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

Influenza A
In Infants and Children

Volume XVII | Friday, February 15, 1946 | Number 14

STAFF MEETING BULLETIN
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INDEX

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William A. O'Brien, M.D.

I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS
Feb. 16 - Feb. 22, 1946
Medical Visitors Welcome

No. 102

Saturdaya Feb. 16

9:00 - 9:50 Pediatrics Grand Rounds; I. McQuarrie and Staff; W-205 U. H.

9:15 - 10:20 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, and Staff; Todd Amphitheater, U. H.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-515 U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

11:30 - 12:20 Anatomy Seminar; Reaction of Injured Cells to Vital Dyes; W. L. Williams; I.A. 226.

Sunday, Feb. 17

11:00 - 1:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

Monday, Feb. 18

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns Quarters, U. H.

12:15 - 1:15 Pediatrics Seminar; Irvine McQuarrie and Staff; 6th Floor Eustis.

12:15 - 1:15 Obstetrics and Gynecology Journal Club; M-435, U. H.

12:30 - 1:20 Pathology Seminar; Cystic Tumors of the Jaw; Dr. Donald Peterson; 104 I. A.

12:30 - 1:20 Physiology Seminar; Inanition Edema; Dr. Ancel Keys; 214 M. H.

4:00 - School of Public Health Seminar; Study of Public Health Nursing Case Loads; Miss Isadora Denike; 6th Floor Student Health Service Bldg., Women's Lounge.

Tuesday, Feb. 19

9:00 - 9:50 Roentgenology-Pediatrics Conference; Solveig Bergh; Stanley Peterson, and Thomas Morner; Eustis Amphitheater, U. H.

3:15 - 4:15 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

4:00 - 4:50 Surgery-Physiology Conference; Operations Involving Whole Blood and Blood Substitutes; Eustis Amphitheater.

8:00 - Minnesota Pathologic Society; Medical Science Amphitheater.

Wednesday, Feb. 20

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515 U. H.

9:00 - 10:30 Pediatrics Staff Rounds; W-205 U. H.

9:00 - 10:50 Neuropsychiatry Seminar; Staff; Station 60 Lounge, U. H.

11:00 - 11:50 Pathology-Medicine-Surgery Conference; Gastric Carcinoma; E. T. Bell, C. J. Watson, O. H. Wangensteen and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Physiology Chemistry Journal Club; Staff; 116 M. H.

4:00 - 6:00 Medicine and Pediatrics Infectious Disease Rounds; W-205 U. H.

Thursday, Feb. 21

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.

12:30 - 1:20 Physiological Chemistry; Cyrus P. Barnum; 116 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling Hansen and Staff; E-534, U. H.

4:30 - Bacteriology Seminar; Rabbit Papilloma; Robert Fischer; 214 M. H.

5:00 - 5:50 Roentgenology Seminar; Hodgkin's Disease; T. B. Merner, M-515 U. H.

Friday, Feb. 22 - Holiday

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221 U. H.

10:30 - 12:20 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Otolaryngology Department; U. H.

1:00 - 2:00 Dermatologic Allergy; Dr. Stepan Epstein; W-312 U. H.

2:00 - 3:20 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312 U. H.

1:30 - 2:20 Roentgenology-Neurosurgery Conference; H. O. Peterson, W. T. Peyton, and Staff; Todd Amphitheater, U. H.

II. INFLUENZA A IN INFANTS AND CHILDREN

John M. Adams

Introduction

Influenza is an epidemic virus disease, highly communicable, which primarily affects the respiratory passages. Epidemics of influenza A are now established as occurring at fairly regular intervals of two or three years, usually beginning in the late fall or winter months. The last few epidemics of influenza B have occurred at approximately four year intervals. It is important to recognize this fact as the diagnosis of influenza should not be made except during an epidemic. Its sporadic incidence is known to be rare.

Pandemic influenza still remains as a great threat to the world. Newman estimated 22 million deaths and approximately 500 million additional persons were attacked in a period of about 3 months in the last great pandemic of 1918.[1] Pandemics usually occur in 3 waves, of about 6 weeks each, separated by an interval of a few months. The outbreaks are sharp in character and end almost as abruptly. This is also characteristic of single epidemics of influenza.

The method of spread is still fairly obscure. During the pandemics of 1789-90, its simultaneous appearance in several isolated spots on land and sea is recorded. In 1917-18 it was considered to be spread by direct contact. Air-borne spread has been shown to occur experimentally. Loosli and co-workers[2] have demonstrated that the relative humidity of the air greatly influences the persistence of the influenza virus, the lower the humidity the longer the virus is present. Its persistence in the air at a high relative humidity is greatly reduced. These same workers have studied the air-sterilizing activity of propylene and triethylene glycol and have shown them to be very effective against the influenza virus. Studies such as these should prove helpful in the control of epidemics of influenza in the future.

Since the discovery of the virus in 1933, a great volume of literature has accumulated. It can be readily propagated in the embryonated chicken egg. By means of the ultra centrifuge and electron microscope, many of its characteristics are being identified. The size of the influenza A virus is about 80 mμ particle-diameter as shown by the electron microscope. Chemically the virus consists of lipoprotein-carbohydrate complexes containing nucleic acid of the desoxypentose type.[3]

Hirst[4] discovered that influenza A and B viruses would agglutinate chickens' red cells. This fact has greatly aided the diagnosis of influenza in the laboratory as the serum causes a direct inhibition of the phenomenon and quantitative titers can thus be determined readily.

Rickard and his associates[5] found that unfiltered throat washings could be inoculated directly into embryonated eggs and the virus identified by the aid of the Hirst test in the allantoic fluid of the incubated egg.

An epidemic of Influenza A occurring among infants and children in the University of Minnesota Hospitals in November and December, 1943, was studied; the laboratory investigations were done in the Influenza Laboratory of the State Board of Health. Doctors E. R. Rickard and M.P. Thigpen were co-workers in this study. The diagnosis was made by isolating influenza A virus directly from unfiltered throat washings inoculated intra-allantoically in the developing chick embryo. Further confirmation of the diagnosis was accomplished by demonstrating a significant increase in specific neutralizing antibodies in the patients' serums as measured by the hemagglutinin-inhibition test.

Epidemiology

The last known epidemic prior to this study occurred in Minneapolis in the winter of 1940-41. The first case in the present epidemic was recognized in the pediatric wards of the University Hospitals on November 25, 1943. This indicates an interim of approximately 3 years between epidemics, which is of special interest in connection with the

present study because we can be reasonably sure that infants under 3 years of age are having their first experience with the disease. We know of no reports on the study of quantitative antibody response of infants who have recently experienced their first infection with influenza virus.

A special effort was made, therefore, to study infants under 3 years of age. All children 10 years of age or below were included in the series, however. With few exceptions, throat washings for virus identification were taken, and specimens of serums for antibody determinations were obtained early in the illness and again at 2 to 3 week intervals after the onset of the disease. Throat cultures and blood counts were done routinely.

The epidemic lasted from November 25 to December 17. There were 24 cases under 11 years of age with an attack rate of a little less than 50 per cent.

Clinical Observations

The onset of the disease was sudden in nearly all cases. An unusual opportunity was presented to observe this, as nearly all the patients were already in the hospital and under care for other conditions at the time of onset of their influenza.

A biphasic or irregular fever curve was noted in two thirds of the cases, and only the milder cases appeared to show the usual "three day fever" which is considered characteristic of the disease among patients without complications. In general, the clinical course and severity of symptoms was the same in the infants and younger children as in the older children. Biphasic temperature curves were observed at all ages in this study of infants and children. This feature was noted only rarely in a study of an epidemic of influenza among young adults which was carried on at the same time and which was caused by the same type of virus. Brightman and Trask[6] refer to the "familiar syndrome of high, irregular or biphasic fever, lassitude and prostration....." They state that leukopenia by no means separates influenza from other diseases involving the respiratory system. The white blood cell counts in our cases rarely showed leukopenia early, with the exception of 1 case. The average of the early counts was 9,047 cells per cubic millimeter, and the counts later, usually after defervescence, gave an average of 7,887 cells. We were not able to confirm the current opinion that leukopenia is a characteristic of influenza.

The infants and children had few subjective complaints. Some of the older children complained of sore throat and headache. Lassitude was rather striking in both groups, while restlessness predominated with the infants. Flushing, cough, mild conjunctival injection and acute pharyngitis were the main physical findings. One patient had a severe epistaxis, and swabbing of the throat initiated some mild bleeding in a few patients. The hyperemia of the pharyngeal spaces stood out as a cardinal finding. This was accompanied by mild laryngeal symptoms and cough in some of the younger patients, not unlike the characteristic brassy cough associated with measles.

The complications were surprisingly mild in spite of the fact that the throat cultures revealed hemolytic streptococci in 7 children. There were 6 patients from whom nonhemolytic streptococci were isolated in the throat culture. Two patients developed otitis media. None of the patients developed pneumonia, although S. H., aged 18 months, on Dec. 15, 1943, showed a moderate increase in bronchovascular markings in a roentgenogram of the lungs, interpreted as acute bronchitis. Diarrhea was not observed.

Laboratory Findings

Serum specimens were examined for neutralizing antibodies to influenza A and B viruses by the red blood cell agglutination-inhibition test.[4] Serial twofold dilutions of serum in isotonic solution of sodium chloride were mixed with four minimal agglutinating doses of influenza virus in 0.5 cc. amounts of the virus dilution in isotonic solution

of sodium chloride. To the serum-virus mixtures were added 1 cc. amounts of a 1.5 per cent suspension of adult chicken red blood cells in isotonic solution of sodium chloride. At the end of 75 minutes the end points of the serum titrations were determined by use of the photodensitometer.[8] The end point of the titration was taken as the serum dilution in which 50 per cent of the cells had sedimented. In case this did not occur in any given serum dilution, the end point was determined by interpolation of the dilution above and the dilution below 50 per cent red cell sedimentation. In al. instances the acute and convalescent phase serums from the same patient were examined in the same test.

The serums were tested against the PR8 strain[9] of influenza A virus which had undergone 250 passages in mice followed by 30 intra-allantoic passages in chick embryos and against the Lee[10] strain of influenza B virus, which had been received from the International Health Division Laboratories and had undergone 6 subsequent intra-allantoic passages in chick embryos. The red blood cell agglutination titer of each virus was determined previous to the use of the virus in the test. One c.c. quantities of serial two-fold dilutions of the virus were mixed with equal quantities of a 1.5 per cent chicken red blood cell suspension in isotonic solution of sodium chloride. The end points of the virus titrations were determined in the same manner as the serum titrations.

Throat washings were obtained from 19 of the 24 patients at the time at which acute phase serum specimens were taken. All washings were obtained during the febrile course of the disease, and the majority were taken within 24 hours of onset of illness. A small amount of isotonic solution of sodium chloride was instilled into the patient's nostrils and was recovered together with mucus from the nasopharynx by means of a soft tubber ear syringe. The washings were placed in unbreakable lusteroid tubes, were frozen on solidified carbon dioxide without delay and were so kept until examined.

Each washing was inoculated in the unfiltered state intra-allantoically into 6 eleven-day chick embryos according to the technic described in another publication.[5] After 48 hours' incubation at 37 C. the allantoic fluids of living embryos were tested for agglutination of chicken red blood cells. If such agglutination was not observed, the fluids were pooled and subsequent passage made to six other eleven-day embryos, which were incubated and tested in an identical manner. A minimum of 5 serial passages was performed with all throat washings examined before considering them negative.

When agglutination was observed, the positive allantoic fluids were pooled and the agglutinating titer of the pool was determined in the manner previously described. If this titer was of low order, an additional passage was made in chick embryos, which passage always produced a fluid containing sufficient agglutinating antigen to permit the identification of the virus type.

Unknown viruses were identified as influenza A by determining the titers of the following two serum pools against the unknown strains:

Serum 1. A pool of serums taken from several human subjects during the acute phase of influenza A. The titer of this serum against the PR8 strain of influenza A virus was 1:256 and against the Lee strain of influenza B virus 1:128.

Serum 2. A pool of convalescent phase serums taken from the same patients as serum 1 at approximately 2 or 3 weeks after onset of illness. The titer of serum 2 against PR8 influenza A virus was 1:3,010, against the Lee influenza B virus 1:128.

When tested against an unknown virus, an increase in titer of serum 2 of more than four times over serum 1 was taken to indicate that the unknown virus was influenza A.

In the accompanying table are given details concerning antibodies to influenza A in the serums examined and details concerning isolation and identi-

Table 1

Serologic Response and Virus Isolation and Identification
Among Infants and Children Ill with Clinical Influenza

		Serologic Response Influenza A				Virus Isolation and Identification			
							Titers with Human Serum Pools		
Patient	Age	Titers Acute Phase Serums	Titers Convalescent Phase Serums	Times Increase Convalescent Over Acute Titer	Serologic Diagnosis Influenza A	Egg Passage in Which Agglutination Was First Observed	Acute Phase Influenza A	Convalescent Phase Influenza A	Identification Influenza A
	1 mo.	1:20	1:11	0	-	Negative			
	5 mos.	1:16	1:16	0	-	Negative			
	9 mos.	1:52	1:588	11	+				
	10 mos.	1:10	1:8	0	-	Negative			
	12 mos.	1:26	1:1,270	40	+				
	31 mos.	1:60	1:4,096	68	+	Negative			
	18 mos.	1:49	1:2,048	41	+	First	1:208	1:3,010	+
	22 mos.	1:79	1:676	9	+				
	22 mos.	<1:32	1:3,330	>100	+	Negative			
	33 mos.	....	....	..	..	Negative			
	35 mos.	1:84	1:1,270	15	+	Third	1:23	1:835	+
	3 yrs.	1:128	1:779	6	+	Negative			
	3 yrs.	1:64	1:338	5	+				
	3 yrs.	1:120	1:1,450	12	+	Fourth	1:60	1:512	+
	3 yrs.	1:74	1:2,048	28	+	Negative			
	4 yrs.	1:128	1:1,270	10	+	Second	1:315	1:3,820	+
	5 yrs.	1:294	1:1,175	4	+	Third	1:256	1:1,910	+
	5 yrs.	1:194	1:6,220	32	+	Negative			
	6 yrs.	1:417	1:112	0	-	Third	1:32	1:722	+
	7 yrs.	1:722	1:779	0	-	Negative			
	7 yrs.	1:223	1:26,600	120	+	Negative			
	8 yrs.	1:32	1:958	30	+				
	9 yrs.	1:45	1:6,700	130	+	Negative			
	10 yrs.	1:45	1:1,560	35	+	Sixth	1:128	1:2,048	+

fication of virus strains. All pairs of serums examined for antibodies against influenza A were also examined for antibodies against influenza B. In no instance was any significant increase in titer noted against the latter virus. This agent was therefore considered to be excluded as the cause of illness of any of the patients.

It may be observed that of 23 pairs of serum specimens examined, 18, or 78 per cent, of the specimens showed fourfold or greater increases in antibodies to influenza A virus in the convalescent phase serums. In 19 throat washings examined for the presence of virus, 7, or 37 per cent, yielded a virus which was identified as influenza A by neutralization with the aforementioned known human antiserums. These percentages were very similar to those obtained for positive serologic diagnoses and virus isolation among a much larger series of specimens taken from the adult population during the same epidemic.

In the serum of S.B., from whose throat influenza virus A was isolated and identified, no increase in antibodies was noted. Rather there appeared a drop in titer, which was verified by repeating the examination of this patient's serum several times and by determining the titer of a second convalescent serum specimen. Isolated instances of virus isolation without serologic response have been previously reported. The apparent drop in titer observed in this patient's serum cannot be explained at present.

Among infants of less than 23 months of age, who to the best of our knowledge had had no previous infection with influenza A virus, the preinfection antibody titers were appreciably lower than in the group from 35 months to 10 years of age. All the members of the latter group had presumably had opportunity to be infected with this virus. Including only individuals with positive serologic diagnosis, the average preinfection titer of the first group was 1:50 and that of the second was 1:119. In this respect it should be noted that the hemagglutinin-inhibition test may not be capable of determining very low neutralizing antibody titers in certain serums. In low dilutions, serums containing no specific antibodies whatever may cause inhibition of agglutination. This nonspecific effect generally disappears in serum dilutions over 1:64.[4]

The average postinfection antibody levels of the two groups were 1:2,000 and 1:4,189, which indicated that the older children had produced only slightly greater antibody titers than the younger. The average incremental antibody rise of the titers of convalescent serums of the two groups were 40 and 35 times the average preinfection titers in the younger and older groups respectively. Were it possible to eliminate the factor of nonspecific inhibition in the preinfection serums of the first group, it would seem likely that the incremental rise of this group would have been far greater. Previous studies in which neutralization tests were done in mice[11] have shown that the serums of children of this age, who have had no infection with influenza virus, possess almost no demonstrable neutralizing antibodies.

Comment

By the use of recently developed laboratory technics, it has been possible to diagnose an epidemic of influenza A in a group of infants and children. The antibody response in infants who were, in all probability, having their first experience with the disease has been studied. Although previous investigators have successfully infected ferrets with influenza by inoculation of throat washings taken from infants ill with influenza[6], neutralizing antibodies were not demonstrated in the convalescent serums of the patients from whom the washings were obtained.[7] In the pediatric literature, several references to the inability of infants to develop neutralizing antibody titers are recorded. The observations recorded here show that, following infection with influenza A virus, infants develop antibody responses of approximately the same magnitude as do older children.

Throughout the epidemic, all cases

suspected of being influenza on clinical evidence alone were included in the series studied. Four of the patients showed no antibody response, nor was virus isolated from these patients' throats. Symptoms and findings in these cases did not differ appreciably fro m those of the cases in which positive serologic diagnosis or virus isolation was obtained. Previous investigators have observed in the study of epidemics of influenza A among adults that persons ill during an epidemic do not all present positive serologic findings nor may virus isolated from the patient's throat washing in every instance.[16]

By means of throat washings which were inoculated in the unfiltered state intra-allantoically into eleven-day chick embryos, the early identification of the virus was made possible. In 1 instance in this epidemic the virus was isolated in the first passage 48 hours after the washing was inoculated. Rickard, Thigpen and Crowley[5] found 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.

Clinically this study confirms the observations of Brightman and Trask[6] that infants and young children with influenza have high, irregular or biphasic fevers. These were the predominant types of temperature curves recorded in these patients and seem significant in contract to febrile curves recorded on young adults in the same epidemic. The outstanding response in the latter group was a fever rising abruptly and falling rather rapidly, generally in 2 to 4 days.

Aldrich[12] calls attention to the association of grip and laryngitis, which in his study ran a close parallel, "making it seem possible that croup is a manifestation of grip in infancy". It would seem probable that other infectious agents responsible for certain upper respiratory diseases of undetermined etiology, which in practice are commonly designated as grip, may be the cause of laryngitis or croup in infants. In the present study, however, influenza A virus was not found to cause such symptoms.

Antibody Response to Various Strains of Influenza in the Serums of Infants Experiencing Their First Infection with Influenza A:

Doctors E. R. Rickard, M. P. Thigpen and I made observations on the antibody responses of young infants below the age of 20 months to widely different strains of influenza A and swine influenza. Many similar observations are recorded on animals and in human adults who more than likely have had previous infection with influenza A.[13-22] It seemed to be of some interest to determine the response of infants who, largely because of their age, we could be reasonably sure were having their first contact with the disease.

I shall not record the details of the study here as it is published in a recent issue, May-June, 1945, of the Journal of Infectious Diseases. The results are recorded in the accompanying table 2.

The antibody response of infants who according to best available evidence were experiencing their first infection with influenza A virus was remarkably similar to the response of ferrets immunized with PR8 virus and subsequently tested for antibodies to the PR8, W.S., and swine influenza viruses by the agglutination inhibition test as reported by Hirst.[4]

The lower titers attained against the swine strain and the rapid and almost complete loss of antibodies against this strain as compared with the various strains of influenza A, particularly the PR8 and the epidemic strain S.H., might explain the original findings of Shope,[23] who observed a lack of swine neutralizing antibodies in the serums of younger children with almost universal presence of such antibodies in the serums of adults.

Table 2

Titers of Convalescent and Late Convalescent Phase Serum Specimens against Different Strains of Influenza A and Swine Influenza Viruses as Determined by the Agglutination Inhibition Test.

Patient	Age at Onset	Time after onset specimen obtained	**Titers against different strains S.H.	PRS	W.S.	Sw.
,	9 Mo.	19 days	676	722	362	64
		5 Mo.	147	104	30	16
	12 Mo.	51 days	1450	512	64	56
		5 Mo.	512	223	42	16
.	18 Mo.	24 days	3580	1560	1270	315
		5 Mo.	1100	362	60	18
*	18 Mo.	15 days	1670	891	1024	294
		4 Mo.	208	128	28	16
,	19 Mo.	14 days	479	194	79	49
		4 Mo.	479	128	23	16
Geometric Means		Convalescent	1270	632	294	104
		Late Convalescent	362	158	34	16

* Virus isolated from this patient.
**Titers are given in reciprocals of serum dilutions.

A Clinico-Pathologic Study of Smears from the Acutely Inflamed Human Pharynx in Influenza A Infection:

(With M. M. Pennoyer and A. M. Whiting)

This study was undertaken because we were impressed with the fact that influenza A infection was primarily a disease of the upper respiratory passages. Francis[24] has stated that the influenza virus exerts its initial and primary effect upon the epithelium of the upper respiratory tract. MacCallum[25] states in the latest edition of his textbook that "no one died of influenza alone without secondary infection with bacteria,"....and also that they were "entirely uninformed as to the nature of any changes in the internal organs which may result from influenza as such." It seemed worthwhile, therefore, to have a look at the changes which might be taking place in the pharynx.

Francis and Stuart-Harris[26] have described the nasal histology of epidemic influenza infection in the ferret. They state in summary, "During the acute stage of infection the respiratory epithelium of the nasal mucous membrane undergoes necrosis with desquamation of the superficial cells, and exudation into the air passages, and an inflammatory reaction occurs in the submucosa."

Further details of the methods employed will not be recorded here as they are now in press in the American Journal of Diseases of Children.

Over 300 smears were made of the pharynx in young adults and children in the acute stage of influenza A infection. The hematoxylin and eosin stain was used throughout.

The low power inspection of the smears revealed large numbers of sloughing epithelial cells, frequently large sheets of epithelial cells were observed. Dividing nuclei were commonly seen.

McNamara[27] reported in a study of lung exudate that "the earliest lesions show epithelial cells to be more granular than usual, and their nuclei are pyknotic." He stated that in the early stages the lack of polymorphonuclear leucocytes in the exudate was very noticeable. He likewise called attention to actively dividing young epithelial cells in which mitotic figures abound.

A mononuclear exudate stood out as the most singular pathologic change in the human pharyngeal exudate. This type of cellular response is quite consistent with the pathologic findings recorded in other types of virus infections, and of influenza itself in lower animals. In microscopic examinations of the lungs of mice and ferrets, McIntosh and Selbie[28] found a great increase of mononuclear cells in the alveolar walls. Francis and Stuart-Harris,[24] however, using "relatively large doses" of epidemic influenza virus in the ferret, record a high degree of destruction of respiratory epithelium and "a rich exudate chiefly polymorphonuclear in type in the air passages." McCordock and Muckenfuss[29] using vaccinia virus in the experimental animal, found the reaction to vary with the quantity of virus used. The concentrated dose produces an acute hemorrhagic type of histologic response with necrosis, whereas the more dilute dose produces a proliferative response with mononuclear cellular infiltration. Francis and Stuart-Harris[24] do call attention to mononuclear infiltrations during the stages of repair and regeneration in ferret epithelium. Rivers[30] has pointed out that acute inflammations occur in many virus diseases and if secondary infections do not intervene, the inflammatory process is usually characterized by an infiltration of mononuclear cells.

In our experience the mononuclear exudate, made up mostly of small lymphocytes, histiocytes, and plasma cells, varied in amount and was often mixed with a few polymorphonuclear cells, many of which were degenerating with pyknotic nuclei. Early in the course of the infection, the mononuclear exudate was frequently the predominate cellular reaction. These cells varied in size from small to very large.

In order to determine the quantitative leucocyte reactions, the smears of 35 patients with definite serologic responses were studied in detail. Sixty-eight per cent of the patients had a predominant mononuclear exudate. No leucocytes could be found on 8 of the specimens and 3 of the smears had a predominant polymorphonuclear reaction, one only showing a marked change. It is of interest that this patient subsequently developed pneumonia. Smears from well persons, prepared in May and June, were analyzed for leucocytic responses. No mononuclear reaction was seen and 17 per cent were found to have a slight to moderate polymorphonuclear exudate.

An exudate, made up almost entirely of polymorphonuclear cells, was found in 18 per cent of the total specimens. In many of these patients a subsequent complication such as follicular tonsillitis, sinusitis, or pneumonia was recorded. We considered this of interest as a possible index of secondary bacterial invasion. Twenty-two cases exhibited secondary bacterial complications (otitis media, follicular tonsillitis, scarlet fever, or pneumonia). Of these, a mononuclear exudate was recorded in 18 per cent in the early stages of the disease, whereas 82 per cent had a predominant polymorphonuclear response at the same period. Fifty-five per cent of the slides were prepared in the first two days of illness.

This mononuclear reaction is not considered specific for influenza A infection. There are very few diseases of the upper respiratory passages that can at present be diagnosed accurately. Undifferentiated respiratory disease still makes up the greatest number of respiratory diseases. It would be of interest to study the pharyngeal exudate in rubeola, or measles, and this we plan to do. A mononuclear exudate might predominate in many other virus diseases of the upper respiratory passages and we have observed it in a few instances of atypical pneumonia. We can be quite certain that most bacterial

infections have a predominant polymorphonuclear response in the pharyngeal exudate.

Influenza Virus Vaccine, Types A and B

During the widespread epidemic of influenza in November and December 1943, the influenza commission investigated the influence of the concentrated, inactivated vaccine on the incidence of clinical influenza[31]. About 12,500 A.S.T.P. men were given mixed influenza virus vaccine types A and B. Among 6,211 unvaccinated controls, the attack rate was 7.11 per cent while among 6,263 vaccinated subjects the rate was 2.22 per cent. Since this striking result was reported, several others have reported confirmatory results.(32-36) Eaton and Meiklejohn (37) failed to confirm these results.

The dosage recommended is one subcutaneous injection of 1 c.c. The duration of immunity is probably not longer than several months. Reactions have been recorded and the vaccine should not be given to egg sensitive individuals.

Summary:

In the study of an epidemic of influenza occurring in infants and children, the disease was characterized by irregular or biphasic fever curves. Leukopenia was not found to be present. Acute pharyngitis, often hyperemic, and lassitude were the most prominent physical findings. None of the patients manifested severe laryngitis or croup.

Influenza A virus was isolated from throat washings taken from a number of the patients and inoculated intra-allantoically into developing chick embryos. The serologic diagnosis of the epidemic was established by the demonstration of significant increases in neutralizing antibodies by means of the hemagglutinin inhibition test in the serums of 18 out of 23 patients so examined. The neutralizing antibody response of infants, who in all probability were having their first infection with influenza A virus, was found to be of approximately the same magnitude as that of older children.

In the serums of 5 infants who experienced their first known attack of influenza A, antibody response as measured by the agglutination inhibition test was greatest to the strain of influenza virus isolated from the nasopharynx of 1 of the infants. Mean antibody levels attained were progressively lower to the PR8 and W. S. strains of influenza A virus and swine influenza virus, respectively, although some antibody was formed against all of the viruses tested.

The most characteristic clinicopathological feature of epidemic influenza as seen in a recent proven epidemic was an acute pharyngitis. The pharyngeal smears of over 300 young adults and children suffering from influenzal A infection were studied, as well as similar tissues from control groups during, and six months after the epidemic. Increased destruction of pharyngeal epithelial tissues was definite as compared to the control specimens. The single most important micropathological feature of the pharyngeal exudate of these influenza patients was a mononuclear exudate, which is consistent with the pathologic findings in certain other types of virus infections, both in man and animals. In our study a polymorphonuclear exudate frequently presaged a complicating secondary bacterial infection.

Influenza virus vaccine, types A and B is now available, and has been shown by others to be effective in protecting against the disease.

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III. GOSSIP

February 10, 4 p.m. On the Burlington Zepher to Chicago to attend the 42nd Annual Congress on Medical Education and Licensure, February 10, 11, and 12, 1946, Red Lacquer Room, Palmer House. I am late as usual in deciding which train I intend to take so I miss out on seat reservations. We locate a spot on the coach with the assistance of a Red Cap, and by the time we reach St. Paul every seat is taken. From Winona on, the crowds increase in size until all standing room is utilized. Everyone is good natured about it, but the diner does not do much business with those who are seated as they most surely will lose their place if they leave. Some passengers hold their places by letting those who are standing sit while they go back. 11 p. m. Chicago and a belated dinner at the Harvey House which always serves good food. The resturants in the western section of the United States seem to have more color than the Chicago place; the Harvey girls who wait on us are a far cry from the Hollywood version. Midnight at the Palmer House to find one advantage in taking an afternoon train in that you do not have to stand in line for your room. Quickly to bed and a refreshing sleep. Some travelers tell me that they wear ear plugs in hotel rooms to induce sleep, but I can imagine what could happen if the place caught fire; others woo sleep when away from home by taking sedatives, but most of us, who are being chased by our jobs, do not have any sleeping difficulties away from home. February 11, 9 a.m. to the Palmer House coffee shop for breakfast, and this is always a treat because of the specialties which are featured. Every place is taken except one near a couple who are just ordering their breakfast. She is the overweight, baby-voiced type and he is the solicitous man of the world traveler type. With a great florish he orders broiled mackeral because he never gets it at home. As we wait for our breakfasts, he talks up his mackeral. He urges her to promise to take a taste, but she refuses. The man on the other side tries to help him by urging her to try it and I put in my two-bits. Finally his mackeral arrives and it is a work of art, but still she refuses. In the middle of all the argumentation, she suddenly announces that she wishes he would get her some coffee cake like mine and that seems to settle everything. The big rolled pancake is another feature so many people order here. Many Minnesotans are eating their breakfast now and at this point Sister Patricia, the able administrator of St. Mary's Hospital, Duluth, and a companion arrive. A word of greeting and on to the morning session at 9:30, where Perrin H. Long, Johns Hopkins University School of Medicine discourses at length on "Medical Progress during the War". He reads his remarks with vigor and distinction. His story covers large areas with heavy sweeps and at times with more emphasis on the all over picture than the exact details of success or failure. He doubts that much of the work done with the sulfa drugs in wounds or by mouth is of value or blood levels were not measured for comparative purpose. He liked the work on typhus and had many good things to say about the program in preventive medicine. At times one detected criticism of the general staff which apparently controls the destiny of medical service as it gave belated approval to tetanus toxoid immunization which later proved so effective. With little warning Doctor Long swung away from scientific subjects and invaded the field of medical education. He felt that the medical product of the wartime years could not be as good as in the past because less time was spent on his development. He admitted that few men on medical duty saw medicine but did see much waiting. Three chief additions to the medical officers training and experience were the organized handling of the sick and injured, psychiatry, and preventive medicine. His remarks were well received and he was full of his subject. (He held forth four hours at an informal bull session the previous day with equal effectiveness.) He is certainly the man to address an organization on medical progress during the war and he would make a good convocation speaker. Wilburt C. Davison, Dean of Duke University School of Medicine, the "Orson Wells" of the deans, gave an informative talk on medical education in Europe. He knew it before the war and

saw it afterward. He rated well the efforts in the Scandanavian countries, Holland, Switzerland, and part of England. Russia has gone farthest in the shortest time, but still has room for improvement. The rest of it was too sad to contemplate. Politics, intrique, commercialism, adherence to the past, isolationism, characterized the medical education of most places. Most arrogant and most overrated were German. Flexner's book on Medical Education still reposes on the German medical leaders' tables with many of the leaves uncut. Thousands of students flock to lectures, none go to the wards. Professors are paid in some places by the number of students they instruct and have little interest in anything else. Facilities are poor, but most serious is the lack of interest in doing much about it or accepting advice from us. He feels that until we are asked, we cannot do anything. His best story was of the Dane who was always popping up to tell the audience how they did it in this country where public health and medical service are closely related. The American Public Health Officer finally told the Dane that if the United States was as small as Denmark they could fumigate it and whitewash it every week. He learned much about trends in medical education from Dan O'Brien and also saw Starplar (the Serbian) who visited us before the war. He is an enormous fellow with explosive ways of expression. When he was here we tried to impress him with how much we had accomplished in public health, but he didn't think it was much. Finally someone asked him what he thought was the greatest public health achievement and he said "rural electrification". The light means opportunity to study, the power to run machines, refrigerate food, heat water, prevent accidents (lights in barns and other places), and many other things. Water purification also occupies a similar position in disease prevention, for not only are water borne diseases prevented, but all other health conditions improve after good sanitation. Davison is another ideal speaker for a group interested in analyzing its own achievements in medical education. He stresses the importance of our appreciation of the responsible position we occupy in this field and warns us that we must not drift toward European ideals in medical education (exceptions noted). Paul B. Magnuson told of the Veterans' plans and did a good job. The whole program is so complex that it is difficult to visualize how a uniform result can be obtained. Eastern medical groups who are distinctly antigovernment are not going to cooperate to any great extent. Physicians busy with practices on part time teaching positions aren't too greatly interested. This leaves the field to full time teaching groups like ours to pave the way. This symposium was discussed by C. Sidney Burwell, Boston, and Williams Middleton, Wisconsin. Doctor Middleton is one of my favorite people, as he never fails to deliver a dignified, thoughtful presentation of facts. George F. Lull, Associate General Manager of the American Medical Association, former Major General in the Medical Corps, spoke on Medicine in the Future. He made a favorable impression except when he said the added burden of attempting to care for the educational needs of the returning medical officer was only a temporary problem and everything would soon be back to the way it was. What I wanted to know is when is the emergency over and when does the change start. At noon to luncheon with the other speakers as a guest of the American Medical Association and Doctor Middleton sat on my right and Doctor Davison on my left. (Dr. Morris Fishbein sat at the speakers' table.) At the close of the luncheon Doctor Diehl and two of his associates were honored with large scrolls and special medals for their work in connection with the war effort. This met with general favor and congratulations all around followed. After the meetings at 2 to hear Paul Titus, M.D., President, Advisory Board for Medical Specialties defend the specialists. He did it well but in the course of his remarks in referring to the shorter opportunities for training for general men, he used the term "refresher courses". I spoke on the Practise of General Medicine. I apologized for not having a southern accent or an eastern accent as most of the speakers before me had had, I apologized for not having a Scandanavian accent coming from Minnesota, and for

not being a general practitioner, I approached the subject from an academic standpoint. Eighty per cent of our last two senior classes plan to qualify for Specialty Boards, 10 per cent are going into practice without it, and 10 per cent are undecided. Only 1 man of the 212 graduates said he was going into practice after a 1-year internship. At the present time there are 15 specialty boards with various sub-boards. I proposed the establishment of a 16th board for general medical service. Undergraduates should have more opportunity to do clinical work before graduation (longer school years). Undergraduate emphasis should be placed on training in medicine, obstetrics, pediatrics, and the medical aspects of the other specialties. Technical training in surgery and the surgical fields should be reserved for graduate students. The first year of internship would be straight medicine, the second year, obstetrics and pediatrics, and this would be followed by a 1-year residency in internal medicine or alternate choices would be obstetrics or pediatrics. The physician would receive recognition for his training and the public would receive the kind of service it needs, as surgery and the surgical specialties would be practiced by the specialties in these fields and they would cease practicing general medicine. This division would simplify undergraduate, graduate, and continuation training. It meets with least favor by the general practitioners who practice surgery (operating general practitioners) and specialists who have no interest in the general medical man. I was surprised at the reception it received for everyone has been thinking in this way about it, but no one has been doing much about it. I made my usual plea to cease and decist the use of the term "refresher course" for continuation study courses. Frankly the use of the term cannot be justified. I also mentioned that we have 150,000 doctors in the United States, 30,000 are specialized (Board recognition), 40,000 are beyond the time when these changes will make any difference, while 80,000 are either practising general medicine and the specialties, or are just "docs". This large group may provide the leadership for specialism in general medicine (general practice), or it may have to come from the internists, obstetricians, and pediatricians. First effort should be to reorganize our thinking in regard to the teaching of undergraduates, and next to provide a program of study beyond graduation, set up courses at the center, and work toward Board recognition. We are a State University and we are more conscious of our practitioner who fulfilled all the requirements and Ajax Carlson said that no training program produced that man as he was just that a sort of person. A symposium on Medical Education and Research followed and I was called out in the middle of it to air my views so I didn't get back. At 5 o'clock to call at the Nebraska Headquarters where many old friends were gathered. I haven't been around as much as Morris Fishbein whose style I am supposed to be pirating, as at this stage he always tells of seeing Hildegard and later on of having lunch with Lou Weed. At 8 to the Empire Room where the floor show was unusually good. Saw many Minnesotans in the crowd, including several staid gentlemen who were tripping the light fantastic toe. Late to bed and up the next morning to have breakfast with Dean Diehl, Lester Evans, and Rhod Heffron, to discuss plans for the Course in the Psychoneurosis for the General Practitioner at the Center for Continuation Study April 1-13. And pleased to learn that John Murray, John Ramono, Tom Rennie, Ralph Kauffman, Harold Wolff, Doug Bond, William Dunn, would be here. Plan is to use ordinary cases as teaching material and to instruct 30 physicians in ways and means of handling the neurotics. Later on in the morning to gossip with people from here and there, and then to lunch with my good wife and finally to the train to return home. Now we have reserved seats and so we ride in comfort, but feeling sorry for the train man who has to stick his head out in the cold breeze to catch a possible hoop containing orders as we pass each station; it was cold when we arrived, and I wondered if the stimulating climate in this north country was responsible for the greater energy and enthusiasm which many from here display in attacking our problems. It is always good to realize that the efforts of so many of our staff are so widely known and so favorably received.

IV. SUMMARY OF DEATHS

FROM JULY FIRST THROUGH DECEMBER THIRTY-FIRST, 1945

MONTH	TOTAL DEATHS	CORONER'S CASES	STILL BIRTHS	REMAINING	AUTOPSIES	PER CENT
July	39	2	0	37	25	67.6
August	38	1	2	35	27	77.1
September	33	1	1	31	21	67.7
October	33	3	0	30	17	56.6
November	41	2	2	37	27	72.9
December	40	2	1	37	24	64.9
TOTAL	224	11	6	207	141	68.1