THE RELATIONSHIP BETWEEN INFLUENZA AND PNEUMONIA

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(With 3 Figures in the Text)

Several observers have drawn attention recently to a possible connexion between influenza and pneumonia (Commission on Acute Respiratory Diseases, 1945; Finland, Ory, Meads & Barnes, 1948; Maxwell, Ward & van Metre, 1949). It has of course long been known that a general relationship exists between influenza and pneumonia in that an increase in incidence of pneumonia occurs during outbreaks of influenza, but the exact role of the virus infection in such cases is obscure. In recent outbreaks of influenza, moreover, the incidence of complications has been low, and outbreaks such as that recorded by Jackson (1946) in which 10% of cases of influenza developed pneumonia have been exceptional. Direct search for influenza virus in the lung lesions and sputa in cases of pneumonia encountered during the outbreak of influenza in 1937 indicated that virus was not easily demonstrated in cases with actual consolidation of the lungs, but antibodies to the virus were often present in the blood in high titre at the time of admission of the patient to hospital. The view was taken that many cases of 'influenzal pneumonia' were in fact post-influenzal in time, and that the role of the virus was essentially preparatory to the bacterial attack (Stuart-Harris, Andrewes & Smith, 1938). In contrast, the ease of recovery of virus from the lungs of rapidly fatal cases of pneumonia associated with *Staphylococcus aureus* infection indicated that a more direct relationship of virus and bacterial infection did occasionally exist. In the winter of 1946–7 a number of cases of pneumonia were studied clinically and bacteriologically in Sheffield both before and during a mild outbreak of influenza A (Stuart-Harris, 1947). About half of the twenty-three cases of pneumonia admitted to hospital and studied during the period of the outbreak exhibited high antibody titres to the virus on admission; the sputa from six cases were tested in eggs but virus was not recovered by this procedure. Because of the prevalence of subclinical infection during an outbreak of influenza, no specific relationship was deduced between the recent virus infection probably responsible for these high antibody titres and the occurrence of bacterial pneumonia. The latter was associated with a pneumococcus in most cases, and no example of acute staphylococcal pneumonia was seen.

The present investigation was planned to extend the study to cases of pneumonia, and the family contacts of such cases both before and during a period when influenza was prevalent in the community. The investigation extended from October 1947 to April 1949.

METHODS

Clinical material

Cases of pneumonia were selected for study who exhibited clinical evidence of consolidation and in whom the disease was thought not to have been in existence for more than a week. Clinical examination included in most cases an X-ray of the chest, a blood count and blood culture. During the period of known prevalence of influenza, the range of patients studied was widened to include acute illnesses of the lower respiratory tract other than those with signs of consolidation and also cases of congestive heart failure. Autopsy material from cases of acute pneumonia and certain other acute illnesses was obtained during the period of the influenza outbreak.

Patients from an explosive outbreak of influenza in February 1949 at a military camp at Catterick were studied by the same methods as those employed in the cases of pneumonia. Other sporadic influenza-like illnesses amongst nurses in Sheffield and Leicester and amongst a few patients under the care of general practitioners both before and during the outbreak of influenza were also studied. The findings in these patients were of importance in establishing the frequency of virus isolation and the pattern of serological response in uncomplicated cases of influenza.

https://doi.org/10.1017/S0022172400014789 Published online by Cambridge University Press

Family contacts of a few selected cases of pneumonia were also studied. Only families of a reasonably large size were in general chosen, and families from whom the patient was admitted more than a week after the onset of illness were excluded.

Techniques

Sputum mixed with saline garglings and broth was obtained within a few hours of admission of the patient to hospital and was stored frozen at − 70° C. until tested for the presence of virus by egg inoculation. Penicillin (500 units/ml.) and streptomycin (1000 units/ml.) were added to the sputum before storage. Thirteen-day old fertile hen's eggs were inoculated amniotically and incubated at 37° C. for 4 days. Amniotic and allantoic fluids obtained after chilling the eggs were titrated with 1% guinea-pig and fowl red cell suspensions. Passage to further eggs was carried out in many cases but not beyond the second generation of eggs unless the agglutination tests in the second generation were positive. Viruses established in eggs were studied further by ferret inoculation in certain instances. Human lung material obtained at autopsy was emulsified in 50% broth saline, cultured on blood agar, frozen and stored. Tests for the presence of virus were carried out as in the case of sputum. Sputum was cultured and an emulsion was inoculated intraperitoneally into mice. Mouse peritoneal fluid was examined for pneumococci, and these, if present, were typed when possible by the aid of antipneumococcal diagnostic sera kindly given by Dr E. Mørch of the State Serum Institute, Copenhagen. Pharyngeal swabs from the family contacts and throat swabs from infants or children with pneumonia were incubated in Avery tubes containing rabbit blood glucose broth for 4 hr. Mice were then inoculated with the resulting culture, and attempts were made to type the pneumococci obtained in the peritoneal fluid.

Two specimens of serum were obtained from each patient excepting those who died; the first specimen was collected within 24 hr. of admission to hospital, and the second 10–14 days later. Sera were examined by the agglutination-inhibition test (Salk, 1944) utilizing the pattern technique and four final minimal agglutinating doses of virus antigen in the presence of a final concentration of 0·125% fowl red cells. The virus antigens used in the agglutination-inhibition tests were eluates from pooled allantoic fluids concentrated on red cells and comprised the PR 8 and Lee viruses. The batches of antigen used in 1947–8 and 1948–9 were different, but the same batch was employed during any one season. Batches of antigen prepared from the NED/1/1949 strain isolated in January 1949 in Holland (Mulder, van der Veen, Brans & Enserink, 1949) were used in tests on sera collected after January 1949. Complement-fixation (C.F.) tests were performed in the manner of the macro-method of Hoyle (1948), except that a simple unconcentrated allantoic fluid antigen of the PR 8 influenza virus was employed. All dilutions were made in barbituric acid buffered saline containing calcium and magnesium as recommended by Mayer, Osler, Bier & Heidelberger (1946). This was prepared as a stock solution and diluted freshly on the day of test (Fulton & Dumbell, 1949). 2½ M.H.D. of complement (Lyovac) were used. Immune ferret sera homologous to the particular virus were always included in the agglutination tests, and in the case of complement-fixation tests, two convalescent human sera were employed as standards.

Epidemiology

Following the mild outbreak in January 1947, the prevalence of influenza, as judged by the notification of deaths from influenza in the great towns, remained at a very low level from October 1947 until January 1949. From the middle of January until April 1949 outbreaks of influenza occurred in Great Britain, and the peak in deaths from influenza was reached in the week ending 19 March 1949. Pneumonia notifications in Sheffield (Fig. 1) showed a contrast between the two winter seasons 1947–8 and 1948–9, indicating an excess of pneumonia in the early months of 1949 compared with that experienced in the same period of 1948. Subdivision of the notifications of pneumonia into age groups (Fig. 2) showed that the general excess of numbers in March and April of 1949 was largely due to an increase in pneumonia at ages of 45 and over. In the case of children under 5 the experience in the two years varied. More cases occurred in the months of February and March 1949 than in the same months of 1948, but the converse held for the months of December and January. Thus, in December 1947 and January 1948, there were more cases of pneumonia in children under 5 and particularly in babies less than 1 year of age, than in the corresponding periods of December 1948 and January 1949.

The recorded deaths from pneumonia in Sheffield during the same period of time are shown in Fig. 3. It will be seen that a large increase in deaths occurred in those over 65 during the months of March and April 1949. Calculation of deaths in relation to number of notified cases showed, however, that the number of deaths was not disproportionate to the incidence of pneumonia. The ratio of deaths to notifications of pneumonia was actually higher both at ages 45–65 and in those 65 and over in the non-epidemic months of January to March 1948 than during February to April 1949. Deaths from pneumonia in babies did not increase during the prevalence of influenza in March and April 1949; they were in fact more numerous in December 1947 and

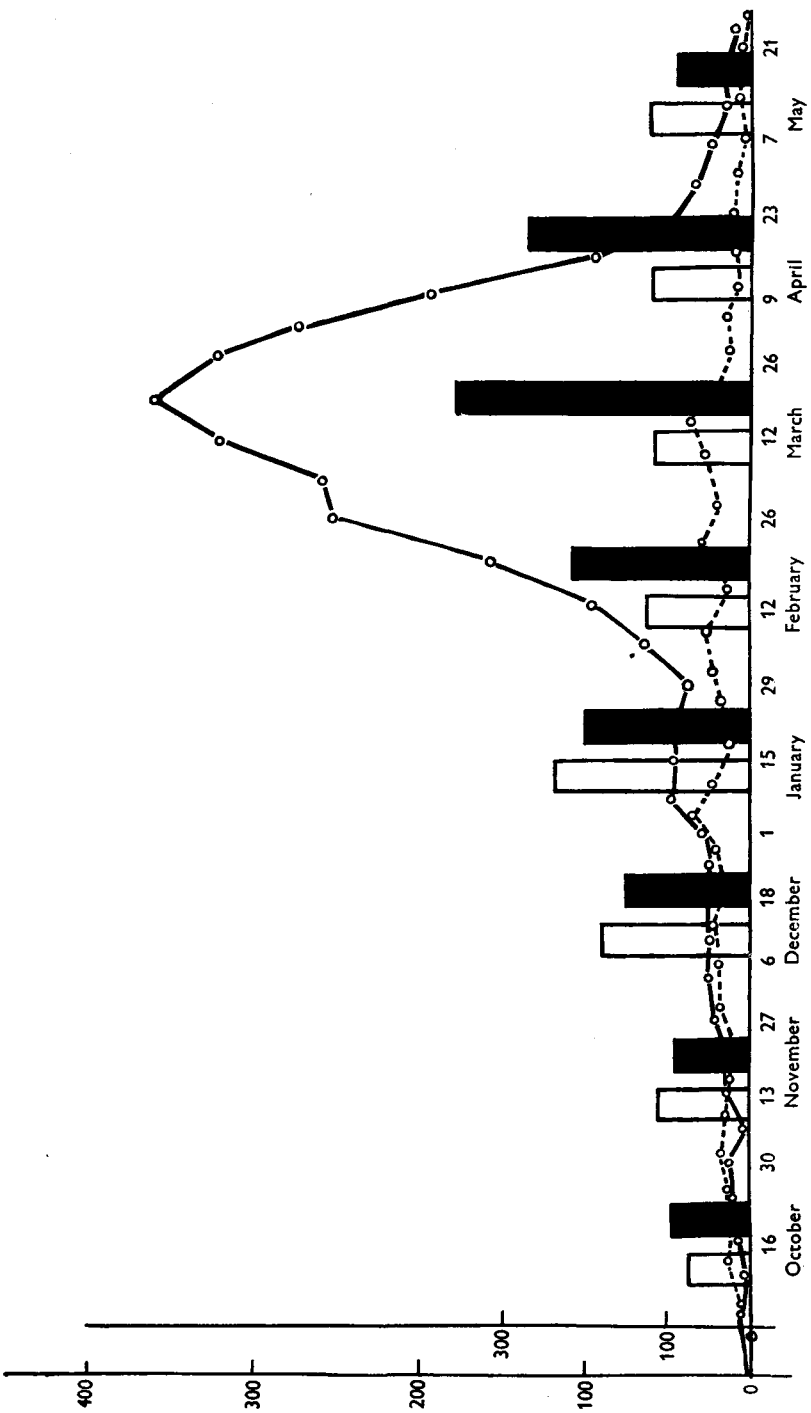

Fig. 1. Influenza deaths (England and Wales), pneumonia notifications (Sheffield), 1947–9. Pneumonia notifications, Sheffield: □, 1947–8; ■, 1948–9. Influenza deaths, great towns: o – – – o, 1947–8; o——o, 1948–9.

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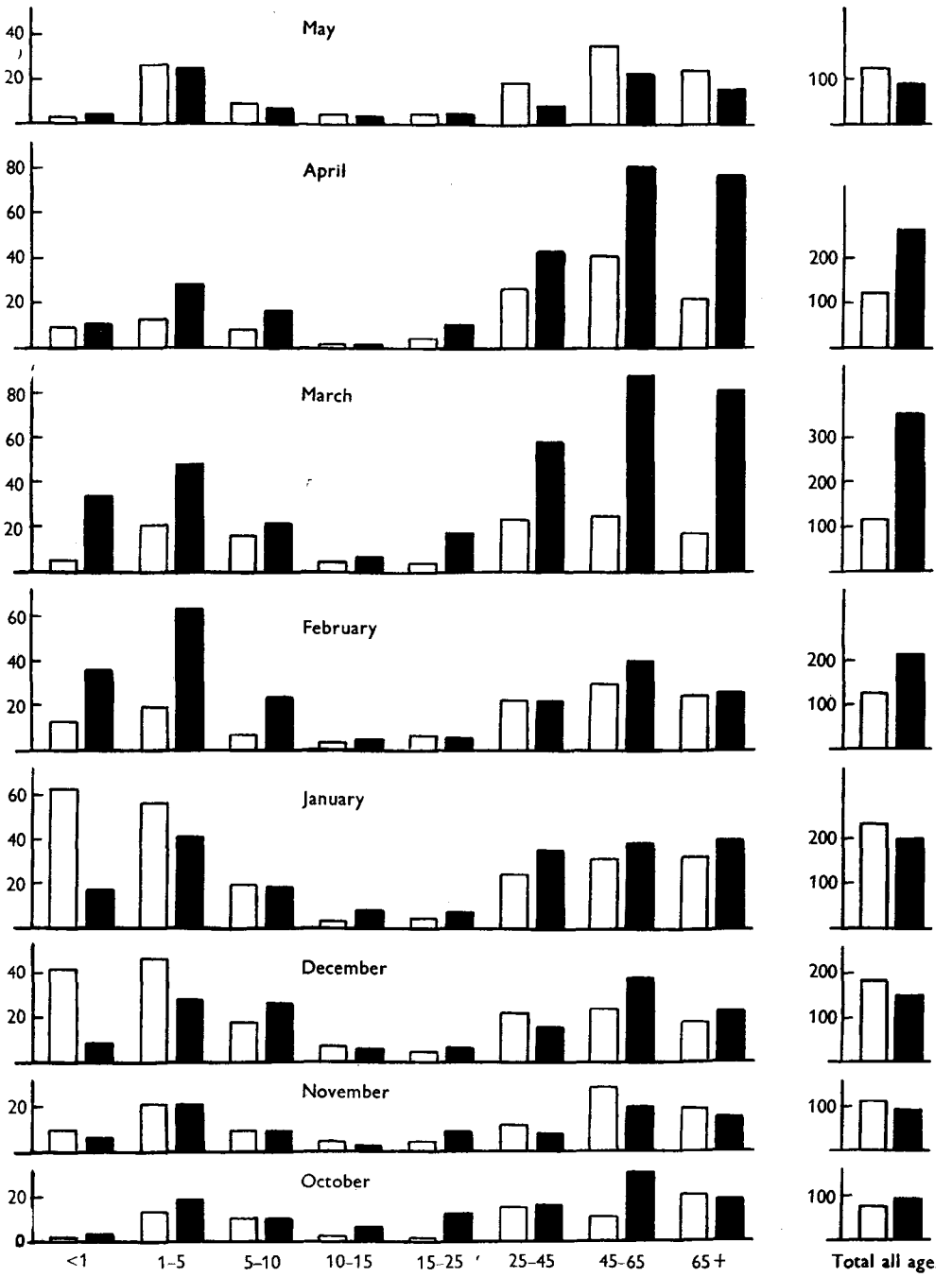

Fig. 2. Pneumonia notifications, Sheffield, 1947–9. □, 1947–8; ■, 1948–9.

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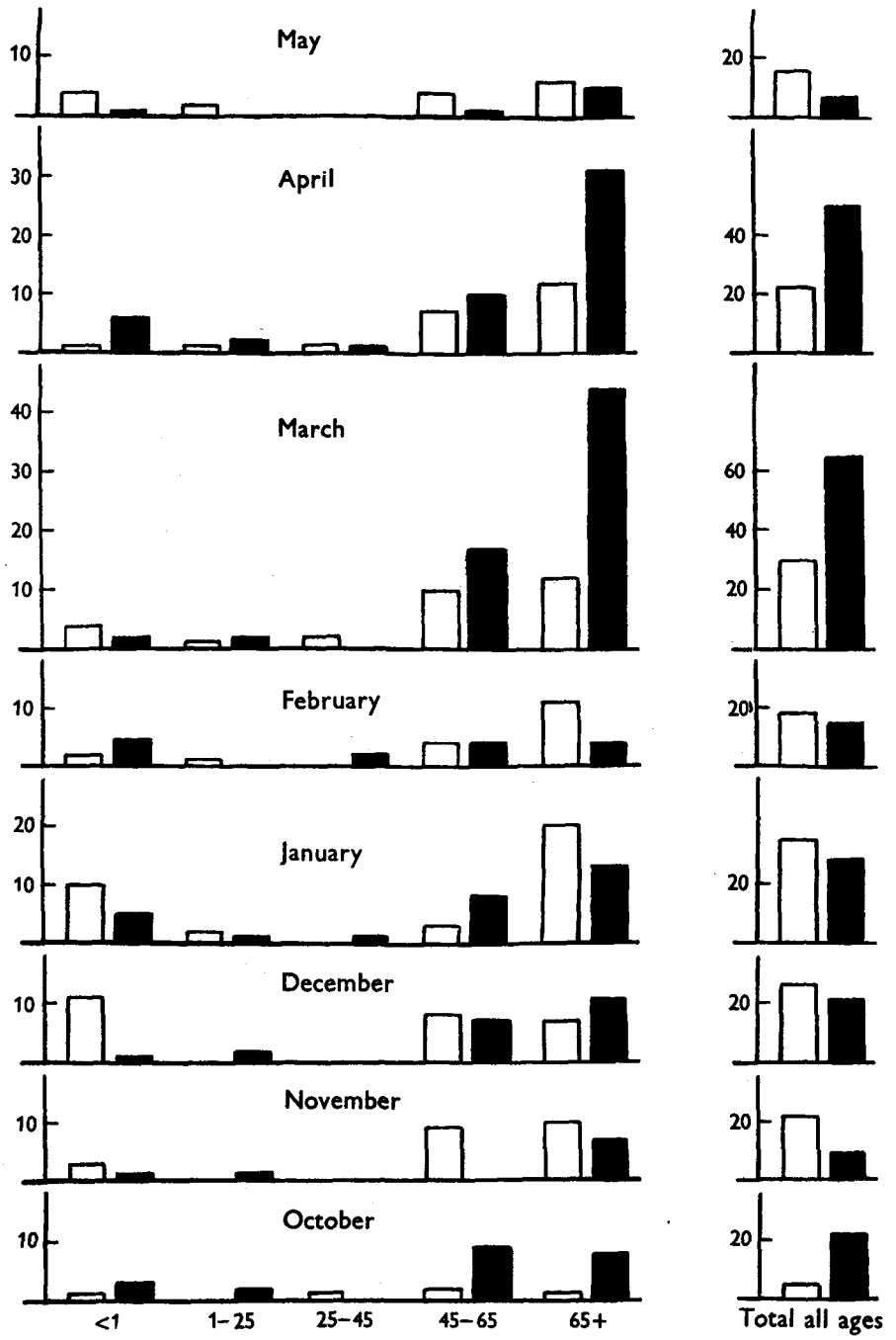

Fig. 3. Deaths from pneumonia, Sheffield, 1947–9. □, 1947–8; ■, 1948–9.

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January 1948 than in the corresponding months of the succeeding year.

Thus, the age incidence of pneumonia before the influenza epidemic was altered by a sharp increase in those over 45 during the outbreak. In February 1949, before any general rise in adult pneumonia had occurred, there was an increase in cases of pneumonia in children aged 1–5, but in view of the occurrence of an excess of pneumonia in babies and infants in the previous winter when influenza was not prevalent, no deduction is possible concerning this rise.

Clinical and bacteriological results

For comparison, the patients investigated between October 1947 and December 1948 have been separated from those studied between January and April 1949. The first period was inter-epidemic in regard to influenza prevalence in Great Britain, and during this time ninety-five patients, including sixty-five between October 1947 and May 1948 and thirty between October and December 1948, were studied (Table 1). Ten of the cases were examples of sporadic lobar or segmental consolidation, though the distinction from broncho-pneumonia was not a sharp one. No particular attempt was made during this period to select cases of pneumonia likely to prove fatal. Also included in the series were five cases of acute bronchitis and two of bronchiectasis; there were no examples of congestive heart failure. The age and sex distribution of these patients with lower respiratory tract disease is shown in Table 2. Sixteen of the patients were female and sixty-nine were male.

Table 1. *Clinical material studied between October* 1947 *and April* 1949

Clinical category	October 1947–December 1948 (inter-epidemic)	January–April 1949 (epidemic)
Pneumonia (fatal)	4	17
Pneumonia (non-fatal)	74	53
Bronchitis	5	16
Bronchiectasis	2	2
Congestive heart failure	0	7
Total	85	95
Upper respiratory tract (clinical influenza)	10	57
Total patients studied	95	152
Family contacts (pneumonia)	63	24
Grand total	158	176

From 1 January 1949 onwards the patients investigated clinically and bacteriologically were grouped in an 'epidemic' series because influenza virus infection had become widespread in Europe and virus had been recovered from cases of influenza in London. In fact, influenza did not become prevalent in the north of England until the middle of February, and the peak in incidence in Sheffield occurred in March. During the epidemic period 152 patients were studied (Table 1), of whom fifty-seven were cases of clinical influenza, seventy of pneumonia, sixteen of bronchitis, two of bronchiectasis and seven of congestive heart failure. The age and sex distribution of the cases, excluding those with clinical influenza, is shown in Table 2. The chief difference from the inter-epidemic series was that in the latter males predominated, but there were nearly equal numbers of males and females during the epidemic period. The next point of contrast lay in the fact that in 1949 seventeen of the cases of pneumonia terminated fatally, although in comparing these figures with 1947–8, it should be remembered that severely ill patients with pneumonia attracted more attention during the epidemic period. However, the increased number of deaths from pneumonia in Sheffield in March 1949 was an obvious reason for the greater number of fatal cases in hospital at that time. Among the seventy cases of pneumonia during the epidemic period forty-one were classified as being lobar in distribution, but the distinction from broncho-pneumonia was not sharp. However, there appeared to be a greater

Table 2. *Age and sex distribution (pneumonia, bronchitis and heart failure)*

	Age groups										Sex		
	<1	1–5	6–10	11–20	21–30	31–40	41–50	51–60	61–70	71 and over	M.	F.	Total
Inter-epidemic	1	4	4	5	10	7	12	24	16	2	69	16	85
Epidemic	1	0	0	3	11	18	9	25	21	7	46	49	95

upper respiratory tract infection and eighty-five were examples of various types of lower respiratory tract disease. There were seventy-eight examples of pneumonia, four of which terminated fatally; sixty-seven cases of pneumonia were judged to exhibit number of cases of broncho-pneumonia during January to April 1949 than previously. More cases of bronchitis and of congestive heart failure were included for study during the latter period, but this was in part due to a desire to spread the investigation

fairly widely during actual prevalence of influenza. The fifty-seven cases of clinical influenza and upper respiratory tract infection were gathered partly from sporadic cases in Sheffield and environs, and partly from an explosive outbreak of influenza at Catterick and a localized outbreak among nurses at Leicester. The latter outbreaks occurred in February and March 1949.

In addition to patients with clinical illness, a study was made of family contacts of cases of pneumonia so that sixty-three contacts of twenty-two cases of pneumonia were investigated serologically and by throat swab during the inter-epidemic period, compared with twenty-four contacts of seven cases of pneumonia during the 'epidemic' period. Pressure of work made it impossible to study more families during the latter period.

THE RESULTS OF TESTS FOR INFLUENZA VIRUS INFECTION

(*a*) '*Inter-epidemic*' *period*

Ninety-two patients were tested serologically or by attempts to recover virus during this period (Table 3).

Table 3. *Tests for influenza virus infection (inter-epidemic period)*

	Oct. 1947–May 1948		Oct.–Dec. 1948		Whole period		
Clinical category	Negative	Positive	Negative	Positive	Negative	Positive	Total
Pneumonia (fatal)	—	—	1	0	1	0	1
Pneumonia (non-fatal)	52	1	21	0	73	1	74
Bronchitis	3	0	2	0	5	0	5
Bronchiectasis	—	—	2	0	2	0	2
Total	55	1	26	0	81	1	82
Upper respiratory	7	0	3	0	10	0	10
Family contacts (pneumonia)	40	1	22	0	62	1	63

Three cases of fatal pneumonia were not tested for virus infection because death precluded collection of a convalescent sample of serum. Cultural tests in eggs were made in only five cases, all of pneumonia; they were negative. All the ninety-two patients were studied serologically. The Salk tests made in the ten cases of upper respiratory infection did not show any rise in antibody titre either to influenza virus A or B. One only of the cases of lower respiratory tract infection showed an antibody rise to an influenza virus. The patient, a boy of 5 years, with lobar pneumonia in November 1947 had no history of influenza. Both Salk and complement-fixation tests showed a fourfold rise in antibody titre to influenza virus A. A type VIII pneumococcus was obtained from the throat swab, but because two carriers of type I pneumococci were found among the family contacts, none of whom yielded type VIII pneumococci, a search for pneumococcal agglutinins was made. Agglutinins to type I pneumococci increased from a titre of 1 : 4 in the serum taken during the acute phase to 1 : 32 in the convalescent sample. No agglutinins to type VIII pneumococci were demonstrated. The case was therefore considered to be probably one of type I pneumococcal infection. Six of the twelve family contacts were tested serologically for influenza, but none showed a rise in titre of antibodies.

Only one of the family contacts of cases of pneumonia gave evidence of influenza virus infection. The contact was the mother of an infant of 2 years with pneumonia in November 1947. The mother showed no illness but her serum developed an eightfold increase in titre of antibodies to influenza virus A by Salk test and a fourfold rise by C.F. test. The patient with pneumonia was not studied serologically, but throat swab culture yielded type I and type VI pneumococci.

Thus during the entire 'inter-epidemic' period two instances, one in a case of pneumonia and the other in a contact of a case of pneumonia, showed evidence of sporadic influenza virus A infection.

(*b*) *Epidemic period*

Tables 4–7 indicate the results obtained during January to April 1949. The findings were regarded as indicative of influenza virus infection on one of two grounds. First, if a virus with the characteristics of influenza virus was recovered from garglings, sputum or lung emulsion, then the case was regarded as 'positive'. Table 4 shows that of a total of sixty-eight specimens examined by egg cultivation, those from eight fatal cases of pneumonia, ten non-fatal cases of pneumonia or bronchitis, one from fatal heart-failure and five cases of upper respiratory disease yielded positive results. It was important to know whether such cases gave serological evidence also of virus infection. Serological tests could not be made on any of the fatal cases because no

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Table 4. *Epidemic period. Results of direct test for virus in eggs. January–April* 1949

	January		February		March		April		Total period		
Clinical category	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Total
Pneumonia (fatal)	1	0	1	1	4	6	3	1	9	8	17
Pneumonia (non-fatal), bronchitis and heart failure	5	0	8	3	9	8	1	0	23	11	34
Upper respiratory disease	4	0	4	3	4	2	—	—	12	5	17

Table 5. *Epidemic period. Tests for influenza virus infection (serological and cultural)*

	January		February		March		April		Total period		
Clinical category	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Total
Pneumonia (fatal)	1	0	1	1	4	6	3	1	9	8	17
Pneumonia (non-fatal)	13	1	12	3	12	6	5	1	42	11	53
Bronchitis	1	0	5	1	2	7	—	—	8	8	16
Bronchiectasis	—	—	1	0	0	1	—	—	1	1	2
Congestive heart failure	1	0	—	—	2	4	—	—	3	4	7
Total	16	1	19	5	20	24	8	2	63	32	95
Upper respiratory	16	0	3	12	9	14	2	1	30	27	57
Family contacts	2	0	20	0	1	1	—	—	23	1	24

convalescent sample could be obtained, nor were samples of serum available from five other cases, four of which were negative and one positive by egg cultivation. But in the fourteen cases from which viruses were recovered in eggs and in which serological tests were also available all but one (no. 168, Table 6) gave positive results either in the Salk or complement-fixation tests or by both methods. The results of these tests strengthened the conclusion that isolation of virus from human specimens indicated influenza virus infection.

Secondly, a case was regarded as 'positive' if the serological tests fulfilled certain criteria irrespective of the results of the egg cultivation. The serological tests which were made on the cases of clinical influenza revealed, however, the complexity of the antibody response evoked by the particular strain of virus causative of the epidemic. Table 6 shows the results obtained in ten soldiers from Catterick and four nurses from Leicester. It will be seen that in some cases a good rise of antibodies occurred to the PR 8 virus as demonstrated by one or other of the Salk or C.F. tests but not necessarily by both. Salk tests with the NED/1/49 strain of virus A usually confirmed one or other of the tests with PR 8 antigen. Therefore more than one test was employed in the examination of all the sera collected between January and April 1949. Cases showing no change in antibody titre between acute and convalescent samples and those in whom a twofold rise of antibodies in the convalescent serum was found in only one test, were regarded as 'negative'. No case was labelled 'positive' on serological grounds unless a combination of at least two tests agreed in result and each showed a rise of at least fourfold in degree in titre, or else that one test had shown a rise of at least eightfold in degree. Five cases of pneumonia and one case of influenza which gave equivocal results by these criteria were excluded from the series altogether and are not included in the tables. There remained for consideration fifty-seven cases of clinical influenza, fifty-five of which were tested serologically and two other cases submitted only to direct test for virus in garglings; the results were also unequivocal in seventy-three cases of pneumonia, bronchitis and congestive heart failure tested serologically or by direct cultivation in addition to five cases tested by cultural methods only (Table 5). Among the cases regarded as positive by serological methods, there were five patients, two with an upper respiratory infection and three with pneumonia or bronchitis in whom the egg tests with garglings or sputum were negative. Table 5 shows the combined results of the cultural and serological tests in the entire group of cases during the epidemic period.

(i) *Cases of pneumonia, bronchitis and congestive heart failure*

Thirty-two cases were judged positive for influenza virus A infection among the ninety-five cases. Table 5 shows that the largest number of positive results was obtained in March. A greater proportion of negative results were obtained amongst the non-

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Table 6. *Laboratory tests in fourteen cases of clinical influenza*

Case no.	Location	Garglings in eggs	Serum tests influenza A			Serum tests influenza B
			PR8 (Salk)	PR8 (C.F.)	NED/1/49 (Salk)	Lee (Salk)
117	Catterick	*Positive*	160/160	*2/8*	20/40	< 20/ < 20
118	Catterick	N.T.	*40/160*	2/6	*< 20/80*	40/40
119	Catterick	N.T.	*< 20/320*	*2/32*	*< 20/320*	< 20/ < 20
120	Catterick	Negative	80/80	12/8	40/40	< 20/ < 20
121	Catterick	N.T.	*160/1280*	*16/256*	*< 20/320*	< 20/ < 40
122	Catterick	N.T.	*20/80*	*< 2/32*	160/320	40/40
126	Catterick	N.T.	*40/320*	*6/64*	*40/160*	< 20/ < 40
128	Catterick	*Positive*	< 20/20	*< 2/32*	*40/1280*	40/80
167	Catterick	Negative	320/320	64/48	80/160	20/20
168	Catterick	*Positive*	80/80	2/2	20/20	80/160
193	Leicester	N.T.	80/160	*8/32*	*< 20/40*	< 20/ < 20
204	Leicester	N.T.	< 20/ < 20	*< 2/16*	< 20/ < 20	< 20/ < 20
222	Leicester	N.T.	< 20/ < 20	*< 2/16*	< 20/ < 20	< 20/ < 20
241	Leicester	N.T.	40/40	8/8	40/40	*< 20/320*

N.T. Not tested.

Cases 120 and 167 were considered negative; all the others were positive.

Case 241 was the only case of influenza B encountered.

Numbers are ratios of reciprocals of dilutions of acute and convalescent samples of sera at the end-point of the reactions. End-point in Salk test was complete inhibition of agglutination; that in the C.F. test was 50 % haemolysis. Italicized data considered as significant of an increase in antibody titre.

fatal cases in whom pneumonia was present clinically and radiologically than amongst either the cases of bronchitis or the cases of pneumonia terminating fatally. The latter furnished a particular group of severely ill patients with signs of extensive pneumonia at the time of admission and were clinically recognizable as a distinct group. They are further discussed in relation to the problem of death from influenza by Stuart-Harris, Franks & Tyrrell (1950). In the fatal cases, the pneumonia was lobar in two, broncho-pneumonic in seven and unspecified in eight. Post-mortem examination confirmed the clinical findings in those thirteen cases in which it was made. An influenza virus strain was recovered from the lungs of four at autopsy and from the sputum of four other cases before death. Because of the absence of serological data and to guard against laboratory contamination, a second independent test of stored material from each case was again made some months after the first. Virus was again recovered in each case by egg inoculation, or in two instances by inoculating hamsters intranasally and subinoculating hamster lung emulsions into eggs. The eight virus strains from the fatal cases are being studied in detail, but so far five have proved to be serologically closely related to the viruses recovered from cases of influenza and to belong to the influenza A '*prime*' group (personal communication from Dr C. M. Chu, World Influenza Centre). It will be recalled that this antigenic group of influenza A was also responsible for the 1947 epidemic of influenza in Great Britain (Stuart-Harris & Miller, 1947; Dudgeon, Mellanby, Glover & Andrewes, 1948) and in the U.S.A. (Francis, Salk & Quilligan, 1947; Sigel, Shaffer, Kirber, Light & Henle, 1948). The NED/1/49 virus is a member of the same group (Mulder *et al.* 1949).

Table 7 shows the clinical diagnosis, result of virus tests and bacteriological findings in all virus-positive cases excepting those in the category of fatal pneumonia. The results of the cultural tests supported a belief that the virus infection responsible for the serological changes was in existence at the time of admission of the patient to hospital, for the specimen of sputum or garglings was collected within a few hours of this event. Hospital cross-infection was not therefore likely to have been concerned in the results. The serological findings agreed closely with the results obtained in cases of clinical influenza (Table 6). The cases clinically comprised a heterogenous group, but it will be observed that the pneumonia was considered to be lobar in six instances, in five of which it was associated with pneumococci in the sputum. The three instances of clinical pneumonia were cases considered to have the signs of consolidation but in whom the X-ray findings were not confirmatory. Some of the cases of bronchitis represented severe illnesses, probably with bronchiolar involvement, others were more trivial, or accompanied chronic disease such as fibroid tuberculosis or a mitral stenosis. The cases of congestive heart failure were secondary to mitral stenosis or to hypertension, but in two instances the patients had also suffered recent febrile illnesses. In

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Table 7. *Serological and cultural findings in twenty-three virus-positive cases of pneumonia and other conditions*

No.	Age	Month	Clinical diagnosis	Bacteria sputum	Egg culture	Influenza A virus serological tests (PR8) Salk	(PR8) C.F.	(NED/1/49) Salk	Influenza B (Lee) Salk
32	56	Jan.	Lobar pneumonia	Pn. VI	N.T.	*< 20/80*	*< 2/2*	160/160	< 20/< 20
81	70	Feb.	Lobar pneumonia	Pn. U.T.	*Positive*	—	—	—	—
107	15	Feb.	Lobar pneumonia	Pn. I St.A	Negative	160/320	*2/> 16*	*160/1280*	40/40
178	60	Mar.	Broncho-pneumonia	N.T.	N.T.	160/160	*16/48*	*< 20/160*	40/40
201	28	Mar.	Lobar pneumonia	No. pn.	N.T.	*80/1280*	*16/256*	*80/1280*	20/< 20
206	43	Mar.	Lobar pneumonia	Pn. III St.A	N.T.	*40/640*	*8/96*	*40/640*	< 20/< 20
208	22	Mar.	Broncho-pneumonia	Pn. XIX St.A H.Str.	*Positive*	*20/160*	*4/64*	*40/160*	40/20
230	30	Mar.	Lobar pneumonia	Pn. II	N.T.	*20/160*	64/64	*40/160*	40/40
115	45	Feb.	Clinical pn.	Pn. XVIII	*Positive*	*< 20/40*	*4/64*	*40/160*	< 20/< 20
197	31	Mar.	Clinical pn.	No. pn.	N.T.	*< 20/160*	*< 2/48*	*< 20/160*	< 20/< 20
260	52	Apr.	Clinical pn.	N.T.	N.T.	*20/80*	*4/> 64*	*80/640*	< 20/< 20
106	50	Feb.	Bronchitis	Pn. III St.A	*Positive*	*40/320*	*< 2/128*	*20/640*	20/< 20
136	68	Mar.	Bronchitis	Pn. XIII	*Positive*	< 20/< 20	*2/16*	*< 40/1280*	< 20/< 20
170	34	Mar.	Bronchitis	No pn.	Negative	*80/1280*	*16/256*	*< 20/320*	< 20/< 20
152	40	Mar.	Bronchitis	No pn.	*Positive*	*30/640*	*2/64*	*40/320*	< 20/< 20
176	54	Mar.	Bronchitis	Pn. XIX	Negative	*80/320*	*8/64*	*< 20/320*	< 20/< 20
177	25	Mar.	Bronchitis	Pn. XIX	N.T.	160/160	*< 2/32*	*< 20/80*	< 20/< 20
228	56	Mar.	Bronchitis	Pn. XIX	*Positive*	*< 20/640*	*6/128*	*< 20/160*	40/40
233	46	Mar.	Bronchitis	N.T.	*Positive*	*< 20/160*	*12/64*	*20/160*	< 20/20
173	32	Mar.	Bronchiectasis	H.Inf.	*Positive*	*40/160*	*8/96*	*20/2560*	80/80
169	54	Mar.	Congestive heart failure	Pn. IV	N.T.	*20/80*	*< 2/4*	40/40	< 20/< 20
182	76	Mar.	Congestive heart failure	No pn.	*Positive*	*< 20/40*	*< 2/> 64*	*80/1280*	80/80
186	6	Mar.	Congestive heart failure	Pn. VIII	N.T.	< 20/< 20	*< 6/32*	*40/320*	< 20/< 20
159	66	Mar.	Congestive heart failure	Coliform	*Positive*	with lung emulsion.			—

N.T. Not tested.

Numbers are ratio of reciprocals of dilutions at end-point in acute and convalescent serum samples. Data italicized considered as significant of an increase in antibody titre.

Pn. Pneumococcus.

St.A. Staphylococcus (coagulase-positive).

H.Str. Haemolytic streptococcus.

H.Inf. *Haemophilus influenzae*.

U.T. Untypable.

one fatal case of heart failure (no. 159) a virus was recovered from the lung at autopsy; serological tests were not made on this patient.

Finally, apart from the cases of fatal pneumonia and the few instances of severe acute bronchitis, there were no sharp clinical differences between these 'virus-positive' cases, and the 'virus-negative' cases in the epidemic or inter-epidemic series. A further study of the clinical data is being made by one of us (D.T.). Eleven of the virus-negative cases of pneumonia and bronchitis admitted to hospital in March and April exhibited the feature of high antibody titre to influenza A in the 'acute' sample of serum. Such should probably have been classified as 'post-influenzal' pneumonia as indicated in the introduction.

https://doi.org/10.1017/S0022172400014789 Published online by Cambridge University Press

(ii) *Cases of clinical influenza*

Table 5 indicates the findings in regard to the cases of clinical influenza or upper respiratory infection studied between January and April 1949. Sixteen cases of sporadic infection were tested in January with entirely negative results. In four cases, three of which were also tested serologically, virus was not recovered from garglings. Positive results by both methods were obtained in February and March both from sporadic cases of clinical influenza in Sheffield and from outbreaks of influenza in Catterick and Leicester. The serological and cultural tests were positive in eleven of thirteen cases from Catterick. The Catterick outbreak was particularly severe, and several hundred cases of influenza were admitted to a Military Hospital in February and March. The majority of the cases were uncomplicated and clinically typical of influenza. A few developed lower respiratory tract complications, and it is of interest that the chest condition in case no. 126 (Table 6) was diagnosed radiologically as an atypical pneumonia. The outbreak in nurses at the Leicester Royal Infirmary was a small one and the majority of the cases were uncomplicated. Dr J. Walker kindly informed us that four cases had, however, developed the radiological appearances of atypical pneumonia. Three of these were tested serologically, one was positive for influenza A (no. 193, Table 6), the others were negative. Of fourteen pairs of sera from Leicester, ten were serologically positive, nine for influenza A and one (no. 241, Table 6) for influenza B. The latter was the only instance of influenza B encountered during the entire study. The remaining virus-positive and negative cases in February, March and April were sporadic cases of clinical influenza in Sheffield.

(iii) *Family contacts*

The one instance of influenza among the twenty-four contacts studied serologically was the wife of a patient with pneumonia (no. 201, Table 7). She did not experience any clinical illness but developed an eightfold rise in antibody titre to influenza A synchronously with the stay of her husband in hospital. The families studied in February were not contacts of cases of pneumonia with laboratory findings indicative of influenza. No other instance of influenzal infection was encountered in this small series which is admittedly an inadequate survey.

THE BACTERIOLOGICAL RESULTS IN THE CASES OF PNEUMONIA, BRONCHITIS, ETC.

The results of an examination of the sputum for pathogenic bacteria and also of pneumococcus typing are shown in Tables 8 and 9. Eighty-one of the inter-epidemic cases of pneumonia and bronchitis and eighty-three of the epidemic cases were thus examined. Pneumococci were prevalent in both series and showed no significant differences in type either between the two series or between the small number of virus-positive and the larger group of virus-negative cases. The haemolytic streptococcus was an unimportant organism numerically in both series of cases; it was present in the sputa of one inter-epidemic and two epidemic cases and was in each case accompanied by a pneumococcus. A difference, however, existed in regard to the staphylococci which were encountered in the two series of cases. Twenty of the epidemic series yielded coagulase-positive staphylococci compared with two of the inter-epidemic cases, though particular care was not taken to note presence of the staphylococcus in the earlier cases. Nevertheless, the significant fact in the epidemic series lay in the occurrence of eleven cases of staphylococcal infection in which the sputum in life contained enormous numbers of cocci and at autopsy a pure culture of the staphylococcus was obtained. Of the eleven cases, ten died and the clinical and autopsy findings were typical of influenzal staphylococcal pneumonia as described by Chickering & Park (1919), Stuart-Harris *et al.* (1938),

Table 8. *Bacteriological results on cases of pneumonia, etc.*

Category	Total cases	Pneumococci	Staphylococci*	Haemolytic streptococci	No pathogenic bacteria
'Inter-epidemic'	81	66	2	1	15
'Epidemic'	83	51	20	2	12

* Coagulase-positive.

Table 9. *Type distribution of strains of pneumococci*

Category	Total cases	Total strains	I	II	III	IV	V	VI	VII	VIII	IX	XI	XII	XIII	XIV	XV	XVIII	XIX	XXII–XXXIV
'Inter-epidemic'	66	67	12	12	8	2	0	4	8	3	1	3	1	1	1	1	—	1	6
'Epidemic'	51	55	7	7	11	3	2	3	2	4	1	—	—	1	1	—	2	5	5

https://doi.org/10.1017/S0022172400014789 Published online by Cambridge University Press

Finland, Peterson & Strauss (1942), Wollenman & Finland (1943), Straub & Mulder (1948) and Mulder & Verdonk (1949). A strain of influenza virus was recovered from the sputum in two instances and from the lung in four cases of this type. Proof of the existence of influenza-virus infection was not obtained in four fatal cases or in the one patient who recovered. In one instance a pneumococcus (type XIX) was also present in the sputum in life but was not demonstrated in the lung at autopsy. In nine other non-fatal cases of pneumonia or bronchitis in which staphylococci were present in the sputum, a pneumococcus was present as well in seven instances. The staphylococcus was not present in such massive concentration in the sputum in any of the nine cases.

Phage-typing of the staphylococci was carried out on thirteen strains of staphylococci sent to the Central Public Health Laboratory, Colindale, and Dr R. E. O. Williams reported that six of the strains belonged to the phage-type 52A. Five of these were from fatal cases of pneumonia. The remaining strains included several different phage types.

DISCUSSION

The results of this investigation are in general similar to those of the only other large-scale studies on pneumonia and influenza yet reported (Finland *et al.* 1948; Maxwell *et al.* 1949). Finland *et al.* (1948) studied sixty-nine cases of bacterial and other pneumonias in Boston during and shortly after an epidemic of influenza B in December 1945. They reported that about one-half of the cases that occurred during the period of the epidemic, irrespective of the clinical character or bacteriological findings, yielded serological evidence of infection with influenza B. Maxwell *et al.* (1949) studied thirty-six cases of pneumococcal pneumonia occurring during an epidemic of influenza A in Baltimore in March and April 1947 and obtained serological evidence of influenza virus infection or isolation of influenza virus in seventeen instances. In the present series eighteen of fifty-five cases of pneumonia during February, March and April 1949 gave evidence of influenza virus A infection either serologically or by isolation of viruses. The positive results were largely confined to the period of prevalence of influenza A as shown by the tests on cases of clinical influenza. In view of the character of the antibody response to the particular strain of virus responsible for this epidemic and the stringency of the criteria adopted before accepting a result as 'positive', the number of cases of pneumonia accepted as having evidence of influenza virus infection is probably a minimal one. The epidemiological data clearly indicate the scope of the outbreak in regard to numbers of reported cases of pneumonia, and considered together with the laboratory results suggest that influenza-virus infection was concerned in a large number of cases with lower respiratory tract involvement in Sheffield during the outbreak. The data in regard to congestive heart failure, though much smaller in number, indicate that during an epidemic influenza-virus infection is also concerned in the respiratory infection commonly encountered in cases of heart failure.

A point of contrast between the results of the present investigation and those of the Baltimore workers lay in the nature of the bacteria present in the sputum or lung. All of the virus-positive cases of pneumonia identified in Baltimore during the epidemic yielded pneumococci, whereas the staphylococcus was an important organism in our own cases and particularly in the fatal illnesses. Our findings agreed, however, with those of the Boston workers (Finland *et al.* 1948), who also found that the *Staphylococcus aureus* was an important organism during the outbreak of influenza B in 1945. Staphylococcal pneumonia during an influenza outbreak is thus frequently a synchronous virus and bacterial infection which may resist current methods of chemotherapy. The exact role of virus and staphylococcus in the causation of the lung lesions is still far from clear, though the work of Straub & Mulder (1948) and Mulder & Verdonk (1949) suggests that the virus is responsible for epithelial lesions in trachea and bronchi. It is possible that a synergism exists between the virus and the staphylococcus, and that production of spreading factor (hyaluronidase) by the latter enhances the virus infection as demonstrated in the case of vaccinia infection in experimental animals (Lack, 1948).

In regard to the interrelationship of the influenza virus infection with pneumococcal pneumonia it is still more difficult to visualize the precise march of events. As stated, the clinical disease is not strikingly different from pneumonia without influenza nor is the response to chemotherapy unusual. But a simultaneous virus and bacterial infection certainly seems to exist in some cases, whilst in others the bacterial infection develops during convalescence from the virus attack. It is particularly in the latter cases which are post-influenzal in time that the role of virus infection could be essentially preparatory to bacterial attack possibly by damaging the natural defence mechanism of the respiratory tract. Harford Leidler & Hara (1949) have furnished experimental evidence that pneumococcal infection in mice is 'potentiated' by simultaneous influenza virus infection because of the actual lung lesions produced by the virus. These workers found that the power of the normal lung to reduce its content of inhaled pneumococci was lost in the presence of simultaneous influenza-virus infection, and the lungs not only contained but actually supported the growth of pneumococci. The influence of the bacteria upon the spread of virus to uninfected cells is a converse pheno-

menon which may also be of importance as suggested in the case of the staphylococcus. According to these theories, the development of influenza in an individual who is a healthy carrier for a pneumococcus might occasionally result in conversion of the carrier state into one of pneumococcal pneumonia with accompanying virus lesions in the lower respiratory tract.

Without denying the possibility of this mechanism, the view which must also be considered is that during an outbreak of influenza, organisms present in the nasopharynx in a state of passive carriage may be transferred and 'passaged' from human to human together with the virus. If this be so, the carrier rates for pneumococci would increase during the outbreak and more cases of actual pneumococcal infection would arise. According to this view, the occurrence of virus in the throat or sputum and the development of antibodies during convalescence would be the result of the virus infection in the upper respiratory tract and might be independent of the process developing in the lung and due to the pneumococcus. The pneumococcal infection in the lung would be the same as in ordinary cases of pneumonia unaccompanied by influenza and would be checked by chemotherapy as effectively as in these. In addition, however, to the combined transfer of bacterium and virus during an epidemic, it is possible to conceive that, as a result of passage from host to host, certain strains of bacteria might develop powers of invasion common to what are sometimes termed 'epidemic strains'. If this happened, more cases of pneumonia associated with a particular strain of bacterium would occur than before the outbreak and would be, at any rate in the early phase of epidemicity, combined with simultaneous influenza-virus infection. No evidence for increased prevalence of particular strains of pneumococci in the cases of pneumonia during the outbreak was obtained in the present investigation, but in the experience recorded by Smillie, Warnock & White (1938), an influenza outbreak in 1937 was closely associated with an epidemic of type I pneumococcal pneumonia which continued after the influenza had ceased. In regard to the staphylococcal cases of pneumonia, some evidence suggesting an increased prevalence of lung infection by the staphylococcus during an influenza outbreak certainly exists. The results of phage-testing the staphylococci recovered from cases of pneumonia were also suggestive that a particular strain of staphylococcus had become prevalent in Sheffield and might therefore be considered as an epidemic strain. More evidence, however, is necessary before this possibility can be accepted.

The data obtained during the inter-epidemic period of influenza indicate that influenza virus is not normally associated with pneumococcal pneumonia unless an epidemic is present. Only one case of pneumococcal pneumonia with simultaneous influenza virus A infection was encountered by us. Maxwell *et al.* (1949) similarly studied thirty-three cases of bacterial pneumonia during an inter-epidemic period and isolated virus from one patient. They also recovered four strains of virus from the lungs of four fatal cases of pneumonia during an inter-epidemic period. It is difficult to believe that these strains of virus represented passive carriage of influenza virus, particularly because of the experience of other workers. In a recent study for instance, McKee & Hale (1949) tested the nose and throat washings from fifty volunteers for influenza virus by a special technique but obtained no virus. They also studied 100 tracheal specimens obtained at autopsy in Iowa in a similar way. Only one specimen, the trachea from a case of bronchiectasis, yielded a strain of influenza virus A. The findings of other workers (Commission on Acute Respiratory Diseases, 1948) indicate that sporadic influenza virus infection is uncommonly encountered when study is made of cases of upper respiratory tract infection. Taylor (1949) has recently reported a 2-year study of nasopharyngeal specimens from individuals who were normal or who had upper respiratory tract symptoms. 141 pools from 793 specimens were tested in eggs, but only four strains of influenza virus were recovered. All were from specimens collected in the few weeks immediately preceding or during an outbreak of influenza. The study of family contacts of cases of pneumonia reported in the present investigation was made because it was thought possible that influenza virus might be one of the respiratory viruses concerned in the infection which commonly precedes ordinary lobar pneumonia. That only one case of virus A infection was encountered in the inter-epidemic period is of little significance either in support or otherwise of this view because of the small numbers which were examined. Nevertheless, it is clear that sporadic virus A infection does occur during an inter-epidemic period and is detectable by present methods. There is, however, every reason for belief that such endemic infection is not necessarily concerned in the genesis of a new outbreak of influenza. In the 1949 epidemic strong epidemiological evidence existed of a spread of infection from Europe to this country (Andrewes, 1949), and the time lag between the appearance of influenza in the south of England and the outbreak in the north confirmed this. The close antigenic relationship between the strains of virus recovered on the Continent and in Britain (Chu, Dawson & Elford, 1949) agreed with this suggestion. The present study of pneumonia is thus of particular significance in indicating the phenomena experienced in a community during an epidemic which almost certainly travelled to the area from elsewhere.

SUMMARY

1. The results are reported of a study of cases of pneumonia, of upper respiratory infection and of family contacts of cases of pneumonia for evidence of influenza-virus infection between October 1947 and April 1949.

2. During an inter-epidemic period in relation to influenza, two sporadic cases of influenza-virus A infection were detected, one in a case of pneumococcal pneumonia and the other in a family contact of a case of pneumonia. These were the only instances of virus infection detected among 158 individuals including seventy-eight cases of pneumonia.

3. The epidemic of influenza from February to April 1949 was associated with an increase in number of notified cases of pneumonia, particularly in those over 45 years of age compared with the notifications in 1948. Deaths from pneumonia also increased, particularly in those of 65 years or over.

4. During the period of influenza prevalence, direct tests of specimens in eggs and serological tests gave positive evidence of influenza virus A infection in many instances. Twenty-six of forty-one cases of upper respiratory infection between February and April 1949 were positive for influenza A and one was a case of influenza B.

5. Eighteen of fifty-five cases of pneumococcal and staphylococcal pneumonia, eight of fifteen cases of bronchitis, one of two cases of bronchiectasis and four of six cases of congestive heart failure gave serological or cultural evidence of influenza virus A infection during the period of February to April 1949.

6. The mechanism of influenza-virus infection in relation to bacterial infection of the lower respiratory tract is discussed.

Many of the patients with pneumonia on whom the above investigations were made were under the care of Dr K. J. G. Milne and Dr E. G. G. Rhind of the City General Hospital, Sheffield, to whom we are deeply indebted for kind and willing co-operation. A few patients under the care of Dr C. Gray Imrie, Prof. E. J. Wayne, Prof. R. S. Illingworth and Dr A. W. D. Leishman at the United Sheffield Hospitals were also studied. Cases of influenza were studied by the courtesy and help of the Staff of the Military Hospital, Catterick, and particularly Major D. Dexter, R.A.M.C., and Lieutenant-Colonel R. S. Vine, R.A.M.C., of the Army Pathology Service. Dr Joan Walker and Dr P. W. W. Gifford provided specimens and clinical details from nurses at the Leicester Royal Infirmary and United Sheffield Hospitals respectively who were under their care. A number of general practitioners provided us with specimens. Autopsy specimens were obtained by the help and permission of Dr L. G. Cook, Dr L. C. D. Hermitte and Dr J. L. Edwards, Pathologists to the City General and United Sheffield Hospitals. To all these we wish to extend thanks. One of us (C.H.S.-H.) wishes to thank Dr E. Mørch, of the State Serum Institute, Copenhagen, for a gift of pneumococcus typing serum.

The expenses of this investigation were defrayed by an expenses grant from the Medical Research Council who also provided one of us (C.H.S.-H.) with a grant for scientific assistance.

The statistical data concerning pneumonia notifications in Sheffield are quoted by kind permission of Dr Llywelyn Roberts, Medical Officer of Health for Sheffield.

REFERENCES

ANDREWES, C. H. (1949). *Edin. Med. Journ.* **56**, 337.

CHICKERING, H. T. & PARK, J. H. (1919). *J. Amer. Med. Ass.* **72**, 617.

CHU, C. M., DAWSON, I. M. & ELFORD, W. J. (1949). *Lancet*, **1**, 602.

Commission on Acute Respiratory Diseases (1945). *Science*, **102**, 561.

Commission on Acute Respiratory Diseases (1948). *Amer. J. Hyg.* **47**, 290.

DUDGEON, J. A., MELLANBY, H., GLOVER, R. E. & ANDREWES, C. H. (1948). *Brit. J. Exp. Path.* **29**, 132.

FINLAND, M., ORY, E. M., MEADS, M. & BARNES, M. W. (1948). *J. Lab. Clin. Med.* **33**, 32.

FINLAND, M., PETERSON, O. L. & STRAUSS, E. (1942). *Arch. Int. Med.* **70**, 183.

FRANCIS, T., junr., SALK, J. E. & QUILLIGAN, J. J. (1947). *Amer. J. Publ. Hlth*, **37**, 1013.

FULTON, F. & DUMBELL, K. R. (1949). *J. Gen. Microbiol.* **3**, 97.

HARFORD, C. G., LEIDLER, V. & HARA, M. (1949). *J. Exp. Med.* **89**, 53.

HOYLE, L. (1948). *Monthly Bull. Minist. Hlth Publ. Hlth Lab. Serv.* no. 114.

JACKSON, W. P. U. (1946). *Lancet*, **2**, 631.

LACK, C. H. (1948). *Brit. J. Exp. Path.* **29**, 191.

MCKEE, A. P. & HALE, W. M. (1949). *J. Immunol.* **61**, 369.

MAXWELL, E. S., WARD, T. G. & VAN METRE, T. E. (1949). *J. Clin. Invest.* **28**, 307.

MAYER, M. M., OSLER, A. G., BIER, O. G. & HEIDELBERGER, M. (1946). *J. Exp. Med.* **84**, 535.

MULDER, J., VAN DER VEEN, J., BRANS, J. J. & ENSERINK, S. W. (1949). *Ant. van Leeuwenhoek*, **15**, 125.

MULDER, J. & VERDONK, G. J. (1949). *J. Path. Bact.* **61**, 55.

SALK, J. E. (1944). *J. Immunol.* **49**, 87.

SIGEL, M. M., SHAFFER, F. W., KIRBER, M. W., LIGHT, A. B. & HENLE, W. (1948). *J. Amer. Med. Ass.* **136**, 437.

SMILLIE, W. G., WARNOCK, G. H. & WHITE, H. J. (1938). *Amer. J. Publ. Hlth*, **28**, 293.
STRAUB, M. & MULDER, J. (1948). *J. Path. Bact.* **60**, 429.
STUART-HARRIS, C. H. (1947). *Brit. Med. J.* **2**, 994.
STUART-HARRIS, C. H., ANDREWES, C. H. & SMITH, W. (1938). *Spec. Rep. Ser. Med. Res. Coun., Lond.*, no. 228.
STUART-HARRIS, C. H., FRANKS, Z. & TYRRELL, D. (1950). In the Press.
STUART-HARRIS, C. H. & MILLER, M. H. (1947). *Brit. J. Exp. Path.* **28**, 394.
TAYLOR, R. M. (1949). *Amer. J. Publ. Hlth*, **39**, 171.
WOLLENMAN, O. J. & FINLAND, M. (1943). *Amer. J. Path.* **19**, 23.

(*MS. received for publication* 1. XI. 49.—Ed.)

CORRIGENDUM

'The Association of certain types (α and β) of *Bact. coli* with infantile gastro-enteritis'

By J. SMITH

p. 222, column 1, five lines from the bottom of the page, should read:

'that the α type should be given the antigenic formula 0 111 B4 and the β type 0 55 B5, since Dr Kauffmann is now satisfied that what was provisionally called 0 112 should now be termed 0 55.'