Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Epidemic Influenza

Volume XV | Friday, March 10, 1944 | Number 19

STAFF MEETING BULLETIN
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Volume XV | Friday, March 10, 1944 | Number 19

INDEX

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
March 13 - March 18

Visitors Welcome

Monday, March 13

9:00 - 10:00 Roentgenology Medicine Conference; L. G. Rigler, C. J. Watson and Staff, Todd Amphitheater, U.H.

9:00 - 11:00 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Interns Quarters, U.H.

12:30 - 1:30 Pediatrics Seminar; Tetanus Prevention and Treatment; E. P. Crump; W-205 U.H.

12:30 - 1:30 Pathology Seminar; Hemoglobinuria; E. Flink, 104 I.A.

Tuesday, March 14

8:00 - 9:00 Surgery Journal Club; O. H. Wangensteen and Staff, Main 515, U.H.

9:00 - 10:00 Roentgenology-Pediatrics Conference; L. G. Rigler, I. McQuarrie and Staff, Eustis Amphitheater, U.H.

11:00 - 12:00 Urology Conference; C. D. Creevy and Staff, Main 515, U.H.

12:30 - 1:30 Pathology Conference; Autopsies; Pathology Staff, 104 I. A.

4:30 - 5:30 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff, Station 54, U. H.

4:00 - 5:00 Pediatrics Grand Rounds; I. McQuarrie and Staff, W-205 U.H.

5:00 - 6:00 Roentgen Diagnosis Conference; A.T. Stenstrom, M-515 U.H.

Wednesday, March 15

9:00 - 11:00 Neuropsychiatry Seminar; Please arrange with department for attendance at these exercises; J. C. McKinley and Staff, Station 60, Lounge U. H.

10:30 - 12:00 Otolaryngology Case Studies; Out Patient Ear, Nose and Throat Department; L. R. Boies and Staff.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; Refractory Anemia; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff, Todd Amphitheater, U. H.

4:00 - 5:00 Obstetrics and Gynecology Journal Club; J. L. McKelvey and Staff; Station 54, U. H.

Thursday, March 16

9:00 - 10:00 Medicine Case Presentation; C. J. Watson and Staff, Todd Amphitheater U. H.

10:00 - 12:00 Medicine Rounds; C. J. Watson and Staff, East 214 U. H.

12:30 - 1:30 Physiological Chemistry Seminar; Oral and Dental Biochemistry; W. D. Armstrong, 116 M. H.

5:00 - 6:00 Roentgenology Seminar; Radiation Necrosis of Bone; T. B. Merner; M-515 U. H.

Friday, March 17

9:00 - 10:00 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

8:30 - 10:00 Pediatrics Grand Rounds; I. McQuarrie and Staff

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff; East 214 U.H.

1:30 - 2:30 Medicine Case Presentation; C. J. Watson and Staff; Eustis Amphitheater.

1:00 - 2:30 Dermatology and Syphilology; Presentation of selected cases of the week; Henry E. Michelson and Staff; W-306 U.H.

1:30 - 3:00 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff, Todd Amphitheater, U. H.

Saturday, March 18

9:00 - 10:00 Medicine Case Presentation, C. J. Watson and Staff, Main 515 U. H.

9:15 - 11:30 Surgery-Roentgenology Conference; O. H. Wangensteen, L. C. Rigler and Staff, Todd Amphitheater, U. H.

10:00 - 12:00 Medicine Ward Rounds; C. J. Watson and Staff, E-214 U. H.

II. EPIDEMIC INFLUENZA
With Reference to the Virus Etiology

E. R. Rickard

The beginning of a discussion of epidemic influenza almost automatically turns to the great influenza pandemic of 1918. Although previous pandemics of similar illness have been recorded (1), the morbidity and mortality associated with the scourge which occurred at the close of World War I have left a very deep impression on the mind of the public in all parts of the civilized world.

During 1918, and in the years immediately succeeding, in spite of most competent investigation, the etiological agent responsible for the pandemic was not demonstrated. One school of thought argued that the Pfeiffer's bacillus, the Hemophilus influenzae, was the causative organism. Today this infectious agent is known to be associated with certain types pneumonia and meningitis (2). It would seem reasonable to presume that during 1918, the Hemophilus influenzae may have been the cause of some of the pneumonias secondary to influenzal infection. Other investigators believed that primary infection was due to a filterable virus. To prove this point, apparently normal human volunteers were inoculated with naso-pharyngeal washings taken from persons ill with influenza (1,3,4). These experiements were negative. For many reasons, man himself is not always the best experimental animal. Particularly during epidemics of diseases of undetermined etiology, the selection of known non-immune subjects may be a problem of no easy solution.

Demonstration of the Virus Etiology of Epidemic Influenza

In 1933, a group of English investigators who were using the ferret as an experiment animal in the study of canine distemper, made the important observation that if ferrets were inoculated intranasally with nasopharyngeal washings from patients ill during epidemics of influenza, a disease similar to human influenza was produced in the ferrets so inoculated (5). The disease could be passed in series from ferret to ferret by subinoculation of lung and turbinate suspensions from the infected animals. Likewise, this same serial passage could be accomplished, if the inocula were passed through filters capable of retaining all microscopically visible forms of life.

This same group of investigators observed that if suspensions of infected ferret lungs and turbinates were given intranasally to mice under light either anesthesia and if serial passage were done, a fatal, bacterially sterile, interstitial, pneumonia could be produced in the mice (6). By mixing the immune serum of ferrets or men recovered from influenza infection with the infectious material the virus could be neutralized and the mice protected from lung lesions or death. These neutralization tests were later perfected by using serial dilutions of serum with a constant number of infectious units of virus (7). By this means it was possible to demonstrate a definite increase in the neutralizing capacities of the sera of ferrets or men taken early in the course of infection as compared to the neutralizing capacities of sera of the same individuals taken two or three weeks after onset of illness. These findings served as good evidence that the infectious agent causing illness in ferrets was the same which had caused illness in men, rather than some adventitious agent accidently harbored by the ferrets themselves. Moreover, the demonstration of an increase of titer of neutralizing antibodies in the acute and convalescent phase serum specimens of patients ill with clinical influenza has served as a reliable diagnostic test for the etiological agent responsible for th illness (8).

Neutralizing Antibodies in Human Sera

Studies of levels of neutralizing antibodies in the sera of the general population during intervals when influenza was not epidemic (9,10) have revealed that almost all individuals possess at least some of these substances in their

sera. Titers vary greatly from one individual to another, but any given individual's titer tends to remain relatively constant over considerable periods of time (10). Studies have been made of the relationship of neutralizing antibody levels and immunity to infection with influenza virus. These studies have indicated that while low antibody titers and susceptibility are correlated, high antibody levels are not an absolute guarantee of immunity (10,11,12,13,14). Cases of influenza, characterized by the typical clinical and epidemiological syndrome and confirmed by the demonstration of significant increases in antibody titers, have been observed in individuals possessing pre-infection antibody levels considerably higher than other individuals have been found to possess immediately following infection (10).

By the study of the pre- and post-epidemic levels of persons who have passed through influenza epidemics, but who give no history of illness, subclinical infections with influenza virus have been demonstrated to be very common (11). In one community epidemic, the numbers of subclinical and clinical cases were equal (10). Moreover, there was no great variation between the pre-epidemic antibody levels noted among individuals who had experienced a clinical illness and those who evidently had been infected but had not become ill. This finding would indicate that pre-infection antibody levels and severity of illness were not closely related.

Duration of Immunity

Considerable study has been given to the determination of the length of immunity conferred by one attack of influenza. All available evidence suggests that this immunity is of relatively short duration. Although there is great variation in individual antibody response, the sera of most persons infected with influenza virus reach their maximum neutralizing antibody titers at approximately two weeks from the day of onset of illness. From there on there is a progressive decrease in titer which likewise varies greatly in different individuals but in a given community tends to return to the pre-epidemic period at the end of approximately two years (10). Second clinical attacks of influenza, as proved by significant antibody responses, have been reported in the same individuals at the end of a two-year interval (15). These observations tend to explain the apparent approximate two-year periodicity of influenza of the type under discussion. This periodicity has been noted with but few exceptions during the past decade during which the virus has been recognized.

Characteristics of the Virus and Mechanism of Immunity

Influenza virus is highly pneumotropic in nature. Unless inoculation is done with overwhelming doses (16), infection may only be produced by introducing the virus into the respiratory system.

The inoculation of fully active influenza virus parenterally in ordinary doses into mice, ferrets, or men does not result in the infection of any of these subjects; rather an increase in neutralizing antibodies is almost always produced. Virus from a number of sources may be used for the production of neutralizing antibodies. That produced in infected mouse or ferret lungs or that grown tissue cultures of living chick tissues or in the developing chick embryo all have been successfully employed for this purpose (17 to 27 incl.). Likewise it has been found that virus inactivated by heat or chemicals is as good an antigen as living virus (28). The antibody response produced varies roughly with the amount of virus given. As in the case of natural infection with the virus, antibodies produced by parenteral inoculation reach their peak at approximately 15 days following inoculation and then begin to decline. Also, as in natural infection, there is considerable individual variation in antibody production and antibody loss. Nevertheless, in the study of the sera of a group of 43 subjects who had received a highly concentrated

vaccine which had produced an 11 times average increase in neutralizing antibody level at 15 days following inoculation, it was found that at the end of 5 months the average titer of the group had fallen to only 3 times the average pre-vaccination level (28).

In considering the mechanism of immunity of influenza it must be born in mind that the virus has opportunity to alight directly upon the susceptible cells without having to traverse the blood stream which may be charged with virucidal substances as in the case of persons immune to yellow fever or equine encephalomyelitis. Francis (29) has observed that the nasal secretions of most individuals contain substances lethal to the virus of influenza. These inactivating substances appear to be identical to neutralizing antibodies found in the sera. The titers of the substances are correlated in a rough way to the titers of neutralizing antibodies in the same patients' sera (30). It would not seem unreasonable to believe that measures aimed at increasing the titer of the nasal inactivating substances might be more effective in preventing influenza than those which result in an increase of titer of neutralizing antibodies in the blood stream.

Influenza A and Influenza B

In 1940, two independent workers (31,32) discovered simultaneously another type of influenza virus. This second virus, which was obtained from cases of typical influenza occurring in frank epidemics, affected laboratory animals in a manner almost identical to the virus discovered in 1933. Nevertheless, the viruses were antigenically completely distinct. Animals immune to one type of virus were fully susceptible to the other and human beings whose sera showed increases in specific antibodies because of infection with one of the viruses showed no such increases when tested against the other virus (33). For clarity of terminology, it was suggested that the virus discovered in 1933 be called influenza A and that isolated in 1940, influenza B (34).

Although less time has been available for the study of influenza B virus than of influenza A, there are many indications that the two entities are remarkably similar in the clinical and epidemiological picture produced, in the production of specific antibodies, in pathogenesis, and mechanism of immunity. Influenza B virus has been established as the etiological agent in epidemics in California during 1936, in Minnesota during 1939 (35) and in North Carolina during 1940 (13). The etiology of these epidemics was demonstrated in retrospect by the examination of preserved naso-pharyngeal washings and serum specimens. During the summer of 1940, influenza A and B were observed and diagnosed occurring concurrently in Havana, Cuba (13).

Swine Influenza

In 1931, Shope (36) demonstrated that pigs were affected with a disease called swine influenza, which was quite similar to the human disease. The disease of pigs was remarkable in that the true clinical and epidemiological picture was produced by a filterable virus acting in synergism with a bacterial agent. The virus produced only a mild febrile reaction when inoculated alone. When inoculated together with the Hemophilus influenzae suis (37), the swine influenza virus produced a more severe disease with pneumonia which sometimes resulted fatally.

Swine influenza virus is closely related antigenically to influenza A virus. Infections in human beings with influenza A virus results in an increase in antibodies to swine influenza virus (11,38). Study of antibodies against swine influenza in the sera of the general population has revealed that almost all adults possess some of these antibodies (39). There has been no demonstrated instances, however, of the isolation of swine influenza virus from cases of influenza occurring in human beings. It would seem quite reasonable to presume, therefore, that swine influenza antibodies found in human sera

are present as a result of overlapping antigencity of the swine and influenza A viruses.

Influenza Viruses in the Developing Chick Embryo

All of the known influenza viruses grow readily in the developing chick embryo. In 1940, Hirst (40) made the important observation that influenza viruses, A, B, or swine, when mixed with avian red blood cells caused an agglutination of these cells. The mixture of specific immune serum with the virus-cell combination caused an inhibition of this agglutination. From these phenomena it has been possible to perfect agglutination-inhibition tests (41) as a substitute for the more time consuming and expensive neutralization tests done in mice.

Another important recent observation has been the discovery that influenza A virus could be isolated by direct intra-embryonic inoculation of filtered throat washings in fertile eggs (42). The avian red blood cell agglutination phenomenon is used as an indicator of the presence of virus. It has been found in the Influenza Laboratory of the Minnesota Department of Health that throat washings need not be filtered to permit direct embryonated egg inoculation and that the simple intra-allantoic route of inoculation serves as well as the intra-embryonic (44). By this latter precedure, it was possible to isolate and identify influenza A virus during the recent influenza epidemic on the University Campus from the naso-pharyngeal washings of patients within 48 hours after the observation of the first cases in the epidemic (43).

Clinical Picture of Influenza A and Influenza B

The clinical picture of influenza A, and that of influenza B as far as we know it, is that of a rather mild disease of short duration with relatively few complications. The onset is generally sudden with chills or chilliness, fever of from 101 to 103, headache, body pains and malaise. Upper respiratory symptoms do not predominate, but mild sore throat and dry cough may be frequent symptoms. With the exception of a slightly infected throat, physical findings are generally negative. Leucopoenia, commonly observed in certain virus diseases, is not a characteristic of influenza (11). The blood picture might be described as a lack of leucocytosis in the presence of fever. The course is generally from 2 to 4 days with rapid defervescence of fever following rest in bed (11,12).

Epidemilogy

Influenza A, and influenza B as far as the latter disease has been observed, are characterized by sharp epidemics. Attack rates vary greatly in different units of the population. Rates as low as 2 or 3 per cent to as high as 38 per cent (45) have been recorded. Institutional outbreaks are often very explosive, sometimes being over within 14 days (52). In any given community the epidemic will generally pass in a period of from 4 to 6 weeks. Apparently, persons accustomed to living dispersedly are considerably more susceptible to infection when brought into crowded environments than those already accustomed to these environments.

Influenza at these latitudes is characteristically a disease of the colder seasons. The same holds true of the southern hemisphere (46). There, however, due to reversal of seasons, the epidemics may be at their height during the quiescent period in the northern hemisphere. Influenza epidemics of both types A and B have been observed in the subtropics during the hottests, most humid seasons (13,47).

During later November and December, 1943, a widespread epidemic of influenza occurred in Minneapolis as part of a similar epidemic which affected the entire United States. Clinical observation revealed that this epidemic was of the same mild clinical nature and explosive character (45) which have been typical of Influenza A during the past several years. Examination by the agglutination-inhibition test of 335

pairs of acute and convalescent phase serum specimens taken during the epidemic in Minneapolis and various other Midwestern localities has revealed that approximately 73 per cent of the paired serum specimens showed significant antibody increases to influenza A virus (52). The same specimens tested against influenza B virus showed no significant increases in antibodies. Influenza A virus has been isolated and identified from a considerable number of naso-pharyngeal washings obtained in this epidemic.

Prevention of Influenza

The control of influenza is one of the health officer's most difficult problems. In consideration of the high percentage of subclinical cases, the futility of isolation or of the quarantine in preventing the spread of the disease becomes apparent. Prohibition of unnecessary public meetings probably would never control an epidemic, but might conceivably slow down the spread.

Masks were used extensively during the 1918 influenza pandemic. It would seem possible that properly constructed and properly used masks might be of some benefit. Here, however, we must deal with the human factor of forgetfulness or carelessness. The high infectivity of virus diseases in the susceptible host also must be considered. Moreover, it should be remembered that the conjunctival sacks are in direct communication with the respiratory passages. Therefore, masks that do not cover the eyes as well as the nose and mouth cannot be considered to afford complete protection to the entrance of material highly infectious to the respiratory organs.

Various air sprays (aerosols) have been proposed for the control of influenza in limited populations such as those of hospitals, barracks, etc. Experimental work has indicated that these agents are effective in controlling infection in laboratory animals (48). If aerosols are proved to be of value in the control of human infection, the administrative difficulties inherent to sterilizing the air in all places where mankind might congregate during influenza epidemics would seem to be apparent.

Animal experimentation has indicated that the parenteral administration of immune serum in practicable doses is of little value in preventing influenza or modifying the disease. In view of what is known of the neutralizing antibodies already contained in the serum of persons who contract influenza, there would be little reason to expect that the administration of small additional amounts of antibody would appreciably alter the course of events. Experiments on the administration of immune sera intranasally to laboratory animals before inoculation with influenza virus have demonstrated that infection may be prevented or considerably modified by this means (49). The literature contains one report of a reduction in attack rates by approximately 90 per cent among human volunteers so treated as compared to untreated controls passing through the same epidemic. This method of prophylaxis would seem worthy of further trial in human beings (50).

The most extensively studied measure for the prevention of influenza has been active immunization by the parenteral administration of influenza A or combined influenza A and B viruses. From what has preceeded it is obvious that this method of immunization has several practical limitations. Antibody titers following parenteral administration of influenza virus do not reach their maximum until approximately 2 weeks after immunization. In dealing with an explosively epidemic disease this fact may prevent the effective immunization of any community until the epidemic has passed its peak. On the other hand, antibody titers following artificial immunization are relatively evanescent and last only a few months. It would follow that in order to afford protection to any group immunization should take place shortly before the expected epidemic season. Although considerable knowledge has been accumulated in regard the periodicity of influenza A, epidemic waves of this disease in any given region are still

not entirely predictable. As yet, very little is known of the periodicity of influenza B.

Up until very recently the results of all experimental trials of influenza vaccination in human beings under natural conditions of infection had been negative or, at the best, of equivocal interpretation (17 to 25 incl.). During the recent influenza A epidemic Commission of the Board for the Investigation of Epidemic Diseases in the United States Army demonstrated conclusively that influenzal vaccines given shortly before an epidemic of influenza A are effective in preventing that disease (51). Approximately 6000 individuals in different parts of the country were inoculated with a combined influenza A and B vaccine during November, 1943, and an equal number of persons living under identical conditions were given injections of inert material to serve as controls. Epidemics of influenza A appeared in all the units vaccinated, in most instances at approximately two weeks following the administration of the vaccine. The general attack rate among the controls was 7.22 %; among vaccinated, 2.22. This represented a reduction of 70% in case incidence of vaccinated as compared to controls. Among the 1200 students at the University of Minnesota who took part in this study, almost an identical reduction in attack rate was noted.

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III. EDITORIAL

When A University Needs A Friend*

The University of Minnesota has just passed through an acute episode which bears some resemblance to an intestinal obstruction. There has been fecal vomiting and severe colic, but the patient appears now to be on the road to recovery. However, the danger of recurrence is very real, and major surgery may be required if the trouble recurs.

The recent strike of non-academic employees at the University of Minnesota is an evidence of a deep-seated disturbance which cannot be passed off as simply another evidence of the irresponsibility of labor groups. The work stoppage in the University Hospitals was unpardonable, and there is much doubt as to whether any strike against the State is legitimate. But neither of those questions negates the fact that the wages of many University employees are too low and that their hours of service are in many instances unusually high. The basic difficulties have not yet been settled.

The physicians of Minnesota and the Northwest have two grounds for interest in the present University situation: first, they have a right to concern themselves about the disruption of hospital service to sick people; and second, they are vitally concerned in the maintenance of a high calibre medical school in this region. Therefore, even the conditions of labor of the non-academic employees in the University of Minnesota are not outside their sphere of personal interest.

Aside from unfortunate attitudes toward the personnel problem, the major fundamental difficulty at the University of Minnesota is a shortage of funds to do its job. The State appropriation for the maintenance of its University is just a little more than half of the appropriation made by other States for the support of universities of comparable size. One of three things must happen at the University of Minnesota. Either it must give up its attempt to do high quality work and let its more valuable staff members go, thus lowering its academic staff budget costs, or it must sharply limit its enrollment, denying a college education to many properly qualified, intelligent young people in the State who desire it, or it must obtain additional funds for support. There are no other possibilities.

To adopt the first of the three alternatives would be to abandon the whole purpose of a University. To adopt the second would be a denial of one of the major premises of a democracy. One is left only with the alternative necessity of finding more funds for support.

A great University is not a luxury. It is a sina qua non for survival of the people. About 0.2 per cent of the total income of the people of the State of Minnesota now goes for public higher education. In these terms it appears to be but a pittance compared with its value to the State. Less than 0.02 per cent goes into medical education, education which supplies much more than half of the physicians of the State. The great question which physicians and other friends of the people of the State of Minnesota must answer is whether they can honestly tolerate spending so little on the greatest investment any community can make, the education of the coming generation for service and progress.

Education is a capital investment. It is the greatest capital investment a community can make for its people. It pays dividends in healthier, happier, fuller lives.

The University of Minnesota is at a turning point. It needs friends, friends who will make it their business to help prevent the deterioration that is certain unless positive leadership turns the tide that is now running it towards its ruin. It needs friends who will help it to double its currently available funds for support.

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