THE CORRELATION OF CLINICAL AND PATHOLOGICAL FINDINGS IN TWO CASES OF PARKINSONIANISM.*

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We are all familar with the clinical picture of a case of epidemic encephalitis of the Parkinsonian type: the fixed flexion attitude, festinating gait, mask-like face and general slowing of all voluntary movement. What is the explanatory pathology of each and all of these physical signs?

This joint paper is an attempt to elucidate in detail the pathology of the two cases under consideration, correlating the clinical picture with the pathological findings and putting forward a few suggestions and possible explanations of some of the changes.

The paper is divided into three sections:

(*a*) Clinical notes.

(*b*) Detailed pathological report.

(*c*) Correlation of physical signs and pathology.

(*a*) Clinical Notes.

The first case was that of a male, C. H—, æt. 28, diagnosed on admission as suffering from dementia præcox with high-grade imbecility, while the second case was a male, M. McC—, æt. 42, admitted as a case of melancholia, the symptoms of which persisted until shortly before death.

In neither case was there any history of an acute febrile illness, and it was only after a residence of months in the hospital that the symptoms and signs of encephalitis made their appearance.

Both cases showed the typical attitude and appearance of "Parkinsonianism" with sialorrhœa and persistent increase of the pulse-rate, while in addition the younger case had a bilateral extensor plantar reflex and the older man showed absence of pupillary response to accommodation.

(*b*) Pathological Report.

Although no part of the nervous system examined can be considered normal, yet the greatest morbid changes are found in the

* Abstract of a paper read at a Divisional Clinical Meeting held at Rainhill Mental Hospital, May 2, 1928.

https://doi.org/10.1192/bjp.74.306.400 Published online by Cambridge University Press

crura, pons, medulla and basal ganglia, and least in the cerebral cortex (with the exception of a well-marked lesion of the Betz cells).

Further, although there are some differences in detail in the pathological findings in the two cases, yet these are generally similar and may be briefly summarized as follows:

(1) *The cerebral cortex.*—From the examination of various regions it appears obvious that the first patient was a mental defective, though not of low grade, and was probably suffering from dementia præcox, whilst the second patient was of at least average intelligence and did not suffer from any marked degree of dementia.

There is a certain amount of chronic thickening of the membranes, but no evidence (either here or in the nervous tissue) of acute inflammatory reaction, past or present.

The most striking lesion of the cerebral cortex is seen in the Betz cells, practically all of these examined being affected, but in a different way, in the two cases. In the first case the cells are more or less shrunken, often vacuolated, with irregularly swollen and fragmented dendrites and a small, darkly staining nucleus, usually centrally placed. There is well-marked satellitosis. In the second case the change closely resembles that seen in "central neuritis," with swelling of the cell (body and nucleus) and marked eccentricity of the latter, but without satellitosis. The amount of "Marchi" degeneration of the nerve-fibres in the precentral region is less than might have been expected from the condition of the Betz cells, as also are the number of areas of chronic fibre degeneration. Reference to the condition of the blood-vessels, etc., of the nervous system as a whole will be made later.

(2) *Basal ganglia.*—As regards the ventricular ependyma, whilst there is no general proliferation, yet there are, in Case 2, several local streaks of ependymal cells penetrating a long distance into the nervous substance.

The *corpus striatum* shows a gross degeneration of all types of nerve cells, especially in Case 2. The larger are mostly reduced to fragments of ragged cytoplasm and nucleus, while the majority of the smaller ones are barely recognizable as nerve-cells. The putamen of the lenticular nucleus is rather more affected than the pallidum in Case 2; the reverse is true of Case 1. There is marked generalized satellitosis. Numerous scattered areas of nerve-fibre atrophy are seen in all parts, and in various stages, but these are particularly prominent in the internal capsule.

The changes in the *optic thalamus* on the whole are much less pronounced than in the corpus striatum.

(3) *Crus cerebri.*—In the *substantia nigra* very few cells approaching to normality are seen. Most have entirely disappeared as

functioning cells, their former stations being merely represented by irregular, broken-up masses of pigment. Although numerous round-cells are present, these bear no definite relationship to the disintegrated nerve-cells.

In the *nucleus ruber*, although occasional individual cells appear fairly normal, most show chronic degeneration, the dendrites being swollen, with ragged edges and often fragmented. The number of small round-cells seen is extraordinary, especially in Case 1, eight, ten, or even up to twenty being present in satellite relation to one nerve-cell.

The *tegmentum* shows generalized degeneration of nerve-cells, though much less pronounced than in the substantia nigra and nucleus ruber.

In the *crusta* there are numerous scattered areas of nerve-fibre atrophy seen in all parts and in all stages, but chiefly affecting the middle third or so in Case 1 and the inner two-thirds in Case 2.

(4) *Pons and medulla.*—In the upper part of the pons there is marked proliferation of the aqueductal ependyma extending into the subjacent nervous tissue. There is gross degeneration of the nerve-cells of the raphe and to a much lesser degree of those of the tegmentum. Numerous scattered areas of nerve-fibre atrophy are seen in all parts, including the cerebellar peduncles and the pyramidal bundles.

The cells of origin of the third and fourth nerves in Case 1 are practically normal. Owing to an unfortunate accident these nuclei were missing in the sections obtained from Case 2, but the third nerves themselves showed definite areas of patchy sclerosis both before and after emergence.

While the cells of origin of the fifth nerve are fairly normal, those of the sixth to the twelfth inclusive are grossly degenerated.

(5) *Spinal cord.*—The cervical region only was examined, and here the most noteworthy change is degeneration of some, though not all, of the anterior cornual cells.

(6) *The cerebellar cortex.*—A point of importance is that a large number of Purkinjë cells have undergone atrophy in the absence of any inflammatory reaction.

(7) *Extra-neuronic changes.*—In the cornu ammonis in Case 1 some blood-crystals are seen—an indication of an old hæmorrhage—and in both cases there are a number of recent small hæmorrhages, in various parts, which must be regarded as terminal and as having no bearing on the symptomatology.

Although there is, in places, some peri-vascular glial proliferation (*e.g.*, in the red nuclei), there is no " cuffing " of vessels, such as is seen in certain acute inflammatory processes, nor is there any

polymorphonuclear leucocyte exudation into the tissues, nor yet any large phagocytic cells. Numbers of "rod" cells are seen in parts, but there is no amœboid glial proliferation. The presence of large numbers of round-cells, especially in Case I, has already been alluded to, and the satellite relation of these to the nerve-cells, particularly in the red nuclei, has been noted.

There is no pathological evidence of any acute inflammatory process having taken place at any time. The changes are essentially those of a chronic degenerative nature combined with a low type of inflammatory reaction.

(*c*) Correlation of Physical Signs and Pathology.

It has already been noted that the general pathological appearance of the cortex in Case I confirmed the clinical diagnosis of high-grade imbecility with dementia præcox.

The general clinical features, summed up in the term "Parkinsonianism," common to both cases and diagnostic of the condition, are represented pathologically by the widespread changes in the red nucleus, substantia nigra and associated parts of the central nervous system. How does this destructive lesion bring about this plastic generalized hypertonus and fixed flexion attitude? We believe it is due to the release of a primitive postural reflex (such as determines the fœtal position of flexion and the anthropoid habitus).

The experimental work of Hunter and Royle furnishes us with the best explanation of the phenomena here described. Hunter performed unilateral removal of the corpus striatum in birds and produced a diffuse muscular rigidity of the corresponding wing, exactly similar to the type of muscular hypertonus occurring in man in the condition called "Parkinsonianism." This and other experimental work has been elaborated to formulate what has been described as a "dualistic theory of muscular tonus."

Tonus we can consider as being composed of two distinct elements:

(*a*) Contractile tone subserved by large striped muscle-fibres and innervated by somatic nerves.

(*b*) Plastic or postural tone subserved by smaller striped muscle-fibres and innervated by post-ganglionic sympathetic nerves accompanying the somatic nerves.

Now we know that contractile tone is controlled and inhibited by the pyramidal tracts and motor cortex. Plastic or postural tone is controlled and inhibited by the rubro-spinal tract and the centres in the crus cerebri and basal ganglia. If these latter (red nucleus, substantia nigra and basal ganglia) are diseased or degenerated, cerebral control over the lower pre-spinal sympathetic

reflex arc is removed, and so we get manifestations of continuous sympathetic overaction, *e.g.*, sialorrhœa, increased frequency of the heart-rate and generalized vaso-constriction. In addition there is a point of bio-chemical interest which demands explanation, *viz.*, the fact that in practically all cases of encephalitis there is a slight persistent hyperglycæmia of blood and cerebro-spinal fluid.

Here let us refer to a fragment of physiological history. One of the pioneers in the elucidation of the problem of glycosuria was Claude Bernard, whose production of experimental glycosuria by puncture of the floor of the fourth ventricle has become a classic. The explanations of the production of experimental puncture glycosuria and that of epidemic encephalitis are one and the same. In both types we have lesions of the brain-stem, the one traumatic and the other degenerative, which sever the paths of communication between the basal ganglia and crural centres and the lower para-sympathetic (autonomic) reflex arc, resulting in a removal of cerebral inhibition and an overaction of the sympathetic nerves regulating the output of glycogen from the liver. In support of this contention we would cite the control experiment in which the glycogenetic nerve-fibres supplying the liver are cut prior to puncturing the floor of the fourth ventricle, in which case no glycosuria results.

Finally the condition of the reflexes and their pathological equivalents require attention.

Case 1 showed no alteration in the pupillary responses, whereas Case 2 showed a sluggish reaction to light and complete absence of response to accommodation. Pathologically we found that the third nucleus of Case 1 was normal, while the fibres of the third nerve in Case 2 showed advanced sclerosis.

The only other reflex of note was the plantar response in Case 1, labelled as ambiguous extensor. This latter observation was almost certainly correct, and is endorsed by the advanced degeneration of the Betz cells found in this case.

In conclusion we wish to affirm that as far as the clinical history and pathological findings are concerned, we can find no evidence of any acute inflammatory process having occurred at any time, and we consider these cases to be examples of a chronic progressive encephalitis rather than the sequelæ of an acute illness. In other words, to apply the term "post-encephalitic" to these and similar cases is in our opinion a misnomer, and we suggest the adoption of the term " chronic progressive encephalitis."