Parkinson's Disease: Looking Back, Looking Forward

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> "If you were to rush into this room right now and announce that you had struck a deal – with God, Allah, Buddha, Christ, Krishna, Bill Gates, whomever – in which the ten years since my diagnosis could be magically taken away, traded in for ten more years as the person I was before, I would, without a moment's hesitation, tell you to take a hike. The ten years since my diagnosis have been the best ten years of my life, and I consider myself a lucky man."
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> **Michael J Fox, on the decade since he was diagnosed with Parkinson's disease.**

April is significant to sufferers and supporters of Parkinson's disease (PD) for two events: the death of Karol Wojtyla, Pope John Paul II on 2 April 2005, and the birthday (April 11) of Dr James Parkinson, the British surgeon for whom the disease is named, and who described the clinical features of PD in 1817 in "*An Essay on the Shaking Palsy*".[1] April 11 also marks World Parkinson's Disease Day. Launched in 1997, its celebration worldwide aims to raise the profile and enhance public awareness of the disease. With celebrities like Michael J Fox and Muhammad Ali being diagnosed with PD and raising funds to support Parkinson's research, much has been done to enable clinicians and scientists to understand and treat the disease.

The treatment of PD was revolutionised by the discovery, by Ehringer and Hornykiewicz, that patients with PD showed marked dopaminergic cell loss in the striatum.[2] This led to clinical trials with levodopa, resulting in reduced mortality and clinical benefit to virtually all patients who were given the drug.[2] Pharmacotherapy, with monoamine oxidase inhibitors, anticholinergic agents, dopamine agonists and, lately, catechol o-methyltransferase (COMT) inhibitors, has long been the mainstay of treatment,[3] but new modalities of treatment have emerged.

A serendipitous accidental ligation of the anterior choroidal artery[4] by Cooper in the 1950s led to the development of surgery, first by lesioning, then (thanks to the seminal work of Benabid and others) by implanting electrical stimulators to the thalamus, globus pallidus and subthalamic nucleus to treat the motor symptoms and complications of the disease.[5] Both lesioning and deep brain stimulation surgeries are performed worldwide (with Singapore being no exception) and offer hope to sufferers of the disease.

Neuroprotective agents, such as monoamine oxidase inhibitors (selegiline and rasagiline),[2] coenzyme-Q10,[2,3] and dopamine agonists,[2,3] are purported to protect the dopaminergic cells against further cell death, and offer hope that the progression of the disease can be slowed, if not halted. Recently, Patel et al[6] reported benefit from intraparenchymal infusions of glial cell-derived neurotrophic factor (GDNF) infusions into the posterior putamen in 5 patients. Though still in its infancy, the field of neuroprotection offers hope against the inexorable destruction of dopaminergic neurons that results in progression of the disease.

Much has been learned about levodopa-induced dyskinesias, once thought to be inevitable in the disease. We now know that as dopaminergic cell loss occurs with progression of the disease, there is less intrinsic dopamine to buffer fluctuating levels and the brain becomes dependent on exogenous dopamine. The motor response fluctuates accordingly, and this pulsatility leads to the development of dyskinesias.[2,3] As such, continuous dopaminergic stimulation with long-acting dopamine agonists, more frequent administration of levodopa or the co-administration of levodopa with a COMT inhibitor such as entacapone[2,3,7] has been advocated as a strategy to delay the development of dyskinesias. Rotigotine, a long-acting dopamine agonist, has been administered transdermally in patients with early PD.[8] This strategy offers yet another means to conveniently deliver exogenous dopamine continuously. New

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developments in the management of levodopa-induced dyskinesia include the administration of levetiracetam, amantadine and zolpidem,[3] as well as deep brain stimulation to the globus pallidus pars interna.[5]

Much progress has been made in elucidating the causation and pathogenesis of PD. For the most part, we know that PD, like most diseases, is complex, and it is likely that both genetics and the environment have a part to play.[2]

The role of environmental toxins is well illustrated by the development of PD in drug addicts who consumed an illicit drug contaminated with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP).[9] Recently, McNaught et al[10] have described how systemic exposure of rats to naturally occurring and synthetic proteasome inhibitors caused them to develop progressive parkinsonism, with cells resembling Lewy bodies being found in surviving neurons.

Though rare, a number of genes (alpha-synuclein, parkin, DJ-1, UCHL-1 and PINK1) have been identified in association with PD, and have yielded insights into the pathogenesis of the disease.[11] These heritable forms of PD should only be considered, for the most part, in young-onset PD or in the presence of a strong family history.

Ongoing PD research, it can be seen, offers tremendous hope for both patient and clinician. Although ventral mesencephalic cell transplantation has not quite lived up to its earlier promise of restoring dopaminergic cell numbers in patients with PD,[12] researchers in the field are pressing onward in the hope that as we learn more, the present difficulties, including the development of "runaway dyskinesias",[13] can be overcome. The field of stem cell research shows great promise, but it is unlikely that human stem cell transplants will take place in the immediate future, although transplants in a primate model of PD are currently under way.[14]

Newer symptomatic medications offer hope that both motor and non-motor manifestations of PD can be treated. Istradefylline, a selective adenosine A_{2A} receptor antagonist is believed to attenuate the overactivity of the striatopallidal pathway in PD, allowing antiparkinsonian benefit without exacerbating dyskinesias.[15] Triple monoamine reuptake inhibitors (blocking reuptake of dopamine, serotonin and noradrenaline) such as NS-2330 are undergoing Phase II trials and allow motor benefit whilst improving cognition and depression.[15]

At present, pharmacotherapeutic strategies allow the amelioration of motor manifestations of PD. Unfortunately, a lot of the non-motor manifestations such as dementia, constipation, sleep disorders, erectile dysfunction and drooling are not helped by dopamine replacement strategies, and research is now being directed at these aspects as well. Sustained interest in the disease will hopefully allow increased funding of research. We-move (www.wemove.org), a website whose aim is "*worldwide education and awareness of movement disorders*" and other such patient-centred sites do much to educate and provide updates to patients, physicians and carers alike. The dignity and indefatigability of PD sufferers such as Janet Reno, Pope John Paul II, and non-celebrity patients remind us that patients can lead inspiring and fulfilling lives. To quote Michael J Fox again, on living with dignity in the face of PD, "*One's dignity may be assaulted, vandalized and cruelly mocked, but cannot be taken away unless it is surrendered.*"

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