A CASE OF ENCEPHALITIS LETHARGICA INVOLVING CHIEFLY THE CEREBRAL CORTEX.

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In the majority of the cases of encephalitis lethargica previously described, the main incidence of the disease has fallen upon the brain stem. The following case appears to resemble so closely clinically, and in many respects pathologically, the interesting cases of this disease recently described by Dr. Farquhar Buzzard[1] in which the *cerebral cortex* was chiefly affected, that it seems worthy of being recorded.

Although I saw the case several times myself, I am indebted to Drs. Cowen, Reeve, and Gott for the notes upon which the clinical history is founded.

Clinical History.—E. J., female, age 28, single, of no occupation. Admitted to Rainhill Asylum, April 18, 1918. Her father is a patient in Lancaster Asylum at the present time.

On admission she was in a condition of agitated melancholia. She had an extensive wound across the throat, self-inflicted with a razor nine days previously. She was in poor health and very anæmic, but with no signs of cardiovascular disease. She had complained of headache and inability to sleep for some weeks, and said she cut her throat because she feared she was becoming insane.

Two days after admission the patient tore open the wound in her throat and lost a good deal of blood, and had some slight rise of temperature after this. The wound in her throat gradually healed, but she remained very anæmic and improved but little mentally, being often very agitated and actively suicidal. From August 21 to 23 she vomited several times, and appeared to be ill. She improved somewhat until October 19, when she complained of pain in the back and down the left thigh, limped in walking, and became confined to bed. She remained in much the same state until December 24, when, after being visited by her friends, she suddenly lost speech, and seemed unable to utter any sound beyond a monotonous ' Ah, ah ! ', although she appeared to understand what was said to her. The right side of the tongue was apparently paralyzed, and she was unable to protrude it. This inability to speak remained until the death of the patient, but at no time was there any difficulty in swallowing. At this time she lay in bed in a drowsy, disinterested state, and seemed very ill.

The word 'lethargic' aptly describes her general appearance, but she could be roused to give fairly accurate responses. She was somewhat difficult to examine satisfactorily, but by January 4 the paralysis had undoubtedly extended. There was complete right hemiplegia affecting the face, arm, and leg, with insensibility to pin-pricks on the same side (including the right half of the tongue and the right side of the chest and abdomen), excepting over a patch in the centre of the groin, a small area over the upper fibular region, and the sole of the foot. The knee-jerks were brisk, especially the right; tendon-jerks of the right arm brisk; no clonus. The right plantar reflex was absent; on the left side a flexor response was obtained; abdominal reflexes were absent on the right side. There was no squint, but the left eyelid drooped slightly. Optic neuritis of medium intensity was present at this time, but there was no apparent deafness. On January 11, one week later, marked wasting of the muscles of the right arm, forearm, and hand was noted; also of the left calf and thigh, although there appeared to be no definite palsy of this limb. The patient died exhausted the next day.

The temperature was subnormal throughout this last illness. The skin generally became markedly pigmented some months before death, but there was no rash, and no ulceration about the mouth. Though constantly drowsy, she retained consciousness throughout, nor did convulsions occur at any time. On December 26, blood-films were examined, but these showed no abnormality beyond an excess of leucocytes, especially of the polynuclear and large hyaline varieties.

It is not easy to date exactly the commencement of the last illness. Although the patient had attacks of vomiting in August, it was not until October 19 that she was noticed to limp in walking, and not until December 24—twenty days before death—that she became afflicted with loss of speech and right hemiplegia.

A tentative diagnosis of cerebral tumour was first made, but later the diagnosis of encephalitis lethargica was suggested by Dr. Cowen.

Post-mortem Examination.—The body was poorly nourished, and there were slight bedsores on the hips and sacrum. The lungs and all the solid viscera were much congested, but otherwise normal. The heart was moderately dilated, but there was no valvular lesion; the larger arteries were normal.

The brain was of about average female size and complexity. There was slight excess of clear subdural fluid. The pia-arachnoid was intensely congested generally, but there was only slight and patchy macroscopic effusion of blood into and below this. The veins were greatly engorged, but there was no obvious thrombosis of these or the sinuses. The cerebral arteries appeared normal to the naked eye,

and showed no signs of thrombosis. There was no flattening of the cerebral gyri; the brain generally was soft. In the fresh specimen a large area of recent softening was seen in the left hemisphere. The softened area involved about the lower two-thirds of the central gyri, the extreme hinder and lower part of the subfrontal region, the extreme hinder part of the orbital surface external to the olfactory tract, the whole of the insula except its extreme anterior end, all the brain substance between this and the lenticular nucleus, and the whole of the putamen except its anterior fifth or so; but not the globus pallidus (*Figs.* 1, 1*a*). In the fresh specimen the affected area was very soft,

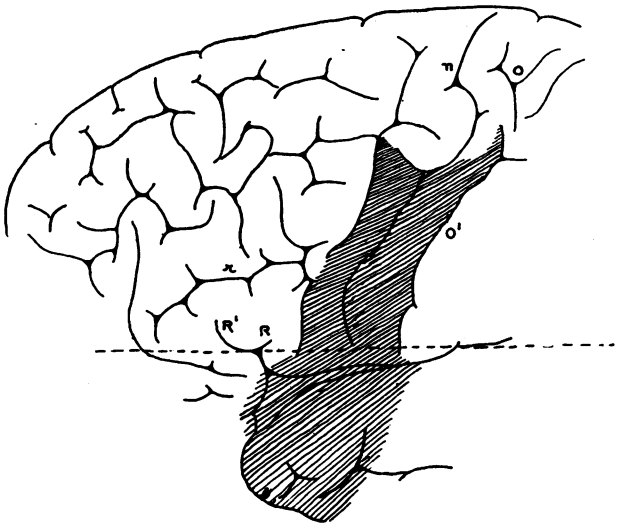

FIG. 1.—Drawing of part of the left cerebral hemisphere. The site of the softened area, as seen macroscopically, is heavily shaded.

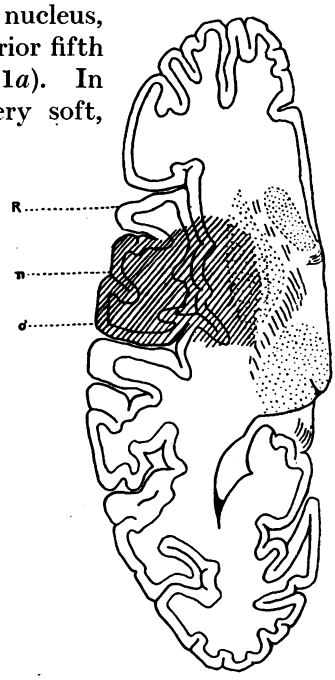

FIG. 1*a*.—Drawing of a cross-section of left cerebral hemisphere at the level indicated by the dotted ine in *Fig.* 1.

n The sulcus centralis; O, O¹ The sulcus postcentralis; *r* The sulcus frontalis inferior; R R¹ The anterior Sylvian rami.

especially in the temporal, insular, and lower central regions. When stripping was attempted, the membranes were adherent over the softened area, and the colour of the surface was a pale yellow tinged with red in places. After the hemisphere in the hardened specimen was sectioned, the cortex of the affected parts appeared somewhat swollen, and numerous fine streaks of intensely congested vessels were visible, but there was no macroscopic hæmorrhage. There was no similar affection of any part of the right cerebral hemisphere, nor of the cerebellum, pons, or medulla. The membranes of the spinal cord were congested, but the cord itself appeared normal to the naked eye.

Microscopical Examination.—*The Cerebral Hemispheres.*—In all parts examined, but especially in the softened area, the membranes are thickened and infiltrated with cells of various form and staining reaction. The vessels have thickened walls and are intensely engorged. Here and there are small hæmorrhages both into the substance of the membranes and below them. Some veins contain clots—hyaline or fibrinous—but these rarely occlude the vessels completely. In places, organizing thrombi are seen in the arterioles.

The appearances of the brain substance in the softened area differ somewhat in different parts, but the most striking general features are (1) the enormous increase in vessels, and (2) the great cellular proliferation. The vessels are mostly thickened, tortuous, and varicose, and part of the wall of many of them has a hyaline appearance. The cellular proliferation may be confined to the neighbourhood of a vessel (*Fig.* 2), but in the most affected parts this proliferation has spread widely into the surrounding tissues. It involves chiefly the veins and capillaries, but the arterioles have not escaped. Although numbers of lymphocytoid cells, plasma cells in various stages of formation, and pseudoplasma cells are seen, the majority of the cells are of the polyblast, epithelioid, and reticulate types. The predominating cells show great variety in shape and staining reaction, both of the cell body and nucleus, and many have two nuclei. Numbers might be described as polyblast-epithelioid—intermediate forms between polyblast and epithelioid cells—which suggest that the latter are derived from the former. Few cells are very definitely granular. It is obvious that these cells have arisen mainly from proliferation of the cells of the adventitial coat of the vessels. Neuroglia proliferation is not a prominent general feature, although here and there, and chiefly in the outer layers of the cortex, collections of large fibril-forming 'glia' cells are seen, showing some differentiation

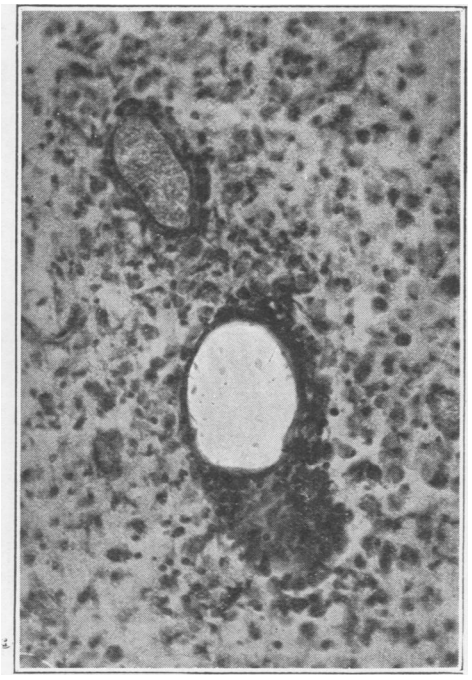

FIG. 2.—Left precentral gyrus; grey matter; cellular proliferation, most marked in the neighbourhood of vessels.

of their processes into fibrils. It does not appear, however, that the cells of the inflammatory reaction have arisen to any great extent from neuroglia cells. The vascular endothelium has also taken a part, though not an extensive one, in the reaction. In some instances proliferated cells of this coat can be seen projecting into the vessel or actually lying free within it.

The veins and capillaries are intensely congested, and there are small hæmorrhages around the vessels in places; but these are not numerous anywhere excepting in the putamen, and in parts of the precentral gyrus, where the hæmorrhages are larger and have torn up the tissues to some extent (*Fig.* 3). A superficial appearance of hæmorrhage has, however, often been produced by blood-cells which

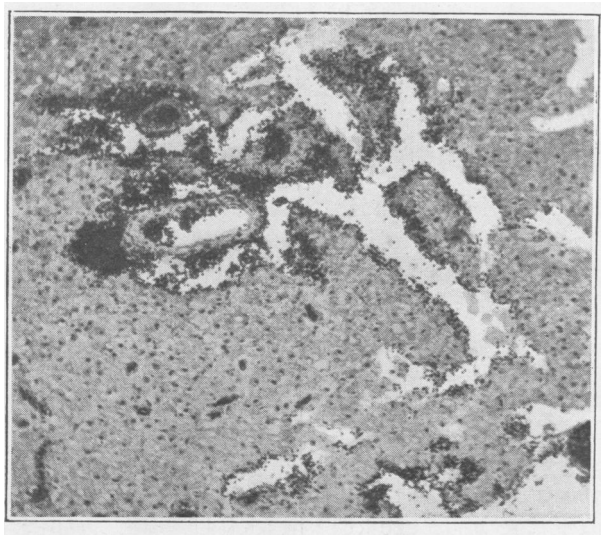

FIG. 3.—Left postcentral gyrus; white matter; hæmorrhage and rupture of tissues.

have come over with the knife in the process of section cutting. Some veins in both the grey and white matter contain clots—hyaline or fibrinous—which usually only partially fill the vessel. In places, also, organizing thrombi are seen in arterioles. A marked feature is the presence in the neighbourhood of many vessels of rarefied sieve-like areas (*Fig.* 4). These frequently contain an amorphous deposit amongst which are scattered proliferated cells. This deposit in some instances forms a fairly regular ring around the vessel; in others the vessel is only partially surrounded by it, whilst in still others it is more irregularly arranged, and spreads into the surrounding tissues some distance away from the vessel. The deposit

stains deep mauve with toluidin blue, a lighter mauve in van Gieson preparations, and brownish orange with pyronin-methyl green. It occurs chiefly about the vessels of the white matter, more rarely in the grey, but occasionally it is seen around a vessel just entering the cortex from the pia. It appears to be an exudate of some kind, for at times similar-looking material is seen within a vessel. In places these sieve-like areas have almost the appearance of actual cavities.

In addition to the above changes, others have occurred in certain parts. Areas of what seem to be partial necrosis are seen where the cells of the inflammatory reaction are themselves in process of dissolution. In such areas there are much darkly-staining débris and many palely-stained cells of various kinds, or fragments of these and nuclei, together with mulberry-like bodies which are probably degenerating cells. The greater part of the insula shows this condition. Whilst in some places the cells of the reaction have the ordinary appearance, in others either one or two broad bands or streaks of degenerating cells are seen—in the lower part of the cortex chiefly. In still other places these occur as isolated clumps. Similar streaks or clumps are found in the neighbouring subfrontal region, and, more rarely, clumps of the same change in parts of the precentral gyrus. They occur only in the grey matter, and there is no sign of hæmorrhage around the areas; but where they are present, many small vessels, both in the pia and the cortex, which appear to be arterioles, contain organizing thrombi, wholly or partially occluding the vessel.

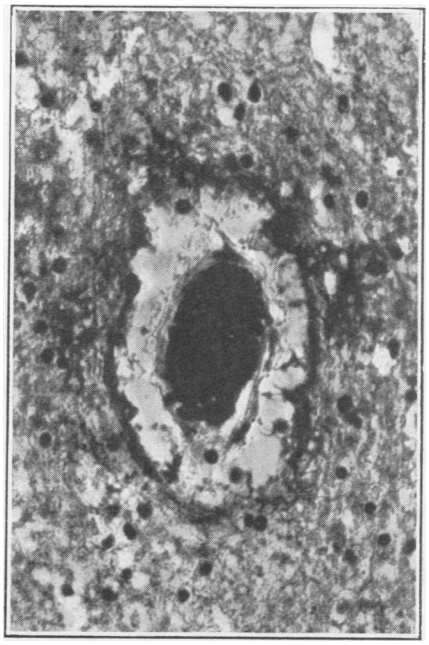

FIG. 4.—Left postcentral gyrus; white matter; perivascular sieve-like area containing exudate.

Mention may now be made of the distribution of the lesion in the softened area and of the condition of the nerve cells. The variability in the intensity of the disease process in different parts is shown both by the patchy character of the inflammatory reaction, and by the state of the nerve cells. Even in the same section, in one part the whole depth of the grey matter is fairly equally affected by the vascular and cellular increase, whilst in an adjacent part the

upper layers of the cortex are comparatively little involved, and the hyperplasia occurs chiefly as a broad band in the deeper layers (*Fig.* 5). In fact it is always most in the latter situation, where the anastomosing network formed by the short cortical arteries is richest, and where also there is probably some anastomosis between these vessels and branches of the long medullary arteries. It must be admitted, however, that in certain parts the proliferation is very marked in the subcortical white matter also, although here it is usually more diffuse than in the grey.

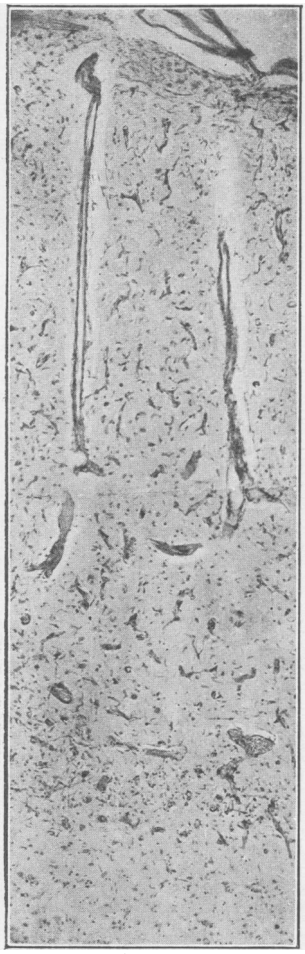

FIG. 5.—Strip of cortex from the middle of the left precentral gyrus. In this situation the inflammatory reaction has affected the entire cortex fairly equally.

The nerve cells in all parts of the region of softening are grossly affected, especially those of the lower cortical layers. In places they are unrecognizable, or stain so faintly as to be scarcely visible. Their condition varies with the intensity of the inflammatory reaction, and is always worst below the level of the granule layer, where this reaction is greatest. There is also considerable variability of implication in different parts of the gyri. In the subfrontal and lower central regions the reaction is most marked and generalized along the bottoms and sides of the gyri, and few nerve cells can be seen in those situations, whilst along the apices and flat surfaces the hyperplasia is much the greatest in the deeper layers, and the smaller nerve cells in the upper layers have remained in comparatively good condition. On the other hand, in the middle of the precentral region the inflammatory process has affected all parts of the gyrus and all levels of the grey matter more equally, excepting the lower half of its posterior wall, and it is only here that practically any nerve cells can be seen. In fact, in no other part of the softened precentral gyrus examined but this could any Betz cells be found, and even here these are so ghost-like that they are only just visible.

The postcentral gyrus about its middle is less affected than the precentral, and its flat surface and posterior side less than its anterior side. The patchy character of the lesion is also demonstrated by the

fact that while the postcentral gyrus is on the whole less affected than the precentral, a small portion of the parietal region, for a variable distance behind the sulcus postcentralis, is severely involved, and a narrow strip of comparatively healthy cortex, containing nerve cells much less changed, intervenes in places between this severely involved region and the postcentral gyrus. The softened area is thus not strictly bounded posteriorly by the sulcus postcentralis. The condition of the upper part of the central region, where there is no obvious softening, will be described presently.

In the putamen there is an enormous amount of vascular and cellular increase, with great destruction of nerve cells, hæmorrhages, thromboses, and perivascular sieve-like areas. The globus pallidus, internal capsule, and optic thalamus are little affected.

In the temporal region the changes appear to be older, or at least less acute than in other parts of the softened area. There are great numbers of vessels with thickened walls, but, on the whole, less cellular proliferation beyond the immediate neighbourhood of the vessels, and the latter are not very greatly congested. The nerve cells, however, are much degenerated, and stain very faintly.

About the upper end of the central gyri, where there is no obvious softening, the membranes are moderately thickened and infiltrated, and the vessels very congested. The vessels throughout the brain substance are much less numerous than in the softened area; there is, however, some adventitial proliferation and increase of 'glia' in the neighbourhood of the vessels. The latter are intensely congested, and some are partially plugged with hyaline clot. In the lower part of the grey matter, and in the white, are a few small sieve-like areas. There are marked changes in the nerve cells; many of the small and medium pyramids, and the polymorphs, are swollen and disintegrated, but the larger pyramids are less affected. The Betz cells are all grossly altered; some are swollen, others shrunken, with ragged edges and defective processes; the nucleus is often indistinct, and is commonly displaced towards the apex or side of the cell. The cytoplasm stains more or less diffusely; there are seldom well-defined Nissl bodies, and the greater part of the cell body usually has a homogeneous and somewhat glassy appearance. The satellite cells are increased in numbers, especially at the level of the medium and larger pyramids, but to a less extent about the Betz cells. On the whole the morbid changes are more marked in the precentral than in the postcentral gyrus.

In the upper, middle, and lower central regions of the opposite hemisphere—the right—the appearance of the vessels is much the same as in the upper central region of the left hemisphere, but there is more small-celled 'glia' proliferation. The condition of the nerve

cells is also much about the same, with the exception of the Betz cells. None of these latter are normal; many show chromatolysis of the axonal type, with fairly good Nissl bodies about the apex of the cell; others stain darkly and diffusely, and appear to be in an earlier stage of the same morbid process as that which has so grossly altered the remaining Betz cells of the opposite hemisphere (*Fig.* 6). The upper part of the central region on this side is more affected than is the middle and lower.

In the prefrontal, the greater part of the parietal, and in the calcarine and hippocampal regions of the left side—the side on which

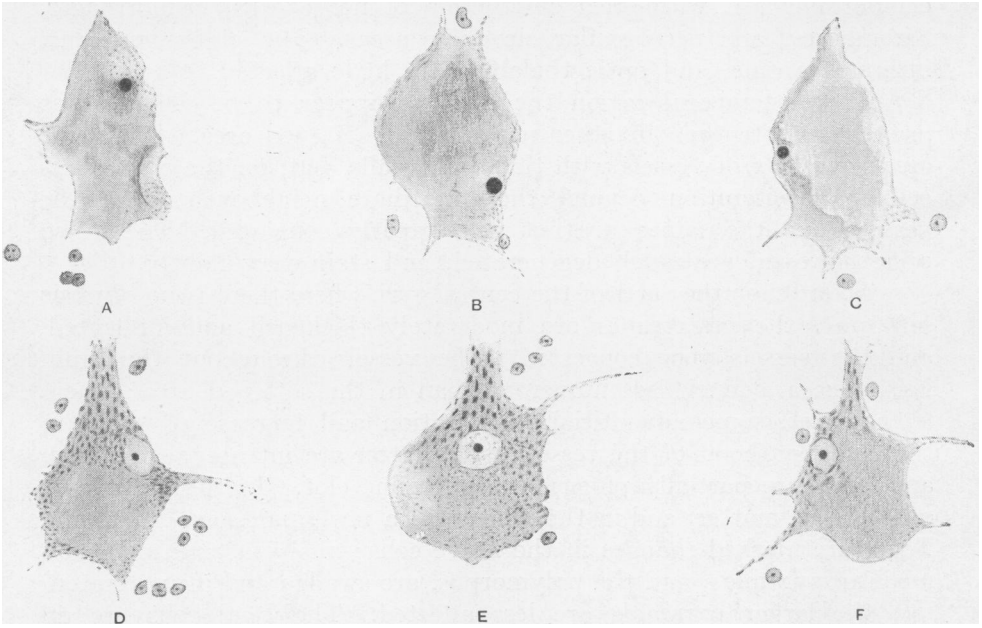

FIG. 6.—Drawings of Betz cells. The upper three (A, B, C) are from the top of the left precentral gyrus, which was not obviously affected by the softening. The lower three (D, E, F) are from the same situation in the opposite hemisphere.

the softening occurred—there are signs of meningitis and a few small hæmorrhages; also great congestion of vessels, some of which contain hyaline clots, and a few small sieve-like areas in the white matter. There is, further, a certain amount of adventitial proliferation, but to nothing like the same extent as in the softened area. Much degeneration of nerve cells, however, exists, with considerable satellitosis, most marked in the prefrontal region.

The Medulla and Pons at various levels.—The membranes are thickened and infiltrated, and the vessels in all parts very congested. Some of the vessels show hyaline thrombi, and there are a few small hæmorrhages in the medulla. There is some adventitial

proliferation, some 'glia' proliferation, especially at the periphery, and much infiltration of small round cells generally. These changes are more marked in the medulla than in the pons. Scattered nerve cells in almost all groups show more or less degeneration, but no one nucleus seems much more affected than another.

The Spinal Cord at Various Levels in the Cervical, Dorsal, and Lumbosacral Regions.—There is considerable thickening of membranes and vessels throughout, but no great amount of active cellular proliferation. The vessels are intensely congested, but few thrombi or hæmorrhages are seen. Much small-round-celled infiltration has occurred in the grey and white matter, with proliferation of large 'glia' cells, especially about the periphery of the cord, but there is no definite sclerosis of any particular tract. Regarding the anterior horn cells, some of these in the cervical region appear fairly normal, but others are stunted and stain diffusely; the lateroventral and laterodorsal groups are most affected, and particularly on one side. In the upper and mid-dorsal regions there is little affection of the cells of the nucleus motorius, but many cells of the nucleus dorsalis on both sides show moderate chromatolysis. In the lower dorsal region several cells of the lateroventral groups are grossly affected. In the lumbar and sacral regions there is degeneration of many cells with displacement of their nuclei in all the groups, but especially in the laterodorsal and retrodorsal on both sides.

The nerve roots and *posterior root ganglia* examined are very congested and show considerable cellular proliferation, and the latter some small hæmorrhages.

The Cerebellum.—There is little alteration in the parts examined, beyond congestion and slight meningitis.

No organisms of any kind were found in the tissues.

General Observations.—Although the condition has been termed 'encephalitis', it is really a widespread meningo-encephalo-myelitis affecting practically all parts of the central nervous system. But the chief stress of the lesion has fallen upon the left cerebral hemisphere, involving principally the lower part of the subfrontal region, the middle and lower central regions, the greater part of the insula, and the putamen, as well as part of the temporal region. Where it is most gross it consists of a great increase of vessels, with marked proliferation of the adventitial, and to a less extent of the endothelial, cells of the vessel walls, together with neuroglial proliferation, thrombosis, hæmorrhage, softening, and much destruction of the nervous tissues. The lesion, however, even in the parts most affected, is patchy in the intensity of its distribution, and also does not seem to have been all lit up at the same time; in some places the reaction appears to be acute, in others less acute, in character. In the soft-

ened area the picture is a very complex one, for, besides the primary inflammatory process, there is a secondary one called forth by the destruction of the nervous tissues and the attempt at removal of the degeneration products. This latter is evidenced by the enormous numbers of phagocytic cells of the epithelioid and reticulate types.

The case differs from those of acute encephalomyelitis described by Cleland and Campbell[2] as occurring in a recent Australian epidemic —clinically, in that it was of longer duration and also presented signs of definite paralysis; and pathologically, in that the changes in the nervous system were more gross, areas of destructive softening being present. On the other hand, the case closely resembles clinically those described by Farquhar Buzzard,[1] the chief symptoms being lethargy, with hemiplegia, hemianæsthesia, and aphasia. Pathologically it seems to be of a similar nature. The chief difference between the morbid findings in this case and in the majority of those previously recorded appears to be that here the changes were more of the so-called hyperplastic type than the hæmorrhagic. Hæmorrhage was not a particularly prominent feature, and this may perhaps be partly accounted for by the rarity of complete venous thrombosis, and perhaps also by the absence of a predisposing fragility on the part of the blood-vessels, owing to the comparative youth of the patient.

I agree with Dr. Buzzard in thinking that 'encephalitis lethargica' is not a new disease; nor probably is its chief incidence in the cerebral cortex very uncommon. I can recall several cases from my own experience which were clinically and pathologically very similar to that above described. I believe, however, that the condition is apt to be overlooked.

With regard to the view that 'encephalitis lethargica' is associated in some intimate causal manner with influenza, the only observation which can be made in connection with this case is that a severe epidemic of influenza occurred on the female side of the institution during the months of September and October, 1918. Over 200 patients and 70 nurses were attacked, and there were many fatalities. The disease continued more or less sporadically until the following March, but the patient E. J. was not definitely known to have suffered from an attack at any time.

I am indebted to Miss A. B. Taylor for some of the drawings, and to Mr. F. J. Abram for the photomicrographs.

REFERENCES.

[1] Buzzard, E. Farquhar, *Lancet*, 1918, ii, 835.
[2] Cleland and Campbell, *Brit. Med. Jour.*, 1919, i, 663.