

DORSAL COLUMN

Grey Matter

An essay on the shaking palsy

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Two hundred years ago at the age of 62, James Parkinson wrote a 66 page treatise entitled *An Essay on the Shaking Palsy*. He believed that he had identified a new ‘medical species’ that had ‘not yet obtained a place in the classification of nosologists’ (Parkinson, 1817).

As a young apothecary Parkinson had attended a course of evening lectures given by the eminent surgeon-anatomist, John Hunter and taken copious shorthand notes. Long after Hunter’s death, Dr John Parkinson collated his father’s notes and published them under the title of *Hunterian Reminiscences, Being the Substance of a Course of Lectures on the Principles and Practice of Surgery Delivered by the Late Mr John Hunter*.

In one of the transcripts the following case is reported:

‘A lady, at the age of seventy-one, had universal palsy: every part of the body shook which was not fully supported. The muscles of respiration were so affected, that respiration was with difficulty effected; but in sleep the vibratory motions of the muscles ceased, and the respiration was performed more equably: any endeavour of the will to alter these morbid actions increased them.’

In Hunter’s opinion palpitations present only when an arm was totally at rest behaved differently from the trembling seen when a limb was not fully supported.

We will now never know what stimulated Parkinson to write his medical classic but perhaps the subliminal influence of his hero and fellow geologist was a factor. Probably unbeknown to Parkinson, John Hunter had earlier described a patient who may well have had the shaking palsy in his Croonian Lecture of 1776 (Hunter, 1837):

‘Lord L—’s hands are almost perpetually in motion, and he never feels the sensation in them being tired. When he is asleep his hands, &c. are perfectly at rest; but when he wakes, in a little time they begin to move.’

What did James Parkinson (1755–1824) describe?

Parkinson defined the shaking palsy as a nervous disorder characterized by a trembling of the limbs at rest, lessened muscular power and a stooped posture associated with a propulsive, festinant gait.

Chapter 1 of *The Essay* concludes with six clinical vignettes. All the cases were men who had noticed the first signs of the malady between the age of 50 and 65 years. Case VI provides the most edifying description but Case I, which Parkinson had seen ‘several years back’ was probably the most carefully studied patient and the one he relied most heavily on in the collage at the start of the chapter.

Parkinson emphasizes that the weakness is specific and differs from that seen in other forms of palsy. Its onset is gradual and is in one patient attributed to the advancement of age rather than illness:

‘So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow is its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement.’

Slowly the weakness worsens leading to difficulties with dexterous activities such as holding a fork or pen:

‘The submission of the limbs to the directions of the will can hardly ever be obtained in the performance of the most ordinary offices of life. The fingers cannot be disposed of in the proposed directions, and applied with certainty to any proposed point.’

‘The dictates of the will’, he wrote, ‘are even, in the last stages of the disease, conveyed to the muscles...but their actions are perverted’.

The tremor is coarse and on occasions violent and is always maximal when the limb is at rest. In Case III it affects the head, which nowadays would raise suspicion of an essential or dystonic tremor. He notes that the tremor usually begins in one limb and then spreads to involve the other limbs over several years. Case VI informs Parkinson that he is able to interrupt the interminable shaking for a few minutes by a brief sudden voluntary movement of the affected arm.

‘... he first perceived weakness in the left hand and arm, and soon after found the trembling commence. In about three years afterwards the right arm became affected in a similar manner: and soon after the convulsive motions affected the whole body, and began to interrupt the speech. In about three years from that time the legs became affected.’

The patient also mentions that at the age of 71 he had experienced a sudden onset of right-sided limb weakness, which had temporarily abolished his tremor. As his strength returned over the ensuing weeks so did his shake. The patient’s attendant then adds that the trembling is sometimes evident even in the lighter stages of his master’s sleep.

Parkinson clearly describes the characteristic festinant gait of the fully established case but there is no clear description of either start hesitation or freezing (blocking) of gait.

‘Case VI- On being asked if he walked under much apprehension of falling forwards? he said he suffered much from it; and replied in the affirmative to the question, whether he experienced any difficulty in restraining himself from getting into a running pace? It being asked if whilst walking he felt much apprehension from the difficulty of raising his feet, if he saw a rising pebble in his path? he avowed, in a strong manner, his alarm on such occasions; and it was observed by his wife, that she believed, that in walking across the room, he would consider as a difficulty the having to step over a pin.’

Case II walks almost entirely on the soles of his feet and depends on a stick to avert falls. Case IV who had only been seen at a distance requires support by an attendant:

‘...standing before him with a hand placed on each shoulder, until by gently swaying backward and forward, he had placed himself in equipoise; when giving the word, he would start in a running pace, the attendant sliding from before him and running forward, being ready to receive him and prevent his falling, after his having run about twenty paces.’

Parkinson also mentions profound fatigue in the legs and motor impatience in which the patient is compelled to walk around endlessly to assuage his tremor. He describes severe constipation requiring mechanical removal of the faeces and continuous drooling of saliva. He hints at depression (‘the unhappy sufferer’) and suggests that rheumatism can precede the trembling. In the terminal phase of the illness he reports that the speech is reduced to a slur and swallowing becomes

difficult. The patient lies motionless, the limbs are contracted and there is incontinence of the sphincters. The patients’ last days are passed in a delirious state.

His *post hoc* review of the available literature in Chapter II is thorough and scholarly but somewhat surprisingly makes no mention of John Hunter’s observations. Parkinson credits François Boissier de Sauvages de Lacroix (1706–67), a botanist and physician for having identified some key elements of the shaking palsy. Sauvages’ separate descriptions of *tremor coactus* and *scelotyrbé festinantem* in *Methodical Nosology* (1763) corresponded to rest tremor and a propulsive or hurrying gait but he had failed to see them as part and parcel of a single syndrome.

Parkinson’s prose is still easy to read and as refreshing as wine. In 1820 James Cooke, a physician to the London Hospital, contended that ‘Mr Parkinson’s Treatise’ was ‘highly deserving’ of attention. John Elliotson, soon to become the Professor of Medicine at University College Hospital, credited Parkinson with nearly all of his knowledge on the subject in a series of case reports purported to represent cases of paralysis agitans in the *Lancet* in 1830 and 1831. None of Parkinson’s findings were contested by the British medical establishment and his monograph attracted interest on the continent. It was almost as if his observations came as no surprise to anyone, yet nobody before him had put two and two together.

In the year of Parkinson’s death Wilhelm von Humboldt (1767–1835), German statesman and humanity scholar, wrote insightfully about his ‘special clumsiness’ and its effect on his handwriting (Horowski *et al.*, 1995). Humboldt believed he was describing the motor deficits of senility whereas Parkinson considered the shaking palsy to be a medical disorder rather than an extreme version of normal ageing.

In 1868 in a clinical lecture on paralysis agitans at the Hôtel Dieu, Trousseau demonstrated to his class that the movements of one of his patients, when instructed to repetitively open and close his hand, became slower and slower (Trousseau, 1868). This observation underpinned the modern definition of bradykinesia (progressive reduction in speed and amplitude after 20 s of sequential finger taps) (Gibb and Lees, 1988). Trousseau also taught, ‘the intellect...gets weakened at last; the patient loses his memory, and his friends notice soon that his mind is not as clear, precocious caducity sets in’.

Charcot had experienced some difficulty in obtaining a copy of Parkinson’s monograph. He acknowledged Parkinson’s ‘descriptive and vivid definition’ but found it incomplete in some aspects and encouraged his students at the Salpêtrière to translate it into French:

‘It will provide you with the satisfaction and knowledge that one always gleans from a direct clinical description made by an honest and careful observer.’

Charcot carried out a number of highly publicized studies on tremor including the mechanical recording of

myographic curves. He also distinguished slowness of movement from weakness and was the first to insist upon muscular rigidity as a cardinal sign. In his Tuesday afternoon lectures he made the point that the tremor was the least handicapping of the motor symptoms and drew his students' attention to the characteristic facial mask, wrinkled forehead and raised eyebrows (Charcot, 1872). He considered paralysis agitans a misnomer. The patients were not paralysed and tremor was not an invariable finding. On 12 June 1888 he proposed 'maladie de Parkinson' as an alternative rubric emphasizing that the disorder was a 'nevrose' without demonstrable pathology.

James Parkinson was an early exponent of field neurology (clinical observation and diagnosis outside the consulting room). Two of his cases he met casually in the street and then questioned (Cases II and III), while Case V was only seen at a distance (Fig. 1). Charcot also drew the attention of his students to the potential for instant neurological diagnosis of the shaking palsy in its fully established form (Fig. 2):

'I have seen such patients everywhere, on the streets of Rome, of Amsterdam, in Spain; it is always the same picture. They can be identified from afar; you do not need a medical history.'

By the late 19th century, the disorder had more or less reached its modern state of clinical recognition. In 1882 Thomas Buzzard, one of a coterie of physicians who helped the National Hospital for the Paralysed and Epileptic in Queen Square to acquire an international reputation, published a collection of 25 lectures, most of which had been delivered at the hospital. The one on paralysis agitans was duplicated without attribution and became the first article accepted by *Brain* on Parkinson's disease (Buzzard, 1882).

Buzzard endorsed Charcot's view that although rest tremor was an important component of the shaking palsy it was not specific or invariable and that postural limb tremor and quivering of the lips could also be seen. He also drew attention to bradyphrenia:

'There is an aspect of marked mental hebetude, or at all events an extreme slowness of expression, so that it is difficult to elicit answers to questions about his history... Yet we contrive to get, in process of time, though the task is laborious, a fair amount of information from him. The face wears a peculiarly stolid expression.'

Buzzard believed that a piping voice was a distinctive feature of the shaking palsy and one that he compared to the voice affected by actors to transmit an appearance of senility to their audience. A gap of 35 years then occurred before *Brain* published a second paper on the topic. Dr J. Ramsay Hunt began his article *Progressive Atrophy of the Globus Pallidus* (Ramsay Hunt, 1917) as follows:

'It is now a century since James Parkinson wrote his celebrated essay on the 'shaking palsy' and with the skill of a master outlined the chief clinical features of the disease which justly bears

his name. There are few, if any contributions to medical literature which excel in exactness of observation and clarity of expression Parkinson's original communication on paralysis agitans.'

Hunt believed that over the course of time the clinical syndrome described by Parkinson would be shown to be caused by a variety of pathological lesions including damage to the globus pallidus. Two or three years after Hunt's paper the thousands of survivors of epidemic encephalitis lethargica with Parkinson's syndrome stimulated debate as to whether Parkinson's disease existed and at the Paris Neurological Association meeting of 1921 attended by several international authorities, including Kinnier Wilson—the matter was hotly debated. In their introduction to the published Proceedings L'Hermitte and Cornil summarized the key issue of the day:

'We must either admit that there exists in addition to multiple Parkinsonian syndromes, an authentic Parkinson's disease with particular lesions and a characteristic evolution and symptomatology or we must say that there is no Parkinson's disease just as there is no hemiplegic disease or pseudo-bulbar disease.' (L'Hermitte and Cornil, 1921)

In 1955 the Guarantors of *Brain* funded a bicentenary volume to commemorate James Parkinson's birth that included a gratefully received reprint of *An Essay on the Shaking Palsy* and essays by W. H. McMenemey, W. G. Greenfield and F. M. R. Walshe (Critchley and McMenemey, 1955). In his introduction MacDonald Critchley showed that the debate in Paris as to whether Parkinson's disease existed had moved on to some extent:

'One of the major developments in our attitude towards Parkinson's disease has been the growth of a concept of Parkinsonism as a syndrome- a symptom-complex which may emanate from various causations. The 'shaking palsy' of James Parkinson is now looked upon as merely one representative (though still the most important) of a number of clinical events.'

Walshe defended the shaking palsy as a syndrome distinguishable from other known causes of parkinsonism by history and examination alone (Critchley and McMenemey, 1955):

'To ignore these differences in the interests of what is a false simplicity is not to make useful generalizations, but to blur the fine points of clinical discrimination and to regress to a lower level of observational precision.'

The technological add-ons

Histopathology

In Chapter IV of the *Essay* Parkinson cautiously proposes the possible site of damage leading to the symptoms of the shaking palsy.

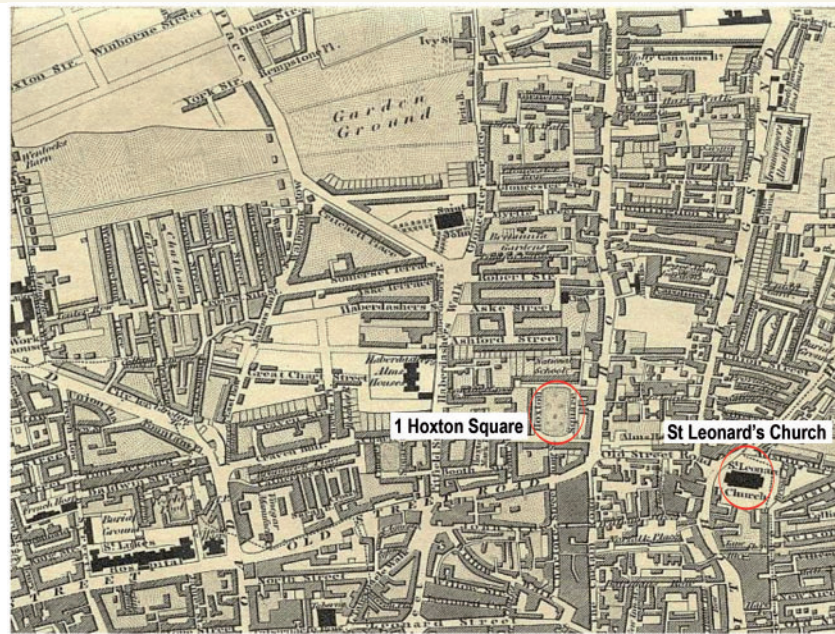


Figure 1 A street map showing Hoxton, Shoreditch, as it was in James Parkinson's time. | Hoxton Street was the site of Parkinson's practice, and St Leonard's Church was where he was baptized and buried.

'A diseased state of the *medulla spinalis*, in that part which is contained in the canal, formed by the superior cervical vertebrae, and extending, as the disease proceeds, to the *medulla oblongata*.'

As his monograph comes to an end Parkinson explains his main reason for writing up his observations:

'Before concluding these pages, it may be proper to observe once more, that an important object proposed to be obtained by them is, the leading of the attention of those who humanely employ anatomical examination in detecting the causes and nature of diseases, particularly to this malady.'

When Parkinson described the shaking palsy pathology had not yet become the anchor for disease classification. In contrast to Alzheimer's disease, which emerged later from a single detailed clinicopathological case report of Auguste D presented at the South West German Psychiatric Association in Tübingen in 1906, the shaking palsy survived as a clinical syndrome for a century.

No agreement concerning the pathological signature of Parkinson's disease existed even after the report in 1912 of eosinophilic inclusions in the medulla oblongata (Lewy bodies) and the discovery by Tretiakoff in his doctoral thesis of moderate-to-severe nerve cell loss in the pars compacta of the substantia nigra. The influential studies of Hassler (1938) and Greenfield and Bosanquet (1953) would belatedly lead to acceptance of brainstem Lewy bodies as a prerequisite for the post-mortem confirmation of Parkinson's disease. More recently syndromes of dementia, visual pseudo-hallucinations and primary cardiovascular

autonomic failure have all been associated with Lewy body and Lewy neurite pathology.

The development of more precise clinical diagnostic criteria in the 1980s and 90s capable of a higher degree of correlation with typical pathological findings derives from a determination to preserve the shaking palsy as a clinicopathological entity within the growing quantity of neuropathologically distinct parkinsonian syndromes (Gibb and Lees, 1988). Remarkably there had been no previous published reports of Parkinson's pathology that included adequate clinical detail. The primacy of the physical sign of bradykinesia in the clinical diagnosis, and the reaffirmation of the fuzzy borderland between ageing-related tremor and Parkinson's disease arose from this phase of clinico-pathological research.

These correlative brain bank studies also drew attention to what I have called 'The Other Parkinson's Disease'. These individuals fulfil pathological criteria for the diagnosis but differ substantially in their clinical presentation from the shaking palsy. They present at an older age with axial and bulbar symptoms and early falls (in the first 5 years). They have a more rapid deterioration. Some have executive and visuo-spatial dysfunction at presentation and many go on to develop early autonomic dysfunction including orthostatic hypotension. Tremor is not prominent but if looked for carefully may be present in a finger or in the lips or chin.

It seems likely that a biological interaction between the primary neurodegenerative process in Parkinson's disease and the effects of ageing and cerebrovascular disease on non-dopaminergic structures is responsible for this 'other Lewy body parkinsonism'.



Figure 2 A picture by Augustus Pugh and Thomas Rowlandson of the Kings' Bench Prison yard, Southwark 1808–1811. In the forefront of the picture and in the enlarged inset is a man who may have the shaking palsy.

Neurochemistry

The discovery in 1960 of severe depletion of dopamine in the corpus striatum stemming from new anatomical and chemical techniques was the sort of advance that Parkinson had hoped for (Ehringer and Hornykiewicz, 1960). The shaking palsy could now be classified as a striatal dopamine deficiency and even as a neurohumoral disorder. L-DOPA, the natural amino acid precursor of dopamine reduced motor handicap in almost all patients and also those with post-encephalitic parkinsonism whereas the majority of patients with vascular parkinsonism, the Westphal variant of Huntington's disease, chronic manganese and Wilson's disease and the atypical parkinsonian syndromes (multiple system atrophy: MSA-P; progressive supranuclear palsy: PSP-P; corticobasal degeneration; and parkinsonism due to abnormal iron accumulation) were only exceptionally improved in a sustained fashion. This provided the opportunity for a new clinical description of L-DOPA responsive Parkinson's syndrome and the physiological replacement of the diseased dopaminergic nigrostriatal bundle by cell-based therapies and neurotrophins remains an important therapeutic target in Parkinson's disease research.

Molecular pathology and genetics

The neuronal protein α -synuclein is an important constituent of the Lewy body and rare mutations of the α -synuclein (*SNCA*) gene have been associated with parkinsonism and dementia (Spillantini *et al.*, 1997). The autosomal dominant forms of parkinsonism, including that resulting from the commoner mutation of dardarin, are clinically

indistinguishable from the shaking palsy. These findings have led to the suggestion that abnormal aggregation of α -synuclein might be important in causing cell death in Parkinson's disease. Based on regional Lewy body and neurite distribution at autopsy, Braak and colleagues have suggested that Parkinson's disease might start in the olfactory bulb or even the enteric nervous system and spread rostrally from nerve cell to nerve cell in the brain from the dorsal nucleus of the vagus and other medullary nuclei to involve the cerebral neocortex. This attractive hypothesis captured neurologists' imagination and led to a search for clinical correlates. As a result, REM sleep disorder, reduced sense of smell, constipation and depression have been proposed as risk factors for the shaking palsy.

Unfortunately there are many exceptions to the classical spreading distribution of Lewy bodies and 10-times more people have α -synuclein pathology in their neurons than ever develop Parkinson's disease (Gibb and Lees, 1988). It seems likely that the Lewy body is a protective mechanism created to shield the neuron from further toxic insults. To embrace a prodromal phase and a terminal dementia in the clinical definition of Parkinson's disease will require a great deal more pathological research to confirm strong clinical correlation with extra-nigral neuronal dysfunction.

Conclusions

Nosography reflects the history of medicine and what has emerged over the last two centuries is a parkinsonian hybrid informed by clinical methods and patients' accounts combined with basic and applied science (Aronowitz, 2001). Histopathological, neurochemical and molecular

genetic technologies have given James Parkinson's clinical syndrome a solidity that semiotics alone could never have achieved. R. E. Kendall in his attempt to define illness drew an analogy between established disease states and the furniture in an old house (Kendall, 1975):

'... each generation has acquired a few new pieces of its own but has never [fully] disposed of those it inherited from its predecessors, so that amongst the inflatable plastic settees and glass coffee tables are still scattered a few old Tudor stools, Jacobean dressers and Regency commodes, and a great deal of Victoriana. A logician would have started by defining what he meant by disease as a whole and then produced individual diseases by sub-dividing the territory whose boundaries he had thus defined. Medicine... proceeded the other way and started with individual diseases.'

As our notions of neurological disease continue to extend beyond the traditional clinicopathological paradigm to embrace a more dynamic consideration of pathological events and chemical processes, neurologists may be forced more and more to fall back on classical clinical methods in which scrupulous observation and description is combined with modern techniques of longitudinal neuroimaging and laboratory biomarkers. Starting from scratch with an open mind may open up new vistas of understanding and finally lead to the cure that Parkinson hoped his essay would pave the way for.

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