# Research Programs on Asian Influenza

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NEARLY a month before the first group of cases of Asian strain influenza were diagnosed in American civilians (high school conference at Davis, Calif., June 21–30, 1957), special research on various aspects of this disease had been started at the National Institutes of Health of the Public Health Service. Since then, 6 of its 13 major subdivisions, the Division of Biologics Standards, the National Institute of Allergy and Infectious Diseases, the National Heart Institute, the National Institute of Mental Health, the Clinical Center, and the National Institute of Neurological Diseases and Blindness, have participated in meeting this investigational exigency.

In late August, a special conference of State and Territorial health officers was called by the Surgeon General to review developments and to coordinate and plan future activities relative to the epidemic. At this meeting, the recommendation was made that a group of outstanding medical scientists representing the several areas of specialized knowledge associated with influenza be appointed to advise the Surgeon General regarding research planned to minimize the morbidity and mortality resulting from Asian influenza. This suggestion was implemented in September.

The following is a brief recapitulation of influenza research being carried on or supported by the National Institutes of Health and of the organization and accomplishments of the Public Health Service Influenza Research Committee.

## Division of Biologics Standards

While influenza vaccine is not a new product and new strains have been added to the vaccine in the past, the vaccine situation faced by the Division of Biologics Standards and by the manufacturers in the early summer of 1957 differed from previous ones in the degree of urgency and in the size of the production goal.

Various isolates of the Asian influenza virus were supplied to licensed manufacturers of influenza vaccine by the Division of Biologics Standards as soon as they were received. The first of these, A/Jap/305/57, was sent out by the division on May 12, 1957. One of the immediate problems encountered with the new strain was the selection of a particular isolate which could be best adapted to producing satisfactory virus growth in the chick embryo. In addition to Japan 305, A/Jap/306/57, A/Jap/307/57, A/Formosa/1/57, and A/Singapore/1/57 were studied by both the division and the manufacturers for growth potential and other characteristics. As a result of these studies, it was decided that no particular isolate would be designated for vaccine production, but that the manufacturer would use, from among those distributed by the Division of Biologics Standards, the Asian strain isolate showing the best growth characteristics in the hands of the individual manufacturer. The type of potency test used with previous influenza vaccines had been of the mouse protection type which requires 4 weeks or longer to complete.

Initially, it was not possible to use this test for the Asian strain vaccine since a strain lethal for mice in sufficient titer had not been developed. Neither had there been sufficient

*Dr. Andrews, director of the National Institute of Allergy and Infectious Diseases, was requested by the director of the National Institutes of Health, Public Health Service, to act as the focal point for all of the Institutes' activities concerning influenza.*

time to develop information as to what constitutes an adequate level of antigenicity as demonstrated by such a test. In these circumstances, it was decided that since chicken cell agglutination (CCA) units per milliliter are related to antibody response, Asian strain influenza vaccine would be released on CCA values alone. This necessitated the development by the division of a CCA reference standard, which was furnished all manufacturers. It was then necessary for the professional staff of the division to work closely with the technical staffs of industry in order to standardize techniques and obtain uniform results in the performance of this test.

While vaccine continued to be released during the emergency on the basis of CCA values alone, efforts continued on the development of a mouse-adapted Asian strain and of a standard reference vaccine. By mid-August such a strain was developed and was furnished the manufacturers for trial potency tests in mice. By mid-November, when the production cycle of monovalent Asian strain vaccine was nearing conclusion and a return to production of a polyvalent vaccine was near, the division had developed and given the manufacturers a standard reference vaccine containing the Asian strain. On December 1, 1957, it was, therefore, possible to require again that potency determination be based upon the same antigenicity tests in mice as were required for all influenza vaccines prior to July 1957.

### NIAID Projects

Scientists at the National Institute of Allergy and Infectious Diseases have a well-established and time-honored record of research activity on respiratory ailments, including influenza. Their current interest in the latter has resulted (*a*) in the development of a hemadsorption-tissue culture technique which facilitates and expedites the recognition of type A influenza virus (*1*), and (*b*) in the demonstration, by means of live-virus challenge experience in human volunteers, that the Asian influenza vaccines available in July 1957 conferred definite but not complete protection against infection and reduced the severity of infection (*2*).

For several years, studies of the characterization and epidemiology of viral agents have been conducted in three local orphanages or homes for children. In these institutions new respiratory and enteric disease agents are being introduced by newcomers and transmitted continually within the closed populations. Periodically, inmates are systematically sampled for pathogenic microbiota on arrival and during and after clinical episodes. Thus, it has been possible to follow with considerable precision the entrance, spread, and departure of specific microagents of disease. It was assumed in advance that these institutions would be invaded by Asian strains of influenza. Plans were made and are now being implemented for determining the epidemiological patterns of influenza outbreaks and the relation and significance to influenza of complicating disease agents under conditions of different levels of vaccination. The etiology of all severe and fatal cases will be studied intensively with particular reference to antibiotic-resistant bacteria.

Cases of unusual interest will be admitted to the Clinical Center for more sophisticated clinical investigations and determinations than are possible elsewhere.

Limited studies on pregnant women and infants are also under way at hospitals in the metropolitan Washington area. Hemagglutination antibody responses and local and systematic reactions to 1.0 ml. subcutaneous injections of 200 CCA units Asian strain vaccine are being evaluated in 51 women vaccinated during the 36th week of pregnancy. Their infants will be examined at delivery for hemagglutination inhibition antibodies. Some 30 newborn babies have been vaccinated with 0.1 ml. of 200 CCA units Asian strain vaccine, half of them subcutaneously and the rest intradermally. They, too, are being followed in order to detect antibody responses and reactions.

The National Advisory Allergy and Infectious Diseases Council at its meeting on June 27–28, 1957, exhibited lively interest and concern in the impending epidemic. The council unanimously affirmed a resolution proposed by its Ad Hoc Committee on Influenza emphasizing the moral obligation of the council to make available the means for studying the diagnostic,

clinical, epidemiological, therapeutic, and prophylactic aspects of the prospective epidemic. The council recommended to the Surgeon General that the national supply of reagents needed for the diagnosis of influenzal and complicating disease agents be augmented, and that additional support be sought for extending research grants and increasing the intramural influenza investigations of the institute. It further proposed that a conference of key research personnel be called to assist in planning and designing influenza studies.

Administrative plans for implementing these recommendations were approved promptly by the Surgeon General. Funds for intramural influenza research were made available, and the sum of $350,000 was reserved for influenza research grants. Laboratories and individuals with special interest and competence in respiratory disease study were encouraged to submit applications for research on various aspects of Asian influenza, with special emphasis on staphylococcal complications, and on evaluative studies of antibiotic prophylaxis against post-influenza pneumonia in high-risk patients, as recommended by the Public Health Service Influenza Research Committee. Some 40 requests for $618,566 were received and reviewed promptly by the Microbiology Study Section and the National Advisory Allergy and Infectious Diseases Council. Of these, 13 for $187,347 were approved for immediate payment. Subjects of investigation include serologic diagnostic technology, clinical aspects, therapy, basic viral studies, vaccine effectiveness under varying conditions of concentration and injection, complicating agents and conditions, etiology and virulence, epidemiology in community and institutional populations, and establishment in lower animals.

### Heart Research Grants

At its meeting on June 20–22, 1957, the National Advisory Heart Council, recognizing the opportunity for studying some of the unsolved problems presented by the 1918–19 influenza epidemic concerning sudden, unexplained collapse and death, suggested that cardiovascular studies relating to influenza be encouraged. On July 12, 1957, a group of medical specialists was convened to discuss and advise regarding specific areas of research which should be supported. As the result of recommendations of this group, the council subsequently reserved $250,000 for special research grants for cardiovascular-renal studies of influenza and approved the establishment of a four-member Ad Hoc Committee on Influenza Studies under the chairmanship of Dr. George E. Burch, to stimulate, review, and make recommendations regarding grant requests.

This committee has recommended and the council has approved 6 research grants, 2 with supplements, in the prescribed subject area, committing $70,840.

### NIMH Projects

The National Institute of Mental Health has joined with the Health Emergency Planning Unit of the Office of the Surgeon General, the Division of General Health Services of the Bureau of State Services, and the Army Chemical Corps in a cooperative study of the impact of influenza epidemics on community life.

The mental health and health educational authorities are interested in ascertaining group behavior, panic reactions, individual and mass motivations in the face of severe epidemics, and the capability under these conditions of the local government and voluntary groups of adapting their activities to cope effectively with the situation. The emergency planners want to determine the special health needs which must be met during unsuppressed outbreaks of disease, and the Army Chemical Corps is interested in ascertaining the levels of disability and absenteeism at which essential community services fail.

It is planned to hold periodic interviews with members of randomized samples of households in 3 cities of about 50,000 population in Pennsylvania and 2 more in North Carolina. Initial baseline data have already been obtained. Special contacts will be maintained with community health personnel, including physicians, nurses, and pharmacists as well as local health department representatives. The study will include similar consideration of transportation, communication, police and fire protection, school and industrial absenteeism, industrial

productivity and costs during epidemic conditions, accident rates and other circumstances and events reflective of the stresses, failures, and compensatory counteractions which occur during epidemics.

The National Institute of Mental Health has made a grant of $50,000 to a professional information-collecting agency which is conducting the weekly family interviews. Another $50,000 has been contributed by the Army Chemical Corps to help defray the costs of this research. Professional skills and services valued at $35,000 are being supplied by the Bureau of State Services for the direction, coordination, and analysis of this study.

### Study of Vaccination Results

From September 3 to October 26, the Employee Health Service Branch at the Clinical Center of the National Institutes of Health offered Asian strain influenza vaccine to employees of the Institutes desiring vaccination.

Careful individual records have been maintained of the manufacturer, lot number, and concentration of the vaccine administered to each person. From subsequent reports of reactions, absenteeism, and the occurrence of influenza-like illness, it is hoped that information will be obtained on the frequency and severity of reactions and the relative effectiveness of the two concentrations of the vaccine in preventing lost work days due to influenza.

Some 6,000 adults of both sexes are involved, about 4,000 of whom were vaccinated subcutaneously at the Employee Health Service with material containing 200 or 500 CCA units. The nonvaccinated group is being sampled to determine the proportion vaccinated outside the clinical center. If this number is sizable, a survey will be made to separate the vaccinated from the nonvaccinated employees.

### NINDB Projects

Knowledge of the well-established etiological role of certain filtrable agents, such as rubella and salivary gland virus, in congenital defects and abnormalities, led the National Institute of Neurological Diseases and Blindness to consider supporting extramural studies to determine whether or not influenza virus also may cause prenatal anomalies, especially of a neuropathic type. On November 16, 1957, a meeting of advisers was held at the National Institutes of Health to discuss plans and procedures for testing this hypothesis.

The group recommended that pregnancies be followed at large obstetrical services to find out whether prenatal abnormality rates were significantly higher if influenza occurred during pregnancy, especially in the first trimester. It was assumed that evidence of prenatal abnormality, including abortion, stillbirth, and fetal and neonatal malformations and anomalies, would be provided by the attending obstetricians, pathologists, and pediatricians. It was concluded that diagnoses of influenza could be made satisfactorily on the basis of standardized serologic tests supported by clinical evidence and certain knowledge that influenza was epidemic in the community when the respiratory illness occurred. The group advised that serum specimens be obtained from the pregnant women at least at registration or the first prenatal visit, at delivery, and, desirably, shortly after convalescence from any upper respiratory episode with fever. Conclusions regarding valid associations of influenza and prenatal anomalies would be based on carefully controlled statistical correlations.

In order to simplify and expedite supplementary financing for this study, it was agreed that these observations should be made, as far as feasible, at the five hospitals where NINDB cerebral palsy project collaborative studies are being made. Other institutions may be invited to cooperate later if additional data are required. The institute will act as the collecting and coordinating agency in handling and analyzing the pooled data.

Support of these studies is expected to be by contract during the initial phase of the project, later by research grants if feasible and indicated. Initiating expenses will probably not exceed $50,000. A large proportion of the total costs will be borne by the cerebral palsy project, of which these investigations are an integral part.

### Research Committee Contributions

The Public Health Service Influenza Research Committee was established on September

26, 1957, in response to a recommendation made to the Surgeon General by the State and Territorial health officers at the special conference on influenza held August 27–28. The committee chairman is Dr. Colin M. MacLeod and there are 14 members. The purposes of this committee are (*a*) to review influenza research conducted or supported by the Public Health Service and other Federal organizations, (*b*) to identify areas where current research on influenza is lacking or deficient, and to make recommendations regarding more adequate coverage, and (*c*) to act in a liaison capacity between influenza research workers in or supported by the Public Health Service and those in or supported by other Federal agencies.

At its first meeting, held September 27, 1957, the committee heard and discussed detailed reports of various representatives of groups engaged in or planning research on influenza in 1957–58. On the basis of these presentations, the committee was able to identify areas of subjects in which more work should be undertaken. These included (*a*) the standardization of hemagglutination inhibition test reporting and methods of determining CCA values of vaccine, (*b*) assessment of the stability of Asian influenza vaccines in terms of CCA unit values, (*c*) animal tests for the antigenicity of these vaccines, (*d*) the efficacy of intracutaneous vaccination, (*e*) data concerning bacterial complications, especially staphylococcal, (*f*) clinical management of influenza patients with complicating infections or conditions, (*g*) controlled studies of Asian strain vaccination in patients with chronic pulmonary and cardiac diseases, (*h*) possible use of attenuated live virus influenza vaccines, (*i*) effectiveness of available vaccines in protecting against natural infection with Asian influenza virus, and (*j*) problems of vaccinating children against this strain of influenza.

The committee recommended that (*a*) the Public Health Service make adequate funds available as soon as possible to collaborating, nongovernmental laboratories for utilizing their resources in a collaborative study on epidemic influenza on a nationwide basis, (*b*) the National Institute of Allergy and Infectious Diseases use remaining reserved influenza research grant funds for studying staphylococcal complications of influenza, and (*c*) the Communicable Disease Center supply on request information concerning laboratories in the United States willing and able to provide reference staphylococcal typing service.

A Subcommittee on Therapy and Management of Asian Influenza and Its Complications was formed with Dr. George E. Burch as chairman. This was co-sponsored by the American Medical Association through its Committee on Influenza. A meeting of the subcommittee was held in New Orleans on October 29, 1957. The extent and pattern of the epidemic and of associated mortality was reviewed. Information was presented and discussed concerning the more common clinical manifestations and serious complications. The following recommendations were made and transmitted to the Public Health Service Committee on Influenza Research:

1. High-risk influenza patients—that is, those with chronic cardiac or pulmonary disease, persons over 60, and pregnant women—should receive prompt and adequate therapy at the first sign of influenza.

2. Grants should be stimulated for controlled studies to evaluate in high-risk patients the prophylactic administration of antibiotics (erythromycin and chloramphenicol advocated) or other chemotherapeutic agents to prevent complicating bacterial pneumonia.

3. An ad hoc committee should be appointed on pneumonia and deaths associated with Asian influenza to establish standard clinical, microbiological, and pathological criteria for determining influenza association, etiology of pneumonia, and cause of death, and to compile the results of applying these criteria during the current epidemic year.

4. Numerous small clinical studies should be made of the pathological physiology, course, and management of Asian influenza.

5. Serious consideration and long-term support should be given to research on the acute infections in people of middle age or over, studies being made to determine physiological and biochemical alterations to be derived therefrom.

The committee emphasized need for thorough and early diagnostic procedures, particularly chest X-rays, in persons presenting pro-

longed and complicated courses following influenza.


REFERENCES

(1) Vogel, J., and Shelokov, A. I.: Adsorption-hemagglutination test for influenza virus in monkey tissue culture. Science 126: 358–359, Aug. 23, 1957.

(2) Bell, J. A., Ward, T. G., Kapikian, A. Z., Shelokov, A. I., Reichelderfer, T. E., and Heubner, R. J.: Artificially induced Asian influenza in vaccinated and unvaccinated volunteers. J. A. M. A. 165: 1366–1377, Nov. 16, 1957.


# films

## "For the Nation's Health"

**16-mm. filmograph, color, sound, 15 minutes. 1957.**

**Audience: Personnel in the health, medical, and allied professions, students, parents, teachers, counselors, civic groups, and the general public.**

This Public Health Service orientation film presents a panoramic view of the activities of the principal health agency of the Federal Government. Combining photographs and motion picture film, it shows the growth of the Public Health Service from its inception in 1798, with limited care of sick and stranded merchant seamen, to its farflung programs today in hospital and medical care, in medical and biological research, and in public health.

Physicians, nurses, dentists, sanitary engineers, pharmacists, veterinarians, and a host of other skilled specialists are shown at work at home and abroad.

In Public Health Service hospitals and clinics, in well-equipped laboratories, on Indian reservations and other field assignments, and on Coast Guard duty, the range and variety of the work of the Public Health Service rarely fails to arouse interest.

Public Health Service personnel have been notified that the film is available to them, principally for training and orientation purposes, through the Communicable Disease Center, Public Health Service, 50 7th Street NE., Atlanta 5, Ga.

Others interested and Service personnel also may order the film on a short-term loan from the Surgeon General, Public Health Service (P), Washington 25, D. C. The filmograph may be purchased from Byron, Inc., 1226 Wisconsin Avenue, Washington 7, D. C. Cost of the print, $62.07, includes reel can, shipping case, and service charge.

## Backsiphonage and Cross Connections: An Introduction

**35-mm. filmstrip, color, sound, 11 minutes, 75 frames, 1957.**

**Audience: Sanitarian trainees and other public health personnel, including food handlers, and custodial and dining car personnel.**

Many plumbing systems suffer from defects in design and installation. Backsiphonage and cross connections, two such defects, are both potential sources of waterborne disease epidemics.

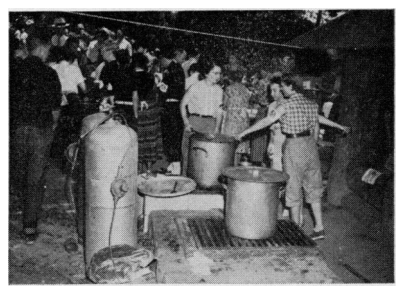
This series of graphics, cleared for television, illustrates the significance to public health of backisphonage and cross connections, tells how to identify the basic causes, and shows the methods of prevention. It surveys the major situation in which the two defects occur.

This filmstrip may be obtained on loan from the Communicable Disease Center, Public Health Service, 50 7th Street NE., Atlanta 5, Ga., or by purchase from United World Films, Inc., 1445 Park Avenue, New York 29, N. Y.

## Public Health Problems In Mass Evacuation

**16-mm. film, black and white, sound, 13 minutes, 462 feet. 1957.**

**Audience: Civil defense trainees in all phases of public health, schools, PTA groups, civic club members, and television viewers.**



**Mass feeding of evacuees poses serious public health problems**

This motion picture showing public health problems attending the mass evacuation of an urban population emphasizes the magnitude of such problems as mass feeding, water supply, medical care, waste and sewage disposal, consequent disease outbreaks. Its objective is the motivation of discussion rather than the solving of problems.

This film may be obtained on loan from the Communicable Disease Center, Public Health Service, 50 7th Street NE., Atlanta 5, Ga., or by purchase from United World Films, Inc., 1445 Park Avenue, New York 29, N. Y.