PARKINSON'S DISEASE

SPOTLIGHT ON PARKINSON'S DISEASE: SEARCHING FOR WAYS TO STOP DISEASE PROGRESSION

MONDAY, MARCH 22, 2021

AMERICAN PARKINSON DISEASE ASSOCIATION
Strength in optimism. Hope in progress.

Support for this program provided by: Genentech, A Member of the Roche Group; Lundbeck

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WELCOME AND INTRODUCTIONS

Rebecca Gilbert, MD, PhD
Vice President, Chief Scientific Officer
American Parkinson Disease Association

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PRESENTATION

David G. Standaert, MD, PhD
John N. Whitaker Professor and Chair of Neurology
The University of Alabama at Birmingham School of Medicine
Birmingham, AL
Chair, APDA Scientific Advisory Board

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FINANCIAL DISCLOSURES

Commercial Research Support: AbbVie Inc.

Consultant: AbbVie Inc., Theravance Inc., Sanofi-Aventis, Appello Pharmaceuticals, Grey Matter Technologies

Speakers Bureaus: none

Equity: none

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THE MANY FACES OF PARKINSON DISEASE

James Parkinson 1817

AN
ESSAY
ON THE
SHAKING PALSY.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

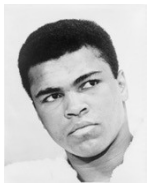
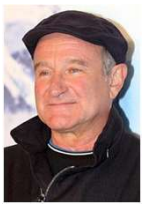
SHAKING PALSY. *(Paralysis Agitans.)*

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.







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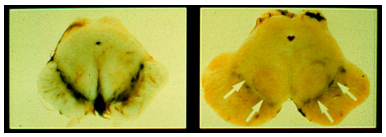
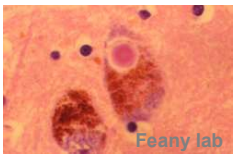
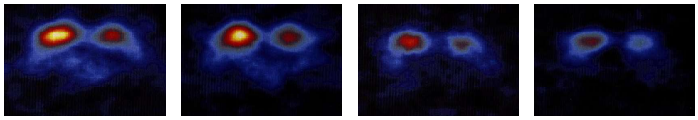
CLASSICAL FEATURES OF PARKINSON DISEASE

- Rest Tremor
- Bradykinesia
- Rigidity
- Postural Imbalance



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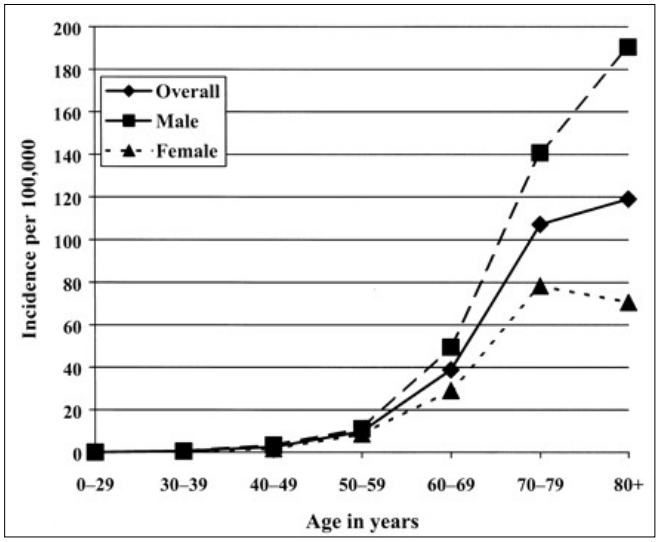
AGE AND PARKINSON DISEASE

The Good News:
We are living longer. Most Americans alive today can expect to live to at least 80 years.

Not So Good News:
The older we get, the more likely we are to get Parkinson Disease.



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PROGRESSION OF PARKINSON DISEASE

At Risk

- No symptoms
- Genetic risk factors

Prodromal "Pre-PD"

- Hyposmia – loss of the sense of smell
- REM Behavior Disorder – "acting out dreams"
- Constipation

Early PD

- Tremor
- Bradykinesia
- Rigidity
- Fatigue

Advanced PD

- Impaired balance
- Wearing off
- Dyskinesia
- Memory problems
- Hallucinations

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SEARCHING FOR WAYS TO STOP DISEASE PROGRESSION

How can we slow or stop the progression of PD?

- Genetic discoveries
  - Alpha-synuclein
  - LRRK2
  - GBA
- Immunology
- Exercise

What will the future of PD therapy look like?

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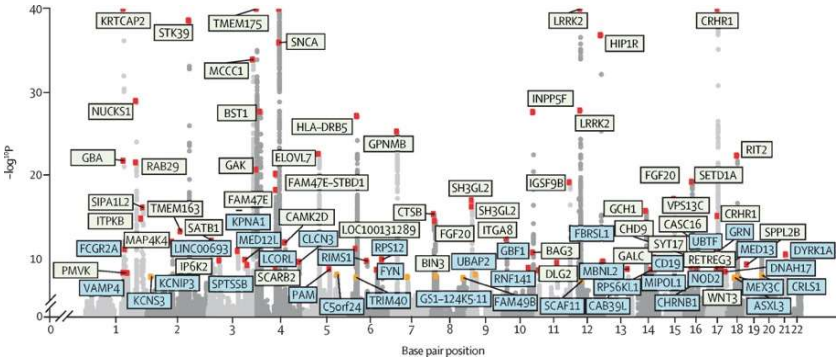
STOPPING PROGRESSION: GENETIC DISCOVERIES

Prime targets emerge from genetic studies of PD:

- Alpha-synuclein
- LRRK2
- GBA

90 genes linked to loci with genome-wide significance in PD



Nalls et al., *Lancet Neurol* 2019; 18: 1091–102

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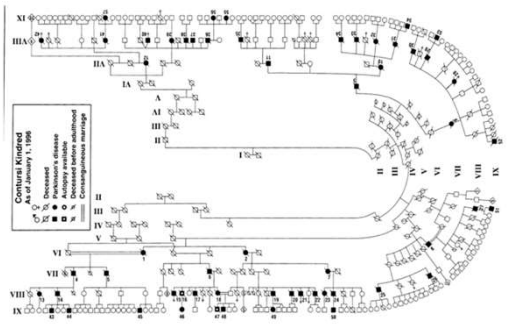
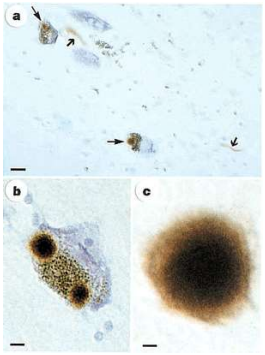
ALPHA-SYNUCLEIN AND PD

- Linked to PD through the large families
- Mutations and gene duplications cause autosomal dominant PD
- A principal component of Lewy bodies





Spillantini et al., Nature, 1997

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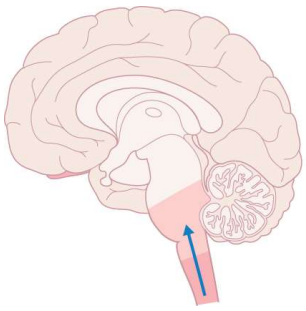
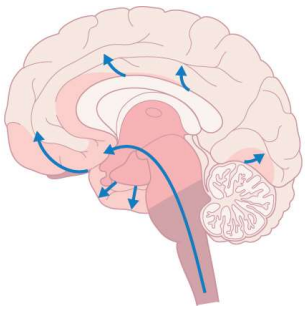
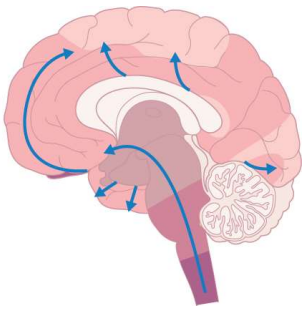
BRAAK HYPOTHESIS: PROGRESSION OF LEWY PATHOLOGY



Prodromal: Braak stages 1 and 2



Early PD: Braak stages 3 and 4



Advanced PD: Braak stages 5 and 6

Braak 2003

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Olanow et al. Neurology 2009;72(Suppl 4):S1–136 (© Wolters Kluwer Health)

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HOW CAN WE TARGET ALPHA-SYNUCLEIN FOR PD THERAPY

Reducing synuclein production

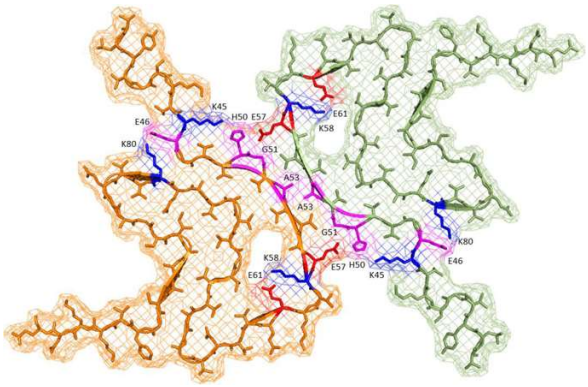
- Antisense strategies
- Transcriptional Inhibitors

Enhancing synuclein removal

- Enhances of autophagy and lysosomal function
- Antibody mediated clearance

Targeting abnormal forms

- Anti-aggregation strategies
- Antibodies specific for misfolded forms



Meade et al., *Mol Neurodegeneration* **14,** 29 (2019)

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CLINICAL TRIALS OF IMMUNOTHERAPY FOR ALPHA-SYNUCLEIN

JAMA Neurology | Original Investigation

Safety and Tolerability of Multiple Ascending Doses of PRX002/RG7935, an Anti–α-Synuclein Monoclonal Antibody, in Patients With Parkinson Disease
A Randomized Clinical Trial

Joseph Jankovic, MD; Ira Goodman, MD; Beth Safirstein, MD; Tonya K. Marmon, DrPH; Dale B. Schenk, PhD; Martin Koller, MD, MPH; Wagner Zago, PhD; Daniel K. Ness, DVM, PhD; Sue G. Griffith, MD, PhD, MRCP; Michael Grundman, MD, MPH; Jay Soto, BS; Susanne Ostrowitzki, MD, PhD; Frank G. Boess, PhD; Meret Martin-Facklam, PhD; Joseph F. Quinn, MD; Stuart H. Isaacson, MD; Omid Omidvar, MD; Aaron Ellenbogen, DO; Gene G. Kinney, PhD

Roche/Prothena, humanized mouse monoclonal targeting aggregated α-synuclein

Safety and immunogenicity of the α-synuclein active immunotherapeutic PD01A in patients with Parkinson's disease: a randomised, single-blinded, phase 1 trial

Dieter Volc, Werner Poewe, Alexandra Kutzelnigg, Petra Lührs, Caroline Thun-Hohenstein, Achim Schneeberger, Gergana Galabova, Nour Majbour, Nishant Vaikath, Omar El-Agnaf, Dorian Winter, Eva Mihalovska, Andreas Mairhofer, Carsten Schwenke, Günther Staffler, Rossella Medori

AFFiRiS, Michael J Fox Foundation, vaccine produced using a peptide from the C-terminal of α-synuclein

Others still in Phase I:

- LU AF82422 (Lundbeck)
- ABBV-0805 (Abbvie)
- MEDI1341 (AstraZeneca)

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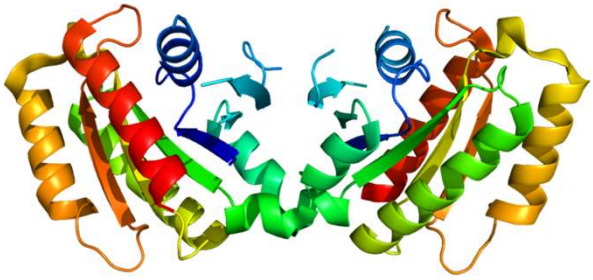
LRRK2

Leucine-rich repeat kinase 2 (LRRK2) mutations are a common cause of PD

- Most common mutation is G2019S
- Up to 4% of sporadic PD in North American clinic populations
- 25% of sporadic PD in Ashkenazi Jews

Mutations increase kinase activity



[1]Healy et al. Lancet Neurol 2008;7:583–90; for a review, see Schapira. Neurol Clin 2009;27:583–603

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CLINICAL TRIALS OF LRRK2 INHIBITORS

- Three different drugs targeting LRRK2 has reached Phase I or Phase II
- None of the studies are published yet
- Lingering concerns about safety have not been fully resolved

Clinicaltrials.gov	Drug	Method of Action	Sponsor/ Contributor
NCT03976349	**BIIB094**	Antisense Oligonucleotide	Biogen/Ionis
NCT04056689	**DNL151**	LRRK2 inhibitor	Denali Therapeutics
NCT03710707	**DNL201**	LRRK2 inhibitor	Denali Therapeutics

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GLUCOCEREBROSIDASE (GBA) AND PD

- Mutations of *GBA1 (*coding for β-glucocerebrosidase) cause Gaucher disease, a storage disorder with neurological symptoms.
- 1996: Neudorfer et al. described parkinsonism in 6 Gaucher patients.
- Heterozygous mutations in *GBA1* can be found in 4% to 7% of PD cases.
- Reduced activity of β-glucocerebrosidase appears to be a common feature of many cases of PD, even without a mutation.
- Can we increase or activate GBA in PD?

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CLINICAL TRIALS IN GBA-PD

JAMA Neurology | Original Investigation

Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations
A Nonrandomized, Noncontrolled Trial

Stephen Mullin, PhD, MRCP; Laura Smith, MSc; Katherine Lee, MRes; Gayle D'Souza, MSc; Philip Woodgate, PhD; Josh Elflein, MSc; Jenny Hällqvist, BSc; Marco Toffoli, MD; Adam Streeter, PhD; Joanne Hosking, PhD; Wendy E. Heywood, PhD; Rajeshree Khengar, PhD; Philip Campbell, MRCP; Jason Hehir, BSc; Sarah Cable, BSc; Kevin Mills, PhD; Henrik Zetterberg, PhD, MD; Patricia Limousin, PhD, MD; Vincenzo Libri, MD, FRCP; Tom Foltynie, PhD, MRCP; Anthony H. V. Schapira, MD, DSc, FRCP, FMedSci

- Ambroxol is used for treatment of cough
- Chaperone, improves GBA function
- Currently in Phase 2 for PD

propel

Prevail Therapeutics

- Gene Therapy
- Direct injection of a virus encoding GBA into the brain
- Study is recruiting participants

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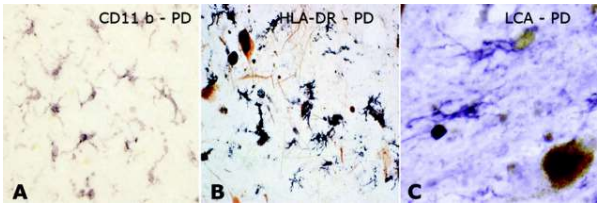
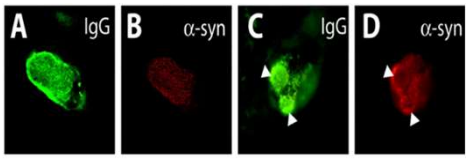
IMMUNE SYSTEM INVOLVEMENT IN HUMAN PARKINSON DISEASE

Microglia Activation in Human PD



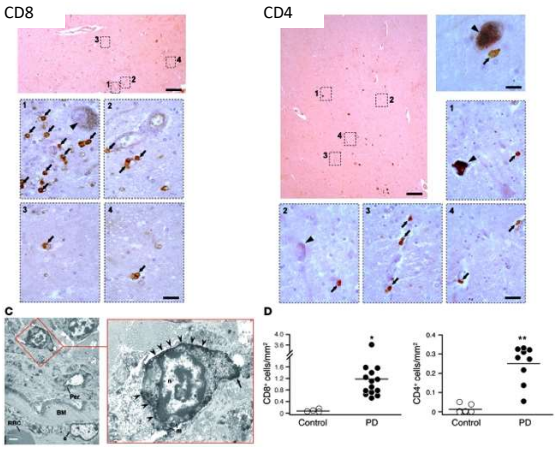
McGeer and McGeer, 2008

IgG Deposition on Nigral Neurons



Orr et al., 2007

CD4 and CD8 T Cells in Human PD brain



Brochard et al., 2009

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SYNUCLEIN REACTIVE T CELLS FROM BLOOD IN PD

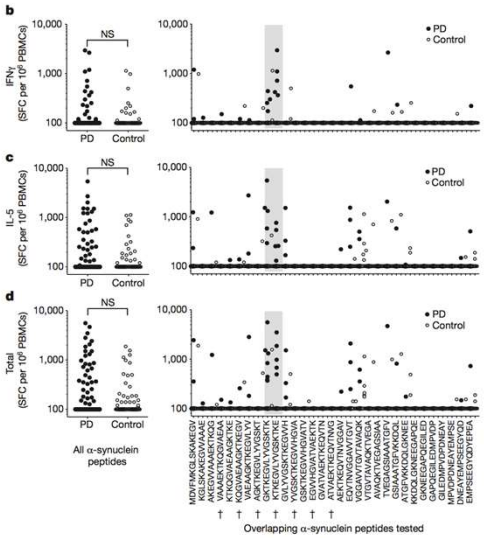
LETTER

doi:10.1038/nature22815

T cells from patients with Parkinson's disease recognize α-synuclein peptides

David Sulzer[1,2,3], Roy N. Alcalay[2], Francesca Garretti[1], Lucien Cote[2], Ellen Kanter[1], Julian Agin-Liebes[1], Christopher Liong[2], Curtis McMurtrey[4], William H. Hildebrand[4], Xiaobo Mao[5,6], Valina L. Dawson[5,6,7,8], Ted M. Dawson[5,6,8,9], Carla Oseroff[10], John Pham[10], John Sidney[10], Myles B. Dillon[10], Chelsea Carpenter[10], Daniela Weiskopf[10], Elizabeth Phillips[11,1,2], Simon Mallal[11,1,2], Bjoern Peters[10], April Frazier[10], Cecilia S. Lindestam Arlehamn[10] & Alessandro Sette[10]

- T cells isolated from blood from patients with PD
- Screened for reactivity to peptide fragments of synuclein
- In one case, reactive T cells found years before onset of PD



Nature 546, 656–661 (29 June 2017)

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IMMUNOMODULATORY THERAPY FOR PD

- Can immune modulation modify the course of PD?
- What are the targets for immune modulating therapy?
- When in the course of the disease is immune modulation effective?

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IMMUNOMODULATION: ANTI-TNF THERAPY

JAMA Neurology | Original Investigation

Anti-Tumor Necrosis Factor Therapy and Incidence of Parkinson Disease Among Patients With Inflammatory Bowel Disease

Inga Peter, PhD; Marla Dubinsky, MD; Susan Bressman, MD; Andrew Park, PhD, MPH; Changyue Lu, MS; Naijun Chen, MS; Anthony Wang, PhD, MPH

- Medicare Supplemental Database, 2000-2016.
- 144,018 individuals with IBD matched with 720,090 controls
- 1,796 with PD
- IBD increases the risk of PD
- Anti-TNF treatment of IBD is associated with a nearly 10-fold reduction in the risk of PD

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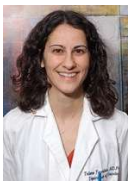
ALABAMA MORRIS K. UDALL CENTER OF EXCELLENCE IN PARKINSON'S DISEASE RESEARCH
NIH AWARD P50NS108675

Alabama Udall Center

David Standaert
Program Director
Project 1
Admin Core

Tika Benveniste
Project 2

Andy West
Project 3
Duke UNIVERSITY



Talene Yacoubian
Clinical Core

Laura Volpicelli-Daley
Animal Model Core

Katherine Belue
Administrator

David Geldmacher
Project 4

Our central hypothesis is that immune cells are activated early in PD, and that inhibiting their pro-inflammatory activities will protect from neurodegeneration

Studying inflammation in early PD patients using PET imaging, blood and CSF studies

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EXERCISE IN PD

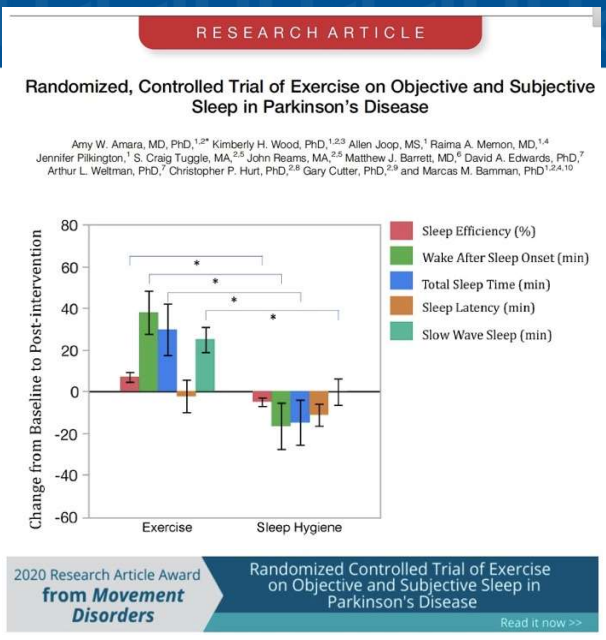
Has established ability to improve PD symptoms:

Park-In-Shape: Remote-based, stationary trainer, 30-45 min three times per week for 6 months. UPDRS improved by 4.2 points.

van der Kolk et al., Lancet Neurol 2019 11:998-1008.

SPARX High-intensity treadmill exercise 4 days per week, 80%-85% maximum heart rate for 6 months. 2.9 point improvement in UPDRS

Schenkman et al., JAMA Neurol 2018 75:219-226.



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WHAT WILL THE PD THERAPY OF THE FUTURE LOOK LIKE?

At-Risk	Prodromal "Pre-PD"	Early PD	Advanced PD

- Gene Specific Therapies (GBA, LRRK2)
- Anti-Synuclein Therapies
- Exercise
- Anti-inflammatory therapies
- Levodopa and other medications
- DBS and other Surgical

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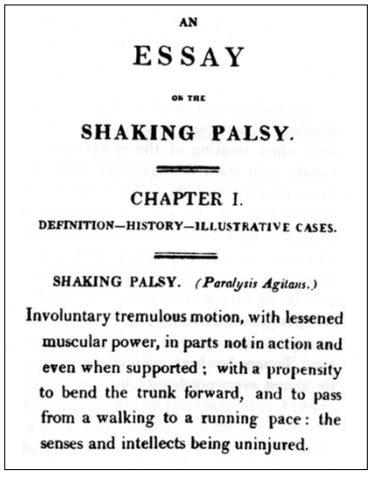
DR. PARKINSON'S 1817 PREDICTION:



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Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

"There appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped."

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QUESTION & ANSWER

David G. Standaert, MD, PhD
John N. Whitaker Professor and Chair of Neurology
The University of Alabama at Birmingham School of Medicine
Birmingham, AL
Chair, APDA Scientific Advisory Board

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CLOSING REMARKS

Rebecca Gilbert, MD, PhD
Vice President, Chief Scientific Officer
American Parkinson Disease Association

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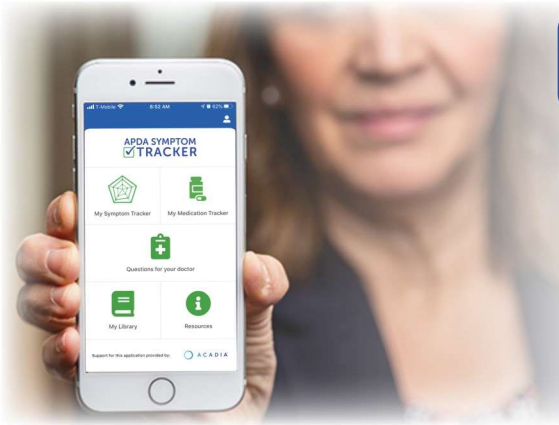
APDA SYMPTOM TRACKER APP



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Introducing an easier way to track your symptoms and manage your care.

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Now Available in Spanish!

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