The Latest Research in Parkinson’s Disease

Lawrence Elmer, MD, PhD
Professor, Dept. of Neurology
University of Toledo
OR….. Rethinking Parkinson’s Disease

Lawrence Elmer, MD, PhD
Professor, Dept. of Neurology
University of Toledo
Earliest areas of Lewy body appearance

**Olfactory mucosa** -
in contact with air, aerosols, fumes, etc.

**Gastrointestinal tract** -
in contact with liquids, solids, medications, toxins, etc. - inhabited by bacteria, fungi, etc.

*Not your father’s Parkinson’s Disease!!*
Genetic Discoveries Paved the Way

Figure 1. Molecular mechanisms leading to neuronal cell death. The grey boxes encompass the independent pathways that can lead to cell death, i.e., mitochondrial dysfunction, ubiquitin–proteasomal dysfunction and alpha-synuclein aggregation. The red circles highlight the primary aberrations that affect each pathway to trigger cell death, such as mutations in the Mendelian genes, or administration of toxins in animal models. The blue arrows indicate the convergence of these pathways: impairment of the UPS has adverse effects on mitochondrial function and the generation of ROS, and similarly, oxidative stress alters the function of the UPS. Oxidative stress may increase alpha-synuclein aggregation, and aggregated alpha-synuclein inhibits the function of the UPS. Note that it is not yet known how LRRK2 mutations cause nigral neuronal loss in PD.

Ghandi and Wood, Human Molecular Genetics, 14:2749 (2005)
Radical Hypothesis of Braak and Colleagues

Revolutionary PD Pathology

Lewy Body Pathology in the Olfactory Bulb and The Dorsal Motor Nucleus of the Vagus Nerve


(A) Incidental Lewy neurites (LNs) (stage 1 brain pathology). The network of LNs almost completely fills out the contours of the entire nucleus in the following stages: (B) 68-year-old woman, stage 3 brain pathology; (C) age and gender unknown, stage 6 brain pathology. Note the severe end stage pathology at stage 6. (D) Dorsal motor nucleus of the vagal nerve in an 85-year-old asymptomatic man. In stage 1, the pathologic process can commence with a single LN (arrow and inset). Note that the melanoneurons (lower left, A2 group) are fully intact. (E) In the course of Parkinson disease, the visceromotor preganglionic projection neurons of this nucleus develop LBs in their somata (upper right) and LNs in their axons (lower left). Note the thick network of axonal LNs in the catecholaminergic tract of the intermediate reticular zone (lower right) in a 61-year-old man with stage 5 brain pathology. Syn-1 (BD Biosciences Laboratories) immunoreactions and blue chromogen SK-4700 [Vector] in unconventionally thick (1.00 µm) polyethylene glycol-embedded sections.
Lewy Body Pathology in the Enteric Nervous System

Nervous system pathology in sporadic Parkinson disease. 
Braak H, Del Tredici K. 
### Incidence of NMS in PD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory dysfunction*</td>
<td>90%</td>
</tr>
<tr>
<td>Dementia</td>
<td>78%</td>
</tr>
<tr>
<td>Depression*</td>
<td>40-50%</td>
</tr>
<tr>
<td>Autonomic nervous system dysfunction</td>
<td>80%</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>50%</td>
</tr>
<tr>
<td>Gastrointestinal symptoms*</td>
<td>50-95%</td>
</tr>
<tr>
<td>Urogenital dysfunction</td>
<td>57-83%</td>
</tr>
<tr>
<td>Pain</td>
<td>40-50%</td>
</tr>
<tr>
<td>Sleep disorders*</td>
<td>66%</td>
</tr>
<tr>
<td>Impulse control disorders</td>
<td>7-14%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>50%</td>
</tr>
</tbody>
</table>

*Identified as possible premotor symptoms

---

A Timeline for Parkinson's Disease

Clinical Manifestations

20-year Prodrome | Onset | Disease Progression
--- | --- | ---
Hyposmia | Unilateral | Poor balance | Bedbound
Constipation | Bilateral | Falls | Dementia
Bladder dysfunction | Tremor | Dependency |
Sleep disorder | Rigidity | Cognitive decline |
Obesity | Akinesia | |
Depression | |

Pathological Changes

Enteric plexus | Substantia nigra | Temporal lobe | Prefrontal cortex
Olfactory bulb | Amygdala | TEC | Tertiary sensory-associated areas
CN X | Meynert’s nucleus | Ca-2 plexus | |
Coeruleus | PPN | Intralaminar thalamic nuclei | |
Caudal raphe | Magnocellular cf. | |

CN X, cranial nerve X; PPN, peripeduncular nucleus; TEC, transentorhinal cortex

Premotor Parkinson’s Disease
Clinical Manifestations

Strongest Evidence (as reviewed by Lang et al. 2011):

- Olfactory deficits (Hyposmia)
- Constipation
- Sleep disorders (RBD, Excessive Daytime Sleepiness)
- Depression

Suggested Links/Investigative:

- Other autonomic disturbances: Heart rate variability
- Other mood and behavioral: Anxiety, apathy, personality characteristics
- Cognitive changes
- Visual disturbances
- Restless legs syndrome
- Fatigue

Premotor Parkinson’s Disease
Clinical Manifestations: Olfaction

- Olfactory bulb may be earliest site of brain pathology in PD, based on Braak Hypothesis
- A recent multi-center study of 400 patients with PD found that 74.5% had an olfactory deficit, as measured by the University of Pennsylvania Smell Identification Test (UPSIT) and corrected for age
- Longitudinal Honolulu-Asia Aging Study showed odds ratio of 5.2 of developing PD among those in the lowest quartile of smell identification, compared to those in the upper quartile
- Easy and relatively inexpensive to test, but low specificity:
  - Smell deficits also occur with normal aging, smoking, head injury, and other neurodegenerative disease (Alzheimer’s disease and PSP)

Autonomic Dysfunction

- **Constipation**
  - Can predate motor symptoms by 18 years
  - Men with less than one bowel movement per day show a 2.7-fold greater risk of developing PD
  - Lewy bodies have been found postmortem in 12.5% of patients with constipation who were not diagnosed with PD or dementia

- **Altered cardiac sympathetic input**
  - Results in loss of heart rate variability
Autonomic Dysfunction: Loss of Heart Rate Variability

- Patients with PD or RBD had lower amounts of sympathetic cardiac terminals as measured by MIBG scintigraphy compared to controls.
- Correlates with changes in cardiac variability.

Sleep Disorders: REM Behavior Disorder (RBD) and Excessive Daytime Sleepiness (EDS)

- 20% of PD patients with RBD report that RBD predated diagnosis by several years
- RBD patients have about a 40% chance of later PD development
- One report suggests that RBD is predictive of PD only when patients develop PD after the age of 50
- RBD is less common in patients with tremor and may predict the development of cognitive decline
- EDS patients also show a 3-fold greater risk for the development of PD

Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder
Neurology. 2009 Apr 14;72(15):1296-300.
Premotor PD and RBD

- Patients with RBD and no motor abnormality have nonmotor PD features
  - Impaired olfaction
  - Cardiac sympathetic denervation
  - Abnormal dopamine imaging

PD Incidence/10,000 Person-Years by Number of Symptoms Present For:

- Excessive daytime sleepiness
- Poor olfaction
- Slow reaction time

*Cases of PD / Subjects at risk

p=0.007 trend
Imaging Evidence of Premotor PD

The concept of biomarkers for the premotor phase have been studied using:

- $^{18}$F-Dopa PET
- DAT SPECT (esp. $^{123}$I-β-CIT)
- Cardiac Sympathetic SPECT Imaging (MIBG) [norepinephrine]
- Transcranial Sonography
- Magnetic resonance Imaging
- Other radioligands representing serotonergic and cholinergic function as well as microglial activation (peripheral benzodiazepine receptor targets) and synuclein tracers
Imaging Evidence of Premotor PD
DAT SPECT Imaging

- $^{123}$I-$\beta$-CIT (Carbomethoxy Iodophenol Tropane) SPECT imaging of the dopamine transport (DAT) system has demonstrated bilateral abnormalities in uptake in patients with hemi-parkinsonism (unilateral motor symptoms)$^1$

- Prospectively followed at-risk individuals have been shown to have abnormally decreased DAT uptake prior to the onset of overt motor symptoms (up to 5 years)$^2$

---

What’s the Benefit if PD is Diagnosed “Early”?

- Exercise is emerging as potentially “disease-modifying”
- Growth factors – i.e. “gene therapy” are available
- Numerous new molecules potentially modify disease progression
Moving from Symptomatic to Disease-Modifying

**Substantia Nigra**
- levodopa
- Parcopa®
- Stalevo®
  (carbidopa/levodopa/entacapone)

**Striatum**
- DA
- GABA
- ACh

**Dopamine agonists**
- apomorphine
- bromocriptine
- pergolide
- pramipexole
- pramipexole ER
- ropinirole
- ropinirole XL
- rotigotine

**Anti-cholinergics**
- baclofen

**MAO-B**
- selegiline
- zydis selegiline
- rasagiline

**BBB**
- carbidopa
- benserazide
- tolcapone
- entacapone

**Moving from Symptomatic to Disease-Modifying**

(Deep Brain Stimulation)
Role of Forced Exercise on PD Progression

Neurology®

Does vigorous exercise have a neuroprotective effect in Parkinson disease?
J. Eric Ahlskog
Neurology 2011;77:288
DOI 10.1212/WNL.0b013e318225ab66

This information is current as of August 3, 2011
Chronic MPTP Model and Exercise

Chronic MPTP Model and Exercise

*European Journal of Neuroscience, Vol. 33, pp. 1264–1274, 2011*
Disease Modification in PD

Sites of Action of PD Drugs: Emerging

- **Dopamine agonists**
  - Controlled-release
  - Novel DA’s
  - Nasal sprays
  - Other transdermal

- **Multifunctional MAO-B Inhibitors**

- **Serotonergic Antagonists**

- **Extended levodopa delivery systems**

- **Adenosine Antagonists**
  - AMPA Antagonists
  - Adrenergic Antagonists

- **Substantia Nigra**

- **Striatum**

- **MAO-B**

- **DA**

- **GABA**
Multi-functional effects of rasagiline in neurons
ADAGIO: Post-Hoc Analysis, Rasagiline 2 mg/day
Patients with Baseline UPDRS Scores >25.5

Growth Factors in Parkinson’s Disease

AAV2-GAD gene therapy for advanced Parkinson’s disease: a double-blind, sham-surgery controlled, randomised trial


Lancet Neurol 2011; 10: 309–19
Growth Factors in Parkinson’s Disease

Lancet Neurol 2011; 10: 309–19
Growth Factors in Parkinson’s Disease

Figure 3: Selected secondary endpoints
(A) Global rating of parkinsonism (a question from the brief parkinsonism rating scale) showed a significant difference between groups (p=0.02, RMA NOVA). Although not compared using statistical tests, more patients in the AAV2-GAD group seemed to report favourable clinical outcomes than did patients in the sham group in the questionnaire to assess motor fluctuations at 6 months. (B) Two patients of 21 in the sham group vs five of 16 in the AAV2-GAD group reported a consistent medication effect; (C) ten of 21 in the sham group vs six of 16 in the AAV2-GAD group reported on-off fluctuations; and (D) 13 of 21 in the sham group vs five of 16 in the AAV2-GAD reported freezing gait. AAV2-GAD=adeno-associated virus serotype 2-glutamic acid decarboxylase.

Lancet Neurol 2011; 10: 309–19
A Timeline for Parkinson's Disease

Clinical Manifestations

- **20-year Prodrome**
  - Hyposmia
  - Constipation
  - Bladder dysfunction
  - Sleep disorder
  - Obesity
  - Depression

- **Onset**
  - Unilateral
    - Tremor
  - Bilateral
    - Rigidity
    - Akinesia

- **Disease Progression**
  - Poor balance
  - Falls
  - Dependency
  - Cognitive decline
  - Bedbound
  - Dementia

Pathological Changes

- Enteric plexus
- Olfactory bulb
- CN X
- Coeruleus
- Caudal raphe
- Magnocellular cf.
- Substantia nigra
- Amygdala
- Meynert’s nucleus
- PPN
- Temporal lobe
- TEC
- Ca-2 plexus
- Intralaminar thalamic nuclei
- Prefrontal cortex
- Tertiary sensory-associated areas

CN X, cranial nerve X; PPN, peripeduncular nucleus; TEC, transentorhinal cortex

Summary

- We are redefining the diagnosis of “Parkinson’s Disease”
- Overwhelming evidence of a “Pre-PD” state
- Multifaceted approaches to therapy are obviously needed
- With hard work, extreme research and a lot of luck, we may see PD “cured” in our lifetime
Thank you!

lawrence.elmer@utoledo.edu