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DEATHS FROM INFLUENZA-A STATISTICAL AND LABORATORY **INVESTIGATION***

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[WITH PHOTOGRAVURE PLATE]

The reason for this investigation was the correlation, abundantly demonstrated in the past fifteen years, between the height of the recorded deaths from influenza in the great towns of England and Wales and the ability to incriminate by laboratory procedures one or other of the influenza viruses in cases of clinical influenza. When the deaths from influenza in the great towns have exceeded in the aggregate a weekly total of 100, positive evidence of virus infection has been obtained in the laboratory, whereas when the weekly total has not risen above 100 the laboratory search for influenza virus has usually been fruitless (Stuart-Harris, 1947).

It seemed possible that an analysis of the clinical findings in cases recorded by practitioners as deaths from influenza obtained from 29 notifications. During this period influenza deaths remained at a very low level and no outbreaks of influenza were encountered. This investigation furnished only a very small sample for comparison with the data obtained during the epidemic period of January to April, 1949, when 192 notifications were received and a total of 85 record sheets were completed; 46 of these were from Sheffield practitioners. The time of occurrence of these deaths from influenza is shown in the Chart in relation to the total weekly figures for England and Wales.

Because of the smallness of the control series no detailed comparison was possible between the practitioners' records in the two series. But the data recorded on the death certifi-

during an epidemic year might disclose points of contrast resimilarly with corded deaths in nonepidemic years. In planning the investigation care had to be taken not to influence the decision of the practitioner at the time of death by prior warning, and the records about to be described were obtained by writing to practitioners in urban areas of the Sheffield and East Midlands



cate enabled the age and sex and seasonal distribution and classification of 'the causes of death in the 29 inter-epidemic cases to be compared with the similar data in the 85 epidemic cases (Tables I and II). Each group was subdivided into four categories according immediate the to cause of death recorded on the death under I certificate (a): (1) cardiac, including the diagnoses

Chart showing the number of deaths from influenza in the East Midlands region in relation to the total weekly figures for England and Wales from January to April, 1949.

Region when a certification of a death from influenza had reached the medical officer of health concerned. A postcard was first sent to such practitioners asking if they were willing to supply further clinical details; to those replying in the affirmative a record sheet was sent which could be filled in simply by ringing code numbers. The completed sheets were then transcribed on to punch-cards, and these were analysed by the aid of a Powers machine in the usual wav.

The investigation began in September, 1947, and from then until December, 1948, a total of 11 record sheets were

of heart failure, myocarditis, and myocardial degeneration ; (2) influenza and influenzal pneumonia; (3) pneumoniaincluding lobar pneumonia, bronchopneumonia, and unspecified varieties; and (4) bronchitis.

It should be noted that the Registrar-General's weekly records of deaths from influenza in the great towns include all cases with mention of influenza anywhere on the death certificate except London. In that town and in all annual figures influenza deaths are considered to be only those in which influenza is reported as the primary cause of death and therefore entered under I (b) or I (c) on the death certificate (personal communication from Dr. W. P. D. Logan, of the General Register Office). As the weekly 4648

^{*}Based on a communication read to the Pathological Society of Great Britain and Ireland in July, 1949.

Age	JanApril, 1949 Epidemic					Sept., 1947-Dec., 1948 Inter- epidemic				
	Car- diac	Influ- enza	Pneu- monia	Bron- chitis	Total	Car- diac	Influ- enza	Pneu- monia	Bron- chitis	Tota
0-9 10-19 20-29 30-39 40-49 50-59 60-69 70-79 80-89 90+	1 4 2 10 12 5		 		3 2 2 9 3 22 30 12 2	 				2 5 4 8 8 2
All ages	34	26	15	10	85	12	3	10	4	29
Male Female	15 19	7 19	6 9	5 5	33 52	75	1 2	2 8	· 2 · 2	12 17

TABLE	I 4 ap	and Ser	Distribution
IABLE	I.—Ave	ana sex	Distribution

	Seasonal Distribution									
	Jan.	Feb.	Mar.	Apr.	May-Aug.	Sept.	Oct.	Nov.	Dec.	
1947 1948 1949	4 7	33		 27	1	1	1 2	4	2 4	Inter- epidemic Epidemic

TABLE II.—Primary and Secondary Causes

	Immediate Cause of Death I (a)								
	85	Epider	nic Cas	es	29 Iı	29 Inter-epidemic Cases			
	Car- diac	Car- Influ- Pneu- Bron- diac enza monia chitis				Influ- enza	Pneu- monia	Bron- chitis	
	34	26	15	10	12	3	10	4	
I (b) (c) Primary: Cardiac Influenza Pneumonia Bronchitis II Secondary or con- tributory:	8 27 4 7	$\frac{7}{1}$	15		$\frac{2}{9}$	$\frac{-}{1}$	10 -	$\frac{1}{3}$	
Cardiac Influenza Chronic bronchitis	3 6 1	$\frac{5}{1}$	$\frac{2}{1}$	2 1 1	3		$\frac{1}{2}$	$\left \begin{array}{c} \overline{1} \\ \overline{1} \end{array} \right $	

records have chiefly been used in connexion with our own laboratory data, no case was excluded from the present series because of remoteness of influenza as a cause of death.

Table I shows that in both series the majority of the deaths occurred in those aged 60 and over, but that there were no differences between the age distributions in the two series. In both series the sex distributions showed a larger number of females than males, but the excess of females was chiefly in those aged 60 and over, and was only slightly disproportionate in comparison with the sex distribution of the population at these ages. Table II gives a further subdivision of each series which indicates the frequency of the primary and secondary causes of death, again classified into the four main groups of cardiac, influenza, pneumonia, and bronchitis. The frequent occurrence of influenza and other respiratory conditions as primary causes of death where the immediate cause of death was classified under "cardiac" was noted in both series. However, this analysis of the data recorded on the death certificates failed to reveal any obvious differences between the inter-epidemic and the epidemic series of cases.

The circumstances recorded by the practitioners on the record sheets sent to them were examined in detail only in the 85 epidemic cases. It was first noted that the practitioners considered that a local outbreak of influenza existed in 69 instances (81%), and that equal numbers considered this outbreak to be mild and sharp respectively. Because the cases were mostly in old people, the size of the family was small and children resident in the house were few in number in the majority of cases. Indeed,

in 46 instances no children were resident in the house at all. Two types of illness had been considered as possible the one in which the illness was continued from onset to death, and the other in which a complication occurring after an interval had been the cause of death. In 73 cases (85%) the illness was recorded as being continuous from start to finish, and in 9 (10%) it was interrupted. The duration of illness was one to five days in 26 (30%), six to ten days in 35 (41%), and more than ten days in 22 (26%). The fact that only one-third of the illnesses lasted for one to five days was surprising, and indicated that the majority were less acute than had been expected.

Table III analyses the cases according to the character of the principal initial illness and the principal respiratory and cardiovascular complications. The same four major

 TABLE III.—Principal Initial Illness and Principal Complications of 85 Epidemic Cases

	Immediate Cause of Death						
/	Cardiac (34)	Influenza (26)	Pneumonia (15)	Bronchitis (10)	Total (85)		
Principal initial illness: (a) Influenza (b) Bronchitis	30 16	19 11	15 2	8 3	72 32		
Respiratory complications: (a) Bronchitis (b) Pneumonia—acute (c) Pneumonia—terminal (d) Pulmonary oedema Cardiovascular complica-	16 6 4 2	12 7 7 2	1 11 3 1	7 1 1 —	36 25 15 5		
tions: (a) Heart failure—acute	19	10	5	3	37		
 (b) Heart failure—long- standing (c) Arteriosclerosis 	12 9	6 6	3 2	2 1	23 18		

subdivisions were used in the sorting of the cards in an attempt to determine whether or not the entire group was reasonably homogeneous in regard to these characters or whether it included a series of cases with special charac-Influenza, either alone or with bronchitis, teristics. occurred in 72 cases as the initial illness, and bronchitis, either alone or with influenza, in 32. Of the respiratory complications, pneumonia was mentioned in 40 instances, being of a terminal character in 15. Of the cardiac complication's, heart failure, either acute or long-standing, was mentioned in 60 instances. Consideration of the complications in the various groups showed that 26 of the 34 cases in which death occurred immediately from a cardiac cause had bronchitis or pneumonia. Conversely, 16 of the 26 cases of influenza, 8 of the 15 cases of pneumonia, and 5 of the 10 cases of bronchitis had what was described as heart failure. It seemed largely to have been a matter of chance whether a practitioner considered death to have been due to the heart failure of myocardial disease resulting from influenza or pneumonia or, conversely, to influenza or pneumonia in a patient exhibiting signs of heart failure.

The remaining data, such as the state of the previous health and the character of previous chest or heart disease, indicated no sharp difference between the various groups, and suggested merely the existence of previous conditions, such as bronchitis, hypertension, or coronary disease, that might be inferred from the ages of the patients.

In regard to treatment, penicillin had been given in 19 instances and sulphonamides in 54.

Thus the picture which emerged from the analysis of the 85 epidemic cases suggested that the illnesses were not widely divergent in clinical type. Written notes supplied by practitioners in comments which could not be analysed statistically suggested that an elderly subject had developed a pyrexial illness accompanied by signs of bronchitis which

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FIG. 1.—Trachea from Case 4. Most of epithelium desquamated and replaced by exudate of leucocytes and fibrin.



FIG. 2.—Trachea from Case 2. More advanced change than Fig. 1. Epithe-lium replaced by a necrotic slough.



FIG. 4.-Lung from Case 2. Edge of area of haemorrhagic infarction with extensive oedema in rest of lung.



FIG. 5.—High-power view of lung of Case 2. Intense congestion and masses of cocci; little leucocytic reaction.



FIG. 1.—Radiograph of chest, December, 1947, showing rounded shadows on the left side.



FIG. 2.—Biopsy specimen showing the spindle-shaped cells in whorled arrangements. $(\times 260.)$



Fig. 3.—Bronchiole from Case 2. Necrosis of entire wall; dark areas of necrotic epithelium are massed cocci.

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FIG. 1.-Right sciatic nerve, showing lymphocytic infiltration with perivas-cular leucocytes and mononuclear cells.



FIG. 2.-Section of lumbar cord showing chromatolysis in anterior horn cells.

may or may not have improved after one or two days. Sudden increase in illness with severe dyspnoea and cyanosis, signs of consolidation, or diffuse rales then supervened, and death occurred relatively quickly in spite of chemotherapy. From the data it was not possible to obtain any picture of the condition of acute heart failure which was mentioned in 37 of the 85 cases, but it may be the state of low blood pressure with tachycardia and feeble heart sounds which is familiar in many grave infections. Though circulatory in origin, it may be due to a peripheral vascular rather than to a central cardiac failure.

Twenty-two Fatal Illnesses During the 1949 Influenza Epidemic

During the same period of the influenza epidemic in Sheffield there occurred an unexpected opportunity of investigating a number of illnesses which had a fatal outcome in hospital. There were 22 such cases, which occurred between January 28 and April 16, 1949. They formed part of a larger investigation of the relationship between influenza and pneumonia (Stuart-Harris et al., 1950). Seventeen of the cases were examples of acute pneumonia, three were of congestive cardiac failure, and there was one case each of diabetic coma and of cerebral haemorrhage. All but five of these cases were submitted to necropsy, and bacteriological examination of portions of lung were carried out ; the sputa from the five on whom post-mortem examinations were not made were examined bacteriologically. Virus tests consisted of amniotic inoculation of 13-day fertile hens' eggs with lung or sputum emulsion to which penicillin and streptomycin had been added in order to suppress bacterial growth.

The distribution of these cases by age and sex (Table IV) gives a somewhat similar pattern to the practitioner series of deaths from influenza, and there was again a pre-

Age		Pneumonia with a History of Influenza	Pneumonia	Congestive Heart Failure	Other Causes	Total
1 1–29 30–39 40–49 50–59 60–69 70–79	· · · · · · · · · · ·	1 1 1 4 	 1 1 3 3 1	 1		$\frac{1}{2}$ 3 4 10 2
All ages		8	9	3	2	22
Male Female	• • •	2 6	5 4	1 2	2	8 14

TABLE IV.—Twenty-two Fatal Illnesses

dominance of female cases. The pneumonia cases could be subdivided according to the presence or absence of a history of influenza, but no sharp clinical differences existed between the subgroups. The bacteriological results enabled the series to be classified into those cases from which a strain of influenza virus was obtained and those which failed to yield virus either from sputum or from the lung.

The virus-positive cases consisted of eight cases of clinical pneumonia and one case of congestive heart failure (Table V). Five of the patients with pneumonia gave a history of influenza at the onset of illness. A virus with the general properties of influenza virus was recovered from the lung in five instances and from the sputum in four. The strains of virus are still being examined serologically, but so far seven have proved to be influenza virus A on the basis of haemagglutination-inhibition tests. Moreover, they belonged to the same serological subgroup as other influenza A strains recovered during the 1949

TABLE V.-Virus-positive Cases

Case No.	Age	Sex	Condition	Duration (Days)	Bacteriology (Lung)
1	46	F	Tracheitis; pneumonia; lung	5	Staph. pyogenes
2	60	F	Tracheitis: pneumonia	7	
3*	49	F	Pneumonia: lung abscesses	8	i
4	36	F	Tracheitis: pneumonia	3	
5*	59	F	Clinical pneumonia; no ne- cropsy	5	Staph. pyogenes (sputum)
6	63	м	Bronchopneumonia (epilepsy; diabetes)	7	Stuph. pyogenes
7*	53	F	Clinical pneumonia: no ne- cropsy	11	No culture
8*	69	м	55 55 55 57	18	Pn. III; strep. haem.
9	66	F	Congestive cardiac failure (hypertension)	7	Bact. coli
	1			1	

* Virus recovered from sputum.

Staph. pyogenes = Coagulase-positive staphylococci.

epidemic in Britain or sent from the continent of Europe to the World Influenza Centre at Hampstead (personal communication from Dr. C. M. Chu).

Coagulase-positive staphylococci were found in lung or sputum of six of the virus-positive cases, being present often in enormous numbers in the sputum and as the sole aerobic organism in the lung. These cases were regarded as staphylococcal pneumonia. A Type III pneumococcus and a haemolytic streptococcus were found in the sputum of one virus-positive case, and *Bact. coli* was present in the lung of the case of congestive cardiac failure. The sputum from the ninth virus-positive case was treated with streptomycin and penicillin before cultivation was carried out, and bacteria were not recovered from this specimen.

TABLE VI.—Virus-negative Cases

Case No.	Age	Sex	Condition	Duration (Days)	Bacteriology (Lung)
10 11 12 13	65 66 71 63	M F M F	Lobar pneumonia (R.L.L.) Bronchopneumonia ",	5 8 3 7	Pn. III <i>H. influenzae</i> Proteus; Bact.
14*	55	м	,,	4	Str. viridans;
15*	61	м	"	7	Pn. XIX (spu- tum); Staph. pyogenes (spu- tum and lung)
16	39	F	Clinical pneumonia; no ne-	3	Staph. pyogenes (sputum)
17	9/12	F	Relapse bronchopneumonia	3	Staph. pyogenes
18	52	м	Lobar pneumonia; aortic stenosis	5	,, ,,
19	77	F	Congestive cardiac failure (bronchopneumonia)	21 mos.	Bact. coli
20	68	М	Congestive cardiac failure. No necropsy	1 mo.	Staph. (sputum)
21 22	68 41	F F	Diabetic coma Cerebral haemorrhage; hyper- tension	5 1	Staph. pyogenes """"

* Sputum as well as lung negative in eggs. Staph. = Coagulase-negative staphylococci. Staph. pyogenes = Coagulase-positive staphylococci.

The virus-negative group included nine cases of pneumonia, two of congestive heart failure, and two of miscellaneous conditions (Table VI). Two of the patients with pneumonia gave a history of influenza. Two patients (Cases 12 and 19) had been in hospital for one month and six weeks before death, which occurred rather unexpectedly. The original diagnosis was chronic bronchitis and emphysema in Case 12 and hypertensive heart failure in Case 19. Analogous conditions for virus isolation existed in all these cases, as in the virus-positive ones, except that the necropsy was carried out in certain instances without preliminary refrigeration of the body, and the necropsy in Case 12 was not done until 24 hours after death, at room temperature.

Coagulase-positive staphylococci were recovered from the lung in five instances, being present in large numbers in three. Smaller numbers of cocci found in the lung of Cases 21 and 22 may have resulted from an aspiration of faucial secretion during the coma which preceded death. One (Case 16) of the two cases which were not submitted to necropsy had enormous numbers of staphylococci in the sputum, and this case and the two others with heavy growth of cocci from the lung were considered to be cases of staphylococcal pneumonia. Case 18 was complicated by the presence of aortic valve disease and may conceivably have been a case of bacterial endocarditis. The bacteriological findings in the remaining virus-negative cases included Type III pneumococci in the lung in two instances (Cases 10 and 11-husband and wife) and a number of other organisms, including coagulase-negative staphylococci, in the remainder.

It must be remembered that all but one of the cases of pneumonia and of cardiac failure had been heavily treated with penicillin, and in some instances with sulphonamides as well. In five the staphylococci recovered from the lung at necropsy were examined by Dr. J. Colquhoun, of the Royal Sheffield Infirmary and Hospital, for sensitivity to Two strains were fully sensitive, but three penicillin. resisted the action of 1,000, 125, and 32 units of penicillin respectively, and were therefore penicillin-resistant. Ten of the strains of staphylococci recovered from sputum or lung were sent to the Central Public Health Laboratory at Colindale for phage-typing by Dr. R. E. O. Williams. The phage type 52A was identified in five of the strains, all of which were recovered from the cases of pneumonia. The prevalence of this type of staphylococcus may have been peculiar to Sheffield, but it was suggestive of a particular relation to the cases of staphylococcal pneumonia.

Discussion

The conclusions drawn from this series of fatal illnesses were that influenza virus was a frequent invader of the lower respiratory tract in cases of fatal pneumonia during the epidemic. The character of the death in such cases was sometimes that of acute pulmonary oedema, but in others circulatory phenomena, such as low blood pressure, feeble heart sounds, or gallop rhythm, suggested the existence of peripheral vascular or myocardial failure. It is probable that some such phenomena would have been described by practitioners as acute heart failure. The possibility exists that the small series of hospital cases was not unrepresentative of the larger series recorded by practitioners as deaths from influenza.

Fatal staphylococcal pneumonia has in the past chiefly excited attention when occurring in subjects younger than the majority of cases of influenzal pneumonia. It is then recognized because of its association with intense dyspnoea and livid "heliotrope" cyanosis. Unless the recent number of cases in Sheffield was an exceptional occurrence, the combined influenza virus and staphylococcal infection of the lung is not rare or confined to young subjects. It seems to resist current methods of chemotherapy. The post-mortem appearances and histology in such cases are striking, and the cases in the present series (Figs. 1-5, Photogravure Plate) showed the necrosing tracheitis and purple oedematous lung described by Winternitz et al. (1920) in the 1918 pandemic and more recently by numerous observers, including Parker et al. (1946). But in the 1918 pandemic the characteristic lesions were not associated solely with staphylococci as they have been in all recent outbreaks. The major difference between recent

epidemics and the 1918 pandemic is the absence of much involvement of the 20-40 age-group-a fact again borne out by the figures recorded above.

Finally, the present investigation has not fulfilled its purpose, because of the small number of inter-epidemic deaths from influenza yet studied. But the laboratory data recorded above seem to justify the use of the phrase "death from influenza" by practitioners, at any rate during an epidemic of influenza.

Summary

A comparison of a group of 29 recorded deaths from influenza during an inter-epidemic period and 85 deaths from influenza during the 1949 influenza epidemic is described. The age and sex distributions and the immediate, primary, and secondary causes of death were not significantly different in the two series.

Analysis of clinical records of the 85 notified deaths during the epidemic period indicated a close relation between respiratory conditions and cardiovascular complications. No evidence was found that the series included a particular clinical group.

Twenty-two fatal illnesses in hospital during the period of the epidemic in Sheffield were investigated for evidence of influenza virus infection. Nine cases yielded influenza virus from sputum or lung, eight were cases of pneumonia, and one was a case of congestive heart failure.

Staphylococcal pneumonia was an important cause of death among the cases admitted to hospital, and six of ten such cases yielded a strain of influenza virus.

This work would not have been possible without the assistance of the many practitioners who supplied details of patients under their care or without the help of the medical officers of health who advised us of the notifications. We are indebted to various physicians and pathologists who permitted us to obtain specimens from patients and at necropsies. We wish to thank particularly Drs. K. J. G. Milne, E. G. G. Rhind, and C. G. Cook, of the City General Hospital. Dr. C. Gray Imrie, Professor E. J. Wayne, Dr. A. W. D. Leishman, and Dr. L. D. Hermitte, of the United Sheffield Hospitals. Dr. J. L. Edwards not only assisted considerably with the post-mortem specimens from patients at the Royal Hospital, Sheffield, but supplied the sections from which the photomicrographs were pre-pared. Lieutenant-Colonel S. M. Vine, R.A.M.C., of the Northern Command Laboratory, Catterick, kindly provided us with specimens from one case. Pneumococcus typing on the cultures indicated was performed by Miss M. Pownall, of the Public Health Laboratory, City General Hospital. To all these we wish to extend thanks. The cost of this investigation was partly defrayed by an expenses grant from the Medical Research Council, which also provided one of us (C. H. S.-H.) with a grant for scientific assistance.

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The British Social Hygiene Council has arranged to hold summer schools in Devon and France this summer. The first will be from July 31 to August 14 at the Seale-Hayne Agricultural College, Newton Abbot, Devon, where a course will be given on "Biology and Rural Life." It is intended for teachers of biology, agricultural students, social workers, and all who are interested in the social and economic conditions of the English countryside. The fee is 16 guineas. The second course will be held on August 16-30 in Paris and have as its theme "The Welfare of the Family." It is intended particularly for children's officers, probation officers, nurses, health visitors, almoners, teachers, and all who are concerned with the educational, communal, and moral aspects of family life. The family welfare services in France will also be studied. Particulars may be obtained from the council at Tavistock House North, Tavistock Square, London, W.C.1.