



# PD & the gut

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# 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.”

James Parkinson, 1817



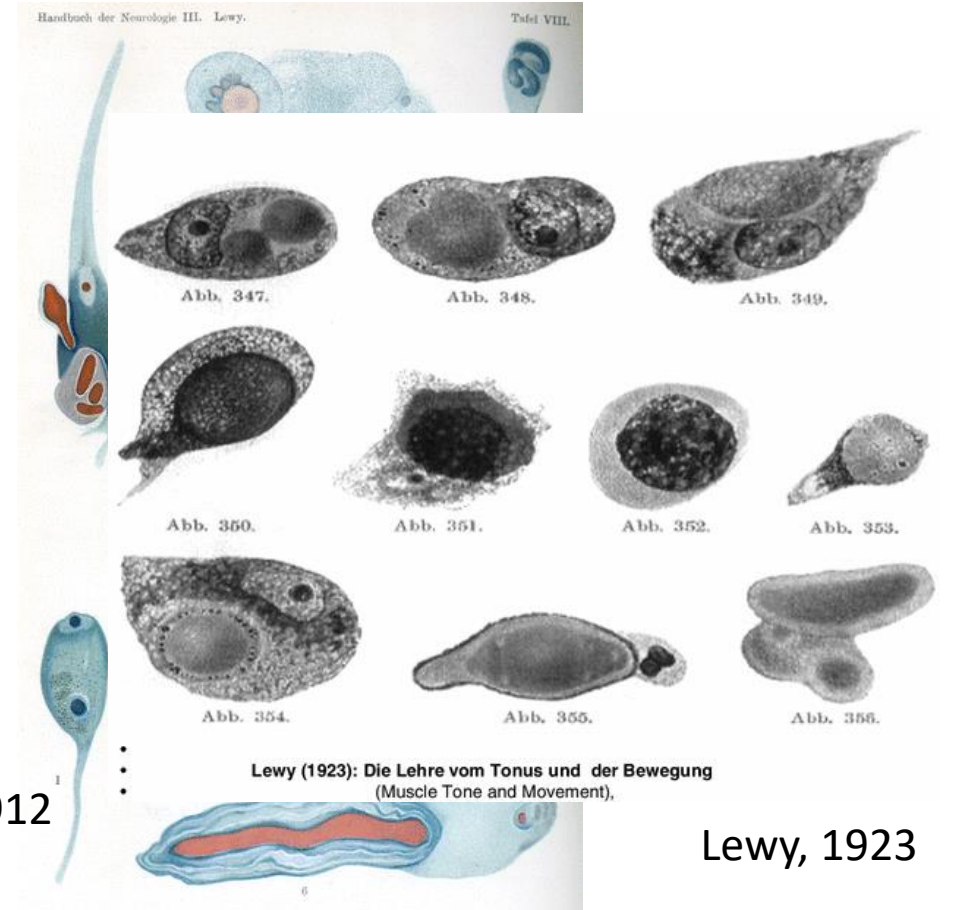
Illustration of Parkinson's disease by [William Richard Gowers](#), which was first published in *A Manual of Diseases of the Nervous System* (1886)

# Pathology of Parkinson's disease

## Lewy body



Lewy, pictured with Alzheimer's crew in 1913

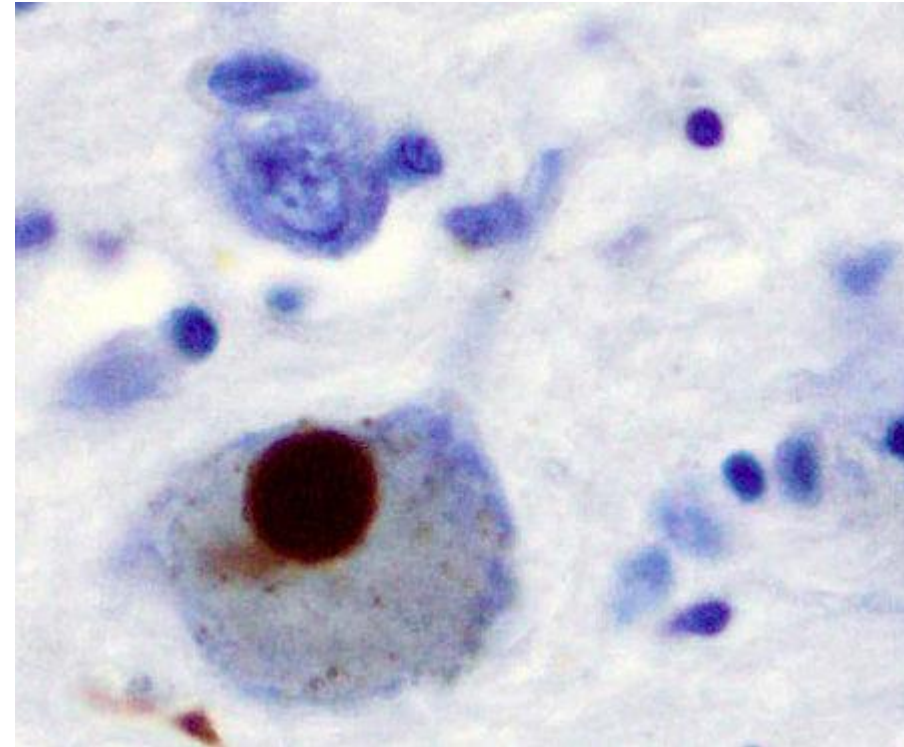
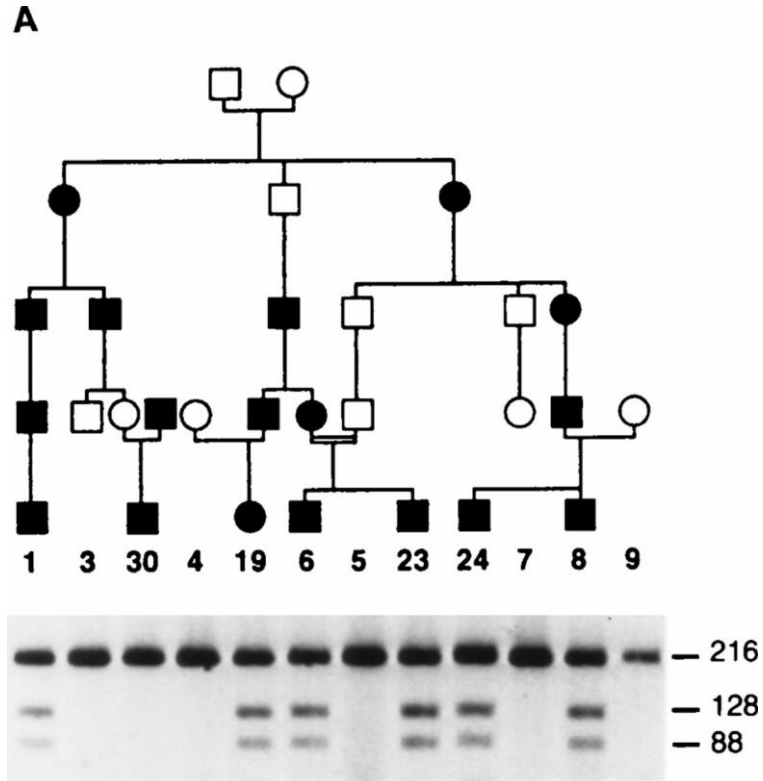


Lewy, 1912

Lewy, 1923



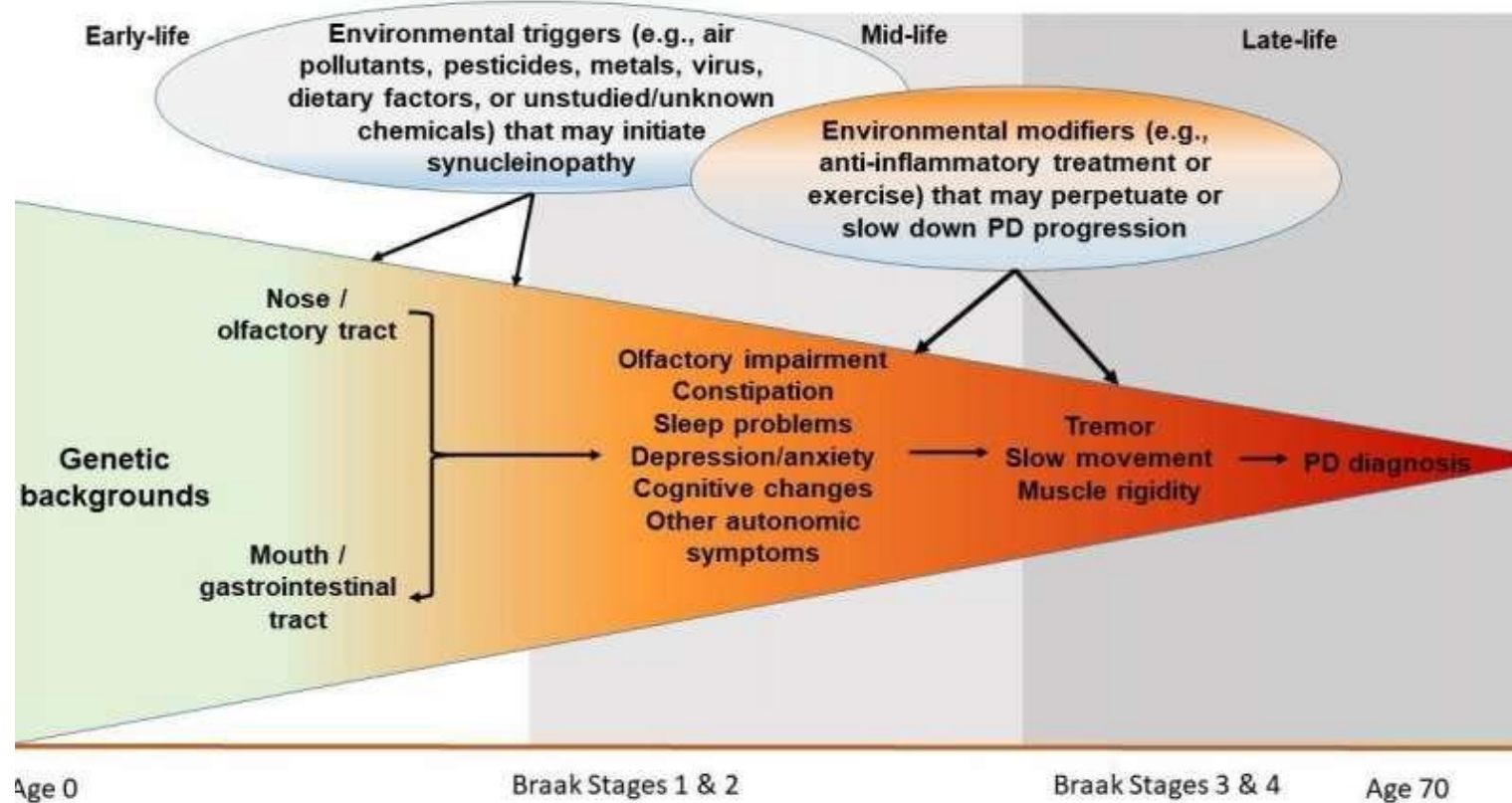
# $\alpha$ -synuclein and PD



Lewy bodies contain  $\alpha$ -synuclein

# The cause(s) of PD

## genetics & environment



# Constipation and PD

BM/day	N	Incident PD #	Incidence, rate/10K person-yrs	
			Unadjusted	Age-adjusted
<1	289	10	19.6	<u>18.9</u>
1	4371	66	8.0	7.9
2	1704	17	5.2	5.4
>2	426	3	3.8	3.9
Test for trend			P=0.002	P=0.005
Overall	6790	96	<u>7.5</u>	

**Appears highest in men with <1BM/day and laxatives > 2/week: 51.6/10,000 person years**

	<i>Prevalence of iLB's in 245 decedents</i>
> 1 BM daily	6.5%
1 BM daily	13.5%
< 1 BM daily	24.1%

Ross et al. *Parkinsonism Rel Disord* 2012;18S1:S199

Abbott RD et al. *Neurology* 2001;57:456.

# Other evidence of gut involvement in PD epidemiology

- Appendectomy may ↓ risk of PD
- Vagotomy (surgical treatment for ulcer) may ↓ risk of PD
- Inflammatory bowel diseases (Crohn's disease & Ulcerative colitis) ↑ the risk of PD
  - But...treatment with certain anti-inflammatory drugs protect against ↑ risk

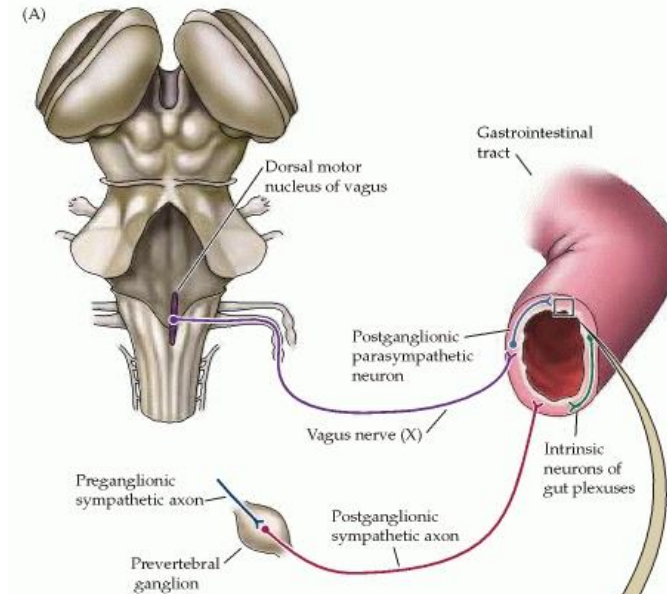
# Why intestines & PD?

Large surface area

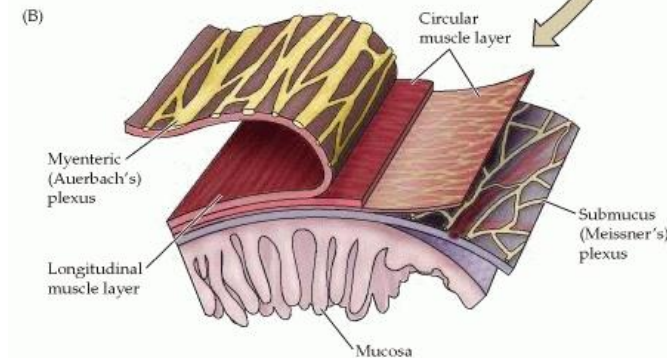


1. Barrier, Immune functions

4. Direct connection to critical brain area



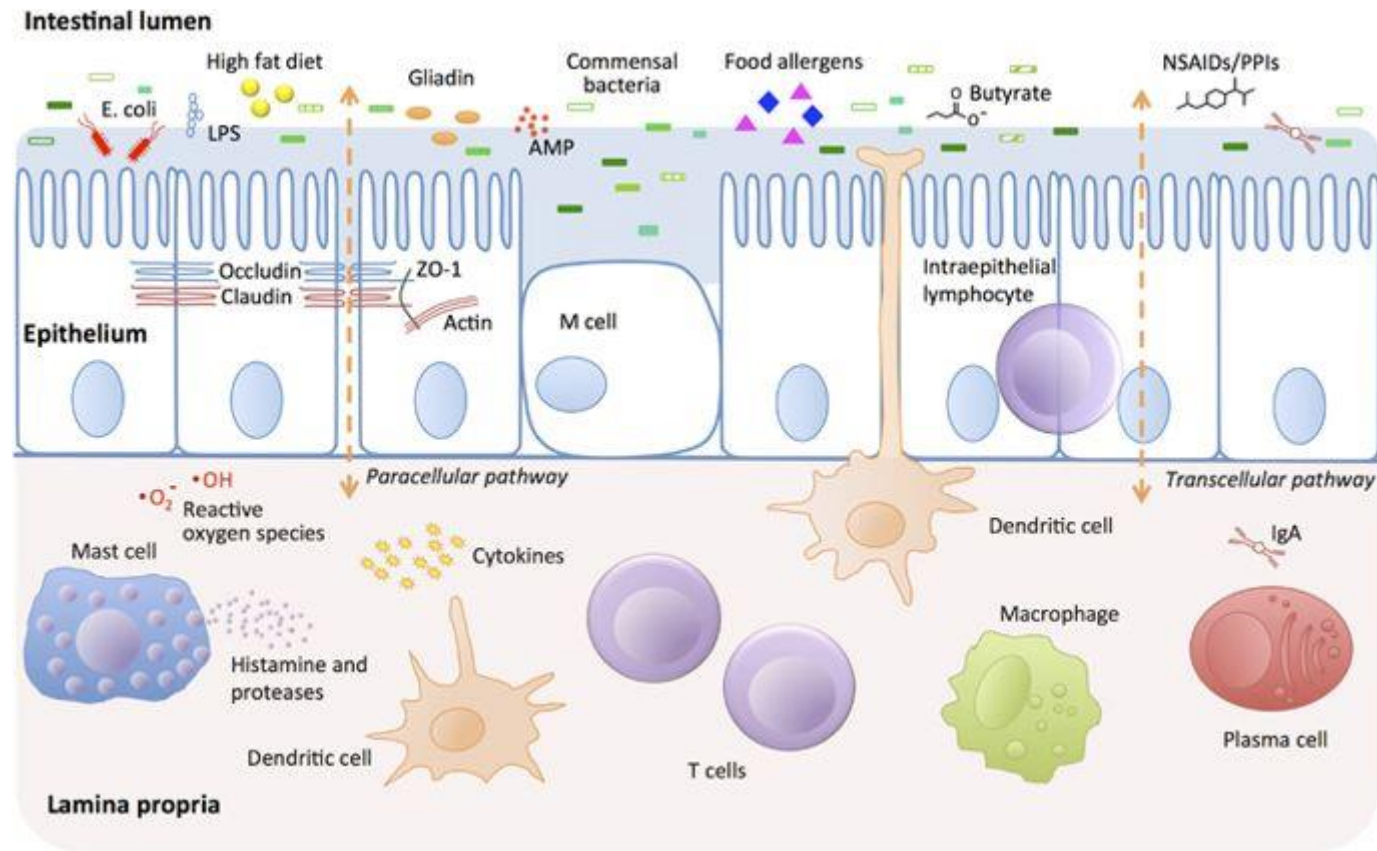
3. 100 million nerve cells



2. 100 trillion bacteria, toxin



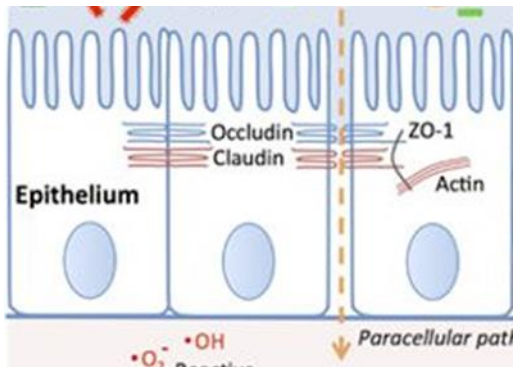
# Intestinal barrier



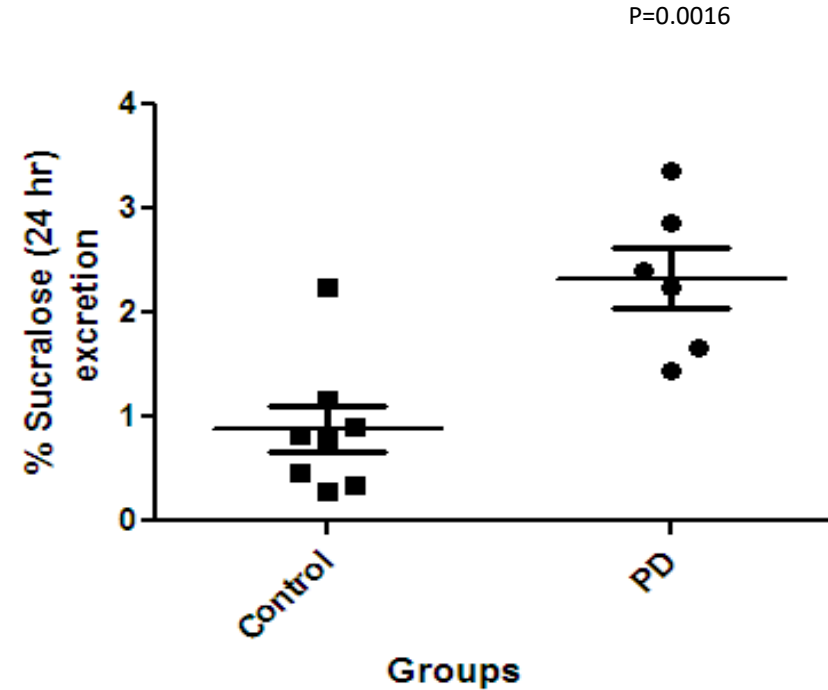
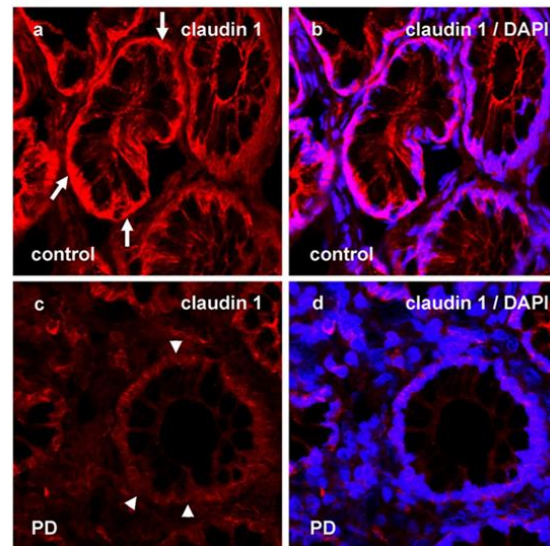
# Testing gut barrier function

## “Leaky gut” & PD

- Testing for “leaky gut”
  - Ingest poorly absorbed sugars
  - Collect 24 hour urine sample
- % of oral load excreted over 24 hours



(A) Histology of claudin 1 in the colon



Unpaired t-test:

significant difference between PD (Mean  $2.331 \pm SEM 0.2945$ ) compared to Control ( $0.8761 \pm 0.2209$ ) groups:  $t(12)=4.040$ ,  $p=0.0016$

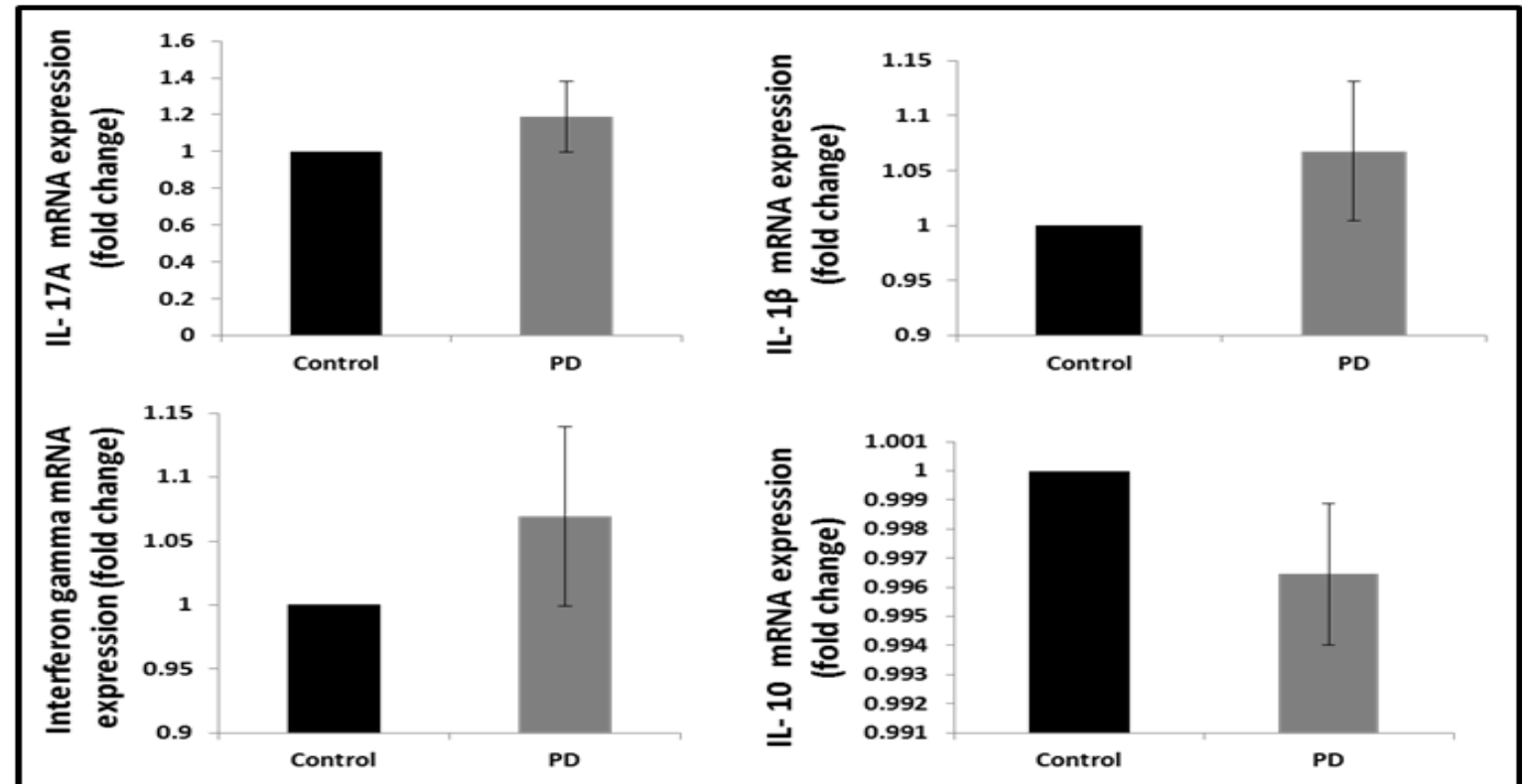
# Testing gut immune function

## cytokine expression and PD

- Cytokine=

substance secreted by immune system cells that has an effect on other cells

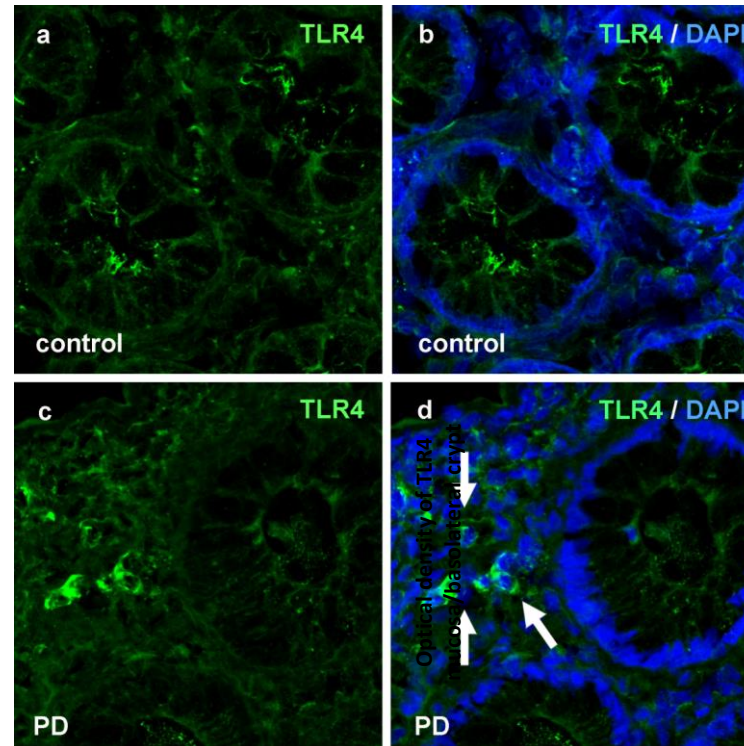
Cytokine expression in colon wall in PD



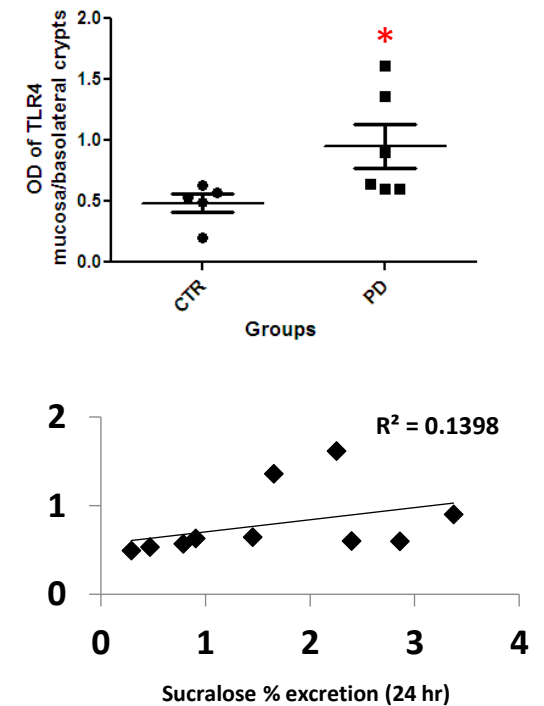
# Toll-like receptors & PD

## TLR 4 expression in colonic mucosa

- Toll-like receptors  
Proteins that sense  
invading microbes and  
initiate immune response

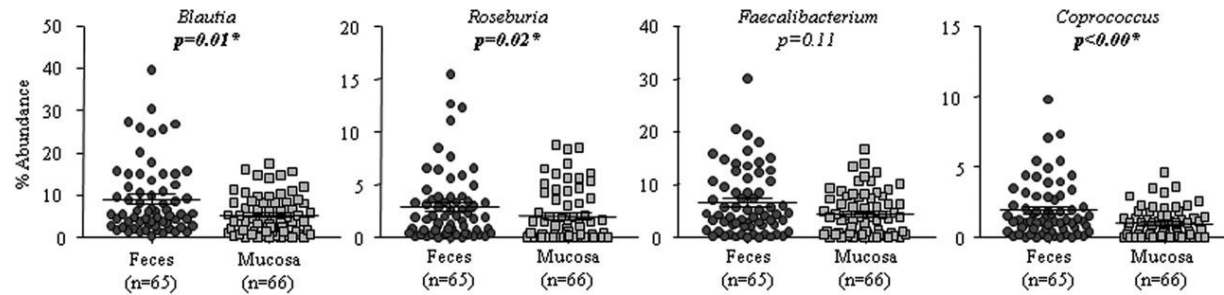


(B) Optical Density of TLR4 in the colon

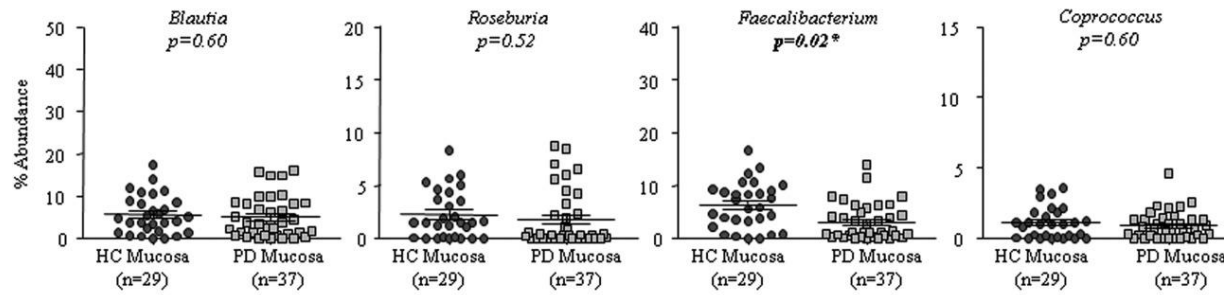




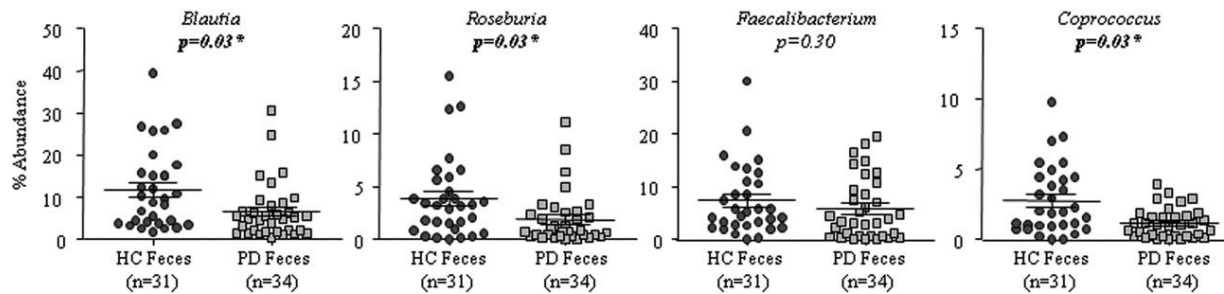
# Microbiota in PD



All cases  
Mucosa vs feces



Mucosa



Feces

# Microbiota in PD

<i>Author, year</i>	<i>N</i>	<i>Findings</i>
Heintz-Buschart, '18 <i>16S &amp; 18S rRNA</i>	76 treated PD 21 iRBD 78 HC	48 OTUs altered in PD; ↑ <b>akkermansia</b> & parent taxa 41 OTUs altered in iRBD; 30 in same direction as PD, 9 shared
Qian, '18 <i>16S rRNA</i>	45 PD 45 HC (spouse)	↑ clostridium, anaerotruncus, aquabacterium, sphingomonas, butryociococcus ↓ lactobacillus, sediminibacterium
Hill-Burns, '17 <i>16S rRNA</i>	212 PD 136 HC	13 OTUs altered in PD ↑ <b>akkermansia</b> , lactobacillus, <b>bifidobacterium</b> ↓ lachnospiracea
Li, '17 <i>16S rRNA</i>	24 PD 14 HC	↑ actinobacteria, proteobacteria (endotoxin producers) ↓ bacteroides, <b>prevotella</b> , ruminococcus (SCFA producers)
Unger, '16 <i>qPCR</i>	34 PD 34 HC	↑ <b>bifidobacterium</b> , enterobacteriaceae ↓ bacteroidetes, <b>prevotellaceae</b> ; faecalibacterium, lactobacillaceae, enterococcaceae ↓ <i>fecal SCFA</i>

# Microbiota in PD

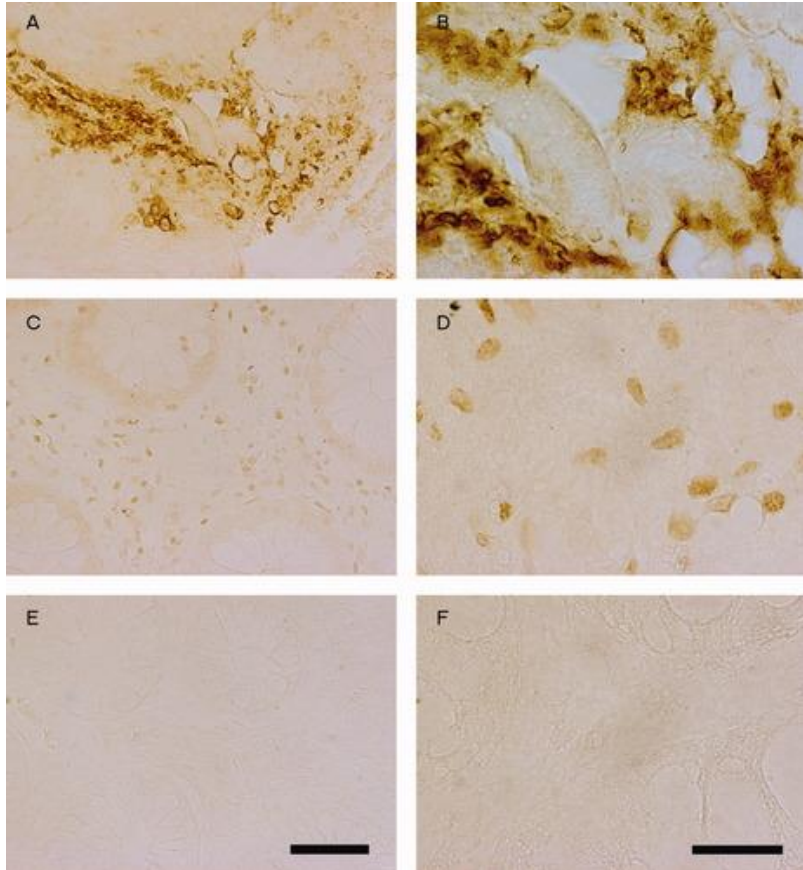
<i>Author, year</i>	<i>N</i>	<i>Findings</i>
Bedarf, '16 <i>Shotgun sequencing</i>	31 PD 28	↑ <b>akkermansia</b> , firmicutes ↓ <b>prevotellaceae</b> , eubacterium
Hopfner, '17 <i>16S rRNA</i>	29 PD 29 HC	↑ <b>lactobacillaceae</b> , enterococcaceae, barnesiellaceae
Petrov, '16 <i>16S rRNA</i>	89 PD 66 HC	↑ christiansella, catabacter, <b>lactobacillus</b> , <b>oscillospira</b> , <b>bifidobacterium</b> ↓ dorea, bacteroides, <b>prevotella</b>
Keshavarzian, '15 <i>16S rRNA</i>	38 PD 34 HC	↑ <b>akkermansia</b> , oscillospira, bacteroides ↓ <b>blautia</b> , coprococcus, roseburia, <b>faecalibacterium</b> , <b>prevotellaceae</b>
Scheperjans, '15 <i>16S rRNA</i>	72 PD 72 HC	↑ <b>lactobacillaceae</b> , verrucomicrobiaceae, bradyrhizobiaceae, clostridiales ↓ <b>prevotella</b>
Hasegawa, '15 <i>qPCR</i>	52 PD 36 HC	↑ <b>lactobacillus</b> , enterococcaceae ↓ clostridium, bacteroides

# What do microbiome studies in PD have in common?

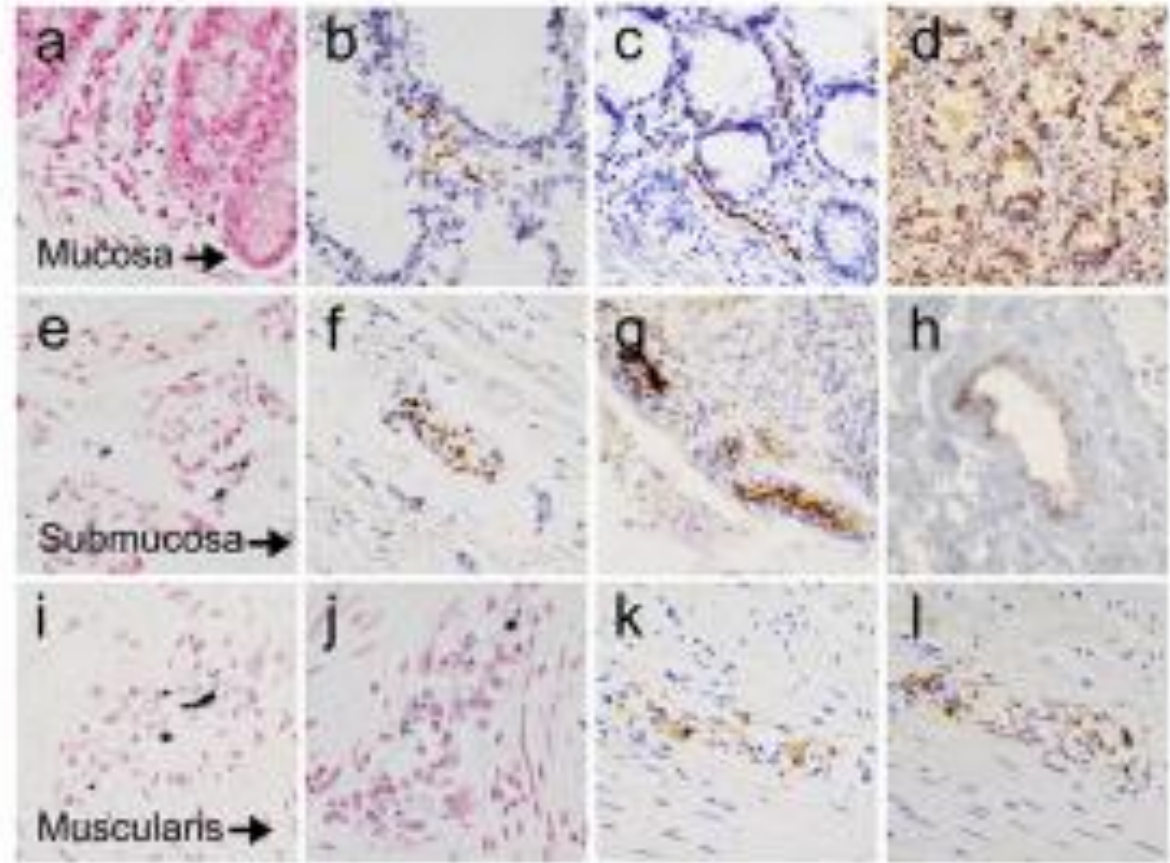
- ↑ inflammatory bacteria
- ↓ anti-inflammatory bacteria



# $\alpha$ -synuclein in colon biopsies



Shannon et al. *Mov Disord* 2012;27(6):709



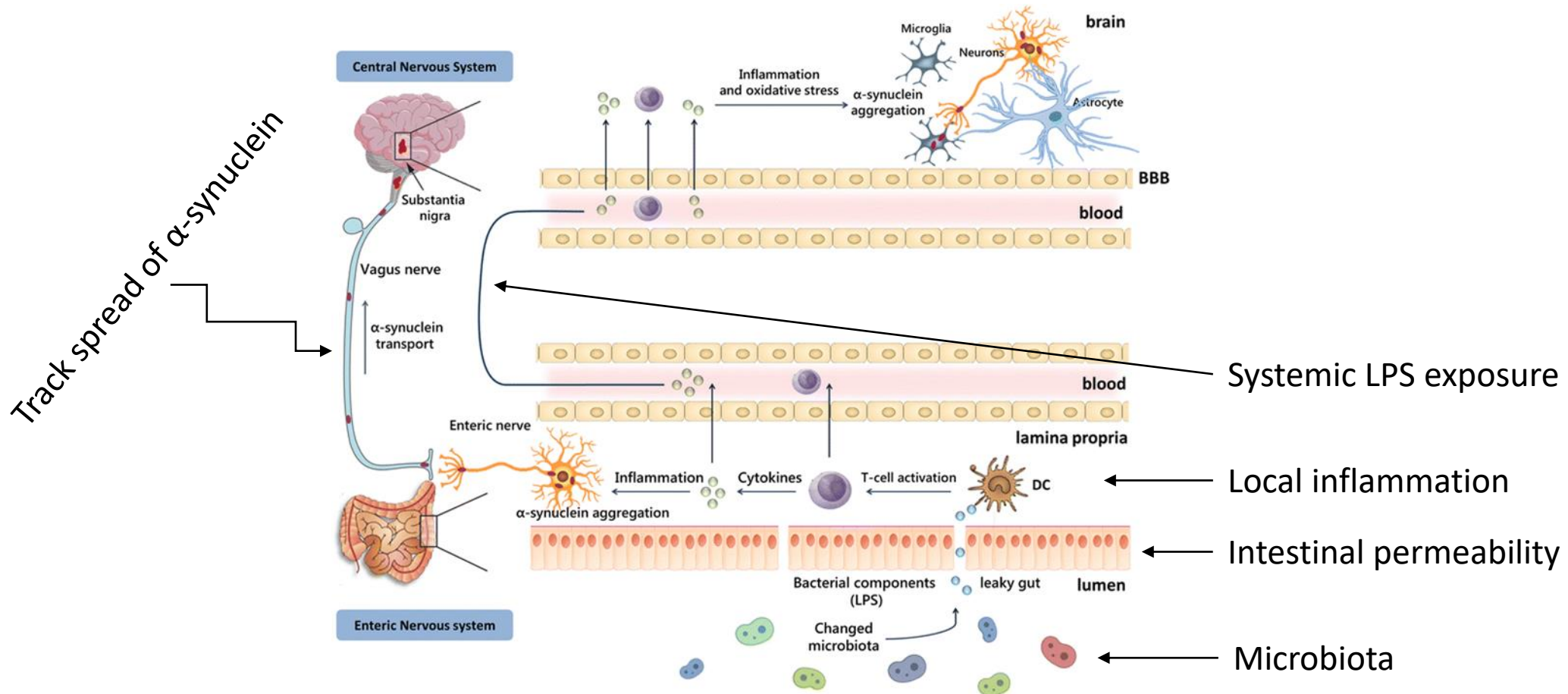
Beach et al (autopsy studies)

# Conclusions about gut function in PD (so far...)

- PD: “leaky gut”
- PD: evidence of immune activation/inflammation in the gut
- PD: altered bacterial composition favoring inflammation
- PD: abnormal  $\alpha$ -synuclein in intestinal wall (??)

**Association does not = causation**

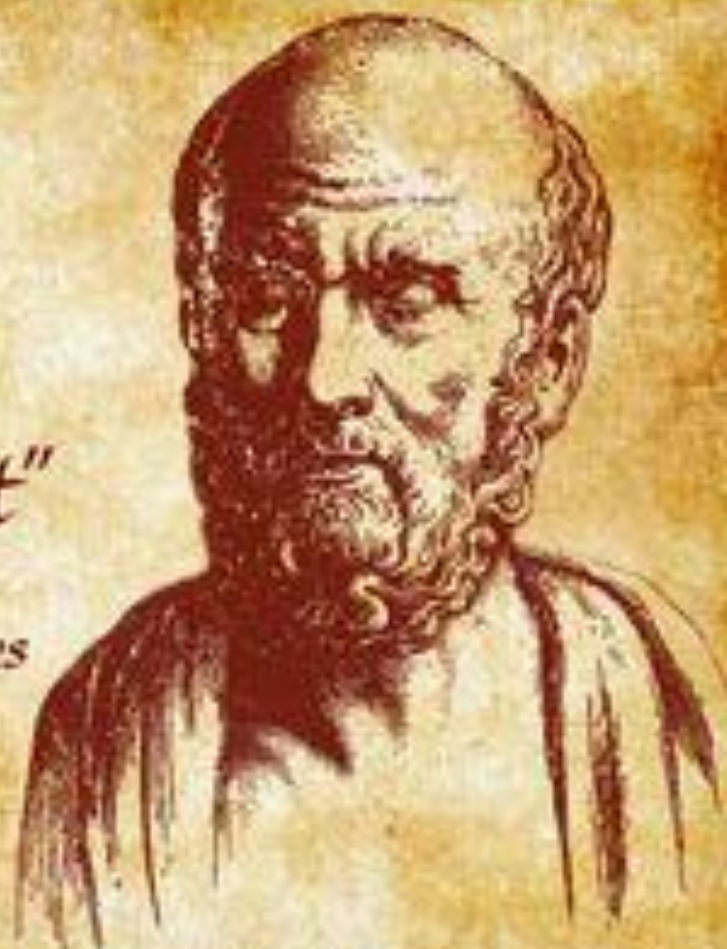
# How might gut changes contribute to PD?



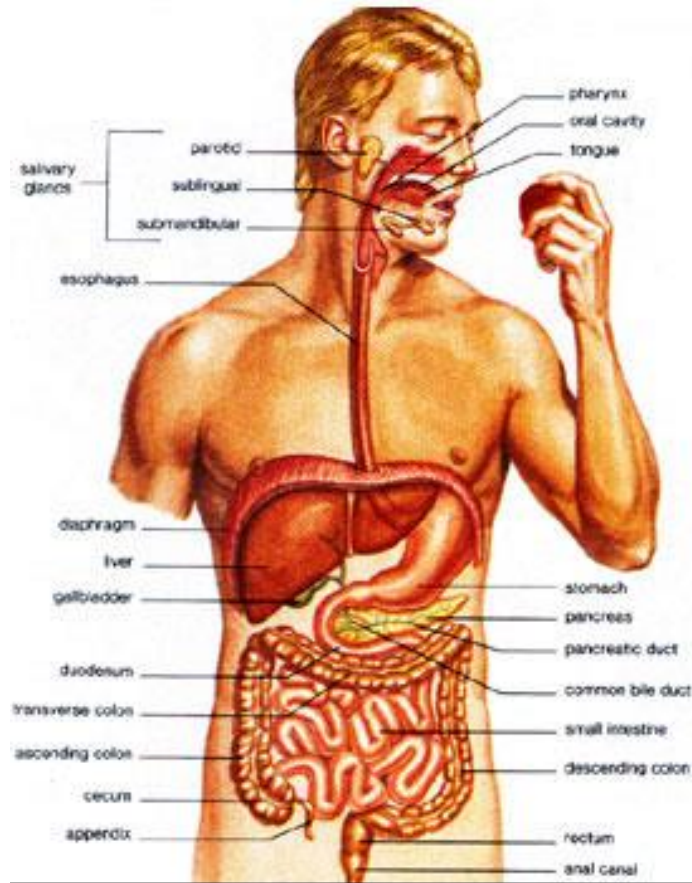


*"All Disease  
begins in  
the gut"*

*~Hippocrates*







# Gastrointestinal dysfunction

- Drooling
  - Abnormal swallowing
  - Bloating
  - Nausea
  - Belching
  - Abdominal pain
  - Constipation
  - Flatulence
  - Defecatory dysfunction
  - Weight loss
- } Slow transit

# Drooling & dysphagia in PD

<i>HY score</i>	<i>N</i>	<i>Drooling</i>	<i>Dysphagia</i>
1	53	25%	8%
1.5	27	19%	11%
2	163	35%	13%
2.5	95	40%	20%
3.0	72	46%	32%
4.0	26	65%	46%
<i>P-value</i>	<0.001	<0.001	<0.001

# Gastrointestinal dysfunction in PD

## Upper GI dysmotility

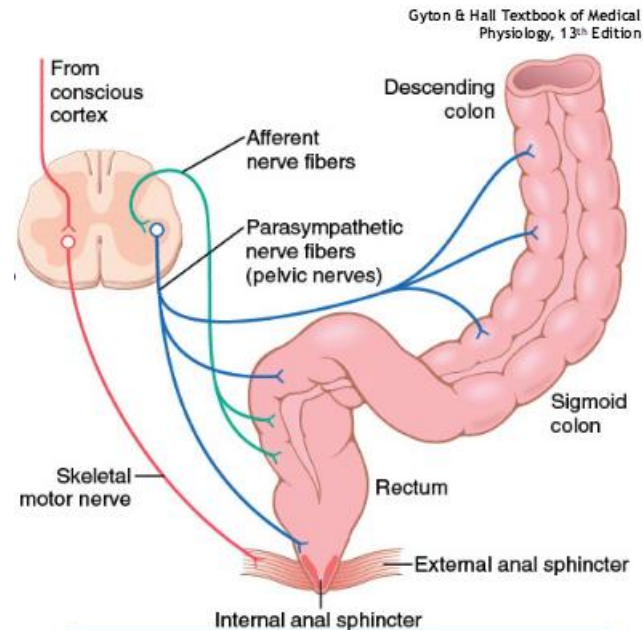
- > 60% of patients
- Esophagus, stomach
  - *Slow* esophageal transit, ↓ efficiency of sphincter
  - *Slow* stomach emptying

## Constipation

- 20-89%
- *Slow* colonic transit

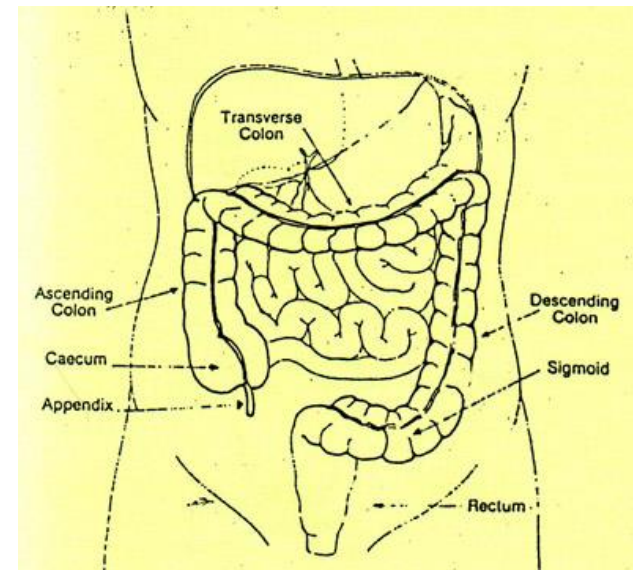
## Defecatory dysfunction

- 57-67%
- Paradoxical muscle contraction
- Spinal cord disease



# Constipation

- 20-81% of PD patients
  - Usual definition < 3 BM per week
- May begin years before motor symptoms
- ↑colonic transit time in 80% of PD
  - Normal: 20-39 hours
  - Early PD: 89 hours
  - Later PD: 44 to 130 hours



# Defecatory dysfunction

- Filling phase in PD
  - Resting anal pressure ↓
  - Smaller ↑ pressure when squeezing
  - Rectal and anal pressures increase together
- Defecation phase in PD
  - ↓ rectal contraction
  - ↓ abdominal straining
  - ↑ anal pressure

# Treatment for drooling

- Hard candy, gum
- Anticholinergic medications
  - Glycopyrrolate
- Botulinum toxin injections





# Common recommendations for swallow

## **Environment**

- Quiet place, no distractions
- Focus on eating
- No talking
- Don't eat when tired
- Eat when "on"

## **Posture & feeding**

- Sit close to the table
- Upright, head up
- Stay up after eating
- Small bites
- Chew thoroughly
- Swallow more than once

# Common recommendations for swallow

## Meal duration

- 30 minute maximum
- Don't rush



## Oral hygiene

- Brush thoroughly after meals
- Brush your tongue
- Remove dentures and clean after every meal
- Clean mouth even if no teeth

# Practical approaches to GI c/o

- Smaller, frequent meals
- Exercise
- Fiber, water, Beano
- Stool softeners, osmotic laxatives, prescription drugs
- Gastro-colic reflex
- “Squatty potty”



# Management of Constipation & Defecatory Dysfunction

## Constipation

- Stool softeners
- Laxatives
  - Senna
  - Polyethylene glycol
  - Lactulose
- Prescription drugs
  - Pyridostigmine bromide
  - Tegaserod
  - Lubiprostone
  - Linactolide

## Defecatory Dysfunction

- Pelvic floor physical therapy\*
- Botulinum toxin injections

# Anti-constipation paste

- Ingredients
  - 1 T Senna tea & 2.5 C boiling water
  - 3 # dried fruit (prunes, figs, raisins etc)
  - 1 C brown sugar
  - 1 C lemon juice
- Directions
  - Steep tea 5 minutes and strain. Boil the fruit in tea to soften (5 mins). Add sugar and lemon juice. Blend into a smooth paste. Store in “Tupperware” in freezer.
- Take 1-2 T daily as needed



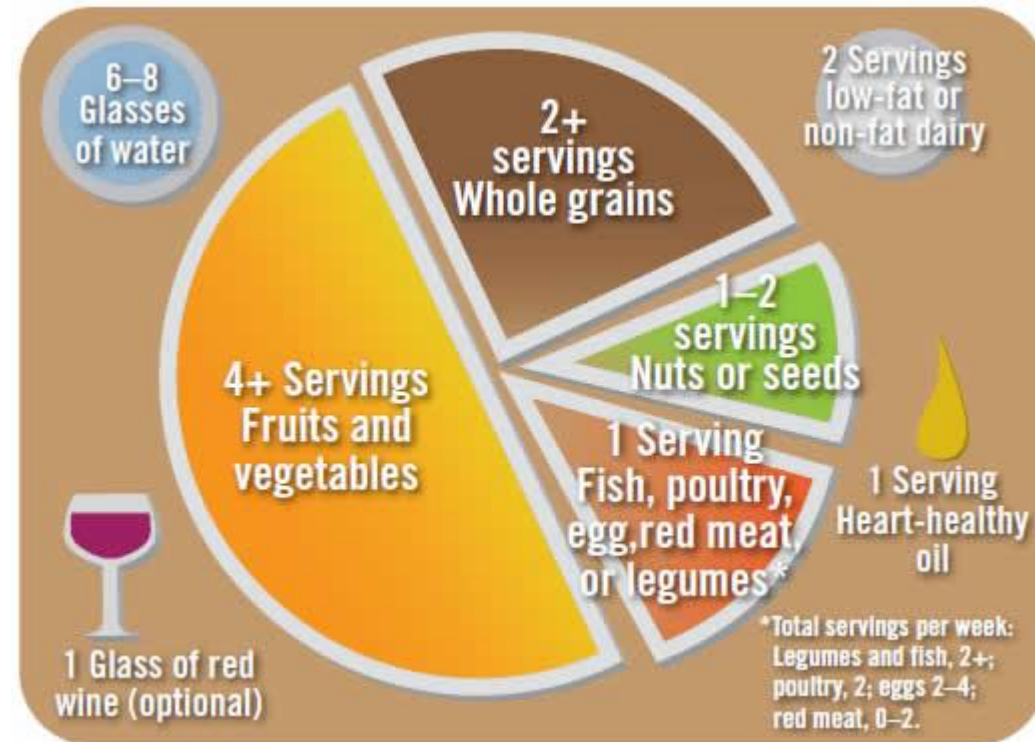
[http://naturalhealthtechniques.com/recipesconstipation\\_paste1\\_filesconstipation\\_paste1/](http://naturalhealthtechniques.com/recipesconstipation_paste1_filesconstipation_paste1/)

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# Diet & PD

- There is no proven Parkinson's diet
- Recommendations should be individualized
- Treat diet like medication: talk to your doctor
- More research is needed...



[https://www.google.com/search?q=what+does+a+mediterranean+diet+look+like+on+a+plate&tbm=isch&tbs=rimg:CVBCrXXXcVkljhfioJUIgEkz2F\\_1PFP-BkQ5IMakpyPlnpxxdxBbXnHsfwWrrW9i5DuqEmeQVml3Yk7T1K-w9OPpgioSCUWI4lQiASTPESZHWfQNJgPvKhIJYX88U\\_14GRDkrNTs4R6H\\_1dzkqEgkGxqSnI-WenBhSLchTER36IyoSCXF3EFteCex\\_1EfKHo-DycsTCKHJBautb2LkO6oRZnLpCbWZh\\_14qEgkSZ5BWYvdiThFwps4FB5dsmyoSCdP Ur7D04-mCEfo0KhgphT1\\_1&tbo=u&sa=X&ved=2ahUKEwi4uMDktOThAhXOna0KHWbPBlkQ9C96BAgBEbs&biw=1528&bih=718&dpr=1.25#imgrc=YYjktV7J94otfM:](https://www.google.com/search?q=what+does+a+mediterranean+diet+look+like+on+a+plate&tbm=isch&tbs=rimg:CVBCrXXXcVkljhfioJUIgEkz2F_1PFP-BkQ5IMakpyPlnpxxdxBbXnHsfwWrrW9i5DuqEmeQVml3Yk7T1K-w9OPpgioSCUWI4lQiASTPESZHWfQNJgPvKhIJYX88U_14GRDkrNTs4R6H_1dzkqEgkGxqSnI-WenBhSLchTER36IyoSCXF3EFteCex_1EfKHo-DycsTCKHJBautb2LkO6oRZnLpCbWZh_14qEgkSZ5BWYvdiThFwps4FB5dsmyoSCdP Ur7D04-mCEfo0KhgphT1_1&tbo=u&sa=X&ved=2ahUKEwi4uMDktOThAhXOna0KHWbPBlkQ9C96BAgBEbs&biw=1528&bih=718&dpr=1.25#imgrc=YYjktV7J94otfM:)

# Probiotics & PD

- No high quality studies...

## PROBIOTIC FOOD



kombucha



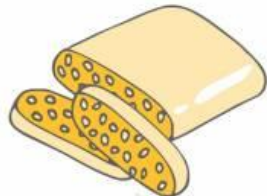
sauerkraut



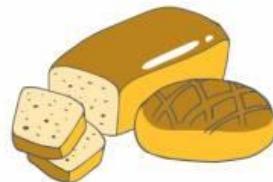
dairy products



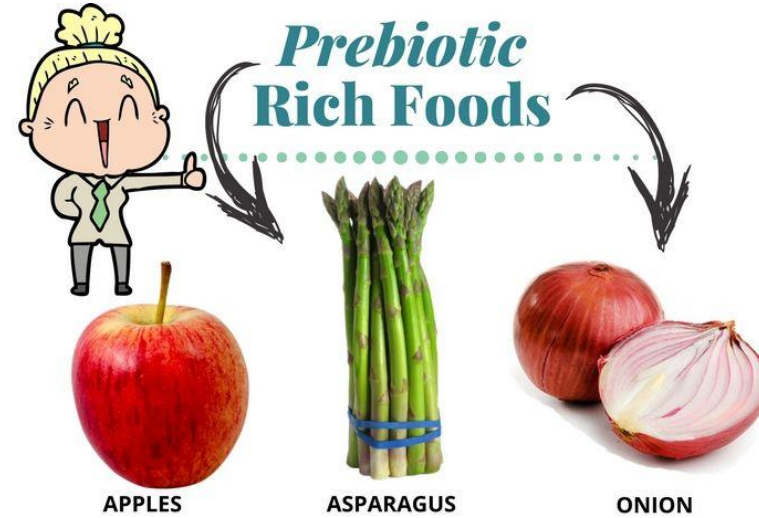
miso soup



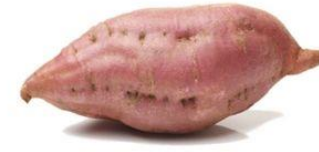
soy tempe



sourdough bread



BERRIES



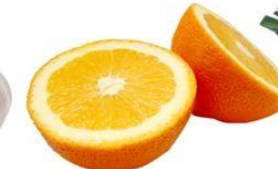
SWEET POTATO



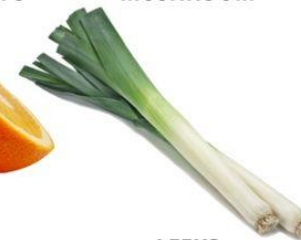
MUSHROOM



GARLIC



ORANGES



LEEKS

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Questions?