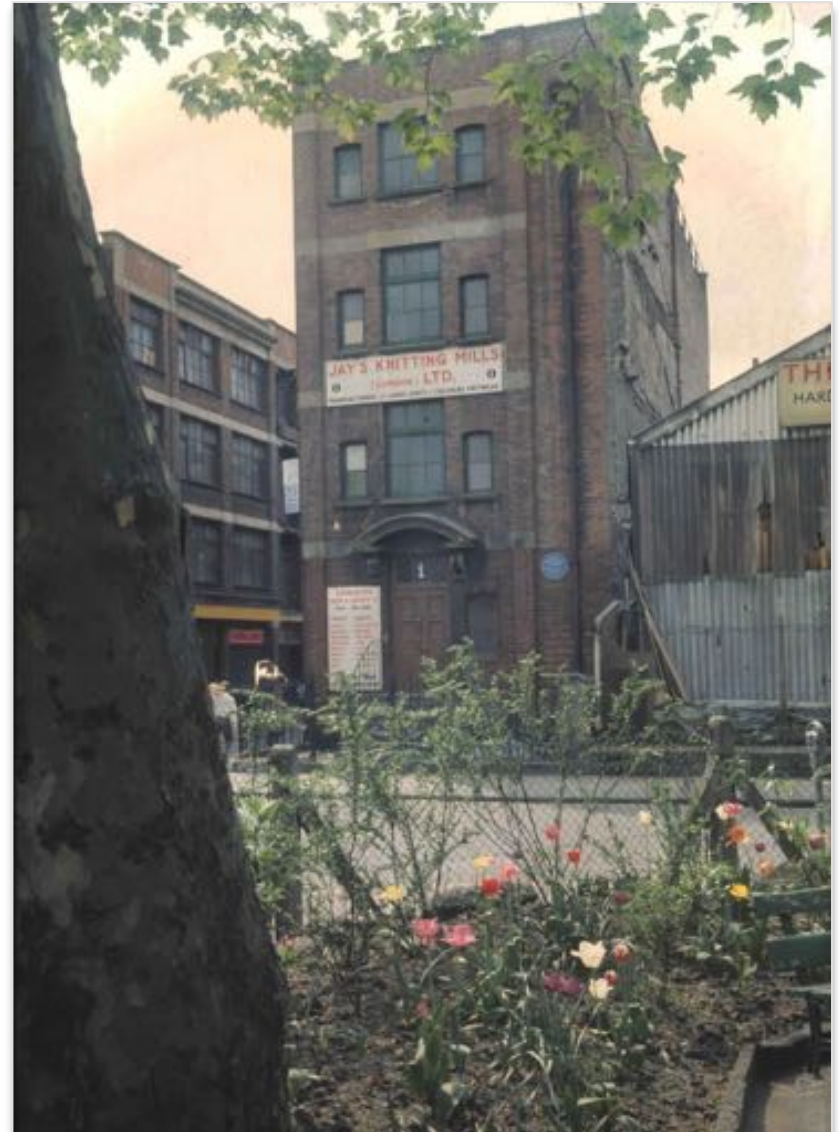


REDEFINING PARKINSON'S DISEASE

Did James Parkinson Get It Right?

Matthew B. Stern, M.D.
University of Pennsylvania
USA

1 Hoxton Square



JAMES
PARKINSON
1755-1824
Physician and
Geologist
lived here



J. Obeso, Spain



W. Poewe,
Austria

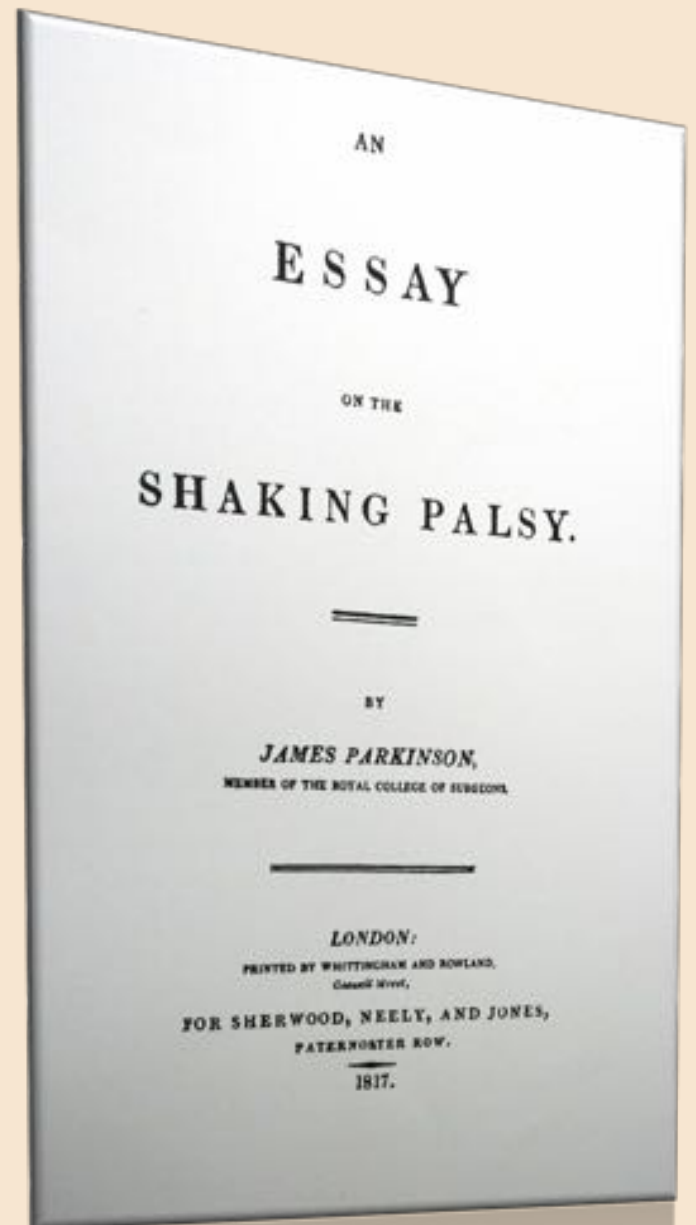


E. Tolosa, Spain

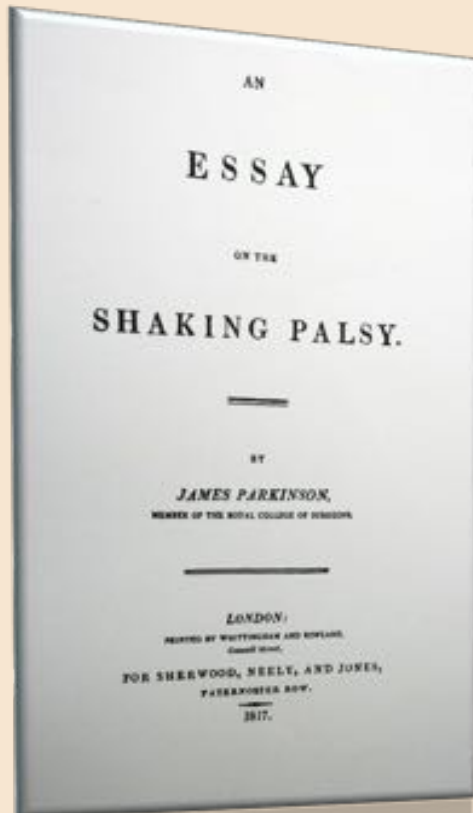


M. Stern, USA

“ To delay their publication did not, indeed appear to be warrantable. The disease had escaped particular notice; and the task of ascertaining its nature and cause by anatomical investigation, did not seem likely to be taken up by those who, from their abilities and opportunities, were most likely to accomplish it.”



James Parkinson's "Shaking Palsy"



The shaking palsy had not yet obtained a place in the classification of nosologists.

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.

An Essay on the Shaking Palsy 1817



ORGANIC REMAINS OF A FOSSIL WORLD.

••

EXAMINATION OF THE MINERALIZED
REMAINS

OF VEGETABLES AND ANIMALS

OF AN ANTI-DILUVIAL WORLD;

OR
OF THE
EXTRANEOUS FOSSILS.

By JAMES SMITH, Esq.
F.R.S.

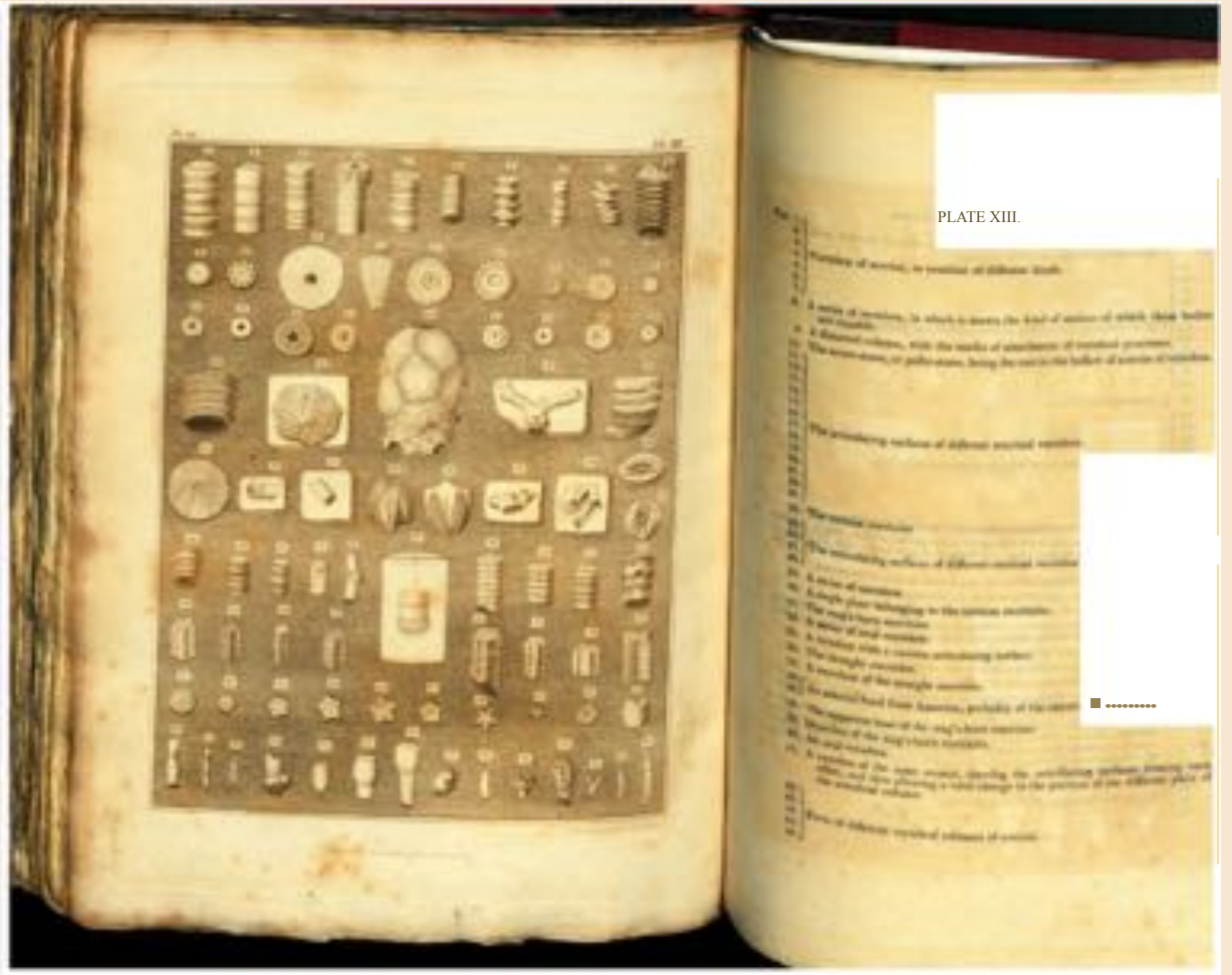


THE FIRST VOLUME;
OF THE VEGETABLE KINGDOM.

LONDON:

Printed by W. B. CLAY, at the New Bath Press, No. 7, St. Dunstons Hill.

1831.



Factoid



James Parkinson 1755-1824

The Ale-House Sermon



“He was rather below the middle stature with an energetic intelligent expression of countenance and of mild and courteous manners. He was always ready to impart information on the subject of medicine and geology.”

Gideon Mantell

Charcot on Parkinson

It will provide you with the satisfaction and knowledge that one always gleans from a direct clinical description made by an honest and careful observer.

Charcot talking about An Essay on the Shaking Palsy



I have seen such patients everywhere on the streets of Rome, of Amsterdam in Spain it is always the same picture they can be identified from afar you do not need a medical history.

Charcot Leçons du Mardi 1888

1^{re} Maladie de Parkinson.

Prendre immédiatement avant chaque repas
un grand 5. Myosyanin (est un mélange
de quatre granules) et 4 autres granules le
soir en se couchant. 6 granules par jour. Le
nombre des granules sera porté progressivement
à 8 et même à 10 dans les 24 heures.

Ces granules sont pris chez Darag,
Pharmacien. 10 Rue de la Harpe, à
Paris.

2^o Immédiatement après chaque repas,
prendre dans un peu de vin, 4 gouttes de
la solution de Pearson. 8 gouttes par

So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement.

The first symptoms... are a slight sense of weakness, with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands and arms.

James Parkinson: *An Essay on the Shaking Palsy*. London 1817

But as the disease proceeds, the hand fails to answer with exactness to the dictates of the will. The legs are not raised to that height, or promptitude which the will directs, so that the utmost care is necessary to prevent frequent falls.

Hitherto the patient will have experienced but little inconvenience; and befriended by the strong influence of habitual endurance, would perhaps seldom think of his being the subject of disease, except when reminded of it by the unsteadiness of his hand, whilst writing or employing himself in any nicer kind of manipulation.

The submission of the limbs to the directions of the will can hardly ever be obtained in the performance of the most ordinary offices of life.' The fingers cannot be disposed of in the proposed directions, and applied with certainty to any proposed point.

The dictates of the will, are even, in the last stages of the disease, conveyed to the muscles... but their actions are perverted.

James Parkinson: *An Essay on the Shaking Palsy*.
London 1817



One of the major developments in our attitude towards Parkinson's disease has been the growth of a concept of Parkinsonism as a syndrome- a symptom- complex which may emanate from various causations. The 'shaking palsy' of James Parkinson is now looked upon as merely one representative (though still the most important) of a number of clinical events.

Critchley 1955

UK Brain Bank Criteria 175 Years Later

Diagnosis of Parkinsonian Syndrome

Bradykinesia and at least one of the following:

- Muscular Rigidity
- 4-6 Hz rest tremor
- Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction

UK Brain Bank Criteria (Cont.)

Supportive prospective positive criteria for Parkinson's disease

Three or more required for diagnosis of definite Parkinson's disease in combination with step one.

- Unilateral onset
- Rest tremor present
- Progressive disorder
- Persistent asymmetry affecting side of onset most
- Excellent response (70-100%) to levodopa
- Severe levodopa-induced chorea
- Levodopa response for 5 years or more
- Clinical course of ten years or more

*From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.

The Last 25 years: Non-motor Symptoms in PD – Prodromal Features?

- Major features of prodromal PD include the following with various combinations:
 - Olfactory dysfunction
 - Autonomic dysfunction (Orthostatic hypotension, constipation, urinary and erectile dysfunctions)
 - Sleep and wake disorders (Insomnia, excessive daytime sleepiness, Rem Sleep Behavior Disorder (RBD))
 - Psychiatric (depression and anxiety) and cognitive impairments (MCI, dementia)
 - Subtle motor dysfunctions

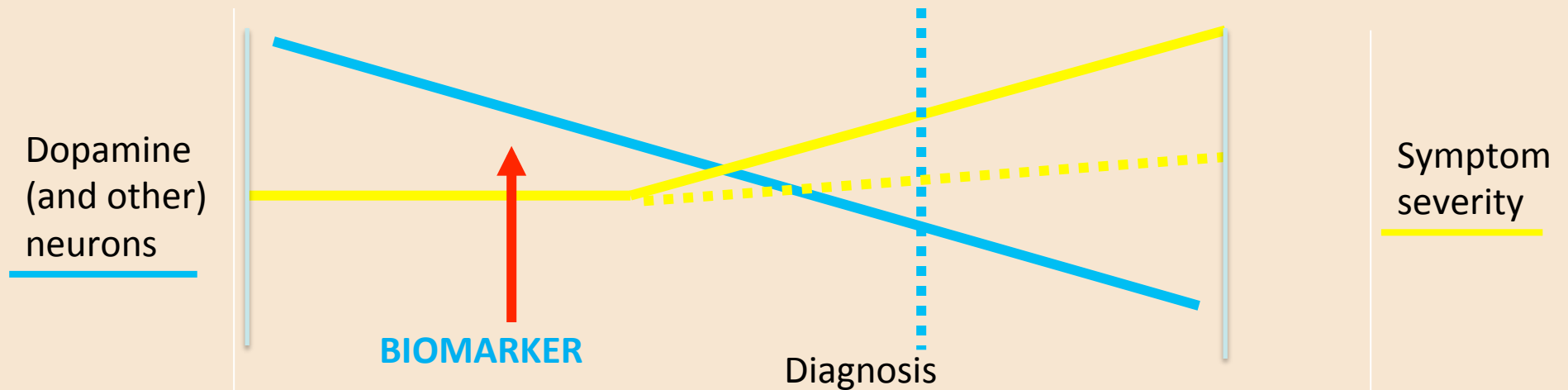
Chaudhuri and Schapira, Lancet Neurol 2009, Berg et al, Mov Disord 2015. Sauerbier et al Park Rel Disorders 2015.

Natural History of Parkinson's Disease



Premanifest Phase

Clinical PD



VIEWPOINT

Toward a Redefinition of Parkinson's Disease

Matthew B. Stern, MD,^{1*} Anthony Lang, MD,² and Werner Poewe, MD³

¹*Penn Comprehensive Neuroscience Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA*

²*Movement Disorders Center and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital and the Division of Neurology, University of Toronto, Toronto, Ontario, Canada*

³*Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria*

Movement Disorders 27:54-60, 2012

PD: A NEW DIAGNOSTIC APPROACH

- PHASE 1** **Preclinical PD**
(molecular markers of PD)
- PHASE 2** **Non-Motor PD**
(hyposmia, Cardiac, GI, RBD, etc)
- PHASE 3** **Motor PD**
(Early Motor, Monosymptomatic)
(Classic Neurologic Manifestations)

The International Parkinson and Movement Disorder Society Task Force

The Definition of Parkinson's Disease

Dr. Ron Postuma (Co-Chair)

Dr. Daniela Berg (Co-Chair)

FEATURED ARTICLE

Time to Redefine PD? Introductory Statement of the MDS Task Force on the Definition of Parkinson's Disease

Daniela Berg, MD,¹⁻⁴ Ronald B. Postuma, MD, MSc,¹⁸ Basiaan Bloem, MD, PhD,³ Piu Chan, MD, PhD,⁴
Bruno Dubois, MD, PhD,⁵ Thomas Gasser, MD,⁷ Christopher G. Goetz, MD,⁶ Glenda M. Halliday, PhD,⁷ John Hardy, PhD,⁸
Anthony E. Lang, MD, FRCPC,⁹ Irene Litvan, MD,¹⁰ Kenneth Marek, MD,¹¹ Jose Obeso, MD, PhD,¹² Wolfgang Oertel, MD,¹³
C. Warren Olanow, MD, FRCPC,¹⁴ Werner Poewe, MD,¹⁵ Matthew Stern, MD,¹⁶ and Gunther Deuschl, MD¹⁷

Mov Disord 2014

With advances in knowledge disease boundaries may change. Occasionally, these changes are of such a magnitude that they require redefinition of the disease. In recognition of the profound changes in our understanding of Parkinson's disease (PD), the International Parkinson and Movement Disorders Society (MDS) commissioned a task force to consider a redefinition of PD.

Major Issues in Redefining PD

- The Clinical vs. Pathologic Gold Standard
- Is PD a syndrome with many causes (genetic, etc)?
- PD versus LBD (cognitive >>motor)
- PD subtypes

Issue 1: What is the Gold Standard?

Current Thinking

- A motor syndrome with levodopa responsive Parkinsonism
- Pathologic confirmation of alpha-synuclein deposition and neuronal loss in the substantia nigra pars compacta

If the pathology is not found, the clinical diagnosis is incorrect.
Similarly, the pathology is “incidental” in the absence of a clinical syndrome

Alternative Gold Standards

- Should we remain true to James Parkinson and define PD as only a clinical syndrome?
- Should genetics be the ultimate standard since pathology can vary among the different genetic causes?

Problems:

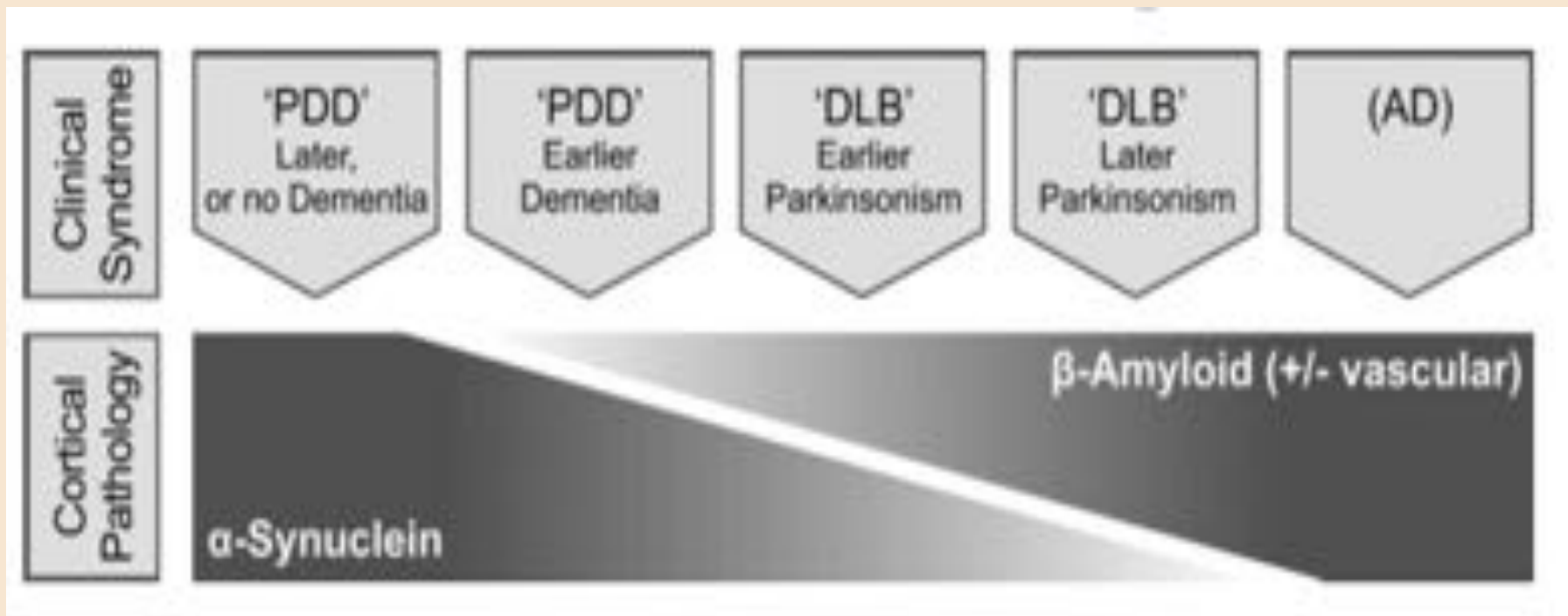
Genetics accounts for a small proportion of all PD cases

Moving Forward: The MDS Task Force

- The core criteria of a clinical syndrome accompanied by SN degeneration and synuclein pathology remain a gold standard until reliable biomarkers of CNS pathology are developed.
- A separate “clinicogenetic” category be established to include those patients with the classic clinical syndrome regardless of synuclein deposition.
- A new approach to genetic classification which differentiates between causative and risk factor genes

Issue #2: What Fits Under the PD Umbrella?

The issue: A patient developed cognitive impairment 18 months after PD diagnosis; he has PD dementia (PDD). Another developed cognitive impairment 10 months after PD diagnosis; according to current definitions, the initial diagnosis was “wrong,” and she has DLB. Does this make sense? (i.e. is the 1 year rule valid?)



Simplified model of how the type of cortical pathology and clinical presentation of PDD and DLB might interact. **Dementia in DLB/PD is associated with two major pathologies: synucleinopathy (i.e., Parkinson pathology) and neuritic amyloidopathy (i.e., Alzheimer pathology).** In PD patients who develop dementia very late in their illness, or not at all (far left), neuritic amyloid deposition is minimal (or absent), and cortical pathology is mainly that of α -Syn deposition. At the other extreme, DLB patients with predominant neuritic amyloid deposition and very minimal α -Syn deposition would usually be diagnosed as AD during life, developing clinical DLB hallmarks late (if at all). Between these two extremes of the spectrum lie the most patients with PD and DLB.

Issue #3: PD Subtypes

The issue: A patient had unilateral tremor onset at age 40, robust L-dopa response with fluctuations and, 20 years later, has few nonmotor features. A second developed bilateral bradykinesia and rigidity at age 80 and had no fluctuations, but had severe constipation, urinary dysfunction, sleep disturbance, and depression, eventually dying with dementia. Do these patients have the same disease?

Moving Forward: the MDS Task Force

- Clinical subtypes should only be delineated if there are clear data that demonstrate consistent, large differences in prognosis, predicted disease manifestations, or treatment. Currently, it is unclear whether any of the current subtype classifications qualify.
- The search for subtypes should not be restricted to clinical features, but should include subtypes of molecular pathogenesis.

Issue #4: The Beginning of PD

The issue: A patient has RBD, olfactory loss, constipation, and depression, but no parkinsonism. Dopaminergic neuroimaging and SN ultrasound are abnormal. Doesn't this patient have PD?

Issue #5: Developing New Diagnostic Criteria

- No standard clinical criteria exist. Many criteria have been proposed for PD, but none have been developed or adopted by an international organization such as the MDS.
- New knowledge: Diagnostic criteria must accommodate new findings. The systemic character of the disease needs to be acknowledged, especially incorporating **nonmotor** symptoms.
- Ancillary testing: Currently, PD diagnoses are generally made clinically, without requiring additional diagnostic tests. Moreover, as knowledge advances, **diagnostic biochemical markers, neuroimaging, or means to document a-Syn deposition may become clinically available.**
- .

MDS Clinical Diagnostic Criteria for Parkinson's Disease

Ronald B. Postuma, MD, MSc,^{1,1*} Daniela Berg, MD,^{2,1*} Matthew Stern, MD,³ Werner Poewe, MD,⁴
C. Warren Olanow, MD, FRCPC,⁵ Wolfgang Oertel, MD,⁶ Jose Obeso, MD, PhD,⁷ Kenneth Marek, MD,⁸ Irene Litvan, MD,⁹
Anthony E. Lang, OC, MD, FRCPC,¹⁰ Glenda Halliday, PhD,¹² Christopher G. Goetz, MD,¹³ Thomas Gasser, MD,²
Bruno Dubois, MD, PhD,¹⁴ Piu Chan, MD, PhD,¹⁵ Bastiaan R. Bloem, MD, PhD,¹⁶ Charles H. Adler, MD, PhD,¹⁷
and Gunther Deuschl, MD¹⁸

2015

DIAGNOSIS OF PD

Parkinsonism (Bradykinesia with either rigidity, tremor or both)

PLUS:

CLINICALLY ESTABLISHED PD:

1. Absence of absolute exclusion criteria
2. At least two supportive criteria (levodopa response, dyskinesia, hyposmia, positive DAT, cardiac sympathetic denervation by SPECT)
3. No red flags

CLINICALLY PROBABLE PD

1. Absence of absolute exclusion criteria (cerebellar signs, vertical gaze abn)
2. Presence of red flags (rapid progression, no progression, falls, autonomic failure counterbalanced by supportive criteria)

The Next Step in Redefining PD:

CASE:

A 55 year old man consults a sleep specialist for treatment of REM Sleep Behavior Disorder. Additional studies by a forward thinking Neurologist reveal severe hyposmia and significantly reduced dopamine transporter binding (<65% of normal) bilaterally. He has misfolded alpha synuclein aggregates detected in the CSF. He has never had neurologic symptoms although has had periods of depression and constipation.

QUESTION:

Does this patient have Parkinson's Disease?

ANSWER: **YES!!!!**

The year is 2027.

The patient is now 65 and has been treated with anti-synuclein agents, antioxidants and mitochondrial membrane stabilizers combined into 1 capsule.

He has been advised to drink coffee (and start smoking).

He rides his bike 10 miles every day.

He has never developed neurologic symptoms....

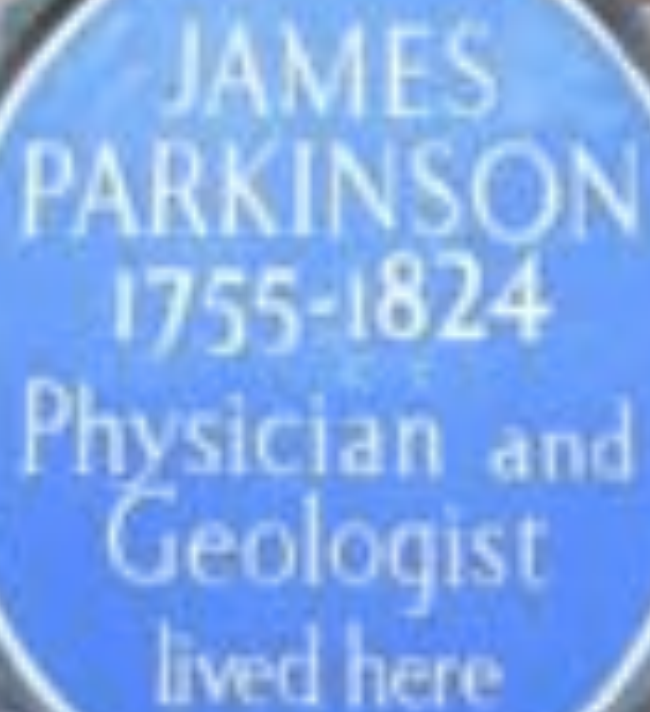
But he still has Parkinson's disease

Did James Parkinson Get It Right?

Not exactly, but regardless of our refinements in definition, he came pretty close!!!!

**"Progress is impossible
without change, and those who
cannot change their minds
cannot change anything."**

-- George Bernard Shaw

A blue oval plaque with a white border is mounted on a red brick wall. The plaque contains white text identifying James Parkinson, a physician and geologist, and his dates of birth and death. To the right of the plaque, a black downspout pipe is visible, and to the left, a brick pillar is partially seen.

JAMES
PARKINSON
1755-1824
Physician and
Geologist
lived here

The Parkinson's Complex

Parkinsonism
Substantia Nigra

Pons

Basal Forebrain

Medulla

Amygdala

Hypothalamus

Olfactory bulb

Spinal Cord (intermediolateral column)

Peripheral Autonomic Nervous System
(heart, intestinal tract, bladder)

Neocortex

Olfactory Cortex

Temporal Cortex