Attention was drawn by us in 1943 (Brain, Greenfield and Russell, 1943) to a form of subacute ingravescent encephalitis which had been described by Dawson in the United States in 1933 and 1934. At that time we reported briefly on the examination of two cases which had occurred in the London district during the previous three years. Since that time we have had the opportunity of making a post-mortem examination of two further cases and in recording these take the opportunity of giving a fuller description of the two cases we had previously recorded, and of discussing the position of the disease in relation to other forms of encephalitis.

**Inclusion Encephalitis**

**Case 1.**—D. B., male, aged 4 years and 4 months, was admitted to the Queen's Hospital for Children, Hackney Road, on September 4, 1939, under the care of Dr. Alice King to whom we are indebted for the clinical notes.

**Clinical history.**—Six or seven weeks before admission the child was noticed to limp with his right leg. Two weeks before admission there was weakness of the upper limbs, and incontinence of urine. Loss of power in all four limbs developed one to two weeks and fecal incontinence three days before admission. No changes in mentality or behaviour had been noted.

**On examination** the child was unable to stand or sit up. Speech was indistinct. Periods of irritability alternated with lethargy. No defect was found in any of the cranial nerves. There was no wasting. On the motor side there was flaccidity and diminished power in the arms; the legs were spastic. All reflexes were present, being brisk in the legs. The plantar reflexes were flexor. No sensory changes could be elicited owing to lack of co-operation. **Lumbar puncture** on the day after admission yielded clear colourless cerebrospinal fluid under a pressure of 120 mm. and containing 10 mg. per cent. of protein, 0.7 per cent. of chlorides and 1 lymphocyte per 2 c.mm. Cultures of the fluid were negative.

**Progress.**—During the period in hospital there was an occasional rise in temperature of 99° and 100° F. On September 6, ataxy of both arms was noted and a slight internal strabismus of the left eye. September 7: There was right wrist-drop. September 19: There appeared to be slight general improvement and he could lift his head off the pillow. On September 30, however, swallowing became difficult and he was apparently blind and spastic with a bilateral extensor plantar response.

Death took place on October 6, 1939, eleven weeks after the onset of the illness; a rise of temperature to 106° F. was recorded on this day.

A necropsy was performed twenty-four hours later by the late Dr. Elizabeth
O'Flynn. Examination showed the body of a well-nourished boy. There were emphysema of the lungs, slight fatty degeneration of the liver and a cortical scar in the right kidney. No further abnormality in chest and abdomen was found.

Brain (weight 1,441 grammes).—The cerebral hemispheres were symmetrical and all convolutions full. The meninges were moist. On horizontal section through one hemisphere the white matter was homogeneous and felt somewhat rubbery. The grey matter and ventricles appeared normal.

The spinal cord was not removed.

No additional macroscopic changes were found on further section of the brain when hardened in formaldehyde.

Microscopic examination.—Blocks from both Rolandic areas, left frontal cortex, right hippocampus, right occipital (area striata), left occipital (convexity), right basal ganglia, mid-brain through anterior corpora quadrigemina, pons through fifth roots, upper medulla oblongata, dentate nucleus, cerebellar cortex and the choroid plexus from a lateral ventricle were embedded in paraffin. Sections were stained with Ehrlich's hematoxylin and eosin, Weigert's iron hematoxylin and van Gieson's mixture, and with phosphotungstic-acid hematoxylin. Some sections from the cerebral cortex were also stained for Nissl substance and by Loyez' hematoxylin for myelin.

Frozen sections from the left Rolandic and occipital cortex were stained by silver carbonate for astrocytes and microglia, a few of the latter sections being counterstained with Sudan III.

Over the cerebral cortex the leptomeninges were slightly thickened by fibrosis, and sparsely infiltrated with small groups of lymphocytes and plasma cells which tended to lie near blood-vessels in the depths of the sulci. A similar, more abundant infiltration was present in the adventitial sheaths of the perforating vessels, and conspicuous cuffs of the cells were often found in the sheaths towards the junction of the grey and white matter. Both veins and arterioles were affected.

A large proportion of the pyramidal cells exhibited stages of chromatolysis leading to necrosis. Such changes were often associated with the presence within the nucleus, and sometimes within the cytoplasm also, of oval or round inclusions or eosinophil material. The intranuclear inclusion was usually solitary, but occasionally two or more were present. It generally lay at the centre of the nucleus while the nucleolus and nucleoplasm were displaced to the periphery, being separated from the inclusion body by a clear halo. In the earlier stages the inclusion was about the same size as the nucleolus (fig. 1) but later it increased until almost the whole of the nucleus was occupied. It was then outlined by a dense ring of chromatin applied to the nuclear membrane (fig. 3). With high magnifications the inclusion appeared finely granular but showed no further structural details. It showed no affinity for silver carbonate, but was pale bluish-green in Nissl preparations and faint purple with phosphotungstic-acid hematoxylin. It had a variable affinity for phloxin in sections stained by Lendrum's phloxin-tartrazine method.

The cytoplasmic eosinophil inclusions were of irregular shape, accommodating themselves to the confines of the cell. Occasionally they occupied the adjacent axis cylinder. They appeared hyaline, non-granular and deep purple with phosphotungstic-acid hematoxylin, though they took the same tint as the intranuclear inclusions in Nissl preparations. Their affinity for silver carbonate was not determined. They were strongly phloxinophil in sections stained by Lendrum's phloxin-tartrazine method.

The degeneration of the pyramidal cells was associated with a conspicuous proliferation of the microglial cells, many of which were rod-shaped (figs. 1 and 2). No inclusion bodies were identified in these cells. A few, however, were present
in the nuclei of the oligodendroglial cells which showed, in general, advanced stages of acute swelling.

In the deeper layers of the cortex the astrocytes had undergone slight proliferation and this was more intense in the immediately subjacent white matter. No inclusion bodies were found within these cells. Although individual axis cylinders and their sheaths had frequently undergone degeneration there were no patches or zones of demyelination in the centrum ovale. Sparsely distributed fat-granule cells, and cuffs of similar cells in the Virchow-Robin spaces of blood-vessels penetrating the white matter, provided evidence of the more diffuse character of the degeneration.

Distribution of changes in cerebral cortex.—Although all parts of the cerebral hemispheres examined were affected, the distribution of inclusion bodies and severity of the changes was uneven. The cortex of the occipital and motor areas was more affected than the hippocampal and frontal regions.

In the basal ganglia perivascular cuffing was of moderate severity and there was considerable generalized degeneration of the neurones. Only one intranuclear inclusion was found occupying a ganglion cell in the caudate nucleus. Slight gliosis was present in the thalamus.

In the mid-brain, pons and medulla oblongata meningitis was absent but there was focal cuffing of the perforating vessels associated with degeneration of neurones. A few intranuclear inclusion bodies were found in the olives only. The neurones of the substantia nigra showed severe chromatolysis without inclusion bodies. A few small lymphocytes were present in the nervous tissues here and in the nuclei of the third nerve.

No histological changes were present in the cerebellum apart from severe chromatolysis in the Purkinje cells, many of which had disappeared, and in the dentate nucleus.

There was severe degeneration, with pyknosis and karyorrhexis, of the epithelium of the choroid plexus in the lateral ventricle. The stroma appeared normal. No inclusion bodies were identified.

Case 2.—History.—D. H., male, aged 11 years. On July 7, 1942, he received his first inoculation of 0.2 c.c. of alum-precipitated toxoid against diphtheria. Three or four days later his parents noticed that he had become forgetful and when sent on an errand could not remember what to do unless it was written down. He became a messy eater and lolléd at the table and was nervous when on his bicycle. These symptoms continued until August 11 when he had his second inoculation of 0.5 c.c. of A.P.T. On August 13 while getting into bed he fell out on to his head, cutting the right side of his forehead which required to be stitched. On August 15 he was noticed to be unsteady in walking and the next day had to hold on to things to prevent himself from falling. He could not see his dominoes nor find the electric light switch. On August 17 he was admitted to the Connaught Hospital, Walthamstow, under the care of Dr. Kenneth Perry and on August 31 he was transferred to Chase Farm Hospital, Enfield. During his stay in the Connaught Hospital his speech became increasingly indistinct and he became incontinent.

Condition on September 4, 1942.—Conscious but unco-operative. Speech slurred and almost unintelligible. Optic discs normal. Visual fields appear full on confrontation. Pupils moderately dilated, reacting briskly to light and accommodation. Ocular movements full; slight bilateral ptosis. Moderate trismus. Bilateral facial spasm producing a risus sardonicus. Weakness of voluntary movement of left side of face. Soft palate and tongue normal. There were intermittent attacks of clonic spasms of the flexors of the right upper and lower limbs, synchronous in both. Between these attacks voluntary movement of these limbs was fairly strong. A grasp reflex was obtainable from the right hand. There was spastic weakness of
the left upper and lower limbs with an intermittent tremor of the left upper limb. The tendon reflexes were exaggerated but equal on the two sides in both upper and lower limbs. The right plantar reflex was flexor and the left extensor. Pin-prick was felt on both sides of the body, possibly more keenly on the right than on the left. No other form of sensibility could be tested. Cervical rigidity and Kernig's sign absent. Temperature 99°, pulse 72, respirations 18.

September 8, 1942, lumbar punctured: C.S.F. pressure 100 mm. 4 c.c. slightly blood-stained fluid. Cells 3 per c.mm. all lymphocytes. Red cells—1,000 per c.mm. Globulin negative. Total protein 30 mg. per cent. Chloride 0·72 per cent. Culture sterile.


Subsequent history.—By September 7 he was completely unconscious and nasal feeding was begun. In both fundi to the temporal side of the optic disc a round white patch of choroidoretinitis about double the diameter of the disc was seen. Both upper limbs were now spastic in flexion and both lower limbs in extension, both plantar reflexes being extensor. Towards the end of the second week in September the temperature rose and at the end of the third week reached 103·5°. It remained with slight variations at about 102°, and the pulse-rate about 120 until October 13 when he died, three months after the onset of his illness. During the last five weeks of his life his nervous condition resembled that of decortication.

On September 15 he was given 15,000 units of diphtheria antitoxin and on September 16 a further 10,000 units and 10,000 units were given on September 22, 23, 24, 25 and 26 without any apparent result. On September 30, October 1 and 2, 21 grammes of sulphapyridine were given, also without result.

A post-mortem examination was made on 14.10.42, twenty-one hours after death.

The liver, spleen, kidneys and suprarenal bodies appeared normal microscopically.

The lungs showed patchy collapse of both lower lobes, with small foci up to half an inch in diameter of bronchopneumonia.

No intranuclear inclusions or foci of necrosis were found in the abdominal organs.

Apart from unusual firmness the brain appeared quite normal. There was no congestion of the cortex or opacity of the meninges.

Pieces were taken for section from the frontal pole, motor, hippocampal and inferior temporal cortex, occipital cortex including the striate area, the basal ganglia, mid-brain, pons, medulla, cerebellum and spinal cord (sixth, seventh and eighth cervical, first and sixth thoracic and second lumbar).

Definite lesions of encephalitis were seen in all parts examined except the cerebellum and the lower thoracic and lumbar levels of the spinal cord. These consisted of degeneration of neurons, many of which in all affected areas contained intranuclear and cytoplasmic inclusion bodies; microglial increase with accumulation of these cells in clusters in the medulla and spinal cord (glial-star formation): perivascular lymphocytic infiltration and astrocytic hyperplasia (neuroglial sclerosis). These reactions and degenerations varied in degree and in proportion to one another in different areas examined, probably according to the age of the process in that area. Neuronal degeneration and neuroglial sclerosis preponderated in the cerebral cortex, microglial proliferation and lymphocytic infiltration in the cervical cord, but all four types of change were seen in greater or less degree in all the affected regions.

A more detailed description of the appearances in each area will indicate these variations.

Motor cortex.—Here there was a general loss of nerve cells and those that remained had shrunken cell bodies so that it was impossible to distinguish the cortical layers. A few Betz cells were present. Some looked almost normal:
others showed central chromatolysis or irregular shrinkage with loss of Nissl granules. None of those seen had intranuclear inclusion bodies. The smaller pyramidal cells were widely affected, many having disappeared, and all having a very shrunken cell body and a hyperchromic nucleus. A considerable number contained intranuclear inclusion bodies, and the cytoplasm of these cells was always very shrunken or ragged and usually showed eosinophilic degeneration. All the astrocytes had large cell bodies, passing off into processes which were readily seen in paraffin sections stained with haematoxylin and eosin, but only a few of the thicker processes, especially those going to the blood-vessels (vascular foot processes), contained neuroglial fibres stainable by phosphotungstic acid haematoxylin. Paired astrocytes indicating multiplication were numerous.

There was great overgrowth of neuroglial fibres both in the subpial zone and in the deepest layer of the cortex and the neighbouring white matter. There was also enlargement both of the nuclei and processes of the microglial cells, and a few of these cells had a rounded, rather foamy cell body. A few vessels were ringed by a single layer of lymphocytes within the perivascular sheath, but this was not very prominent in the cerebral cortex.

In some areas, more in the superficial cortex than in that bordering the sulci, most of the nerve cells had disappeared, and astrocytes were more numerous than neurons. In the underlying white matter all the astrocytes had swollen cell bodies giving rise to fine fibrous processes, and there was a considerable excess of neuroglial fibres.

Prefrontal cortex.—Conditions here were similar to those in the motor cortex, with even more destruction of neurons and more gliosis and increase in rod cells and other microglial forms.

Hippocampal cortex.—Here there was an almost complete destruction of the layer of pyramidal cells in the zone lying nearest to the ventricle; elsewhere it was fairly well preserved. In the area of maximal destruction almost every one of the few remaining neurons contained an intranuclear inclusion body, and showed severe degeneration of the cell body. The fascia dentata was only slightly affected. There was heavy gliosis with swollen astrocytes in the affected zone of pyramidal cells. The neighbouring part of the hippocampal gyrus showed a degree of neuronal degeneration comparable with that in the motor cortex, with very many intranuclear inclusion bodies.

On the inferior surface of the temporal lobe near its external border there were areas in which the majority of the nerve cells contained intranuclear inclusion bodies and were severely degenerated. Slight perivascular lymphocytic infiltration was seen in this region round the cortical veins.

Occipital cortex.—Here there was little destruction of neurons and the general architecture and cortical layers were little disturbed. No marked neuroglial or microglial proliferation was present here, although in the underlying white matter the astrocytes had rather swollen cell bodies and some increase of fibres. In one sulcus there was considerable lymphocytic infiltration of the pia-arachnoid. However, with higher magnification many nerve cells were found to be in various stages of degeneration and many intranuclear inclusion bodies were seen in them.

Thalamus.—The whole nucleus was fairly severely involved but in a somewhat patchy manner. In the most severely affected areas most of the nerve cells had disappeared. A few were recognizable as such, and presented various degrees of chromatolytic degeneration, many having their nuclei flattened under the cell membrane, others were only recognizable as nuclei containing inclusion bodies with a shred of cytoplasm round them. There was considerable gliosis and increase in number and size of microglial nuclei. There was also considerable lymphocytic cuffing round many of the veins. In places the tissue was vacuolated, even in celloidin sections.
Caudate nucleus and putamen.—These nuclei were only slightly affected but showed slight gliosis with the presence of a number of neuroglial fibres in all areas. These were chiefly vascular processes but several others were seen. Occasional nerve cells contained intranuclear inclusions but most were normal. Slight lymphocytic cuffing was seen round a few veins.

Globus pallidus.—This was in general fairly normal, but a considerable proportion of neurons appeared degenerated and contained intranuclear inclusions. Owing to the absence of small nerve cells in this nucleus it was possible to establish with certainty that occasional oligodendroglial nuclei contained inclusion bodies. Occasional plasma cells were seen here close to the wall of capillary vessels. There was slight swelling of the bodies of the astrocytes.

Mid-brain.—Both in the substantia nigra and the nucleus ruber there was some excess of microglial nuclei and numerous vessels in the latter situation showed perivascular lymphocytic infiltration. A few nerve cells were degenerated and contained intranuclear inclusion bodies. The cells of the substantia nigra thus affected had begun to shed their granules which were loosely grouped round the cytoplasm of the cell.

Pons.—Here also there was gliosis and increase of microglial cells in the ventral portion, especially round the nuclei pontis. The astrocytes were all swollen and their neuroglial fibres more numerous and rather thicker than normal, producing a gliosis in the ventral part of the pons. Degenerated nerve cells containing intranuclear inclusions were more numerous there than in the mid-brain nuclei, and occasional nuclei, indistinguishable from oligodendroglial nuclei, also contained small inclusion bodies.

Medulla.—A considerable number of degenerated nerve cells with intranuclear inclusions were found in the inferior olive. One contained two inclusion bodies. In the lower medulla the nuclei gracilis and cuneatus also contained many degenerated neurons with intranuclear inclusions.

Spinal cord.—As has been stated the lower thoracic and lumbar segments examined showed no abnormality. In the cervical segments and first thoracic segment, however, a few nerve cells both in the ventral and dorsal horns were degenerated and contained intranuclear inclusions. Several of the large ventral horn cells contained more than one inclusion body; as many as six were seen in one cell, and in others the inclusion body was lobulated as though it had resulted from the fusion of several smaller bodies (figs. 5 to 8). Occasional degenerated cells were surrounded or overlaid by microglial cells, a condition of early neuronophagy.

The cytoplasm of many of the affected ventral horn cells contained a few granules which stained with cosin a bright red colour, almost as bright as that of red blood cells. The larger of these usually lay in the periphery of the cell. With phosphotungstic acid haematoxylin these granules stained pink, but many other granules and curled thread-like structures were also seen, chiefly towards the centre of the cytoplasm, which took a deep purple colour with this stain. Granules of the latter kind are seen in many forms of neuronal degeneration, but they were specially abundant in this case. The cells with these purple-staining cytoplasmic granules were usually found to contain one or more intranuclear inclusion bodies. Although more easily seen in the large ventral horn cells, intranuclear inclusion bodies were present in a larger proportion of the neurons of the dorsal horns (figs. 9 and 10).

Quite intense perivascular lymphocytic infiltration was present in several of the lower cervical segments of the cord. The larger veins in the grey matter and grey commissure were chiefly involved. A few glial stars composed chiefly of microglial cells were also present in the grey matter in these segments.

Pieces of fresh tissue were sent in buffered glycerine saline to the late Professor J. McIntosh of the Bland-Sutton Institute, who with Dr. F. R. Selbie injected them
intracerebrally into mice and rabbits and inoculated them also on to the scarified cornea of rabbits, without result.


Clinical history.—At the age of 2 she had measles and "kidney trouble"; at 3 years two attacks of pneumonia; at 5 years bilateral otitis media. One month before the onset of her terminal illness there had been recurrence of earache, but after three days she was able to return to school. Apart from these illnesses she seems to have been a normal child until nine weeks before death when her work at school became slovenly. This was followed by rapid mental deterioration; she soon became unable to dress herself and her speech was unintelligible. There was no complaint of headache. A month later she was brought home to London from the country district to which she had been evacuated during the war; she then did not recognize her mother.

On admission to the London Hospital under Dr. Henry Wilson, four weeks before death, she appeared well nourished. She was never obstreperous but was unco-operative, and would sit silent and morose, and slept for long periods.

On examination.—The fundi showed pallor of the discs, but were otherwise normal. Pupils: sluggish reaction to light. No abnormality in any of the cranial nerves. No nystagmus. Limbs: resistance to passive movement. Occasional involuntary twitchings. Tendon reflexes normal in upper limbs; increased in lower limbs. Flexor plantar responses.

Blood: slight leucocytosis. Wassermann reaction negative.

Lumbar puncture yielded cerebrospinal fluid under increased pressure, with normal protein and no excess of cells. Wassermann reaction negative. Lange: paretic type of curve. Urine: a trace of albumen present.

Progress.—Temperature swinging between 97° and 103°. She steadily deteriorated and, two weeks before death, became unable to feed herself or to recognize anybody. She lapsed into a state of decerebrate rigidity with spasticity of the limbs and finally periodic convulsive attacks which affected the whole body. At this time she showed a divergent squint; the pupils were unequal and reacted poorly to light, especially the left. Death took place from respiratory failure.


Weights.—Body, 14-88 kg.; length, 1-3 m.; heart, 99 grammes; liver, 483 grammes; kidneys, 92 grammes; suprarenals, 7-6 grammes; spleen, 35 grammes; pituitary, 0-3 gramme; thyroid, 3-05 grammes; thymus, 3-1 grammes; pancreas, 27-1 grammes; ovaries, 1-5 grammes.

Examination of brain.—With aseptic precautions portions of the left frontal and right occipital cortex, the left basal ganglia, upper pons, and cerebellum were removed for experimental transmission to laboratory animals. The rest of the brain was fixed in formaldehyde. On section there was diffuse engorgement and
numerous pin-point haemorrhages formed an ill-defined zone in the subcortical white matter in many parts of the cerebrum. In these areas the white matter often showed a diffuse yellowish-grey discoloration but without obvious alteration in texture. In a few areas, however, there was obvious friable softening of the white matter, namely in the left post-central gyrus, the left occipital and occipito-parietal convexity extending medially to the parasagittal region, and the medial surface to the calcarine fissure. The right occipital convexity was similarly affected in the area from which bits had been removed for animal-transmission. No naked eye changes were found in the basal ganglia, brain-stem or spinal cord.

Microscopic examination.—Blocks from the left frontal convexity, inferior surface of right frontal lobe including the olfactory tract, left temporal region including Ammon's horn, right Rolandic cortex, right occipital cortex, left post-central cortex; basal ganglia on both sides, mid-brain,pons, cerebellum, medulla oblongata, posterior part of left eyeball and representative levels of the cord, and the left ventricular choroid plexus were embedded in paraffin. The posterior root ganglion of the twelfth thoracic segment on the right, a Gasserian ganglion, the semilunar ganglion and right sympathetic chain were similarly treated. Frozen sections were prepared and stained by a variety of silver techniques from the left frontal and right occipital regions, the blocks being adjacent to those taken for paraffin sections. The stains used were the same as in Case 1.

The greatest changes were in the cerebral cortex and the immediately subjacent white matter. All parts of the cortex were affected, but the changes varied considerably in intensity in different areas. The most severe were in the right occipital lobe and left post-central region. Both here and elsewhere meningitis was slight and was confined to a sparse infiltration with a mixture of small lymphocytes, large mononuclear cells and occasional neutrophil leucocytes. There was slight cuffing of a moderate number of the perforating vessels in the occipital lobe with similar cells, predominantly lymphocytes. Elsewhere cuffing was very scanty or absent. The most conspicuous changes were in the pyramidal cells, a variable proportion of which were affected in the same manner as in Case I. In general the cytoplasmic and intranuclear inclusion bodies were more numerous in the present case; in some areas, for example the occipital cortex, almost every neurone was so affected. The microglial response, with the production of transitional forms and rod-cells was proportionate to the neuronal degeneration and destruction. In the subcortical white matter there was correspondingly a variable loss of axis-cylinders associated with aggregates of foam-cells which, in silver preparations, were demonstrated as rounded-up microglial cells laden with sudanophil lipoid. In situations where the bodies of the neurones were most heavily occupied by inclusions the subcortical white matter, as noted macroscopically, was obviously softened. But in Loyez préparations the demyelination in such areas was poorly defined and incomplete. Gliosis of the subcortical white matter, and of the deeper layers of the cortex, was usually conspicuous. Fresh haemorrhages, which tended to be perivascular, were present in the white matter in some areas. No inclusion bodies were identified with certainty in the neuroglia, ependyma or choroid-plexus epithelium.

In the basal ganglia there was slight perivascular cuffing in the corpus striatum, and a very few intranuclear inclusion bodies were present in neurones in the lenticular nuclei and thalamus.

The mid-brain showed uneven chromatolysis of the neurones in the substantia nigra, with one doubtful intranuclear inclusion body, and slight cuffing of an adjacent perforating vessel. There was no meningitis over the cerebellum. Chromatolysis affected many of the Purkinje cells and these were missing in some areas, while the Bergmann cells had undergone focal proliferation. No inclusion bodies were present. Chromatolysis was present in the nuclei pontis and a few inclusion bodies were identified within these neurones. Two also were found in...
nuclei that appeared to belong to oligodendroglial cells. There was slight cuffing of the perforating vessels in the ventral half of the pons, but no evidence of meningitis. The neurons of the inferior olives showed considerable pyknosis and there was slight chromatolysis in the tegmental nuclei of the medulla oblongata. In this region there was some microglial proliferation, but no inclusion bodies were found at this level.

The seventh cervical, third and ninth thoracic and second lumbar segments of the spinal cord showed no histological abnormality.

In the twelfth thoracic right posterior root ganglion there was chromatolysis and some ganglion cells were shrunk and deeply haematoxyphil. No inclusion bodies were present.

The Gasserian ganglion and semilunar ganglion appeared normal.

Portions of the right sympathetic chain showed chromatolysis of some ganglion cells, and one was largely replaced by polymorphonuclear leucocytes. No inclusion bodies were found.

Inclusion bodies in other tissues.—A special search was made for these in sections of the nasal mucosa, pharynx, stomach, small intestine, liver, pancreas, and lung with negative results.

Experimental transmission to animals.—Samples of brain tissue, as already indicated, were sent to three different laboratories. Intracerebral inoculations were made into rabbits, guinea-pigs, mice and two hamsters with negative results.

Case 4.—M. J. (male) was seen in the Out-Patient Department of the National Hospital on April 25, 1947, by Dr. Macdonald Critchley to whom he had been sent from Charing Cross Hospital by Dr. Doyne Bell for an opinion. He was at that time 5 years and 11 months old. The boy's history was that he had developed normally till September 1946 when he had a febrile illness diagnosed as acute rheumatism. In January 1947 he began to make unsteady movements of the hands and head, he tended to stumble and drop his cup out of his hands. Incontinence of urine appeared at this time and persisted. By March he was much worse, and was having attacks with a frequency of about one a minute in which he fell forwards with an apparent relaxation of the skeletal muscles for a fraction of a second, but did not actually fall. His speech also deteriorated. He had vomited several times during the week previous to his visit to the National Hospital. Paresis of the facial musculature on the right side had appeared in March 1947, and for about four months there had been incontinence of urine.

While in Charing Cross Hospital in March a lumbar puncture had been performed, the fluid being found to be quite normal. (The Lange reaction was not performed on the fluid.) A blood-count and X-ray examinations of the head and chest also gave normal results.

When seen in the National Hospital he lay on his back with his legs flexed, making large flexion athetotic movements more with the right than with the left leg. There were also constant myoclonic jerks of all his limbs, sometimes small in amplitude and at other times coarser and more violent. There appeared to be transitory losses of consciousness. He was apathetic, and showed little if any voluntary movement except feebly to clutch his teddy bear when it was put in his arms. He could follow a light or the noise of jangling keys. When anything approached his lips he was apt to open his mouth and if the object was brought into contact with it to suck or bite at it. The nurse had noticed that when he was fed with a spoon even if his mouth was already full he would open his lips at the sight of food. The pupils reacted to light and accommodation. His eyes followed moving objects without evident hesitation; there was no nystagmus. There was evident weakness of the right lower face. He ate extremely slowly but did not choke. He did not speak but occasionally made a slight whining noise, as for example when he was tested by pin-prick, which he resented on all parts of the
body. He withdrew his feet when they were pinched. The tendon-jerks were all present, the ankle-jerks being very feeble. The abdominal reflexes were absent and the plantars gave a flexor type of response. The examination showed a general picture of progressive dementia, with apathy, speechlessness, paralysis and rigidity and the diagnosis rested between a post-encephalitic state and a form of progressive cerebral degeneration. An electro-encephalographic examination was made a week later by Dr. Denis Williams who reported "A grossly abnormal E.E.G. Episodes of high-voltage spikes showing a sharp phase reversal were present in the posterior parietal regions. They were synchronous with the myoclonic jerks. Transverse leads showed persistent phase reversal in the left hemisphere and all the evidence pointed to a severe biparietal abnormality more evident on the left side."

He returned to Dr. Doyne Bell's ward in Charing Cross Hospital and during the subsequent weeks his condition deteriorated very rapidly. He went home in May, but was sent into Hillingdon County Hospital on June 3, 1947. On examination there the patient was lightly comatose responding to the stimulus of noise by convulsive movements of the right hand and arm and resisting attempts to open the mouth. There was generalized spasticity and the jerks were equal on the two sides, there was a bilateral extensor plantar response and ankle clonus was present on both sides. He deteriorated steadily and developed bronchopneumonia from which he died on July 7 having been ill for about six months.

We are greatly indebted to Dr. Herbert Rogers for sending us notes of his post-mortem examination and half the brain.

A post-mortem examination was carried out by Dr. Rogers on July 8, fourteen hours after death.

*External appearance.*—An emaciated boy. Bedsore over sacrum.

*Internal examination.*—Head: Scalp and skull are normal.

Brain: The pial veins are congested. No evidence of meningitis. The left half was sectioned through the basal ganglia; the small vessels are unduly prominent in the basal ganglia. No other visible abnormality.

Mouth: Tongue normal. Tonsils somewhat enlarged.

Thyroid: Normal appearances.

Chest: No fluid exudates or adhesions are present. Thymic tissue is small in amount.

Lungs: Larynx normal. Trachea and larger bronchi normal. Both lungs appear to be normal. No consolidation and no evidence of tuberculosis. No enlargement of mediastinal or hilar glands.


Liver: Normal size. No visible lesions. Gall-bladder and ducts normal.

Pancreas: Appears to be normal.

Adrenals: Small, but normal.

Spleen: Normal appearance.


Cæsophagus: Normal.

Stomach: Normal size. There is a small submucous nodule near the pylorus which may be an adenomyoma or some similar tumour.

Intestine: Normal throughout. Peritoneum healthy.

The right cerebral hemisphere, with the right half of the mid-brain, pons and cerebellum were received from Hillingdon County Hospital. There was definite thickening and opacity of the pia-arachnoid over the fronto-parietal region of the convexity of the cerebrum, with some widening of sulci. The hemisphere was firm, but showed no macroscopic abnormality on section.

Large pieces of cortex measuring 4 cm. in diameter were taken from the frontal
and occipital poles, from the pre- and post-central regions including the corpus callosum about its central part, and from the temporal lobe at right angles to the hippocampus. Horizontal sections were also taken from the basal ganglia at two levels and from several levels of the mid-brain and pons. The cerebellar hemisphere was cut in a sagittal plane through the nucleus dentatus. These pieces were embedded in celloidin and stained by Ehrlich’s haematoxylin with eosin, iron haematoxylin with van Gieson’s counterstain, Mallory’s phosphotungstic acid haematoxylin, Loyez stain for myelin, Heidenhain’s azan and thionin blue for Nissl granules. Pieces of frontal and central cortex were also cut frozen, and stained by Scharlach R. with Ehrlich’s haematoxylin, Cajal’s gold sublimate for astrocytes, and the Weil Davenport method for microglia. Paraffin sections of frontal cortex and pulvinar of thalamus were also stained by Lendrum’s method for intracellular inclusions.

These sections showed the same general appearances as were seen in the previous three cases. In spite of the longer duration of the disease the degree of gliosis and of destruction of cortical neurons was very similar to that in Case 2. There was, however, rather more microglial hyperplasia with formation of rod cells which in places was very striking and the perivascular infiltration, in this case predominanty with plasma cells, was more prominent both in the grey and white matter. Under the most affected areas of cortex there was considerable gliosis of the white matter, with the formation of swollen-bodied astrocytes and considerable increase in number of microglia. Swollen myelin sheaths, a few of which contained one or more myelophages, were seen in these areas.

While the inflammatory process was diffuse and some degree of it was seen in most of the areas examined, it varied greatly from one area to another without obvious reason. In the frontal pole it was greater on the convexity than on the mesial surface. The precentral gyrus was severely affected. Here only an occasional Betz cell was recognizable, but in the fifth layer there was a number of large cells with a rounded hyaline highly refractile cell body and an eccentric nucleus which in every case contained an inclusion body. These appeared to represent the remains of Betz cells. The significance of this hyaline change will be discussed later. In a few, short thick processes of similar hyalinized appearance ran out a short distance from the cell body. Here and in other severely affected parts of the cortex it was difficult to recognize the layers owing to loss and degeneration of neurons and proliferation of astrocytes and microglia. Two or four closely set astrocytic nuclei were often seen, and there was great hypertrophy of the neuroglial processes, but except in those running to the larger vessels there was little tendency to the formation of Ranvier-Weigert fibres. Fibrous gliosis was, however, well developed in the molecular layer and at the junction of cortex and white matter.

The number of intranuclear inclusion bodies also varied greatly from place to place. In the less affected areas they were scanty, although degenerated neurons were not infrequent. In the more affected areas of the frontal lobe they were numerous, four or five cells containing inclusion bodies of varying size being seen in most high power fields. In the calcarine cortex, which was comparatively slightly damaged, inclusion bodies were not difficult to find in the larger neurons, some filling the nucleus completely, others being quite small, with a diameter about a quarter of that of the nucleus. In the occipital as in the frontal lobe the outer or convex surface was more severely affected than the mesial cortex.

The temporal cortex also was only slightly damaged. In the hippocampus there was slight diffuse fibrous gliosis with an occasional glial star in the pyramidal layer. In Sommer’s sector a few neurons were degenerated and undergoing neuronophagy. Some of these contained inclusion bodies.

In the basal ganglia the large neurons of the caudate nucleus and putamen were rather shrunken with a granular cytoplasm, but no inclusion bodies were seen in them. There was slight fibrous gliosis in these nuclei. The globus pallidus showed
little alteration except a slight excess of microglia and swelling of the astrocytic nuclei, without any formation of fibres in their processes.

The thalamus was affected in an irregular manner, but everywhere the gliosis and microglial overgrowth tended to be greater than the loss or degeneration of neurons, most of which were fairly normal. However, in the pulvinar and dorsal nucleus some neurons were reduced to the hyaline conditions seen in the Betz cells, and others consisted of a mass of granules staining purple with Mallory's phosphotungstic acid haematoxylin, and their nucleus contained an inclusion body. In the corpora mammillaria the changes were similar but rather more intense.

When sections of the pre-frontal and pre-central gyri and the pulvinar of the optic thalamus were examined with the oil immersion objective, inclusion bodies were seen also in the cytoplasm of the affected nerve cells. These varied greatly in size. All were eosinophilic, and with Lendrum's phloxin tartrazine method the smaller bodies had a bright red colour, and appeared more sharply defined than with eosin staining. It was also possible to pick out with ease the more granular bodies which were difficult to distinguish from the cytoplasm of degenerated cells in sections stained with eosin. The smallest bodies resembled those illustrated in figs 1 to 4 and usually lay at the periphery of the cell. As these bodies became more numerous they appeared to become collected in a mass most often near the cell margin in one sector of its circumference, but not infrequently they formed a streak along the centre of the apical dendrite (fig. 14). Later the granules appeared to fuse into a hyaline mass which took a more orange stain with Lendrum's method; this might form a horseshoe round the outer half of the cell body with its ends based on the eccentrically displaced nucleus (fig. 15). Finally the nucleus and the cell body appeared to be lying side by side, the latter having been entirely transformed into a hyalinized shrunken mass (fig. 16). The two latter stages appeared under rather lower magnifications as the eosinophilic hyalinization of the cytoplasm already described.

The cells showing these larger cytoplasmic inclusions always also contained intranuclear inclusions, which in general were smaller in cells with small intracytoplasmic inclusions, and filled the nucleus more completely in cells with larger cytoplasmic inclusions. Cells containing the smaller, more granular inclusions might have one or more small intranuclear inclusions, but some appeared to have quite normal nuclei.

In the corpus luysii, substantia nigra and nucleus ruber there was some fibrous gliosis with slight increase of microglia, but no degeneration of neurons was seen.

In the pons there was rather severe perivascular infiltration and microglial proliferation in the nuclei pontis with slight fibrous gliosis. In some of these neurons intranuclear inclusion bodies were seen, and they were often associated with the presence of cytoplasmic granules which stained purple with Mallory's phosphotungstic acid haematoxylin. The tegmentum and its nuclei were little affected.

The cerebellar cortex showed more obvious changes in this case than in the others. Although the Purkinje cells showed little change and no inclusion bodies were seen in them, many had probably disappeared and there was a fairly diffuse fibrous gliosis of the molecular layer. This was in most places slight in degree, but in some places was rather more definite and was associated with a local excess of microglial cells, which either formed a fairly narrow band passing through the thickness of the molecular layer, or a wider area confined to the inner half or two-thirds of this layer. In the thionin-blue sections the cells sometimes showed their cytoplasm in the fashion described by Spielmeyer as "bush work" (gliastrauhwerk). In most cases, however, only the nuclei were seen. The former appearance which was seen by Spielmeyer in typhus fever probably represents the earlier stages of a local microglial reaction secondary to the degeneration of Purkinje cells.
THE INCLUSION BODIES

In Case 1 only could any granularity be seen in the intranuclear inclusions. In the other three cases they appeared quite hyaline in magnifications up to \( \times 900 \). They were round or oval with a well-defined highly refractile margin. When they were smaller than the nucleus of the cell they usually lay centrally, pushing the nucleolus to one side and leaving a clear zone between them and the nuclear membrane on which the remaining chromatin was condensed. Many inclusion bodies filled the nucleus completely and only a few granules of chromatin could be seen on their surface. The smallest single inclusions, e.g. those in the inferior olives of Case 2, were about 3 \( \mu \) in their narrower diameter; the majority of those in the cortical pyramids varied from 5 to 6 \( \mu \) and the largest, i.e. those in the ventral horns of Case 2, reached 10 \( \mu \) in their narrower diameter. The small multiple bodies seen in the ventral horn cells in this case were less than 1 \( \mu \) in diameter. None of these inclusions was stained by Bielschowsky's silver method. With Ehrlich's haematoxylin and eosin they were eosinophilic, but did not stain quite so brightly as red blood cells, and they often appeared rose pink or even mauve in colour, according to the intensity of the eosin stain. With Mallory's phosphotungstic acid haematoxylin they stained purple or lavender contrasting with the pink-staining nucleolus and the reddish-purple cytoplasmic granules. These last were considered to be degeneration products, and as quite different from the eosinophilic intra-cytoplasmic inclusions, which were not easily recognizable by this stain.

In sections from Cases 1, 3 and 4 stained by Lendrum's phloxintartrazine method the intranuclear inclusions showed a variable affinity for the phloxin; some were quite brightly stained but many showed gradations to orange. The orange examples were usually those that filled the nucleus completely. Sections from Case 1 have also been stained and examined by Lendrum, who reports (1947), "a relatively poor phloxinophilia." The smaller cytoplasmic inclusions on the other hand were uniformly and brilliantly phloxinophil in all three cases.

The cytoplasmic inclusions also stained with eosin rather more brightly than the intranuclear inclusions, i.e. almost as brightly as the red blood corpuscles. The multiple intranuclear inclusions seen in the inferior olives and ventral horn cells of the cervical cord in Case 2 appeared to represent an earlier stage than the larger single bodies, as the cells in which they were found often showed little evidence of degeneration. It appeared probable that the larger bodies were formed by coalescence of small bodies and some evidence of this in the form of lobulated inclusion bodies was seen in a few cells of the cervical cord of Case 2.

Similarly the cytoplasmic inclusions, of which the smaller examples
were usually multiple, appeared to fuse into larger bodies and eventually replaced the whole of the cytoplasm in many cells in the cortex and optic thalamus of Case IV.

**DISCUSSION**

The clinical picture in the four patients reported in this paper showed certain common features which may possess diagnostic value: in fact it was experience of Case 2 that enabled the diagnosis to be made in Case 3 during life. All four patients were children between the ages of 4 and 11 years and in each case the illness ran a subacute course ending fatally between nine weeks and six months after the onset. In Cases 2 and 3 the first abnormality noticed was psychological—a change in temperament; in all four the disease produced dementia and quadriplegia, and finally a condition of decortication. Persistent or intermittent muscular spasms were present in Nos. 2, 3 and 4. Signs of meningeal irritation were absent and the cerebrospinal fluid showed no increase in the cellular or protein content, but a Lange reaction of paretic type was found in Case 3, the only one in which fluid was thus tested. The onset and course of this disorder, then, was more insidious than is usual in the forms of encephalitis due to neurotropic viruses in general.

*Other cases of subacute inclusion encephalitis.*—Our four patients appear to have suffered from the type of encephalitis which was first described by Dawson in 1933, and called by him "inclusion encephalitis." His patient was a boy of 16 whose illness started with involuntary jerking movements of the arms and legs, along with loss of self-control. The illness lasted about seven weeks till death. On post-mortem examination the brain was described as congested and oedematous and on microscopical examination, in addition to the usual evidence of encephalitis, eosinophilic inclusion bodies were found in the nuclei of degenerated nerve cells, and also refractile hyaline eosinophilic inclusion bodies in the cytoplasm. Similar intranuclear inclusions were seen in swollen astrocytes. A year later Dawson published a second case in a girl of 5 years in whom also the early stages of the disease were characterized by peculiar jerkings of the limbs. When admitted to hospital three months later, these jerkings had become more frequent and severe, she had lost the ability to speak and was so stuporose that she did not eat. The cerebrospinal fluid in this case was normal. As in the previous case the limbs assumed a lead-pipe rigidity before death, which occurred four months from the date of the first symptoms. The post-mortem findings in this case were similar to those in the previous one. Injections of brain emulsion from both cases were made into rabbits by the intracerebral, subcutaneous and corneal routes without result. Inoculations were also made into mice, rats, monkeys, dogs, cats and chickens without any effect.
In 1942 a similar case was published by Akelaitis and Zeldis. The patient was a boy of 5 years, whose illness started twelve days before admission. One night he had awakened crying and frightened and the next morning there was stiffness and twitching of the left arm. Five days later the left leg began to twitch and became rigid and these movements progressed to severe dystonic movements causing him to fall backwards. On admission to hospital he was semistuporose and dysarthric, but was well orientated and responded slowly to questioning. There were hyperkinetic seizures like rapid torsion spasms on the left side, with arching of the back, but not of the neck, to the left. Between the seizures the left arm and leg were spastic, the leg in extension, the arm in flexion and adduction. The cerebrospinal fluid was normal, except for the presence of a strong paretic curve in the Lange reaction. A week after admission to hospital the jerking spread to the right limbs and there was dystonia of both sides of the body. Dysphagia and dysphonia supervened with transient ocular palsies. He died nine weeks after the onset of the illness. Post-mortem, the brain was swollen and soft with large areas of cortical necrosis on the lateral and inferior surfaces of the right frontal lobe, in which irregular cyst-like spaces were also seen, and there were smaller discrete areas of necrosis in the left occipital cortex. The microscopical examination of the less-affected areas of the cortex gave similar results to those in Dawson’s cases, inclusion bodies being seen in many degenerated neurons and also in oligodendroglial cells. There were also cytoplasmic inclusions of doubtful nature in the nerve cells. These did not resemble the intranuclear inclusions. No attempt to isolate the virus was made in this case.

Acute forms of inclusion encephalitis.—Under the title “Intranuclear inclusions in infancy,” Kinney published in 1942 the case of a child of 3 years. The illness began with a convulsion, and attacks of trembling and crying. Three days later more convulsions occurred. The child was admitted in a semistuporose condition to hospital, where no abnormal physical signs were found except constant twitching of the lips. Convulsions became more severe, the child became comatose and died about seven days after the onset of illness.

Post-mortem examination showed no gross abnormality, but microscopical lesions of encephalitis were found in all areas of the brain; none was seen in the spinal cord. In the cortex and subcortical white matter there were focal areas infiltrated with polymorphonuclear and mononuclear cells. These were perivascular in the white matter, but more diffuse in the grey, a few areas of which were partially necrotic. In some areas intranuclear inclusions were seen in the nerve cells. The walls of some blood-vessels in this case were necrotic and infiltrated by polymorphonuclear cells and macrophages, and one intranuclear inclusion
was found in a cell of the vessel wall. The inclusion bodies were acidophilic and granular. No inoculation experiments were made in this case. No disease was found at a lower level in the brain than the substantia nigra.

Another acute case in a male aged 21 was published in Australia in 1943 by Swann. The patient was a diabetic, but under control with protamin-zinc-insulin. A fortnight before admission he had had a severe cold with herpes labialis. The illness began with 12 "spasms" during one night in which the patient felt his tongue swollen. He was admitted to hospital next day with left-sided facial paralysis. Glucose and acetone were found in the urine. He had attacks of twitching and two epileptiform attacks when in hospital, and he died nine days after the onset of the illness. Post-mortem examination showed foci of necrosis in the deeper layers of the cortex, often perivascular in distribution and associated with total destruction or partial degeneration of axons and myelin. There was also degeneration of the walls of many vessels, associated with a fibrinous exudate with degenerated polymorphonuclear and microglial cells in the extra-adventitial tissues. The coalescence of necrotic foci led to larger areas of softening under the most severely damaged areas of cortex, similar perivascular areas of degeneration were seen in the white matter. Intranuclear inclusion bodies were found both in nerve cells and in astrocytes and oligodendroglia.

These last two cases have several points in common and differ from the other three in the acuteness of their course and in the evidences of necrotic changes in the walls of the blood-vessels. As no inoculation experiments appear to have been made in either case it is impossible to state whether or not they may have been the results of infection by the virus of herpes febrilis; the occurrence of herpes simplex on the lips in the Australian case a fortnight before the onset of the encephalitis is suggestive in this respect. This suggestion is supported by a case published by Smith, Lennette and Reames in 1941. An infant 4 weeks old was well till four days before admission to hospital when it became irritable and fretful. On the day before admission to hospital there was twitching of the left arm and leg which continued. There were also occasional convulsions. Death occurred on the ninth day of illness. Microscopically the brain showed an extensive inflammatory process in the brain tissue and around the meningeal vessels. Apart from slight swelling of endothelial cells no vascular changes were seen, but areas of frank necrosis were seen in the cerebrum and cerebellum. The intranuclear inclusion bodies varied from four to five times the width of the nucleolus to the whole width of the nucleus and as in Swann's case fine radiating lines were sometimes seen connecting the body with the nuclear membrane.
The larger bodies were often granular. In this case inoculation of brain emulsions into mice, rabbits, rats and guinea-pigs gave a virus indistinguishable from that of herpes febrilis.

A similar case of acute encephalitis due to a virus identical with that of herpes simplex was reported in 1944 by Zarafonetis, Smadel, Adams and Haymaker. The patient was a 25-year-old soldier, who complained of headache three days before he was first examined and during that time became slow and incoherent in speech. On examination he was conscious, but apathetic and febrile, with a temperature of 103°F. and a pulse of 108 per minute. Kernig's sign was positive and there was stiffness of the neck. The spinal fluid contained 175 lymphocytes per c.mm. and 44 mg. of protein, with normal glucose. Three days later the fluid was flocculent with over 300 cells, chiefly lymphocytes. The temperature rose to 105°F., he became delirious but no further neurological signs developed. He died eight days after the onset of the disease. Post-mortem examination showed an area of softening along the inferior margin of the left temporal lobe, 4 cm. in diameter. This area was studded with small haemorrhages. Elsewhere there was intense vascular congestion with small ecchymoses and petechiae. A meningeal exudate was seen especially round the vessels. The cerebral cortex, mid-brain and pons showed perivascular cuffing, and there was some proliferation of glial cells round the cuffed vessels. Many scattered cortical neurons were in a condition of ischaemic necrosis, even in places at a distance from the area of necrosis. Intranuclear inclusions were present in profusion in the most affected areas, chiefly in the glial cells but a few also in neurons. They were also seen in cells deep in the brain tissue in the areas of glial proliferation. Brain emulsion preserved in buffered glycerine produced encephalitis in mice, hamsters, guinea-pigs and rabbits, but inoculation into a monkey was without result.

Cases of encephalitis in which Type A inclusion bodies have been found thus separate themselves into the relatively subacute type examined by Dawson (1933 and 1934), Akelaitis and Zeldis (1942) and ourselves, and the more acute cases of Smith, Lennette and Reames (1941), Swann (1943), Kinney (1942) and Zarafonetis, Smadel, Adams and Haymaker (1944). In two cases of the latter group inoculation into animals proved that the encephalitis was caused by the virus of herpes simplex. In the former group attempts to inoculate animals in both Dawson's case and in our Cases 2 and 3 were without result. Dawson appears to have used mice, rats, rabbits, cats, dogs, monkeys and chickens without result. In our Case 2 intracerebral injections were made into mice and rabbits both by the intracerebral and corneal routes and in Case 3 into rabbits, mice, guinea-pigs and hamsters also without result. It is possible that after so
prolonged an illness the virus might have been fixed to the nerve cells in such a way as to render its passage to animals more difficult. However, it remains true that three workers failed to transmit the virus to animals from our Case 3 although the case was recognized before death as probably one of inclusion encephalitis and every care was taken to ensure a passage to animals if this were possible. It is to be noted also that Akelaitis and Zeldis state in their paper that Dr. Marguerite Smith considered that the inclusion bodies in their case were "quite distinct morphologically from those in which she isolated the herpes simplex virus."

The cytoplasmic inclusions seen by Dawson and by ourselves are also unlike anything seen after infection with the virus of herpes febrilis. Although these differ to some degree in staining reactions from the intra-nuclear inclusions, they resemble the inclusion bodies of other virus diseases, and do not appear to be purely degenerative in character. The evidence, therefore, is in favour of the view that the subacute type of case described by Dawson, Akelaitis and Zeldis and ourselves differs aetiologicaly from the acute cases in which the virus of herpes febrilis has been incriminated.

It is also to be noted that the cerebral lesions in these seven subacute cases were more confined to the grey matter than those in the acute cases. Even though, as in the case of Akelaitis and Zeldis, there may be extensive necrosis of the cortex, it is noted that this "stopped short of the white matter." In the cases we examined it was evident that the encephalitis had attacked the grey matter primarily and that the changes seen in the white matter were secondary to damage to cortical nerve cells.

In this respect the disease contrasts with that of "subacute necrosing leuco-encephalitis" recently described by van Bogaert, in which both white and grey matter appear to be primarily affected, but with much less severe destruction of nerve cells than in Dawson's type. The occasional presence of inclusion bodies in the oligodendroglial cells suggests, however, that the virus responsible for this type of encephalitis may be less strictly neurotropic than, for example, that of rabies.

It is of course possible that more than one form of virus may be responsible for these seven cases, although the close similarity of their histological appearances makes this unlikely. Until further evidence of their aetiology is forthcoming, it would seem advisable to group them together, and to separate them both from the acute cases in which inclusion bodies are present, and from the subacute cases, both of van Bogaert's type, and the other rare subacute cases in which the encephalitis is confined to the grey matter. The term "inclusion encephalitis" suggested by Dawson is therefore not sufficiently distinctive by itself, and we suggest the name "subacute inclusion encephalitis (Dawson type)."
To illustrate article by W. Russell Brain, J. G. Greenfield and Dorothy S. Russell.
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We desire to thank Dr. Macdonald Critchley, whose interest in the case enabled us to obtain material from Case 4, and also Dr. Doyne Bell, under whom the patient was in Charing Cross Hospital, for clinical notes of this case.

SUMMARY

Four cases of subacute encephalitis corresponding to Dawson's "inclusion encephalitis" type are described. The illness ran an ingravescent course, being fatal in from nine weeks to six months, and was characterized by progressive dementia, and in three cases by myoclonic jerking movements of the limbs and face. The cerebrospinal fluid was normal in all four cases except for the presence of a Lange reaction of paretic type in the only case in which it was thus examined.

Post-mortem examination showed subacute lesions of encephalitis which appeared to involve the grey matter primarily, the changes in the white matter being secondary to destruction of cortical nerve cells. Many degenerated nerve cells in the cortex, brain-stem and (in one case) in the spinal cord contained intranuclear inclusion bodies, and inclusion bodies were also seen in the cytoplasm of nerve cells and in the nuclei of oligodendroglial cells. Microglial reaction and perivascular infiltration by lymphocytes and plasma cells were also prominent.

The nature of this form of encephalitis is discussed. It is considered that it differs aetiologically from the acute form of encephalitis associated with Type A intranuclear inclusions, in which the virus of herpes febrilis has been incriminated in all the cases in which animal inoculations have been made. It also differs from the subacute type of encephalitis described by van Bogaert under the name of "subacute sclerosing leuco-encephalitis."

REFERENCES

LEGENDS FOR ILLUSTRATIONS

PLATE XVIII

Fig. 1 (Case 1).—Cortical neuron containing an inclusion surrounded by the typical halo. The nucleolus (darker) is displaced towards the upper right hand part of the nucleus.

Fig. 2 (Case 1).—Two cortical neurons of which the upper contains an inclusion similar to that in fig. 1. The lower cell is at a later stage of degeneration and the inclusion occupies the nucleus more completely. Acidophilic cytoplasmic inclusions are also seen near the lower margin of the cell.

Fig. 3 (Case 1).—Advanced degeneration in two cortical neurons, in which inclusions fill the greater part of the nucleus. Acidophilic masses are seen in the cytoplasm of the lower cell.

Fig. 4 (Case 2).—Two neurons from pyramidal layer of hippocampal cortex, containing intranuclear acidophilic inclusions surrounded by a halo. Acidophilic inclusions are also seen at the margin of the cytoplasm of both cells.

All sections stained with Ehrlich's haematoxylin and eosin and magnified x 900.

PLATE XIX

Case 2.—Neurons from the anterior horns of the seventh and eighth cervical segments of the cord; stained by Ehrlich's hematoxylin and eosin to show varying numbers and appearances of intranuclear inclusions. All neurons show varying degrees of chromatolysis.

Fig. 5.—Neuron showing three small intranuclear inclusions. Other small inclusions are not clearly in focus. x 800.

Fig. 6.—Neuron showing a larger and a smaller rounded intranuclear inclusion (grey). x 600.

Fig. 7.—Neuron with a lobulated intranuclear inclusion suggesting the fusion of several smaller bodies. x 500.

Fig. 8.—Neuron with a single large hyaline inclusion. x 750.

PLATE XX

Fig. 9.—Anterior horn neuron from eighth cervical segment of Case 2 stained by phosphotungstic acid haematoxylin and showing an intranuclear inclusion (grey violet) and numerous degeneration granules in the cytoplasm (reddish purple). To contrast with the acidophilic cytoplasmic inclusions in fig. 10. x 900.

Fig. 10.—Anterior horn neuron from eighth cervical segment of Case 2, stained by Ehrlich's hematoxylin and eosin and showing four rounded eosinophil bodies along the right-hand margin of the cell. The nucleus is not present in this section. x 700.

In both figs. 9 and 10 a Wratten B (green) filter was used.

Fig. 11 (Case 3).—Cortical neuron stained by Lendrum's phloxin-tartrazine method, x 1750. There is a medium-sized intranuclear inclusion. A fairly large phloxinophilic cytoplasmic inclusion is seen on either side of the nucleus and several small granular inclusions in the cytoplasm near the base of the cell. Yellow filter.

Fig. 12 (Case 4).—Pyramidal neurons from motor cortex stained by Ehrlich's haematoxylin and eosin and showing intranuclear inclusions and a shrunken hyaline cytoplasm. Note also the microglial hyperplasia. x 800.
PLATE XXI

Case 4.—Neurons stained by Lendrum's phloxin-tartrazine method to show inclusion bodies. Figs. 13, 14 and 15 from frontal cortex. Fig. 16 from pulvinar of optic thalamus.

In fig. 13 the bodies are small, granular or fleck like and lie on the margin of the cytoplasm. A group of plasma cells is included in the photograph. × 1150.

Fig. 14 shows a less common arrangement of granular inclusion bodies round the nuclear membrane and running up the centre of the cytoplasm towards the apical dendrite. × 750.

In both figs. 13 and 14 the cytoplasmic inclusions were stained bright red.

Figs. 15 and 16 show later stages of neuronal degeneration with both cytoplasmic and intranuclear inclusions. × 1100.

In fig. 15 there is a horseshoe-shaped group of hyaline flocculent inclusions in the cytoplasm and a medium-sized intranuclear inclusion.

In fig. 16 the cytoplasm contains a more rounded hyaline mass and the very eccentric nucleus is filled by the inclusion body. In figs. 15 and 16 the inclusions are stained orange.