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James Parkinson's chimera: syndrome or disease?

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ABSTRACT

It is two hundred years since James Parkinson published *An Essay on the Shaking Palsy*. While his monograph continues to be acclaimed for its precedence and clarity of description, what is often overlooked is the originality of Parkinson's ideas. We show that he appreciated the weakness of the systematic eighteenth century nosologies, which presupposed that medical species, the building blocks of these Linnaean taxonomic schemes, were as distinct as plant and animal species; and that Parkinson made a conceptual leap about combinations of clinical phenomena in recurring patterns, now recognized to be one of the germs of neurological thinking about syndromes. The *Essay's* written style underpins another aspect of significance to contemporary neurological practice—an inherent intellectual humility. In this commemorative year we locate the continuing importance of the related notions of syndrome and disease in successive frameworks of knowledge about the Shaking Palsy. Syndrome and disease are interpreted as dual character concepts, one clinically-based and the other restricted to pathophysiological causation. They both remain fundamental to understanding Parkinson's syndrome-disease today.

171 words.

Introduction

James Parkinson (1755 – 1824), who published *An Essay on the Shaking Palsy* two hundred years ago, owes his lasting reputation to the disease which it described.[1] As a result of the universality of the name and the frequency of the disorder, Parkinson has been hailed as the world's best-known neurologist,[2] though he designated himself, in both his publications and his will, as a 'surgeon-apothecary' (his main medical affiliations were to the Company of Surgeons, later the Royal College of Surgeons, and from 1814 to the Association of Apothecaries and Apothecary Surgeons of England and Wales). Despite his eponymous fame, the originality of his ideas about how clinical observations could be segregated into diagnostic entities is often overlooked.

Parkinson went beyond previous taxonomic approaches to tremor that relied on classification by sub-division, and thought instead in terms of combinations of clinical phenomena recurring in recognisable spatio-temporal patterns. This is the conceptual leap of his monograph, and it represents one of the germs of neurological thinking about syndromes. Its innovatory nature explains why the shaking palsy had not hitherto 'obtained a place in the classification of nosologists' despite its distinctive appearance.[1] Although he did not employ the word syndrome, his *Essay* illustrated how the linking together of a set of disparate clinical features can serve as a valuable template of deferred understanding. As it happened, more than a century elapsed before a lesion in the pars compacta of the substantia nigra was accepted as the single most consistent site of brain damage associated with the cardinal clinical features described in the Introduction to his monograph.

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Terminology inevitably reflects the evolution of our knowledge in medicine. This article argues for the continuing intellectual importance of James Parkinson's contribution to contemporary neurological practice by placing the related notions of syndrome and disease in the successive frameworks of knowledge which developed out of his *Essay*.

Syndrome and disease as constructs

The Greek source word *σύνδρομον* has the sense of a concurrence of things. One popular modern definition of a syndrome is a collective manifestation or pattern of clinical phenomena that is repeatedly observed but not completely understood or explained. It is a configuration of components or parts which is assumed to reflect a more fundamental process, such as a type or class of pathological mechanism.

The literary philosopher Kenneth Burke (1897-1993) in his *A Grammar of Motives* wrote that while 'much service has been got by following Occam's law to the effect that *Entities should not be multiplied beyond necessity*, much of disservice has arisen through ignoring a contrary precept, which states: *Entities should not be reduced beyond necessity*.' [3] Syndromes insist that some discernibly discrete elements 'belong together'. They invoke a combinatory process that reduces the 'blooming, buzzing confusion' of clinical phenomena [4] to a smaller number of compound forms ('atoms to molecules', 'letters to words').

Disease entities are held to have more credence and conceptual solidity than syndromes because awareness of their pathological, biochemical or genetic aetiology is implied. In clinical medicine, however, distinction between denotative and connotative descriptors is blurred, disease and syndrome frequently being used

synonymously. A syndrome can refer to a constellation of clinical features that has more than one defined cause, and the term is now also used to describe a single complex symptom such as chronic fatigue.

James Parkinson's *Essay*: a composition of its time

James Parkinson's *Essay* was a work in an older tradition of enquiry in which observation and classification were the foundation for new medical knowledge. Like many doctors of his generation, Parkinson's scientific interests were not restricted to medicine. He wrote treatises and papers on geology, fossils and chemistry, and was well acquainted with the principles of study of chemical and earth sciences. The development of palaeontology occurred in his lifetime, as did the botanical discoveries of the voyages of James Cook (1728-1779) and the French navigator-scientists Lapérouse, d'Entrecasteaux (1737-93) and Nicolas Baudin (1754-1803), the resultant knowledge being given classificatory structure by the Linnaean taxonomy of the living world; and William 'Strata' Smith conferred order on the subterranean world when he published his first geological map of Britain in 1815.

The idea of identifying defining characteristics of a specific biological entity would have been familiar to Parkinson from his work on fossilised marine animals. His *Essay* argued that certain disparate clinical phenomena should be joined together: tremor 'of parts not in action'; what we now call a propulsive shuffling gait; and a weakness or failure of 'dictates of the will' to achieve movement. He also realised that the shaking palsy had a visible presence on the busy streets of London (see Figures 1 and 2).

Figures 1 and 2 about here

Though the medical knowledge of the ancient world had lost much of its relevance, Parkinson respectfully mentioned Galen's ideas on tremor. Since the mid-1700s, classification of diseases had tended to follow the Linnaean binomial system of genus and species.

Parkinson's *Essay* refers to Carl Linnaeus's (1707 – 1778) generic term for involuntary movement, which he thought was separate from the shaking palsy (Linnaeus's system of disease classification was much less successful than his *Systema Naturae* of 1735 for botany and zoology). François Boissier de Sauvages de Lacroix (1706 - 1767), who was a botanist before becoming a physician, and was a friend of Linnaeus, was credited by Parkinson for having identified some elements of the shaking palsy in his *Methodical Nosology* (1763).[5] Sauvages's separate species of *tremor coactus* and *sclerotyrbē festinantem* seemed to correspond to rest tremor and a hurrying or propulsive gait, but he had made no attempt to see them as part and parcel of a single entity.

The systematic eighteenth century nosologies which the *Essay* reviews—those of Linnaeus, Vogel, Sauvages and Cullen—were vertical arrangements of categories such as Class, Order, Genus and Species which presupposed that medical species, the building blocks of these taxonomic rankings, were as distinct as plant and animal species appeared to be. Parkinson realised that some medical phenomena did not reflect a unitary significance and that cross-genera grouping was needed to account for his observations.

The term *paralysis agitans*, which Parkinson uses sparsely in his *Essay*, maintained continuity with the Latin binomials of the Linnaean nosologists, but his preference for the plain English of 'the Shaking

Palsy' represents a further point of departure. His 'assemblage of symptoms' took on the status of a syndrome which in this instance combined different genera and species, and thereby transcended the prevailing hierarchical system used to categorize clinical signs and symptoms.

Parkinson identified constipation, drooling of saliva, sleep disturbance and, possibly, psychological changes as clinical phenomena seen in sufferers of the shaking palsy. It was twentieth century neurologists who played down these symptoms, particularly in textbook descriptions.[6,7] Parkinson also made pertinent observations on the course of the condition. Its insidious onset, he thought, could have a prodromal phase of regional rheumatism.[1] He had an approximate idea of the course of the illness and its spread to different body parts and functions, and he also recognised some of the features of its advanced stage. Although he noted that delirium could occur terminally, he emphasised 'the absence of any injury to the senses and to the intellect, [and] that the morbid state does not extend to the encephalon'.[1] This contention may not have been inaccurate bearing in mind the duration of disease and the average age of the patients he observed.[8]

The evolution of James Parkinson's syndrome-disease

James Parkinson published information on six individuals who suffered from the shaking palsy, one of whom he had only seen at a distance. Parkinson thought the patients he described were affected by a weakness, which he distinguished from other forms of palsy. 'The dictates of the will,' he wrote, 'are even, in the last stages of the disease, conveyed to the muscles... but their actions are perverted'.[1] He saw weakness as an early and defining sign of the condition. Charcot (1825-1893) said that weakness in the shaking

palsy was largely illusory since patients could produce good muscular power when encouraged to do so, which he verified with a dynamometer.[9] In his Tuesday lectures Charcot emphasised slowness of movement and muscle rigidity as defining characteristics, which he distinguished from the spasticity of a spinal cord lesion. Trousseau was even more incisive about the particularity of the movement disorder, noting that one of his patients became progressively slower when asked to repeatedly open and close his hand, thus anticipating the modern concept of bradykinesia (progressive reduction in speed and amplitude of sequential voluntary movement).[10]

Parkinson identified some of the changes in posture associated with the condition: 'After a few more months the patient is found to be less strict than usual in preserving an upright posture: this being most observable whilst walking'.[1] Facial freezing, a clinical sign that potentially could have been identified by Parkinson's field work, was described by Charcot. Trousseau and some of the French alienists like Ball and Naville appreciated that eventual intellectual weakening could occur in older patients.[11,12]

Charcot coined the term *maladie de Parkinson*. He paid tribute to Parkinson's 'vivid and descriptive definition'[13] but he was also seeking a new terminology that reflected his realisation that tremor was not an obligatory component of the syndrome. William Gowers (1845 - 1915) disliked eponyms and preferred 'the shaking palsy' although in his *Manual* of 1878 he reverted to the then more widely accepted term *paralysis agitans*. [14]

In 1919 Konstantin Tretiakoff (1892 – 1958) identified a loss of pigmented substantia nigra neurons[15] in association with the same intracellular inclusions that Lewy had reported seven years before.[16] Neither of these findings was universally agreed to be pathognomonic for Parkinson's disease (PD) until the influential

confirmatory papers published by Hassler and then by Greenfield and Bosanquet.[17,18] The acknowledgement of secondary causes of the condition such as post-encephalitic parkinsonism, vascular parkinsonism and parkinsonism in manganese miners brought into sharp focus the distinctions between syndrome and disease. While clinicians were generally able to distinguish these disorders from one another, some authors questioned whether the *maladie de Parkinson* was really a disease at all.[19,20]

Progressive supranuclear palsy and multiple system atrophy, delineated in the 1960s as a result of clinico-pathological studies, are now established as distinct diseases that frequently present with bradykinesia, rigidity and postural deformity. Brain bank research showed that in routine clinical practice more than 15% of patients diagnosed with PD and who retained that diagnosis until the end of their lives, have an alternative pathological explanation, mostly either progressive supranuclear palsy or multiple system atrophy.[21] The development of clinical diagnostic criteria capable of a higher degree of correlation with typical pathological findings derives from a determination to preserve PD as a distinct clinical identity within a growing number of neuropathologically distinct parkinsonian syndromes. The primacy of the physical sign of bradykinesia in the clinical diagnosis of PD stems from this phase of clinico-pathological research. The disorder now also encompasses biochemical parkinsonism (nigrostriatal dopamine deficiency from enzyme defects, with levodopa responsiveness) and monogenetic parkinsonism with and without typical Lewy pathology. In contrast, the eponym Alzheimer's disease stemmed from a single detailed clinico-pathological case report and, until the nineteen sixties, described a rare degenerative amnesia.[22] The realisation that the

pathological lesion was identical to the commonest cause of dementia led to a broadening of its use.

The Braak model of topographic pathological progression hinges on the acceptance of Lewy bodies as a harbinger of selective neuronal loss,[23] and on this basis proposes that the pathological process of Parkinson's disease involves the olfactory, autonomic and enteric nervous systems. This notion has further destabilised the word 'disease' as designating a specific relationship between clinical features and pathophysiology in PD. If regional neuronal degeneration is confirmed to begin *outside* the substantia nigra and to spread eventually far beyond it, a new concept for James Parkinson's syndrome-disease may be needed.

From a clinical perspective, this approach runs into the difficulty that hyposmia, constipation and sleep disorders do not reliably predict the development of tremor, bradykinesia and rigidity. Furthermore, the majority of people with these non-motor complaints have no nigral degeneration or Lewy body pathology.

Syndrome and disease as dual characteristics

There is a dynamic tension between syndrome and disease, which can inspire new thinking about clinical entities. Syndromes embody the clinical approaches of phenomenology, fieldwork, semiotics and pattern recognition, and preserve an impression of how a disorder is experienced by a patient and encountered in the clinic. Diseases, on the other hand, conform more closely to knowledge about aetiology and mechanisms which carries implications for the development of possible treatments.

Evidence-based approaches or consensus diagnostic criteria drafted by expert committees are now the favoured approach to maintain nosological rigour and consistency of disease diagnosis, but this process has the drawback of relying heavily on review articles and meta-analyses rather than on individual clinicians' accumulated diagnostic acumen or a patient's subjective experience. In a sense they have replaced the older, respected text book descriptions of disease states.

There are many situations in which something may be characterised in two different ways when deciding whether it belongs to a particular grouping.[24] One person might have superior technical ability to apply pigments to canvas but not progress beyond a limited repertoire of images. Another, without particular training or skill in painting, may have a talent for visual creativity and a commitment to express it. Both could be called artists, each embodying a certain sense of the word. Dual characterisations usually operate at two contrasting levels—concrete and abstract, superficial and profound, or sensual and contemplative. They reveal different judgement frames about what defines membership of a category. Although dual character analyses may generate contradictions, the end result can be one of greater understanding. This way of thinking illuminates how syndromes and diseases mesh together within the structure of medical knowledge. In approaching the diagnosis of PD, disease character should be formulated according to the probability that a patient has the typical pathology of severe but not complete loss of pigmented neurons in the substantia nigra in association with brain stem Lewy bodies. Its syndromic character pertains to the clinical domain, being composed of specific motor deficits that would have been recognisable to Charcot and Gowers.

Two new sets of diagnostic criteria for use in PD research, published in the same 2015 issue of *Movement Disorders*, can be looked at in terms of this dual syndrome-disease relationship. In the MDS Clinical Diagnostic Criteria, motor deficits of bradykinesia, rigidity and tremor remain indispensable for the diagnosis of PD, anchoring the scheme within a syndromic construct.[25] Other criteria have then been overlaid, including responses to pharmacological therapy, clinical features more suggestive of other disorders (red flags) and ancillary investigations such as neuroimaging; these support a probabilistic estimate of typical underlying pathology, and hence disease character. Inter-penetration of syndrome and disease characters is one source of strength in this new working classification. To prove their usefulness in clinical practice and research the criteria now need to be validated against expert clinical opinion and existing scales.[26]

The creation of the MDS Research Criteria for Prodromal PD presents many more challenges.[27] Such an alignment of the dual characteristics is denied by the task itself, since it is an attempt to engage with a pre-diagnostic phase of the disorder. A proxy syndrome made up of clinical features that might anticipate the fully fledged motor syndrome has been drawn up. A disease construct, created by Bayesian statistics using prior demographic probabilities and likelihood ratios drawn from earlier clinical research, is used to try to predict Lewy pathology in the absence of cardinal motor signs. It seems clear that a demarcation of PD that encompasses a prodromal phase in its syndromic character needs to establish a strong correlation with pathologically-based disease character to satisfactorily redefine the disorder.

Pride and humility

An Essay on the Shaking Palsy, with its organised approach and astute analysis, is often admired as an early contribution to the project of scientific modernity in medicine. Some self-effacing and deferential comments that begin and end the *Essay* are attributable perhaps to the courteous turn of phrase of an educated Englishman of the Georgian era. But one reason that *An Essay on the Shaking Palsy* strikes a different tone from much modern scientific writing is its inherent humility. James Parkinson never wrote in a manner of superiority or self-worth, or to emphasise the importance of his opinions. The origins of Parkinson's humility are not easily appreciated from the *Essay* itself, but probably belong to the philosophical and medical climate of his era.

At the end of the eighteenth century, religious belief had to contend with several sources of doubt. Rationalist and humanist writers had undermined the position of theological learning, while political developments like the French Revolution were violently antagonistic to the authority of Church. In the long run though, scientific advances in natural sciences —especially geology and palaeontology—had the most corrosive effects on religious faith. The stratification of rock formations seen in coal mines and canal excavations and the fossilised remains of strange plants and animals found in various geological layers appeared to imply many different eras in the history of the earth each of which must have lasted for a very long time, which was inconsistent with the straightforward interpretation of the biblical account of Creation.

Some writers at the turn of the nineteenth century thought that religion and the new scientific knowledge could yet be reconciled. The clergyman William Paley's influential *Natural Theology; or,*

Evidences of the Existence and Attributes of the Deity (1802)[28] had updated a traditional Christian idea about nature—that in all its recently discovered complexity, it revealed the scheme of its Creator and continued to complement the divine revelations contained in the scriptures. Paley (1743-1805) began with the argument that as a watch implies the existence of a watchmaker, so the natural world implies the existence of God. James Parkinson shared these beliefs in natural theology, and his *Organic Remains of a Former World*, published nine years after Paley's volume, attempts to follow the Old Testament prehistoric chronology. The subtitle of Parkinson's book refers to the fossilised plants and animals of the antediluvian world; in the volume he explained how the stratification of rocks and fossils and the deposition of coal could have been formed by the Deluge. New discoveries about Nature, he wrote, 'cannot fail to excite a reverential awe, and dispose to the adoration of the Great Supreme'[29] (see Figure 3) Natural theological ideas extended to medical knowledge, Paley having also written about diseases and their different phenomenological and temporal patterns representing God's grand plan for human experience.[28]

Even though Parkinson's *Organic Remains of a Former World* treats fossils as natural formations which are to be investigated empirically through experimental investigation and chemical analysis, and displays a powerful drive to classify based on form and pattern, it retains a Mosaic schema in which each day of creation has become an indeterminately long period of time.

Figure 3 about here

As the nineteenth century progressed, even before Darwin published *On the Origin of Species* (1859), these ideas were becoming less tenable. As a source of intellectual humility in scientific writing, this form of religious feeling was abandoned by most people, then largely forgotten. It has become necessary to find other counterweights to our pride in the achievements of modern medicine.

Conclusions

In his *Essay*, James Parkinson set out observations that lacked an overarching theory to hold all their components together. His cases presented a chronicle of physical decline from which he developed a generic clinical history that conferred a narrative structure on the course of the malady. The *Essay* came to function as a conduit through which older ideas about collecting and categorising clinical information made their way into medical practice, ideas which continue to complement modern neuroscience. Although Parkinson clearly believed he had identified something more than a loose collection of symptoms and signs—in his words, the ‘Shaking Palsy’ was ‘a species of disease’—our consideration of how the modern concept of PD has developed has not identified a single version of the condition. Today’s concept or ‘unit-idea’[30] of it is not an unchanging one; there is no clinically based definition of the condition continuous across two centuries that have elapsed since the *Essay* appeared. What has been inherited is an evolving hybrid concept informed by patient accounts, clinical methods and basic and applied science, reminiscent of R. E. Kendall’s analogy of how furniture finds a place in a modern household:

‘... each generation has acquired a few new pieces of its own but has never [fully] disposed of those it inherited from its

predecessors, so that amongst the inflatable plastic settees and glass coffee tables are still scattered a few old Tudor stools, Jacobean dressers and Regency commodes, and a great deal of Victoriana. A logician would have started by defining what he meant by disease as a whole and then produced individual diseases by sub-dividing the territory whose boundaries he had thus defined. Medicine ... proceeded the other way and started with individual diseases.’[31]

Although the tendency over the twentieth-century has been for symptoms and signs to play a subordinate role to measures and markers of cellular disruption and derangement in the diagnosis of most diseases, new medical conditions have continued to gain credence without meeting Parkinson’s ideal of an anatomy based diagnosis. Aronowitz cites disease-syndromes such as Still’s disease, Reiter’s syndrome and Behcet’s syndrome as examples of clusters of symptoms, physical signs and biochemical and immunological markers, that have gained in both clinical and conceptual coherence since their original descriptions were first formulated.[32]

Parkinson’s careful characterisation of a cluster of clinical features in a small number of patients has continued to advance medical understanding into the new millenium. Traces of the creative tensions which he faced when he wrote his *Essay* are still felt within neurology’s dimer of syndrome-disease. We have argued for a non-doctrinal commitment to both sides of the interaction and for continuing intellectual and conceptual fluidity between them. Time will tell if a new construction of PD’s syndromic character which now embraces a defined prodromal phase and terminal dementia will supplant the one so memorably sketched in 1817 by James Parkinson.

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CAPTIONS

Figures 1 and 2 [please place side-by side in text].

Junction by St Leonard's Church Shoreditch (both c.1800), showing the striking variety of postures and gaits visible at this busy intersection, only a stone's throw from Parkinson's childhood home and surgeon-apothecary's practice in Hoxton Square.

Figure 3

Frontispiece to James Parkinson's *Organic Remains of a Former World* (3 vol, 1804-11). With shells of antediluvian invertebrates in the foreground, Noah's Ark rests on Mount Ararat. The rainbow reminds readers of God's promise: 'I do set my bow in the cloud, and it shall be for a token of a covenant between me and the earth' (Genesis 9:13).