

## Parkinson's Disease: from *paralysis agitans* to *parkin*

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Parkinson's disease is one of the most common chronic neurological disorders in the world, with a lifetime risk of developing the condition of 1.5%. It is primarily a disorder of movement, characterised by resting tremor, rigidity, bradykinesia, loss of postural reflexes, and asymmetry at onset.

The first published description of a series of cases of the disease is contained in *An Essay on the Shaking Palsy*, published in 1817 by James Parkinson, a man who, as the historian Roy Porter put it, was a “doctor with impeccably enlightened credentials”. Parkinson was a surgeon-apothecary (the prototype of the modern general practitioner) in Regency London, inheriting his practice in Hoxton Square from his father in the 1780s. After a precarious flirtation with radical politics, Parkinson settled into the life of doctor and natural philosopher, publishing widely both on medical and geological topics. This breadth of interest was not unusual for the period - as a student Parkinson had attended lectures of the most famous surgeon and natural philosopher of the day, John Hunter. Like Hunter, Parkinson was a doctor with a naturalist's view of the world. Thus the *Essay* contains both snapshots of the condition in people who Parkinson simply approached in the street and interviewed, and a detailed natural history of the condition in one patient over the course of 12 years.

In the *Essay*, Parkinson defined the shaking palsy (*paralysis agitans*) as a condition in which sufferers exhibited “involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured”. The *Essay* was not the first to describe the pathognomonic symptoms of the condition - the involuntary tremor (*tremor coactus*) and hurrying gait (*scelotyrbe festinans*) - but it was the first to emphasise the fact that they existed together as manifestations of a single disease.

### Understanding the pathology

Considering the causes of the shaking palsy, Parkinson stated that it should not be confused with palsies “consequent to indulgence in the drinking of spiritous liquors... [or] from the immoderate enjoyment of tea and coffee”, or with the tremors of advanced age. Parkinson believed that the shaking palsy arose from pathology in the medulla and the upper portion of the spinal cord, a notion consistent with contemporary understanding of the functions of different parts of the brain. This theory underpinned his therapeutic approach, which was to let blood from the upper part of the neck, followed by the application of blisters,

liniments, and - if necessary - a 1.5 inch issue (a wound formed with caustic and kept open with cork) on each side of the vertebral column, to obtain a purulent discharge.

Parkinson did not coin his own eponym. This was bestowed by the most famous of all 19th century neurologists, Jean-Martin Charcot, who christened it 'la maladie de Parkinson'. Charcot's clinical lectures of the 1860s and 1870s stressed the importance of rigidity, distinguished bradykinesia from weakness and the 'pill-rolling' tremor of Parkinson's disease from the intention tremor of disseminated (later, multiple) sclerosis. Charcot proposed various treatments, including - after observing that the tremor of the condition diminished when sufferers travelled on the railway - a trembling armchair.

The clinical descriptions of Parkinson's disease contained in the works of the great 19th century clinicians such as Charcot and Trousseau are readily recognisable to modern eyes. Clinico-anatomical correlative research, the bedrock of 19th century scientific medicine, struggled to find a cause for the disease, however; Charcot, for example, considered that there was no lesion to find. Advances in techniques of preserving and staining brains *post-mortem* led in 1912 to Kinnier Wilson coining the term 'extrapyramidal pathway' to describe the areas damaged in the disease, areas which he believed exerted a steadying influence on the corticospinal pathways. As early as the 1940s, neurosurgeons attempted to use this anatomical information to devise surgical treatments for Parkinson's disease, with variable degrees of success.

Subsequent developments originated far away from the hospitals and laboratories of Western Europe. In India, the root of the plant *Rauwolfia serpentina* had been used since ancient times as an antidote to insect and reptile bites, a treatment for fever, a hypnotic and a treatment for insanity. Experiments performed on extracts of the root in the 1930s showed that it had, in addition to the above, a significant effect in lowering blood pressure, culminating in the publication in 1949 of a clinical trial of *Rauwolfia* in hypertension by Rustom Jal Vakil, a Bombay cardiologist. By 1954, the active principle of the root - reserpine - had been isolated, its structure determined, and the drug introduced into clinical practice as both an antihypertensive and antipsychotic. The following year the first reports appeared of the drug's Parkinson's-like side effects. The discovery, by the Swedish biochemist Arvid Carlsson, of what caused these side-effects, revolutionised the understanding and treatment of Parkinson's disease.

Building on the work of the American chemical pharmacologist, Bernard Brodie, who had demonstrated that reserpine caused serotonin to disappear from the brain and other tissues, Carlsson and his colleagues showed that reserpine also depleted the brain's store of catecholamines. They postulated that this might be the cause of adverse behavioural and physical effects of the drug, and found that these effects could be reversed in experimental animals by giving the catecholamine precursor 3,4-dihydroxyphenylalanine (DOPA), an improvement that did not occur when the animals were given the serotonin precursor, 5-hydroxytryptophan. To their surprise, however, they did not find that giving L-DOPA restored normal noradrenaline levels in the brains of these animals. Their attention then switched to the substance intermediate between DOPA and noradrenaline: dopamine.

## The role of dopamine

Carlsson showed that dopamine was also depleted by reserpine, and that the action of L-DOPA was mediated by restoring normal levels of dopamine. Subsequent demonstrations that brain dopamine is concentrated in the basal ganglia suggested a central role for its depletion in Parkinson's disease, and raised the possibility that L-DOPA might be useful therapy. Carlsson presented this hypothesis at international meetings in 1958 and 1960, though at one meeting he met opposition from the octogenarian *eminence grise* of pharmacology, Sir Henry Dale, who stated that L-DOPA was a poison!

By this stage, however, evidence was mounting for the role of dopamine in Parkinson's disease, and within two years this evidence was incontrovertible. In Germany, Hornykiewicz's group demonstrated the absence of dopamine from the *post mortem* brains of patients with Parkinson's disease, and reported improvement in akinesia in a patient given intravenous L-DOPA. Sano replicated these findings in Japan; in Canada, Barbeau's group showed that oral treatment with L-DOPA could reduce rigidity.

## Therapeutic advances

After such an extraordinary flurry of activity, the next few years were disappointing. Therapeutically useful doses of L-DOPA induced tachycardia, sweating, nausea and vomiting, as well as elevating blood pressure. This problem was eventually solved by the American neurologist George Cotzias, who in 1967 introduced an escalating regime of treatment that enabled patients to develop tolerance to the unwanted side effects. Scepticism dwindled following the widespread introduction of Cotzias' technique. However, it was not until the mid-1970s, when combination treatments containing L-DOPA and a dopa decarboxylase inhibitor (DDI) became commercially available, and the dopamine agonist bromocriptine was shown to be effective in Parkinson's disease, that therapeutic nihilism turned to enthusiasm.

Recent decades have seen a steady expansion of the pharmaceutical armamentarium, which now includes new formulations of the L-DOPA/DDI combinations, new dopamine agonists, monoamine oxidase and catechol-O-methyltransferase inhibitors, and new uses for old drugs, such as amantadine. There is increased awareness of, and willingness to treat non-motor manifestations of the disease, such as depression, urinary and sleep disturbances. Surgery has made a comeback, with deep brain stimulation in many cases superseding the older, ablative procedures.

## Genetic factors

Understanding of the pathology of Parkinson's disease has been enhanced by molecular approaches to cellular biochemistry, genetics, and genomics. Parkinson's disease is becoming understood as a failure of a complex web of interlinking processes within brain cells, leading to the accumulation of faulty proteins within the cell, mitochondrial failure, and ultimately cell death. In 1997, it was shown that cytoplasmic inclusion bodies characteristic of Parkinson's disease, which were first described by Lewy in 1912, consist primarily of an abnormal form of a protein called  $\alpha$ -synuclein. In the same year, mis-sense mutations in the  $\alpha$ -synuclein gene were shown to cause a form of familial Parkinson's disease. A second gene, *parkin*, was identified the following year, and many more have followed, one of which - LRRK-2 - accounts for 1% of sporadic cases and 4% of hereditary cases worldwide.

In spite of all this progress, there remain unmet needs: there is no effective treatment for postural instability, or for the cognitive decline which is a frequent accompaniment of the disease in its advanced stages. And finally, despite the hopes attendant on gene therapy, there are, as yet, no treatments that reverse or even slow the underlying processes that cause this fascinating, common neurological disorder.