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Unresolved Issues Relating to the Shaking Palsy on the Celebration of James Parkinson's 250th Birthday

Andrew J. Lees, MD, FRCP

Reta Lila Weston Institute for Neurological Disorders, Institute of Neurology, University College London, London, United Kingdom

Abstract: James Parkinson's Essay on the Shaking Palsy published in 1817 provided the first clear clinical description for the disorder now known throughout the world by his name. His primary reason for publishing his monograph shortly before his retirement from medical practice was to draw the medical profession's attention to a malady, which had not yet been defined as a nosological entity. He also hoped that the eminent anatomists of the day would be stimulated to elucidate the pathological lesion responsible for the clinical picture and that this in turn might lead to a rational cure. The concept of Parkinson's disease remains clinically based and successive generations of neurologists have refined and embellished Parkinson's seminal descriptions. Narrative accounts by affected individuals have also helped physicians understand what it is like to live with Parkinson's disease. For many years, the pathological hallmarks of Parkinson's disease were disputed and there were few clinico-pathological reports with adequate clinical description. However, most neurologists now link severe loss of nigral cells in the ventrolateral tier of the pars compacta of the substantia nigra with bradykinesia and the presence of Lewy bodies in a number of discrete brain stem and cortical regions with Parkinson's disease. There are many unanswered clinical questions relating to Parkinson's disease including the striking heterogeneity and frequent limb asymmetry. It also remains somewhat uncertain whether Parkinson's disease is ever truly unilateral by the time of clinical presentation and whether the hand rather than the foot is the most common site of onset. Hyposmia and visual hallucinations are helpful pointers in distinguishing Parkinson's disease from atypical Parkinsonism and should be specifically enquired about in the history. Simple reliable cultural-specific smell identification batteries are an urgent need and target of clinical research. It remains to be determined whether Alzheimer type dementia as opposed to a dysexecutive syndrome should be considered a part of Parkinson's disease and further detailed clinico-pathological correlative studies are needed. It is also unclear whether autosomal dominant monogenetic Parkinsonism due to synuclein or LRRK-2 mutations will prove to be identical clinically with Parkinson's disease and for the present it is wiser to regard Parkinson's disease as a sporadic disorder. Parkinson was an active political reformer and if alive today would certainly be campaigning to translate more effectively the rich seam of neuroscientific research of the last decade into therapeutic benefits for the rising number of people who are developing the shaking palsy as a result of increasing longevity in the developed world.

Key words: James Parkinson; clinical features; Parkinson's disease; substantia nigra; neuropathology.

In 1911, James Parkinson's first biographer Leonard G Rowntree addressed the Johns Hopkins Hospital Historical Society as follows "English born, English bred, forgotten by the English and the world at large such was the fate of James Parkinson."[1] Two hundred and fifty years after Parkinson's birth this can no longer be said to be the case. The disease, which thanks to Charcot, now carries the Hoxton apothecary's name, is increasingly recognized throughout the world and his birthday April 11 has become World Parkinson's Day, symbolized by the James Parkinson tulip. In 1817 Parkinson published a slim monograph entitled "An Essay on the Shaking Palsy" based on the clinical description of 6 patients he had seen either as patients, or on his peregrinations through the streets close to his home in Hoxton Square. He was already in his sixty second year and starting to wind down his medical work, leaving more and more of the duties of his busy general practice to his son, thus allowing himself more time to devote to his passion for

Correspondence to: A.J. Lees, Reta Lila Weston Institute for Neurological Disorders, Institute of Neurology, University College London, London, United Kingdom. E-mail: alees@ion.ucl.ac.uk
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paleontology. However, he felt that the complex of symptoms so eloquently recorded in his essay had not yet obtained a place in the classification of nosologists and were therefore worthy of putting on record. He also hoped that their publication would stimulate the anatomists and eminent physicians of the day to search for the site of the pathological lesion within the brain.[2] James would have been embarrassed to have the label "maladie de Parkinson" bestowed on his labors by Charcot, the father of neurology, in 1877 and if still alive might well have defended the continuing usage of the ancient term of "shaking palsy." His modesty and decency are reflected by the fact that, although, during his life he was held in respect in both medical and geological circles, no portrait has as yet come to light. Parkinson also chose to write his critical and often acerbic polemical pamphlets under the nom de plume of Old Hubert, although this may have been more to preserve his anonymity in turbulent times.

His treatise on the shaking palsy begins with the succinct summary of the distinctive features of the malady. "Involuntary tremulous motion with lessened muscular power, in parts not in action and even when supported: with a propensity to bend the trunk forwards and to pass from a walking to a running pace: the senses and intellect being uninjured."

He graciously and studiously acknowledged the earlier descriptions by Galen, Gaubius, Juncker, Cullen, Boissier de Sauvages and Sylvius de la Boe and speculated that trauma to the top of the cervical cord might be a possible cause.[2] There has been much interest and speculation as to why James Parkinson might have been particularly drawn to describe the shaking palsy; his medical writings were wide ranging and pragmatic as befits a busy general practitioner and drew directly on the experiences of his clinical practice. He was also a liberal social reformer who railed against the dreadful public health issues and the treatment of the insane. He attended the inspirational lectures of the eminent anatomist and surgeon John Hunter at the Leicester Square Lyceum and at the London Hospital, and Parkinson's son John transcribed his father's shorthand notes into a book entitled "Hunterian Reminiscences" published after his father's death in 1833. It is intriguing that an important omission from James Parkinson's historical bibliography was the description by Hunter in his Croonian Lecture: "Lord L-'s hands are perpetually in motion, and he never feels the sensation of them being tired. When he is asleep his hands are perfectly at rest but when he wakes in a little time they begin to move." It is probable this description had escaped Parkinson's attention, but perhaps Hunter had mentioned Lord L at one of his demonstrations, which had subliminally sensitized Parkinson's lively mind to the disorder. There is no evidence to support that he or any of his family were afflicted with the malady and his own justification for his monograph was simply that the disorder had so far escaped notice in much the same way as some of the fossils he and his friends in the Geological Society were recording for the first time.[3]

Subsequent generations of physicians have searched for additional descriptions of Parkinson's disease, but while fragmentary accounts have come to light in biblical texts, the Ayurvedic and among the hieroglyphics of the Great Pyramids, none are as satisfying or complete as that provided by Parkinson.[47] For example, there is an Egyptian papyrus of the nineteenth dynasty (ca. 1350–1200 BC), which describes a king as follows "divine old age had slackened his mouth. He cast his spittle upon the ground and spit it out"—a possible early reference to Parkinsonian drooling. In the Hindu library of the University of Benares among the Sanskrit texts is the Charakasamhita compiled around 2500 BC by Agnivesha; Chapter 20, entitled Vepathu contains a comprehensive account of tremors, some of which are linked with one of the Vatas or palsies.[3] In Ecclesiastes 12:3 a description can be found of the fate of the young as they inevitably age "In the day when the keepers of the house shall tremble." Leonardo da Vinci had a great interest in the workings of the nervous system and on a page of anatomical drawing in the collection of the Queen of England at Windsor Castle the following explanation of involuntary movements is included[4] "how nerves sometimes operate by themselves without any command from other functioning parts or the soul. This is clearly apparent for you will see paralytics and those who are shivering and benumbed by cold move their trembling parts, such as their head or hands without permission of the soul; which soul with all its forces cannot prevent these parts from trembling."

In 1776 Johannes Baptiste Sagar in his treatise "An Ariadne's Thread for Students of the Sick" included the following commentary: "In Vienna, I saw a man above the age of 50 who was running involuntarily, being also unable of keeping direction so as to avoid obstacles; in addition he suffered from ptyalism."[5] These tantalizing but ultimately unsatisfying descriptions are worth recording if only to support Parkinson's contention that he was not describing a newly emerging disease caused by industrialization. What also sets Parkinson's monograph apart from these interesting "snap shots" is his attempt to describe the natural history of the malady—"The disease is of long duration: to connect, therefore, the symptoms which occur in its later stages with those which mark its commencement, requires a continuance of observation of

the same case, or at least a correct history of its symptoms, even for several years."[2]

It is a favorite pastime and preoccupation of neurologists to discern neurological disease concealed in the paintings of the Old Masters. Because the cardinal features of Parkinson's disease include a poverty and slowness of voluntary movement and a pill rolling resting tremor, absolute diagnostic certainty can never be achieved from inspection of a canvas or from a photograph, whereas cinematographic evidence has provided convincing footage supporting a diagnosis of Parkinsonism in Adolf Hitler, General Franco, and Chairman Mao Tse Tung. What may be discerned in a still picture, however, is the characteristic flexion of the trunk, neck, elbow, and knees suggesting a weary "hang dog" body language. The physiognomy may suggest a mixture of mild anxiety with staring eyes and lid retraction and depression with a dull stolidity to the countenance, and there may be further clues in the "rheumatoid" hand posture. However, here the art gallery flaneur must beware the overlapping kinesics of melancholia and senility, both favorite themes of our great painters. A frequently cited example is the innkeeper in Rembrandt's sketch "The Good Samaritan." The appearance of St. Hugo of Grenoble in the Carthusian Refectory in Zurburan's painting, housed in the Museo de Bellas Artes in Sevilla, also strongly suggests Parkinsonism. Another recently reported convincing example is the lithograph of the Lithuanian ham seller Mr. Kulik portrayed by the German artist Isidorus Weiss in 1814.[6]

Narrative accounts of Parkinson's disease can also be informative and the accounts of Wilhelm von Humboldt, the Prussian scholar, reformer and statesman, provide an early insight into what it was like to live with the shaking palsy.[7,48] Among the interesting observations which appeared in his "Letters to a Lady Friend" in 1829 he described his own writing difficulties a tell-tale symptom, which had escaped Parkinson's sharp eye. "I am sorry for having written in such an unclear manner . . . . unfortunately only too often I cause people trouble in deciphering my handwriting. I think about this when I'm writing, but my attention isn't always the same and so I become illegible." A year later he had further illuminations on his difficulty; "you are completely right as my hand's difficulty in writing, this usually accompanies ageing: there occurs either trembling or a situation I prefer calling clumsiness rather than weakness. Writing, if it has to be firm and clear, requires a lot of sometimes very minute and hardly noticeable finger movements that need to be made in rapid sequence but with clear distinction from each other. In ageing, suppleness is missing in this respect. The same applies also to other acts such as buttoning up during dressing . . . . while the hand maintains its strength for grabbing, carrying and holding)." This is a clear description of the components of bradykinesia and Humboldt's script is highly suggestive of Parkinson's disease, although Humboldt himself attributed this affliction to premature ageing triggered by the distress of his wife's death, while his physician had considered he had a "spinal cord weakness." Humboldt was forced in his later years to resort to writing in Latin to try to overcome his loss of writing fluency in German.[8]

In the last 30 years it has become commonplace for patients to give narrative accounts about their Parkinson's disease and although these are by definition idiosyncratic, they provide fascinating insights for the physician as to what it is like to be told you have Parkinson's disease and then live with it. A patient of mine told me "it doesn't kill you but it takes your life away," another woman said Parkinson's made her feel like the damsel held in the grip of King Kong as the monster strode above the Manhattan skyline. Symptoms and signs as described in the biography of the England football player Ray Kennedy, and other patients have encouraged physicians to think more about the prodromal phase of the illness and the latent interval between the inception of the pathological process and the unequivocal emergence of the cardinal motor sign.[9,10] This has become an important and developing clinical research area in preparation for the discovery of treatments that can attenuate the neurodegenerative process.

The early neurologists embellished and refined Parkinson's clinical description and I would particularly single out the writings of Trousseau and Charcot in France,[11] Gowers[12] and Kinnier Wilson[13] in England and Erb[14] in Germany for particular commendation. Parkinson would have chastised himself for missing the drooling of saliva, the oiliness of the skin and the distinctive cramped miniscule vanishing script,[15] but he should be excused from missing the cogwheel phenomenon,[16] and lead pipe rigidity, as the physical examination of the nervous system was not yet part of the doctors' clinical method. He would have been fascinated to learn that the majority of patients find that their sense of smell has declined[17] and that half at least experience phantasmagorical, psychedelic visual illusions, and hallucinations.[18] He did not know that many patients disturb their bedmates with screams and violent flinging movements of the limbs while dreaming and that others are troubled by drenching sweats and urgency of micturition. He would not have been surprised to learn that there are known to be many causes for the shaking palsy, although the pill rolling rest tremor he described remains a reliable marker for Parkinson's disease as opposed to a second-

ary or atypical variety. Parkinson's description of "the hand failing to answer with exactness to the dictates of the will" is now described in medical jargon as bradykinesia, akinesia, or hypokinesia with the three terms often and erroneously being used interchangeably.

Almost two centuries after Parkinson's seminal description, and enormous leaps in our understanding of the pathogenesis and molecular pathology of his malady, rudimentary phenomenological, and semantic issues remain unresolved. Basic observational clinical studies relating to prognostic risk factors, prediction of individual response to therapy, and the variable natural history of the malady have not been given the serious attention they warrant. For example, although most neurologists would concur that it is a quiver in one hand which usually brings the patient to neurological attention, it remains to be confirmed whether—as is commonly believed—the disease is ever truly unilateral. If there is obvious bradykinesia or rest tremor in one hand when the patient is first examined, clinical appreciation of subtle bradykinesia in the hand on the other side may easily be overlooked. More sophisticated clinical methods to detect subtle motor impairment particularly in the legs may change our notion about the site of onset of Parkinson's disease. Functional imaging using dopamine transporter ligands in patients considered to have unilateral very early Parkinson's disease has shown that in many cases the striatal binding index is already markedly reduced to a level where one might have predicted some motor impairments on the apparently unaffected side.[19] Recently Uitti and colleagues have taken another look at the relation of handedness and the side of onset of Parkinson's disease and suggested that at least in left handers, the disease is more likely to start on the left.[20]

At least 60% of patients when they are first seen have a clear asymmetry of motor signs and as a general rule the more striking the difference in symptom severity on the two sides, the more likely an excellent sustained response to levodopa therapy is to be. It is unclear whether the asymmetry index in a particular patient persists throughout the course of the whole illness.[21] My own impression is that the difference in motor disability between the two sides lessens in many patients as the disease progresses and in a few the side of the presenting complaint—especially if tremor was the initial complaint—may actually be paradoxically less affected later in the disease. I have also noted that some patients may appear to have more difficulty on testing fine finger movements in one hand in one consultation and 3 months later it appears the difficulties have become more pronounced on the other side only for the problem to switch back again at the next visit. It is important to carry out more than one sequential motor task with the fingers as there may be quite striking disparities and the correlation with micrographia is also poor. Whereas L-dopa induced peak dose chorea is invariably more severe on the more affected side, off period dystonia may sometimes be more disabling on the less affected side.[22] Axial and bilateral symmetrical presentations of Parkinson's disease are more likely in those over 70 years when the additional confounding effects of diffuse subcortical white matter ischemia and the biological effects of ageing may modify the clinical presentation.[23]

Another interesting and unresolved clinical issue is whether temporary remission may occur in the early stages of the disorder. A few patients describe isolated episodes of tremor which may have occurred up to a decade before the diagnosis becomes unavoidable. I have also seen 2 patients, both who had an associated depression, who once their unhappiness resolved lost their bradykinesia and rigidity. One of these had a F-dopa PET scan while she was suspected of having Parkinsonism and was found to have reduced uptake at a level intermediate between normal controls and PD. The functional imaging changes in this case resembled those reported in some carriers of monogenetic Parkinsonism, some of whom have gone on to express the disease. One might speculate that compensatory measures due to neuronal plasticity may be sufficient to drive the pathogenic process back underground once the chemical changes associated with depression have reversed. At latest follow up more than a decade after first seen, neither of these patients has developed Parkinson's disease. Patients with secondary Parkinsonism due to viral encephalitis or toxic exposure may also have a full recovery despite residual irreversible neuronal death. Conversely, there are a number of reports in which elderly individuals exposed to neuroleptics develop irreversible Parkinsonism. The presumption is that these patients already have Lewy body pathology and the chemical changes induced by the neuroleptic set off a cascade of toxic events which cannot be corrected by drug discontinuation.[24]

Ten times more people have Lewy body pathology than ever develop Parkinson's disease and while it is unclear what protects these individuals from developing the clinical syndrome, it is likely that they are more competent in walling off the pathogenic processes and preventing the disease.[25] Indeed it has been suggested that the Lewy body itself may be a protective mechanism to shield the neurone from further insult. Another unresolved clinical issue is whether the incidence rate of Parkinson's disease actually drops in the ninth decade as is suggested by some epidemiological studies.[26] Diagnosis of Parkinson's disease is difficult in the very old

because soft basal ganglia signs are acknowledged as a frequent component of ageing. If the incidence really falls in the ninth decade then it would provide a strong argument to reject the hypothesis that Parkinson's disease is due to an acute environmental insult compounded by the biology of ageing.

One of the strengths of Parkinson's essay was his accurate description of the course of the shaking palsy. He emphasized the spread of the disease from one limb and that in the early changes it impacted relatively little on the patient's quality of life, but by the end the patient was severely incapacitated, dependent on others for everyday tasks, incontinent and cachectic. Poewe and Wenning have recently reported that the average delay in spread from the affected limb to the unaffected ipsilateral limb is about a year and for spread to the other side two and a half years. They have also shown that the deterioration on the Unified Parkinson's Disease Rating Scale is faster in the first 2 years after diagnosis than later on as bradykinetic and tremulous disabilities bottom out. Analysis of the DATATOP data also provided support for Hoehn and Yahr's contention that there is a marked heterogeneity in disease progression, with young onset and predominant tremor being good prognostic signs.[27,28] Some of the young onset benign tremulous patients are now recognized to carry the parkin or PINK-1 mutations. In contrast, patients with prominent early axial and bulbar signs and cognitive deficits respond less well to L-dopa, progress more rapidly and have a poorer prognosis.[28] However, it is important to be aware that a number of these "axial forms" of PD turn out to have an alternative pathology at autopsy particularly neurofibrillary tangles.

Parkinson's hopes that the publication of his monograph might lead to elucidation of the anatomical substrate had to wait 80 years. Following the publication of Blocq and Marinesco's case report of a tuberculomatous noisette in the midbrain which had caused contralateral Parkinsonism,[29] Edouard Brissaud speculated that the localization must be subthalamic or peduncular and that an ischemic lesion of the locus niger could be responsible for Parkinson's disease. He acknowledged that this was "a theory based on wise ignorance which recognized itself."[30] Constantin Tretiakoff, a Russian working at the Salpetriere Hospital in Paris, was set the task of confirming Brissaud's hypothesis. In his doctoral thesis of 1919 he described his findings following the examination of fifty-four substantia nigras. Nine of these had Parkinson's disease and three von Economo's disease. The substantia was consistently affected in all the Parkinsonian patients and there were also associated "senile lesions." Tretiakoff also noted that six of the brains also had "corps de Lewy" described in the dorsal nucleus of the vagus in Parkinson's disease 7 years earlier by Frederich Lewy.[31,32] Despite Tretiakoff's careful work severe damage to the pars compacta of the substantia nigra was not generally accepted as the critical pathological lesion in Parkinson's disease until the later confirmatory neuropathological studies of Hassler[33] and then Greenfield and Bosanquet[34] led to almost complete universal acceptance.

The ventrolateral tier of the pars compacta bears the brunt of the damage and by the later stages of the disease very few neurones in this zone (Spedd and Spez of Hassler)[35] are still functioning normally. These nerve cells project mainly to the dorsal putamen which is the first and most dopamine depleted area of the corpus striatum. The micro-architecture of the substantia nigra is also now recognized to be extremely complex with a "Swiss cheese" like pattern with calbindin negative nigrosomes and a calbindin rich matrix.[36,37] The nigrosomes correlate closely with the areas of maximal damage in the nigra in Parkinson's disease raising the possibility that calcium binding protein located predominantly, but not exclusively, in the dorsal tier may help to protect these less vulnerable nigral neurones. Another protein called Girk2[38] (G protein coupled inward rectifying current potassium channel type w2) is located only in the ventral tier and it is of interest that the weaver mouse model, better known as a paradigm for cerebellar ataxia, loses 50% of all its dopaminergic nigral neurones in the first weeks of life, all of which are Girk 2 positive. The surviving dopaminergic cells in the weaver mouse all contain calbindin.

It has been estimated that cell loss in the pars compacta starts about 6 years before the first motor signs are clinically detectable by which point at least 75% of neurones in the ventrolateral tier will have been destroyed. Although the lesion of the pars compacta of the substantia nigra is considered the pathological substrate for bradykinesia and rigidity, other brain stem areas, the cerebral cortex, the enteric nervous system and sympathetic ganglia also have Lewy body pathology. Exactly what the relevance of these other damaged areas such as the locus coeruleus, nucleus basalis of Meynert, the dorsal nuclei of the vagus nerve, raphe nuclei and the pedunculopontine nuclei is with respect to the clinical picture remains unclear, but disturbances of the sleep/wake cycle, pain, anxiety and depression, falls and freezing, constipation and dysphagia are common complaints from patients and contribute significantly to morbidity and a reduced quality of life. Parkinson would have been cheered by the recent attention paid by the anatomist Braak and his colleagues to the anatomo–pathology of

the malady. Although it remains unclear whether Lewy bodies represent a defense mechanism to sequester and detoxify potentially noxious proteins in neurones still able to function, or are harbingers of cell death, there is persuasive evidence to suggest that incidental Lewy body pathology is associated with increased oxidative stress, mitochondrial dysfunction and neuronal loss in the nigra. This raises the strong possibility that those elderly individuals who die without signs of Parkinson's disease but with Lewy body pathology in their brain stems might have gone on eventually to develop the disease if they had lived longer. The other intriguing possibility is that these patients, although exposed to cryptic exogenous insults which can lead to the cascade of damage responsible for Parkinson's disease, have the biological capacity to contain it at a level which will not lead to clinically apparent illness. Perhaps the one tenth of cases with severe Lewy body pathology and Parkinson's disease will prove to have a genetic susceptibility to the illness which means their neuro-protective mechanisms fail to cope with the accumulating and varied environmental insults.

Following on from his work in Alzheimer's disease where it is believed that the pathological process begins in the entorhinal cortex and spreads to involve the neocortex, Braak has suggested on the basis of pathological studies on control, incidental dorsal vagal nucleus Lewy body brains and Parkinson's disease tissue, that the pathological process actually begins in the enteric nervous system, dorsal nucleus of the vagus and anterior olfactory areas.[39,40] This notion resonates with clinicians because it is known that disturbances of bowel motility and impairment of olfaction may precede the cardinal motor symptoms in some patients. However, Braak's conclusions are derived from the assumption that Lewy bodies are reliable markers for neuronal loss in Parkinson's disease and brains with Lewy bodies in brain regions other than the dorsal nucleus of the vagus were not considered. A recent study has failed to show any correlation between either the degree of cell loss or Lewy body load in the dorsal nucleus of the vagus and the severity of constipation in Parkinson's disease.[41] There is also no cell loss in the ventrolateral parts of the nucleus ambiguus, the region believed to be important in cardiovascular autonomic function and known to be damaged in multiple system atrophy.[42]

There is also no evidence that the severity of Lewy body pathology in the nigra is correlated with either neuronal loss or more importantly bradykinesia. Before Braak's challenging observations can be accepted cell counts will need to be carried out in the dorsal nucleus of the vagus and olfactory regions in incidental Lewy body brains and age matched controls, as it is known that Lewy bodies may be found in brain regions like the basal nucleus of the amygdala where little or no cell loss occurs. More groups of aged patients need to be prospectively studied at autopsy[43,44] and more brains of young onset PD dying before the age of 55, and young control brains, need to be examined for alpha synuclein pathology. In vivo prospective functional imaging needs to be correlated with pathology and, finally, a series of patients with Lewy body dementia need to be studied to determine if the dorsal nucleus of the vagus and olfactory structures are consistently affected. This latter issue is of considerable importance not least because the correlation of dementia in Parkinson's disease does not correlate closely with neocortical Lewy body burden.[45]

Studies attempting to quantify the impact of Parkinson's disease on quality of life have confirmed that symptoms such as depression, pain, constipation and sleep disturbances contribute importantly to morbidity, and this has led to a renewed interest in these frequently associated symptoms. However, it remains unclear whether these symptoms result as a direct consequence of the primary disease process or whether they are secondary nonspecific findings. Nevertheless, if severe visual failure occurred in 80% of patients with Parkinson's disease as is the case with hyposmia, then it is hard to conceive that it would not have been embraced as a cardinal feature of the illness. One of the problems with respect to the nonmotor symptoms and even some of the motor disabilities like freezing and rest tremor has been to correlate them with the known pathology of the disease. Quantification of neuronal loss in particular nuclear groups is an exacting and imprecise technique although stereoscopic methodology has led to some improvement and an awareness that a number of structures like the pedunculopontine nucleus, nucleus basalis of Meynert and ventral segmental dopaminergic cell groups may have substantially greater neuronal loss than is seen in controls. In fact a neuropathologist who was unaware of the characteristic clinical picture of Parkinson's disease might consider that the pathological lesions might be more likely to produce a disorder with prominent cognitive, neuropsychiatric and autonomic disturbance than one dominated by motor handicap.

However, if one focuses on the relatively few patients who have died from Parkinson's disease under the age of 50, the described lesion is much more restricted and patients with juvenile L-dopa responsive Parkinsonism have not been noted to have Lewy body pathology. After 10 to 15 years of disease bradykinesia, rigidity and tremor deteriorate very little and nigral cell loss is an exponential process with a more rapid fall out in the

early years of disease. Another intriguing observation is that in many patients rest tremor seems to diminish as the disease evolves. Late deterioration in Parkinson's disease is often due to freezing of gait with damaging falls, swallowing and speech deterioration and dementia. Some patients also have disabling autonomic symptoms including bladder and bowel dysfunction and syncope. These axial, bulbar and cognitive deficits may also be prominent in the first 5 years of the disease particularly in patients presenting over the age of 70 years. As a consequence of these observations disease progression in Parkinson's disease depends on the age of the patient and not the disease duration. A biological interaction between the primary neurodegenerative process responsible for Parkinson's disease, and the effects of ageing and co-existing diffuse cerebrovascular pathology on nondopaminergic structures leading to late decompensation, could explain these findings. An alternative explanation might be that the age of onset influences the clinical presentation. There is another interesting suggestion that "atypical features" such as gaze palsies, autonomic failure and gait and bulbar presentations with a poorer response to L-dopa may occur in black Africans and patients originating from the Indian subcontinent, but this needs substantiating with further pathological studies.[46]

As a compassionate physician Parkinson felt helpless in the face of this brutal disease and resorted in desperation to blood letting and the application of vesicatories despite warning colleagues against the irrational use of nostrums. He also wryly commented on the healthy scepticism of his patients who seemed resigned to the incurable nature of the disorder. Despite this he held out hope that a disease-modifying therapy might eventually be discovered. "On the contrary, there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least the progress of the disease may be stopped."

The vital discovery of severe depletion of dopamine in the corpus striatum stemming from new anatomical and chemical techniques was just the sort of advance Parkinson had hoped for when writing his monograph. However, despite our increased understanding of the pathological processes which underlie the shaking palsy, no effective disease modifying therapy has materialized. If alive today Parkinson would be exhorting the leaders of our profession to develop more reliable methods of assessing disease progression and encouraging our great universities to devote more of their time to translational drug discovery. He would caution against the increasing disregard for clinical observational studies which can result in such important advances in patient outcome measures. Old Hubert would also have much advice for governmental agencies and Pharma. He would advise a radical and urgent reform of the Drug Approval process arguing that a relaxation of the current emphasis of proof of efficacy might lead to faster progress. He would recommend that Parkinson's disease could be considered an "orphan disease" and encourage the pharmaceutical industry to invest more in innovative therapies. He would demand a review of the patent laws which no longer protect original drug development and encourage imitators and generic drugs. He would see the harm excessive bureaucratic road blocks have had on clinical research and the reduction in the number of practicing clinicians involved in decision making in academic medicine. He would cajole the pharmaceutical industry to adopt a more flexible approach to drug development and not to rely as heavily on reductionist target driven models for Parkinson's disease at the expense of environmental data, phenotypic screens and serendipitous observations. Despite these concerns the humble London practitioner would no doubt also feel a twinge of pride that the shaking palsy had now established itself as a recognizable nosological entity and that his hopes that his monograph would encourage further study had been fulfilled.

REFERENCES

1. Rowntree L. James Parkinson. Bull Johns Hopkins Hosp 1912;23: 33–35.
2. Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely and Jones; 1817.
3. Currier R. Did John Hunter give James Parkinson an idea? Arch Neurol 1996;53:377-378.
4. Stern GM. James Parkinson 1755-1824. Parkinson's disease. Baltimore: Chapman and Hall; 1990. p XIII-XXVII.
5. Sagar J. Systema morborum symptomaticum ecs. Vienna: Kraus Class; 1771. V11: 4, XX11,3.
6. Budrys V. Parkinson's disease before Parkinson, Vilnius 1814. J R Soc Med 2005;98:178-179.
7. Lakke J. Wilhelm von Humboldt and James Parkinson. An appraisal of observation and creativity. Parkinsonism Relat Disord 1996;2:225-229.
8. Horowski R, Horowski L, Calne SM, Calne DB. From Wilhelm von Humboldt to Hitler—are prominent people more prone to have Parkinson's disease? Parkinsonism Relat Disord 2000;6:205-214.
9. Lees AJ. When did Ray Kennedy's Parkinson's disease begin? Mov Disord 1992;7:110-116.
10. Lees AJ. Ray of hope. The Ray Kennedy story. London: Penguin, 1993.
11. Charcot J. Lecons sur les Maladies du Systeme Nerveux Faites a la Salpetriere. Paris: Masson, 1880.
12. Gowers W. A manual of diseases of the nervous system. London: Churchill, p 1886-1888.
13. Wilson S. Neurology. London: Arnold, 1947.
14. Erb W. Paralysis agitans (Parkinsonische Krankheit). Die deutsche klinik. E. a. K. Leyden, F. Berlin, Urban and Schwarzenberg 1901;6 (Part 1):31-50.
15. McLennan JE, Nakano K, Tyler HR, Schwab RS. Micrographia in Parkinson's disease. J Neurol Sci 1972;15:141-152.
16. Ghiglione P, Mutani R, Chiò A. Cogwheel rigidity. Arch Neurol 2005;62:828-830.

17. Hawkes C. Olfactory testing in parkinsonism. Lancet Neurol 2004; 3:393-394.
18. Williams DR, Lees AJ. Visual hallucinations in the diagnosis of idiopathic Parkinson's disease: a retrospective autopsy study. Lancet Neurol 2005;4:605-610.
19. Pirker W. Correlation of dopamine transporter imaging with parkinsonian motor handicap: how close is it? Mov Disord 2003;18 (Suppl 7):S43–S51.
20. Uitti RJ, Baba Y, Whaley NR, Wszolek ZK, Putzke JD. Parkinson disease: handedness predicts asymmetry. Neurology 2005;64: 1925-1930.
21. Lee CS, Schulzer M, Mak E, Hammerstad JP, Calne S, Calne DB. Patterns of asymmetry do not change over the course of idiopathic parkinsonism: implications for pathogenesis. Neurology 1995; 45(3, Part 1):435-439.
22. Toth C, Rajput M, Rajput AH. Anomalies of asymmetry of clinical signs in parkinsonism. Mov Disord 2004;19:151-157.
23. Jankovic J. Progression of Parkinson disease: are we making progress in charting the course? Arch Neurol 2005;62:351-352.
24. Rajput AH, Rozdilsky B, Hornykiewicz O, Shannak K, Lee T, Seeman P. "Reversible drug-induced parkinsonism. Clinicopathologic study of two cases. Arch Neurol 1982;39:644-646.
25. McNaught KS, Shashidharan P, Perl DP, Jenner P, Olanow CW. Aggresome-related biogenesis of Lewy bodies. Eur J Neurosci 2002;16:2136-2148.
26. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord 2003;18:19-31.
27. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967;17:427-442.
28. Poewe WH, Wenning GK. The natural history of Parkinson's disease. Ann Neurol 1998;44(3 Suppl 1):S1–S9.
29. Blocq P. Sur un cas de tremblement parkinsonien hemiplegique symptomatique d'une tumeur du peduncule cerebrale. Rev Neurol 1894;2.
30. Brissaud E. Nature et pathogenie de la maladie de Parkinson (lecon 23). Lecons sur les Maladies du Systeme Nerveux. Recueilles et publiees par Henry Meige. Paris: Masson; 1895. p 488-501.
31. Lewy F. Paralysis agitans. I. Pathologische anatomie. In: Lewandowsky M, editors. Handbuch der neurologie. Berlin: Springer; 1912. p 920-933.
32. Tretiakoff C. Contribution a l'etude de l'anatomie pathologique du locus niger de Soemmering avec quelques deductions relatives a la athogenie des troubles du tonus musculaire et de la maladie de Parkinson. Paris; Jouve and Co. 1919.
33. Hassler R. Zur Pathologie der paralysis agitans und des postenzephalitschen Parkinsonismus. J f Psychol u Neurol 1938;48: 387-476.
34. Greenfield JG, Bosanquet FD. The brain-stem lesions in Parkinsonism. J Neurol Neurosurg Psychiatry 1953;16:213–226.
35. Hassler R. Zur Normalanatomie der Substantia Nigra. Versuch einer architektonischen Gliederung. J f Psychol u Neurol 1937;48: 1-55.
36. Damier P, Hirsch EC, Agid Y, Greybiel AM. The substantia nigra of the human brain. I. Nigrosomes and the nigral matrix, a compartmental organization based on calbindin D(28K) immunohistochemistry. Brain 1999;122 (Part 8):1421-1436.
37. Damier P, Hirsch EC, Agid Y, Greybiel AM. The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain 1999;122 (Part 8):1437-1448.
38. Mendez I, Sanchez-Pernaute R, Oliver C, et al. Cell type analysis of functional fetal dopamine cell suspension transplants in the striatum and substantia nigra of patients with Parkinson's disease. Brain 2005;128 (Part 7):1498-1510.
39. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197-211.
40. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318:121-134.
41. Benarroch EE, Schmeichel AM, Sandroni P, Low PA, Parisi JE. Involvement of vagal autonomic nuclei in multiple system atrophy and Lewy body disease. Neurology 2006;66:378-383.
42. Benarroch EE, Schmeichel AM, Low PA, Boeve BF, Sandroni P, Parisi JE. Involvement of medullary regions controlling sympathetic output in Lewy body disease. Brain 2005;128 (Part 2):338-344.
43. Parkkinen L, Kauppinen T, Pirttila T, Alafuzoff I. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann Neurol 2005;57:82-91.
44. Parkkinen L, Pirttila T, Tervahauta M, Alafuzoff I. Widespread and abundant α-synuclein pathology in a neurologically unimpaired subject. Neuropathology 2005;25:304-314.
45. Colosimo C, Hughes AJ, Kilford L, Lees AJ. Lewy body cortical involvement may not always predict dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:852-856.
46. Chaudhuri KR, Hu MT, Brooks DJ. Atypical parkinsonism in Afro-Caribbean and Indian origin immigrants to the UK. Mov Disord 2000;15:18-23.
47. Stern GM. Did Parkinsonism occur before1817? J Neurol Neurosurg Psychiatry 1989; (Suppl):11-12.
48. Horowski R, Horowski L, Vogel S, Poewe W, Kielhorn FW. An essay on Wilhelm von Humboldt and the shaking palsy: first comprehensive description of Parkinson's disease by a patient. Neurology 1995;45(3, Part 1):565-568.