Parkinson's Disease: Research update

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Disclosures

- Experimental therapies will be discussed
- Dr. Ross receives grant support from the Institute of Medicine and National Institutes of Health, and salary from the Department of Veterans Affairs
- There are no further disclosures.

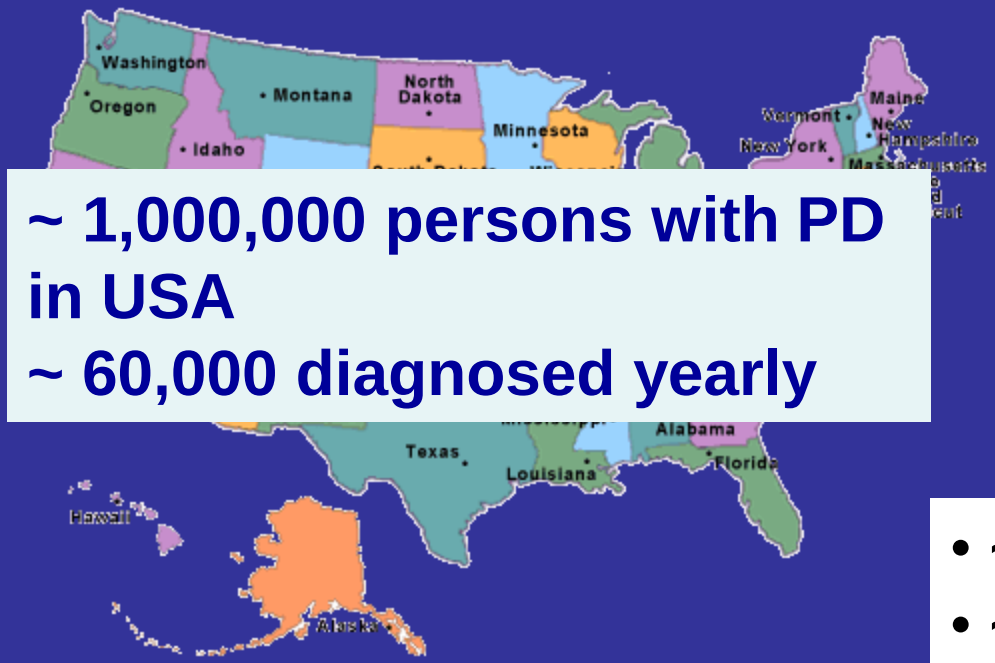
April is Parkinson's Awareness Month

Senate resolution 474

Resolved, That the Senate—

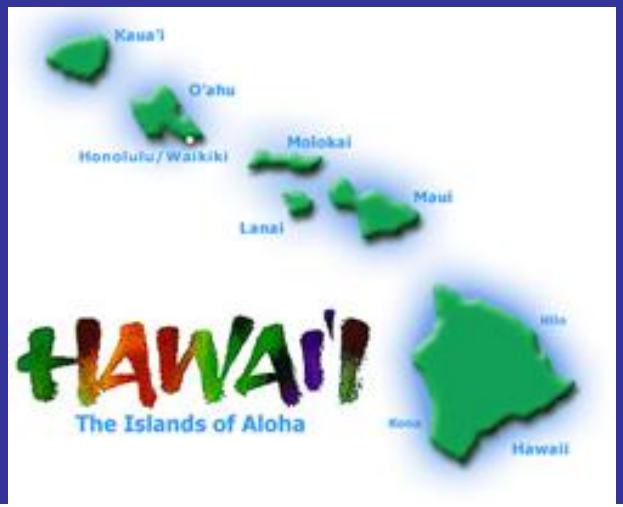
- **supports the designation of April as Parkinson's Awareness Month;**
- **continues to support research to find better treatments, and eventually, a cure for Parkinson's disease;**
- **recognizes the people living with Parkinson's who participate in vital clinical trials to advance our knowledge of this disease**

Parkinson's disease: how common?

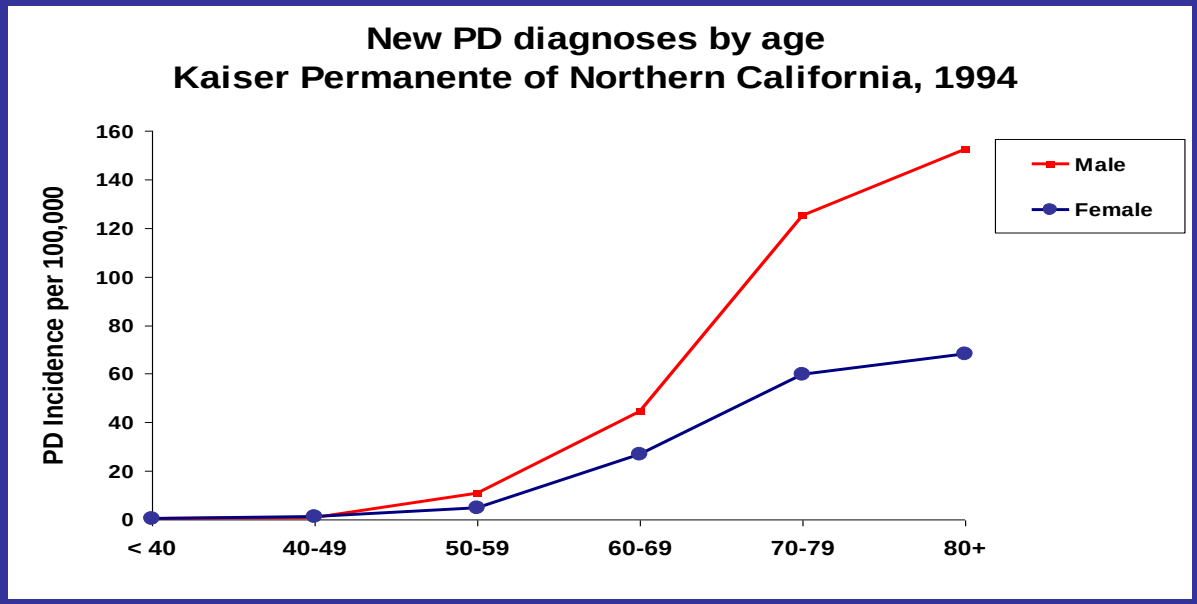


~ 1,000,000 persons with PD in USA

~ 60,000 diagnosed yearly



- **~ 3000 persons in Hawaii**
- **~ 200 diagnosed yearly**



Update of PD research

- Annual cost for PD care in the USA is 14.4 billion dollars with total per patient cost of $20,000 per year.
- The cause of Parkinson's disease is unknown.
- Diagnosis depends on recognition of typical symptoms and clinical features. Currently, there is no diagnostic test.
- There are good medications to treat symptoms but no cure and no way to halt progression of the disease.

Update of PD research:

- **This presentation will discuss recent research on :**
  - **Environmental toxins, genes, and Parkinson's disease**
  - **Methods to diagnose PD earlier**
  - **New treatments in development**

Risk factors for Parkinson's disease

- **Environmental factors associated with increased risk:**
  - **Environmental toxins**
    - **Pesticides**
    - **Trichloroethylene**
  - **Head injury**

- **Environmental factors associated with decreased risk:**
  - **Cigarette smoking**
  - **Coffee drinking**
  - **High uric acid**

Pesticides and PD Link

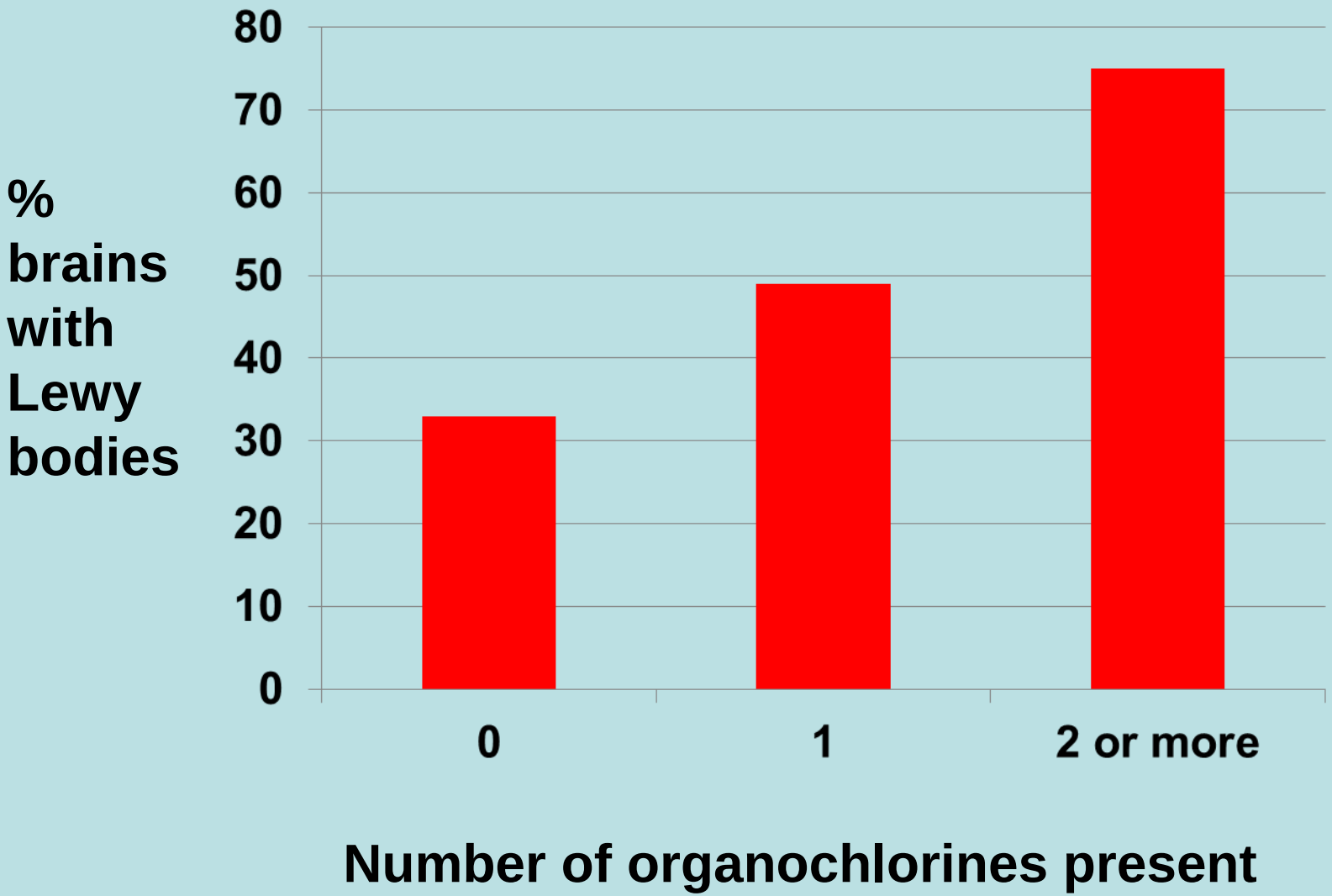
- **Preponderance of evidence indicates pesticide exposure is associated with higher PD risk.**
- **Specific pesticides implicated include:**
  - **Paraquat – commonly used herbicide**
  - **Maneb – commonly used fungicide**
  - **Rotenone – widely used in home gardening, pest control, fish poison, and commercial insecticide**
  - **Organochlorines – banned in US over 30 years ago**
  - **2,4-D - constituent of agent orange**
  - **2,4,5-T - constituent of agent orange**
- **Recommendations:**
  - **Avoid of these chemicals when possible**
  - **When contact is necessary, use protective gear**

Association of brain organochlorines with Lewy pathology in the Honolulu-Asia Aging Study

(*Ross et al, Movement Disorders, 2012)*

- **Brain autopsies sought on all cohort deaths**
- **Organochlorine levels measured in frozen occipital lobe samples by gas chromatography *(Edo Pellizzari, Research Triangle Institute)***
- **Presence of Lewy bodies determined with alpha synuclein staining *(John Duda, Philadelphia VA)***

Per cent of brains with Lewy bodies by detectable levels of 0,1,or 2 organochlorines (hepox-b, methoxychlor, and b-BHC)



Other environmental toxins and PD

- **Trichloroethylene (TCE)**
  - Dry cleaning and degreasing agent and additive in many products such as paints and carpet spot removers
  - TCE causes loss of dopamine nerve cells and accumulation of synuclein in rats
  - PD risk increased 5 times in twins occupationally exposed to TCE
- **Manganese and welding**
  - Symptoms of parkinsonism reported in manganese miners with high exposure
  - Recent report found no increased risk of PD with welding.

Update on Genetics and PD

- About 1 in 7 PD patients have a first degree relative with PD, more than twice that of the general population.
- First degree relatives of PD patients have 2.3 times the risk of developing PD compared to those without relatives.
- Genetic factors play a more obvious role when the onset of disease is young, below the age of 50 years.
- There are a few genetic forms of PD associated with mutations that cause PD, however, these are rare – less than 10%

Genetic forms of PD

Gene	Features	Role in PD
Alpha synuclein	Extremely rare Young onset PD	Synuclein in the protein in Lewy bodies
LRRK2	Most common genetic cause but still < 2% of PD, mid to late onset PD	Modifies other proteins involved in PD
glucocerebrosidase	Increases risk of PD 5 times,	Mutation may block break down of toxins
Parkin	Rare, Young onset PD	Mutation inhibits cells ability to get rid of other proteins
PINK1	Very rare, associated with young onset PD	Helps cell break down faulty parts
DJ-1	Very rare, associated with young onset PD	Protects cell from oxidative stress

Update on Genetics and PD Genetic counseling

- Genetic testing is offered on a commercial basis for the major genetic mutations associated with higher risk of PD
- No formal testing guidelines have been developed
- Testing may be helpful in the following conditions
  - Juvenile onset PD
  - PD with onset younger than age 55 years with a positive family history or atypical features
  - Late onset PD with a strong family history of PD
- Concerns:
  - May affect eligibility for health and life insurance

"Genetic Information you share with others could be used against your interests. You should be careful about sharing your Genetic Information with others." 23 and me website

Gene environment interaction

- Gene-Environment interaction may play a role in causing PD where persons are born with a genetic mutation that makes them more susceptible to the toxic effects of an environmental exposure.
- Genetics loads the gun and environment pulls the trigger
- Gene environment interactions found for:
  - Head injury and genes affecting alpha synuclein accumulation
  - Pesticide exposure and genes affecting absorption, metabolism, and excretion of pesticides

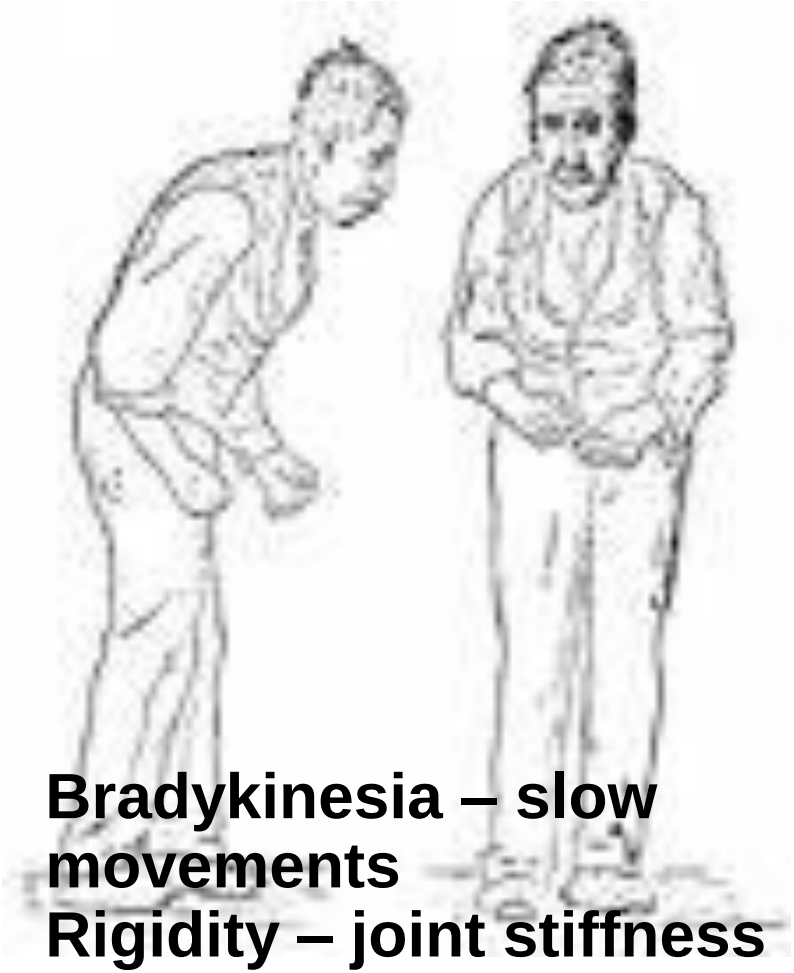
Parkinson's disease diagnosis

- Diagnosis of PD is clinical and we are wrong 10 to 20% of the time
- By the time of diagnosis patients have already lost 50% of the nerve cells that produce dopamine in the substantia nigra.

Tests are needed that improve diagnostic accuracy and allow earlier diagnosis

PD diagnosis confirmation requires:

- **Clinical parkinsonism**
- **Lewy bodies in the dopamine producing nerve cells**



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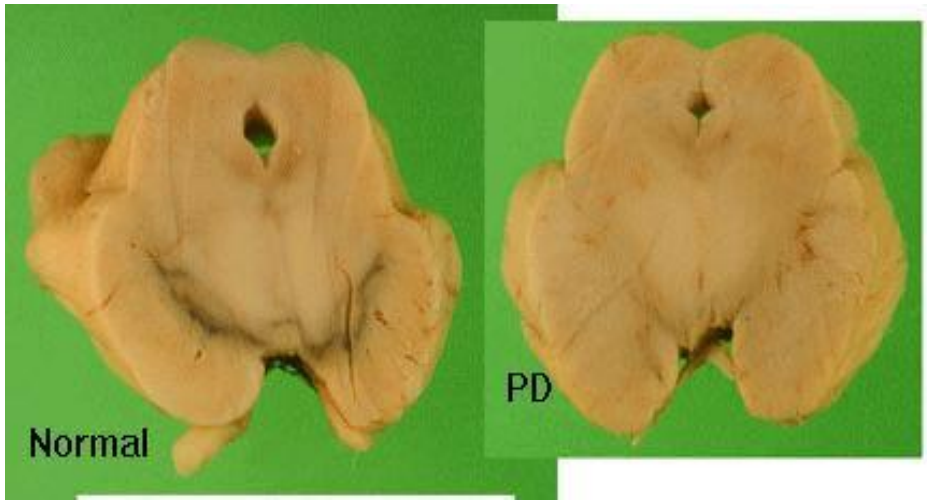
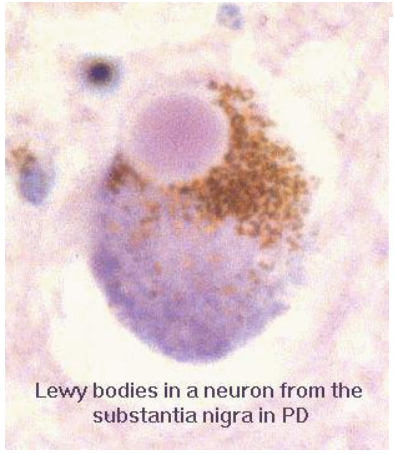
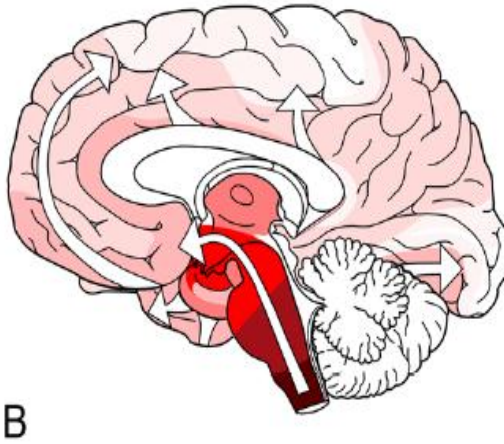






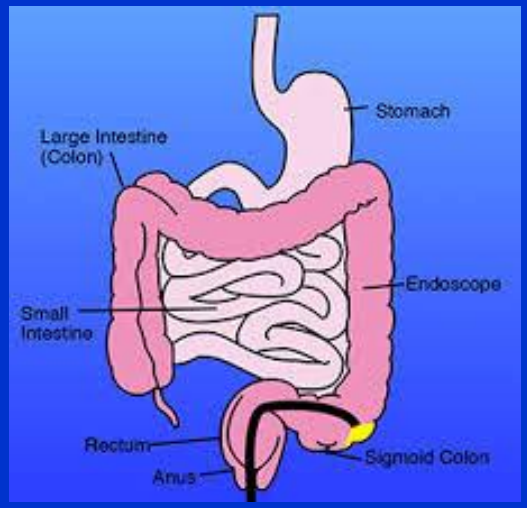
- **Bradykinesia – slow movements**
- **Rigidity – joint stiffness**
- **Rest tremor**
- **Postural instability**

Parkinson's disease: Non-motor features

- Impaired olfaction
- Constipation
- Prolonged Q-T interval
- Excessive daytime sleepiness,
- REM sleep behavior disorder
- Sexual dysfunction
- Fatigue

- Seborrhea
- Dry skin and dry eyes
- Drooling and dysphagia
- Bladder dysfunction
- Major depression
- Dementia
- Psychosis

Biopsy of colon or salivary glands may help to diagnose early PD

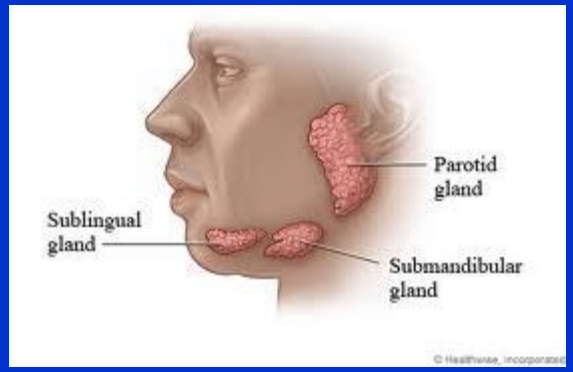


Lewy bodies in the colon

- 9 early PD patients and 46 non-PD controls had sigmoidoscopy and biopsy of the sigmoid colon
- All PD patients had Lewy bodies
- None of the non-PD controls had Lewy bodies

Lewy bodies in the salivary glands

- Submandibular salivary gland biopsied with a needle using local anesthetic
- 9 of 12 biopsies from PD patients had Lewy bodies
- Side effects were minimal.



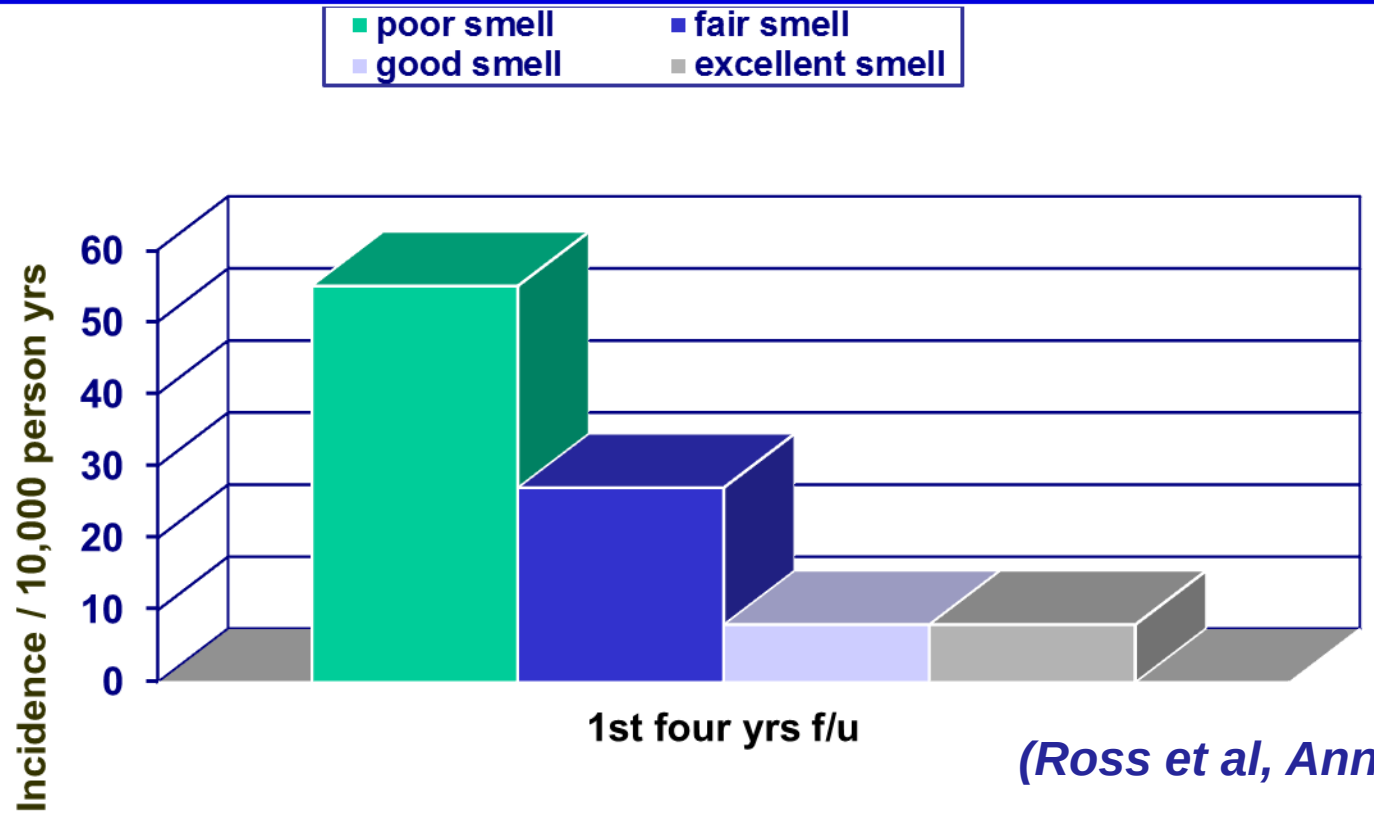
Possible pre-motor symptoms

- Olfaction
- Sleep disorders
  - Rapid eye movement sleep disorder
- Constipation

Olfactory dysfunction in the Honolulu-Asia Aging Study

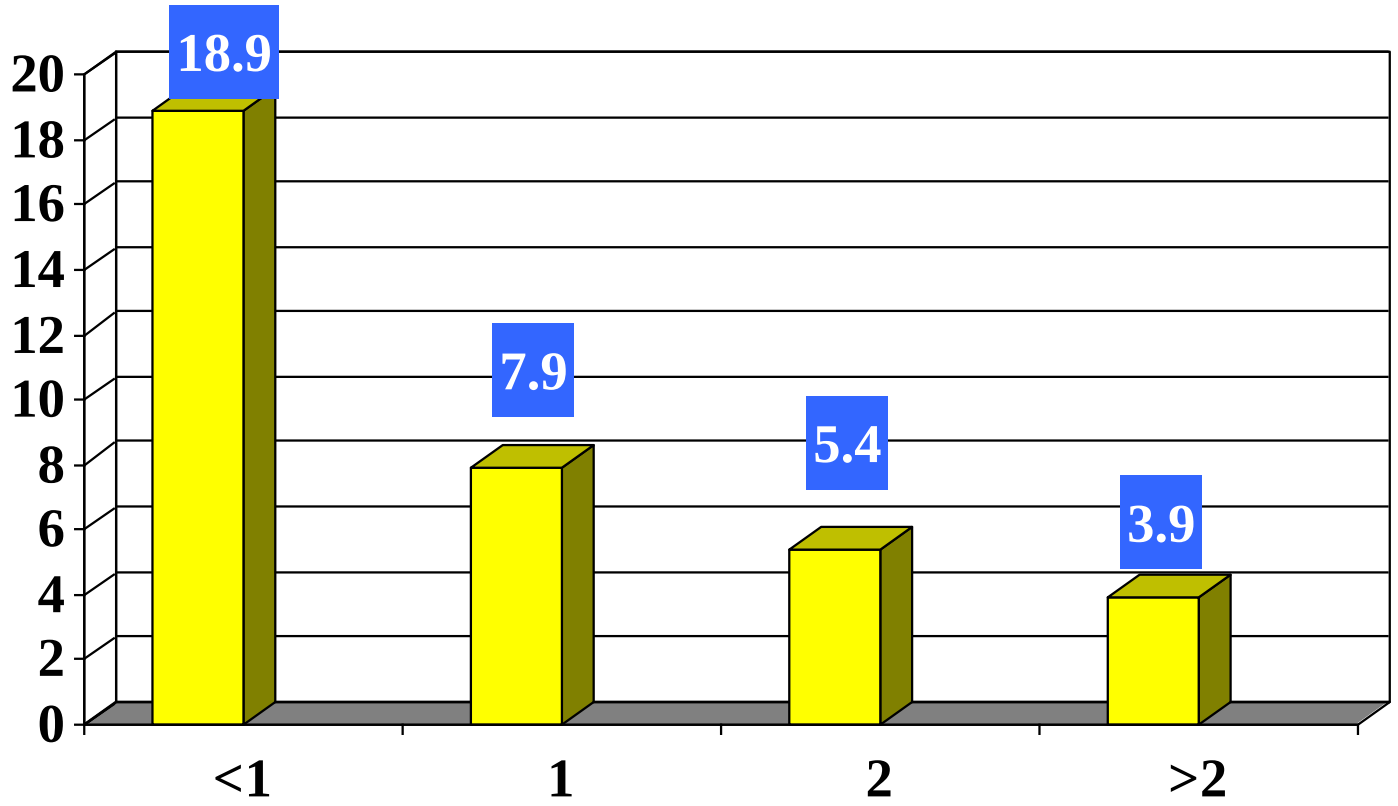
- **Present in 90% of PD patients whether measured by identification, threshold testing or recognition and occurs early**

2263 men in the study given Brief Smell Identification Test



(Ross et al, Ann Neurol 2006)

The fewer bowel movements reported per day at exam time the greater the risk of developing PD in the future: the Honolulu-Asia Aging Study



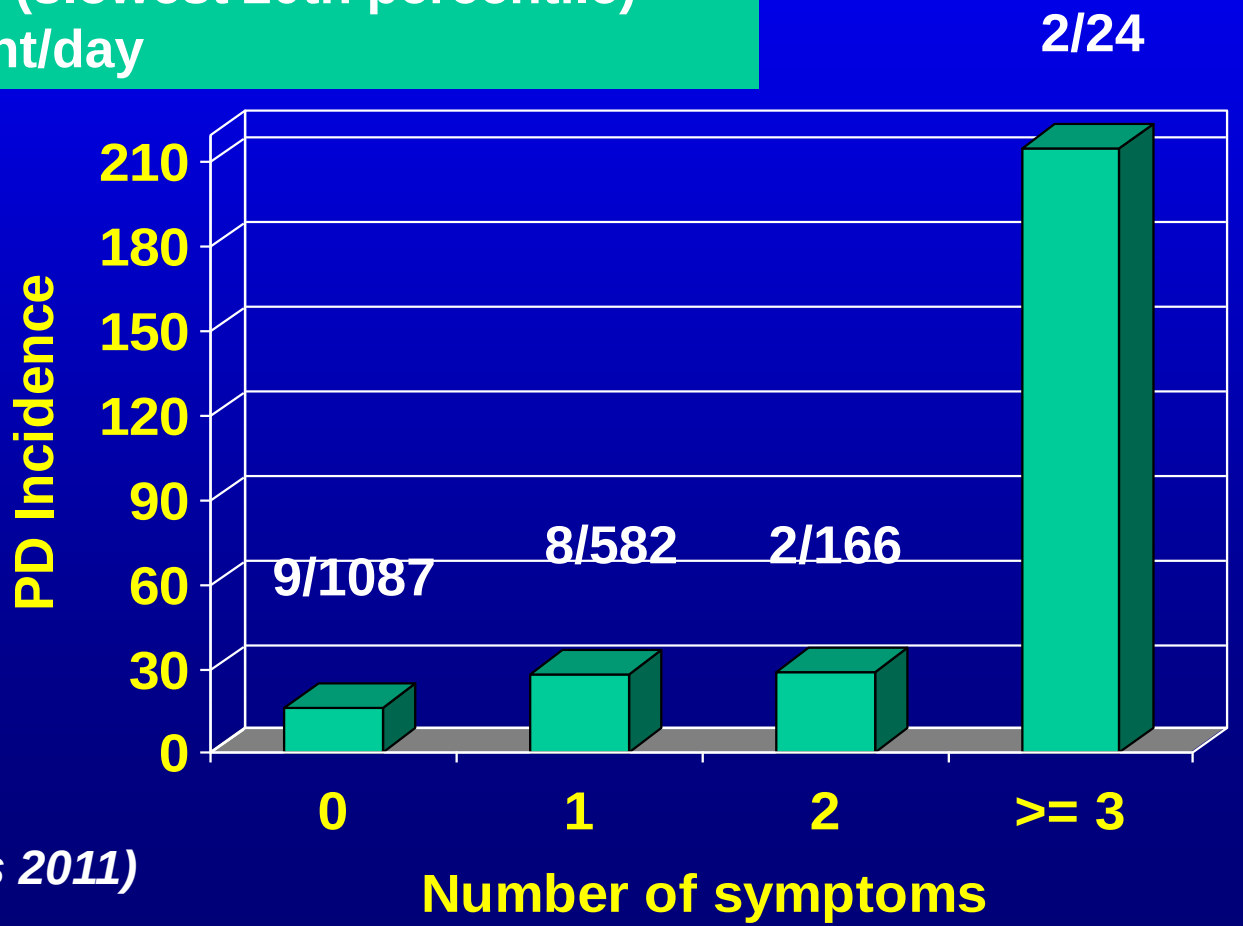
(Abbott et al, Neurol 2001)

REM Sleep behavior disorder

- Loss of normal body paralysis that accompanies dream (rapid eye movement) sleep
- Range of behaviors from talking and gesturing to violent kicking and punching in association with dream content (acting out dreams)
- RBD occurs in up to 60% of those with PD compared to less than 2% in the general public
- Among those who are diagnosed with RBD without PD, 20-45% will develop PD in five years and 40 to 65% in 10 years.

PD incidence/10,000 person-years in the Honolulu-Asia Aging Study by number of early symptoms present

- Excessive Daytime Sleepiness
- Poor olfaction (bottom 20th percentile)
- Slow reaction time (slowest 20th percentile)
- <1 bowel movement/day



(Ross et al, Park Rel Dis 2011)

Parkinson's disease treatment

- Symptomatic treatment helps the motor features
  - Medications:
    - Carbidopa / levodopa
    - Dopamine agonists including ropinirole, pramipexole, rotigotine
    - Entacapone
    - Amantadine / anticholinergic medications
    - Rasagiline and selegiline
  - Surgical: deep brain stimulation
- Disease modifying treatments slow progression of disease. These are not yet available but may in the future include:
  - Medications to protect nerve cells from death
  - Exercise
  - Gene therapy and stem cell therapy

Parkinson's disease clinical trials

- 43 active clinical trials in the United States for Parkinson's disease
  - 30 are still seeking participants
  - 13 are active but not enrolling new participants.

- There are over 35 new medications under development to help patients with Parkinson's disease

Update on medications intended to slow progression of PD

- **Co-enzyme Q-10:**
  - **Trial discontinued early due to lack of efficacy**
- **Creatine: (Honolulu was a site)**
  - **Antioxidant, improves mitochondrial function**
  - **Trial discontinued early due to lack of efficacy**

Isradipine to slow progression of PD

- Approved blood pressure medication that blocks calcium channels
- Substantia Nigra neurons use calcium and sodium channels for normal functioning
- Calcium can harm cells
- Blocking calcium channels is neuroprotective in animal models of PD
- phase II trail completed – isradipine 10 mg was well tolerated in patients with early PD
- Trial to determine whether isradipine slows progression in PD is starting this Summer. Honolulu is a participating site.

Ongoing trials of medications intended to slow progression of PD

- **Pioglitazone –**
  - **Approved drug to treat diabetes**
  - **Reduces insulin resistance in type II diabetes**
  - **Has anti-inflammatory properties and enhances mitochondrial function.**
  - **Protects dopamine nerve cells in animal models of PD**
  - **Multi-center trial (Honolulu is a site) has completed enrollment and trial will end this Fall.**

Ongoing trials of medications intended to slow progression of PD

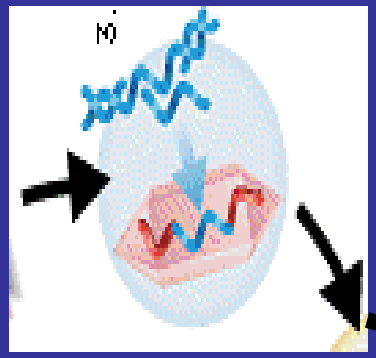
- **Transdermal Nicotine –**
  - **Approved for smoking cessation**
  - **There is a strong association of smoking and reduced PD risk**
  - **Nicotine protects dopamine neurons animal models of PD**
  - **Multi-center (Honolulu is site) trial of nicotine patch in early PD completed enrollment and will finish in a year**

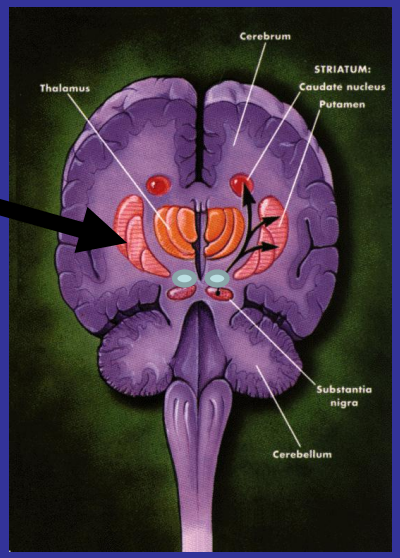
ProSavin® Gene Therapy for PD

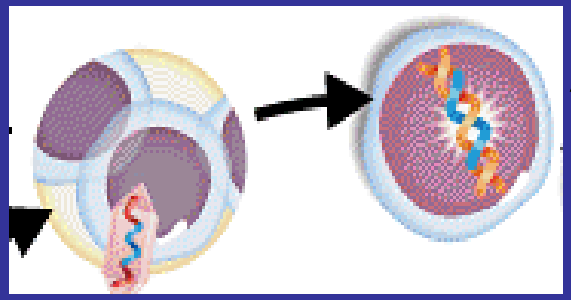
DNA for 3 enzymes required to make dopamine inserted into a virus (ProSavin®)

The virus with the dopamine enzyme DNA is injected into nerve cells of the putamen where dopamine is released.

The infected putamen nerve cells become dopamine producing factories







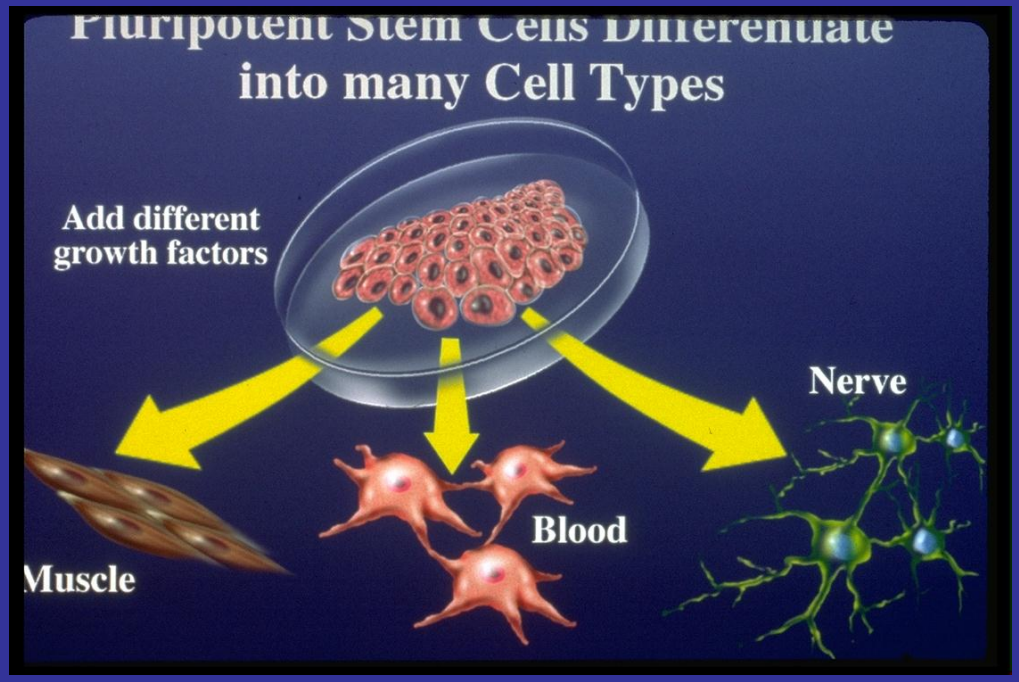
Dopamine

ProSavin Therapy for PD - Results

- 15 PD patients received ProSavin® in an open label trial and were followed for 12 months
- All patients had improvement in motor function at 12 months compared to baseline
- Dyskinesias were increased, but these responded to decreasing levodopa dose.
- Prosavin® was safe and well tolerated.
- Cautionary notes:
  - Small number of patients
  - Open label design and no control group
  - Would not be expected to improve non-motor features of PD such as dementia, freezing, and falling.

Stem cell therapy

- **Stem cells are unspecialized cells that can divide and differentiate into many types of specialized cells.**



Cellular therapy for PD

1. **Multiple cell types may be utilized**
   - embryonic stem cells (ES) isolated from human embryos
   - Induced pluripotent stem cells: (iPS) usually from human skin and re-programmed to have the capability to differentiate into multiple cell types
   - **Mesenchymal stem cells (MSC): derived from bone marrow or fat from the patient**
   - Neural Progenitor cells (NPC): derived from fetal or adult neural tissue including ventricular wall and dentate gyrus

Cellular therapy for PD – mesenchymal stem cells

- Majority of studies have been done with mesenchymal stem cells
- Potential support mechanisms include:
  1. Replenishment of dopaminergic cells
  2. Environmental enrichment through synthesis or delivery of brain chemicals that can protect nerve cells.
  3. Modulation of immune response
- May be delivered by injection into brain or through an artery or vein.

Stem cell therapy for PD

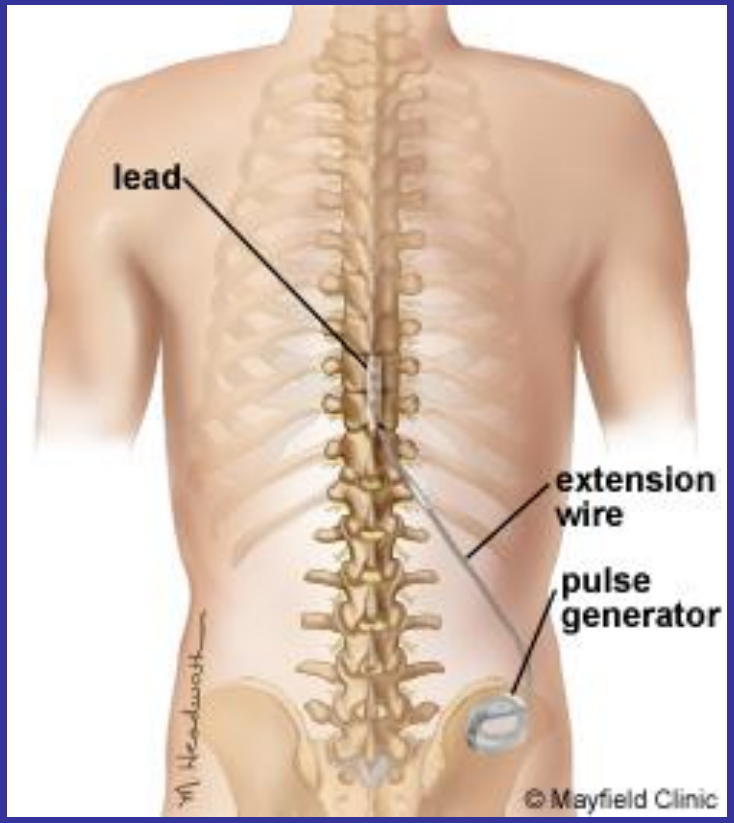
- **Human research**
  - **An open label trial *(Venkataramana et al, Stem Cells International 2012)* of bone marrow derived MSC transplanted into the brain showed**
    - **Motor function in 8 PD patients improved during on and off periods**
    - **Scores did not change for 4 PD-plus patients**
  - **Placebo controlled trial of mesenchymal stem cells injected into vein or artery in 31 patients with multiple system atrophy**
    - **Treated group had better motor function**
    - **Treated group had more small strokes**

Stem cell therapy for PD
Barriers to success

1. Overall quality of life unlikely to improve with replacement therapy alone as PD is a complex disorder with non-motor symptoms unrelated to dopaminergic neuron loss
2. Unregulated release of dopamine from fetal transplants resulted in motor complications
3. Lewy bodies have been found in fetal dopamine cell grafts 14 years after implantation
   - Transplanted cells can survive for years
   - The PD process continues after transplantation and is transmissible to the grafts
4. Some stem cell types capable of producing tumors
5. Helpful effects of transplanted cells often short lived

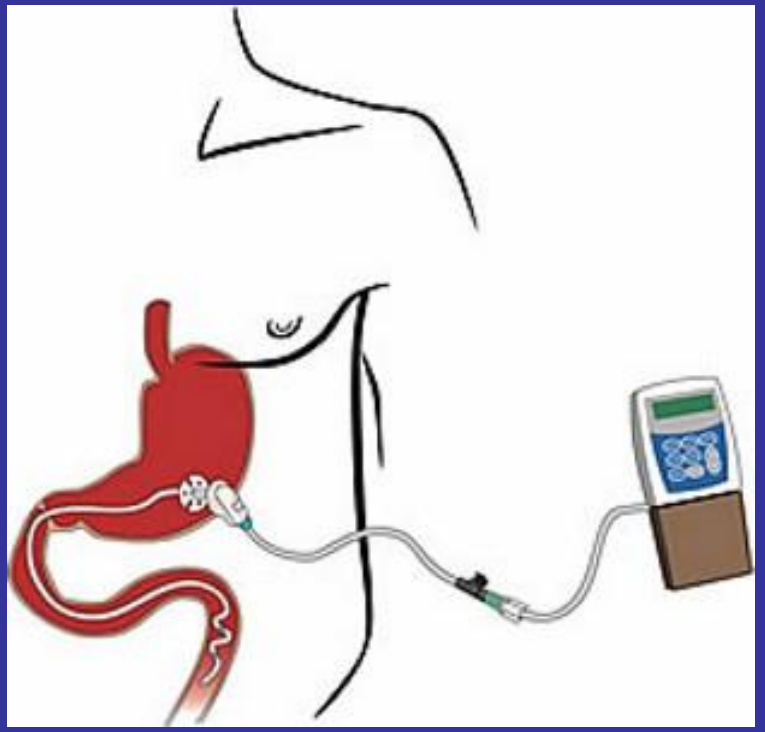
Dorsal column spinal cord stimulation for PD

1. Spinal cord stimulation is used to treat chronic pain
2. Chronic stimulation in a rat PD model associated with improvement in motor symptoms
3. Case reports of PD patients have shown motor improvement
4. Double blind, crossover trial failed to show benefit in two PD patients



Continuous levodopa infusion for PD: Duodopa

1. Continuous carbidopa-levodopa solution is pumped into the small intestine
2. Already approved in Europe for advanced PD and severe motor fluctuations



Continuous levodopa infusion for PD: Duodopa

- Recent randomized controlled trial comparing infusion to oral levodopa found infusion associated with :
  - reduced off time by 2 hours
  - Increased on time without troublesome dyskinesias
  - Significant improvement in activities of daily living
- Adverse events related to surgery or the device were common but rarely serious

If you are interested in ongoing clinical trials for Parkinson's disease in Hawaii…

- **Call 808 636-0681**

- **Resources:**
  - National Parkinson Foundation-Hawaii: parkinsonhawaii.org
  - Parkinson Action Network: parkinsonsaction.org
  - National Parkinson Foundation: www.parkinson.org
  - Parkinson's Disease Foundation: www.pdf.org
  - Information on clinical trials: Clinicaltrials.gov
  - Fox Foundation: www.michaeljfox.org