

tamination procedures must be responsible. A means for interruption of such transmission must be sought. (g) Risk figures for patients of HB Ag-positive physicians, surgeons, and dentists should be developed. If carriage of HG Ag is hazardous to patients, the risk should be defined, and appropriate measures developed for reduction of the risk. (h) The effect of the season on dissemination of herpesviruses should be studied. In addition, the cytomegalovirus group should be evaluated for antigenic variants, since there may be considerable variation in potential for disease among different members of this group. (i) Measures for the increase of specific resistance to representatives of the herpesvirus group should be evaluated. While the effectiveness of specific attenuated or inactivated vaccines may appear to be unlikely on theoretical grounds, transfer factor and other cellular immunological approaches should be studied.

(3) Personnel, physicians, and nurses must be trained in hospital epidemiology, surveillance, and control procedures, to implement and to increase the available knowledge. In addition, innovative approaches to the dissemination of knowledge concerning the usage of antimicrobial agents, hazards of various invasive procedures, and hospital control practices must be encouraged.

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Influenza Research in the Soviet Union—1974

The Agreement on Cultural and Scientific Exchanges between the U.S. and the U.S.S.R. proposed the development of mutual cooperation in

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selected fields of health and medical science. The initial problems selected were malignant neoplasms, cardiovascular diseases, and environmental health. At its second session, the U.S.—U.S.S.R. Joint Committee for Health Cooperation agreed to further exploration in the field of influenza and other viral diseases; recommendations regarding areas of collaboration would be considered at the third session of the Joint Committee in Moscow in June 1974. On behalf of the development of these recommendations, a delegation of scientists from the United States visited the Soviet Union during February 17–27, 1974, for discussions with Soviet scientists in Leningrad and Moscow. The delegation was larger than the small group that had visited several institutes in these two cities in January 1973 [1], and was able to collect additional information on Soviet research. This summary presents a synthesis of information collected by members of the visiting delegation regarding Soviet research in the five principal areas considered for possible joint collaboration.

Specific Immunoprophylaxis

A long historical tradition for the use of live-virus vaccines in the Soviet Union dates from Smorodintsev's experimental infection of volunteers with influenza virus in 1937 [2]. That the success of immunization with live virus has been limited is evidenced by continued research on new methods for attenuation and administration of virus and by the present emphasis on research in chemoprophylaxis. Furthermore, mass immunization is not yet undertaken on more than a city or regional basis, and no more than 50 million doses of vaccine are used each year. The eventual goal is the achievement of mass immunization of about 70% of the population. Such immunization would be nonselective, except that the vaccination of children would be emphasized. There is little interest in the use of inactivated vaccine by parenteral administration, although such vaccine is now being produced experimentally and is to be utilized, if approved, in hyperimmunization of volunteers for the production of immunoglobulin against influenza virus.

Administration and control. The development of new or modified vaccines is chiefly under the aegis of the All-Union Research Institute of Influenza in Leningrad, although the Institute for Viral

Preparations in Moscow also undertakes limited research and development in addition to its production activities.

The initial testing of a new vaccine in volunteers is under the control of the institute involved in its development. Protocols are first reviewed by an Institute Expert Committee, then by a Review Council before testing of vaccines in volunteers. Experimental vaccines are preliminarily tested under standard protocols for mycobacteria, mycoplasmas, and hemadsorbing viruses. Initial testing in volunteers is principally for reactogenicity. Testing is stepwise in relation to volunteer susceptibility and is restricted to young adults. Thus, the live vaccine is successively tested in volunteers (five per group) with high, low, and undetectable levels of serum antibody, and then finally in groups of 20 antibody-negative subjects. Application of the vaccine to non-volunteer populations in field trials requires the permission of the Ministry of Health. Selection of strains for the production of vaccines is made in the November through January period by a committee under the Ministry of Health; results of testing of the first three production batches in a total of 60 volunteers are submitted to the Laboratory of Biologic Control, which is part of the Tarasevich Control Institute for Biological Preparations of the Ministry of Health. Allantoic fluid vaccine is distributed to Sanitary-Epidemiologic Stations that arrange for and direct its use in organized population groups, such as industrial workers. Neither allantoic nor tissue culture vaccines are available directly to polyclinics or other medical facilities.

Production. Experimental vaccines are produced by the institute involved in their development. Thus, Smorodintsev's allantoic fluid vaccines are produced at the All-Union Research Institute of Influenza, while tissue culture vaccines originated by the Institute for Viral Preparations are prepared there. On the other hand, the Smorodintsev vaccine approved for general use is produced by the Institute for Viral Preparations. About 12 million of the 45–50 million doses of influenza vaccine produced each year are produced in the latter institute. Production of the remainder appears to be distributed among institutes in other cities. Chick embryos used at both the All-Union Research Institute and the Institute

for Viral Preparations are furnished from flocks under supervision of the Veterinary Department. However, the All-Union Research Institute minimizes the problem of avian leukosis, citing the negative evidence of 10,000 children who received mumps vaccine and were followed for 12 years, plus the impracticality of testing when 15 million eggs are used annually. The Institute for Viral Preparations reported negative RIF (resistance-inducing factor) tests on periodic testing of eggs.

Research. Research in influenza vaccines appears to be entirely committed to live virus immunization. The primary site of this research is the All-Union Research Institute of Influenza, although some vaccine-related research is undertaken elsewhere, primarily at the Institute for Viral Preparations. A significant amount of the genetic and molecular virologic research at the All-Union Research Institute is oriented to problems of viral attenuation and virulence markers.

Until recently, the attenuation of viruses for use in the production of vaccine has been empirically achieved by serial passage in chick embryos and periodic testing in volunteers for reactogenicity. Attention is now being directed to other means of attenuation and to the effects of employing a changed route of administration of low-passage, virulent virus for the reduction of toxic effects. Preliminary experiments have attempted the recombination of freshly isolated virulent strains with attenuated "laboratory" viruses for the production of so-called "biological recombinants" that possess the antigens of the wild-type parent but are changed in other properties, such as virulence for mice. Cold adaptation of viruses by passage at 25 C is also under study. A rapid-passage method in which allantoic fluids are harvested and passaged every 24 hr is also under investigation as a means of shortening the time required for attenuation.

The greatest emphasis at present is on the use of the peroral (po) route of administration of live vaccine to children as a method of reducing symptoms associated with intranasal administration. Comparative studies of the two routes have been done principally at the All-Union Research Institute with allantoic fluid vaccines. These studies indicate that multiplication of virus is reduced after po administration, as evidenced by recovery

of virus in low concentration only on the fifth day and a delay in antibody response when compared with that to intranasal vaccine. Immunogenicity is also reduced by po administration, so that three separate applications of the virus at 14-day intervals are required to achieve a reasonable rate of seroconversion. At the Institute for Viral Preparations, Dr. A. K. Alexeeva is investigating po live-virus vaccine prepared in tissue culture.

The commitment to live influenza vaccines extends also to the immunoprophylaxis of other diseases, including infections with parainfluenza and respiratory syncytial viruses, adenoviruses, and *Mycoplasma*. The ultimate research objective is the suppression of respiratory diseases, particularly in children, through the use of "combined immunization."

As previously reported [1], passive immunotherapy is carried out through administration of γ -globulin derived after specific immunization of man. Earlier interest in the use of high-titered γ -globulin intranasally as a prophylactic agent seems to have been abandoned. Rather, γ -globulin given parenterally was reported to be efficacious in alleviating high fever and other evidences of "toxicity," particularly in children. No new data on efficacy were provided. The γ -globulin is prepared at the Pasteur Institute in Leningrad from serum drawn from volunteers hyperimmunized with virus vaccines. The γ -globulin is approved for use and is available at pharmacies without prescription at a cost of 3.75 rubles/2 ml.

Epidemiology

Surveillance. Most epidemiologic data presented covered the period from 1957 to the present, with by far the greatest emphasis on influenza A. The Soviet Union experienced major epidemics of influenza in 1957, 1959, 1962 (mixed A and B), 1965, 1967, 1968, and 1970, reflecting roughly a two- to three-year cycle. The epidemics of 1957, 1962, and 1968 appear to have caused the greatest morbidity. Sudden onset of countrywide outbreaks during the late fall or early winter months have characterized most epidemics, and the northern areas and urban populations have been most frequently and most severely affected. Apparently most large cities (population of more than

200,000) experience relatively uniform increased morbidity during epidemics, with little asynchronous occurrence countrywide. Influenza is a disease primarily of children most often affecting those between the ages of nine and 15 years.

Surveillance of influenza and other acute respiratory diseases (ARD) is based on morbidity reports originating at the polyclinic or hospital level. Large factories, mills, etc., also have clinics and provide data for the system. Physicians are required to report cases seen at clinics or on house calls. Report cards are filled out daily, collected by trained health personnel, tabulated, and sent to District Sanitary-Epidemiologic Stations; from here reports are sent to successively higher administrative units: the Rayon, the Oblast, then to the Republics, and finally to the Ministry of Health.

Although this system (which also applies to other reportable communicable diseases) is the formal, regular, national method of morbidity reporting, two other systems of influenza and ARD reporting exist that serve somewhat different functions but utilize the same basic polyclinic source of data. These systems are operated by the All-Union Research Institute, Leningrad, and the Ivanovsky Institute, Moscow. For the last two or three years the former institute has operated a surveillance system for influenza-ARD consisting of regular daily morbidity reporting (by cable or telephone) from the capitals of the 15 republics. Thirty-seven other cities submit regular reports weekly. Another 100 cities are supposed to report weekly, but perhaps only 30-40 of these do so regularly. The morbidity data received by the All-Union Research Institute are identical to data reported in the national system. However, this institute receives these data either one day or one week before the regular system; it uses them primarily to determine the probability of influenza morbidity in the 52 cities under close surveillance.

In 1957 the Ivanovsky Institute began receiving morbidity data every 10 days from 30 towns throughout the Soviet Union. The number of towns reporting grew to 55 but is now only 20. These 20 cities report the same data to the All-Union Research Institute; the cities are distributed widely throughout the Soviet Union and have populations of 200,000 or more. Fourteen of these cities report each week; six cities report by

cable daily. All report the total number of patients seen at polyclinics or at home who are diagnosed as having influenza or ARD plus the same morbidity data for children up to seven years of age. During influenza epidemics the Ivanovsky Institute also receives daily by cable the total number of hospitalized cases of influenza and the total number of deaths attributable to influenza. The daily and weekly morbidity data are considered provisional, and each month the 20 cities send an adjusted tabulation of cases which is final. A monthly summary of these data, along with laboratory results, is mailed to each city. A quarterly report is compiled and sent to the World Health Organization for publication.

Physicians are required to report all cases of influenza and ARD they diagnose, and most do so; many ill persons are never seen by physicians. As a result of several apartment house surveys after two major epidemics, a rough estimate of overall morbidity of 35% was obtained. Approximately 50%–60% of these cases were seen by a physician.

Laboratory surveillance. The All-Union and Ivanovsky Institutes receive regular laboratory reports from the 53 and 20 reporting cities, respectively. Although it was not clearly confirmed, it appears that the Gamaleya Institute presently serves as a resource and administrative headquarters for most if not all of the laboratories that provide input to all three institutes. Serologic tests are performed at the Gamaleya Institute on sera received weekly from 20 Sanitary-Epidemiologic Stations. Sera are obtained from patients of all ages presenting at clinics with noninfectious diseases, from blood donors, from military populations, and from children attending day-care centers and schools. The sera are examined by HAI tests for antibodies to the following viruses: influenza A/England/42/72, A/Hong Kong/1/68, A/Singapore/1/57, B/Dushavbe/65, and B/Moscow/69; parainfluenza 1, 2, 3, 4A, and 4B; and coronavirus OC43. Antibodies to adenovirus (group-specific) and respiratory syncytial virus are assayed by the CF test. The metabolic inhibition and colony reduction tests are used for *Mycoplasma pneumoniae* and *Mycoplasma hominis*, respectively. Approximately 4,000 sera are examined annually. Results are sent to the All-Union Research Institute of Influenza.

Adenovirus, influenza virus, parainfluenza virus (1, 2, and 3), and mycoplasma infections also are diagnosed by direct fluorescent antibody staining of nasal smears. The reagents are thought to be prepared at the All-Union Research Institute and distributed to its stations. Some of the stations also perform serodiagnostic tests, but many forward paired sera to the Gamaleya Institute for examination. Paired sera are said to be difficult to obtain. Some stations may attempt virus isolation in tissue culture; many apparently employ embryonated eggs for isolation of influenza viruses.

Computer modeling. Soviet epidemiologists have devoted considerable effort to the development of a model for the prediction of registered numbers of cases of influenza or ARD for 128 geographic units within the Soviet Union. Since registered morbidity rather than a more direct measure of real influenza-ARD morbidity is used, the model probably has more applicability for health planners, who need to anticipate increased requirements for delivery of health care associated with epidemics, and for industrial organizations that face future production losses, than for those concerned with anticipating changes in the health status of the population per se.

Critical to the quality of the data input is the proportion of the cases registered. Many behavioral factors affect the proportion of cases registered. Among these is probably the cost of illness. Although both inpatient and outpatient services are provided at no direct cost to the patient, sick leave benefits do not always cover absences from work because of illness. For the first five years of employment, benefits cover 50% of the employee's salary; for the next three, the percentage increases to 80%; only after eight years on the job does sick leave cover the employee's entire salary during illness. Thus, influenza imposes an indirect cost on many in terms of lost income. Some may be reluctant to declare themselves ill because they do not want to incur this loss.

Once an influenza-ARD epidemic has been identified in one location, the model enables one to predict future registrations for 128 observational units, encompassing 99% of the Soviet population. The model serves two roles: (1) prediction of daily registrations in a large number

of locations; (2) evaluation of the effects of specific public programs (e.g., vaccination). The former application is particularly important in the Soviet Union, since physicians from all types of specialties and even medical students in advanced stages of training are mobilized to treat influenza during epidemics.

Although data from the morbidity registration system in the Soviet Union provide the basic information for this model, data from the 52 All-Union reporting centers appear to be used as well, particularly for obtaining early warning of the location of the initial epidemic outbreak in the country.

The model's theoretical structure was developed at the Gamaleya Institute by L. V. Rvachev. Rvachev's academic training is in mathematics and physics; the model is based on principles from physics. The basic equations have been presented by Baroyan et al. [3]; a much more rigorous theoretical development of the model has been published by Rvachev [4]. The formal structure of the model will not be presented here, but brief mention will be made of the independent variables and parameters that serve as the basis for predictions.

Movement of persons among geographic areas provides the mechanism for the spread of influenza-ARD. The model contains a large number of transportation coefficients (based on sales of airline, bus, and railroad tickets) relating inter-locational flows of people. These data have been assembled through rather painstaking efforts on the part of staff. One of the Soviet scientists estimated that it took three man-years to secure this information alone.

Two epidemic-specific parameters reflect the initial (i.e., at the time of epidemic outbreak) density of influenza-susceptible individuals and the speed of transmission within a location. These are estimated from data on registered morbidity in the location in which the initial outbreak occurs. It appears that data must be obtained for five to 14 days. Rvachev maintains that the estimates are maximal likelihood estimates. Once the epidemic-specific parameters have been estimated, predictions can be made for all locations in the Soviet Union. The interval between the date predictions are made and the peak of the influenza-ARD epidemic in the median location is about

1.5 months. These two parameters are said to embody virological and immunological factors associated with the epidemic. The model, however, does not consider such factors explicitly. Other variables and parameters in the model are the area's population and frequency distribution of length of influenza illness, obtained by averaging of data from a monograph by Zhdanov et al. [5].

The predictive ability of the model has been evaluated with use of both historical data (for outbreaks in 1957, 1959, 1962, 1965, 1967, 1969, and 1970) and data generated for two years since the model was developed. The Soviets show extensive plots of actual vs. predicted values of influenza-ARD morbidity; these plots indicate that the model predicts quite well. Timing of the epidemic and its intensity (measured by the number of registered cases in the location) have been used to assess predictive accuracy. A prediction is considered "accurate" if two conditions are satisfied. First, the day on which influenza-ARD reaches its highest level must be within five days of the day on which the peak is predicted to occur. Second, the following inequality must be satisfied: $0.7 < (\text{highest predicted registered morbidity in location}) / (\text{highest actual registered morbidity in location}) < 1.5$. Using this definition of accuracy, recent tests have shown the model to be "accurate" 80% of the time.

Compared with similar models in other fields, the model for prediction of influenza-ARD epidemiology provides reasonably good predictions of the dependent variable. However, at present it provides very little time between the date on which predictions are made and the date on which epidemics occur. This interval might, of course, be lengthened if the epidemic-specific parameters were estimates based on influenza data from another country, at a time before the epidemic reached the Soviet Union. For this reason, there is some interest among the Soviets in having the United States and other countries implement the model. Discussions along this line are now underway with the German Democratic Republic and Bulgaria.

Animal Influenza

Research on the ecology of influenza viruses is done at the Ivanovsky Institute under the direc-

tion of D. K. Lvov in collaboration with L. Y. Zakstelskaya. Dr. Lvov indicated that most of the work had been done since 1970. While there were earlier reports on animal influenza viruses, there appears to have been no organized program until 1970. Dr. Lvov has been investigating the ecology of arthropod-borne viruses for some time; he now is using some of the same procedures and materials in studying the ecology of influenza. Most of his efforts have been directed toward avian species. Thus far, most of these studies have been conducted in the far east of the Soviet Union (specifically, the Kamchatka Region and the Komandorskiye Islands). Other areas have included the Eastern Arctic, West Central Arctic, Murmansk Regions, Byelorussia, and the Caspian Sea. All of the areas studied so far have been on the perimeter of the country. While the field aspects have been directed by Drs. Lvov and A. A. Sazonov, the antigenic and serologic analyses and virus characterizations have been done under the direction of Dr. Zakstelskaya.

Viruses characterized as H3N2 have been isolated from the chicken, pig, dog, calf, and wild birds (terns and herons) in various parts of the Soviet Union. In the far east, antibody to the H3 antigen has been found in wild birds, fur seals, cattle, and mink. While there is serological evidence for the H3N2 virus in the far east, the only isolations of that virus from wild birds (terns and herons) have been in the Caspian Sea area. Other information includes: (1) the demonstration of A/equine/Miami/63 (Heq2Neq2) antibody in bird sera, (2) the demonstration of A/swine/Iowa/30 (Hsw1N1) antibody in seal and some bird sera, (3) the presence of fowl plague virus (Hav1) in chickens in 1970 and the presence of that antibody in wild birds in 1972, and (4) the isolation of swine influenza virus (A/swine/Tartu/1/70) from pigs in 1970.

A virus (Hav7N2) was isolated from terns in the Caspian Sea area in June 1973. It is also interesting to note that Newcastle disease virus was isolated from wild birds (species not indicated) on Kamchatka in 1972, the same year it was isolated from wild ducks in California by workers in the United States.

Interferon Chemoprophylaxis and Therapy

Several Soviet scientists are interested in antiviral chemoprophylaxis and therapy, including use of

interferon and interferon inducers against influenza, and there is some overlap of interests by scientists at various institutions. However, there was little evidence of formal collaboration in this area of influenza research in the Soviet Union.

Laboratory research with anti-influenza drugs. Dr. G. A. Galegov of the Ivanovsky Institute, a biochemist, leads a group of scientists interested in testing antiviral agents. He hopes to achieve additive therapeutic effects without additive toxicity by using combinations of drugs or interferon plus a drug. Dr. Galegov has been a coauthor of several publications in this area [6] and is currently seeking an agent that will interfere with the RNA polymerase of influenza virus. He is studying a disulfide agent that decreases the RNA polymerase activity by about 40%. The name of the agent and the concentration required to produce this effect were not stated; no studies have been performed with it in animals. His laboratory apparently does not perform animal experiments with anti-influenza drugs but does measure their antiviral effects in tissue culture while attempting to delineate mechanisms of action.

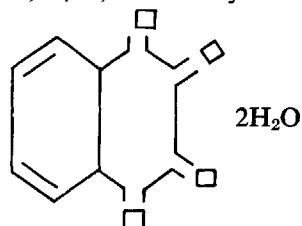
Development of new anti-influenza drugs. Very little information was acquired in this area. The two new chemical agents used in the Soviet Union to prevent influenza, Oxolin and Bonaph-ton, were supplied to clinicians for testing in volunteers by Dr. Pershin of the Institute for Chemo-Therapeutic Preparations in Moscow; unfortunately, he was not a participant in the discussions. Dr. D. M. Zlydnikov of the All-Union Research Institute had used these drugs to prevent or treat influenza but did not know what effect they had on influenza virus in vitro or on influenza infection in animal models. Dr. Zlydnikov suggested that Dr. Pershin might have done some studies in cell cultures or animals. The scientists who are concerned with influenza chemoprophylaxis and chemotherapy obtain the agents used from manufacturing facilities, such as Dr. Pershin's institute in Moscow, or from outside the Soviet Union. The clinical investigators who used these agents in volunteers apparently had not done independent in vitro or animal studies.

Clinical studies. The research performed in the large and active volunteer unit at the All-Union Research Institute of Influenza can be briefly summarized.

(1) *Amantadine.* The observation made by

scientists in the United States that amantadine was partially effective for prophylaxis against influenza type A2 infection in human volunteers was confirmed.

(2) *Oxolin*. Tetraoxytetrahydronaphthalenedihydrate, or 1, 2, 3, 4 Tetrahydro naftalin is a



nasal ointment now widely available in the Soviet Union; it is said to prevent morbidity (39%) in volunteers infected with influenza. Details of the volunteer experiments were not given, but morbidity was the only parameter studied. No virus isolation or serological confirmation of infection was supplied. No information was obtained about its mechanism of action in tissue culture or in animals. This drug has been used widely in epidemiologic field trials and is now approved for general use. The package insert states: "For the purpose of individual prophylaxis of influenza, the 0.25% ointment is used in the form of daily two fold application to the nasal mucosa during the period of elevation and maximum development of the epidemic outbreak of influenza (for 25 days) or upon contact with an influenza patient."

(3) *Bonaphton* (called 6 *Bromonaphthoquinone-1, 2* [MO-855]). Dr. Zlydnikov obtained this agent from Dr. Pershin and studied its effect in human volunteers challenged with partially attenuated influenza virus [A₂/Hong Kong/68 (H3N2)]. The drug was given the day before challenge and daily for six days after challenge. Controls received a placebo. Safety was studied in a total of 363 volunteers in many experiments. Efficacy studies were limited to evaluation of clinical morbidity; no virus isolation or antibody studies were performed. A regimen of 50 mg given po two times daily, from the day before to six days after challenge, was said to decrease morbidity (e.g., 38.4% of 13 volunteers given Bonaphton vs. 78.6% of 14 volunteers given placebo). Large epidemiologic field trials were done, and approval for general use was obtained. As was the case with Oxolin, no data were presented about the mechanism of Bonaphton's effect, and

it was not learned whether animal studies had been performed with this drug.

(4) *Interferon and interferon inducers*. Soviet scientists are interested in the use of interferon, either by aerosolization of exogenous human interferon (widely used to treat influenza) or by induction with viral vaccines or chemical inducers. These studies were reviewed in detail in 1973 [1]; no new information has been acquired.

Some interesting research is being done by two laboratories in the general area of nonspecific resistance to influenza. Drs. T. G. Orlova and L. M. Mentkevich at the Ivanovsky Institute have studied the effects of interferon induction by viruses (including influenza) and nucleotides in irradiated CBA mice, which received transplants of either syngeneic bone marrow or rat bone marrow [7]. Induction of interferon by all inducers except influenza virus appeared to be related to production of interferon in bone marrow cells as measured by species specificity. Influenza virus induced mouse interferon in irradiated mice that had received rat bone marrow transplants, a fact suggesting the possibility of extramedullary interferon induction by influenza.

Genetics and Biology of Influenza Viruses

Few laboratories in the Soviet Union appear to be concerned primarily with basic genetic studies of influenza viruses. Recently, as noted, laboratories in the All-Union Research Institute have begun to apply techniques of cold adaptation and recombination to attenuation of strains used for production of live-virus vaccine. In the laboratory of Dr. D. B. Golubev, antigenic and other variation of the neuraminidase antigens of H3N2 influenza viruses have been under study; his demonstration of differing temperature inactivation and temperature optima of these neuraminidases provides interesting genetic markers. This laboratory has continued studies on the possible relation between temperature optima of neuraminidase and virulence. A lower temperature optimum was described as characteristic of attenuated strains.

Dr. Golubev also reported that, by use of the CF test and purified neuraminidase (N2) proteins, three major antigenic subgroups could be distinguished among influenza strains isolated since 1957. He described these groups as repre-

senting "semi-shifts"; the three groups include strains isolated from 1957 to 1965, from 1967 to 1971, and from 1972 to the present, respectively. Each semi-shift was accompanied by a change in neuraminidase inactivation temperature. Each semi-shift also occurred at the time of a major epidemic in the Soviet Union.

At the Ivanovsky Institute of Virology, studies of influenza virus RNA polymerase have been undertaken by Dr. Galegov, but these studies apparently are in their early stages. Dr. U. Z. Ghendon's group at the Institute for Viral Preparations has worked extensively with temperature-sensitive mutants of fowl plague virus since shifting attention from polioviruses to influenza. Results of the assortment of the fowl plague *ts* mutants into five complementation groups have been published. More recently, Ghendon has found evidence of variation in RNA polymerase activity among wild-type strains of virus associated with epidemics in December 1971, January 1973, and early 1968. In contrast to observations of workers in the United States, Ghendon has evidence against the association of RNA virion polymerase activity with the ribonuclear protein.

Dr. F. I. Yershov of the Ivanovsky Institute is attempting to establish persistent *in vitro* infections with influenza viruses. Such studies may relate to possible mechanisms for survival of the virus during epidemic periods and for antigenic variation. Work on such persistent infections with influenza viruses has just begun; major effort in the past involved tick-borne encephalitis virus and parainfluenza viruses.

General Comment

This report, without critique, has attempted to summarize objectively information helpfully provided by Soviet colleagues. Because of the press of time, important contributions may well have been missed by such a brief survey, and the possibility is acknowledged that some of the presented facts may have been misunderstood and are, therefore, misrepresented. Apologies are offered for all such errors, with the expectation that they will be corrected as the collaboration recommended by the delegations from the United States and the Soviet Union becomes a reality.

To these observers, it appears that the recognition given by the Ministry of Health of the Soviet Union to influenza as an important national

health problem exceeds that given by health authorities in the United States. The Soviet investment in research on influenza probably exceeds investment in the United States. The development of a national system of morbidity surveillance and of computer forecasting as a means of allowing local health authorities to prepare for an increased demand for medical services recognizes the impact of the disease in the community. Such morbidity reporting is superior to that in the United States and provides a hard-data base for the concern evidenced by the Soviet Ministry. Clearly, neither country has solved the complex problem of influenza prevention; there is much to be gained through mutual cooperation.

References

1. Jordan, W. S., Jr., Hopps, H. E., Merigan, T. C. Influenza and interferon research in the Soviet Union—January 1973. *J. Infect. Dis.* 128:261-264, 1973.
2. Smorodintseff, A. A., Tushinsky, M. D., Drobyshchskaya, A. I., Korovin, A. A., Osetroff, A. I. Investigation of volunteers infected with the influenza virus. *Am. J. Med. Sci.* 194:159-170, 1937.
3. Baroyan, O. V., Zhdanov, V. M., Soloven, V. D., Zakstels, L. Y., Rvachev, L. V., Urbakh, Y. V., Ermakov, V. V., Antonova, I. V. Possibilities for computer modeling of influenza epidemics in the U.S.S.R. *Zh. Mikrobiol. Epidemiol. Immunobiol.* 5:3, 1972.
4. Rvachev, L. V. Report on a visit to Bulgaria, December 1-29, 1972. World Health Organization (Bulletin-UNDP/BUL/68/502).
5. Zhdanov, V. M., Soleviev, V. D., Epshtein, F. G. *Uchenie O Grippe*. Moscow, Medgiz, 1958.
6. Galegov, G. A. Review of problems in viral chemotherapy. *J. Chem. Assoc. U.S.S.R.* 2:200-207, 1973.
7. Mentkevich, L. M., Orlova, T. G., Shcheglovitova, O. N. Interferon production and infection caused by influenza virus in radiation chimeras. *Acta Virol. (Praha)* 17:435-438, 1973.

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