MEDICAL GRAND ROUNDS

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INFLUENZA: CONSIDERATION OF HONG KONG-68 VARIANT

Influenza is an acute respiratory disease of man and animals caused by certain myxoviruses. The influenza viruses are spherical particles of medium size (80-120 mμ in diameter), contain a single stranded RNA core which constitutes the type-specific antigen within a capsid of helical symmetry which is surrounded by a lipoprotein envelope. The envelope is studded with surface projections which possess hemagglutinating activity. The virus matures at the cell surface but is complete only outside of the cell. Human influenza viruses comprise 3 groups (A, B and C) which are completely unrelated antigenically, do not induce cross-immunity and differ in epidemiological and clinical characteristics. The 3 types of influenza virus are distinguished from each other by their type-specific soluble complement-fixing (CF) antigens. All members of a particular type share the same soluble CF antigens. Subtypes are differentiated by antigens associated with the virus particles themselves, strain-specific CF antigens or hemagglutinating (HA) antigens which are detected by hemagglutination inhibition (HAI) tests or neutralization tests (1,2). The neutralization test designed to measure the presence of influenza virus neutralizing antibody in the sera of vaccinated mice using hemadsorption as an endpoint indicator is more discriminating in detecting antigenic variation than conventional hemagglutination inhibition or strain-specific complement fixation tests (Table 1) (2,3). The interpretation of the significance of these data is open to speculation; however, from the influenza vaccine experience in 1963 it became apparent that re-evaluation of the techniques employed to detect antigenic changes in prevalent influenza viruses was of major clinical importance and necessary for the formulation of effective vaccines (4-6).

Epidemiology:

Critical assessment of the patterns of prior outbreaks of influenza afford the basis from which speculation or predications regarding future outbreaks, in this discussion A2/Hong Kong/68, are drawn. For this reason it would appear advantageous to review and categorize features which may enable better understanding of the current problem. While Hippocrates reported an infection resembling flu which obliterated the Athenian army in 412 B.C. and approximately 30 pandemics have been described between 1510 and 1930, data sufficiently accurate from which to base predictions can be obtained only after 1900 and even then information prior to the identification of the influenza virus by Smith, Andrews and Laidlaw in 1933 is more speculative (1, 7-10).

The etiologic agent of the 1918-20 pandemic was never isolated, but serological evidence suggests that it was closely related to the virus isolated from swine influenza (11-12). However, it cannot be determined with certainty as to whether or not the pandemic of 1918-20 was associated with the introduction of a new antigenic variant or not. If it had been associated with appearance of a new

variant, the epidemiological cycle would have been quite unusual, since serological studies in individuals of various ages suggest that human contact with the antigen has not been common since 1920 (12-13). Thus, the epidemiologic life of the 1918-20 influenza A variant would have been of several years' duration, rather than the decade or longer seen with more recent isolates. Despite this missing piece, assessment of other features is of value in defining the potential impact of influenza.

The initial recognition in the U.S. and, for that matter, in the world, was on March 11, 1918, at Camp Funston, Fort Riley, Kansas, when classical clinical influenza abruptly broke out. It is interesting and perhaps relevant in view of the present problems with air pollution that the outbreak occurred two days following a severe dust storm. This initial outbreak lasted 5 weeks, involved 1,127 patients (hospitalized), and there were 46 deaths (a case fatality ratio of 4%) (7). Subsequently, influenza appeared in other portions of the U.S., Europe, Japan and China with remarkable rapidity. The prominence it received in Spain gave rise to its designation as "Spanish influenza". It affected simultaneously a large percentage of the population with an overall morbidity rate in the U.S. of 23.9%, with rates varying from 15% in Louisville, Kentucky, to 53.5% in San Antonio and showed a predilection for the 5- to 35-year age group (14). The spring wave missed many areas of the world. The second wave is stated to have appeared in Europe in the last week in August, 1918 (8). It supposedly appeared in Boston at approximately the same time. Between the first and middle of September, hundreds of new foci appeared and by the first week in October, the pandemic was worldwide. The peak in the U.S. occurred between October 12 and 26, 1918 (15, 15a). In the second wave, there were many mild cases, but more severe forms became prominent; patients who started abruptly with pulmonary congestion, profound cyanosis and died within a few days and patients who on the fourth or fifth day of seemingly mild influenza developed a bacterial bronchopneumonia with either death or prolonged convalescence. During the 31 weeks between September 15, 1918, and April 19, 1919, approximately 21,000,000 deaths occurred in the world and in the United States, approximately 550,000 deaths occurred. The excess mortality was 550.5/100,000, or approximately 0.5% (16). During this interval the overall case fatality ratio was as high as 3.14% in New London, Connecticut (14). The age-specific mortality was highest in the 15- to 45-year age groups (Figure 1). A marked increase in mortality during pregnancy was observed (17).

Certain epidemiological and clinical features stand out: the initial outbreaks in the Northern Hemisphere occurred in the spring, attack rates were high (approximately 25%) with the highest rates in the young adults, pandemic disease had occurred by the first week in October and the peak was reached the last two weeks in October (approximately 8 weeks after reintroduction), and the case fatality ratio was very high with the clinical pictures of both primary influenzal pneumonia and superimposed bacterial pneumonia. While the specific antigenic variant has remained elusive, there are features, as will be seen later, which suggest the pandemic followed introduction of a new variant into a susceptible population.

Following the 1918-19 pandemic, influenza outbreaks associated with excess mortality, a feature which is primarily seen with influenza A, occurred in February 1922, February 1923, March 1926 and January 1929 (18, 19). The 1929

epidemic was associated with approximately 50,000 excess deaths. The morbidity rate was 145/1000, or approximately one-half that of 1918-19. A striking difference was the rather constant age-specific attack rate, in contrast to the increased incidence in younger ages in 1918-19 (14). Also in contrast to 1918-19, the death rate was increased at the extremes of life, less than 5 years and progressively increased beyond 55 years. This pattern of constant age-specific attack rate was seen in 1963, in contrast to 1957 with influenza A2, and suggests prior contact with the antigen (Figure 2) (20). This would suggest that the strain prevalent in 1929 had been previously encountered and did not represent a major new variant, although a decade had passed since the 1918-19 pandemic.

Following isolation of influenza A or A0 in 1933, epidemics and local outbreaks occurred but no major pandemic ensued. In 1947, a major antigenic change in the influenza virus unexpectedly occurred. This agent was originally designated as A' and more recently as A1. Because of this major antigenic shift, persons immunized with vaccines containing only A antigenic components were not protected (21). It is noteworthy that despite this major antigenic change pandemic disease did not ensue (22). Sudden marked shifts in antigenic characteristics would be expected to be accompanied by outbreaks with high attack rates. Yet the epidemic of 1943 (A0 with a minor antigenic drift) had much higher attack rates than the outbreak of A1 in 1947 (22a). In fact, pandemic disease did not appear at any time with the A1 strain of influenza despite the observation that it replaced the prototype strain PR8-WS of A0 throughout the world. Thus, major antigenic changes are not <u>per se</u> associated with pandemic influenza.

In late February 1957, epidemic influenza apparently began in Kweichow Province in Southwest China (8). It became known to the rest of the world when epidemic influenza occurred in Hong Kong in April 1957, then rapidly spread to Singapore, Manila and Taiwan (23, 24). In Hong Kong disease spread rapidly, with a 15-20% attack rate and almost no mortality. An officer from the U.S. Army 406th Medical Laboratory in Japan traveled to Hong Kong upon initial reports and by May 22, Meyer and associates had characterized the causative agent as a new type, designated as Asian, then A2, of which A2/Japan/305/57 has become the prototype (25). In the U.S., initial recognition occurred among military personnel, first at Newport, R.I., on June 2, then almost simultaneously in San Francisco (23). During late June and early July, 15 outbreaks were recognized in children's camps in California. In late June, a conference was held in Grinnell, Iowa, involving 1,500 young persons from 43 states and several foreign countries. Several participants had been in prior contact with A2 influenza in California and an outbreak of 200 cases occurred at Grinnell with 50 subsequent cases. By September, epidemic spread occurred in almost all parts of the country.

It is beyond the scope of this discussion to cover all facets of the experience in 1957-58, during the pandemic of Asian influenza. Several epidemiologic features deserve comment. Numerous epidemics were recognized in many parts of the country in September and the epidemic reached an initial peak by mid-October, 1957 (23). Excess mortality, the traditional index of epidemic influenza, follows the peak occurrence of cases by an interval of 3-4 weeks (23). Peak excess mortality was at its peak in November. By December all indices of influenza had declined. Age-specific attack rates were low among preschool children, rose markedly among school children, reaching a peak among high school students and young adults (Figure 2) (26, 27). In the Cleveland family study, attack rates

were 73% in school children, 30-32% in mothers and preschool children and 16% in fathers (27a). The initial sparing of younger children and older adults cannot relate to immune status, as was to be well demonstrated with the second wave, but must have represented less opportunity for exposure.

Recurrence of a second wave had been striking in 1918-19. During the Asian epidemic, between January and March 1958 a second wave of influenza occurred (28). During the second wave, populations with higher attack rates during the first wave were spared. For example, in studies in a children's institution, during the initial wave 69% of 223 children had clinical influenza. During the second wave in January-February 1958 (5 months later), only 11% of the old residents became ill (29). Thus, natural infection induced immunity which lasted at least 5 months. During the first wave, 40,000 excess deaths were recorded and 20,000 during the second wave. The shape of the histogram of age-specific mortality is in general a skewed "U" with peaks at either end (Figure 3). This type of curve has characterized all influenza outbreaks except for the 1918-19 pandemic. Eickhoff and associates demonstrated that certain individuals were at increased risk of death from influenza. Three broad groups, two of which overlap, can be identified: persons over 65 years of age, persons with certain "associated chronic diseases" and pregnant women (28). Associated chronic diseases of significance include cardiovascular renal disease, particularly rheumatic heart disease with mitral stenosis, chronic pulmonary diseases, e.g., bronchial asthma, chronic obstructive lung disease, pulmonary tuberculosis and metabolic diseases such as diabetes mellitus. There was no excess mortality in patients with malignant neoplasms. The mortality rate from influenza was reported to be twice as high among pregnant women as compared with non-pregnant women in the same age group in 1957-58 (28). Widelock, et al. reported a 9.4-fold increase in mortality when influenza occurred in the last half of pregnancy in October-November 1957 in comparison to the same months of 1958-60 (71). Increased mortality in pregnant women has not been encountered in subsequent A2 epidemics.

Subsequent influenza A2 outbreaks of epidemic proportions occurred in 1960, 1963 and 1967. In these subsequent outbreaks (1960, 1963), the peak morbidity rates in school children and young adults had vanished (Figure 2) (20, 28). An immunologic explanation of the change in age distribution of morbidity rates is afforded by the studies of Widelock, et al. (30). In long-term serological studies they found that the incidence of antibody levels (HA antibody) in the 15-19 age group never fell below 75% positive, while in the age group over 40 the monthly incidence of significant levels fell to as low as only 40% and fluctuated between 40 and 75%.

Based upon surveillance of outbreaks and antigenic changes, influenza A outbreaks occur at 2- to 3-year intervals and are associated with excess mortality. In contrast, influenza B outbreaks occur every three to six years and are not associated with excess mortality but can be measured by excess absenteeism. It was against this background, and an epidemic of influenza A2 in all but four states in 1967-68, that little or no A2 influenza was anticipated in 1968-69, unless a major antigenic change occurred (31).

However, on July 27, 1968, an epidemic of influenza affecting an estimated 300,000 persons in Hong Kong was reported (32). The first cases became evident on July 13, 1968, with a rapid increase in incidence reaching an apparent peak on

July 25-26, 1968. The disease was clinically mild, lasting 3 to 4 days. Estimates of overall attack rates have varied from 10 to 30%, or 400,000 cases, with 22 deaths unofficially reported (33). Study of the viruses isolated in Hong Kong in various centers has revealed major dissimilarities between these strains and earlier A2 strains. Because they were identified with WHO reference A2 polyvalent antisera, they have been classified as A2 viruses by the world influenza center in London and NCDC in Atlanta (34, 35). However, Fukumi of Japan considers it sufficiently dissimilar to be designated as A3 (36). The magnitude of the antigenic differences can be illustrated by serological strain relationships (Table 2) and study of the HI antibody response against A/Hong Kong/68 strains by individuals who had either clinical influenza due to A2 in 1967-68 or had received vaccine in 1967 (Table 3). Subsequent outbreaks have been reported in Singapore, Taiwan, the Philippines, Indonesia and Thailand. The outbreak in Manila began about the first week in August and reached a peak by August 24, 1968 (Table 4) (37). In that excess mortality follows the clinical peak by 3 to 4 weeks, the impact of A/Hong Kong/68 in Manila cannot yet be fully assessed. On September 2, 1968, 2 cases of influenza-like illness in Atlanta, Georgia, were reported and confirmed as A2/Hong Kong/68 strains; the index case had returned from the Far East 4 days prior to onset of symptoms (38). Also, on September 6, a Merchant Marine vessel docked at Vancouver, Washington, having had an outbreak of influenza-like illness after leaving Saigon on August 18 (39).

Thus, there is little question that influenza A/Hong Kong/68 has been introduced into the U.S. The major question is whether or not pandemic disease will ensue. From prior experience, when major antigenic shifts have occurred widespread disease usually, although not necessarily, follows. Pandemicity is most probably related to antigenic novelty of the virus and lack of specific immunity rather than to virulence of the agent. In a population with very low levels of immunity, a high attack rate in school-age children and young adults would be anticipated. The late initial occurrence in Hong Kong (July 1968 in contrast to April 1957) and the late introduction into the U.S. (September 1968 in contrast to June 1957) might influence pandemic occurrence. In both 1918 and 1957, the epidemic was well advanced by late September. The apparent mild nature of the disease in Hong Kong cannot be taken to indicate lack of virulence, since in 1957 the same observations were made. Even in the absence of pandemic disease epidemic disease with excess mortality in older persons and individuals with associated chronic diseases would seem more likely than not.

In addition to examining the epidemiology of influenza with particular reference to A/Hong Kong/68, there are several other aspects which are of general interest. The sporadic occurrence of pandemics, seemingly almost at 10-year intervals, and epidemics of influenza A at 2- to 3-year intervals does not account for the persistence of the influenza virus in interepidemic periods. Hayslett, et al. presented evidence of the sequential acquisition of antibody in a population with no clinical influenza (40). From such data, they postulate that interepidemic spread is by inapparent man-to-man transmission. An additional mechanism for maintenance in man might involve overt clinical infection which was not recognized as influenza; for example, influenza may be associated with a clinical picture of segmental or bronchopneumonia (41, 42).

The fascinating observations of Shope regarding swine influenza raise interesting questions regarding human disease. Shope has demonstrated that the

swine lung worm (Metastrongylus spp.), a nematode parasite which resides in the bronchioles of swine, under natural conditions can serve as a reservoir and intermediate host for the swine influenza virus (43, 44). The virus can persist in a masked form within its worm host for long periods of time and even years may elapse between its transmission from one swine to the next. The virus is present in a non-infective form and a provocative stimulus is necessary to initiate infection. Injections of Hemophilus influenza suis or the migration of ascaris larvae furnished the needed provocation (43-46). While there is no evidence of a similar mechanism of masked infection which is pre-seeded and then provoked in man, there are epidemiological features which are not well explained by man-to-man transmission with a relatively high rate of apparent to inapparent infection. For example, the 1789 outbreak of influenza appeared to spread more rapidly than available transportation, and in 1918 Boston and Bombay had their epidemic peaks in the same week, while New York did not have its peak until 3 weeks later (8).

While pandemics with high attack rates and relatively high mortality may appear following major antigenic change, a background of some degree of prior heterotypic exposure apparently provides some degree of protection. Brown, Gajdusek and Morris described an epidemic of A2 influenza which swept through several isolated islands belonging to the Yap district of the western Caroline Islands (47). Three islands were involved, attack rates were virtually 100 per cent and the mortality ranged from 1.0 to 6.5 per cent. None of the populations had had any experience with A2 influenza, and the younger half of the population had no antibody to any strain of influenza virus. Yet despite no prior exposure, 23% developed low levels of antibody against A and A1 antigens, indicating the potentiality of some relative degree of cross-immunity between types.

Pathogenesis:

The review by Davenport brings together the current understanding of pathogenesis; following is a brief resume of his review (48). Infection can be initiated in man by virus in the wet or dry state, in small or large aggregates, and when lodged on the upper as well as on the lower respiratory passages, assuming that the virus settles first on the mucous film covering the respiratory epithelium of the nasopharynx or bronchi or bronchioles. The first event in likelihood is the combination with an alpha type inhibitor of hemagglutination. Alpha inhibitors are heat-stable mucoproteins found in serum and in a wide variety of tissue secretions including those of the lung. They are believed to be structurally analogous to the erythrocyte and tissue receptors for influenza virus. If the hemagglutinin of influenza viruses did not possess another important property, it seems most likely that the outcome of this initial event would be extrusion of the virus, since ciliary action would favor movement of the potential invader on the mucous film toward the exterior. Gottschalk has shown that the neuraminidase activity of influenza viruses rapidly lowers the viscosity of mucus (49). Conversion of this viscous material to a watery fluid lays bare cellular surface receptors and promotes the spread of virus by flow of virus-containing fluids to lower portions of the pulmonary apparatus. Virus enzyme action not only liquefies mucus, but also results in release of virus in a fully active state from combination with inhibitors. The stage is now set for penetration of virus. Fazekas de St. Groth concluded that viral enzyme activity was not essential for penetration since virus heated sufficiently to inactivate the enzyme was apparently engulfed (50). He called the process "viropexis", implying that intact virus particles

were taken into cells much as are colloidal dyes. The scheme of attachment, liquefaction of mucus and penetration of cells described here can be interrupted by either of two humoral factors. The first is a heat-labile proteinaceous substance called beta inhibitor, and the second is specific antibody. Beta inhibitor is present in serum at low concentrations and presumably by diffusion may come to bathe the surfaces of respiratory epithelium and mix with mucus. Beta inhibitor is capable of inactivating in vitro the infectivity of low concentrations of influenza viruses. More certain is the function of anti-influenzal antibodies. Neutralization of virus will occur if a sufficient concentration of antibody reaches virus prior to penetration of cells and under these circumstances infection can be prevented. However, the antibody mechanism of resistance can be partially overcome if the challenge is severe enough. Cellular factors may also condition the outcome of exposure to virus, although unequivocal experiments have not been designed. If infection is initiated, the virus multiplies and eventually emerges from the invaded cells. The inflammatory process which follows cell injury results in increased diffusion of plasma constituents to the area of invasion. If the diffusate contains a sufficient amount of virus inactivating substances, infection will be aborted. If not, the outpouring of fluid may favor dispersion of virus and hence increase the extent and severity of infection. Isaacs and Hitchcock demonstrated that the concentration of interferon, a substance apparently formed in infected cells that contributes to cellular resistance, increases rapidly in the lungs of infected mice and remains at high levels for several days before specific antibody can be detected either in serum or in lung extracts (51). Whether interferon or its absence may play a role in infections in humans has not yet been clearly established.

The pathophysiology of influenza is usually described in terms of viral action on the respiratory tract. The virus might be expected to penetrate beyond the alveolar cells and enter the capillaries, but the generalized symptoms are usually ascribed to "toxic" effects from the absorption into the blood of the breakdown products of infected cells. In mice, viremia and isolation of virus from the spleen, liver and kidney have been shown (52). Virus has been isolated from the brain of a patient with acute influenzal encephalitis (53). Influenza virus has also been recovered from the spleen, lymph nodes, liver and other tissues in three fatal cases, apparently under circumstances in which meticulous care to avoid contamination was taken (54). In addition, A2 influenza virus has been reported isolated from peripheral blood of a patient hospitalized with afebrile illness. The illness was associated with a significant rise in HAI antibody both to the isolated agent and to standard influenzal antigen (55). These reports suggest that on occasion extrapulmonary dissemination may occur and lend credence to some of the extrapulmonary influenzal complications which have been reported.

Pathology:

More or less extensive destruction, consisting of degeneration and desquamation of the ciliated epithelium of the trachea and bronchi, occurs in the acute stage of influenza. An early lesion appears to be a swelling of the cell with a swollen oval nucleus situated transversely in the cytoplasm. The normal palisade structure of the epithelium vanishes. Structures resembling basophilic and eosinophilic inclusion bodies are sometimes found in the cytoplasm. These inclusions are mainly phagocytized cellular and nuclear debris derived from unknown necrotic cells. At more or less the same time, the structure of the epithelium is

altered by the development of intercellular spaces, probably due to release and shrinkage of cells. In addition, real eosinophilic inclusion bodies may also be demonstrated in the cytoplasm. Neither the eosinophilic inclusion bodies nor the small shrunken cells are considered by Hers to be pathognomonic for influenza (56). Finally, one or two rows of a flattened layer of cells sometimes remain, covering the basement membrane. In the latter stages, this epithelium changes into a stratified-like epithelium in which the normal structure of the epithelial lining can rarely be found. Because a complete growth cycle of influenza virus is very short, about 8 hours, the death and desquamation of the affected cells occurs very early in the disease. The change of the ciliated epithelium into a stratified layer of cells had been mentioned as early as 1899 and had been observed by many investigators in 1918 (56). Similar changes were demonstrated by Burch, Walsh and Mogabgab on bronchial biopsy obtained from 9 patients at the height of illness (57). The pathology of human influenza virus pneumonia has been less clearcut. In a study of 148 virologically confirmed fatal cases of Asian influenza, it was found in many instances that damage extended to the epithelial lining of the resiratory bronchioles; in 30 of these cases without co-existent bacterial inflammation, a peculiar form of focal pneumonia was present which could be readily recognized to be identical with the pneumonic lesions found in certain cases by American pathologists in 1918 and considered by them to be true influenzal pneumonia. In the early stage of the disease, the microscopic lesions included: a) severe hyperemia and broadening of the alveolar walls with interstitial leucocytic infiltration; b) alveolar hemorrhage; c) capillary thrombosis with increased focal leucocytic exudate; d) dilatation of alveolar ducts and the presence of so-called hyaline membranes. In addition, cells characterized by small round nuclei showing striking pyknosis or coarse particles of chromatin at the nuclear membrane are found attached to the alveolar wall or lying within the exudate in the alveoli. Vacuoles are common (58). MacCallum described the same type of cell in the alveolar exudate of 13 of 44 cases of influenza pneumonia in 1918 (59). The importance of pre-existing disease as well as the importance of superimposed bacterial infections in predisposing to fatal influenza is illustrated in the summary of the studies by Hers and Mulder (Figure 4).

Clinical Features:

Influenza is a disease with few characteristic signs, hence symptoms are particularly important. A tabulation of both symptomatology and signs is taken from the summary paper by Dr. Stuart-Harris (Tables 5, 6) (27a, 61, 62).

Although respiratory tract symptoms frequently dominate the clinical picture of even mild influenza, little is known about the alterations in pulmonary function associated with this common infection. That functional impairment may occur despite normal chest radiographs is suggested by the observation that many patients with influenza have clinical findings indicative of lower respiratory tract disease (63, 64). The only study of pulmonary functions in patients with uncomplicated proven influenza was performed in a group of 30 military recruits (65). A transient but significant reduction in ventilatory function as measured by the indirect maximum breathing capacity calculated from the forced expiratory volume during 0.75 second was reported. Blood gas studies were not performed. During the epidemic of 1967-68, Drs. Johanson and Pierce at this institution investigated the effect of uncomplicated (non-pneumonic) influenza on the pulmonary function of previously healthy, non-hospitalized adult patients (66). Of the

patients studied, 10 had confirmed influenza. They ranged in age from 23 to 61 years. There were 4 women and 6 men, only 3 of whom were cigarette smokers. All were febrile and despite normal chest radiographs, 5 had some minor abnormality on auscultation of the chest. In the acute study, the ratio of residual volume (RV) to TLC was elevated in 6 patients. The FVC of 4 patients was less than 85% of their predicted value with proportionate decreases in $FEV_{1.0}$, one patient having a normal FVC but a reduced $FEV_{1.0}$. During the acute illness, arterial pO_2 was low in 7 patients (< 80 mm Hg) and this reduction was associated with an increased alveolar-arterial O_2 tension gradient in the 6 patients in whom this calculation was possible. Repeat studies at 2 and 6 weeks revealed return to or toward normal. Inhalation of a bronchodilator aerosol had no significant effect on ventilatory function at either the acute or the 2-week follow-up study. These data are compatible with bronchiolitis with partial obstruction of small airways and altered ventilation-perfusion relationships or involvement of the pulmonary parenchyma. While not allowing a differentiation between small airways and parenchymal disease, the data indicate that pulmonary involvement frequently occurs during apparently uncomplicated influenza (66).

Complications:

Although the mortality has varied considerably between outbreaks of pandemic influenza, Kilbourne has suggested that the influenza virus has not altered appreciably in regard to its intrinsic virulence for man in the past 50 years, morbidity being determined by immunologic factors and mortality by abnormalities of the host and his environment (67). The importance of associated chronic disease as a determinant in fatal progression was discussed in the sections on epidemiology and on pathology (28, 59). The studies of Louria and associates during the 1957 A2 influenza epidemic emphasize the importance of underlying disease in the pathogenesis of both pulmonary complications and fatality (68). 21 of the 30 patients with serious pulmonary complications, including 9 of the 11 who died, had underlying illness or were pregnant. 14 of the patients had cardiovascular disease, 10 of the 14 having rheumatic heart disease. Concurrently, Martin and associates studied a series of 32 influenza-associated deaths in the Boston area (69). Of these, 24 had some type of antecedent disease; heart disease 12 (rheumatic 5, hypertensive 4, coronary 2, congenital 1), pulmonary disease or respiratory insufficiency 10 (bronchial asthma 4), diabetes 2, cirrhosis of the liver 2, pregnancy 4, miscellaneous 4. Harford has suggested that the increased mortality observed in patients with cardiovascular disease may be due to edema which enhances the spread of influenza virus in the human lung similar to the observations on the spread of pneumococci (70). Assessment of environmental factors is considerably more difficult. Several air pollution studies have demonstrated that increases in morbidity and mortality of the exposed population are related to excessively high levels of air contamination. The role of other, simultaneously acting, environmental stresses such as cold weather and epidemic disease have been difficult to assess. Greenberg and associates have reported on the interrelationships between air pollution, influenza and mortality in New York City during January-February 1963 (72). The air pollutant which is common to most urban areas is sulfur dioxide. The maximal permissible 1-hour level of sulfur dioxide is considered to be 0.40 ppm. In their analysis, air pollution (> 0.40 ppm sulfur dioxide) in the presence of cold and A2 influenza resulted in 200 to 400 excess deaths over a similar period when influenza and cold of comparable degree were present in the absence of air pollution. While studies such as these are

extremely difficult to interpret, they emphasize the increasing complexity of assessing causality in problems faced by urban societies.

Respiratory complications of influenza: The most important complications are those involving the lower respiratory tract which may be divided into cases of tracheobronchitis and bronchiolitis and those with pneumonia. Influenzal pneumonia is of two main varieties, primary influenza virus pneumonia and late bacterial pneumonia, with admixtures of both. The relative frequency of each apparently varies during different epidemics and in different locations (58, 68, 69). These studies of Louria and associates are illustrated in Figure 4A. In this series, it is of note that 8 of the 15 late bacterial pneumonias were of pneumococcal etiology. These findings are in accord with the observations of Stuart-Harris in the A1 influenzal era. During this time, in 166 cases of pneumonia, pneumococci were recovered in 69% (73). In contrast, Hers and associates demonstrated staphylococci in 69 of 103 fatal cases of influenza (74). Likewise, Martin and associates demonstrated staphylococci in 11 of 17 fatal post-influenzal bacterial pneumonias (69). Major features of the polar syndromes of bacterial pneumonia following influenza and primary influenza virus pneumonia have been summarized by Rogers (Tables 7, 8) (75).

Delayed convalescence: One of the major complications following influenza is that of prolonged weakness and asthenia. The studies of Imboden, Canter and Cluff strongly suggested that symptomatic recovery from acute brucellosis was critically dependent upon the emotional state of the person. In August of 1957, prior to the occurrence of A2 influenza, the MMPI and CMI tests were administered to a total of 600 subjects. In the winter of 1957-58, 26 of these persons reported to the dispensary with an illness that was diagnosed as influenza. The 26 persons with influenza were divided into two groups: a) recovered group, 14 persons, who became asymptomatic 3-14 days, with an average of 7.9 days after the onset of illness, and b) symptomatic group, 12 persons who retained symptoms beyond 3 weeks (76). These two groups did not differ from each other with respect to clinical characteristics of their acute illness. Significant differences were observed, however, in the psychologic test results in that delayed recovery following acute self-limited illness occurred in persons who respond to psychologic tests in patterns characteristic of depression-prone patients. Since the psychologic data in this study were obtained prior to the illness, the evidence supports the view that this emotional state or attitude is not secondary to the illness but existed prior to it and in significant measure was a determining factor in delaying symptomatic recovery from acute illness. In addition, psychologic vulnerability increased the risk of "apparent" illness 2.4 times above that of the non-vulnerable group (77). Serologic studies suggested that the infection rate in both groups was the same. It was suggested that increased reporting of illness by vulnerable persons rather than increased frequency of disease seemed the most likely explanation.

Cardiac: Influenzal myocarditis, although demonstrated pathologically, proved virologically and described as a clinical entity probably occurs infrequently (78). Electrocardiographic changes include T wave flattening and inversion in addition to arrhythmias (79). Whether such changes, when minor, should be taken as indicative of definite myocardial involvement remains the subject of debate. SGOT may be elevated and reach a maximum on the tenth day. Other studies have suggested that SGOT elevations do not occur in mild influenza without myocarditis, but that they may be elevated in the face of influenzal pneumonia. Studies of LDH isozymes should shed additional light on this question. Clinically recognized pericarditis

subsequently proved to be due to influenza virus occurs, but is also rare. Instances of viral isolation from pericardial fluid have been reported. Burch and associates demonstrated decreased digital blood flow during the height of the illness in 15 of 20 patients with A2 influenza (57).

Neurological complications: The evidence for association between influenza and neurological disease has generally been rather circumstantial. Such cases may be divided into a) cases of encephalitis occurring concomitantly with influenza, b) cases of encephalitis occurring 3 days to 2 weeks after influenza, c) Guillain-Barre syndrome, and d) cases of mixed character (53). The frequency of encephalitis is listed as 0.8 to 1.2 cases per 1000 influenzal deaths (73). This is probably similar to the reported frequency of measles encephalitis. The patient reported by Flewett and Hoult from whom virus was isolated from the brain is quite convincing. Manifestations included confusion, convulsions, coma and at least three patients showed heat regulatory disturbances. Cerebrospinal fluids revealed lymphocytic pleocytosis with normal levels of sugar and some elevations of protein. Additional small series and case reports reveal similar manifestations which include loss of vertical conjugate gaze and oculogyric spasms (80, 81). In addition, during 1957 there were several less than convincing reports on acute psychosis following Asian influenza (82, 83).

Influenza in pregnancy and congenital defects: The increased maternal mortality observed both during the pandemic of 1918-20 and of 1957-58 when influenza was acquired during pregnancy has been discussed. In Maryland, Harris observed a gross mortality of 27% in patients developing influenza during pregnancy (17). Widelock, et al. calculated 9.4 times as many deaths as anticipated when influenza occurred in the second half of pregnancy. During subsequent years, i.e., 1958, 1959 and 1960, the numbers returned to expected values (71). The same investigators noted no increase in premature births associated with periods of increased occurrence of A2 influenza. Likewise, no increase in fetal deaths occurred. Coffey and Jessup concluded that during the early waves of A2 influenza in Ireland, congenital anomalies had resulted from infection of pregnant women (84). These investigators questioned mothers prior to delivery and reported that 3.6% of the 663 mothers with influenza had abnormal children (1.5% anencephaly) compared with 1.5% (0.45% anencephaly) in the randomly paired control group. Numerous other investigators have reported no significant differences in congenital malformations in infants whose mothers had had influenza and those who had not (71, 85-89).

Miscellaneous complications: Other rarely reported abnormalities include renal complications, purpura, labyrinthitis and otitis media (81, 90). From the negative standpoint, in an extensive study of 1,855 men who had had pneumonia during the influenza pandemic of 1919, when traced through 1955 no relationship was seen between pneumonia in 1918 and the subsequent development of carcinoma of the lung (91).

Prevention:

Environmental protection: During the 1957-58 influenza pandemic, a study was implemented at the Veterans Administration Hospital, Livermore, California, to determine whether the ultraviolet disinfection of droplet nuclei would block the transmission of influenza to a susceptible population during an epidemic (92). The radiated patient group remained virtually free of infection (Table 9). However,

implementation of such a program poses serious logistic problems.

Immunization: The value of influenza immunization has been seriously questioned on many occasions. Yet it has been recognized that recovery from influenza is associated with at least temporary resistance to reinfection, hence regularly effective protection through immunization must be an attainable reality. Before considering the results of various influenza vaccine studies, it would be advantageous to examine some of the characteristics of commercial vaccines. Freshly isolated strains of influenza virus produce very low titers of hemagglutinating activity when tested by the chicken erythrocyte agglutination (CCA) technique. Thus, a new antigenic variant must be egg adapted and stabilized for vaccine production. Good production strains yield 150-300 CCA units/ml of allantoic fluid (93). In 1957 it was estimated that one dose of vaccine containing 200 CCA units of antigen could be produced per egg (94). It is obvious that vaccine production requires large numbers of embryonated eggs from flocks which are free of avian leukosis. The virus particles are then concentrated by using a Sharples centrifuge, then usually inactivated with formalin. Throughout, potency must be maintained. Production of influenza vaccine does not involve the use of penicillin or other antibiotics.

1. Vaccine characteristics: Most commercial "purified" vaccines are in reality extremely crude (Table 10) (95). In studies on purification of vaccine, most of the pyrogenicity is associated with the soluble contaminant fraction, rather than the virus (95). These observations suggest that the earlier data reported by Salk, that reactions to vaccine increased as the concentration of virus was increased, may have been a chance occurrence (96).

2. Route of administration: One very confusing situation encountered in 1957 concerned dosage recommendations. The subcutaneous (s.c.) or intramuscular route of administration was recommended except for very small children. Nevertheless, large numbers of physicians chose to administer fractions of a milliliter (usually 0.1 ml or 20 CCA of antigen) intradermally (i.d.). These decisions were based on experience with pre-epidemic strains to which some prior immunity existed, upon a desire to minimize reactions and as a means of extending the limited supply of vaccine. Since the same situation exists in regard to A/Hong Kong/68 vaccine, the data from 1957-58 should be re-examined. Unfortunately, the results are conflicting. Boger and Liu reported poor results after i.d. administration: 8 of 22 individuals developed HAI titers in contrast to 20 of 22 individuals after the s.c. route (97). Subsequently Boger and associates revaccinated a group of 30 patients with 0.1 ml (20 CCA units) of commercial polyvalent vaccine i.d. and demonstrated a rise in HAI titer in only 25% in contrast to 87 to 100% following s.c. administration of 1.0 ml (200 CCA) of the same vaccines (98). Sanger performed similar studies in a group of 72 subjects who received s.c. influenza vaccine and 204 subjects who received 0.1 ml i.d. (99). Significant increases in either HAI or CF titers occurred in 92% of those who received s.c. vaccine and 86% of those who received i.d. vaccine. In a more recent report, Brown noted the antibody response following either s.c. or i.d. polyvalent vaccine to be poor; 17% had a 4-fold rise to A2 following s.c. with 13% following i.d. injection (100). Even following two injections, only 27% have a 4-fold increase.

3. Reactions: Reactions to influenza vaccine have been noted since the early trials. It has been suggested that they relate to the lipoprotein envelope

and are inherent in influenza vaccine. The observations of Reimer suggest this not to be the case (95). In 1957-58 the problem arose concerning the possible presence of penicillin in influenza vaccine. Instances were reported in which penicillin-like sensitivity reactions had developed following the administration of influenza vaccine. While no penicillin was actually added to the vaccine itself, traces of penicillin were present in some of the seed virus which had been used in production. While the amounts were less than 0.001 unit per dose of vaccine, manufacturers agreed to discontinue the use of penicillin in their seed virus (94). During 1943-45, the rate of reactions reported by the military in use of the vaccine was 20%, with reports varying from 7 to 85% (101). Several fatal anaphylactoid reactions have been recorded. In another study on reactions to influenza vaccine in military populations, Griffin analyzed reactions to more than 3,400,000 vaccine injections. The total reaction rate was 6.29%, of which 0.03% were considered severe. In 1957, 0.3 per 1000 individuals had moderate reactions and were placed on quarters. These rates compare with 6.89% with typhoid vaccine boosters, 24.4% with smallpox revaccination and 7.18% with tetanus toxoid boosters. Boger and associates studied reactions in 1,032 patients who received one of 6 lots of commercial polyvalent influenza vaccine (500 CCA) and observed systemic reactions consisting of fever in only 1 patient and local reactions in 26.2% of patients (98). In contrast to this very low frequency of reactions, Hulka studied 395 women during pregnancy (6). Individuals who were immunized spent an average of 0.4 patient days in bed because of reactions. While the number of patient days in bed due to influenza in the control group was 1.05 and in the vaccinees 0.38 days, when 0.4 days for reaction was added the overall effectiveness became less. In an industrial program, 2.5% of individuals reported the loss of at least 1 workday (100). Recently the NCDC has more extensively studied the relationship between vaccine dosage, antibody response and reactions (102). A vaccine reaction study has been carried out at the Atlanta Federal Penitentiary. Each subject was asked immediately prior to injection and 8 hours, 24 hours and 48 hours after injection whether he had developed headache, malaise, muscular pain, loss of appetite, nausea and/or chills. Oral temperatures were taken at each of these times. Local reactions were measured at each of these times. Erythema of greater than 50 mm or induration greater than 20 mm was classified as severe. In assessing these data, it should be realized that the element of secondary gain is present in this population group. The frequency of systemic reactions was quite constant in each group, as was the percentage of individuals with temperature changes of greater than 1.5° (Figures 5-6). These data are quite striking in that the reaction rate did not appear significantly related to dosage even when extremely high concentrations were utilized, although these latter vaccines were prepared by zonal ultracentrifugation. In addition, it was observed that antibody responses were greater when the dosage of antigen was increased (Figure 7). Thus, while there is no question that reactions to influenza vaccine, both systemic and local, occur, their actual frequency differs considerably and recent studies suggest that they are not inseparably related to antigen dose.

4. Vaccine effectiveness: Evaluation of vaccine effectiveness is complicated by continued antigenic variability of the influenza virus, particularly influenza A. The results of field trials conducted by the Commission on Influenza, Armed Forces Epidemiologic Board, have been summarized by Davenport (Figure 8) (21). In this figure, the major antigenic change in 1947 is apparent. The relative lack of protection in one of the studies in 1957 is also striking. From these data, it appeared that surveillance of influenza viruses with the incorporation of current strains into the vaccine should enable the continued supply of

potent vaccine unless an abrupt antigenic shift occurred. Influenza was predicted for the 1962-63 winter season. During the period of July 1-December 31, 1962, a total of 47,000,000 doses of polyvalent influenza vaccine were distributed in the United States (2). The extent to which this vaccine was used among the important high-risk groups is not known with accuracy, although it is estimated that between 20 and 25% of those over 65 years of age had received vaccine. In mid-January 1963, an epidemic of A2 influenza began and within the next 3 months approximately 72,000 excess deaths occurred. During this same epidemic, two additional control studies reported essentially vaccine failure. In the Baltimore City Fire Department family influenza study, questionable protection was demonstrated in individuals over 45 years of age and the vaccine efficacy was calculated at 33% (4). Bashe and associates in a similar study demonstrated clinical influenza attack rates of 37.8% in a group of immunized children in comparison with 50% in the controls, resulting in an effectiveness ratio of 24.4% (5). These investigators felt it was unlikely that the 1963 outbreak of A2 influenza was due to strains of sufficient antigenic drift to account for vaccine ineffectiveness; however, as pointed out by Robinson, depending upon the technique for laboratory evaluation, one could predict rather marked antigenic drift. Thus, it could be concluded that the failure of vaccine to afford protection in 1963 should not have been unexpected in view of the antigenic change in the virus; however, from the operational standpoint, this had not been appreciated prospectively despite intensive antigenic surveillance.

Subsequent vaccine modification and evaluation has included study not only of the polyvalent influenza vaccines, but also a reconsideration of monovalent vaccines in an attempt to increase the antigenic mass of prevalent strains, yet to remain within a total dose of 600 CCA. In a study of students aged 14-18 years in Anchorage, Alaska, in 1965-66, Maynard and associates demonstrated that monovalent A2 (A2/Taiwan/1-64, 400 CCA) was more effective than a commercial polyvalent vaccine containing 100 CCA of the same A2 antigen (103). The clinical efficacy of the monovalent A vaccine was 57%, in contrast to 47% with the polyvalent. Based upon serologic evaluation, the efficacy of the monovalent vaccine was 100%, in contrast to 57% with the polyvalent vaccine. Again, these observations illustrated the occurrence of both inapparent influenza as well as influenzal illness due to additional agents. Additional serologic studies have been performed to compare the serologic responses to bivalent as compared to polyvalent vaccines (104). The initial studies carried out in 1966-67 revealed greater antibody responses as well as higher titers (Table 11). These studies involved experimental vaccines. When commercial vaccines were evaluated in the retirement community of Seal Beach, California, in 1967, the previously observed differences were less (104). Based upon the observations, the use of bivalent vaccine has been recommended to enable an increase in the amount of antigen effective against current strains. As will be seen, the effectiveness is difficult to evaluate.

5. Considerations regarding vaccine developments: One approach which has been utilized is through the use of immunologic adjuvants to achieve a more durable immunity of higher level, employing a smaller antigenic mass. Freund's incomplete mineral oil adjuvant has been used in experimental vaccines. This has not been utilized extensively in man because of a body of data relating to induction of potentiation of plasma cell tumors in some experimental animals, induction of autoimmune reactions and formation of disseminated focal granulomata in animals injected with mineral oil alone, although studies in man have indicated relatively few adverse effects except for local reactions. In addition, there is the suggestion that the adjuvant vaccine sensitized individuals to penicillin and the possibility

of sensitivity to other allergens cannot be excluded (105). At the time these experimental vaccines were manufactured, it was the practice of the manufacturer to add penicillin to seed virus. Subsequently, a metabolizable adjuvant consisting of peanut oil, mannide monooleate and aluminum monostearate has been evaluated (106). Initial studies demonstrated the adjuvant was associated with rapid and prolonged elevation of antibody titers with local and systemic reactions which did not significantly exceed those associated with aqueous vaccines. Subsequent difficulties in production and confirmation of early results have precluded its present availability.

Recent interest has centered on consideration of local or aerosol immunization as a more effective approach to the prevention of influenza. While of recent interest, the initial observations relative to local secretory antibody were reported by Burnet, Lush and Jackson and by Francis in 1940 (107, 108). Francis suggested that mechanisms resident in the respiratory tract itself might play a significant role in the prevention of natural disease. He demonstrated that nasal secretions from approximately half of normal individuals caused complete or almost complete inactivation of a reasonably large viral inoculum, whereas saliva was ineffective. Little further interest in local immunity in influenza was evident until the series of papers by Fazekas de St. Groth and Donnelley (109-111). These investigators reported that antibody circulating in the vascular system was not directly involved in protection, since the virus approached and selectively attacked the susceptible cell from its mucosal surface without previously entering the bloodstream. Judged by the criterion of serum antibody level, they demonstrated that peritoneal vaccination should be the most and intranasal vaccination the least proficient method. In contrast, intranasal administration of either attenuated live or formalized virus either type B or A gave much greater protection than intraperitoneal, and both were more effective than subcutaneous. While live vaccine was more effective than the formalinized killed vaccine, significant protection could be achieved with formalinized vaccines. They demonstrated that resistance to experimental influenza infection showed a strict positive correlation with the amount of specific anti-hemagglutinin present in the respiratory tract. They further demonstrated that specific resistance could be enhanced by the simultaneous nasal administration of a heterologous virus by enhancing the apparent transfer of homotypic antibody from serum to bronchial secretions. In recent studies, it has been demonstrated that both the HAI activity and specific influenza virus neutralizing activity of nasal secretions from individuals who are free of infection are associated with IgA (112). The subsequent studies by Alford and associates demonstrated that nasal wash IgA was predominantly 11S, whereas IgG in nasal secretions was 7S. Neutralizing activity was associated with the 11S IgA in 2 subjects and the 7S globulins in 1 subject. They propose that nasal secretory IgA may function as a non-specific inhibitor of hemagglutination inhibition due to its high sialic acid content (113). Mann and associates studied the antibody response in respiratory secretions of volunteers given either live or dead influenza virus (114). In the live virus group, 9 of 12 developed antibody, whereas in those receiving vaccine (600 CCA), 10 of 10 developed serum antibody. Both sputum and nasal wash antibody levels were higher in the group which received the live virus, whereas the level of salivary antibody was equal in both. Absorption of sputum or nasal washings with IgG resulted in no decrease in antibody, whereas absorption with IgA removed the antibody. Furthermore, antibody persisted longer following live virus inoculation. It is these studies which suggest that nasopharyngeal or aerosol administration of inactivated vaccine may prove useful as an immunization procedure. Field trials were initiated during 1967-68; however,

the results have not been published to enable critical evaluation. However, this would appear to represent a most promising approach to immunization.

Live attenuated influenza vaccine has been utilized in the U.S.S.R. since the late 1950s. The results of atomization of attenuated vaccine into the upper respiratory tract have been extensively evaluated and provide quite striking protection (Table 12) (115). While these studies clearly demonstrate the efficacy of attenuated influenza vaccine following nasal administration, they do not settle whether the protection is due primarily to the attenuated vaccine or to the route of administration. In England, five trials of the attenuated live influenza virus vaccine have been made since 1960 (116, 117). The vaccine used in the trials was prepared from the Russian A2 strain, Iksha attenuated by passage in eggs and given by drops intranasally. The findings in the first three trials were encouraging in that serologic evidence of symptomless infection was produced by the vaccine in most recipients (57% and 63% demonstrating HAI antibody responses) and the volunteers were apparently resistant to reinfection with a challenging dose of live virus given intranasally one month later. In the fourth and fifth trials, the HAI antibody response in serum was unsatisfactory (11-38%), and was inferior to that observed in the three earlier trials. It was felt that the reduction in response was probably due to an alteration in the virus during further passage.

6. Recommendations, 1968-69: The Public Health Service Advisory Committee on Immunization Practices has recently recommended that bivalent and polyvalent influenza vaccine be given to persons at highest risk of mortality or severe complications as a result of influenza. When the new monovalent vaccine, A2/Aichi/2/68 (Hong Kong variant) becomes available, the same groups should be vaccinated or revaccinated with it. High risk groups include persons with chronic illnesses as defined below, and all persons in the older age group.

> Chronically ill: Persons of all ages who suffer from chronic debilitating diseases including cardiovascular, pulmonary, renal or metabolic disorders: 1) Patients with rheumatic heart disease, especially with mitral stenosis; 2) Patients with such cardiovascular disorders as arteriosclerotic heart disease and hypertension, especially those showing evidence of frank or incipient cardiac insufficiency; 3) Patients with chronic bronchopulmonary diseases such as asthma, chronic bronchitis, cystic fibrosis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema or pulmonary tuberculosis; 4) Metabolic diseases such as diabetes mellitus.
>
> Older age groups: During major influenza outbreaks, especially those caused by type A viruses, increased mortality has regularly been recognized in persons over 45 years of age and even more notably, for those over 65. This association has been particularly marked in individuals with underlying chronic disease. Based upon previous experience with other A2 strains, 2 doses of the monovalent vaccine 2 months apart should afford optimal protection. However, a single dose should produce significant protection and in view of the expected limited supply of this vaccine in the fall of 1968, the administration of a single dose should be seriously considered so that protection for the greatest number of persons can be achieved. Immunization should begin as soon as practicable after the vaccine becomes available. It is important that immunization be carried out before influenza occurs in the immediate area because there is at least a 2-week interval between vaccination and development of antibodies. Despite the expected

limited supply of vaccine, the intradermal route of administration is not recommended. Based upon observations obtained with the apperance of the A2 strain in 1957, antibody responses to the intradermal administration are much less predictable.

Chemoprophylaxis: Amantadine hydrochloride is a synthetic salt of a symmetrical primary amine shown first by Davies, et al. to have a selective and dose-related inhibitory activity against influenza group A viruses, especially type A2 strains (118). This compound, which is not virucidal, blocked or slowed viral penetration into host cells. Since these original observations, a number of studies in tissue cultures, eggs and experimental animals has been performed, as well as studies in human beings which involve both experimental and natural infections. The earlier studies are summarized in detail by the critical review of Sabin (119). Sabin concluded that tissue culture studies showed that amantadine hydrochloride had a minimal effect on all type A influenza viruses as well as on influenza C, the Sendai strain of parainfluenza virus, rubella virus and pseudorabies virus. It is possible that different strains had different proportions of drug-resistant virus particles, and one study demonstrated the loss of susceptibility to the drug of an A2 influenza strain under a single passage in primary calf kidney cells in the presence of the drug. The test in eggs and mice, even with massive doses of drug, showed significant though minimal effects only when the smallest doses of virus were used for infection. The studies on small numbers of human volunteers experimentally infected with two different disease-producing strains of A2 virus showed a reduction in the number of illnesses with one strain but not with the other. Tests with attenuated A2 influenza virus showed a significant but relatively slight reduction in subclinical infection. Sabin feels there is only one valid investigation in human adults (prisoner volunteers) exposed to natural infection with influenza A2 virus and this shows a reduction in subclinical infection without a significant reduction in the number of clinical illnesses. The two studies in institutions for mentally retarded children are considered inconclusive. No evidence of significant organ toxicity has been observed thus far. In certain groups of adults (college students and people engaged in certain specialized activities in industry), subjective transitory side-effects involving cerebration have been observed with a frequency of 4 to 27% among those receiving 200 mg per day. He finally concluded that no field trials of the effect of the drug under conditions of its proposed use in an open community having an extensive outbreak of A2 influenza have as yet been carried out, and until that is done under carefully controlled conditions, general use of the drug does not appear warranted (Table 13, Figs. 9, 10). More recently, the completed studies of Togo, Hornick and Dawkins on induced influenza in prisoner volunteers have been reported (120). This report, which Sabin recognizes as "the most significant", presents evidence that the prophylactic administration of amantadine hydrochloride (Symmetrel) significantly diminished the occurrence and severity of experimentally induced Asian influenza in a double-blind study. No difference in seroconversion rates was observed, but serum neutralizing antibody titers were significantly lower in men receiving amantadine (120). An ideal antiviral drug would be one which would prevent the annoying or occasional serious manifestations of the infection without interfering with immune mechanisms. These studies suggest this to be the case. The same investigators report similar results employing an analog of amantadine hydrochloride designated rimantadine hydrochloride (121).

The major side-effects of amantadine are those listed previously. Jackson and associates have utilized the agent in Navy recruits without interference in their ability to perform mechanical tasks (122). In an uncontrolled study of its efficacy in a group of nurses, Schiff reported reactions similar to amphetamine, i.e., jumpiness and a sensation of "disconnected" in patients receiving 100 mg b.i.d. One girl with a past history of a seizure disorder developed a grand mal seizure and one patient with diabetes mellitus developed a severe insulin reaction possibly associated with amantadine. The symptoms decreased when the dosage was discontinued and then reinstituted at 100 mg daily. Following discontinuation of the drug after 16-21 days of therapy, approximately one-fifth of the individuals felt a sensation of depression which persisted for as long as one week. Despite these side-effects, he gained the impression that it decreased the attack rate of clinical influenza (123).

The available data suggest that amantadine is effective only in the prevention, not in the treatment, of respiratory infections caused by susceptible influenza A strains. Additional studies will be necessary to define its efficacy inasmuch as it would have to be taken at the time of exposure and presumably continued throughout the epidemic period, 4-8 weeks. According to Schiff, preliminary studies with at least one of the Hong Kong variants suggests that amantadine is effective *in vitro* against this strain and may demonstrate greater activity than against other A2 strains.

From review of the data on chemoprophylaxis with amantadine, it appears that appropriately controlled studies should be initiated. The circumstances are ideal in that immunization can be performed and yet the drug evaluated both for clinical illness as well as inapparent illness as detected by seroconversions. Decisions regarding its general use should await better estimations of the virulence of infection. In the event that extremely virulent disease ensues, its use in high risk individuals might be justified with the realization that an increased frequency of adverse reactions may be encountered in this group. It does, however, provide a potential agent to supplement vaccine prophylaxis.

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TABLE 1

Antigenic Relationships Among A2 Influenza Viruses

A. Hemagglutination Inhibition Test:

Virus Antigen	Ferret Immune Sera	
	Japan 305/57	Japan 170/62
A2/Japan/305/57	320	320
A2/Japan/170/62	80	640

B. Neutralization Tests of Inhibition of Hemadsorption of Mouse Sera Following Injection of Reference Influenza Vaccine

Dilution of Vaccine Injected	Antibodies Against A2 Virus	
	Japan 305/57	Japan 170/62
1:5	+	0
1:25	+	0
1:125	+	0
1:625	+	0
1:3125	0	0

(From Ref. 2)

TABLE 2

Strain Relationships* of Type A2 Influenza Viruses With 1968 Hong Kong Isolates

	A2/Japan/305/57	A2/Japan/170/62	A2/Taiwan/1/64	A2/Georgia/1/67	A2/Tokyo/3/67	A2/Ann Arbor/7/67	A2/Texas/2/68	A2/Hong Kong/1/68	A2/Hong Kong/8/68
A2/Japan/305/57	1.0								
A2/Japan/170/62	1.4	1.0							
A2/Taiwan/1/64	4.0	2.8	1.0						
A2/Georgia/1/67	4.0	4.0	2.8	1.0					
A2/Tokyo/3/67	16.0	5.7	8.0	5.7	1.0				
A2/Ann Arbor/7/67	5.7	2.8	5.7	4.0	4.0	1.0			
A2/Texas/2/68	22.6	5.7	4.0	2.8	4.0	4.0	1.0		
A2/Hong Kong/1/68	i‡	22.6	i	i	i	i	i	1.0	
A2/Hong Kong/8/68	i	11.3	22.6	22.6	i	11.3	64.0	1.0	1.0

* Similarity coefficients (r) according to the formula of Archetti and Horsfall, J. Exp. Med. 92:441, 1950.

‡ i = indeterminate

TABLE 3

HI Antibody Response to Hong Kong/8/68 and Selected Influenza Virus Strains

Group	No. in Group	Antigen	Serum Pairs - % > 4-Fold Increase
I. Clinical Illness (4-75 years)	32	A2/Jap/170/62	100
		A2/Ga/19/67	100
		A2/Tokyo/3/67	88
		Hong Kong/8/68	19
II. Vaccine (elderly)	36	A2/Jap/170/62	92
		A2/Tokyo/3/67	53
		Hong Kong/8/68	12
III. Vaccine (prison, high dose)	44	A2/Jap/170/62	90
		A2/Tokyo/3/67	71
		Hong Kong/8/68	11

From NCDC:ACIP:4 Sept. 1968

TABLE 4

Weekly Cases of Influenza-Like Illness Reported From Public Health Facilities in Greater Manila (Approx. 1.5 million pop.)

Year	Week Number													
	27	28	39	30	31	32	33	34	35	36	37	38	39	40
1965	65	46	42	54	50	61	46	32	47	43	22	52	35	
1966	44	40	42	78	46	58	87	174	96	167	119	254	243	107
1967	46	29	69	130	57	85	152	250	255	251	214	230	140	144
1968	53	48	46	65	59	162	1,882	20,346	11,285	5,812				

TABLE 5

Symptomatology of Influenza A, A1, and A2 in Adults
(Percentage Frequency)

	1937, 1939, 1941 Influenza A (60 cases*)	1950, 1951, 1953, 1956 Influenza A1 (28 cases‡)	1957 Influenza A2 (30 cases‡)
	%	%	%
Sudden onset	75	32	46
Premonitory	18	—	—
Constitutional symptoms:			
Malaise	87	71	66
Headache	85	82	72
Shivering	80	78	64
Anorexia	71	64	37
Muscular pains	60	78	62
Dizziness	32	—	—
Ocular symptoms	20	—	—
Respiratory symptoms:			
Cough	88	93	90
Coryza or nasal obstruction	80	93	82
Sore throat	48	75	62
Expectoration	31	55	40
Chest pain	11	—	—
Hoarse voice	10	32	37
Miscellaneous:			
Insomnia	38	0	0
Nausea or vomiting	17	3	11
Abdominal pain	0	0	0
Diarrhea	0	11	0
Irritability	0	43	22

* Reported in J. Roy. Army Med. Corps 77:123, 1941

‡ Reported in Am. J. Hyg. 68:190, 1958

TABLE 6

Percentage of Abnormalities in Uncomplicated Influenza

	1937 Influenza A (England) (82 cases)	1943 Influenza A (U.S. Army) (74 cases)	1950-56 Influenza A1 (Cleveland) (28 cases)	1957 Asian Influenza (Cleveland) (30 cases)
Fever:				
Mean duration	3.6 days	—	—	—
Highest temperature (average)	101.2°F	< 100°F 11 100-101.9°F 38 102°F + 50	< 100°F 13.1 101-101.9°F 47.8 102°F + 39.1	< 100°F 12.5 100-101.9°F 58.3 102°F + 29.2
Flushed face	69	45	8.7	24.0
Conjunctival abnormalities	89	46	13.0	56.0
Nasal discharge	24	61	30.4	20.0
Nasal obstruction	58	68	28.6 (injection)	64.0 (injection)
Fauces:				
Injected	73	6	73.9	68.0
Dry pharynx	41	Lymph follicles 33	39.1	32.0
Exudate	1		0	0
Chest signs:				
Rales	14	11	0	0
Rhonchi	20	29	0	0

TABLE 7

Syndrome of Bacterial Pneumonia Following Influenza
(15 Patients)

History:

1. Typical influenzal syndrome
2. Improvement for one to four days
3. Fever, chills, pleural pain, bloody sputum

Examination:

1. Local consolidation
2. Bacteria in sputum smears and culture (pneumococci, staphylococci, H. influenzae)
3. Response to antimicrobials
4. Low mortality (1/15)

TABLE 8

Syndrome of Influenza Virus Pneumonia
(6 Patients)

History:
1. Age 30 to 50, rheumatic heart disease
2. Typical influenza
3. No remission, increasing fever, dyspnea, scant bloody sputum

Examination:
1. Extreme tachypnea, cyanosis
2. Poor air exchange, diffuse findings, expiratory wheezing, no local consolidation
3. Scant bacteria on smear, no pathogens on culture
4. No response to antimicrobials
5. High mortality (5/6)

TABLE 9

Serologic Data for Entire Period of Study

	Initial Negative	Fourfold Rise	Per Cent Positive
Patients:			
Radiated	209	4	2
Nonradiated	396	75	19
Personnel	511	92	18

TABLE 10

Influenza Vaccine Development

Sample		CCA units/mg Protein	µg Protein/ 1000 CCA	% Purity
"Absolute"		25,000	approx. 40	100
"Zonommune" (Lilly)		15,000	approx. 67	60
Sharples: Stanley et al. 44-47		1000-2000	500-1000	4-8
1967-68	A	3630	275	8.5
	B	2860	350	
	C	1570	636	
	D	600-2000	500-1670	

From: NCDC - C. Reimer
May 1968

TABLE 11

Serologic Response to Bivalent vs Polyvalent Influenza Vaccine 1966-67 and 1967-68

Population	Vaccine* Group	No. of Persons	% 4-Fold Ab Response		Fold Increase in GMT	
			A_2-Tai	B-Md	A_2-Tai	B-Md
Cape May	E. Bi 66	39	85	44	19.7	3.0
	E. Poly 66	44	61	32	6.1	2.7
Hopeville	E. Bi 66	45	91	45	15.1	4.4
	E. Poly 66	42	76	53	8.2	4.2
	Placebo	40	5	0	—	—
Seal Beach	C. Bi 67	48	81	90	9.2	9.7
	C. Poly 67	50	62	88	5.7	7.5

* E - experimental, C - commercial

From: NCDC - S. Schoenbaum, M.D.
May 1968

TABLE 12

Efficacy of Live Influenza Vaccine During 1962 Outbreaks of Influenza A2 and B

Antigen	No. Immunized	Attack Rate (cases/1000)
A-2	12,501	41.3
Control	16,052	156.8
B	10,473	4.7
Control	18,180	58.7

TABLE 13

Evaluation of Amantadine in Humans

Study	Dose/Day (mg)	No. Cases	Pre-Antibody Titer	4-Fold Ab (%)	Illness (%)
Jackson A2/134 attenuated	200	41	≤ 10 HI	37	2.4
	P	85	≤ 10 HI	71	9.5
	200	24	≥ 20 HI	16	0
	P	63	≥ 20 HI	27	6.3
Togo A2/Rockville/1/65	200	29	< 1:2 NT	100	28
	P	29	< 1:2 NT	97	62
Keating (natural A2 infection)	200	216	≤ 16 HI-72%	12.0	5.1
	P	460	≤ 16 HI-70%	36.6	5.9

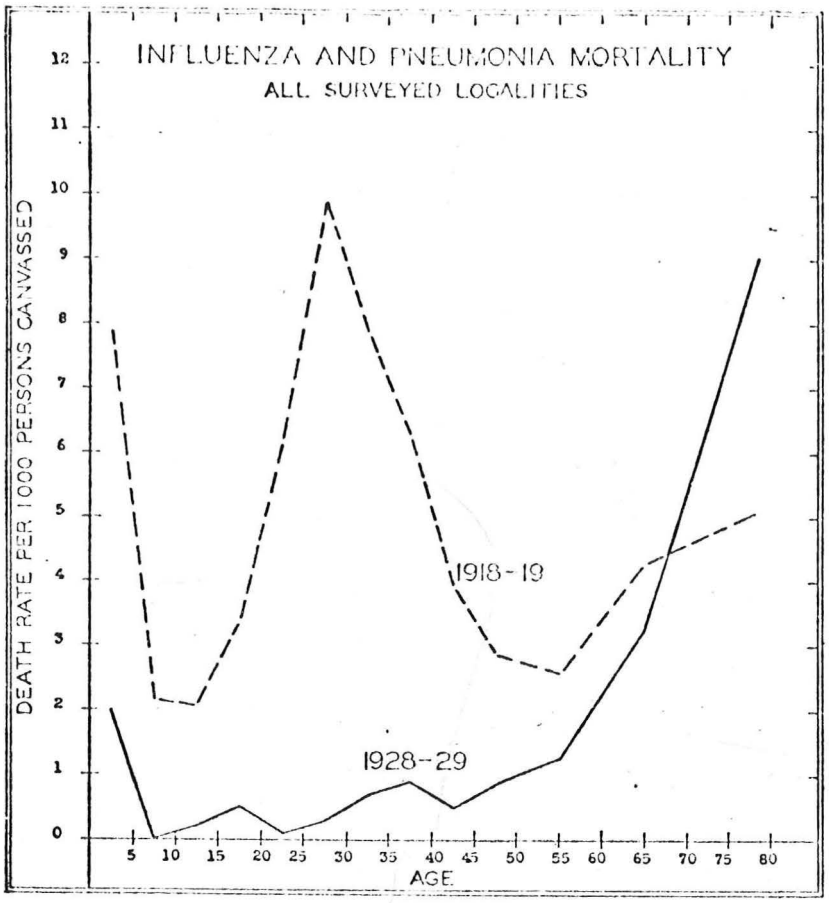


FIGURE 1

Mortality from influenza and pneumonia at specific ages in surveyed groups during the epidemics of 1928-29 and 1918-19

AGE SPECIFIC ATTACK RATES

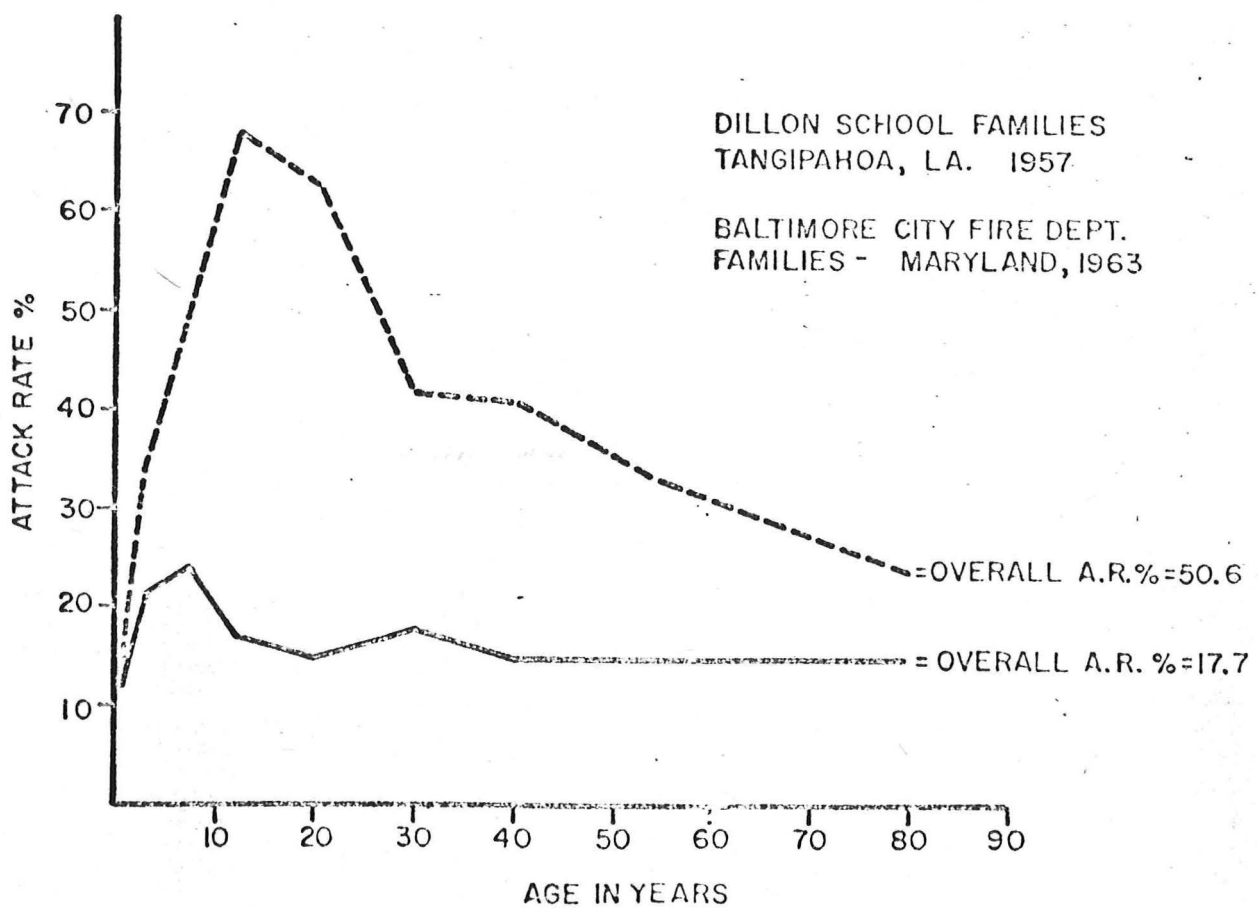


FIGURE 2

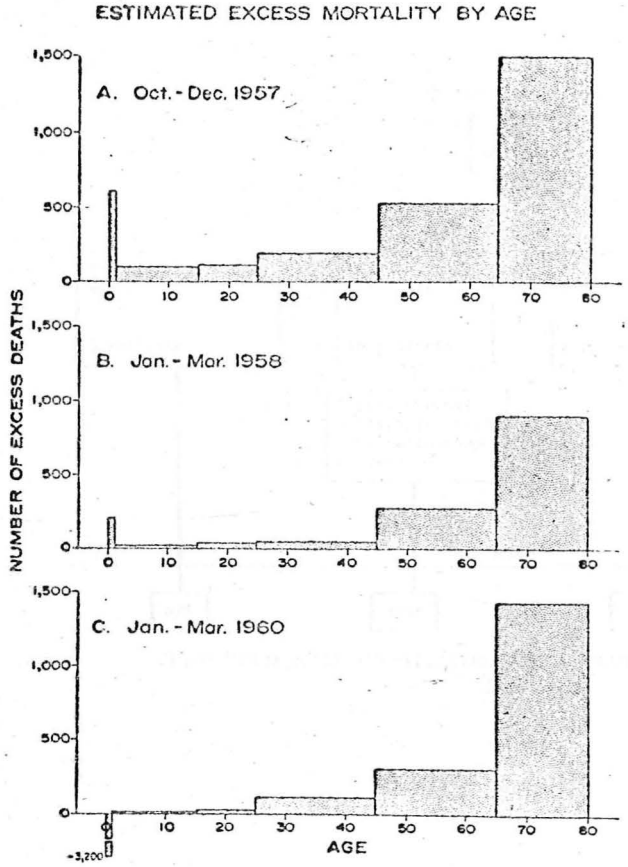
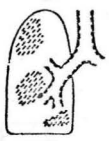
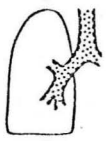
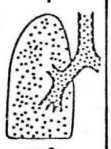
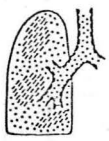


FIGURE 3

TYPES OF HISTOPATHOLOGIC LESIONS IN 148 VIROLOGICALLY CONFIRMED CASES OF ASIAN INFLUENZA

Virus lesion in respiratory tract; Virus lesion in lung; Bacterial inflammation	1  4%	2  20%	3  5%	4  40%	5  31%
Preexisting disease:					
Kyphoscoliosis		1		1	
Tuberculosis	1	1*	2		1
Emphysema and chronic bronchitis	1	2	1	8	2
Anthracosilicosis		1		3	1
Mitral stenosis		10†		1	
Aortic "	2	1			
Myocardial fibrosis		5		5	2
Other heart-disease		1			1
Multiple sclerosis				1	
Epilepsy				1	1
Idiocy				4	1
Other neurological disease			1	1	
Other disease	1	2		3	6
Pregnancy		1			1
Previously healthy	1	5	3	31	30

* Associated with pregnancy.
† 4 cases associated with pregnancy.

FIGURE 4

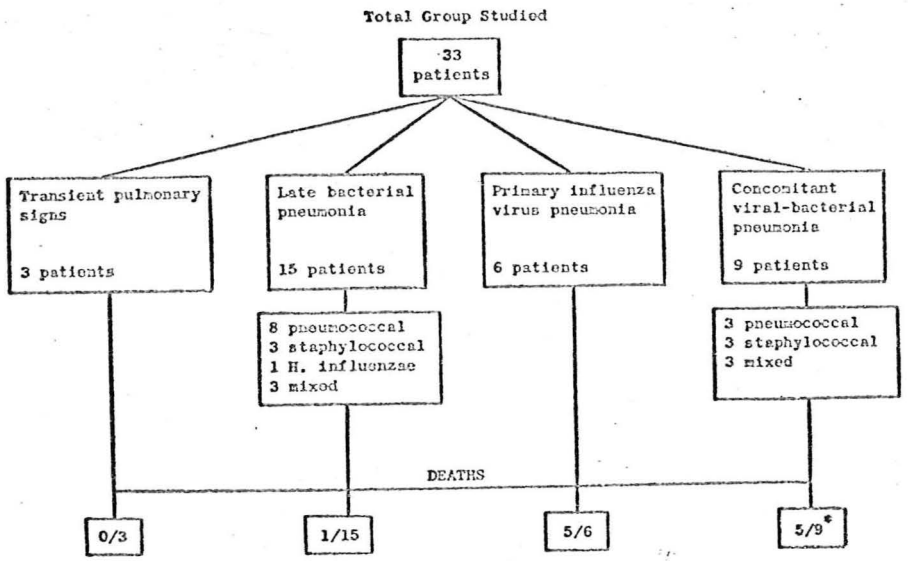


FIGURE 4A

THE PULMONARY COMPLICATIONS OF INFLUENZA, THE NEW YORK HOSPITAL, 1957-58

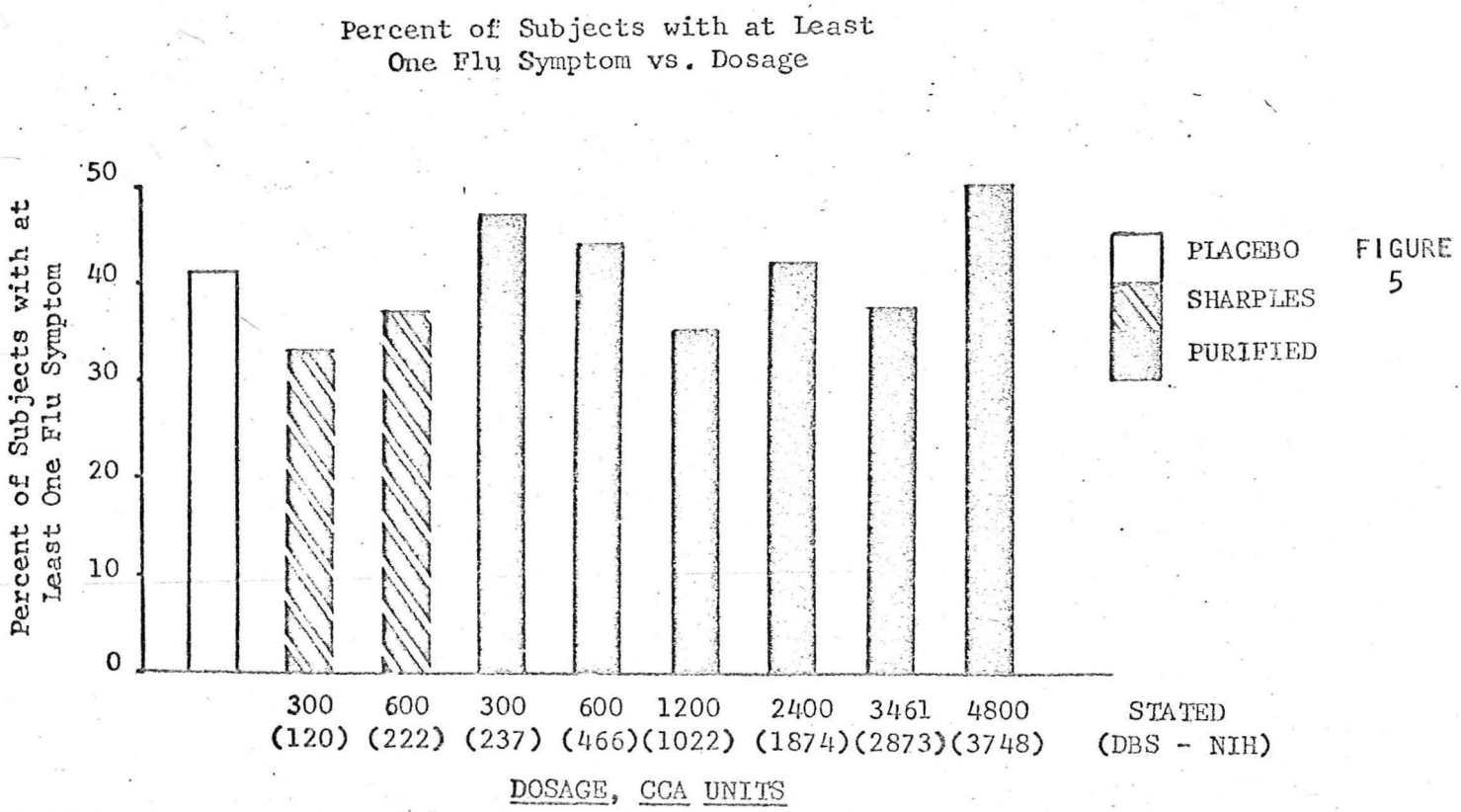


FIGURE 5

Percent of Subjects with Temperature
Changes of > 1.5° vs. Dosage

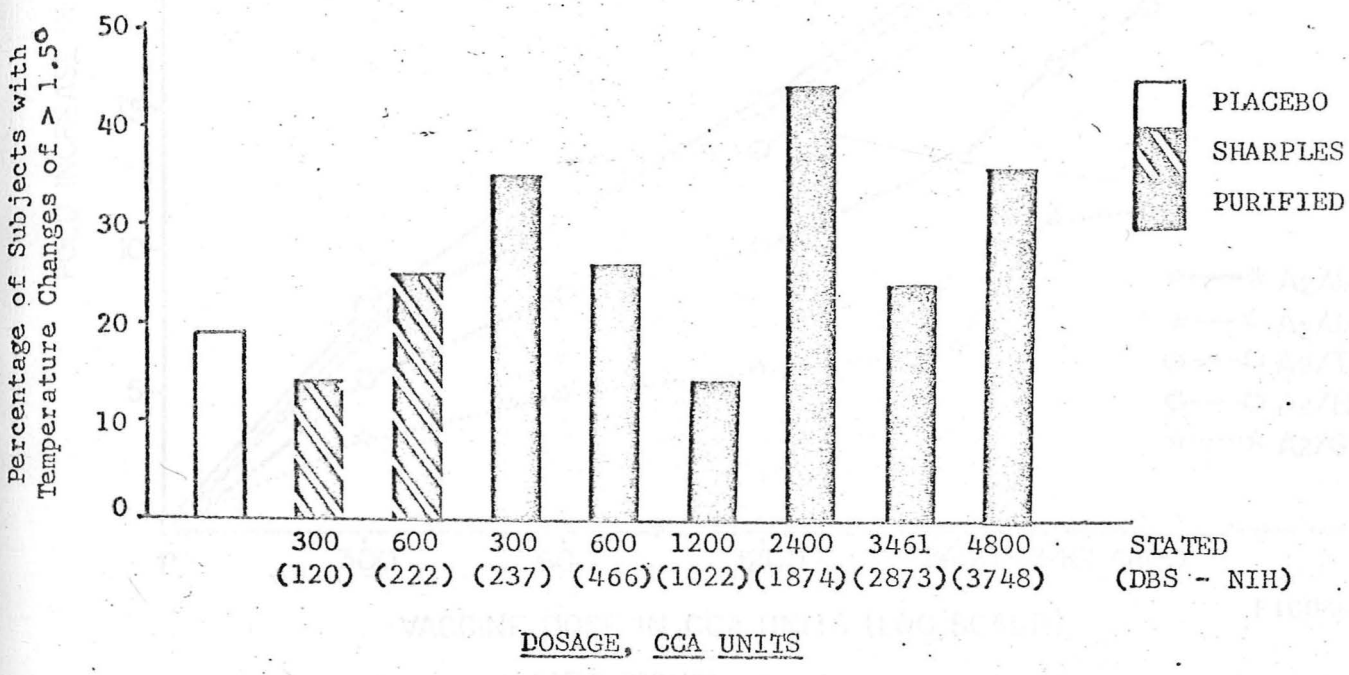


FIGURE 6

Fold Increase Geometric Mean Antibody Titer Three Weeks Following Subcutaneous Administration of Varying Doses of Zonal Purified A_2/JAP/305/57 Influenza Virus Vaccine

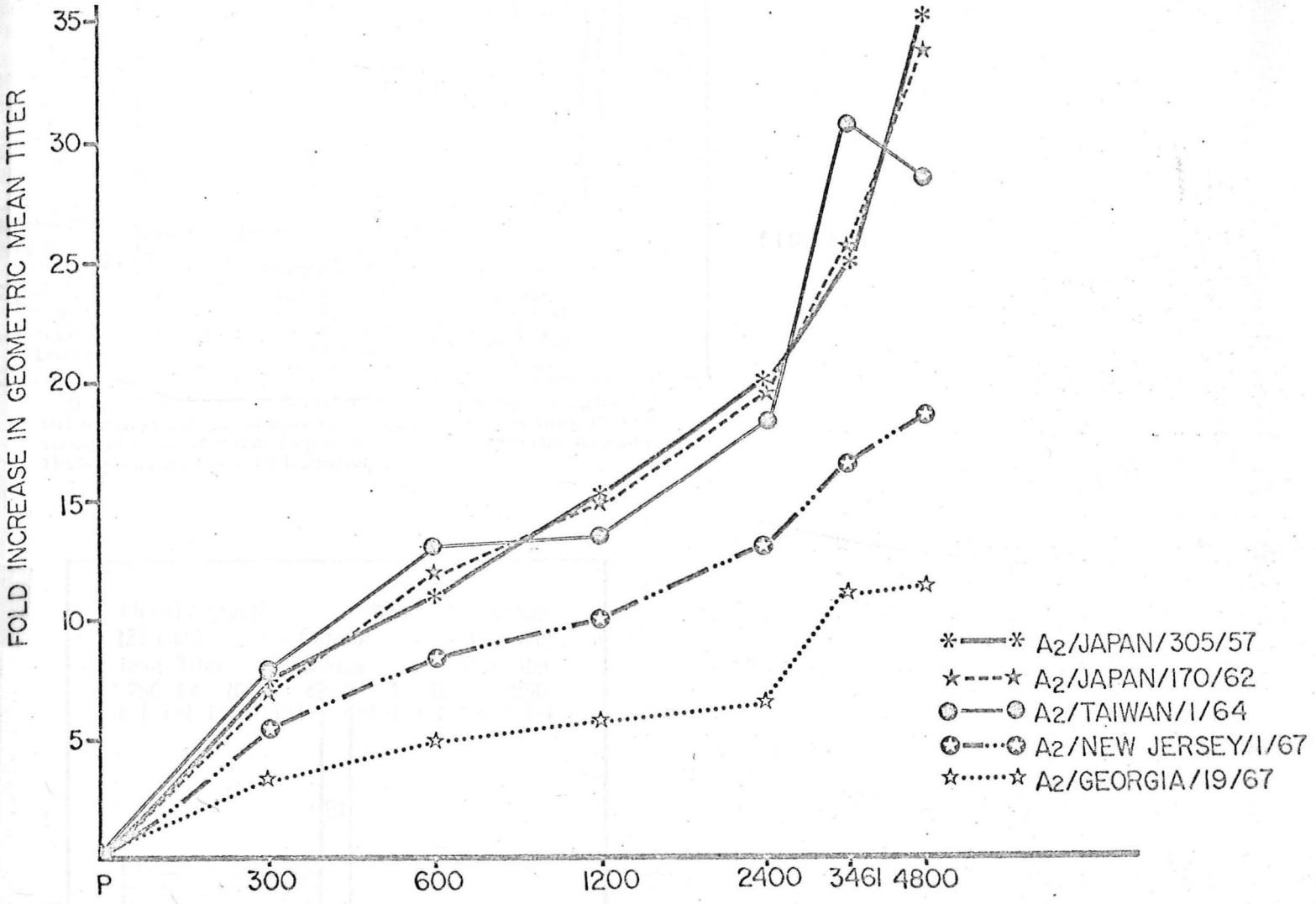


FIGURE 7

YEAR	PREVAILING VIRUS	CASES PER 100 VACCINEES	CONTROLS	PROTECTION RATIO
1943	A	1.96	7.06	3.6
1947	A′	7.19	8.09	1.1
1950	A′	1.2	3.7	3.1
1951	A′	0.5	2.01	4.0
1953	A′	0.95	5.7	8.1
1953	A′	0.61	2.77	4.5
1957	A′	0.92	5.1	5.5
1957	ASIAN	2.18	3.79	1.7
		5.93	15.01	2.5
		1.73	5.25	3.0
		3.32	7.61	2.3
		1.74	7.61	4.4
		3.98	16.2	4.1

FIGURE 8

. Results of field trials on vaccination against influenza A, conducted by the Commission on Influenza, Armed Forces Epidemiological Board.

YEAR	PREVAILING VIRUS	CASES PER 100 VACCINEES	CONTROLS	PROTECTION RATIO
1945	B	0.87	11.21	12.9
1952	B	7.24	19.32	2.7
1955	B′	2.2	3.5	1.6
1958	B′	0.43	2.49	5.8

Results of field trials on vaccination against influenza B, conducted by the Commission on Influenza, Armed Forces Epidemiological Board.

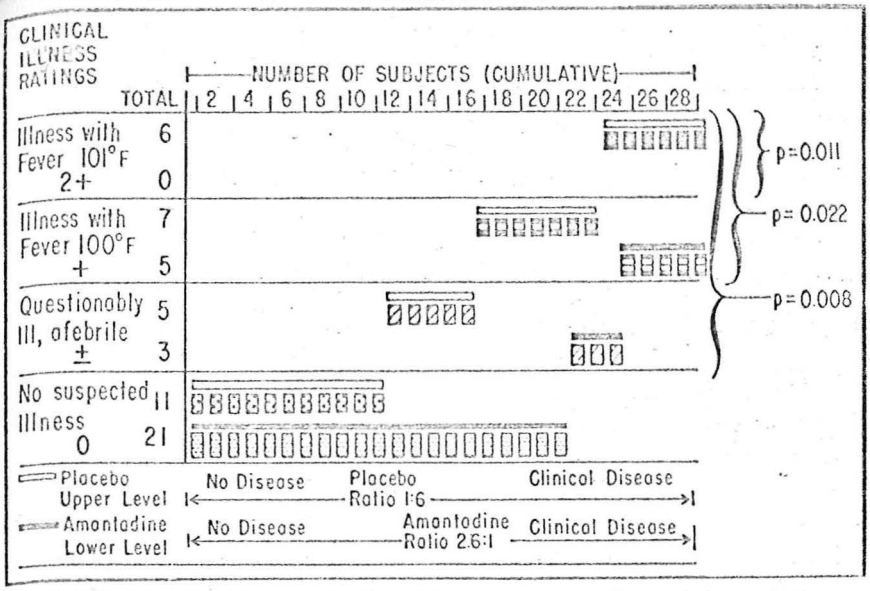


FIGURE 9

Distribution of types of clinical responses occurring in drug-treated and placebo-treated volunteers exposed to A2 influenza virus. Men receiving placebo medication (blocks in upper half of each classification). Those given amantadine (in lower half).

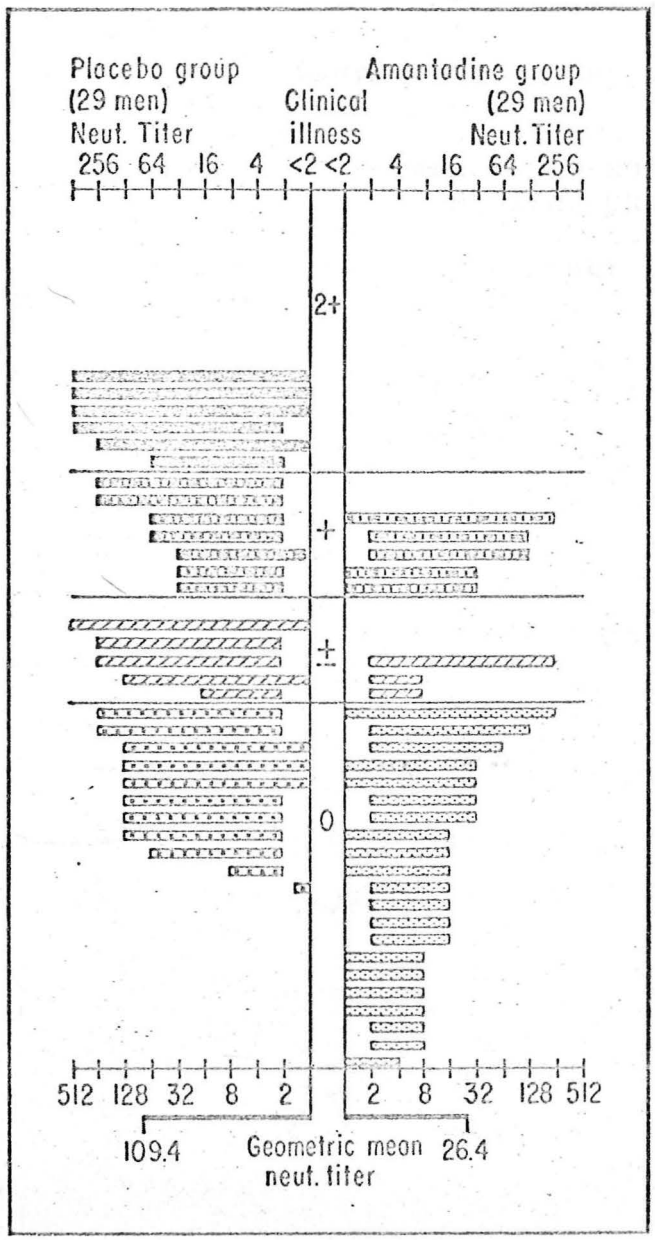


FIGURE 10

Correlation between clinical and serological responses in volunteers exposed to A2 influenza virus. Length of each bar corresponds to magnitude of antibody titer increase. Placebo-treated volunteers are listed on left and drug-treated, on right.