Review Article

Parkinson and his disease revisited

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Introduction

The late Dr Arthur Morris (1889–1980) was appointed Medical Superintendent of St Leonard's Hospital, Shoreditch in 1935, and developed a lifelong interest in James Parkinson, who had been a parish doctor to the workhouse which stood on the site of St Leonard's Hospital. The idea of a biography led him to become an avid collector of his life and times. He became an informed historian on London in 1800, Parkinson's descendants, palaeontology, politics and the pop-gun plot, and absolutely anything connected with Parkinson. He died before the biography was completed but it has at last been published. This was due to the determination and dedication of his widow, Dorothy Morris. The result is a classic of our times, and an overdue tribute to our national medical hero, James Parkinson, and to his devoted biographer, Arthur Morris.¹

James Parkinson (1755–1824)

Four generations of the Parkinson family were surgeon-apothecaries in Hoxton where James Parkinson was born on 11 April 1755. He was baptized, married and buried in Shoreditch's St Leonard's Church. Initially a medical apprentice with his father, thereafter he became a medical student at the London Hospital (1776), a post-graduate with John Hunter (1794), gaining a diploma of the Company of Surgeons (1784), a Fellow of the Medical Society of London (1787), founding member of the Medico-Chirurgical Society (1812), founding member of the Hunterian Society (1819) and Gold Medallist of the Royal College of Surgeons (1822). He died on the 21 December 1824 and is buried alongside his grandfather, father and son in St Leonard's Church.

The shaking palsy (paralysis agitans)

Medical classics are often brief and concise. William Harvey's *De Motu Cordis* was a slim 72 pages

(68 pages of type), which had no immediate acceptance. It caused a storm of controversy between 'circulators' and 'non-circulators', and the last rumble of criticisms did not die away for the best part of a century. Parkinson's '*Essay on the Shaking Palsy*' (1817) was also a slim text of 66 pages divided into five chapters on definition and history, pathognomonic features, differential diagnosis, causes and treatment. It is based on his experience of six patients over many years. The disorder was not granted its eponymous title until the 1860s when Charot coined the term '*la maladie de Parkinson*'.

Pathophysiology

The melanin-containing cells of the substantia nigra terminate in the caudate nucleus and putamen. Dopamine was found to be a neurotransmitter and its lack was noted to cause akinesia and rigidity. Levodopa revolutionized both our understanding and the management of Parkinson's disease in the 1960s. In 1979 another biochemical milestone was noted in Californian drug abusers who developed a form of Parkinson's disease due to an illicit pethidine derivative, methyl phenyl tetrahydropyridine (MPTP) which is specific to the nigrostriatum.³ It causes biochemical changes within mitochondria where it inhibits the enzymic respiratory chain. The biochemical process also leads to the generation of highly reactive free radicals which oxidize cellular lipids and cause extensive cell death in the nigrostriatum. Tocopherol is a scavenger of free radicals and may avert these catastrophic biochemical changes.

Treatment (Table I)

Levodopa

Levodopa has revolutionized the management of Parkinson's disease by restoring dopamine deficiency which is the basis of the disorder; L-dopa overcomes disability and extends life expectancy.⁴ It is now routinely administered in combination

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Table I Drugs for Parkinson's disease

Generic name	Trade name	Mode of action	Tablet size (mg)	Remarks
Levodopa	Brocadopa Larodopa	Dopamine precursor	125, 250 500 500	Initially 250 mg daily increasing by 250 mg every 4 days
Levodopa plus benserazide	Madopar	Dopamine precursor + decarboxylase inhibitor	62.5 125 250	Initially 62.5 three times daily after food
Levodopa plus carbidopa	Sinemet		62.5 (LS) 110 275 (PLUS)	Initially 1 × PLUS daily
Bromocriptine mesylate	Parlodel	Dopamine agonist	1, 2.5 5, 10	Initially 1 mg at bedtime, increasing every 2 weeks
Amantadine	Symmetrel	Dopaminergic	100	Also protects against influenza A
Selegiline hydrochloride	Eldepryl Deprenyl	Monoamine oxidase inhibitor	5	With levodopa particularly for 'on-off' symptoms
Benzhexol	Artane Bentex Broflex	Anticholinergic	2, 5 2, 5 5	Beware of gastro-intestinal obstruction, narrow angle glaucoma, prostatic
Benztropine	Cogentin		2	hypertrophy, cardiac
Biperiden	Akineton		2	arrhythmia, dry mouth,
Methixene	Tremonil		5	blurred vision, drowsiness
Orphenadrine	Biorphen Disipal		25/5 ml 50	
Prochloridone	Arpicolin Kemadrin		2.5, 5 5	

with a peripheral decarboxylase inhibitor which allows a smaller dose, prevents its wasteful peripheral metabolism and thereby fewer side effects. Nausea is minimized by its administration after food in a ratio of 1:4 peripheral decarboxylase inhibitor: levodopa. The two commonly used inhibitors are carbidopa and benserazide.

The 'on-off' syndrome describes the all-or-none clinical response and its management relies on improved delivery of L-dopa to the brain by oral sustained-release preparations, subcutaneous infusions of such dopamine agonists as lisuride and apomorphine or transdermal delivery.⁵

Bromocriptine

Bromocriptine is a dopamine agonist used in acromegaly and for neutralizing prolactin secretion. It has been administered in low dosage in combination with levodopa to prolong the benefits of the latter.⁶ However, its adverse effects may force it to be discontinued.

Selegiline (Deprenyl; Eldepryl)

Monoamine oxidase breaks down dopamine so it was rational to try monoamine oxidase inhibitors to prevent the dopamine deficit; and in practice to allow a reduction in levodopa dosage. A controlled trial suggests that selegiline, given with tocopherol anti-oxidative therapy, slows the development of disability by approximately one year; it slows disease progression and may reduce the rate of neuronal degeneration.^{7,8} It is recommended in a dose of 5 to 10 mg daily in the earliest stage of the disease, together with tocopherol to offset damaging superoxides and peroxides.

Unlike other monoamine oxidase inhibitors, it can be safely used with levodopa. Side effects are rare, but it should be avoided in patients with peptic ulceration.

Amantadine

This drug was originally introduced as prophylaxis for influenza A virus infection, and by serendipity it

was noted to be useful in a woman with Parkinson's disease, causing remission of rigidity, tremor and akinesia. When the drug was discontinued, she experienced a relapse.⁹ It is often used in the early stage of the disease. It is likely that it stimulates the release of dopamine.

Surgery

Leslie Oliver¹⁰ was an early enthusiast for stereotactic surgery. Serendipity led to the interesting observation that the tremor and rigidity of Parkinson's disease disappeared after accidental tearing of the anterior choroidal artery.¹¹ It was due to infarction of the substantia nigra and medial part of the globus pallidus. Transplantation^{1,5} of adrenal medulla or human fetal mesencephalic tissue remains an experimental procedure. The most promising results of surgery have followed fetal mesencephalic grafts into the putamen where dopamine deficiency is most severe. The present clear message is to use fetal grafts rather than adrenal autografts, and into the putamen rather than the caudate nucleus.^{12,13} All techniques will surely provide data and a better understanding of a disorder which Parkinson described so accurately 173 years ago.

Management

Once the clinical diagnosis is established with confidence, consider the following lines of management:

1. Selegiline is indicated at the earliest stage of the disease. Clinical trials indicate that it will delay the development of disability by approximately one year and it also slows disease progression.^{7,8} Tocopherol should also be given as a free radical scavenger.
2. The disabled patient should be given the benefit of levodopa together with benserazide or carbidopa (Madopar or Sinemet).
3. Amantadine is weakly dopaminergic and offers slight additional benefit. Consider it particularly during the influenza season for it protects against influenza A.
4. Bromocriptine is dopaminergic and combines well with levodopa in the patient who suffers fluctuations of response with levodopa alone. This combination serves to minimize 'on-off' attacks.
5. Anticholinergic drugs combine well with levodopa in reducing salivation and dribbling, tremor and rigidity. Their side effects of dry mouth, constipation, blurring of vision and hesitancy of micturition may prove unacceptable to the patient. They are contraindicated in patients with prostatism and glaucoma.
6. Neurosurgery remains a promising but still experimental procedure. Stereotactic procedures are used to implant fetal mesencephalic tissue into the putamen. Surely this experimental work will provide an answer during this decade.^{12,13,14}

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