

that the constrictor action of nicotine was present in the rabbit ear three weeks after sympathectomy, and this action was blocked by hexamethonium. This might suggest the existence of peripherally situated ganglia which were unaffected by "sympathectomy." Then chromaffin tissue was found in the rabbit ear as it was found in human skin. It is clear that we have as yet incomplete knowledge of sources of noradrenaline and adrenaline which may affect vascular tone. It seems, however, that they can all be dispersed by the action of reserpine.

The use of reserpine for peripheral conditions is, however, limited by its effect on the central nervous system. What is needed is a quaternary compound which will not penetrate the blood-brain barrier. Unfortunately neither serpentine nor serpentine, which are quaternary, has the same effect as reserpine. It may be that either choline 2:6-xylylether bromide, synthesized by Hey and Willey (1954) and investigated by Exley (1957), or a quaternary form of one of the benzoquinolizine derivatives described by Pletscher, Besendorf, and Bächtold (1958), or a quaternary form of reserpine itself would have the action desired.

### Summary

The work of Schmitterlöw showed that noradrenaline is present in artery walls, but hitherto it has not been considered to affect vascular tone. Certain substances such as nicotine, and (in the presence of atropine) acetylcholine, cause vasoconstriction in the vessels of the rabbit ear, and the mechanism of their action has not been understood hitherto. This vasoconstriction has now been shown to be due to the release of noradrenaline from the artery wall, since the vasoconstriction was absent in the ears from rabbits treated with reserpine.

When the skin of rabbit ears was extracted it was found to contain a substance like noradrenaline, but ears from rabbits treated with reserpine did not contain it. Mr. E. H. Leach demonstrated the presence of chromaffin cells in the ears of normal rabbits. These cells were absent in the ears of rabbits treated with reserpine.

Strips of aorta from normal rabbits, when suspended in a bath, contracted on addition of nicotine. They were found to contain noradrenaline in a mean amount of 0.5 µg./g. Strips of aorta from rabbits treated with reserpine did not contract on addition of nicotine. They contained only traces of noradrenaline.

Nicotine had a constrictor action on the perfused vessels of the dog's hind leg, though not in all preparations.

Strips of aorta from rabbits treated with reserpine were highly sensitive to noradrenaline. From this it appeared that the store of noradrenaline in the vessel wall must normally reduce the effect of noradrenaline, and probably the effect of sympathetic impulses also.

Conditions such as Raynaud's disease may be due to a release of noradrenaline from the store in the artery wall, and might therefore benefit from the treatment with reserpine, which would reduce the store.

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## SOME ASPECTS OF THE RECENT EPIDEMIC OF INFLUENZA IN DUNDEE

BY

### A COMBINED STUDY GROUP\*

The need for epidemiological intelligence reports from representative places in different countries on the progress and varying behaviour in influenza during an epidemic or pandemic has long been felt and sometimes stressed. The present communication from Dundee is intended as a contribution to the further development of such an intelligence service in the United Kingdom. Dundee appears to have suffered relatively late in the recent epidemic, and if, as some authorities fear, this epidemic is the first wave of a series our observations may be of special interest.

In assessing the time when the influenza reached epidemic proportions in Dundee the following three sets of weekly returns were useful: first certificates received by the Ministry of National Insurance; records of absenteeism kindly provided by various large industrial establishments; and returns of weekly percentage absence of pupils in local authority schools.

Sporadic cases of influenza were reported from housing districts as early as mid-August, and there was serological evidence of influenza A in a few cases dating from this time, but the disease did not reach epidemic proportions until the beginning of October; this was possibly about a fortnight later than in Edinburgh and Glasgow but about the same time as in Aberdeen.

The maximum figure for the weekly returns of "first certificates" received by the Ministry of National Insur-

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ance was 4,014 (usual range of figures for this season is 580-710). This was attained in the week ending October 18th and is the highest so far recorded for Dundee. The previous maximum recorded was 2,005 in January, 1951. Particularly high peaks of absenteeism were recorded in various large industrial establishments and in the schools of the city. The mortality rate for the period October 5 to November 16 is estimated to have been 19 per 100,000.

The inquiry was conducted by a combined study group which included clinicians, epidemiologists, bacteriologists, and pathologists. The investigation was greatly facilitated by the decision of the Eastern Regional Hospital Board to admit all influenzal patients to one hospital—namely, King's Cross Infectious Diseases Hospital, Dundee.

In reading the literature of the 1918 pandemic (M.R.C., 1919; Ministry of Health, 1920), we were impressed by the high mortality in certain places and not in others, which suggested that local environmental factors may be of greater significance than variation in the virulence of the virus as the cause of a high mortality in different localities during an epidemic of influenza. We present evidence to show that the most important factors responsible for the mortality in the recent outbreak in Dundee were staphylococcal infection of the lungs and the presence of pre-existing disease.

**Analysis of Hospital Admissions**

The usual reason advanced by general practitioners for sending patients to hospital was influenzal pneumonia, but some elderly patients with uncomplicated influenza were sent to hospital because of difficulty of treatment at home. During the 6-weeks period commencing October 1, 541 patients (263 males and 278 females) were admitted to hospital. An analysis of the sex distribution of patients by age groups revealed no difference.

During the first week of the epidemic patients under 20 years of age predominated (59%). This contrasted with subsequent weeks when the number of patients over 50 increased, reaching a maximum of 55% in the fifth week (Table I). The hospital assessment of the incidence of influenzal pneumonia, based on clinical and radiological evidence, was 262 out of 541 patients (48%).

**Clinical Features**

(a) *Influenza Uncomplicated by Pneumonia* (279 cases).—The commonest symptoms complained of were cough (152), headache (139), nausea or vomiting (93), chest pain (88), generalized aches and pains, especially limb pains (55), and sore throat (59). Coryzal symptoms were present in 35 patients. Abdominal pain and diarrhoea occurred in a small number. There were 14 instances of severe epistaxis, and in some of these the epistaxis was the reason for admission to hospital. Haemoptysis (8), fainting attacks (10), and

signs of meningeal irritation without changes in cerebrospinal fluid (3) were also observed. Pyrexia was present in most cases, and the temperatures recorded in hospital ranged from 100 to 103° F. (37.8 to 39.4° C.). Usually the temperature returned to normal in a few days. In a number of patients an intermittent type of pyrexia was observed;

Dyspnoea occurred in 48 patients and abnormal chest signs were noted in 135 (48%). Since many of these patients in addition looked extremely toxic, it is easy to understand the difficulties of practitioners in deciding whether or not there was superadded pneumonia.

(b) *Influenza Complicated by Pneumonia* (262 cases).—The features already described in the uncomplicated cases were also prominent in the pneumonia group, but, as might be expected, there was an increased incidence of signs referable to the pneumonic process. Thus cough was present in 207, and 134 complained of chest pain. The chest pain was of two types—substernal, which was presumably the clinical reflection of the tracheitis so commonly seen at necropsy, and pleuritic pain occurring in relation to the pneumonia. Haemoptysis occurred in 19 patients. Pyrexia was more pronounced in the complicated cases, and, as might be expected, there was a greater incidence of shivering, sweating, and delirium. One patient had intractable hiccups which lasted about 14 days. Well-marked pneumonic signs were present in the majority of this group. Dyspnoea was observed in 156 and cyanosis in 77 patients. Typical heliotrope cyanosis was seen in three patients who died from fulminant pneumonia.

(c) *Factors Other than Influenza and Pneumonia*.—Influenzal pneumonia was particularly severe on patients with pre-existing disease, and 70 patients were so affected. In 28 there was known cardiac disease, including mitral lesions, cardiac failure, and congenital heart disease. Thirty-six patients were already respiratory cripples from chronic bronchitis, asthma, bronchiectasis, pulmonary tuberculosis, bronchial carcinoma, or cystic lung disease. A miscellaneous group included Parkinsonism, chronic muscular dystrophy, myeloid leukaemia, diabetes, marasmus, and mental defect. Four patients were admitted with status asthmaticus, but these responded rapidly to treatment with cortisone. Cerebral thrombosis was a complication in two patients, and one elderly man developed severe septic parotitis. Encephalitis was observed in one patient with otherwise uncomplicated influenza, and in one with influenzal pneumonia.

(d) *X-ray Findings*.—X-ray examination was not carried out on all patients, so that no detailed analysis relating the findings to the duration of illness and to the different age groups is considered worth while. Nevertheless some of the results in the clinical pneumonia group have been selected for presentation. In this group of 262, 20% were not x-rayed, 30% showed no abnormal radiological signs at the time of examination, 20% had radiological signs of bronchopneumonia, and 30% had radiological evidence of segmental or lobar pneumonia. Pulmonary abscesses were observed in five and pleural effusion in four patients.

*Treatment of Pneumonia*.—In view of the fact that influenzal pneumonia was likely to be associated with a variety of organisms, and more especially in view of the possible occurrence of penicillin-resistant staphylococci, we decided to use chlortetracycline. We have analysed the results of

TABLE I.—Total Admissions to Hospital for Influenza and its Complications Presented by Age Groups and by Weeks from October 1, 1957

Age in Years	Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		6-weeks Period	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-19 .. ..	52	59	51	39	44	34	29	31	11	18	13	32	200	37
20-49 .. ..	25	28	34	26	34	26	19	21	16	27	7	17	135	25
50+ .. ..	11	13	45	35	52	40	44	48	33	55	21	51	206	38
All ages ..	88	100	130	100	130	100	92	100	60	100	41	100	541	100

this experience but wish to stress that this was not a controlled clinical trial and that apparent discrepancies in the figures are due to small numbers in which for clinical reasons the standard treatment was not followed. The standard dosage schedule of chlortetracycline for an adult was 1 g. a day for five days, occasionally extended for a further two days, and 231 out of 262 patients (88%) were treated in this way. In a further 27 patients the treatment started by the general practitioner was continued, and in four seriously ill patients erythromycin was given. A second course of antibiotic treatment had to be given to 33 patients who failed to respond satisfactorily to treatment with chlortetracycline. Of these, 29 were given erythromycin and 4 novobiocin.

**Side-effects Associated with Chlortetracycline Treatment.**—Side-effects were observed in 44 patients out of 319 who were treated with chlortetracycline. No deaths could be attributed to side-effects. They did not appear until the fourth day from the start of treatment, and most occurred between the fourth and seventh days; the remainder were longer in appearing. The commonest side-effect was diarrhoea (36 patients). Rectal swabs were taken from 19 of these, and in 12 *Staphylococcus aureus* was isolated which was sensitive to chloramphenicol and erythromycin only. Eight patients developed stomatitis, and staphylococcal scarlet fever occurred in a boy aged 6 years. A staphylococcus with the same antibiotic sensitivity pattern was isolated from the throat of this boy. Brodie *et al.* (1955) described staphylococcal scarlet fever in 7 out of 48 children showing side-effects following treatment with tetracycline for Sonne dysentery. It is noteworthy that in the present series, in which there is a higher age incidence than in the dysentery series, there is only one case of scarlatinal rash in the 44 patients showing side-effects. Possibly this low incidence is due to the fact that owing to previous streptococcal infection the older patients had immunity against erythrogenic toxin.

### Bacteriological Investigations

The bacteriological investigations included the examination of sputa or pharyngeal swabs of all patients in one ward of the hospital on admission, after 96 hours' and after one week's stay in hospital. Pharyngeal swabs were taken if sputa could not be obtained. The lungs of a number of fatal cases were also examined.

TABLE II.—Frequency of Isolations of Various Organisms from Sputum or Pharyngeal Swabs from Patients on Admission and During Stay in Hospital

Isolations from Sputum or Pharyngeal Swabs	On Admission		After 96 Hours		After 1 Week	
	No.	%	No.	%	No.	%
Staphylococci ..	2	2.5	16*	32	8*	36
Pneumococci ..	10	13	0	0	1	5
<i>H. influenzae</i> ..	6	8	2	4	0	0
<i>Str. haemolyticus</i> ..	1	1.5	0	0	0	0
Normal flora ..	51	65	24	50	13	59
No growth ..	8†	10	7‡	14	0	0
Total ..	78	100	49	100	22	100

\* With one exception these strains were "hospital" strains and resistant to penicillin, chlortetracycline, streptomycin, and oxytetracycline, but sensitive to chloramphenicol and erythromycin.

† Including 2 pharyngeal swabs.

‡ All sputa.

Table II shows the frequency of the isolation of various organisms on admission and after 96 hours' and one week's stay in hospital. The term "normal flora" signifies the cultivation of those organisms which are normally present in the mouth and throat and in normal proportions. Attention is specially drawn to the following points in Table II: (a) the high frequency of isolation of normal flora on admission 51/78 (65%) and after 96 hours' and one week's stay in hospital—namely, 24/49 (50%) and 13/22 (59%) respectively; (b) the frequency of isolation of almost pure growths of *pneumococcus* and *Haemophilus influenzae* on admission—namely, 10/78 (13%) and 6/78 (8%) respectively—and the

fall in the isolation rate of these organisms during treatment; (c) the rise in the isolation rate of coagulase-positive staphylococci from 2/78 (2.5%) on admission to 16/49 (32%) after 96 hours' stay in hospital; and (d) the fact that the type of staphylococcus isolated from patients in hospital was sensitive only to chloramphenicol and erythromycin.

**Virus Isolation.**—An attempt was made to isolate virus from pharyngeal washings of 10 patients not more than three days after the onset of symptoms. Included were three patients in the ward survey, two of whom died four days after the onset of symptoms. The pharyngeal washings were inoculated by the allantoic route, and 8 out of 10 fluids haemagglutinated 1% guinea-pig cells at a dilution of at least 1/512. An additional isolation was obtained from pharyngeal washings inoculated into roller tube cultures of 13-day chick lung tissue and then injecting the nutrient fluid by the allantoic route. Complement-fixation reactions showed that the allantoic fluids contained influenza A antigen. Three of the strains were submitted to the World Influenza Centre of the W.H.O. and confirmed as being influenza A of the Asian type. No attempt was made to isolate virus from the lungs of fatal cases.

### Serology

At the start of the investigation a sample of serum for complement-fixation tests against influenza A was obtained from 32 patients in the ward; thereafter serum was obtained from each new patient on admission to this ward. The sera obtained on admission were considered as of the first rather than of the acute phase, since 53 out of the 93 patients admitted had been ill for more than five days. A second specimen was obtained between 15 and 40 days after the onset of symptoms. Pairs of first and second specimens were obtained from 77 out of 125 (61%) patients.

The complement-fixation reactions were carried out in "perspex" plates by the small-volume technique, using 0.1 ml. of influenza A antigen, patient's serum, complement 2 M.H.D., and 0.2 ml. of sensitized 1% sheep-cell suspension.

Demonstrable complement-fixing antibodies (>1/8) against influenza A were found in 67 out of 93 patients at the time of admission. The examination of paired sera from 77 patients gave the following results: (a) a fourfold rise in complement-fixing antibodies in 63 patients; (b) a first reading positive at a serum dilution of 1/128 followed by less than a fourfold rise in seven cases; (c) no antibodies demonstrated in either of the paired specimens in two patients; and (d) a titre of 1/8–1/32 in a first specimen taken 6 to 11 days after onset and no significant rise in a second specimen taken more than 30 days after onset in five patients.

Either a fourfold rise in complement-fixing antibodies or a significant initial titre was demonstrated in 70 out of 77 (91%) patients. It is also of interest that 10 patients had serum complement-fixing antibodies at a dilution of 1/8 or 1/16 on the third or fourth day from onset of symptoms. From other observations not detailed here it was noted that, of 40 hospital personnel (medical and nursing staff) who did not develop clinical influenza, only 18 failed to show complement-fixing antibodies at a serum dilution of 1/8. Thus such low levels of complement-fixing antibodies that may be detected in patients less than five days after onset may indicate previous exposure to the virus. In this epidemic a fourfold rise during the course of the disease and subsequent convalescence was taken to be of greater significance in the serological diagnosis of influenza than an initial low level of complement-fixing antibody.

### Analysis of Deaths

Table III presents the analysis of influenza deaths which occurred in hospital. It will be seen that the overall death rate was 6%; that in the pneumonia group it was 11%; that in the uncomplicated influenza group it was less than

TABLE III.—Analysis of Influenzal Deaths in Hospital by Various Categories

Total Deaths	Number of Deaths					Distribution of Deaths in Days After Admission to Hospital										
	Pneumonia	Uncomplicated Influenza	Age Groups in Years			Group with Pre-existing Disease	1	2	3	4	5	6	7	8	9	>9
			< 20	20-49	50 and Over											
33/541 (6.1%)	30/262 (11.4%)	3/279 (1%)	1/200 (0.5%)	3/135 (2.2%)	29/206 (14%)	17/33 (51%)	8	3	2	5	2	1	1	4	2	5

The numerators signify the number of deaths and the denominators the number of patients in the group.

1% ; that the group aged 50 and over had the highest death rate, 14% ; and that half of those who died had pre-existing chronic disease. The pre-existing diseases included pulmonary tuberculosis, mitral stenosis, bronchiectasis, chronic bronchitis with emphysema, and chronic lymphatic leukaemia ; and included in a small group from other hospitals in the region was a case of Huntington's chorea and renal amyloidosis. Although there was little difference in age between the previously healthy group and the group with pre-existing disease, the duration of the influenza illness was much longer in the latter. It is of some interest that three cases of influenzal bronchopneumonia were found at necropsy, where no clinical evidence of influenza or pneumonia had been recognized during life.

Eight of the deaths occurred within 24 hours of admission and 18 within 96 hours. Several patients in this group were elderly people who lived alone, and who were found more or less moribund by neighbours. The commonest organism isolated from the lungs was the "hospital" staphylococcus (Table IV). In all these cases large numbers

TABLE IV.—Organisms Isolated from Lungs of Fatal Cases

Organisms, total 11:	
Staphylococcus .. ..	8 (1 penicillin resistant—sensitive to others ; 7 resistant to penicillin, chlortetracycline, streptomycin, and oxytetracycline)
Pneumococcus .. ..	1 (pneumococcus isolated from right lung and staphylococcus from left lung)
Proteus .. ..	2
No isolation .. ..	2

of staphylococci were seen in impression smears of the lungs. One case seems worthy of special mention, in that a pneumococcus was isolated from a consolidated lobe of one lung and a "hospital" staphylococcus from a bronchopneumonic area in the other lung.

#### Pathological Observations (24 Necropsies)

The main feature of interest in the naked-eye examination of the lungs was the intense dark-purple haemorrhagic oedema, in some cases focal, in others involving the whole lung so that on many occasions the weight of a lung was over 1 kg. In cases with a focal distribution of haemorrhagic oedema lower lobes were more often involved than upper, and posterior parts more than anterior. The amount of haemorrhage and oedema varied, so that some areas had the appearance and feel of red hepatization, and others were solid with oedema from which a moderately blood-stained fluid exuded when the lung was sectioned. In the haemorrhagic and oedematous areas, focal bronchopneumonia and compensatory emphysema were present. In two cases there was also mediastinal emphysema, while 17 showed bronchopneumonic consolidation and eight had small abscesses scattered throughout the lungs. In general, the larynx was not involved, but oedematous obstruction was found in two cases.

The parenchymatous changes in the lungs were not related to the length of the illness, but changes in certain other organs did appear to be so. Patients with a short history (less than 10 days) showed a false membrane lining the tracheo-bronchial tract, easily identified by naked eye down to the third-order bronchi. Fatty liver and septic spleen were also noted. A feature of nine cases was extreme pallor of the kidneys. In three of these cases, microscopical evidence of bilateral necrosis of proximal tubules was later

found, although the renal changes in the remaining six cases consisted of cloudy swelling and post-mortem autolysis only. In one case encephalitis was the cause of death. Patients with a longer history (more than 10 days) showed congestion and thinning of the tracheo-bronchial mucosa and a congested liver, but no other constant changes were found.

Another feature of special interest was the frequency with which petechiae were observed. In 10 cases they were present in the fundus of the stomach, sometimes associated with coffee-ground material. In two of these cases acute gastric erosions, and, in a third, mucosal haemorrhages 1 cm. in diameter, were present. Occasional petechiae were also found in the subpleura, pericardium, and brain.

The microscopical appearances in the lungs were of the following common pattern. There was invariably great congestion of the lung capillaries, associated with purulent bronchopneumonia surrounded by oedematous lung tissue with little fibrin, varying degrees of red-cell extravasation and macrophage infiltration. In all cases a pyogenic reaction was present varying from early bronchopneumonia to abscess formation.

The changes in the trachea and bronchi were similar to those described by Hers (1955)—namely, erosion of the mucous membrane, hyaline thickening of the basement membrane, and oedema of the submucosa associated with varying degrees of secondary pyogenic infection.

#### Note on the Occurrence of Influenza in Two Student Halls of Residence

One hall had 165 male students and the other 75 female students. When the academic year began, 19% of the males and 8% of the females had had an attack of influenza. There appeared to be no geographical distribution to account for this difference. Over a period of 42 days the incidence was as follows:

October 8 to 21 .. ..	13% males ..	24% females
October 22 to November 4 ..	6% ..	13% ..
November 5 to 18 .. ..	3% ..	24% ..

It will be seen that the outbreak amongst the males died out gradually, whereas there was a rise during the last fortnight among the females. The incidence among the females declined in step with that in the male hall of residence until early in November, when a "residence party" was held. At least four of the young women who attended were probably infectious, and in view of the crowded conditions it is not surprising that a sharp rise in the incidence of influenza occurred thereafter.

The substantially higher incidence of influenza in the case of the female students, 60%, compared with the male students, 22%, appears to be due to two main factors: (1) the lower proportion of female students who had already had influenza before the beginning of term, and (2) the sharp rise in incidence following the residence party.

*Second Attacks of Influenza.*—The six students who came into this category were seen by one of us (J. J. A. R.). In assessing what constituted a second attack, all instances of single relapses within a period of a month were rejected, as were those in which one or other of the attacks had not been typical. Of the six students concerned, five had their first attack in England and one in Scotland. Influenza had been epidemic at the time in the areas concerned, and their medical practitioners had been quite definite about the diagnosis. Four of them were male students and two female.

The mean period from the beginning of the first to the onset of the second attack was seven weeks, in the range of five to nine weeks.

### Discussion

Although in this epidemic the pathological findings in fatal cases were similar to those of previous pandemics and epidemics, there were only three cases of fulminant influenza pneumonia with heliotrope cyanosis and peripheral vascular collapse. We feel this should be stressed, as it is an incidence of less than 1% of the hospital admissions. It is clear, however, that two factors were of considerable importance in precipitating a fatal issue—namely, the age of the patient and the presence of pre-existing disease. Only four patients dying from pneumonia were below the age of 50 years, a fatality rate of less than 3%: this figure contrasts markedly with a rate of 22% in the group aged 50 and over. In more than half of the deaths there was evidence of pre-existing disease, usually of cardiac or respiratory nature, suggesting that such individuals contract influenza pneumonia more readily and succumb to a prolonged illness of only moderate severity. Giles and Shuttleworth (1957) also found that 35 of their 46 fatal cases had pre-existing disease.

It is generally accepted that influenza pneumonia is the commonest cause of death during epidemics of influenza. The evidence from post-mortem examination of the lungs suggests the view that influenza pneumonia is the result of combined virus-bacterial infection (Stuart-Harris, 1953). Since it is generally accepted that virus vaccines are of limited value in the prevention of influenza, treatment of the secondary infection becomes of the greatest importance.

In considering the treatment of bacterial infection it is essential to appreciate that the bacterial component varies not only from epidemic to epidemic but also from place to place during the same epidemic. This we would call the *variability principle* in the local epidemiology of influenza pneumonia. We feel that at present there is a danger of overemphasis of the international aspects of influenza brought about by the informative studies on virus spread and virus variability by the World Influenza Centre, with consequent neglect of local factors which may be responsible for the observed variation in mortality rates in different places during the same epidemic. Patrick (1919), working in Malta during the pandemic, drew attention to the importance of *Staphylococcus aureus* in influenza pneumonia, while in other places the importance of *Haemophilus influenzae* was stressed.

Stuart-Harris (1953) has incriminated *Staph. aureus*, and in the present epidemic this organism was found in the lungs of 69 of 103 virologically confirmed fatal cases of Asiatic influenza in Holland (Hers *et al.*, 1957) and in 31 of 36 fatal cases in England (Jevons *et al.*, 1957).

In our experience the staphylococcus was associated with the most severe cases of pneumonia, but was not the most common cause of pneumonia. There was a much higher incidence of segmental and lobar pneumonia than we had anticipated, and it was therefore not surprising to find that pneumococci were the most common pathogens isolated on admission. Our investigation showed that within 96 hours of admission to hospital a considerable number of patients had acquired staphylococci, often of the highly resistant type now associated with hospitals. It should be pointed out that, of 30 patients dying from pneumonia, 8 died within 24 hours of admission, 11 within 48 hours, and 18 within 96 hours. All these patients were gravely ill on admission and the part played by acquisition of "hospital" staphylococci is difficult to assess.

It seems worthy of note that the supporters of the view that *Staph. aureus* is important have been reporting the experience gained in hospital practice. We have been impressed by the isolation of pure growth of *H. influenzae* and pneumococci from the sputum of some patients in the initial stages of the disease and their replacement by *Staph. aureus* after a short period in hospital (Table II). This seems to

indicate that the bacterial component of influenza pneumonia varies in the home and in the hospital. Further, it illustrates that staphylococcal influenza pneumonia may be another facet of the vexed problem of staphylococcal disease in hospital.

Ideally, any attempt to prevent the spread of influenza pneumonia in the community should, in our opinion, be conducted on a rational basis, of which the early recognition of the responsible bacterial component and its antibiotic sensitivity pattern are essential parts. This early recognition allows the choice of a suitable antibiotic. In fulminating influenza pneumonia resulting from the combined action of virus and staphylococcus, it would seem reasonable to use an antibiotic such as erythromycin or novobiocin if, as is the position in Dundee, most strains of staphylococci are still sensitive to these antibiotics. Further, since in these cases there are indications that the toxin of the staphylococcus may be a factor, the use of staphylococcal antitoxin might be considered. It is also probably worth considering corticosteroids in combating peripheral vascular collapse.

We appreciate the difficulties in differentiating uncomplicated influenza and influenza pneumonia in the home, but we would suggest that patients over 50 and those with pre-existing cardiac or respiratory disease should be given a broad-spectrum antibiotic.

We draw attention to the fact that, while we used chlortetracycline in hospital for "routine" treatment, we found it necessary to give erythromycin on occasions when chlortetracycline failed to control the infection. It is not easy to suggest how the mortality could be reduced in the group of non-fulminating influenza pneumonias. When one considers such factors as the elderly patient, the occurrence of pre-existing cardiac and respiratory disease, and the patients who for one reason or another arrive at hospital in a moribund condition, there is left a comparatively small number of patients who have died for the sole reason that the pneumonia has resisted therapeutic measures. Chlortetracycline was used as the "routine" antibiotic in this epidemic in the knowledge that the organisms isolated from sputum obtained on admission were fully sensitive to this drug. Is the use of an antibiotic such as erythromycin justifiable for all cases when there is demonstrable sputum conversion to the carriage of "hospital" staphylococci? In this series, erythromycin was used only in emergency for dangerously ill patients, since it was thought unwise to use this antibiotic to the exclusion of all others, in view of the danger of the emergence of erythromycin-resistant strains.

There is little doubt that the staphylococcus was responsible for most of the side-effects noted under treatment with chlortetracycline, including the case of scarlet fever. Such side-effects could be lethal in a gravely ill patient, who might otherwise recover. This risk must be calculated when assessing the antibiotic to be used in hospital, but is probably no greater than that involved in deciding the line of treatment to be adopted in any serious illness.

### Summary

This is a report of the recent epidemic of influenza in Dundee by a combined study group consisting of epidemiologists, clinicians, bacteriologists, and pathologists. During the six-weeks period beginning on October 1, 541 patients were admitted to hospital. There were 33 deaths. An analysis showed that the majority of those who died were aged 50 and over, and many had pre-existing disease of cardiac or respiratory nature.

Influenza virus A of the Asian type was isolated from selected cases. The demonstration of either a fourfold rise in titre or a significant initial titre of complement-fixing antibodies to influenza A virus was obtained in 70 out of 77 (91%) patients examined.

Staphylococci were the most commonly isolated organisms from post-mortem material. In a proportion

of cases the staphylococci were of the resistant type generally associated with hospitals.

Second attacks of influenza within a period of seven weeks are reported. Attention is drawn to two cases of encephalitis which are possibly influenzal in origin.

Measures for the treatment of influenzal pneumonia are discussed. A plea is made for further studies on the local epidemiology of influenzal pneumonia, especially from the point of view of the bacterial component.

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## ENCEPHALITIS AND INFLUENZA

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Sporadic cases of encephalitis of uncertain aetiology, although rare, may occur at any season of the year. There is a suggestion that encephalitis is recognized more often during an epidemic of influenza (Leigh, 1946; Jennings, 1952; Dubowitz, 1958), and this raises the possible relationship between these two conditions. Stuart-Harris (1939) showed that strains of influenza virus could be rendered neurotropic in the laboratory, but was sceptical about influenza as a cause of encephalitis in natural circumstances (Stuart-Harris, 1953).

During the recent epidemic of influenza in Dundee all patients requiring hospital treatment were admitted to one centre, King's Cross Hospital, and 468 patients were investigated during the months of October and November, 1957. In the same period the total of patients with signs and symptoms of encephalitis was four, but only two of these cases were recognized clinically to be associated with influenza. In the other two

the predominant features were referable to the central nervous system; one was admitted to the meningitis unit of King's Cross Hospital and the other to a general medical ward in Maryfield Hospital. Three of the patients recovered completely, but one died with purulent bronchopneumonia and encephalitis.

An attempt was made to assess the incidence of influenza in Dundee during the epidemic period. Ten general practitioners representing various districts within the city kindly supplied information from their records on the total number of influenzal patients examined, and, further, estimated the probable total number of persons with influenza occurring in their practices. The figures based on records were much lower than had been the impression of the incidence during the outbreak. Despite the obvious difficulties of such an inquiry, the results were remarkably constant and revealed that the incidence of patients examined was approximately 15%, while the estimated probable total was 20% of the patients in each practice. Based on the population of Dundee, this gives a total of 27,000 patients clinically diagnosed as cases of influenza and an estimated overall figure of 36,000. The incidence of encephalitis would therefore appear to be of the order of 1 in 120 for hospital admissions and 1 in nearly 10,000 of all patients with influenza during an epidemic period.

### Case 1

A boy aged 14 became ill on October 17, 1957. He had previously been healthy, his only illnesses being measles, whooping-cough, and chicken-pox. For three days before sickening he had been "off colour," and on October 17 he was febrile and was vomiting. These signs persisted, and the general condition deteriorated. On October 20 he became unconscious and was admitted to King's Cross Hospital with a provisional diagnosis of meningitis.

He was found to be acutely ill and in coma, lying on his back with arms spastic and flexed at the elbows, and legs extended and also in spasm. The degree of spasm was greater on the left than on the right side of the body. Deep reflexes were uniformly exaggerated, plantar responses were extensor, and abdominal reflexes were absent. Pupils were equal and dilated, and the response to light was sluggish. He had left external strabismus and right internal strabismus. Papilloedema was present, more marked on the left side. The cerebrospinal fluid was under increased tension; there were 46 red blood cells per c.mm. but no increase in white cells; biochemical examination showed nothing abnormal.

Examination of systems other than the central nervous system showed them to be normal. In particular, no abnormal signs were detected in the lungs, apart from a harsh broncho-vesicular murmur at the apex of the right lung. On admission his temperature was 104° F. (40° C.), pulse rate 114, and respiratory rate 30. The leucocyte count was 19,000 per c.mm., with polymorphonuclear preponderance (87%). A provisional diagnosis of cerebral abscess was made, and treatment with combined streptomycin and penicillin was begun.

The following day (October 21) he was more deeply unconscious. Respirations were rapid and irregular and his colour poor. The eyes were deviated downwards with vertical nystagmus. His temperature rose to 105.6° F. (40.9° C.) and he died during the afternoon.

### Post-mortem Findings

The most striking changes were found in the brain and respiratory system. The brain (weight 1,500 g.) was swollen and showed marked flattening of the convolutions. There was intense hyperaemia of the meninges, and on section the