Parkinson's Disease

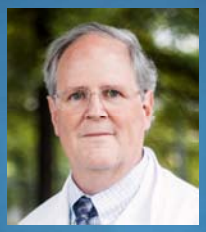
Spotlight on Treatment Advances

Tuesday, January 26, 2016

Welcome and Introductions

Stephanie Paul
Vice President Development and Marketing
American Parkinson Disease Association

Presenter



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

Disclosures: In the last year, Dr. Standaert has served as a consultant for Teva Neuroscience Inc. and Abbvie, Inc.

Parkinson Disease

James Parkinson 1817

AN
ESSAY
ON THE
SHAKING PALSY.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

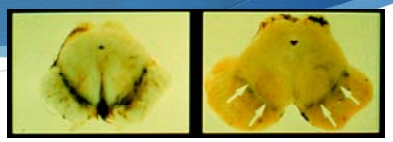
SHAKING PALSY. (*Paralysis Agitans.*)

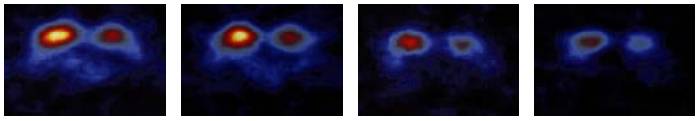
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

4

Classical Features of Parkinson Disease

- Rest Tremor
- Bradykinesia
- Rigidity
- Postural Imbalance

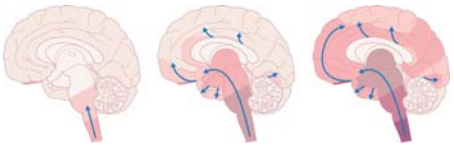




5

Parkinson Disease: Non-motor Features

- **Early (premotor) Features**
  - **Hyposmia – loss of the sense of smell**
  - **REM Behavior Disorder – "acting out dreams"**
  - **Autonomic disturbances – low blood pressure, constipation**
- **Late Features**
  - **Excessive sleepiness**
  - **Depression and anxiety**
  - **Dementia**



6

PD Treatments

Symptomatic Treatments

- Goal is to correct or suppress specific symptoms
- Some good existing treatments of this kind
- Examples
  - levodopa
  - ropinerole
  - pramipexole

7

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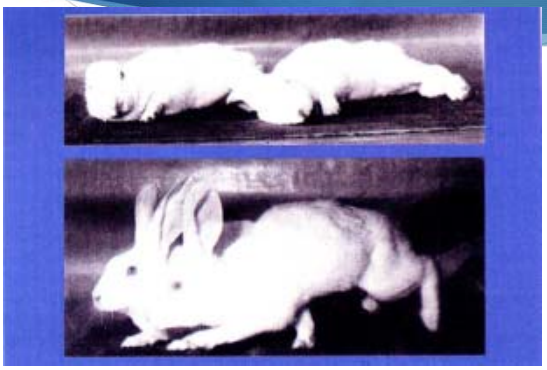
Neuroprotective Treatments

- Goal is to slow or prevent progression of PD
- No proven therapies in this category yet
- Need is increasing:
  - 2016 : 1,500,000
  - 2050: 4,000,000

Estimated PD cases in the US

8

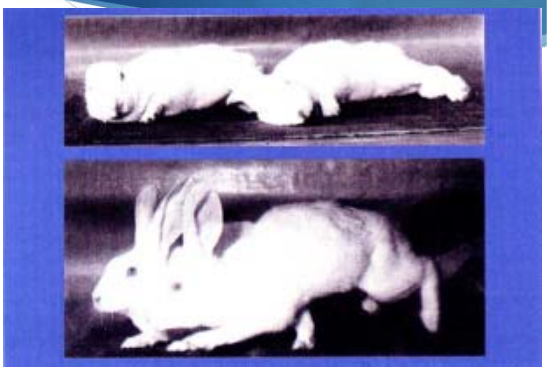
Discovery of Levodopa



Rabbits that became immobile (akinetic) after being reserpinized (upper panel) and then were restored to good mobility after being treated with l-dopa (Figure from Carlsson's Nobel Lecture).

9

Discovery of Levodopa



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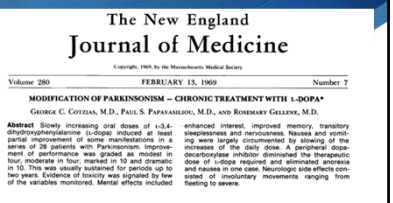
10



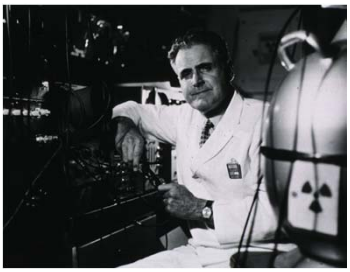
The New England
Journal of Medicine

Volume 280 FEBRUARY 13, 1969 Number 7

MODIFICATION OF PARKINSONISM – CHRONIC TREATMENT WITH L-DOPA*

GEORGE C. COTZIAS, M.D., PAUL S. PAPAVASILIOU, M.D., AND ROSEMARY GELLENE, M.D.

Abstract Slowly increasing oral doses of L-3,4-dihydroxyphenylalanine (L-dopa) induced at least partial improvement of some manifestations in a series of 28 patients with Parkinsonism. Improvement of performance was graded as modest in four, moderate in four, marked in 10 and dramatic in 10. This was usually sustained for periods up to two years. Evidence of toxicity was signaled by few of the variables monitored. Mental effects included enhanced interest, improved memory, transitory sleeplessness and nervousness. Nausea and vomiting were largely circumvented by slowing of the increases of the daily dose. A peripheral dopa-decarboxylase inhibitor diminished the therapeutic dose of L-dopa required and eliminated anorexia and nausea in one case. Neurologic side effects consisted of involuntary movements ranging from fleeting to severe.



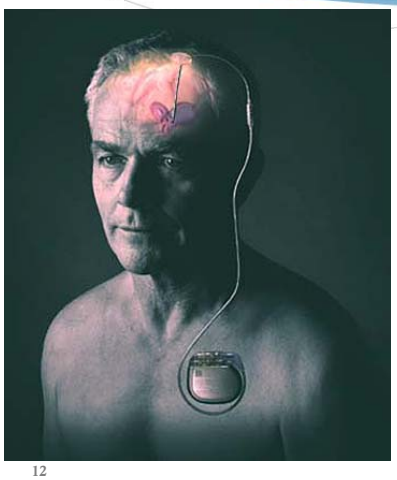
Dr. George C. Cotzias
Brookhaven Lab, 1970

Dopaminergic Treatments for PD

- **Levodopa/carbidopa (Sinemet®)**
- **Pramipexole (Mirapex®)**
- **Ropinerole (Requip®)**
- **Rotigitine (Neupro®)**
- **Apomorphine (Apokyn®)**
- **Others that affect dopamine indirectly:**
  - **Rasagiline (Azilect®)**
  - **Entacapone (Comtan®, Stalevo®)**

11

Deep Brain Stimulation



Mahlon R. DeLong
Emory University
School of Medicine

Alim Louis Benabid
Joseph Fourier University

2014 Lasker Foundation
DeBakey Clinical Medical Research Award

12

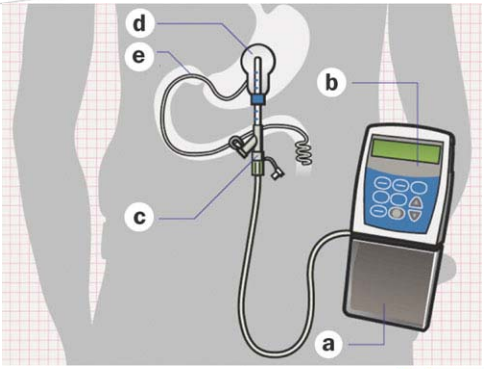
New Treatments – Approved in the Last Year

- Duopa™ - Levodopa/Carbidopa Intestinal Gel
- Rytary™ - Extended Release Levodopa/Carbidopa
- Northera™ - droxidopa

13

Duopa™ Carbidopa/Levodopa Gel

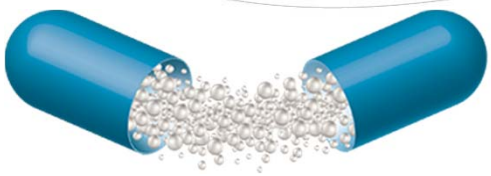
- Carbidopa/Levodopa in a gel form, infused in to the intestines using a pump.
- Intended for patients with wearing off and fluctuations



Richards, L. (2009) Intrajejunal duodopa improves non-motor symptoms *Nat. Rev. Neurol.* doi:10.1038/nrneurol.2009.84

14

Rytary™



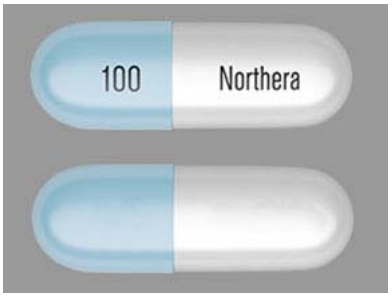
Each capsule contains both:
- Immediate-release beads.
- Extended-release beads.[2]

- Controlled release levodopa/carbidopa
- Controls symptoms in early PD
- Reduces wearing off in advanced PD
- Side effects similar to levodopa/carbidopa

15

Northera™ (droxidopa)

- Approved for treatment of orthostatic hypotension in Parkinson disease
- One of several treatments for low blood pressure and dizziness in PD



16

What is Coming Soon?

Some Highlights From Clinicaltrials.gov

17

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Some Highlights From Clinicaltrials.gov

- More ways to deliver dopamine
  - Inhaled levodopa
  - Levodopa "accordion pill"
  - Apomorphine – infusion, nasal, "strips"

18

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- Treatments for wearing off and dyskinesia
  - Improved amantidine
  - A2a antagonists – Istradefyline, Tozadenant

19

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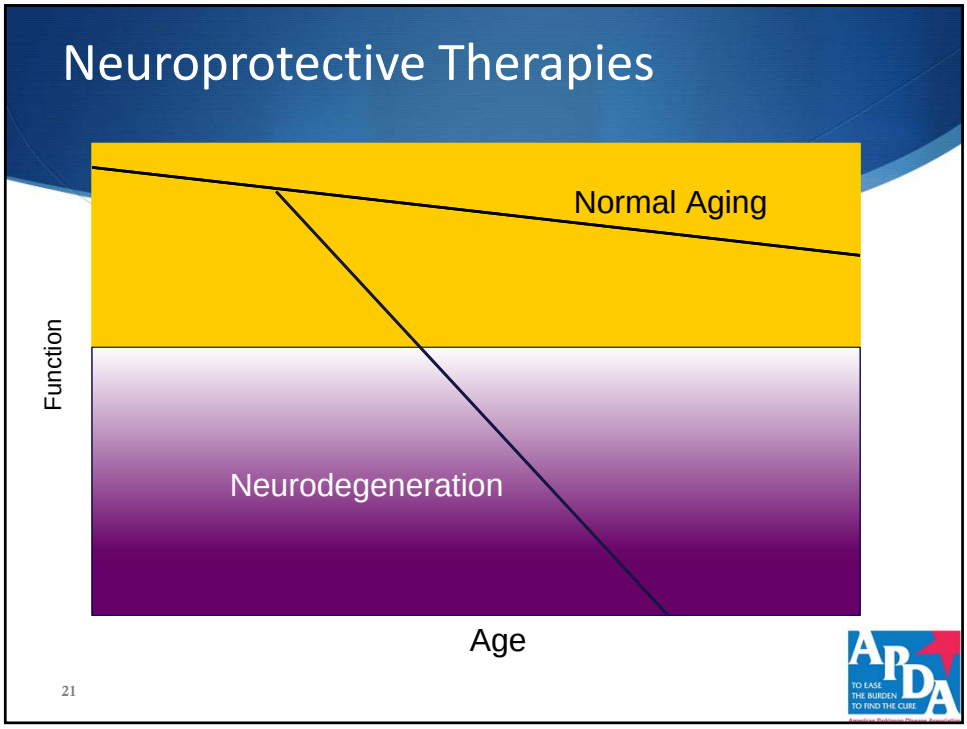
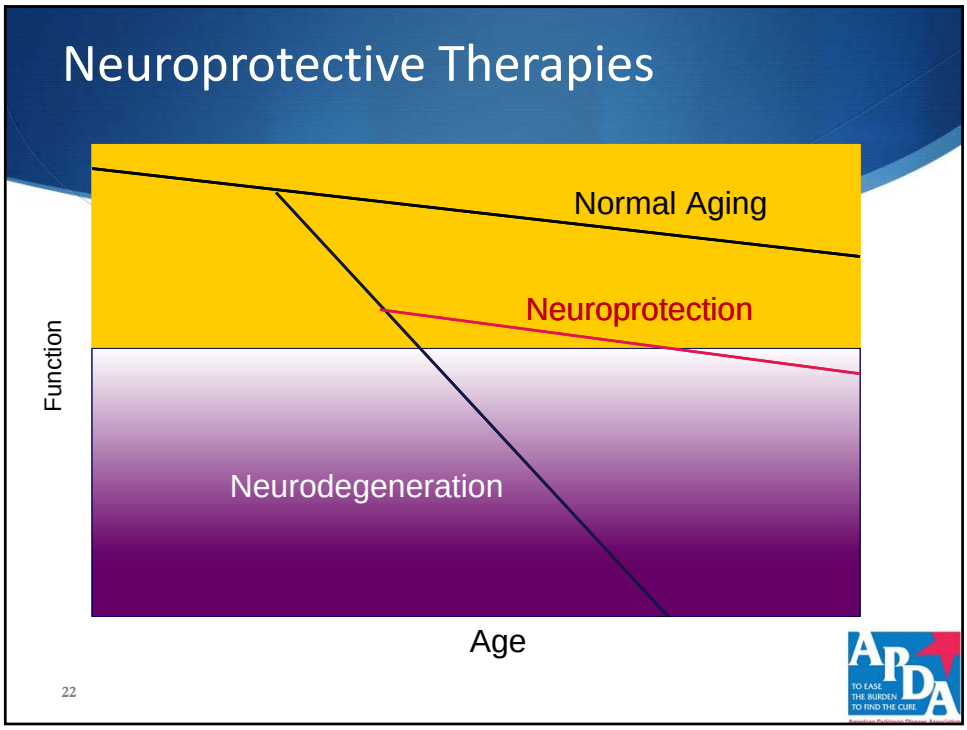
- Exercise
  - What is the right "prescription" for exercise?

20


Neuroprotective Therapies
Normal Aging
Function
Neurodegeneration
Age
21


Neuroprotective Therapies
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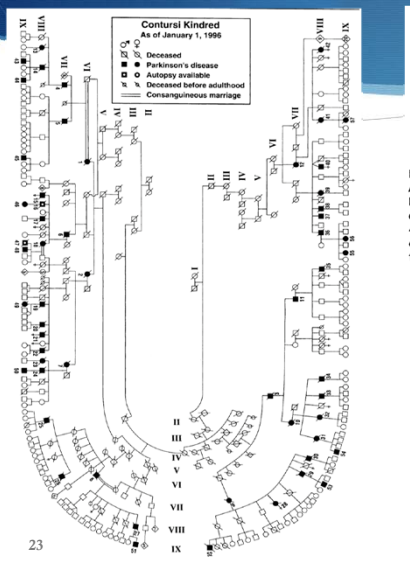
22

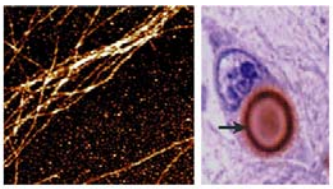
Alpha-synuclein, a Gene for PD



Mapping of a Gene for Parkinson's Disease to Chromosome 4q21–q23

Mihael H. Polymeropoulos,* Joseph J. Higgins, Lawrence I. Golbe, William G. Johnson, Susan E. Ide, Giuseppe Di Iorio, Giuseppe Sanges, Edward S. Stenroos, Lana T. Pho, Alejandro A. Schaffer, Alice M. Lazzarini, Robert L. Nussbaum, Roger C. Duvoisin

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting approximately 1 percent of the population over age 50. Recent studies have confirmed significant familial aggregation of PD and a large number of large multicase families have been documented. Genetic markers on chromosome 4q21–q23 were found to be linked to the PD phenotype in a large kindred with autosomal dominant PD, with a $Z_{max} = 6.00$ for marker *D4S2380*. This finding will facilitate identification of the gene and research on the pathogenesis of PD.

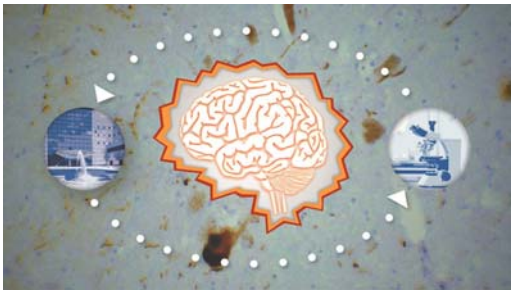


Science; Nov 15, 1996; 274, 5290

23

PD and Inflammation: *turning down the heat*

- Too much synuclein in the brain activates the immune system
- Immune cells and antibodies damage dopamine neurons
- Would blocking inflammation slow the progress of PD?



24

Current Trials of Neuroprotection

- **Isradipine – drug used for hypertension**
- **Urate – an antioxidant found in blood**

25

Neuroprotection: The Next wave

- **Treatments to reduce alpha-synuclein in the brain**
  - **Vaccines**
  - **Drugs that activate clearance (nilotinib?)**

26

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27

Neuroprotection: The Next wave

- Treatments to reduce alpha-synuclein in the brain
  - Vaccines
  - Drugs that activate clearance (nilotinib?)
- Drugs that block inflammation
- Neuro-restoration
  - Growth Factors (GDNF?)
  - Transplants (Stem Cells?)

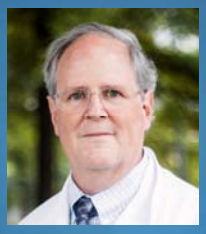
28

Summary

- We are fortunate that we already have treatments that can help with many of the symptoms of PD
  - Dopamine-based treatments
  - DBS
- Soon, we will see better treatments for PD symptoms
  - More effective ways to deliver dopaminergic drugs
  - Treatments for non-motor symptoms
- The "cutting edge" of research is the search for neuroprotection
  - Anti-oxidant
  - Anti-synuclein
  - Anti-inflammatory
  - Others

29

Question & Answer



David G. Standaert, MD, PhD
John N. Whitaker Professor and Chair of Neurology
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Closing Remarks

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For additional information, answers to your questions, or resources

Please visit our website
www.apdaparkinson.org

Or call us
1-800-223-2732

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