Many Causes of Parkinson's Disease: An Epidemiologist's Perspective

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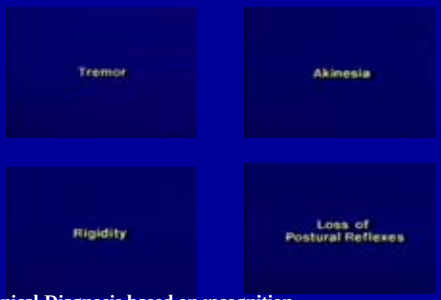
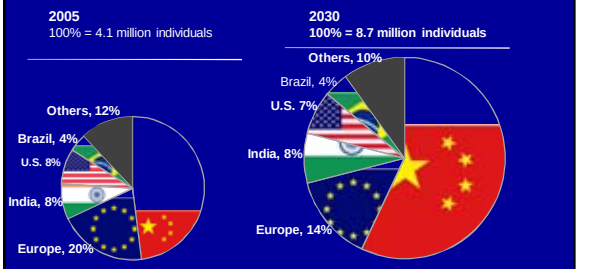
Disclosures: Consultant to Impax, Adamas & Abbvie Pharmaceuticals

Parkinson's Disease: Cardinal Signs



- Clinical Diagnosis based on recognition
- Differentiate from other disorders causing tremor, slowness, imbalance

PD expected to more than double by 2030



PD projections for persons aged > 50 in the world's ten most and Western Europe's five most populous nations

(Dorsey et al, 2007)

PD expected to more than double by 2030

2005
100% = 4.1 million individuals

2030
100% = 8.7 million individuals

CRITICAL NEEDS:

Understand PD etiology to:

-Identify ways to slow or prevent PD onset

-Identify people at risk for PD to allow early intervention à "prodromal PD"

PD projections for persons aged > 50 in the world's ten most and Western Europe's five most populous nations

(Dorsey et al, 2007)

What Causes Parkinson's Disease?

MPTP-Induced Parkinsonism

The First Big Clue Langston, Ballard, Tetrud 1983

Cluster of subacute parkinsonism in young narcotics addicts

Similar to PD:

- Same signs as PD
- Progressive worsening in some
- Improves with l-dopa
- Same side effects from l-dopa

BUT

- MPTP injection is rare
- Not a likely cause of PD

MPTP-Induced Parkinsonism

The toxicologic effects of MPTP suggested that similar chemicals, present in the environment, could cause PD

A Large Kindred with Autosomal Dominant Parkinson's Disease

Lawrence I. Golbe, MD,* Giuseppe Di Iorio, MD,† Vincenzo Bonavita, MD,† Douglas C. Miller, MD, PhD,‡ and Roger C. Duvoisin, MD*

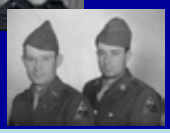
Ann Neurol 1990;27:276–282

"These findings favor monogenic autosomal dominant inheritance and show reason to argue against a multifactorial etiology or heteroplasmy."

Duvoisin & Johnson Brain Pathology 1992

Is Parkinson's Disease a monogenic disorder?

Twins: Mother Nature's Controlled Study



NAS/NRC WWII VETERAN TWINS ROSTER 31,848 TWINS BORN 1917 - 1927

- MZ twins share ~100% of genes
- DZ twins share ~50% of genes

Hypothesis: If Parkinson's disease is primarily a genetic disorder, then concordance in MZ twins should be > than in DZ twins

Results: MZ & DZ concordance similar ;
Except young onset MZ > DZ

Conclusion: Environment is an important contributor to the cause of most PD

Tanner, et al, JAMA, 1999

Genes and PD – Monogenic Forms

Well – Validated Parkinson's Disease Associated Genes Dominant Inheritance

GENE	ONSET	MUTATIONS	RISK VARIANTS	
SNCA	Early 40 – 50 years	A53T, A30P, E46K , Duplications, triplications	Promotor Rep 1, 5', 3'	Alpha-synuclein protein product; Mutation Penetrance ~100%
LRRK2	Typical/late > 50 years	G2019S(AJ, Arab),R1441x (Basque), ?	G2385R, R1628P (Asian)	Most common; 1-2% U.S. PD ; Mutation Penetrance 30-70%

Corti et el, Physiol Rev 2011; Lesage, Brice , Park Relat Disord 2012

Well – Validated Parkinson's Disease Associated Genes Recessive Inheritance

GENE	ONSET	MUTATIONS	RISK VARIANTS	
parkin	Juvenile (age <40) Early (age 40-50)	~170 mutations (point, exon rearrangement)	Promoter variants, heterozygotes ñ late onset PD ?	80% of onset < age 20, rare after age 50
PINK1	Early (age 40-50)	~ 50 point mutations	Heterozygotes ñ late onset PD?	Rare
DJ-1	Early (age 40-50)	~ 15 mutations, large deletions	Heterozygotes ñ late onset PD?	Rare
ATP13A2	Juvenile (Kufor-Rakeb, atypical PD)	>5 point mutations	heterozygotes, early onset PD??	Rare
GBA	recessive à Gaucher's Dis	>300 mutations (point, insertions, deletions, complex)	GD, Heterozygotes ñ late onset PD, DLB	â-glucocerebrosidase gene product; AJ most common group

Corti et el, Physiol Rev 2011; Lesage, Brice , Park Relat Disord 2012

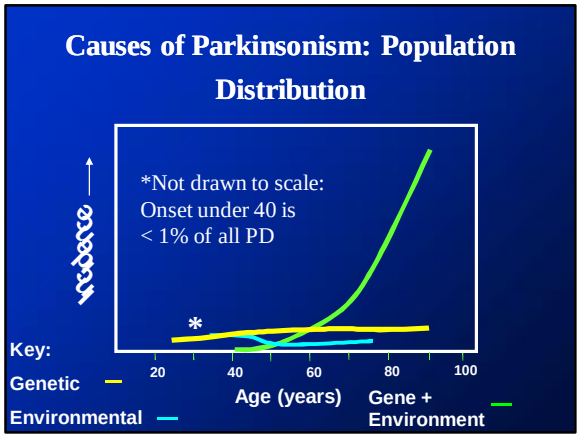
Heritability of PD

Heritability estimates

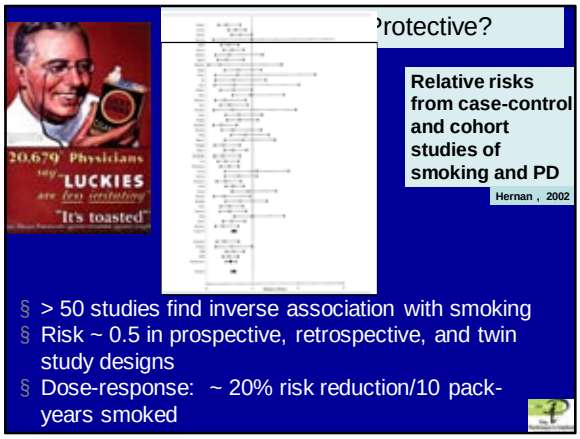
- Twin studies: 25% overall, higher in young onset PD, lower in typical onset
- GWAS studies: 25% overall, higher in young onset PD, lower in typical onset

Therefore

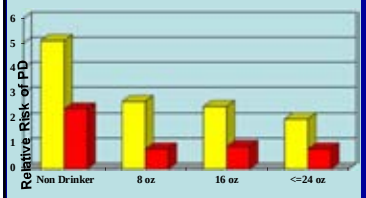
Up to 75% of disease liability in typical PD is non-heritable: *environment*



What Are the Environmental Determinants of Parkinson's Disease?



Greater Midlife Coffee & Tea Drinking is Associated with a Lower Risk of PD
(Ross et al, 2000)



Adjusted for age and pack-years of smoking

Test for Trend - p=0.001 Test for Trend p=0.079

Reference Group Drinks ≥28 oz/day
Reference Group Drinks ≥24 oz/day

Proposed Explanations:

- Adenosine A2A receptor blockers protect against MPTP-induced injury in animals
- Green tea polyphenols protect in animal models

OR

- Coffee drinking &/or cigarette smoking may reflect "preparkinsonian" personality

Pesticides – Increased Risk:
Since the 1990s, over 20 case-control studies have shown an association of PD and pesticides. PD risk is usually about twice as high in pesticide exposed persons.

BUT

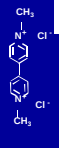
- Broad chemical categories
- Few specific agents identified

SEARCH Study: Case Control Study of Occupational Risk Factors
Tanner et al, Arch Neurol, 2009;66(9):1106-1113

519 PD cases, 511 controls in 8 MD centers

Lifelong, job-task-based occupational histories; other risk factors

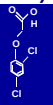
Paraquat: OR* = 2.8 (95% C.I.: 0.8, 9.7)



Mechanism

? ROS

2,4-Diphenoxyacetic acid (2,4-D) : OR* = 2.6 (95% C.I.: 1.03, 6.48)



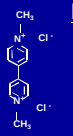
Mechanism

? Alpha Synuclein aggregation

*adjusted for age, gender , smoking

FAME Study: PD in Agricultural Health Study Tanner, Kamel et al, 2011

52,000 farmers, 32,000 spouses in Iowa & N Carolina screened for PD
112 PD cases, 368 controls
In-person examination, videotape, blood, dust, soil
Lifelong history: occupation, pesticides, other risks



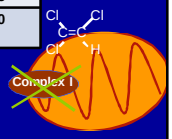
Paraquat à **Increased Risk of PD:**
All OR = 2.3 (95% C.I. 1.45, 4.3)
Men OR = 2.5 (95% C.I. 1.3, 4.7)

Rotenone à **Increased Risk of PD:**
All OR = 2.3 (95% C.I.: 1.2, 4.3)
Men OR = 2.8 (95% C.I.: 1.4, 5.8)

Models adjusted for age, gender, state, ever smoking, ever pesticide use

Solvent Exposures in 99 Twin Pairs Discordant for PD *Goldman et al , 2010*

Compound	Odds ratio	95% Confidence Interval	P-value
N-hexane	1.27	0.40-4.07	0.69
Toluene	1.28	0.49-3.31	0.61
Xylene	2.24	0.43-11.6	0.34
CCl_4	2.32	0.88-6.11	0.088
TCE	**6.11**	1.15-32.5	**0.034**
PERC	**10.5**	0.97-113	**0.053**
TCE or PERC	**8.94**	1.70-47.0	**0.010**



Consistent with occupational cluster (Gash et al 2008) **& TCE rat model** (Liu et al, 2010)

Is There Biologic Plausibility? Laboratory Studies of Toxicants:

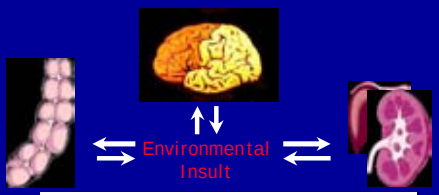
***In vitro* & in animal models, toxicant exposure can cause:**

	Para-quat	Rote-none	Diel-drin	TCE
?% synuclein fibrillary aggregates	+		+	+
Mitochondrial dysfunction	+	+	+	+
Oxidative stress	+	+	+	+
Nigral injury	+	+	+	+
Behavioral changes		+	+	+

BUT

Not all people exposed to these toxicants get PD. **Why?**

Exposure of the brain to environmental toxicants is controlled by genetically-determined enzymes and transporters throughout the body



Gene-Environment Interaction

An exposure may cause disease in persons unable to metabolize a toxicant while others are not affected

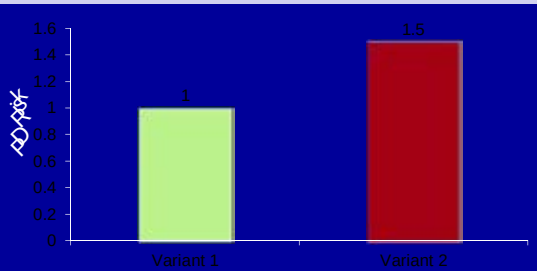
Example 1: Gene-Environment Interaction in PD

Goldman, Tanner, et al, Annals of Neurology 2012

Gene: α-synuclein

Environment: Head injury

Alpha-Synuclein Rep 1 Gene Variant is Associated with *Small* Increase in PD Risk



Gene Variant 2 makes more alpha-synuclein protein than Variant 1

Head Injury & PD

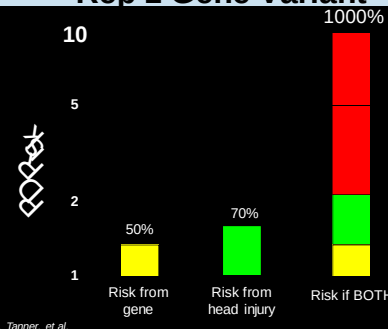
- Mild-moderate head injury associated with PD in >70% of studies.

Dr. J. William Langston and Mohammad Ali

- 2-3 fold increased risk
- Biologic Plausibility:
  - Triggers chronic inflammatory process
  - Oxidative stress
  - Protein aggregation
  - Mitochondrial damage

BUT only some people with head injuries develop PD
Why?

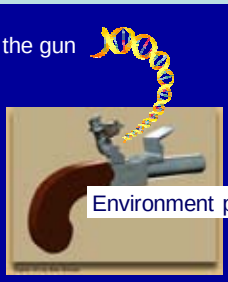
BOTH Head Injury & ?TS Synuclein Rep 1 Gene Variant



Goldman, Tanner, et al, Ann Neurol, 2012

Parkinson's Disease : A Complex Disorder

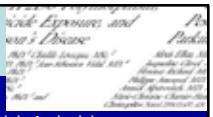
Genetics loads the gun



Environment pulls the trigger

Example 2a: Pesticides, Genes & Parkinson's Disease

Elbaz et al, 2004



•French Farmers Health Insurance (Mutualité Sociale Agricole):
190 PD cases 419 matched controls

•Pesticide use judged by occupational health physician:
Never used, exposed by gardening or professional use

CYP2D6*4 allele genotyping ("poor metabolizer") = 2 alleles

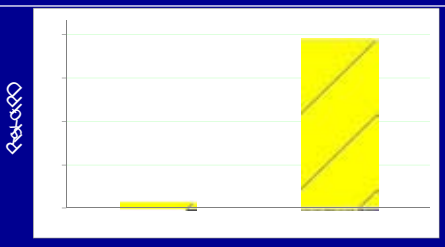
RESULTS:

	Odds Ratio		
	Never	Exposed	p
0 - 1 CYP2D6*4 alleles:	1.00	1.5 (0.92, 2.93)	0.1
2 CYP2D6*4 alleles:	1.00	3.28 (1.16, 9.27)	0.02

à Only the poor metabolizers exposed to pesticides had increased risk of PD

Example 2b: Paraquat, GST-T1 and Parkinson's Disease

Risk of PD Associated with Joint Occurrence of Paraquat Exposure and a Variant of the GST-T1 Gene



Goldman et al, 2012

Monogenic Parkinsonism & Environmental Factors: Does Environment Influence LRRK2 Associated Parkinsonism?

- **Most common genetic cause, ~1% - 2% of all parkinsonism**
- **Dominantly inherited**
- **Penetrance is incomplete, about 30%.**

à **Implication: Environmental factors &/or other genes determine who is affected**

Monogenic Parkinsonism & Environmental Factors: Does Environment Influence LRRK2 Associated Parkinsonism?

- Most common genetic

Even in genetic forms of parkinsonism, multiple determinants are likely .

Next step: Investigate environmental exposures in LRRK2 affected and unaffected carriers

Nonsmoking Carriers of LRRK2 Gly2385Arg Have Increased Risk of PD

An example of gene-environment interaction

Journal of the Neurological Sciences

LRRK2 Gly2385Arg polymorphism, cigarette smoking, and risk of sporadic Parkinson's disease: A case–control study in Japan

GA à OR 2.06

Nonsmoking Carriers of LRRK2 Gly2385Arg Have Increased Risk of PD

An example of gene-environment interaction

Journal of the Neurological Sciences

LRRK2 Gly2385Arg polymorphism, cigarette smoking, and risk of sporadic Parkinson's disease: A case–control study in Japa

GA EVER SMOKERS à OR 1.47, NS

GA NONSMOKERS à OR 5.76

GA à OR 2.06

Can Combined Effects of Environmental Factors Influence Risk of Parkinson's Disease ?

Head Injury, Paraquat Use and Risk of PD

Goldman et al, Mov Disord 2012

83 PD and 328 controls with complete data in FAME
- **Head injury in 19%**
- **Paraquat used by 17%, all men**

Head injury	Paraquat Use	Odds Ratio
No	No	1.0 (ref)
Yes	No	1.2
No	Yes	1.8
Yes	**Yes**	**4.2**

Head injury and paraquat use were synergistically associated with increased PD risk
Both cause oxidative stress
Joint effects are synergistic in a recent animal model (Hutson, 2011).

Risk of Parkinson's disease associated with the herbicide paraquat is attenuated by high dietary intake of polyunsaturated fatty acids

Kamel et al, submitted

•89 confirmed cases and 336 matched controls in FAME
•Diet before diagnosis from a food frequency questionnaire

- Parkinson's disease inversely associated with polyunsaturated fatty acids, notably ?3linolenic acid
  (OR 0.4, 95% CI 0.2-0.8)
- Association of Parkinson's disease with paraquat stronger in those with low intake of ??3linolenic acid

High intake, - paraquat	1.0 (referent)
Low intake, + paraquat	1.3 (0.7-2.5)
High intake, - paraquat	1.4 (0.5-3.9)
Low intake, + paraquat	4.5 (1.7-12)

Purely Genetic PD is Rare
Purely Environmental PD is Rare

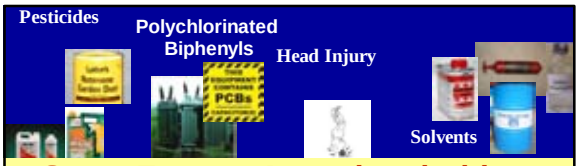
Most PD is likely due to the combined effects of genetic predisposition and environmental exposures

This is a hopeful finding, because environment can be changed!

NEXT STEP: Secondary Prevention of PD ?

à **Identify persons "at risk" for PD *before symptoms manifest*: efficient screening critical**

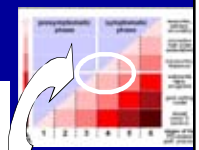
à **Intervene to prevent the development of PD: a safe treatment critical**



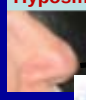
Some Factors Associated with a Higher Risk of Parkinson's Disease : Clues to Identify Persons at Risk?

Can an "at risk" profile for PD be identified?

Braak Stages of CNS Pathology for PD



Hyposmia



REM Sleep BD

?Heart Rate Variability

Constipation

Substantia nigra not first site of injury in PD

Lewy neurites found in olfactory bulb & autonomic nervous system

Should neuroprotective trials target persons with these signs?

Some Factors Associated with a Lower Risk of Parkinson's Disease: Clues for Preventative Therapies?

Physical activity

Cigarette smoking

Flavonoids?

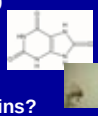
PUFAs?

Coffee & Tea Drinking

Anti-inflammatory drugs (ibuprofen)

Ca channel blockers

Statins?



Higher serum urate

Higher Vitamin D

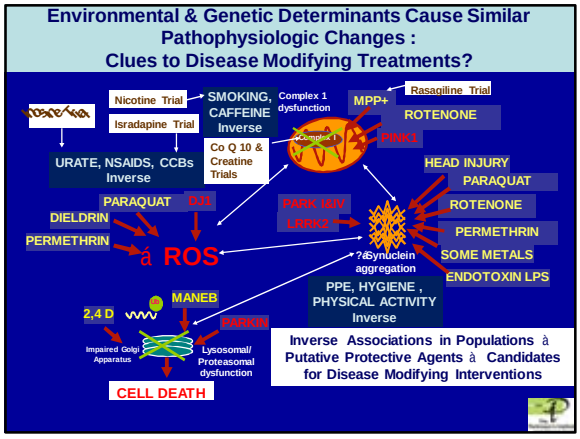
Female gender; Estrogens?

Association Does Not Prove Causation

Laboratory Studies Needed:

- à Determine pathophysiologic mechanisms
- à Develop candidate treatments

Are you sure about this? It seems odd that a pointy head and long beak is what makes birds fly.


Environmental & Genetic Determinants Cause Similar Pathophysiologic Changes :
Clues to Disease Modifying Treatments?
Nicotine Trial
Isradapine Trial
SMOKING, CAFFEINE Inverse
Co Q 10 & Creatine Trials
URATE, NSAIDS, CCBs Inverse
Complex 1 dysfunction
Complex I
Rasagiline Trial
MPP+
ROTENONE
PINK1
HEAD INJURY
PARAQUAT
ROTENONE
PERMETHRIN
SOME METALS
ENDOTOXIN LPS
PARAQUAT
DJ1
DIELDRIN
PERMETHRIN
á ROS
PARK 1&IV
LRRK2
?á Synuclein aggregation
PPE, HYGIENE , PHYSICAL ACTIVITY Inverse
2,4 D
MANEB
PARKIN
Impaired Golgi Apparatus
Lysosomal/ Proteasomal dysfunction
CELL DEATH
Inverse Associations in Populations à Putative Protective Agents à Candidates for Disease Modifying Interventions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