# Neurological Complications of so-called "Influenza" A Winter Study in South-east Wales*

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## Summary

**Acute neurological disorder followed an upper respiratory infection in 19 patients in south-east Wales during the winter of 1969-70. Spinal and radicular syndromes predominated and included seven cases of transverse myelopathy. Serological tests suggested that the preceding infection was due to influenza A virus in eight cases, to other viruses in six, and were negative in five.**


## Introduction

Influenza and the flu are umbrella-words which are used to headline epidemics of upper respiratory infection. A host of viruses, besides the ubiquitous streptococcus, can mimic clinical influenza, whereas the myxovirus of influenza itself may cause no more than a passing cold (Stuart-Harris, 1965; Tyrrell, 1965). The exact diagnosis of each case, short of post-mortem proof, requires culture of virus from infected tissues together with complementary serological tests. As these criteria may be difficult to fulfil, a clinical diagnosis is often based on data which are scientifically inadequate but which are wrongly assumed to be definitive.

Influenza due to the Hong Kong variant of A2 virus was epidemic in Great Britain from November 1969 to March 1970 (*British Medical Journal*, 1969, 1970a). In the first week of 1970 alone 3,170 deaths were attributed to it in official notifications. The virus, however, was positively identified in only 2,072 cases throughout the epidemic period, though other types of respiratory virus were isolated from more than 1,000 cases (*British Medical Journal*. 1970b). The chance, therefore, of a mistaken clinical diagnosis was considerable.

## Present Investigation

In the region around Cardiff the pattern of acute neurological illness in the wake of so-called influenza was distinctive. All types of disorder were seen, but the brunt seemed to fall on the spinal cord and proximal nerve roots. During the winter months of 1969-70, when Hong Kong influenza was epidemic, 19 cases were admitted to hospitals in south-east Wales and followed up into the late summer. All cases were examined by me; of these 13 were admitted to the departments of neurology at Cardiff Royal Infirmary and at St. David's Hospital, Cardiff, and six, who were under the care of physicians, surgeons, or paediatricians, were seen in consultation.

### VIRUS SEROLOGY

All the patients gave a story of influenza, or of an upper respiratory infection which they called "the flu," in the days before the onset of their neurological illness (Table I). In many cases the general practitioner had requested admission on the grounds of severe or complicated influenza.

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### *Influenza A Virus*

Seven patients, who had serological evidence of exposure to influenza A virus developed neurological symptoms between 26 December and 9 January. In an eighth, who had been ill in January, symptoms of myelopathy started on 2 March, three days after a further infection (Table I). Excluding the four patients whose illness began before 1 December or after 3 March, there were seven either with negative virus serology or with evidence of exposure to other viruses (Table I).

### *Adenovirus*

Two patients with titres to adenovirus had early symptoms typical of that infection: sore throat, running eyes, and enlarged glands in the neck. A third was admitted to hospital with haemolytic anaemia of undetermined aetiology. Signs of polyradiculopathy developed within days, respiratory failure quickly supervening.

### *Herpes Zoster*

Herpes zoster was followed by myelopathy in two cases. In both the spinal fluid was normal (Table II) and cultures were sterile. One case of myeloradiculopathy had a low but persistent titre to *Mycoplasma pneumoniae*, which disappeared during convalescence. All this patient's family had had "the flu."

### NEUROLOGICAL INVOLVEMENT

Of the 13 patients with a predominantly spinal disorder (Tables I and II) eight, including the two cases of zoster, had myelopathy, four had a combination of signs indicating both spinal and radicular disease, and one with encephalopathy was found to have a diffuse myelopathy when she emerged from coma.

In the four patients with polyradiculopathy involvement of cranial nerves was unusually frequent; one had total ophthalmoplegia, facial diplegia, and bulbar palsy, one bilateral facial weakness, and one dysphagia with paralysis of soft palate and vocal cords (Tables I and II). A fifth patient with myeloradiculopathy had bilateral facial weakness and the patient with encephalomyelopathy had bilateral optic neuropathy. In addition to generalized radiculopathy one case had typical symptoms of localized brachial neuropathy, later developing amyotrophy of the shoulder girdle. Another patient with a severe demyelinating polyneuropathy had dense sensory loss in her hands resembling cases of myeloradiculopathy.

Three patients developed respiratory paralysis and required ventilation. All were transferred to the assisted respiration

*Based on a communication to the Society of Physicians in Wales at Portmeirion on 8 May 1970.

TABLE I—*Virus Serology of 19 Cases of Acute Para-infectious Neurological Disorder*

| Case No. | Sex | Age | Diagnosis | Prodromal Illness | Neurological Illness | Virus C.F.T. | Date | Titre | H.I. titre |
|---|---|---|---|---|---|---|---|---|---|
| 1 .. .. | F. | 67 | Polyradiculopathy | 23 Oct. | 31 Oct. | Adenovirus | 1 Nov. | 1/128 | |
| | | | | | | | 11 Nov. | 1/64 | |
| | | | | | | | 1 Dec. | 1/32 | |
| 2 .. .. | M. | 67 | Polyradiculopathy and brachial neuropathy | 30 Oct. | | | | | |
| | | | | 20 Nov. | 4 Dec. | Negative | 11 Dec. | | |
| 3 .. .. | M. | 55 | Myeloradiculopathy | 11 Dec. | 22 Dec. | Negative | 6 Mar. | | |
| 4 .. .. | M. | 45 | Myelopathy | 18 Dec. | 26 Dec. | Influenza A | 31 Dec. | 1/128 | 1/512 |
| | | | | | | ,, ,, | 20 Jan. | 1/128 | |
| | | | | | | ,, ,, | 8 Feb. | 1/128 | |
| 5 .. .. | F. | 18 | Myeloradiculopathy | 23 Dec. | 27 Dec. | Influenza A | 25 Mar. | 1/32 | Anti/c |
| | | | | | | Negative | 5 May | | |
| 6 .. .. | F. | 72 | Myelopathy | 20 Dec. | 28 Dec. | Influenza A | 19 May | 1/32 | 1/4,096 |
| 7 .. .. | F. | 55 | Polyradiculopathy | 15 Dec. | 29 Dec. | Influenza A | 18 Mar. | 1/64 | 1/128 |
| | | | | | | ,, ,, | 22 Apr. | 1/32 | 1/32 |
| 8 .. .. | M. | 59 | Polyradiculopathy | 18 Dec. | 1 Jan. | Anti/c | 6 Jan. | | |
| | | | | | | Influenza A | 24 Jan. | 1/128 | 1/256 |
| 9 .. .. | F. | 49 | Myeloradiculopathy | 20 Dec. | 1 Jan. | *Myco. pneum.* | 6 Jan. | 1/32 | |
| | | | | | | ,, ,, | 19 Jan. | 1/32 | |
| | | | | | | Negative | 18 May | | |
| 10 .. .. | F. | 12 | Subdural empyema | 19 Dec. | 2 Jan. | Influenza A | 7 Jan. | 1/64 | 1/256 |
| 11 .. .. | F. | 66 | Myelopathy | 20 Dec. | 5 Jan. | Var.-zoster | 22 Jan. | 1/128 | |
| | | | | | | ,, ,, | 28 Jan. | 1/64 | |
| | | | | | | ,, ,, | 2 Mar. | 1/32 | |
| 12 .. .. | M. | 20 | Myelopathy | 20 Dec. | 9 Jan. | Influenza A | 14 Jan. | 1/64 | 1/128 |
| | | | | | | ,, ,, | 20 Feb. | 1/32 | 1/128 |
| 13 .. .. | M. | 30 | Myelopathy | 9 Feb. | 12 Feb. | Negative | 19 Feb. | | |
| | | | | | | Negative | 3 Mar. | | |
| 14 .. .. | M. | 34 | Myelopathy | 23 Jan. | 13 Feb. | Negative | 14 Feb. | | |
| | | | | | | Negative | 16 Feb. | | |
| | | | | | | Negative | 19 Feb. | | |
| | | | | | | Negative | 13 Mar. | | |
| | | | | | | Influenza A | 24 June. | 1/32 | 1/128 |
| | | | | | | Adenovirus | ,, ,, | 1/16 | |
| | | | | | | *Myco. pneum.* | ,, ,, | 1/16 | |
| 15 .. .. | M. | 28 | Myelopathy | 1 Jan. | | Resp. syncyt. | 6 Mar. | 1/32 | |
| | | | | 28 Feb. | 2 Mar. | *Myco. pneum.* | ,, ,, | 1/16 | |
| | | | | | | Parainfl. 3 | ,, ,, | 1/16 | |
| | | | | | | Influenza A | 15 Apr. | 1/64 | 1/1,024 |
| 16 .. .. | M. | 46 | Myeloradiculopathy | 15 Feb. | 2 Mar. | Negative | 10 Apr. | | |
| | | | | | | Negative | 17 Jun. | | |
| 17 .. .. | F. | 27 | Encephalomyelopathy | 29 Mar. | 2 Apr. | Adenovirus | 15 Apr. | 1/64 | |
| 18 .. .. | F. | 78 | Myelopathy | 18 Mar. | 6 Apr. | Var.-zoster | 27 Apr. | 1/256 | |
| 19 .. .. | M. | 23 | Encephalopathy | 8 Apr. | 13 Apr. | Adenovirus | 16 Apr. | 1/64 | |
| | | | | | | ,, | 26 Apr. | 1/64 | |

Cases were numbered according to the day of onset of neurological symptoms. This order did not always coincide with the order of admission to hospital.
Case 2 developed herpes simplex of the lip on 30 October and on 20 November 1969 approximately. Case 15 had upper respiratory symptoms on 1 January and on 28 February 1970.
In all cases complement fixation tests were performed for influenza A, B, and C; psittacosis/L.G.V.; *Coxiella burneti*; adenovirus; respiratory syncytial virus; *Mycoplasma pneumoniae*; parainfluenza 1, 2, and 3. Additional tests for varicella-zoster were performed in Cases 11 and 18 only.
Haemagglutination-inhibition was measured on the stored frozen sera of all cases with a titre to influenza A > 1/8.
Prodromal illness = actual, or estimated, day of onset of upper respiratory symptoms.
Neurological illness = actual, or estimated, day of onset of neurological symptoms.
Virus C.F.T. = virus complement fixation test. All titres > 1/8 are tabulated. Negative = all titres < 1/8. Anti/c = serum anti-complementary.
H.I. titre = titre of haemagglutination-inhibition for influenza A.

unit at Llandough Hospital and all three survived. A child, at first suspected of encephalopathy, proved to have a pyogenic infection and died of relapsing subdural empyema.

## Transverse Myelopathy

Transverse myelopathy may follow an infection, jennerian vaccination, and other medical and surgical procedures (Turnbull and McIntosh, 1926; Greenfield, 1930; Altrocchi, 1963b). It occurs also without prodromal illness and has been described in association with a remote cancer (Mancall and Rosales, 1964) and in drug addicts (Richter and Rosenberg, 1968). The basic morbidity is that of an acute disseminated encephalomyelitis (Adams and Kubik, 1952). Swelling of the cord may trap and compress radicular veins within the canal and lead to further congestion, the clinical level marking the upper boundary of their drainage. This mechanical effect of oedema distinguishes transverse from the ascending and descending varieties of myelopathy. At necropsy lesions are seen to extend throughout all levels of the central nervous system (Greenfield, 1930). The process is reversible (Herkenrath, 1935), and clinical recovery is often complete (Altrocchi, 1963b).

Transverse myelopathy was diagnosed in seven cases (Tables I and II). Two (Cases 4 and 12) had titres suggestive of contemporary infection with influenza A virus. The serum of another (Case 6) was lost during the acute illness but showed a low titre to influenza A during convalescence. A fourth patient (Case 15) had low titres to several viruses at the onset of his neurological illness, which had followed a succession of colds, but showed a small titre to influenza A as he recovered. Two patients (Cases 13 and 14) had negative virus serology.

In the less severe of the two cases of herpes zoster (Case 18) symptoms were unilateral but persisted, whereas the patient (Case 11) with transverse myelopathy made a slow but nearly total recovery. This latter syndrome is a rare complication of zoster (Gordon and Tucker, 1945; Altrocchi, 1963b) and has been attributed to thrombosis of a radicular vessel with spinal infarction (Hughes, 1966). Her recovery from tetra-

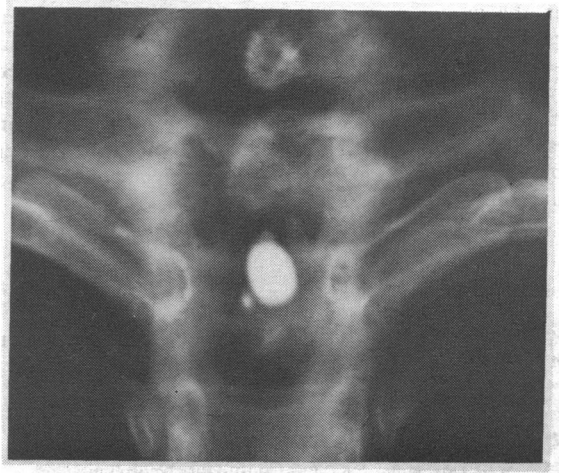

FIG. 1—Myelogram (Case 4). Globule of contrast medium trapped by swollen cord at level of second dorsal vertebra.

plegia with a mid-cervical sensory level was consistent with extraspinal thrombosis, but infarction was improbable.

Early symptoms of myelopathy were weakness of the legs, retention of urine, and chest pain. Two patients (Cases 6 and 12) complained of intense paraesthesiae. One (Case 14) developed symptoms abruptly; seized with increasing pain in his chest, he returned to bed and within five minutes he was paraplegic. Spinal pain was severe in one patient (Case 4) who was admitted with retention of urine. He was febrile, with a peripheral leucocytosis, and over the second dorsal vertebra the area was acutely tender. Epidural abscess was excluded by myelography, though a globule of contrast medium was trapped by the oedematous cord (Fig. 1). Paraplegia developed rapidly, reaching a peak within 48 hours. Fluctuation was common. Altrocchi (1963a, 1963b) found that nearly half of his 67 cases were paralysed within a day of the onset, whereas in epidural abscess signs advanced relentlessly over several days.

In six cases the spinal fluid was abnormal (Table II). The two cases of zoster myelopathy, in one of whom (Case 18) signs were confined to a single limb, had a normal fluid. Myelography excluded compression in two cases, but in both the cord was oedematous (Cases 4 and 11). Plain *x*-ray films of the spine were normal in all cases.

Five patients were treated with corticotrophin and steroids. All did well. At the end of the follow-up period three (Cases 12, 13, and 15) had recovered completely and had no residual signs, but two (Cases 4 and 14) were still troubled by hesitancy of micturition and by persisting impotence. The elderly patient (Case 6) who had not had steroids had also made a complete recovery.

TABLE II—*Examination of Cerebrospinal Fluid*

| Case No. | Diagnosis | Days after onset | Cells/mm³ | Protein/100 ml | Glucose/100 ml | Virus Culture |
|---|---|---|---|---|---|---|
| 4 .. | Transverse myelopathy | 3 | 54 | 47 | 70 | Negative |
| 6 .. | ,, ,, | 17 | 0 | 152 | 63 | |
| 12 .. | ,, ,, | 4 | 110 | 86 | 56 | Negative |
| 13 .. | ,, ,, | 9 | 12 | 66 | 68 | Negative |
| 14 .. | ,, ,, | 1 | 3 | 120 | 73 | |
| 15 .. | ,, ,, | 2 | 0 | 105 | 70 | |
| 11 .. | Zoster myelopathy | 17 | 0 | 28 | — | Negative |
| 18 .. | ,, ,, | 21 | 2 | 40 | 60 | Negative |
| 1 .. | Polyradiculopathy | 4 | 0 | 200 | 70 | Negative |
| 2 .. | ,, | 7 | 0 | 60 | 70 | Negative |
| 7 .. | ,, | 41 | 0 | 50 | 70 | Negative |
| | | 112 | 0 | 20 | 50 | |
| 8 .. | ,, | 6 | 0 | 30 | — | Negative |
| | | 18 | 0 | 120 | 75 | |
| 3 .. | Myeloradiculopathy | 5 | 0 | 56 | 97 | |
| | | 25 | 2 | 405 | 124 | |
| 5 .. | ,, | 82 | 7 | 30 | 65 | |
| 9 .. | ,, | 4 | 0 | 20 | 59 | Negative |
| 16 .. | ,, | 36 | 0 | 20 | — | |
| 17 .. | Encephalomyelopathy | 3 | 0 | 40 | 68 | |
| | | 4 | 22 | 15 | 67 | |
| | | 5 | 40 | 15 | — | Negative |
| 19 .. | Encephalopathy | 2 | 5 | 80 | 79 | Negative |
| 10 .. | Subdural empyema | 6 | 12 | — | 76 | Negative * |
| | | 11 | 10 | 50 | 64 | |

*Culture negative for both bacteria and viruses.

## Polyradiculopathy

Haymaker and Kernohan (1949) firmly established polyradiculopathy as the anatomical basis of the Landry-Guillain-Barré syndrome (Landry, 1859; Guillain, Barré, and Strohl, 1916). Twenty years later Asbury, Arnason, and Adams (1969) found that the earliest histological change was a migration of lymphocytes from the vasa nervorum into nerve roots, peripheral nerves, and limited areas of the central nervous system. Myelin was the target of the lymphocytes' attack, and segmental demyelination was a typical finding of the fully developed case. They suggested that "idiopathic polyneuritis" was an immune disorder mediated by clones of abnormally sensitized lymphocytes.

Four patients had polyradiculopathy (Table I), and in three the protein content of the spinal fluid was raised (Table II). In the fourth case the fluid was not examined until six weeks after the onset of symptoms, by which time the protein level was 50 mg/100 ml. Ten weeks later it had fallen to 20 mg/100 ml. One patient (Case 8) had inconclusive evidence of influenza A, and falling titres to this virus were recorded in another (Case 7) many weeks after the onset of her illness. In one (Case 2) the virus serology was negative. The fourth patient (Case 1) was admitted at the end of October 1969 with haemolytic anaemia of unknown aetiology. She complained of tingling in her fingers, and by the end of the week developed a severe polyradiculopathy with respiratory paralysis. Serological tests showed a high titre to adenovirus, which fell progressively over the next month (Table I).

Leigh (1946) described similar cases during an epidemic of influenza B but without proof of infection. The three patients of Gibberd and Kelly (1964) had positive complement fixation tests for mumps which were thought to indicate non-specific myxovirus infection.

Severe chest pain was so striking a feature of one patient (Case 2), a retired doctor, that coronary thrombosis was suspected. Serial electrocardiograms and serum enzyme levels were normal. When he developed localized neuropathy of the shoulder girdle, as well as signs of symmetrical polyradiculopathy, the cause of his pain became clear. Arthropathy of the affected shoulder was a further complication. Nerve conduction studies on three patients (Cases 1, 2, and 7) confirmed peripheral neuropathy. In two (Cases 1 and 7) the degree of slowing of motor conduction was great enough to suggest segmental demyelination.

Corticotrophin or steroids were given to three patients (Cases 1, 2, and 7). They had no effect on the course of the neuropathy of the patient with adenovirus infection (Case 1) though her anaemia steadily recovered. Corticotrophin quickly relieved the doctor's coronary-like pain but did not prevent amyotrophy of the shoulder girdle. On the other hand, the signs of polyradiculopathy did not progress, and this aspect of his illness soon improved. Though the third patient (Case 7) was not seen until many weeks after the onset of symptoms, she was relieved of pain within 24 hours of starting prednisone and was able to dress and feed herself and to write letters for the first time in four months.

The details of another case of Guillain-Barré syndrome occurring in the period under review were kindly given to me by Dr. Gerald Anderson. This patient denied previous infection, but virus studies were not available. Dr. Anderson observed improvement within a week of starting prednisolone, five days after the onset of paralysis and 10 days after the initial paraesthesiae. She recovered fully after four months.

## Myeloradiculopathy

Four patients had an unusual illness with symptoms of both spinal and radicular disorder (Tables I and II). Soon after a feverish cold three experienced intense discomfort of limbs and trunk, particularly of the hands, which caused many sleepless nights. Exceptional clumsiness soon followed. The housewife (Case 9) could neither dress nor do her hair, nor wash up nor make a bed—she lost her fingers in the bedclothes; the fitter (Case 16) had to abandon work, which he could not see to do; the secretary (Case 5) was reduced to one-finger typing. Their "dumb hands" were due to loss of spatial sense with almost total inability to recognize the shape, texture, and nature of objects placed in the palm and moved across the pads of fingers and thumb. This striking physical sign has been named achoraesthesia by Renfrew (1962). The outstretched fingers were constantly on the move, so-called

"pseudo-athetosis," and position sense of their distal joints was lost. Apart from a weak grip power was unaffected. Tendon reflexes were absent.

The lower limbs were less severely affected. One patient (Case 9) had bilateral partial foot-drop, two (Cases 5 and 9) had loss of tendon jerks, but in all three the plantar responses were flexor. In one patient (Case 9) distal sensory impairment extended on to the lower left abdomen, where the cutaneous reflex also was absent.

The fourth patient (Case 3) had returned to work after influenza when increasing clumsiness took him back to his doctor. Flaccid weakness of all four limbs, absent tendon jerks, and rising protein in the spinal fluid (Table II) led to a diagnosis of Guillain-Barré syndrome. Mild delirium and the amnesia of encephalopathy were mistaken for toxic confusion. In the second week he developed spinal signs, including retention of urine and achoraesthesia of his hands. Soon after he started taking corticotrophin his vital capacity improved and ventilation was avoided. Facial diplegia and upper limb weakness cleared quickly, sensory loss recovering more slowly. Six months later he had a flaccid paraplegia and could only hobble around on elbow-crutches. Knee and ankle jerks were absent but the plantar responses were extensor. Sensation was intact.

Though all four patients had had a previous respiratory infection none had strongly positive virus serology. Two (Cases 3 and 16) had negative tests. One (Case 5), months later, had a decreasing titre to influenza A, and another (Case 9) had a low titre to *Myco. pneumoniae* which disappeared during convalescence.

The important differential diagnosis in three patients (Cases 5, 9, and 16), all of whom recovered fully, was multiple sclerosis. None had a story of previous episodes and two were already over 45 years of age. In one patient (Case 9) nerve conduction studies confirmed peripheral dysfunction, making a diagnosis of multiple sclerosis most improbable. Whether the illness of the other two was really a sequel to virus infection or whether it was a first episode of demyelination will be decided only by prolonged follow-up.

In 4 out of 31 early cases of multiple sclerosis McAlpine, Compston, and Lumsden (1955) found that both posterior columns were simultaneously affected and that depression of reflexes, always unusual, was more common in upper than in lower limbs during the first year of the disease. A similar picture of clumsy useless hands which were intensely painful was seen in one of the patients with polyradiculopathy (Case 7). She was also dysphagic and had lost 20 kg. She responded promptly to prednisone, her cranial nerve palsies recovering first.

A fatal case of myeloradiculopathy, with no story of respiratory infection, occurred during the epidemic period. In mid-November 1969 the patient was seized with girdle pain and weakness of his legs. He had a flaccid paraplegia with absent reflexes and a sensory level at the umbilicus. His arms became mildly affected during the next week. He responded initially to corticotrophin but relapsed twice despite continued therapy, finally dying of bronchopneumonia. On four occasions his spinal fluid showed a mild pleocytosis and increased protein, with upper limits of 34 white cells per $mm^3$ and 196 mg of protein per 100 ml. Nerve conduction studies in April 1970 suggested that the changes of peripheral neuropathy were more proximal than distal. At necropsy on 8 May 1970 Dr. R. C. Ryder confirmed that death was due to pneumonia on a background of pneumoconiosis and chronic bronchitis. Search for a cryptic cancer was negative. The brain and spinal cord were later examined by Dr. D. G. F. Harriman. He found changes throughout the cord (Fig. 2) maximal in the dorsal region, in dorsal roots and ganglia, and to a less degree in the brain-stem and in the periventricular areas of the cerebrum. Perivascular cuffs of small mononuclear cells were associated with pallor of myelin, particularly of the posterior and posterolateral columns. His final comment was: "This is predominantly a radiculomyelitis, and as in some forms of polyneuritis there is simultaneous involvement of cerebral periventricular tissue."

## Encephalopathy

Two patients (Cases 17 and 19) were seen in the throes of encephalopathy, and one of the cases of myeloradiculopathy (Case 3) had mild cerebral involvement. Two had significant titres to adenovirus (Table 1) and a preceding respiratory infection which was typical (Stuart-Harris, 1965). Though neither patient had conspicuous conjunctivitis, soreness of the eyes was an early symptom and in both examination was difficult because of photophobia. The husband of one (Case 17) described her eyes as "looking like a coloured road map" during the week before her admission.

Amnesia was a cardinal symptom after recovery. This ranged from four days (Case 19) to eight days (Case 17), being uncertain in one (Case 3). During the period under review two other patients, both elderly women, were seen when they were convalescent from an obscure illness which followed "influenza." One had a five-week gap in her memory which ended on Christmas eve and began again, in hospital, during the first week of February. The other had amnesia for about a week. Neither of these cases had virus studies. The illness of one patient (Case 19) was relatively mild. As he was clearly getting better within hours of admission to hospital, after lapse into coma, corticotrophin was not advised. Recovery was complete within a fortnight.

The patient with encephalomyelopathy (Case 17) was stuporous when she was examined on the eighth day of illness. Corticotrophin, 100 units 12-hourly, was begun, and within 48 hours she was fully conscious and rational. She was found then to have a severe tetraplegia with absent reflexes but no sensory loss. She was doubly incontinent. She complained of impaired vision and her optic discs, initially normal, became unduly pale. Visual acuity fell slightly but

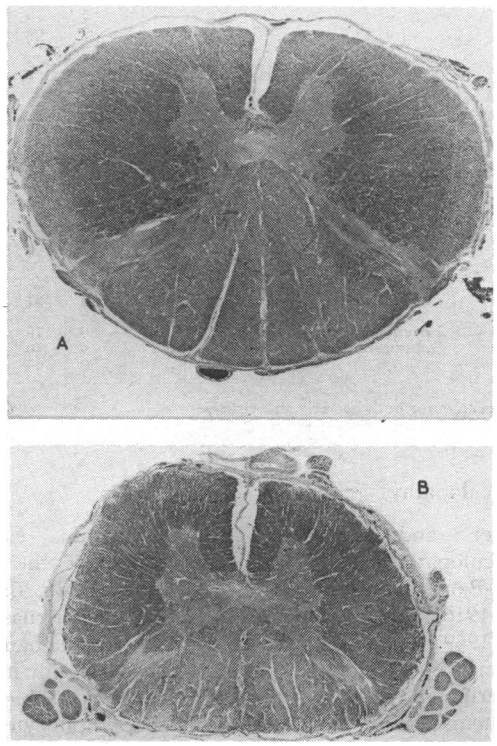


FIG. 2—Transverse sections of cervical (A) and dorsal cord (B) of case of relapsing myeloradiculopathy. Demyelination of posterior and of posterolateral columns. (×5).

scotoma was not present. After three months she made a remarkable recovery. Despite a waddling gait she was able to walk a mile (1,600 m), individual muscles were strong and had regained their normal size, and her vision had returned to normal. Her only complaints were of slowness of micturition and total loss of libido.

Electroencephalograms were performed on both patients during the acute stage of illness and showed diffuse slow-wave activity at theta and delta frequencies. Subsequent records showed progressive return to normal. The spinal fluid findings were abnormal in both cases (Table II).

### Pyogenic Encephalopathy

The association of pyogenic infections with influenza is a potent cause of morbidity and death (Stuart-Harris, 1965). Subdural empyema, however, is rarely described. In a recent review of this condition Hitchcock and Andreadis (1964) found that the overall mortality rate was 34% since the introduction of antibiotics and that it was particularly lethal in children. Four out of 11 patients aged 10 to 20 years died. In 10 the source of infection was a paranasal sinus and in the eleventh a flare-up of chronic middle ear disease.

The child (case 10) with subdural empyema had been ill during Christmas week with influenza, confirmed a fortnight later by a titre of 1:64 to influenza A virus (Table I). Shortly before New Year's Day she became listless and complained of headache and on 7 January 1970 had a single generalized convulsion. On admission to hospital she was fully conscious and had a fever of 39°C, but otherwise had no abnormal signs. Ampicillin and erythromycin were given. Twitching without loss of consciousness was reported during the first night and next morning lumbar puncture showed a few lymphocytes but normal protein and sugar. A second puncture a week later was similar (Table II). Her temperature returned quickly to normal but she remained listless and generally unwell without specific signs. On 26 January sudden recrudescence of fever was followed by dense left hemiplegia. Burr holes were made and a large subdural empyema was drained from the right parietal area. The pus was sterile. Recovery was at first satisfactory but relapse followed and she died suddenly on 6 March. At necropsy pus was loculated in and around the occipital lobe but no source of infection was found in her ears and paranasal sinuses, which in life had seemed normal.

### Discussion

Two points of interest emerged from this record of acute neurological illness in the wake of the winter epidemics of 1969-70. The first was neurological. Myelopathy is an uncommon disease: in this subregion of Wales in 1957 only 2 out of 13 neurological cases associated with Asian influenza had signs of myelopathy (McConkey and Daws, 1958; Wells, James, and Evans, 1959); and during the 1962 smallpox epidemic, out of 20 cases with central nervous disorder which followed 800,000 vaccinations only one had transverse myelopathy (Spillane and Wells, 1964).

Six cases of transverse myelopathy within the space of 10 weeks (from 26 December 1969 to 2 March 1970) among a population of one and a quarter millions would be unusual at any time (Table I). Over a slightly longer period (from 22 December 1969 to 6 April 1970) there were, in addition, four cases of myeloradiculopathy, two cases of postherpetic myelopathy—a complication of shingles in less than 7% of cases (Gupta, Helal, and Kiely, 1969)—one case of encephalomyelopathy, and three cases of polyradiculopathy with unusual features suggesting spinal involvement.

Thus 16 of the 19 cases displayed special susceptibility of the spinal cord and dorsal nerve roots to the effects of influenza and of other winter infections. The histological findings of the fatal case, excluded from the main series owing to the absence of prodromal infection, underlined the selective distribution of lesions in these same areas of the nervous system.

The second focus of interest was epidemiological. Though all 19 patients had a story of preceding respiratory illness, the evidence for a virus infection was often incomplete and no case had a positive virus culture. Eight had serological support for infection with influenza A, and in a ninth case this had clearly followed the onset of neurological symptoms (Table I). Three patients had clinical and serological evidence of adenovirus infection, two had herpes zoster, and one had a falling titre to *Myco. pneumoniae*.

During the winter the unusual number of postinfectious syndromes had suggested a causal relationship between influenza and the neurological disorder. Afterwards the evidence seemed tenuous, indicating at most that the greater density of cases during the influenza epidemic was related only to upper respiratory infection and not to a specific organism.

Many colleagues have contributed generously to this report and I am deeply indebted to them. Particular thanks are due to Dr. G. Anderson for his account of his patient with polyneuropathy; to Dr. D. M. Williams for details of the patient with relapsing myeloradiculopathy; to Dr. J. D. Spillane for permission to quote the details of Cases 4, 11, 12, and 13; to Dr. J. D. Ball for details of Cases 1, 8, and 11 while they were treated in the assisted respiration unit; to the many general practitioners, physicians, surgeons, and paediatricians who referred their patients to me; to Dr. A. D. Evans, who provided the information on virus serology and culture; to Dr. A. S. Bligh for the myelogram of Case 4; to Dr. J. G. Graham for the electromyograms and studies of nerve conduction; to Dr. R. C. Ryder, who performed the necropsy on the fatal case of myeloradiculopathy; and to Dr. D. G. F. Harrisman, who examined the brain and spinal cord and provided the illustrations of histological sections.

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