THE COMPLICATIONS OF INFLUENZA

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EPIDEMIC influenza has been characterized throughout history by its ability to kill. The extent of this mortality has, of course, varied from outbreak to outbreak so that it is impossible to provide any meaningful statistics. Indeed, so far as the entire country is concerned, the number of deaths appears to be determined as much by the total morbidity as by the time of year of the outbreak or the particular population group. Kilbourne (1960) has gone so far as to suggest 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 immunological factors and mortality by abnormalities of the host or his environment. This is a suggestion which might well occasion a heated debate particularly as we have yet to decide upon a laboratory method of defining virus virulence which would enable us to classify strains. It is, however worthwhile emphasizing the point which emerged abundantly during the first waves of the A2 influenza era, namely that complications then occurred particularly among those in the older age-groups with chronic disease of the heart or lung. The host appears therefore to be all important in the determination of the incidence of fatal complications of influenza. This was indeed obvious even before the Asian virus era, for during influenza epidemics deaths from all causes rise and although the largest separate increase is in respiratory complications, deaths due to hypertension, rheumatic heart disease, chronic nephritis, and diabetes, all show an increase often known as the excess mortality of influenza. The ages of those who died during 1957 in the Asian outbreak of the U.S.A. were such that over one-half of the excess mortality occasioned by the October-December wave occurred in those over 65 years of age and the proportion of these rose to 80% in the third wave of January-March 1960 (Eickhoff, Sherman, and Serfling, 1961).

The 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. The distinction of the bronchitis patients from those with uncomplicated influenza may be difficult to make and is in any case somewhat artificial. Because we have lacked information on the pathology of human influenza in the past, it is difficult to know the exact area of the respiratory tract affected by virus lesions. Thus although the focus is usually assumed to be the nasopharynx and nasal turbinates, the high proportion of patients with cough and the frequent occurrence of substernal soreness or huskiness of the voice suggest that the virus does not limit its attack to the upper respiratory tract. Burnet indeed often writes of influenza as essentially a disease of the bronchial epithelium and thinks of spread as occurring primarily in an upward direction. Recent work published by Walsh, Dietlein, Low, Burch and Mogabgab (1961), which was based upon tracheal and bronchial biopsies obtained by bronchoscopy in six patients with uncomplicated influenza, certainly seems to confirm at least the presence of epithelial lesions. There are no clinical signs of this tracheo-bronchitis in simple influenza but the frequent development of added sounds in the chest and even the raising of sputum in previously healthy persons is a pointer in the same direction. In 1937, I found rales or rhonchi in 53 of 82 patients (64%). Of the 53, 19 patients showed abnormalities for several days, such as fine or medium basal râles with or without rhonchi elsewhere (Stuart-Harris, Andrewes and Smith, 1938); 31% of the patients produced sputum in the form of pellets or nummules of white to green mucopus. All these abnormalities were found in patients thought to have uncomplicated disease except that in one patient previously affected by asthma, generalized wheezing rhonchi indicated that a general broncho-constriction had occurred. It is, in fact, the asthmatic patient who during influenza develops wheezing rhonchi suggesting widespread bronchial involvement, and a similar picture occurs in the ordinary case of chronic bronchitis. Much more serious are the cases of severe laryngo-tracheo-bronchitis which occur relatively infrequently but which were seen in schoolchildren during the first Asian epidemic. Obstruction in these cases was severe enough to necessitate tracheostomy.

Influenzal bronchiolitis is characterized by a more prolonged pyrexia than the ordinary case, by dyspnœa and slight cyanosis and by abundant râles varying from fine to coarse over wide areas of the lung. Cough is productive of a muco-purulent or frankly purulent sputum. Sometimes the sputum is viscid, the bronchioles are plugged with secretion, and breath-sounds over the affected area are reduced. The radiograph is essentially normal. Virus is readily demonstrable in patients with bronchiolitis, for the air-passage involve-

ment occurs synchronously with the disease. The sputum does not usually contain pneumococci but *Hæmophilus influenzae* may or may not be present. In a series of 17 cases of bronchiolitis seen in 1937 the past histories of the patients were examined carefully in order to determine whether the complication was the result of previous chest disease. Four patients only gave a history of such illness; two had had previous bronchitis, one an attack of pneumonia in childhood and one had pleurisy a year before the influenza. Perhaps the important fact is that 13 patients had no previous chest abnormality and that influenzal bronchiolitis ought to be regarded as a feature of the virus infection in previously well adults.

Influenzal pneumonia is of two main varieties occurring respectively synchronously with and after the influenza virus infection. The clinical picture first of all of post-influenzal pneumonia is little if at all different from ordinary pneumococcal pneumonia. These are the patients who have been up for a day or two or are about to be discharged and who develop a sudden pleural pain, fever and dyspnœa. They are perhaps iller than most cases of pneumococcal pneumonia at times other than during epidemics of influenza. They tend to have classical signs of consolidation, pneumococci are the chief cause of the condition and chemotherapy is eminently satisfactory. The synchronous cases of influenzal pneumonia are a different problem. These patients begin to be ill with the normal symptoms of influenza but soon become dyspnœic and cyanosed. Chest pain of a pleural character may or may not be present. Cough is often present but may be unproductive in spite of abundant râles in more than one area. The appearance of severe illnesses and the fact that the patients are often mentally disturbed and disorientated are points of distinction from cases of uncomplicated influenza. The pulse also is usually rapid, the blood pressure low, and the patient may be sweating and thus present the appearance of shock.

The clinical picture is seen in its most striking form in patients who become gravely ill within a matter of 36 hours of the onset of illness. Such fulminant pneumonia is characteristic of staphylococcal infection.

Table 1 shows the bacteria recovered from cases of all varieties of pneumonia admitted to hospital under my care during the A1 virus era (Stuart-Harris, 1953). The non-influenzal periods consisted of one of three months and one of six months during which 130 cases of pneumonia were investigated; 166 cases of pneumonia were studied in two separate influenzal A1 periods of three months' duration. The great difference between the bacteria concerned in these two seasons is, of course. the increase in number of staphylococcal cases. It is, in fact, the *Staphylococcus pyogenes* which constitutes the main bacterial threat to cases of influenza in this day and age. This is well shown by the species of bacteria recovered from the sputum or lung of fatal cases of pneumonia during the first Asian wave in England and in Holland (Report of the Public Health Laboratory Service, 1958; Hers, Goslings, Masurel and Mulder, 1957). In both series of cases there were a number of fatalities in which no pathogenic bacteria were recovered from the lung. The Leyden workers (Hers, Masurel and Mulder, 1958) have made an excellent study of such cases and have proved to my mind conclusively that virus alone can cause an actual pneumonitis. The most important pathological findings are that the alveolar cells are desquamated and necrotic and the pulmonary capillaries show thrombosis, necrosis and hæmorrhage; in addition there is a hyaline membrane which lines the alveolar ducts and alveoli. It seems strange that the best demonstration of this lesion, proven as viral by means of staining with fluorescent-

TABLE 1

BACTERIA RECOVERED IN CASES OF PNEUMONIA IN SHEFFIELD
(*Influenzal and Non-influenzal Periods*)

Period	No. of Cases	Pneumo-cocci	*Staph. pyogenes*	*Hæm. strep.*	Fried-lander	No Patho-genic Bacteria
1. Non-influenzal:						
(*a*) October 1947 to December 1948 ..	81	66 (81)	2	1	0	15
(*b*) July to December 1950..	49	38 (77)	5	1	0	10
2. Influenzal:						
(*a*) January to March 1949	83	51 (61)	20	2	0	12
(*b*) January to March 1951	83	63 (76)	13	1	3	8
(*c*) Both influenzal periods. Serologically and culturally positive cases of influenza virus infection only	55	39 (70)	20*	2	0	3

* 7 had pneumococci as well.   (Figures in brackets are percentages.)

tagged immune serum, has been obtained in patients with mitral stenosis. Superadded to this virus lesion are the necrotizing and toxic effects of the carpet of staphylococci which extends from the larynx down to the alveoli in those patients who die from influenza-staphylococcal pneumonia.

One cannot conclude this account of the pulmonary complications without reference to the importance of the host in their determination. Pregnancy, heart disease and chronic bronchitis are the three chief associates of severe or fatal influenzal pneumonia (Louria, Blumenfeld, Ellis, Kilbourne and Rogers, 1959; Robertson, Caley and Moore, 1958). Whether the virus lesions of the respiratory tract cause death from obstructive bronchitis or because of an effect on the circulation remains to be considered.

Cardiac Complications

It has always been known that patients with existing heart disease such as mitral stenosis, hypertension or ischæmia tolerate influenza poorly. Perhaps the extent of the deterioration likely to occur was not adequately appreciated before 1957 but numerous papers appeared after the first wave indicating the gravity of influenzal pneumonia in cardiac cases. In Leeds the distinctive character of the clinical picture of influenzal pneumonia in mitral stenosis was pictured by Newcombe, Nixon and Thompson (1958). Severe dyspnœa, hæmoptysis and congestive heart failure were noted. Radiological opacities of a multiple and ill-defined character resembling pulmonary œdema were seen. Three of the nine patients died. The effect of influenza in patients with other forms of pre-existing heart disease has not attracted so much attention as that of mitral stenosis. However, congestive cardiac failure at times is clearly dated from an attack of influenza in patients with any form of heart disease and particularly with chronic cor pulmonale. The mechanism of this does not appear to be a specific effect of influenza virus infection.

Cardiac complications in patients without pre-existing heart disease are, however, uncommon. Pericarditis and myocarditis have been described infrequently (Finland, Parker, Barnes and Joliffe, 1945). Adams (1959) described eight cases of so-called benign non-specific pericarditis occurring after either influenza B or influenza A infection. Bacteria did not appear to be concerned in these abnormalities but pericarditis certainly occurs in some patients with staphylococcal pneumonia. Studies of the effect of Asian influenza on the normal circulatory system were made by Walsh, Burch, White, Mogabgab and Dietlein (1958). The first study of 30 patients with influenza admitted to hospital included 20 with uncompli-

cated disease and ten with pulmonary involvement. Abnormal electrocardiographic findings consisting of T-wave changes without any impairment of conduction and changes in the vectorcardiogram were noted in a proportion of the patients including uncomplicated cases. Gibson, Arnold, Craige, and Curnen (1959) studied 87 university students and found 12 with electrocardiograms which were rated abnormal because of S-T segment deviations, T-wave depression and arrhythmias. Four of the 12 patients had abnormalities only during convalescence. These American authors think that their findings support the existence of a myocarditis due to influenza virus which is clinically overlooked. Probably this is a matter requiring much more work for though influenza virus has been recovered from the heart muscle in patients dying from influenzal pneumonia (Kaji, Oseasohn, Jordan and Dingle, 1959) it seems probable that this is due to an agonal viræmia. The more plausible effect of 'toxæmia' is equally difficult to sustain. Apart from its pyrogenic action, influenza virus requires to be given in enormous doses to demonstrate a toxic effect in mice and then the liver, the brain and lung appear to be the chief targets (Henle and Henle, 1946).

Neurological Complications

The evidence for association between influenza and neurological disease has in the past been circumstantial and untrustworthy because of the lack of laboratory data. Encephalitis as a cause of death has occurred after 0.8 to 1.2 cases per 1,000 influenza deaths in the years from 1950 onwards. This is probably similar to the reported frequency of measles encephalitis of 1 per 1,000 cases though these are not of course all fatal. In 1957, a new phenomenon appeared, namely an incidence of fatal encephalitis of 3.6 per 1,000 influenza deaths. Numerous articles appeared in the press and none were more convincing than the papers by Flewett and Hoult (1958) and Hoult and Flewett (1960) from this hospital. I shall follow their suggestions for the classification of cases of encephalitis occurring synchronously with influenza, cases of encephalitis occurring three days to two weeks after influenza, the Guillain-Barré syndrome and cases of a mixed character probably with only a coincidental link with influenza. It is chiefly cases of a synchronous character which have been widely described as acute influenzal encephalitis by other authors. This disease is sometimes hæmorrhagic in character but lesions at autopsy are not impressive even though influenza virus was recovered from either brain or CSF in isolated instances. It is generally agreed that the post-influenzal cases of encephalitis are of the demyelinating type which occur after

other acute infections such as measles, rubella and varicella. Their relationship to the virus infection is obscure. Thirdly, Guillain-Barré syndrome certainly has no specific relation to influenza and may indeed have an origin in auto-immunization. Nevertheless, Wells, James and Evans (1959) recovered influenza virus from the CSF taken at autopsy in two fatal cases occurring in Cardiff in 1957. I find the whole question of virus recovery from post-mortem specimens difficult to evaluate unless the brain is opened prior to the examination of the thorax. This has seldom been done.

Finally, there seems no particular point in describing the various types of neurological disease casually related to influenza. I would like to point out the undoubted existence of acute organic psychoses in influenza particularly in adults in 1957. Delirium, mania and convulsions with few or absent neurological signs were all described (Friedman and Cancellieri, 1958) and may perhaps represent a true toxic effect of influenza. One can only conclude by reference to the extremely low frequency of all neurological abnormalities occurring as complications of influenza. It is difficult to maintain the perspective required to contrast their rarity with the frequency of depression during convalescence particularly in the elderly.

Conclusion

Influenza virus infection falls on the healthy and abnormal population equally. Though it causes complications much more frequently in those with pre-existing heart or chest disease, its effect as an initiator of disease of the lungs in those with previously good health must not be overlooked. This summary of the chief clinical complications has left little time to refer to otitis media, labyrinthitis or sinusitis. Of these perhaps acute labyrinthitis is a syndrome following upper respiratory disease which has a particularly striking character. Like otitis media however, there is no evidence linking it specifically with influenza virus.

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