MEDICAL GRAND ROUNDS

THE UNIVERSITY OF TEXAS HEALTH SCIENCE CENTER AT DALLAS

July 22, 1976

INFLUENZA

James P. Luby, M.D.

"If we do not vaccinate widely and effectively and . . . influenza should appear, then undoubtedly we shall have copious opportunity again to study pandemic influenza. If we do vaccinate now, the most valuable information that can be derived will be whether or not we have finally gotten ourselves into a situation where we know that we can protect against outbreaks of pandemic influenza."

Richard E. Shope (1957).

TABLE OF CONTENTS

INTRODUCTION

A nationwide immunization campaign is being planned for the United States beginning in September to prevent the morbidity and mortality associated with pandemic influenza. Plans for this campaign began after the documentation of human to human transfer of an antigenically novel influenza A virus at Fort Dix, New Jersey this spring. The influenza A virus isolated at Fort Dix has the antigenic constitution of the virus that most probably caused the 1918-1919 pandemic and which has circulated in the American Midwest in swine since 1918. The virus has been called swine influenza virus (HSw1N1). In this report we will set out to explore the scientific rationale for the immunization campaign as well as to delineate the major recent advances that have been made in our understanding of inluenza virus. We will concentrate on influenza A virus althouhg it is to be noted that because of its usual periodicity an epidemic of influenza B is possible this spring.

HISTORY

Epidemic influenza has been recognized from medical writings since at least the twelfth century. For the purposes of the present discussion we will concentrate on the occurrence of influenza A in the period beginning in 1889-1890. During this period of time an unquestioned pandemic of influenza struck the world. Morbidity related to the pandemic spread of this virus occurred at least through 1892. Excess mortality was noted but was nowhere near the level seen during 1918-1919. This pandemic is notable in that it occurred in a pre-antibiotic interval and for that reason can be compared to the 1918-1919 pandemic of influenza. From serological studies performed on people living through the 1889-1890 pandemic it has been ascertained that they were most probably infected with a virus that had a hemagglutinin with the antigenic characteristics of the Asian strain of influenza virus (H2). In the early 1900s another epidemic of influenza occurred. From seriological studies performed on persons living through this epidemic it has been ascertained that they were infected with a virus with a hemagglutinin that closely resembled the Hong Kong strain of influenza A virus (H3). Table 1, Figure 1 (71, 143).

In the spring of 1918, epidemic influenza occurred again. Although its origin will never be known with certainty, the first documentation of its occurrence was at an army camp, Camp Funston in Fort Riley, Kansas. Excess mortality was noted in the United States that spring. It has been established that persons who had influenza that spring were immune to attacks of influenza later to occur that fall and winter. Epidemics of influenza occurred throughout that summer but there was no demonstrable effect on excess mortality during that period of time. Troop movements related to the closing phases of World War I undoubtedly aided the spread of the virus. Then in the autumn of 1918 there occurred a worldwide pandemic of

TABLE 1

Periods of Possible Pandemic Occurrence of Influenza In Recent History

Date	Unquestioned pandemic	Pandemic interval (years)	Major epidemic interval (years)
1847			
1855			8
1875			20
1889	+		14
1900			11
1918	+	29	18
1929			11
1946	+	28	17
1957	+	11	11
1968	+	11	11

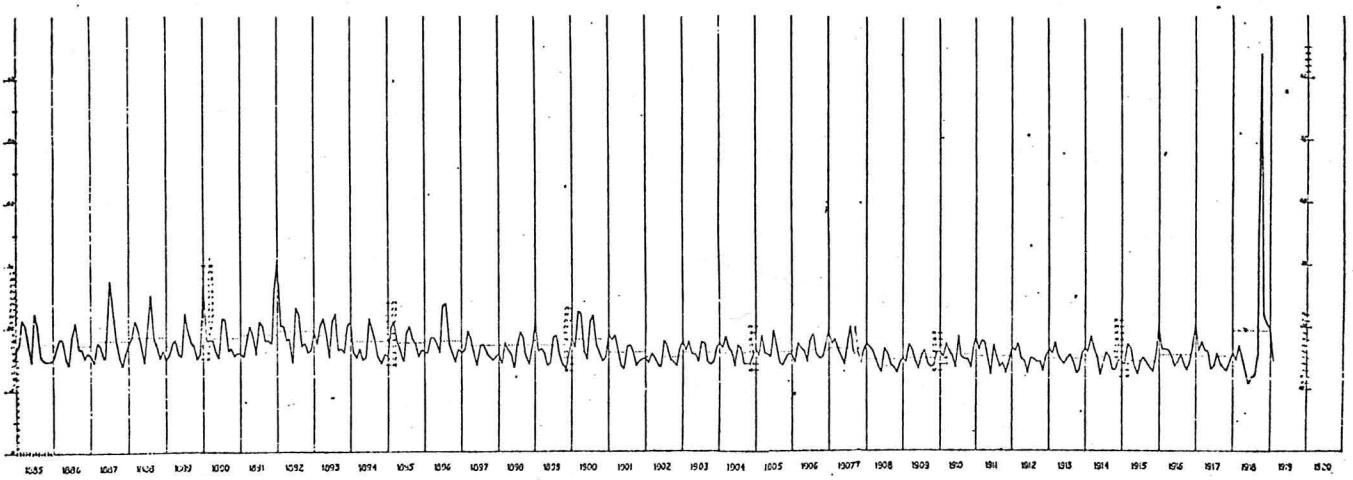
[a] Including undisputed pandemics of and major (possible pandemic) outbreaks with high excess mortality. For example, the mortality in England and Wales and in Victoria in 1899-1900 was almost as high as observed with 1889-1891 pandemic [League of Nations' data cited by Burnet and Clark (1942)]. Thirty "pandemics" occurred between 1510 and 1930; the mean interpandemic interval for this period is 14 years [data from Francis and Maassab (1965), interpretation the author's].

influenza that was to cause 500,000 deaths in the United States and 20 million deaths worldwide. It had a peak month in October although a second wave occurred in the early portion of 1919. The 1918-1919 pandemic is notable in many instances. It struck with alarming ferocity involving many geographically disparate areas at approximately the same period of time (Figure 2)(16). Although total case rates were probably no greater than the 1889-1890 pandemic and the later 1928-1929 epidemic of influenza, the pneumonia attack rates were significantly increased. The percent of cases complicated by pneumonia ranged from approximately three to ten per cent. Case rates of influenza declined with advancing age although pneumonia case fatality ratios indicated proportionately more severe disease with advanced age. The 1918-1919 pandemic was especially noted for the striking involvement of persons in the twenty to forty year age group. The deline of influenza case rates with advancing age has been postulated to have resulted from pre-existing exposure of elderly persons to an influenza virus that had the same antigenic characteristics as the one that circulated during the great epidemic (Figures 3, 4) (38).

Although it cannot be proven, the striking increase in excess mortality of the 1918-1919 pandemic as compared to the epidemics occurring 1889-1890 and 1928-1929 may have resulted from an intrinsic virulence of the virus. Other explanations such as dislocations brought on by the World War or of excessively virulent strains of bacteria do not seem applicable in that World War II was accompanied by as much disruption of civilized life and 1946 saw the emergence of another pandemic strain of influenza virus. The bacteriology of cases of

FIGURE 1

THE 1918 EPIDEMIC OF INFLUENZA IN CONNECTICUT

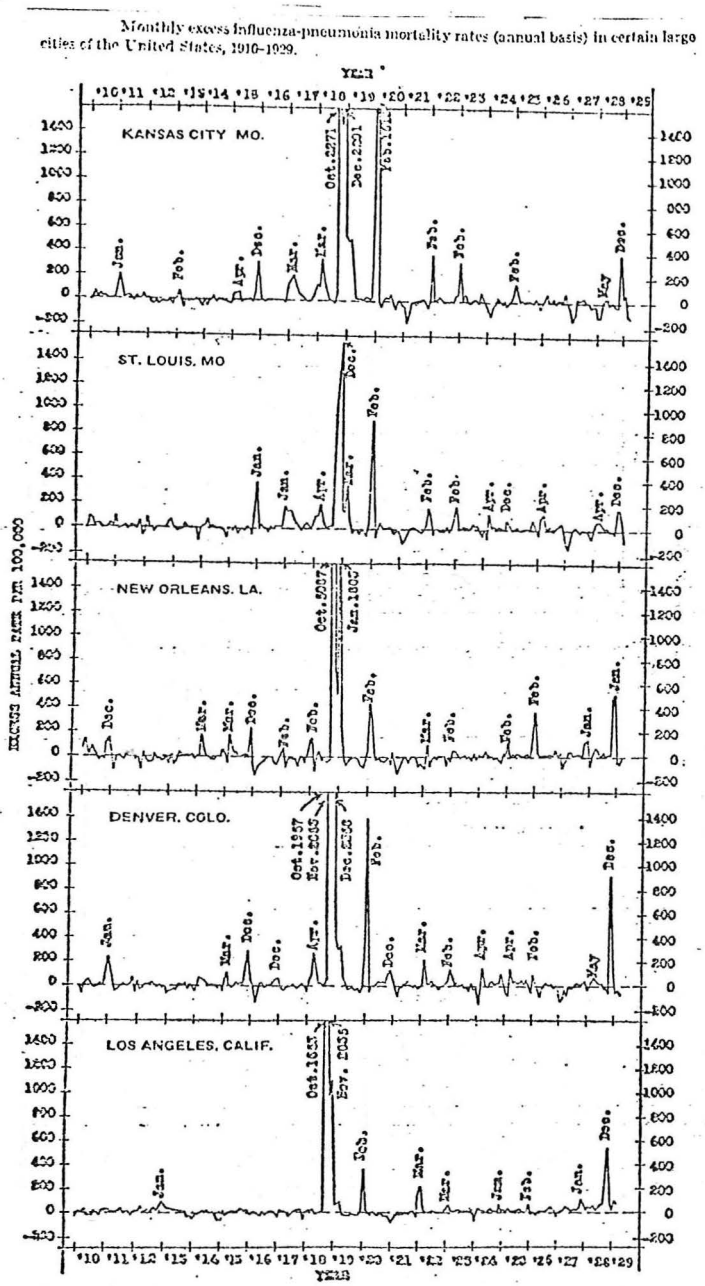


Monthly death rate from all causes per 1,000 population in Connecticut (on annual basis).

pneumonia was extensively studied during the 1918-1919 epidemic. Multiple bacterial species were found, most commonly Pneumococcus but also Group A Streptococcus and *Staphylococcus aureus*. *Hemophilus influenzae* (Pfeiffer's bacillus), the agent postulated to have caused the 1889-1890 pandemic, was found inconsistently among specimens during the 1918-1919 pandemic. Bacteriological studies in 1918-1919 thus effectively disproved the hypothesis that *Hemophilus influenzae* was the cause of epidemic influenza.

All authorities now agree that the tremendous excess mortality associated with the 1918-1919 pandemic could not occur again simply because of our capacity to combat bacterial suprainfection with potent antimicrobial substances. It seems unlikely, however, that antibiotics would have much effect on the incidence of pneumonia complicating influenza. With an attack rate approximating 30% and with 5% of the cases complicated by pneumonia, it is easy to comprehend why the 1918-1919 pandemic and its fulminant occurrence in October-November, 1918

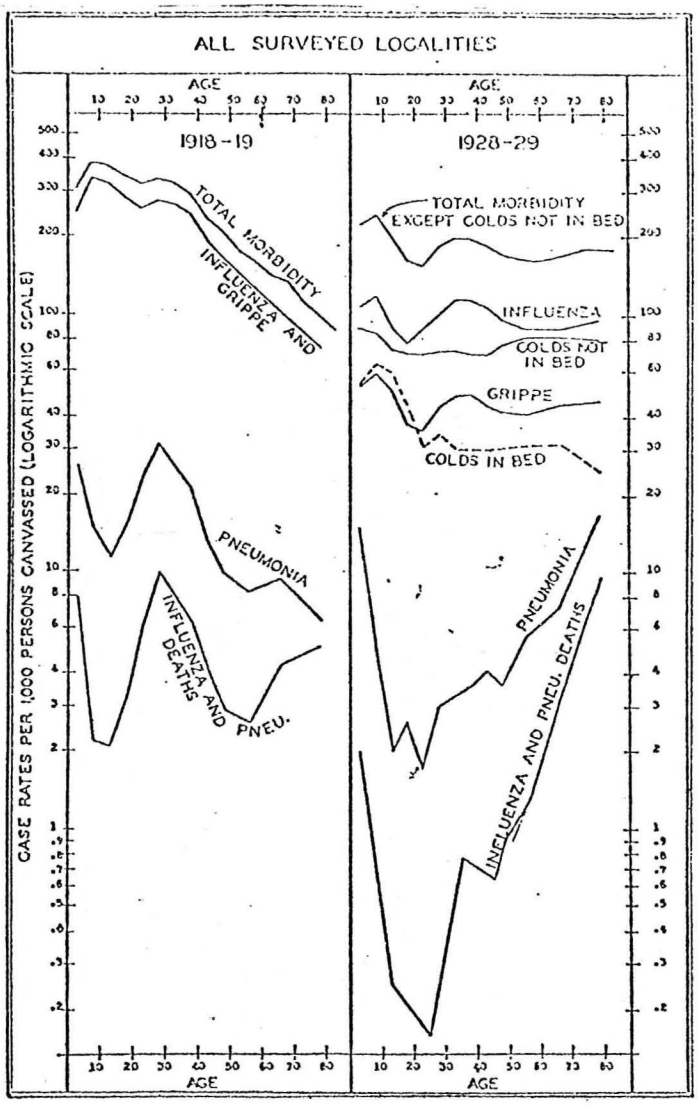
FIGURE 2



literally overwhelmed the medical facilities of the U. S. and the world. Although a virus having the antigenic characteristics of the 1918-1919 pandemic strain (HswlN1), may circulate in the coming year, it must be stressed that the antigenic characteristics of a virus may be separate from the factors which determine its virulence. Thus, the 1889-1890 pandemic was caused by a novel antigenic agent; however, this pandemic was not associated with the lethality caused by the 1918-1919 virus. Both pandemics occurred before the advent of antibiotics. The 1918-1919 pandemic stresses the tremendous potential of this virus to inflict damage on human populations.

FIGURE 3

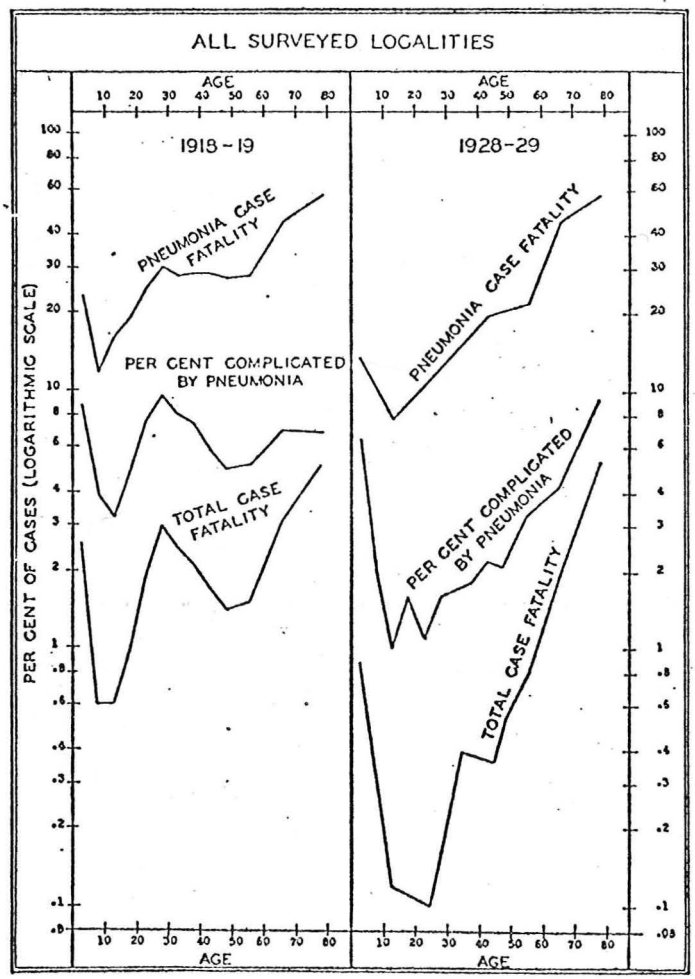
Relative change with age in the incidence of the various types of respiratory illness in surveyed groups during the epidemics of 1928–29 and 1918–19.



At the time of the occurrence of the 1918-1919 epidemic, farmers in the American Midwest noted for the first time a clinically similar disease in swine and called it "Hog Flu." This disease, swine influenza, is considered so striking in its epidemic form that it is unlikely to have been missed and now continues to occur endemically in the U. S. Only occasional instances of its transmission to humans have occurred and prior to this spring, there has been no documented human to human transmission.

FIGURE 4

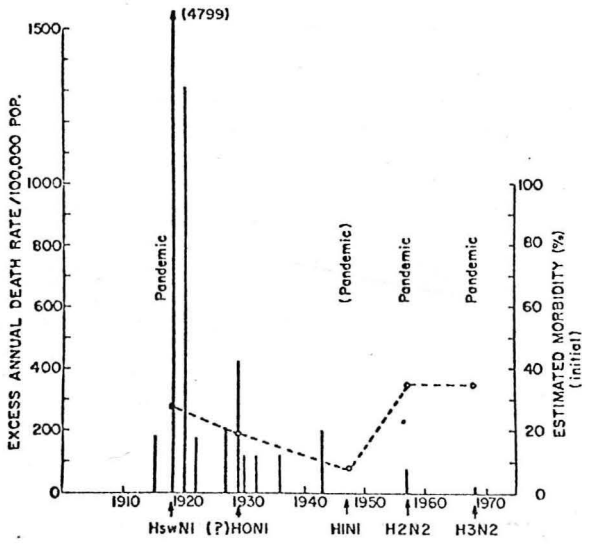
Relative change with age in the severity of the various types of respiratory illness in surveyed groups during the epidemics of 1928–29 and 1918–19.



In 1931, Shope isolated the agent of swine influenza and later showed that persons who lived during the 1918-1919 pandemic possessed antibody to this virus. Later, in 1933 Laidlaw, Andrews and Smith isolated the influenza A virus from human cases by inoculation in ferrets. This opened the way to the modern era of virology of influenza. Francis was later to isolate influenza B virus. This virus was shown later to cause geographically restricted disease occurring every four to six years without much excess mortality and having as its most significant lethal complication the induction of Reye's syndrome. The agent isolated by Laidlaw, Andrews and Smith is now designated antigenically H0N1. In 1946 another

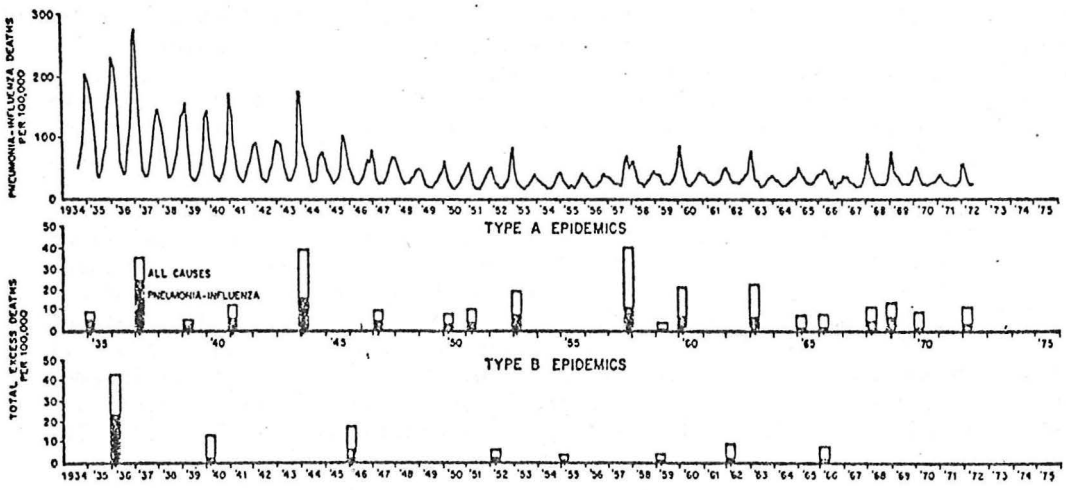
pandemic occurred caused by H1N1 influenza A virus. Then in 1957 another pandemic occurred caused by Asian influenza virus designated antigenically as H2N2. In 1968-69 the Hong Kong strain of influenza virus circulated around the world causing another pandemic and it has been antigenically denoted as H3N2 (Figures 5, 6) (71). The epidemiologic pattern of the occurrence of

FIGURE 5



Profile of major epidemics of influenza in the United States during the twentieth century. Open circles estimated morbidity in initial wave; vertical lines, excess annual death rate per 100,000 population.

FIGURE 6



Pneumonia–influenza death rates by month and excess mortality during epidemic periods, United States, 1934–1972. (Influenza-Respiratory Disease Surveillance. U.S. Department of Health, Education and Welfare, Public Health Service, Report No. 88. Center for Disease Control, 1973, p. 8.)

Influenza A now appears to be that of pandemic disease every ten to eleven years followed by epidemic disease every two to three years at a fairly regular periodicity. The elucidation of this epidemiologic pattern has enabled the U.S. Public Health Service to make predictions of epidemics and this stimulated the administration of vaccine. The study of influenza virus has been enormously eased by the discovery of Burnet that it could be cultivated in the amniotic and chorioallantois sacs of embryonated chicken eggs and later its demonstration that it could be grown in monkey kidney tissue culture.

With increasing world travel, antigenic variants of influenza A virus have a greater likelihood of spreading through the world population. The speed with which such a virus can spread is illustrated in relationship to the recent experience with the Victoria strain of influenza A virus. The first documented cases of influenza in the U. S. caused by the Victoria strain of influenza virus had onsets in Oregon beginning January 7, 1976 and in California beginning January 13th, 1976. During the week ending February 7, adult admissions to the major medical emergency room at Parkland Memorial Hospital, Dallas, Texas for influenza-like illnesses reached epidemic levels. It has been estimated that there were 11,000 pneumonia and influenza deaths attributed to the influenza A epidemic caused by the Victoria strain in the U. S. This is the highest number since the Hong Kong 1968-1969 epidemic when an estimated 12,700 pneumonia and influenza deaths occurred.

VIROLOGY

Influenza virus has three subtypes: A, B and C. The subtypes of influenza virus differ in having distinguishable soluble antigens which fix complement. It is now known that such antigens are largely composed of the ribonucleoprotein and the Membrane (M) protein of the virion. Influenza B causes geographically restricted disease at usual periodic intervals of four to six years. It causes absenteeism at work, school and affects excess mortality slightly. Aside from morbidity, its major clinical import is that of the induction of Reye's syndrome. Influenza C causes a common cold syndrome without being associated with significant epidemic disease. Most of the modern work in the virology of influenza virus has been determined with influenza A virus and therefore, this discussion will concentrate on that agent.

The structure of influenza A virus is either that of a sperical or filamentous particle. Filamentous forms often predominate when taken directly from clinical material. The spherical form represents the mature fully infectious particle and can be selected for by serial transfer. The filamentous form is thought to be lacking in M protein and is not considered infectious. Both the spherical and the filamentous particles possess surface projections or spikes. These spikes are the hemagglutinin and the neuraminidase and are attached by hydrophobic ends to the underlying lipid bilayer derived from host cell cytoplasmic membrane (Figures 7, 8) (15, 140). The hemagglutinin is actually a trimer of a single polypeptide (HA)

FIGURE 7

THE STRUCTURE OF INFLUENZA VIRUS

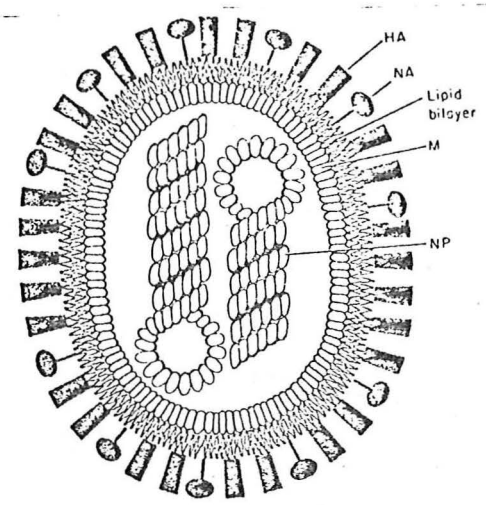
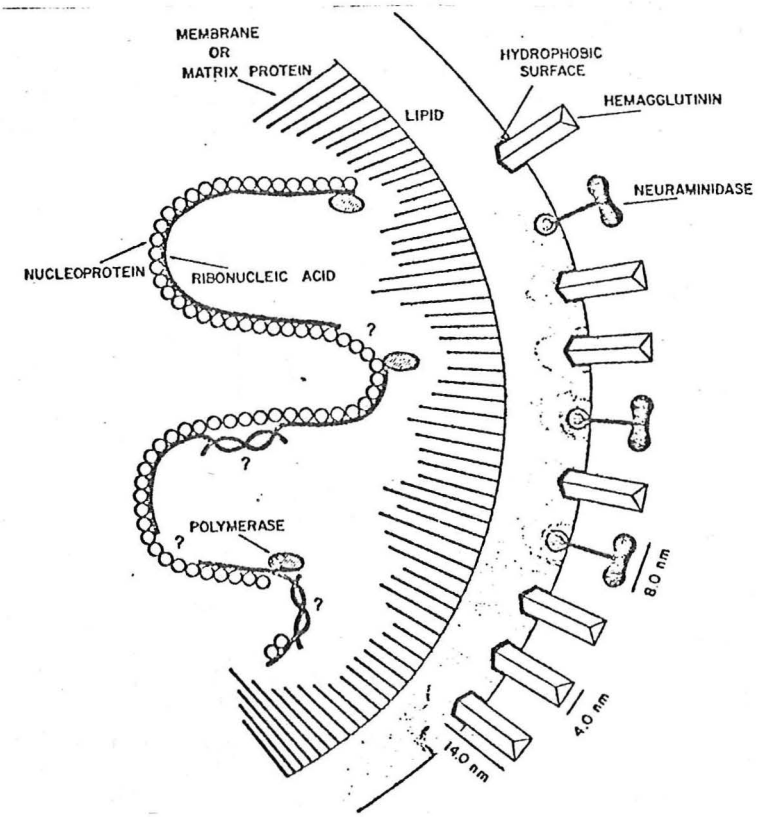


FIGURE 8

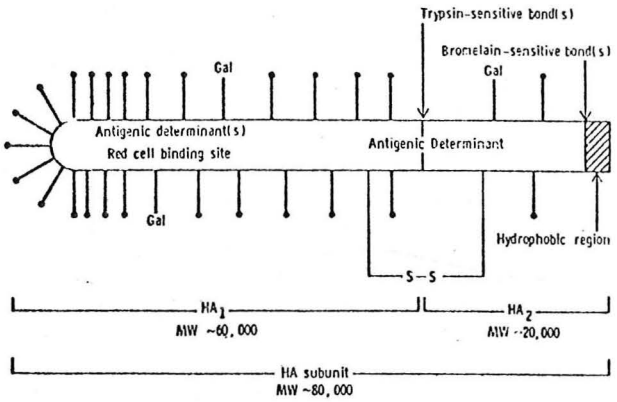
THE STRUCTURE OF INFLUENZA VIRUS



while the neuraminidase is a tetramer. The hemagglutinin can be cleaved by trypsin into two components: HA_1 and HA_2 (Figure 9) (116). The HA_2 portion of

FIGURE 9

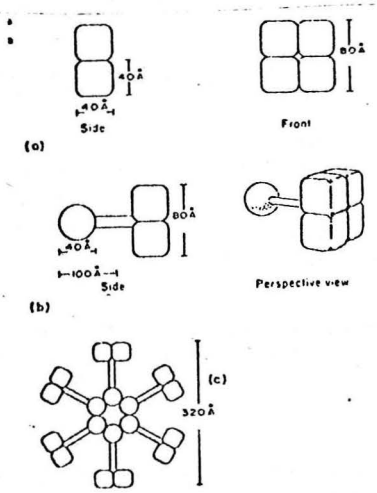
A DIAGRAM OF THE HA SUBUNIT



of the hemagglutinin trimer is inserted into the lipid bilayer. The antigenically more important end of the hemagglutinin trimer is designated as HA_1 and is actually the site of attachment of the virion to the host cell. The hemagglutinin subunit is a glycosylated protein which does not contain any neuraminic acid residues. Antibody directed against the hemagglutinin portion of the virion is considered to be protective, preventing attachment of the virion to the cell. The neuraminidase spike is a tetramer of a single polypeptide (NA), is located on the surface of the virion and has the capacity of cleaving N-acetylneuraminic acid from glycoprotein substrates (Figure 10) (10). It has at least three known functions. 1.) The first

FIGURE 10

NEURAMINIDASE STRUCTURE



of these is to aid in the budding process severing the attachment of the virion from the cell and thus aiding its release and exit. 2.) It also can separate the attachment of the virion from mucoproteins found in the saliva and in respiratory secretions. 3.) It has the additional function of preventing auto-aggregation of influenza virions. Antibody to the neuraminidase is thought to be protective. In tissue culture systems under agarose overlays antibody to the neuraminidase portion of the virion does not prevent attachment or infection but limits plaque size. The mechanism of plaque size limitation represents an inhibition of neuraminidase function by antibody and consequent prevention of virion release and subsequent infection of adjacent cells. The antigenic constitution of the hemagglutinin and neuraminidase are denoted by numerals. The virus originally isolated by Laidlaw, Andrews and Smith is known as HONl. The virus isolated in the pandemic of 1946 is known as HlNl. The virus isolated in 1957 is known as H2N2 and the virion isolated in the Hong Kong pandemic is known as H3N2. The virus of swine influenza is denoted as HswlNl. Other animal species also have influenza viruses of their own. Amongst the animals affected are horses, swine and various avian species. The hemagglutinins of these animal species are denoted also in terms of their antigenic characteristics. For example, the viruses that circulate in horses have hemagglutinins that are denoted as HEql and HEq2.

Underlying the lipid bilayer is a rim of M protein which may operate to orient the structures on the surface and probably directs the inclusions of ribonucleic acid (RNA) segments. The core of the virion is made up of at least 8 separable segments of RNA. These separable RNA segments are wound back upon each other in the form of a double helix with a hairpin turn. One of the problems in viral assembly necessitates getting all eight of these individual segments packaged into each virion. The M protein may function to aid in this packaging process. The packaging problem is such that certain of these nucleic acid segments can be absent from individual particles and more than eight segments can be included in other virions. There are at least two and perhaps three proteins in the core of the virion (P_1, P_2, P_3). One of these proteins serves as an RNA directed RNA polymerase (Table 2) (15).

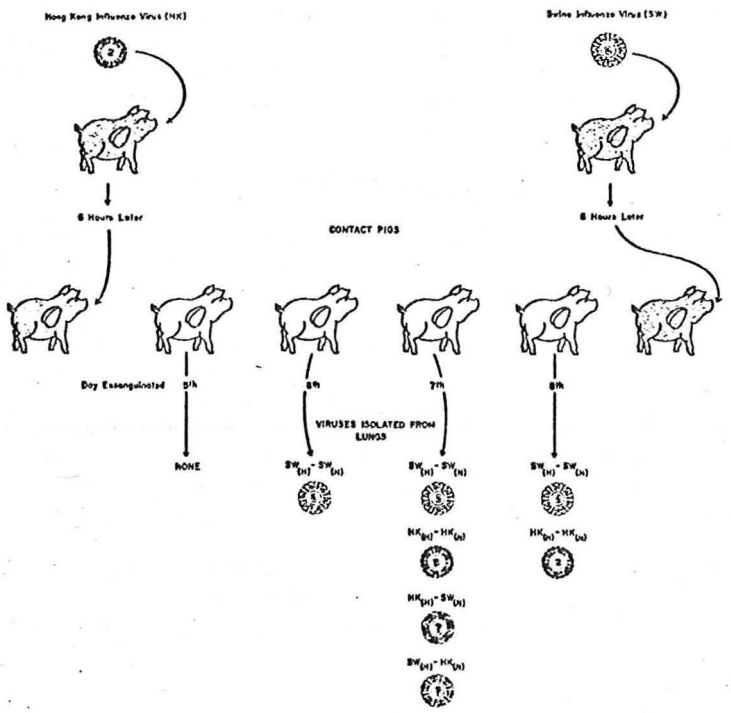
TABLE 2

The Proteins of the Influenza Virion

Designation	Molecular weight (daltons)	Location in virion	Function	Comments
P_1, P_2	81,000-94,000	Internal	Involved in RNA transcription?	Two polypeptides have been resolved in some, but not all strains
HA	75,000-80,000	Spikes on surface	Binding to cellular receptors	Glycoprotein. May be cleaved to yield HA_1 and HA_2
NP	55,000-65,000	Internal	Subunit of nucleocapsid	Strains of the same type share a common nucleoprotein antigen
NA	55,000-70,000	Spikes on surface	Neuraminidase	Glycoprotein
HA_1	49,000-58,000	Spikes on surface	Binding to cellular receptors	Glycoproteins, derived from HA by proteolytic cleavage and linked by disulfide bonds
HA_2	25,000-30,000	Spikes on surface		
M	21,000-27,000	Beneath lipid bilayer in envelope	Major structural component of envelope	Nonglycosylated membrane protein

Since there are multiple segments of RNA included with each virion, each coding for a specific protein, influenza A virus is the prototype of a virus in which genetic recombination occurs. Genetic recombination is that phenomena resulting after dual infection of a cell wherein the RNA segments of one virus particle may be packaged with the nucleic acid segments of the other virion. The progeny virion can be passaged in tissue culture and isolated under selective conditions. Genetic recombination has been shown to occur experimentally in animals under natural transmission conditions. One such experiment is pertinent and is depicted in Figure 11 (140).

FIGURE 11



Recombination between Hong Kong and SW influenza viruses under conditions of natural transmission. One pig was infected with HK influenza virus and a second pig was infected with SW influenza virus. Six hours later the infected animals were put into a room with four contact pigs. Beginning on the fifth day after introduction of the infected animals, one pig was exsanguinated each day and lung suspensions were examined for recombinant viruses as described in Materials and Methods. No viruses were detected in lung suspensions on the fifth day; on the sixth day parental SW virus was present, and on the seventh day both parental viruses and recombinant viruses possessing SW(H)-HK(N) and HK(H)-SW(N) were isolated. On the eighth day both parental viruses were present but no recombinant viruses were detected. From Webster *et al.* (1973).

Between pandemics the hemagglutinin and neuraminidase are undergoing constant change spoken of in terms of antigenic drift. A major change in the hemagglutinin particularly, or the neuraminidase results in the formation of a virion that has the capacity for pandemic spread. It has been postulated that such a change could not occur by mutation alone but might occur through genetic recombination wherein the recombinant may have the hemagglutinin of another species (equine, swine, avian) and the capacity to spread in populations characteristic of the human

parental strain. Although genetic recombination is the leading postulate to explain the mechanism of the induction of pandemic strains, this hypothesis has not been proven and other explanations are possible. Such explanations involve chance mutational events similar to but of a more profound magnitude to the mutations causing antigenic drift and the unlikely but still possible reactivation of a latent influenza A virus from a human host. It has recently been demonstrated that temperate RNA virus host cell interactions can result in DNA proviral copies of the virion. After multiple passages in tissue culture without apparent change in cell morphology, the virus can be rescued or reactivated by isolation of the cellular DNA and subsequent transfection of suitable cells in which viral replication can occur.

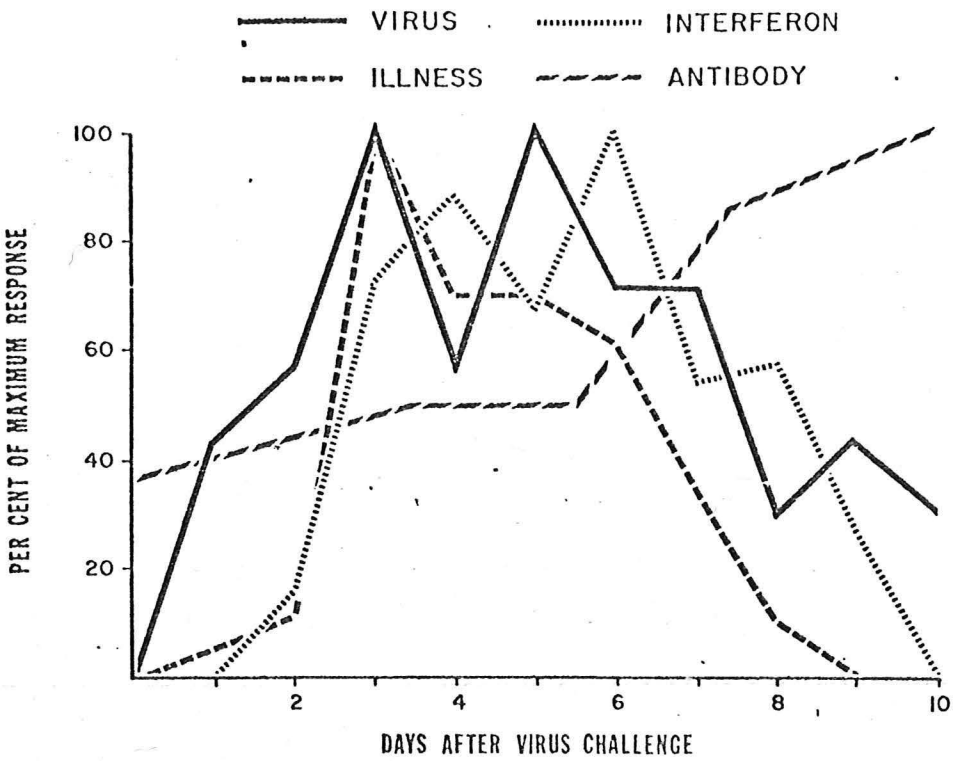
The phenomena of genetic recombination has been utilized to produce viruses for vaccine manufacture. Early passage isolates of influenza virus may not replicate well in the chorioallantoic sac of embryonated chicken eggs. By genetic recombination, strains that are adapted for growth in eggs can be placed in cell culture with a current novel antigenic isolate. Under proper selection techniques, progeny virus having the current antigenic characteristic and the capacity to replicate well in eggs can be produced.

Replication of the influenza virion involves attachment, penetration and uncoating followed by induction of complementary RNA directed by the enzyme, RNA directed RNA polymerase and which is contained in its core. The complementary RNA can now act as messenger RNA directing the synthesis of viral proteins. Viral RNA is then produced. Synthesis of the virion requires an intact host cell nucleus and ribonucleoprotein accumulates in that structure in the early phases of viral assembly. The other components of the virion are synthesized in the cytoplasmic compartment and appear later at the cytoplasmic membrane where M protein has been postulated to orient their configuration. Then, packaging of RNA segments occurs perhaps again aided by M protein. Finally, budding results in the release of infective virus, aided by neuraminidase function. This summary of viral replication is predicated on the thesis that the RNA segments contained in the virion are negative stranded, i.e., that cannot directly code for viral protein synthesis. Amantadine interferes with influenza A viral synthesis in the penetration and uncoating steps of replication.

IMMUNOLOGY

In challenge experiments with normal volunteers the virus titer in nasal wash material reaches its peak on the third to fifth day after infection (Figure 12) (60). The first detectable host defense response is that of interferon production. Later both nasal wash and serum antibody determinations become positive. The role of cell-mediated responses in limiting the infection is under active investigation but is not clear at the present time. Nasal wash antibody can be detected by hemagglutination inhibition (HAI) and neutralization test techniques and may be the critical determinant in the prevention of reinfection. Serum antibody can be detected by HAI, neutralization, antineuraminidase and complement fixation test techniques. The complement fixation test determining antibody to the soluble protein constituents of the virus, viz., ribonucleoprotein and M protein, is type specific and becomes positive after all influenza A viral infections. Since the complement fixation test is type

FIGURE 12

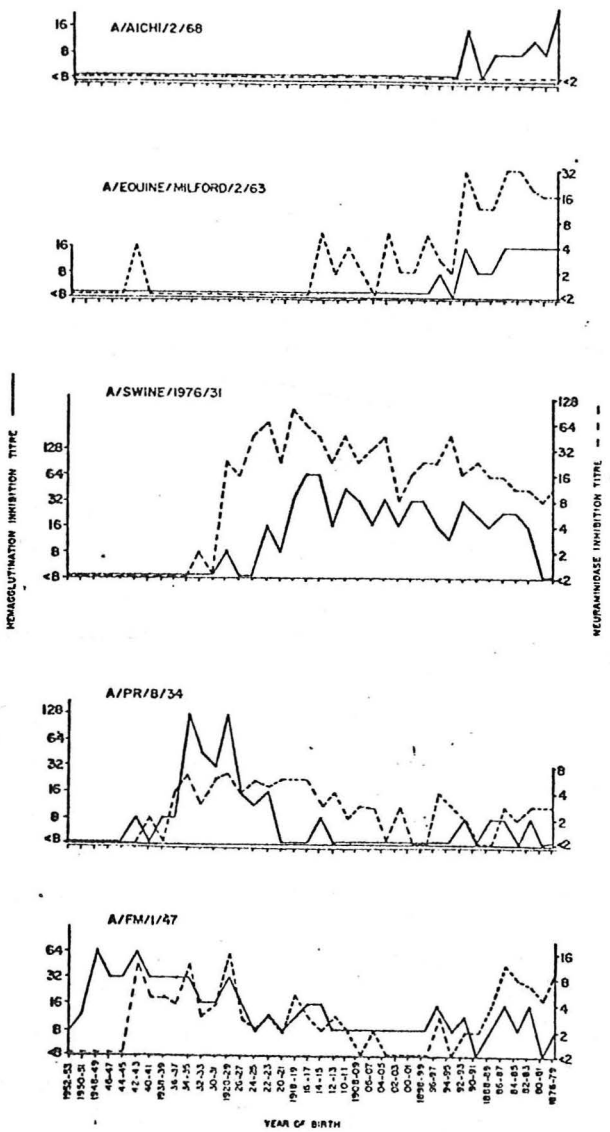


A graphic correlation of the clinical, virologic, and serologic results with interferon in the nasal washings after challenge of volunteers with influenza A_2 virus.

specific and is independent of the antigenic changes in the hemagglutinin and the neuraminidase, it is the most-widely used test in the viral diagnostic laboratory.

A critical concept in understanding immunology and the serological epidemiology of influenza A in human populations is that coined under the phrase, "Original Antigenic Sin." This concept presupposes that a clone of antibody producing cells is selected and permanently oriented by the first influenza A viral infection. Subsequent influenza infections result in an anamnestic response to that original infecting virus plus the expected response to the current infecting agent. Through recurrent infections and subsequent anamnestic boosts in titer, the person retains his level of antibody to the hemagglutinin and the neuraminidase of the original infecting virus. By examining serum pools from cohorts born during different periods of time, it is thus possible to ascertain by antibody studies, the antigenic characteristics of the infecting viruses. Thus, before the 1957 Asian influenza epidemic, it was found that people living during the 1889-1890 pandemic actually had antibodies directed toward the hemagglutinin of the Asian strain of influenza virus (H2). In subsequent analyses, it has been found that a cohort of persons likely to have experienced influenza infection in or around 1900 had antibodies to the Hong Kong virus hemagglutinin (H3). (Figure 13) (68). By analysis of this data, investigators have concluded that influenza A virus may have a limited or finite number of antigenic possibilities and that that antigenic type circulates in the population

FIGURE 13



The distribution of influenza virus antibodies in human serum. Sera were collected in 1955 and pools for each age group prepared from equal aliquots of 25 specimens. Pools were titrated for anti-hemagglutinin antibodies (——) using as antigens the wild-type virus indicated in each panel. Anti-neuraminidase antibodies (·– – –·) were determined by a neuraminidase-inhibition (NI) test using fetuin as substrate. Antigens employed in NI tests to obtain results shown in the panels of figure 1, listed from top to bottom, were: A/Prague (Heq1)-Hong Kong (N2); A/Milford/63 soluble neuraminidase (Neq2); A/swine/31 soluble neuraminidase (N1); A/Milford (Heq2)-PR8 (N1); A/Hong Kong (H3)-FM1 (N1).

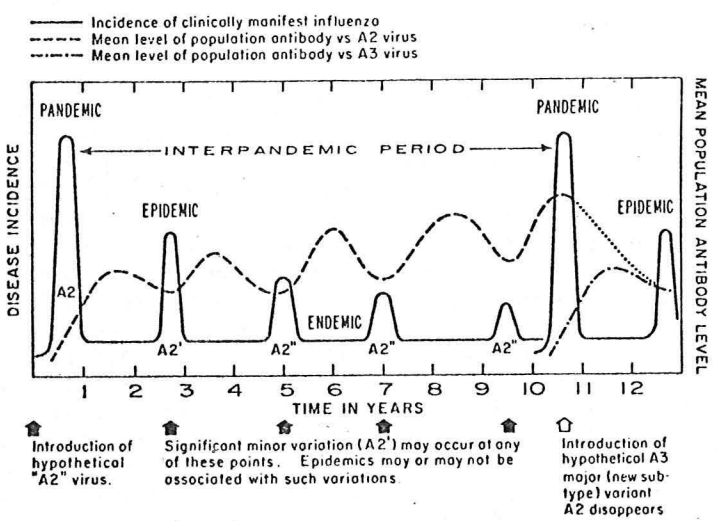
to which there is the least immunity. This "recycling" hypothesis includes the prediction made in the early 1970s that a swine-like influenza A virus may recur in man in the late 1970s or early 1980s.

EPIDEMIOLOGY

Influenza A and B viruses spread rapidly through the population during epidemic times. The mode of transmission is via the respiratory route; the involvement of so many of the population during a short period of time connotes that significant transmission must occur by the creation of infected aerosols. In this regard influenza A and B viruses are comparable to rubeola and varicella-zoster virus. Influenza B virus tends to occur in geographically restricted epidemics usually during early springtime at four to six year intervals. School and work absenteeism result but generally there is not any exceptional increase in excess mortality. Although there are antigenic shifts in both the hemagglutinin and neuraminidase pandemic influenza B has not been described. Secondary infection is common and usually does not result in serious illness. The most significant clinical manifestation of inluenza B viral infections is the association with Reye's syndrome. Since the last epidemic influenza B year was 1973-1974, there is a reasonable possibility that an influenza B epidemic might occur in 1976-1977 or shortly thereafter. During that time an excess incidence of Reye's syndrome should be expected.

At the present time, influenza A pandemics occur approximately every eleven years. In between pandemics, influenza A epidemics occur every two to three years. With increasing world travel, there may be a recent tendency for influenza A epidemics to occur each year. Prior to the present it was noted that just prior to the next pandemic there was a relative absence of influenza A viral activity. This period has been called the "salubrious interval." It is during this interval that population immunity levels have reached a state that epidemic viral activity is thwarted (Figure 14) (71). Teleologically, it has been reasoned that pandemic

FIGURE 14



antigenic changes in the virion occur with increasing population immunity to insure the survival of the virus. In interepidemic periods, influenza A virus persists by non-epidemic human to human transfer. In the interpandemic period, secondary infection with influenza A virus appears to be common, especially in children. These secondary infections may be relatively asymptomatic but serve to boost total population immunity.

Measurements indicating the presence of influenza A virus epidemic activity in populations include school and work absenteeism, visits to primary care physicians, visits to emergency rooms of city and county hospitals, numbers of persons presenting to such emergency rooms with febrile upper respiratory tract infections and later by parameters such as total excess mortality, mortality in persons 65 years of age or older and deaths due to pneumonia and influenza. Influenza A virus is unique in that the most current strain tends to eliminate other strains of virus from circulation in the population.

Serological studies on population groups living through the 1889-1890 pandemic and the 1900 epidemic have supported the thesis that there are a limited number of influenza A antigenic variants. These variants have been postulated to recycle in accordance with population immunity levels. It is possible that the decline in age specific incidence with advancing age encountered during the 1918-1919 epidemic may have resulted from previous exposure of elderly persons in the population to an antigenically similar virus. The recycling hypothesis offers a conceptual framework to enable prediction of the antigenic constitution of future pandemic strains. On this basis it was postulated that a swine-like influenza A virus would circulate in man in the 1970s and 1980s.

It is in this epidemiological context that the Fort Dix, New Jersey experience must be interpreted. Although there have been instances of swine to human transmission of swine influenza A virus in the American Midwest, there are no documented occurrences of human to human transmission of this virus (Table 3) (135). During 1975-1976, there were at least two instances of human to human transmission of swine influenza A virus. The first occurred in Charlottesville, Virginia in which two patients developed pneumonia and serological evidence of infection with swine influenza A virus. The Fort Dix, New Jersey experience is significant in that there were at least 11 virologically diagnosed cases of swine influenza A infection, including one death. 273/1321 sera drawn from persons at Fort Dix were positive for HAI test antibodies to swine influenza A virus. Persons with positive titers tended to occur in platoons with confirmed cases. Spread of this strain of virus was documented in at least one family of a Fort Dix recruit (Table 4) (135). The origin of the virus that caused the Virginia and New Jersey cases is not known. There is no evidence whatsoever that it originated from transfer to humans from swine. Although knowledge of the principles of genetic recombination might predict the occasional occurrence of such an event, the evidence must be interpreted as being most consonant with the emergence of an antigenically novel human influenza A virus having the antigenic characteristics of the strain causeing the 1918-1919 pandemic. As far as is presently known, there have been no additional cases of swine influenza A viral infection in this country. Low-level transmission and seeding of population groups may be occurring this summer but there is no evidence that this has in fact been happening. It is noteworthy that all apparent influenza A viral activity has ceased in this country this summer although no one suggests that this virus is really absent from human populations. The history of all the influenza pandemics in this century (1918-1919, 1957-1958, 1968-1969) has included the demonstration of summertime regional epidemic activity. However, it should also be noted that after the introduction of Hong Kong influenza A virus in Seattle, there was a 1-2 month hiatus before the occurrence of further cases even though a Virus Watch program was in operation to closely monitor the occurrence of infection with influenza A virus.

It was faced with such information (the recycling hypothesis, the consistent emergence to dominance of the most antigenically novel influenza A virus), that led to the meeting wherein experts recommended that swine influenza A virus vaccine be prepared and stockpiled. Since one could not exclude the possibility

TABLE 3

Summary of Cases of Influenza Due to A(HswlN1)-like Viruses and of Investigations of Human-to-Human Transmission

Location	Patient	Age	Sex	Onset	Diagnostic Test	Investigation of Spread: Household Contacts	Local Contacts	Other parts of Community
Mayo Clinic, MN		13	M	July-Sept. 1974	Virus isolation on post-mortem exam	2 breeder sows had antibodies. Parents were negative	-	-
Sheboygan, WI	S.B.	8	M	Oct. 1975	Seroconversion	5 of 7 household members had HI titers ≥20	0/24 classmates had titers	Age >50: Pos/tested 33/38, % 87; Age 15-49: 4/44, 9; Age <15: 4/156, 3
Ft. Dix, NJ	D.L. (fatal)	19	M	Feb. 1976	Virus isolation on post-mortem	34% positive titers in platoons with confirmed cases	273/1321 (21%) single sera positive	6% positive titers in platoons without confirmed cases
	4 cases				Isolations			
	6 cases				Seroconversion			
Charlottesville, Virginia	M.D.	40	F	Dec 5 1975	Pneumonia & seroconversion	0/5 children positive	0/6 cases in nearby household	
	C.F.	55	M	Dec 27 1975	Pneumonia & seroconversion	0/4 cases in household	0/2 positive	4/12 culture's positive for A/Victoria

TABLE 4

Investigation of Close Contacts of 22 Ft. Dix Recruits with History of Swine Contact and Swine Antibody

Community	# Tested	# HI ≥20 (Ages)
Arley, Ala.	4	1 (42)
Headland, Ala.	4	1 (61)
Thornton, Colo.	9	1 (50)
Lyons, Colo.	3	0
Laurel, Del.	4	0
Kellog, Iowa	5	0
Franklyn, Mass.	4	0
Belding, Mich.	13	0
Munnsville, NY	9	0
Everington, Ohio	1	0
Columbus, Ohio	2	0
Valencia, Penn.	4	0
Erie, Penn.	7	0
Fayettesville, Penn.	11	4* (11,12,20,25)
Newville, Penn.	4	1 (50)
Hemmingway, SC	4	2 (60,18**)
Bristol, Tenn.	2	0
Woodstock, Virg.	10	3 (47,49,75)
Toppenish, Wash.	20	2 (56,32)
Tacoma, Wash.	35	3 (60,53,59)
Mannington, W. Virg.	11	1 (59)
TOTAL	168	19

* 3 siblings and 1 friend living in household
**Girlfriend of recruit

that a Victoria-like strain would circulate in the population and give rise to excess mortality in persons predisposed to the serious consequences of influenza it was recommended that that strain of influenza A also be given in a bivalent vaccine to those particular persons. A nationwide immunization campaign has been scheduled for the U.S., beginning in September. In the state of Texas it is estimated that it would require 90 days to immunize the population. In the absence of the continued occurrence of cases, alternate plans have been devised. The most cogent of these plans is to delay the immunization campaign until further swine influenza A viral activity can be documented. It should be stressed that the experience with the Victoria strain of influenza A virus is instructive in that with modern travel it was only a period of 2-3 weeks before epidemic influenza was being detected in most portions of the country following its initial documentation on the western coast of the United States in January, 1976.

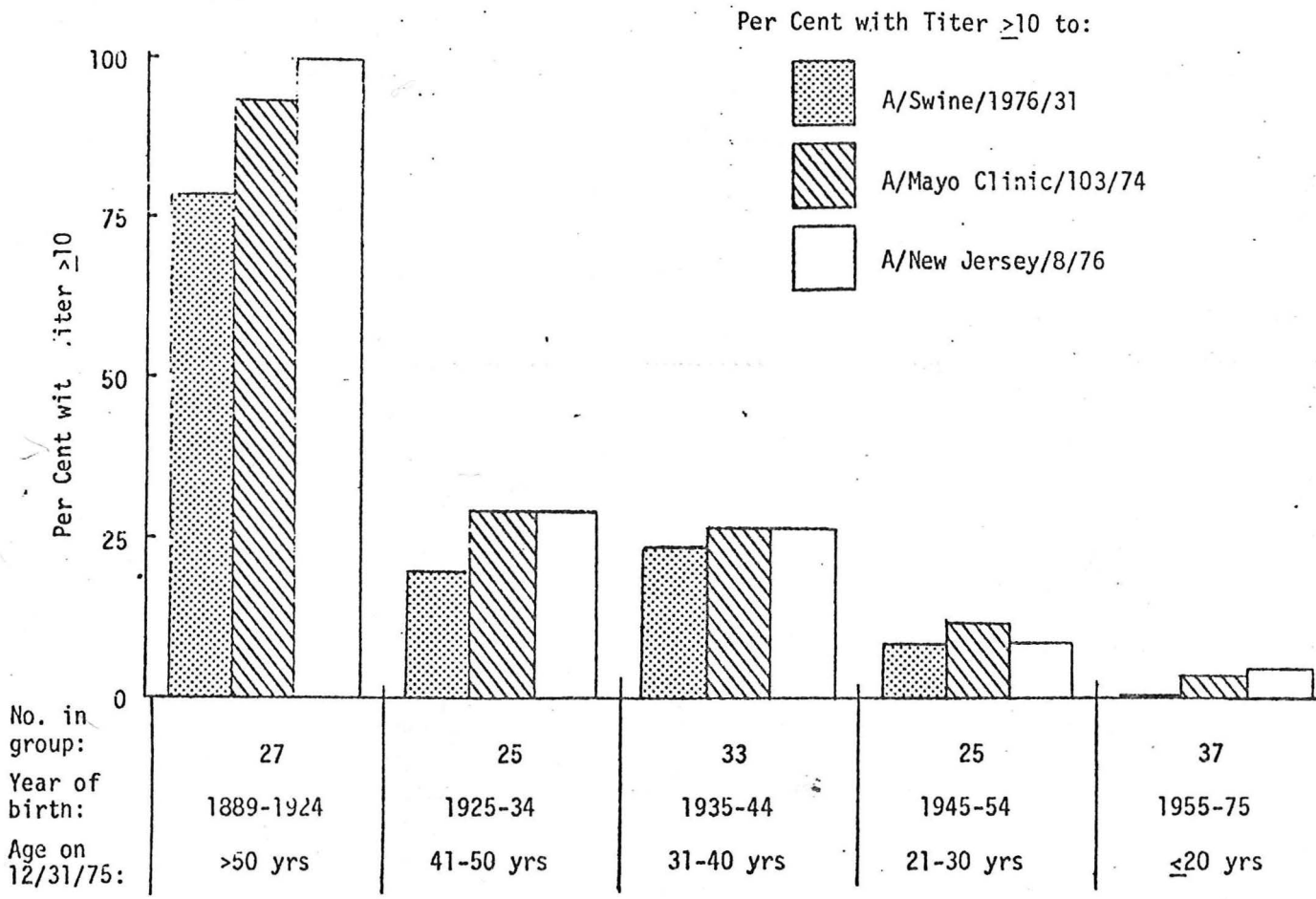
The New Jersey strain of swine influenza A virus has been designated as HswlN1. The hemagglutinin of the New Jersey strain is very closely related to the Mayo Clinic isolate encountered in 1974 and the original prototype virus isolated by Richard Shope in 1931. Most probably, swine influenza A virus circulated from 1918 until the late 1920s when it was replaced in the epidemic of 1928-1929 by the HON1 virus. The neuraminidase of the New Jersey isolate is antigenically similar

to the neuraminidase that circulated from 1918 until 1957. However, antibody to N1 does not prevent the activity of neuraminidase as an enzyme. A high percentage of patients who lived through the 1918-1919 epidemic and shortly thereafter have HAI test antibodies against the A/New Jersey/8/76 virus (Figure 15) (135). It

FIGURE 15

SWINE INFLUENZA HI TITERS IN 147 INDIVIDUALS

ATLANTA, FEBRUARY 1976



could be reasoned that such persons might be protected during any ensuing epidemic season and this would be a situation comparable to the 1918-1919 epidemic in which case rates fell off with advancing age. It is impossible to gauge what the effect of antibody toward the neuraminidase constituent may be. It has been postulated that the 1968-1969 Hong Kong influenza A epidemic was less severe than the 1957 Asian influenza A epidemic because the neuraminidase had not changed its antigenic constitution.

CLINICAL

Except for a tendency to cause croup which may be severe enough to require tracheostomy, influenza A viral infections in the pediatric age group cannot be reliably distinguished from other viral upper respiratory tract infections. Similarly, secondary infection in the adult with a closely related strain causes a relatively non-specific upper respiratory tract illness or may be asymptomatic. Influenza B viral infections although inducing school and work absenteeism usually are not associated with secondary pneumonia or with much increase in excess mortality. Influenza B viral infections are, however, closely associated with Reye's syndrome. Influenza C infections are uncommon, may be asymptomatic or may cause a picture similar to the common cold.

Primary infection with influenza A virus causes a clinical syndrome in adults which in epidemics is quite distinct (Tables 5, 6) (25). After a short incubation

TABLE 5

Symptoms in Proven Adult Cases of Influenza A Virus Infection

Symptoms	H0N1 1937, 1939, 1941 (60 cases)[a]	H1N1 1947 (76 cases)[b]	H2N2 1957 (30 cases)[c]
Sudden onset	75[d]	67	46
Systemic symptoms			
Chilliness	80	85	64
Feverishness	--[e]	99	71
Headache	85	86	72
Myalgia	60	60	62
Malaise	87	—	67
Anorexia	71	—	37
Respiratory symptoms			
Sneezing	—	—	67
Nasal obstruction	80	—	52
Nasal discharge		70	82
Sore throat	48	49	62
Hoarseness	10	—	37
Cough	88	97	90
Sputum	31	32	41
Other			
Photophobia	20		—
Nausea	17	29	4
Vomiting		9	7
Diarrhea	—	4	0
Abdominal pain	—	15	0

[a] From Stuart-Harris (1961).
[b] From Kilbourne and Loge (1950).
[c] From Jordan *et al.* (1958).
[d] Percent with indicated symptom.
[e] No data.

period of two to three days, the patient has a sudden onset of fever and marked prostration. The time of onset can oftentimes be closely dated. Headache and generalized myalgias are present along with malaise. Prostration is a striking feature of the illness causing the patient to miss school or work and remain in

TABLE 6

Physical Findings in Proven Adult Cases of Influenza A Virus Infection

Signs	H0N1 1937 (82 cases)[a]	H1N1 1947 (76 cases)[b]	H2N2 1957 (30 cases)[c]
Maximum temperature			
100°F			13[d]
100°–101.9°F	101.2°F (average)	101.3°F (average)	58
≥102°F			29
Flushed face	67	58	24
Conjunctival abnormalities	89	66	56
Nasal discharge	22	52	20
Nasal injection/edema	—[e]	—	64
Nasal obstruction	51	—	—
Pharyngeal infection	73	72	68
Pharyngeal exudate	1	0	0
Cervical adenopathy	—	22	8
Rhonchi and/or rales	20	4	0

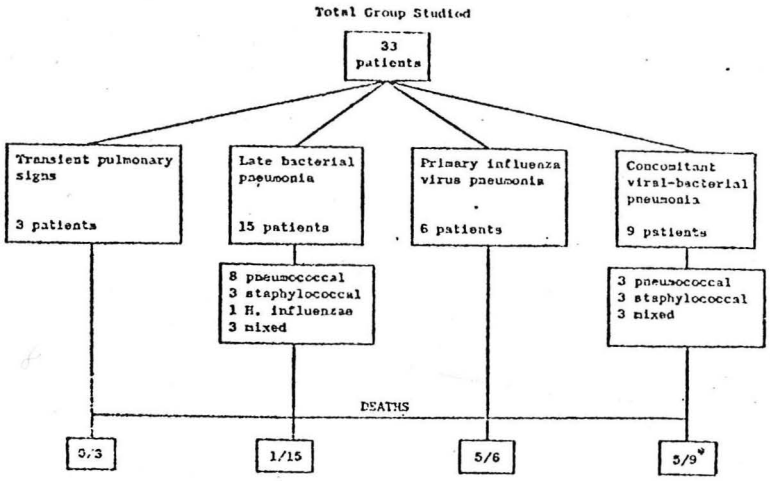
[a] From Stuart-Harris (1961).
[b] From Kilbourne and Loge (1950).
[c] From Jordan *et al.* (1958).
[d] Percent with indicated symptoms.
[e] No data.

bed for at least the initial portions of the illness. A cough is present as well as a sore throat. Rhinorrhea is not a striking manifestation of influenzal infections. On physical examiniation, the patient usually at some time has a temperature equal to or greater than 101°. The face is flushed, the conjunctivae are injected and the pharynx is red. A pharyngeal exudate is uncommon in the course of ordinary influenzal infections. In cases that seek medical attention, a certain percentage will have end-inspiratory sticky rales usually relatively well localized. Such patients usually have negative chest x-rays. After three to five days the patient usually has recovered to the extent that he can return to work but weakness and malaise may persist.

Pulmonary manifestations of influenza A viral infection have been divided by etiology into pure viral, viral plus bacterial or bacterial suprainfection (Figure 16) (79). A patient with pure influenza viral pneumonia develops dyspnea during the early course of illness. A cough is present oftentimes associated with hemoptysis. On physical examination the patients are tachypneic and in severe cases cyanotic. They may be extremely agitated. Physical examination reveals tachypnea, cyanosis and diffuse end-inspiratory sticky rales. When the involvement by roentgenogram is extensive, the case fatality ratio may exceed 60%. Less extensive pure viral pneumonia has also been described. Chest x-ray reveals either a diffuse or localized increase in interstitial markings. With severe influenzal pneumonia, the patients may progress to diffuse alveolar infiltrates indistinguishable roentgenographically from the adult respiratory distress syndrome. Therapy with intermittent positive pressure breathing and positive end-expiratory pressure ventilatory assistance has improved the survival rate in influenzal pneumonia. The resolution of the alveolar infiltrates may be slow and protracted. Influenzal pneumonia may be complicated by bacterial suprainfection in which the sputum becomes

FIGURE 16

THE PULMONARY COMPLICATIONS OF INFLUENZA



purulent and areas of consolidation are evident upon physical examination and on chest x-ray. Bacterial pneumonia complicating influenza oftentimes occurs after a latent period during which time the patient appears to be recovering from his primary illness. He then develops an acute onset of illness with purulent sputum which may be blood streaked and discrete areas of consolidation. The usual infecting organism is Pneumococcus. However, *Hemophilus influenzae*, Group A Streptococcus, *Staphylococcus aureus* and gram negative bacilli may be the etiologic organisms. Staphylococcal pneumonia may be extensive, involve multiple lobes and be associated with cavitation and the development of pyopneumothoraces.

Pathological findings in influenzal pneumonia relate to a destruction of the normal tracheal epithelium with subsequent squamous metaplasia. The interstitium of the lung contains a mononuclear cell inflammatory infiltrate. Hyaline membranes line the alveoli and can be seen in the absence of oxygen therapy. Goodpasture noted in the 1918-1919 epidemic that hyaline membranes were a characteristic feature of some of the cases that were autopsied. Damage to the alveolar capillary membrane results in the development of alveolar edema fluid. Mononuclear cells and erythrocytes also fill the alveoli. With bacterial suprainfection the trachea may be filled with a neutrophilic inflammatory exudate. Bronchopneumonia or lobar pneumonia may be present with the characteristic pathological alterations associated with these entities.

Pneumonia complicating influenza has a particular predilection for the aged and for persons with underlying cardiovascular and pulmonary disease problems. Noteworthy, in the induction of the pure viral pneumonia associated with influenza is the high proportion of patients with chronic rheumatic heart disease, particularly mitral stenosis. It has been postulated that persons with some element of chronic pulmonary edema are particularly prone to influenza pneumonia because of the ease with which the virus may spread through alveolar edema fluid. Drs. Johanson, Pierce

and Sanford were among the first to document that with uncomplicated influenza there was an abnormality in pulmonary function predominantly related to disease of small airways and associated with increased alveolar-arterial oxygen gradients. This has subsequently been confirmed by a number of other investigators.

Viremia has been documented in overwhelming influenzal virus infections. It has also been substantiated under conditions of artificial challenge. As a result of this viremia involvement of the myocardium and pericardium may occur. Myocarditis and pericarditis are usually manifest by electrocardiographic findings of ST-T wave changes. Conduction disturbances may be present. Pericardial effusions are rare but influenza A virus has been grown from the pericardial fluid in at least one report. Significant myocarditis is infrequent but can lead to progressive cardiac dilatation, failure and rarely, death. The central nervous system may be involved. Studies related to involvement of the central nervous system have been clouded because of the lack of laboratory documentation of influenza A infection. The manifestations related to central nervous system involvement that appear relatively well documented include disseminated encephalomyelitis, transverse myelitis, the Guillan-Barré syndrome, encephalopathy and encephalitis. Reye's syndrome can follow influenza A viral infections and is characterized by diffuse cerebral edema and visceral fatty metamorphosis. Reye's syndrome in particular is associated with influenzal B viral infection. Of great recent interest but yet to be confirmed is the report showing influenza A viral antigens in the affected areas of the brain of patients with post-encephalitic Parkinson's disease. This finding again raises the question of the possible association of Von Economo's encephalitis and influenza A infection.

Massive rhabdomyolysis may complicate influenza A viral infection. Its mechanism is unknown but elevated serum levels of muscle enzymes and myoglobinuria can occur and result in renal failure. Uric acid concentrations are increased as a result of the diffuse muscle damage and may contribute to the acute renal failure accompanying this syndrome. Disseminated intravascular coagulation with acute renal failure can also complicate influenza A virus infection. Of interest is the recent demonstration that meningococcal carriage is enhanced by preceding influenza A viral infection. Outbreaks of meningococcal disease have also been associated with epidemics of influenza A.

CASE HISTORIES

CASE #1. Influenza A viral pneumonia complicating pregnancy.

The patient was a 24 year old woman in the second trimester of pregnancy. On February 20, 1976 she developed influenza with a fever to 101°. On February 23, she presented to a suburban hospital with fever and dyspnea. On February 26, because of increasing pulmonary infilatrates on antibiotic therapy, increasing dyspnea and decreased pO_2 levels, she was intubated and subsequently transferred to PMH. Chest x-rays revealed diffuse interstitial and alveolar infiltrates. No bacterial pathogens were ever grown from the patient's sputum or tracheal secretions either at the suburban hospital or PMH. On March 1, she had the onset

of labor and delivered a premature infant that died on the third day of life. Before and after transfer to PMH she was obtunded: EEG revealed evidence of anoxic encephalopathy. However, on March 9, she had become alert and responsive but blood gas values continued to deteriorate. In preparation for her placement on the membrane oxygenator, a lung biopsy was performed which revealed diffuse, severe interstitial fibrosis. This precluded use of the membrane oxygenator. She developed progressive pulmonary hypertension and died on March 11. Influenza A CF titers drawn on admission to PMH and subsequently thereafter were $\geq$ 1:256.

CASE #2. *Combined pneumonia due to influenza A and Streptococcus pneumoniae.*

The patient was a 38 year old man who had a diagnosis of discoid lupus and who had previously been worked up for dermatomyositis (elevated eosinophile count, increased ESR, SGOT, CPK). He developed influenza on February 4, 1976. Five days later he presented to the PMH EOR with shaking chills, fever, pleuritic chest pain and a productive cough. Physical examination on admission revealed a temperature of 102° and bilateral rales, more prominent on the left. The pO_2 = 45, pCO_2 = 16 and the pH = 7.39. Chest x-ray revealed left lower lobe consolidation and diffuse interstitial infiltrates. Blood cultures taken on admission were positive for *Streptococcus pneumoniae.* Shortly after admission to the hospital he had a cardiac arrest and aspirated. He was resuscitated but never developed consciousness. Post-resuscitation, his hospital course was complicated by shock, rhabdomyolysis (CPK values $\sim$ 12,000), disseminated intravascular coagulation, acute renal failure and symmetrical peripheral gangrene. He died 11 days after admission with influenza A CF titers rising to $\geq$ 1:256. Autopsy revealed resolving bacterial pneumonia and interstitial proliferative pneumonitis; the latter thought, in part, to be related to oxygen toxicity.

CASE #3. *Influenza A and meningococcal disease. Adult respiratory distress syndrome possibly related to viral pneumonia.*

The patient is a 24 year old man who was first seen in the PMH EOR on February 7, 1976 with a temperature of 103°, diffuse myalgias, arthralgias and sore throat. He had been placed in jail that morning. He was treated with acetoaminophen and returned to jail. On February 16, he was again brought to PMH for fever, confusion, combativeness. He was found to have muchal rigidity and papilledema. LP revealed 1100 cells, 95% of which were polymorphonuclear leucocytes. The CSF glucose was decreased and cultures later grew *Neisseria menigitidis.* Chest x-rays showed diffuse bilateral pulmonary infiltrates with a normal cardiac silhouette. Influenza A CF titers performed on sera taken on admission and shortly thereafter were $\geq$ 1:256. He was treated with high dose penicillin and required intubation and PEEP therapy for eventual resolution of his adult respiratory distress syndrome. At discharge, he was alert and oriented and his chest x-ray revealed only a residual infiltrate in the left base.

CASE #4. *Encephalitis associated with influenza A infection.*

The patient is a 36 year old man who was well until one week prior to admission to PMH. At that time he developed a "flu"-like syndrome with fever, chills,

malaise, cough. He continued with these symptoms until the day of admission when he became confused, tremulous and could not recognize family members. Physical examination on admission revealed a temperature of 101.4°. He was tremulous, confused, disoriented, unable to respond coherently and combative when aroused. There was an almost continuous myoclonic jerking of muscle groups, particularly around the shoulders and head. There were no focal neurological signs. Laboratory studies revealed a WBC of 6500, the hemoglobin was 14.8 gm.%. CSF revealed 152 WBC's, 88% lymphocytes, a CSF/plasma glucose ratio of 64/92 and a protein concentration of 100 mg. %. EEG showed a diffuse abnormality consistent with encephalitis. The patient continued febrile, disoriented, tremulous until the fifth hospital day when he became more alert and the focal myoclonic seizure activity disappeared. His fever continued until the seventh hospital day. On discharge he was completely alert and oriented and able to ambulate without problems. On follow-up visit three weeks later he was considered neurologically normal with his only symptoms being aches in his calves after moderate exercise. Influenza CF titers revealed a rise from 1:16 to ≧ 1:256.

PREVENTION AND THERAPY

In the United States immunization with inactivated influenza viral vaccines has long been an integral part of good medical practice. The United States Public Health Service has always conservatively recommended the selective immunization of our aged population and of those with illnesses that may make them particularly predisposed to the serious consequences of influenza. These illnesses include persons with chronic cardiovascular diseases, chronic lung diseases and persons with metabolic diseases such as diabetes mellitus and chronic renal failure. The United States Public Health Service has never recommended widescale immunization to prevent total respiratory illness rates in the community. In the military, however, influenza immunization has long been regularly practiced and given to most personnel in order to prevent morbidity in this population. With the present selective immunization policy, it has been estimated that only 20-25% of the target population in the U. S. is reached each year. Pandemic disease or periodic epidemic disease has never been prevented.

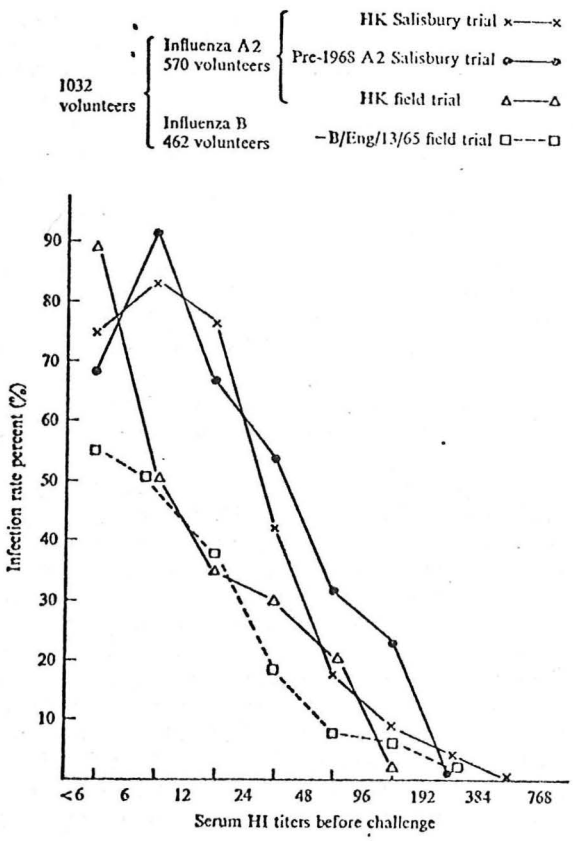
The use of monovalent or bivalent vaccines has replaced the older polyvalent vaccines. There have been advances in the purification of the vaccine virus. These advances have included zonal ultracentrifugation and treatment of the virus with detergents or ether with subsequent purification. Thus, present vaccines contain either intact virus or chemically disrupted (split) viral constituents. The present vaccines are inactivated by formalin after having been prepared in eggs. With purification techniques, egg constituents can now be removed to a greater extent but never entirely from the vaccine and hence this product should not be given to persons with allergies to egg products. In terms of potency, the vaccines are titered in antigenic units, chicken red blood cell agglutinating units (chick cell agglutinating, CCA units).

Minor side-reactions, local erythema, swelling, tenderness, fever are encountered to a lesser extent than previously. With the vaccines presently in preparation, fever to 101°, in persons ≧ 24 years of age was encountered only

slightly more commonly than that seen in persons given placebo but this difference was not considered statistically significant. Since their inception, inactivated influenza vaccines have been given to millions of persons. They have an impressive safety record with regard to serious side-effects. In fact, it is considered standard and good medical practice to administer the inactivated vaccine yearly to the aged and to persons with chronic diseases in the population. Speculation concerning untoward late complications of the vaccine appear totally unwarranted in view of their common usage in medicine for at least 25 years.

Inactivated influenza vaccines have been shown to be at least 70% effective if they contain enough antigenic mass to raise circulating antibody levels to a certain titer against the virus strain that subsequently ciruculates in the ensuing year (Figure 17). For present vaccines, one dose is considered sufficient for that purpose. If the person has some degree of pre-existing immunity, the efficacy of the vaccine is enhanced. If the serum antibody level is sufficiently high, nasal wash antibody also appears in persons given inactivated influenza vaccine. There are studies that indicate that protection may persist for longer than a year. However, yearly immunization of susceptible population groups has been recommended by the U. S. Public Health Service.

FIGURE 17



Infection rate of volunteers challenged with various influenza viruses in relation to their prechallenge titers or homologous serum HI antibody. From Hobson *et al.* (1973). *J. Hyg., Camb.* Copyright 1973 Cambridge

Critical to the successful application of monovalent and bivalent inactivated influenza vaccines is their formulation. They are evaluated yearly so that the most current antigenically different strain is included. The formulation of the vaccine requires an intact, comprehensive and vigilant surveillance system so that antigenic changes in the virion can be detected promptly. The present immunization policy of the Public Health Service also is partly predicated on the basis that significant influenza activity in the population can be predicted to a certain extent. The prediction of such epidemic activity has stimulated an increased use of influenza vaccine in those years. Prediction of epidemic influenza and the formulation of the vaccine revolves around certain principles. 1.) Pandemic variants of influenza A virus occur every decade (10-11 years). 2.) In between pendemics, epidemic influenza A activity occurs every 2-3 years and influenza B activity every 4-6 years. 3.) The most antigenically novel influenza A strain (the strain to which there is the least population immunity) encountered in the previous year is the strain which will displace the others and circulate in the ensuing year. With regard to pandemics; although new strains encountered in 1957 and 1968 were recognized and realized capable of pandemic spread, it proved difficult to manufacture enough vaccine quickly to prevent significant morbidity and excess mortality.

During the present spring and summer, inactivated influenza vaccines have been prepared (Tables 7, 8) (136). These appear potent and safe for adult use. Further studies will have to be conducted regarding their use in children. A monovalent vaccine (HswlN1) is anticipated for widescale use while a bivalent vaccine (HswlN1, H3N2-Victoria) has been prepared for persons most likely to have serious influenza complications. The public must be cognizant that these vaccines are associated with a finite side-reaction rate and will not prevent upper respiratory tract infections caused by other viruses.

There have been intensive efforts to improve influenza vaccines. These have revolved around whether inactivated vaccines can be administered more effectively, i.e., intranasally to induce greater local immunity or the development of live, attenuated vaccines (Table 9) (71). The development of live virus vaccines for general use has been hampered by the occasional demonstration of reversion to wild-type virus, the lead time to manufacture enough vaccine given the emergence of a pandemic variant, and the demonstration that temperate RNA-host cell interactions may give rise to proviral DNA copies which may integrate with cellular DNA and, <u>in vitro</u>, be rescued under appropriate conditions.

It has now been shown conclusively under both artificial and natural challenge circumstances that amantadine is an effective prophylactic drug against influenza A infection. The estimated protective efficacy of this drug given in adult dosages of 100 mg. twice a day approximates that of the inactivated vaccine. If illnesses do result they tend to be milder. It has not been substantiated that amantadine given as a prophylactic agent protects against the purulent complications of influenza A virus. Its action, that of preventing penetration of the virus into the cell and its uncoating, is enhanced in the presence of a pre-existing level of circulating antibody. Amantadine must be given throughout the length of the influenza season (4-6 weeks). It is a safe drug and has been administered on a protracted basis to alleviate Parkinson's disease. Its side effects are central nervous system in origin and include jitteriness, insomnia, inability to concentrate, etc. The side effects are generally dose related and are oftentimes slightly more

TABLE 7

Monovalent A/N.J./76 (Hsw1N1) Vaccine Study

Three Week Post-vaccination Antibody Status[a]

Manufacturer	Dose[b] (CCA)	% With HI Antibody Titer ≥40 Age: 3-6	6-10	17-24	≥25[c]
Wyeth	50(48)[d]	0			
(Split)	100(96)	0	0		
	200(192)		3	28(15)[e]	76(114)
	400(360)		5	39(27)	90(216)
	800(708)			36(26)	93(337)
Parke-Davis	50(57)	11			
(Split)	100(114)	9	2		
	200(228)		9	38(26)	93(214)
	400(444)		2	21(13)	92(225)
	800(792)			46(40)	94(320)
Merrell-National	50(33)	62			
(Whole)	100(66)	39	44		
	200(132)		50	47(23)	72(78)
	400(312)		59	54(40)	85(121)
	800(708)			53(37)	88(187)
Merck, Sharp	50 (48)	50			
& Dohme	100(96)	100	77		
(Whole)	200(192)			58(44)	92(168)
	400(360)			85(69)	92(223)
	800(744)			91(92)	93(220)
Placebo		0	0	0	12

[a]Hemagglutination inhibition tests with A/swine/1976/31 (Hsw1N1) for Parke-Davis and A/N.J./8/76 (Hsw1N1) for all others.

[b]Average no. subjects/vaccine dose in each age group: 3-6 (17), 6-10 (40), 17-23 (37), ≥24 (100).

[c]Less than 10% were age ≥52.

[e]( ) Geometric mean titers.

[d]( ) Actual CCA value.

TABLE 8

Monovalent A/N.J./76(HswlN1) Vaccine Study

Fever[a]

Manufacturer	Dose[b] (CCA)	Percent with Temp. (°F) Age: 3-6 ≥100	3-6 ≥102	6-10 ≥100	6-10 ≥102	≥17[c] ≥100	≥17[c] ≥102
Wyeth (Split)	50[f]	4	[d]				
	100	2		6	2		
	200	15		2		4	
	400			4		2	
	800					3	
Parke-Davis (Split)	50	8					
	100	3		6			
	200	0		2		2	
	400			2		1	
	800					5	
Merrell-National (Whole)	50	11	4				
	100	18	3	12	2		
	200			23	8	2	
	400			35	9	2	
	800					5	
Merck, Sharp & Dohme (Whole)	50	26	6				
	100	6		25	15		
	200					1	
	400					4	
	800					13	4
Placebo		8	3	4		2	

[a]At any time 6-48 hrs. post-vaccination.

[b]Average No. subjects/vaccine dose in each age group: 3-6 (17), 6-10 (40), ≥17 (135).

[c]Less than 8% in this group were age ≥52.

[d]No fever ≥102°F if not indicated.

[f]Actual CCA values given in Table 1.

TABLE 9

Types of Influenza Vaccines—Actual and Potential[a]

I. Inactivated or noninfective
  A. Whole virus—formalin-inactivated
    1. Conventional empirically selected[b]
    2. Recombinant for high yield characteristic[b]
    3. Recombinant antigenic hybrid specific for neuraminidase antigen
    4. Any of the above plus adjuvant
  B. Disrupted or "split" virus[b]
    1. Presently made from (1) or (2) above
    2. Contains all viral proteins but are usually less toxic and less antigenic
  C. Isolated purified antigens
    1. Hemagglutinin
    2. Neuraminidase
    3. Above in combination
    } May require adjuvant
II. Live virus (infective)
  A. Empirically selected by passage and spontaneous attenuation[c]
  B. Selected mutants
    1. Inhibitor-resistant (thought to correlate with attenuation)[b]
    2. Temperature sensitive (ts)
    3. Cold-adapted
  C. Recombinant
    1. Hybrid derived from virulent (wild type) and avirulent viruses, usually intermediate in virulence
    2. Properties of (2) and (3) (selected mutants) can be transferred to new serotype by recombination
    3. Any of above variants can be conferred with "high yield" genes by recombination (2) (whole virus-formalin-inactivated)

[a] From Kilbourne (1975).
[b] Currently in use and commercially available.
[c] In intermittent use in U.S.S.R. for many years.

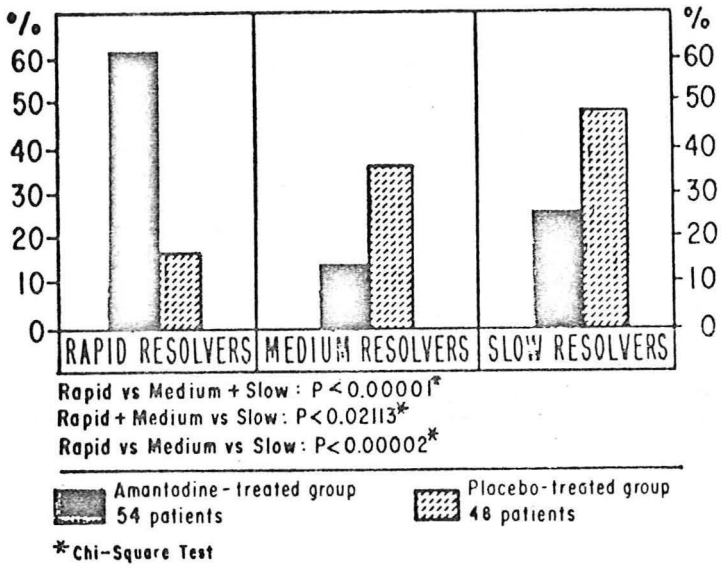
severe in older persons. Under such circumstances the dose can be reduced. Most people can take amantadine for fairly long periods without difficulty. Amantadine is not metabolized and is excreted almost entirely in the urine. Patients with renal failure should be given amantadine with caution because of the possibility of accumulation and enhanced central nervous system related side-effects.

Amantadine must be considered as an adjunct to influenza immunization. If a pandemic occurs and there have been substantial numbers of the population that have not been immunized, it should be considered for use to prevent influenza. Population groups that might be given amantadine include family members of cases, particularly when those persons are aged or have pre-existing disease, medical personnel working in emergency rooms of hospitals, population groups whose services are essential for the maintenance of civilized life and to prevent the occurrence of nosocomial influenza infections.

Amantadine has been used therapeutically. One study has demonstrated that if given to patients within 20 hours after the onset of illness, it enhanced early recovery (Figure 18) (132). Other studies have not been as convincing that amantadine has a significant therapeutic effect and most authorities at the present time would not use amantadine as a treatment regimen.

FIGURE 18

Incidence of Amantadine- and Placebo-Treated Patients Who Had Rapid, Medium, or Slow Resolution of Influenza



SHOULD THE POPULATION OF THE UNITED STATES BE IMMUNIZED AGAINST SWINE INFLUENZA A VIRUS?

The recycling hypothesis predicts the next circulating strain of Influenza A virus will have an antigenic constitution similar to that causing the 1918-1919 epidemic. Experience has shown that when an influenza A virus with a novel antigenic constitution appears and circulates in the human population it usually becomes the predominant virus in the ensuing year. The United States Public Health Service has always been extremely conservative in its recommendations for immunization of the population against influenza. They have never previously recommended widescale immunization. Immunization with influenza A viral vaccines have been shown to be at least 70% effective when the vaccine has been directed against the strain that subsequently circulates in the population. Protection lasts for at least a year. Although minor side effects should be expected, it must be emphasized that the medical profession has long accepted the safety of influenza immunization so that it is considered good medical practice to immunize yearly the portion of our population with chronic disease states and our aged citizens. Consternation about the unforeseen effects of influenza immunization has no basis in reality based upon the safe administration of comparable vaccines over at least a 25 year interval. Since the vaccine in children (at the present stage of development) is associated with a relatively high reaction rate and less than acceptable serological evidence of protection, a cogent argument can be made to delay their immunization until a safer preparation can be produced.

We must live with the constant specter of pandemic influenza unless we can find means of accurately predicting the strains that will circulate in the population and circumvent the lead time necessary to manufacture effective vaccines. During 1957-1958 and in 1968-1969 substantial disease had already occurred by the time that vaccines were available for widescale use. Although potent antimicrobials would certainly prevent the catastrophic excess mortality seen during the 1918-1919 pandemic, we must remain cognizant that worldwide circulation of an intrinsically more virulent virus may one day recur. Since it is estimated that it would take approximately 3 months to immunize our population and an additional month after immunization to confer protection, stockpiling of vaccine until the first occurrence of cases of influenza does not seem the wisest course. This is attested to by the rapid spread recently of the Victoria strain of influenza A virus in the U. S. and the 1918-1919 experience where fulminant epidemic activity occurred simultaneously at geographically separate areas of the world. Widespread use of amantadine has been suggested until vaccine can be delivered to the population. The logistics of this proposal argue against this alternative as do the associated implications of cost and drug side-effects. We must ask ourselves, given the problems of time related to vaccine manufacture, assurance of safety and delivery to the population, what signals would we accept before committing our resources in an attempt to prevent pandemic influenza? If the signal is the actual occurrence of pandemic influenza, it is already too late as the 1957-1958, 1968-1969 experiences illustrate.

A confident prediction of an influenza A pandemic during 1976-1977 cannot now be made. The public must be aware of this and informed that upper respiratory tract infections caused by other viruses will continue to occur and that there may be an influenza B epidemic this spring. The option must be left open that more selective but still relatively widescale immunization campaigns may be necessary to prevent the excess mortality associated with the emergence of a new pandemic strain, an event experience has taught that occurs each decade. Indeed, it is the possibility of the pandemic spread of influenza A virus, the knowledge that there may be alterations in its intrinsic virulence, our present groping attempts to predict its occurrence and prevent it by immunization, that make influenza the "last great plague of mankind."

REFERENCES

1. Austin, D.F., Karp, S., Dworsky, R., Henderson, B.E.: Excess leukemia in cohorts of children born following influenza epidemics. Am. J. Epidemiol. 101:77-83, 1975.

2. Baron, S., du Buy, H.G., Buckler, C.E., Johnson, M.L.: Relationship of interferon production to virus growth in vivo. Proc. Soc. Exp. Biol. Med. 117:338-341, 1964.

3. Beare, A.S., et al.: Reactions and antibody response to live influenza vaccine prepared from the Iksha (A2) strain (A report to the Medical Research Council by their Committee on influenza and other respiratory virus vaccines). J. Hyg. 65:245-254, 1967.

4. Bental, E.: Acute psychoses due to encephalitis following Asian influenza. Lancet 2:18-20, 1958.

5. Berlin, B.S., Pirojboot, N.: A rapid method for demonstration of precipitating antibody against influenza virus by counterimmunoelectrophoresis. J. Infect. Dis. 126:345-347, 1972.

6. Berlin, B.S., Simon, N.M., and Bovner, R.N.: Myoglobinuria precipitated by viral infection. JAMA 227:1414-1415, 1974

7. Beveridge, W.I.: The origin of influenza pandemics. Who Chron. 29:471-473, 1975.

8. Bogart, D.B., Liu, C., Ruth, W.E., Kerby, G.R., and Williams, C.H.: Rapid diagnosis of primary influenza pneumonia. Chest 68:513-517, 1975.

9. Broun, G.O., et al.: Characteristics of influenza virus infections observed in St. Louis from 1943 to 1957. I. Arch. Int. Med. 101:203-210, 1958.

10. Bucher, D. and Palese, P.: THE INFLUENZA VIRUSES AND INFLUENZA. "The Biologically Active Proteins of Influenza Virus: Neuraminidase," Academic Press, Inc., New York, 1975.

11. Buebendorf, D.P., Carson, T.E., Cooper, N.R., Moynihan, M.J., and Yankee, R.A.: Asian influenza: a study of 150 persons during the 1957 pandemic. Yale J. Biol. 31:14-28, 1958.

12. Burch, G.E., Walsh, J.J., Mogabgab, W.A.: Study of the response of the cardiovascular system to Asian influenza. Am. Rev. Resp. Dis. 83:68-78, 1961.

13. Burk, R.F., Schaffner, W., Koenig, M.G.: Severe influenza virus pneumonia in the pandemic of 1968-69. Arch. Int. Med. 127:1122-1128, 1971.

14. Carey, D.E., Dunn, F.L., Robinson, R.Q., Jensen, K.E., and Martin, J.D.: Community-wide epidemic of Asian strain influenza. Clinical and sub-clinical illnesses among school children. JAMA 167:1459-1463, 1958.

15. Choppin, P.W. and Compans, R.W.: THE INFLUENZA VIRUSES AND INFLUENZA. "The structure of influenza virus," Academic Press, Inc., New York, 1975.

16. Collins, S.D., et al.: Mortality from influenza and pneumonia in 50 large cities of the United States, 1910-1929. Pub. Health Rep. 45:2277-2328, 1930.

17. The Commission on Acute Respiratory Diseases, Fort Bragg, North Carolina: Endemic influenza. Am. J. Hyg. 47:290-296, 1948.

18. Couch, R.B., Kasel, J.A., Gerin, J.L., Schulman, J.L., Kilbourne, E.D.: Induction of partial immunity to influenza by a neuraminidase-specific vaccine. J. Infect. Dis. 129:411-420, 1974.

19. Daugharty, H.: Immunoprecipitin reaction of influenza virus-antibody complex with anti-IgG. J. Imm. 107:802-809, 1971.

20. Davenport, F.M.: Inactivated influenza virus vaccines. Am. Rev. Resp. Dis. 83:146-150, 1961.

21. Davenport, F.M., Hennessy, A.V., and Francis, T., Jr.: Epidemiologic and immunologic significance of age distribution of antibody to antigenic variants of influenza virus. J. Exp. Med. 98:641, 1953.

22. Davenport, F.M., Hennessy, A.V., Drescher, J., Mulder, J., Francis, T., Jr.: Further observations on the relevance of serologic recapitulations of human infection with influenza viruses. J. Exp. Med. 120:1087-1097, 1964.

23. Davenport, F.M., Minuse, E., Hennessy, A.V., and Francis, T., Jr.: Interpretations of influenza antibody patterns of man. Bull. W.H.O. 41:453-460, 1969.

24. Davison, A.M., Thomson, D., Robson, J.S.: Intravascular coagulation complicating influenza A virus infection. Brit. Med. J. 1:654-655, 1973.

25. Douglas, R.G., Jr. Alfrod, R.H., Cate, T.R., and Couch, R.B.: The leukocyte response during viral respiratory illness in man. Ann. Intern. Med. 64:521-530, 1966.

26. Douglas, R.G., Jr.: THE INFLUENZA VIRUSES AND INFLUENZA. "Influenza in Man," Academic Press, Inc., New York, 1975.

27. Dowdle, W.R.: Editorial: Inactivated influenza vaccines. NEJM 289:1309-1310, 1973.

28. Dowdle, W.R., Schild, G.C.: THE INFLUENZA VIRUSES AND INFLUENZA. "Laboratory Propagation of Human Influenza Viruses, Experimental Host Range, and Isolation from Clinical Materials," Academic Press, Inc., New York, 1975.

29. Dull, H.B., Jensen, K.E., Rakich, J.H., Cohen, A., Henderson, D.A., Pirkle, C.I.: Monovalent Asian influenza vaccine. JAMA 172:1223-1229, 1960.

30. Easterday, B.C.: THE INFLUENZA VIRUSES AND INFLUENZA. "Animal influenza," Academic Press, Inc., New York, 1975.

31. Ebisawa, I.T., Kitamoto, O.: Persistence of viral antigen in the nasal epithelium in complicated influenza. Am. Rev. Resp. Dis. 99:275-278, 1969.

32. Eickhoff, T.C.: Committee on Immunization against influenza: rationale and recommendations. J. Infect. Dis. 123:446-454, 1971.

33. Eickhoff, T.C.: Sero-epidemiologic studies of meningococcal infection with the indirect hemagglutination test. J. Infect. Dis. 123:519-526, 1971.

34. Eickhoff, T.C., Sherman, I.L., Serfling, R.E.: Observations on excess mortality associated with epidemic influenza. JAMA 176:776-782, 1961.

35. Finland, M., Parker, F., Barnes, N.W., et al.: Acute myocarditis in influenza A infections: Two cases of non-bacterial myocarditis, with isolation of virus from the lungs. Amer. J. Med. Sci. 209:455-468, 1945.

36. Flewett, T.H., Hoult, J.G.: Influenzal encephalopathy and postinfluenzal encephalitis. Lancet 2:11-15, 1958.

37. Foy, H.M., Cooney, M.K., McMahan, R., Bor, E., Grayston, J.T.: Single-dose monovalent A_2 Hong Kong influenza vaccine. Efficacy 14 months after immunization. JAMA 217:1067-1071, 1971.

38. Francis, T. Jr.: Influenza: the newe acquayantance. Ann. Int. Med. 39:203-221, 1953.

39. Freihofer, A.F., Brooks, S.M., Loudon, R.G., May, D.B., and Settle, H.P., Jr.: Functional effects of influenzal pneumonia. Chest 66: Suppl.:36S-37S, 1974.

40. Gamboa, E.T., Wolf, A., Yahr, M.D., Barden, H., Hsu, C.C., Duffy, P.E. and Harter, D.H.: Influenza A virus as a possible cause of postencephalitic Parkinsonism. Trans. Am Neurol. Ass. 98:177-180, 1973.

41. Garrett Adams, H.: A local chronicle of the influenza epidemic of 1918. N. Carolina Med. J. 25:397-400, 1964.

42. Goodpasture, E.W.: The significance of certain pulmonary lesions in relation to the etiology of influenza. Amer. J. Med. Sci. 158:863-870, 1919.

43. Griffin, H.E.: Reactions to influenza vaccine. Ann. Allergy 17:179-187, 1959.

44. Hakulinen, T., Hovi, L., Karkinen, J.A., Askel Ainen, and Penttinen, K., and Sax, En L: Association between influenza during pregnancy and childhood leukemia. Brit. Med. J. 4:265-267, 1973.

45. Hall, C.B., and Douglas, R.G., Jr.: Nosocomial influenza infection as a cause of intercurrent fevers in infants. Pediatrics 55:673-677, 1975.

46. Hall, C.E., Cooney, M.K., and Fox, J.P.: The Seattle virus watch. IV. Comparative epidemiologic observations of infections with influenza A and B viruses, 1965-1969, in families with young children. Am. J. Epidemiol. 98: 365-380, 1973.

47. Hall, W.J., Douglas, R.G., Jr., Hyde, R.W., Roth, F.K., Cross, A.S., and Speers, D.M.: Pulmonary mechanics after uncomplicated influenza A infection. Am. Rev. Resp. Dis. 113:141-148, 1976.

48. Hardy, J.M.B., Azarowicz, E.N., Maninni, A., Medearis, D.N., Jr., Cooke, R.E.: The effect of Asian influenza on the outcome of pregnancy, Baltimore 1957-1958. Am. J. Pub. Health 51:1182-1188, 1961.

49. Harford, C.G.: Influenza viral pneumonia of human beings. Am. J. Med. 29:907-909, 1960.

50. Hayslett, J., et al.: Endemic influenza. I. Serological evidence of continuing and subclinical infection in disparate populations in the post-pandemic period. Am. R. Resp. Dis. 85:1-8, 1962.

51. Hers, J.F., Goslings, W.R.O., Masurel, N., Mulder, J.: Death from Asiatic influenza in the Netherlands. Lancet 2:1164-1165, 1957.

52. Higgins, P.B.: Viruses associated with acute respiratory infections 1961-1971. J. Hyg. (Camb) 72:425-432, 1974.

53. Hildebrandt, H.M., Maassab, H.F., Willis, P.W.: Influenza virus pericarditis. Amer. J. Dis. Child. 104:579-582, 1962.

54. Hoehling, A.A.: THE GREAT EPIDEMIC. When the Spanish influenza struck, Little Brown and Co., 1st Edition, Canada Ltd., 1961.

55. Horner, G.J., and Gray, F.D., Jr.: Effect of uncomplicated presumptive influenza on the diffusing capacity of the lung. Am. Rev. Resp. Dis. 108:866-869, 1973.

56. Houseworth, J., and Langmuir, A.D.: Excess mortality from epidemic influenza, 1957-1966. Am. J. Epidemiol. 100:40-48, 1974.

57. Hulka, J.F.: Effectiveness of polyvalent influenza vaccine in pregnancy. Obst. and Gyn. 23:830-837, 1964.

58.

59. Jackson, G.G., and Muldoon, R.L.: Viruses causing common respiratory infections in man. V. Influenza A (Asian). J. Infect. Dis. 131:308-357, 1975.

60. Jao, R.L., Wheelock, E.F., Jackson, G.G.: Production of interferon in volunteers infected with Asian influenza. J. Infect. Dis. 121:419-426, 1970.

61. Jarstrand, C. and Tunevall, G.: The significance of bacterial superinfection in influenza. Scand. J. Infect. Dis. 6:137-144, 1974.

62. Johanson, W.G., Pierce, A.K., Sanford, J.P.: Pulmonary function in uncomplicated influenza. Am. Rev. Resp. Dis. 100:141-146, 1969.

63. Jordan, M.C., Rousseau, W.E., Tegtmeter, G.E., Noble, G.R., Muth, R.G., and Chin, T.D.: Immunogenicity of inactivated influenza virus vaccine in chronic renal failure. Ann. Int. Med. 79:790-794, 1973.

64. Jordan, W.S., Jr., Badger, G.F., Dingle, J.H.: A study of illness in a group of Cleveland families. XVI. The epidemiology of influenza, 1948-1953. Am. J. Hyg. 68:169-189, 1958.

65. Jordan, W.S., Jr., Dowdle, W.R., Easterday, B.C., Ennis, F.A., Gregg, B.M., Kilbourne, E.D., Seal, J.A., Sloan, F.A.: Influenza research in the Soviet Union--1974. J. Infect. Dis. 130:686-693, 1974.

66. Kaji, M., et al. Isolation of Asian virus from extrapulmonary tissues in fatal human influenza. Proc. Soc. Exp. Biol. and Med. 100:272-275, 1959.

67. Kaye, D., Rosenbluth, M., Hook, E.W.: Endemic influenza. II. The nature of the disease in the post-pandemic period. Amer. Rev. Resp. Dis. 85:9-21, 1962.

68. Kendal, A.P., Minuse, E., Maassab, H.F., Hennessy, A.V., and Davenport, F.M.: Influenza neuraminidase antibody patterns of man. Am. J. Epidemiol. 98:96-103, 1973.

69. Kilbourne, E.D., Loge, J.P.: Influenza A: A clinical study of an epidemic caused by a new strain of virus. Ann. Int. Med. 33:371, 1950.

70. Kilbourne, E.D.: THE INFLUENZA VIRUSES AND INFLUENZA. "The influenza viruses and influenza -- an introduction," Academic Press, Inc., New York, 1975.

71. Kilbourne, E.D.: THE INFLUENZA VIRUSES AND INFLUENZA. "Epidemiology of influenza," Academic Press, Inc., New York, 1975.

72. Knight, V., Couch, R.B., Douglas, R.G., Tauraso, N.M.: Serologic responses and results of natural infectious challenge of recipients of zonal ultra-centrifuged influenza A_2/Aichi/2/68 vaccine. Bull W.H.O. 45:767-771, 1971.

73. Langmuir, A.D., Henderson, D.A., Serfling, R.E.: The epidemiological basis for the control of influenza. Am. J. Pub. Health 54:563-571, 1964.

74. Ledder, S.R., Gill, P.W., and Peat, J.K.: Short and long term effects on influenza A on lung function. Med. J. Australia 2:812-814, 1974.

75. Lehmann, N.I., Gust, I.D.: Viraemia in influenza. Med. J. Australia 2:1166-1169, 1971.

76. Lewes, D., Rainford, D.J., and Lane, W.F.: Symptomless myocarditis and myalgia in viral and mycoplasma pneumoniae infections. Brit. Heart J. 36:924-932, 1974.

77. Lindsay, M.I., Herrman, E.C., Morrow, G.W., et al.: Hong Kong influenza: Clinical, microbiology and pathologic features in 127 cases. JAMA 214:1825-1832, 1970.

78. Linnemann, C.C., Jr., Shea, L., Partin, J.C., Schubert, W.K., and Schiff, G.M.: Reye's syndrome: epidemiologic and viral studies, 1963-1974. Am. J. Epidemiol. 101:517-526, 1975.

79. Louria, D.B., Blumenfield, H.L., Ellis, J.T., et al.: Studies on influenza in the pandemic of 1957-58. II. Pulmonary complications of influenza. J.C.I. 38:213-265, 1959.

80. Luby, J.P., Johnson, M.T., and Jones, S.R.: Antiviral chemotherapy. Ann. Rev. of Med. 25:251-268, 1974.

81. McHenry, M.C., Alfidi, R.J., Diodhar, S.D., Braun, W.E., Popowniak, K.L.: Hospital-acquired pneumonia. Med. Clin. North Amer. 58:565-580, 1974.

82. MacCallum, W.G.: Pathological anatomy of pneumonia associated with influenza. Johns Hopkins Hosp. Rep. 20:149, 1921.

83. Mackenzie, J.S., Mackenzie, I., Lloyd, J., Dent, V.: Comparative trials of live attenuated and detergent split influenza virus vaccines. J. Hyg. (Camb) 75:425-443, 1975.

84. Masurel, N., Marine, W.M.: Recycling of Asian and Hong Kong influenza A virus hemagglutinin in man. Am. J. Epidemiol. 97:44-49, 1973.

85. Maynard, J.E., et al.: Evaluation of monovalent and polyvalent influenza vaccines during an epidemic of type A2 and B influenza. Am. J. Epidemiol. 87:148-157, 1968.

86. Medearis, D.N., Jr., Neill, C.A., and Markowitz, M.: Influenza and cardiopulmonary disease. II. Mod. Concepts Cardiovasc. Dis. 32:813-816, 1963.

87. Mejlszenkier, J.D., Safran, A.P., Healy, J.J., Embree, L., Duellette, E.M.: The myositis of influenza. Arch. Neurol. 29:441-443, 1973.

88. Middleton, P.J., Alexander, Szymanski: Severe myositis during recovery from influenza. Lancet 2:533-535, 1970.

89. Miller, L.W., Hume, E.B., O'Brien, F.R., Togo, Y., and Hornick, R.B.: Alice strain live attenuated influenza (H3N2) vaccine in an elderly population. Am. J. Epidemiol. 101:340-346, 1975.

90. Mills, J., Chanock, R.M.: Temperature-sensitive mutants of influenza virus. I. Behavior in tissue culture and in experimental animals. J. Infect. Dis. 123:145-157, 1971.

91. Minow, R.A., Gorbach, S., Johnson, B.L., Jr., Dornfeld, L.: Myoglobinuria associated with influenza A infection. Ann. Intern. Med. 80:359-361, 1974.

92. Monto, A.S., Kendal, A.P.: Effect of neuraminidase antibody on Hong Kong influenza. Lancet 1:623-625, 1973.

93. Monto, A.S., and Kioumehr, F.: The Tecumseh study of respiratory illness. IX. Occurrence of influenza in the community, 1966-1971. Am. J. Epidemiol. 102:553-563, 1975.

94. Monto, A.S., Davenport, F.M., Napier, J.A., et al.: Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. J. Infect. Dis. 122:16-25, 1970.

95. Morgensen, J.L.: Myoglobinuria and renal failure associated with influenza. Ann. Intern. Med. 80:362, 1974.

96. Mostow, S.R.,Schoenbaum, S.C.,Dowdle, W.R.: Studies with inactivated influenza vaccines purified by zonal centrifugation. I. Adverse reactions and serologic responses. Bull. W.H.O. 41:525-530, 1969.

97. Mufson, M.A., et al.: The role of viruses, mycoplasmas and bacteria in acute pneumonia in civilian adults. Am. J. Epidemiol. 86:526-544, 1967.

98. Murphy, B.R., Chalhub, E.G., Nusinoff, S.R., Chanock, R.M.: Attenuation of ts recombinants for man. J. Infect. Dis. 126:170-178, 1972.

99. Murphy, B.R., Kasel, J.A., Chanock, R.M.: Association of serum anti-neuraminidase antibody with resistance to influenza in man. NEJM 286:1329-1332, 1972.

100. Myking, O. and Schreiner, A.: Case Report: Influenza virus infection complicated by severe renal failure. Scand. J. Infect. Dis. 6:205-207, 1974.

101. Naficy, K.: Human influenza infection with proven viremia. NEJM 269:964-966, 1963.

102. Oseasohn, R., Adelson, L., Kaji, M.: Clinicopathologic study of thirty-three fatal cases of Asian influenza. NEJM 260:509-518, 1959.

103. Pearl, R.: Influenza studies. II. Further data on the correlation of explosiveness of outbreak of the 1918 epidemic. Pub. Health Rep. 36:273-298, 1921.

104. Pons, M.W.: THE INFLUENZA VIRUSES AND INFLUENZA. "Influenza virus RNA(s)," Academic Press, Inc., New York, 1975.

105. Randolph, V.L. and Heath, C.W., Jr.: Influenza during pregnancy in relation to subsequent childhood leukemia and lymphoma. Am. J. Epidemiol. 100:399-409, 1974.

106. Reed, W.P., Olds, J.W., Kesch, A.L.: Decreased skin-test reactivity associated with influenza. J. Infect. Dis. 125:398-402, 1972.

107. Riski, H. and Alanko, K.: Mycoplasma and influenza pneumonia in a series of 214 adults. Scand. J. Respir. Dis. Suppl.89:235-245, 1974.

108. Ruben, F.L., Jackson, G.G.: A new subunit influenza vaccine: acceptability compared with standard vaccines and effect of dose on antigenicity. J. Infect. Dis. 125:656-664, 1972.

109. Rubin, R.J. and Gregg, M.B.: Influenza surveillance in the United States 1972-1974. Am. J. Epidemiol. 102:225-232, 1975

110. Rytel, M.W., Jackson, L.J., Ferstenfeld, J.E., Rosenkranz, M.A.: New live attenuated influenza A/England/42/72 (H3N2) vaccine (Alice): Reactogenicity, immunogenicity, and protection efficacy. J. Infect. Dis. 132:652-659, 1975.

111. Schambelan, M., and Sussman, S.: Encephalitis and purpura with influenza infection. Am. J. Dis. Child. 111:302-303, 1966.

112. Schild, G.C.: Antibody against influenza A_2 virus neuraminidase in human sera. J. Hyg, (Camb) 67:353-365, 1969.

113. Schild, G.C., Dowdle, W.R.: THE INFLUENZA VIRUSES AND INFLUENZA. "Influenza virus characterization and diagnostic serology," Academic Press, Inc., New York, 1975.

114. Scholtissek, C., Klenk, H.: THE INFLUENZA VIRUSES AND INFLUENZA. "Influenza virus replication," Academic Press, Inc., New York, 1975.

115. Schulman, J.L.: THE INFLUENZA VIRUSES AND INFLUENZA. "Immunology of influenza," Academic Press, Inc., New York, 1975.

116. Schulze, Irene T.: THE INFLUENZA VIRUSES AND INFLUENZA. "The biologically active proteins of influenza virus: The hemagglutinin," Academic Press, Inc., New York, 1975.

117. Schnurrenberger, P.R., Woods, G.T., Martin, R.J.: Serologic evidence of human infection with swine influenza virus. Am. Rev. Resp. Dis. 102:356-361, 1970.

118. Schulman, J.L.: The role of antineuraminidase antibody in immunity to influenza virus infection. Bull. W.H.O. 41:647-650, 1969.

119. Schwarzmann, S.W., Adler, J.L., Sullivan, R.J., et al.: Bacterial pneumonia during the Hong Kong influenza epidemic of 1968-1969. Arch. Int. Med. 127:1037-1041, 1971.

120. Seltser, R., Sartwell, P.E., Bell, J.A.: A controlled test of Asian influenza vaccine in a population of families. Am. J. Hyg. 75:112-135, 1962.

121. Shope, R.E.: The incidence of neutralizing antibodies for swine influenza virus in the sera of human beings of different ages. J. Exp. Med. 63:669, 1936.

122. Shope, R.E.: The swine lungworm as a reservoir and intermediate host for swine influenza virus in healthy and susceptible pigs. J. Exp. Med. 74:41-47, 1941.

123. Shope, R.E.: Influenza. History, epidemiology and speculation. Pub. Health Rep. 73:165-178, 1958.

124. Simon, N.M., Rovner, R.N., Berlin, B.S.: Acute myoglobinuria associated with type A_2 (Hong Kong) influenza. JAMA 212:1704-1705, 1970.

125. Simpson, R.W., Bean, W.J.: THE INFLUENZA VIRUSES AND INFLUENZA. "The biologically active proteins of influenza virus: Influenza transcriptase activity of cells and virions," Academic Press, Inc., New York, 1975.

126. Smith, W., Andrewes, C.H., and Laidlaw, P.P.: A virus obtained from influenzal patients. Lancet 2:66, 1933.

127. Spencer, M.J., Cherry, J.D., Powell, K.R., Sumaya, C.V., Garakian, A.J.: Clinical trials with Alice strain, live, attenuated, serum inhibitor-resistant intranasal influenza A vaccine. J. Infect. Dis. 132:415-420, 1975.

128. Stanley, E.D., Jackson, G.G.: Viremia in Asian influenza. Trans. Assoc. Amer. Phys. 79:376-387, 1966.

129. Still, R.M.L.: Psychosis following Asian influenza in Barbados. Lancet 2: 20-21, 1958.

130. Stiver, H.G., Graves, P., Elckhoff, T.C., Meiklejohn, G.: Efficacy of "Hong Kong vaccine in preventing" England variant influenza A in 1927. NEJM 289: 1267-1271, 1973.

131. Sugiura, A.: THE INFLUENZA VIRUSES AND INFLUENZA. "Influenza virus genetics," Academic Press, Inc., New York, 1975.

132. Togo, Y., Hornick, R.B., and Dawkins, A.T., Jr.: Studies on induced influenza in man. I. Double blind studies designed to assess prophylactic efficacy of amantadine hydrochloride against A2/Rockville/1/65 strain. JAMA 203:1089-1094, 1968.

133. Togo, Y., Hornick, R.B., Felitti, V.J., Kaufman, M.L., Dawkins, A.T., Kelpe, V.E. and Claghorn, J.L.: Evaluation of therapeutic efficacy of amantadine in patients with naturally occurring A_2 influenza. JAMA 211:1149-1156, 1970.

134. Trimble, G.X.: Maternal influenza and congenital defects. JAMA 172:2109-2110, 1960.

135. U. S. Dept. of Health, Education and Welfare. Center for Disease Control. Annual EIS Conference. April, 1976.

136. U. S. Dept. of Health, Education and Welfare. Center for Disease Control. Summary of vaccine trials - conf. June 20-21, 1976.

137. Walker, W.C., Douglas, A.C., Leckie, W.J., Pines, A., Grant, I.W.: Respiratory complications of influenza. Lancet 1:449-454, 1958.

138. Walsh, J.J., Dietlein, L.F., Low, F.N., Burch, G.E., Mogabgag, W.J.: Broncho-tracheal response in human influenza. Type A, Asian strain, as studied by light and electron microscopic examination of bronchoscopic biopsies. Arch. Intern. Med. 108:376-388, 1961.

139. Webster, R.G., Laver, W.G., Tumova, B.: Studies on the origin of pandemic influenza viruses V. Persistence of Asian influenza virus hemagglutinin (H2) antigen in nature? Virology 67:534-543, 1975.

140. Webster, R.G., Laver, W.G.: THE INFLUENZA VIRUSES AND INFLUENZA. "Antigenic variation of influenza," Academic Press, Inc., New York, 1975.

141. Wenzel, R.P., Hendley, J.O., Sande, M.A., Gwaltney, J.M.: Revised (1972-1973) bivalent influenza vaccine. Serum and nasal antibody responses to parenteral vaccination. JAMA 226:435-438, 1973.

142. Wilson, M.G., Stein, A.M.: Teratogenic effects of Asian influenza. An extended study. JAMA 210:336-337, 1969.

143. Winslow, C.E.A., and Rogers, J.F.: Statistics of the 1918 epidemic of influenza in Connecticut. J. Infect. Dis. 26:185-216, 1920.

144. Yawn, D.H., Pyeatte, J.C., Joseph, J.M., Eichler, S.L., Garcia-Bunuel, R.: Transplacental transfer of influenza virus. JAMA 216:1022-1023, 1971.

145. Young, L.S., LaForce, F.M., Head, J.J., et al.: A simultaneous outbreak of meningococcal and influenza infections. NEJM 287:5-9, 1972.

146. Zalan, E., Borman, E., Labzoffsky, N.A.: Infectious influenza virus-antibody complex. Arch. Gesamte Virusforsch. 34:209-213, 1971.