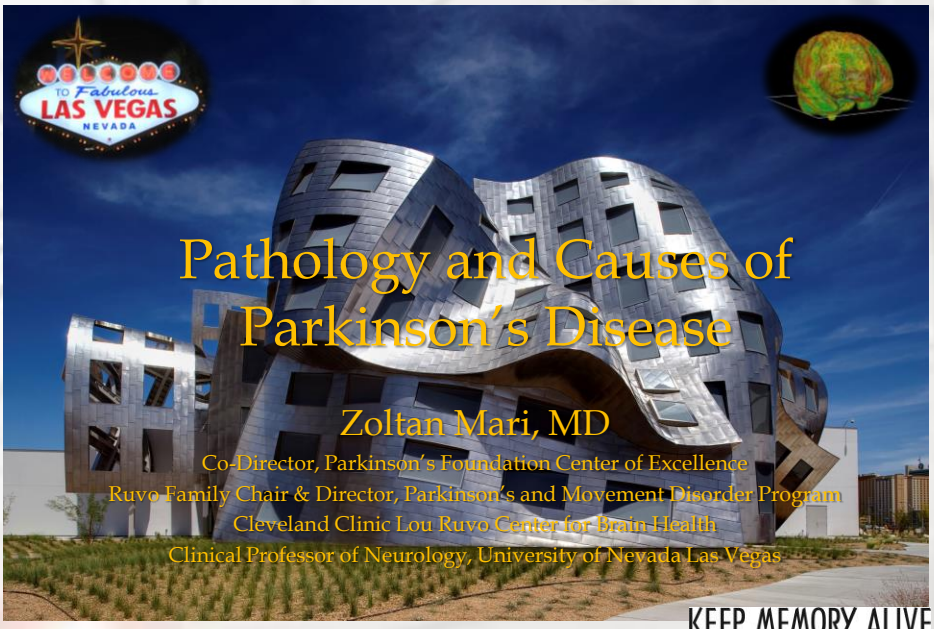

Pathology and Causes of Parkinson's Disease

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Ruvo Family Chair & Director, Parkinson's and Movement Disorder Program
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Cleveland Clinic

KEEP MEMORY ALIVE
Supporting the Mission of Cleveland Clinic Lou Ruvo Center for Brain Health
ALZHEIMER'S | HUNTINGTON'S | PARKINSON'S
MULTIPLE SYSTEM ATROPHY | MULTIPLE SCLEROSIS

Disclosures

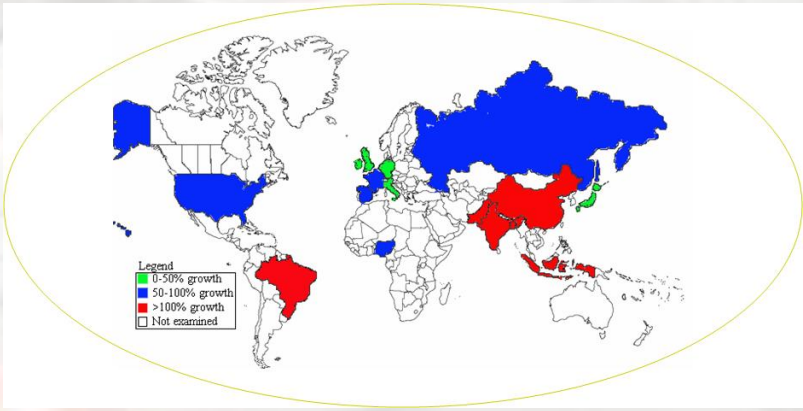
- Z. Mari is a full-time staff at Cleveland Clinic and is representing his own opinions and NOT that of CC
- Z. Mari received (institutional) research support from:
  - National Institutes of Health
  - Michael J. Fox Foundation
  - National Parkinson Foundation (including PKG)
  - AbbVie/Solvay Pharmaceuticals
  - Great Lakes Neurotechnologies
  - AVID Radiopharmaceuticals
- Z. Mari has served as a paid consultant for GB Sciences, Sanofi Genzyme, NeuroReserve, Sensory Cloud, and Global Kinetics Corporation
- Z. Mari is founder and CMO for Neuraly, Inc & Z NeuroSciences, LLC

Overview

- The growing public health impact of Parkinson disease worldwide
- Some historical concepts – how long have we recognized PD?

The Burden of Parkinson Disease Is Growing

Change in number of people with Parkinson disease in the world's most populous nations from 2005 to 2030*

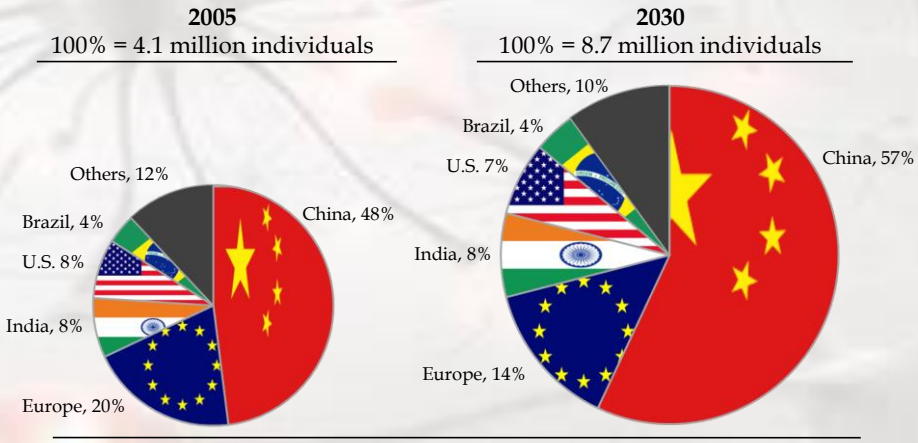


*Among individuals over 50 in the world's ten most and Western Europe's five most populous nations

Source: Neurology 2007;68:384-6

The Burden Affects the Whole World

Distribution of individuals with Parkinson disease by country, 2005 and 2030*



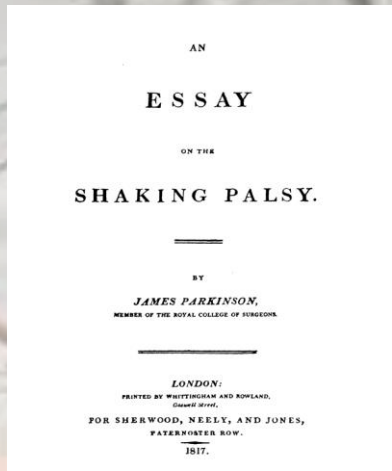
*Among individuals over 50 in the world's ten most and Western Europe's five most populous nations

Source: Neurology 2007;68:384-6

History of Parkinson Disease & Its Treatments

- Reviewing the history of treatment is a source of optimism
- No treatment was available at all throughout most of human history
- Few people in ancient and medieval times actually lived long to have PD (mean age of onset 60)
- Today, we have a host of treatment options including surgical and non-surgical
- The pace of discovery accelerates and "disease modifying" or "neuroprotective" treatments, which remain elusive, are the "holy grail" of present day therapy research efforts

Averroes, the Islamic philosopher who was one of the first to study Parkinson's disease.



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Goswell Street,

FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

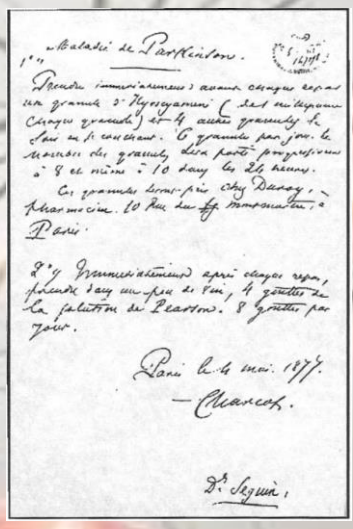
"But although, at present, uninformed as to the precise nature of the disease, still it ought not to be considered as one against which there exists no countervailing remedy. On the contrary, there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped." James Parkinson, An Essay on the Shaking Palsy, 1817

First Parkinson Therapies

FAUTEUIL TRÉPIDANT EN USAGE A LA SALPÊTRIÈRE POUR LE TRAITEMENT DE LA PARALYSIE AGITANTE

FIGURE 19 Vibratory therapy. Charcot observed that patients with Parkinson's disease experienced a reduction in their rest tremor, after taking a carriage ride or after horseback riding. He developed a therapeutic vibratory chair that simulated the rhythmic shaking of a carriage (18). A vibratory helmet to shake the head and brain was later developed. Such therapies were not utilized widely and have not been studied in modern times.

First Parkinson Therapies



Prescription dated 1877. Treating Parkinson's disease, Charcot used belladonna alkaloids (agents with potent anticholinergic properties) as well as rye-based products that had ergot activity, a feature of some currently available dopamine agonists (21). Charcot's advice was empiric and preceded the recognition of the well-known dopaminergic/cholinergic balance that is implicit to normal striatal neurochemical activity.

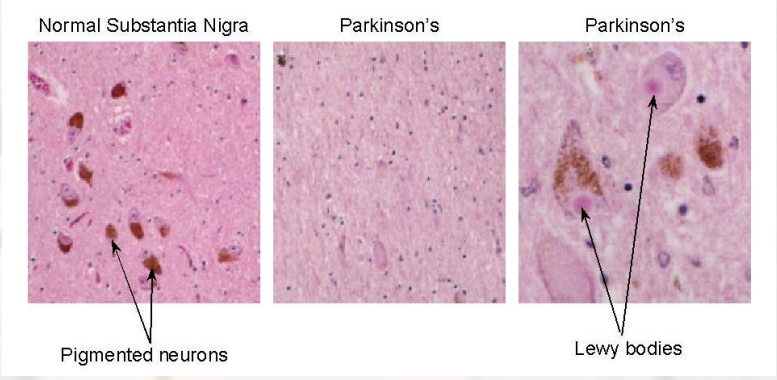
Review of the Development of Modern Parkinson Therapies

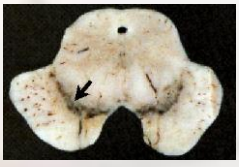
- By the 1940s and 50s, neurosurgical treatments were being used to treat PD
- In 1960, dopamine was found to be decreased in the brains of people with PD
- In 1961 to 1962, we get the first successful trials of levodopa
- By 1968, levodopa pills were available for use. This of course was a dramatic breakthrough in treatment for PD. Levodopa therapy worked so well for some patients that they could live relatively normal lives. It was soon discovered, however, that levodopa had unpleasant side effects and could not prevent progression of the disease so new drugs were developed to treat these side effects and to slow progression of the disease
- Bromocriptine and the MAO-B inhibitor deprenyl were developed in the 1970s
- Pergolide, selegiline and antioxidant therapies were developed in the 1980s
- Meanwhile, deep brain stimulation therapies were introduced in the late 1980s and neurosurgical techniques were refined in the 80s and 90sThe FDA approved use of deep brain stimulation of the subthalamic nucleus for treatment of tremor in 1997
- New dopamine agonists, pramipexole and ropinirole were approved for use in that year as well
- Tolcapone and Entacapone were approved for use in the following year 1998
- In 2006, a new MAO-B inhibitor was developed called rasagiline
- In 2007 a dopamine patch was developed (rotigotine) to deliver dopamine to the bloodstream in a more uniform manner thus reducing side effects
- Many experimental approaches being tested

Introduction to PD: the Concept of a "Disease" and Its Pathology

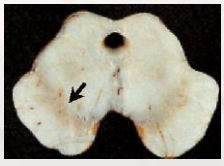
- Population versus individual-level etiology and the forever debate between "splitters" & "lumpers"
  - Each individual patient is different from another, genetically, epigenetically, environmentally, and from the perspective of interactions between these – the significance of comorbidities, "phenocopies", and natural variation of the "same thing"
  - Understanding the concept of "risk" as opposed to "cause"
  - Risk is a probability, which is affected by a number of factors, many of which we know, many more we do not know
  - Risk can be conceptualized at birth (based on genetic/epigenetic factors and embryonic exposures), but it is not stable, it is a dynamic concept – risk typically grows during lifetime, but hopefully it can also be reduced
  - The proper understanding of risk and factors that affect it is critical for our better approaches to altering disease risk
  - While we may understand and describe these factors at the population level and in general terms for PD in general, there is a loose connection between such information and how that applies specifically in cases of individual patients
  - Science is not yet developed to fully and accurately characterize and describe all of these factors and determine risk at the individual level or attribute proportional and specific causal relationship between every genetic and environmental factor at play – it is a process too complex for our current state of science
  - As this is becoming possible, our disease modifying trials will increasingly apply "stratified" recruitment; rather than enrolling entire populations or inclusion based on medical and clinical criteria irrelevant to the mechanism of therapy
- Pathology – the historical primary pillar of defining "disease" while more specific than clinical phenotype, it still is "just" part of the phenotype, which may be subject to the same challenges (phenocopies, etc) and while undoubtedly a crucial part of disease, may not automatically be the be-all/end-all ultimate correlate of specific disease modification

PD Basics: Pathology



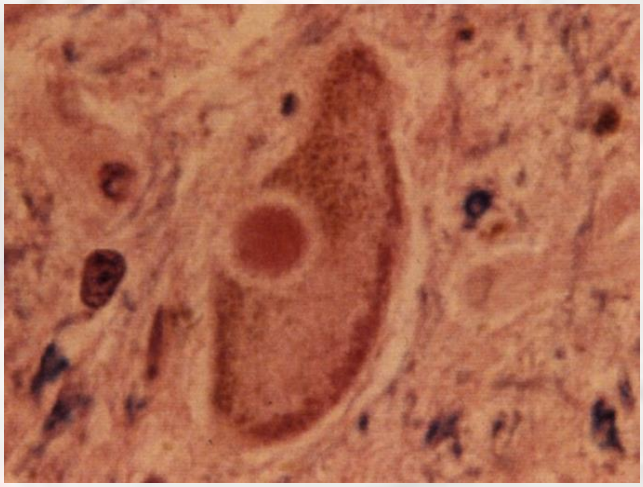


Normal: Nigra (pigment)



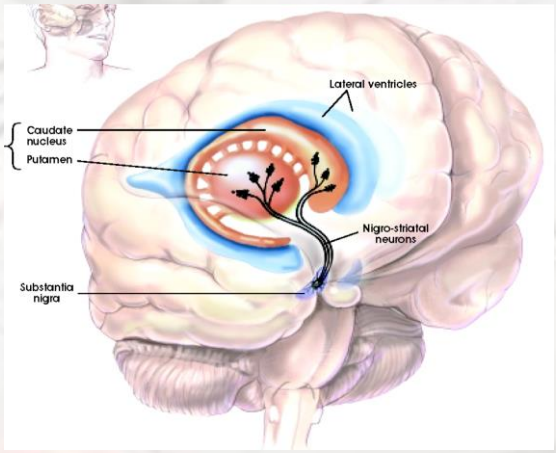
Parkinson: Nigra (lost pigment)

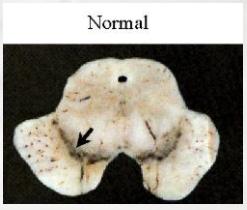
Cellular Pathology of Parkinson's disease: the Lewy Body

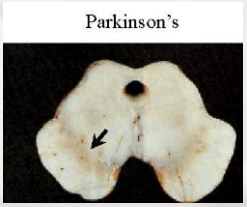


Lang & Lozano 1998

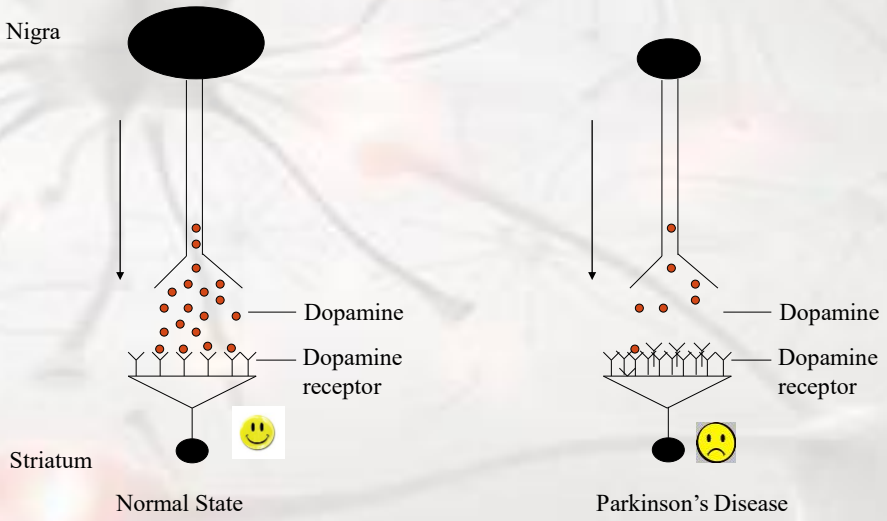
Gross Pathology of Parkinson's Disease



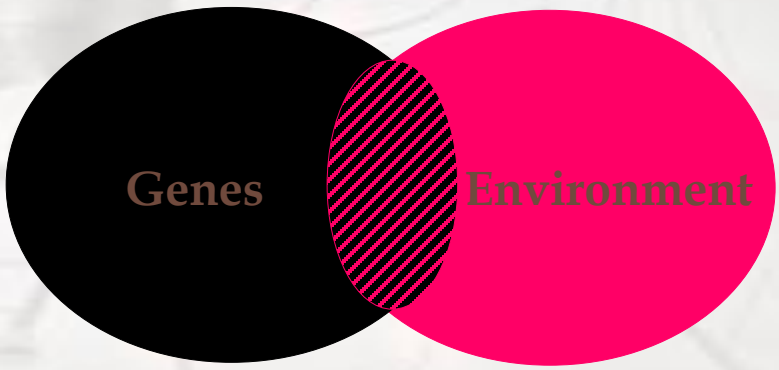




Neuropharmacology of PD



Parkinson's Disease Etiology



$$P = G + E$$

Parkinson disease: Causes

(for individual patients we can NOT say why they have PD)

GENETIC FACTORS?

- Single genes that cause PD, passed down in families (rare): see next slide
- Risk factors genes, more common and likely a large number of these
- Twins: identical more than fraternal twins will have similar PD risk
- 10% have a first degree relative with PD
- Young onset is more likely to have genetic factors

ENVIRONMENTAL FACTORS?

- Increasing age
- Brain trauma?
- Previous infections, other health conditions?
- Toxins: pesticides, metals, carbon monoxide, MPTP drug
- Rural living, well water
- Delaying PD?: smoking (whites, Asians), coffee?

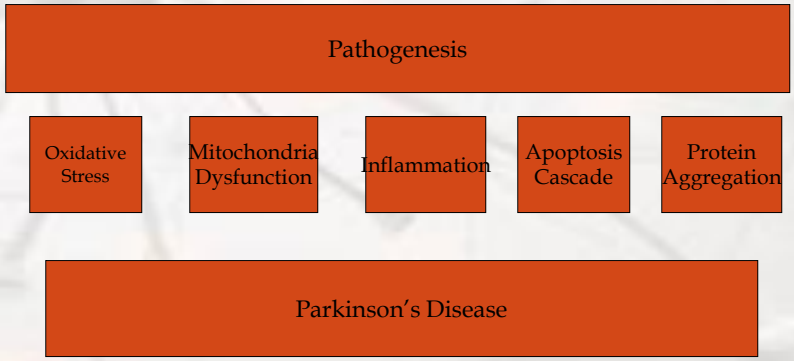
Causes of PD: Genes

Proteins & Gene loci:

- Alpha-synuclein (PARK1,4)
- LRRK2 (PARK8)
- Parkin (PARK2)
- PINK1 (PARK6)
- DJ-1 (PARK7)
- ATP13A2 (PARK9)

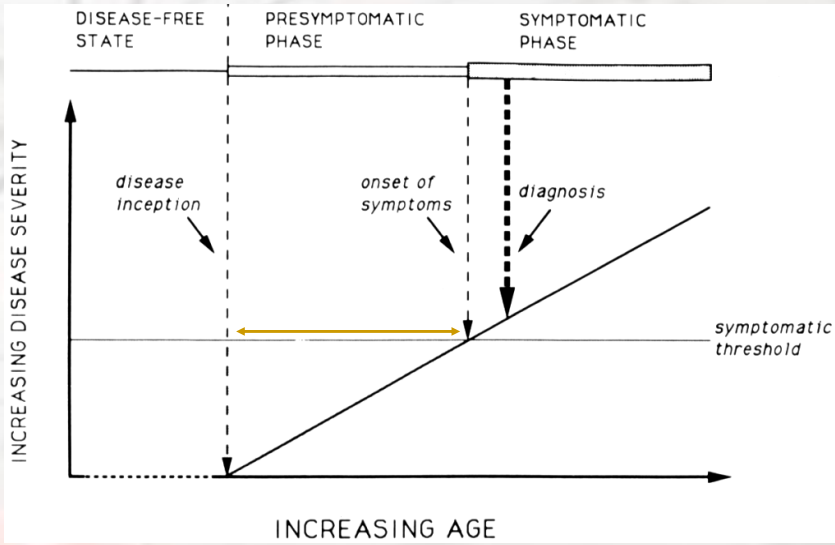
Cause of Parkinson's Disease

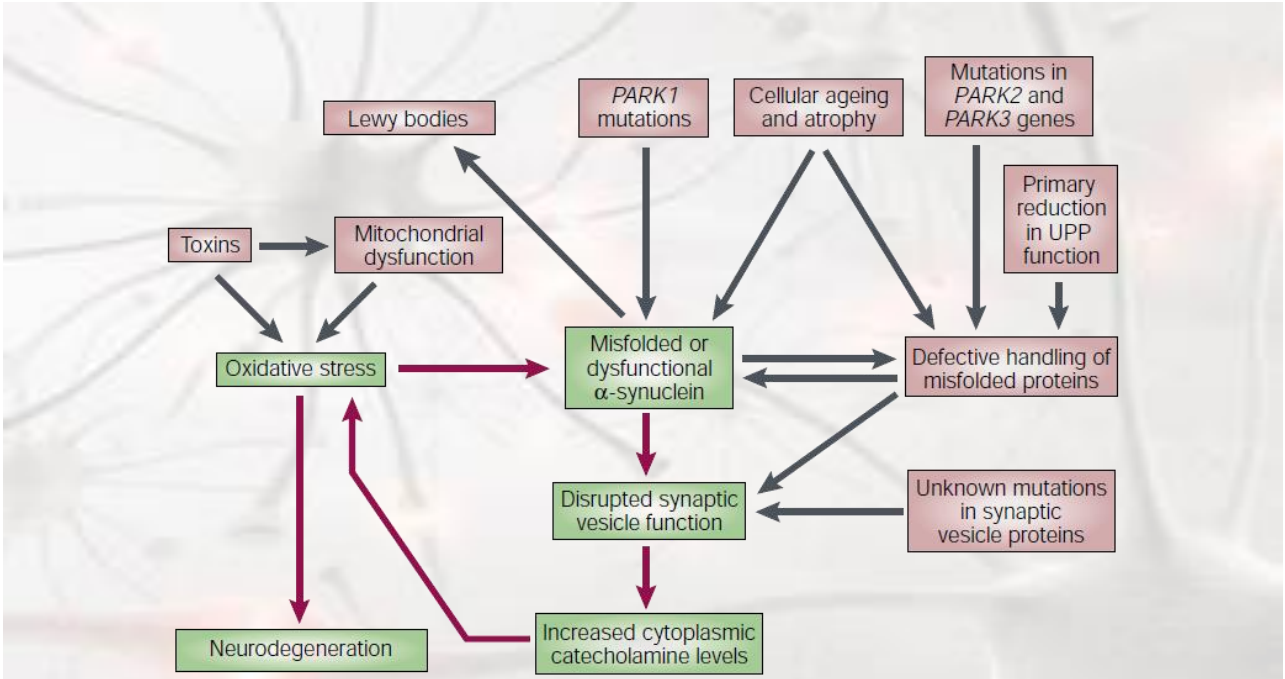
*Genetics *Age *Environment



"Parkinson's Disease: The Life Cycle of the Dopamine Neuron", The New York Academy of Sciences, 2003

Progression of Parkinson's disease

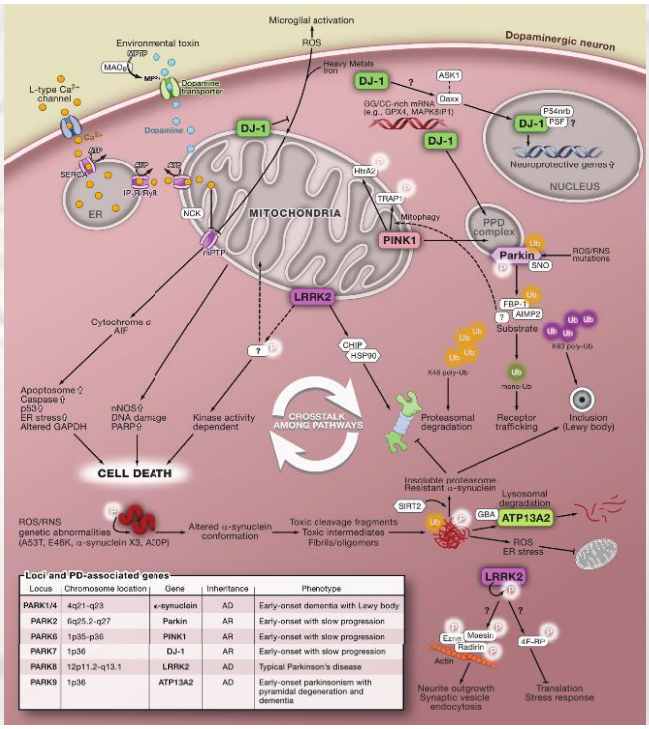




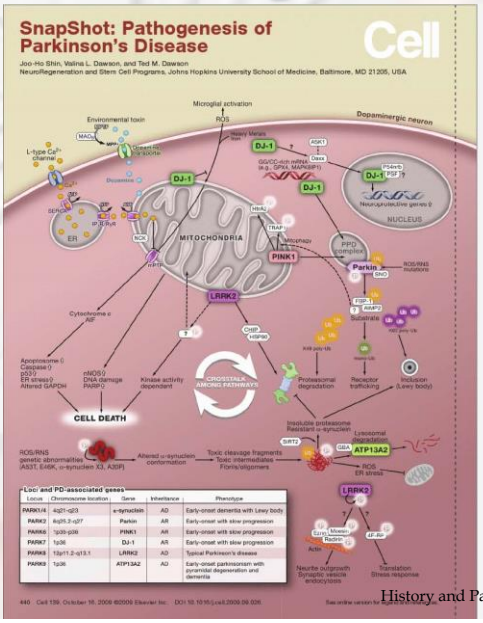
Basic Science: Inside the Neurons

1. DNA (rough recipe)
2. mRNA (compact recipe)
3. unfolded protein (string-like)
4. folded protein (3-D *functioning* structure)

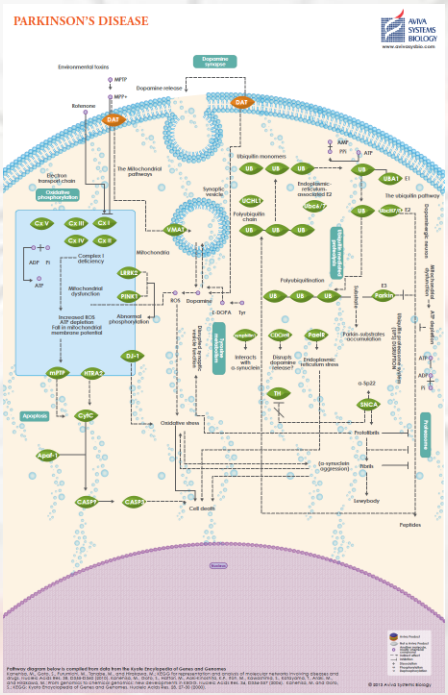
Problem: Misfolded proteins can group together and gum-up the cell (toxic aggregation)



Pathogenesis of PD: in 2009



History and Pathology of PD

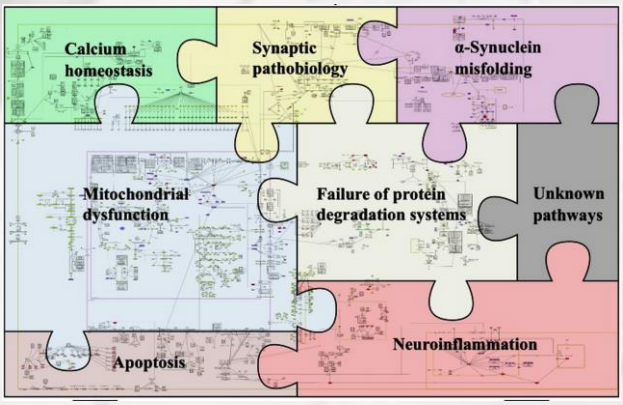


PD Molecular Pathways (as of 2013)

- Oxidative phosphorylation
- Apoptosis
- Tyrosine metabolism
- Ubiquitin mediated proteolysis
- Proteasome system

History and Pathology of PD

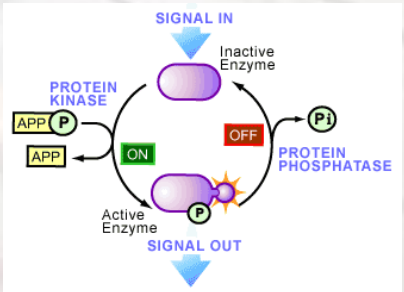
Neuroprotection: Biological systems involved in PD



Fujita KA, Ostaszewski M, Matsuoka Y, Ghosh S, Glaab E, Trefois C, et al. Integrating pathways of parkinson's disease in a molecular interaction map. *Mol. Neurobiol.* 2014;49:88-102

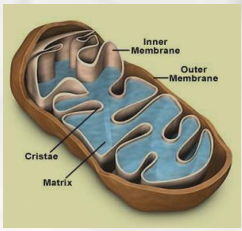
Cell Damage: Protein Activation

- Proteins are activated (turned "on") by Kinases and deactivated (turned "off") by Phosphatases, by adding or removing a "tag"
- Known genes and toxins can have bad effects on these kinases and phosphatases.
- However, these may become medication targets



Cell Damage: Mitochondria

- Mitochondria: the cell's power plant
  - In the process of creating energy for the cell, mitochondria can produce harmful byproducts: free radicals and reactive oxidative molecules (especially if not working properly)
  - Mitochondrial are dysfunctional in PD either because of genetic, toxic, or other reasons

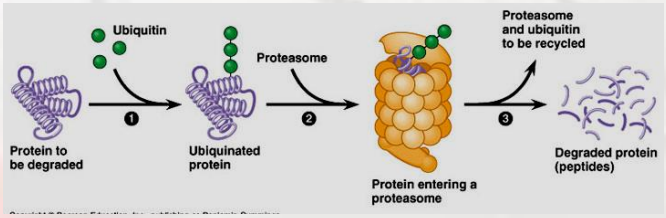


Cell Damage: Trafficking

- A "highway" system of microtubules exists to direct things where they need to go
- Other targeting systems are utilized
- Known genes and toxins in PD damage this system

Cell Damage: Waste System

- Proteasomes: the trash system that break down worn out parts of the cell including proteins
- Genetic and toxic factors can injure proteasomes
- Improper disposal of worn out cellular parts can lead to abnormal protein aggregation and mitochondrial dysfunction.



Prion Hypothesis

- Recent reports demonstrate that a single intracerebral inoculation of misfolded a-synuclein can induce Lewy-like pathology in cells that can spread from affected to unaffected regions and can induce neurodegeneration with motor disturbances in both transgenic and normal mice.
- Further, inoculates derived from the brains of elderly a-synuclein–overexpressing transgenic mice have now been shown to accelerate the disease process when injected into the brains of young transgenic animals.

PNAS

CrossMark

Evidence for α-synuclein prions causing multiple system atrophy in humans with parkinsonism

Stanley B. Prusiner[a,b,c,1], Amanda L. Woerman[a], Daniel A. Mordes[d], Joel C. Watts[a,b,2], Ryan Rampersaud[e], David B. Berry[e], Smita Patel[e], Abby Oehler[e], Jennifer K. Lowe[f], Stephanie N. Kravitz[f], Daniel H. Geschwind[f,g], David V. Glidden[h], Glenda M. Halliday[i], Lefkos T. Middleton[j], Steve M. Gentleman[k], Lea T. Grinberg[b,l], and Kurt Giles[a,b]

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Contributed by Stanley B. Prusiner, July 22, 2015 (sent for review May 19, 2015)

Prions are proteins that adopt alternative conformations that become self-propagating; the PrP^{Sc} prion causes the rare human disorder Creutzfeldt–Jakob disease (CJD). We report here that multiple system atrophy (MSA) is caused by a different human prion composed of the α-synuclein protein. MSA is a slowly evolving disorder characterized by progressive loss of autonomic nervous system function and often signs of parkinsonism; the neuropathological hallmark of MSA is glial cytoplasmic inclusions consisting of filaments of α-synuclein. To determine whether human α-synuclein forms prions, we examined 14 human brain homogenates for transmission to cultured human embryonic kidney (HEK) cells expressing full-length, mutant human α-synuclein fused to yellow fluorescent protein (α-syn140*A53T–YFP) and TgM83$^{+/-}$ mice expressing α-synuclein (A53T). The TgM83$^{+/-}$ mice that were hemizygous for the mutant transgene did not develop spontaneous illness; in contrast, the TgM83$^{+/+}$ mice that were homozygous developed neurological dysfunction. Brain extracts from 14 MSA cases all transmitted neurodegeneration to TgM83$^{+/-}$ mice after incubation periods of ∼120 d, which was accompanied by deposition of α-synuclein within neuronal cell bodies and axons. All of the MSA extracts also induced aggregation of α-syn*A53T–YFP in cultured cells, whereas none of six Parkinson's disease (PD) extracts or a control sample did so. Our findings argue that MSA is caused by a unique strain of α-synuclein prions, which is different from the putative prions causing PD and from those causing spontaneous neurodegeneration in TgM83$^{+/-}$ mice. Remarkably, α-synuclein is the first new human prion to be identified, to our knowledge, since the discovery a half century ago that CJD was transmissible.

neurodegeneration | Parkinson's disease | synucleinopathies | strains

Looking back almost 50 y ago, kuru was the first human prion disease to be transmitted to an experimental animal (1). Subsequently, Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker disease, and fatal familial insomnia were transmitted to nonhuman primates or transgenic (Tg) mice; all of these disorders were eventually found to be caused by PrP^{Sc} prions that were initially discovered in hamsters with experimental scrapie. Attempts to transmit other neurodegenerative diseases, including Alzheimer's and Parkinson's, to monkeys were disappointing; none of the animals developed signs of neurological dysfunction, and none showed recognizable neuropathological changes at autopsy (2).

In 1960, Milton Shy and Glenn Drager described two male patients suffering from orthostatic hypotension, additional forms of autonomic insufficiency, and a movement disorder resembling Parkinson's disease (PD). They also found an additional 40 cases of idiopathic hypotension in the literature, which shared many features with their patients. Nine years later, Graham and Oppenheimer suggested that Shy–Drager syndrome should be combined with striatonigral degeneration and olivopontocerebellar atrophy and that these three entities should be called multiple system atrophy (MSA) (3). They presciently argued that all three disorders were likely caused by a similar neurodegenerative process. Two decades passed before support for this hypothesis began to emerge when the brains of 11 MSA patients were reported to contain silver-positive accumulations or glial cytoplasmic inclusions (GCIs) primarily in oligodendrocytes (4). The nature of these GCIs remained elusive for another decade until three groups reported that GCIs exhibited positive immunostaining for α-synuclein (5–7). The discovery that MSA is a synucleinopathy followed a study reported 1 y earlier showing that Lewy bodies in PD contain α-synuclein by immunostaining (8). Such investigations were prompted by molecular genetic studies showing genetic linkage between the A53T point mutation in α-synuclein and inherited PD (9).

MSA is a sporadic, adult-onset, progressive neurodegenerative disorder with an annual incidence of ∼3 per 100,000 individuals over the age of 50 (10, 11). The duration of MSA is generally 5–10 y and is substantially shorter than most cases of PD, which

Significance

Prions are proteins that assume alternate shapes that become self-propagating, and while some prions perform normal physiological functions, others cause disease. Prions were discovered while studying the cause of rare neurodegenerative diseases of animals and humans called scrapie and Creutzfeldt–Jakob disease, respectively. We report here the discovery of α-synuclein prions that cause a more common neurodegenerative disease in humans called multiple system atrophy (MSA). In contrast to MSA, brain extracts from Parkinson's disease (PD) patients were not transmissible to genetically engineered cells or mice, although much evidence argues that PD is also caused by α-synuclein, suggesting that this strain (or variant) is different from those that cause MSA.

Author contributions: S.B.P., A.L.W., and K.G. designed research; A.L.W., J.C.W., R.R., D.B.B., S.P., A.O., and S.N.K. performed research; D.A.M., G.M.H., L.T.M., and S.M.G. contributed new reagents/analytic tools; S.B.P., A.L.W., J.C.W., R.R., D.B.B., J.K.L., D.H.G., D.V.G., L.T.G., and K.G. analyzed data; and S.B.P., A.L.W., R.R., and K.G. wrote the paper.

The authors declare no conflict of interest.

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www.pnas.org/cgi/doi/10.1073/pnas.1514475112

Prion Hypothesis

- Fetal adrenal graft cells develop Lewy bodies

nature medicine

Brief Communication

Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation

Jia-Yi Li, Elisabet Englund, Janice L Holton, Denis Soulet, Peter Hagell, Andrew J Lees, Tammaryn Lashley, Niall P Quinn, Stig Rehncrona, Anders Björklund, Håkan Widner, Tamas Revesz & Olle Lindvall & Patrik Brundin

Two subjects with Parkinson's disease who had long-term survival of transplanted fetal mesencephalic dopaminergic neurons (11–16 years) developed α-synuclein–positive Lewy bodies in grafted neurons. Our observation has key implications for understanding Parkinson's pathogenesis by providing the first evidence, to our knowledge, that the disease can propagate from host to graft cells. However, available data suggest that the majority of grafted cells are functionally unimpaired after a decade, and recipients can still experience long-term symptomatic relief.

Prion Hypothesis

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Spreading of pathology in neurodegenerative diseases: a focus on human studies

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Abstract

The progression of many neurodegenerative diseases is thought to be driven by the template-directed misfolding, seeded aggregation and cell–cell transmission of characteristic disease-related proteins, leading to the sequential dissemination of pathological protein aggregates. Recent evidence strongly suggests that the anatomical connections made by neurons — in addition to the intrinsic characteristics of neurons, such as morphology and gene expression profile — determine whether they are vulnerable to degeneration in these disorders. Notably, this common pathogenic principle opens up opportunities for pursuing novel targets for therapeutic interventions for these neurodegenerative disorders. We review recent evidence that supports the notion of neuron–neuron protein propagation, with a focus on neuropathological and positron emission tomography imaging studies in humans.

Neurodegenerative diseases are a major cause of disability and premature death among older people worldwide[1–3]. Although these diseases, for which there are currently no disease-modifying therapies, show a great diversity of clinical phenotypes, they share a common pathological hallmark — the accumulation of characteristic proteins into insoluble aggregates in or among selectively vulnerable neurons and glial cells.

Aggregates of the phosphorylated microtubule-associated protein tau in neurofibrillary tangles and neuropil threads, together with deposits of amyloid-β (Aβ), are characteristic of sporadic Alzheimer disease (AD). Tau pathology alone also characterizes a subgroup of

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Competing interests statement
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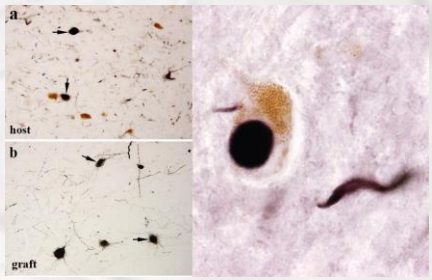

- **(Left)** Alpha-synuclein–stained Lewy bodies and Lewy neurites are shown in (a) host substantia nigra neurons and (b) embryonic dopamine neurons that had been implanted into the striatum of a PD patient 14 years earlier.
- **(Right)** This is a high-power view of an a-synuclein–stained Lewy body and a Lewy neurite in grafted mesencephalic dopamine neurons.

Reading on history of PD therapies:

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2. Goetz, C.G. (2007). Early Iconography of Parkinson's Disease. In: *Handbook of Parkinson's Disease: Fourth Edition*, Edited by Rajesh Pahwa, MD and Kelly E. Lyons, MD. New York: Informa Healthcare; pps. 1-17.
3. The Pace of Innovation in Treatment of Parkinson's Disease; from Patrick McNamara, Ph.D., former About.com Guide Updated April 14, 2009