Parkinson's disease

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Natural history of Parkinson's disease

Parkinson's disease is a movement disorder that mainly affects those of middle to old age. It is progressive over many decades and is characterised by bradykinesia, resting tremor, stiffness, and postural instability. The bradykinesias are associated with initiation of movement—thus, Zimmer frames without wheels are harmful because they can interrupt the flow of motion. Tremor tends to be worse at rest, and initially unilateral; even when invisible it can often be detected on examination as cog wheeling (the combination of tremor and increased muscle tone).

Levodopa therapy lengthens the life of people with the disorder. The effects of this treatment and the extended natural history of the disease (resulting from treatment of the underlying problem) cannot be distinguished precisely. However, with time, patients begin to have motor fluctuations between on and off states, and drug-resistant periods become more frequent and longer. Dyskinesias, which are sometimes painful, can develop. Over half of patients have cognitive decline in the later stages of the disease. Depression is common. Psychotic events are prevalent and made worse by dopaminergic drugs, which often prompt treatment withdrawal. Death is usually due to a cause other than Parkinson's disease.

Case presentation

A 65-year-old priest had noticed himself becoming increasingly slow when he began to walk. He also complained of a tremor in his right hand when not in use. A diagnosis of idiopathic Parkinson's disease was made and he was started on levodopa therapy. Over the next 5 years, his symptoms worsened despite treatment. His difficulty in initiating movements escalated, his face became increasingly expressionless, and his handwriting smaller and more difficult to read. From his early 70s, he began to suffer progressively more from fluctuations between on states (in which he was able to move but was greatly afflicted by drug-induced dyskinesias), and off states, in which he was stiff and inactive. His off states increased in frequency and duration, and his dyskinesias became painful and distressing. These dyskinesias were most striking immediately after taking his medication and towards the end of its time of action. He inquired as to the availability of neurosurgery to treat his dyskinesias but, while the procedure was being considered, he contracted bronchopneumonia and died, aged 76 years. At no time did he have cognitive decline, but the last years of his life were troubled by depression.

Cause

No reliable diagnostic test exists to distinguish Parkinson's disease from other causes of parkinsonism, such as vascular parkinsonism, dementia pugilistica, encephalitis lethargica, progressive supranuclear palsy, corticobasal degeneration, and multisystem atrophy.[1] However, all have dysfunction of the basal ganglia and their white-matter connections. The substantia nigra pars compacta could be an area vulnerable to various injuries, but the precise one that causes Parkinson's disease is not known.

In the early 1980s, a group of drug addicts attempting to produce their own heroin mistakenly gave themselves N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and developed parkinson-like symptoms.[2] A metabolite of this drug, generated by the action of monoamine oxidase B, is toxic to the dopaminergic cells of the substantia nigra pars compacta. The resulting parkinsonism responds well to levodopa therapy. Similarity between the metabolite and the pesticide paraquat raised fears that this poison could be a cause of Parkinson's disease. These fears were supported by a link between disease incidence and paraquat use, as well as by a heightened risk of the disease in rural areas. However, the progressive nature of Parkinson's disease has not been seen in those affected by MPTP, and argues against a toxic effect.

α-synuclein and parkin gene mutations have been shown to cause parkinsonism in several families.[3] The products of these genes are thought to have an important role in the recycling of oxidised cytosomal and membrane-bound proteins. Mitochondrial defects and oxidative stress have also been suggested as mechanisms of neuronal damage.

Pathophysiology

Histologically, Parkinson's disease consists of the loss of dopaminergic neurons of the nigrostriatal pathway (and to a lesser extent those of the locus coeruleus). Lewy bodies (intracytoplasmic eosinophilic inclusions found in injured or fragmented neurons) are a constant feature of the disease. Their pathogenesis remains elusive and whether they are a cause or result is unclear. One possibility is that they result from a defective response to oxidative neuronal injury.

The basal ganglia are a group of subcortical nuclei that control voluntary movements (figure 1). They consist of the striatum (putamen and caudate), globus pallidus externa and interna, subthalamic nucleus, and substantia nigra pars compacta and reticularis. The basal ganglia have no direct connections with the descending tracts of the spinal cord. Instead they form neural loops extending from the motor cortex to the motor thalamus and back to the cortex. The loops have been anatomically divided into four groups—motor, occulomotor,

premotor, and limbic loops—which run in parallel without much collateral branching. The limbic (allocortical) projections tend to synapse in cellular islands in the caudate known as striosomes, whereas the motor loops (neocortex) synapse in the homogeneous matrix of the putamen. Within the motor loop, the somatotropic arrangement of the cortex is preserved throughout the circuit. These different loops seem to control movements at varying levels of complexity, as well as in different anatomical areas. The primary neurotransmitters within these loops are glutamate and γ-aminobutyric acid (GABA). These loops contain direct (excitatory) and indirect (inhibitory) pathways; the excitatory pathway passes via the subthalamic nucleus as shown in figure 1.[4] The dopaminergic input from the substantia nigra pars compacta seems to modulate the balance between the inhibitory and excitatory motor loops. The resulting disinhibition of neuron populations in the motor cortex seems to enable certain physical movements to occur.

Parkinson's disease could represent the supraphysiological end of the spectrum of postural tone—caused by oversuppression of the basal ganglia output, resulting in bradykinesia. As depicted in figure 2, a reduced number of dopaminergic fibres from the substantia nigra pars compacta results in activation of the inhibitory pathway. Dysfunction of movement that occurs in the disease is peculiar, consisting of both movement loss and gain (increased tone and tremor). In affected patients, the basal ganglia are not simply switched off through lack of dopamine. Single-cell recordings have shown that in Parkinson's disease the subthalamic nucleus discharges abnormally in pulses of 4–8 Hz; the frequency of the characteristic pill-rolling tremor. Clearly, not only the quantity but also the quality of neuronal signalling is altered.[5] The panel shows the various treatments available for Parkinson's disease.

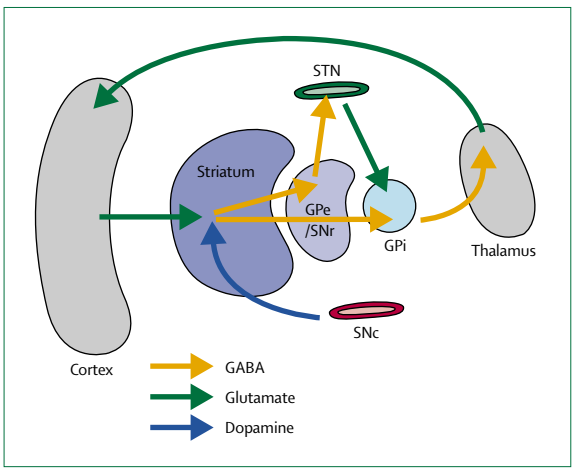


Figure 1: **Model for normal basal-ganglia function**
GPe=globus pallidus externa. GPi=globus pallidus interna. STN=subthalamic nucleus. SNc=substantia nigra pars compacta. SNr=substantia nigra pars reticularis.

James Parkinson

James Parkinson was born in 1755 in Shoreditch, then a semi-urban borough on the outskirts of London. The area was a well-known theatre district: Parkinson's house in Hoxton Square was on the site of a field, where, in 1598, Ben Jonson killed a fellow actor in a duel. Shakespeare lived and worked in Shoreditch, and many of his plays were performed for the first time in a theatre in the grounds of a ruined priory. Near this site, in 1736–40, a pupil of Christopher Wren rebuilt the dilapidated St Leonard's Church (figure 3) in the Palladian style. It was here, in the original Actors' Church, that James Parkinson was christened, married, and buried.

Parkinson's father, John, was the first of four generations of Parkinson surgeon–apothecaries. Parkinson's own apprenticeship (to his father) began at the age of 16 years, and was rounded off by 6 months as a dresser (house surgeon) at the nearby London Hospital. In 1781, virtually in charge of the family practice because of his father's disability from gout, James married Mary Dale, the daughter of a local silk manufacturer. In 1782–85, Parkinson saw the consecutive deaths of his younger brother, his father, and—after a few months of life—his first son. However, his career prospered. In 1784 (as a result of his hospital experience and an oral examination), James was admitted to the Company of Surgeons. He attended lectures by John Hunter the next year, and in 1787 was made a member of the Medical Society of London after his presentation to them of a paper on the effect of lightning strikes.

The orderly progression of Parkinson's career suffered no visible disruption in the 1790s, a turbulent decade in revolutionary politics. The world was a dangerously changing place. The British electorate in 1788 was actually smaller than it had been before the Civil War

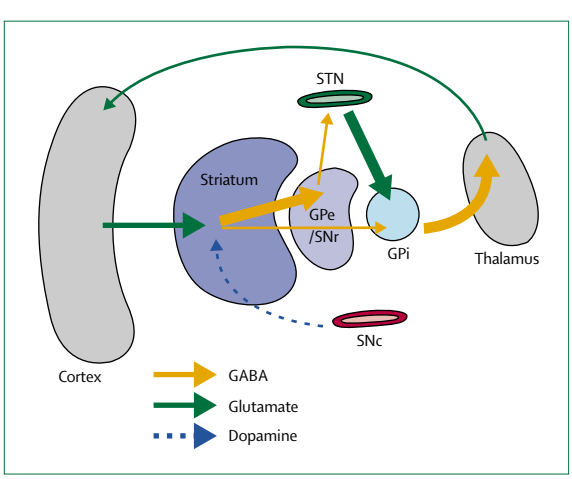


Figure 2: **Model for basal-ganglia dysfunction in Parkinson's disease**
GPe=globus pallidus externa. GPi=globus pallidus interna. STN=subthalamic nucleus. SNc=substantia nigra pars compacta. SNr=substantia nigra pars reticularis. Thin arrows correspond to reduced release of neurotransmitter.

Panel: Treatment for Parkinson's disease

Drugs

Levodopa

The mainstay of Parkinson's disease treatment—used in conjunction with a dopa-decarboxylase inhibitor. Levodopa is taken up and converted into dopamine that is then released physiologically. Later in the disease, motor fluctuations occur, probably because of continued loss of nigrostriatal neurons, effect of the pulsatile nature of levodopa levels on postsynaptic dopamine receptors, or both.

Dopamine agonists

Act mainly on postsynaptic dopamine receptors and result in fewer motor fluctuations because they do not require the buffering capacity of nigrostriatal neurons. They are less effective than levodopa. One of them (apomorphine) can be given in a subcutaneous infusion, thereby producing a steady plasma concentration.

Catechol-o-methyltransferase (COMT) inhibitors

These drugs prevent the breakdown of dopamine and hence extend its availability. They are especially useful in increasing the duration of on time gained from levodopa therapy. They might worsen the side-effects of levodopa.

Anticholinergic drugs

They have a low efficacy and a high side-effect profile. They might have some benefit in treating tremor.

Amantadine

A novel anti-Parkinson's drug. It could improve symptoms partly by N-methyl-D-aspartate (NMDA) receptor antagonism and partly by increasing dopamine release; it is now used largely to alleviate dyskinesias. Amantadine might provide some symptomatic benefit for patients with multisystem atrophy or progressive supranuclear palsy.

Surgery

Thalamotomy

A useful treatment for tremor but has little effect on bradykinesia or rigidity.

Pallidotomy

A treatment that can be useful in the reduction of rigidity, dyskinesia, and tremor. Bilateral pallidotomy is not recommended because of the heightened mortality in patients.

Deep brain stimulation (DBS)

Procedure involving stereotactic implantation of electrodes into various subcortical structures (commonly the ventral intermediate nucleus of the thalamus, globus pallidus interna, and subthalamus nucleus). DBS induces inhibition within these structures. Subthalamus nuclear stimulation produces the best result in patients with Parkinson's disease (>80% reduction in patients' unified Parkinson's disease rating scale scores [UPDRS]), reducing both rigidity and bradykinesias. It can also lead to treatment reduction, whereas globus pallidus interna stimulation probably does not. However, subthalamus nuclear stimulation is the most technically difficult, since the subthalamus nucleus is the size of a grain of rice.[6]

New treatments

Neuroprotective

Selegiline, an irreversible monoamine oxidase B (MAO–B) inhibitor, was thought to retard the progression of neuronal loss in Parkinson's disease, because the MAO-B enzyme is responsible for the production of MPTP's toxic metabolite. Selegiline seems to delay the need for levodopa therapy, but whether it has any neuroprotective effect is unclear. New strategies aim to prevent the progressive loss of nigrostriatal neurons. These include iron chelators, antioxidants, glutamate antagonists, tyrosine-kinase antagonists, nitric-oxide-synthase inhibitors, and trophic factors. Despite success in animal studies, clinical effects so far have been disappointing.

Restorative therapy

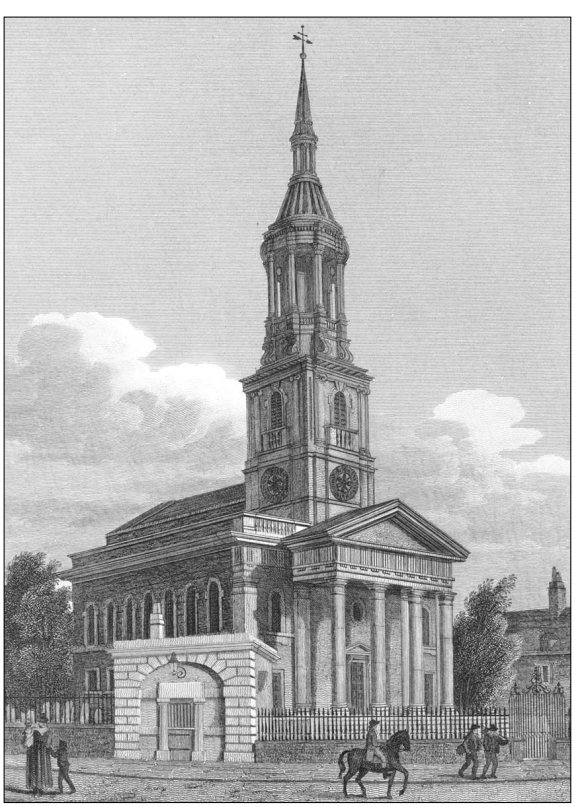
Stem-cell therapy for idiopathic Parkinson's disease has been considered since the 1980s. Several case series of patients undergoing implantation of dopamine-producing stem cells into various parts of the striatum have shown improvements in patients' UPDRS scores. A post-mortem study has shown long-term survival of the implanted graft. Randomised controlled trials involving sham surgery have been less promising, at best some benefits for young patients with Parkinson's disease. These techniques still need to be developed further and could prove a major benefit to those with the disease.

150 years before. The swelling urban centres of the country had little representation and fewer voters; mortality and poverty were both on the rise. To make the situation more unstable, there had been revolutions in America and France. Britain seemed set to follow. In 1792, Parkinson joined the London Corresponding Society, a group committed to bringing about profound egalitarian changes in society, such as universal democracy. From 1793, Parkinson became a prolific political pamphleteer, producing sheet after sheet of

arguments (often bitterly sarcastic) in favour of revolutionary change. That same year saw the pop-gun plot; an invention of government agents aimed at condemning the Society as well as rousing up popular opinion against reform. Members of the Society were alleged to have planned to assassinate King George III by firing a poisoned dart at him from the pit of a theatre. Parkinson himself was not charged, but appeared before the Privy Council to account for himself. There he was cross-examined by the Attorney General and the then Prime Minister, William Pitt. The episode neither intimidated Parkinson nor damped his ardour in the years thereafter. However, towards the end of the 1790s, the political phase of his life finished. There were to be no more pamphlets and no further involvement in any societies more revolutionary than Sunday schools (albeit at a time when these schools were attempting the inflammatory act of bringing literacy to the masses). Instead, James Parkinson, with the obligations of his practice and his now growing family, took up writing textbooks.

His first effort was a medical textbook aimed at the lay reader. It was a popular success, running to five editions. The paternalistic and slightly patronising tone was a vast change from the pithy polemics and naked anger of his political writings. The book was followed in the last year of the century by one on chemistry—a neat bridge between Parkinson's profession and his new interest in geology. In quick succession, he wrote on medical education, on the manufacture of trusses for hernias, and on how to be a good parent. The parenting book (figure 4) contains a last trace of politics: Parkinson detested the fashionable turn-of-the century idea that children should not be disciplined, lest it blunt their natural sensitivities. Parents were responsible, he wrote, for ensuring that their children did not grow into "hateful little tyrants".[7] He wrote a book for a medical audience on gout, which he had had himself from the age of 30 years. In his description of the dissection of a gouty big toe (which he compares to the extraction of a fossil), one can see his medical, chemical, and geological interests achieving a rare combination.

Although Parkinson remained active in medical practice, his professional passion from the start of the 19th century until his death seems to have been, above all things, for fossils. Perhaps, after the death of the early



London Ancestor

Figure 3: St Leonard's Church, Shoreditch

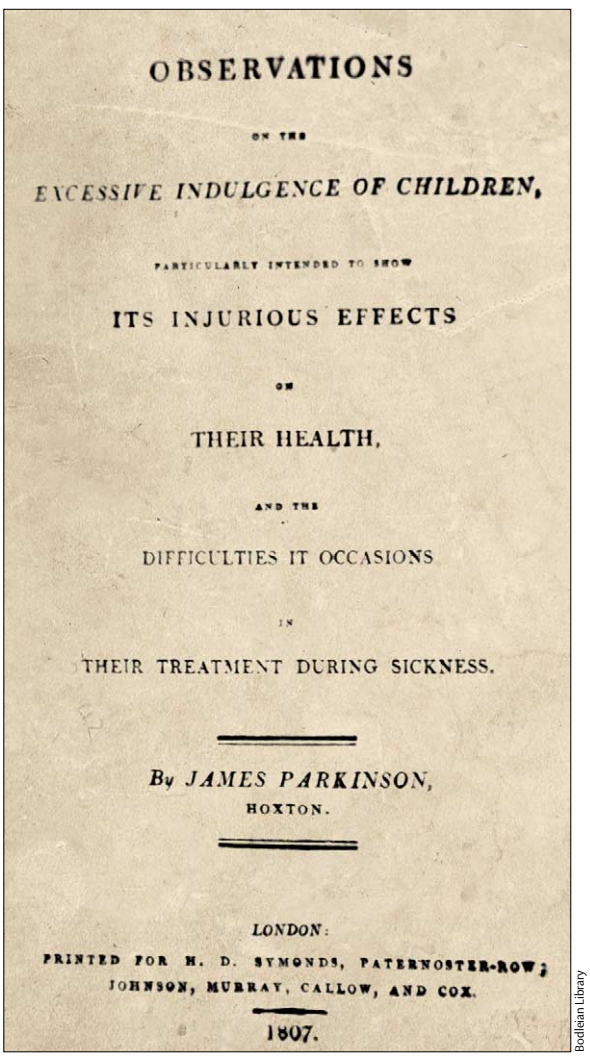


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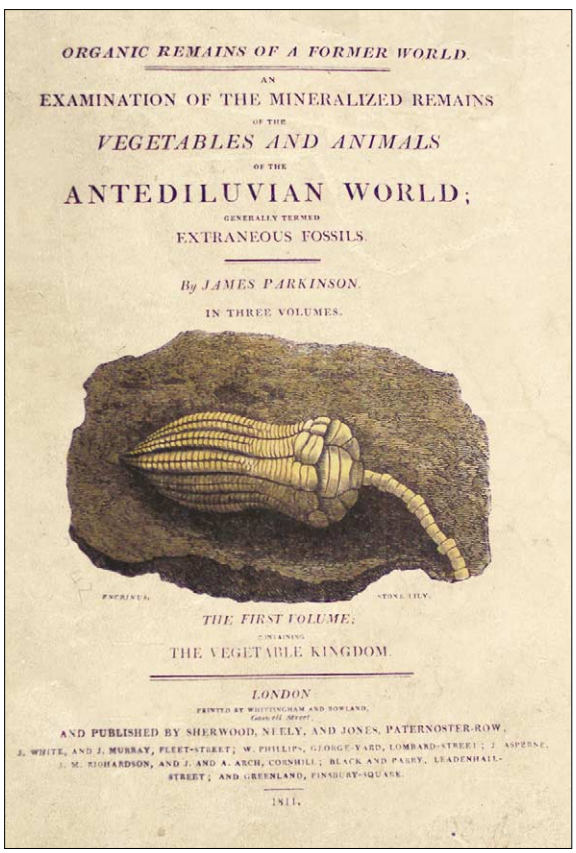
Figure 4: Title sheet of *Observations on the excessive indulgence of children*


ORGANIC REMAINS OF A FORMER WORLD.

AN

EXAMINATION OF THE MINERALIZED REMAINS

OF THE

VEGETABLES AND ANIMALS

OF THE

ANTEDILUVIAN WORLD;

GENERALLY TERMED

EXTRANEOUS FOSSILS.

By JAMES PARKINSON.

IN THREE VOLUMES.

ENCRINUS. STONE LILY.

THE FIRST VOLUME;

CONTAINING

THE VEGETABLE KINGDOM.

LONDON

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street.

AND PUBLISHED BY SHERWOOD, NEELY, AND JONES, PATERNOSTER-ROW;

J. WHITE, AND J. MURRAY, FLEET-STREET; W. PHILLIPS, GEORGE-YARD, LOMBARD-STREET; J. ASPERNE,

J. M. RICHARDSON, AND J. AND A. ARCH, CORNHILL; BLACK AND PARRY, LEADENHALL-

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1811.

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Figure 5: Title sheet of *Organic remains of a former world*

optimism that had come with the French Revolution, he believed more fertile ground for revolution existed beneath the soil than above it. Parkinson began his fossil collection in 1799. By 1811 he had published the three volumes of *Organic remains of a former world*[8] (figure 5)—the first comprehensive review in English of what would come to be called palaeontology. At the time it was hailed as a classic, leading to Parkinson's honorary election to societies as far away as Russia, and the naming of an ammonite, palm, and gastropod after him.

In his research, Parkinson found evidence for the biblical account of creation, noting that the order of fossils in the strata followed that of creation as described by Moses (ie, the separation of rocks from water, and the creation of vegetable life, inhabitants of water and air, terrestrial animals, and finally man). With his optimistic faith in human progression (and fondness for commas), Parkinson wrote,

> "From these several creations it appears that beings have proceeded, gradually increasing in superiority, from testaceous animals to reptiles, fish, marine and fresh-water amphibia, quadrupeds, and lastly to man, who, in his turn, is destined, with the earth he inhabits, to pass away, and be succeeded by a new heaven and a new earth".

That Moses declared this process had taken only 6 days did not trouble Parkinson, who felt the prophet had never meant such a description to be taken literally. Parkinson found evidence that the tops of mountains had once been the beds of seas and that many creatures that had once lived were now extinct. He noted that these truths were consistent with the flood, and that nowhere in the Bible did it say other creatures had not walked the earth before those now existing. He wrote:

> "Many have been led to doubt the total extinction of some species, and the late creation of others, as circumstances which would be incompatible with the power and wisdom of the Almighty, who, they conceive, would have formed a creation so complete at first, as to have required no subsequent change. Without dwelling on the impropriety of such modes of reasoning, it must be observed, that the facts are indubitable, and afford a direct proof of the Creator of the universe continuing a superintending providence over the works of his hands".

In 1812, Parkinson and his son John published the first report of death from perforation of the appendix. In 1817, at the late age of 62 years, Parkinson became the second president of the Association of Apothecaries and Surgeon Apothecaries of England and Wales, which had been founded in 1812. The association aimed to regulate apothecaries, which it achieved through the Apothecaries Act of 1815. This regulation laid the groundwork for development of the specialty that was beginning to be known as general practice.

In the same year, Parkinson published *An essay on the shaking palsy*. Although shaking palsy had been used before, Parkinson, with the same interest in precise classification that marked his work on fossils, felt that the term had previously been used vaguely. He was specific in talking about a resting tremor. The slowly progressive nature of this tremor, along with the hurried (festinant) gait of patients, made up the bulk of his description of the disease he called paralysis agitans. His detailed account of its natural history was based on only six cases, some of which he had only glimpsed. In a description of a particular case, he wrote:

> "The next case was also noticed casually in the street. The subject of it was a man of about sixty-five years of age, of a remarkable athletic frame. The agitation of the limbs, and indeed of the head and of the whole body, was too vehement to allow it to be designated as trembling. He was entirely unable to walk; the body being so bowed, and the head thrown so forward, as to oblige him to go on a continued run, and to employ his stick every five or six steps to force him more into an upright posture, by projecting the point of it with great force against the pavement. He stated, that he had been a sailor, and attributed his complaints to having been for several months confined in a Spanish prison, where he had, during the whole period of his confinement, lain upon the bare damp earth."

Of the disease, Parkinson wrote:

> "As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him for a moment; but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room. The chin is now almost immoveably bent down upon the sternum. The slops with which he is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost. The urine and faeces are passed involuntarily; and at the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release".

His work had little effect until the Parisian physician Jean-Martin Charcot[9] took it up half a century later. Although Parkinson's description had been incomplete (making no note of rigidity or of a Parkinsonian mask, for example), Charcot was convinced that the Englishman had been a crucial pioneer. Hence, he referred to "maladie de Parkinson".

James Parkinson was a mix of the conventional and the innovative. He was a revolutionary campaigner who loathed inherited privilege and the undemocratic and unequal society of his day. He was heavily involved in traditional church life, yet supportive of non-conformists. He was an educated man who took a keen interest in events overseas, yet he rarely strayed from the small suburb where he was born and died. His essay on the shaking palsy contains some wonderful descriptions of the disease that bears his name, yet also has many omissions. By contrast with the general perception that eponyms were much more popular historically than they are in modern medicine, paralysis agitans was still the accepted name for Parkinson's disease as late as 1920. James Parkinson died of a stroke on Dec 21, 1824, and was buried 4 days later at St Leonard's in Shoreditch. No images of him survive.

Conflict of interest statement

We declare that we have no conflict of interest.

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