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.

We wish to thank Professor W. J. Tulloch for facilities, and to express our gratitude to the nursing staff of King's Cross Hospital for their care of the patients and to Sister Alma Mitchell for her help in the collection of specimens for bacteriological examination. Dr. A. Isaacs very kindly typed the influenza strains submitted to the World Influenza Centre of the World Health Organization, London. The antigens and convalescent positive sera used in the complement-fixation test were supplied by the Standards Laboratory for Serological Reagents, Colindale.

REFERENCES

- Brodie, J., Jamieson, W., and Sommerville, T. (1955). *Lancet*, 2, 223.
 Giles, C., and Shuttleworth, E. M. (1957). *Ibid.*, 2, 1224.
 Hers, J. F. Ph. (1955). *The Histopathology of the Respiratory Tract in Human Influenza*. Stenfert Kroese, Leyden.
 — Gosling, W. R. O., Masurel, N., and Mulder, J. (1957). *Lancet*, 2, 1164.
 Jevons, M. P., Taylor, C. E. D., and Williams, R. E. O. (1957). *Ibid.*, 2, 891.
 Medical Research Committee (1919). Report No. 36.
 Ministry of Health (1920). Reports on Public Health and Medical Subjects, No. 4.
 Patrick, A. (1919). *Lancet*, 1, 137.
 Stuart-Harris, C. H. (1953). *Influenza and Other Virus Infections of the Respiratory Tract*. Arnold, London.

ENCEPHALITIS AND INFLUENZA

BY

J. M. DUNBAR, M.D., B.Sc.

*Lecturer in Bacteriology, University of St. Andrews,
Queen's College, Dundee*

W. M. JAMIESON, M.D., M.R.C.P.Ed., D.P.H.

Physician-Superintendent, King's Cross Hospital, Dundee

JEAN H. M. LANGLANDS, M.B., Ch.B.

*Registrar, Medical Professorial Unit, Maryfield General
Hospital, Dundee*

AND

G. H. SMITH, T.D., M.D.

Consultant Pathologist, Maryfield General Hospital, Dundee

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

grey matter of the cortex was pale mauve in colour, while the cut surface of the white matter was congested.

Blocks were examined microscopically from various areas of cortex, basal ganglia, mid-brain, and medulla. The appearances were similar in all areas examined, and consisted mainly of intense congestion and occasional small haemorrhages, many of which spread along the perivascular space. There was no evidence of perivascular cuffing, but in relation to the perivascular haemorrhages there was a suggestion of early microglial proliferation in the adjacent collar of white matter, although it was not certain that there was any demyelination. There was a red-cell reaction in the olivary nuclei, and degenerative neuronal changes were evident, with accompanying satellitosis of the oligodendroglia, which also showed acute swelling.

The trachea and bronchi showed intense hyperaemia and contained copious pink-stained frothy fluid.

There were solid haemorrhagic patches in both lungs, with pus extending from the smaller bronchioles. Examination of various blocks of lung tissue and trachea showed intense congestion, oedema, haemorrhages, and mononuclear infiltration. Patches of purulent consolidation were also evident. The trachea and bronchi showed loss of epithelium, thickening and hyalinization of the basement membrane, and mononuclear infiltration. The appearances were typical of influenza with superadded purulent bronchopneumonia.

All other organs were normal, apart from venous congestion.

Case 2

On October 13, 1957, a girl aged 14 was admitted to the medical professorial unit, Maryfield Hospital, Dundee. Three weeks before admission she had a head cold severe enough to keep her off school for two days. Four days before admission another upper respiratory tract infection started, and we date the onset of her illness from this time (October 9). The following day she stayed in bed and in the evening developed nausea, vomiting, and colicky abdominal pain. On the third day she felt better, but in the evening abdominal pain and vomiting recurred. On the fourth day she seemed drowsy and confused, and was admitted to hospital.

On admission she was stuporous, agitated, with purposeless movements of the limbs, and did not respond to questions. The pupils were dilated and reacted sluggishly to light; there was no papilloedema or any abnormality in the tendon and plantar reflexes. At this time she was afebrile and the haemoglobin and E.S.R. were normal. The leucocyte count was 7,500 per c.mm. Next day, the fifth of her illness, she became comatose, responding only to supraorbital pressure. Plantar reflexes were extensor and abdominal reflexes were absent. A lumbar puncture yielded C.S.F. at normal pressure with no pleocytosis and 40 mg. of protein per 100 ml. X-ray examination of the chest, skull, and sinuses gave normal results. A neurosurgeon was asked to see her to exclude the presence of a cerebral tumour; he agreed that this was unlikely.

Treatment with penicillin and streptomycin was begun. On the sixth day the only abnormality on lumbar puncture was a protein of 60 mg. per 100 ml. Tendon reflexes were now absent, and on the evening of the seventh day of illness she was deeply unconscious. Early the next morning she was seen to stir, and when a nurse went to her she asked for her handkerchief. Her cerebration was slow and speech slurred; she was ataxic, and tendon and abdominal reflexes were still absent with extensor plantar responses. She gradually improved until on the eleventh day of illness there were no abnormal signs referable to the central nervous system. An electroencephalogram at this time was within normal limits.

On the 14th day she complained of pain in the back of the neck and her temperature was raised. In the next few days she developed neck rigidity and Kernig's sign was present. On lumbar puncture the C.S.F. pressure was

normal; protein, 15 mg. per 100 ml.; and cells, 13 per c.mm., mainly lymphocytes. The blood leucocyte count was 9,700 cells per c.mm., the differential count being within normal limits. Her temperature returned to normal after a week. She was transferred to a convalescent home four weeks after the onset of her illness, and later returned to school fully recovered and with no sequelae.

Serology

Complement-fixation tests on six specimens of sera gave the following results. The titres against influenza A antigen obtained on sera taken on the 8th, 26th, and 35th days after onset of symptoms ranged from 32 to 64. Two further samples of sera submitted on the 54th and 90th days yielded the same titre (32), while serum taken almost five months after the onset of symptoms failed to yield a titre of >8. The first three sera were confirmed at the Virus Diagnostic Laboratory, Colindale, as containing antibodies to influenza A to a titre of 32. The first two sera (8th and 26th days) both had a titre of <8 against influenza B, influenza C, sendai, adenovirus group, psittacosis-L.G.V., mumps V, and lymphochoriomeningitis virus antigens. *Leptospira* agglutinins were negative against *L. icterohaemorrhagiae* and *L. canicola*. No *Streptococcus M.G.* agglutinins were detected at a serum dilution of 1/20.

Case 3

On October 21, 1957, a man aged 48 was admitted to hospital suffering from influenza. The illness had started three days previously with typical "influenzal" symptoms—pyrexia, shivering, cough, and malaise. On the day of admission his temperature was 104° F. (40° C.) and he was very drowsy. On physical examination the only abnormality was in the respiratory system, where there were generalized rhonchi and some basal crepitations. On October 22 there was considerable mental derangement, with confusion and hallucinations. Next day he was unconscious. By October 25 he could be roused with difficulty and was becoming rather violent. Lumbar puncture showed the cerebrospinal fluid to be normal, although the sugar content was high (105 mg. per 100 ml.). Blood urea was 40 mg. per 100 ml. During the next few days he continued to improve, and by October 28 was very much better. Examination of the central nervous system showed nothing abnormal. He made an uneventful recovery.

Case 4

On October 25, 1957, a male child aged 20 months became suddenly ill. He was febrile and listless, and had a convulsion. He was admitted to hospital the same day, the provisional diagnosis being "influenza and convulsion." Other members of the household were suffering from influenza at this time.

On admission to hospital the child's temperature was 101° F. (38.3° C.) and he was having a generalized convulsion. Respirations were 72, and there were low-pitched rhonchi throughout the lungs. He vomited on several occasions. The convulsion ceased after 15 minutes, and examination of the central nervous system showed no abnormality apart from some increase in muscular tone generally. Lumbar puncture revealed normal cerebrospinal fluid. On October 29 he had a further convulsion lasting seven minutes. Lumbar puncture again showed normal cerebrospinal fluid. The blood leucocyte count was 6,000 per c.mm. (polymorphs 48%). Examination of the ocular fundi revealed neither papilloedema nor venous congestion. The child was drowsy and generally spastic. He was disinclined to move around in bed, and in particular showed reluctance to move the right leg. Deep reflexes were generally exaggerated and plantar responses were extensor. By November 13 he was mentally more alert, but was still spastic and not moving the right leg. By November 27 he was able to

sit up in bed, and at the time of discharge from hospital (December 11) he appeared fully recovered mentally, but some degree of spasm persisted in both legs. He was observed for several weeks as an out-patient and improved steadily. When last seen (January 12, 1958) he was completely recovered.

Discussion

It is fortunately rare for influenzal patients to die from cerebral complications, and the pathological changes are by no means constant. The main types described by Crome (1954) and Crawford (1954) are: (1) a haemorrhagic encephalitis in which haemorrhages may be severe and extensive enough to destroy parts of the brain and are associated with proliferation of neuroglia and mild meningitis; and (2) perivascular demyelination, the changes being similar to those of post-vaccinal encephalitis.

Case 1 does not appear to belong clearly to either of these types. This case occurred during the epidemic in Dundee, and the post-mortem appearances of the lungs, both macroscopically and microscopically, were typical of those seen in 23 other necropsies during a six-weeks period. The appearances are also described in detail by Hers (1955). It is therefore reasonable to assume that the primary illness was in fact influenza and that the cerebral condition was a complication of influenza. The appearances in the lungs were also similar to those in which staphylococci were isolated, and it is likely that the secondary purulent bronchopneumonia was of staphylococcal type, although no bacteriological investigation was carried out.

Morgan and Pickup (1958), in their series of influenzal bronchopneumonia in children, describe a case which closely resembles this patient both clinically and pathologically. They were also impressed by the paucity of physical signs in the chest, as was Atkinson (1957) and Mann and Pasha (1957).

In the second case, although a fourfold rise in complement-fixing antibodies against influenza A was not demonstrated, a titre of 32 or 64 is regarded as evidence of recent infection. The failure to demonstrate a rise in titre may be due to the fact that the first specimen was taken eight days after onset of symptoms, so that development of complement-fixing antibodies may already have started. One point of note is the persistence of the antibodies at a constant titre of 32 for over three months, although they fell to less than 8 after five months.

Cases 3 and 4 differ from the first two cases in that the patients were admitted to hospital with a firm diagnosis of influenza. In Case 3 pharyngeal washings taken two days after onset yielded influenza virus identified serologically as type A. This strain was confirmed by Dr. A. Isaacs at the World Influenza Centre, London, as being characteristic of Asian influenza. Serum obtained 32 days after onset was found to have a complement-fixing antibody titre of at least 256. Isolation of the epidemic strain of virus from the throat, followed by the finding of a significant level of complement-fixing antibody to influenza A in a convalescent specimen of serum, confirms the diagnosis of influenza. The cerebral upset which rapidly overshadowed the respiratory infection was thought to be due to an associated encephalitis, since the patient was a man of temperate habits and there was no indication that the chest infection was severe enough to give signs of anoxia. In Case 4 the diagnosis of influenza was based on a febrile illness occurring in a baby from a household in which other members were suffering from influenza. The nature of the signs in the central nervous system were consistent with encephalitis.

While the evidence presented is not conclusive, we believe that all four cases described were in fact suffering from influenza and encephalitis. We would echo the wish expressed by Stephens and Cappell (1958), that in the future "every opportunity will be taken by all who observe such cases to search for an infecting virus both during life and at necropsy."

Summary

Four cases showing features of encephalitis and associated with influenza are described. They were all diagnosed during the recent epidemic and represent an incidence of approximately 1 in 10,000 of all patients with influenza. Two presented marked symptoms of respiratory infection, while two were not recognized on admission to be associated with influenza. One patient died, and at necropsy the findings were consistent with a diagnosis of encephalitis as a complication of influenza. Influenza A virus of the Asian type was isolated from pharyngeal washings of one case, while complement-fixation tests yielded significant titres against influenza A antigen in the sera of two patients.

The need for detailed investigation of similar cases in the future is stressed.

Our thanks are due to Professor I. G. W. Hill and Dr. J. Stowers for permission to publish details from the clinical notes on Case 2, and to Dr. R. S. Bluglass for co-operation.

REFERENCES

- Atkinson, E. C. (1957). *Brit. med. J.*, 2, 821.
Crawford, T. (1954). *J. clin. Path.*, 7, 1.
Crome, L. (1954). *Msch. Psychiat. Neurol.*, 128, 159.
Dubowitz, V. (1958). *Lancet*, 1, 140.
Hers, J. F. Ph. (1955). *The Histopathology of the Respiratory Tract in Human Influenza*. Stenfert Kroese, Leyden.
Jennings, G. H. (1952). *Brit. med. J.*, 1, 123.
Leigh, A. D. (1946). *Ibid.*, 2, 936.
Mann, B., and Pasha, M. A. (1957). *Ibid.*, 2, 939.
Morgan, D. M., and Pickup, J. D. (1958). *Ibid.*, 1, 263.
Stephens, J. H., and Cappell, D. F. (1958). *Lancet*, 1, 381.
Stuart-Harris, C. H. (1939). *Ibid.*, 1, 497.
— (1953). *Influenza and Other Virus Infections of the Respiratory Tract*. Arnold, London.

DEATHS FROM ASIAN INFLUENZA, 1957

A REPORT BY THE PUBLIC HEALTH LABORATORY SERVICE BASED ON RECORDS FROM HOSPITAL AND PUBLIC HEALTH LABORATORIES

When the autumn epidemic of Asian influenza began hospital and public health laboratories in England, Wales, and Northern Ireland were invited to contribute brief standard records of fatal or serious cases of influenzal pneumonia in persons under the age of 45 years. The age limit was later extended to include all patients, and, in addition, a few laboratories engaged in special investigations of influenza deaths kindly supplied information on their cases in an abbreviated and consolidated form, omitting certain clinical and pathological details. A full description of one such series of patients has already been published (Giles and Shuttleworth, 1957). The results obtained from the analysis of records sent before January 15, 1958, are presented below.

Patients Studied

Records were received for 477 fatal and 43 non-fatal cases; the non-fatal cases were too few for full analysis and are not considered further in this paper. The age and sex distribution of the fatal cases is shown in Table I. Almost all (467) were investigated bacteriologically, and influenza virus A was isolated in 195 (63%) of 310 cases tested. Of those dying within five days of onset of illness the proportion confirmed by virus isolation was 80%. Almost all the virus strains were typed, and belonged without exception to the Asian group. A full clinical record was available for about half the cases and the abbreviated record mentioned above for the remainder.

From figures published in the Weekly Returns of the Registrar-General it is estimated that there were approxi-