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Research Article

STUDIES ON INFLUENZA IN THE PANDEMIC OF 1957–1958. I. AN EPIDEMIOLOGIC, CLINICAL AND SEROLOGIC INVESTIGATION OF AN INTRAHOSPITAL EPIDEMIC, WITH A NOTE ON VACCINATION EFFICACY *

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Influenza caused by a new variant of influenza A virus assumed epidemic proportions in southwest China in late February, 1957 (1). During the next three months influenza outbreaks occurred widely throughout the Orient and first appeared in the United States in the middle of May. During the summer the disease spread slowly and sporadically within the United States, initially involved military establishments which received military personnel from the Orient, and later attacked various civilian groups collected in summer camps and conferences. From September through December, 1957, there was a rapid and diffuse spread of influenza, and epidemics were observed in most cities throughout the country (2).

In late August, 1957, it was predicted that influenza would probably be seen in epidemic proportions within New York City. At this time a prospective interdepartmental study was organized at The New York Hospital-Cornell Medical Center with the belief that the pending epidemic might present a unique opportunity to study influenza by a multidisciplined approach not often possible under epidemic conditions.

The present series of three papers is a report of these studies. The first paper details observations on an intrahospital epidemic arising within a single medical ward. Included in this initial paper of the report are the results of studies of the clinical syndrome and the clinical pathology of uncomplicated influenza, the results of different serologic methods for the diagnosis of influenza, and observations on the efficacy of prior influenza vaccination in protecting a small group of personnel heavily exposed to the infection. The second paper (3) analyzes the clinical course and the microbiological and pathologic characteristics of pneumonia arising in patients with Asian influenza A virus infection as witnessed at The New York Hospital from September, 1957, through January, 1958. The final paper (4) reports in detail the techniques used in the isolation of influenza virus and the laboratory characteristics of the strains of Asian influenza A virus recovered from patients during the present study.

METHOD OF STUDY

1. Persons included in the study group. Sixty-two persons were confined within, or working on, Ward H5 at the time of the epidemic. All were included in the present study. This group consisted of 29 male and female patients over 16 years of age admitted because of medical illnesses and a ward staff of 33 persons employed on various shifts. The personnel included four physicians, five medical students, seven registered nurses, five student nurses, nine nurses' aides, and three floor clerks.

2. Vaccination status of group. None of the 29 medical patients had received influenza vaccine. Twenty members of the H5 staff had received one or more injections of a monovalent vaccine containing 200 chicken-red cell-agglutinating (CCA) units per ml. of the Asian strain of influenza A virus. Sixteen persons had been given 1.0 ml. (200 CCA units) of vaccine subcutaneously 19 days before the appearance of influenza on the ward. Three persons had received intradermal injections of 0.1 ml. (20 CCA units) of vaccine 19 and 12 days prior to the influenza outbreak. One additional staff member received 0.2 ml. (40 CCA units) intradermally 2 days after the epidemic began.

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3. Clinical data. Daily observations were made by the house staff and influenza study group on all patients who developed symptoms suggestive of influenza. A check sheet was used to facilitate uniform tabulation of daily symptoms and signs. Rectal temperatures and pulse rates were recorded every four hours. Similar studies were carried out on personnel who developed influenzal symptoms, but were of necessity less complete.

4. Routine laboratory tests. Total and differential leukocyte counts, hematocrit values, and erythrocyte sedimentation rates were determined every three days on subjects who developed influenza. Studies of liver and renal function, chest roentgenograms, and special serologic and bacteriologic studies were obtained in selected cases.

5. Viral and bacteriologic studies. Fifteen ml. of phosphate buffered saline solution (0.85 per cent NaCl) was gargled and collected for recovery of influenza virus. These washings were obtained from five patients within 24 to 96 hours after the onset of influenza symptoms. Techniques of virus isolation are described in a succeeding paper (4).

Nose and throat cultures were obtained from 53 of the 62 individuals on the third day of the epidemic whether or not symptoms or signs of influenza were apparent. Sputum specimens were obtained from all patients with productive cough. Sputum smears were stained by the Gram method and examined microscopically. Throat swabs and sputum specimens were streaked on blood agar plates and inoculated into beef heart infusion broth. Particular attention was given to the isolation and identification of coagulase positive staphylococci, pneumococci, *Hemophilus influenzae,* and beta hemolytic streptococci.

6. Serologic studies. Two or more specimens of serum were obtained from 55 of the 62 subjects of the study. Initial blood specimens were drawn on the fourth day following admission of the initial case of influenza. Subsequent blood specimens were obtained 5 to 21 days after this initial bleeding. Blood was allowed to clot at room temperature; the serum was separated and stored at −20° C. until studies were performed. Three serologic tests for influenza were performed on each set of sera, and paired sera were titrated simultaneously. Complement fixing (CF) antibodies were measured by a standard procedure (5), using as the test antigen an A/

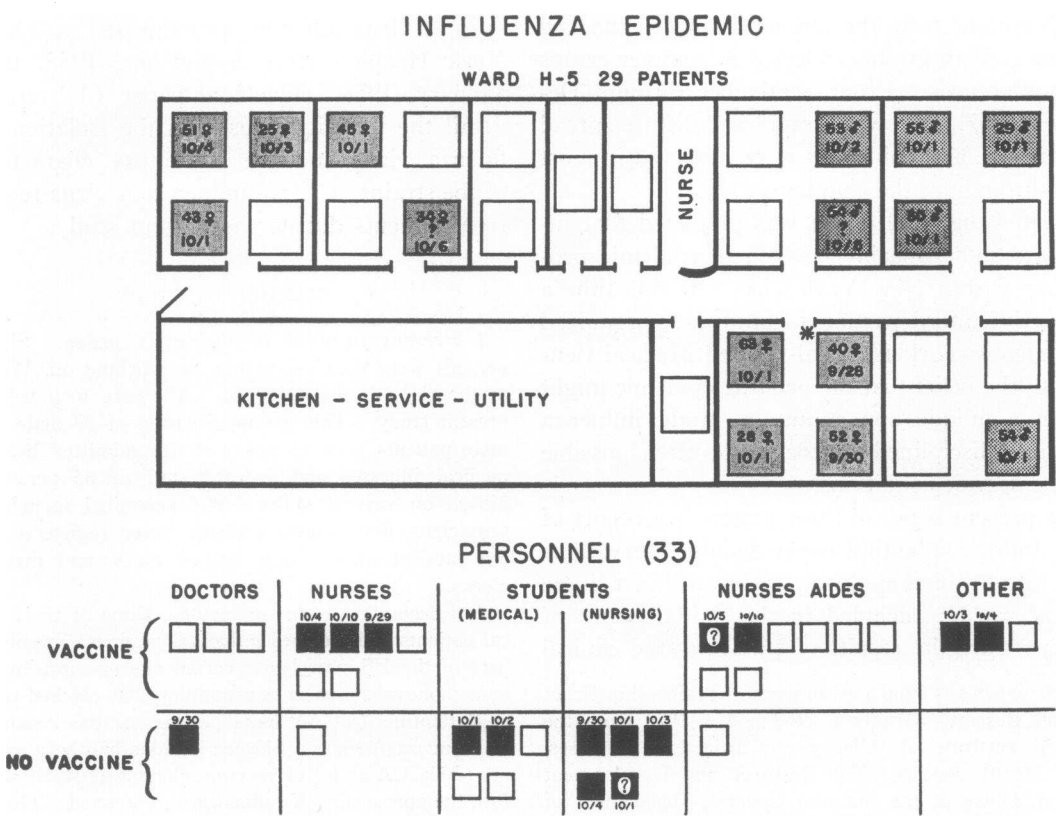

FIG. 1. TOPOGRAPHY OF WARD H5 AND MAKE-UP OF WARD PERSONNEL

Shaded blocks represent individual patients and personnel who developed influenza symptoms. The date of appearance of symptoms is indicated within or above the blocks. The location of the initial case is indicated by an asterisk.

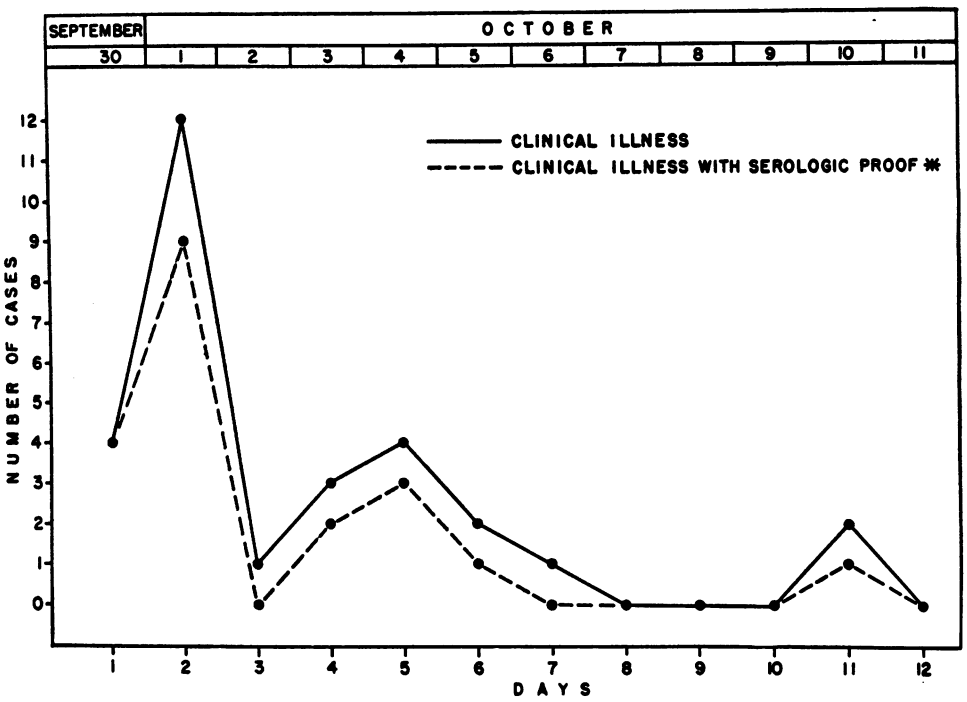

FIG. 2. DAILY APPEARANCE OF NEW CASES OF INFLUENZA ON WARD H5 BY DATE OF MONTH AND DAY OF EPIDEMIC

The term "serologic proof" is equated with a demonstrated fourfold or greater rise in hemagglutination-inhibiting or complement fixing antibodies.

Japan/305/57 strain which had been passaged only in eggs.[1]

Titration of hemagglutination-inhibiting (HI) antibody. Early in the present study HI antibody was measured with the egg-line strain of the Japan 305 (Asian strain) virus and trypsin inactivated sera. The relative insensitivity of this antigen to nonspecific serum inhibitor obviated the use of the more effective periodate method (see below) for the destruction of inhibitor. The egg-line virus was also relatively insensitive to inhibition by antibody, however, so that few antibody rises were demonstrated with this virus. Accordingly, most sera were re-titrated with an inhibitor and antibody-sensitive variant of the Japan 305 strain which had been passed through ferrets and mice (Japan 305 $E_4F_1M_3E_8$, obtained through the courtesy of Dr. Keith Jensen). In these latter titrations, preliminary destruction of inhibitor was effected with periodate as described below.

a) Inhibitor-resistant virus/trypsin inactivation of serum inhibitor. Equal parts of serum and two per cent trypsin in phosphate buffered saline (PBS) were heated together at 56° C. for 30 minutes. Serial twofold dilutions of 0.2 ml. volume of the inactivated serum were made in PBS. Two-tenths ml. of "egg-line" Asian influenza virus strain A/Japan/305/57 containing 16 to 32 hemagglutinating units was added to each tube. After 15 minutes' incubation at 22° C., 0.4 ml. of a 0.5 per cent suspension of human "O" red cells was added. The test was observed for inhibition of red cell agglutination after 40 minutes' incubation at 22° C.

b) Inhibitor-sensitive (mouse-ferret passaged) virus/periodate inactivation of serum inhibitor. Two-tenths ml. of serum was heated at 56° C. for 30 minutes. Four-tenths ml. of M/90 potassium periodate solution in distilled water was added to the serum after cooling, and the mixture refrigerated at 4° C. for 18 hours. Four-tenths ml. of 1 per cent glycerol in PBS was then added and the mixture maintained at room temperature for one hour to neutralize further periodate action. Serial dilutions and the remainder of the test procedure were the same as those used following treatment with trypsin. This method represents a modification of a procedure originally proposed by Burnet and Lind (6) and adapted by Jensen (7).

[1] This strain, obtained from Dr. John Y. Sugg, was initially isolated at the Army Medical School, Washington, D. C. It had been passaged once by the allantoic route in eggs prior to receipt. Three additional egg passages were carried out prior to its use in these studies.

RESULTS

Epidemiology

Ward H5 is composed of 29 beds arranged in one, two and four bed units as diagrammed in

TABLE I

Summary of information on individuals on Ward H5 developing influenzal symptoms

No.	Patient, Age, Sex	Status	Underlying disease*	Vaccine route,† Date	Date, onset of clinical symptoms	Duration of clinical symptoms	Severity of illness	Max. temp.	WBC/1,000 (range)	Specific antibody rise
						days		°C.		
1	R. S. 40 F	Patient	RHD, MS, MI, Auric. fibril.		9/28	8	3+	40.6	2.0–11.9	+
2	D. B. 24 M	MD	None		9/30	4	1+	39.0		+
3	L. F. 18 F	RN	None	S.C. 9/11	9/30	5	2+		13.9	+
4	S. F. 23 F	Stud. nurse	None		9/30	3	2+	38.3	5.1	+
5	B. N. 52 F	Patient	RHD, MS, MI, Heart failure		9/30	31	3+	39.8	6.3–11.4	+
6	J. B. 22 M	Med. stud.	None		10/1	1	1+			0
7	C. C. 63 M	Patient	Rheumatoid arthritis		10/1	6	1+	38.8	10.8	+
8	G. C. 54 M	Patient	Cirrhosis, Diabetes mellitus		10/1	2	1+	39.5	4.1– 6.7	+
9	M. D. 20 F	Stud. nurse	None		10/1	1	1+			0
10	S. D. 45 F	Patient	RHD, MI, Heart failure		10/1	7	2+	39.8	4.9– 7.3	+
11	J. G. 19 F	Stud. nurse	None		10/1	2	2+	39.6	3.7	+
12	V. G. 43 F	Patient	Hodgkin's dis., Rt. pleural effusion		10/1	7	2+	39.5	6.8– 9.2	0
13	E. L. 55 M	Patient	RHD, MS, MI, Auric. fibril., Ht. fail.		10/1	3	1+	39.3	6.9–11.5	+
14	R. K. 29 M	Patient	Rheumatic fever		10/1	6	1+	38.8	7.2–10.4	+
15	A. M. 28 F	Patient	Serum sickness		10/1	8	3+	40.0	5.2–14	+
16	K. N. 63 F	Patient	Myocardial infarction		10/1	2	1+	38.5	4.3– 5.3	+
17	G. V. 30 M	Patient	RHD, AI, Heart failure		10/1	8	3+	40.2	6.5–11.4	+
18	J. S. 23 M	Med. stud.	None		10/2	4	1+			?
19	E. C. 21 F	Stud. nurse	None		10/3	3	2+	38.3	9.6	+
20	M. R. 38 F	Ward clerk	None	S.C. 9/11	10/3	6	2+			+
21	M. T. 25 F	Patient	Anemia, Fever unknown origin		10/3	3	1+	38.5		?
22	M. E. 23 F	Stud. nurse	None		10/4	5	2+	38.6	6.2– 6.5	+
23	A. F. 24 F	RN	None	S.C. 9/11	10/4	4	2+			0
24	E. H. 51 F	Patient	Hypertension, Periph. vascular dis.		10/4	3	1+	39.3	9.2–10.3	+
25	L. S. 36 F	Ward clerk	None	S.C. 9/11	10/4	4	2+			+
26	I. C. 54 M	Patient	Hypertension, CVA, Pulm. insuff.		10/5	2	1+	39.6	8.1– 9.9	+
27	J. L. 25 F	Nurses' aide	None	S.C. 9/11	10/5	?	?			?
28	A. P. 34 F	Patient	Ulcerative colitis		10/6	4	1+	39.8		0
29	M. B. 30 F	RN	None	S.C. 9/11	10/10	4	1+			+
30	L. J. 21 F	Nurses' aide	None	I.D. 10/2	10/10	5	1+			?

* Abbreviations are as follows: RHD, rheumatic heart disease; MS, mitral stenosis; MI, mitral insufficiency; AI, aortic insufficiency; CVA, cerebrovascular accident.

† S.C., subcutaneous; I.D., intradermal.

Figure 1. Rooms open into a central ward corridor which communicates with the main hospital corridor by a single door. Patients leave the ward for special study procedures in other parts of the hospital, but many remain within the confines of the ward during their entire hospital stay. Personnel move freely between the ward, other parts of the hospital, and the outside community. At the time of the epidemic, all 29 beds were occupied.

On September 28, 1957, a 40 year old woman (R. S.) with known rheumatic heart disease was admitted to a four bed room on H5 with an undiagnosed acute febrile illness subsequently proved to be influenza complicated by bacterial pneumonia. Isolation procedures were not instituted. Within 24 hours symptoms of influenzal nature developed in the patient in the adjacent bed and in three of the ward staff. The subsequent spread of disease within the ward and the daily appearance of new cases are depicted in Figures 1 and 2.

During the next 24 hour period an additional 12 individuals developed an acute febrile illness believed to be influenza. Within seven days, 28 persons had developed symptoms consistent with a diagnosis of influenza. Two others developed symptoms typical of influenza on the eleventh day after the admission of the index case, but by this time influenza was prevalent within the community and the hospital, and these two cases may have arisen from an external source. Data on the 30 individuals who developed clinical influenza are recorded in Table 1.

Clinical manifestations of influenza

The clinical manifestations of influenza were strikingly uniform, and few differences were noted in the symptom complex manifested by patients or personnel. The incidence of predominating symptoms is given in Table II. In 29 of 30 individuals developing influenza, the onset was characterized by the relatively abrupt appearance of fever; temperature rose rapidly to maximum levels, commonly above 39° C., during the first 24 to 48 hours. Fever then subsided rapidly. Temperature elevations persisted from 48 to 96 hours in the absence of complications. Eight persons noted chilly sensations during the period of rising temperature. Cough of varying severity appeared within the first 24 hours in 25 individuals but was productive of sputum in only four. Three patients complained of moderate substernal pain associated with severe and protracted cough.

TABLE II

Incidence of symptoms in 30 individuals on Ward H5 manifesting influenza symptoms

Symptom	With significant antibody titer rise (21)	Without significant antibody titer rise (9)	Total (30)	
			Number	Per cent
Fever	20	9	29	97
Cough	17	8	25	80
Headache	15	2	17	63
Nasal discharge	12	2	14	47
Sore throat	11	2	13	43
Gastrointestinal symptoms	7	3	10	33
Generalized aching	7	2	9	30
Chills	8	0	8	27
Chest pain	3	0	3	10
Epistaxis	2	0	2	7

During the first 24 hours of illness, 17 individuals developed frontal headache which appeared related in intensity to the height of the temperature rise. Generalized muscle aches were noted more frequently by personnel than by bed patients and were not a prominent feature of this illness. Thirteen persons complained of a scratchy sore throat, but on examination only minimal inflammation of the pharyngeal mucosa was noted in 10. Mild nasal discharge appeared in 14 individuals; the nasal mucosa was visibly inflamed in six. Two patients with rhinitis had single episodes of epistaxis.

Ten persons with influenza had complaints referable to the gastrointestinal system; of these persons, seven were previously hospitalized bed patients and three were members of ward personnel. Although two previously healthy persons suffered nausea and vomiting, the occurrence of diarrhea or abdominal pain was restricted in all but one case to bed patients with antecedent disease. Similarly, the incidence of nausea and vomiting was two to three times higher among bed patients than in personnel. Of the seven of 15 bed patients with gastrointestinal symptoms, four had rheumatic heart disease (three with cardiac failure), and others had diagnoses of serum sickness, Hodgkins disease, and rheumatic fever. In addition, all but one patient were receiving medication of possible importance in the genesis of gastrointestinal symptomatology. These drugs included

oral penicillin, sulfonamides, erythromycin, codeine sulfate, and tetracycline, as well as digitalis in those patients with heart failure.

The occurrence of mild gastrointestinal symptoms in only three of 15 ward personnel is more in keeping with the rarity of abdominal complaints observed in previous clinical studies of influenza (8, 9).

Prostration, depression, and malaise which appeared out of proportion to the severity of the illness were more common in patients than in personnel. Of interest was the relatively greater severity of illness in those patients with underlying rheumatic heart disease. As shown in Table I, of the 30 persons manifesting symptoms of influenza, five had rheumatic heart disease, 10 had been hospitalized for other disease processes, and 15 were previously healthy personnel. Three of the five patients with rheumatic heart disease had severe influenza symptoms and developed pulmonary complications. Among the other 25 individuals studied, 10 with nonrheumatic illness and 15 without underlying disease, only one case of severe influenza occurred. This patient did not develop manifest pulmonary disease. Although the personnel group was younger, the patients with chronic nonrheumatic illnesses were of an age comparable to those with rheumatic heart disease.

Physical findings of lower respiratory tract involvement were noted in five individuals. Two patients developed fine, moist bilateral basilar rales without roentgenographic evidence of pulmonary infiltrates. These signs disappeared spontaneously within three days. Two bed patients with severe rheumatic heart disease developed clinical roentgenographic evidence of pneumonia during the course of influenza. A third patient with rheumatic heart disease developed persistent pleural pain with an audible friction rub bilaterally. These three patients (R. S., G. V. and B. N.) are discussed in the succeeding paper (3).

Laboratory studies

Leukocyte counts. As noted in Figure 3, no consistent changes in leukocyte counts were noted in patients with influenza. Total leukocyte counts

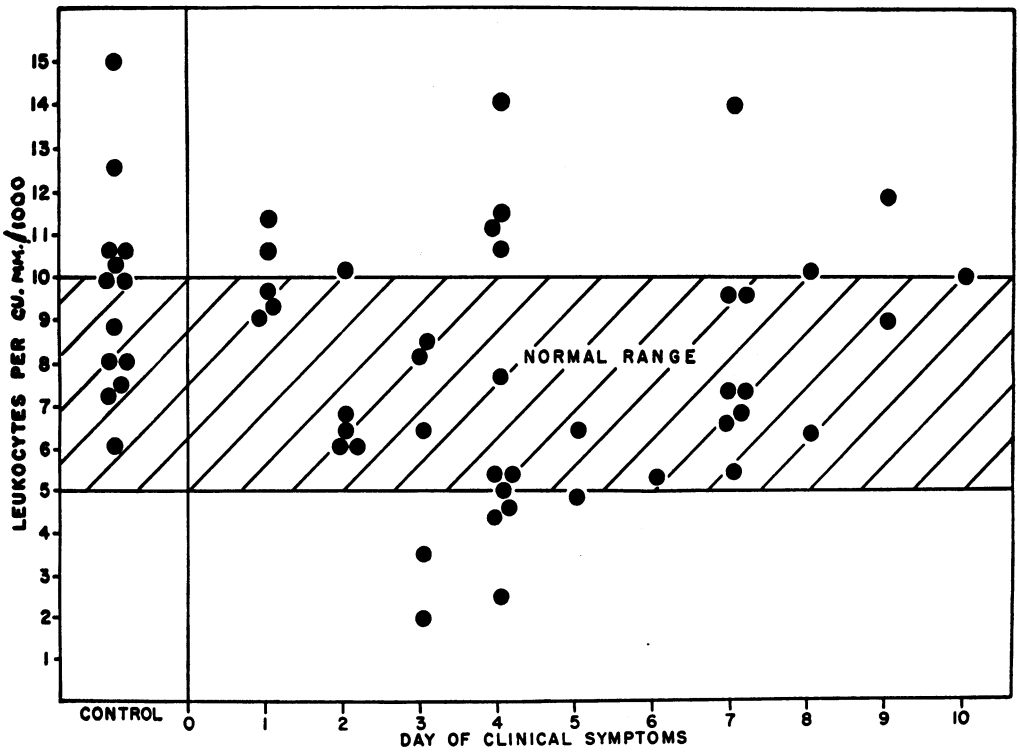

FIG. 3. TOTAL LEUKOCYTE COUNTS IN INDIVIDUALS WITH INFLUENZA IN RELATION TO ONSET OF SYMPTOMS

Values of leukocyte counts obtained on this group prior to influenza are also given.

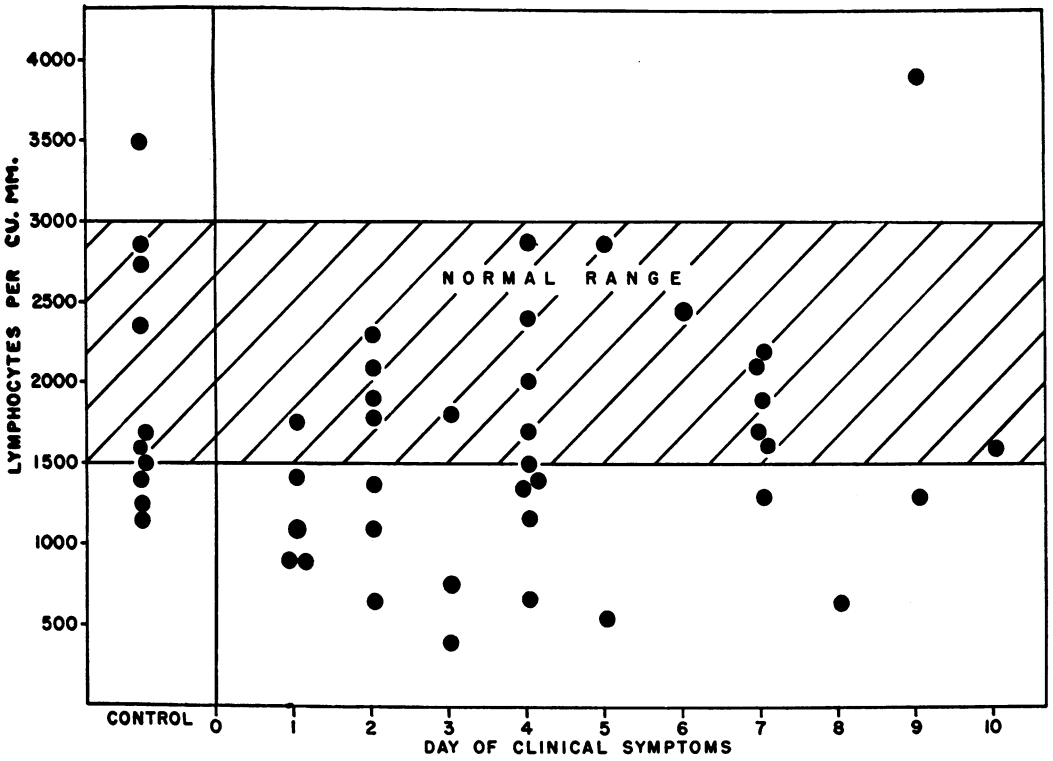

FIG. 4. TOTAL LYMPHOCYTE COUNTS IN INDIVIDUALS WITH INFLUENZA IN RELATION TO ONSET OF SYMPTOMS

Values of lymphocyte counts obtained on this group prior to influenza are also given.

obtained during the disease period varied from 2,000 to 14,000 cells per cu. mm. Nine of 18 patients had leukocyte counts which remained consistently within the normal range. Four persons had transient leukopenia which occurred on the third and fourth day of illness. A leukocytosis of 14,000 cells per cu. mm. was encountered in two patients. The three patients who developed pulmonary bacterial complications could not be differentiated on the basis of leukocytic response. Lymphopenia was common during the first four days of influenza in the face of normal total leukocyte values. Lymphocyte counts are graphed in Figure 4. Striking lymphopenia was noted in four individuals. The single instance of sustained lymphopenia was associated with a normal total leukocyte count.

Erythrocyte sedimentation rates. Erythrocyte sedimentation rates were commonly elevated during the course of influenza, but a significant number of hospitalized patients had increased sedimentation rates prior to the onset of influenza, rendering uncertain the significance of this observation.

Bacteriologic studies

Nose and throat cultures were obtained from 53 persons during the course of the epidemic. These cultures did not demonstrate significant differences in the recovery of potential pathogens from individuals with influenza and those without influenzal symptoms. Cultural data are presented in Table III. Pneumococci and *Hemophilus influenzae*

TABLE III

Bacteriologic findings in nose and throat cultures obtained from 53 individuals

Organism	With influenzal symptoms (24)	Without influenzal symptoms (29)
Coagulase positive staphylococcus aureus	8	13
Pneumococcus	4	1
Hemophilus influenzae	4	0
Group A streptococcus	0	0

were isolated from four persons with influenza. Pneumococcal pneumonia was present in one of these patients. Coagulase positive staphylococci were isolated from eight persons with influenza and 13 without evidence of disease. Beta hemolytic streptococci were not recovered from any patient.

Virologic studies

Virus isolation. Because of the explosive nature of the outbreak, specimens for virus isolation were not obtained until 96 to 120 hours after the onset of the epidemic, and only five attempts at virus isolation were performed on selected recent cases. The Asian strain of influenza A virus was recovered from a throat washing obtained 96 hours after the onset of influenza in one patient. Throat washings obtained from the remaining four patients, 24 to 96 hours after the onset of symptoms, did not yield influenza virus.

Serologic studies. Fifty-five paired serum specimens were available for serologic study. A fourfold rise in antibody titer between acute and convalescent serums was considered evidence of influenza virus infection.

Fifty-four pairs of sera were tested for hemagglutination-inhibiting antibodies using trypsinized sera and egg-line, inhibitor-resistant virus. Initial titers were low, ranging from less than 1 : 8 to 1 : 32, and in none of the convalescent sera did the anti-

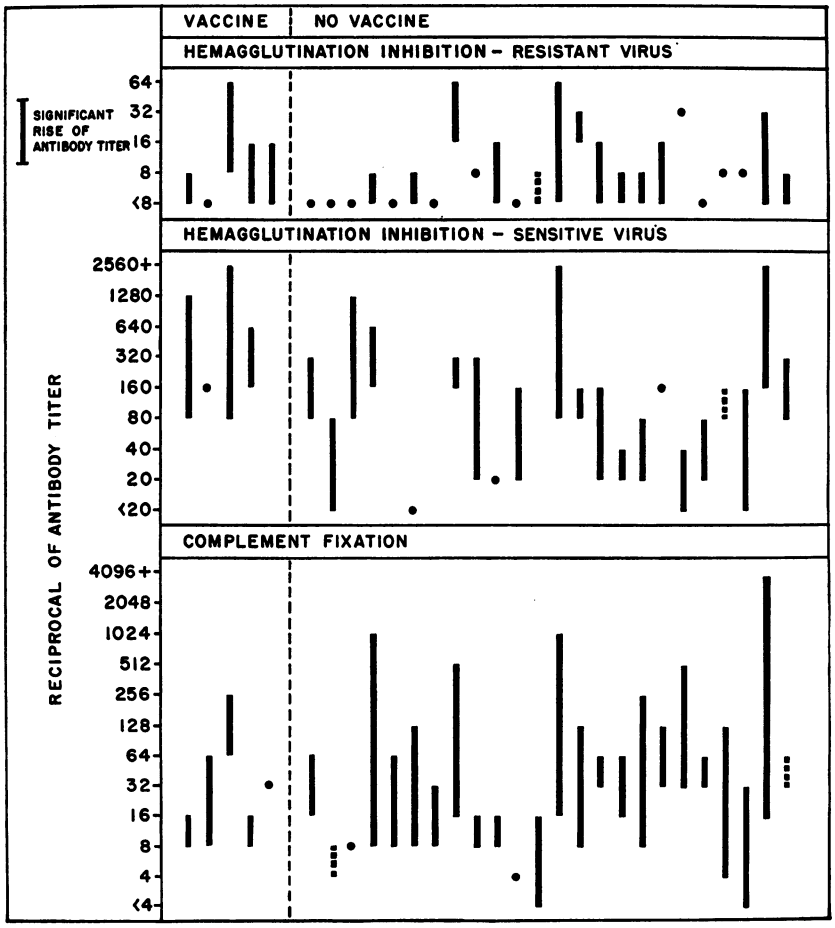

FIG. 5. COMPARISON OF CHANGES IN ANTIBODY TITER BY THREE SEROLOGIC METHODS IN INDIVIDUALS IN WHOM ANTIBODY TITER RISE WAS DEMONSTRATED BY ANY ONE OF THESE METHODS

A solid line indicates a rise in titer, a dotted line a fall, and a single dot denotes that no change in titer occurred.

TABLE IV

Serologic findings on individuals manifesting clinical influenza and/or significant antibody rise

No.	Case	Date, onset of symptoms	Vaccination route, Date	Date of sera		Reciprocal of antibody titers						Significant antibody rise		
				Early	Convalescent	HI-inhibit. resis. virus		HI-inhibit. sens. virus		Comp. fix.		HI-resis. virus	HI-sens. virus	Comp. fix.
1	R. S.	9/28		10/3	10/16	<8	32	160	2,560+	16	4,096+	+	+	+
2	D. B.	9/30		10/3	10/16	<8	<8	80	320	16	64	0	+	+
3	L. F.	9/30	S.C. 9/11	10/4	10/16	<8	16			32	32	+		0
4	S. F.	9/30		10/4	10/16	<8	8	<20	<20	8	128	0	0	+
5	B. N.	9/30		10/3	10/16	<8	64	80	2,560+	16	1,024	+	+	+
6	J. B.	10/1		10/3	10/16	<8	<8	80	80	16	16	0	0	0
7	C. C.	10/1		10/3	10/8	<8	<8	20	160	4	4	0	+	0
8	G. C.	10/1		10/3	10/16	8	<8			<4	16	0		+
9	M. D.	10/1		10/3	10/16	8	<8	<20	<20	8	8	0	0	0
10	S. D.	10/1		10/3	10/16	<8	16	20	20	8	16	+	0	0
11	J. G.	10/1		10/4	10/16	<8	<8			8	32	0		+
12	V. G.	10/1		10/3	10/16	16	<8			<4	<4	0		0
13	E. L.	10/1		10/3	10/16	16	64	160	320	16	512	+	0	+
14	R. K.	10/1		10/3	10/24	<8	<8	20	80	32	64	0	+	0
15	A. M.	10/1		10/3	10/8	16	32	80	160	8	128	0	0	+
16	K. N.	10/1		10/3	10/24	<8	16	160	160	32	128	+	0	+
17	G. V.	10/1		10/3	10/16	32	32	<20	40	32	512	0	+	+
18	J. S.	10/2												
19	E. C.	10/3		10/3	10/16	<8	<8	160	640	8	1,024	0	+	+
20	M. R.	10/3	S.C. 9/11	10/3	10/16	<8	<8	160	160	8	64	0	0	+
21	M. T.	10/3												
22	M. E.	10/4		10/3	10/16	<8	<8			8	64	0		+
23	A. F.	10/4	S.C. 9/11	10/3	10/16	<8	<8	80	80	64	64	0	0	0
24	E. H.	10/4		10/3	10/16	8	8	20	320	8	16	0	+	0
25	L. S.	10/4	S.C. 9/11	10/3	10/24	8	64	80	2,560+	64	256	+	+	+
26	I. C.	10/5		10/3	10/24	<8	8	20	80	8	256	0	+	+
27	J. L.	10/5	S.C. 9/11											
28	A. P.	10/6		10/3	10/16	16	8	320	320	16	16	0	0	0
29	M. B.	10/10	S.C. 9/11	10/3	10/17	<8	16	160	640	8	16	+	+	0
30	L. J.	10/10	I.D. 10/2	10/2	11/1			40	160				+*	
31	G. B.		I.D. 9/11	10/3	10/16	<8	8	80	1,280	8	16	0	+	0
32	D. D.			10/3	10/16	<8	<8	80	1,280	8	8	0	+	0
33	Z. H.			10/3	10/16	<8	16	20	160	32	64	+	+	0
34	R. K.			10/3	10/16	<8	<8	<20	80	8	4	0	+	0
35	F. L.			10/3	10/16	<8	8	20	40	16	64	0	0	+
36	V. N.			10/3	10/16	8	8	160	80	4	128	0	0	+
37	A. S.			10/3	10/16	8	8	<20	160	<4	32	0	+	+
38	K. W.			10/3	10/17	<8	8	80	320	64	32	0	+	0

* This antibody rise was assumed to be due to vaccination.

body titer rise above 1:64. A significant rise in antibody titer was demonstrated in only nine pairs of sera by this method. All titers in this paper are expressed as final dilutions of serum.

Because of the apparent insensitivity of the egg-line virus in demonstrating antibody response, tests were repeated using potassium periodate for inhibitor destruction and a ferret-mouse passaged virus sensitive to both inhibitor and antibody. Forty-eight tests on paired sera were performed by this method which proved a more sensitive technique for the demonstration of influenza infection. Significant titer rises were demonstrated in 18 cases. The high initial titers of apparent antibody in some sera suggest that all inhibitor was not necessarily destroyed with periodate. However, the increased number of titer increases demonstrated with this method affirm its usefulness. Titration of antibody with a virus strain isolated from the epidemic (Case S. D.) did not demonstrate additional serologic responses in cases negative with the ferret-mouse line (inhibitor-sensitive) virus.

Fifty-two pairs of sera were tested for the presence of complement fixing antibody with viral antigen of the egg-line Japan 305 influenza virus. Significant increases in titer were evident with 18 pairs of sera.

Increases in both hemagglutination-inhibiting and complement fixing antibodies were noted as early as seven days after the onset of influenza symptoms, in accord with earlier observations on the appearance of neutralizing antibodies in influenza (10).

As noted in Figure 5, patients manifesting significant antibody response by one method did not necessarily demonstrate antibody rise by other serologic methods. Utilizing all three serologic tests for diagnosis, proof of influenza infection was obtained in 21 of 30 individuals developing clinical disease. In addition, eight persons who showed no clinical manifestations of disease had significant rises in antibody titers, indicating that inapparent influenza infection occurred during the epidemic period. A full summary of serologic data obtained on all individuals manifesting either the clinical syndrome or serologic evidence of recent influenza infection is presented in Table IV.

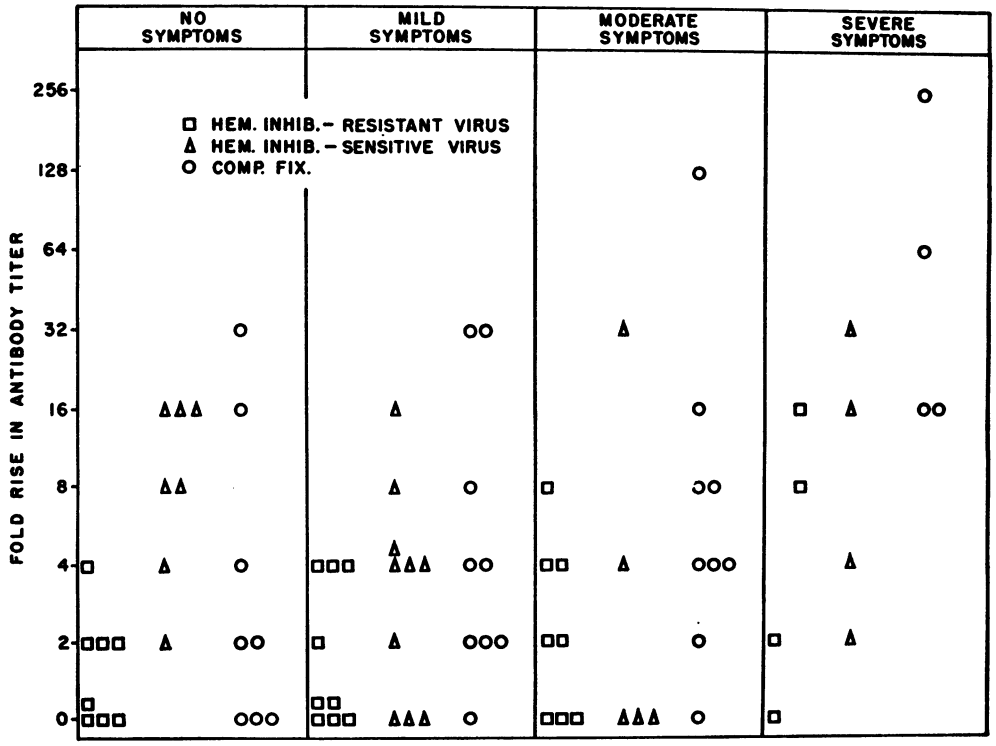

FIG. 6. CORRELATION OF FOLD RISE IN ANTIBODY TITER AND THE SEVERITY OF CLINICAL ILLNESS

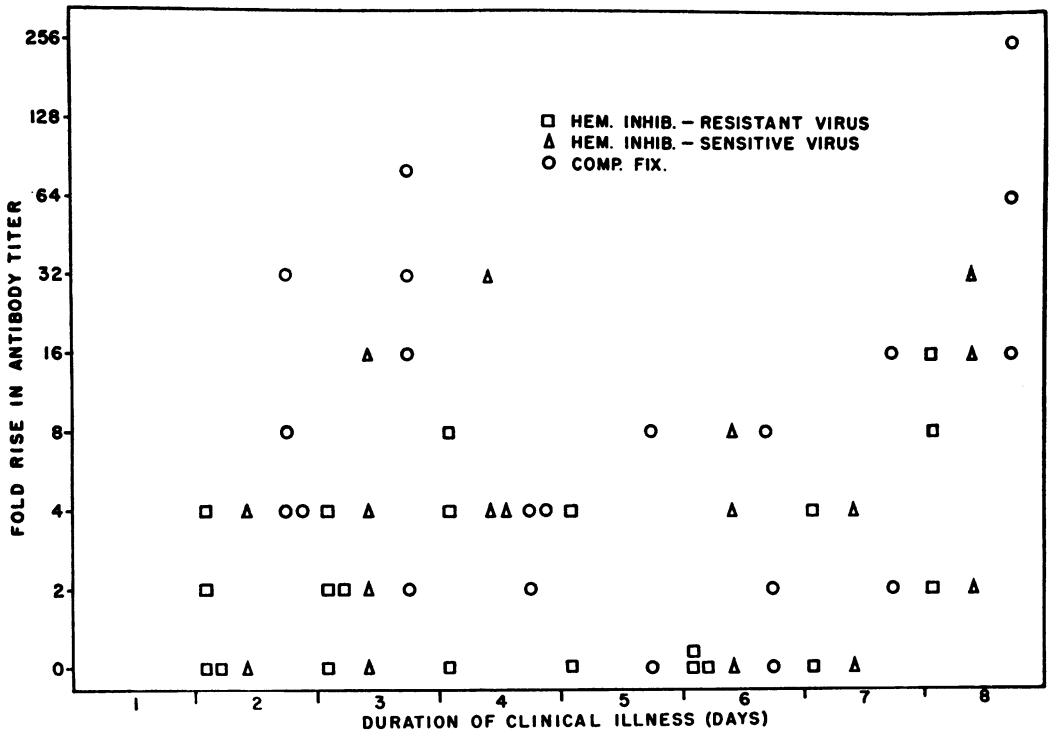

FIG. 7. CORRELATION OF FOLD RISE IN ANTIBODY TITER AND THE TOTAL DURATION OF THE CLINICAL ILLNESS

The relation of the degree of antibody rise to the severity and duration of influenza symptoms

The relation of antibody response to the severity and duration of influenzal symptoms was examined. The relevant data are presented in Figures 6 and 7. It is evident that the spread of antibody response is broad and the data scattered, particularly when antibody response and duration of illness are correlated. However, if attention is directed to individual CF antibody responses of fourfold or more, a definite trend is noted in those cases with proved infection. This trend of *increasing incidence of significant antibody response with increasing severity of infection* could merely indicate *more accurate clinical diagnosis* in the more severely ill. That this interpretation is partially correct is shown by comparison of the geometric means of the antibody responses of fourfold or more in the various categories of illness. It is found that these average fold increases are 12.1 in patients with "no symptoms," 10.6 in patients with "mild symptoms," and 9.2 in patients with "moderate symptoms." In the few patients with "severe symptoms," however, significantly greater response, averaging 45-fold, was found. Thus the antibody response of seriously ill patients clearly exceeded that of patients with milder symptoms even when comparison was restricted to those with serologically proved influenza.

Incidence of influenza in vaccinated and nonvaccinated individuals

As previously noted, 20 staff members had received influenza vaccine prior to the appearance of influenza on H5. In 19, sufficient time (19 days) had elapsed for the development of measurable antibody (11).

Pre-epidemic antibody levels in vaccinated individuals were comparable to those demonstrated in nonvaccinated individuals when determined by complement fixation or hemagglutination-inhibiting antibody studies using inhibitor-resistant virus. Higher levels of pre-epidemic antibody were noted in the majority of vaccinated individuals when hemagglutination-inhibiting antibody was determined with the inhibitor-sensitive virus antigen

TABLE V

Incidence of influenza in vaccinated and nonvaccinated individuals

Group	No. developing clinical influenza / No. at risk	No. with significant antibody titer rise / No. tested
Vaccinated	7/20 (35%)	5/16 (31%)
Nonvaccinated	23/42 (55%)	24/37 (65%)

(Figure 5, Table IV). Nevertheless, there was considerable overlap with the titers obtained in nonvaccinated individuals.

Despite the equivocal nature of antibody increase in vaccinated individuals, suggestive evidence of vaccine protection was obtained. As noted in Table V, seven of 20, or 35 per cent of the vaccinated personnel developed clinical influenza compared with 23 of 42, or 55 per cent of the total nonvaccinated group. If only individuals developing significant antibody response were included in the analysis, 5 of 16, or 31 per cent of the vaccinated and 24 of 37, or 65 per cent of the total nonvaccinated group had documented influenza infection. If the 33 ward personnel were considered separately, 8 of 13 nonvaccinated staff members manifested clinical influenza in contrast to 7 of 20 individuals receiving influenza vaccination. Thus although the groups were small, the results suggest protection by immunization in a situation of concentrated exposure.

Miscellaneous laboratory studies

Laboratory studies did not reveal evidence of significant changes in liver or renal function. None of the patients tested developed serum cold agglutinins during influenza.

Studies on certain experimental bacterial infections suggest that profound changes in serum amino acids can occur during the course of generalized infection (12). The prostration associated with influenza led us to determine whether gross changes in serum proteins or serum amino acid levels accompanied the acute illness. Sera obtained from eight acutely ill patients were paired with sera from the same patients obtained following recovery and subjected to protein electrophoresis and paper chromatography. No differences could be detected in the patterns obtained during acute and recovery phases.

DISCUSSION

Explosive onset and swift spread of the infection in crowded populations are cardinal features of epidemic influenza. These characteristics suggested the etiology of the present epidemic and retrospectively led to the diagnosis of the patient admitted with fever of unknown origin who represented the primary case. The high attack rate of symptomatic infection produced by the pandemic virus of 1957 which involved 30 of 62 persons in this institutionalized group also resembled previous epidemics caused by other strains of influenza A virus (10). So, too, the incidence of clinically inapparent infection detected by specific antibody response (28 per cent) corresponded exactly with past experience reported by Horsfall, Hahn and Rickard (10) and closely with the 32 per cent incidence of inapparent influenza A noted by Kilbourne, Anderson and Horsfall in a mixed A and B epidemic in children (13).

The present outbreak occurred in a heterogeneous group containing both healthy and sick adults of widely differing ages. It can be assumed with reasonable certainty that infection was produced by a single strain of virus. It thus seems of particular interest to note the varying disease syndromes observed in different individuals. In young and previously healthy adults influenza virus infection caused the expected acute and prostrating but brief and benign illness typical of past epidemics of influenza A (8–10). In patients hospitalized with debilitating disease states, severe and unusual symptomatology and illness occurred. In these individuals, already ill, an undue incidence of gastrointestinal symptomatology was associated with the more usual symptoms of influenza virus infection. Furthermore, five hospitalized patients developed evidence of lower respiratory tract involvement. Although bacteriologic studies failed to reveal changes in the bacterial flora of the nasopharynx in the majority of persons developing influenza, three of these five patients developed definite bacterial pneumonia. Each of these three patients had underlying chronic rheumatic heart disease. The relationship between serious pulmonary complications of influenza and underlying illness is discussed in detail in the succeeding paper (3).

It thus appeared that the variations in severity

of influenza observed among members of this semi-closed community were probably related to differences in host management of infection rather than to variations in viral virulence during this small explosive outbreak.

While total leukopenia was uncommon, an absolute lymphocytopenia was noted to occur during the first four days of illness in many patients. This finding, reported in experimental influenza in human volunteers (14) and in murine infection (15, 16), deserves further investigation as a difference in the host reaction to viral and bacterial infections of possible diagnostic value. An extensive series of other laboratory studies did not reveal consistent or diagnostically useful abnormalities.

The present study supports the finding of Jensen and Hogan that multiple serologic methods are necessary for the maximum diagnosis of cases of influenza (17). Despite the use of three methods, significant antibody response was not demonstrated in nine patients who developed clinical illness indistinguishable from the serologically confirmed influenza of others. Although it is possible that these individuals contracted a respiratory infection of other etiology, the clinical syndrome and the setting in which it arose make it more likely that the serologic techniques used were inadequate to detect the presence of influenza in 30 per cent of those who contracted the disease.

Patients who were severely ill showed a greater antibody response than patients with mild or moderate symptomatology. This finding has not been previously documented in human influenza. Greater antigenic stimulation produced by the protracted presence of the virus or the attainment of greater viral (antigenic) mass during the course of the infection appear the most likely explanations of this phenomenon.

Evidence obtained in the present outbreak suggests that prior vaccination with small amounts of specific monovalent influenza vaccine may exert a protective effect in a group subjected to concentrated exposure. Serologically documented influenza infection occurred in 31 per cent of vaccinated individuals, as contrasted with 65 per cent of persons who had not received the vaccine. Although the difference in attack rate is not marked, this decrease in incidence of infection correlates well with previous studies on vaccine efficacy in small closed populations (18).

Thus in the present experience, the epidemiology and clinical nature of a small epidemic of influenza A within the 1957–58 pandemic resembled previous outbreaks occurring in interpandemic years. Detailed study of this epidemic has emphasized the influence of the underlying status of the human host on the severity of the disease, the frequency of lymphopenia early in the course of influenza, and a correlation between the severity of the illness and the magnitude of specific antibody response.

SUMMARY

1. An epidemic of influenza A on a hospital ward during the pandemic of 1957–58 caused illness in 30 persons of a total population of 62. Serologic evidence of influenza infection was obtained in eight persons who did not manifest symptoms of influenza.

2. The disease closely resembled previous descriptions of typical influenza, except for the occurrence of a high rate of gastrointestinal symptoms in patients with underlying disease. Three patients with rheumatic heart disease developed pulmonary complications of influenza.

3. Except for inconstantly observed lymphocytopenia during the first four days of illness, consistent abnormalities were not found with routine and special laboratory tests.

4. The incidence of serologically confirmed influenza was 34 per cent less in vaccinated than in nonvaccinated subjects.

5. Determination of both hemagglutination-inhibiting and complement fixing antibodies increased the number of cases diagnosed.

6. Although the severity and duration of illness were not correlated with antibody response as a straight line function, the mean magnitude of complement fixing antibody increase in seriously ill patients was almost fourfold greater than in other patients with significant serologic response to infection.

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