THE PATHOLOGY OF CHRONIC EPIDEMIC ENCEPHALITIS: A HISTOLOGICAL STUDY OF FOUR CASES WITH WIDESPREAD CEREBRAL LESIONS.*

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THE predominant importance of the Parkinsonian syndrome amongst the later manifestations of epidemic encephalitis has caused a considerable number of observers to direct their efforts towards the finding of an anatomical basis for the development of this symptom-complex. As a result, attention has been focussed upon the substantia nigra, in which severe destructive changes are constantly found in these cases and the rest of the central nervous system is commonly described as showing changes of only slight significance (McAlpine¹²). In the present study, on the other hand, attention has been given to the disease-process and its effects upon the nervous tissues as a whole rather than to the results of destructive changes in definite areas.

Two of the four cases which were available for study were of the ordinary Parkinsonian type and the other two were selected because they showed, during life, symptoms of severe cerebral disturbance, compatible with a diagnosis of chronic encephalitis, although not definitely indicative of this condition: and because examination of the brain revealed marked destructive alterations in the substantia nigra and failed to reveal the anatomical changes characteristic of any other recognised disease.

Material and Methods.—The brain and spinal cord were fixed entire in either formalin or formalin-ammonium-bromide solution. The brain-stem was cut transversely into a series of thin slices and each alternate fragment embedded in celloidin, the remainder being used for frozen sections. Pieces of tissue from the pre-frontal, pre- and post-central, occipital and temporal cortex, basal ganglia and thalamus of each hemisphere, from the cerebellum and from the four principal regions of the cord were also cut both in celloidin and after freezing. Celloidin sections, cut at about 15 micra, were stained by Masson's hæmatoxylin-eosin-safran method and by thionin or toluidin blue. Scharlach R. staining for fats, silver impregnations for the demonstration of axis-cylinders, Cajal's gold-sublimate method and Anderson's Victoria-blue technique for the neuroglia were carried out upon frozen sections. Several other methods were also used for special purposes.

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CHANGES IN THE INDIVIDUAL TISSUE ELEMENTS.

A brief account of the alterations in the individual tissue elements will save unnecessary repetition in the description of the individual cases.

Nerve-Cells.—As the localisation of the lesions in the grey matter would lead one to expect, the perikarya of the neurones are commonly severely affected while their axis-cylinders and myelin sheaths usually escape damage. Regressive alterations in the former are frequently observed whereas signs of injury to the latter are rarely noted and, when they do occur, are probably always secondary to the destruction of the cell from which the fibre originates.

In every part of the nervous system the smaller nerve-cells show more conspicuous degenerative changes and are surrounded by larger groups of perineuronal satellites than the larger elements in their neighbourhood. Thus the small stellate and polymorphic cells in the cerebral cortex suffer more severely than the larger pyramidal cells; the small polygonal cells in the lentiform nucleus present more marked alterations than the large pallidal cells; the small cells forming the sensory nuclei of the brain-stem are often severely damaged, while the large multipolar elements of the motor nuclei are little affected.

The extensive destruction of the large multipolar cells of the substantia nigra may suggest that the presence of a considerable quantity of melanin pigment in the cytoplasm makes the cell particularly vulnerable, but outfall of pigmented cells in other regions, notably the substantia ferruginea and dorsal motor nucleus of the vagus, is generally inconspicuous.

The degenerative changes in the cells present no noteworthy peculiarities. Chromatolysis occurs, as in other conditions. The Nissl bodies break up into coarser and then into finer granular fragments, first near the nucleus and later throughout the cell-body and dendrites; the nucleus loses its central position in the cell and becomes slightly swollen; the nuclear membrane stains rather less distinctly while there may be a faint colouration of the intranuclear network; the nucleolus is somewhat reduced in size, loses its sharp contour, becomes vacuolated and stains more feebly.

In more severely damaged cells the cytoplasm and dendrites may take a faint, homogeneous stain and the cell-body and processes appear much distorted, while smaller and larger vacuoles appear in the cytoplasm and, if numerous, give the whole cell a foamy appearance. More commonly the Nissl substance disappears almost entirely from the cytoplasm, the cell loses its clear-cut outline, and a small amount of faintly-staining, granular material which appears to be disintegrating at the periphery is all that is visible around the nucleus.

But even in the presence of the most severe alterations in the cytoplasm of the nerve-cells, changes in the nucleus are seldom more marked than those already described. Complete solution of the nuclear chromatin, fragmentation of the nucleus or nucleolus and extrusion of the nucleus from the body of the cell are all extremely rare phenomena. It seems reasonable to conclude,

therefore, that the majority of the cells which are severely damaged are not necessarily on the way to complete destruction but are, under favourable conditions, capable of recovery.

Granule-Cells.—Cells of this type play a very prominent part in the reactive processes in these cases and are usually found in large numbers clustered about the cell-bodies of the neurones, wandering free in the tissues or lying in rows along the smaller vessels. Their nucleus, which is small, deeply-staining and rounded or slightly ovoid, closely resembles the nucleus of the ordinary

FIG. 1.—a. and b. are altered microglia cells; c.-g., granule cells; c., stained by toluidin blue; d.-f., contain granules of lipochrome, melanin and iron-containing pigments; g., a typical 'fat granule cell'. (x 1,000).

lymphocyte, but their cytoplasm, which is abundant and stains very feebly, is often only delimited by the granular content of the cell. This granular material within the cytoplasm of these cells appears to be part of the product of disintegration of the nerve-cell cytoplasm, which is transported by them through the tissues to be deposited in the lymph spaces surrounding the blood-vessels. This is shown by the fact that substances present in the healthy nerve-cells gradually disappear from their cytoplasm during degeneration and

are found instead in the perineuronal satellites, in the granule-cells wandering in the tissues, in those lying along the blood-vessels and in the perivascular spaces of these vessels, whereas in healthier areas granules of such material are not found in the satellite cells or perivascular spaces. Much of this granular material is of indefinite nature, the particles being recognisable only by reason of their affinity for some aniline dye or because they become deeply impregnated in silver preparations, but a number of fairly well-defined substances are also present in abundance. Thus, wherever nerve-cells containing much

FIG. 2.—Showing the situation of the granule-cells in relation to a small capillary; they lie outside the membrana limitans perivascularis. Prefrontal cortex; Case III. Cajal's gold-sublimate method. ($\times 275$).

lipochrome are degenerating, granules of this yellow pigment are readily recognisable in the granule-cells; many of the granule-cells in the substantia nigra are packed with fine granules of melanin; a few of these cells in the basal region contain granules which give a well-marked Prussian-blue reaction. In these cases the ordinary fat granule-cell was found in small numbers only in the region of the substantia nigra, where there had been a considerable amount of myelin sheath destruction. (Fig. 1).

The parineuronal satellites* may lie at a little distance from the nerve-cell but are usually situated very close to it, frequently in little bays at its periphery but never entirely within its cytoplasm. The granule-cells in relation to the precapillary and capillary vessels lie in the nervous tissues, between the vascular foot-processes of the astrocytes; they are closely applied to the glial membrana limitans perivascularis but lie outside it, and not in the perivascular spaces as the expression 'perivascular round-cell infiltration' would imply. (Fig. 2).

(In describing the pathological appearances in individual cases, figures

FIG. 3.—Disintegration of small granule-cells within the lymph space of a small subcortical artery. Prefrontal cortex: Case III. Hæmatoxylin-eosin-safran. ($\times 500$).

will frequently be given indicating the numbers of these small cells in the groups about the nerve-cells and in the rows along the precapillary vessels, since this probably gives the clearest indication of the intensity of the reactive processes in different areas.)

In areas in which active changes have evidently been in progress for some time, very degenerate granule-cells with small, deeply-staining, gnarled,

* This expression will, in general, be used in referring to the small cells clustered about the nerve-cell bodies since, in routine preparations, the abnormal elements cannot usually be distinguished from the normal microglial and oligodendroglial 'satellites' of the neurones.

pyknotic nuclei may be found in the adventitial spaces of the larger vessels and can, very rarely, be seen penetrating the adventitia to reach the lymph spaces, in which they disintegrate. (Fig. 3).

Since most of the material had been fixed in bulk, extensive investigation by the methods of Rio Hortega could not be carried out, but sufficiently good preparations were obtained to suggest that the granule-cells in these cases arise from the microglia.[†]

FIG. 4.—Large astrocytes with thick, fleshy, branching processes in which fibres are becoming differentiated. a., from the nucleus of the spinal tract of the trigeminal; Case III. b., from the globus pallidus; Case II. Anderson's Victoria blue method. ($\times 500$).

Astrocytes.—In certain areas in which nerve-cell degeneration and granule-cell reaction are well-marked, as in the deeper layers of the cortex, changes in the astrocytes are insignificant; there is only a slight hypertrophy of a small proportion of the cells. In parts of the brain-stem, on the other hand, where other alterations are not so striking, the astrocytes are increased in number and many of them are greatly enlarged and actively engaged in glia-fibre

[†] Excellent descriptions and illustrations of microglia will be found in the papers of Penfield^{15,16} and of Reynolds and Slater¹⁹.

production, while the very occasional presence of bi-nucleated cells indicates that slow proliferation is still occurring.

The earlier stages in the development of the hypertrophic fibrous astrocyte are not very frequently seen, but occasionally, especially in the nucleus of the spinal tract of the trigeminal, large glia-cells are encountered in which the cytoplasm of the cell-body and long, thick, branching processes stains very deeply with the aniline dye but contains no fibres. (Fig. 4a.) At a somewhat later stage the cell-body and processes take the stain rather less intensely,

FIG. 5.—A hypertrophic astrocyte with voluminous bundles of well-formed fibres. From the substantia nigra: Case III. Anderson's Victoria blue method. ($\times 800$).

while fibres make their appearance as deeply-staining condensations of the cytoplasm running along the edges of the processes and passing through the perinuclear zone from one process to another. (Fig. 4b.)

In the progressively altered cells most commonly met with, however, abundant fibre-formation has already taken place. The most striking examples of this type of cell are found in the substantia nigra of the Parkinsonian cases. The nucleus of these cells is usually large, oval or slightly irregular, with scanty

chromatin, arranged in a thin layer about the nuclear membrane, clumped into one or more nucleolus-like masses and scattered in fine granules throughout the karyoplasm. The cytoplasm, which stains very faintly with the aniline dye, is visible only in the voluminous cell-body and in the bases of the more massive protoplasmic processes. The long, stout, well-formed glia fibres, sweeping in graceful curves through the perinuclear zone, pass out through the larger processes in compact bundles or leave the cell-body singly or in little groups. In the larger processes several fibre bundles run along entwined together for a short distance and then turn off in different directions into the neighbouring tissues where they rapidly become resolved into spreading leashes of individual fibres, which mingle inextricably with those of adjacent astrocytes. (Fig. 5). At a later stage, particularly in areas in which much fibre-formation has taken place, the nuclei of the astrocytes are shrunken and the individuality of cells is lost in the dense fibre feltwork.

There can be no doubt that hypertrophy and proliferation of the glia-cells are a late component of the whole pathological process. Their absence in certain situations where other alterations are intense indicates this quite clearly. On the other hand such proliferation may be an active accompaniment of other changes, as in the nucleus of the spinal tract of the trigeminal, or may remain active in areas in which the granule-cell reaction is dying down and the majority of the surviving cells are healthy, as in the substantia nigra.

It seems probable that the astrocytic reaction is a purely reparative process, although it may vary, perhaps, in effectiveness in different situations or in different individuals. In certain little patches of grey matter in the thalamus which had been almost completely denuded of nerve-cells, gliosis was intense, whereas there was little alteration in the astrocytes in the surrounding nerve substance. The marked gliosis in the substantia nigra, also, was quite evidently related to an outfall of nerve-cells and fibres. But, of course, in a disease such as this, in which the grey matter is so diffusely affected, there may be obvious glial proliferation without any apparent outfall of specific nervous structures, and therefore the possibility that a late stimulating effect of the irritant itself may influence the astrocytic reaction cannot be wholly excluded.

Blood-Vessels.—Changes in the walls of the blood-vessels in these cases are confined to the region of the adventitial (Virchow-Robin) spaces and are largely, if not entirely, secondary to the alterations in the nervous tissues proper.

When numerous granule-cells are collected about the precapillary vessels the adventitial cells of these channels invariably show slight swelling and contain granular fragments and irregular masses of debris. This debris, which corresponds in character with the material found in the cytoplasm of the granule-cells and derived by them, in turn, from the degenerating nervous elements, includes fats, pigments and various other substances. Presumably these pass from the granule-cells lying in close apposition to the membrana limitans perivascularis through that membrane into the cytoplasm of the

adventitial cells. As already mentioned, a few degenerate granule-cells may be found in the lymph spaces of the larger vessels. In the substantia nigra there is usually well-marked perivascular infiltration, the infiltrate consisting of large and medium-sized mononuclear cells together with a large number of small cells. The nature of these small cells cannot always be determined when the infiltration is dense; some of them are probably granule-cells and the remainder lymphocytes.

FIG. 6.—Large deposits of an iron-containing pigment in the media of a medium-sized artery; marked hyaline thickening of the intima. Globus pallidus; Case II. Hæmatoxylin-eosin-safran. ($\times 200$).

Subsidiary Features. Hæmorrhages.—In the pia-arachnoid over the hemispheres, brain-stem and spinal cord small areas of hæmorrhage are often noted in the meningeal meshes close to the nervous tissues. In the cerebral cortex, where such extravasations are especially common, blood is frequently found tracking along outside the wall of a small cortical vessel to form a little pool beneath the pia or along its adventitial spaces to escape into the subarachnoid space. In the latter situation there is usually a great collection of larger and smaller mononuclear cells around the area of hæmorrhage, there is active phagocytosis of the remnants of the red cells and the cytoplasm of the macro-

phages contains granules of hæmatogenous pigment. Since there is never any indication of repair of the tissues following such hæmorrhages during the course of the illness it is concluded that they are merely terminal.

Vascular 'Siderosis,' etc.—Impregnation of the media of the arteries in the anterior half of the globus pallidus by an iron-containing pigment was noted in all four cases. In the first two cases described the pigmentary deposit was copious throughout the muscular layer of the vessel walls and there was usually a partial impregnation of the internal elastic lamina and of the region of the adventitial lymph spaces. A large proportion of the vessels were affected and, when marked, the condition was associated with great hyaline thickening of the intima, the lumen of the vessel being frequently reduced to less than half its original calibre. (Fig. 6). In the other cases the vessels showed only a partial impregnation of the media.

A number of 'degeneration bodies' were found in the region of the basal nuclei. Most of these were irregular, lobulated masses of large size (15-50 micra in diameter) which stained very deeply with hæmatoxylin and usually gave a well-marked Prussian-blue reaction. Smaller spherical granules were occasionally found near the capillaries.

These concretions are described in detail by McAlpine¹¹, Hurst⁸ and others who have studied them extensively along with the arterial lesions. According to Hadfield⁴, the latter are found in at least 60 per cent. of people over the age of 30, but are uncommon in younger individuals. The only remarkable feature here, therefore, is the great severity of the condition in a child of 13. (Case II).

HISTOLOGICAL FINDINGS IN THE INDIVIDUAL CASES.

CASE I.

Clinical History.—A female, aged 37, was admitted to the Royal Infirmary, Edinburgh, under the care of Professor W. T. Ritchie, in June, 1924; she complained of lethargy, insomnia and nocturnal restlessness which had persisted since a typical lethargic attack of epidemic encephalitis two months previously.

She had the characteristic Parkinsonian facies, attitude and gait; her voice was weak and toneless and her articulation slow; there was slight enfeeblement of the muscles of the left side of the face, affecting especially the left angle of the mouth, but no paresis of the limbs was noted and no abnormal movements were present.

She was finally discharged but was readmitted for a period of three weeks, some ten months later. By that time the signs of Parkinsonism had become more pronounced, salivation was constantly excessive, and the patient had become depressed and emotionally unstable.

In June, 1925, she entered the Royal Edinburgh Hospital for Mental Disorders as a voluntary patient. She was dull and depressed, apathetic and drowsy, and lay in bed almost stuporose, paying no attention to anything and often refusing to be fed; yet she was sometimes capable of conversing quite rationally with her husband.

Eventually she developed a septic broncho-pneumonia and died on December 28, 1925.

FIG. 7.—A group of small granule-cells in the fork of a precapillary vessel. Layer of medium-sized pyramidal cells; precentral cortex; Case I. Haematoxylin-eosin-safran. (x75).

FIG. 8.—Cell degeneration and neuronophagia in the layer of polymorphic cells; prefrontal cortex; Case I. Toluidin blue. (x200).

Histological Findings.—Cerebral Cortex.—Beginning in patches in the layer of medium-sized pyramidal cells, severe degenerative alterations in the nerve-cells became increasingly prominent at deeper levels and reached their maximum intensity in the deepest cortical zone. Pericellular groups of satellites commonly numbered 6–8, and occasionally as many as 10–14 small cells were found clustered about a very degenerate nerve-cell deep in the polymorph layer. (Fig. 8). Large numbers of small granule-cells were grouped about the dilated precapillary and capillary vessels in the deeper cortex, rows of 12–15 being commonly encountered alongside these channels. (Fig. 7). A number of the astrocytes in the deeper cortex and adjacent white matter were slightly enlarged. Degenerate granule-cells were present in considerable numbers in the nervous tissues around the larger subcortical vessels but were rarely found within their perivascular spaces. There were numerous small areas of hæmorrhage in the pial meshes.

The changes outlined above were rather more marked in the prefrontal and temporal cortex than in the region of the fissure of Rolando, while in the occipital region only patches of the deeper cortex were severely affected.

Basal Region. Putamen and Caudate Nucleus.—Most of the small polygonal cells in these nuclei were very degenerate but the large multipolar cells generally showed only mild central chromatolysis. Neuronophagia was marked and as many as 14–20 satellites were occasionally found clustered about a disintegrating nerve-cell. Along the precapillary arterioles and venules there were frequently continuous rows of 10–15 granule cells. Many of the astrocytes were slightly enlarged.

Clastrum.—The changes resembled those in the putamen but were more severe.

Globus Pallidus.—Most of the large pallidal cells were fairly healthy and satellites were present only in relation to rare degenerate cells. Many of the astrocytes were slightly hypertrophic.

Thalamus.—There were a number of small foci of intense gliosis in the grey matter and in these foci the nerve-cells were conspicuously reduced in number. Elsewhere the thalamus was affected to about the same extent as the globus pallidus.

Within the perivascular spaces of the larger vessels in the basal region of the brain there were a few degenerate granule-cells and mononuclear phagocytes and a large amount of lipochrome pigment.

Midbrain.—There were alterations of varying degrees of intensity in many of the grey masses at this level. Severe nerve-cell degeneration was most frequent in the colliculi and reticular substance and only slightly less marked in the red nucleus and central grey matter. Collections of satellites about the damaged cells frequently numbered 5–7 or more, and there was a slight diffuse increase in the number of small cells along the adjacent capillaries. The large nerve-cells of the oculomotor nucleus and of the mesencephalic nucleus of the trigeminal were uniformly healthy.

In place of the normal large cell-islets of the substantia nigra only a few scattered pigmented cells remained. The majority of the surviving elements were perfectly healthy, however, and satellites were present only in relation to a few damaged cells. Large hypertrophic fibrous astrocytes were numerous in the substantia nigra and central grey matter, and the glia-fibre meshwork in these regions was abnormally dense. In the other grey masses of the midbrain area hypertrophic fibrous glia-cells were sparsely distributed.

Many of the larger vessels in the midbrain showed slight fibrous thickening of the outer adventitia and some swelling of the adventitial cells. In the region of the substantia nigra the dilated perivascular spaces contained a number of small degenerate cells, a few large mononuclear phagocytes and a large amount of melanin pigment.

Pons and Medulla.—Severe degenerative changes, accompanied by an increase in the number of perineuronal satellites, sometimes up to 7 or 8, were frequent in the cells of the nuclei of the spinal tract of the trigeminal and tractus solitarius and in the reticular

substance. Occasional degenerate or atrophic nerve-cells were found in many other nuclei, but the large multipolar cells of the somatic motor nuclei of the lower cranial nerves were uniformly healthy. There was no definite excess of satellites along the capillaries. Only a small number of hypertrophic fibrous astrocytes were found in the grey matter.

Cerebellum.—Showed no pathological changes of importance.

CASE II.

Clinical History.—A female child, aged 13, was admitted to Edinburgh Royal Infirmary, under the care of Professor Murray Lyon, in September, 1926. Her complaint was that, since an attack of 'influenza' in February, 1926, she had become progressively thinner and weaker and had developed occasional backward twitchings of the head. She was found to be extremely emaciated and so weak that she could not sit up or feed herself without shaking all over, but no definite signs of organic disease were elicited. Moro's test and the Wassermann reaction were negative. On lumbar puncture, a clear fluid, containing a few lymphocytes but no organisms, came out under pressure. On October 24 she developed severe myoclonic movements of the face, arms and legs; five days later a spastic paralysis of the left side appeared; still later dysphagia and complete anarthria developed in turn and she became completely comatose on November 3, the day before her death.

Histological Findings. Cerebral Cortex.—In the superficial half of the cortex the nerve-cells showed only mild chronic changes, but from the level of the medium pyramids downwards severe degenerative alterations in the cells became increasingly prominent. As a rule perineuronal accumulations of satellites numbered only 3-4, but groups of 8-9 or more were quite commonly found around the deeper polymorphs. About the pre-capillary arterioles and venules little rows of 6-8 granule-cells in single layers, or groups of 9-10 where the vessel bifurcated, usually represented a maximum accumulation. A few of the astrocytes in the deeper cortex were slightly enlarged. Granule-cells were present in large numbers in the nervous tissues around the larger subcortical vessels and were occasionally found within their perivascular spaces. There were a few small areas of hæmorrhage in the arachnoid meshes and in the superficial cortex beneath the pia.

The pathological changes in the cortex of this brain were less extensive than in the other three cases, only patches of the deeper layers being severely damaged. Such patches usually shaded off through a zone of less intense reaction into tissue which was little affected.

Basal Region. Putamen and Caudate Nucleus.—There was widespread degeneration of nerve-cells throughout these grey masses, the small polygonal cells being much more severely damaged than the large pallidal cells. Around the degenerate nerve-cells there were groups of 5-6 or more satellites and along the small vessels rows of up to 10-12 granule-cells. A few of the astrocytes were slightly enlarged.

Clastrum.—The changes here resembled those in the putamen.

Globus Pallidus.—Only a few of the large pallidal cells were degenerate; there was little neuronophagia and only a slight increase in the number of satellites along the capillaries.

Thalamus.—Many of the nerve-cells showed degenerative alterations of moderate intensity. Accumulations of 6-9 satellites were found about some of the more degenerate cells and there were occasional rows of 5-7 granule-cells along the precapillary vessels. Many of the astrocytes in the thalamus were enlarged and a few hypertrophic fibrous cells of medium size were found here and there near the larger vessels. There was marked hypertrophy and proliferation of fibrous astrocytes in a few tiny foci which had become almost entirely denuded of nerve cells.

A few small pyknotic nuclei were found in the adventitial spaces of many of the larger vessels in the basal region of the brain.

FIG. 9.—A small group of healthy surviving cells in the substantia nigra. Case II. Toluidin blue. ($\times 275$).

FIG. 10.—Cell degeneration and neuronophagia in the red nucleus. Case II. Toluidin blue. ($\times 275$).

Midbrain and Hypothalamic Region.—In the colliculi, red nucleus, central grey matter and reticular substance nerve-cell degeneration was both frequent and severe and pericellular satellites were greatly increased in number, as many as 8–10 being frequently found in relation to the smaller nerve-cells. (Fig. 10). The large multipolar cells of the nuclei of the third and fourth cranial nerves, the mesencephalic nucleus of the trigeminal, the locus coeruleus, nucleus hypothalamicus and lateral geniculate body had almost all escaped damage but a number of cells in the medial geniculate body and substantia innominata were degenerate. The substantia nigra had sustained great cell loss but was much less completely denuded of cells than in the Parkinsonian cases. The majority of the surviving cells, moreover, were remarkably healthy in appearance and satellites were present only in relation to a few degenerate cells. (Fig. 9).

Compact rows of 6–8 granule-cells were present in relation to the precapillary vessels only where other alterations were well-marked. Elsewhere there was merely a slight diffuse increase in the number of satellites about the small vessels.

There was a considerable amount of glial proliferation in the substantia nigra, central grey matter and reticular substance, most of the astrocytes being fibre-forming cells of medium size. Elsewhere the astrocytes commonly showed some enlargement but fibre-forming cells were only occasionally noted near the vessels.

In most areas the lumina of the Virchow-Robin spaces contained only a few degenerate granule-cells but in the substantia nigra there were many large and small mononuclear cells within the meshes of the adventitia.

Pons and Medulla.—Only a small proportion of the cells of the motor nuclei of the lower cranial nerves were degenerate but in the sensory nuclei and, in particular, in the nucleus of the spinal tract of the trigeminal, many of the nerve-cells were severely damaged. Neuronophagia was usually very slight and there was nowhere any considerable excess of satellites along the smaller vessels. Many granule-cells were present in the tissues around the larger vessels, however, and small cells were occasionally found within the perivascular spaces. Many of the astrocytes in the posterior column nuclei and in the nucleus of the spinal tract of the trigeminal showed marked progressive alterations; occasional hypertrophic glia-cells were found in other parts of the grey matter especially in the floor of the fourth ventricle.

The *cerebellum* and *spinal cord* showed no noteworthy changes.

CASE III.

Clinical History.—A male, aged 62, was admitted to the Royal Infirmary, Edinburgh, under the care of Professor Edwin Bramwell, on November 13, 1927. Three years before he had had a typical, acute, lethargic attack of epidemic encephalitis; since then, he stated, he had felt very listless and his friends had noticed that his facial expression had changed, that his movements had become very slow and that he held his arms rigid in walking.

Fourteen days before admission he started to become progressively weaker so that after a few days he had to remain in bed and still later he became so weak that he could not feed himself or read for long; he had also developed incontinence of urine and faeces.

On examination the patient appeared dull, drowsy and confused; his memory was somewhat impaired but he answered questions intelligently, although with an effort and in a slow, monotonous voice. His face was immobile; the right naso-labial fold was smoothed out and the mouth drawn over to the left; saliva dribbled from his lips. His eyelids drooped markedly and he could not move his eyes upwards and only slightly from side to side. The masseters were weak, the tongue deviated to the right and was tremulous. There was no obvious weakness of the limbs but the muscles of both upper and lower limbs were hypertonic and there was a marked tremor of the hands on movement. Bed-sores were present over the sacrum and right malar eminence.

He gradually became more drowsy, developed a hypostatic pneumonia and died on November 20, 1927.

Histological Findings. Cerebral Cortex.—Degenerative changes were present in the nerve-cells in all layers of the cortex but were invariably slight in the cells of the superficial half, whereas in the deeper layers a large proportion of the nerve-cells were severely damaged. Collections of satellites about the degenerate cells varied in number from 3 up to 9 or 10, and continuous rows of 6–10 small granule-cells, with groups of 10–12 where the vessel bifurcated, were found in relation to the precapillary arterioles and venules. A small proportion of the astrocytes in the deeper cortex and adjacent white matter showed slight hypertrophy.

There were many degenerate granule-cells in the tissues around the larger subcortical vessels and a few of these cells were seen in the perivascular lymph spaces. At the surface of the brain there were a few areas of subpial and meningeal hæmorrhage.

The changes outlined above were fairly constant in extent and severity in all the regions examined with the exception of the occipital cortex, in which only patches of the deeper layers had been severely implicated.

Basal Region. Putamen, Caudate Nucleus and Claustrum.—The nerve-cells in these nuclei showed marked degenerative changes, more severe in the small polygonal cells than in the large multipolar elements. Around the degenerate cells there were groups of up to 8–9 satellites and along the precapillary vessels rows of 7–8 cells with occasional groups of 20 or more in double and treble layers. Many of the astrocytes were slightly enlarged.

Globus Pallidus.—Most of the large multipolar cells of this nucleus showed only slight chromatolysis but in a few, degenerative changes were more severe and about these small groups of satellites were collected. There was marked hypertrophy of a very few of the astrocytes.

Thalamus.—Most of the nerve-cells showed degenerative changes of moderate severity and satellites were collected in groups of 5–6 about the more degenerate cells and in rows of 6–7 along the small vessels. Only a few of the astrocytes were enlarged.

The larger vessels in the basal region of the hemispheres displayed marked swelling of the adventitial cells in the region of the perivascular lymph spaces. The cytoplasm of these cells contained a small amount of lipochrome pigment and a few degenerate granule-cells were present in the lumina of the spaces.

Midbrain.—Degenerative changes of varying degrees of severity were present in many of the nerve-cells forming the various grey masses at this level. In the colliculi, reticular substance and central grey matter, where almost all the nerve-cells were implicated, perineuronal satellites usually numbered 3–5, but quite commonly collections of 8–10 were present about badly damaged cells. The alterations in the medial geniculate body and red nucleus were only slightly less marked. Many of the large cells in the oculomotor nucleus showed slight central chromatolysis but only a few of these cells were more severely damaged. The substantia nigra had sustained great cell loss, for only a few scattered cells occupied the site of this large nucleus. Most of the remaining cells appeared fairly healthy, however, and satellites were present only in relation to occasional degenerate elements. In the tissues there were little groups of granule-cells collected around masses of melanin pigment, the remains of dead pigmented nerve-cells. Suitable preparations showed a marked outfall of axis-cylinders and myelin sheaths, particularly in the medial part of the nucleus. In most of the midbrain nuclei the perivascular satellites were increased in number but they rarely formed long continuous chains. The astrocytes in the substantia nigra were considerably increased in number; most of the cells were of the hypertrophic fibrous type and they had produced voluminous

bundles of fibres. (Fig. 11). The feltwork of glial fibres was very dense in the medial part of the nucleus. A number of hypertrophic fibrous astrocytes of a somewhat smaller type were present in the central grey matter, colliculi and reticular substance.

In the substantia nigra the perivascular spaces of the larger vessels contained many larger and smaller mononuclear cells and large amounts of melanin pigment and fat. Elsewhere very few granule-cells were found within the adventitial channels, although they were usually plentiful in the surrounding tissues.

Pons.—The large cells forming the motor nuclei of the fifth, sixth and seventh cranial nerves were generally fairly healthy but a few showed degeneration and around these small numbers of satellites were grouped. Degenerative changes of great severity were common in the cells of the superior olivary nucleus and nucleus of the lateral lemniscus,

FIG. 11.—Gliosis in the substantia nigra. Case III. Anderson's Victoria blue method. ($\times 275$).

in the reticular nuclei and, in particular, in the main sensory and spinal nuclei of the trigeminal nerve. Five or six satellites were usually collected about the degenerate cells, but the satellites along the small vessels were only slightly increased in number. A number of hypertrophic fibrous astrocytes were scattered throughout the tissues.

Medulla.—The large multipolar cells of the hypoglossal nucleus, nucleus ambiguus and anterior column were almost all perfectly healthy. A number of cells in other groups showed mild degenerative changes but severe alterations were practically confined to the cells of the dorsal motor nucleus of the vagus, the nucleus of the tractus solitarius, the reticular nuclei and the nucleus of the spinal tract of the trigeminal, the last being most

extensively affected. Many hypertrophic fibrous astrocytes were found in this nucleus and in the grey matter in the floor of the fourth ventricle.

Cerebellum.—Showed no noteworthy alterations.

Spinal Cord.—Severe degeneration and neuronophagia were noted in a few of the nerve-cells in both anterior and posterior horns in the cervical enlargement and in many of the cells of the intermedio-lateral column in the midthoracic region. In this part of the grey matter the network of glial fibres was unusually dense; elsewhere only occasional fibrous astrocytes were found.

CASE IV.

Clinical History.—A female, aged 30, was admitted to the Royal Infirmary, Edinburgh, under the care of Dr. Chalmers Watson, in December, 1927. Following a slight

FIG. 12.—Marked accumulation of small granule-cells along a precapillary venule in the deeper layers of the prefrontal cortex. Case IV. Hæmatoxylin-eosin-safran. ($\times 200$).

illness in January, 1927, she had become increasingly dull, listless, apathetic and irritable. No definite signs of organic disease of the central nervous system could be elicited. While in hospital she had occasional rigors during which the temperature rose to 105°F ., but she stated that these did not cause her any discomfort. Numerous trophic sores developed during the few days preceding her death, which took place on December 19, 1927.

At autopsy no pathological changes in the organs were noted and there was no naked-eye indication of intracranial disease.

Histological Findings.—A slight degree of chromatolysis was apparent in almost all the nerve-cells throughout the central nervous system but this was regarded simply as the result of the fever and toxæmia accompanying the terminal illness.

Cerebral Cortex.—Nerve-cells showing severe degenerative changes were present in the second and third layers of the cortex but were much more numerous in the cortical zones at a deeper level. Neuronophagia was not usually very marked but groups of 8–10 pericellular satellites were not uncommon. Collections of 10–15 granule-cells, arranged in double or treble rows, were frequently found along the smaller vessels in the deeper cortex. (Fig. 12). A few of the deeper cortical and subcortical astrocytes were slightly hypertrophied.

Granule-cells were found in large numbers in the nervous tissues around the larger subcortical vessels but were rarely seen within the perivascular lymph spaces. In all areas there were many small hæmorrhages along the superficial cortical arterioles, at the surface of the brain beneath the pia, and in the meninges.

These alterations were all more intense in the prefrontal and temporal regions, particularly on the left side, than in the sensorimotor and occipital cortex.

Basal Region. Putamen and Caudate Nucleus.—Severe degenerative changes were present in the small polygonal and large multipolar cells throughout these nuclei. Groups of pericellular satellites usually numbered 3–12 and there were rows of 9–12 small granule-cells along many of the small arterioles and venules. Many of the astrocytes were slightly enlarged.

Globus Pallidus.—Many of the large pallidal cells showed moderately severe degenerative changes and had groups of up to 7–8 satellites around them. Along the precapillary vessels there were sparse, short chains of, at most, 4–5 granule-cells. Many of the astrocytes were enlarged and very rare large fibre-forming cells were encountered.

Clastrum and Thalamus.—The conditions in these nuclei resembled those in the globus pallidus but there were larger collections of satellites along the smaller vessels and no fibre-forming astrocytes were found.

The adventitial cells lining the lymph spaces of the larger vessels in the basal region of the brain were markedly swollen and within the lumen there were a number of degenerate granule-cells and a few macrophages laden with lipochrome pigment.

Midbrain.—A large proportion of the nerve-cells in the colliculi, red nucleus and central grey matter and a somewhat smaller number in the reticular substance and medial geniculate body showed severe degenerative changes. Groups of up to 9–10 satellites were collected about the damaged cells. Many of the large multipolar cells of the third and fourth cranial nerve nuclei were shrunken and atrophic. The substantia nigra of both sides showed a marked outfall of nerve-cells and fibres. Most of the remaining nerve-cells were shrunken and depigmented and there were groups of 5–6 satellites around a few very degenerate cells. There was a slight increase in the number of satellites along the small vessels throughout the midbrain area, always most marked where neuronophagia was most severe.

There was marked hypertrophy and proliferation of the astrocytes of the substantia nigra and a few large fibre-forming cells were also found in the central grey matter, colliculi and reticular substance.

Many granule-cells were found infiltrating the tissues around the larger vessels in the midbrain area but large numbers of small cells were found within the perivascular spaces only in the substantia nigra. Here the adventitial spaces also contained many large mononuclear cells and much melanin pigment and fat.

Pons and Medulla.—The large multipolar cells of the somatic motor nuclei of the lower cranial nerves were healthy. Severe degenerative changes were noted in the nerve-cells in the other grey masses in the lower part of the brain-stem but were frequent only in the nuclei pontis, in the main sensory and spinal nuclei of the trigeminal, in the nucleus of the tractus solitarius and in the reticular substance. Little groups of 5–6 satellites were usually present around the degenerate cells but there was no marked accumulation of

granule-cells along the precapillary vessels. A small number of hypertrophic fibrous astrocytes were scattered at wide intervals throughout the grey matter. They were most numerous in the nucleus of the spinal tract of the trigeminal and in the central grey matter in the closed portion of the medulla.

Cerebellum.—Showed no noteworthy alterations.

Spinal Cord.—A few scattered cells in both anterior and posterior columns in the cervical region showed severe degenerative changes; the mid-thoracic region had escaped with little damage; only a small group of cells in the middle of the anterior column in the lumbar region was implicated; in the sacral region a number of cells in the anterior column and a considerable proportion of those in the posterior column showed marked alterations. The satellite groups about the degenerate cells were large (9–10) in the sacral region, elsewhere they were much smaller. There was no definite increase in the number of satellites about the precapillary vessels and no marked alteration in the astrocytes at any level.

COMMENTARY.

When encephalitis became prevalent in Europe in 1917, it was quickly realised that the condition must be infective in origin. Two features, in particular, gave support to this conclusion: the disease showed a tendency to occur in small localised epidemics, and the cerebral lesions were definitely inflammatory in nature. But histological and experimental research, though vast in amount, has failed to place our knowledge of the etiology of the condition upon a substantial foundation. The precise nature of the causal agent of the infection remains obscure.

Attempts to explain the disease by attributing the lesions to organisms of well-defined morphological type have not been lacking. Rosenow and Jackson²⁰, for example, described a diplostreptococcus which occurred around the vessels in the diseased nervous tissues. Hilgermann, Lauxen and Shaw⁶ reported the finding of protozoa, resembling the parasites of coast fever of cattle, in the blood, marrow, spleen, liver and ventricular fluid of fatal cases. These and other similar observations have not been confirmed extensively, however, and the great majority of workers believe that the causal agent of epidemic encephalitis belongs to the group of ultramicroscopic viruses.

But it has never been actually demonstrated that a filterable virus is the cause of the disease. Many experienced workers have made repeated attempts to infect animals with material from cases of human encephalitis and have failed to transmit an infection. The positive findings of other workers are inconclusive because they may be interpreted in different ways.

The earlier workers often relied upon the presence of histological lesions in the brains of inoculated rabbits as evidence of the transmission of the infection. This work is difficult to evaluate because the lesions described cannot always be distinguished from those of the spontaneous chronic encephalitis

of rabbits. This disease is characterised by the presence of meningeal, cortical, perivascular and subependymal collections of small round cells in the brains of affected animals. Only rarely does it betray its presence during life by producing cerebral symptoms. The condition is apparently rare in Great Britain, but is common in Sweden and in some parts of America. McCartney¹³, working at the Rockefeller Institute, found that 55 per cent. of a group of 372 rabbits were affected. None of these animals had been injected intracerebrally. It is obvious, therefore, that unless it can be shown that the laboratory stock is free from this condition, the histological appearances in inoculated animals must be interpreted with great reserve.

During the Paris epidemic of 1919-20, Levaditi¹⁰ and his fellow workers attempted to infect animals with cerebrospinal fluid, blood, brain emulsion and filtrates of the saliva and nasal mucus of a number of cases of the disease. A fixed virus was obtained by inoculating rabbits with brain emulsion from one case. The cerebral tissues of another case gave an attenuated virus. In their numerous other inoculation experiments the results were negative. The fixed virus, when inoculated intracranially or by various extracranial routes, produces a rapidly fatal acute encephalitis in the rabbit. This disease is identical, clinically and pathologically, with the encephalitis produced in the rabbit by inoculation with the herpes virus. And, moreover, it has been shown by cross immunity experiments that the virus itself is identical with the virus of herpes. Levaditi concludes, therefore, that the causal agent of epidemic encephalitis in man is the herpes virus or a special strain of this virus which has developed 'neurotropic' tendencies.

Flexner and Amoss² have confirmed most of Levaditi's experimental findings, but question the validity of his conclusions. They inoculated animals with nasopharyngeal washings and brain emulsion from many cases of encephalitis with uniformly negative results. In addition, they tested a series of 100 specimens of cerebrospinal fluid (27 of which came from cases of encephalitis) for the presence of the herpes virus. These fluids were injected intracerebrally in rabbits and only one of them proved virulent. This specimen was obtained from a case of neurosyphilis which had been under observation for several years and had never shown any sign of encephalitis. These workers infer that the herpes virus may occasionally invade the fluids and tissues of the human body without producing pathogenic effects and that the occasional presence of this virus in the brain of human cases of encephalitis is quite accidental.

Further work, without pointing to a definite solution, has served to show how complex the problem is. On the whole, it may be said that it is still possible that the causal agent of epidemic encephalitis is a special strain of the herpes virus which has acquired a marked virulence for human nervous tissues. But it is more probable that the disease is due to a totally different virus which has never been transmitted to animals. All our definite informa-

tion about the pathogenic properties of this virus has been obtained from the study of the disease which it produces in the human subject.

An analysis of the pathological findings in the four chronic cases described brings to light several interesting features of the chronic stage of the malady.

(1) *The lesions are widespread in the central nervous system.*—In most of the work which has been carried out on the pathological anatomy of chronic encephalitis the main object has been the elucidation of anatomical and physiological problems. The aim of the observers was to determine the site of the lesion which caused the development of post-encephalitic Parkinsonism. The presence of marked destructive lesions in the substantia nigra in this disease was used as a basis for conclusions regarding the functions of this cell-mass and attempts were made to determine the course of the fibre-tracts connecting it with other nuclei. Naturally, attention was focussed upon the substantia nigra and less regard paid to other areas. McAlpine¹² and other authors quoted by him are in substantial agreement that the changes in the substantia nigra are of great importance. Lesions elsewhere in the brain-stem or basal nuclei if present, are generally regarded as insignificant. No important cortical alterations were found by any of these writers.

More recently, however, a few observers have reported single cases of chronic encephalitis in which the lesions were much more widespread. In some of these cases very marked cortical changes were found, in addition to the advanced lesions in the brain-stem. Chronic degenerative changes in the ganglion-cells of the cortex with perivascular infiltration and overgrowth of protoplasmic neuroglia were noted by Pjatnizky, Pawljutschenko and Michejew¹⁷. Zucker²² described a case in which there was a marked outfall of nerve-cells with disturbance of the cellular architecture and marked proliferation of microglia and neuroglia in the cerebral cortex. He noted the absence of inflammatory changes. Holzer⁷ and Meyer¹⁴ described cases in children in whom the acute disease had been followed by changes in character. Curiously enough, although very marked lesions were found in the midbrain and hindbrain in both cases and in the thalami in one, neither of them showed any noteworthy alterations in the cerebral cortex.

The findings in the short series of cases described in this paper show that a widespread distribution of lesions in chronic encephalitis is by no means exceptional. In all of these cases the substantia nigra was most markedly affected, but lesions of varying degrees of severity were found in almost all the other nuclei of the brain-stem and in the basal nuclei and thalami. The spinal cord showed definite alterations in two cases and in all four the deeper layers of the cerebral cortex were markedly implicated. The cerebellum alone had escaped damage in every case.

It is clear that in chronic encephalitis the lesions are not confined to a limited area. Practically the whole of the central nervous system is affected.

(2) *The disease is active.*—From the pathological standpoint, the active nature of the lesions is the most important feature of the disease. Yet few writers on chronic encephalitis give much attention to this aspect of the subject. Zucker²², however, pointed out that the lesions in the brain-stem and cerebral cortex of his case were by no means quiescent. Reynolds and Slater¹⁹, in a recent paper, lay stress upon the progressive nature of the astrocytic reaction in the midbrain of a patient who died eight years after the primary acute attack.

In the four cases under discussion the lesions are undoubtedly active. This is equally true of every case, whatever the duration of the illness (longest—three years; shortest—nine months). The nerve-cells show degenerative alterations; granule-cells are assembled in large numbers about the nerve-cells and small blood-vessels; large fibre-forming astrocytes are present in many areas. These appearances are to be regarded as unmistakable evidence of an active pathological process. They offer a vivid contrast to the findings in the nervous system in old-standing cases of paralysis following poliomyelitis. Here a glial scar takes the place of nerve-cells which have been destroyed while the surrounding tissues are healthy. The lesions of 'chronic' poliomyelitis are healed lesions; the lesions of chronic encephalitis are actively progressive.

(3) *The grey matter of the central nervous system is affected diffusely but the lesions vary in intensity and in degree of development in different grey masses.*—The histological findings differ in different parts of the brain. But it is reasonable to assume that the underlying pathological process is essentially the same in all. It has simply advanced further in some regions than in others. Different nuclei, even when lying close to each other, may be very differently affected. The lesions may be severe in the substantia nigra, for example, and relatively slight in the adjacent red nucleus. Moreover, the appearances suggest that the process is increasing in intensity in some areas, while it is becoming more quiescent in others.

In every cell-mass affected, the lesions are diffusely distributed. In a given area, minor variations in the intensity of the reactive processes are frequently noted. But the disease is rarely definitely focal. A few small foci of intense gliosis, associated with a marked local outfall of nerve-cells, were found in the thalami of two cases. But elsewhere the disease always affected the tissues diffusely.

The variations in the intensity and in the stage of development of the pathological process in different areas may be illustrated by a comparison of the findings in the cerebral cortex with those in the substantia nigra.

Throughout the deeper layers of the cortex, degenerative changes in nerve-cells are frequent and severe, but there is little indication of actual cell-destruction; marked neuronophagia is common; granule-cells are accumulated about

the precapillary vessels in large numbers but are seldom found within the lymph spaces of the larger arteries and veins; the astrocytes show little alteration.

In the substantia nigra there has been a considerable outfall of nerve-cells and fibres; the remaining cells are frequently depigmented but, in the majority, the Nissl granules and neurofibrils appear fairly healthy; neurophagia is seldom marked; the number of satellites along the smaller vessels is not excessive, but numerous degenerate granule-cells are present in the lymph spaces of the larger arteries and veins; the astrocytes are markedly increased in numbers and most of the cells are of the large fibre-forming type.

In the cortex there is a process of intense nerve-cell degeneration accompanied by a marked reaction of the phagocytic granule-cells, while the astrocytes remain practically unchanged.

In the substantia nigra this stage is almost over. Many of the nerve-cells have been destroyed; a few are degenerate; but the majority of those that remain have either escaped damage or have recovered. The astrocytes are engaged in the repair of the tissues.

These are the extremes. The conditions in other areas illustrate intermediate stages.

(4) *The pathological process is a relatively simple one, implicating only the nervous tissues proper.*—A study of the lesions at different stages of development enables us to obtain some idea of the sequence of changes occurring in the diseased nervous tissues.

Degeneration of nerve-cells may be noted in areas in which there is no neuronophagia, no increase in the number of satellites about the nerve-cells or along the blood-vessels and no proliferative changes in the astrocytes. But such cell degeneration is never absent when other changes are present. It must be regarded, therefore, as the primary alteration in the nervous tissues.

In most areas, however, the degenerating nerve-cells are surrounded by a number of small granule-cells, and there is a marked increase in the number of small cells along the adjacent precapillary and capillary vessels. These small granule-cells apparently arise from the microglia. They probably act simply as scavenger cells, absorbing the debris cast out of the disintegrating nerve-cell cytoplasm and depositing it in the adventitial spaces of the smaller vessels. Finally they degenerate and die, the nucleus becoming broken up or undergoing gradual lysis. This may occur in the nervous tissues, but very frequently the granule-cell passes into the lymph spaces of one of the larger vessels before disintegrating. Many of these cells are seen in this situation in areas in which an intense reaction has been in progress for some time.

The degenerative changes in the nerve-cells may become more and more severe and finally lead to the death of the cell. This is a frequent occurrence

amongst the large pigmented cells of the substantia nigra. But, in other areas, although degeneration of cells is common, complete destruction appears to be relatively slight. There is rarely any direct evidence of outfall of neurones.

When nerve-cells have been destroyed the astrocytes enlarge and may proliferate. They develop long, thick, branching cytoplasmic processes in which bundles of fibrils become differentiated. In this way a network of glia fibres is laid down and this repairs the gaps in the tissues resulting from the destruction of neurones.

This process involves essentially only the nervous tissues proper. Cellular elements derived from the bloodstream, from the walls of the blood-vessels or from the meninges, do not play any active part in it. The slight alterations in the region of the perivascular spaces are such as may result simply from the accumulation of debris in this situation. And this debris is brought to the lymph spaces by phagocytes originating in the nervous tissues themselves. These phagocytes were formerly termed 'gliogenic granule-cells' because they were believed to arise from the ectodermal astrocytes. Hence it was supposed that all the elements involved—the nerve-cells or their processes, which degenerate, the granule-cells which remove the debris, and the astrocytes which repair the tissues—were ectodermal in origin. The whole process was accordingly spoken of as an 'ectodermal reaction.' Within recent years, however, Rio Hortega, Penfield¹⁶, Hurst⁹ and others have demonstrated that the 'gliogenic granule-cells' arise, not from the astrocytes, but from the microglia. This is a special category of cells which is found only within the nervous tissues but is believed to be of mesodermal origin (Penfield⁹). The expression 'ectodermal reaction' can therefore no longer be regarded as accurate. But it may still be retained as a useful term indicating that the pathological processes are confined to the nervous tissues proper.

A pure 'ectodermal reaction' of this type follows injuries which inflict damage upon the nerve-cells or their processes without affecting the blood-vessels. When the vessels are injured, reactive processes of a totally different character are set in motion. These will be considered later in discussing the acute stage of the disease. In chronic encephalitis the perikarya of the neurones alone are severely affected. There is no evidence of direct damage to the axicylinders or their myelin sheaths.

The cause of this severe injury to the nerve-cells merits consideration. Toxic substances, finding their way into the nervous tissues from the circulating blood, might be expected to affect susceptible areas fairly uniformly. Any deficiency, in the circulating fluids, of substances necessary for the nutrition of the nerve-cells would likewise produce effects simultaneously in all areas. But, as has been pointed out already, the lesions in different areas vary greatly in severity. Moreover, in some cell-masses the disease processes are at an early stage of development, in others they have advanced far towards healing.

It would be difficult to attribute such lesions to injurious agents reaching the tissues through the circulating blood.

A great variety of local tissue alterations are capable of causing damage to the neighbouring nerve-cells. Local defects in the circulation of fluids, for example, resulting from disease of the walls of the blood-vessels, might cause local injury to the nerve-cells. But, in general, the walls of the vessels are healthy. Toxic substances might find their way into the adjacent nervous tissues from inflammatory foci in the walls of the vessels or elsewhere. But such inflammatory foci are absent. Living organisms could injure the nerve-cells very readily. But, if these are present, they cannot be demonstrated.

There is, in short, no evidence regarding any local or general factor, nutritional or toxic, to which the nerve-cell degeneration can be attributed. But it is reasonable to assume that the progressive lesions of the chronic stage of encephalitis are due to the action of the virus which caused the primary acute attack ; that this virus lingers on in the tissues after the acute stage of the disease is over ; and that it exerts a direct injurious effect upon the nerve-cells.

The severity of the lesions in the chronic stage of the disease may depend to some extent upon the particular strain of the virus which reaches the nervous tissues and upon its ability to survive and multiply there. It may depend upon varying degrees of susceptibility of the nerve-cells in different individuals. But it certainly does depend upon differences in susceptibility of different types of nerve-cell in the same brain, for some cell types are always much more severely affected than others. Many of the large pigmented cells of the substantia nigra are always destroyed, whereas there is no evidence of outfall of cells in the adjacent red nucleus. The small cells of the sensory nuclei of the cranial nerves are severely damaged, the large multipolar cells of the motor nuclei very slightly. And since these cell-masses lie very close to each other, it is obvious that the virus may reach any of them equally readily. The differences in the effects produced must, therefore, depend upon differences in the susceptibility of different types of nerve-cell.

A number of other problems still remain to be considered. Does the virus exert its action upon the nerve-cells slowly and continuously from the time it first gains entrance to the tissues ? Or may it, in some cases or in some situations, remain for a time latent and practically inert, until circumstances favour the progress of the infection ? In the case of the very chronic lesions in the midbrain region it seems impossible to choose between these alternative possibilities. The lesions in the cerebral cortex, in the basal ganglia and in some of the nuclei of the brain-stem, on the other hand, appear to be of fairly recent origin. If they had been in progress very long, some destruction of nerve-cells and some proliferation of astrocytes must almost certainly have resulted. Then how do such lesions arise ? Are they caused by a fresh spread of the virus from some part of the brain-stem in which the disease has been progressing ? Or are they due to the activation of a local infection that has

previously been latent? The histological data do not provide us with any information bearing upon these questions.

COMPARISON OF ACUTE AND CHRONIC STAGES.

It has already been pointed out that in these cases of chronic encephalitis the lesions are concentrated in the nervous tissues. The blood-vessels are little affected by comparison. In the acute stage of the disease, on the other hand, inflammatory changes affecting the walls of the vessels are the most striking feature. Cellular elements derived from the tissues of the vessel wall and from the circulating blood become heaped up in the perivascular lymph spaces and emigrate into the adjacent tissues. Lymphocytes, larger and smaller mononuclear cells, endothelial and adventitial cells, mast-cells, plasma-cells and even polymorph leucocytes may all participate (Da Fano¹).

This type of tissue alteration falls into the general group of 'mesodermal' types of reaction, which are characterised by the activity of cellular elements derived from the connective tissue—vascular system. Such reactions are known to follow upon injury to the walls of the blood-vessels. Accordingly Guizetti² has suggested that the perivascular inflammatory changes in acute epidemic encephalitis are due to the "direct localisation of the germs of the infection on the walls of the veins."

There is, of course, a considerable amount of nerve-cell degeneration even in the acute stage of the disease, but this is usually a much less conspicuous feature than the alterations associated with the vessels. Indeed, it is generally agreed that damage to nerve-cells is usually not nearly so marked as the clinical features would lead one to expect (Hall³). And, moreover, much of the cell degeneration that does occur may well be due rather to intoxication and interference with the nutrition of the cells than to the direct action of the virus. This is suggested by the fact that recovery from the symptoms of the acute stage of the disease may be rapid and complete, whereas recovery from symptoms of the chronic stage either does not occur at all or is tedious and, usually, incomplete. And in the chronic stage, as has been pointed out, the degeneration of the nerve-cells is probably due to a direct attack of the virus upon the cells themselves.

As the disease passes into its chronic stages the alterations in the nervous tissues progress while the perivascular inflammation subsides. In this respect chronic encephalitis differs essentially from general paralysis of the insane, a disease which resembles the chronic stage of encephalitis in that the nerve-cells are attacked and destroyed by a virus which is present in the nervous tissues. The destructive effects upon the nerve-cells and the associated degeneration of fibres in general paralysis are, of course, much more extensive and severe. But the most striking difference between the two diseases is this: in general

paralysis the perivascular inflammatory condition persists, the lymph spaces of many of the vessels being crowded with proliferated endothelial cells, lymphocytes and plasma-cells, while in chronic encephalitis the 'mesodermal reaction' in the walls of the vessels has died away.

From the foregoing it will be apparent that the acute and chronic stages of epidemic encephalitis differ markedly in their pathology as well as in their clinical features.

In the acute stage of the disease both the ectodermal and the mesodermal tissues of the brain are affected. The virus attacks the walls of the blood-vessels and stirs up a brisk reaction of the mesodermal type in the region of their adventitial lymph spaces. Such an inflammatory process must affect the adjacent nerve-cells by poisoning the fluids upon which they depend for their nourishment and by interfering with the circulation of these fluids. No doubt a number of cells are also injured by the direct action of the virus. But after a time the perivascular inflammatory reaction dies down. Probably a few of the nerve-cells have been destroyed but the remainder recover and resume their normal functions.

Whether recovery is permanent or not will now depend upon the susceptibility of the nervous tissues proper. If these tissues prove very resistant to the action of the virus there will be no chronic phase. If they are very susceptible, chronic symptoms may appear as a continuation of the acute disease. But usually there is an interval of apparently good health before the chronic disease develops clinically.

In the chronic stage of encephalitis the ectodermal tissues alone are affected. The symptoms are due to the direct action of the virus upon the nerve cells. The reactive processes which develop are of the ectodermal type. If the nerve-cells prove very susceptible the symptoms of the chronic stage will appear during the course of the acute attack or soon after it is over. If they are less vulnerable a long time may elapse before the damage is severe enough to cause any functional derangement. The virus may even remain latent for a time, doing little or no damage. Hence the possible interval of months or years between the acute attack and the appearance of symptoms of the chronic stage.

In many cases encephalitis develops as a chronic disease from the outset. There is no recognisable acute phase. In these cases, we may suppose, the virus does not provoke a widespread perivascular inflammatory reaction but enters the nervous tissues and slowly attacks the susceptible nerve-cells.

PROGNOSIS IN CHRONIC ENCEPHALITIS.

Certain of the data gathered during the course of this study have a bearing upon the question of the prognosis in chronic encephalitis.

It has been pointed out that the lesions are not simply the result of the primary acute attack of the disease but are progressive in nature. And although no dogmatic assertion can be made regarding the causation of these chronic progressive lesions, it is reasonable to assume that they are due to the prolonged action of the virus which was responsible for the primary acute attack. This virus, apparently acting directly upon the nerve-cells, may destroy them completely ; or it may damage them in such a way as to interfere with their function without causing complete destruction. The prognosis will be favourable only if the progress of the infection can be permanently arrested. The chief aim of therapeutic measures should be the complete destruction of the virus. Attempts to relieve symptoms may only injure the nerve-cells and render them more liable to attack.

Even the complete elimination of the virus, however, will not ensure complete recovery. Nerve-cells which have been destroyed cannot be replaced either anatomically or functionally. In other organs destruction of cells is made good either by proliferation or by hypertrophy of surviving elements. But there is no evidence that nerve-cells can ever be replaced by regeneration or that surviving cells undergo hypertrophy. Even if regeneration did occur it would be useless unless the newly formed cells could re-establish the connections of those which had been destroyed and take their place in the formation of functioning nervous arcs. Similarly, hypertrophy of the surviving cells would probably not assist in the restoration of function.

The grouping together of nerve-cells in masses subserving a definite function has also an important bearing upon the results of disease in the central nervous system. The patient in whom the apex of a lung or the lower pole of a kidney has been destroyed by disease will suffer no inconvenience, provided the remainder of these organs is healthy. But the destruction of a small portion of the nervous system, containing a nucleus with important functions, will produce grave disabilities, however healthy the rest of the nervous tissues.

The great majority of workers (McAlpine¹² and others) agree that the lesions in the substantia nigra are the cause of post-encephalitic Parkinsonism. In every case in the present series there was a well-marked reduction in the number of cells in this nucleus. In every case the surviving cells appeared fairly healthy. Two of the cases, in which the outfall of cells was especially marked, had well-developed Parkinsonism. The other two cases, in which a much larger proportion of cells had escaped destruction, had not developed the Parkinsonian syndrome. It is apparent, therefore, that symptoms of Parkinsonism will not necessarily develop if a sufficient number of cells in the substantia nigra remain intact. But it is equally evident that once Parkinsonism develops, recovery is not to be expected since the nerve-cells in this nucleus are not simply damaged but are completely destroyed.

These remarks apply to the substantia nigra only. A very large number of other cell-groups were examined in the cases under discussion and lesions

were found in almost all. But in these a varying amount of nerve-cell degeneration was the rule, marked cell destruction the exception. Nowhere was there any evidence of an outfall of cells comparable with that in the substantia nigra. And, moreover, the damaged cells almost all appeared to be capable of recovery. There is reason to believe, therefore, that if the infection could be eliminated, recovery from symptom-complexes other than that of Parkinsonism would readily take place.

It is clear that in many cases of chronic encephalitis the virus remains active in the nervous tissues for years. Whether the infective process ever becomes arrested spontaneously is an open question. Many infections terminate naturally because the serum of the host develops substances or properties which are antagonistic to the parasite. It is possible that the serum of encephalitics may be capable of destroying the virus. But this would not necessarily affect the chronic disease, since it is probable that little, if any, of the blood serum finds its way into the nervous tissues. The experiments of Teale and Embleton²¹ show that a foreign serum, at any rate, does not penetrate into the nervous parenchyma. These workers injected guinea-pigs with large doses of horse serum and, after bleeding them thoroughly, tested their organs for the presence of this serum by delicate anaphylactic methods. It was found that the horse serum was present in the liver, spleen and omentum, but could not be detected in the brain or spinal cord. It is quite likely that the serum proteins of the animal itself are likewise excluded from the nervous tissues proper.

The adventitial spaces of the blood-vessels act as the lymph channels of the central nervous system. These spaces are in free communication with the subarachnoid space and drain into it. And since the cerebrospinal fluid normally contains only a small amount of protein (.018 per cent.), it is obvious that only a very small amount of serum protein passes from the interior of the vessels into the perivascular channels. This has an important bearing upon the progress of inflammatory conditions in the meninges and perivascular spaces because protective substances in the serum will reach the affected tissues in a state of high dilution. In bacterial meningitis the permeability of the vessel walls is altered during the course of the acute inflammatory reaction and a fluid rich in plasma proteins is exuded. But in epidemic encephalitis the protein concentration in the cerebrospinal fluid is normal or only slightly increased. Antibodies must therefore reach a high concentration in the blood serum before they can become effective in the dilute fluid of the perivascular spaces. It is possible that, in acute encephalitis, such effective concentration of antibodies is finally attained and the virus in the walls of the vessels destroyed. It is certain that the perivascular inflammatory reaction subsides. But the degenerative changes in the nervous tissues continue, possibly because the serum does not reach these tissues at all.

The important differences between the acute and chronic stages of the disease might be more readily explained on the supposition that a local cellular immunity developed in the tissues of the vascular adventitia but failed to develop in the nervous parenchyma. This may indeed be the correct explanation of the phenomena. It is obvious that all tissues must have some natural resistance to the action of irritants. But it is not certain that an increased resistance can be acquired by the tissues apart from the fluids in which they are bathed. In the present state of our knowledge, therefore, it appears better not to invoke theories of local immunity in suggesting a possible explanation of the findings.

No matter how immunity is produced, the virus, although still present in the brain, no longer injures the walls of the vessels or excites an inflammatory reaction in their adventitia. The inflammatory infiltrate of the acute stage is absorbed, the endothelial and adventitial cells regenerate and the vessels resume their former healthy state. But the disease processes in the nervous tissues continue, nerve cells are destroyed and, since regeneration of neurones cannot take place, complete restoration of these tissues is impossible.

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