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## PNEUMONIA COMPLICATING ASIAN INFLUENZA

BY

NEVILLE C. OSWALD, T.D., M.D., F.R.C.P.,  
*Physician*

R. A. SHOOTER, M.D.,  
*Bacteriologist*

M. P. CURWEN, M.A.  
*Statistician*

*St. Bartholomew's Hospital, London*

The epidemic of influenza which later became known as "Asian 'flu" apparently originated in China in February, 1957, and its causative organism, a new variant of influenza virus A, was first identified in cases which occurred in Hong Kong in April, 1957 (Meyer, Hilleman, Miesse, Crawford and Bankhead, 1957). The epidemic spread rapidly across Asia and Europe, and appeared sporadically in Britain during the summer months. The first wave of infection occurred in Yorkshire; it spread almost immediately to the North and more slowly to the South, the North having the more severe experience (Martin, 1958). Local outbreaks developed in many places in the latter half of August, but October was the peak month, and the infection had virtually disappeared by the end of November.

Asian influenza attacked an estimated twelve million people in Britain, and was directly or indirectly responsible for about 16,000 deaths, two-thirds of the fatalities being in persons over the age of 55 (W.H.O. Weekly Epidemiological Record, 1958). The mortality rate was not exceptional, possibly owing in part to the outbreak having passed its peak before the usual minor respiratory infections and winter ailments had become widespread. The incidence of pulmonary complications, principally pneumonia, was also low, figures for general practices being 3.5% of 750 (Fry and Hume, 1957) and 5% of 542 (Edmundson and Hodgkin, 1957), and amongst R.A.F. recruits 5% of 391 (Gilroy, 1957); it increased steadily as the epidemic progressed (Cantor, 1957; Gilroy, 1957). No accurate figures are available to indicate the frequency of pneumonia amongst emergency hospital admissions for Asian 'flu, but it is unlikely to have been much in excess of one-half, at least so far as London hospitals were concerned; this was also the experience of Walker, Douglas, Leckie, Pines, and Grant (1958) in Edinburgh.

Early in the epidemic it became evident that no single hospital was likely to have sufficient clinical material for a comprehensive study of the various pulmonary complications. Also, with much interest attaching to the significance of superinfection by *Staphylococcus aureus*, a special investigation of staphylococcal pneumonia would necessitate the inclusion of a large number of hospitals.

### Material

Two surveys were devised—one to examine the general pattern of all influenzal pneumonias admitted to a group

of hospitals, and the other to assess the clinical significance of secondary invasion by *Staph. aureus* by collecting instances of staphylococcal pneumonia from a wide range of hospitals. The following comprised the material.

1. The clinical, radiological, and pathological records of all cases of pneumonia occurring in the ten London undergraduate teaching hospitals during the autumn of 1957. Firm clinical evidence of influenza was required in each case, together with radiological or pathological proof of pneumonia, except in a very few in which the clinical evidence appeared to be unquestionable. Many doubtful cases were discarded, including some with probable pneumonia which were not x-rayed at the height of the disease. A total of 165 cases satisfied these criteria, of which 20 (12%) were regarded as instances of staphylococcal pneumonia. The design of the survey was such that viral identification could not be insisted upon.

2. The clinical, radiological, and pathological records of cases of staphylococcal pneumonia admitted to hospitals in the London area, mainly in the North-east Metropolitan Region (93), the Royal Navy (8) the Army (13), and the Royal Air Force (21), making 135 cases altogether, during the autumn of 1957. The criteria of influenza were the same as for the teaching hospitals.

### Comparison between Staphylococcal and non-Staphylococcal Pneumonia

In order to compare staphylococcal and non-staphylococcal pneumonia, the 20 staphylococcal cases have been extracted from the teaching hospital series and added to those from non-teaching hospitals, so that the comparison is between 145 non-staphylococcal pneumonias from teaching hospitals and 155 staphylococcal pneumonias from all sources.

The serious consequences of secondary infection by *Staph. aureus*, particularly in children and young adults, are amply confirmed by this investigation. Table I shows the mortality rates by age and sex in the two groups. The high proportion aged 15-34 in the staphylococcal group is partly accounted for by the inclusion of Service patients. The most striking feature is that for staphylococcal pneumonia age had no effect upon mortality, whilst for non-staphylococcal pneumonia almost all the deaths were in the oldest age group.

TABLE I.—Mortality in Relation to Age and Sex

	Total	Age (Years)				Sex	
		0-14	15-34	35-54	55-	Male	Female
Staphylococcal pneumonia	No. . . 155	10	74	28	43	98	57
	Deaths 44	3	19	8	14	25	19
	%.. 28	30	26	29	33	26	33
Non-staphylococcal pneumonia	No. . . 145	10	38	35	62	86	59
	Deaths 18	—	1	1	16	11	7
	%.. 12	—	3	3	26	13	12

An attempt was made to grade the severity of the infection in each case into mild, moderate, or severe. Although complete accuracy was not possible, mainly because of difficulties in definition, consideration of the various clinical aspects and their responses to treatment resulted in the allocation of individual cases to one or other of the three categories with reasonable confidence. Table II shows the distribution. In the staphylococcal

TABLE II.—Severity of Infection in Staphylococcal and Non-staphylococcal Pneumonia Complicating Asian Influenza

	Mild	Moderate	Severe
Staphylococcal pneumonia . . .	19	65	71
Non-staphylococcal pneumonia . . .	42	69	34

group, 71 (46%) of the patients were severely ill, compared with 34 (23%) of those with non-staphylococcal pneumonia, many of whom were elderly and had associated chronic bronchitis or cardiac disease.

In a review of the various clinical features the staphylococcal series consistently showed the severer reaction. The median duration of symptoms before admission was five days for the patient with staphylococcal pneumonia and four days for the others; 18% of each group had symptoms for less than two days, and their mortality was higher than those with longer histories. The median duration of stay in hospital of the survivors in the staphylococcal group was 26 days, compared with 16 days for the others. Only 12 of the staphylococcal patients were in hospital for less than a fortnight, compared with 50 of the others. Part of this difference is accounted for by the long stay of the Service patients; of the 42 with staphylococcal pneumonia, 25 were in hospital for four weeks or more, but, even excluding these, the median for the remainder was 24 days.

Examination of temperature charts showed that deaths occurred in patients with maximum recorded temperatures ranging from 99° F. (37.2° C.) to over 105° F. (40.6° C.), and that a high temperature by itself did not carry a poor prognosis. However, the median duration of fever in the survivors was twice as long in the staphylococcal group (eight compared with four days), as was the duration of a temperature above 100° F. (37.8° C.) (four compared with two days); 32% of the staphylococcal and 4% of the non-staphylococcal patients had a temperature of 100° F. (37.8° C.) or over for more than a week. In assessing the total length of fever, some account must be taken of the four to five days' duration of symptoms before admission, which, so far as could be determined from the notes, was usually a febrile period. Hence the total duration of fever in the survivors was probably of the order of two weeks for the staphylococcal cases and eight days for the others.

There was a sharp difference in the radiological features in the two groups (Table III). In the staphylococcal pneumonias 37% of all patients had three or

more zones involved, compared with 19% for the others. In each group mortality increased sharply with the number of zones affected. Although no radiographs were taken of almost half the patients who died, necropsy proof of extensive pulmonary involvement was almost invariable when this examination was performed. The excess of lung abscesses in the staphylococcal series is to be expected.

TABLE III.—Radiology at Height of Disease

	Total	No. of Zones Involved				Abscess	No Radiograph Taken
		1	2	3	4 or More		
Staphylococcal pneumonia	No. . . 155	27	44	27	30	21	27
	Deaths 44	2	4	4	11	—	23
	%.. 28	7	9	15	37	—	85
Non-staphylococcal pneumonia	No. . . 145	65	38	16	12	2	14
	Deaths 18	—	4	3	6	—	5
	%.. 12	—	11	19	50	—	36

These findings amply confirm the virulent nature of staphylococcal pneumonia complicating Asian influenza. Compared with non-staphylococcal pneumonia, it caused a severer and longer illness, with a higher and more prolonged fever, radiological evidence of more extensive pulmonary involvement, and, most important of all, a high mortality in children and young adults.

### Pathological Aspects

#### Bacteriology

Table IV shows the principal pathogenic bacteria which were isolated from sputum. In the staphylococcal series, *Str. pneumoniae* and *H. influenzae* were found on a few

TABLE IV.—Principal Pathogenic Bacteria in Sputum

Cases	Organisms*						Not Tested
	<i>Staph. aureus</i>	<i>Str. pneumoniae</i>	<i>Strep. pyogenes</i>	<i>H. influenzae</i>	<i>Kleb. friedländeri</i>	Non-pathogens	
Staphylococcal pneumonia	155	151	7	—	6	—	4
Non-staphylococcal pneumonia	145	—	24	2	23	2	74

\* More than one organism was cultured from several cases in both series. Of the four cases in the first series in which the sputum was not tested the diagnosis was made in one from a blood culture and in three at necropsy.

occasions. Whether *H. influenzae* should be regarded as a pathogen in this context is not clear; certainly it is capable of producing pneumonia, but the evidence that it does so very often is uncertain. In the non-staphylococcal group, almost exactly one-half yielded no pathogens, and a further 21% either had no sputum or did not have it examined; of the remainder *Str. pneumoniae* and *H. influenzae* occurred with equal frequency (16 and 17% respectively), and *Str. pyogenes* and *Kleb. friedländeri* were found on two occasions each.

#### Antibacterial Therapy

Table V shows the frequency with which the various antibacterial drugs were used. In the non-staphylococcal series, penicillin was administered to no less than 74% of the patients and one or other of the tetracycline group to 32%. Most of the patients had an illness of only mild or moderate severity, and a single drug sufficed to effect a cure in most of these. Indeed, 60% of patients had only one antibacterial drug. The other remedies, such as streptomycin and chloramphenicol, were usually reserved for severe infections and were given either in conjunction with the first choice or after it had failed.

In the staphylococcal series, the pattern of chemotherapy was rather different. Although penicillin (76%) and the

TABLE V.—Number of Patients Treated with Various Drugs

	No. of Patients Treated	
	Non-staphylococcal	Staphylococcal
Sulphonamides .. .. .	16	12
Penicillin .. .. .	108	118
Tetracycline .. .. .	47	76
Chloramphenicol .. .. .	13	25
Streptomycin .. .. .	20	37
Erythromycin .. .. .	2	39
Novobiocin .. .. .	—	3

tetracycline group (49%) were the most popular, erythromycin, streptomycin, and chloramphenicol were used much more frequently than in the non-staphylococcal series. Only 28% were given a single drug. The great majority had at least two of the remedies listed in Table V, and two had as many as five. These were usually given either in an effort to overcome fulminating influenza or in order to conform with the results of tests for drug sensitivity. The sensitivities of the various staphylococci are given in Table VI, according to whether they were isolated (a) within four

TABLE VI.—Sensitivities of Staphylococci Isolated from Patients with Staphylococcal Pneumonia Following Influenza

	(a) Isolated Within 4 Days of Admission			(b) Isolated More Than 4 Days After Admission		(c) Influenza Contracted in Hospital		% Resistant (b+c)
	No.	Resistant	%	No.	Resistant	No.	Resistant	
Sulphonamides ..	34	15	44	5	4	1	0	67
Penicillin ..	113	55	49	18	16	9	9	93
Streptomycin ..	89	11	12	17	9	7	6	62
Tetracycline ..	94	21	22	18	12	9	8	74
Chloramphenicol..	96	6	6	16	1	7	1	9
Erythromycin ..	60	4	7	17	1	8	0	4

days of admission and were presumably acquired outside hospital, (b) more than four days after admission and could well have been acquired within hospital, and (c) from patients already in hospital when they contracted influenza. As might be expected, the latter groups show a considerably higher resistance rate to the more commonly used antibiotics, penicillin, streptomycin, and tetracycline, the figures being 93%, 62%, and 74% respectively, compared with 49%, 12%, and 22% of strains isolated within four days of admission. The low rate of resistance to chloramphenicol and erythromycin probably reflects the relatively restricted use of these drugs in the past. An attempt was made to correlate the *in vitro* sensitivities with therapeutic responses, but, chiefly because of the many occasions on which two or more drugs were prescribed either together or in succession, no valid conclusions could be drawn.

**White Blood Cell Count**

In almost all hospitals a white blood cell count was done as a routine, usually with a differential count in addition. In 26 patients the count was repeated after an interval, but the great majority had only a single observation. Table VII shows that the test was carried out in all but 40 of the

TABLE VII.—White Blood Cell Counts Within Five Days of Admission to Hospital Related to Deaths and Survivors from Severe Infections

	W.B.C.	Cases	Deaths (a)	Survivors from Severe Infections (b)	% of Deaths and Survivors from Severe Infections (a+b)
	6,000— ..	63	17	10	43
	14,000— ..	34	6	9	44
	Not known..	40	18	5	57
Non-staphylococcal pneumonia	<6,000 ..	34	5	3	24
	6,000— ..	71	5	9	20
	14,000— ..	23	1	5	26
	Not known..	17	7	2	53

155 staphylococcal patients and all but 17 of the 145 non-staphylococcal patients. In both groups counts were omitted in several patients who died shortly after admission. The findings strongly suggest that no relationship exists between a white cell count taken within five days of admission and either the severity of the illness or the mortality. Despite the theoretical argument that it might help to differentiate a predominantly viral infection from one with secondary invasion by a pyogenic organism, this examination, at least so far as pneumonia complicating influenza is concerned, seems to provide little information of value, and the rarity of serial counts confirms this view.

**Clinical Aspects**

Although the majority of patients overcame their infections without causing undue alarm, many had features which are associated with a grave prognosis, such as mental changes, prostration, pallor, cyanosis, and excessive dyspnoea. In a number of instances the influenza was superimposed upon other diseases—for example, chronic bronchitis and cardiovascular disorders. In order to enlarge the experience of these more formidable aspects, a further 79 cases of non-staphylococcal pneumonia have been added to the staphylococcal and non-staphylococcal groups compared above, making 379 cases altogether. The further 79 cases were from non-teaching hospitals; some were thought originally to be instances of staphylococcal pneumonia, the others were from hospitals which supplied non-staphylococcal in addition to staphylococcal material. They were to some extent a selected group with severe infections, and so could not be included in the foregoing comparison between staphylococcal and non-staphylococcal pneumonias.

**Previous History**

*Chronic Bronchitis and Emphysema.*—A previous history of chronic bronchitis was noted in 84 patients, and of these 25 (30%) died. The great majority were over the age of 55, and this mortality is similar to the overall rate within this age range. Almost certainly more would have died if the epidemic had reached its height in the winter months, but some credit must be given to their medical attendants, principally general practitioners, for instituting early and effective treatment in this vulnerable group. The pattern of infection did not differ appreciably from that in non-bronchitics, but any tendency to asthma or bronchospasm exaggerated the degree of dyspnoea.

*Ischaemic heart disease* was present in 11 patients, of whom six died, and hypertensive heart disease in six, with two deaths. Cardiac failure contributed to a fatal outcome in several of these.

Several authors have been impressed by the seriousness of Asian influenza in patients with *chronic rheumatic carditis*, particularly mitral stenosis. Reid (1957) saw nine such patients with two deaths, and Govan and Macdonald (1957) had experience of nine patients who were also pregnant, of whom four died. Hers, Goslings, Masurel, and Mulder (1957) found 10 rheumatic hearts in 252 necropsies, and Giles and Shuttleworth (1957) seven in 46 necropsies; Roberts (1957), examining 12 cases of fatal fulminating influenza, noted mitral stenosis in three. In our series, eight patients had chronic rheumatic carditis (six mitral stenosis, two aortic incompetence), of whom four died. These figures are well in excess of the expected mortality, and associated rheumatic heart disease must be regarded as a serious disadvantage.

*Pregnancy.*—In its later stages, pregnancy certainly constitutes a hazard when influenzal pneumonia is superimposed. Of seven pregnant women in this series, two died, one having mitral stenosis in addition. The others were all very ill, and four delivered their babies at the height of the infection.

*Diabetes.*—Of nine diabetics, six died, four of whom were admitted in a state of coma with grossly disordered carbohydrate metabolism.

### Nervous Features

Mental changes are among the most alarming features of influenzal pneumonia. They vary from confusion to delirium and coma, and were present in some degree in 15% of this series. They can be accounted for by three entirely different mechanisms—namely, by anoxia and carbon dioxide retention resulting from pre-existing chronic pulmonary disease or extensive involvement of the lungs and air passages; by “general toxæmia,” in which case the adrenals may play a part; or by direct invasion of the brain by viruses or bacteria. The invasive nature of influenzal pneumonia is such that gaseous exchange in the lungs may easily become inadequate, particularly in patients with pre-existing chronic pulmonary diseases, and the resulting acute anoxia will readily contribute to mental impairment. “General Toxæmia” is discussed later in relation to fulminating influenza. Evidence of direct microbial invasion of the brain is fragmentary.

Although the existence of true influenzal encephalitis remains somewhat nebulous, the clinical features in several of the cases reported in the present outbreak have been typical of a viral encephalitis; but the organism has not been found in the brain, and the changes in the cerebrospinal fluid have been scanty or absent (Dubowitz, 1958; Smith, 1958; Dunbar, Jamieson, Langlands, and Smith, 1958). McGill and Goodbody (1958) report an instance with extensive haemorrhages in the white matter, conforming to the acute haemorrhagic leuco-encephalitis described by Crawford (1954), but Giles and Shuttleworth (1957) were unable to find any microscopical evidence of encephalitis in two patients admitted to hospital in coma and whose brains showed intense congestion and oedema. Perhaps further evidence of the possible neurotropic properties of the Asian strain will be forthcoming. The following are instances of neurological involvement in this series.

L. S., male aged 44. On admission, two days' history of cough, sputum, pleurisy, stiffness of neck, and mental confusion. Temperature 104° F. (40° C.); purulent sputum containing *H. influenzae*; radiological consolidation in three zones. Diagnosed as “meningism,” the cerebrospinal fluid containing 27 cells per c.mm., 90% lymphocytes, 10% polymorphs. Treatment with penicillin and “sulphatriad” resulted in a complete clinical recovery in six days; discharged from hospital after 16 days.

A. M., male aged 17. Admitted to hospital on day of onset, with general aches, cough, and mental confusion. Temperature 103° F. (39.4° C.), scanty mucopurulent sputum containing no pathogens, radiological consolidation right base. Treated with penicillin, but fever persisted with increasing delirium leading to coma and generalized convulsions. Died on the tenth day. Post-mortem examination showed deeply congested superficial cerebral veins with slightly blood-stained fluid in both ventricles; no microscopical evidence of haemorrhage or encephalitis.

T. B., male aged 22. On admission, six days' history of increasing illness with moderate fever and delirium. Radiological consolidation of right middle and lower zones; *Staph. aureus* isolated from thin right purulent effusion on day of admission. Treated with penicillin, streptomycin, and erythromycin in full doses. Became rapidly comatose, the cerebrospinal fluid being purulent and containing 2,160 cells per c.mm., mainly polymorphs. Died on tenth day of illness. Necropsy showed extensive pneumonia of both lungs with multiple small staphylococcal abscesses. The brain contained several septic infarcts in addition to meningitis.

D. C., male aged 22. On admission, three days' history of increasing headache, dyspnoea, and mental confusion. Temperature 104° F. (40° C.); purulent sputum contained *Staph. aureus* sensitive to all drugs; patchy radiological consolidation in all zones of both lungs. Stiffness of the neck led to a diagnosis of meningism, and the cerebrospinal fluid contained 12 cells per c.mm., of which 11 were lymphocytes. Treated with penicillin, tetracycline, and chloramphenicol, he made a complete recovery in a month.

The third of these patients evidently died from septic emboli which derived from the lungs. The others had fairly firm clinical evidence of encephalitis, but pathological proof was lacking.

Amongst the minor neurological disorders, one young adult, who had a sharp attack of influenza, developed weakness and tingling of one leg which was attributed to a toxic neuritis; it resolved completely in three weeks. Another had a transient weakness of one arm.

Post-influenzal depression was noted on a number of occasions.

### Fulminating Influenza

A diagnosis of fulminating influenza is often made in patients whose clinical features are alarming and in whom the degree of toxæmia is extreme. Despite the lack of a clear definition, the term is a useful one. In the 1918–19 epidemic the graver forms were referred to as “pneumonic influenza,” the course of the illness being regarded as “fulminating” (French, 1920). Clearly, emphasis upon the pulmonary component to the exclusion of the state of the air passages and the degree of toxæmia is undesirable, and the somewhat non-committal term fulminating influenza is now generally used to describe the severest forms of this infection (Scadding, 1937; Stuart-Harris, 1953).

In this series 132 patients were judged to have been gravely ill, of whom 76 (58%) died. How many of these should be regarded as instances of fulminating influenza is a matter of opinion, but, so far as could be judged from the records, they all fell within the category. They had the features ordinarily associated with this diagnosis in the following proportions: prostration (55%), cyanosis (80%), pallor (12%), mental disturbance (48%), excessive dyspnoea (62%), and blood-stained sputum (36%). The figures are comparable to those from previous epidemics, and the reason for the large total is that the cases were derived from a considerable number of sources and contained a high proportion (71, or 54%) of instances of staphylococcal pneumonia.

Perhaps the outstanding qualities of fulminating influenza are the short duration of the acute illness and the severe degree of toxæmia, so that effective treatment to combat collapse must necessarily be given quickly. In addition to oxygen therapy, antibacterial drugs, and the maintenance of a clear airway, which are considered elsewhere, the possibility of steroid therapy arises, the value of which in the present epidemic has produced conflicting opinions. Plaza de los Reyes and Cruz-Coke (1957) and Rotem (1957) claim to have obtained good results; Walker *et al.* (1958) are not particularly impressed; and Gunn (1957), after observing four fatal cases treated in this way, thinks that they should not be given and suggests that they may interfere with immunity mechanisms. Librach (1957), summarizing the evidence for and against steroid therapy in acute infections, advocates caution. Before passing final judgment, three aspects need to be considered.

(a) *Evidence of Adrenal Damage.*—Macroscopic evidence of damage was rarely encountered in the present epidemic. Amongst the necropsies in this series, the state of the adrenals was recorded on 24 occasions. None showed gross changes, but the following were observed: acute congestion (2), loss of cortical lipoid (2), enlargement and tenseness (1), and a few focal haemorrhages (1). Warrack (1957) cites an instance of fulminating influenza in which the adrenals showed only a minimal amount of functional tissue, with heavy intercellular haemorrhage. Adrenal haemorrhage was noted on only eight occasions in a survey of 219 necropsies undertaken by the Public Health Laboratory Service (1958). Hence evidence of structural damage is not impressive.

(b) *Effect of Toxæmia upon the Adrenals.*—Adrenal impairment, which need not necessarily be accompanied by evidence of macroscopic or microscopic damage, may prevent the output of large quantities of hydrocortisone and thus lead to a relative failure. The acute toxæmia of fulminating influenza rarely lasts for more than a few days, so that the administration of hydrocortisone would be no more than a form of substitution therapy. Its frequent use in similar crises, such as post-operative states, suggests that it does not interfere with the processes

of inflammation and healing provided that it is used for a short time only.

(c) *Nature of Fulminating Influenza.*—The essential components are inflammation and obstruction of the airway to the lungs, pulmonary oedema, haemorrhage and pneumonia, and toxæmia. Steroid drugs can hardly be expected to relieve tracheobronchial obstruction, and their ability to restrict the spread of infection in the lungs is doubtful. Where they are most likely to succeed is in the suppression of circulatory collapse resulting from toxæmia, and this is the purpose for which they are given.

Biochemical proof of inadequate adrenal response to fulminating influenza is not so far forthcoming, and when we are faced with a desperately ill patient the results of such tests as are available cannot be awaited. Surely the best policy is to give hydrocortisone for a few days in the reasonable hope that it will be effective and the almost certain knowledge that it will do no harm.

In this series some 27 patients had steroid therapy in adequate dosage, usually 100 mg. of hydrocortisone intravenously, followed by 50 mg. 6- or 12-hourly; of these, 17 died. The relative importance of obstructed airway, loss of effective alveolar surface, and toxæmia in each case cannot be accurately assessed from the notes. Also, eight of the deaths occurred within 24 hours of admission to hospital. However, the impression is that the survivors were those with a reasonably free airway and comparatively little radiological evidence of consolidation who responded promptly to a combination of hydrocortisone and antibiotics.

The following case illustrates the difficulties of clinical assessment.

L. S., female aged 16. Influenza started with a cough, sore throat, and left pleuritic pain. She remained at home, feeling reasonably well with a mild fever, until the fifth day, when she was admitted to hospital with a few hours' history of increasing illness and delirium. On examination she was prostrate, pale, and semicomatose. She had a tachycardia and a temperature of 104° F. (40° C.). Her breathing was unembarrassed, she had no sputum, and there were signs of bronchitis in her lungs; a radiograph of her chest showed patchy consolidation at the left base. Within an hour of admission she had had 50 mg. of hydrocortisone and 250 mg. of erythromycin intravenously, and 20 ml. of anti-staphylococcal gamma-globulin. After four hours she was much improved, and at the end of 24 hours she seemed to have fully recovered. Erythromycin was continued, by mouth, for a further two days, and she was discharged from hospital perfectly well after 16 days.

#### Obstructed Air-passages

In the early stages of influenza the brunt of the infection often falls upon the epithelium of the trachea and bronchi. The inflammatory reaction may be severe enough to cause obstruction to airflow, with consequent stridor and indrawing of the soft tissues of the neck during inspiration; if unrelieved, it can by itself lead to a fatal outcome. On reaching the lungs the infection characteristically passes through the phase of oedema and haemorrhage before frank consolidation develops. Hence, from the therapeutic standpoint, the need to relieve respiratory obstruction occasionally overshadows all other measures, and this particularly applies in fulminating influenza.

*Tracheobronchial intubation* serves the dual purpose of enlargement of the airway by the removal of debris, usually at the expense of damage to the acutely inflamed respiratory epithelium, and the aspiration of inflammatory products and oedema which derive from the lungs; these latter may not amount to more than an ounce or two at a single aspiration, but their removal often gives considerable symptomatic relief. Therefore, adequate clinical and, if possible, radiological assessment must be made before intubation in order to determine so far as is possible the extent both of the obstruction to airflow and of the pulmonary oedema.

Bronchoscopy, perhaps because it is the commoner procedure, can often be performed more quickly and easily than tracheotomy. It has the advantage that the larger bronchi can be aspirated under direct vision, but it is dis-

treassing and exhausting, and the inevitable epithelial damage is such that the instrument should not be passed more than once. Indeed, bronchoscopy should probably be reserved for acute emergencies only.

Tracheotomy, the treatment of choice in tracheobronchial intubation, is a minor procedure in the hands of experts, and enables the nursing staff to carry out repeated suction by catheterization.

Despite the theoretical objections of some authors (Sheldon, 1957), intubation was regarded as a life-saving procedure in the present epidemic by the majority (Anderson and Niblock, 1957; Rawlins, 1957; Walker *et al.*, 1958). Almost certainly it should have been performed earlier and more frequently. In this series bronchoscopy was carried out three times (no deaths) and tracheotomy six times (three deaths). Several other patients had clinical evidence of a stridor, which usually resolved with antibiotic therapy; but a very large number had extensive pulmonary oedema, and upon them aspiration was not attempted.

L. P., female aged 9. Admitted with two days' history of increasing dyspnoea, sore throat, and vomiting. On examination temperature 104° F. (40° C.), extreme dyspnoea, cyanosis, stridor, and sucking in of soft tissues of the neck during inspiration. Lung fields radiologically clear; purulent sputum contained scanty *Staph. aureus*. Dramatic recovery in four days with antibiotics, tracheotomy, and repeated tracheobronchial aspiration.

D. P., female aged 8. Admitted with two days' history of general aches, rigor, and increasing dyspnoea. On examination temperature 104° F. (40° C.), she was collapsed, cyanosed, and breathless with stridor. Extensive confluent radiological opacities in all zones of the right lung. Purulent sputum contained *Staph. aureus*. Failed to respond to tetracycline and erythromycin, becoming increasingly breathless, and died on the sixth day of her illness. No bronchoscopy or tracheotomy. Necropsy showed that the whole of the trachea and main bronchi were filled with thick tenacious yellowish-brown mucopus. The lungs showed extensive haemorrhagic oedema and bronchopneumonia with multiple small abscesses.

#### Lung Abscess

Radiology cannot reflect the true incidence of abscess formation in the acute stages, because the ring shadows are often obliterated by surrounding pneumonia and oedema. This was frequently seen when comparing radiographs with necropsy specimens, and applied particularly to the smaller abscesses which occur so commonly in acute staphylococcal pneumonia. However, radiological cavitation was observed on 25 occasions—staphylococcal 21 (14%), others 4 (2%). There were no deaths in this group, principally because they could not be diagnosed in the acute stage.

In the staphylococcal series, several of the large lung abscesses were diagnosed two weeks or more after the onset of influenza in patients who felt that they had more or less recovered from their infections but who were troubled by excessive purulent sputum. Most of the abscesses responded rapidly to antibiotic therapy. During the short period of observation available, 13 resolved completely, 5 became hairline cysts of which 2 persisted, 2 continued as thin-walled cavity systems, and 1 remained a rather thick-walled cavity after two months. The four lung abscesses in patients from whom *Staph. aureus* was not isolated resolved with treatment; staphylococci might well have been found in these if they had been looked for earlier and more thoroughly.

#### Pleural Effusion

Pleural effusions occurred in 24 patients: staphylococcal 18 (12%), and others 6 (3%). For the most part they were small and serous, and resolved without treatment or following simple aspiration. There were four empyemata, three of which were successfully treated by aspiration and the instillation of penicillin. The fourth was a classical example of an acute staphylococcal lung abscess which ruptured into the pleural cavity and produced a pyopneumothorax. Aspiration was followed by pleural decortication and a full recovery.

### Cardiovascular Complications

*Acute myocarditis* may have been the precipitating cause of death in a few cases of fulminating influenza, probably resulting more from the general toxæmia than from any specific effect of the virus upon the myocardium. Giles and Shuttleworth (1957), in a series of 46 post-mortem examinations, frequently encountered cardiac enlargement for which there seemed to be no adequate explanation, and myocardial oedema was in their opinion the most constant microscopical finding. The following are instances of myocardial involvement.

P. M., female aged 19. Admitted to hospital with one day's history of general aches, lassitude, cough, and pleuritic pain. During the next six days her condition gave rise to no anxiety, her temperature did not exceed 100° F. (37.8° C.), and a radiograph of her chest after four days showed no abnormality. Her scanty sputum was not examined. On the seventh day of her illness she rapidly became worse, with delirium leading to coma, and died on the eighth day, despite large doses of penicillin, chloramphenicol, intravenous steroids, and staphylococcal antitoxin. Post-mortem examination revealed extensive pneumonia and haemorrhagic oedema of both lungs, a culture growing *Staph. albus* only. The pericardial sac contained a few ounces of clear yellow fluid, and there were a few subpericardial petechiae. The heart was dilated, weighed 251 g., and the myocardium was pale, soft, and claylike in consistency. Subendocardial haemorrhages were seen throughout the left ventricle.

P. McL., female aged 23. Admitted to hospital with seven days' history of lassitude, general aches, and pleurisy. On examination she was semicomatose, cyanosed, breathless, and had a temperature of 102° F. (38.9° C.). She was treated with intramuscular chloramphenicol and intravenous hydrocortisone, but died 30 hours later. Necropsy showed extensive bronchopneumonia and haemorrhagic oedema of the lungs with one acute abscess, measuring an inch (2.5 cm.) across. The pericardium contained 400 ml. of green purulent fluid with rough fibrin deposits. The heart was dilated, weighed 300 g., and the myocardium was creamy white, very soft, and of claylike consistency; there were a few small abscesses in the wall of the left ventricle. Coagulase-positive staphylococci and haemolytic streptococci group A were cultured from the trachea, the lungs, and the lung abscess; the streptococci were also grown from the blood and the pericardial fluid.

*Embolic Phenomena.*—Instances of embolic spread to sites outside the thorax were seen only in the staphylococcal series, and then only on four occasions (3%). An example of multiple cerebral infarcts has already been cited. Another patient developed several emboli of his fingers and toes, and acute arthritis of the knee. *Staph. aureus* was cultured from his blood, and he recovered completely in three weeks with appropriate antibiotics. A third patient developed a septic infarct of his foot which required incision and from which *Staph. aureus* was isolated.

J. C., male aged 23. Admitted to hospital with a history of influenza two weeks previously, from which he never fully recovered. Three days before admission he developed acute arthritis of the ankle. A radiograph of his chest showed confluent consolidation of the greater part of the left lower lobe, and his purulent sputum contained *Staph. aureus*. He responded well to antibiotics, and was discharged from hospital after three weeks with his foot in plaster.

### Discussion

Every few years epidemic influenza presents its challenge to medical resources. Reports of outbreaks of Asian influenza during its passage from the Far East suggested that the pulmonary complications were few and the mortality rates low (Guthrie, Forsyth, and Montgomery, 1957; Lim, Smith, Hale, and Glass, 1957; Rowland, 1958). In Britain several problems associated with the pneumonic forms were anticipated, such as the possible number of deaths in the various age groups, particularly in the elderly with pre-existing cardiac and pulmonary diseases, the frequency of the fulminating variety, the nature of the complications, the pattern of secondary bacterial invasion, and the efficiency of the newer remedies such as tetracyclines, chloramphenicol, erythromycin, and the corticosteroids.

The mortality among the 165 patients in London undergraduate teaching hospitals was 10%, the majority of deaths

occurring at or after the age of 55; this compares with 11% of 262 pneumonic patients analysed by the Combined Study Group, Dundee (1958), and 17% of 69 similar patients seen by Walker *et al.* (1958) in Edinburgh. Death rates from pneumonic influenza before antibiotics were discovered were 27.5–40% in the pandemic of 1918–19 (Brem, Bolling and Casper, 1918; Opie, Freeman, Blake, Small, and Rivers, 1919; Chickering and Park, 1919; French, 1920), with no improvement in later epidemics (Collins, 1931; Scadding, 1937). Direct comparisons between Asian influenza and pre-antibiotic epidemics are naturally hazardous, owing to differences in virulence of the viruses concerned and of associated bacteria, and the variable times of onset and duration; but if they are limited to cases with pneumonia, these difficulties are to some extent overcome. Certainly, the consistently lower death rates in recent years cannot easily be explained other than by attributing them to improved methods of treatment.

Instances of fulminating influenza occur in all major epidemics and constitute a considerable clinical problem. Owing to the lack of a satisfactory definition, their frequency in this or other epidemics cannot be determined. In the present context they seemed to occur unevenly in and near London, some large hospitals admitting none and others as many as five or six. Of the 132 patients whose influenza was regarded as fulminating, 58% died; 30% of the deaths occurred within 24 hours and 80% within a week of admission. At the height of the outbreak many hospitals were crowded with patients. The medical and nursing staffs, often depleted by the infection, had to care for many influenza patients, one or two of whom might be suffering from this acute medical emergency, against which some of the newer remedies had not been adequately tested. As the epidemic progressed, the pattern of infection became clear and the treatment more definitive. Several hospitals formulated emergency plans for the very ill which were carried out on admission, and consisted in the main of oxygen therapy, intravenous erythromycin and hydrocortisone, and, if available, staphylococcal antitoxin. These measures almost certainly saved lives in the present series, but a study of the records suggested that insufficient use was probably made of early intratracheal intubation.

Secondary invasion by *Staph. aureus*, as had been anticipated, undoubtedly added materially to the severity of the outbreak. It was encountered in 12% of the 165 patients in London undergraduate teaching hospitals, and was very common in pathological series from other sources. Roberts (1957) found *Staph. aureus*, usually in pure culture, in 8 out of 9 cases of fulminating influenzal pneumonia. Hers *et al.* (1957) in 61% of 103 fatal cases of influenza, Giles and Shuttleworth (1957) in 33% of 46 influenza deaths, and the Public Health Laboratory Service (1958) in 62% of 477 fatalities.

Experience in this epidemic has left the question of the choice of antibiotics for routine use to some extent unsolved. The majority of patients overcame their pneumonia uneventfully, and penicillin and tetracycline appeared to be equally effective. The problem lay with the 10–15% who developed staphylococcal pneumonia. Patients treated at home in the first instance, as were one-third in this series, may reasonably be given penicillin or tetracycline in the knowledge that it is suitable for non-staphylococcal infections, and will rapidly resolve about one-half of the staphylococcal infections. Once patients have been admitted to hospital, close co-operation with the laboratory is necessary, so that staphylococci may be identified in direct smears of sputum within two hours and their sensitivities reported from primary cultures in 24 hours. This system was in use in many hospitals taking part in this investigation, and accounts partly for the frequent changes in antibiotic therapy within 48 hours of admission in the staphylococcal series.

The complications were remarkably few. Pleural effusions, with one exception, responded to simple measures, and antibiotics were almost uniformly successful in resolving



lung abscesses. Isolated instances of direct spread of infection to the heart and embolic spread to the brain occurred, with fatal consequences.

### Summary

The clinical and pathological records and radiographs of 165 patients with pneumonia complicating influenza admitted to the 10 London undergraduate teaching hospitals in the autumn of 1957 are reviewed. Of these, 20 (12%) were instances of staphylococcal pneumonia.

The non-staphylococcal cases are compared with the staphylococcal cases, together with a further 135 instances of staphylococcal pneumonia complicating influenza during the same period which were derived from hospitals in and near London, mainly in the North-east Metropolitan Region and from the three armed Services.

The severer course and higher mortality in the staphylococcal series are discussed.

The clinical assessment and emergency treatment of fulminating influenza are described, with special reference to bacteriology, choice of antibiotics, steroid therapy, and tracheobronchial intubation.

In order to enlarge experience of the severer forms of influenzal pneumonia and the less common forms of treatment, the records of 79 cases were added to the above series, making a total of 379 cases.

We record our sincere thanks to the many physicians and pathologists who made the collection of so large a series possible, particularly the medical committees of the 10 London undergraduate teaching hospitals, the Senior Administrative Medical Officer, and the medical committees of the hospitals in the North-east Metropolitan Region, and the Medical Directors General and medical officers of the Royal Navy, Army, and Royal Air Force. We are also indebted to individual physicians and pathologists at the following hospitals—Bedford General, Brompton, Buchanan, Lister, Mount Pleasant, North Herts, Royal East Sussex, Royal Northern, Schrodelles, St. Andrew's, Bow, St. Helier, and St. Olave's.

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## NEUROLOGICAL AND HEPATIC DISORDERS ASSOCIATED WITH INFLUENZA

BY

C. C. KAPILA, O.B.E., M.B., M.R.C.P., D.T.M.&H.  
Brigadier

S. KAUL, M.D., M.R.C.P.  
Lieutenant-Colonel, A.M.C.

S. C. KAPUR, M.D.  
Major, A.M.C.

T. S. KALAYANAM, M.B., B.S., M.R.C.P.Ed.  
D.T.M.&H.  
Major, A.M.C.

AND

D. BANERJEE, M.B., B.S., M.R.C.P.Ed., D.T.M.&H.  
Captain, A.M.C.

From time to time in the history of mankind influenza has taken its toll in terms of human life and suffering. The present pandemic, which appears to have started in North China in the early spring of 1957, spread to Hong Kong, and was first reported from Singapore in May. Cases started to appear in Madras in the same month, after the arrival in the port of s.s. *Rajula* from Singapore. Very soon after, other Indian ports also reported the occurrence of cases. The epidemic thence spread fanwise throughout the country, and by the end of the month most of the towns of South India were affected. The vast majority of these cases conformed to the usual clinical picture associated with influenza and described in previous epidemics (Abrahams *et al.*, 1919; Stuart-Harris, 1945). Early in this epidemic we realized that some of the cases showed unusual clinical features referable to the central nervous system and the liver. These cases were therefore studied in detail, and the observations form the subject of this paper.

### Present Investigation

Out of 9,459 cases of influenza admitted to the various military hospitals in South India, a total of 30 showed the features mentioned. All the cases occurred during the peak period of the epidemic in the stations. Sixteen occurred in one station in 17 days. The usual incidence of encephalitis in this station is one or two cases a year. Five cases occurred in another station in 27 days, whereas the usual incidence of encephalitis there is about one a year.

*Clinical Features.*—These are shown in Table I. They do not pertain to the initial signs and symptoms of influenza but to those of the subsequent illness, during which neurological and hepatic manifestations developed. In a typical case after an attack of influenza the patient was afebrile and progressing well, when suddenly there was an onset of severe persistent vomiting followed very soon by delirium, boisterousness, and coma. Some of these cases had convulsions. In a few, localizing neurological signs were noted. A third of these cases had raised serum bilirubin. Complete recovery occurred in 13, and 17 proved fatal.

*Age-and-Sex Incidence.*—Age varied from about 14 to 26 years, except one case of a child aged 2 years and 9 months and another of an adult aged 36. All the patients were males. No inference can, however, be drawn from this age-and-sex incidence, since the number of cases affected was small, and the community at risk was of a similar age-and-sex group.

*Onset.*—As already indicated, after a typical attack of influenza there was an afebrile period varying from one to