Parkinson’s Disease at 200 Years: Progress, New Faces, and Unmet Needs

Anthony E. Lang, OC, MD, FRCPC, FAAN, FCAHS, FRSC, Professor, University of Toronto, Department of Medicine; Director, Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson’s Disease, Toronto Western Hospital; Director, Division of Neurology, University of Toronto

Parkinson’s disease (PD) is an extremely common neurodegenerative disorder, second only to Alzheimer’s disease, affecting 1 in 1000 individuals in the general population. Classically, PD has been considered a “movement disorder”, manifesting the hallmark features of Tremor, Rigidity, Akinesia/bradykinesia and Postural disturbances, comprising the acronym known to most medical students, TRAP. Age is the single most common risk factor and the incidence rises to 1 in 100 over the age of 60. Due to the increasing longevity of the world’s population it has been predicted that the number of individuals with PD over age 50 in Western Europe’s five most and the world’s 10 most populous nations will double from 2005 estimates of 4.1-4.6 million in 2005 to between 8.7-9.3 million by 2030.1 Next year will mark the 200th anniversary of the seminal publication of the “Essay on the Shaking Palsy” in which James Parkinson described six cases of the disorder that the famed French neurologist, Jean-Martin Charcot, named after him some 50 years later. Remarkably, although Parkinson evaluated only three patients in his clinic and observed the other 3 on the street, he accurately described almost all the classical clinical features. In the intervening 200 years, there have been a number of landmark developments but many remaining critical unmet needs.

Early in the 20th century the neuropathological substrate of the disorder was recognized to be degeneration of the substantia nigra pars compacta (SNc) of the midbrain and neurons in this and other areas were found to contain characteristic inclu-

sions termed Lewy bodies. Dopamine was eventually defined as an active neurotransmitter in its own right (apart from its intermediate role in noradrenaline metabolism). Degeneration of the dopaminergic nigrostriatal pathway was subsequently demonstrated to result in dopamine deficiency in the brains of PD patients and approximately 50 years ago, dopamine replacement using its precursor, levodopa, revolutionized the management of Parkinson’s disease (PD).2 However, the short plasma half-life of levodopa brought with it new, unexpected problems including profound hour-to-hour fluctuations in levels of mobility and abnormal involuntary movements (dyskinesias) which vary depending on fluctuating plasma and resultant brain levodopa levels.

The cause of PD has been a source of intense investigation since James Parkinson’s first description and, as with most diseases, the pendulum has variably swayed between nurture and nature.3 The potential role of environmental toxins has been repeatedly considered, particularly since Parkinson described his patients at the time of the Industrial Revolution. However, it is now known that cases of the disorder were documented in the writings of ancient Egypt and India. Probably the strongest evidence for environmental toxins came with the discovery in the early 1980s of a small cluster of heroin addicts who developed acute, severe permanent parkinsonism (in contrast to reversible parkinsonism well known to be caused by dopamine receptor blocking agents such as antipsychotic drugs and dopamine depleting drugs such as reserpine) due to the injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). This was subsequently demonstrated to be the precursor of MPP+, an inhibitor of complex 1 of the mitochondrial respiratory chain, which was found to be capable of inducing profound damage to the dopamine neurons of the SNc. This discovery has had a remarkable impact on the field, driving a search for similar toxins that are more widely present in the environment (e.g. pesticides and herbicides), generating extensive research into the pathogenesis of dopamine neuronal degeneration (particularly the role of mitochondrial dysfunction), and creating animal models that have been used quite effectively in evaluating treatments for the symptoms of dopamine deficiency as well as the complications of levodopa therapy. Unfortunately, these models have uniformly failed to predict response to experimental disease modifying therapies (i.e. treatments designed to alter the course of the disease) raising questions about the relevance of the acute toxin model to the pathogenesis of the human disease.4

Corresponding Author:
Anthony E. Lang
lang@uhnresearch.ca
Although the discovery of MPTP pushed the etiology pendulum strongly toward the environmental extreme, work on possible genetic factors was encouraged by studies of families where PD seemed to be inherited in an autosomal dominant fashion. The next major revolution occurred in 1997 with the discovery of a mutation in the gene for a poorly understood protein, alpha synuclein, in a large family originating from the town of Contursi in Italy (later demonstrated to have originated from Greece).\(^5\) Subsequently it was shown that not only mutations in the alpha synuclein gene were causative but production of too much of the normal protein through inheritance of duplications and triplications of the normal gene were similarly pathogenic. As in all fields of medicine, recent advances in genetics have completely revised concepts of the etiology and pathogenesis of Parkinson’s disease, now with several well-defined monogenic forms and a number of genetic risk factors, most notably mutations in the GBA gene which encodes beta-glucocerebrosidase, the lysosomal enzyme deficient in Gaucher’s disease.\(^3\) In addition to abnormalities of mitochondrial function and processing, genetic discoveries and other lines of research have emphasized potential roles for other pathogenic mechanisms contributing to neuronal death including disturbances of the ubiquitin-proteasome system, the lysosome-autophagy pathway, and neuroinflammation.\(^3\) The discovery of alpha synuclein has particularly emphasized the role of protein aggregation and protein membrane trafficking contributing to disease pathogenesis and has also completely revised concepts about how and where the disease begins and how it spreads.

Shortly after the discovery of the alpha synuclein mutation in the Contursi pedigree it was shown that this protein is a principal constituent of the neuropathological hallmark of Parkinson’s disease, the Lewy body.\(^6\) The development of antibodies to alpha synuclein demonstrated the presence of “Lewy pathology” (Lewy bodies and Lewy neurites) far more widespread than had been previously appreciated. Immunohistochemical studies led the neuroanatomist Heiko Braak and his colleagues to postulate that, in the central nervous system (CNS) the disease begins in the dorsal motor nucleus of the vagus (i.e. the low brainstem) and olfactory bulb and spreads from there, only affecting the dopaminergic SNc at the third of their proposed six stages of the disease.\(^7,8\) They also postulated that the disease actually begins outside the CNS, possibly in the enteric nervous system, spreading from the gut to the brain via the vagus nerve. The Braak model combined with the subsequent fascinating observation of Lewy pathology in a proportion of fetal nigral cells transplanted into the brains of patients with Parkinson’s disease many years earlier (in a therapeutic attempt to restore nigro-striatal dopaminergic innervation) have driven the concept that misfolded alpha synuclein can spread from one cell to another, subsequently recruiting the neighbor cell’s normal alpha synuclein, in a process known as permissive templating, comparable to prion diseases such as Creutzfeldt-Jakob disease.\(^9\) Recent animal studies using alpha synuclein fibrils as well as Lewy body extracts from PD brains support this prion-like mechanism of spread of disease.\(^10\) It is now believed that the process of cell to cell transmission of misfolded protein followed by recruit-ment and abnormal folding of wild type protein is not unique to Parkinson’s disease but applies widely in the field of neurodegeneration, including Alzheimer’s disease and frontotemporal dementias.\(^11\)

These and other developments have had a huge impact on our current concepts about the disorder and research directions. The introduction of “advanced therapies” such as deep brain stimulation (DBS) and infusion therapies (for example, duodenal infusion of levodopa via a pump (“Duodopa”)), designed to provide more consistent and continuous dopaminergic stimulation, are quite effective in managing problematic motor complications (i.e. motor fluctuations and dyskinesias) and further considerable research efforts are actively attempting to address the pharmacokinetic shortcomings of levodopa that cause these problems in the first place. However, it is now widely appreciated that Parkinson’s disease is not simply a motor disorder due to dopamine deficiency.\(^12\) The widespread, multi-systems central and peripheral nervous system pathology results in a large number of non-motor symptoms. Some of these, such as olfactory dysfunction, constipation, depression, anxiety and sleep disorders (e.g., rapid eye movement behavioral disorder), may precede the motor features of dopamine deficiency by many years and even decades.\(^13\) Others, such as dysautonomia (orthostatic hypotension, bowel, bladder and sexual dysfunction) and cognitive dysfunction, tend to occur later and contribute greatly to disability and compromise of quality of life in the later stages of the disease. These are combined with motor symptoms that respond poorly if at all to dopaminergic therapy, including speech and swallowing disturbances and gait dysfunction with postural instability and falls. These so-called “non-dopaminergic features” remain a huge unmet need in the management of Parkinson’s disease,\(^14\) refractory to most of our current therapies including DBS, despite it’s truly revolutionary effects in the treatment of dopaminergic motor complications in properly selected patients. The non-dopaminergic basis of these later-stage treatment-resistant problems also predicts the failure of these symptoms to benefit from future attempts to replace lost dopamine cells, for example, using stem cell technology.\(^15\)

It is now widely recognized that at the other (initial) end of the disease spectrum, PD has a prolonged “premotor” or “prodromal” stage before the classical motor features become evident. New diagnostic criteria, recently proposed by a task force of the International Parkinson and Movement Disorder Society, continue to emphasize the classical clinical features of Parkinsonism (combining these with additional supportive and exclusionary criteria)\(^16\) but new research criteria for prodromal PD have also been proposed,\(^17\) including those features outlined above that commonly precede the development of motor Parkinsonism. A major obstacle to further advances in this field is the lack of reliable biomarkers that could be used for early diagnosis, tracking of disease progression, target engagement in trials of disease modifying therapies and eventually surrogates of desired treatment effects.\(^18\) This field is extremely active, using a variety of novel imaging techniques as well as studies in all areas of “omics” (e.g., genomics, epigenomics, transcriptomics, proteomics, metabolomics, lipiddomics, microbiomics). Recognizing the important role of alpha
synuclein in the disease pathogenesis, research efforts have been actively pursuing the possibility of demonstrating this protein in biological fluids (e.g., blood, cerebrospinal fluid) as well as in biopsies of peripheral autonomic nerves in the colon, skin and salivary glands.19

The Holy Grail of Parkinson’s disease is the development of effective neuroprotective therapy which, in the future if introduced early enough in the disease course (i.e. in the prodromal stage) could even prevent the eventual development of those features that we now require to make a diagnosis.20 To date, all attempts to define effective neuroprotective/disease modifying therapy have failed. There are probably many reasons for this that are beyond the scope of this brief commentary. One critical factor, applicable to all neurodegenerative diseases, is when in the course of the disease process the treatment is applied. Indeed, it has been known for some time that the classical motor features of PD don’t become manifest until 50-70% of nigral dopaminergic cells are lost and Braak’s work has emphasized that the disease is entrenched in other areas well before the nigra is first affected. Beginning neuroprotective therapy even at the first appearance of clinical features of PD (Braak’s Stage 3) may be analogous to closing the barn door long after the horse has bolted. Thus, the clear need for various biomarkers of early disease mentioned above. As indicated, there is current widespread enthusiasm for a central role of mis-folding and trafficking of abnormal alpha synuclein in “species” in the pathogenesis and spread of the disease and general consensus that this field needs to be aggressively pursued, including the exciting early clinical trials of passive and active immunization therapy that are now underway.

Separate from the role of alpha synuclein, which may be common to all patients with so-called “Lewy body Parkinson’s disease”, other pathogenic factors may vary considerably from patient to patient. Indeed, rather than considering Parkinson’s disease as a uniform, homogeneous disease entity it may be more appropriate to think in terms of Parkinson’s disease,21 each possibly having a distinct biomarker signature and requiring some variation in approaches to disease modifying therapy. The recognition of the heterogeneity of the disease will necessitate changes in approaches to evaluating putative neuroprotective therapies (targeting specific patient populations rather than the current inclusion of all cases diagnosed as having early “Parkinson’s disease”) and, as in the field of cancer therapy, the current single-target pharmacologic approach will need to be expanded to involve biology-specific, multi-targeted strategies (“cocktails”) in selected, well-defined patient subgroups.4

As one can see from this brief commentary, the past 200 years have seen many exciting developments in our understanding of the condition first formally described by James Parkinson in 1817. These developments have given many new faces to the disorder. The introduction of levodopa provided the clear recognition of the non-dopaminergic features in a new face of motor fluctuations and dyskinesias. It also permitted the clear recognition of the non-dopaminergic features with another face of PD arising in the later stages, one now dominated by dementia (occurring in up to 80% of patients living long enough) as well as other treatment-resistant motor and non-motor problems. This face has been further refined in patients receiving advanced therapies (DBS, infusion therapies) in whom the classical dopaminergic motor features are minimally evident. The recognition that the disorder is clinically and potentially pathogenetically heterogeneous also forces us to further consider subtle differences in the facial characteristics of distinct Parkinson’s diseases. Finally, the recognition of long-standing prodromal disease and the prospect of being able to reliably diagnose this in the future, long before any of the TRAP features become evident, promises to give a very new and different face to the disorder, one which has little or no recognizable relationship to the cases described by James Parkinson. We can be hopeful that advances in diagnosis and management, based in part on developments reviewed here, will eliminate the earlier faces of the disorder that now compromise the quality of life of so many of the world’s population.

References
2. Special Issue: Levodopa: 50 years of a Revolutionary Drug for Parkinson Disease. Mov Disord 2015;30:1-120.