Public Health Monograph No. 50

United States-U.S.S.R. Medical Exchange Missions 1956

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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

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United States-U.S.S.R. Medical Exchange Missions 1956

Microbiology and Epidemiology

Part I

Visit of the Soviet Poliomyelitis Team to the United States, January 18–February 22, 1956

Part II

American Medical Mission on Microbiology and Epidemiology to the Soviet Union February 27-March 28, 1956

Public Health Monograph No. 50

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EARLY IN 1956, the Public Health Service was called upon to organize a program of exchanges in medicine between the United States and the Soviet Union.

The Soviet Government had made a request to the United States Department of State for a mission on poliomyelitis to the United States, and the first step in the exchange program was to devise and supervise a schedule for this mission. The mission arrived in the United States on January 18 and left on February 25, 1956.

The second step was the formulation and accomplishment of a reciprocal mission to the Soviet Union. This mission left the United States on February 25 and completed its tour on March 28, 1956.

The third step of the program, as yet incomplete, was the development of a plan for a long-term exchange of information and personnel between the United States and the Soviet Union. At this time, it seems appropriate to review the results of the first completed exchange mission. To this end, the various reports of the American personnel participating in the missions are combined in this monograph.

Dr. Alexis Shelokov of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Public Health Service, acted as tour conductor and interpreter for the Soviet Poliomyelitis Team when they visited the United States. As part I of this monograph, his report covers all aspects of the Russian visit and gives some insight into the impression the Russian scientists made upon their American colleagues.

Members of the Soviet team, all representing the Academy of Medical Sciences of the U.S.S.R., were:

Professor Mikhail P. Chumakov, director, Poliomyelitis Research Institute, Academy of Medical Sciences, Moscow, formerly director of the Institute of Virology imeni [in the name of] Ivanovsky, Academy of Medical Sciences U.S.S.R.

Professor Anatoli A. Smorodintsev, director, department of virusology, Institute of Experimental Medicine, Academy of Medical Sciences, Leningrad.

Dr. Marina K. Voroshilova, senior research worker, Poliomyelitis Research Institute, Academy of Medical Sciences U.S.S.R., Moscow.

Dr. Lev I. Lukin, epidemiologist, Poliomyelitis Research Institute, Academy of Medical Sciences U.S.S.R., Moscow.

The American Mission on Microbiology and Epidemiology to the Soviet Union consisted of the following persons:

Colin M. MacLeod, M.D., professor of microbiology, New York University College of Medicine, New York, N. Y., now professor of microbiology, University of Pennsylvania, Philadelphia, Pa.

Karl F. Meyer, M.D., director, the George W. Hooper Foundation, University of California Medical Center, San Francisco, Calif., and professor of experimental pathology, University of California, Berkeley, Calif.

John R. Paul, M.D., professor of preventive medicine, Yale University, New Haven, Conn.

Richard E. Shope, M.D., member, Rockefeller Institute for Medical Research, New York, N. Y.

Michael B. Shimkin, M.D., chief, Biometry and Epidemiology Branch, National Cancer Institute, National Institutes of Health, Public Health Service, Bethesda, Md. (In 1944, Dr. Shimkin had a similar assignment. A report of this mission was published in *Science*: 605,637, 1946.)

Part II of this monograph is a compilation of reports by the five members of the American delegation.

Following their return to the United States, by prior arrangement members of the mission prepared individual reports on certain aspects of the trip. In order to document as much information as possible in this publication and at the same time to avoid unnecessary repetition, these trip reports have been consolidated into a single chronological account. Meanwhile, a short report by the group was published in the October 13, 1956, issue of the *Journal of the American Medical Association*.

Whatever may be the future fate of the U.S.–U.S.S.R. medical exchanges, the present report should serve to document the conclusions of the members of the American mission, who state ". . . it would be arrogant, stupid, and even dangerous for the United States to ignore Soviet medicine and research . . . ." and that "appropriate steps be taken to develop channels of communication between the medical scientists of the Soviet Union and the United States."

Contents

Contents—Continued

Part I

Visit of the Soviet Poliomyelitis Team to the United States

January 18—February 22, 1956

THE PURPOSE of this report is to record information of medical and scientific interest offered by the Soviet virologists who visited the United States January 18–February 22, 1956. Some of the impressions made upon them and by them during the meetings with a number of our prominent scientists are also mentioned. Because of the nature of the tour, the major portion of the time was devoted to presenting the progress of the scientific work in the United States. Since each presentation was followed by questions, relatively little time was available for us to ask the visitors about their work or for them to discuss it.

The section of the report briefly dealing with some aspects of the Soviet medical system is included because, in spite of its being essentially "hearsay" information, some readers may find it useful.

General Aspects of the Tour

The four Russian virologists who made up the Soviet Poliomyelitis Team represented the Academy of Medical Sciences (AMS) of the Union of Soviet Socialist Republics. Professor Mikhail P. Chumakov, leader of the group, and his senior colleague, Professor Anatoli A. Smorodintsev, have received special recognition for their work on Russian spring-summer encephalitis and Russian hemorrhagic fevers. However, while poliomyelitis has occupied Chumakov's attention for a number of years, Smorodintsev is only now beginning his work in this field, having previously concentrated on the respiratory viruses, influenza especially. Dr. Marina K. Voroshilova, Chumakov's wife, has been his collaborator for many years, primarily in poliomyelitis research, and is an outstanding Soviet poliomyelitis virus specialist. Dr. Lev I. Lukin, who represented the Soviet Medical Association, is an epidemiologist by training and is employed in Chumakov's Poliomyelitis Research Institute.

The four Russians were accompanied on the tour by two commissioned officers of the Public Health Service. William S. Wilson, a sanitary engineer, served as the travel administrator throughout most of the trip, and Dr. Shelokov acted as the scientific interpreter.

The purpose of the tour was to visit some of the outstanding poliomyelitis research laboratories specifically listed by the Russians, in order to meet the responsible investigators, to discuss their current research programs, and to examine the physical facilities of these laboratories. The itinerary was as follows:

January 18	Arrive New York. Delegates met by Dr. Shelokov.
January 19	Arrive Washington, D. C. Department of Health, Education, and Welfare. Met by Surgeon General Leonard A. Scheele of the Public Health Service, who took them to meet Secretary Marion B. Folsom and Special Assistant for Health and Medical Affairs Dr. L. T. Coggeshall. Members of the Surgeon General's staff discussed the broad aspects of the poliomyelitis problem in the United States.
January 20–21	National Institutes of Health, Bethesda, Md. Met by Dr. James Shannon, the director. Brief visits to several virus laboratories of the National Institute of Allergy and Infectious Diseases and of the Division of Bio-

logical Standards. Deposited Russian virus strains for study and distribution by the National Institutes of Health.

January 23–25 Boston, Mass.
Children's Hospital and Harvard School of Public Health: Dr. John F. Enders, Dr. Thomas H. Weller, and their staff. Tissue culture in research on poliomyelitis and other viruses. Visits to poliomyelitis wards and respirator center. Lecture by Professor Smorodintsev.

January 26–27 New Haven, Conn.
Yale University School of Medicine: Dr. John R. Paul and staff. Virus research techniques and epidemiology of poliomyelitis.

January 28–February 1 Pittsburgh, Pa.
University of Pittsburgh: Dr. Jonas Salk and staff. Poliomyelitis vaccine, application of tissue culture to research on other viruses. Lecture by Professor Smorodintsev.

February 2–3 Baltimore, Md.
Johns Hopkins University: Dr. Howard Howe and Dr. David Bodian. Epidemiology and pathogenesis of poliomyelitis.

February 5–7 Cincinnati, Ohio.
Children's Hospital Research Foundation: Dr. Albert B. Sabin and staff. Research on live poliomyelitis virus vaccine, enteric cytopathogenic human orphan (ECHO) viruses, and so forth.

February 9–10 Minneapolis, Minn.
University of Minnesota: Dr. Jerome T. Syverton. Techniques of poliomyelitis virus research; emphasis on use of special cell strains, for example, HeLa cells. Visit to Mayo Clinic.

February 13 Indianapolis, Ind.
Pitman-Moore Co.: Dr. Samuel Bozeman. Commercial production of poliomyelitis vaccine.

February 15–16 Bethesda, Md.
National Institutes of Health. Further conferences with staffs of National Institute of Allergy and Infectious Diseases and Division of Biological Standards. Seminars by Professor Chumakov and Dr. Voroshilova; lecture by Professor Smorodintsev.

February 17 New York, N. Y.
Rockefeller Institute for Medical Research: Dr. Richard Shope. Meetings with the institute staff on a variety of research problems related to the delegates' interest. Lecture by Professor Smorodintsev.

February 20 National Foundation for Infantile Paralysis: Dr. Hart Van Riper, Dr. Thomas Rivers, and others. Poliomyelitis in the United States and the role of the foundation.

February 22 Leave New York for Canada.

As noted, in Boston, Pittsburgh, Bethesda, and New York, Professor Smorodintsev gave a formal lecture. His subject was "Some Problems of Immunity Against Virus Diseases." In Bethesda, Professor Chumakov presented a paper on the "Etiology, Epidemiology, and Prophylaxis of Hemorrhagic Fevers," during a conference organized by Dr. Joseph Smadel, and Dr. Voroshilova presented a paper entitled "Isolation and Studies of Type 4 Poliomyelitis Virus" at a small seminar. Translations of these three presentations are appended to this report as supplements Nos. 1, 2, and 3, and their contents are summarized in the appropriate sections.

There was no question in the minds of the people who met the Soviet delegates as to their competence, as indicated by a thorough scientific background, extensive knowledge of the field of virology, and awareness of recent developments. It was obvious that the three senior members of the group have intimate familiarity with the virus laboratory and have not been restricting their activities to administrative matters. They were a hard-working group, who, because they had little time available, would forego the opportunities for entertainment, sightseeing, or shopping, even though they made it clear that they would have liked to engage in these activities. They worked long hours, late into the night, reorganizing their daily notes and discussing what they had seen.

The interests of the delegates were broad, although they tried to restrict most of their activities to the problems of poliomyelitis. Even though thoroughly familiar with the American scientific literature related to their work, they were anxious to obtain as many reprints as possible for their own working files as well as for the use of their colleagues and as additional copies for the libraries.

At every scheduled visit, they looked forward to meeting personally the American hosts whom they knew well from their publications. Invariably they were interested in reviewing the historical development of the research projects of each laboratory and the direction in which work was progressing. They asked detailed questions not only about the specific procedures and methods employed by a laboratory, but also about the organizational and administrative details assuring efficient functioning of the research group. They paid a great deal of attention to the general and specialized laboratory equipment shown to them: it was apparent that they are concerned with procurement of modern virus laboratory equipment for their own institutes.

Probably because Professor Chumakov will have under his direction a section of the Poliomyelitis Research Institute devoted to clinical research and care of severely paralyzed patients, he was greatly interested in the clinical aspects of this disease. He requested visits to the respirator and rehabilitation centers, where he concerned himself with the medical, social, and psychiatric aspects of clinical poliomyelitis.

The mission was quite anxious to initiate an exchange of virus strains and antiserums. With this in mind, they brought with them several viruses, which will be discussed later, and offered any other material of interest to American microbiologists for future exchanges. In return they requested a number of virus strains and serums, including all the official prototypes of Coxsackie groups A and B, the enteric cytopathogenic human orphan (ECHO) virus group, the adenoviruses, and others.

Specific Comments by the Russian Delegates

Virus Diseases

Poliomyelitis

Usually Professor Chumakov was the spokesman for the group on the subject of poliomyelitis, stating that, as compared with the disease in the United States, poliomyelitis has not presented much of a problem in the Soviet Union. During most press interviews he mentioned the incidence rate in the U.S.S.R. as being approximately one-tenth as high as in the United States. On one occasion, however, he cited the usual annual rate as 0.8 cases per 100,000 population, with the peak incidence in children under the age of 5 years. Since about 1950 the disease has become more common and there have been several serious outbreaks in certain of the Soviet republics, with the incidence rising to 5 or 6 cases per 100,000. The Soviet Government is aware that, following the usual course of events in other countries, a possibility exists that poliomyelitis will become a public health problem. Hence the delegates' concern with the vaccine as well as the new government-sponsored interest in the entire field of poliomyelitis as evidenced by the formation of a special Poliomyelitis Research Institute under Professor Chumakov's direction.

When Professor Chumakov was asked what in his opinion is responsible for the increasing incidence of poliomyelitis in the Soviet Union, he stated that possible factors include the spread of poliomyelitis viruses to the U.S.S.R. from the countries where poliomyelitis has become a serious and common problem (he cited the probable introduction of poliomyelitis into the United States by the Scandinavian immigrants towards the end of the last century), and that the opportunities for virus spread from one country to another are rather favorable in this age of rapid and extensive travel throughout the world. Professor Chumakov disagreed with the commonly given explanation of shifting incidence of poliomyelitis toward older age groups because he did not think that improved sanitary conditions can possibly explain the whole picture and stated that it is too simple and convenient a hypothesis. At different times he developed this theme in different ways, emphasizing such other factors as possible change in virulence of epidemic strains, differences in mechanisms of susceptibility, and resistance determined by the individual's physiological status. He also cited experiences in 1952 in Karaganda (Kazakhstan S.S.R.), where a very severe epidemic, affecting many adults, occurred under conditions that were unsanitary, in comparison with most of the Soviet Union.

Virologic investigations of poliomyelitis in the U.S.S.R. were begun in 1945 by Chumakov, Belyaeva, and Voroshilova, who isolated the first strain of poliovirus from the brain of a child dead from this disease. From 1945 to 1954, using monkeys, cotton rats, and mice, Chumakov and his co-workers isolated 32 strains of poliovirus from several Soviet outbreaks. They specifically mentioned studies in the Baltic republics, the Kazakhstan Republic, Western Siberia, and Byelorussian Republic, as well as the thorough investigation of the Berlin epidemic of 1947–48. In 1954 and 1955, using human embryonic fibroblasts in tissue culture, Chumakov's group isolated 192 virus strains, the majority of which came from diagnosed clinical cases of poliomyelitis. (Apparently, in the summer of 1955, there was a severe outbreak of poliomyelitis in Moscow and, as a result, the Soviet physicians have renewed their interest in this disease.) Thus, to date the total number of strains isolated was given as 224, of which 187 of the 198 typable strains (94 percent) belong to type 1, 8 strains (4 percent) belong to type 2, and 3 strains were classified as belonging to the new type 4 poliovirus. In addition 14 other cytopathogenic agents, which so far have not been classified, were isolated from the patients' stools. Also, 12 virus strains as yet not typed were isolated in monkeys. It was specifically stated that Chumakov and his colleagues have never isolated any strains of poliovirus belonging to type 3.

The three strains of virus which Chumakov, Belyaeva, and Voroshilova call the type 4 poliovirus were discussed in detail by Dr. Voroshilova in her report given at the National Institutes of Health. (A complete translation appears in supplement No. 3).

The following is a brief summary of her presentation: The three strains of poliomyelitis virus were isolated from stools of six children during the 1952 epidemic in Karaganda. The stools were pooled in pairs according to the clinical disease of the donors: 2 children had severe involvement and eventually died; 2 had typical spinal form of paralysis; and 2 were nonparalytic cases. All three fecal pools yielded virus strains which were found to belong to the same apparently new type of poliovirus. These strains possess high pathogenicity for monkeys and for newborn and adult cotton rats. Newborn white mice were somewhat less susceptible. Unlike type 2 polioviruses these strains were totally nonpathogenic for adult white mice. The histopathological lesions in the brains and spinal cords of infected monkeys and cotton rats corresponded closely to those of experimental poliomyelities. Definite differences were found in the antigenic structure of the Russian strains compared with the standard polioviruses of types 1, 2, and 3. Therefore, she postulated that they have discovered a new immunological type of poliovirus.

Emphasizing that type 4 poliovirus was isolated only during one of the many outbreaks investigated, Voroshilova suggested that this is not a common cause of clinical poliomyelitis, although they were able to show the presence of neutralizing antibodies in the serums collected from other parts of the Soviet Union, including the Moscow district.

Although tissue culture procedures have been used in Russia for many years, their specific application to poliomyelitis research and diagnostic procedures dates back only to early 1954. Primarily, Soviet investigators have relied upon cultures of human fibroblasts derived from fragments of fetal tissues, obtained through therapeutic abortions performed in hospitals, and to some extent HeLa cell strain obtained from one of the

Scandinavian laboratories. They have had little experience with monkey kidney tissue and have not as yet begun mass preparation of cells by trypsinization procedures and similar methods. They have had difficulties in procuring monkeys in sufficient numbers. Apparently their own monkey nursery at the Sukhumi Biological Station cannot produce monkeys rapidly enough and it has been almost impossible to import the animals from India or the Philippines. Most of the monkeys the Soviets have are rhesus but small numbers of cynomolgus, African, and New World species are kept at Sukhumi for selective breeding in order to produce a species which can withstand the rigors of the northern climate and still be useful in poliomyelitis studies.

It was said that Soviet laboratories have small amounts of experimental poliomyelitis vaccine, of both killed and live virus types, which are used for animal experimentation. In regard to the American progress in development of an effective vaccine, the delegates stated that they were greatly impressed with the efficacy of the Salk vaccine employing formalin-killed poliovirus; nevertheless they felt that the living virus vaccine should be further developed for possible practical use. They considered a possibility that it might be desirable to use living virus vaccine for the second injection once a margin of safety through antibody response to the first injection of killed virus is assured, even if it may not be feasible to use living virus vaccine exclusively.

The delegates were very much interested in the steps Dr. Salk is taking to improve the present poliomyelitis vaccine as well as in Dr. Sabin's progress toward a living attenuated vaccine for oral use. They were concerned with the details of vaccine production, including particularly safety and potency controls and the problems inherent in large-scale application of custom techniques and procedures, originally worked out under highly controlled conditions of a research laboratory.

It was apparent that the Russian virologists are considering and planning to organize pilot plants for production of small quantities of experimental vaccine for human use in field trials. In fact, the delegates stated somewhat optimistically that before the next poliomyelitis season they hope to use their own vaccine in a field trial similar to the 1954 trials in the United States but on a smaller scale.

Because the peak incidence of poliomyelitis occurs before the age of 5 years in the Soviet Union, the delegates considered it important to know whether the evidence so far accumulated in the United States would apply to their home situation; that is, they wish to know whether the Salk vaccine successfully immunizes very young children and infants. On the basis of the data demonstrated to them they thought that it probably does.

Professor Chumakov was interested in setting up new laboratories at the Poliomyelitis Research Institute; he spoke of the laboratory equipment and the clinical equipment for a respirator center, including a rehabilitation service for severely paralyzed patients, such as tank and chest respirators, and other devices for the care of patients with respiratory embarrassment, such as rocking beds, electrophrenic respirators, vital capacity meters, or oximeters. (Apparently no clinical facilities are planned for the Leningrad Institute; the Moscow Center will conduct all of the clinical research on poliomyelitis.)

In summary, Soviet research on poliomyelitis is undoubtedly in the early stages of technical development; even so, it offers certain important contributions, such as the possible discovery of type 4 poliovirus. With the modern methods available, and with an adequate supply of susceptible cells for tissue culture work, it can be expected that within a short time Soviet workers will be able to do large-scale diagnostic work, including virus isolations and serologic procedures, as well as competent fundamental research and development of applied techniques, such as a poliomyelitis vaccine.

Living Virus Vaccines

Live virus vaccines against influenza, measles, and mumps were discussed several times as important Soviet contributions to preventive medicine. According to Professor Smorodintsev, usually the spokesman for the group on this subject, details of the technical procedures in their preparation have been published during the past several years in Soviet journals.

Smorodintsev stated that all three vaccines are prepared in embryonated eggs and that the measles vaccine virus now adapted to chick embryos originally was cultivated in tissue culture. The measles vaccine has been developed by Professor Sergiev, who has perfected it sufficiently to consider its large-scale use in children within a short time. The mumps vaccine was mentioned as a promising preparation though it is still in an experimental stage and is not ready for wide practical application.

Professor Smorodintsev stated that live influenza virus vaccine is prepared from the allantoic fluid of chick embryos infected with several standard strains of epidemic influenza, including, I believe, 1 strain of type A, 1 of A prime, and 2 or 3 strains of group B. The vaccine is provided as a lyophilized powder which can be insufflated directly into the nasal passages or, if a liquid atomizer is used, it is reconstituted with sterile water.

Vaccination has to be repeated approximately every 12 to 18 months in order to maintain adequate immunity. Smorodintsev stated that influenza morbidity can be tremendously diminished with this vaccine and that "the body selects the strains of the living virus types to which it has no preexisting immunity, allowing these strains to multiply in the respiratory passages while the 'useless' strains, that is, those to which the patient is immune, are suppressed and cannot propagate in the patient's tissues." According to Smorodintsev, during the past few years more than 10,000,000 individuals have received this vaccine annually. He believes that, with increasing use of the vaccine, a great proportion of the population eventually will be protected.

The list of contraindications to vaccination includes the more general types of undesirable conditions such as acute febrile or respiratory diseases, chronic lung diseases, cardiovascular insufficiency, marked debilitation of the patient, and the late months of pregnancy. Not mentioned in this list is the fact that the vaccine should not be used in children under the age of 7 years because of the frequency and severity of undesirable side reactions, a point which Professor Smorodintsev specifically discussed. He was enthusiastic about the possibility of using the killed virus influenza vaccine developed in the United States for immunization of the Soviet preschool children.

The anti-influenza serum was described as a polyvalent serum prepared in horses (?) against the strains of influenza, including A, A prime, and B. The serum is provided in dry powder form. Professor Smorodintsev felt that this serum has a definite therapeutic efficacy if administered sufficiently early (on the first or second day of disease), or when administered to members of a family which needs protection because of a case of influenza in the household. For therapeutic purposes, the serum has to be administered several times each day. For prophylaxis, it is given about once a week during the entire period of the epidemic outbreak. According to Smorodintsev, there are no contraindications to its use at any time or at any age [other than sensitization to horse serum?].

Early laboratory diagnosis of epidemic influenza was another topic mentioned several times by Professor Smorodintsev. He pointed out that often it is important for the epidemiologist to establish early the fact that an outbreak of influenza is occurring, whatever virus type is eventually established as the cause of the outbreak. Such a diagnosis, he claims, can be accomplished by impression smears of nasal secretions from the clinical cases of influenza. According to Smorodintsev, in 50 to 60 percent of influenza cases it can be specifically established that the patient is suffering from influenza by the presence of characteristic eosinophilic inclusion bodies in the nasal epithelial cells. The technique of making impression smears consists of introducing a narrow thin cover slip into the posterior nares, allowing the removed secretions to dry, and staining the preparation with a differential stain for inclusion bodies. (As already noted, Smorodintsev said that these methods and procedures have been adequately described in their publications during the past 5 or 7 years).

Viral Hemorrhagic Fevers

While the subject of hemorrhagic fever was discussed many times, the best organized summary of the Soviet studies was given by Professor Chumakov in his presentation at the National Institutes of Health, under the title, "Etiology, Epidemiology, and Prophylaxis of Hemorrhagic Fevers" (supplement No. 1). This was a brief but lucid summary of Soviet work on the three specific and distinct clinical entities (Far Eastern, Crimean, and Omsk hemorrhagic fevers) which he groups under a general name of "viral hemorrhagic fevers" because of the similarity in their hemorrhagic manifestations, even though there is little question that they are caused by entirely different etiological agents.

Chumakov reviewed the history of the name "hemorrhagic fever," which he introduced to describe the Crimean disease. (The Soviets were calling the Far Eastern form "hemorrhagic nephroso-nephritis" or "hemorrhagic fever with renal syndrome," unaware that the Japanese named the same disease "epidemic hemorrhagic fever," the term adopted later by the American investigators to describe the disease as encountered in Korea at the 38th parallel.) Professor Chumakov is convinced that all three hemorrhagic fevers are due to filtrable viruses. (The causal agent of the Far Eastern form so far has not been definitely established although the probable etiological agent was isolated from three species of Gamasoidea mites.)

Referring to the original observations made by Smorodintsev in 1940, when "hemorrhagic nephroso-nephritis" was first discovered and described, Professor Chumakov stated that he was able to repeat that work in 1954–55, since almost every year, beginning with 1948, cases of undoubtedly the same disease have occurred in the European U.S.S.R., with the largest outbreak, about 300 cases in the Yaroslavl area. In the body of this section of his report he reviewed the clinical and pathological findings and the epidemiological and virologic studies, with results essentially similar to those of the Japanese and the American studies. He concluded by saying that, unfortunately, thus far it has not been possible to find convenient laboratory methods for isolation and identification of the etiological viral agent; that there are no serologic means of diagnosis of this disease, no methods of specific prophylaxis or treatment; and that only general prophylactic measures can be recommended, such as destruction of the rodent population and protection of humans against contact with rodents and their ectoparasites. (Chumakov feels that the human infection occurs upon direct contact with excreta of infected rodents.)

The next section of Chumakov's paper deals with the Crimean hemorrhagic fever. This disease was originally studied and described by Chumakov in 1944. It occurs primarily in the steppes of the Russian republics from Crimea through the middle Asiatic areas. It is caused by a specific viral agent which has been repeatedly isolated from the bloodstream of febrile patients, as well as from infected *Hyalomma* ticks, which serve as vectors. Diagnosis is usually established by complement-fixation and neutralization reactions. At the present time a vaccine is being developed to prevent Crimean fever, using heat-killed virus which, under proper conditions, retains its immunogenic properties.

The Omsk hemorrhagic fever also was originally discovered and described by Chumakov and co-workers in 1947. It occurs in a relatively small area of the Barabin steppes about the Omsk and Novosibirsk regions. It is a milder disease than the other two and is caused by a filtrable virus which is highly pathogenic for a number of rodents. The ticks of *Dermacentor* species are the natural reservoir and vectors of the infection. This virus was found to be antigenically related to other viruses transmitted by the *Ixodides* ticks, namely the viruses of spring-summer tick encephalitis, of Scotch "louping-ill" encephalomyelitis, and the so-called "viral milk fever with double period of pyrexia" occurring in Central Europe. Laboratory diagnosis of the Omsk disease is made by means of complement fixation or neutralization reactions or through easily accomplished isolation of the virus from the blood stream. There is an effective formalin-killed virus vaccine, made from the brains of mice, which is the most effective method of prophylaxis against this disease.

Some of Professor Chumakov's informal comments on the hemorrhagic fevers, made during the trip and reported below, reemphasize some of the points made in his report (supplement No. 1), elucidate others, and supply some additional new information.

As already mentioned, in 1955 Professor Chumakov repeated the work originally done by Smorodintsev on the Far Eastern hemorrhagic fever, except that Chumakov used "filtered material" from clinical cases observed in the European U.S.S.R. The filtrate was inoculated into human volunteers, some of them his laboratory personnel, and the results of this experiment were said to confirm that Far Eastern hemorrhagic fever is not a rickettsial but a viral disease. Chumakov mentioned that these filtered materials were also inoculated into human embryonic fibroblast tissue cultures, with production of a cytopathogenic effect consisting of "central degeneration" around the fragment and some "focal degeneration" at the periphery of the outgrowth. This effect could be observed in the inoculated tubes only (the controls remained normal) for a total of three passages in fibroblast cultures, after which it was apparently lost.

Professor Chumakov's feeling is that the effect probably was due to the virus of epidemic hemorrhagic fever. (Besides the many usual virus laboratory animals which proved negative for isolation or propagation of the virus of the Far Eastern fever, Dr. Voroshilova mentioned that she and Professor Chumakov had tried repeatedly to adapt hemorrhagic fever to cats with no success.) Professor Chumakov could not account easily for the localization of Yaroslavl hemorrhagic fever in the small geographic area, except for such factors as topographic conditions favoring the prevalence of the particular tick carrier, even though he did not think that this is a completely adequate explanation.

In regard to Omsk hemorrhagic fever, Professor Chumakov said that it is a mild, benign disease with mortality amounting only to 1 or 2 percent. The clinical course is characterized by headache, fever with the temperature reaching 39.5°–40°C., often with a double hump, considerable systemic toxicity, occasional petechiae, and no true purpura hemorrhagica except on very rare occasions, and usually only microscopic hematuria. The course of the acute case is usually about 2 weeks, and recovery is gradual. The virus can be isolated from the blood of the patient throughout the febrile period, up to the sixth or seventh day of the disease.

The muskrat is the best experimental animal for the investigation of Omsk hemorrhagic fever. Upon infection, it reproduces the clinical picture of the disease in man, including thrombopenia, shift to the left in the white blood cell count, and leukopenia.

The virus can also be propagated successfully in white mice by the intracerebral route, with production of hemorrhagic encephalitis, paralysis, and death.

The disease is usually transmitted by two species of *Dermacentor* ticks and, under special conditions, by a species of muskrat which serves as the vector in some explosive outbreaks in the absence of ticks.

The vaccine against Omsk hemorrhagic fever is made from mouse brain and it is said to be very effective. In the first field trials, three cases of the disease occurred in some 1,280 vaccinees, while about 137 cases occurred in approximately 1,200 unvaccinated persons.

The localization of Omsk hemorrhagic fever within a small area of something like 30 by 70 kilometers remains unexplained. Professor Chumakov suggested that in reality the Omsk disease may be occurring elsewhere in the Soviet Union but so far the cases have not been recognized.

In regard to the Crimean hemorrhagic fever, Professor Chumakov stated that this is a much more severe and serious infection than the Omsk type, with a high mortality and frequently complicated course. Viremia is also present during the febrile course of the disease. Intravenous inoculation of serum or blood of acutely ill persons into monkeys produces fever only and the disease cannot be reproduced in this species nor can the virus be passaged more than a few times.

The virus of Crimean hemorrhagic fever

has to be kept alive by passaging in human beings by such means as inoculation of institutionalized psychiatric patients, primarily schizophrenics, who are carefully selected from the group needing pyrogenic therapy as part of their regimen and who receive a "controlled dose" of the virus. The blood of these inoculated patients contains appreciable quantities of the virus, which can be neutralized, losing its pathogenicity for the human if it is mixed with convalescent serum obtained at 4 or 6 weeks from recovering human volunteers.

A diagnostic complement fixation test can be performed using serum from acutely ill patients which contains enough virus to serve as a satisfactory antigen against convalescent serum from patients, which contains antibodies.

The psychiatric patients who are serving as media for passage of the Crimean virus and at the same time are receiving pyrogenic therapy are protected with human immune convalescent serum when it appears that they may be developing a severe form of the disease. In this regard Professor Chumakov stated unequivocally that administration of the serum to such ill patients developing serious toxic symptoms of the Crimean fever resulted in a most dramatic alleviation of their distress within 12 or 18 hours. Generally, the patients remain under close observation to determine whether they might need the therapeutic serum, and it was said that there has never been a fatality in a patient receiving the experimental infection with the Crimean hemorrhagic fever.

Viral Chorioencephalitis

During one visit, Professor Chumakov described an interesting disease entity. The Soviet virologists call the disease viral chorioencephalitis, while the psychiatrists and neurologists prefer to use the descriptive "psychosensory neuroinfection of school children." The disease begins with a week or so of mild influenzalike illness, often followed by a period of remission, after which the characteristic syndrome appears. The complaints often refer to odd disturbances in perception of space relations associated with difficulty in mental concentration. Professor Chumakov described the most characteristic complaint of school children as a sensation that either one side of the body is asymmetrical in size or in shape as compared with the other, or that the other people and objects around the patient have become asymmetrical. Some patients experience the sensation of objects rotating in space as much as 180°.

Apparently this is not a psychiatric disturbance but represents an organic lesion in the appropriate portion of the brain resulting in the specific disturbances of perception of physical dimensions. On lumbar puncture a marked elevation of cerebrospinal fluid pressure is often found with little if any other change.

Professor Chumakov stated that a virus was isolated in 1948 from individual pools of blood and cerebrospinal fluids of three patients. The virus can be easily passaged by intracerebral inoculation of white mice. Chumakov felt that this is the specific etiological agent, related to, but not identical with, the virus of lymphocytic choriomeningitis (Armstrong).

Usually the course of viral chorioencephalitis is rather benign and often the outbreaks are detected from reports of school teachers who become concerned by the sudden deterioration of some of their outstanding students, who, on investigation, can be shown to be suffering from this disease.

No human material has been available for histological studies. In animals there is considerable edema of the white matter and distinct lesions of the choroid plexi.

Professor Chumakov stated that viral chorioencephalitis has become less prevalent since its recognition in the 1940's and not many cases can now be found. A strain of this virus was brought to the National Institutes of Health for study and a description of this strain supplied by Professor Chumakov is appended to this report (supplement 2).

Some Briefly Noted Topics

Other Viruses

Professor Smorodintsev mentioned that several immunologically distinct types of what appear to be the APC viruses have been isolated in the Soviet Union, but that these cannot be correlated with the officially recognized American types for lack of serums and viruses for comparison. Similarly Voroshilova and Chumakov have isolated a number of cytopathogenic agents which were not typable with the usual poliomyelitis hyperimmune serums; not being pathogenic for suckling mice, they apparently are new agents. Some of these, they feel, would probably fall into the orphan ECHO virus groups, had they the means for proper comparison of the strains.

Voroshilova and Chumakov have also isolated several virus strains undoubtedly belonging to the group A Coxsackie, but these also have not been compared with the internationally accepted types. They were not certain that they have isolated any strains belonging to group B Coxsackie virus.

Both Professor Chumakov and Professor Smorodintsev stated that in Russia at present there is no effective vaccine against infectious hepatitis, nor were they aware of anyone who has definitely isolated the causal agent of infectious hepatitis.

The problem of classification of one of the strains of the virus causing Russian spring-summer tick encephalitis was discussed because of the strain brought by the delegation for study to the United States. Some workers in Russia have had evidence that this strain is identical or related to the virus of the Scotch "louping-ill" while others are not convinced of such close relationship.

The virus of foot-and-mouth disease of cattle was the only animal virus specifically mentioned because of the effective vaccine available against this disease.

Multiple Sclerosis Vaccine

The Soviet vaccine against multiple sclerosis was briefly discussed on several occasions. It was stated that this is not a prophylactic preparation and seems to be useful in therapy of the disease (that is, its use is a procedure amounting to "postinfectious immunization" using a vaccine for treatment). The vaccine is prepared from rat brains which contain what is thought to be the virus of multiple sclerosis. The results with the use of this vaccine are somewhat equivocal and while a remission rate of about 30 percent seems to be associated with it, the mortality rate due to multiple sclerosis apparently is not affected. It was noted that it is extremely difficult to evaluate the efficacy of any preparation when the natural course of this chronic disease is characterized by spontaneous remissions, but some data indicate that the vaccine can be successfully used for its early diagnosis. This is accomplished by injecting a small amount intracutaneously to serve as a skin test, thus presumably eliminating the necessity of waiting for the clinically recognizable characteristic symptoms and signs.

Bacterial Vaccines

While the group did not include a bacteriologist, the delegates spoke of some of the Russian accomplishments in the development of effective bacterial vaccines, particularly those using live attenuated strains of organisms. Professor Smorodintsev mentioned the highly satisfactory vaccine produced against tularemia. The vaccine is prepared by attenuating live strain of *Pasteurella tularense* "by the classical method of Pasteur using heat." It is employed only in endemic areas, specifically in individuals occupationally exposed to tularemia, with a drastic reduction in incidence of the disease.

Two other successful vaccines mentioned were the preparations against brucellosis and anthrax.

Incidentally, in reply to a question about the use of typhoid vaccine in the Soviet Union, Professor Smorodintsev stated that typhoid inoculations are given only when specifically indicated in the civilian population, but members of the armed services routinely receive classical typhoid-paratyphoid vaccine combined with tetanus toxoid.

Professor Smorodintsev mentioned that the BCG vaccine against tuberculosis is widely used in the Soviet Union with excellent results, that is, a considerable reduction of morbidity due to tuberculosis. Dr. Voroshilova added that the BCG vaccine is now routinely administered in the Soviet nurseries, a teaspoonful by mouth prior to the infant's departure from the hospital.

Antiviral Immunity

The formal lecture delivered by Professor Smorodintsev in several cities was entitled "Some Problems of Immunity Against Virus Diseases." This presentation did not lend itself to brief summaries, and the reader is referred to the complete text (supplement No. 2), which deals with some of the work conducted in Smorodintsev's laboratory during the past 15 years on the differences between the mechanisms of antiviral and antibacterial immunity, including the role of phagocytosis.

Smorodintsev believes that it has been established that one of the most important physiological defense factors against viruses is the destructive effect of normal body temperature of warm-blooded animals on the extracellular virus particles. He believes this to be the most universal and constant direct cause of the death of viruses outside of the susceptible cells in naturally insusceptible animals. He considered the role of the virus-neutralizing antibodies, describing the discovery of thermolabile antibodies. These can be demonstrated in very small amounts only in fresh serums of animals hyperimmunized with live virus, and the thermolabile antibodies are lost not only with heating but on prolonged storage in ordinary refrigerators. These antibodies lyse the virus irreversibly and are present in insignificantly small amounts as compared with heat-stable antibodies which cause reversible neutralization of the virus.

Professor Smorodintsev left with the library of the National Institutes of Health a freshly printed copy of Voprosi Patogeneza i Immunologii Viruskhnikh Bolezney (Problems of Pathogenesis and Immunology of Virus Diseases), published by Medgiz, Leningrad, 1955 (478 pp.) This is a collection of articles written by several Soviet authorities of the Leningrad school, with Professor Smorodintsev as the editor. The titles of the five sections indicate the subject matter:

I. Problems of pathogenesis of virus infections.
II. Mechanisms of natural antiviral immunity.
III. Specific mechanisms of antiviral immunity.
IV. Problems of virus nature of bacterial phage.
V. Problems of immunity to individual virus infections.

This appears to be an excellent book, summarizing the recent Soviet experimental work and the Leningrad group's concept of the pathogenesis and immunogenesis of virus diseases.

Some General Aspects of Soviet Medicine

This section is included because some of the comments of the delegates about their medical education, their virologic institutes, and their media for dissemination of scientific information may be of interest. No organized discussion of these topics took place during the trip. The following notes represent a few impressions gathered during informal conversation.

Apparently the modern trend in the Soviet Union is to separate the medical school, physically as well as administratively, from the rest of the university because, in the experience of the Soviets, the medical school benefits from such separation. The medical school staff, both in basic and clinical medical sciences, are encouraged to do independent research, but the research activities conducted in the various scientific institutes are removed from the medical schools and from the universities to insure the research scientist freedom from formal teaching. However, the younger staff members of the research institutes have an academic standing as candidates for higher degrees ("aspirants") and are the future professorial and senior research staff of the medical schools and the institutes.

The general structure of the Soviet medical research institutes as functionaries of the Academy of Medical Sciences U.S.S.R. is well known. The newest organization is the Poliomyelitis Research Institute under Professor Chumakov's directorship. Apparently this particular institute will be charged with directing poliomyelitis research in the Soviet Union in its virologic, epidemiological, and clinical aspects, including development of an effective vaccine of either killed or living virus type. It was implied that this will be a major institute with a large budget and a large staff of professional and technical personnel. Previously both Professor Chumakov and Dr. Voroshilova were associated with the Institute of Virusology imeni Ivanovsky, the other prominent virologic institute under the Academy of Medical Sciences, also located in Moscow. Some of the other major institutions referred to as *the* virologic centers were: the Institute of Epidemiology and Microbiology imeni Gamaleya, and the Leningrad Institute of Experimental Medicine, where the department of virusology is under the directorship of Professor Smorodintsev.

Professor Chumakov indicated that efforts are being made to establish a network of smaller independent virologic centers suitable for advanced training of young virologists and for carrying out independent research. He stated that several such institutes have been in existence for a number of years doing first-class work but on a smaller scale and with a lesser concentration of prominent talent than the central institutes in Moscow and Leningrad. The following were named as outstanding examples of fine peripheral laboratories: Kharkov, Tiflis, Kiev, and Tashkent.

Because of the interest of the delegates in monkeys as animals essential in poliomyelitis research, the Sukhumi Biological Station was repeatedly mentioned, with its experimental monkey breeding nursery.

The only institute of strictly clinical nature referred to by the delegates was the Central Institute for Advanced Medical Studies, or, differently translated, the Central Institute for Professional Advancement of Physicians, also located in Moscow. The function of this institute is to provide specialty training in the clinical and fundamental aspects of the various specialty fields of medicine and surgery and the subspecialties. The training provided there is not generally comparable to our program of residency training; it is intended for postgraduate education of physicians already engaged in practice of clinical medicine. Apparently, this particular program is more comparable with our university postgraduate medical courses offered for physicians who return for a specific study of a certain aspect of medicine without necessarily direct responsibility for hospital patients.

The delegates' thorough knowledge of our scientific literature served as convincing evidence of the efforts of their scientific community to keep up with advances in the United States. Most of the Soviet workers, even if they cannot speak English, are able to read scientific English with the help of a dictionary; abstracts and translations of our significant publications apparently are available to them as issued by the Institute of Scientific Information of the Academy of Sciences of the U.S.S.R. It was mentioned that this institute employs about 200 people, who are engaged in abstracting Russian, Eastern European, and Western scientific publications and supplying full translations when needed. Apparently they regularly publish a set of abstracts of both Soviet and non-Soviet papers in various fields under the title, "*Referativny Zhurnal*," similar in nature to our *Biological Abstracts*. It was said that there is a surprisingly short lag between the publication of a Soviet scientific article and its inclusion in the abstracts.

The visitors often inquired of our scientists about their knowledge of Soviet work in a particular field, and usually the answer was that very little is known because few of our scientists can either read Russian or have access to translations of Soviet articles. The Soviet visitors, on the other hand, stated that not only are all of the Soviet medical libraries supplied with most of the standard and some of the more obscure scientific publications from the United States but also that many individual scientists privately subscribe to American journals. Both Professor Smorodintsev and Professor Chumakov receive five of our journals, including *Journal of Bacteriology, Proceedings of the Society for Experimental Biology and Medicine, Journal of Immunology, American Journal of Hygiene,* and *American Journal of Public Health.* One of the members of the group listed some of the Soviet medical journals which in his opinion are especially outstanding. These included *Mikrobiologiya, Klinicheskaya Meditsina (Clinical Medicine), Kazanskyi Meditsinskyi Zhurnal (Medical Journal of the University of Kazan),* and the *Vestnik Akademii Meditzinskikh Nauk (Bulletin of the Academy of Medical Sciences).*

The delegates mentioned that a new journal dealing with virology exclusively was to appear in January 1956, with the first issue devoted to poliomyelitis research. The name of this new journal is *Voprosy Virusologii (Problems of Virology).*

Chumakov stated that the best Soviet virology text is Virus and Rickettsial Infections of Man, edited by Thomas Rivers, second edition, 1952. This was translated by Voroshilova and brought up to date by Chumakov by means of annotations, footnotes, and additional bibliography, covering recent advances in Soviet work in the field of virology.

Results of the Tour

It was obvious that the Soviet delegation was impressed by the competence and productivity of our professional scientific workers, as well as by the efficiency and skills of the supporting technical personnel. They repeatedly commented on the large number of virologic centers in the United States and on the quality and abundance of equipment in our well-designed laboratories. The way they put it on one of the occasions was that it is fortunate that, at a time when a revolution had taken place in the whole field of virology because of tissue culture techniques, the United States had on hand a constellation of unusually competent individuals to pick up these techniques and immediately apply them, developing the science of virology beyond the dreams of a few years past.

The breadth of interests of many of our prominent virologists also impressed the Soviet visitors. They commented on the fact that, in each one of the laboratories they visited, not one but a number of related but not necessarily dependent projects are pursued by various members of the research group. The quality of our equipment, which they found was available with relative ease at prices which are not prohibitive, and the abundance of such equipment in all of the better virologic laboratories evoked favorable comment, as did the physical layout of the laboratories. Their admiration was evident not only in the spoken words: Professor Smorodintsev's camera clicked incessantly and time and time again members of the delegation made sketches of individual pieces of equipment demonstrated to them as well as of the physical setup of the laboratories. There is no question in my mind that these delegates will carry away with them a highly favorable impression of the status of virologic research in the United States.

As to the impressions the visitors made on the majority of the Americans, I believe that the consensus can be summarized as follows: The three senior members of the group are highly competent virologists, thoroughly familiar with our published scientific work. They were most receptive to the information imparted and evaluated it in an objectively critical, but friendly, way. For the most part, their questions and comments were informed and to the point. They repeatedly declared their belief in the value of freedom of scientific thought and exchange of ideas as the cornerstone of international and national science. They felt sure that the situation in the Soviet Union today is such as to warrant mutual understanding and close relation between the scientists of the two nations.

The delegates invited their hosts to come to the Soviet Union, assuring them of a warm welcome and total freedom to visit anywhere and to see, hear, and discuss anything they wish. They appeared anxious to set up an open exchange of published materials, as well as of manuscripts for publication in the journals of the other country, and to set up reciprocal exchanges of virus strains, serums, vaccines, and other biological materials. They also expressed a hope that it will be possible to exchange younger scientific personnel on fellowships as well as to exchange senior scientists in the field of microbiology as visiting lecturers and consultants.

What can be said about the direction that is being taken by Soviet virology today? It is obvious that in the field of poliomyelitis they are going to follow the pattern so well established during the last few years by the American school of virology: mass production of tissue culture cells for diagnosis by virus isolation, neutralization, complement-fixation procedures, and so forth. This will automatically involve them in separation and identification of other cytopathogenic agents, that is, Coxsackie, *Herpes simplex*, APC, ECHO viruses, and so forth. Even though during their discussions here the delegates emphasized the use of rodents for isolation and identification of new viruses, it is likely that once engaged in tissue culture work their emphasis will shift to routine neglect of these animals for no other reason than the sheer numbers of specimens. Finally, it is also evident that they intend to begin production of formalin-killed poliomyelitis vaccine for field trial use while extending their early interests in the possibilities of an attenuated live virus vaccine.

The above statements, especially in regard to vaccine production, are based on the assumption that the Soviet scientists will be able to find a steady supply of susceptible animal cells for tissue culture work. It is conceivable that they may find it impossible to obtain monkey kidneys in sufficient numbers, in which case their workers would have to rely on cultures of stable cell lines (such as HeLa cells), human amnion cells, or other human and animal tissues, with certain inherent disadvantages.

Whatever tissues the Russian scientists use, their virologic research is bound to undergo a revolution similar to that which we have witnessed in the United States during the past few years. It would be difficult to predict what directions this work will follow because the horizons may be unlimited. With the modern tools of virologic research in their hands, undoubtedly the Russians will also delve into the fundamental aspects of immunology, virus-cell relationships, and similar basic problems. It is safe to say that they have the scientific competence and the imagination to produce significant contributions to virology.

We, too, have benefited from the visit of this delegation, and not only through acquisition of a few Russian virus strains, including the possibly important so-called type 4 poliomyelitis virus. For one thing, the Soviet delegation paved the way for our mission to the Soviet Union to visit their scientific institutes and virologic centers. Most important, their visit may have initiated exchange of scientific information, virus strains, vaccine, and so forth, which would benefit both countries.

Finally, the favorable impression created by these scientific delegates, who served as ambassadors of good will on behalf of the Soviet scientists, will probably result in a reawakened interest of American research workers in Soviet scientific literature, which, according to the visitors, is entering a period of new vigor and productivity.

Supplements to Part 1

The material in these supplements was translated by Dr. Alexis Shelokov, the Public Health Service officer who acted as interpreter for the Soviet delegation. No effort was made to edit the original reports from a literary standpoint, and this has occasionally resulted in unusual turns of speech.

Professor Chumakov's and Dr. Voroshilova's reports were written under most adverse circumstances. The decision to give these talks was made while on tour and the presentations were composed at odd hours and written in longhand aboard moving trains. Neither author had the opportunity to reread his Russian text, which was prepared from memory and from notations in notebooks. Since the translations were done under similar circumstances and the typing could not be finished until almost the moment of delivery, the authors did not have an opportunity to see the final English versions.

Professor Smorodintsev's lecture was based on an earlier and considerably longer lecture originally entitled, "The Mechanism of Suppression of Viral Agents in the Immune Organism." The present text was translated from his abridged manuscript in time to begin the actual presentation.

Etiology, Epidemiology, and Prophylaxis of Hemorrhagic Fevers

M. P. Chumakov

During the past 10 or 20 years, Soviet scientists have studied and described a group of new endemic virus diseases of man for which I propose a general name of "viral hemorrhagic fevers." Various manifestations of the hemorrhagic syndrome appear rather frequently (in over 50 percent of all cases) during the course of these infections, regular changes take place in the blood picture, and there are certain symptoms attributable to lesions in the nervous system and internal organs.

Incidentally, the name "hemorrhagic fever" was first introduced by us in 1944, to indicate a peculiar infectious hemorrhagic disease seen in Crimea. We were completely unaware of the fact that the Japanese authors in 1942–44 also used the term "hemorrhagic fever" or "epidemic hemorrhagic fever," to describe another infectious disease observed by them during the period of 1936–43 in North Manchuria. We learned of these Japanese studies only in 1946, when we received from Japan the articles by Kitano and others on "purpura hemorrhagica fever," which, in our country, was called "hemorrhagic nephroso-nephritis," or "hemorrhagic fever with renal syndrome," while the American authors (Smadel and others) referred to it as the "Far Eastern hemorrhagic fever."

Thus, quite independently of each other, Soviet and Japanese authors introduced the name "hemorrhagic fever" to indicate two entirely different infectious diseases, different in their etiology and clinical pictures, even though similar in some respects, such as regularly occurring hemorrhagic symptoms during the acute febrile state or soon after defervescence.

At the present time, there are reasons to distinguish three independent types of human disease within the group of virus hemorrhagic fevers, namely, (*a*) hemorrhagic nephroso-nephritis (or as we still sometimes refer to it, "hemorrhagic fever with renal syndrome" or "epidemic hemorrhagic fever"), (*b*) Crimean hemorrhagic fever, and (*c*) Omsk hemorrhagic fever.

These three types of epidemic hemorrhagic fevers are due to entirely different and unrelated filtrable viruses. In spite of the frequency of association with the hemorrhagic syndrome common to them, the three diseases differ significantly in their clinical picture and their course; similarly, the regional distribution of their natural foci, their virus reservoirs, the mechanisms of their transmission, are all quite different.

There is some evidence of the existence of other still little-studied hemorrhagic fevers (for instance, North Bukhovinian, and so forth). The etiological variety of all of the representatives of this group should be further investigated.

In view of the lack of true uniformity

This paper was presented at a seminar on hemorrhagic fevers held at the National Institutes of Health, Public Health Service, Bethesda, Md., on February 16, 1956. The seminar was organized by Dr. Joseph E. Smadel, associate director of NIH.

The first portion of the seminar was devoted to showing a motion picture produced by the United States Government on the Far Eastern hemorrhagic fevers encountered by American troops in Korea. Professor Chumakov's paper followed. The presentation was interspersed with questions from the audience concerning specific points mentioned in the talk. Some of the answers to these questions, enclosed in brackets, are incorporated into appropriate paragraphs in the text.

characteristic of this group, let us discuss them separately. At this time I shall comment upon only the more general aspects of the complex investigations of the etiology of hemorrhagic fevers, their epidemiology, and their prophylaxis as studied in the Soviet Union.

Hemorrhagic fever with renal syndrome (hemorrhagic nephroso-nephritis, also referred to by Japanese and American authors as epidemic hemorrhagic fever), first attracted the attention of Soviet physicians in 1936 or a little earlier. The descriptions of this disease as an entity in the Far East appeared in 1940–41 (Churilov, Tzigankov, Reznikov, and many others).

The work of Smorodintsev and his coworkers (1940) on the virus etiology of hemorrhagic nephroso-nephritis, played a particularly important role in defining this disease. I shall not discuss the history nor the results of the studies done by American, Japanese, Canadian, and other authors, as those were presented by Dr. Smadel in his motion picture film and discussion.

Fundamental information on this disease as studied in the Soviet Far East is contained in the monograph by Smorodintsev, Churilov, and Chudakov, entitled "Hemorrhagic Nephroso-Nephritis," published by Medgiz, 1953. In addition to their data, I shall only state that beginning with 1948 almost every year we observed similar cases of this disease in the central portion of the European U.S.S.R., mostly in the form of small outbreaks during the autumn and winter months in certain areas of Yaroslavl and Kalinin regions ("oblasts"). The cases in the upper Volga Basin were studied by Chumakov, Reznikov, Avakian, Lebedev, Dzachurov, Povalishina, Uspensky, and others. Similar outbreaks were also described near the Ural area (1951–53), in Trans-Carpathian Ukraine (1952), in Southern Ukraine, and in Karelia (1945–53). The largest outbreak was in 5 areas of Yaroslavl and 2 areas of Kalinin regions, where about 300 cases were reported during the fall and winter of 1953–54. [These cases ocurred among both sexes and affected individuals of all ages, but in the Yaroslavl area the individuals attending forage cattle were especially involved.]

Clinical-pathological studies of this type of hemorrhagic fever in the European foci permit us to state that these cases were almost identical in their course and outcome with those noted by other authors in the Soviet Far East, Northern China, and at the 38th parallel in South Korea. [Cross-immunity studies to prove the identity of the Far Eastern and the European hemorrhagic fevers have not been performed.]

Occurrence of fatal cases of hemorrhagic nephro-nephritis associated with the characteristic picture of hemorrhagic renal lesions is the most typical feature of this disease, irrespective of the geographic location of the outbreak. [On the basis of histopathological findings, and partly on the basis of physiological or functional clinical investigations by Sergeyeva and others, the observed vascular lesions were attributed to autonomic nervous system dysfunction.] The clinical features of the European cases correspond exactly to the Far Eastern cases. During different years, the mortality in the European outbreaks varied from 1 percent to 7 or 8 percent, averaging 4 to 5 percent.

Often repeated attempts to produce experimental infection in various laboratory and wild animals, and also in chick embryos and cultures of human and monkey tissues, gave either completely negative or questionable results. In this respect, our data are not an exception and correspond with the majority of other reports. We did obtain successful results in inoculation of psychiatric patients with infectious materials from cases of hemorrhagic fever as a form of pyrogenic therapy in place of malaria. All such observations were conducted under strictly controlled conditions and were concluded quite favorably and successfully.

In 1954–55, while working along these lines with Belyaveva and Leschinskaya on the materials obtained from Kalinin and Yaroslavl regions, we confirmed the fundamental facts of the virus etiology of this form of hemorrhagic fever as established previously by Smorodintsev. Again, in 1955, we were able to prove the presence of the etiological agent of this disease in an emulsion of three species of Gamasoidae mites collected from mouseholes and nests [frequently sheltering *Microtus arvalis* and three other species of small rodents, namely, *Micromys minutus*, *Apodemus agrarius*, and *Sorex araneus*] in the homes where hemorrhagic fever cases occurred. [The isolation of the virus was accomplished by intramuscular inoculation of psychiatric patients (who received this as a form of pyrogenic therapy for which they were scheduled) with emulsions of mites sterilized by addition of antibiotics; the symptoms produced were typical of hemorrhagic fever.] The proper names of these mites are *Euhaemogamasus nidi*, *Haemogamasus glasgowi*, and *Hirstionyssus (Liponyssus) arvicolae*.

Isolation of the virus from these mites confirms our suggestion of "relay transmission" of the viral agent by way of nestled or "settled" mites, and possibly explains why for many years the infection has been endemic during fall and winter months in certain specific households, while absent in neighboring homes even though in the fall the mouselike rodent population in these homes equally increased by migration from the fields. [The peak incidence of cases was during the months of November and December as contrasted with a double peak case incidence observed by American investigators in Korea.]

At the same time, our data do not offer any evidence as to the role of the Gamasoides mites, or any other bloodsucking arthropod, in direct transmission of this infection to man. It is probable that human infection occurs upon direct contact with excreta of infected mouselike rodents.

Seasonal occurrence during autumn and winter further suggests that mites serve as a virus reservoir for mice but play no direct role in human infection. [The Gamasoides family of mites includes many forms parasitic on birds and mammals; however, mites of this group only occasionally parasitize man and then only in a transitory manner.]

Unfortunately, so far, it has not been possible to find convenient laboratory methods for the isolation and identification of the viral agent of hemorrhagic fever with renal syndrome; there are no practical serologic means for its diagnosis. [. . . nevertheless, complement fixation antigens in low and often inadequate titer, which react specifically with antibodies in convalescent serums, have been demonstrated in acute serums], no methods of specific prophylaxis have been developed as yet, nor are there any specific methods of treatment — for instance, antibiotics, including the newer broad-spectrum ones, are totally ineffective. General prophylaxtic measures against hemorrhagic fever with renal syndrome should be directed toward (*a*) destruction of rodent population in the areas of observed human infections, (*b*) chemical acaricidal measures in the vicinity of rodent holes and nests, and (*c*) protection of humans against contact with rodents and their ectoparasites.

The first fundamental data about Crimean hemorrhagic fever[1] were obtained in Crimea in 1944–46 as a result of scientific expeditions of the Academy of the Medical Sciences of the U.S.S.R. under Professor Chumakov's direction, with active participation (in 1944) of the military physicians.[2] The work of Professor N. I. Khodukin and associates in Usbekistan (1948–52) was also of fundamental importance.

Crimean hemorrhagic fever is an acute systemic infection of man, with a relatively short febrile period, accompanied rather frequently by a variety of bleeding phenomena (nasal, uterine, gastrointestinal, sometimes renal) and also by characteristic changes in the blood picture, cardiovascular and nervous systems, as well as some internal organs; it is characterized by spring-summer seasonal occurrence. It occurs primarily in the steppes areas (Crimea, Krasnodar area, Southern Ukraine, entire Bulgaria, Astrakhan region, and five Soviet Middle Asiatic Republics), these being the sites of geographic distribution of the ticks *Hyalomma plumbeum* and *Hyalomma anatolicum*, which are the natural reservoirs and vectors of this infection.

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[1] (Chumakov, 1944). Synonyms: Acute infectious capillaro-toxicosis (Sipovsky, P. V., 1944); hemorrhagic fever of Uzbekistan (Khodukin, N. I., and others, 1949–52; Katzenovich, A. L., and Itzkovich, I. D., 1949–52); acute infectious hemorrhagic disease of Turkmenia (Mikhailov, G. M., 1946); infectious hemorrhagic fever of Tadjikistan (Semyatkovskaya, Z. V., and Sirdikova, N. K., 1950).

[2] A. E. Sokolov, S. I. Griftzev, A. A. Kolachev, I. R. Drobinsky, and I. O. Mirsky.

In the greater majority of cases, the infection is not contagious in the sense of transmission from patient to a healthy contact but occasionally an exception to this rule was observed, with rather serious consequences. Thus, for instance, in the Uzbeck, Turkmen, and Tadjik A.S.S.R. (according to the data of Khoudukin, Mikhailov, and Zhitomirsky) and also in Bulgaria (Chumakov, 1953) there were repeated instances of intrahospital infections in the medical personnel as a result of exposing minor skin wounds to the acutely hemorrhaging patients or from unsuccessful attempts at direct blood transfusions or sometimes following routine skin puncture with the "Francke" needle for blood studies. The causes of this transformation of a normally not contagious tickborne hemorrhagic fever to a highly contagious form of infection and resulting in grave [... usually fatal] cases among the hospital personnel still are not clear; it is possible that in these cases, there was a mixed double infection with the hemorraghic fever virus associated with some septic micro-organisms which played the role of "transporters" of this virus and were simultaneously introduced by the tick vector into the blood stream of the patients.

The clinical course of Crimean hemorrhagic fever usually begins with a sudden rise in temperature (to 39°–40°C.), chilliness, headache, and waistline muscular pains, malaise, weakness, sometimes vomiting, hyperemia of eyes, face and throat, and mouth dryness. The fever continues steadily for 5–12 days; the temperature then drops in stepwise fashion; in approximately 80 percent of cases there are two phases of temperature elevation (a double-humped curve with a single-day drop to subfebrile levels on the third to the fifth days of illness); in contradistinction to malaria, there are no shaking chills or sweats. During the second half of the febrile period (beginning with the fourth to the fifth or sixth day) very often (in 75 percent to 90 percent of cases) new symptoms of one type or another make their appearance, such as a pharyngeal enanthem, or tiny sparse petechial exanthem over the trunk, or purpuric skin hemorrhages, gum bleeding, epistaxis, and in severe cases hematemesis, and repeated nasal, intestinal, uterine, renal, and other bleeding of diapedesis type.

In the lighter and abortive cases of the disease, bleeding may be absent, but the characteristic changes in the blood picture, disturbances in the sympathetic nervous system, and to some extent in the internal organs, are always present. As a rule, Crimean hemorrhagic fever is not accompanied by jaundice or by severe renal disturbances, but some evidence of hepatic and renal involvement is not rare, including tenderness on palpation, bilirubinemia, scanty albuminuria and microhematuria. Usually, once the temperature returns to normal, acute symptoms subside and relapses are not observed.

The blood picture in Crimean hemorrhagic fever, combined with the clinical and epidemiological data, has important diagnostic significance. Quite regularly leukopenia is observed with levels of 3.5 to 1.5 thousand per cubic millimeter, as well as a sharp drop in eosinophils, neutropenia, marked increase in the percentage of stab forms, lymphopenia (usually absolute) replaced soon by a relative lymphocytosis (40 percent–55 percent). During the acute stage, leukopenia is frequently accompanied by thrombopenia (with levels as low as 150,000–60,000 and even 18,000, instead of the usual 250,000–350,000) and, what is especially important in cases with hemorrhagic syndrome, there is a marked quantitative decrease in prothrombin and, for a short while, a prolongation of blood clotting [. . . and bleeding] time as compared to normal.

Appearance of leukocytosis in Crimean hemorrhagic fever usually signals the beginning of inflammatory processes caused by hemorrhages in lungs or elsewhere. In fatal cases (comprising on the average 2 percent to 8 percent of total annual cases) autopsy may disclose as much as a liter of blood in the gastric cavity, a bloody mass in the intestines, numerous minor hemorrhages into the lungs and other organs and tissues, as well as inflammatory phenomena in the lungs, and degenerative changes in the liver and ganglia of the vegetative nervous systems. (In some individual cases, hemorrhages into the renal pelvis were also found).

Epidemiology of the Crimean hemorrhagic

fever may be characterized as follows: endemicity in certain areas, primarily in the steppes, for example, Crimea; seasonal occurrence during spring and summer months; rural type of cases (individuals working in or visiting the steppes); presence of immunity to those who had once convalesced from the disease; complete lack of spread by contagion among humans; lack of evidence favoring alimentary or droplet aerosol route of spread, with the exception of laboratory cases under special conditions; lack of spread of infection from domestic animals or through bites of mosquitoes, sandflies, flies, and common parasites generally; proved connection between the spread of this infection through *Hyalomma* ticks and the natural endemic foci of the virus.

The causal viral agent of Crimean hemorrhagic fever is regularly found in the bloodstream of febrile patients and in the bodies of the appropriate species of ticks. The virus passes through bacterial filters such as Seitz "SF" asbestos filter, Berkefeld candles, types V and N; it can be preserved for a long time (about 2 years) as dry powder under vacuum; and it does not produce any microscopically visible formations reminiscent of rickettsia or elementary bodies, when cultivated under a variety of conditions in animals, chick embryos, and so forth, or upon artificial infection of lice and ticks. The virus of Crimean hemorrhagic fever was found to be nonpathogenic or very weakly pathogenic for the 11 types of laboratory and domestic animals tested. Its basic properties (including ease of filtrability, spontaneous infectivity for tick vectors, antigenic specificity, and so forth) were thoroughly studied experimentally in monkeys and later when this virus was utilized for fever therapy in specifically indicated psychiatric cases. In all cases of such therapeutic inoculations with the virus of Crimean hemorrhagic fever, the outcome was favorable, with stable improvement in many cases in the psychiatric state of schizophrenic patients.

Repeated reinoculations of the virus into volunteers convalescing from Crimean hemorrhagic fever demonstrated very solid specific immunity, which appears soon after defeverescence (4–8–10 days) and lasts not less than 11 months. It was possible to establish the immunological identity of all four virus strains of Crimean hemorrhagic fever isolated in 1945–46 from patients and from *Hyalomma plumbeum* ticks (adults as well as nymphs). Other human volunteer experiments demonstrated that individuals convalescing from Crimean hemorrhagic fever did not possess immunity against sandfly fever just as convalescents from sandfly fever were susceptible to Crimean hemorrhagic fever, thus demonstrating the immunological distinction between the two etiological agents. It is important to note that in some of our experiments, heat (25° C. for 3 days) completely inactivated the Crimean hemorrhagic fever virus and no infection could be produced with this virus, although the immunogenic properties were preserved, as proved by subsequent challenge of the inoculated individuals. This opens up the possibility of killed virus vaccines against the Crimean hemorrhagic fever. The virus was repeatedly isolated from the filtered emulsions of *Hyalomma plumbeum* ticks caught in the steppes, thus firmly establishing the tick transmission theory of this infection and warranting the prophylactic measures directed against the tick. [The ticks were found to contain considerable quantities of virus; the virus has been isolated from adults and nymphs, thus suggesting probable transovarial passage. Larvae were not tested.]

The Crimean virus has not been demonstrated in the blood of rabbits which were used to feed a mass of young forms of *Hyalomma plumbeum* ticks, both nymphs and larvae, while at the same time we established the fact that this virus winters in adult ticks. This indicates that the virus may be preserved in nature within the tick vector for long periods of time during the interepidemic periods.

In 1955 we succeeded in isolating a strain of this virus outside the borders of Crimea, namely, from a perfectly typical case of the disease that occurred in the Astrakhan region.

We were regularly able to make specific etiological serodiagnosis by means of neutralization reaction and complement fixation reaction. [Neutralization reactions were performed employing human volunteers as the indicator host; they were inoculated with a mixture of 1 volume of acute virus-bearing serum and 5 volumes of convalescent immune serum (0.01–0.05 ml. acute serum and 0.05–0.25 ml. convalescent serum). The complement fixation reaction utilized the antigen present in the acute serum obtained during the first 3 days of illness.] Thus, practical diagnosis of sporadic and epidemic cases became possible, early in the disease by complement fixation tests, and retrospectively by neutralization reaction of paired serums. Special experiments, such as those with monkeys, disclosed absence of cross-immunity between the viruses of Omsk and Crimean hemorrhagic fever as well as the virus of sandfly fever, demonstrating that these infections are separate entities. [These experiments employed rhesus monkeys. After experimental inoculation with Crimean virus, the monkeys developed low-grade fever and an intense viremia. Hence, the serum obtained from monkeys during the early febrile period can be successfully used as a complement fixation antigen. The experimentally inoculated monkeys often exhibited exanthemata of questionable significance but they did not develop syndromes suggestive of the human disease.]

We were able to show that the gravely ill cases of Crimean hemorrhagic fever can be successfully treated with serums from convalescent patients.

In conclusion, we shall briefly characterize the third type of the virus hemorrhagic fever group, namely, the Omsk hemorrhagic fever, which was distinguished as a nosologic entity in 1947 by M. P. Chumakov, R. M. Akhrem-Akhremovich, A. F. Bilibin, and others. The main foci of endemic disease are in the areas of the Great Barabin steppes (Omsk and Novosibirsk regions) [...an area measuring 70 × 200 km.]. The Omsk fever is characterized by fewer hemorrhagic manifestations and lesser mortality than the other two types of hemorrhagic fever. In about half the cases, there is a double-humped fever curve with an afebrile period (3–14 days); not rarely, there is meningismus, but always without paralysis; jaundice or severe renal disturbances do not occur; the fever is accompanied by leukopenia, thrombocytopenia, and a shift to the left in the leukocyte count.

The specific etiological agent of the Omsk hemorrhagic fever is a filtrable virus (isolated by M. P. Chumakov, A. P. Belyaeva, A. V. Gagarina, and N. S. Slavina, 1947). The virus is highly pathogenic for mice, field mice, [...including *Microtus, Stenocranius gregalis, Ondratha tibetica*], monkeys, and many other animals. The ticks *Dermacentor pictus* and *Dermacentor marginatus* were shown to be the natural reservoirs and vectors of the infection.

The infection can be transmitted via the respiratory route by inhalation of infected dust particles suspended in air (for example, under laboratory conditions) and apparently also via the alimentary route. [About 20 cases of laboratory infections had occurred. It is interesting that not one of them was associated with clinical encephalitis, which is a characteristic feature of infections with Russian spring-summer encephalitis or louping ill encephalomyelitis.]

It was discovered that the virus of Omsk hemorrhagic fever is antigenically related to a number of other viruses transmitted by *Ixodides* ticks, namely, the viruses of spring-summer tick encephalitis, louping ill encephalomyelitis of Scotland, and the so-called "viral milk fever with double period of pyrexia" occurring in Central Europe. [Minor but definite quantitative differences can be demonstrated by mouse neutralization tests, using human convalescent serums; mouse neutralization tests, using animal immune and hyperimmune serums; cross-immunity in vaccinated mice; and cross-relationship by complement fixation tests using immune serums. This tick-borne family can be contrasted with a family of mosquito-borne viral neurotropic infections of the Japanese B-Murray Valley encephalitis group.]

Laboratory diagnosis of the Omsk disease is made by complement fixation or neutralization reactions with the virus, and isolation of the virus from the blood stream. [Complement fixation tests employ antigens prepared from infected mouse brain or acute phase human serum.]

The most effective antiepidemic measure against the Omsk hemorrhagic fever is prophylactic vaccination of the population in the endemic areas with a formalin-killed virus vaccine made from the brains of mice inoculated with passaged virus.

Some Problems of Immunity Against Virus Diseases

A. A. Smorodintsev

The work conducted in our laboratory during the past 15 years demonstrated the difference between the mechanisms of antiviral and antibacterial immunity. Antiviral immunity depends on qualitatively unique defense mechanisms which reflect the peculiarities of the pathogenesis of virus infections and the biology of their causal agents. This applies equally well to acute virus diseases as well as to diseases characterized by a chronic course. This assumption was apparently adequate to explain the naturally inborn antiviral immunity which we studied first.

The causal agents of ultravirus infections differ radically from pathogenic bacteria by their obligatory intracellular parasitism selectively adapted to a limited number of tissues or organs. In the absence of tissues susceptible to a given virus, there exists a state of complete and solid insusceptibility: such inborn species immunity cannot be overcome either by increasing the dose of the infectious agent or by weakening the overall resistance of the animal. The question is, what mechanisms are responsible for the uniformly observed rapid and complete disappearance of the infective virus even when tremendous doses of it are artificially introduced into an insusceptible organism? What role is played in this process by phagocytosis and nonspecific lysis, that is, the chief mechanisms of natural antibacterial immunity?

Our investigations, employing the viruses of ectromelia, vaccinia, influenza, tick and Japanese encephalitides, have shown the inertness of phagocytosis in all virus infections so far studied. It was found that leukocytes obtained from naturally resistant as well as from susceptible animals do not cause intracellular destruction of these viruses even when the latter were sensitized beforehand with specific antibodies and complement. Inactivation of the virus within the body of naturally insusceptible animals and the outcome of infection of susceptible animals are not changed by interreaction of the virus with the abundant leukocytic exudate mobilized by means of injection of broth or aluronate into the peritoneal cavity. If bacteria are used in such an experiment, the protective role of phagocytosis can be clearly demonstrated.

There is no destruction of the virus by phagocytes even when the virus is artificially introduced into the leukocytes; for instance, using chick erythrocytes with adsorbed influenza virus. Such erythrocytes are rapidly phagocytized upon their introduction into the animal's peritoneal cavity by leukocytes which had accumulated in the peritoneal exudate as a result of preliminary broth injection. Thus, the virus adsorbed by erythrocytes readily penetrates within the phagocytes. It was found that after a 4-hour sojourn within the leukocytes, the viruses of influenza, vaccinia, and ectromelia could be detected in these phagocytes in the same concentration as in the peritoneal cavity of control animals (injected with the virus unadsorbed by erythrocytes). It was apparent that even under conditions of artificial penetration of virus inside the phagocytes of a normal organism, the viruses are not destroyed but preserve their initial biological activity.

No changes in susceptibility to the influenza virus were observed in animals with partial or complete blocking of the reticulo-endothelial system. Immunized animals did not display an increase in the barrier function of the regional lymphatic nodes as compared with susceptible animals in which these protective mechanisms do not take part in the reaction toward the viral agents.

The results of our investigations suggest that the phagocytic mechanisms are incapable of direct destruction of smallest, medium, and large-sized ultravirus agents in naturally insusceptible animals as well as in immune animals.

We are now continuing to study the role of phagocytosis in antiviral immunity, using a group of large viruses (psittacosis-lymphogranuloma venereum) and also the rickettsiae, which possess a most complex morphological organization and are capable of causing irritation of phagocytes. It is most likely that the larger viruses are also subjected to incomplete phagocytosis, having adapted themselves to intracellular parasitism through high resistance to the action of tissue enzymes.

A most important role among the general physiological defense factors against viruses is played by the destructive effect of normal body temperature of warm-blooded animals on the extracellular virus particles — a mechanism we first observed. It was found that the temperature of 37°–38° C., optimal for intracellular reproduction of viruses, can be destructive for them under extracellular conditions. This is observed not only in test tube experiments but in the naturally susceptible and immunized animals.

Whenever viruses are outside of the susceptible cells, the normal body temperature of warm-blooded animals causes their spontaneous rapid thermal inactivation. The following basic factors prove the validity of this theory:

(*a*) The majority of viruses pathogenic for man and animals are characterized by high thermal lability and perish at 37° C. within 1 to 3 days even in highly infectious suspensions of infected organs.

(*b*) The rate of inactivation of the virus in brain and subcutaneous tissue removed from infected animals and placed under sterile conditions in an incubator at 37° C. approaches the rate of disappearance of the virus in the same organs of infected insusceptible animals during in vivo experiments.

(*c*) Changes in the body temperature of inoculated insusceptible animals greatly affect the death rate of the virus. A lowering of the temperature of such insusceptible animals favors virus survival while an increase in the temperature accelerates its destruction. Thus, inactivation of the influenza virus introduced into the hind leg muscles of white mice or guinea pigs partially decreases with artificial cooling and increases when the infected parts are warmed. The virus introduced into the peritoneal cavity of frogs or fish, which are exceptionally well suited for experimental changes in body temperature, survives for a long time when the animals are in cold water and rapidly dies off when they are placed in a warm aquarium.

(*d*) Observations on the viruses characterized by different initial in vitro resistance to thermal changes offer particularly convincing proof of thermal virus inactivation as a mechanism of natural antiviral immunity.

By means of prolonged adaptation of influenza virus to the action of high temperature, we have obtained a thermoresistant strain which survives about 3 hours of heating at 52° C. It was found that the original influenza virus strain perished in subcutaneous tissue of white mice within 3 days while the thermoresistant variant survived for about 10 days. The thermoresistant variant did not change in its biological or antigenic properties as compared with the original strain.

Bacteriophages represent a most favorable opportunity for a comparative study of the rates of virus destruction within insusceptible animals in relation to their thermal stability, being completely harmless for laboratory animals and most advantageous as models of a typical virus subject to a most precise quantitative detection in the animal organism. Bacteriophages possess a broad range of thermal stability and thus allow selection of the more thermolabile as well as the more thermostable types as models to study their destruction.

We were able to demonstrate an exceptionally clear-cut correlation between the stability of the phages upon heating and the length of their survival within warm-blooded animals. The important role of the thermoresistant bacterial virus in the duration of their survival within warm-blooded animals was also established through experiments with a strain of mycoides-phage which was obtained by controlled changes in the thermal resistance of the initial thermolabile strain.

The original thermolabile strain survived at 37° C. for 6 days, the variant strain for some 12 days. The original strain survived for 4 days upon intravenous inoculation and the variant, for 11 days. Upon subcutaneous inoculation, the original strain could be detected in the subcutaneous focus for 3 or 4 days while the variant could be detected for 10 days. The other properties of the thermostable strain did not seem to differ from the original strain. Thus, it was established that increase in the thermal stability of the phage led to considerable increase in the duration of its survival within the warm-blooded animals.

These investigations confirm the important defense role of normal body temperature of warm-blooded animals as a natural physiological factor which enhances spontaneous destruction of viruses if they are outside the susceptible cells of the animal's body.

A close correlation that exists between the intensity of virus destruction and the body temperature of a naturally resistant host cannot be explained through the action of enzymatic processes accelerated by raising the outside temperature. In the light of our data concerning the action of tissue enzymes on the influenza virus, there is no reason to attach too much significance to the role of such enzymatic action in the destruction of biological activity of viruses. Thus, it was found that during interaction of influenza virus with concentrated crude tissue emulsions of chick embryos or internal organs of white mice, guinea pigs, or rabbits at 37° C., the time to complete virus inactivation correlates exactly with control experiments in which the influenza virus was mixed with identical tissue emulsions which were inactivated at 100° C.

The rates of virus inactivation in crude tissue emulsions at different temperature levels do not seem to follow any of the uniform laws established for the action of enzymes at different temperatures. Thus, an increase in temperature by 10° C. was not accompanied by a twofold increase in the rate of virus inactivation, as would be characteristic of an enzyme reaction, but by a multiple of tenfold. This tremendous acceleration of virus destruction with an increase in external temperature is characteristic of thermal effect which, as we have shown, is capable of causing spontaneous destruction of the virus without enzyme participation.

Our investigations have demonstrated that the first stage of virus inactivation in an insusceptible animal (that is, loss of its biological activity) takes place without tissue enzymes, to the action of which the native virus particle is quite resistant. It seems that this first stage is dependent upon a combined effect of direct thermal inactivation of the virus particle by the normal body temperature of warm-blooded animals and the nonspecific thermolabile factors, that is, neutralizing substances present in the animal.

The second stage of virus inactivation — the loss of immunogenic and hemagglutinating properties by the biologically inactivated virus — is the result of a direct effect of tissue enzymes to which the inactivated influenza virus particle becomes sensitive. Therefore, fresh emulsions of different tissues rich in enzymes allow this process to take place much more rapidly than inactivated emulsions.

Thus, the action of normal body temperature of warm-blooded animals is the most universal and constantly acting direct cause of the death of viruses outside of susceptible cells in naturally insusceptible animals.

This fate of extracellular sojourn of virus is observed not only in naturally resistant animals but in immunized animals as well. As will be shown, virus loses its access to susceptible tissues after interaction with the virus neutralizing antibodies. In this state, it rapidly perishes because of thermal denaturation.

Rapid inactivation of biological activity of viral agents in naturally resistant animals is not infrequently associated with the presence of thermolabile inhibitors in normal serums of different animals. Such substances have been detected by a number of investigators in the serums of many animals and of man.

The major role of serum thermolabile substances in natural antiviral immunity is emphasized by our observations using, as a model, bacterial phages inoculated into white mice. It was found that some proteus and staphylococcus phages, while possessing high thermal resistance in vitro, generally die off in white mice within 6 to 72 hours. Taking into account the high thermal resistance of these phages, we could not explain this fact through injurious effects of temperature changes in the experimental animal.

Staphylococcus and proteus phages possess high sensitivity to the inactivating effect of fresh animal blood and serum. On the other hand, intestinal phages and mycoides-phage are completely resistant to this factor. Thus, we could associate rapid disappearance of these thermoresistant phages with the inactivating action of thermolabile inhibitors present in the normal serum of white mice.

The thermolabile inhibitors of blood, tissue, and various secretions play an important role in the mechanism of asymptomatic experimental influenza infections of white mice. Fresh serums of normal white mice are totally inert toward virulent strains, but possess high neutralizing activity toward all nonpathogenic strains which cause asymptomatic infection of these mice. With increased adaptation of nonpathogenic strains to lungs of white mice, accompanied by an increase in the virulence of these strains, there is a continuous diminution in the sensitivity of adapted strains to the action of normal mouse serum in the reaction of thermolabile inhibitors. Knowing the sensitivity of certain strains to the action of normal mouse serum in the reaction of hemagglutination-inhibition and in the biological neutralization of the virus in developing chick embryo, we can fairly precisely predict the actual pathogenicity of these virus strains for white mice.

This suggests that the thermolabile serum inhibitors possess protective properties and that in overcoming the sensitivity of the virus to these substances, it is changed from a nonpathogenic into a pathogenic variant.

Another important natural defense mechanism is the active reaction of the susceptible cells to penetration of the virus, manifested as a "walling-off" of multiplying particles into isolated inclusion bodies which may be discharged outside the infected cells. As was shown by Pigarevsky, using experimental influenza infection of white mice and hamsters as a model, the inclusion bodies formed within the cells of ciliated epithelium are actively discharged by the infected cells into the lumen of trachea and bronchi. The presence of inclusion formations, which isolates virus particles within cytoplasm or nucleus, and its subsequent evacuation on to the mucous membranes of the respiratory tract, where the virus rapidly perishes, takes place more actively in asymptomatic forms of influenza virus infections than in severe fatal infections. The ability of the susceptible cells to rid themselves of virus particles has to be considered an important defense mechanism against viral agents which is mobilized during the very early stages of virus development prior to the appearance of specific immune factors.

In this fashion, rapid and complete destruction of virus within resistant animals takes place without phagocytosis, that is, without the basic factor of antibacterial immunity. The phagocytes apparently are incapable of biological inactivation of most viruses even after the virus is artificially introduced into the protoplasm of the phagocytes.

For example, apparently intensive destruction of influenza virus in total and partially insusceptible animals is associated with an interreaction of a number of physiological factors, among which the fundamental role is played by thermal denaturation of the extracellular virus and also the action of the nonspecific thermolabile blood substances, as well as active defense by the susceptible cells through the formation of virus inclusions.

Besides the general defense mechanisms, the specifically immune animal is also protected by a new factor, the specific virus-neutralizing antibodies. Their protective action during virus infections in the majority of cases is not connected with susceptibility of the virus to phagocytosis or to specific lysis. By combining with the specific antibodies, the viruses lose their major aggressive function, that is, the ability of attaching themselves to and penetrating within a susceptible cell. Thus, the defensive action of antibodies is not due to destruction of the virus particle but is due to its capacity for intracellular parasitism. Under these conditions, viruses are rapidly destroyed through the action of normal body temperature of warm-blooded animals.

Many facts point to the important role of neutralizing antibodies as a direct defensive factor in specific antiviral immunity:

1. The existing correlation between the amount of neutralizing antibodies in convalescent persons and animals, and their resistance to the viruses of influenza, encephalitides, vaccinia, ectromelia, and mumps.

The high level and duration of acquired immunity so characteristic of many virus infections is explained by an incessant replacement of virus-neutralizing antibodies in convalescent animals. Correlating the level of resistance of an animal with the amount of antibody, one has to take into account not only the blood antibodies but also the antibodies present in other fluids bathing the susceptible tissue (in influenza, the secretions of the respiratory mucous membranes; in virus encephalitides, the cerebrospinal fluid; in mumps, saliva) and also the possible production of antibodies or their intermediaries by epithelial and other infected tissues (histiogenic or tissue immunity).

2. Chronic course of those virus infections which do not cause formation of specific antibodies (or their formation in negligible amounts only). For instance, lymphocytic choriomeningitis of white mice, not associated with any protective blood substances, tends to be a chronic infection. The same virus of lymphocytic choriomeningitis produces humoral immunity in guinea pigs and, therefore, rapidly disappears.

3. The possibility of artificially producing potent immunity by means of active immunization of susceptible animals with inactivated vaccines, that is, when there is no possibility of multiplication of the virus in susceptible cells or of related changes in tissue immunity.

4. The marked prophylactic effect of immune serums in the majority of virus infections with demonstrably high titers of neutralizing antibodies comparable in their effect to the defensive action of antitoxic serums in toxic bacterial infections.

The mechanism of action of virus-neutralizing antibodies has been a subject of some controversy in the literature. According to some authors, antibodies are not capable of combining with viruses but act directly on the cells susceptible to the virus by blocking the cells of the immune animal and preventing the virus from combining with the susceptible tissues. This point of view has been abandoned as of the present time. It has been proved that viruses combine avidly with specific antibodies and exhaust specific serums. The results of interaction of viruses with antibodies are differently evaluated by individual investigators. One group of authors concludes that immune serum causes a morphological breakdown of viruses resulting in a complete loss of viral biological activity. Others defend the reversibility of the virus-antibody complex as proved by the fact that it is possible to isolate active virus from the neutral mixture through application of certain procedures facilitating disassociation of the virus from the antibodies (cataphoresis, dilution of the neutral mixture, elution of the virus by ultracentrifugation).

We have studied the mechanism of virus-neutralizing antibody reaction using a number of viruses of various complexity of their particle organization. Included were viruses of smallest and medium sizes (virus encephalitides, influenza, rabies) and viruses which form optically visible elementary bodies (vaccinia, ectromelia).

It was shown that the mechanism of defensive action of virus-neutralizing antibodies varies with the complexity of organization of the virus. Viruses of the smallest and medium sizes enter a reversible union with antibodies while completely preserving their initial biological activity. When combined with antibodies the viruses of this group are not capable of entering and multiplying within the susceptible cells but upon artificial removal of the antibodies they regain their initial activity.

Large-sized viruses which form optically visible elementary bodies stimulate formation of two different types of antibodies:

1. Thermostable antibodies which resist heating at 56° C. and which form a reversible union with the virus, and

2. The thermolabile antibodies which irreversibly destroy the biological activity of the virus without participation of complement. These conclusions are based on the following data.

By combining the viruses of influenza, Russian tick and Japanese encephalitides, and rabies with the excess of hyperimmune serums, we created biologically inactive mixtures in which no free virus could be demonstrated by repeated passages through highly susceptible animals. From the literature, we know that viruses can be reactivated from such neutral mixtures by freeing the virus through electrocatophoresis, or selective adsorption with kaolin, or ultracentrifugation.

The problem of quantitative limits of virus reactivation remains obscure. Most authors suppose that the bulk of the virus perishes in the neutral mixture with but a small percentage of virus particles, particularly resistant to the effect of antibodies, actually surviving the reaction. Using virus models, a number of foreign authors observed complete or partial destruction of viruses following contact with neutralizing antibodies. According to our studies, the quantitative aspects of reactivation of the viruses studied depended in the main upon the efficiency of the methods employed to separate the virus from the antibodies. The most commonly employed techniques of freeing viruses from neutral mixtures by means of their serial dilution, electrophoresis, and adsorption with kaolin and charcoal, do not insure optimal opportunities for separation of the virus from the antibodies and allow isolation of only a negligibly small portion of the virus contained in the biologically neutral mixture.

The most precise results of reactivation of viruses from neutral mixtures are obtained with the aid of intensive elution of virus particles from antibodies by ultracentrifugation and on the surface of Elford membrane filters. Application of the latter methods showed that the quantities of the viruses of influenza, rabies, and arthropod-borne seasonal encephalitides, reinactivated from neutral mixtures, closely approached their concentration in control mixtures with normal serums.

Progressive reactivation of the virus of encephalitis, influenza, and rabies from respective neutral mixtures does not negate the possibility of direct interaction between viruses and antibodies. Viruses combine avidly with the specific antibodies and regularly exhaust specific serums.

When a virus is blocked by antibodies, it is not capable of attaching to and penetrating within a susceptible cell, and therefore, cannot multiply. This very mechanism, according to our data, is the most universal one in the action of virus-neutralizing antibodies. However, it was found that the result of interreaction between different viruses and hyperimmune serums depends on the complexity of organization of its particle. When such an organization is of the simplest kind, for example, with the viruses of Russian tick and Japanese encephalitides, and influenza, even high concentration of virus-neutralizing antibodies does not exert a destructive effect on homologous virus upon prolonged contact with it at incubation temperatures. Viruses of more complex organization, for instance, the vaccinia virus, yield to the lytic effect of immune serums.

Our laboratory investigations with vaccinia and ectromelia viruses demonstrated that the interreaction of these viruses with the immune serums of laboratory animals produced different results depending upon the methods used in producing the serum. If the animals (rabbits, guinea pigs, white rats) were immunized with a formalin-killed virus, the serums, whether active or heated, neutralized the biological activity of the virus consistently well. However, upon elution of the virus by ultracentrifugation it was possible to isolate it without loss of any of its original activity. Similar results were obtained when serums of animals immunized with a live active virus, but of low titer, were used or when the serums were subjected to a preliminary heating at 56°C. for 30 minutes.

On the contrary, serums of rabbits hyperimmunized subcutaneously with living vaccinia virus or serums of white rats hyperimmunized with the ectromelia virus, and possessing high titer of specific antibodies, were found to contain a new previously unknown variety of antibodies. These antibodies irreversibly lysed homologous viruses; they were found to be thermolabile, and to be present in comparatively insignificant amounts as compared to thermostable antibodies which caused reversible neutralization of the virus. Thus, it became clear why previous work by various authors with the vaccinia virus was characterized by a number of contradictions. No irreversible inactivation of the virus could take place if such investigations were conducted using immune serums of low titers and subjected to preliminary dilution, heating, or prolonged storage, whether the virus used for immunization was live or killed. The described effect could be demonstrated only in fresh serums of animals hyperimmunized with live virus and not subjected to either heat or prolonged storage in ordinary refrigerators. Thermolabile antibodies act upon the virus only when the serum is used either undiluted or in low dilution, since their concentration in the serum is not very great.

The action of thermolabile antibodies absolutely does not depend on the presence of complement — its preliminary removal from the fresh hyperimmunized serum does not affect its activity. Addition of complement to heated serum did not restore its activity. The bulk of thermolabile virus-lysing antibodies was bound with the labile fraction of serum globulin. The same fraction was devoid of neutralizing activity in animals which were vaccinated with formalin-killed virus.

It is very likely that still more sharply lysing action of immune serums will be eventually demonstrated in relation to the still little-studied group of psittacosis-lymphogranuloma venereum viruses, which are of the largest particle size.

Our test tube experiments on the action of specific antibodies on different viruses were also confirmed under the conditions of the intact animal. Application of specially developed methods insured the opportunity of checking the action of different types of antibodies on viruses within intact immunized animals.

We found that in mice immunized actively with live or inactivated influenza virus and also passively with anti-influenzal serum, no virus could be detected even after a few hours following its inoculation. Such negative result was not due to actual death of the virus in the intact immunized animal but was due to masking of the virus by the antibodies, present in excess in the tissues studied. Thus, the curve of influenza virus inactivation in an immune animal infected subcutaneously, intraperitoneally, and intracerebrally, that is, bypassing the respiratory routes, was essentially identical with the curve of virus inactivation in insusceptible normal animals.

Even though virus-neutralizing antibodies do not destroy influenza virus, even under optimal conditions present in the immune animal, they successfully paralyze its fundamental aggressive function, that is, its ability to multiply rapidly in susceptible tissues. In combining with the specific antibodies the virus loses the ability to fix itself onto the susceptible cells and therefore cannot penetrate within such cells. When the virus is outside the susceptible tissue, it is rapidly destroyed due to the unfavorable environmental conditions. These conditions, according to our data, depend first of all on thermal factors which initiate inactivation of thermolabile viruses in the naturally resistant animals and also on the nonspecific thermolabile virolytic blood substances.

Other interesting results were obtained in our laboratory when we studied the fate of a pneumotropic strain of ectromelia virus in immunized rats. Irreversible inactivation of this ectromelia virus took place within 2 to 3 hours after its inoculation into white rats immunized with formalin-killed virus.

Valuable facts favoring the important defense role of virus-neutralizing antibodies in the mechanism of antiviral immunity were uncovered during studies of animals with experimentally produced irradiation illness. Sharp depression of immunogenesis and of virus-neutralizing antibody production were noted in convalescent and vaccinated animals. Under these conditions acute virus infections acquire a chronic character and progress to a much more grave form. Thus, we think that the mechanism of tissue immunity, which is still unclear, is associated with participation of specific antibodies. These antibodies are produced not only by the reticuloendothelial cells but also by some other kind of tissue cells, such as the ciliary epithelium in case of influenza infection. According to our data, mouse lung cells obtained from immune animals and grown in tissue culture are completely resistant to their homologous virus strain but are susceptible to immunologically distinct influenza viruses.

Isolation and Studies of Type 4 Poliomyelitis Virus

M. K. Voroshilova

Virologic investigations of poliomyelitis in the U.S.S.R. were first begun in 1945. Chumakov, Belyaeva, and Voroshilova isolated in a monkey the first strain of poliovirus from the brain of a child with a clinical diagnosis of fatal poliomyelitis. During the period 1945 to 1954, investigations were conducted in a number of areas of the Soviet Union: the Baltic Republics, Western Siberia, Kazakhstan, Byelorussian Republic, and, in 1947–48, the Berlin epidemic. By using animals, including monkeys, cotton rats, and mice, 32 strains of poliovirus were isolated.

In 1954–55, as a result of application of tissue culture for laboratory investigations, 192 virus strains were isolated (including 151 strains from stools of patients with paralytic, nonparalytic, and abortive poliomyelitis, 37 strains from stools of children in contact with cases of poliomyelitis, 2 strains from throat washings, and 2 strains from brains of fatal cases of the disease).

Thus, the total number of poliovirus strains isolated was 224. Study of these strains showed that 187 of the 198 typable strains (94 percent) belonged to type 1, and 8 strains (4 percent) to type 2, while 3 strains were classified by us as type 4. In addition, 14 cytopathogenic agents from patients' stools remain still unclassified, and finally, 12 strains isolated directly in monkeys have not been typed so far.

It follows that the majority of strains of poliovirus isolated in the U.S.S.R. belong to type 1 (about 94 percent), while only a small number belong to either type 2 or type 4. Until now, none of our strains belong to type 3. We are particularly interested in our isolation and studies of the so-called fourth immunological type of poliovirus.

In 1952, while studying materials obtained during a poliomyelitis outbreak in the city of Karaganda, we isolated three virus strains which possess all of the typical properties of poliovirus but differ sharply from all of the known strains by their immunological properties and pathogenicity for laboratory animals.

Strain AB was isolated in monkeys from pooled feces of two sick children who died of bulbospinal form of poliomyelitis. This strain was found to be highly pathogenic for monkeys by any route of infection. The primary isolation was in a monkey by intraperitoneal (30 ml.) and intranasal routes over a period of 5 days. The monkey became ill on the fifth postinoculation day: There was a rise in temperature followed by flaccid paresis of lower extremities. This monkey's brain was successfully used to infect the next monkey intracerebrally, as well as some suckling cotton rats.

During the first 2 years there were four successful monkey-to-monkey passages, indicating the high pathogenicity of this strain for monkeys. Beginning with the second monkey passage, brain and spinal cord emulsions were used to inoculate concurrently adult and newborn cotton rats and white mice. Both adult and suckling cotton rats were highly susceptible, as were newborn white mice, but adult white mice never became ill. Suckling cotton rat brain emulsions from the 10th and 24th passages were used to infect two monkeys which developed typical experimental poliomyelitis.

Strain MK was isolated from the pooled feces of two children ill with a typical spinal form of poliomyelitis by inoculation of adult cotton rats and newborn white mice. Subsequently, suckling cotton rats were found to be most susceptible and were used for over 25 consecutive passages. Rhesus monkeys were successfully infected with brains of suckling cotton rats as well as with their muscle suspensions. Many attempts to infect adult white mice gave negative results.

Strain GZ was isolated in September 1952 from feces of two sick children by intracerebral inoculation of monkeys and was subsequently passaged twice in monkeys. Adult and newborn cotton rats and suckling white mice were also successfully infected with the brain of the first-passage monkey. Attempts to infect small laboratory animals with the monkey brain from the second and third passages were not successful, possibly because of prolonged storage of the material in glycerine.

Strains AB and MK can be easily filtered through Berkefeld candles V, N, and W and Seitz asbestos pads without appreciable loss of activity. The virus can be preserved in glycerine at +4° C. or as a frozen emulsion for at least a year. Neither penicillin in concentrations of 1,000–2,000 units per milliliter nor streptomycin at about 0.1 mgm. per milliliter had any deleterious effect on this virus. Activity of the virus was not effected by ethyl-ether. Emulsions of central nervous system tissue containing strain AB when stored at room temperature preserved their activity for at least 2½ months.

Studies of the distribution of strain AB in the tissues of sick cotton rat sucklings showed its regular presence in considerable concentration (up to 10^{-5} and 10^{-6}) not only in the brain and spinal cord but also in muscles (10^{-5}), liver (10^{-4}), spleen, kidneys, lungs (10^{-3}–10^{-4}), and also in the intestines (10^{-2}–10^{-4}), in blood (diluted 1:2), and in undiluted urine.

The picture of histopathological lesions in brains and spinal cords of monkeys infected with strains AB, GZ, and MK, and in the cotton rats infected with strains AB and MK, corresponds to that of experimental poliomyelitis caused by other immunological strains.

Immunological properties of the newly isolated strains were studied in cross-immunity experiments in immunized cotton rats, monkeys convalescent from experimental poliomyelitis, and by cross-neutralization experiments in cotton rats. Combined formalinized vaccines and live virus (using strains AB, MK, GZ, OVCH, and Lansing), were used for immunization of cotton rats.

Cotton rats were used for cross-titration of strains AB, MK, OVCH, and Lansing 20 days after completion of the course of immunization. Cross-immunity experiments were performed in monkeys convalescent from experimental infection with strains of poliomyelitis virus types 1, 2, and 4, and known to be immune to infection with homologous strains. The results of these tests demonstrated complete immunological independence of strains AB, MK, and GZ from poliomyelitis virus of first, second, and third types. It was also shown during these tests of cross-immunity in monkeys that one of the Karaganda strains (strain YV) was a poliomyelitis virus type 1. Serums from immunized cotton rats, rabbits, guinea pigs, and monkeys were used in cross-neutralization studies of strains belonging to types 2 and 4 of poliomyelitis virus. The immune serums against strains AB and MK had high neutralization indexes against homologous strains but did not neutralize strains of type 2 virus (OVCH and Lansing). Conversely, serums prepared against type 2, which had high neutralization indexes against strains OVCH and Lansing, did not neutralize strains AB and MK.

Thus, cross-immunity tests in monkeys and cotton rats, and cross-neutralizations in cotton rats, confirm complete immunological independence of strains AB and MK and, less completely, that of strain GZ, as well as their difference from the three immunological types of poliomyelitis virus known until now. Increase in titer of neutralizing antibodies was demonstrated in the paired serums of both children from whose pooled fecal specimens the virus strain MK was isolated.

Small-scale investigations of human serums detected virus neutralizing antibodies against type 4 virus, not only in specimens from Karaganda but also in those from Western Siberia, Moscow, Yaroslav regions, and Alma-Ata (thus suggesting possible presence of infection of this type elsewhere).

In recent years, as a result of large-scale studies of poliovirus carrier state, there have been frequent reports of isolation of so-called "orphan" viruses, not pathogenic for monkeys or mice, and differing immunologically from the known types of poliomyelitis virus. Strains AB, MK, and GZ differ from these viruses in their pathogenicity for monkeys and rodents. Our strains seem to resemble the Redwood strain isolated by Stanley and Dorman in 1953 in Australia from the brain of a child who died of bulbar poliomyelitis. Strain Redwood was reported to be pathogenic for monkeys and newborn mice, causing a disease typical of poliomyelitis in its clinical and pathological pictures. It was said to be nonpathogenic for adult mice but to differ immunologically from strains of types 1 and 2. It was not studied in relation to type 3 strains nor were cotton rats investigated as experimental hosts.

Conclusions

1. In 1952, while examining materials from a poliomyelitis outbreak in Karaganda, we isolated from the stools of several children three strains of virus which differ immunologically from the known poliomyelitis types.
2. Newly isolated strains possess high pathogenicity for monkeys and for newborn and adult cotton rats; they are somewhat less pathogenic for newborn white mice and, unlike type 2 poliomyelitis virus, are totally nonpathogenic for adult white mice. In being nonpathogenic for adult white mice, these strains differ from the viruses of the encephalomyocarditis groups, the seasonal encephalitis group, and a number of other viruses. Our newly isolated strains are pathogenic for adult cotton rats and monkeys, which differentiates them from the Coxsackie viruses.
3. Histopathological central nervous system lesions in infected monkeys and cotton rats correspond to those of experimental poliomyelitis.
4. Clear-cut proof of existing differences in antigenic structure of strains AB, MK, and GZ from poliomyelitis virus types 1, 2, and 3 can be seen in cross-immunity and cross-neutralization experiments in cotton rats and monkeys.
5. The results of various experiments allow us to postulate the existence of a new immunological type 4 poliomyelitis virus.

Addendum

The following additional information was not included by Dr. Voroshilova in her talk, but was mentioned to Dr. Shelokov:

1. Some of the monkeys with paralysis due to infection with type 4 strains also showed "diffuse interstitial myocarditis."
2. Suckling mice did not show lesions of myositis. Their pancreatic tissues were not examined for possible pancreatitis.
3. None of the three strains of "type 4" could be checked against Coxsackie group B antiserums.
4. One or more of the type 4 strains were grown with difficulty in cultures of human fibroblasts producing cytopathogenic effect at about the 10th or 12th day with incomplete degeneration of cells and passaged only with difficulty.
5. Paired serums only from the children whose pooled feces yielded strain MK could be tested and shown to have rising titers of neutralizing antibodies. The children from whom strain AB was isolated both died, while the two from whom the strain GZ was obtained moved away and could not be traced.
6. No virus isolations from the brains of children dead with strain AB could be attempted since the material was shipped to Moscow in formalin only.
7. Additional details concerning specifically the prototype strain AB can be found in Professor Chumakov's strain description (supplement 4).

The Russian Virus Strains

M. P. Chumakov

Poliovirus, Type 1

Strain KRF–1. The "KRF–1" strain of poliovirus, type 1, was isolated in 1950 in Moscow from the stools of two patients with nonparalytic poliomyelitis by means of rhesus monkey inoculation. This strain has been maintained by serial passage in monkeys and in tissue cultures of human fibroblasts, where it causes cytopathogenic effects after 3 to 4 days. It is not pathogenic for rodents.

Strain KRF–1 was shown to be indistinguishable (by monkey cross-immunity experiments) from the Brunhilde strain of type 1 poliovirus in its antigenic properties, and it was found to differ radically from the type 3 virus (Leon), type 2 virus (strain "OVCH"), and the type 4 virus (strain AB). Analogous results were obtained in tissue culture.

Strain Loug. The Loug strain of poliovirus, type 1, also referred to as "Loug-Mindalina," was isolated from the tonsil (tr: "mindalina") of an infant dead of bulbar poliomyelitis on the third day of illness in the city of Alma-Ata (Kazakhstan) in 1954.

The virus is pathogenic for monkeys; it is not pathogenic for rodents. It grows well in tissue culture of human fibroblasts. It was typed in tissue cultures as a type 1 poliovirus.

Strain 3KVII. Strain 3KVII of poliovirus, type 1, was isolated in 1954 by means of inoculation of a rhesus monkey with an emulsion of pooled stools from three children in the city of Alma-Ata, all of whom had isolated monoparesis of the facial nerve. Sent as monkey brain.

Poliovirus, Type 2

Strain OVCH. Strain OVCH, or Ovchinnikov, a poliovirus, type 2, was isolated from the feces of a spinal paralytic poliomyelitis patient in Moscow in 1953 by inoculation of cotton rats with an antibiotic-treated stool emulsion. This strain is highly pathogenic for cotton rats, white mice of all ages, and monkeys, and grows well in tissue cultures of human embryonic fibroblasts. Its cytopathogenic effect is complete within 48 hours. Histology is quite typical of experimental poliomyelitis.

Two tubes of this virus strain are provided. These are labeled: Nos. 1852 and 1853, November 4, 1955, "cotton rat brain, consecutive passage."

Immunologically, in experiments of cross-neutralization and cross-immunity in cotton rats and mice, strain OVCH was found to correspond completely to the poliovirus, type 2, Lansing strain.

Strain Alexeyeva. The Alexeyeva strain of poliovirus, type 2, was isolated from the feces of a patient with spinal paralytic form of poliomyelitis in Moscow in 1954 by means of cotton rat inoculation with antibiotic-treated fecal emulsion.

This strain is highly pathogenic for cotton rats and white mice of all ages. Histologically, the infection in rodents is quite typical of experimental poliomyelitis. It grows well in human embryonic fibroblast cultures. The

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The accompanying information on Russian virus strains was hurriedly compiled by Professor Chumakov in an effort to help the laboratory workers at the National Institutes of Health in their work with the Russian virus strains. The strain histories as given represent what Professor Chumakov thought to be some of the more salient points indispensable in initiating our studies of these viruses.

cytopathogenic effect is complete after 48–72 hours.

The virus is provided in two tubes, labeled: No. 1862 and No. 1863, November 4, 1955, "cotton rat brain."

Immunologically, the virus corresponds completely to poliovirus, type 2, by means of experiments with immune serums in animals and in tissue cultures.

Strain Smirnova. Strain Smirnova, a poliovirus, type 2, was isolated in 1948 in the city of Minsk (Byelorussia) from a stool of a child suffering from spinal paralytic disease by direct inoculation of white mice with antibiotic-treated stool emulsion.

This strain is highly pathogenic for white mice, cotton rats, and monkeys. It causes typical clinical and histopathological pictures of experimental poliomyelitis. It grows well in human fibroblast cultures with a clear-cut cytopathogenic effect.

Immunologically, this strain corresponds to poliovirus, type 2, strain Lansing.

The virus is provided in two tubes, labeled: No. 1837 and No. 1838, November 4, 1955, "cotton rat brain, consecutive passage."

Poliovirus, Strain AB

Strain AB poliovirus, is poliovirus, type 4, Moscow, U.S.S.R., by Dr. M. P. Chumakov and Dr. M. K. Voroshilova.

Isolation. The cases from which this poliovirus type was isolated occurred in the summer of 1950 during an epidemic of poliomyelitis in the city of Karaganda (Kazakhstan, S.S.R.). The virus was initially isolated in October 1952 by intracerebral inoculation of a rhesus monkey with a pooled mixture of stools collected during the first week of illness from two children, paralyzed with poliomyelitis. The children, Akhundov and Byelik, were aged 1½ months and 3 years, respectively.

Adaptation. Beginning with the second passage, the virus has been passed simultaneously in monkeys and in rodents (suckling cotton rats, adult cotton rats, and suckling white mice). It is not pathogenic for adult white mice, guinea pigs of all ages, rabbits, chick embryos, and so forth.

The virus is grown with difficulty in cultures of human fibroblasts, producing cytopathogenic effect at about the 10th to the 12th day with incomplete degeneration of cells.

Titers. In cotton rats, up to 10^{-5} $10^{-6.5}$.

Means of maintenance of strain AB. Strain AB is maintained by cerebral passages (10-percent brain emulsion) in suckling or young cotton rats, in suckling white mice, or in rhesus or cynomolgus monkeys.

Immunological Identification. In its antigenic relationships, strain AB has been found to be completely different from the three known types of polioviruses, as follows:

(*a*) Antiserums produced with strain AB do not neutralize polioviruses of the first, second, and third types in tissue culture nor upon testing against type 2 virus in neutralization experiments in cotton rats or mice.

(*b*) In monkey experiments, no cross-immunity could be demonstrated between the strain AB and the viruses of the first, second, and third types.

(*c*) The same is true in experiments using cotton rats, for example, a complete lack of cross-immunity between strain AB and poliovirus, strain Lansing.

Strain No. 256

Strain No. 256, *Ixodes ricinus,* B.S.S.R., 1940, is the virus of Russian tick spring-summer encephalitis isolated by M. P. Chumakov in 1940 from adult *Ixodes ricinus* ticks collected in the forests of the Byelorussian S.S.R. (Minsk oblast). This virus strain is quite characteristic of the etiological agent of tick encephalitis. Professors Zilber and Shubladze relate this strain to the virus of louping ill, but Professors Chumakov and Belyaeva do not consider this proved. Discussions of this controversial point were published in the U.S.S.R. between 1940 and 1950. The sample of this virus supplied to the National Institutes of Health consists of lyophilized mouse brain in two ampules.

Strain BBBF

Strain BBBF is the virus of chorioencephalitis, "psychosensory neuroinfection of school children," isolated in 1948 from separate pools of blood and spinal fluid of four children with typical illnesses. The virus can be passaged in white mice by the intracerebral route of injection. In guinea pigs, it causes only a benign fever lasting 1 or 2 days.

In many ways the virus of chorioencephalitis resembles the virus of lymphocytic choriomeningitis but differs from it by its low pathogenicity for guinea pigs and monkeys and by the absence of bilateral cross-immunity (unilateral cross-reactions). The virus of chorioencephalitis is not related to any other known neuroviruses.

The clinical picture in children seen as ambulatory cases is characterized by a prolonged undulant course or, more precisely, by remittent attacks, associated with increased cerebrospinal fluid pressure, various psychosensory disturbances without symptoms of true psychosis, or organic encephalitis. The outcome is generally favorable, but in school children there is a notable failure to succeed in their studies.

The virus was supplied to the National Institutes of Health as two ampules of lyophilized mouse brain.

Part II

The American Medical Mission On Microbiology and Epidemiology To the Soviet Union

February 27–March 28, 1956

THE UNITED STATES Mission on Microbiology and Epidemiology assembled in Washington on February 23, 1956, and met with Dr. Lowell T. Coggeshall, Special Assistant for Health and Medical Affairs, Department of Health, Education, and Welfare, and Dr. Leonard A. Scheele, Surgeon General of the United States Public Health Service. We were briefed by personnel of several agencies the next day, and on February 25, we assembled in New York and departed for Moscow via the Scandinavian Air System. We spent 30 days, February 27–March 28, in the Soviet Union, visiting some 25 medical institutes and organizations in Moscow, Leningrad, Kiev, Kharkov, and Sukhumi, where we met and talked with more than 200 Soviet scientists and other medical men and women.

The mission operated as a group. Dr. John R. Paul acted as spokesman until he left Moscow on March 18. The rest of the mission, with Dr. Colin MacLeod as chairman, was together until March 25. Dr. MacLeod and Dr. Shope left Moscow on March 25. Dr. Meyer and Dr. Shimkin visited two more institutions and completed the business of the mission by March 28.

The initerary of the mission follows:

February 25	16:00 Leave New York.
February 26	21:30 Arrive Helsinki.
February 27	15:15 Leave Helsinki. 21:00 Arrive Moscow.
February 28	United States Embassy. The Honorable Charles Bohlen; Hayward Isham, second secretary.
February 29	Ministry of Health, U.S.S.R., Rachmanovsky Pereulok.
March 1–2	Central Institute of Epidemiology and Microbiology imeni Gamaleya (Academy of Medical Sciences, U.S.S.R.), 182-D, Shukinskaya 33, U.S.S.R.
March 3	Central State Control Institute imeni Tarasevich, (Ministry of Health, U.S.S.R.), Sivtzev Vrazhek 41
March 4	Sunday.
March 5	Institute of Virusology imeni Ivanovsky (Academy of Medical Sciences, U.S.S.R.)
March 6	State Institute of Vaccines and Sera imeni Metchnikov (Ministry of Health U.S.S.R.) Chernoshevskaya 44
March 7	Neurology Clinic, Botkin Hospital Academy of Medical Sciences, U.S.S.R.)
March 8	First Moscow Medical Institute (Ministry of Health, U.S.S.R.)
March 9	Institute of Experimental Pathology and Therapy of Cancer (Academy of Medical Sciences, U.S.S.R., Moscow, Tretia Meschanskaya Ulitsa 61.
March 10	Central Institute for Qualification of Physicians (Ministry of Health, U.S.S.R.) Pl. Vosstania ½.
March 11	0:25 Leave Moscow. 10:05 Arrive Leningrad.
March 12	Leningrad Sanitary-Hygiene Medical Institute (Ministry of Health, U.S.S.R.)
March 13	Zoological Institute (Academy of Science, U.S.S.R.), Universitetskaya Nabrizhnaya 1.
March 14	Institute of Experimental Medicine (Academy of Medical Sciences U.S.S.R.), Kirovsky Prospect 66/71. Oncology Institute (Academy of Medical Sciences U.S.S.R.)
March 15	8:45 Leave Leningrad. 15:25 Arrive Kharkov, Ukraine.
March 16	State Institute of Vaccines and Sera imeni Metchnikov (Ministry of Health U.S.S.R.), Pushkinskaya 14.
March 17	Kharkov Zootechnical Institute, Lozovenki.
March 18	10:40 Leave Kharkov. 12:40 Arrive Kiev, Ukraine.
March 19	Ukraine Institute of Epidemiology and Microbiology. Institute of Infectious Diseases (Academy of Medical Sciences U.S.S.R.)
March 20	Institute of Microbiology (Academy of Science Ukraine). 17:50 Leave Kiev. 22:55 Arrive Rostov-on-the-Don.

March 21	At airport: Anti-Plague Institute (Ministry of Health U.S.S.R.)
	9:20 Leave Rostov-on-the-Don.
	12:10 Arrive Sukhumi.
	Medical Biological Station (Academy of Medical Sciences U.S.S.R.)
March 22	12:10 Leave Sukhumi.
	18:15 Arrive Moscow.
March 23	Academy of Medical Sciences U.S.S.R.
	All-Union Scientific Institute of Veterinary Ectoparasitology, Mycology, and Sanitation.
	Institute for the Study of Poliomyelitis (Academy of Medical Sciences U.S.S.R.)
March 24	Central State Control Institute imeni Tavasevich (Academy of Medical Sciences U.S.S.R.)
	Academy of Medical Sciences U.S.S.R.
March 25	Sunday.
March 26	Institute of Organization of Public Health and History of Medicine imeni Semashko (Academy of Medical Sciences U.S.S.R.)
March 27	State Central Medical Library (Ministry of Health U.S.S.R.), Ploschad Vosstaniya ½.
March 28	8:45 Leave Moscow.
	12:50 Arrive Stockholm.
March 29	17:00 Leave Stockholm.
	9:10 Arrive New York.

General Observations

Twentieth Communist Congress

The period that the mission spent in the Soviet Union, between February 27 and March 28, 1956, witnessed some important events in the history of the Soviet Union. These events undoubtedly influenced not only the Soviet attitudes toward the mission but also our reactions and impression to such attitudes.

We were in the Soviet Union shortly after the completion of the Twentieth Session of the Communist Party of the Soviet Union, at which the sixth 5–year plan was presented and accepted.

Several statements of direct interest to science and its course in the Soviet Union were made at this session. In his speech, Premier Bulganin referred to the detrimental features of overcentralization and secrecy. He noted that the Soviet Union has nearly 3,000 institutions of research and education but that more than one-third of them were in Moscow and Leningrad, and that 60 percent of the scientists under the ministries and 85 percent of the members of academies were to be found in these two cities. He encouraged exchanges of opinion, development of research at universities, and relaxation of secrecy measures.

Dr. Maria K. Kovrigina, the Minister of Health, gave an address at the session. She indicated that the mortality rate in the Soviet Union in 1954 was lower than in the United States, Britain, or France. (This rate probably indicates a younger population.) The chief causes of death were cardiovascular disease (including rheumatic heart disease, hypertension, and coronary occlusion) and cancer. The rates for both diseases were stated to be lower in Russia than in the "capitalist" countries. (Again, the rate is probably a reflection of a young population.) Kovringa also commented upon overcentralization, noting that 51 of the 76 medical institutes (schools) were in the European part of the country.

Conferences

The conferences at the institutes we visited were carefully arranged and were quite similar. They usually continued for 3 to 5 hours, during which we met the staff, heard a general description of the institute, and visited the laboratories.

Our impression is that most of the information we received on scientific work had already been published. This would probably be true of laboratory visitors in the

United States also, particularly if they were uninformed about published work.

It was our intent to see as much as possible rather than to delve deeply into any one subject and as a result, our interpretations in many situations are undoubtedly based on superficial analysis.

A fact that stood out was how well the Soviet scientists were acquainted with our work, and how poorly we knew theirs. All their institutes had excellent representations of our scientific publications. Books that are considered important are translated and published in Russian.

Equipment

We found the Soviet research institutes satisfactorily equipped in that all the basic equipment was available. It was obvious that many items had been manufactured by the Soviets for only a few years. For example, the microscopes of Soviet make are copies of the Zeiss model of 2 or 3 years ago.

Late in 1955 a book was published which listed and illustrated much of the laboratory equipment of Soviet manufacture. This is "Sovremenniye metodi i technika morphologitcheskikh issledovanye," (Modern methods and technology of morphological investigations), edited by D. A. Zhdanov.

Several Soviet investigators remarked that technical equipment was still hard to get and in short supply and that rare chemicals were also extremely difficult to procure.

The institutes in Moscow, Kiev, and Leningrad had electron microscopes of modern design, centrifuges, Geiger counters, incubators, and the usual biochemical equipment. The serum and virus institutes had freezing-drying equipment, deep aeration tanks of several hundred to a thousand liters, tablet-press machines, and the usual equipment for making and sealing vials. All of the equipment had a rough, unfinished, handmade look, and the products issuing from the preparation were in rough, hand-sealed vials with poorly printed labels.

There was little question that the Soviet institutes were equipped and able to turn out any biological that was really required. However, the system was crude, and had far to go in the matters of packaging, marketing, and distribution. We saw no metal containers for medicinal products; all packages were of paper.

We had no way of assessing how well the needs of the Soviet physicians were met. However, there were ample pharmacies in the towns, and drugs and equipment did not appear to be short.

Medical publications are handicapped by the quality of paper available, which makes reproductions of histological details difficult, particularly since preparation and staining of the material is not always satisfactory.

We did not see any modern calculating machines, indexing systems (other than alphabetical hand cards), or statistical approach to records in any of the laboratories we visited.

Medical Scientists

We believe that the leading figures in Soviet medical science would enjoy the same relative status in other countries as well. We met many talented, original workers who were well acquainted with modern techniques and instrumentation. These workers were well supported in their facilities, their assistants, and their opportunities and social status. There are many able technicians in Soviet laboratories, usually women in their middle years.

Science has a preferred status in Soviet society. Every activity in science and related technology is grouped into institutes—educational, research, production. Most of these institutes have no fewer than 100 or even 500 people in their organizations. In Moscow, many large buildings have signs which proclaim them to house the institute of medical cosmetology, or virology, or vaccines and serums.

Many scientists in the Soviet Union hold at least two posts, head of a laboratory in a research institute and a "chair" on the faculty of a medical or postgraduate educational institute. Both posts pay full salaries for a 6-hour day. Membership in an academy also carries financial emolument, as does the writing of articles and books or translation of foreign scientific material. A college-trained biochemist earns, say, 1,000 rubles a month as a technician. If she obtains the degree of candidate of medical science, the salary is doubled; with the degree of doctor, it is doubled again. If she occupies two posts, writes, and is a member of an academy, she may receive a salary of more than 10,000 rubles, at least 10 times the salary of a technician.

In presenting us with scientific material, several Soviet scientists offered to make arrangements to exchange reprints, journals, and catalogs. A number of Soviet investigators were invited to submit articles for consideration for publication in American journals, with the explanation that such articles would be carefully reviewed before acceptance. All tentatively accepted the invitation.

Soviet scientists asked us to write to them at their institutes or through the Academy of Medical Sciences or the Ministry of Health.

Press Relations

Soviet papers and magazines made numerous requests for us to prepare articles, to appear on the radio, and to give interviews. Dr. Paul prepared a short question-and-answer piece on poliomyelitis, and we had an interview on cancer.

Requests for Materials

Soviet scientists supplied us with almost all the materials which we requested. These included viruses, as well as published and unpublished data on specific topics of interest to the mission. We took with us a large number of viruses, in partial fulfillment of a list submitted by Professors Chumakov and Smorodintzev on their visit to the United States. In Moscow, on March 23, we received the Army film on Korean hemorrhagic fever, which Dr. MacLeod turned over to Professor Chumakov. In exchange, a Russian film on tick encephalitis was being cleared for transmission to us but clearance was not completed before we left.

We did not receive the viruses of hepatitis and encephalomyelitis. The Soviets had not isolated hepatitis virus successfully, and the validity of the encephalomyelitis virus was still in doubt. We were also unable to obtain epidemiological data on certain diseases.

Lists of biological materials and of typewritten and printed materials obtained by the mission are appended as addenda 1 and 2.

Chronological Report

A day-by-day account of events pertinent to the purpose of the mission follows.

February 27 (Monday)

The mission spent a half day in Helsinki, where Dr. Nils Oker-Blom, microbiologist at the Laboratories of the City of Helsinki, and Dr. Penttinich, of the National Serum Institute of Finland, assisted us in replenishing our supply of dry ice for the preservation of biological specimens being taken to the Soviet Union.

When we arrived at the Moscow airport, we were greeted by several persons from the American Embassy and the Soviet Ministry of Health. At the Hotel National we met Leo Nikolaevich Mekhedov, an English-speaking biochemist who acted as our liaison officer and technical and scientific interpreter. We are indebted to Mr. Mekhedov not only for his services as interpreter but as our guide and companion throughout our visit in the Soviet Union.

February 28 (Tuesday)

On the morning after our arrival in Moscow we were driven around the city on a sightseeing tour. In the afternoon we were received by Ambassador Bohlen and discussed our itinerary with him.

February 29 (Wednesday)

Ministry of Health U.S.S.R. In the morning, we were officially received at the Ministry of Health U.S.S.R., with Professor V. M. Zhdanov, one of the deputy ministers, acting as our host. Professor Zhdanov has been head of the Kharkov Institute of Vaccines and Sera and has worked on influenza vaccine there; since at least 1952, he has been one of the deputies to the minister of health, Madame Kovrigina; and he is the author of a number of medical texts, including a recent one on infectious disease. Copies of this text were given to our mission.

Professor Zhdanov gave the mission a brief general account of the organization of public health, medical practice, medical education, and research in the Soviet Union. In general, the system is same as it was in 1944.[1]

The capital authority on medicine and public health is the Ministerstvo Zdravookhranenia U.S.S.R. (literal translation, Ministry of Health Protection, hereafter referred to as the Ministry of Health). Substituent ministries are reduplicated in the 16 republics of the U.S.S.R. and in oblasts (regions) and rayons (districts), when the size of the area indicates a need for such organizations. All services, including the salaries of physicians and ancillary personnel, are on government budget.

The services of the substituent ministries may be divided into two parts, therapy and sanitary epidemic work. All services are free. Both forms of service are organized along district lines. The function of the Ministry of Health is supervision.

The expressed principle of the Ministry of Health is to provide equal services throughout the country and yet to allow maximal local freedom of initiative. Certain measures are therefore legally prescribed for the whole country, but their practical uses are modified by local conditions because Russia is such a vast and, from a health standpoint, variable country.

[1] See *Am. Rev. Soviet M.* 1: 465, 1944; 3: 453, 1946; 4:271, 1947; and 5: 82, 1947.

Many of these public health measures are codified in four volumes, the "Sbornik Vazhneishikh Ofitsialnikh Materialov po Sanitarnim i Protivepidemicheskim Voprosam" (Collection of Important Official Materials on Sanitation and Anti-epidemic Questions, Medgiz, 1953–55), of which Zhdanov is an editor. All four volumes were presented to us on our departure.

Zhdanov stated that it is desirable that all methods of prophylaxis be based on a firm scientific foundation. One of the purposes of the Ministry of Health is to see that this is done. Another principle that Zhdanov expressed is the early application of scientific findings to practice. As soon as certain procedures are established, the ministry applies them to general use.

Sanitary-Epidemiological Stations. The key unit of Soviet preventive medicine is the sanitary-epidemiological station. These stations are organized and set up in compliance with the particular requirements of the region in which they are located. Each station has four departments: sanitation, antiepidemic, disinfection, and laboratory. In addition, some districts may have special services, depending upon local needs, and in large areas there may be, in addition, food, school, and industrial hygiene sanitation groups.

The size of the unit depends on the area and the local problems and may vary from a dozen individuals headed by a physician (vrach) to several hundred workers. The stations are distributed geographically and in industries and schools. The station can issue orders to other agencies in the field of health, enforce sanitary regulations, and impose fines or, for health reasons, it can even close factories.

The Sanitary Antiepidemic Services of the Ministry of Health play an important role in the planning and building of new enterprises. For instance, when dams or reservoirs are constructed, they are built with a view to facilitating malaria control.

The Ministry of Health gives directives to all economic groups in the country in the form of State laws; for instance, there is a law against the pollution of air and water by industries liable to such regulations. Along with the general laws promulgated by the Ministry of Health, local regulations are prescribed.

The ministry periodically reexamines its regulations as new information becomes available. For example, the regulations on scarlet fever were recently changed on the basis of published American experience.

On the other hand, the Soviet workers did not find the American influenza vaccine successful, and they proceeded toward the use of live attenuated strains. Their experience in vaccinating 10 to 12 million persons during the past 2 years indicates the satisfactory protective effects. The vaccine they have developed is comprised of living strains of influenza virus which have been attenuated by passage through human embryo tissue culture and egg culture. The material is freeze-dried. The vaccine is administered by way of the respiratory tract. It is considered safe for anyone over 5 years of age. If the vaccine is used in children under the age of 5 years, the dose has to be decreased materially. Reactions are mild and occur in about 1 percent of individuals. The vaccine is now widely used, but Soviet workers have run into problems with new strains.

Preventive Plans. Antiepidemic work is planned and carried out, using world experience in executing and adapting practices to the needs of their own special conditions. For instance, in some areas of Russia there are natural reservoirs for tularemia, and this situation is controlled either by the elimination of the reservoir or by the development and application of a vaccine. This vaccine is a living, attenuated one, and in many areas of Russia vaccination of total populations has proved more economical and feasible than elimination of the reservoirs. The population in these areas is periodically immunized to maintain a good level of immunity.

Zhdanov stated that among their chief problems are childhood infections, except diphtheria, and sanitation situations occasioned by housing shortages.

Medical Education. All medical education is under the jurisdiction of the Ministry of Health. Medical schools are not affiliated with the university system in Russia. There are 78 medical schools located in different parts of the country. (Kovrigina in her speech gave 76 as the number). Each Republic and each large city has at least one medical school. The multinational character of the country has to be taken into consideration in the establishment of medical schools. However, the teaching methods are unified so far as is possible and are modified in different areas only to coincide with local conditions; that is, in schools in the southern part of Russia, tropical diseases are emphasized more than they are in schools in the north.

Medicine is a 6–year course after 10 years of primary and secondary education. During the last years almost no lectures are given; the student's time is largely devoted to practical experience. At the end of 6 years, the student receives a diploma and is then entitled to begin practice.

Some departments in the medical schools are considerably more specialized than those in most other parts of the world; for instance, instead of having a single chair of hygiene in a school, there is frequently a separate chair for industrial hygiene, food hygiene, school hygiene, and so on.

A medical student can earn one of three types of diploma, depending upon the type of medical school he attends. The three general categories are sanitation (preventive medicine), pediatrics, and general therapeutic medicine. Some medical schools have 2 or 3 faculties, while others have only 1 faculty, and graduate doctors of only one category.

There are about a dozen postgraduate medical schools, which train physicians for more narrowed specialization. Ordinarily, the physician attends such postgraduate schools after about 3 years of practice. Teaching in these postgraduate schools is largely by seminar. All physicians, but particularly those who need such refresher courses, are supposed to attend a postgraduate school for 3 to 12 months every 5 years.

About 65 percent of the physicians in Russia and the students in the medical schools are women.

Medical research is carried out in medical schools, but is largely under three systems of institutes. Some are under the Academy of Medical Sciences, where the accent is on theoretical (i.e., basic) questions. Others are under the U.S.S.R. Ministry of Health where practical questions are emphasized, and others are under the Republics, for special local problems.

Research in general is correlated by the Medical Research Council of the Ministry of Health U.S.S.R. (N. I. Graschenkov, chairman). This group makes decisions concerning the overall direction and objectives of the investigations, and finer details are determined by various subcouncils. Professor Zhdanov remarked that in planning and outlining the work of various institutes, the capabilities and talents of individual scientists were taken into account.

The institutes of the local republics and certain individual institutes plan their own work, taking cognizance of health conditions peculiar to the areas in which they are located. Institutes under the Academy of Medical Science plan their work in compliance with the individual character of the various institutes.

After an individual has finished medical school and has become a physician, there are two further degrees that he can achieve, candidate of medical sciences and doctor of medical sciences.

The candidate of medical sciences degree can be earned in one of two ways. The individual may carry on studies for 3 additional years in the medical school; as an "aspirant" he is selected for this privilege by competitive examination. At the end of the 3-year period, he writes a thesis and defends it before a board of professors. If he is successful, he wins his degree, and he can then work in a research institute. Another way in which the candidate of medical sciences degree can be achieved is by working as an assistant in a medical research institute with an established scientific worker as preceptor. Upon achieving the degree of candidate of medical sciences, the physician's salary is doubled.

The doctor of medical sciences degree is achieved by independent work. To earn this, an individual must show ability to conduct good research without the assistance of his professor. He writes a thesis on his investigative work and defends this. If successful, he is passed by a special scientific commission. The achievement of the degree of doctor of medical sciences bestows upon the individual the right to become a professor and to supervise the work of others, and gives him various special privileges; in addition, it doubles his salary.

Beyond the achievement of doctor of medical sciences, there are various other honorary titles that can be earned. A few outstandingly able physicians are appointed to the Academy of Sciences or to the Academy of Medical Sciences. In these there are two grades, corresponding member and full member, or academician. The achievement of the grade of academician automatically adds 3,000 rubles to a man's salary. Certain of the larger republics have their own academies to which local physicians can aspire.

Central Institute of Epidemiology and Microbiology (Gamaleya). In the afternoon, we paid our first visit to the Central Institute of Epidemiology and Microbiology (Gamaleya), which is situated on the outskirts of Moscow. This institute, named after a famous Russian virologist, is perhaps the largest and most active institute for medical research in Moscow. Patterned after the Pasteur Institute, it has a number of departments and is a major production and research center of the Academy of Medical Sciences as well as of the Ministry of Health.

The institute consists of 6 or 8 large buildings, with another in the process of construction, and covers several acres. The apartments for the staff are in the same area. There are stables for a few animals at the institute, but most of the animals for serum and vaccine production are kept on a farm some 30 kilometers away.

The members of the mission met in the office of the director, Dr. Vershilova, where 30 or more scientists, representing a senior staff, were gathered. They not only represented the Gamaleya Institute but also some other Moscow research institutes. We met the majority of them, and mention was made of their fields or specialties.

March 1 and 2 (Thursday and Friday)

The second visit to Gamaleya was a full-day inspection of the laboratories. Preliminary discussions were held with regard to the functions and administration of the institute. Professor Vershilova said the institute had a staff of over 500 workers, of whom one-third were of professional rank (including technicians). About 100 of these are directly concerned with the preparation of biologicals. The Ministry of Health annually orders certain amounts of these products, for which funds are deposited in the institute's account. Vershilova stated that the profit of the business annually was 10 to 12 million rubles, in addition to the basic 15 million ruble annual budget from the government. She drew a fine distinction between this operation and American commercial production for profit. The practical work done is similar to that carried out by commercial laboratories in our country.

In October the institute receives estimates of the amounts of serums and vaccines that will be required of it for the year. It prepares its quota of these products and distributes them through pharmacies, either in hospitals or in the cities. The main products made at the Gamaleya Institute are living vaccines against brucellosis and tularemia; the standard calf lymph vaccine virus; typhoid vaccine; tetanus, diphtheria, and botulinus antitoxins; and a vaccine against Q fever.

Emphasis was placed on the fact that this is an institute of the Academy of Medical Sciences, so that research is the largest part of its activity. Much of this research is concerned with efforts to produce new and better vaccine preparations. Here was developed the dry, live vaccine for brucellosis and tularemia, the rickettsia vaccines for Soviet use, the dysentery vaccines, and the egg-grown Q fever vaccine.

Dr. Vershilova pointed out that the institute had to be evacuated during the war and that it was still suffering from shortages. They were not yet satisfied with their equipment, but the government was giving considerable help in the form of funds for instruments and a new building. The apparatus is in part made locally, but during the past year some equipment has been imported.

We were told that the only compulsory immunization in the Soviet Union is smallpox vaccination. It is given first at 1 to 2 months and repeated at school age. The vaccine is the standard calf preparation. Professor M. A. Morozov is in charge of this activity. In Russia, vaccination against whooping cough has recently been initiated on a routine basis. The vaccine is administered either as a monovalent one or in combination with diphtheria toxoid. Whooping cough is not a reportable disease in Russia. There are free baby clinics throughout Russia, to which all babies are taken, and at which all necessary vaccinations are conducted routinely. Diphtheria was stated not to be a problem, and wide use is made of immunization as part of well-baby care in dispensaries. Tetanus toxoid is not employed; antitoxin is used when clinically indicated.

Laboratory Processes. The activities of the specific laboratories and units visited by the mission are described below.

1. Preparation of antitoxic serums and globulin. The principal serums made at the Gamaleya Institute are those against *Clostridium oedematiens* gas gangrene, tetanus, *Clostridium botulinum* A and B, diphtheria, and scarlet fever. Professor Beylinson, a woman, is the originator of a method for clarifying, concentrating, and drying serums, a process which requires 6 days for completion. Blood is drawn into citrate and the plasma is separated in a De Laval type of separator. The plasma is treated with ammonium sulfate to precipitate all the globulin. The precipitate is then collected by filtration, pressed, and stored as 50 percent globulin, 20 percent salts, and 30 percent water, and is digested with pepsin at the proper pH. Later, the temperature is raised high enough to destroy deleterious thermolabile elements. The solution is again salted out, collected by filter, redissolved, and dialyzed. It is then concentrated by Beylinson's own method as follows:

Chloroform is added in excess to the dialyzed solution. This makes an emulsion. Then hydrochloric acid is added, dropwise, to bring the pH to between 5.1 and 5.4. This precipitates the foreign nonantitoxin protein. The chloroform is removed by separator, while the precipitated protein is also removed by separator run at a different speed. The clarified antitoxin is neutralized with sodium hydroxide to pH 6.9. The process is known as the Diaferm–3 process and is capable of concentrating globulin 6 to 10 times. There is considerable loss of antibodies in this procedure, and one of Beylinson's main research projects now is to attempt to improve the methods to a point where this loss will be minimized.

2. Preparation of dried living virus vaccines, essentially by the freeze-dry method, using stabilizers. Professor Dolinov, who is in charge, is an engineer as well as a biologist. He was particularly interested in methods for automatically sealing ampules under gas, the one step which has to be done by hand at present. The scheme of drying live viruses was made available to us in writing and has been translated.

The chief reason for the success of this method appears to lie in the stabilizer used in the drying process. For instance, in drying vaccinia virus, the stabilizer used is 10 percent sucrose and 10 percent egg white. In drying living brucellosis vaccine, the stabilizer is 10 percent sucrose and 2 percent gelatin. The BCG vaccine is freeze-dried in a stabilizer containing 10 percent sucrose and 1 percent gelatin. Using the Dolinov method of drying, a value of 80 percent viability can be achieved, for instance, with the *Brucella* organism on commercial production.

3. Department of Oncology. A longer conference was held with Professor Zilber on his studies in the virus theory of cancer and his detection of apparently unique tumor antigens by the guinea pig anaphylaxis reaction. This work has been published and translated. (Zilber, L. A.: The specific component of malignant tumors. Uspekhi Sovremennoi Biologii 30, 2 (5) : 188–221, 1950.)

Zilber isolates nucleoprotein fractions from various tumors by a method which will be described later. By the same method, he also isolates nucleoproteins from normal tissues of the same type as those from which the tumors were derived. Then he immunizes guinea pigs with the tumor nucleoprotein preparations. In order to do this, he gives guinea pigs a single subcutaneous injection containing about 6 mg. of nucleoprotein. Twenty-two days later, Zilber desensitizes these guinea pigs by giving them a 2 mg. to 3 mg. injection of the normal tissue nucleoprotein intravenously. He waits for the manifestations of shock to come to an end and the temperature to return to normal. He then gives the guinea pigs a second intravenous dose of the normal tissue nucleoprotein that is somewhat larger than the initial one (4 mg. to 5 mg.). If the animal still shows manifestations of anaphylaxis, he gives a third intravenous injection, this time of 6 mg. of normal tissue nucleoprotein. When he reaches a point at which normal tissue nucleoprotein no longer gives an anaphylactic reaction, and when the temperature from the last shocking injection has returned to normal, he gives an intravenous injection of 6 mg. of tumor tissue nucleoprotein. The animals go into shock of varying severity, which Professor Zilber considers evidence of the presence of some nucleoprotein substance in tumor tissue that is not present in normal tissue of the same tissue origin.

Professor Zilber has isolated nucleoprotein fractions from a large series of human tumors from various sources. When he carries out this experiment with either the rabbit papilloma virus or the Rous sarcoma virus, he gets a good reaction, and he believes, in the case of these two tumors, that the different nucleoprotein in the tumor tissue is actually the virus. He further believes that similar evidence that he gets with human tumors suggests that the foreign nucleoprotein in them may also be a virus.

The method by which Professor Zilber prepares his nucleoprotein extracts is as follows: The tumor tissue or normal tissue is homogenized in alkaline distilled water (pH 8–8.5). This mixture is stirred for 2 hours in a cold room, allowed to stand overnight, and then centrifuged. To the decanted supernatant is added enough HCl to lower the pH to 6, and a protein precipitate results. This is discarded. The supernatant is adjusted to pH 4–4.5, and another precipitate results. This is washed with water of the same pH (4–4.5), and then is dissolved in an alkaline solution at pH 7. This is the material that Zilber uses to sensitize his guinea pigs.

Another line of investigation developed by Professor Zilber to produce evidence which he thinks indicates that many human tumors may be of viral etiology is as follows: A suspension of rabbit papilloma virus is prepared (clarified by centrifugation, etc.), and mixed with guinea pig red blood cells. The guinea pig cells adsorb the virus to such a degree that the adsorbed fluid no longer contains any of the virus. These guinea pig cells, to which the papilloma virus is adsorbed, are then injected into guinea pigs subcutaneously to immunize them. Twenty-two days later guinea pigs can be put into anaphylactic shock (frequently fatal) by intravenous injection of cells of the same animal to which papilloma virus has been adsorbed. Carrying out the same sort of an experiment with many human tumors, Zilber can obtain the same results that he gets with papilloma, suggesting to him that, just as the guinea pig red cells adsorb papilloma virus, they also adsorb a virus or viruslike material from human tumors (this by analogy with the similarity of results obtained with the papilloma virus.)

Unfortunately, the issue is a little confused at the moment, because, according to Professor Zilber, nucleoprotein obtained from a suspension of tumors which have previously been adsorbed with guinea pig red cells still yields the foreign nucleoprotein mentioned in an earlier paragraph. Thus, Professor Zilber is faced with the dilemma of the presence of two substances in many human tumors which are not present in normal tissue of the same origin. One of these is a viruslike substance which can be adsorbed to guinea pig red cells, while the other is nucleoprotein, evidently not adsorbed by guinea pig red cells, which differs from the nucleoprotein present in normal tissues. Professor Zilber's imaginative approach to the tumor problem is being pursued vigorously in a large, well-staffed, and well-equipped laboratory. Other experiments in Professor Zilber's department included those by Dr. Medvedev. These consisted of an apparent transfer of human mammary tumors to mice and experiments on leukemia in mice.

In another section of the oncology division, work on antigens from tumors was in progress under Dr. Narzissov. This work was concerned with transmissible spontaneous tumors in mice, and from the tumors antigens were prepared and complement-fixation tests were carried out with the homologous mouse serum.

In still another section of the institute studies on immunity in cancer were being carried out, notably the demonstration of immune effects in transplantable cancer. In general, the technique consisted of preparation of an immune serum of high potency by immunizing horses with tumor cell suspension. The serum lyses the tumor cells very well, and to the lysate (freed from the remainder of these cells) 2 percent formalin is added. This is used as a vaccine for animals. Fifty to 80 percent of vaccinated animals become immune to the Brown-Pearce tumor of rabbits.

Dr. Zilber pointed out that he possessed and was using an example of the Carell-Lindbergh apparatus for the maintenance of whole organs, and that he had begun to use tissue culture techniques and was studying HeLa tissue culture cells. The department was equipped with an electron microscope and an ultracentrifuge made is Moscow.

4. Conference on childhood infections, with Professor Pavlov. In Pavlov's department, vaccines against organisms causing enteric disease are produced. There are several types of vaccine, one of them known as the tetra, which contains typhoid, paratyphoid A and B, and dysentery bacilli in which are incorporated strains of Flexner and Sonne bacilli. There are facilities for growing enteric bacteria for vaccine in tank culture. We saw tanks of 1,000-, 500-, and 250-liter capacity. Organisms grown on culture media containing casein and a peptone base were killed with formalin, dried with hot air in ovens, and bottled in the form of flakes.

One of their vaccines is administered orally. The killed organisms are made into pills, and these pills are administered to individuals suffering from chronic dysentery. The principle on which this treatment is based was reiterated several times, namely, that some Russian scientists believe that there is such a thing as local immunity of an epithelial surface, and that by applying the antigen to the surface, a certain degree of "resistance" can be created. This resistance is conditioned perhaps by local lymphoid tissue. Theoretically, this should inhibit penetration of the agent through this barrier. Ordinarily, the vaccine is given parenterally for prophylaxis.

The workers in the Gamaleya Institute did not believe that their dysentery vaccine, used orally for therapeutic purposes, had any real effects but its manufacture was being continued on a small scale because some clinicians considered it useful. The laboratory is working with diphtheria, whooping cough, scarlet fever, and coccal infections. Diphtheria toxoid adsorbed on alum is made here.

In the case of scarlet fever, Professor Pavlov's laboratory is studying the chemistry of the streptococcus from the standpoint of the development of diagnostic substances and procedures. We were informed that in Russia streptococci had been known to be the cause of scarlet fever since 1905. (In other Soviet institutions, the direct relationship of streptococci to scarlet fever was not completely accepted.) In Russia scarlet fever is treated with aqueous penicillin,—200,000 units twice daily for 6 days. This was stated to reduce complications by 5 to 7 times.

Dr. Lampert, one of Professor Pavlov's associates, has been studying the diagnosis of scarlet fever, using the urine of patients. She states that various antigens of streptococci are excreted in the urine during the early days of infection and give precipitin reactions. She stated that there is no group C antigen present in urine, but T antigens are present and probably M antigens. The M antigen is currently under study. Dr. Lampert takes fresh, whole urine, centrifuged without pH adjustment, and layers it directly over rabbit antiserum. The reaction is read in 15 minutes and again after 2 hours at 37° C. Dr. Lampert stated that by this method one can tell if the patient has streptococcal infection, and that the method can be used in early diagnosis of complications in scarlet fever and in carrier studies.

Dr. Lampert has been preparing a scarlet fever toxin for human immunization, employing Veldee's method of precipitation with tannate. She said that tannate-precipitated toxin is injected three times intracutaneously, that the situation is a complicated one, and that immunity is not durable, lasting only about 6 months. She has tried unsuccessfully to make a toxoid.

To prepare scarletinal toxin, Dochez N. Y. 5 strain is cultivated in cellophane sacks (according to the American method for *botulinus* toxin). By this means, toxin concentrates of 5,000,000 units per milliliter can be obtained. Dr. Lampert stated that in Professor Pavlov's department they have now prepared a toxin of a purity of 23,000,000 units per milligram of nitrogen, that the purified material is absorbed well on aluminum hydroxide at pH 7.4 to 7.6, and that this material is now being tested for its capacity to immunize. Children in one of the collectives are being used in this test.

The Dick test is used to select "susceptibles." The test population is evenly divided between the immunized children and the controls. Dr. Lampert stated that during a 7-month period after immunization the incidence of scarlet fever was reduced eightfold in immunized children. The department's present plan is to reimmunize these children at intervals of 6 months. To date, 1,000 children have been immunized.

Dr. Lampert stated that, in Moscow, for many years the leading types of group A streptococci have been 1, 2, 4, 6, and 27. Types 8, 10, 12, and 26 have occurred, but infrequently.

Dr. Lampert said that rheumatic fever was a serious problem among children in Russia, as elsewhere in the world. Despite the fact that type 12 infections have occurred, she remarked that acute nephritis is very rare in Moscow; also, that no epidemics have occurred in children's collectives.

Professor Pavlov stated that immunization against scarlet fever is not carried out generally in the Soviet Union.

5. Conference on the attenuated tularemia vaccine with Professor Olsufiev. The strain used has been forced to attenuate through variation in the culture medium.

The living cultures are freeze-dried and reconstituted for use. The culture is applied to the scarified skin in much the same manner as is vaccinia virus. The reaction begins on the fourth or fifth day, may be quite severe, and may last for as long as 4 weeks. Immunity is stated to persist at an effective level for 5 to 6 years. The vaccine strain of *Bacterium tularense* used is stated to be stable. This vaccine is prepared at the Gamaleya Institute, as well as in other laboratories in Russia. The institute's data, which appear quite reliable, indicate that this vaccine is highly effective, maintaining immunity for at least 6 years. We obtained samples of the material, and the official instructions for its preparation.

6. Conference on the live attenuated brucellosis vaccine with Professor Vershilova and her laboratory assistants, including Dr. Semecheva. Published data and our impressions suggest that this is an interesting preparation and an effective one. The living *Brucella* vaccine was developed from our strain 19 culture. The organism was passed through animals of low susceptibility, grown on agar, and S-form colonies were selected. When the culture became stabilized, it was tried on guinea pigs and was found to produce a good immunity which persisted for a year or longer. The living vaccine, when used on a small scale in areas where *Brucella melitensis* prevailed, was found to be effective in preventing undulant fever.

The vaccine is administered to man subcutaneously as a single injection of 150 million organisms. It appears to be completely safe, resulting in only a weak local reaction. When the immune titer of the vaccinated individual drops, reimmunization is effected by scarification, applying the living culture in much the same manner as vaccinia virus is applied. The Russian vaccine strain which was developed by Professor Vershilova is called strain 68. In veterinary practice, a very similar, but not identical, strain is used in immunizing cattle. We brought back a sample of the vaccine and instructions for its production.

7. Conference on rickettsioses. This conference was conducted by Professor Zdodrovsky, who had worked with Vershilova for many years and whose experience is published in a book, "Studies on Rickettsia and Rickettsioses," by Zdodrovsky and Golinevich (Moscow, Medgiz, 1956).

During the course of this visit, we learned that, in Zdodrovsky's opinion, Siberian tick fever is serologically identical with Rocky Mountain spotted fever. He stated that Q fever is extremely prevalent in Russia and that its incidence parallels the incidence of brucellosis, being high during the lambing and calving seasons. Professor Zdodrovsky has developed an effective vaccine against Q fever. The organism is grown in yolk sac, but we neglected to learn more details about it. It would appear to be a formalin-inactivated rickettsial vaccine.

The Gamaleya Institute seemed to have an adequate number of personnal and technicians. More than half the laboratory technicians were women. The laboratories were apparently well equipped, although some of the equipment looked antiquated. The directors hoped to remedy this situation within the next few years. Journals from the United States were often prominently displayed on the laboratory desks.

The Russian scientists were interested in the place of women in scientific work in the United States, not only as technicians but as administrators. Dr. Vershilova, the director of the Gamaleya Institute, asked, for example, whether her counterpart existed in the United States. The names of Dr. Florence Sabin and Dr. Leona Baumgartner were mentioned as examples of a prominent woman scientist and an administrator.

8. Publications. There was some discussion about the interchange of medical publications and the translation of American texts into Russian.

March 3 (Saturday)

Central State Control Institute (Tarasevich). March 3 was spent at the Central State Control Institute imeni Tarasevich in central Moscow. The administrative director of the institute is Simon I. Dedenko and the scientific director is Professor Nina Klueva.

The total personnel of the Central State Control Institute was stated to be 190, of which 60 were professionals. In addition, 150 inspectors are assigned to various production institutes throughout the U.S.S.R.

The chief duty of the institute is to set and to enforce standards for biological products that are made by the 38 Institutes of Sera and Vaccines under the Ministry of Health. This is done primarily by assignment of professional inspectors to the production centers. These inspectors issue licenses and check the processes in progress in small laboratories provided for the purpose. The central institute checks the products on a sample basis and whenever indications for such checks arise.

We were told that serums for the diagnosis of streptococcal infections are limited and that there are no pneumococcal typing serums available. The institute is planning to extend the list of these serums.

In general, international standards for biological products were said to be followed when these standards are available. We asked for instructions and standards for various biological products, and these were gathered for us by the Ministry of Health.

This institute's responsibilities are in the field of vaccines, serums, and antibiotics. Veterinary preparations are controlled through veterinary institutes, which are under another ministry. Drug standards and standards for hormones are outside the sphere of the institute, being the responsibility of special pharmacopeia commissions and of the factories making the chemicals. All manufactured products in the U.S.S.R. carry the designation "GOST," followed by a number; this is the government's standard designation for the product.

The institute maintains a bacteriological type culture collection, of several thousand strains. Professor Razhberger is the supervisor of this collection.

The virus collection is maintained at the Ivanovsky Institute. During World War II, most of the strain collection was lost or destroyed, and it had to be replaced by obtaining samples from all over the world. Some strains are maintained in other institutes that are actively working with them; a careful card index of these is kept at the Tarasevich Institute. Considerable of the work done here revolves around the development of good methods of preserving and stabilizing the various cultures.

The Tarasevich Institute also is responsible for the standardization of toxoids and living vaccines, and is attempting to set up a workable set of biological standards for these.

The research work of the Central State Control Institute is chiefly concerned with improvement of the stability of biologicals, problems of biological testing, and selection of bacterial strains for various preparations. In the serum laboratories, some antireticular cytotoxic serum is still being made on a small scale. Although little original work was in progress, Klueva is interested in combined vaccines, including one with eight antigens, the purpose of which was not too clear. Yurkovsky talked of smallpox vaccine and of rabies vaccine, which seem to be the standard calf and old Pasteur preparations. Pokrovskaya talked of the institute's plague vaccine, which was of the EV type.

During the discussion, we answered questions on the requirements of control of the Salk-type poliomyelitis vaccine in the United States.

In answer to a question concerning the nature of biomycin, we were told that this is a terramycin-like antibiotic which comes from an actinomycete.

March 5 (Monday)

Institute of Virusology (Ivanovsky). March 5 was spent at the Intitute of Virusology imeni Ivanovsky. This institute is under the Academy of Medical Sciences, and used to be part of the old All-Union Institute of Experimental Medicine (VIEM). It still occupies part of the building in which the Institute of Normal and Pathologic Physiology and the Fundamental Library of the Academy of Medical Sciences are housed.

The director of the Institute of Virusology is Pavel N. Kosyakov. Its personnel numbers about 200, of whom about 80 are professional workers. We were impressed by the quality of the scientists here, and by the work they were doing. Professor Kosyakov was primarily interested in immunology and the clinical application of vaccines. He directs an influenza clinic in one of the city hospitals (on Falcon Hill), and is primarily engaged in studies on influenza, the respiratory catarrhs, and virus hepatitis.

Professor Rishkov works on the problem of viral physiology and is especially interested in the influence of viral hydrolysates on multiplication of viruses. He also studies the effect of certain acridine and proflavine compounds on the inhibition of viral multiplication.

Professor Tavarnitsky is a biochemist, interested in studying the changes taking place in cells during the process of viral infection. In his studies, he uses methods of purification less technical than differential centrifuging. He makes use of tracers and labeled compounds and takes advantage of the selective adsorption of viruses by red cells and by certain bacteria. He is particularly interested in comparing the biochemistry of pathogenic strains of viruses with apathogenic ones. He uses a pathogenic and an apathogenic strain of influenza virus.

Tavarnitsky finds that major changes in host metabolism, especially that involving the metabolism of nucleic acid, takes place during infection with pathogenic viruses. He has studied the effect of adenosine triphosphate (ATP) and has found that it enhances the growth of viruses and increases the rate of incorporation of phosphorus. From this he has concluded that ATP is essential in energizing viral multiplication.

Professor Gorbunova works on influenza and is primarily interested in transformation by artificial means. She isolated 15 strains of type C influenza virus from the Leningrad outbreak last spring and obtained serologic evidence of infection but no isolations from a similar outbreak of influenza in Moscow. She has made extensive studies of the antigenic structure of the various types of influenza viruses and finds that the Russian B strains show great variation from the standard Lee type. On the A strains, it appears that none except A′ have occurred in natural outbreaks in Russia since 1949.

Gorbunova has been searching for something better than the cholera vibrio to use as a source of receptor-destroying enzymes. She has come to the conclusion that the CO_2 method is more satisfactory than the cholera vibrio. The CO_2 method was developed by Friedman of Leningrad and consists essentially of passing CO_2 through serum diluted 1:10 with water for 3 to 5 minutes. When the serum is centrifuged, the supernatant is found to be free of nonspecific inhibitors, although the inhibitors remain active in the sediment. It was with this method that Gorbunova obtained evidence of the presence of C type antibody in many Russian serums. This method is described in a book on laboratory techniques by Shubladze and Gaidamovich entitled "Short Course in Virusology" (Medgiz, Moscow, 1954).

Gorbunova has also been interested in the behavior of mixed strains of influenza virus in culture (embryonated eggs) and has found that if a mixture of A, A′, and B strains is made, the A′ strain will be lost within 30 serial passages. If the mixture contains only A and A′, the latter strain will not be lost in serial passages in eggs.

Gorbunova has also studied the effect of passage of type A influenza virus serially through immune mice and has observed that such passage gives a marked antigenic change in the passaged virus. The change is in the direction of A′.

Gorbunova, with Professor V. M. Zhdanov, has developed a living, attenuated influenza virus vaccine by passing virus through human embryonic lung tissue culture and then growing it in embryonated eggs. This vaccine has been extensively used in Russia to protect human beings against influenza.

We next visited the laboratory of Professor Barian, an epidemiologist. We heard here for the first time that among the arthropod-borne encephalitides of the U.S.S.R., notably the tick-borne spring-summer infections, there was a two-wave form of this disease known as "two-wave milk fever." Apparently the disease is transmitted by goat's milk, although it is due to the same encephalitis virus which is transmitted by the tick. Presumably, the infected milk is collected from the goat during the stage of viremia on the part of the caprine host.

The hemorrhagic diseases are not receiving much attention in the Soviet Union at present and, except for the Omsk group, little information was obtained about them. The Crimean group gives rise to a few epidemics in the Crimea. The hemorrhagic diseases are considered to be of virus etiology; on the other hand, the etiology might be rickettsial. There seems to be no single opinion as yet.

Tick encephalitis is prevalent and is controlled by a specific vaccine and tick prophylaxis.

There was an increase in poliomyelitis in Russia in 1944–45, but the incidence of this disease cannot be compared with the incidence of poliomyelitis in Scandinavia or in the United States. The average incidence in the Soviet Union is not more than 6.2 per 100,000 as compared with 50 to 60 in Scandinavia and 60 to 65 in the United States.

Hepatitis, known in the Soviet Union as Botkin's disease, has shown a small increase in the U.S.S.R., as it has throughout the world. For instance, in the Soviet Union, hepatitis has seemed to increase about 5 to 6 times, presumably since the war. In 1955, the prevalence was 75 to 76 per 100,000 in Europe, 95 to 100 in Western Europe and somewhat lower in Central Europe, and 40 to 45 per 100,000 in the Soviet Union. However, in the U.S.S.R., the distribution of hepatitis is irregular; for instance, the index in the Ukraine and Caucasus is low, 10 to 12 per 100,000, while in some regions—Moldavia, the Baltic Republics, and central Uzbeckistan—it is very high.

Professor Barian was asked to comment on a report that there had been yellow fever in the Soviet Union. His answer was "No," that the insect vector, the mosquito *Aedes aegypti*, had been found at one time but had now disappeared. This led to a discussion of the possible mutual exclusion of dengue and yellow fever, either in the mosquito or in man, and how this might affect southeast Asia and India. Barian commented that dengue had been discovered on the Turkish shore of the Black Sea but not in Russia.

We next visited the laboratory of Professor Sergiev. He is chief of the measles laboratory and is very much interested in active immunization against measles.

In studying measles, Sergiev has taken advantage of the observation that the measles virus can be adsorbed to various bacteria (*Bacillus prodiogiosus, Salmonella typhosa,* etc.), and that these bacteria, to which measles virus has been adsorbed, will then agglutinate with measles immune serum. Using this method, Sergiev has demonstrated that virus multiplies in the blood of various animals, such as turtles, snakes, rabbits, guinea pigs, and monkeys. He has studied the qualities of virus passed through various animals, and he has found that measles virus which has been passed through rabbits multiplies when it is injected into monkeys, but it does not produce clinical disease in the monkey. Furthermore, measles virus passed through puppies also loses its ability to infect monkeys, although it multiplies in them, and monkeys thus injected are immune to virulent monkey or human measles viruses. Sergiev has also grown measles virus in chick embryo and in human tissue culture, and with some of these cultures he was able to immunize monkeys. Sergiev says that even freeze-drying of measles virus destroys its pathogenicity for man.

Measles virus passed through puppies just one time has been used to vaccinate children in collectives. The children in this experiment were only slightly immunized, but the number of complications resulting when they acquired measles was diminished about 15 times.

The immunity induced by the puppy blood vaccine was increased when multiple injections were administered to children. Two injections of a human embryo tissue culture measles vaccine were also used to induce immunity. However, in this experiment, no immunity was established at 13 days but immunity was present 30 days after the second injection.

Sergiev told us that measles virus can be carried through puppies for at least 6 or 7 passages, and that a rash is seen in between 30 and 40 percent of the puppies infected. He routinely uses puppies that are 2 to 3 months old, although he stated that older dogs are also susceptible.

Dr. Sergiev was also asked about sandfly fever. He answered that in many places in previous years this disease had been a problem but that today, like malaria, it is no problem. The Soviets did have a live vaccine which they felt was effective against sandfly fever. The laboratory in which the live vaccine is produced was not specified.

We visited the library, which contained some 250,000 items, including 80,000 foreign books and journals.

Next, we went to the laboratory of Professor Shubladze, the wife of Professor V. D. Soloviev. She works on encephalitis, hepatitis, and tumors, and maintains a special laboratory for the isolation of new virus strains from cases of nonepidemic polyseasonal encephalitis. In this laboratory, Shubladze searches for virus in persons ill with many types of encephalitis. She isolates numbers of well-known viruses, such as lymphocytic choriomeningitis virus and herpes virus.

Among the viruses isolated by Shubladze is one which she calls the acute encephalomyelitis virus. She has isolated this virus 5 times from about 100 cases of acute encephalomyelitis. Isolations have been made from blood, brain, and cerebrospinal fluid. The virus of acute encephalomyelitis, which appears to be distantly related serologically to the rabies virus, grows in most laboratory animals cerebrally. When administered to young chicks, it causes a chronic disease that can last for as long as a year and a half. Pathologically, acute encephalomyelitis in chickens closely resembles multiple sclerosis in man, and it was this resemblance that suggested a possible relationship of the virus to human multiple sclerosis. The virus in chickens causes demyelinating lesions. The virus will kill rabbits and mice by either subcutaneous or intraperitoneal injection but has a longer incubation period by these routes than by the intracerebral route.

Shubladze has never isolated the virus of acute encephalomyelitis from a case of multiple sclerosis, but a fairly high number of multiple sclerosis patients possess antibodies in the blood serum active against the virus, suggesting that this virus may have initially been responsible for the multiple sclerosis syndrome.

Shubladze has prepared a formalin-inactivated vaccine of the acute encephalomyelitis virus, which has been tested in the treatment of multiple sclerosis during the past 10 years. According to her, 30 percent of the individuals thus treated have completely recovered. The vaccine is a formalized suspension of the brain of infected animals (mice or rats). The data that Shubladze gave us indicated that serologic tests were positive in 50 percent of multiple sclerosis cases, and the skin test with the antigen was positive in 96 percent of these cases. Only 3 percent of normal individuals gave positive skin tests. The skin reaction, an area of erythema roughly 1.5 x 1.5 cm., appears in about 24 hours and disappears in 48 hours.

Hepatitis. In Shubladze's laboratory, the great majority of the experiments in hepatitis have been negative. There have been several phases of the work.

From many tests, largely with human feces representing material from hundreds of cases, Shubladze reports that they have isolated a so-called egg form of hepatitis virus in 3 percent of the trials as demonstrated by the presence of an antigen which fixed complement with serums from recovered cases. Apparently, this result was achieved with considerable difficulty. Shubladze admitted that her results were similar to those of Benda, Gerlach, and others, in Vienna (Arch. ges. Virusforsch 4: 2, 89–117, 1949).

Another and more hopeful line of research has been the demonstration of an antigen derived from the livers and spleens of patients who died of hepatitis. The spleen was the better of these two sources of antigen. This antigen was found to be useful as a complement-fixing antigen and in producing hemagglutination. Specific inhibition of this reaction occurs in convalescent hepatitis serums, but it can be demonstrated only after nonspecific inhibitors are eliminated. The best way to do this is through filtration. The test is set up with chicken erythrocytes. When normal liver gives a reaction in these patients, the serum is absorbed first with normal liver.

A third antigen consists of specific bacteria isolated from the blood by Dr. Verankova. This micro-organism has been isolated from the blood in 44 percent of the cases of hepatitis studied in Shubladze's laboratory. The micro-organism grows only in symbiosis with yellow sarcinae, looks like a pleuropneumonialike organism, grows in chains, and has been called the streptobacillus of Botkin's disease. It is apparently grown in a liver-pig stomach medium. Tissue culture studies on hepatitis virus using chick embryo and human embryo have been negative.

In response to a question about the local prevalence of serum hepatitis, Shubladze gave us the impression that this infection was not found in the Soviet Union since blood donors are selected on a very careful basis and individuals suspected of having hepatitis are not accepted. Asked whether information was available on the techniques of sterilization of blood or blood products, she mentioned that this was done with "trypo flavine."

Finally, attempts to reproduce hepatitis experimentally in monkeys have been negative so far, but Shubladze does not consider that her work has been sufficient or that enough animals were used. She does believe that in rhesus monkeys they have produced the disease with so-called microsymptoms, such as enlargement of the liver. Most important of all was the finding that the blood of these infected animals contained antibodies to their antigen, as demonstrated by complement-fixing tests. They have made no attempts to reproduce hepatitis experimentally in man.

Shubladze's laboratory also does work in oncology, a special emphasis being placed on the determination of a virus etiology. In carrying out this work, Shubladze attempts to stimulate growths on chick embryo membranes by means of filtrates of human tumors or by the injection of such filtrates into irradiated animals. Thus far she has had positive results with only one type of tumor, carcinoma of the larynx. Filtrates of these tumors produce tumorlike growths on the chorioallantoic membranes of embryonated eggs.

We next visited the laboratory of Professor Lefkovich, who has collected much useful data on encephalitis over a period of almost 20 years. The three types of encephalitis in the Soviet Union are tickborne encephalitis; so-called Russian spring-summer encephalitis (RSSE), western and eastern types; and Japanese B encephalitis. A map in Professor Levkovitch's room illustrated the geographic distribution of these forms of encephalitis. The western variety of RSSE was confined to the central third of the Soviet Union, that is, to Russia and Siberia, and the western variety to the eastern half of the country. RSSE is characterized clinically by paralysis of the shoulder girdle and neck muscles.

The "American idea" that the western variety of RSSE is a form of the Scottish disease of sheep known as louping ill is not shared by most Russian scientists. They have found serologic differences and differences in the experimental disease. For instance, sheep infected with louping ill suffer severely and usually die, whereas the virus of western RSSE, when injected intracerebrally into sheep, only gives rise to a mild fever without central nervous system symptoms. Up until now Russian scientists have not been able to find any epizootic of this type in sheep in Russia. Although cross-immunity seems to exist between the viruses of louping ill and western RSSE, they are not the same.

A new clinical form of RSSE has been recently demonstrated. This is the alimentary form, often characterized by two bouts of fever. It is produced by the transfer of the eastern variety of the tickborne encephalitis virus to man through raw goat's milk. There is no great difference between this virus and the newly-discoverd virus which causes "two-wave milk fever." Experiments indicate that 20 days after a goat is infected the milk may become infectious. The goat itself is not particularly ill, although it may have some fever. However, when the virus of two-wave milk fever is injected intracerebrally into the goat, serious encephalitis may result. In this respect, RSSE differs from Japanese encephalitis, which is not transmitted by milk. Both the eastern and western forms of RSSE can be transmitted by goat's milk.

Viral studies have been carried out at the Ivanovsky Institute since 1937. The RSSE viruses have been shown to be pathogenic for mice, rats, goats, sheep, guinea pigs, and monkeys, nonpathogenic for rabbits.

Epidemiological studies indicate that the encephalitis virus can be carried by the tick

Dermacentor sylvarum, and that there is transovarian passage of the virus.

The tick is the main reservoir of infection. Other tick vectors include *Ixodes hemaphysalis* in the east and *Ixodes ricinus*, which is the main carrier in the western area. Practically all wild and domestic animals can be carriers. Gophers, field mice, and hedgehogs may develop apparent or inapparent infection. Virus can be found in such animals over a period of 7 to 9 days. In birds there is also a large reservoir of infection, with the virus present (presumably in the blood) for 15 to 20 days. Ticks, in the larval or nymphal stages, bite birds in the nest. It has been shown recently that mites may be carriers of virus for short periods; also that birds of the passeriform type get encephalitis.

Studies also were made of the effect of immune animals on the reservoir of infection. It was found that in immunized animals, the viremia to experimental infection is of shorter length; therefore, it is considered that the presence of immune animals in a given area will decrease the opportunity for transmission of the virus. The workers in Lefkovich's laboratory have undertaken studies on the immunity of the human population within the reservoirs. Persons who have lived there a long time have high titers and immunity. In some reservoirs up to 30 percent of adults have antibodies. As regards natural (animal) reservoirs, adults also have a high percentage of antibody titers. Questions under investigation are concerned with whether or not ticks fed upon immune animals actually become infected; there seems to be some evidence that when an uninfected tick feeds on an immune animal, the tick does not become infected.

Formalinized mouse brain vaccine has proved highly effective. In Lefkovich's laboratory, they have also tried an egg vaccine, which was not as effective as the mouse brain vaccine. It is important to use a booster dose 1 to 2 months after the last injection. There have been no bad reactions, although many thousands have been vaccinated. The vaccines exhibit a high antibody level; if the absence of reactions to mouse brains is correct, this is important.

For the diagnosis of encephalitis, Lefkovich's workers use a mouse brain antigen inactivated with ultraviolet light.

For tick control, various chemicals were mentioned, notably one called hexachlor and gamma hex. Its application, they claim, renders the treated territory clean of ticks for 2 or 3 years.

The work on Japanese encephalitis, a disease which also prevails in Russia, is less actively pursued than work against spring-summer encephalitis. The Russians use a vaccine made of formalin-inactivated infected mouse brain to protect against Japanese encephalitis.

In regard to the equipment or facilities for work in these institutes, we got the general impression that the rooms were rather crowded; that there was no dearth of manpower and womanpower; and that the apparatus, although not as adequate or modern as one might see in this country, was by no means inadequate. Electron microscopes and centrifuges of various kinds were in evidence, usually from quite a variety of sources.

In reviewing the work being carried out by Soviet scientists, the impression is that their relative isolation has in one sense given them a degree of independence that has perhaps enabled them to develop programs quite different from those in the United States. There are many examples in which work in the Soviet Union seems to have gone off on a tangent, but whether this is right or wrong, good or bad, remains to be seen.

March 6 (Tuesday)

Institute of Vaccines and Sera (Metchnikov). The Institute of Vaccines and Sera imeni Metchnikov is one of the older medical institutes in Russia, having been organized soon after the revolution to fight the epidemics that prevailed then. Its director is Andrei P. Muzichenko. He is apparently strictly an administrator; the scientific director is a woman, Professor Greenbaum. Muzichenko described the institute as a scientific center as well as a training institute, and it was stated to have a staff of 150, about half of them of professional rank. Their activities have been concerned with practical work —testing drugs for practical use. Officially it is a vaccine and serum institute whose main work is scientific study of the etiology, epidemiology, and prophylaxis of children's diseases, chiefly those of viral origin.

The institute has four main departments: microbiology and immunology, epidemiology, production, and virology.

The department of microbiology and immunology, under Professor Christovnikova, has to do with bacterial and other vaccines. The research of this department consists of attempts to develop new prophylactic preparations and to improve the old ones.

The department of epidemiology, under Professor Mitayev, deals with the problems of epidemiology of infectious diseases and devises methods of controlling epidemics. This department operates under an outside advisory council.

A discussion on reportable diseases was held with Mitayev. The Russian list of such diseases was very similar to ours. It is not given here since an official statement, including the forms used for such reports, was given to us and has been translated.

The production department, under Dr. Ogloblena, is charged with the production of various biologicals, including living influenza vaccine, smallpox egg vaccine, gamma globulin, antitoxins, antibacterial and antiviral serums, and a leptospiral vaccine. This department cooperates with the epidemiology department in producing and studying, under field conditions, new prophylactic preparations. Current studies of this character have to do with a living influenza vaccine.

The virology department, under Professor Soloviev, is working with influenza, smallpox, and poliomyelitis, and cooperates with the production department in the preparation of viral vaccines. This laboratory is concerned with practical and theoretical aspects of vaccines and serums. The practical aspects are those of vaccine production and serum testing. Theoretical studies include investigation of the transformation of viruses and of immunity.

Apparently influenza and influenza epidemics are particularly common in Russia and represent a considerable menace as a cause of time lost from work. Vaccination against influenza has been practiced in Russia for some years, their particular variety of vaccine being a live virus vaccine administered intranasally. The effectiveness of this vaccine has been demonstrated on more than one occasion (table 1).

Table 1. Effectiveness of vaccination against influenza in a factory population (cotton workers) observed in 1955

Number times vaccinated	Number under observation	Influenza cases		Number days lost from work
		Number	Percent	
Once (1954)	6,056	583	9.6	3,125
Twice (1953, 1954)	3,931	476	12.0	233
Controls:				
Unvaccinated	4,972	1,769	35.0	--------
Vaccinated (1953)	1,901	537	28.0	--------

Some of these workers had been vaccinated in 1953 only, some in 1953 and 1954, and some in 1954 only. The vaccination was usually given during the autumn months. The record of illness was made in the winter months, early in 1955. Various rates are recorded in these four groups of individuals, but there seems to be a difference, which is probably statistically significant, indicating low rates, 9.6 percent to 12 percent in the individuals vaccinated in 1954 and 1953, as compared to the higher rates in the unvaccinated controls and those vaccinated 2 years ago, in which the rates were 35 percent and 28 percent respectively.

Another experiment, also carried out in a population of factory workers, indicated the effectiveness of vaccination in individuals who had been vaccinated once in the fall of 1953 (table 2). These individuals were observed in the winter of 1953–54. A sharp difference in rates between the vaccinated and control groups is noted. When the vaccine is given during an epidemic, the effect is almost immediate, suggesting strongly that interference may play some role in the end result. The immunity following intranasal vaccination lasts only for 1 year, and the following year vaccinated individuals appear to be again fully susceptible to influenza.

In discussing these results a number of questions were raised: Did the live vaccine spread to other members of the family?

Table 2. Effectiveness of vaccination against influenza in a factory population observed in 1953–54

Number times vaccinated	Number under observation	Influenza cases	
		Number	Percent
Once (1953)	9,853	865	8.8
Control	5,436	2,401	44.2

Could the lowered rates be examples of interference, in that vaccination was being practiced at a time when epidemic influenza was beginning? It was again pointed out that the vaccination of young children under 5 years of age was not a simple procedure, since reactions (symptoms of illness) were more apt to be produced in these young children than in children over 5 years of age.

In the preparation of the strains of influenza virus for use in the vaccine there are two lines of investigation; the growth of influenza viruses in tissue cultures of human embryonic lung for attenuation purposes and the conservation of strains and strain properties.

The virology department is also engaged in the adaptation of virus strains from the nasal mucosa. For attenuation, passages are made in eggs only. The degree of attenuation is tested in groups of volunteers, but before the volunteers are used the strains are tried out in tissue culture of human embryo (lung). A good strain for vaccination gives a good growth in the lung of the human embryo.

Virus which grows in eggs but does not grow in human embryonic lung tissue culture is unsatisfactory for use as vaccine. The ideal virus is one which has been well attenuated in the egg but which still maintains its capacity to grow in human cells.

The virology department has attempted to attenuate these strains in mice by adapting the strains to that species, but they have not been successful because mouse-adapted strains will not take in man. In the vaccine they use A and A′ and B strain mixtures obtained from chick embryos. One of their B strains is called Kri; isolated in 1950, it is different from the Lee strain. One chick embryo gives 18 doses of vaccine.

Another interesting phase of Professor Soloviev's work concerns the serial passage of PR8 influenza virus in eggs in the presence of anti-PR8 and anti-WS serum. In such serial passages, three 10-day-old chick embryos in a group are inoculated with varying dilutions of serum and a constant amount of virus. Upon serial passage, the virus gradually acquires the capacity to transmit influenza against higher and higher dilutions of serum, until finally (by the 11th passage) the serum appears to exert no inhibitory effect. At this time, when the virus is typed, it is found to have changed from an A to an A′ type. This variant was still present at the 72d passage.

The use of this vaccine is based on the theory of local immunity, in other words, the creation of a state of resistance in the epithelial lining of the upper respiratory tract. There is relatively little antibody developed in the serum of individuals after intranasal instillation; in other words, you get low antibodies in the blood, but a high degree of resistance is present in the cells, in contrast to parenteral inoculation of influenza vaccine in which you get high titers of antibodies in the blood and low evidence of resistance in the tissues. In rats, this picture of local immunity can be well demonstrated; in ferrets or mice, it has not yet been tested.

Dr. Soloviev demonstrated a chart showing the influenza experience in the Soviet Union covering a period of 7 years, 1949–55. Unfortunately, however, the rates were not shown, because with each year the virology department had started with a figure arbitrarily chosen to represent unity, which was the maximum number of cases observed in the summer; and the winter rates were calculated on the basis of the deviation from this unit. In 1948–49 both "A" and "B" types had been present; in the following winter, "B" alone; in 1950–51, "A" alone; in 1951–52, "A" alone; in 1952–53, "A" and "B"; in 1953–54, "A" alone, and so on. Superficially, one would surmise that the frequency with which epidemics occur in Russia, that is, practically every winter, was far greater than what might be the experience in this country.

We had a very interesting discussion on

leptospirosis. This disease occurs mainly during the summer and is quite prevalent among bathers. Seven types of leptospira have been identified in Russia. All strains isolated are sent to this laboratory for classification. They are identified on the basis of their morphologic, serologic, and biological properties. In classifying them, ecologic as well as serologic data are utilized. The natural reservoir for leptospirosis is thought to be wild animals, while domestic animals apparently serve as supplementary reservoirs.

The field mouse (*Microtus*) is considered to be the natural reservoir of leptospira. Infection of this animal is mainly in the kidneys, and leptospira are spread through its urine. Shrews and water rats also serve as reservoirs in some area. Leptospirosis is known as water fever in Russia. The culture medium used in growing leptospira is Uhlenhuth's medium (H_2O plus rabbit serum and sometimes yeast extract.) Isolations of leptospira are made from rodents by kidney puncture and from the human blood stream (2 to 3 drops of blood to 0.5 cc. of medium in five tubes).

In areas of Russia where leptospirosis is most prevalent, a prophylactic vaccine is used. Cultures for vaccine are grown for 10 days in Uhlenhuth's medium and are inactivated by heat and phenol. A polyvalent vaccine is used (usually at least four strains), and two injections are administered.

Individuals in whom the diagnosis of leptospirosis is made can usually be treated satisfactorily with penicillin or streptomycin up to the first 4 days of illness. Such treatment shortens the period of illness and also shortens the carrier period.

The experimental animal of choice in studying leptospirosis is the suckling rabbit. Rabbits 10 to 12 days old die in about 10 days following inoculation subcutaneously, intraperitoneally, or into the eye, with most field strains of leptospira.

March 7 (Wednesday)

Neurology Clinic, Botkin Hospital. The head of the Neurology Clinic at Botkin Hospital, Professor N. I. Graschenkov, is at present chairman of the Research Council of the Ministry of Health and a member of the Academy of Science. Previously, he held posts as director of VIEM, the All-Union Institute of Experimental Medicine, and as a deputy minister of health.

We saw modern equipment and laboratories here, including one on biophysics in which two aspirants were determining the electromagnetic moment of chemicals.

Graschenkov's approach to his work appeared to be primarily biochemical. His main current interest appeared to be the study of "diencephalic syndromes," which were treated by nasal insertion of tampons soaked in benadryl or novocaine and by application of a weak current between the nose and the occiput to produce ionophoretic permeation of the material to the diencephalon via the olfactory nerves. (Reprints of reports on this approach have been translated into English). We heard later in Leningrad that this form of treatment seemed to have some effect in asthma, but no controlled experimental data were shown.

Professor Graschenkov did not discount the marked psychological effect that this type of treatment might have on his patients.

In discussing the problem of multiple sclerosis, Graschenkov was inclined to agree with the views of Professor Hoff of Vienna that multiple sclerosis is not the same as a chronic form of viral encephalitis. This is in contrast to the views of Professor Margolis, who believes multiple sclerosis to be the late stage of an acute encephalitis.

Professor Graschenkov is inclined to believe that there is an allergic factor. Furthermore, he does not agree with Dr. Shubladze, whose vaccine we have discussed previously. Graschenkov has found that the skin reaction with the Shubladze vaccine is nonspecific, and that he gets positive reactions in tuberculosis and in other chronic diseases. According to Graschenkov, the important neurological problems in Russia can be divided roughly as follows: 40 percent are due to vascular disturbances, virus diseases with secondary changes account for 30 percent, and the remaining 30 percent is made up of neoplastic diseases and other less common conditions.

Professor Graschenkov has done some

work with lymphocytic choriomeningitis and finds the usual epidemiological relationship to the common house mouse. In addition, he has observed outbreaks of the disease in the country at harvest time, in which he has been able to implicate field mice as the reservoir and source of infection.

March 8 (Thursday)

First Moscow Medical Institute. The First Moscow Medical Institute is maintained under the direction of the Ministry of Health. It is one of the largest medical schools in the country, occupying a number of buildings, some grouped in one place and others scattered about the city.

A general survey of the scope and organization of the school was given us first by the present dean and director, Professor Vladimir V. Kovanov, who is professor of surgery. He pointed out that his was not a full-time administrative position, but that he also occupied a clinical chair.

The dean of this institute is elected by the Scientific Council, which not only elects administrative officers but determines the work of the school (or institute), which is concerned with education, scientific research, and clinical responsibilities.

More than 4,000 students are enrolled in the institute and some 500 aspirants are postgraduate students. The faculty numbers some 500, of whom at least 80 are full professors. The number of chairs (departments) is less than 80 because in the larger departments, such as anatomy, there are sometimes two professors for one chair.

The duration of the medical course is 6 years, and, as has been emphasized before, there are two kinds of instruction from which the student may choose; in other words, there are two faculties. One is concerned with general practice and the other, with sanitation and hygiene, which prepares the student for work in industrial hygiene, community hygiene, school hygiene, and so on. The institute maintains a close connection with important clinics, and here the fourth-, fifth-, and sixth-year students are trained in their clinical work.

As previously mentioned, the medical schools exist as organizations distinct from the university. The separation was made in 1930. Previously, the First Moscow Medical Institute was a part of Moscow University; now it is under the Ministry of Health. The dean pointed out that, from his standpoint, this was an advantage; in other words, that this independence from the university played a positive role for the medical school. When it was a part of the university it was only one of the various diversified groups with which it had to compete for funds. "Now we have a separate budget, we have more students, and we have more buildings. Our identity is much better established. When at the university we could take only 800 to 1,000 students; now we have more than 4,000."

Dean Kovanov admitted that they had perhaps lost some opportunities for contact in special departments, but that this was a minor matter in comparison with the material advantages achieved. When asked what was the advantage of having as many as 4,000 students as compared with 1,000, he said that they were glad because they were now better able to meet the demand for physicians. "We need many doctors," he said, "we do not yet have a surplus," and then he went on to point out that with a larger number of students the institute receives more support from the State, its laboratories are bigger, and its scientific staff can be enlarged.

The institute has 1,500 beds for clinical teaching. These are available to students in the sixth year of their course and also when they work in the first-aid hospital.

In response to a question as to how the integration between the medical school and the hospitals was accomplished, Dean Kovanov stated that he was director of the institute and at the same time director of all the clinics. Of course, he has a deputy, whose work is concerned almost entirely with the administration of the clinics, but it was clear that the clinics were an integral part of the teaching institution. He did admit, however, that in his dealings with some of the hospitals where teaching was done, organizational problems has arisen which required "some discussions." We were told here that we would be able to receive a copy of the catalogue of the First Moscow Medical Institute.

In explaining the trends which are now being put into practice by the curriculum commission of this medical school, Dean Kovanov stated that the faculty of the institute believed that in the past they had been attempting too much in the way of specialization, and that they would now attempt to keep their medical education on a broad basis. Not until the trainee had become an aspirant would they plan to begin to specialize. As to the distribution of students in the school, it seems that about 33 per cent choose to elect the sanitary hygiene course and 66 per cent, the course in general practice or therapy. Both groups of students get training in both fields, the difference being quantitative rather than qualitative.

In discussing the allocation of students after they have finished their course, Dean Kovanov pointed out that the students came from many parts of the country and that they usually went back to the area from which they came. The most talented of them remained in Moscow. Certain others were given assigned positions in remote areas. The dean stated that they did have a problem of many students wanting to locate in large cities, and they could not always satisfy these demands.

Only a rough outline of the curriculum will be given here. Each year of the 6-year course is divided into two terms, and in discussing these terms, the number of hours for each course will be given. It was stated that, as a rule about half of the hours were taken up with lectures and the other half with laboratory work or practical demonstration.

In the first 2 years, anatomy covers 3 terms, 392 hours, including 118 hours of lectures; physics, terms 1 and 2, 136 hours; biology, terms 1 and 2, 190; histology, 182; foreign languages, 220; physical education, hours not specified; chemistry (inorganic, organic, and colloid), 140; biological chemistry, beginning in the second and continuing to the third term, 295; physiology, beginning in the second year, that is, the third term, 295; in the fourth and continuing into the fifth term, microbiology, 207 hours.

In the third year, that is, the fifth and sixth terms, the students begin sanitary microbiology, then pharmacology, pathological anatomy, pathological physiology, general surgery, and general treatment.

During the fourth and fifth years they are given introductory instruction in surgery, therapeutics, pediatrics, obstetrics and gynecology, neuropathology, psychiatry, dermatology and venereal disease, laryngology, opthalmology, and various sanitary disciplines. Here the hours differ, depending on what course the students choose. Students specializing in the sanitary hygiene course take instruction in hygiene of industry, 293 hours; school hygiene, 140; epidemiology, 300; community hygiene, 283; and biostatistics. The students in the therapeutic course get a total of 162 hours of general hygiene. Sometime during this period they take a 2-month externship.

During the sixth year, the students in the so-called therapeutic faculty have what amounts to a rotating internship in surgery, medicine, and obstetrics and gynecology, while those in the sanitary hygiene faculty get practical field work at epidemic field stations.

In response to a question as to whether the medical curriculum throughout the whole nation is uniform, it was pointed out that there are certain differences. Some of the faculty specialize in pediatrics, and, attached to some of the medical schools are physicians of oral surgery, or stomatology, presumably dentistry, and also of pharmacy.

Aspirants are taken on by the theoretical departments of the First Moscow Medical Institute after the sixth year. Clinical departments invite students to work for 2 additional years after their sixth year in order that they may become clinical specialists (ordinatori). These ordinatori can then take 3 more years as aspirants to become teachers.

The school year is 10 months, with a 2-month summer vacation. Finally, the dean pointed out that research work is done in all departments of the medical school or institute.

An inspection trip was made to a large museum with a unique collection of models representing a whole variety of dermatological lesions. Many of these gave an extraordinarily lifelike appearance, and were far better than the more familiar wax models which were popular a generation or more ago in some of the medical schools of the United States. In the dermatology department 112 beds were available for the demonstration of patients to the students.

In Dean Kovanov's own department, surgery, a number of experiments were demonstrated illustrating the transplantation of organs. Moving pictures were shown of a dog to which an extra head had been transplanted. The animal lived 7 to 9 days. The transplantation of an extra heart, giving the animal two hearts, was demonstrated. This animal had lived for many months and was still alive at the time of our visit. A good deal of discussion was spent on the delicate surgery necessary for the suture of small vessels and the demonstration of an instrument which achieves this purpose.

We were then taken, under the direction of Professor Yeliseyev, professor of embryology and histology, to his department, which was located in another building some blocks away. Professor Yeliseyev showed us his lecture halls, laboratories, and classrooms. In the lecture hall, we were asked to say a few words to the assembled students. One could not be help but be impressed by the youth of the students who were in their first and second years of medical school. They appeared to average not more than 17 years of age and were most enthusiastic.

Professor Yeliseyev demonstrated some of the work of his department, which consisted of removal (ablation) of the cerebral hemispheres of rats and the subsequent study of the effect of this procedure on the regeneration of tissues. One of the experiments consisted in removing a part of the liver of the decerebrated rat and watching the speed with which the liver regenerated.

In the department of embryology and histology, as in many other medical research departments in Russia, experiments also included studies on conditioned reflexes, which were concerned with rats, both with and without cerebral hemispheres.

In the anatomy department, there was a room for the "scientific society of students," the so-called "Circle." This amounts to a students' club, with membership available to the students who seem to be most proficient and who have shown particular interest in anatomy. About 1 out of 5 students is accepted for membership. These scientific clubs apparently are an important element in the life of the students and are found in several departments. In the clubroom, members are given a desk and a microscope and have more access to personal guidance than the ordinary student gets.

There are 700 students admitted to the First Moscow Medical Institute each year. They are selected by competitive examination and there are roughly 5 applicants for each 1 that is accepted. Once selected, most students complete their 6 years of training. However, on an average, about 40 of the 700 initially chosen drop out during the course of the first 2 years of study.

These failures are seldom the result of poor scholastic ability and usually result from inability of the student to do the things required during the first 2 years, or distaste for work in the dissection room. Students entering medical school range in age from 16 to 18 years. It was our understanding that medical students and university students in general are exempt from military duty.

The chair (or department) of microbiology was next demonstrated by Professor Lebedeva. This course occupies the fourth and fifth terms; 207 hours are assigned to it, of which 80 are lectures. The first half of the course (fourth term) is concerned with general microbiology, theories of immunity and infection; the second half (fifth term) is on special microbiology, with the study of infection and infectious agents. Here, as in the department of anatomy, there were classrooms with about 20 to 30 students in the room receiving practical demonstrations. Professor Lebedeva has written a textbook entitled "Practical Microbiology," which is now in a new edition. In this department, as in a good many others, there was at least one electron microscope.

There are also postgraduate students (candidates) working in the department of microbiology, all of whom prepare a thesis on their work.

In the laboratory, the undergraduate students inoculate culture media and animals. In their courses in virology, they work on influenza virus and are taught the techniques of the inoculation of the incubated egg. They make observations on the diagnosis of smallpox and rabies, and here again the students who show the most interest are admitted to the scientific circle, or students' club, of this department.

It is clear that with 700 students it is necessary to break the class up into small groups. The schedule for these groups was shown us. Obviously, a fairly good-sized faculty is required. This faculty numbered 1 professor, 2 docents, and 10 assistants.

The research work of this department included studies on antibiotics, with particular attention to the resistant forms. Acid-fast bacteria were included in this study; also studied was the role of nucleic acid in the biology of any resistant bacteria. This research work is apparently done by the postgraduate students (aspirants and candidates).

The impression that one gets from seeing this medical school, housed in old buildings and with enormous classes, is that of stepping back into the past. The medical school is separated from the university and is thus more like a trade school. It is clear that a great deal of the teaching is didactic, as it must be with such large classes and a repetitious system of administering instruction.

As Dean Kovanov stated, the country needs doctors. The medical schools must turn them out in large numbers, and the doctor who graduates from the First Moscow Medical Institute is not supposed to be a finished product but rather a practitioner, a so-called vrach. Some 3 years after finishing medical school, he can return for refresher courses and perhaps become a specialist or work into the scientific hierarchy at some later time. Practical working doctors in large numbers is the chief idea.

As has been stressed repeatedly, the number of women students is conspicuously high. About 75 percent of the student groups which we saw were women, and about 10 to 20 percent of the chairs are occupied by women.

Medical education and the organizational patterns of training ancillary personnel were topics somewhat outside our immediate assignment. We saw only two schools.

We left the First Moscow Medical Institute favorably impressed by the intellectual quality of the professors, by their scientific backgrounds, and by the very evident enthusiasm and eagerness of the students whom we had seen in their classes and in their laboratory periods.

The impression was that, although the classes were extremely large, the teaching staffs and the laboratory facilities, including anatomical dissection, were large enough to cope with the load, and it seems likely that the students are getting an amount and quality of instruction that probably compares favorably with our own.

The motivations for service and achievement in medicine are relatively as high and compelling in the Soviet Union as they are in the United States. There are approximately the same number of medical schools in the United States and the U.S.S.R. The difference is that there are stated to be many medical schools in the U.S.S.R. with more than a thousand students whereas the largest medical school in the United States probably has no more than 600 students.

March 9 (Friday)

Institute of Experimental Pathology and Therapy of Cancer. The Institute of Experimental Pathology and Therapy of Cancer, Academy of Medical Sciences, was established in 1952 and occupies a building in the old Ekaterinskaya Hospital area. Its director is Nikolai N. Blokhin, who represents the U.S.S.R. on the International Union Against Cancer. The institute has 380 workers, of whom 140 are of professional status. This new institute is divided into several departments and laboratories, as follows: department of etiology, department of experimental chemotherapy, chemical department, laboratory of pharmacology, laboratory of pathology, laboratory of biochemistry, and the clinic.

The department of etiology, the largest department, investigates the viral etiology of cancer. This department contains a laboratory for the tissue culture of tumor viruses and maintains a laboratory of tumor strains.

The department of experimental chemotherapy is subdivided into three laboratories: experimental chemotherapy, antibiotics and other natural substances, and experimental hormonal therapy.

The chemical department contains the laboratory for the synthesis of chemical substances, the laboratory for the study of the chemistry of natural substances, and the analytical chemistry laboratory.

The clinic is small, having only 60 beds. It is used for treatment of special types of patients that the institute wishes to study.

The Institute of Experimental Pathology and Therapy of Cancer was stated to cooperate closely with the Oncology Institute in Leningrad, but it also appears to have the primary assignment of the Academy of Medical Sciences U.S.S.R. in the field of chemotherapy of cancer. The chemotherapy work is headed by L. F. Larionov.

Considerable time was spent in presenting to us data on several chloroethylamine compounds. These included nitrogen mustards and their derivatives, Novoembikhin and Dopan. A report of these derivatives, including the chemical formulas, was published in the February 4, 1956 (p. 252) issue of the *British Medical Journal.* Dopan contains a pyrimidine nucleus and it seems to be useful in myeloblastic leukemia and Hodgkin's disease. It is given orally and has minimal side effects. Another related compound, called sarcolysine, also has been reported in *Lancet* for July 23, 1955 (p. 169). Sarcolysine has interest because of its clinical effect in seminoma of the testis. It appears to have some effect on primary tumors of the liver, but none on their metastases. The side effects of the drug on the bone marrow may be diminished by administering it intra-arterially. In experimental tumors, the close relationship of sarcolysine to HN2 is shown by the fact that resistance to sarcolysine produces resistance also to triethylene melamine (TEM) and HN2. Clinically, however, it was stated to be quite ineffective in Hodgkin's disease.

The chemotherapy department receives compounds for testing against various tumors. Each compound is first tested for toxicity and to determine its maximum therapeutic dose. The standardized product is then tested for activity against rat sarcoma 45, Ehrlich's sarcoma (ascites form), and a transmissible strain of mouse leukemia. If promising preliminary results are obtained, the testing is extended to rate sarcoma M–1. Judgment as to response is based on a comparison of the tumors in treated and untreated groups of animals. Ordinarily, treatment is begun when the tumors are 1 gram in size. At the end of the experiment they are weighed to determine the percentage of inhibition, and a record is made of the number that have completely regressed.

In initial trials, both Dopan and sarcolysine were found to be very active against rat sarcoma 45, the latter compound causing regression even when the tumor was quite large at the time treatment was initiated. Sarcolysin was also found to be effective against mouse sarcoma 298.

Study of the antimetabolites has revealed some that are slightly effective, but none that is as active as the various mustard derivatives. In using the mustard derivatives, it has seemed best to begin with a large dose and diminish the dose during the course of treatment.

The chief guiding principle in the program of the Institute of Experimental Pathology and Therapy of Cancer is to combine alkylating groups with amino acids and their analogues, in order that they might act as met abolic carriers to the tumor. Empirically, a wide variety of antibiotics, plant derivatives and chemicals are also tested. Professor Menshikov, a chemist, informed us that the recent newspaper account of a Caucasian flower that cured cancer referred to an old friend, *Colchicum autumnale,* which had been used as a paste for skin cancer with some effect. In the work with antibiotics, the chemotherapy department gets the crude culture fluids or the partially purified antibiotic from three different antibiotic institutes for trial.

Of 150 antibiotics which they have tried, workers at the institute have observed 5 or 6 that had some effect on experimental tumors. One, an actinomycin, was particularly interesting in the Ehrlich ascites tumor; the material was stated not to be related to actinomycin C. This effect is most pronounced during the second week of treatment. The antibiotic has now been partially purified and seems to be a great deal more active and more stable than were the initial culture fluids. The active principle of this antibiotic is soluble only in water and not in organic solvents. Therapy seems to be most effective when large doses at wide intervals are used, rather than when a low, continuous level is maintained.

Triethylene melamine has been worked with to some extent and in large doses seems to exert some therapeutic effect. However, of the tumors that have proved resistant to sarcolysin, all have also seemed to be resistant to TEM.

Antimetabolites are also tried; amino adapine and amino glutamine folic acid derivatives had some inhibiting properties against tumors.

A large department on etiology is headed by Professor Timofeyevsky, who also has a laboratory in Kiev. His approach is mostly in the direction of viral etiology and of carcinogenesis in tissue culture. Elena Pogosiantz appears to be the chief biologist and geneticist of the department. The etiology department has had considerable trouble with mouse infections, particularly ectromelia. *Lagurus lagurus,* a small gopher-like animal, is being extensively used as an experimental animal for tumor work. It appears to be very satisfactory in all except two respects; it bites, and it has no tail.

Tissue obtained at biopsy from human tumors goes immediately to the biochemistry laboratory, to the virus laboratory, and to the electron microscope department. The virus laboratory tries to grow it on egg membranes and attempts to see virus-like particles under the electron microscope. The most interesting findings have been with gastric polyps, and here it has been possible to find virus-like particles under the electron microscope up to the 60th serial egg passage. Certain other tumors contain virus-like particles which cannot be transmitted serially through the embryonating egg.

The experimental clinical wards in the cancer institute were pleasant, and the patients were obviously well cared for and satisfied. It is the policy of the institute not to discuss cancer with patients, and no special release forms or other arrangements are used for experimental approaches except the medical opinion that the patient would not be benefited by standard therapy. The surgical suite was good. There are no X-ray therapy facilities here; X-ray therapy is given as needed at the Oncology Institute imeni Gertzen, which we did not see.

Dr. Shimkin spoke to the staff in the auditorium of this institute, on "Some Aspects of Cancer Research in the United States." The speech was made in Russian, and it pleased the audience to hear that Novinsky is now on record in America as having transplanted tumors in 1876, or 12 years before Hanau.

It was on this day that the Ministry of Health held a large dinner for the mission. They had invited a number of the United States Embassy staff to be present also, and Heyward Isham, Second Secretary, attended the dinner. The hosts were the Deputy Minister of Health, Professor Zhdanov, and Professor Timakov, former director of the Gamaleya Institute.

March 10 (Saturday)

Central Institute for Qualification of Physicians. The Central Institute for Qualification of Physicians is located in central Moscow. Formerly a domicile for noble widows, it is now the headquarters of a system of postgraduate medical institutes which arranges courses for physicians. The director is Professor Vera P. Lebedeva.

Such institutions date back to czarist Russia; the Clinical Institute of Queen Helena Pavlova was founded in St. Petersburg in 1885. Soviet law permits doctors to come back for postgraduate education after 5 years in practice, according to Professor Lebedeva. The physician (vrach) is permitted to keep his salary and, in addition, while attending the postgraduate institute, he is given quarters and a stipend of 400 rubles per month.

Immediately following the revolution, four such institutes were founded. There are now about 11. The two largest are this one in Moscow and the original institute in Leningrad. There are 3 in the Ukraine, 2 in the Russian Republic, 1 in Byelorussia, 1 in Tashkent, and 1 in Baku. All told, these postgraduate institutes can accommodate between 15,000 and 16,000 vraches per annum.

In addition to these institutes for the improvement of physicians, there are other postgraduate facilities; for example, vraches may return to the medical schools (institutes) for ordinate training. About 2,500 each year receive this training. Professor Lebedeva also noted that 5 or 6 of the medical institutes have faculties for postgraduate studies separate from the ordinate training. These facilities can accommodate about 1,500 students per annum. All in all, therefore, including the institutes for the improvement of physicians, ordinate training, and the postgraduate faculties in the medical institutes, there are places for between 19,000 and 20,000 per year who wish to take postgraduate medical education. If the total number of qualified medical practitioners in the Soviet Union is between 250,000 and 300,000, as we were informed, it is apparent that not every physician can return for postgraduate education every 5 years as the law permits.

Professor Lebedeva pointed out that, in the first place, it is not necessary to admit all physicians for postgraduate education. For example, the teachers in hospitals do not wish or need to return, and physicians with families and established homes generally do not wish to come. She emphasized that well-trained physicians do not need to return, and in general those with weaker backgrounds constitute the main student group. Approximately 50 percent of the physicians that come to this institute have had up to 10 years of experience in practice; the remainder have had more than 10 years.

The method of admission is as follows:

The individual republics inform the Ministry of Health that they are short of certain specialists and that they would like to send a certain number of doctors for training. Some of these go to the Central Institute and some to the institutes of the various republics. At the Moscow institute, which was organized in 1930, 4,500 vraches are admitted each year and they must have had 5 years in practice to qualify. A quota is set for each republic. The names of the vraches are obtained from the republic and the Central Institute sends them an invitation. Apparently, there is no difficulty in filling classes since doctors prefer to come to Moscow.

The institute has 54 chairs covering all branches of medical science. This is true also for the Leningrad Institute. The clinical chairs are at large hospitals or in research institutes in Moscow, with the preclinical chairs in the central buildings of the institute. Fifteen of the clinical chairs are located at the Botkin Hospital, and professors carrying on double duties, that is, at the Botkin Hospital and at the Central Institute, are paid extra for this extra work.

For example, we learned that Professor Graschenkov was the institute's professor of neuropathology at the Botkin Hospital, and recently Professor V. V. Parin was appointed to the chair of clinical physiology. Professor Lebedeva said that the Central Institute, however, wishes to have its own clinics in all branches under its own supervision, and they believe that this may be accomplished under the present 5-year plan. She described the following programs of instruction:

1. Group studies. A 4- to 5-month course for those wishing to specialize. Three lectures are given on selected clinical topics each week, and students go to the laboratories to learn methods. At the same time, they are assigned 2 or 3 patients whom they follow under supervision.

2. Group studies. Short refresher courses of 10 days to 1 month. Examples of this are contributions of Pavlovian physiology to clinical medicine given for physiology teachers; a 1-month course in anesthesia and analgesia (this is much in demand); and 10-day courses in diseases of the prostate and on radioactive isotopes.

3. Individual doctors who wish to work at a particular institute or clinic. For example, a surgeon who may wish to learn cardiac or pulmonary surgery is assigned to a

particular chair for whatever period is required.

4. Ordinate and aspirant training. The ordinate course occupies 2 years and is concerned with clinical medicine. A certain proportion of ordinates go on to become aspirants. The aspirant course takes 3 years In contrast to ordinate training, the aspirant must do original work and must write a thesis. At the Central Institute there are roughly 60 aspirants, and it was interesting to note that scientific programs are arranged specifically for them twice a year. In these programs original work carried on by the aspirants is presented. The aspirant papers are collected and published in a book. We were also shown a doctoral thesis, "Microflora of the air in Moscow," by Dr. Galekeyev. This is an extensive dissertation copiously illustrated with photographs of various air sampling devices and containing an extensive bibliography of both Russian and foreign papers.

5. General lectures for physicians in Moscow.

6. Correspondence courses. These courses are sent out to physicians, although the composition of the clientele was not clarified. About 400 to 500 physicians per year are on the correspondence school list. The course lasts for a year. In June of each year, correspondence course students come to the institute and make reports of their work. There are no examinations, but if the work has been satisfactory, a diploma is given. Professor Lebedeva stated that one of the drawbacks of the correspondence course is that many physicians drop out.

7. Public health organization. This course is carried out in collaboration with the Moscow Health Department. For those who are already in the field of public health, the course takes 5 months; for those coming newly into the field, a year.

The following administrative matters are of interest. At the Central Institute, in addition to the director, there are two vice directors, one for scientific affairs, the other for education. At all postgraduate institutes in the Soviet Union, there are four faculties: surgery; therapy (general medicine); sanitation; and medical radiology, which is being liquidated. In addition, there is a military faculty for doctors in the military reserve.

The 1956 budget of the Central Institute is 24,000,000 rubles. The physical facilities that we saw were old; the administrative building was constructed in 1812. However, it was maintained in good repair and, as Professor Lebedeva said, "it is a pleasant old place."

With the present shortage of housing, the postgraduate institutes have to maintain hostels and restaurants in Moscow for physicians taking courses here. There are 2 large hostels, 1 for 400 people and 1 for 600. However, these are inadequate; as many as 5 or 6 physicians live in one room. Professor Lebedeva stated that a new animal house and a hostel will be constructed in 1956 and a new building for the theoretical chairs is scheduled for 1957.

Professor Ermolieva, who in 1944 was director of the institute in which the Soviets were producing penicillin, was present at this conference, but we did not have the time to visit her department of microbiology.

In the evening we attended a tea given by an association known as "VOKS," whose purpose is to try to establish contacts with people outside the Soviet Union in various cultural and technical fields.

Professor Sarkisov, the head of the medical section, welcomed us. Guests included Ashurkov, Vershilova, and Negovsky, who is interested in problems of resuscitation.

At the meeting a call was made for suggestions as to how there could best be an exchange of information between the United States and Soviet Russia in the medical field.

March 12 (Monday)

Leningrad Sanitary-Hygiene Medical Institute. The Leningrad Sanitary-Hygiene Medical Institute was stated to be the only medical school in the Soviet Union limited to the sanitary-hygiene course. It is located at least 20 kilometers outside Leningrad in a large "compound." The 30 or 40 buildings which make up the institute were all built in the early 1900's as memorials to and in the architectural style of the time of Peter the Great.

The institute also has clinical facilities at the City Hospital of Leningrad.

The director, or dean, of the institute is Dmitri A. Zhdanov, an anatomist-histologist who was dean of the Tomsk Medical Institute, and who some years ago won a Stalin prize of 200,000 rubles for his lymphatic injection preparations. He had just published a book on Leonardo de Vinci as anatomist and one on Soviet medical laboratory equipment. He later demonstrated some of his preparations to us and spoke of the fact that during the summer of 1955 he had attended the International Congress of Anatomy.

There are three medical teaching institutes in Leningrad. One is mainly devoted to treatment and general practice, one to pediatrics, and this one to sanitation and hygiene. For the first 3 years the curriculum is the same in the three schools. Specialization begins in the fourth year. Starting in that year, the curriculum stresses family and community hygiene, social hygiene, and the organization of public health services. Emphasis was placed upon the fact that practical education and field training is obtained in these fields through contact with the medical department's work in factories and in other areas. The amount of time spent in industrial hygiene amounts to 293 hours of instruction; in epidemiology, 315 hours; in community hygiene, 300 hours; and in sanitary bacteriology, 200 hours, accompanied by 50 hours of practical training.

In response to our queries about text books in epidemiology, two were mentioned. One was by Bashenin of Leningrad (Bashenin, V. A.: A course in special epidemiology. Medgiz, Leningrad, 1955). The other one, on general epidemiology, was by Gromaschevsky of Kiev. These texts contain little or no data dealing with disease prevalence in the U.S.S.R. after 1935.

The faculty of the Leningrad Sanitary-Hygiene Medical Institute consists of some 330 professors and teachers, who are assisted to some extent by 200 aspirants. About 400 physicians are on duty in the clinics; they also have some teaching responsibilities. The students number 3,000, of whom over half are women.

A certain amount of research is also carried out at this institute. In the department of microbiology, for instance, the students are engaged in studies in bacteriophage and methods of serologic diagnosis. In the epidemiological department, they are interested in work on hepatitis. In the laboratory for industrial hygiene, the students are carrying out studies on vibration and its importance to workers, and work is proceeding there in toxicology. In the department of school hygiene, they are working on air pollution and hygiene of the air. In the division of community hygiene, water sanitation is the problem. There is also a chair of general hygiene; its research was not described.

The department of epidemiology seemed to be particularly well equipped. This department was using radioactive tracers, phase contrast microscopes, and luminescent microscopy in its work.

In its work with air and water, the department makes extensive use of Millipore filters, and it provides practical demonstrations for the students.

Professor Bashenin, head of the department of epidemiology is primarily interested in hepatitis, especially as it concerns the existence of virus carriers. The faculty believed that, in about 10 percent of the patients hepatitis is prolonged, with residual manifestations. The department has had occasion to study the contacts of such chronic cases and apparently believed that such patients served as chronic carriers for some time. It had also been interested in detecting hepatitis cases which did not have jaundice.

A method of diagnosis for use in the laboratory had been recently discovered; it concerned the adsorption of hepatitis virus on bacteria. The bacterium used was a special nonpigmented strain of *Bacillus prodigiosus*. The bacterial cells were exposed to material such as blood or feces presumably containing the virus. This material was centrifuged down and then exposed to specific antiserums made from rabbits; if the virus was present, agglutination of the bacteria ensued. Professor Bashenin believed that the reaction was specific up to 90 percent; that is, in samples of blood taken early in the course of acute hepatitis, virus could be demonstrated in this fashion.

As for the manufacture of antiserums in this diagnostic test, the inoculum for immunizing rabbits is the blood of a case of hepatitis in its early stage. Obviously, this is a complex antigen, so complex as to render the procedure a doubtful one. The *B. prodigiosus* method was described by a physician in Odessa in a book which it is stated will be published soon.

The clinical hepatitis studies had been correlated with liver function tests on patients. The department of epidemiology did not have (as was emphasized in Dr. Shubladze's laboratory) a complement-fixing antigen which it could apply.

Professor Bashenin considered that hepatitis might be spread not only through intestinal discharges but also by droplet infections; in other words, by nasal spray. The evidence on which his opinion was based was the fact that review of the epidemiology of hepatitis in children's collective groups had shown that dysentery could be checked by improving the sanitary arrangements; but no decrease in hepatitis could be demonstrated, even though sanitary arrangements had been improved. In other words, the measures effective against dysentery were not effective against infectious hepatitis. The epidemiology department also believed that the high incidence of hepatitis among physicians, particularly stomatologists, was an indication that the disease had been contracted by contact with oral secretion.

Professor Bashenin believed that 5,000 to 6,000 cases of hepatitis a year occurred in Leningrad, most of them during November, December, and January. There was no evidence that the disease was waterborne.

Hepatitis seemed to be most prevalent in crowded places. Special efforts were made to control the carriers, notably, the so-called chronic cases. Although the duration of a carrier state was not established, it only occurred when the convalescent patient had a recurrence of hepatitis. However, heavy work could provoke a recurrence, which might come on at any time within 2 to 4 years following the acute stage of the disease.

Apparently the department was unfamiliar with the problem of the sterilization of blood products for serum hepatitis and had done no work on these products. Professor Bashenin said that cases of serum hepatitis had occurred in Leningrad after blood transfusions but that there is no problem now. Individual syringes are boiled for 20 to 30 minutes, and blood donors are screened.

The Leningrad Sanitary-Hygiene Medical Institute has a department of tuberculosis therapy and control, although tuberculosis was not a big problem. We were told that the use of BCG vaccine in children was in the hands of the clinicians. The antibiotics being used are biomycin, streptomycin, and para-aminosalicylic acid (PAS), and a preparation analogous to isoniazid.

Venereal disease incidence was said to be extremely low. Apparently there are not enough cases to show examples of syphilis to students today.

Professor Bashenin was unable to give us any incidence figures on streptococcal diseases, rheumatic fever, or acute nephritis. He stated that figures on the incidence of scarlet fever were handled in the same way as any incidence figures on streptococcal disease.

The incidence of diphtheria in Leningrad was 1.1 per 10,000, higher than in the United States. In France, the number of cases is 0.2 per 10,000 and the number is still lower in England. Distribution of diphtheria in the Soviet Union depends on local conditions. As for preventive measures, each child receives serial injections of an alum-precipitated toxoid: 2 in the first year, the first at the age of 3 months and the second 4 to 6 months later, as a booster; an injection at 3 to 4 years of age; another at 7 to 8 years; and another at age 12.

The average poliomyelitis experience in Leningrad has been about 10 cases per month. In 1947 and 1955, epidemics occurred in August and September; 235 cases were reported in the 1955 epidemic. The age of the patients was from 1 to 6 years.

It was stated that infectious mononucleosis was not common in the Soviet Union. The disease appeared as individual cases, not in groups, and the age of the patients usually ranged from 20 to 30 years.

We spent some time in the department of microbiology, with Professor Fisher in charge. This department had numerous exhibits on diseases in wall cases. On one wall was a panel showing how some intestinal infections could be spread by airplane, artillery, or sabotage of wells.

A. A. Kedrov, professor of clinical medicine, showed us about the cardiorheumatology clinic, which houses 160 patients on its 5 floors. On the first floor were student laboratories, research laboratories, and X-ray equipment. The clinic was well equipped throughout and spotlessly clean. The patients were comfortable, clean, and well taken care of; the beds were of crude metal and very low. One hundred of the patients in this clinic were advanced rheumatocardiacs, most of whom were being prepared for cardiac surgery. We visited one room where 2 of the 8 patients had obviously severe mitral stenosis.

Professor Kedrov was interested to know what tests were used in the United States to assess activity of rheumatic fever. He was somewhat surprised to hear that the test for C-reactive protein were widely used as one method of evaluation and that antiserums are commercially available. Kedrov thought that Graschenkov's nasal tampon ionophoresis method for asthma was worth further trial.

The general impression of the Leningrad Sanitary-Hygiene Medical Institute was that, like many pre-World War II European hospitals, it looked old and out-of-date. No interns were in evidence, but there seemed to be an adequate supply of nurses.

March 13 (Tuesday)

Zoological Institute of the Academy of Sciences U.S.S.R. The Zoological Institute of the Academy of Sciences, a large museum on the Neva River, was the only Academy of Science institute that we visited. It is headed by Academician E. N. Pavlovsky and is referred to as Pavlovsky's Institute.

The museum was founded in 1831. Brandt was its first director. It has an outstanding collection of preserved zoological specimens, and it attracts 150,000 visitors a year.

We were welcomed here by Academician Pavlovsky, a world authority on zoology, ecology, and geography.

Academician Pavlovsky explained that the function of his institute was to send out expeditions each year all over the length and breadth of the Soviet Union to collect materials, to allow the participating scientists to have contact with nature, and particularly to study the way in which nature is related to the prevalence of diseases of animals and man. These expeditions include young scientists as well as more experienced ones, and the studies cover a large family of some 250,000 species. The work of the institute on the fauna of the U.S.S.R. is covered in 61 volumes. The first volume, "Blood-Sucking Insects," by Shtakelberg, was printed in 1927. In general, the institute prefers to study animals and insects of importance to agriculture and medicine, and this work provides a foundation for work in zoology, parasitology, and epidemiology.

Animals of importance to the country are studied first. This activity of the institute brings it into relationship with other scientific groups, especially the Ministry of Health. Workers at the institute have studied flies, gnats, mosquitoes, ticks, and other species systematically and have written reference books on all of these insects, as well as on the black flies, midges, and many others. Professor Pavlovsky believes that the study of insects forms the basis for the understanding of insect vectors of disease.

Professor Monchadsky is in charge of the parasitology work, and his department has published considerable work on various worm forms.

In addition to publishing accounts of native insects and worms, the institute publishes more inclusive reports of its various expeditions.

The Zoological Institute included a natural history museum. One of the gems of the collection was a large mammoth, dating from 10,000 to 30,000 years ago, which had been found frozen in Siberia, representing an almost complete specimen in a fine state of preservation.

A full collection of Pavlovsky's publications, accounts of expeditions, and handbooks on various insects, must be a rich mine of information on the Soviet Union. Pavlovsky was much interested in exchange of books, insect specimens, and other information. It would be useful to develop such an association, perhaps through one of our museums of natural history.

Discovery of the relationship of the animal kingdom to problems of ecology and epidemiology was obviously the aim of the director and of his institute.

We were impressed not only by the importance of the idea of an "ecological institute" but by its actual reality. To our knowledge, we do not have its counterpart in the United States. The integrating functions which such an institute can exert should be of great assistance to those concerned with epidemiological expeditions and with ecological and zoological exploration. The point of view is important, as well as the collection of new facts.

In the afternoon, we visited one of the shrines of Pavlov, the Institute of Experimental Medicine station at Koltushi, which was built for him in the latter part of his life and is now under the direction of Professor K. M. Bykov. This institute is located some 30 kilometers outside of Leningrad. It consists of 15 or more buildings situated on a hillside, and includes laboratories, animal houses, and homes for the workers, as well as Pavlov's house, surrounded by broad fields and scattered trees. The geographical area covered by the Pavlov Institute was stated to be some 1,400 hectares. Its staff numbered 150 individuals of professional rank and some 300 technical helpers. The institute is part of the Institute for Experimental Medicine at Leningrad but it seems to operate as a separate entity.

The Pavlov Institute is a blend of a research station, a museum, and a temple to Pavlov. Its theme is the development of the conditioned reflex mechanism.

We were told by Professor Bykov that the theme of conditioned reflexes was being investigated in many species of animals, including invertebrates. On the farm, some of the work was directed toward practical problems, such as trying to induce chickens to lay eggs at 12-hour intervals by varying the day-night relationships and establishing conditioned reflexes on that basis.

An aspirant demonstrated to us the establishment of conditioned reflexes in the rat and described experiments which so far have failed to demonstrate that conditioned reflexes are inherited. In another experiment, mice of strain C57 black, divided according to whether they responded slowly or rapidly to establishment of conditioned reflexes, were injected with carcinogens. At the Pavlov Institute, 31 percent of the "fast" mice developed tumors compared with 78 percent of the "slow" mice. Once they arose, however, tumors killed the "fast" mice in shorter periods of time than they killed the "slow" mice. A report of this work has been published (Bull. eksp. biol. med., U.S.S.R. 38: 9, 1954).

Other demonstrations and discussions were presented to us. These included studies going forward on conditioned reflexes, particularly those based on so-called external receptors vs. internal receptors, the former being represented by the eye and the ear and the latter, by bone marrow and lymphatic glands.

March 14 (Wednesday)

Institute of Experimental Medicine. The Institute of Experimental Medicine of the Academy of Medical Sciences U.S.S.R. in Leningrad is housed in several large gray buildings and is being expanded.

This institute is the old Imperial Institute of Experimental Medicine founded 65 years ago. Here Ivan Pavlov did most of his work. Apparently the famous Russian writer, Gorki, took great interest in the concept of medical science and in Pavlov as its exponent. It was somewhat at Gorki's initiation that the All-Union (originally Imperial) Institute of Experimental Medicine (VIEM) was organized. Metchnikoff and Pasteur took part in its organization. For a long time VIEM was one of the main research institutes in Russia. With the organization of the Academy of Medical Sciences, it became one of the institutes under academy jurisdiction. It is still large, with a personnel of over 500 divided among 11 departments whose heads include 7 members of the Academy of Medical Sciences. It has numbered among its staff some great scientists, notably Zabolotny, who worked on plague, Pavlov, and Nienski, the biochemist.

The institute originally had a large plague laboratory, but since plague is no longer important in Russia, this laboratory has been discontinued.

Immunology studies are divided between the virology and microbiology departments. There are no clinics attached to the institute.

We visited the virology department first and were shown around by Professor Drobichevskaya. She is primarily interested in influenza and the seasonal encephalitides. The institute is beginning work with poliomyelitis. The influenza work consists of investigations in the problems of transformation of type and the isolation of new strains. The institute has isolated a number of strains of type C virus.

The C type strains of influenza virus isolated from children during 1954 were difficult to adapt to eggs and were found to develop best when the eggs were held at lower than usual temperatures (32°–33°C.). The C strains isolated in Leningrad were similar serologically to Taylor's original strain. Drobichevskaya reported some work in which attempts have been made to alter the immune response to influenza by manipulation of the so-called higher nervous activity. This was done by developing conditioned reflexes, and in some experimental animals an increase in antibodies developed without a booster shot of vaccine. We are not sure that Drobichevsaya took this work very seriously.

Drobichevskaya has succeeded in conducting recombination experiments with A and A′ influenza strains, but not with A and B, or C strains. Her studies have shown that the antigenic properties of strains of a virus can be changed on passage through immune mice. She could also effect this change passively by growing the virus in the presence of immune serum in eggs. She used PR8 and WS and other A type strains, and the final strain achieved approached the A′ type. The serologic changes induced appear to be stable. Dobrichevskaya has made no effort to transform the swine type virus, and it may be that this should be done in order to see in which direction it goes.

The virology department has done considerable work on seasonal encephalitis and has recently recovered a new virus from a condition known as two-wave encephalomyelitis. The carrier of this virus is a tick, but the virus can also be transmitted through the medium of goat's milk. In its biological properties, this virus is very much like that of Russian spring-summer encephalitis and louping ill. Professor Drobichevskaya told us that the Omsk fever virus was similar to this new virus but was not transmitted in milk. The Omsk fever virus is tick-transmitted but by a different tick than the two-wave encephalitis.

We next met with Dr. Morozinka, the first Russian investigator to isolate C-type influenza virus. She works mainly with children under 3 years of age, and in this age group influenza antiviral titers are very low. Using the complement fixation and neutralization tests, she found that during an outbreak of influenza, antibodies rise in this age group, and are considerably more type specific than antibodies in older individuals. She has been very much interested in learning whether influenza virus reservoirs or carriers exist and has made extensive studies of apparently normal children to determine whether or not virus may be present in some of them.

In September 1952, Morozinka isolated virus from two children in a collective where there was no illness. The specific neutralizing serum titers among the children in this collective was usually 0 up to 1½ years of age, and up to 1–20 in the older age groups. The two viruses isolated were both B types and the children from whom the viruses were isolated had 0 antibody titers. One of these children eventually became sick and, following infection, developed a detectable antibody titer. The other child at no time showed clinical illness but did eventually develop antibodies. An outbreak of B-type influenza occurred in this collective 28 days after the two carriers were detected. Later an epidemic of B-type influenza appeared in the adult population of the city. Virus from the carriers was isolated by inoculating their nasal washings into the amniotic sacs of embryonated eggs.

Professor Smorodintsev, the head of the virology department, has developed an anti-influenza virus horse serum which he uses to treat children. He administers this serum intranasally, usually three times per day for 3 days. Children treated in this way appear to be less ill than untreated ones, and most of the complications of influenza are avoided. The serum is prepared against types A, A′, and B influenza virus by injecting horses with these strains and harvesting the serum when the antiviral titer has reached a level of about 1,200.

The serum is purified by the "Diaferm 3" process and dried. The powdered serum is then mixed with a sulfa preparation, probably sulfanilamide, in roughly 5 parts of serum to 95 parts of sulfa before being put into containers to be dispensed. Apparently this preparation is fairly widely used and well thought of.

We visited the pathology department next, where most of the interest appears to be in atherosclerosis. In the absence of Professor N. N. Anitchkov, demonstrations were made by his assistant, Professor Voinozenedsky. We found that no permission is required to autopsy any person dying in Russia; all are subject to autopsy if the physician so desires, and the rate can approach 100 percent.

The work of the pathology department was concerned with the pathology of blood vessels, particularly as it relates to arteriosclerosis. Professor Anitchkov has studied this situation on a world-wide basis, collecting data from many sources and countries. He believes that coronary occlusion is not only connected with arteriosclerosis but with hypertension, the latter being regarded as a nervous disorder. This department also works on the pathology of vessels in infectious disease.

The department of infectious pathology studies mainly the pathology of neurological and respiratory infections and the diseases of childhood. This department also is conducting extensive work with experimental whooping cough infections in mice. Mice are infected intranasally with small doses of *Hemophilus pertussis* and come down with whooping cough after an incubation period of 2 to 7 days. The disease lasts a month or longer. The organism does not multiply in the bronchi but in the smaller air sacs, so that ciliary damage is not a prominent feature of this experimental infection.

As part of the visit to the Institute of Experimental Medicine, we were shown Pavlov's old laboratory and his chambers for observing animals, and also the Pavlov Museum, which is housed in a separate building. This was a rewarding experience. Here the story of Pavlov's life is told with pictures and diagrams: his boyhood and student days and his early work when he attended the Leningrad Military Medical Institute and worked on the faculty. Troops of school children are brought through this museum daily to learn about the great scientist and his work.

Oncological Institute of Leningrad. In the afternoon, we visited the Oncological Institute of Leningrad. Professor A. I. Serebrov, the director of this institute, had visited America in 1946. The scientific director of the institute is N. N. Petrov. The staff numbers 360, of whom 60 are scientists. Clinical facilities, consisting of 108 beds, are in hospitals elsewhere.

Professor Shabad, whose work is well known in the United States, is continuing work on environmental carcinogens. A recent study involved the isolation of large amounts of 3,4-benzpyrene from the air of Leningrad.

Shabad thinks that industrial atmospheric pollution is the chief factor in the increased lung cancer mortality in Leningrad and Moscow. Personally, he does not believe that smoking has much to do with lung cancer because he failed to produce tumors in mice painted with tobacco tars *(Voprosi Onkologii* 3: 96, 1955). He has been interested also in the systematic search for occult neoplasms and precancerous changes in presumably normal tissues. Shabad holds that the data support the view that cancer is a stepwise alteration and not one sudden change.

The Oncology Institute has also been studying the pathology of tumors of various organs to learn what the potentialities of cancer may be in different tissues of the body.

Shabad showed us their small museum, where exhibits included an induced sarcoma in a hedgehog and papilloma of the lip of a whale.

Professor Glazunov has been working with the rabbit papilloma virus. He found that the addition of the papilloma virus to a tissue culture of rabbit epithelium somewhat increases the rapidity of growth of the epithelium, but apparently very little, if any, multiplication of virus occurs. Glazunov next tried to grow the papilloma virus in tissue cultures of the intima of the aorta, the reticulum of the spleen, and smooth uterine muscle. He found that the addition of the papilloma virus to tissue cultures derived from these tissues markedly slowed down the growth of the cells. It was our understanding that he made his extract of papilloma with glycerine. These connective tissue cultures in the presence of the papilloma virus do not die, but can be maintained indefinitely.

In examining the cultures, Glazunov noted what appeared to be a disorganization of the lipoid metabolism of the cells in that there was considerable modification of the protein and lipoid relationships, and the Schiff reaction was altered. The protoplasm of the cells, especially of smooth muscle cells, appears to be markedly altered, and small vacuoles appear which show small inclusions like those seen in virus diseases. Tissue cultures contain papilloma virus, demonstrable by rabbit inoculation, in both the cellular and liquid phase of the culture, on the 1st, 4th, and 11th days of growth. Eleven-day cultures had had the fluid changed in them at 5 days and replaced with new nutrient fluid. The papillomas produced by the 11-day cultures had a shorter incubation period than those induced by the original material. Glazunov does not yet know whether the virus is just surviving or whether it actually multiplies in mesenchymal tissues. We were told that either spleen or aorta connective tissue cultures were satisfactory for demonstrating this apparent growth of the papilloma virus. Glazunov had not yet tried to transmit the virus in series in mesenchymal cell tissue culture, but he had some very good pictures of the cellular particles which he considers the virus causes in cells of the tissue culture.

Dr. Karastilova was investigating the immunological properties of azo dye-protein combinations. Such combinations retain specificity for the dye.

Dr. Krotkina, Petrov's co-worker, told us of the induction of tumors in monkeys with radium and methylcholanthrene, and of cancerlike lesions in the glandular portion of the stomachs of rats fed barley barbs. Reports of these investigations have been published, and Dr. Krotkina gave us reprints.

The Oncology Institute in Leningrad is not conducting work on chemotherapy. Professor Serebrov is a gynecologist and is interested in radiation therapy, but he did not describe his own work. He is the actual editor of the resumed *Voprosi Onkologii* (Problems of Oncology), an old journal whose publication has been interrupted several times; the present series is now in the second volume. English summaries are being reestablished in the *Voprosi Onkologii* this year. Arrangements were made to exchange *Voprosi Onkologii* for the *Journal of the National Cancer Institute.*

March 15 (Thursday)

We arrived in Kharkov and were met by a delegation which included the health officer of the city, T. H. Sevchenko; the director of the Institute of Vaccines and Sera, Dr. Cherkass; Professor Dirgatch, professor of microbiology, and others.

Kharkov, a city of about a million people, still shows many signs of a vast amount of destruction which resulted from the fighting in the city in World War II. A certain amount of rebuilding is in process.

March 16 (Friday)

Kharkov Institute of Vaccines and Sera (Metchnikov). After a brief visit to the University of Kharkov, which is being rebuilt, we reported to the Kharkov Institute of Vaccines and Sera imeni Metchnikov, which is under the direct control of the Ministry of Health U.S.S.R. The main building is a four-story structure with a large auditorium seating some 500 people.

The director, Dr. Cherkass, pointed out that this is one of the oldest of the institutes; it was founded in 1887, and it had recently numbered among its workers Professor Zhdanov, the Deputy Minister of Health, who had been our host in Moscow.

This institute produces more than 20 bacterial preparations for diagnostic, prophylactic, and treatment purposes. In addition to production facilities, it also has laboratories for research. Among the departments are:

Department of Microbiology, under Professor Dirgatch. This laboratory is engaged in a study of the mechanism of action of various antibiotics. Professor Dirgatch is the originator of a substance known as sanozine, a homologue derivative of pyocyanine. It is produced synthetically from pyocyanine by the substitution of an ethyl for a methyl group. It is less toxic than pyocyanine and has a broad antibacterial spectrum, with some activity against both gram positive and gram negative organisms, including *Brucella*, staphylococcus, streptococcus, and the organisms of cholera, pertussis, diphtheria, tuberculosis, and the dysentery and gas gangrene groups. Its usefulness, however, is mainly in reducing the needed doses of antibiotics which are more specific for such infections. Sanozine is effective by mouth, when applied locally, or when given intravenously.

Sanozine has been used in combination with streptomycin in tuberculous meningitis, with about 90 percent recoveries. It decreases the incidence of toxic manifestations of streptomycin by diminishing the necessary dose of that antibiotic. Sanozine appears to have no advantage over streptomycin in pulmonary tuberculosis, it has almost no side effects and does not depress vitamin levels in man as does streptomycin.

Department of Children's Diseases. This department studies prophylaxis and treatment methods against whooping cough. Various strains of pertussis have been studied and some have been found to produce an endotoxin as well as an exotoxin. Such strains have been used to prepare vaccines which are actually combinations of vaccine and toxoid. When used in animals and children, these combinations have caused a rise of antibodies similar to those following an actual attack of the disease. Horses immunized with the strains of pertussis used for vaccine production yield a serum that is both antibacterial and antitoxic in type. This serum is used therapeutically in children and supposedly diminishes the severity of the disease.

In addition to specific serum for the treatment of whooping cough, a combination of antibiotics is also used; ordinarily, this is a mixture of syntomycin (like chloramphenicol) and sanozine. The antibiotics are given twice a day for 5 days.

In producing pertussis vaccine, the organisms producing the exotoxin are usually grown for 5 to 7 days in a medium containing fresh blood, whereas, to produce corpuscular vaccine, the organism is grown on charcoal agar.

Department of Wound Infections. This laboratory is charged with the development of methods for producing high-titer toxins from *Clostridium perfringens* and *Clostridium oedematiens*. It now produces *C. perfringens* toxins of 600 MLD per cubic centimeter and *C. oedematiens* toxin up to 20,000 MLD per cubic centimeter.

Virology Department. Candidate of Medical Sciences Levy is head of the virology department, which studies the etiology and epidemiology of lymphocytic choriomeningitis and the role played by rodents in this disease. The department is also preparing specific complement-fixing antigens. Another condition studied by Levy has been rickettsialpox.

Both rickettsialpox and choriomeningitis rarely occur in Russia; Levy and his staff could remember perhaps five patients during the past 3 years. Reservoirs of lymphocytic choriomeningitis were found in several species of field mice (*Microtus silvaticus* and *Microtus flavicordis*), which can carry the virus for their whole lifetime and spread it in their excreta. Rats as well as mice form the reservoir of rickettsialpox, which is transmitted to man by a mite (*Allodermanyssus sanguineus*).

The virology department has also been interested in influenza and has carried out fairly extensive tests on live influenza vaccine and on Smorodintsev's prophylactic serum.

Levy has also conducted studies on the multiple sclerosis virus and vaccine, and the data he presented roughly corresponded with that which Schubladze had given us earlier. His data for the skin test and for the efficacy of the vaccine were identical with those of Shubladze.

Dr. Levy reported that, in patients with multiple sclerosis who responded to treatment with the Shubladze vaccine, antibody levels rose. In patients who did not respond to treatment there is ordinarily no rise in antibody titer as the result of administration of vaccine. Levy gave us a treatment schedule for use of the multiple sclerosis vaccine which roughly amounted to administration of increasing doses of vaccine intramuscularly or subcutaneously for a period of time. The vaccine is 15 percent infected mouse brain inactivated with formaldehyde.

Ordinarily there are a few allergic reactions following the administration of the Shubladze vaccine, but there are only slight systemic reactions in about one-half of the cases. Levy indicated that the virus is serologically related both to rabies and fox encephalitis viruses. This relationship is quantitative; for instance, an immune serum that will neutralize the virus of acute encephalomyelitis at a dilution of 1:10,000 is active against rabies virus or fox encephalitis virus at a dilution of ±1:100. We were told that the vaccine was being sent to many foreign countries after export clearance with the proper authorities in Moscow. We did not hear of the safety tests employed to ascertain that the vaccine did not contain live virus.

The health officer of Kharkov, Dr. Sevchenko, accompanied us during our visits to the Kharkov Institute of Vaccines and Sera imeni Metchinkov on March 16 and the Kharkov Zootechnical Institute on March 17. From him we learned that the Ministry of Health of the Ukraine is headed by a Dr. Bratus, with headquarters at Kiev. In Kharkov, as in other areas, the regional health department has three main sections: therapy, which includes hospitals, and clinics; maternal and child health; and public health sanitation.

The regional health department has hospitals and treatment clinics, with teaching beds for the medical institutes. It evolves its methods of procedure in close cooperation with the local research institutes. The department operates under a scientific medical council comprised of about 25 members. The chairman of this council is the chief of the health department.

Sanitary inspections are carried out in schools, factories, and so forth.

Each regional health department has its own laboratory facilities. The city health laboratories are, of course, the largest; the district laboratories are smaller.

Dr. Sevchenko was vague about the incidence of disease in the Kharkov area and about its population. However, he indicated that there were about a million people in the Kharkov area; this seems to be a standard figure given for the larger towns. He said that there were about 22,000 registered cases of tuberculosis and about 100 to 150 cases of diphtheria per year, with 1 or 2 deaths. He told us that there are about 30 to 50 deaths from rheumatic fever annually; that there are about 1,500 new cases of rheumatic fever per year; and that they know of 15,000 cases of rheumatic carditis in Kharkov.

Sevchenko stated that in Kharkov their preventive program consists of physical examinations in the schools, general hygienic measures, and special attention to weak and poorly nourished children, whom he believes to be more susceptible to rheumatic fever. He apparently was unaware of the relationship of antecedent streptococcal disease to rheumatic fever, and it was apparent that no steps are taken to prevent recurrence by chemotherapy. He was much interested in a description of penicillin prophylaxis of rheumatic fever.

No information was available on hepatitis in Kharkov except that there were "dozens of cases in the city." Serum hepatitis had been noted some years ago. The use of gamma globulin has eliminated a certain percentage of cases of hepatitis.

It was stated that the incidence of poliomyelitis is very low in Kharkov. The health department during the past year has become interested in this disease. Apparently there have been only 10 or 20 cases, all of the patients below the age of 10.

We were unable to learn about sandfly (pappataci) fever. Apparently it was not regarded as a disease of importance, although a live vaccine had been prepared and was being used. The mission did secure a copy of the paper-bound booklet by Academician Pavlovsky entitled "Pappataci Fever and its Carrier," Medgiz, Leningrad, 1947.

March 17 (Saturday)

Kharkov Zootechnical Institute. The Kharkov Zootechnical Institute at Lozovenki, is a technical school under the Ministry of Higher Education of Ukraine, founded in 1921, and located on a large experimental farm of 3,000 acres. Its function is to educate and train students of animal husbandry to increase and improve food production. Upon graduation the students go to collective farms to superintend the technical aspects of animal husbandry on these farms. The course of study is 4 years and 7 months, and the educational plan is divided into three parts: general education, physics and chemistry; general biology; and special zootechnical disciplines.

The students come to the institute after 10 years of schooling, and entrance is by competitive examination. Both girls and boys have rooms in large dormitories at the institute, and all students receive a State stipend. The purpose of training these students is to help increase the food production of the country.

One hundred and fifty new students are accepted every year, and a total of about 800 are in residence at all times. Fifty percent of these are women. A correspondence course is also given, and correspondence students are in residence at the institute for 1½ months out of each year. The course is completed in 6 years. Correspondence course graduates also take positions on collective farms or in farm machine factories.

The departments of the institute, all of which do a certain amount of research, are biology, nutrition, zoology, breeding, large animals, small animals (sheep and swine), microbiology and basic veterinary science, agriculture and agronomy, horse breeding, dairy industry, and economy and organization of agriculture. During conversations with the faculty, we obtained the following information.

The important swine diseases in Russia are erysipelas and influenza; there is little, if any, hog cholera. The important diseases of cattle are brucellosis, foot-and-mouth disease, anthrax, tuberculosis, piroplasmosis, and anaplasmosis. It was said that Russia has no rinderpest and very little mastitis. The important poultry diseases are salmonellosis, pullorum disease, fowl plague occasionally, leukemia, and fowl cholera. No Newcastle disease was reported. The important diseases of horses, of which Russia has 16 million head, are strangles, some *Salmonella* abortion, a little dourine, and some swamp fever. It was stated that there is no glanders in Russia, no virus abortion, and no equine encephalitis. Salmonellosis appears to be the only serious disease of ducks.

The director of the institute, M. I. Kniga, introduced us to his department heads.

Professor Gorb, the professor of nutrition, described studies on milk production in goats, using isotopic tracers. Antibiotics are employed in the feed of chickens and pigs, but only at early ages. The institute does not use stilbestrol or other hormones as meat tenderizers.

Artificial insemination was described by Professor Adrievich as having started in the Soviet Union. It is used widely for sheep, cattle, and horses. The diluent is egg yolk, and fructose is used as a stabilizer for rapid freezing. This maintains sperm for approximately one month.

We were shown the cow barns and the milk products department, which the director heads. All milk handled and sold through regular channels is pasteurized (at 67°C, for one-half hour by vat method), as required by law. About 15 million tons of milk and 500,000 tons of butter are produced per year. However, much additional milk, from individually owned cows and sold through individual arrangements, is not pasteurized, and no effective system of control apparently exists.

March 18 (Sunday)

We arrived in Kiev after a 2–hour flight and were met by 6 scientists, including the directors of the 3 institutes we were scheduled to see.

March 19 (Monday)

Ukraine Institute of Epidemiology and Microbiology. The Ukraine Institute of Epidemiology and Microbiology at Kiev was founded in 1896 with the main purpose of producing antirabies vaccine and antidiphtheria serum. It was modeled after the Pasteur Institute. It is similar in its organization and purpose to the Institute of Epidemiology and Microbiology in Moscow. Its director is S. N. Terekhov; its scientific director is Lev Gromashevsky, one of the top epidemiologists of the U.S.S.R. Infections now dealt with at this institute are mainly dysentery and diarrheas, diphtheria, scarlatina, typhoid, influenza, epidemic hepatitis, malaria, helminthiasis, tularemia, brucellosis, and recently poliomyelitis.

Professor Gromashevsky gave a rather favorable account of the occurrence of disease in the Soviet Union, substantiating the expressed view that infectious diseases were under control. Acute hepatitis was recognized as a problem; serum hepatitis is officially not separated from other forms, although Gromashevsky himself recognized it. He thought there were about 100 cases in Kiev last year. Malaria is rarely seen. Even with the Crimea now part of the Ukraine, the institute saw only 14 cases of local origin last year; the others were imported from southern republics. The last cholera was seen in 1925.

Relapsing fever occurs occasionally, and there are small numbers of cases of leptospirosis (8 to 10 cases per year in Kiev). Water fever, on the other hand, is fairly common in rural areas, especially during the harvest season, and is caused by *Leptospira grippotyphosa*. During the harvest season there are as many as 200 cases.

There is some brucellosis, almost always milkborne.

Professor Gromashevsky said that although helminthiasis was prevalent, enterobiasis is extremely rare. We were told that the scarlatina seen at present in Kiev is a very mild form and that there have been 2,000 cases without a fatality. Professor Gromashevsky said that he does not work with rheumatic fever and has no information as to its etiology. He stated that he knows of three cases of acute nephritis in Kiev (population approximately 1 million) during the past 2 years. Of the types of group A streptococci that occur in disease, types 29 and 4 have been observed in Kiev.

We visited Professor Timofeyevsky's department of oncology and talked to his assistant, Professor Teresa Gragerova. Timofeyevsky and Gragerova are investigating viruses in cancer essentially by two approaches: One is to attempt to pass serially viruslike particles in embryonated eggs. Electron microscope studies indicated such particles in 2 cases of human breast cancer out of 20 or so attempts. The viruslike bodies could be maintained only through a few passages.

The second approach was to produce neoplastic changes in tissue culture. It was stated that such in vitro transformation could be achieved with fibroblasts exposed to Rous sarcoma, and also with mouse fibroblasts exposed to the milk factor plus methylcholanthrene. Tissue culture equipment that we saw here and in Moscow was rather primitive and seemingly limited to fairly short-term flask cultures. We saw no roller-tube or large-scale operations.

The institute had 2 electron microscopes, 1 old RCA model and 1 more recent Soviet model, both in operation. Its other equipment was satisfactory and adequate for the work.

Professor Dechenko showed us analyses of fecal samples for various pathogens; the collections were done by Zieman's tube method. Dechenko's laboratory seemed to be a rather routine diagnostic laboratory.

In the not too distant past, dysentery was widespread and had a high incidence in

Russia. At that time studies showed that the ratio of dysentery to diarrhea was about 1:10. The ratio now is about 1:1, due to some improvement in the sanitation and to considerable improvement in bacteriological diagnosis. The numbers of dysentery cases have now diminished. Shiga dysentery is completely gone, only Flexner and Sonne have been recognized during the past 10 years.

The dysentery rate in the Ukraine at present is 8 to 9 per 10,000 per year. This rate has declined 10 to 15 times within the past 10 years.

The institute has done extensive work in attempted immunization against dysentery and has reached the conclusion that immunity to the disease is slow to develop, weak, and not very lasting. The immunity from recovered cases is apparently an infection immunity. There is relatively little typhoid fever in the Ukraine, less than 1 in 10,000 of population per year.

Institute of Infectious Diseases. In the afternoon, we visited the Institute of Infectious Diseases of the Academy of Medical Sciences U.S.S.R., which is located in one of the buildings of the historic Lavra (Cave Monastery). The institute was established in 1949, to work on dysentery, scarlet fever, and influenza in an organization of intimate association between laboratories and clinical facilities. We were told by Professor I. L. Bogdanov, the English-speaking director, that in 1957 poliomyelitis is being substituted for dysentery as one of its chief problems. The institute staff consists of 200, of whom 50 are scientists, and includes 135 beds in 3 hospital wards, outpatient clinics, and diagnostic laboratories.

This institute has eight departments: epidemiology; virology; bacteriology; experimental physiology; pathology; clinical diagnostic laboratory; polyclinic, with an outpatient dispensary for the followup of patients after discharge; and a radiological laboratory.

One of the responsibilities of the institute is writing all instructions on various diseases for the use of physicians in the Ukraine. It also conducts various symposiums on the infectious diseases in its field for physicians in the Ukraine.

Dr. Kornushenko, the epidemiologist at this institute, has made extensive studies of the onset of influenza outbreaks in Kiev and has graphs to demonstrate a marked correlation between changes in the weather and the onset of influenza. She has at no time been able to demonstrate healthy carriers of the virus but, once an epidemic gets under way, she has succeeded in demonstrating virus in the upper respiratory tracts of a few apparently healthy individuals. In studies relating to the period of infection, she has found that virus disappears from the upper respiratory tract of infected individuals on the fourth or fifth day after the onset of illness. This is roughly at the point where serum antibody begins to rise. According to Kornushenko, influenza epidemics in Kiev ordinarily begin in October and are always related to a sudden change in weather (temperature and precipitation).

Dr. Nina Maximovich told us of 8 fatal cases of influenza in children that have come to autopsy; in 5 of these influenza virus only could be isolated from the pneumonic lung, while in the remaining 3, the virus was accompanied by a staphylococcus. From none of the children could the Pfeiffer bacillus be isolated. All cases were very acute, with death taking place during the first 24–48 hours of illness.

Professor N. N. Serotinin is the experimental pathophysiologist whose work included demonstration with electroencephalographs that the alpha rhythm may disappear with severe influenza. Dr. Richenko in this department studied *Candida* mycoses overgrowth following antibiotic therapy, and found that this growth did not occur when antibiotics were used cyclically.

Through the use of labeled amino acids, the biochemistry department has been attempting to study the mechanism of action of different drugs to determine their side effects and has found that both sulfa drugs and antibiotics in therapeutic doses inhibit protein synthesis. Biomycin acts on enzymes with a sulfydryl group, but other antibiotics appear not to act on these enzymes.

At the Kiev Infectious Diseases Institute, Docent Pervachenko stated that she believed in the streptococcal causation of scarlet fever and that during the past 4 years the dominant streptococcal types have been 1, 2, and 4. In 1955, type 8 was also isolated. Type 12 causes some disease, but the institute has seen no acute nephritis during the past 4 years. A chart of frequency of streptococcal types during this time showed 104 cases of type 12 infection. Pervachenko stated that the development of resistance of streptococci to penicillin occurs frequently (almost 50 percent of cases) during therapy. As examples of this, she said that it was not uncommon before treatment to have susceptibility to penicillin of about 0.04 to 0.08 units, whereas frequently after therapy the inhibitory level required was 0.125 to 0.5 units. This institution recommended biomycin or penicillin for the treatment of scarlet fever. Pervachenko stated that biomycin sterilizes the throat of streptococci better than penicillin. Rheumatic fever is seen rarely in the institute hospital after scarlet fever.

Scarlet fever patients are ordinarily released from the hospital after 14 days. The diagnosis is based on the presence of fever, sore throat, and rash, and the isolation of hemolytic streptococci in about 90 percent of the cases. Treatment consists of penicillin or biomycin, and Professor Bogdanov stated that complications following either therapy were reduced 2½ to 3 times. There was no difference between the two antibiotics in reduction of complications.

If penicillin is used in the treatment of scarlet fever, 10,000 units per kilo are given three times a day by mouth, and the treatment is continued for 6 days. If biomycin is used, it is administered by mouth, 20,000 units per kilo, 3 or 4 times per day, and the treatment is continued for 6 days. After an interval of 5 days, the same course of treatment is repeated for a further 4-day period. Professor Bogdanov believes that most antibiotics are more effective when given cyclically like this than when continued over a long period of time.

In general, a wide variety of antibiotics are known and available in the Soviet Union. Among the antibiotics and their Soviet names were Levomycin and Syntomycin, which were described as similar to chloramphenicol, and biomycin, a tetracycline similar to aureomycin.

Infectious disease wards of the hospital are of two types. In one type, individual glassed-in cubicles are used for each patient. The other type is an open ward of about 30 beds. The air in these wards is circulated by fan through an ultraviolet lamp machine set in the middle of the floor. In a short interval of time, this machine completely recirculates the air past the ultraviolet lamps. This method of air sterilization has cut cross infections within the wards to practically nothing.

In the influenza ward, Dr. Hirsonskaya was studying the symptomatology and treatment of influenza. She was not convinced that any treatment had real effect except symptomatic relief. An interesting sign was described and attributed to Morozhkin: the appearance of small vacuolated papules on the soft palate during the first few days of influenza.

In the scarlet fever ward we saw many of the 30 little patients who were hospitalized there. Because of the current mildness of scarlet fever, it is believed that compulsory hospitalization will soon be abandoned. Scarlet fever stopped being a serious disease in the Ukraine about 1940.

Another investigator at the Infectious Diseases Institute has made extensive attempts to produce experimental dysentery in various animals and has found the following animals to be susceptible to dysentery by feeding: Chinese monkeys, bears, cats, dogs, and rodents, in roughly that order of susceptibility. He has found swine and goats to be insusceptible and has failed to establish any phenomena of infection in cold-blooded animals or in invertebrates.

This investigator studied the phenomena of infection by using radioactive phosphorus to label his dysentery bacilli, and, using dogs with various surgically produced fistulas, he studied the distribution of the organism following infection. He found that in the duodenum and small intestine, the dysentery bacilli not only survived but multiplied. Radioactive phosphorus from the bacteria got into the blood stream from the intestinal loops, but he failed to find bacteria themselves in either the blood or liver. He also found that dysentery bacilli multiplied in the large intestine and that their dissociation products (radioactive phosphorus) were found in the liver, but no bacteria were found there.

Another investigator at the institute has been interested in the common cold and has attempted to induce this condition in various ways. He has had patients put their feet in cold water and then has studied the blood vessels in their noses. He has found that first the blood vessels in the nose contract, and that later there is marked dilation. Accompanying dilation of the blood vessels, an inflammatory phenomenon occurs in the nose, but the nasal bacterial flora does not begin to increase for more than 2 hours after this. The subsequent clinical course differs with various individuals; some have only higher nervous activity, others get a coryza.

March 20 (Tuesday)

Institute of Microbiology of Ukraine. The Institute of Microbiology at Kiev is under the Academy of Science of the Ukraine S.S.R. The director of the institute is Victor Drobatchko. The institute's aims are agricultural rather than medical and include search for antibiotic substances from higher plants for control of plant diseases and viruses.

The viruses used as tests in the search for antibiotics included influenza, polyhedral disease of the silkworm, and tobacco mosaic. The program is being expanded next year to try the effect of the materials against some experimental tumors, including Rous sarcoma and a mouse tumor containing the milk factor. The institute is initiating this program because it feels very strongly that an antiviral substance will eventually prove to be effective against tumors.

This institute attempts to get its antibiotic substances from higher plants, such as trees, grass, vegetables, and so forth. A substance known as arinarin, which comes from tomatoes, is one that is promising. Allicin from garlic and a derivative known as pseudoallicin are used to treat seeds before planting to prevent disease. This substance works for wheat, oats, and barley. Ordinarily, the institute, when developing an antibiotic, carries the material only through the laboratory stages and makes only enough for small-scale field trials.

Professor Rubencheck talked to us about bacterial fertilizers, especially nitrogen-fixing organisms that stimulate plant growth. Dr. Frenkel was in charge of bacterial fermentation laboratories, and had worked on botulism before the war. Dr. Rashba, a biochemist, described her work on bacterial transformation.

We left Kiev late because of inclement weather and arrived in Rostov at 11 o'clock in the evening. We were met by Professor A. K. Shiskin, director of the Anti-Plague Institute, eight senior members of his staff, and an interpreter. Since our plane for Sukhumi was scheduled to leave, we and our hosts remained at the airport and did not visit the Anti-Plague Institute as scheduled.

Professor Shishkin recounted that the institute had been established to combat plague and that, although they were still working with *Bacillus pestis*, plague was a problem of the past. The successful tularemia vaccine was discovered at this institute, and they were investigating brucellosis, insect transmission of disease, and ectoparasites.

The group claimed that they had completely eliminated plague by systematic poisoning of the burrowing rodent (suslik) of the Don basin, an area of over 15 million hectares.

March 21 (Wednesday)

Medical-Biological Station. At Sukhumi, we visited the Medical-Biological Station of the Academy of Medical Sciences U.S.S.R. and saw the famous monkey colony, which was founded some 30 years ago. The station occupies an area of 26 hectares in the subtropical foothills of the Caucasus Mountains overlooking the Black Sea.

Originally a branch of the Endocrinology Institute, the Sukhimi station later became a branch of the All-Union Institute of Experimental Medicine. In 1945, it became an independent station affiiliated to the Academy of Medical Sciences. It is scheduled to be elevated from a "station" to the rank of a full institute in the near future. According to the scientific director, Professor Boris A. Lapin, Maxim Gorki was instrumental in setting up this station. It will be recalled that Gorki suffered from advanced tuberculosis and was interested in medical research, for which he acted as a patron in his close friendship with Lenin.

After Professor Lapin had given us a general description of the work of the station, we visited the monkey farm and some of the laboratories.

The laboratory division includes the following laboratories: experimental oncology, infectious pathology, morphology, radiobilogy, biology, physiology and pathology of higher nervous activity, and a monkey clinic for the study and treatment of diseases. The second large division of the station is the farm for breeding monkeys, which has its own staff. The total personnel of the station is about 250 scientific workers and supporting personnel. At present, the monkey population is 600, although we were informed that it is being increased to 1,500. Sixty percent of the monkeys were born at the colony.

The station has specialized in the rearing and study of mandrills and *Macacus rhesus*. These constitute 90 percent of the monkey population. Five to six generations of monkeys have been reared at the station. The increase in the colony by natural reproduction is on the order of 100 to 120 per year. The mortality from all causes is about 15 per year. New monkeys are being added, 50 rhesus monkeys having recently come from China, which was stated to be a better source than India at present.

The station has long been engaged in psychological and physiological studies. For many years, most of the problems dealt with were concerned with higher nervous activity.

However, since 1945, according to Professor Lapin, studies have been more in the medical field, including infectious diseases and experimental oncology. Professor N. N. Petrov is scientific director of the Oncology Institute at Leningrad, but he spends 1 to 2 months a year at Sukhumi. He has studied the production of bone cancer in monkeys, using methylcholanthrene and radium implantation. Malignant tumors with metastases have been produced. The minimum induction period for methylcholanthrene was 3 years. Among spontaneously occurring tumors in monkeys, the workers at the station have observed carcinoma of the kidney and breast and a granulosa cell tumor of the ovary, and one sarcoma. These, as well as severe uterine fibroids and intestinal polyps, were shown to us. The station has also been working rather extensively with the rabbit papilloma virus.

Among the infectious diseases that had been studied at Sukhumi at one time or another are tetanus, tuberculosis, cholera, whooping cough, measles, dysentery, and salmonella infections.

Spontaneous measles has not been observed in the monkeys kept under natural conditions but it has sometimes broken out in monkeys that have been kept confined. Two years ago the station had an epidemic of 30 cases of measles. To study this disease, they have been using the *Bacillus prodigiosus* agglutination technique of Sergiev for antibody determination (adsorbing the measles virus on *B. prodigiosus* and testing for its presence by agglutination with measles immune serum).

Tissue culture techniques have not been used at the station. Dr. Stasinovich, who talked to us about measles, said that the measles virus causes disease in all of the monkey species they have. Tuberculosis at one time was a serious menace, but the colony is now free from it. Control measures included isolation of incoming or infected monkeys, ophthalmic tests with tuberculin, and, more recently, therapy of infections with streptomycin, para-aminosalicylic acid, and a compound of unknown composition "Phthisavid." (This may be isonicotinic acid hydrazide). All employees are given a preemployment examination and regular examinations at 6-month intervals.

Of the spontaneous diseases, dysentery and salmonellosis (paratyphoid B) are now the most important. Spread, the station believes, is by contact. In the control of dysentery, examination is made for carrier states of shigellae and carriers are then treated with different combinations of antibiotics. In addition, the so-called Immunogen of Professor Troyetzky has been used, although one gathered the impression that at Sukhumi reliance is placed on chemotherapy. The dysentery strains have been Flexner and Sonne. Of interest were the observations on superinfection. If dysentery bacilli are carried, it is easy to produce the clinical disease by superinfection, the dose depending on size and weight of the experimental animal. Under these circumstances, 30 billion dysentery bacilli will produce clinical disease regularly, whereas in noncarriers 70 to 80 billion or more bacilli may be necessary to produce disease and the results may be irregular.

The incubation period of dysentery is 1 to 4 days. According to Dr. Dzhikidze, superinfection is a specific effect; that is, *Shigella sonnei* superinfects an *S. sonnei* carrier. A rapid rise in antibody occurs following superinfection. Similar observations have been made with paratyphoid B in that superinfection can be caused with doses of approximately 30 billion organisms. Following recovery from natural infection, a relative state of immunity occurs, which lasts from 3 to 4 months. Immunity is less good and is of shorter duration following immunization with formalin-killed bacteria.

In the Radiobiology Laboratory studies have been made of the pathogenesis of irradiation sickness in monkeys and the role of the central nervous system in this condition. The effects of irradiation on infection, including the production of disease by autogenous bacteria, also have been studied.

In the laboratory for the study of the pathology and physiology of higher nervous activity, investigations have been made of neuroses induced by giving mild electric shocks when the monkeys reach for their food or by sexual frustration. Sexual frustration is the more effective producer of severe neurosis.

One method used was to separate a male and a female monkey who had lived together for a long time and had become attached to one another and place the female in a nearby cage with a new male. The old male gets violently disturbed by what he sees in the other cage. Severe neuroses, which become permanent, may develop in 3 months, depending on the personal characteristics of the monkey. Workers at the station report the development of marked hypertensive changes in some of these monkeys. Two monkeys have died of myocardial infarction. However, spontaneous atherosclerosis also occurs in older monkeys. We were shown one pathology specimen with involvement of the aortic arch.

The monkey station is quite impressive, and we wished that the United States had a similar activity where these species could be observed and studied under seminatural conditions. The work of the station was recently summarized in a book entitled, "Theoretical and Practical Questions of Experimental Medicine and Biology in Monkeys" (Medgiz, Moscow, 1956), which we obtained in Moscow. This book has detailed articles on tumors and on hypertension in monkeys placed under stress conditions. The latter observations were limited to five monkeys, and we understand that several attempts to reproduce the results have not been successful.

On Thursday, March 22, we returned to Moscow.

March 23 (Friday)

All-Union Veterinary Institute. The All-Union Scientific Institute of Veterinary Ectoparasitology, Mycology, and Sanitation has seven laboratories: Laboratory of Prophylaxis and Therapy of Ectoparasitological Diseases of Animals, Laboratory of Entomology and Disinfection, Laboratory of Sanitation, Disinfection Laboratory, Antibiotics Laboratory, Mycology Laboratory, and Chemical Laboratory. Professor A. A. Pollikov is the director of the institute.

This institute has no department dealing with the infectious diseases of animals.

The Laboratory of Prophylaxis and Therapy of Ectoparasitological Diseases of Animals works along two lines. One part of the work is designed to increase the resistance of the skin to skin diseases; the other part is designed to increase and improve the yield of leather and of fur. Skin diseases are the more important problem. One skin disease is caused by infestation with botflies *(Hypoderm bovis)*, the larvae of which get under the skin of the animal and spoil the leather. Treatment of this condition consists of painting the skin with 4 percent DDT in oil. This is done during the winter, and the larvae die under the skin before they have emerged. Where this method of control has been applied on a large scale, the botfly has been almost eradicated.

The other problem concerns improving the character of the fur on fur-bearing animals, and it was our understanding that an approach to this consisted in the application of something known as napthalon oil. This substance apparently modifies the new fur and, in sheep, leads to larger yields of wool.

The Mycology Laboratory is interested in toxic molds and deals largely with alimentary toxicoses, especially those causing forage poisoning. The *Stachybotrys* fungus seems to be the main offender, producing leucopenia, anemia, and sometimes acute intoxication. These fungi thrive best in moist straw or hay. *Stachybotrys* toxin, which can be produced in large quantity by growth of the fungus in Czapek medium, produces severe symptoms of acute intoxication in swine, sheep, and even in cattle, in addition to horses. As small an amount as 200 gm. of well-infected hay is adequate to kill an animal. Ordinarily, the disease kills in from 2 to 3 weeks. The toxin is thermostabile and must be given by mouth. The optimum temperature for the development of the toxin is 24°–26°C.

The Antibiotics Laboratory works in two directions to develop antibiotics that are effective in treating disease and to develop antibiotics which are valuable from a nutrition standpoint. Antibiotics are used in Russian veterinary medicine in about the same manner as in the United States.

The Entomology Laboratory studies methods of controlling biting insects, such as tabanids, mosquitoes, and gnats, with the objective in mind of diminishing livestock losses caused by these blood-sucking insects. Control is either by spraying of individual animals, or by area spraying with atomizers.

Ticks are controlled by dipping in arsenates or chlortan. Thus far, the Russians have not developed an effective repellent.

Histoplasmosis, as well as aspergillosis of poultry, appears to be a problem in Russia. Ringworm of cattle is also serious.

To judge from the fact that there exists a separate laboratory for the purpose, pseudorabies in swine may be an important disease in young pigs in Russia. Russians seem to believe that pigs acquire pseudorabies from cattle, and it appears that many young swine die of the disease, although older animals do not. There is no evidence that cattle do not acquire the disease from pigs. The pseudorabies virus laboratory at the veterinary institute was engaged in studies of methods of disinfecting the pseudorabies virus on the hides and bristles of swine.

Institute for the Study of Poliomyelitis. The Institute for the Study of Poliomyelitis, whose director is Professor M. P. Chumakov, is in temporary quarters and will be there until its new building is completed. The institute is comprised of two laboratories, one for experimental work and the other for epidemiology. During the past 15 years, the personnel of this new institute have been chiefly engaged in a study of hemorrhagic fever and the Russian encephalitides.

Chumakov believes that there are three main etiological types of hemorrhagic fever: Crimean, Omsk, and Far Eastern. The hemorrhagic fevers have been studied extensively because they constitute an important health hazard in Russia.

The small amount of polioyelitis work that has been carried on by workers in this institute since 1945 has had to do largely with consideration of the etiology and laboratory diagnosis of the disease. Up until 1954 most of the work was with monkeys and cotton rats. Now the work is mainly with tissue culture, and most of the investigation has to do with the classification of strains. Of the strains occurring in Russia, 92 percent appear to be type I, 7 percent, type II. Some strains could not be classified. Recently the institute isolated three strains of a new type of poliomyelitis virus, which has been tentatively called type IV. This new virus produces paralysis and characteristic histopathology in monkeys; it is also pathogenic for only very young white mice. It is antigenically distinct from the other three types of poliomyelitis virus. The full extent of the prevalence of type IV poliomyelitis has not yet been studied.

Academy of Medical Sciences U.S.S.R. The Academy of Medical Sciences U.S.S.R. was holding the concluding sessions of its annual meeting, and Dr. Shimkin attended to represent the mission. He was received cordially and met Marie K. Kovrigina, Minister of Health, F. G. Krotov, and V. V. Parin. A copy of the 5-year plan for medical research, 1956–60, was presented to him.

The chief topic at the 1956 meeting of the academy was cancer, with particular interest in the virus aspects of the problem.

Professor Savitsky spoke on the epidemiology of cancer in the Soviet Union and emphasized that cancer of the lung in males was now in second or third place as a cause of death among males, whereas it was in 10th place in 1938. Stomach cancer still maintained first place among males.

March 24 (Saturday)

Members of the mission lectured at the Central Control Institute of Tarasevich. Dr. McLeod spoke on "Effect of Silicates on Gram Staining"; Dr. Shope, on "Virus Reservoirs"; and Dr. Meyer, on "Psittacosis and Ornithosis." Each presentation took 40 minutes; half of which were devoted to Mr. Mekhedov's carefully prepared translations. The meeting was conducted by the director of the institute, Professor Dedenko.

In the evening, the Academy of Medical Sciences U.S.S.R. held a formal reception for the mission, presided over by the president of the academy, A. N. Bakulev, and attended by the officers of the academy.

March 25 (Sunday)

Dr. MacLeod and Dr. Shope left for Helsinki Sunday morning.

March 26 (Monday)

Institute of Organization of Public Health and History of Medicine. The Institute of Organization of Public Health and History of Medicine is located in the First Medical Institute and is under the Ministry of Health and the Academy of Medical Sciences. E. D. Ashurkov is its director. There are 103 people on the staff.

The institute has four divisions: organization of public health, statistics, history of medicine, and history of Soviet public health. The philosophy here is that the organization and history of medicine are disciplines of science as much as are oncology or microbiology and need a similar approach for their best development.

The department of organization tries to formulate the most effective administrative patterns in public health and for work in dispensaries, hospitals, and so forth. Professor Kaliyou showed us a "Handbook on Planning and Equipping Hospitals," published in 1953 in collaboration with the Academy of Architecture. This would be an interesting volume to study.

The department of statistics, under Professor Batkis, is not concerned with vital statistics per se but with the use of statistical methods. Vital statistics is the function of the Ministry of Health. We were presented with two recent monographs from this department, one on "Statistical Methods in Clinical Studies" and the other on "Statistical Methods in Experimental Studies." Professor Merkov is their expert on cancer statistics; in 1941 he published a monograph on "Malignant Neoplasms in the Ukraine."

The department of the history of medicine is concerned with translating medical classics into Russian, developing courses on medical history for the medical schools, and keeping up-to-date various jubilee years as a means of maintaining interest in history. The institute is developing a museum on medical history and is anxious to have a good collection of portraits of foreign scientists of historical importance. Their present collection of portraits of Americans is most meager. We were given a pack of 32 portraits of Russian scientists in exchange for a collection of portraits of historical American medical figures. This exchange could include portraits of contemporary members of the Academy of Science and Academy of Medical Sciences U.S.S.R., for a similar collection from our National Academy of Sciences. Their pack included pictures of Pavlovsky, Bakulev, and several other living Soviet scientists. (This exchange is now proceeding with the National Library of Medicine.)

The department of Soviet medical history, described by Professor Bursukov, is primarily concerned with events under the Soviets, although its studies go back as far as Kiev Russ for background.

March 27 (Tuesday)

Central State Medical Library. At the Central State Medical Library, Dr. P. Kolosov, the librarian, discussed book exchanges primarily, since the arrangement for the exchange of journals was quite satisfactory. Most medical books in the Soviet Union are published by Medgiz, which produces about 500 titles a year. The head of Medgiz is Nikoloi A. Vinogradov.

Commercially, procurement of a selected output of Medgiz would be difficult. Medgiz does not issue prepublication catalogs, and usually the better books are quickly bought up. The best solution would be procurement of the total output of Medgiz for an exchange of equivalent American books through the Central State Medical Library. Kolosov indicated that this was quite possible and that he was interested in such an arrangement.

Medgiz published the "Meditsinskaya Literatura U.S.S.R.," a list of all medical journals, articles, and books, but the last volume covers the period 1945–46. Medgiz is now getting out a 1953 index and hopes to be up to date in a few years.

Because of time limitations, we did not see the actual library, which was stated to have more than a million accessions and to cover the complete Soviet medical literature since 1919. It is adding about a thousand foreign titles each year. A microfilm service will be available shortly.

Later in the day, Professor Chumakov visited us. He told us that the Russian plans for poliomyelitis work call for the production of a Salk-type vaccine "in the best possible way." Some changes in the strains may be made, such as inclusion of the Soviet type IV poliomyelitis. They do not propose to go into large-scale production but to produce enough vaccine for a field trial with about 200,000 children. Arrangements for obtaining monkeys are in progress with China and Abyssinia. The real aim of the poliomyelitis workers, supported by their concepts of other vaccines, is to develop attenuated strains for use in immunization.

In addition to samples of sandfly fever virus and hemorrhagic fever ticks, which Professor Chumakov supplied, we received many books, typewritten materials, and a wooden box containing most of the viruses we had requested, to take back to the United States.

March 28 (Wednesday)

Early in the morning, Mr. Medhedov took us to the airport, where we met Dr. Christov and Galina Namestnikova, of the Ministry of Health. Our baggage was not opened, and the only documents we had to show were our passports and currency declarations.

The American Medical Mission on Microbiology and Epidemiology to the Soviet Union was on its way home.

Recommendation

Members of the American Medical Mission on Microbiology and Epidemiology to the Soviet Union believe that it would be arrogant, stupid, and even dangerous for the United States to ignore Soviet medicine and research. They recommend that all appropriate steps be taken to develop channels of communication between the medical scientists of the Soviet Union and the United States by exchange of literature, materials, and personnel. The mission members point out that the United States can learn from Russian achievements, but that understanding of their medicine and research is even more important than mere knowledge. On the basis of these principles, a rather large-scale plan and a long-range, pliable program of medical exchanges appear clearly indicated. The mission urges the early initiation of such a program.

Opinion may be voiced that medical exchanges with the Soviet Union do not require special approaches and should proceed along the usual lines undertaken with other countries. The facts are, however, that the Soviet Union represents a special problem and one that is of paramount importance to the United States. Special and perhaps unique methods are essential in dealing with the Soviet Union. Official or semiofficial missions under governmental sponsorship are only the first of such steps, to be replaced by informal interchanges as soon as the situation warrants.

The gathering, translating, and evaluating of Soviet medical literature is an important aspect of our information. This aspect must be developed and will be strengthened by first-hand observations; at the same time, the value of such observations will be enhanced by knowledge of the background of published materials. It should be remembered that our ignorance of the Russian medical literature is not entirely due to language barriers; even more important is the psychological barrier of considering this literature not worthy of attention. The development of a center for the evaluation of Soviet medical research and related subjects is recommended.

There seems to be no risk of consequence to the United States involved in getting a clear picture of Soviet medicine and medical research. The benefits to the United States seem real.

In the spring of 1956, at the completion of their visit to Russia, the American Mission on Microbiology and Epidemiology to the Soviet Union brought back to the United States strains of microbial agents supplied by Soviet scientists. These agents and the American scientist who received them are listed in addendum 1.

Biologicals Received From Russian Scientists

Agent	*Recipient*
Bacterial strains for vaccines:	
Bacterium tularense [1]	K. F. Meyer [2]
Brucella [3]	K. F. Meyer [2]
BCG	R. Dubose [4]
Virus strains:	
Chorioencephalitis	A. I. Shelokov [5]
Crimean hemorrhagic fever	J. E. Smadel [5]
Gastroenteritis F 1	A. I. Shelekov [5]
Influenza [6]	B. Eddy [5]
Live polyvalent vaccine	
16 strains of vaccine	
Lymphocytic chriomeningitis virus	National Institutes of Health
Measles	J. F. Enders [7]
Milk fever	J. R. Schmidt [8]
Strain F	
Strain K-57	
Mumps	J. F. Enders [7]
Omsk hemorrhagic fever	J. R. Schmidt [8]
Papilloma	R. E. Shope [4]
Poliomyelitis:	
Type 1	K. Habel,[5] A. I. Shelokov,[5] J. S. Younger [9]
Strain Loug	
Strain KRF-1	
Strain 3K VII	
Virus strains—Continued	
Polyomyelitis—Continued	
Type 2	K. Habel,[5] A. I. Shelokov,[5] J. S. Younger [9]
Strain Alexeyeva	
Strain OVCH	
Strain Smirnova	
Type 4	K. Habel,[5] D. Horstmann,[10] J. S. Bell [5]
Strain AB	
Sandfly fever	A. B. Sabin,[11] J. E. Smadel [5]
Spring-summer encephalitis	J. R. Schmidt [8]

[1] Including mimeographed instructions for use of dried tularemia vaccines.

[2] University of California School of Medicine, San Francisco, Calif.

[3] Including mimeographed instructions for use of dried *Brucella* vaccine.

[4] Rockefeller Institute for Medical Research, New York.

[5] National Institutes of Health, Public Health Service, Bethesda, Med.

[6] Including mimeographed instructions on use of dried influenza vaccine.

[7] Children's Medical Center, Boston, Mass.

[8] Walter Reed Army Medical Center, Washington, D. C.

[9] University of Pittsburgh School of Medicine, Pittsburgh, Pa.

[10] Yale University, New Haven, Conn.

[11] Children's Hospital Research Foundation, Cincinnati, Ohio.

Soviet Printed Materials Received

Books and Pamphlets

Academy of Medical Sciences, U.S.S.R.: Annotations of scientific works of Academy of Medical Sciences, U.S.S.R. during 1954. Moscow, 1956, 544 pp.

Academy of Medical Sciences, U.S.S.R.: Five-year plan for medical research 1956–1960. Moscow, 1956, 110 pp.

Artemev, F. A.: Laws on management of public health in the U.S.S.R. Moscow, Medgiz, 1955, 46 pp.

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- Microbiology.
- Topographic anatomy and operative surgery.
- Histology and embryology.
- Inorganic and analytical chemistry.
- Physics.
- Pathological physiology.
- Pathological anatomy.

Programs for students in pharmaceutical institutes and pharmaceutical faculties of medical institutes, in:
- Pharmacology.
- Legal chemistry.
- Medical economics.
- Inorganic chemistry.
- Technology of prescriptions and Galenic preparations.

Programs on courses for medical schools (feldshers, midwives, and so on) in:
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- Anatomy, histology, and embryology.
- Biology.
- Physiology of man.
- Microbiology.
- Pharmacology and prescriptions.
- Infectious diseases.
- Epidemiology and disinfection.
- Epidemiology and medical parasitology.
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Scheme for purification of plasma by Diaferm 3 IEM AMS method.

Scheme for drying live vaccines by method of Dolinov.

Instructions for preparation, control, and use of:
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- Polyvaccine.
- Cholera monovaccine.
- Percutaneous, dry, live antitularemia vaccine from strains 155 and 15.
- Subcutaneous dry, live antibrucellosis vaccine IEM AMS U.S.S.R.
- Diphtheria native anatoxin.
- Tetanus anatoxin, for active immunization of man.
- Antibotulinus serum, types A and B.
- Antigangrene serum.
- Antitetanus serum.
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- Method of testing the reactivity of corpuscular intestinal vaccines and polyvaccines.

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