Su Ling Yeoh
Entry for the Eleventh Essay Prize of The British Geriatrics Society Movement Disorders Section
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'Walking in the footsteps of James Parkinson 200 years on'

In the waiting room

Shoulders stooped, he slowly rises from the chair.

Heard his name called out just now. From around the corner.

He gestures in the direction of the call for his kind presence. Wife waiting patiently by his side. Just in case.

He's been tripping lately. Since when? Perhaps a year, round about the same time those shakes started.

Trips in the home.
Trips outside the home.
Trips everywhere.

She says.

He smiles. Inside.

Life trips.
Life-changing.
Today is D-Day.

The corridor is long and narrow.
Like a catwalk.
With lush, red carpet laid down just for him.
He knows its seen better days.
Like him, its threads are showing.

Shuffling, *Stuttering*, *Festinating* – he walks in the footsteps of those 200 years before

That's what's done it to the carpet, he thought wryly.

At the end is the stage, where a ready and captive audience awaits.
With arms unnervingly loyal to his sides, he shuffles towards the open door, with small, measured, effortful steps, one in front of the other, hurriedly bringing him closer and closer to his fate. He can feel the eyes of those around him watching with worry, curiosity, judgement – gazing upon his every move.

He's reached the stage. Ready to perform. To face the music.

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A clinical diagnosis

"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 intellects being uninjured." [1]

In a similar manner to that of James Parkinson two centuries ago, honest, and diligent observation has persisted as the mainstay of diagnosis in Parkinson's Disease (PD). The presence of cardinal motor hallmarks of PD – resting tremor, bradykinesia, and rigidity – deduced through the powers of observation and clinical examination, and in the absence of an identifiable agent or other aetiological condition, suffices a diagnosis even today. But though the process of diagnosing PD has scarcely altered, the clinical conceptualisation of this insidious neurodegenerative condition has significantly evolved. Indeed, the only cardinal sign in Parkinson's essay included in the present diagnostic criteria for PD is tremor at rest [2] - aptly reflecting the title of his seminal publication. Whilst the motor presentation dominates the clinical portrait, non-motor manifestations, including cognitive and neuropsychiatric disturbances, have been given increasing recognition in diagnosis. Active screening for cognitive and neuropsychiatric dysfunction will ensure timely intervention, and help lessen the profound impact these symptoms can have on the patient's quality of life.

Understanding disease pathogenesis

"…disease depends not on general weakness, but merely on the interruption of the flow of the nervous influence to the affected parts." [1]

PD is defined as a movement disorder arising from the loss of dopaminergic neurons in the pars compacta of the substantia nigra, with deposition of α-synuclein positive Lewy bodies. The seminal finding that α-synuclein is the major component of Lewy bodies [3], led to a re-evaluation of the traditional paradigm of PD: that motor features stem from the net effect of reduced dopamine in the nigrostriatal pathway, resulting in the inability to reduce the inhibitory output of the basal ganglia, and dopamine deficiency in ventral striatal projections accounts for cognitive dysfunction.

The advent of immunostaining against α-synuclein established that intraneuronal Lewy body inclusions not only affect the dopamine-producing neurons of the nigrostriatal pathway, but a host of other selectively vulnerable neuronal types. This led to a re-staging of PD pathology, with early disease characterised by non-nigral pathology, and substantia nigra pathology only at disease stage 3 [4]; correlating clinically with the predominance of non-motor symptoms in the prodromal phase.

The mechanisms underlying disease propagation, and the reasons this occurs at different rates in different individuals remains undetermined. Understanding the modulating influences of the environment on genetic composition may help bridge this gap, with genome-wide association studies identifying numerous susceptibility genes and loci that contribute to disease risk in idiopathic PD. Furthermore, mechanisms initiating disease are poorly understood. Recent observations of early pathology in the enteric nervous plexus and olfactory bulb in prodromal PD cases suggest that the first insult may be an environmental pathogen [5], triggering the novel conformational change in α-synuclein which unleashes the relentless, self-propagating, cascade of disease.

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Therapeutic interventions

"…to attempt the cure, blood should be first taken from the upper part of the neck…" [1]

Parkinson dedicated the final chapter to 'considerations respecting the means of cure'. Whilst the therapeutic approaches he recommended - venesection and vesicatories to decompress the spinal medulla – reveal the influence of humorism in nineteenth-century medicine, Parkinson's appeals for anatomico-pathological understanding reflect the changing landscape of medicine. Two centuries on, advances in our understanding have shaped the therapeutic interventions available.

Pharmacological therapies currently available for PD are based on the logical understanding of the dopaminergic system. Levodopa remains the most effective oral therapy for the motor manifestations of PD, despite its long-term complications. Debilitating 'on-phase' dyskinesias, the unpredictability of 'offs', and rapid fluctuations in clinical state, known as the 'on-off phenomenon', are the invariable consequence of sustained levodopa use. Not seen in untreated PD patients, or with other PD medications, the 'on-off phenomenon' reflects the fluctuating plasma concentration of levodopa, and reduced therapeutic benefit with progressive disease. This warped success of Levodopa underlines how therapeutic intervention can inadvertently change the face of disease in more than one dimension.

With the recognition that non-motor features are closely related to quality of life, it is important to consider pharmacological and non-pharmacological approaches to symptomatic management. A challenge is that dopaminergic medications can exacerbate postural hypotension, worsen cognition, and aggravate hallucinations and paranoia through enhanced dopamine receptor stimulation in the mesolimbic pathway. Similarly, deep brain stimulation can benefit medication-refractory motor symptoms but worsen speech problems. Therapeutic approaches must therefore strike a delicate balance in the holistic management of the patient.

Future therapeutic directions – the next 200 years?

Complications of existing therapies to enhance dopamine levels has led to interest in direct replacement of dopaminergic neurons into the striatum. Since the first transplantation of foetal midbrain in 1987, there has been significant progress in transferring strategies to the clinic. Currently ongoing is an open-label, multi-centre trial (TRANSEURO) of foetal ventral-mesencephalic tissue transplanted into the striatum of patients with early PD, and stem-cell derived neuronal grafts may soon be ready for clinical trials. Stem-cell sources of dopaminergic neurons are more desirable than those from foetuses because of ethical and practical reasons. However, the advantage of foetal midbrain tissue is that they are already programmed to become mature dopaminergic cells, whilst stem-cells require re-programming, and verification of long-term functional efficacy. Alternatively, gene therapy has been trialled as a strategy for direct and continuous dopamine replacement, with a Phase 1/II dose-escalation, open-label trial reporting promising results. Prosavin®, which delivers genes for enzymes important for dopamine synthesis into the striatum via a lentiviral vector, observed improvements in motor scores at 6 and 12 months' follow-up, and a favourable side-effect profile, with no off-medication dyskinesias [6]. Neuroprotective strategies with GDNF infusions have also been trialled with some success.

Whilst much promise has been demonstrated in this pioneering field, it remains to be seen if cell-based therapies will be competitive in treating PD, with cost likely to be an important determinant.

Additionally, gene and cell-replacement therapies only improve dopaminergic motor symptoms, and are not disease modifying. Thus, patient selection is crucial, with younger patients, with isolated nigrostriatal pathology, most likely to benefit from neuronal grafting. If clinical trials are to demonstrate an observable result, patient stratification is critical as relatively small sample sizes, but individual variation in presentation and response means huge variance is seen at trial end-points. Employing markers to stratify patients by prognosis will ensure that the efficacy of novel therapeutic strategies is demonstrable in clinical trials.

In contrast to cell-replacement strategies, patients at 'high-risk' of rapid disease progression may be more suitable for therapies harnessing the patient's immune system to ameliorate systemic disease propagation, such as vaccine-based approaches targeting α-synuclein aggregation. With Phase I trials of active and passive vaccinations against α-synuclein underway, these may represent the first disease-modifying treatments for PD. Furthermore, recognition that inflammation has a direct pathogenic influence on disease progression in animal and human models makes immunomodulation an attractive therapeutic avenue. An epidemiological study observed that individuals who regularly take non-steroidal anti-inflammatory medications have a reduced risk of PD [7], raising the possibility that pre-existing immunomodulatory or anti-inflammatory medications alter PD risk. More significantly, the suspicion that the immune response determines not only the risk of developing PD, but influences the rate of disease progression after diagnosis, unveils enormous potential for disease-modifying immunotherapies [8].

Whilst translation of novel therapeutic strategies may be years in the pipeline, modelling therapies on our progressive understanding of the initiators, drivers, and players in PD pathogenesis bring us closer to changing the predicament of the "*unhappy sufferer…from the domination of which he had no prospect of escape*" [1]. A hope that may one day become the reality James Parkinson contemplated two centuries ago.

Word count: 1500

References

1. Parkinson, J. An essay on the shaking palsy. Sherwood, Neely and Jones. (1817).
2. Postuma, R. B. et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 30, 1591–1601 (2015).
3. Spillantini, M. G. et al. α-Synuclein in Lewy bodies. Nature 388, 839–840 (1997).
4. Braak, H. et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211 (2003).
5. Del Tredici, K. & Braak, H. Review: Sporadic Parkinson's disease: development and distribution of α-synuclein pathology. Neuropathol. Appl. Neurobiol. 42, 33–50 (2016).
6. Palfi, S. et al. Long-term safety and tolerability of ProSavin, a lentiviral vector-based gene therapy for Parkinson's disease: a dose escalation, open-label, phase 1/2 trial. Lancet 383, 1138–1146 (2014).
7.Gao, X., Chen, H., Schwarzschild, M. A. & Ascherio, A. Use of ibuprofen and risk of Parkinson disease. Neurology 76, 863–869 (2011).
8.Williams-Gray, C. H. et al. Serum immune markers and disease progression in an incident Parkinson's disease cohort (ICICLE-PD). Mov Disord 31, 995–1003 (2016).