Fifty years of Parkinson's disease: one step forwards, two steps back?

The first issue of the *British Journal of Hospital Medicine* was published in October 1966 and included a symposium covering the neuropathology and treatment of Parkinson's disease. Could things have really changed that much in just 50 brief years?

Parkinson's disease poses the clinician with a range of challenges which are not commonly encountered across other clinical conditions. First, there are a range of parkinsonian diseases (e.g. progressive supranuclear palsy, multiple system atrophy, Lewy body dementia) that can all mimic the 'real deal' but unfortunately there is no diagnostic test to confirm Parkinson's disease and/or exclude these other imitators.

Second, the major motor symptoms of Parkinson's disease represent a 'moving target'. While patients generally commence their journey with some combination of slowness, stiffness and/or tremor, as the disease progresses these symptoms are often replaced by more challenging issues like motor fluctuations, dyskinesia and falls, which require other treatment strategies.

Third, as highlighted in the original *Essay on the Shaking Palsy* (Parkinson, 1817), Parkinson's disease is so much more than a movement disorder. Indeed, it is likely that non-motor features account for the greatest degree of disease burden, which means they need to be actively treated. This requires an extensive enquiry across multiple clinical domains including neuropsychiatric features (e.g. affective symptoms, psychosis, impulse control disorders), sleep–wake complaints (e.g. rapid eye movement sleep behaviour disorder, somnolence), sensory abnormalities (e.g. anosmia, pain) and autonomic failure (e.g. postural hypotension, constipation, bladder dysfunction).

Finally, clinicians are confronted by not knowing the cause of Parkinson's disease, its risk factors or any approaches that could ultimately limit progression of the disease.

Interestingly, many of the concepts raised above were not even broached in the original symposium on Parkinson's disease published in this journal 50 years ago. This included articles on the neuropathology of Parkinson's disease (*Figure 1*), the medical management of Parkinson's disease and stereotaxic surgery for Parkinsonism. This update will hopefully encompass the major advances that have occurred over this period while highlighting our current limitations.

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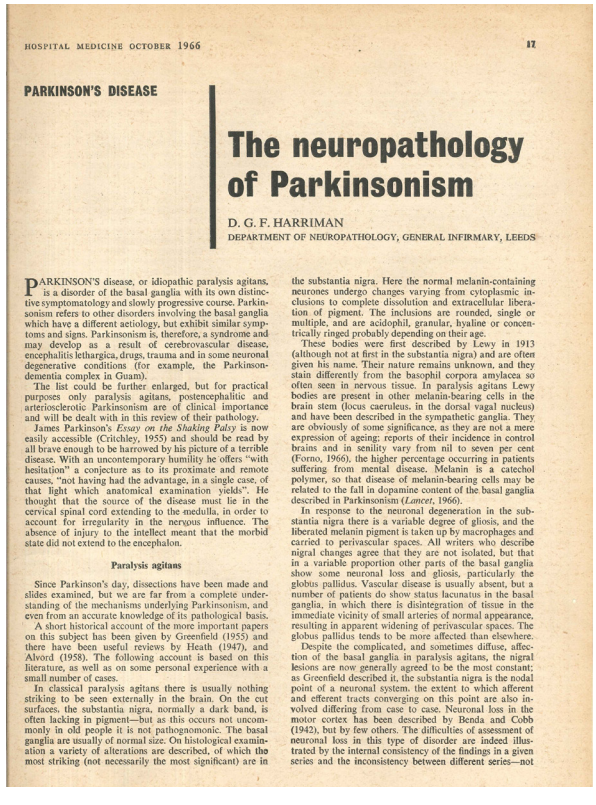
Lumpers and splitters

In the original Parkinson's disease symposium published in the journal 50 years ago much consideration was given to post-encephalitic, cerebrovascular and drug-induced parkinsonism along with Parkinson's disease. The reduction in cases of post-encephalitic parkinsonism (encephalitis lethargica) following the flu pandemic of the early 1900s was also highlighted. Therefore, it is interesting to note that work in paediatric populations has identified the presence of an elevated level of immunoglobulin G to extracellular dopamine-2 receptor in a high proportion of

Figure 1. Symposium article from the first issue of *Hospital Medicine*, in 1966. Full text of all the symposium articles can be accessed on www.bjhm.co.uk



HOSPITAL MEDICINE OCTOBER 1966 17

PARKINSON'S DISEASE

The neuropathology of Parkinsonism

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PARKINSON'S disease, or idiopathic paralysis agitans, is a disorder of the basal ganglia with its own distinctive symptomatology and slowly progressive course. Parkinsonism refers to other disorders involving the basal ganglia which have a different aetiology, but exhibit similar symptoms and signs. Parkinsonism is, therefore, a syndrome and may develop as a result of cerebrovascular disease, encephalitis lethargica, drugs, trauma and in some neuronal degenerative conditions (for example, the Parkinson-dementia complex in Guam).

The list could be further enlarged, but for practical purposes only paralysis agitans, postencephalitic and arteriosclerotic Parkinsonism are of clinical importance and will be dealt with in this review of their pathology.

James Parkinson's *Essay on the Shaking Palsy* is now easily accessible (Critchley, 1955) and should be read by all brave enough to be harrowed by his picture of a terrible disease. With an uncontemporary humility he offers "with hesitation" a conjecture as to its proximate and remote causes, "not having had the advantage, in a single case, of that light which anatomical examination yields". He thought that the source of the disease must lie in the cervical spinal cord extending to the medulla, in order to account for irregularity in the nervous influence. The absence of injury to the intellect meant that the morbid state did not extend to the encephalon.

Paralysis agitans

Since Parkinson's day, dissections have been made and slides examined, but we are far from a complete understanding of the mechanisms underlying Parkinsonism, and even from an accurate knowledge of its pathological basis.

A short historical account of the more important papers on this subject has been given by Greenfield (1955) and there have been useful reviews by Heath (1947), and Alvord (1958). The following account is based on this literature, as well as on some personal experience with a small number of cases.

In classical paralysis agitans there is usually nothing striking to be seen externally in the brain. On the cut surfaces, the substantia nigra, normally a dark band, is often lacking in pigment—but as this occurs not uncommonly in old people it is not pathognomonic. The basal ganglia are usually of normal size. On histological examination a variety of alterations are described, of which the most striking (not necessarily the most significant) are in the substantia nigra. Here the normal melanin-containing neurones undergo changes varying from cytoplasmic inclusions to complete dissolution and extracellular liberation of pigment. The inclusions are rounded, single or multiple, and are acidophil, granular, hyaline or concentrically ringed probably depending on their age.

These bodies were first described by Lewy in 1913 (although not at first in the substantia nigra) and are often given his name. Their nature remains unknown, and they stain differently from the basophil corpora amylacea so often seen in nervous tissue. In paralysis agitans Lewy bodies are present in other melanin-bearing cells in the brain stem (locus caeruleus, in the dorsal vagal nucleus) and have been described in the sympathetic ganglia. They are obviously of some significance, as they are not a mere expression of ageing; reports of their incidence in control brains and in senility vary from nil to seven per cent (Forno, 1966), the higher percentage occurring in patients suffering from mental disease. Melanin is a catechol polymer, so that disease of melanin-bearing cells may be related to the fall in dopamine content of the basal ganglia described in Parkinsonism (*Lancet*, 1966).

In response to the neuronal degeneration in the substantia nigra there is a variable degree of gliosis, and the liberated melanin pigment is taken up by macrophages and carried to perivascular spaces. All writers who describe nigral changes agree that they are not isolated, but that in a variable proportion other parts of the basal ganglia show some neuronal loss and gliosis, particularly the globus pallidus. Vascular disease is usually absent, but a number of patients do show status lacunatus in the basal ganglia, in which there is disintegration of tissue in the immediate vicinity of small arteries of normal appearance, resulting in apparent widening of perivascular spaces. The globus pallidus tends to be more affected than elsewhere.

Despite the complicated, and sometimes diffuse, affection of the basal ganglia in paralysis agitans, the nigral lesions are now generally agreed to be the most constant; as Greenfield described it, the substantia nigra is the nodal point of a neuronal system, the extent to which afferent and efferent tracts converging on this point are also involved differing from case to case. Neuronal loss in the motor cortex has been described by Benda and Cobb (1942), but by few others. The difficulties of assessment of neuronal loss in this type of disorder are indeed illustrated by the internal consistency of the findings in a given series and the inconsistency between different series—not

cases presenting with combined movement disorder and psychiatric features. This suggests that many of the original cases of encephalitis lethargica may in fact have actually represented an autoimmune basal ganglia encephalitis (Dale et al, 2012).

In the symposium from 50 years ago there was no concept of progressive supranuclear palsy, multiple system atrophy or Lewy body dementia, which are probably much more prescient considerations in the clinic these days. Clearly, clinicians are now aware that parkinsonism associated with atypical features such as disrupted eye movements (progressive supranuclear palsy), dysautonomia and ataxia (multiple system atrophy) or rapid dementia (Lewy body dementia) should act as red flags for an alternate diagnosis to Parkinson's disease. However, there is still significant phenotypic overlap between these conditions, and results from clinicopathological series using stringent diagnostic guidelines have failed to yield absolute diagnostic accuracy (Hughes et al, 2002).

It has been recognized that Parkinson's disease, progressive supranuclear palsy, multiple system atrophy and Lewy body dementia are all proteinopathies with a distinct pattern of cell loss. While Parkinson's disease, multiple system atrophy and Lewy body dementia are all associated with abnormal aggregates of insoluble alpha-synuclein within dying brain cells, progressive supranuclear palsy is characterized by neurofibrillary tangles of tau protein, predominantly in the brainstem and basal ganglia. Alpha-synuclein deposits were first described by Friedrich Lewy in 1913 and today Lewy bodies form the pathological hallmark of Parkinson's disease when they are observed within the substantia nigra. Similarly Lewy bodies are seen in the brainstem, limbic system and neocortex in patients with Lewy body dementia, often in association with the amyloid and neurofibrillary tangles characteristic of Alzheimer's disease. In patients with multiple system atrophy, Lewy bodies are seen in both neurones but predominantly within glial cells in the brainstem and cerebellum.

It was hoped that advances in structural and functional neuroimaging may help resolve diagnostic dilemmas across the parkinsonian disorders but unfortunately while at a group level these approaches offer promise, their lack of specificity and sensitivity within an individual has limited their clinical application. For example, the use of dopamine transporter (DaTscan) imaging can usually distinguish Parkinson's disease from conditions where dopamine levels are not depleted like essential and dytonic tremor but unfortunately the technique struggles to discern Parkinson's disease from progressive supranuclear palsy, multiple system atrophy and Lewy body dementia. Therefore, the development of radioligands that are able to reliably bind intracellular epitopes of alpha-synuclein and tau are a hot topic for research. However, in the absence of any proven disease-modifying approaches, this lack of diagnostic acumen is perhaps less important at this time.

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In the absence of a cure

The pharmacological management of Parkinson's disease published in this journal 50 years ago cites the first work identifying the reduction of striatal dopamine in patients with extra-pyramidal features (Ehringer and Hornykiewicz, 1960). In light of their findings the authors had proposed the role of methyl-dopa as a potential treatment in Parkinson's disease, although initial studies had delivered mixed findings and there had also been the suggestion that methyl-dopa might actually induce parkinsonism. However, 50 years later the role of dopamine depletion in Parkinson's disease is no longer disputed and dopaminergic modulation has become the cornerstone of symptomatic treatment.

A little something for the honeymoon

A range of approaches is now available and have all passed level I evidence for the symptomatic management of Parkinson's disease. These are probably all more effective in the earlier stages of disease ('the honeymoon period') than when nigrostriatal degeneration is more advanced. Reassuringly none of the currently approved therapies have been found to accelerate the progression of disease and significantly different classes of treatment may be used in combination given their distinct mechanisms of action. Levodopa (L-dopa) represents the precursor of dopamine that is able to cross the blood–brain barrier whereas catechol-O-methyl transferase and monoamine oxidase type B inhibitors both inhibit enzymes (in the gut and brain respectively) that ultimately allow the more effective delivery of dopamine at the synapse. In contrast, dopamine agonists are able to directly stimulate the dopamine receptors.

It was only after the more prolonged administration of L-dopa that clinicians became aware of the motor complications of Parkinson's disease – namely the 'wearing off' phenomenon where there is a return of symptoms and involuntary dyskinetic movements. For many years it was asserted that these features might represent an effect of prolonged exposure to L-dopa leading to the promotion of other therapeutic strategies. However, evidence from comparative populations in the first and third world (Italy and Ghana respectively) has helped identify that disease duration rather than prolonged exposure to L-dopa is the main driver for the development of motor complications (Cilia et al, 2014). In this work, patients with similar disease durations but markedly differing drug exposure periods demonstrated similar patterns of motor phenomenology.

> ...cohort studies looking at people who are yet to develop Parkinson's disease have demonstrated a range of significant pre-motor associations, which might shed light on the pathogenesis

In a similar vein, clinicians have also considered whether any particular medication regimen is superior when initiating therapy and again research has helped answer this important clinical question (PD Med Collaborative Group et al, 2014). In this study the authors demonstrated that over the 7 years following diagnosis there was very little to choose between patients who had been initiated on L-dopa, monoamine oxidase type B inhibitors or dopamine agonist therapies.

When the going gets tough

The management of patients with motor complications that fail to respond to the symptomatic treatments outlined above has seen significant changes over the last 50 years, with the development of three advanced therapies that can all reduce the periods that a patient will spend switched 'off' and with troublesome dyskinesia. Apomorphine and levodopa-carbidopa intestinal gel are both infusion therapies while deep brain stimulation involves the surgical placement of electrodes, a technique that has by and large replaced previously performed ablative lesion approaches. All of these therapies bypass the need for gastric emptying, which becomes erratic in advancing Parkinson's disease leading to the inconsistent delivery of medications to their site of absorption in the small bowel.

Apomorphine is a potent dopamine agonist that is delivered subcutaneously either intermittently (as a rescue approach) or as a continuous infusion usually only during waking hours. Levodopa-carbidopa intestinal gel is again delivered by a pump where a gel preparation of L-dopa is infused via a percutaneous tube to the jejunum. One level I study has confirmed the benefit of levodopa-carbidopa intestinal gel (Olanow et al, 2014) and this benefit seems to be maintained but patients need to be closely monitored mainly for complications relating to the mechanism of infusion. Several level I studies have been completed that show the safety and benefit of deep brain stimulation with electrode placement both in the subthalamic nucleus and internal segment of the globus pallidus (for review see Fox et al (2011)). In addition, there is now also level I evidence to demonstrate that deep brain stimulation should not be delayed in suitable patients with significant motor complications (Schuepbach et al, 2013).

Insights from non-motor symptoms

Despite the significant burden of non-motor features in Parkinson's disease they had been largely ignored by researchers and clinicians alike until efforts over the last quarter of a century. Much of this work was highlighted by the emergence of longitudinal studies of incident cases, for example the Sydney Multi-Centre Study (Hely et al, 2008). These observations raised awareness about the high rates of non-motor features, particularly in relation to neuropsychiatric features such as the emergence of dementia in 20% of patients over the course of 20 years and 70% of patients experiencing psychosis after 10 years. While there are some emerging novel therapies such as pimavanserin (a selective serotonin 5-HT2A inverse agonist) for treating psychosis in patients with Parkinson's disease, there have been no major breakthroughs in the treatment of the non-motor features. However, it does seem that established therapies used in other populations can be effective for at least some of these symptoms, including depression, psychosis and sialorrhoea, and therefore should not be neglected (for review see Seppi et al (2011)).

In addition to the findings from longitudinal studies of patients with Parkinson's disease, a number of cohort studies looking at people who are yet to develop Parkinson's disease have demonstrated a range of significant pre-motor associations, which might shed light on the pathogenesis of the condition (for review see Postuma et al (2012)). From this work clinicians are now tuning into the relevance of symptoms such as anosmia, constipation, anxiety and rapid eye movement sleep behaviour disorder, which in turn raises three important questions.

1. Are there specific 'at risk' populations who might be able to be identified before they develop Parkinson's disease?
2. Does the pattern of non-motor symptoms predating motor signs that are then in turn 'replaced' by more problematic neocortical features like dementia and psychosis give an indication about the way the pathology of Parkinson's disease is spreading through the brain?
3. If there is a reliable spread of such pathology would it be possible to find an accurate biomarker that could be used to test unaffected people who are going to develop Parkinson's disease?

Predicting Parkinson's disease

One of the common approaches to predicting a disease is to turn to the field of genetics. Over the last 50 years some of the major advances in Parkinson's disease have been through the identification of genetic causes and genetic risks for the disease (for review see Spatola and Wider (2014)). Both autosomal dominant (SNCA, LRRK2, VPS35, EIF4G1) and recessive (PARK2, PINK1, DJ-1) monogenic forms of Parkinson's disease have been reported but these cases probably account for less than 5% of all patients. However, there is a growing appreciation about genes that can increase the risk of developing Parkinson's disease and therefore it is important to understand how they might be exerting this effect. For example, while homozygous mutations within the GBA1 gene lead to Gaucher's disease, heterozygous mutations within this gene, which codes for the lysosomal enzyme glucocerebrosidase, are the most frequent genetic risk factor for developing Parkinson's disease.

An alternative approach to identifying individuals who are at risk of developing Parkinson's disease has been to

stratify people by the presence of non-motor features. Probably the most striking study to date evaluates the combined risk of people with idiopathic rapid eye movement sleep behaviour disorder who also have hyposmia, reduced visual colour discrimination and any motor signs (such as reduced arm swing or micrographia). The researchers identified that over just 3 years, 65% of individuals who had all of these features transitioned to a synucleinopathy (Parkinson's disease or Lewy body dementia) (Postuma et al, 2015).

The concept of Parkinson's disease pathology spreading in stages throughout the brain in a manner that would allow the emergence of pre-motor features (including rapid eye movement sleep behaviour disorder, anosmia, constipation and mood disorder) is now familiar to many (Braak et al, 2004). This has been linked to a dual hit hypothesis where an unknown agent could enter the CNS through nasal (via inhalation) or intestinal (via ingestion) mucosae. This concept has in turn led to a number of studies attempting to confirm the presence of alpha-synuclein at distant sites (e.g. salivary glands, colon) in pre-motor patients. Although many researchers have reported the ability to detect the presence of this protein it remains to be seen whether peripheral tissue biopsy will demonstrate significant accuracy to be of clinical utility (Visanji et al, 2014).

So where is the cure?

Very few conditions can currently be cured and probably clinicians have no right to expect that they will ever see the cure for Parkinson's disease despite the best efforts and desires. Perhaps the most intense area of research relates to the spread of alpha-synuclein pathology (*Figure 2*) and the dual hit hypothesis as mentioned above. This observation suggests that the pathogenesis is an active process with an 'advancing front line' that could theoretically be stopped.

Some key observations that have driven the field in the last few years were the findings that resulted from previous curative efforts in the early 2000s. These studies used fetal grafts as a way of trying to re-establish striatal dopamine levels (Olanow et al, 2003; Freed et al, 2008). Most readers will be aware that both of these studies were discontinued prematurely as patients developed runaway dyskinesias requiring deep brain stimulation. However, several transplanted patients have now come to post mortem and interestingly Lewy body pathology has been identified within fetal grafted cells. This observation has led some to postulate that these cells must have been transfected by the host in a process akin to that which is seen in prion disease (Olanow and Prusiner, 2009).

In this model, the ingestion or inhalation of an agent that could cause a reconfiguration of wild type alpha-synuclein may lead to a cascade with a misfolding of the protein into a non-degradable form that leads to cell death. The concept of transfection would require that this abnormal process could be passed on from cell to cell, perhaps by an exocytic mechanism. A number of animal models have been developed to support this hypothesis and one study has demonstrated that alpha-synuclein derived from the post-mortem brains of patients with multiple system atrophy could induce an alpha-synuclein prion in genetically susceptible mice (Prusiner et al, 2015). Clearly, there is a considerable way to go before drawing more definitive conclusions but already a number of therapies targeting alpha-synuclein have entered phase I clinical human trials.

Modulating alpha-synuclein is not the only therapeutic strategy in the pipeline and a number of other approaches, such as targeting potential deficits within lysosomes, perioxisomes or mitochondria, will be explored. Stem cells remain an active area for many researchers, as does the concept of using growth factors to encourage neuronal survival or gene therapy to change local enzyme activity through a viral vector.

KEY POINTS

- Over the past 50 years Parkinson's disease has become much more of a distinct clinical entity separate to the range of other parkinsonian disorders.
- There is now a strong appreciation of the key role of dopaminergic depletion and this has formed the cornerstone for the array of symptomatic therapies.
- The motor aspects of Parkinson's disease are now seen as a changing spectrum with earlier cardinal signs 'giving way' to motor complications in more advanced disease.
- There is a significant need to recognize and treat non-motor symptoms.
- Understanding how the disease evolves from a pre-motor to motor to neuropsychiatric condition gives insights into the pathogenesis of the disease and how it might be possible to predict cases in future.
- Research has highlighted how the Braak hypothesis of spreading pathology might be linked to an underlying prion process, which in turn potentially offers novel opportunities and strategies for cure.

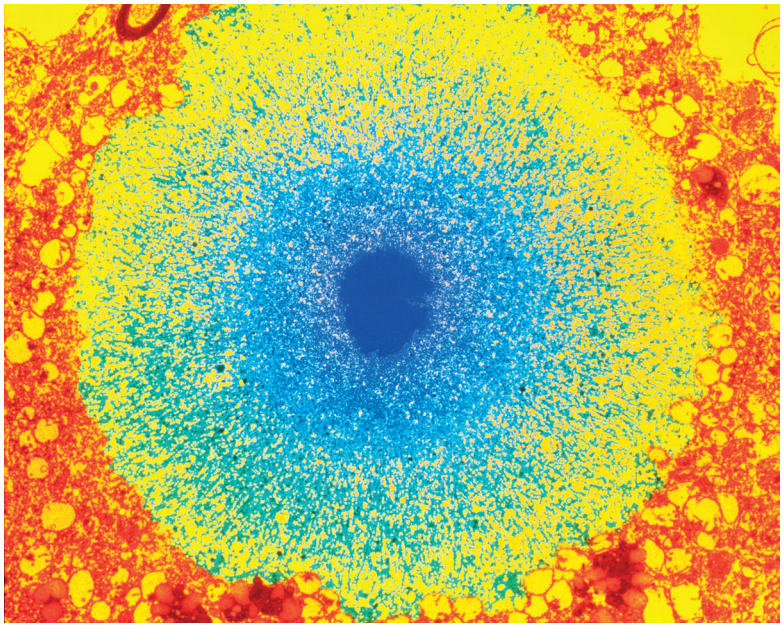

Figure 2. Coloured transmission electron micrograph of a section through a Lewy body in a nerve cell in the brain, a diagnostic feature of Parkinson's disease. Lewy bodies are largely made up of filaments of the brain protein alpha-synuclein (blue). Magnification x2750 at 6x7cm size.

Conclusions

While Parkinson's disease is still a major health and socioeconomic burden we are seeing incremental improvements in our understanding. Given the evolution of the field over the last 50 years, there is much to be hopeful about for the future. **BJHM**

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