Gastrointestinal Dysfunction in Parkinson's Disease

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James Parkinson

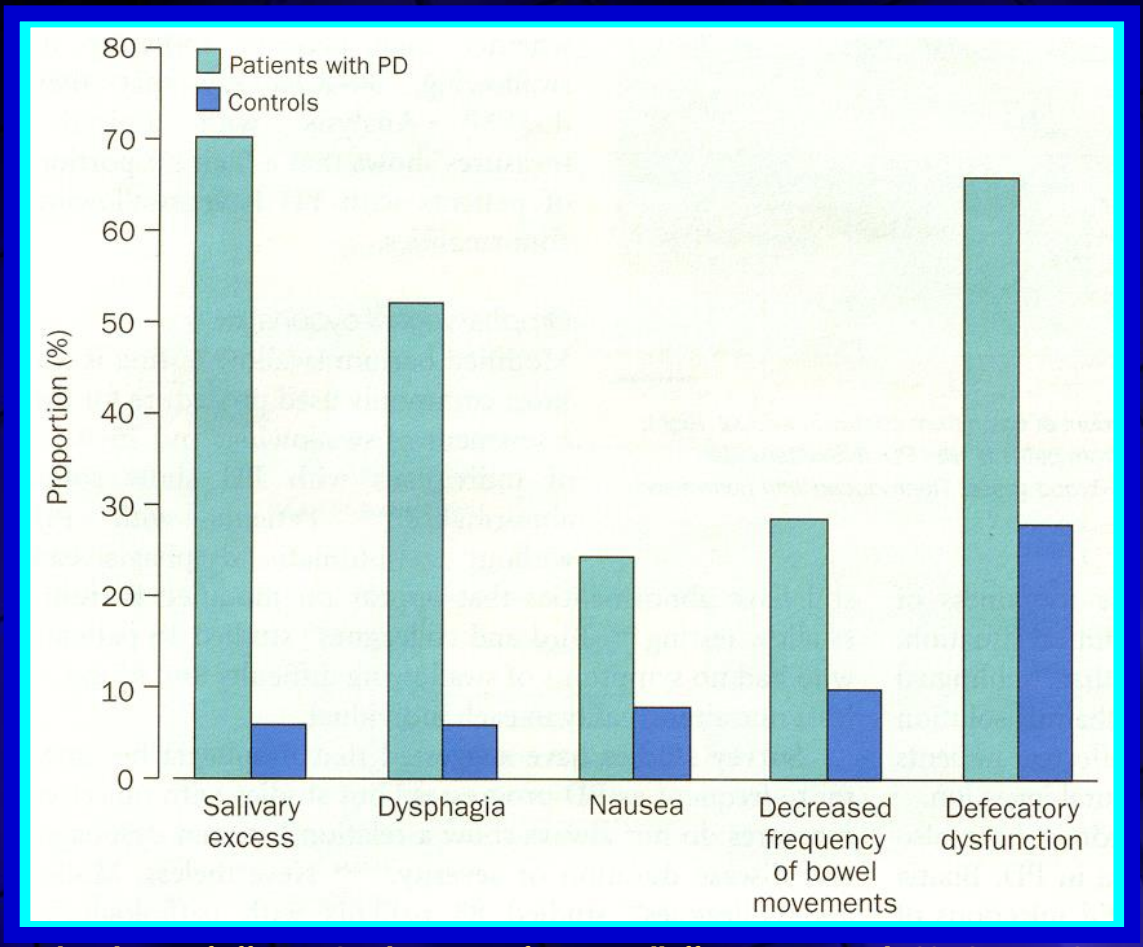
- "….so much are the actions of the muscles of the tongue, pharynx, &c. impeded by impaired action and perpetual agitation, that the food is with difficulty retained in the mouth until masticated; and then as difficultly swallowed"

- "the saliva fails of being directed to the back part of the fauces, and hence is continually draining from the mouth"

- "the bowels, which had been all along torpid, now, in most cases, demand stimulating medicines of very considerable power: the expulsion of faeces from the rectum sometimes requiring mechanical aid"

Parkinson J. An Essay on the Shaking Palsy, 1817.

Gastrointestinal Symptoms in PD



Edwards LL, Pfeiffer RF, Quigley EM, Hofman R, Balluff M. Mov Disord 1991;6:151-156.

Gastrointestinal Symptoms in PD

Table 2 Frequency of nonmotor symptoms in patients with PD and controls[a]

	PD	Control	*p* Value
Total no. (%) of NMS	8.4 (4.3)	2.8 (2.6)	<0.001[b]
Gastrointestinal tract, n (%)			
Sialorrhea	89 (56.0)	6 (6.1)	<0.001[b]
Dysphagia	32 (20.1)	3 (3.0)	<0.001[b]
Nausea	15 (9.4)	4 (4.0)	0.142
Constipation	67 (42.1)	7 (7.1)	<0.001[b]
Bowel incontinence	9 (5.7)	5 (5.1)	1.000
Incomplete bowel emptying	51 (32.1)	12 (12.1)	<0.001[b]

Khoo et al. Neurology 2013:80:276-281

Gastrointestinal Dysfunction

- Excess saliva
- Dysphagia
- Nausea/Gastroparesis
- Bowel dysfunction
  - Decreased frequency
  - Defecatory dysfunction
- **Weight loss**

Salivary Excess

Excess Saliva in PD

- Experienced by 56-78%
- Initially nocturnal drooling
- May progress to “handkerchief” stage
- Saliva production is actually decreased
- Drooling is due to :
  - Decreased swallowing frequency
  - Decreased swallowing efficiency
  - Tendency for mouth to be open
  - Stooped posture

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson’s Disease.
In: Parkinson’s Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.

Treatment of Excess Saliva

- Gum and hard candy
  - Make swallowing more "conscious" and more frequent
- Anticholinergic drugs
  - Avoid systemic drugs such as trihexyphenidyl or benztropine
  - Glycopyrrolate avoids central (brain-related) adverse effects but not peripheral ones
  - **Sublingual atropine ophthalmic solution**
  - Oral tropicamide films also being tested

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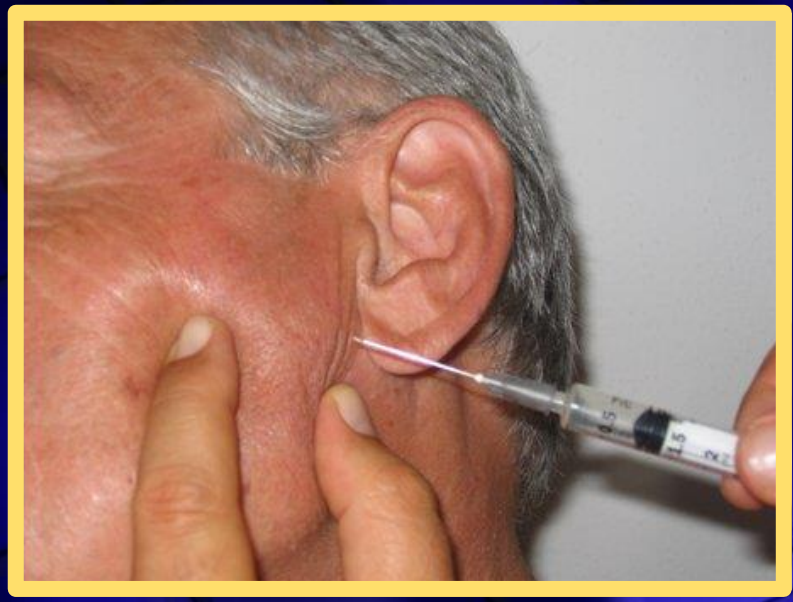
In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.

Treatment of Excess Saliva

- Intraparotid botulinum toxin injections
  - Benefits last for 3-4 months
  - Risk of pharyngeal muscle weakness
- Antiparkinson medication
  - May improve swallowing efficiency
- Behavioral swallowing therapy



Seppi K, et al. Mov Disord 2011;26(Suppl3):S42-S80.
Jost WH. Mov Disord 1999;14:1057.

Treatment of Salivary Excess

Dysphagia

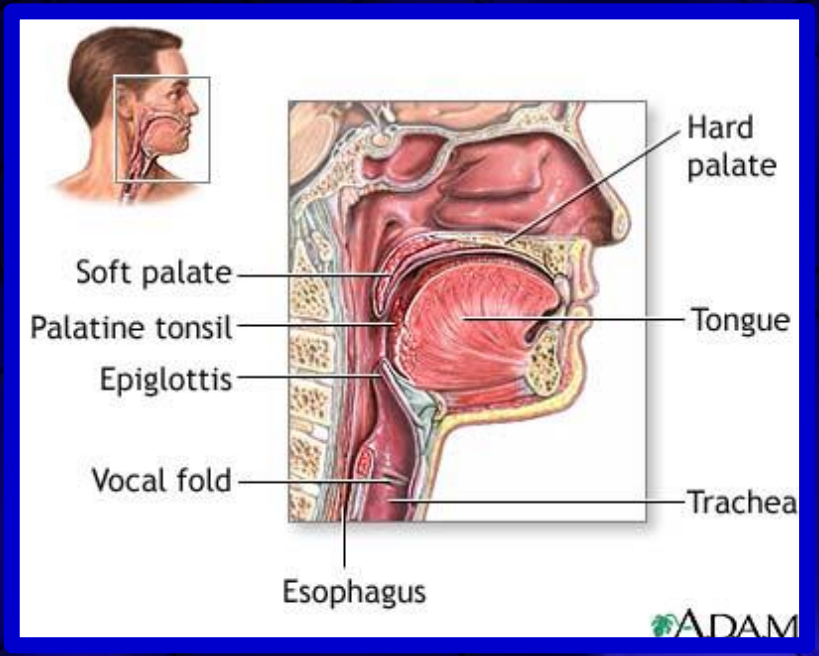
Dysphagia in PD

- Survey studies report dysphagia in 30-82%
  - Broad range probably reflects questionnaire detail
- Objective testing abnormalities range higher
  - MBS shows some abnormality in 75-97%
  - Patients may be clinically asymptomatic
- Aspiration present in 15-56% of patients
- Clinically silent aspiration present in 15-33%

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease.
In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.
Leopold NA. Dysphagia.
In: Parkinson's Disease and Nonmotor dysfunction, 2nd Edition (Pfeiffer RF, Bodis-Wollner I, Eds), 2013, pp. 133-144.

Dysphagia in PD

- Abnormalities at multiple levels
  - Oral - lips, tongue, mouth
  - Pharyngeal - throat
  - Esophageal - esophagus
- Oropharyngeal phase involves:
  - 30 pairs of striated muscles
- Impaired motor control due to:
  - Rigidity
  - Bradykinesia
  - Tremor (lingual)
- Decreased pharyngeal sensation due to pharyngeal sensory nerve involvement may also play a role



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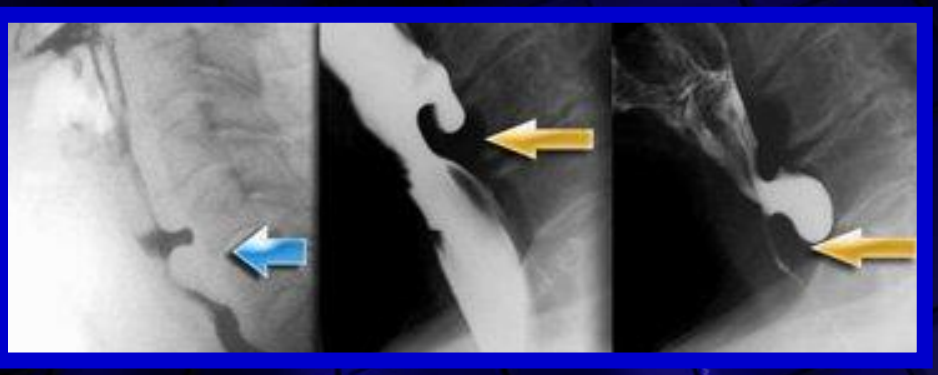
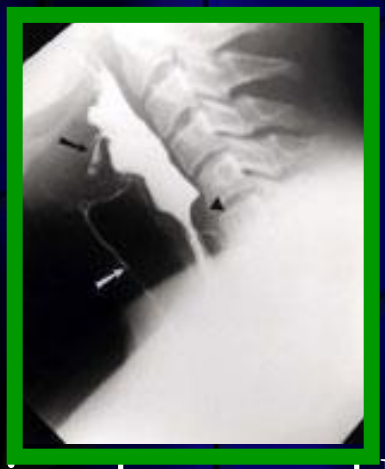
Saeian K, Shaker R. Management of Swallowing Disorders
In: Neurogastroenterology. (Quigley EMM, Pfeiffer RF , Eds), 2004, pp. 275-300.
Mu L, et al. J Neuropathol Exp Neurol 2013;72:614-623.

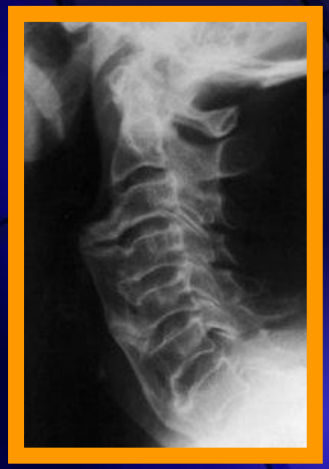
Dysphagia in PD: Other Causes



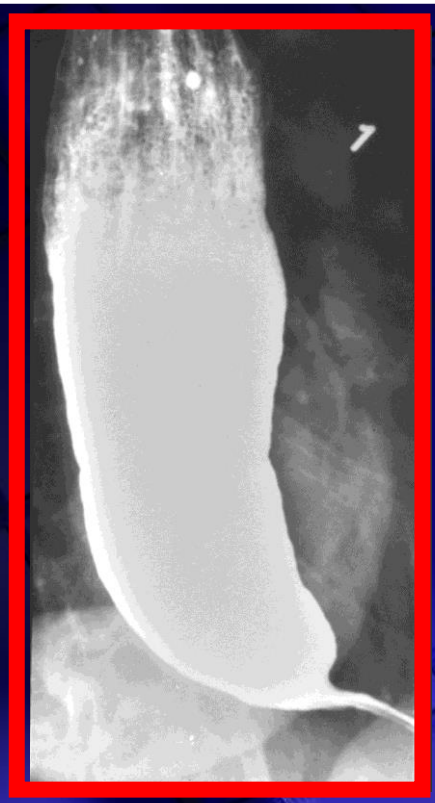
Zenker's diverticulum



Cricopharyngeal bar



Anterior osteophytes

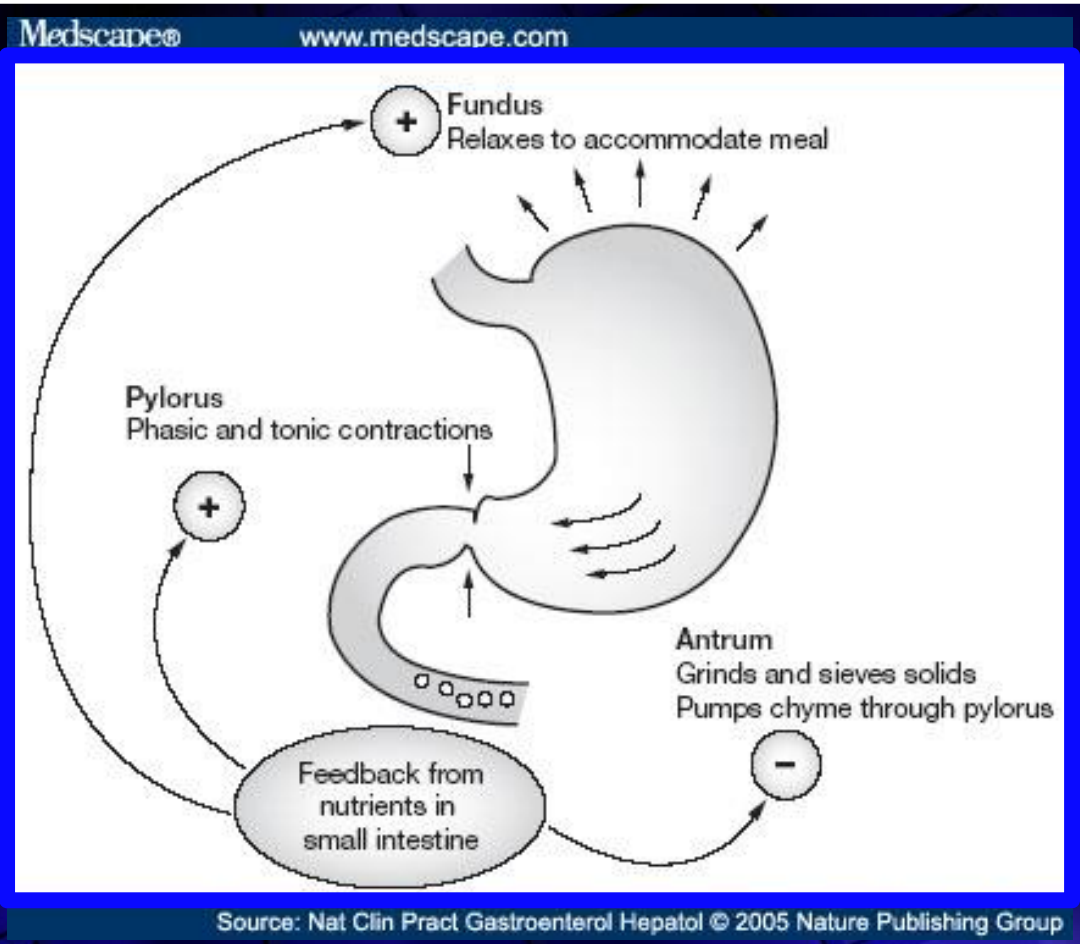


Achalasia

Treatment of Dysphagia

Nausea/Gastroparesis

Gastroparesis



Raynor CK and Horowitz M. Nat Clin Pract Gastroenterol Hepatol 2005;2:454-462.

Gastroparesis Symptoms

- Reduced appetite
- Early satiety (fullness after a few bites)
- Nausea
- Vomiting (sometimes undigested food)
- "Heartburn" (gastroesophageal reflux)
- Abdominal bloating and distension
- Weight loss

Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease.
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Rozenberg A, et al. Gastric Dysfunction in Parkinson's Disease.
In: Parkinson's Disease and Nonmotor Dysfunction, 2nd Edition (Pfeiffer RF, Bodis-Wollner I, Eds), 2013, pp. 145-154.

Gastric Emptying Results of ^{13}C-OBT

- May be evident in early untreated PD
- More prominent as disease advances
- May interfere with absorption of levodopa and other agents

	GEC	$t_{1/2b}$ (min)	t_{lagb} (min)	t_{peak} (min)
Controls (n = 22)	3.00 ± 0.41	107.31 ± 9.9	70.1 ± 10.2	73.6 ± 19.0
PD patients (n = 36)	2.33 ± 0.67***	169.0 ± 42.3***	105.1 ± 32.4***	111.3 ± 28.8***
UPDRS (0–30) (n = 11)	2.50 ± 0.49	147.0 ± 24.2	90.7 ± 14.8	100.9 ± 30.1
UPDRS (31–60) (n = 19)	2.34 ± 0.67	171.00 ± 37.7	106.5 ± 33.8	111.3 ± 28.0
UPDRS (61–92) (n = 6)	1.99 ± 0.93	203.0 ± 61.5†	127.4 ± 41.6‡	130.0 ± 22.6
H&Y (0–2) (n = 21)	2.54 ± 0.57	149.7 ± 28.2	93.5 ± 19.3	102.9 ± 25.2
H&Y (2.5–5) (n = 15)	2.04 ± 0.71*	196.0 ± 44.8**	121.4 ± 39.9**	123.0 ± 30.1*

Tanaka Y, et al. J Neurol 2011;258:421-426.
Heetun ZS, Quigley EMM. Parkinsonism Relat Disord 2012;18:433-440.
Hermanowicz N. Mov Disord 2008;23:152-153

Goetze, et al. Neurosci Lett 2005;375:170-173.

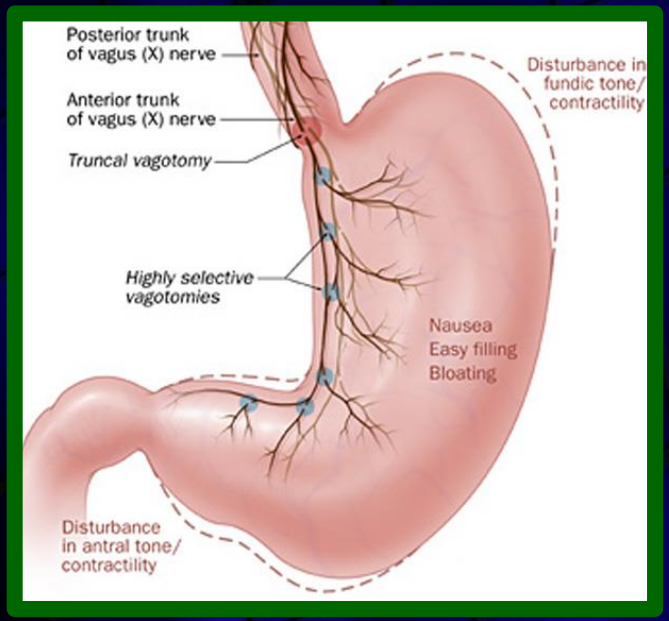
Treatment - Prokinetic Agents

- Dopamine antagonists
  - Domperidone
    - Not available in the USA
    - Rising concern for cardiotoxicity
  - Metoclopramide (Reglan)
    - Do **NOT** use in PD – crosses the BBB
- Motilin agonists
  - Erythromycin
    - Effective acutely when given iv; not appropriate for long term use
- Histamine H2 antagonist/cholinomimetics
  - Nizatidine (Axid)
    - Only one small pilot study
- Ghrelin agonists
  - Relamorelin (RM-131)
    - Still experimental; positive reports in diabetic gastroparesis
- Serotonin 5-HT_4 agonists (increase ACh release)
    - Cisapride and tegaserod withdrawn
    - Mosapride, prucalopride, and renzapride not available

Doi H, et al. Nizatidine ameliorates gastroparesis in Parkinson's disease: a pilot study. Mov Disord 2014;29:562-566.
Pfeiffer RF. Gastrointestinal and Swallowing Disturbances in Parkinson's Disease.
In: Parkinson's Disease: Non-Motor and Non-Dopaminergic Features (Olanow CW, Stocchi F, Lang AE, Eds.). 2011, pp. 257-273.

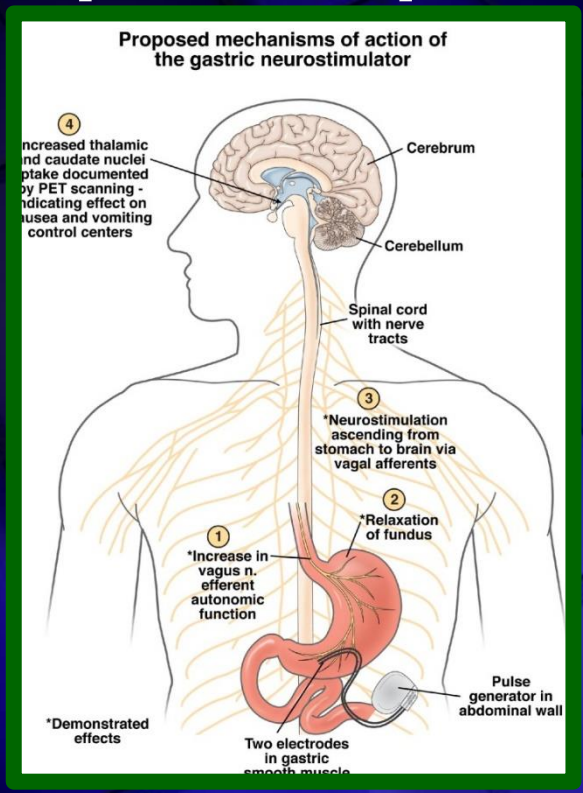
Treatment: Possible Approaches

Botulinum toxin injections of the pyloric sphincter



Gil R, Hwynn N, Fabian T, Joseph S, Fernandez HH. Parkinsonism Relat Disord 2011;17:285-287.

Gastric pacemaker implantation

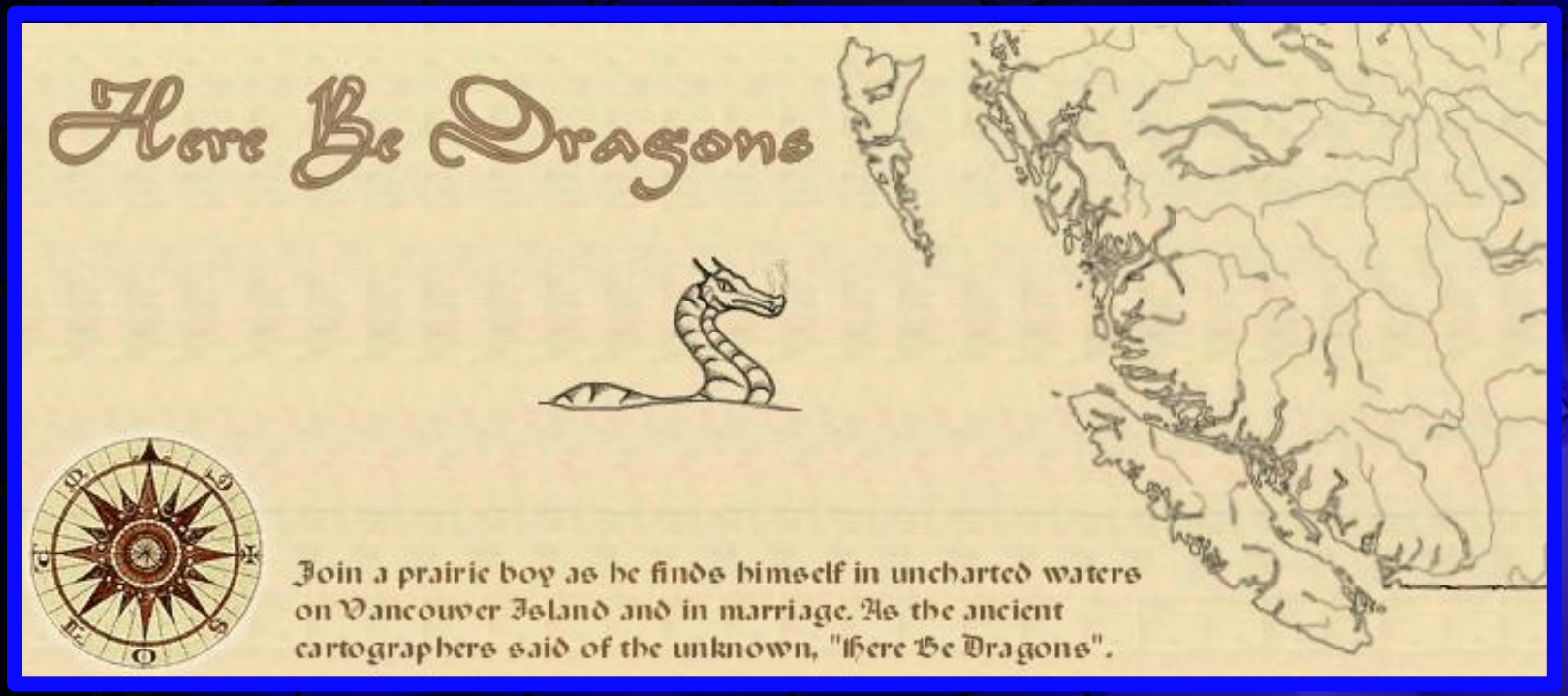


Reddymassu, SC, Sarosiek I, McCallum RW. Clin Gastroenterol Hepatol 2010;8:117-124

Circumventing Gastroparesis

- Bypassing the stomach
  - Levodopa/carbidopa intestinal gel
  - Subcutaneous apomorphine
  - Rotigotine

Small Intestine



Small Intestinal Bacterial Overgrowth in PD

- Not well-studied in PD
- Present in 54% of PD patients in one study
- Is characterized by:
  - Increased bacterial density in SI
  - Presence of colonic-type bacterial species in SI
- Results in malabsorption
  - Might explain weight loss in PD
- Impaired GI motility favors its occurrence

Gabrielli M, et al. Mov Disord 2011;26:889-892

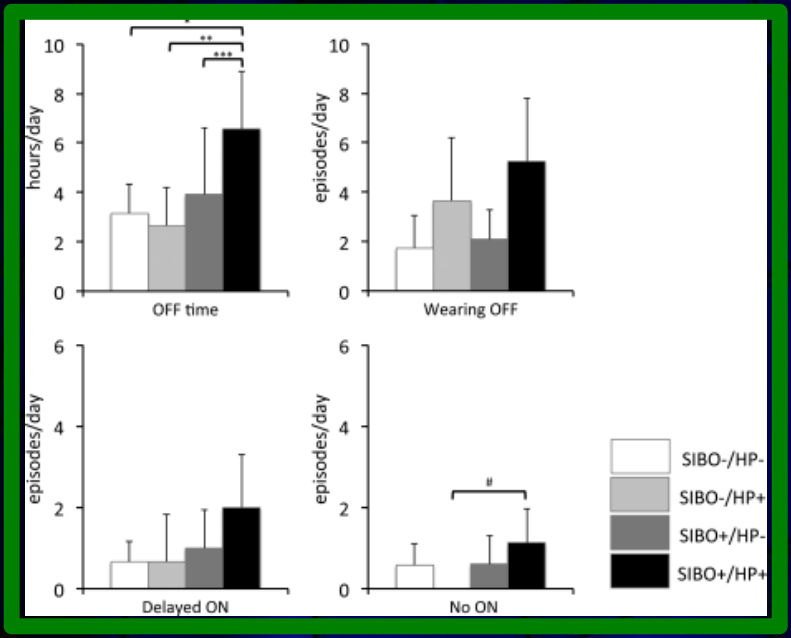
Small Intestinal Bacterial Overgrowth in PD

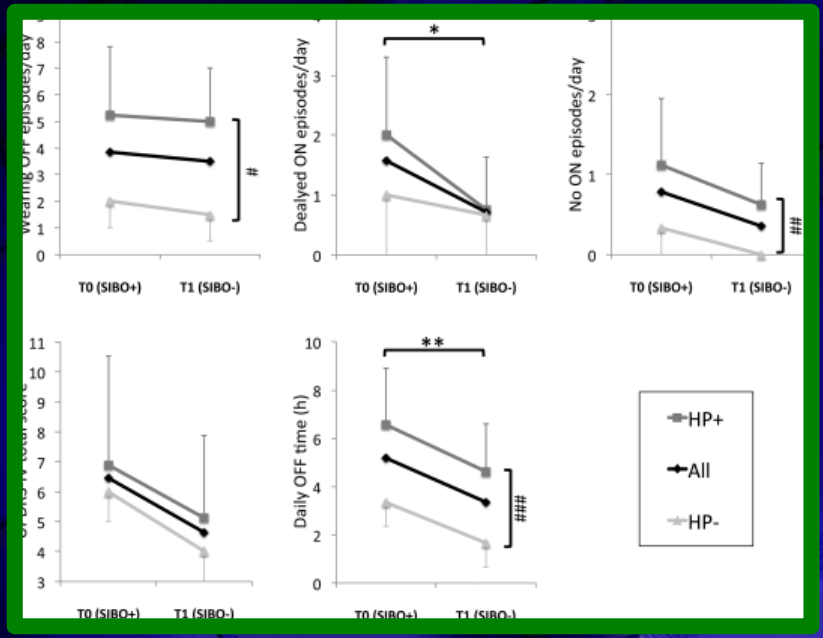
Prevalence of gastrointestinal symptoms in patients with Parkinson's disease affected by SIBO versus those without SIBO

	SIBO positive, % (n = 26)	SIBO negative, % (n = 22)	OR (CI)
Abdominal discomfort	30.8	27.3	ns
Bloating	**69.2**	**31.8**	**2.07 (1.42–16.40)**
Flatulence	**65.4**	**36.4**	**1.74 (1.01–10.83)**
Constipation	73.1	81.8	ns
Diarrhea	19.2	9.1	ns

Gabrielli M, et al. Mov Disord 2011;26:889-892

Small Intestinal Bacterial Overgrowth in PD





Fasano A, Bove F, Gabrielli M, et al. Mov Disord 2013;28:1241-1249.

Bowel Dysfunction

Bowel Dysfunction in PD

- Constipation (colonic inertia)
  - Decreased bowel movement frequency
- Defecatory dysfunction
  - Difficulty with the act of defecation

Constipation

- Defined as follows:
  - Fewer than 3 bowel movements weekly
- Occurs in 20-79% of PD patients

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
Pfeiffer RF. Gastrointestinal Dysfunction in Parkinson's Disease.
In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 309-326.
Pfeiffer RF. Intestinal Dysfunction in Parkinson's Disease.
In: Parkinson's Disease and Nonmotor dysfunction, 2nd Edition (Pfeiffer RF, Bodis-Wollner I, Eds), 2013, pp. 155-171

What Causes Constipation in PD?

- Colon transit time (CTT) is prolonged in PD
- Slowing occurs in 80% of PD patients
- Average CTT in PD is twice as long:

  44 hours vs. 20 hours
- Other investigators report much longer times

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
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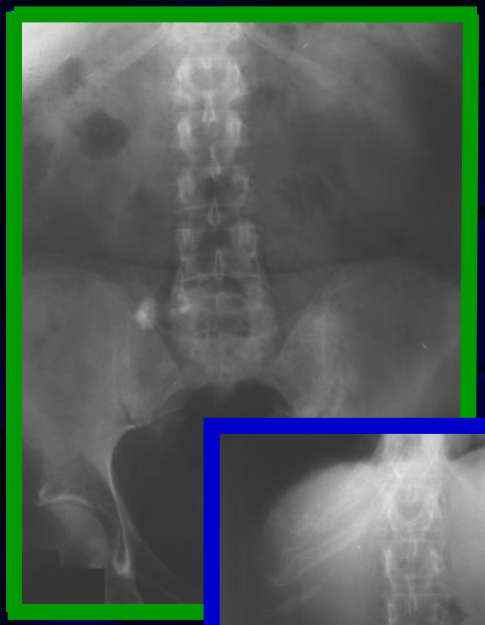
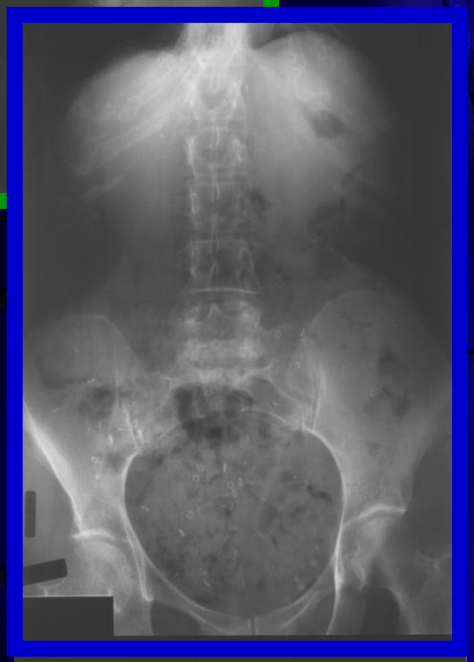
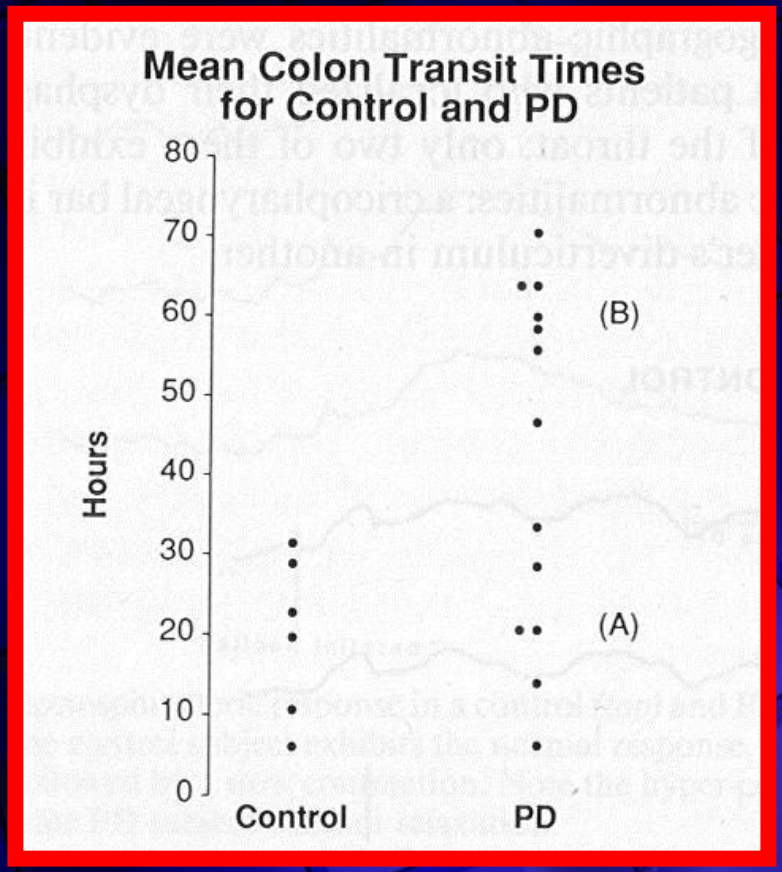
Colon Transit Time in PD

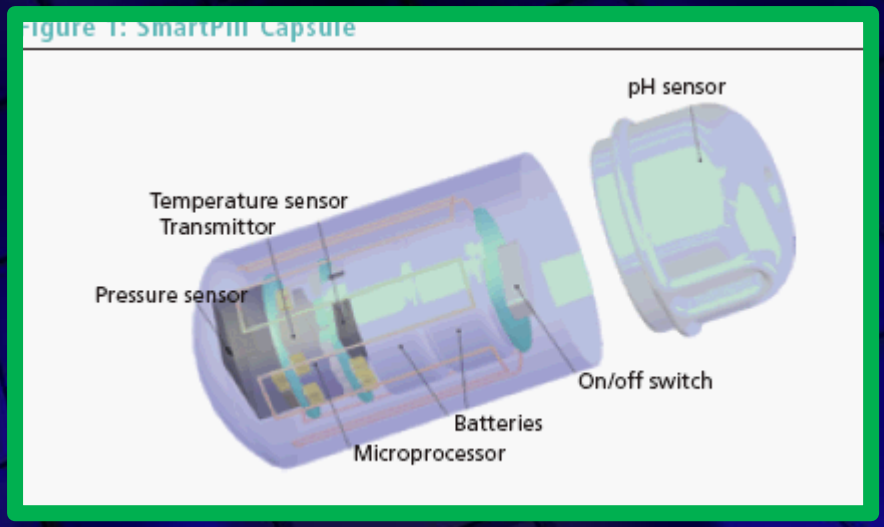






Edwards LL, et al. Am J Gastroenterol 1994;89:15-25.

GI Transit Time – And More



Prokinetic Agents

- Serotonin 5-HT-4 agonists
  - Cisapride
  - Tegaserod
  - Prucalopride
- Type 2 chloride channel activators
  - Lubiprostone (Amitiza)
- Guanylate cyclase 2 agonists
  - Linaclotide (Linzess)
- Cholinesterase inhibitors
  - Pyridostigmine (Mestinon)
- Prostaglandin analogs
  - Misoprostol (Cytotec)
- **Ghrelin agonists**
  - **Relamorelin (RM-131)**
- Surgical approaches
  - Colectomy

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Treatment of Colonic Dysmotility

Defecatory Dysfunction

- Develops in 66% of PD patients
- Characterized by:
  - Increased straining
  - Painful defecation
  - Incomplete emptying

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Normal Defecation

- Relaxation of:
  - Internal anal sphincter
  - External anal sphincter
  - Puborectalis
- Contraction of:
  - Abdominal wall muscles
  - Diaphragm
  - Glottic muscles

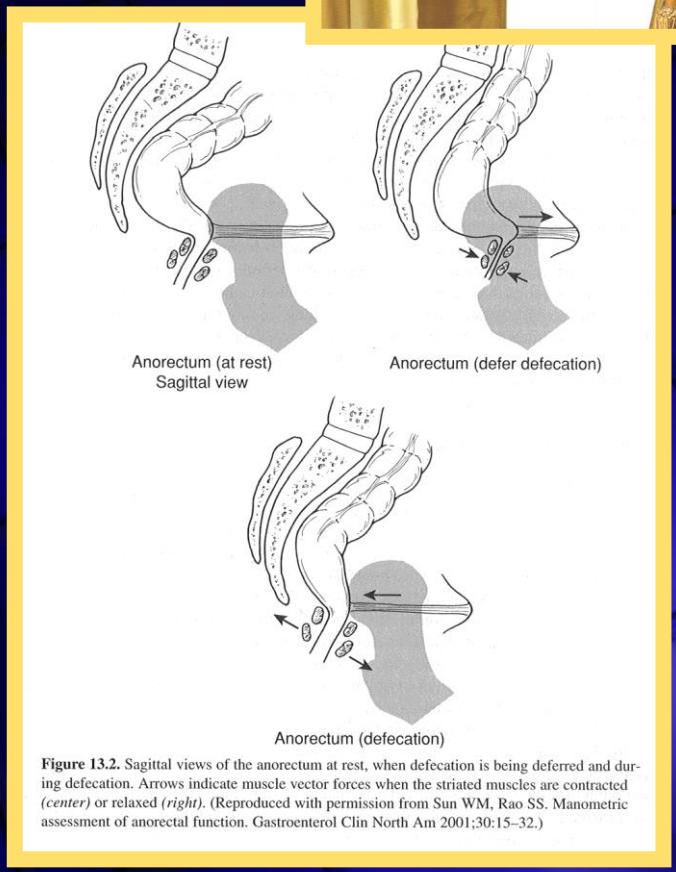

Figure 13.2. Sagittal views of the anorectum at rest, when defecation is being deferred and during defecation. Arrows indicate muscle vector forces when the striated muscles are contracted *(center)* or relaxed *(right)*. (Reproduced with permission from Sun WM, Rao SS. Manometric assessment of anorectal function. Gastroenterol Clin North Am 2001;30:15–32.)

Sun WM, Rao SS. Gastroenterol Clin North Am 2001;30:15-32.

Defecatory Dysfunction: Pathophysiology

- Impaired motor control/coordination:
  - Inadequate sphincter relaxation
  - Failure of anorectal angle to open
  - Insufficient intra-abdominal pressure
- Underlying mechanisms may include:
  - Bradykinesia
  - Rigidity
  - Dystonia (off-period phenomenon)

Pfeiffer RF. Parkinsonism Relat Disord 2011;17:10-15.
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Anorectal Testing in PD

Anorectal manometry

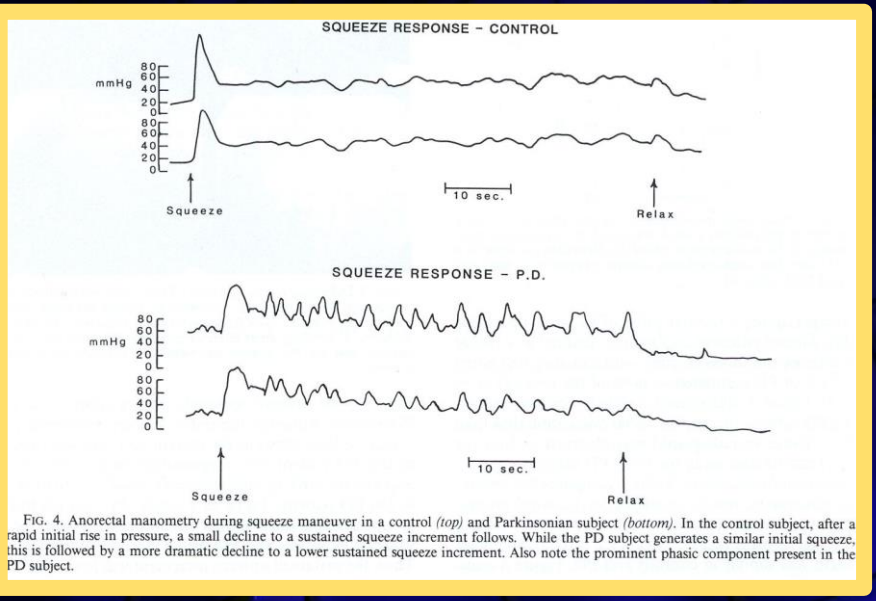


FIG. 4. Anorectal manometry during squeeze maneuver in a control *(top)* and Parkinsonian subject *(bottom)*. In the control subject, after a rapid initial rise in pressure, a small decline to a sustained squeeze increment follows. While the PD subject generates a similar initial squeeze, this is followed by a more dramatic decline to a lower sustained squeeze increment. Also note the prominent phasic component present in the PD subject.

Edwards LL, et al. Ann Neurol 1993;33:490-493
Ashraf, et al. Mov Disord 1994;9:655-663.

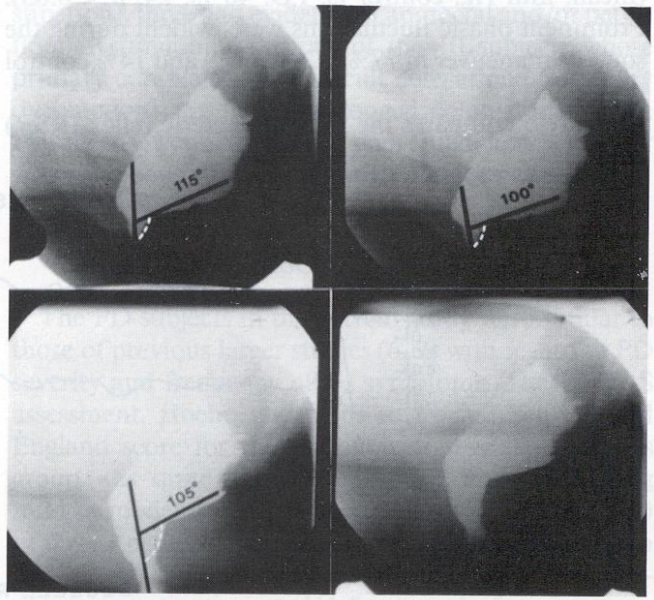
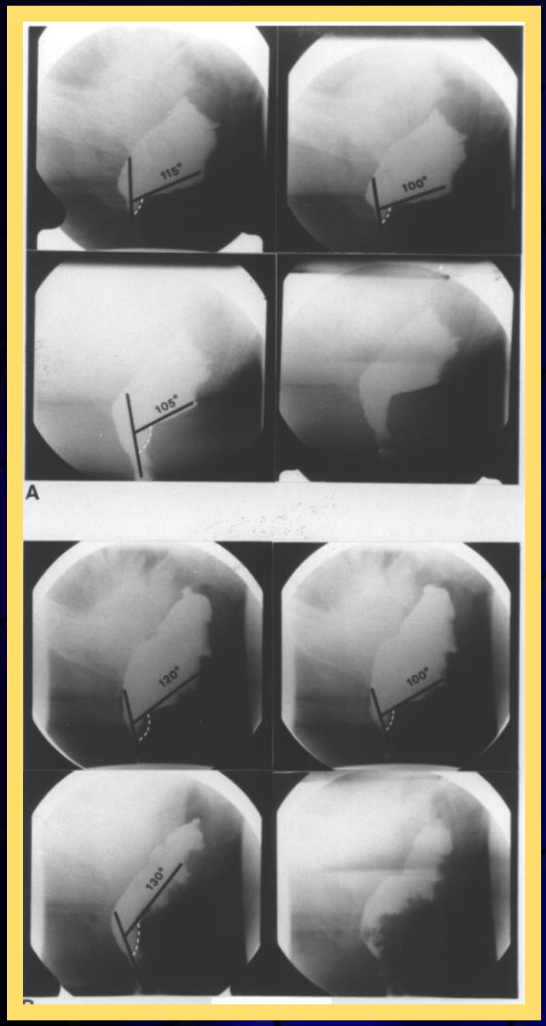


FIG. 3. Defecography in a PD subject. Frames from each maneuver in sequence; *top left,* rest; *top right,* squeeze; *bottom left,* strain; and *bottom right,* evacuate. Note (i) anorectal angle decreases rather than increases on straining, an example of paradoxical puborectalis contraction, and (ii) this subject was unable to evacuate the rectal contents.

Defecography

Anorectal Testing in PD



Before apomorphine

After apomorphine

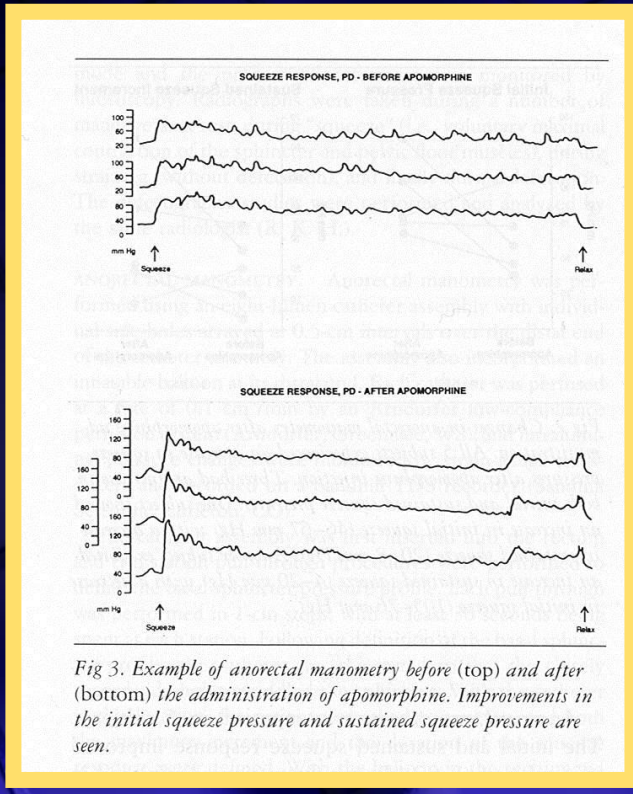


Fig 3. Example of anorectal manometry before (top) *and after* (bottom) *the administration of apomorphine. Improvements in the initial squeeze pressure and sustained squeeze pressure are seen.*

Edwards, et al. Ann Neurol 1993;33:490-493.
Ashraf, et al. Mov Disord 1994;9:655-663.

Treatment of Defecatory Dysfunction

- Dopaminergic medications
  - Apomorphine injections
  - Conventional DA agonists
  - Levodopa
- Botulinum toxin
  - External anal sphincter
  - Puborectalis
- Biofeedback techniques

Mathers SE, et al. Arch Neurol 1989;46:1061-1064.
Edwards LL, et al. Ann Neurol 1993;33:490-493.
Albanese A, et al. Mov Disord 1997;12:764-766.
Albanese A, et al. Am J Gastroenterol 2003;98:1439-1440.
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When, Where and Why Does GI Dysfunction Develop in PD?

Constipation and Risk of PD

Table 3 *Incidence of PD according to frequency of bowel movements*

Bowel movements/d	Sample size	Incident PD cases	Incidence, rate/10,000 person-years	
			Unadjusted	Age-adjusted
<1	289	10	19.6	18.9
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	7.5	—

Abbott, et. al. Neurology 2001;57:456-462.

Onset of Constipation in Relation to Motor Symptoms

Onset of Constipation	Total # (%)	Men # (%)	Women # (%)
Before PD	49 (50.5)	23 (43.4)	26 (59.1)
After PD	14 (14.4)	11 (20.8)	3 (6.8)
Unknown	34 (35.1)	19 (35.8)	15 (34.1)
Total	97 (100.0)	53 (100.0)	44 (100.0)

- In patients who had onset of constipation before onset of PD the mean age at which constipation began was 39.9 years
- In these individuals constipation began a mean of 18.7 years before the appearance of motor symptoms

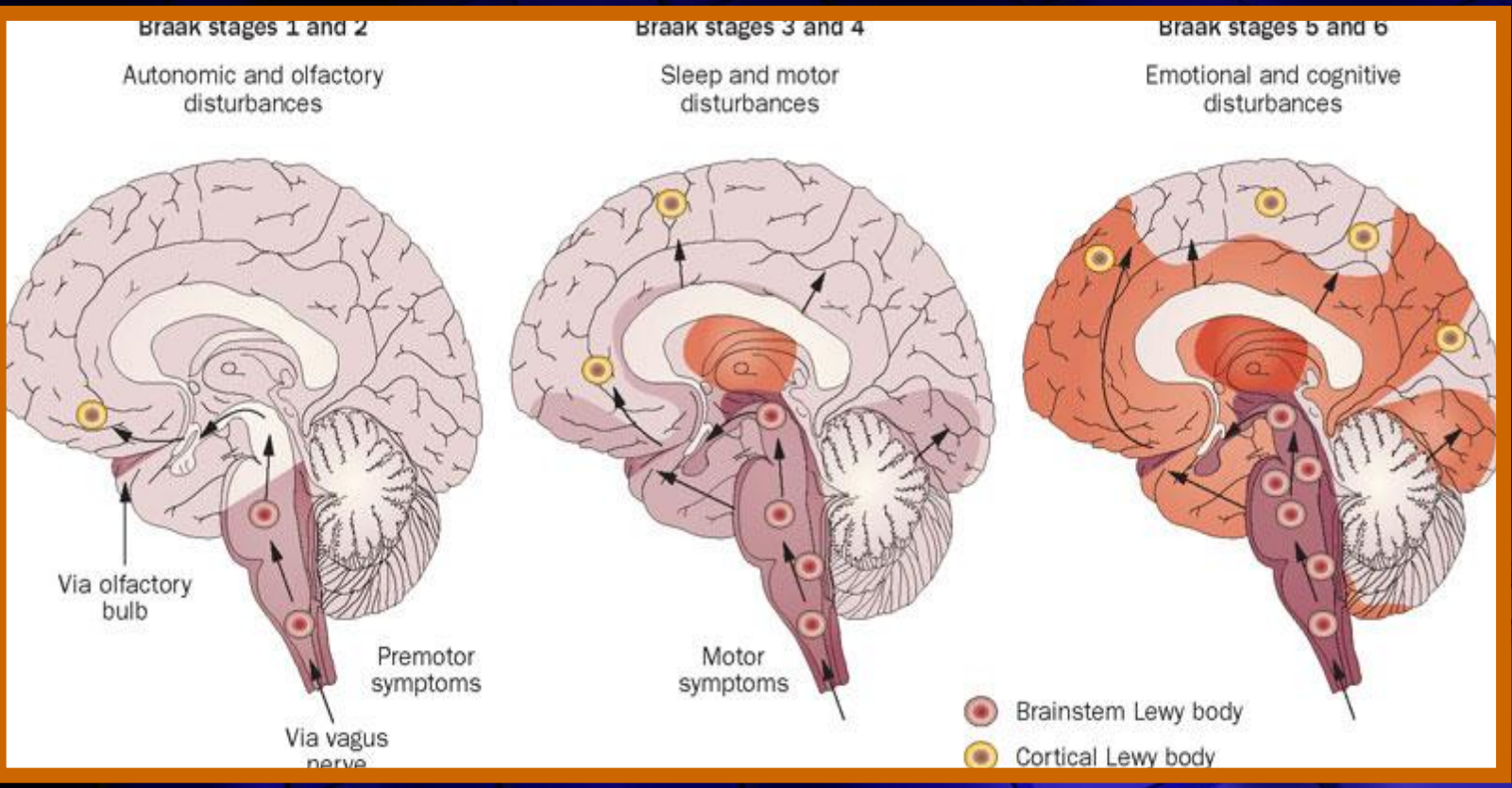
Ueki A, Otsuka M. J Neurol 2004;251(Suppl 7):VII/18-VII/23.

Pathophysiology of GI Dysfunction in PD

- Is it based within the
  - Enteric Nervous System?
- Is it based within the
  - Central Nervous System?

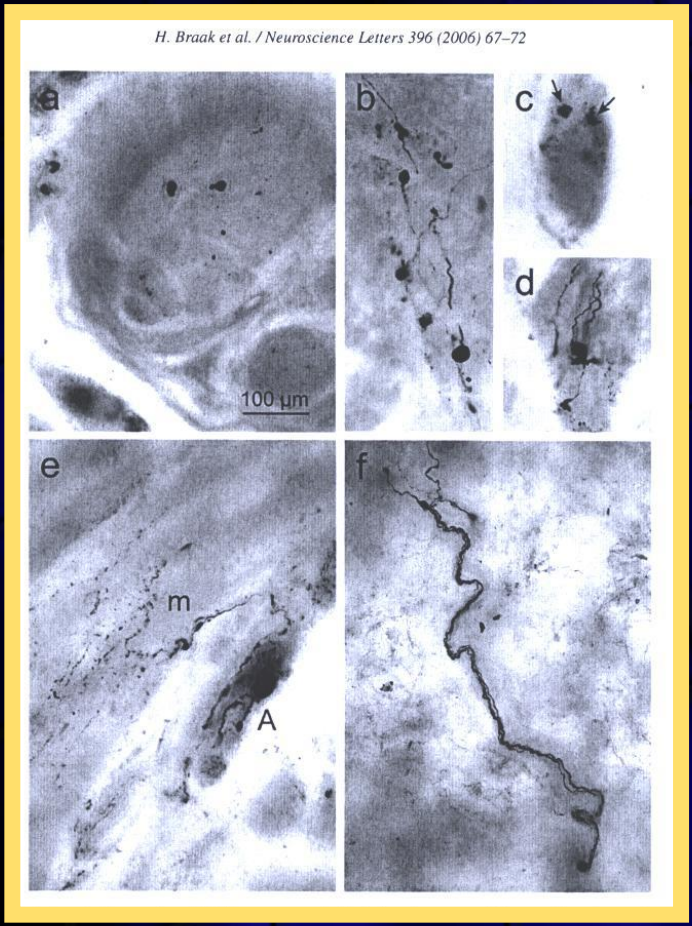
Enteric Nervous System

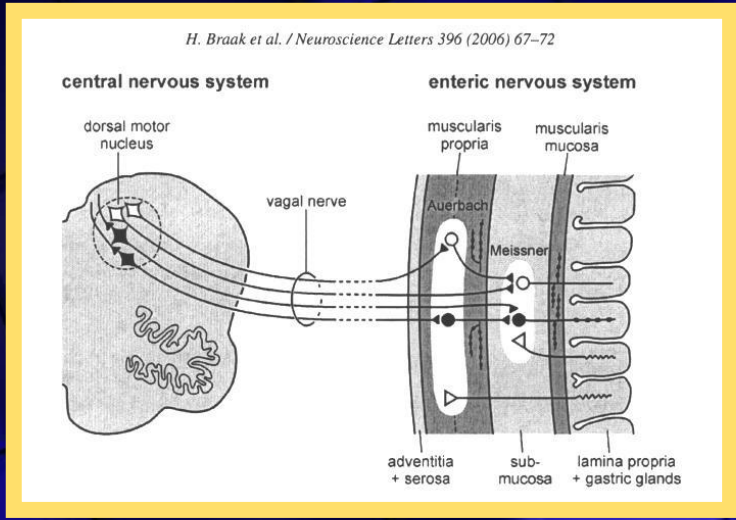
Braak Staging of PD



Doty RL. Nature Reviews Neurology 2012;8:329-339.
Braak H, Del Tredici-Braak K. Neuroanatomy of Parkinson's disease.
In: Parkinson's Disease, 2nd Edition (Pfeiffer RF, Wszolek ZK, Ebadi M, Eds), 2013, pp. 473-492.

Braak: Gastric Involvement

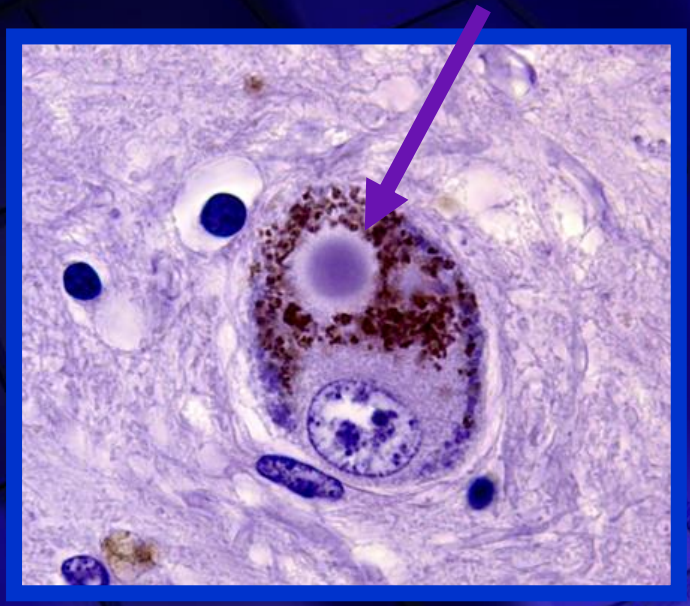




Braak, et al., Neurosci Lett 2006;396:67-72.

Enteric Lewy Bodies in PD

- Esophagus
  - 1984 – Qualman et al.
- Colon
  - 1987 - Kupsky et al.
  - 1990 - Wakabayashi et al.
  - 1995 – Singaram et al.

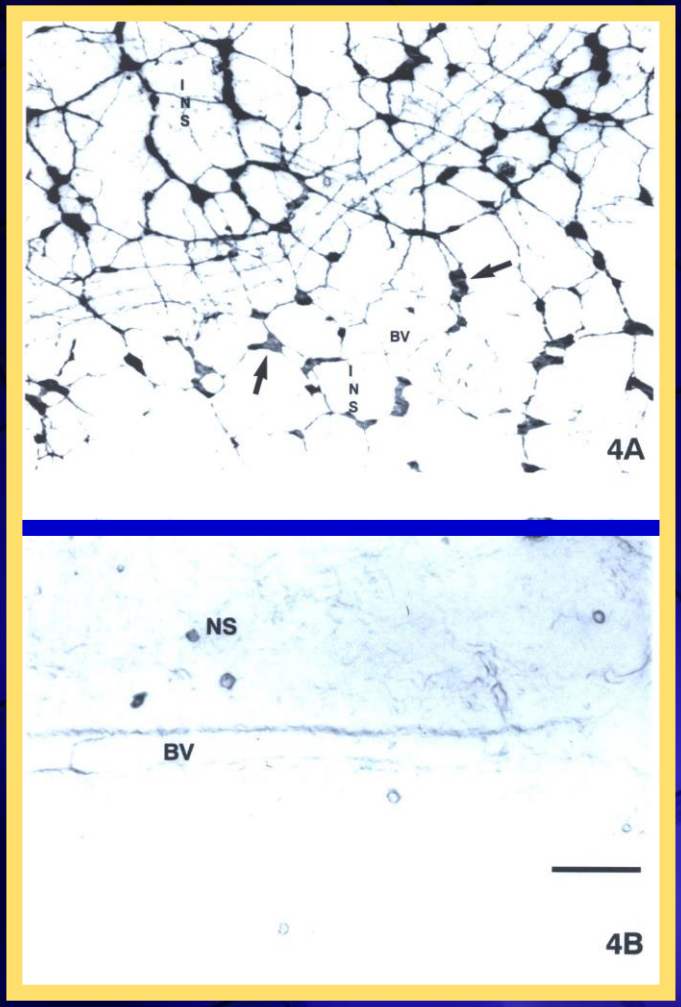


Qualman SJ, et al. Gastroenterology 1984;87:848-856
Kupsky WJ, et al. Neurology 1987;37:1253-1255.
Wakabayashi K, et al. Acta Neuropathol 1990;79:581-583
Singaram C, et al. Lancet 1995;346:861-864.

Dopamine in Whole Mounts of Colon

Control subject

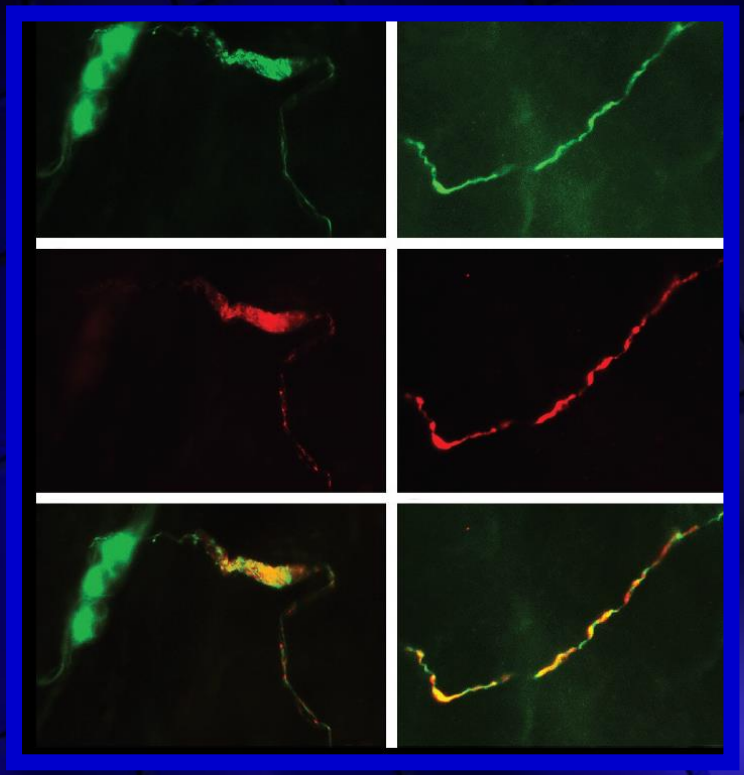
PD patient



Singaram C, et al. Lancet 1995;346:861-864.

Alpha-Synuclein Positive Submucosal Neurites in PD in Humans

Obtained during colonoscopy



Lebouvier et al., Gut 2008;57:1741-1743

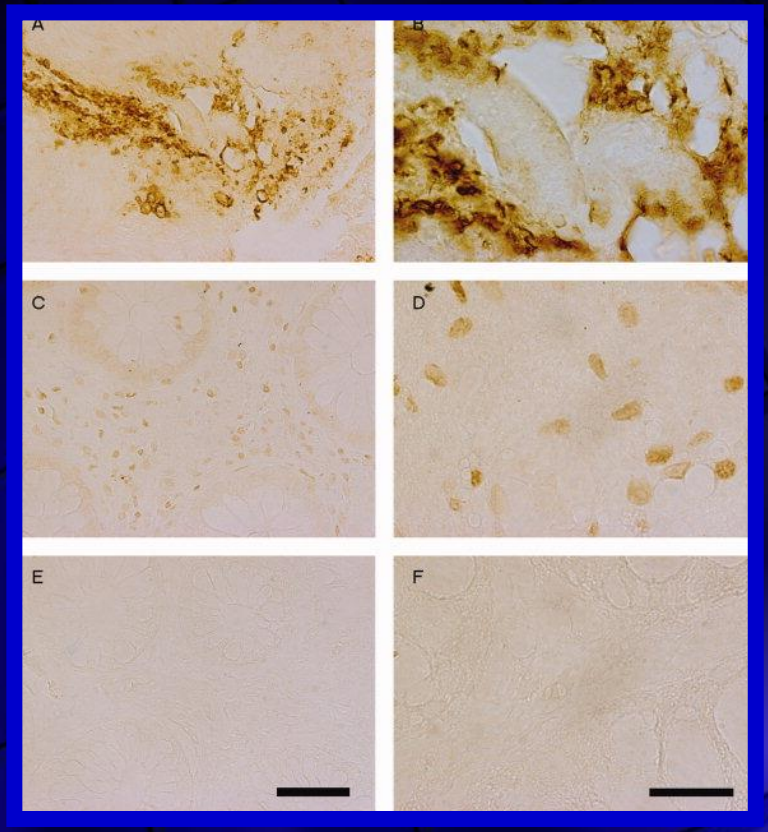
α-Synuclein in Colon Submucosa - Early PD

Obtained during sigmoidoscopy

PD

IBD

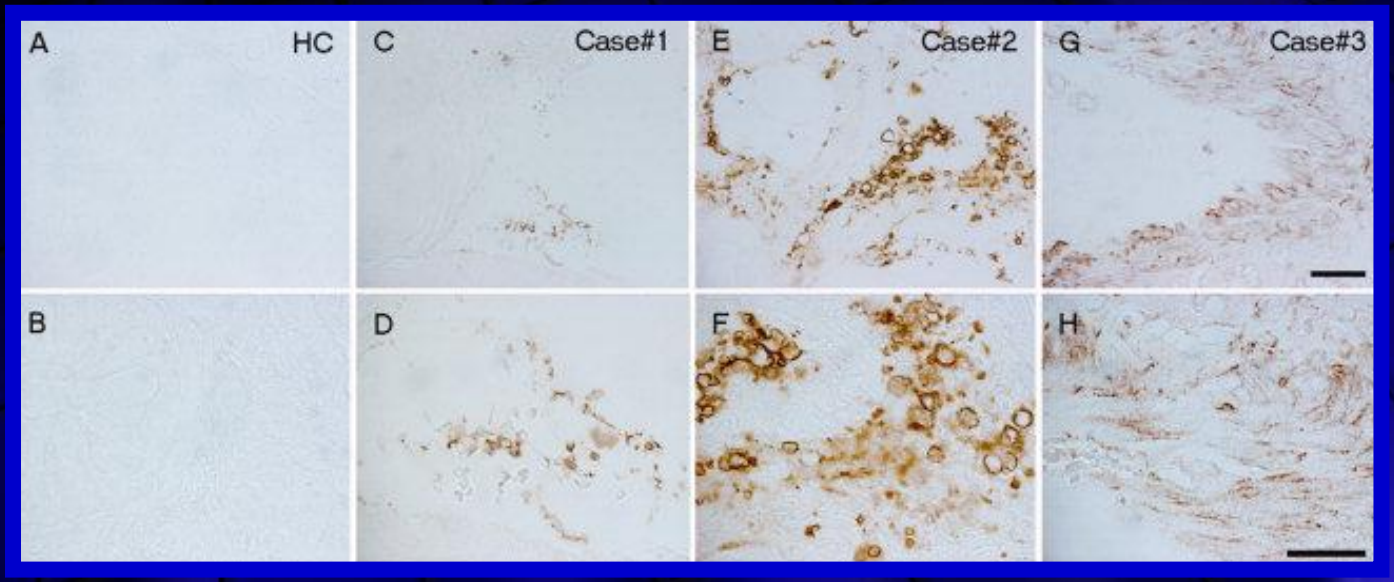
C



Shannon, et al. Mov Disord 2012;27:709-715.

Colonic Biopsy 2-5 Years Before PD Diagnosis

- Low Power

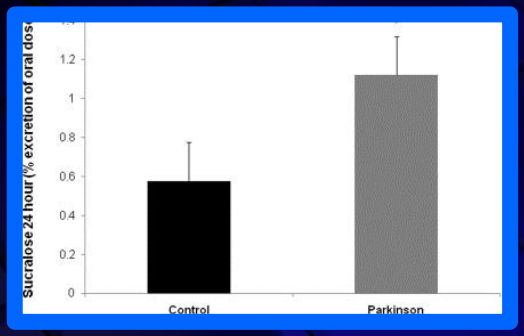


- High Power

Shannon, et al. Mov Disord 2012;27:716-719.

Increased Intestinal Permeability in PD

- PD subjects exhibit increased large intestinal permeability
- They also demonstrate increased intestinal mucosal staining for E. coli, nitrotyrosine and alpha-synuclein



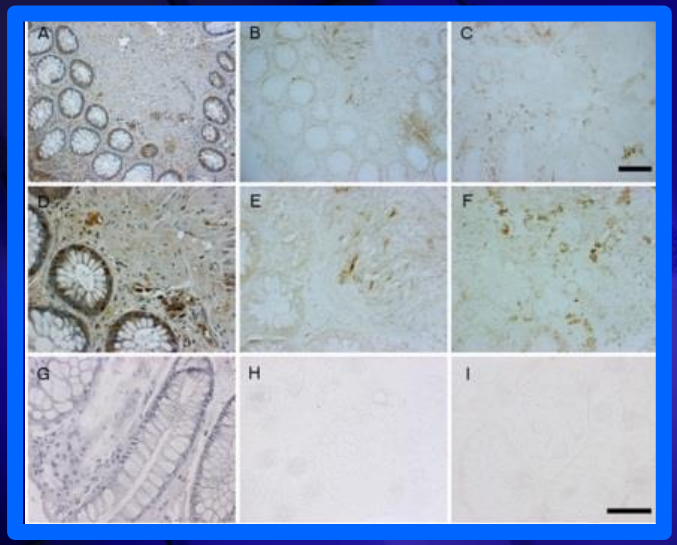
Forsyth CB, et al. PlosOne 2011;6:e28032

E. coli α-synuclein 3-nitrotyrosine

PD 156

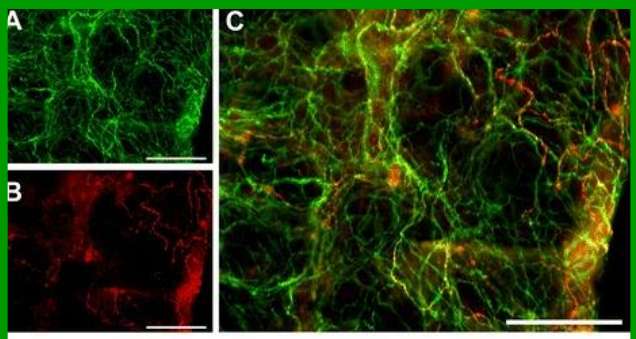
PD 406

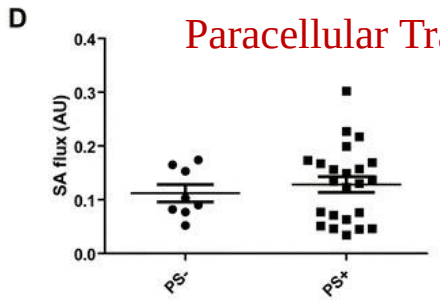
C 406

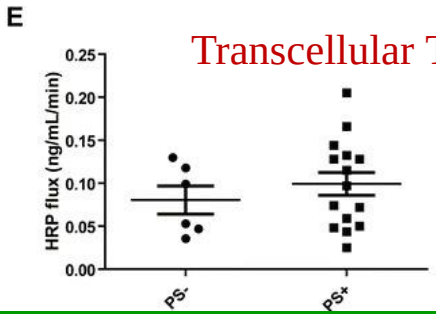


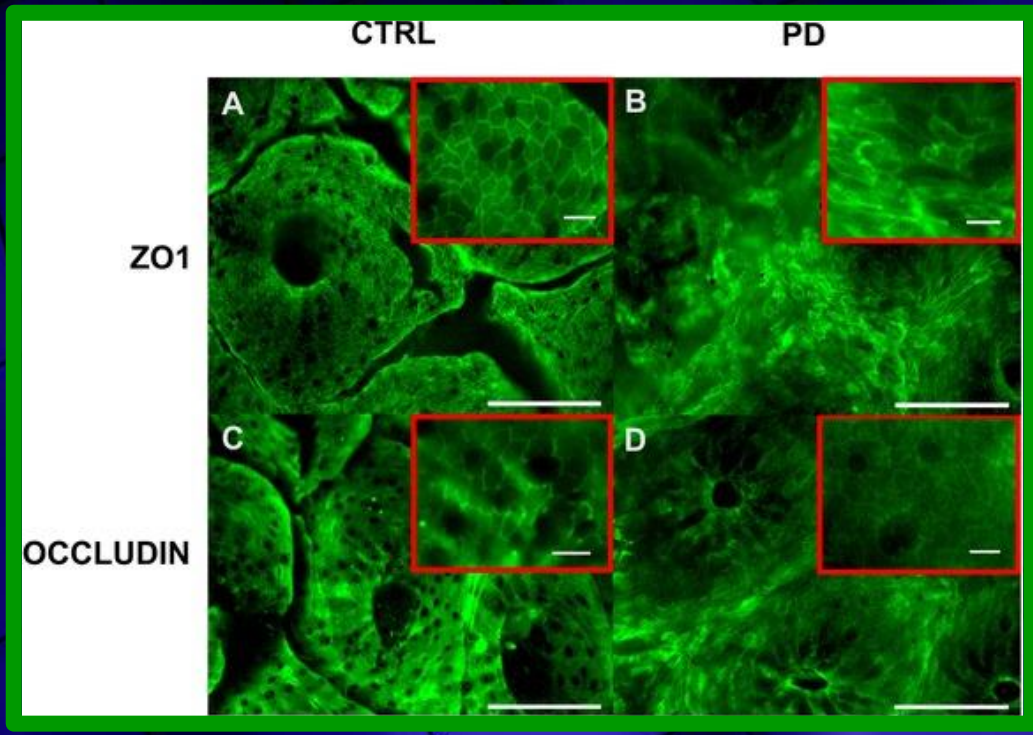
Forsyth CB, et al. PlosOne 2011;6:e28032

Intestinal Epithelial Barrier in PD









Clairembault T, et al. Acta Neuropathologica Communications 2015;3:2

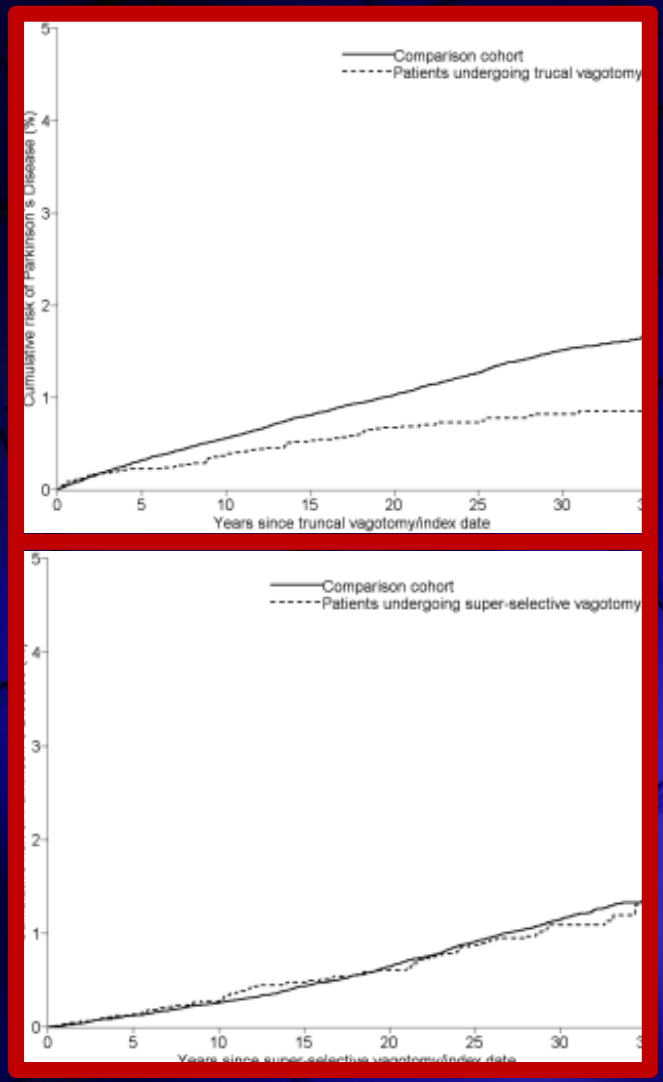
Dysbiosis in PD

- Gut microbiota (100 trillion organisms) and their metabolic products are in close proximity to the ENS
- Certain types of bacteria may be reduced in PD (e.g. Prevotellaceae) and others may be increased (e.g. Enterobacteriaceae)
- May produce an altered, pro-inflammatory chemical environment
- With altered intestinal permeability and increased entry of pathogens
- All of which may trigger ENS pathology
- And this prompts speculation about Fecal Microbiota Transplantation as a treatment for PD

Unger MM, et al. Parkinsonism Relat Disord 2016; doi:10.1016/jparkreldis.2016.08.019.
Scheperjans F, et al. Mov Disord 2015;30:350-358.
Keshavarzian A. et al. Mov Disord 2015;30:1351-1360.

Vagotomy and PD

- The risk of developing PD is reduced in individuals who have undergone full truncal vagotomy
- The risk of developing PD is not reduced in individuals who have undergone superselective vagotomy



Svensson E, et al. Ann Neurol 2015;78:522-529.

James Parkinson

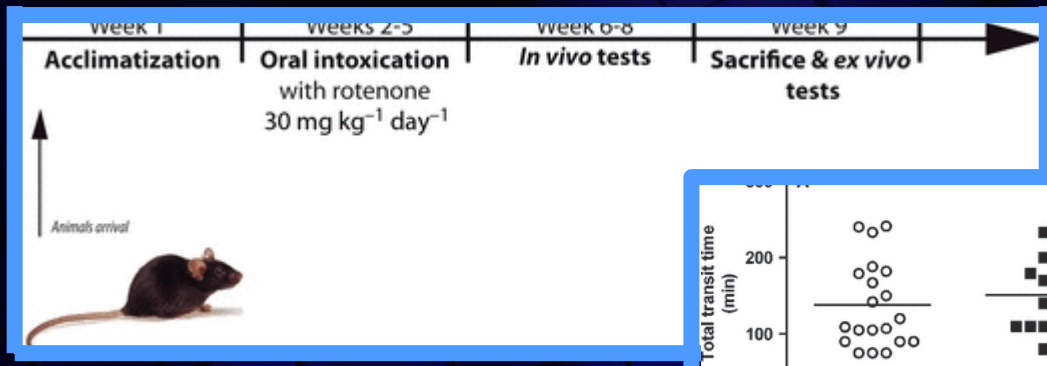
"Although unable to trace the connection by which a disordered state of the stomach and bowels may induce a morbid action in a part of the medulla spinalis, yet taught by the instruction of Mr. Abernethy, little hesitation need be employed before we determine on the probability of such occurrence."

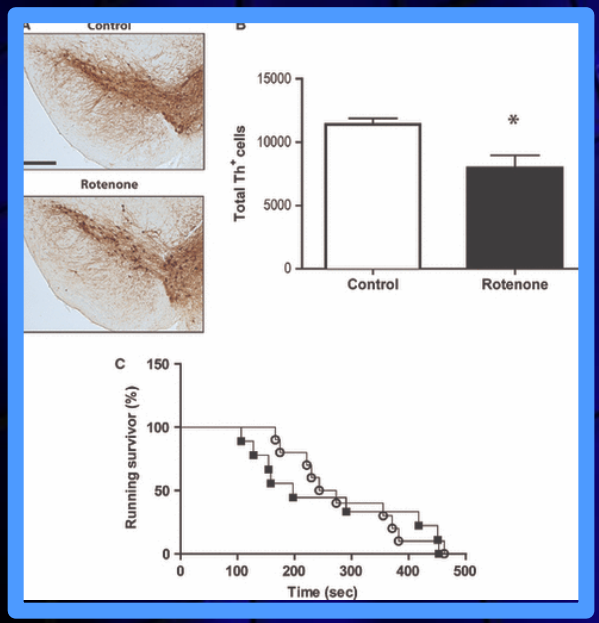
Parkinson J. An Essay on the Shaking Palsy, 1817.

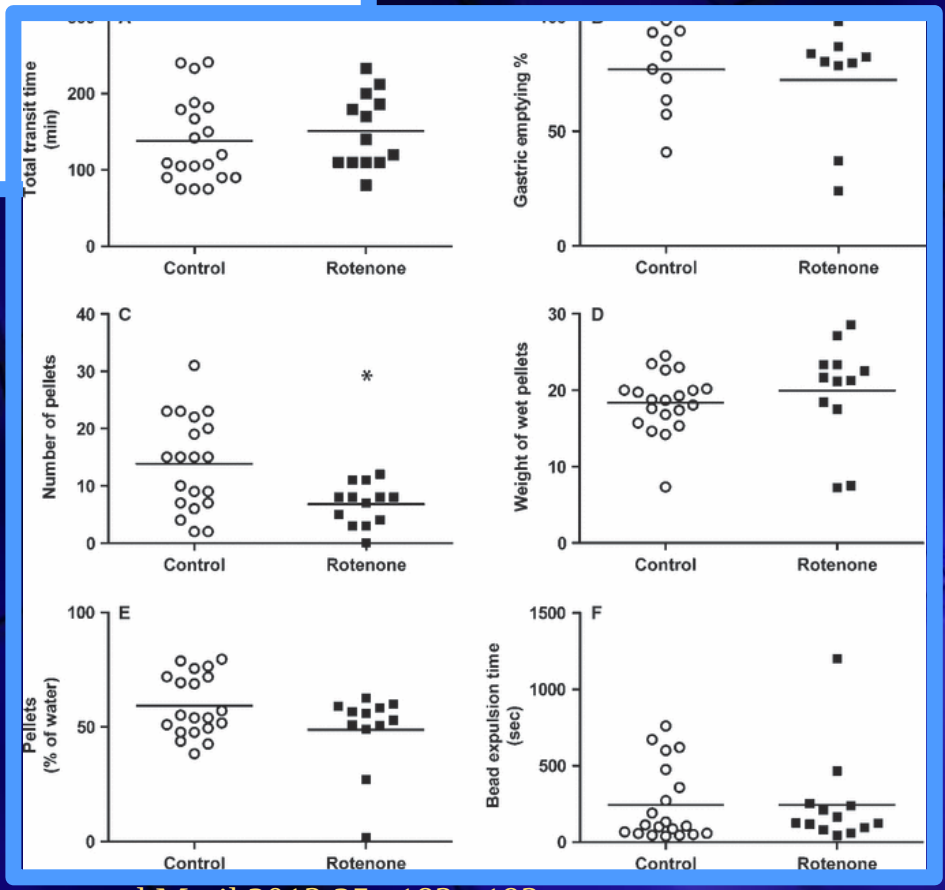
But Wait……

Central Nervous System

Oral Rotenone and GI Functions

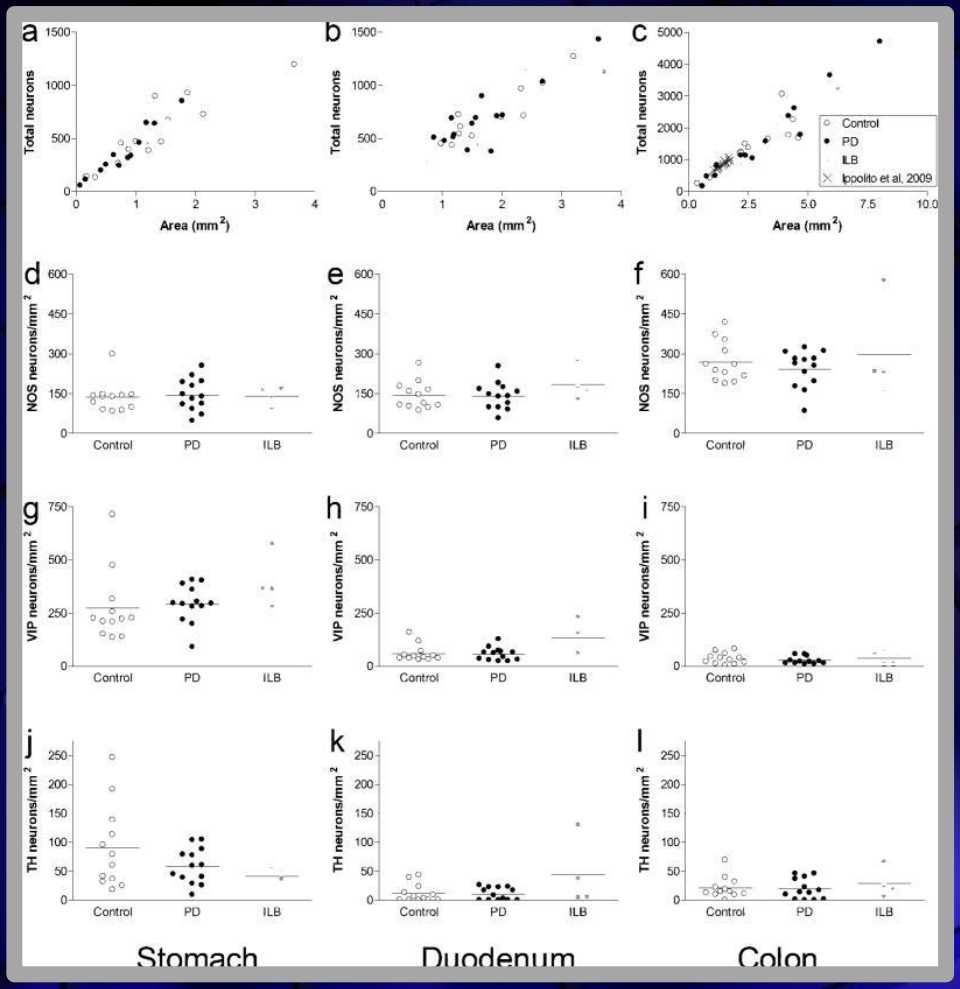






Tasselli M, et al. Neurogastroenterol Motil 2013;25:e183-e193.

No Loss of Enteric Neurons in PD



Annerino DM, et al. Acta Neuropathol 2012;124:665-680.

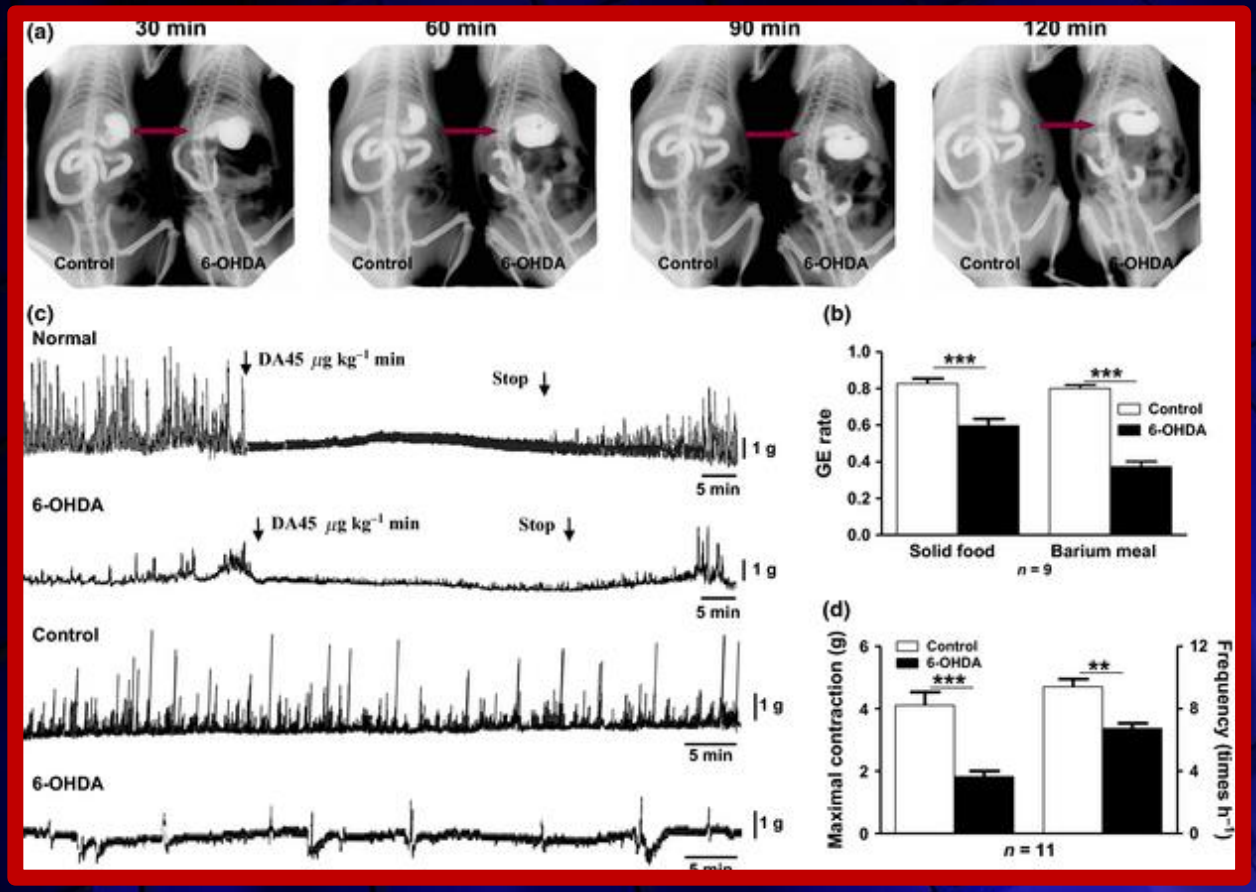
Corbillè AG, et al. J Parkinsons Dis 2014;4:571-576

ENS α-Synuclein

- Phosphorylated α-synuclein deposition
  - Follows a rostral-caudal gradient in the ENS
- Follows the distribution of vagal efferents
  - Lower esophagus and stomach
  - Small intestine and proximal colon
  - Upper esophagus is spared
    - Is supplied from nucleus ambiguus

Beach TG, et al. Acta Neuropathol 2010;119:689-702.

6-OHDA SN Lesion Produces Gastroparesis



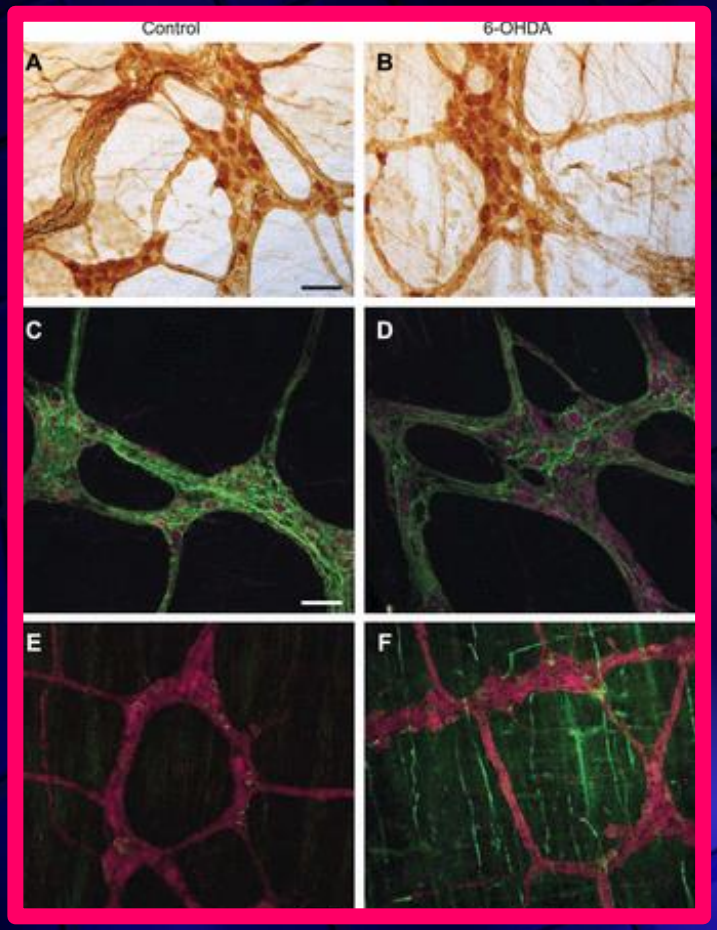
Zheng LF, et al. Acta Physiologica (Oxf) 2014;211:434-446.
Pfeiffer RF. Acta Physiologica (Oxf) 2014; 211:271-272.

SNpc 6-OHDA Alters Neurochemical Phenotypes in Myenteric Plexus

Decrease in TH-IR+ fibers

Decrease in ChAT+ neurons

Increase in nNOS-IR neurons



Myenteric neurons fundus

Myenteric neurons corpus

Myenteric neurons duodenum

Toti L, Travagli A. Am J Physiol Gastrointest Liver Physiol 2014;307:G1013-G1023.


LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED

GI Dysfunction in PD

- There is pathology in the ENS in PD
- There is pathology in the CNS in PD
- PD may well have its genesis in the ENS
- But it is not so clear whether the GI symptoms of PD are ENS or CNS in origin
- Or perhaps they are both

QUESTIONS?