LIVING WELL

PARKINSON'S DISEASE CONFERENCE

PARKINSON FOUNDATION | Western Pennsylvania

What is Your Gut Telling You?

A look at intestinal health in Parkinson's disease

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Living Well Parkinson's Disease Conference

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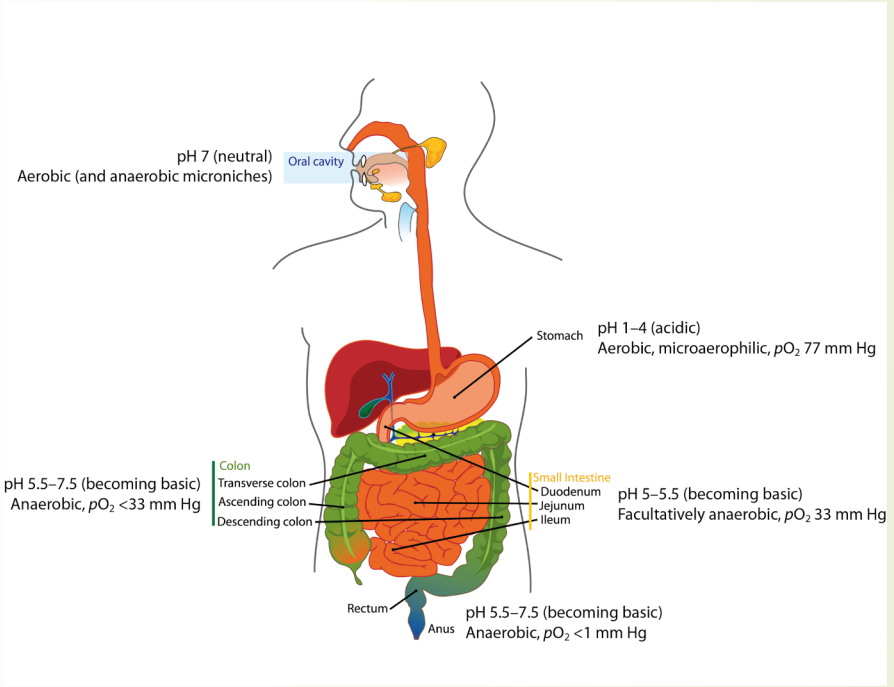
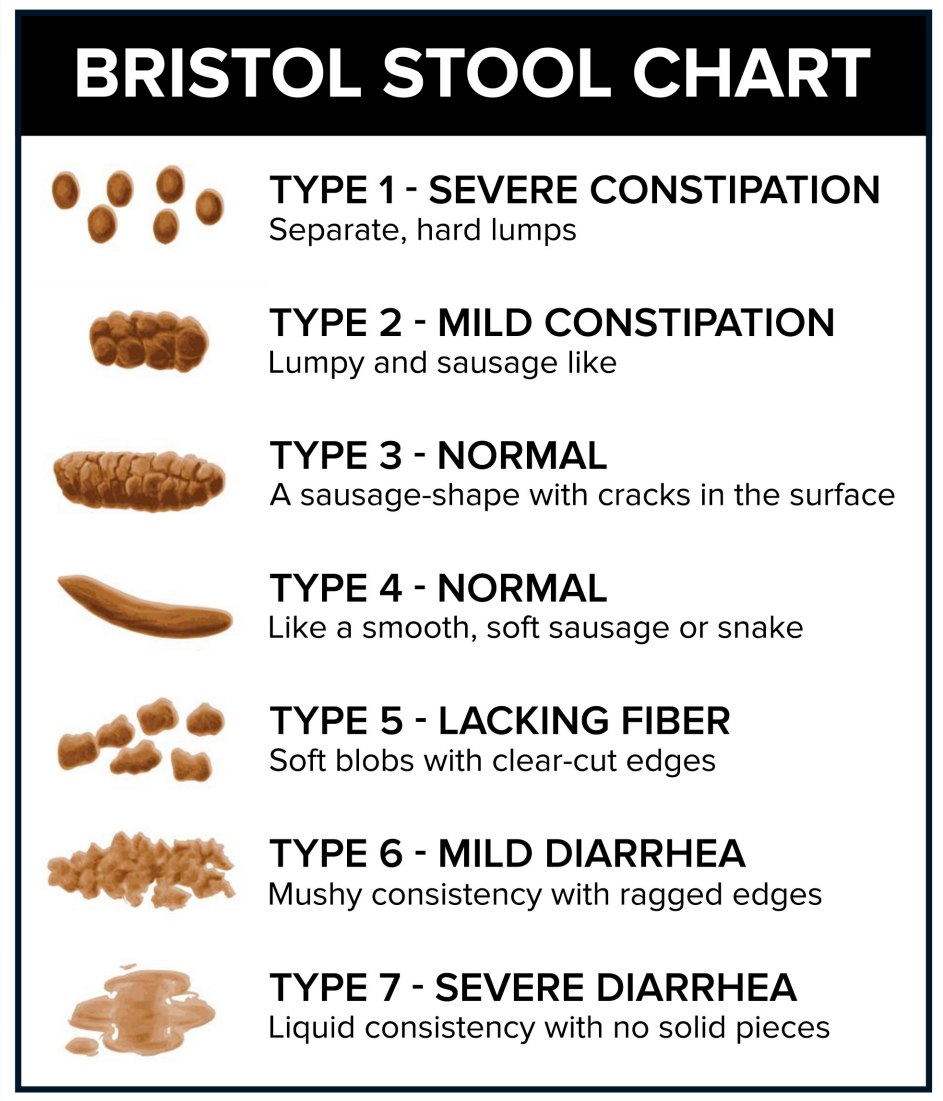
The GI Tract

- The gut: the tube from the mouth to the anus
- GI Non-motor symptoms in PD:
  - Constipation
  - Acid Reflux
  - Nausea
  - Weight Loss
  - Abdominal Pain



Constipation in Parkinson's Disease

- In 1971 6790 men between the ages of 51-75 were followed for 12 years
- What they found:
  - Men having <1 bowel movement increased their risk of developing PD 4 fold compared to men who had 2 BM per day
  - Men having <1 bowel movement increased their risk of developing PD 4.5 fold compared to men who had more than 2 BM per day
  - Even when adjusted for age, pack-years of cigarette smoking, coffee consumption, laxative use, jogging, and the intake of fruits, vegetables, and grains



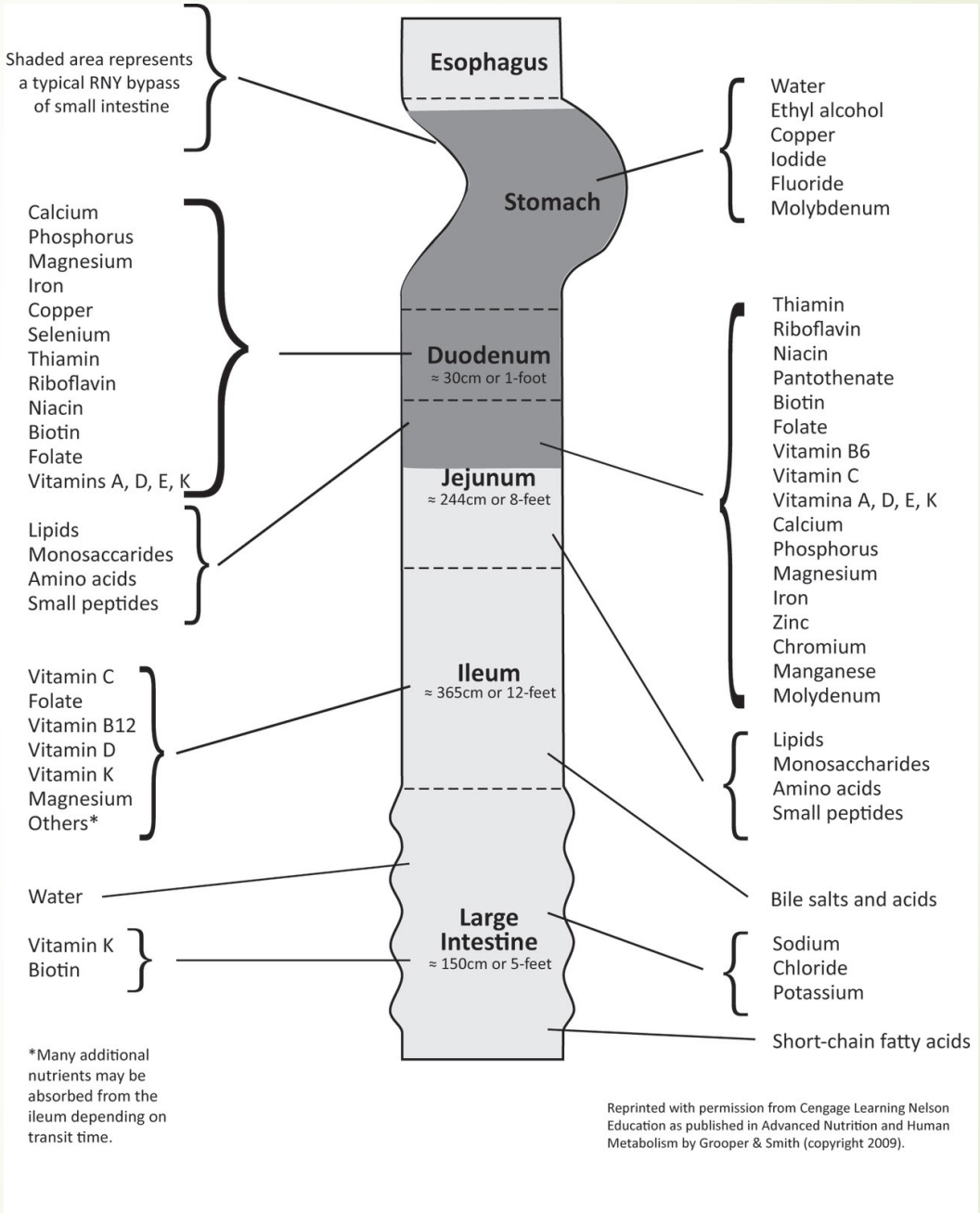
Aboott RD, 2001

Does Parkinson's disease start in the gut?

- There have been multiple studies looking at the link between the gut and the brain in PD
- Two PD subtypes: brain first & gut first (Borghammer 2019)
- They have demonstrated that the misfolding and aggregation of alpha synuclein are seen in the enteric NS and the vagus nerve
- They are acting like a prion (Borghammer 2018)
- Truncal vagotomy as treatment? (Liddle RA 2018)

The basics

- Organs that make it up: mouth, esophagus, stomach, small intestine, large intestine, rectum, anus
- AND salivary glands, liver, gallbladder and pancreas

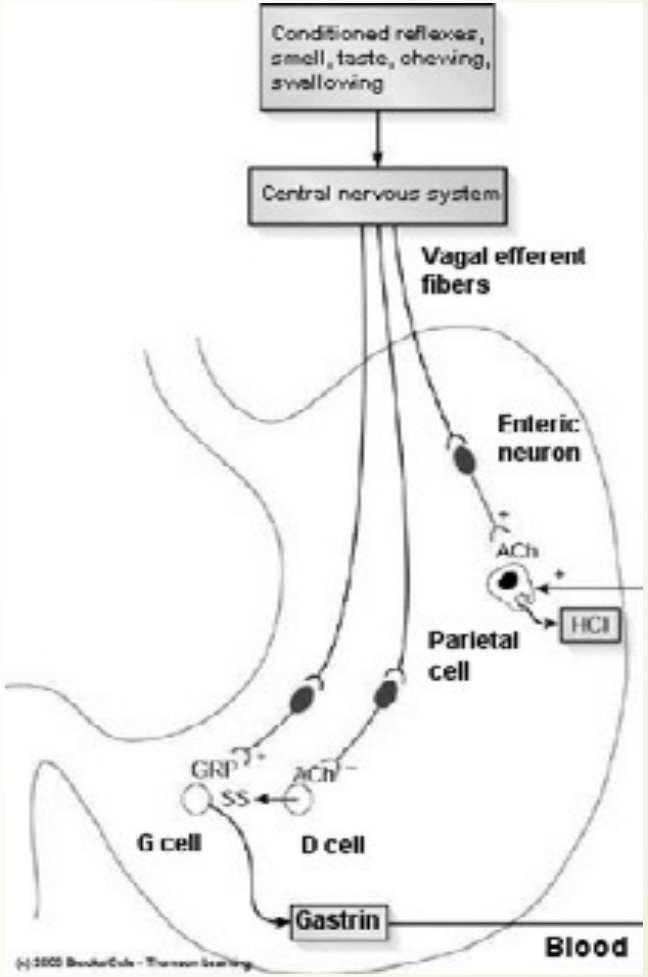


Taste & Smell Part of Digestion

- The mouth is NOT the first place that digestion starts
- You start the digestion process when you think, look & smell your food
- Your saliva has an enzyme called amylase that starts to break down starches before it gets to your stomach

The Stomach & Pancreas

- The pH of your stomach is ~2
- The **vagus nerve** stimulates digestion:
- stomach acid, gastrin and pancreatic enzymes help to breakdown and absorb food
- So how do proton pump inhibitors affect this?



Thompson Learning, 2005

Intestines: Small & Large

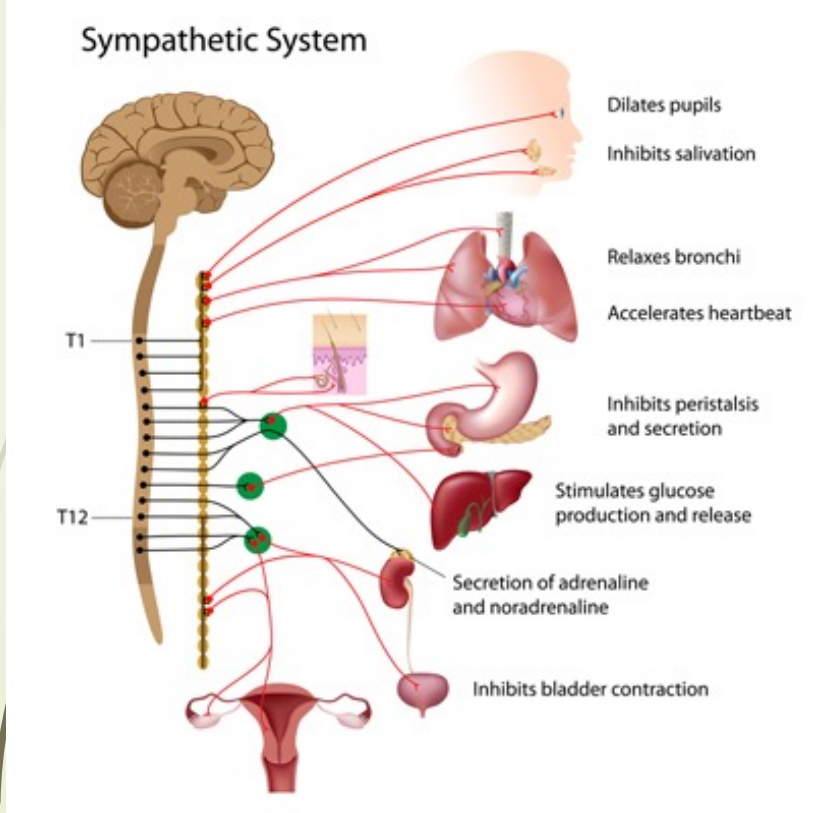
Small

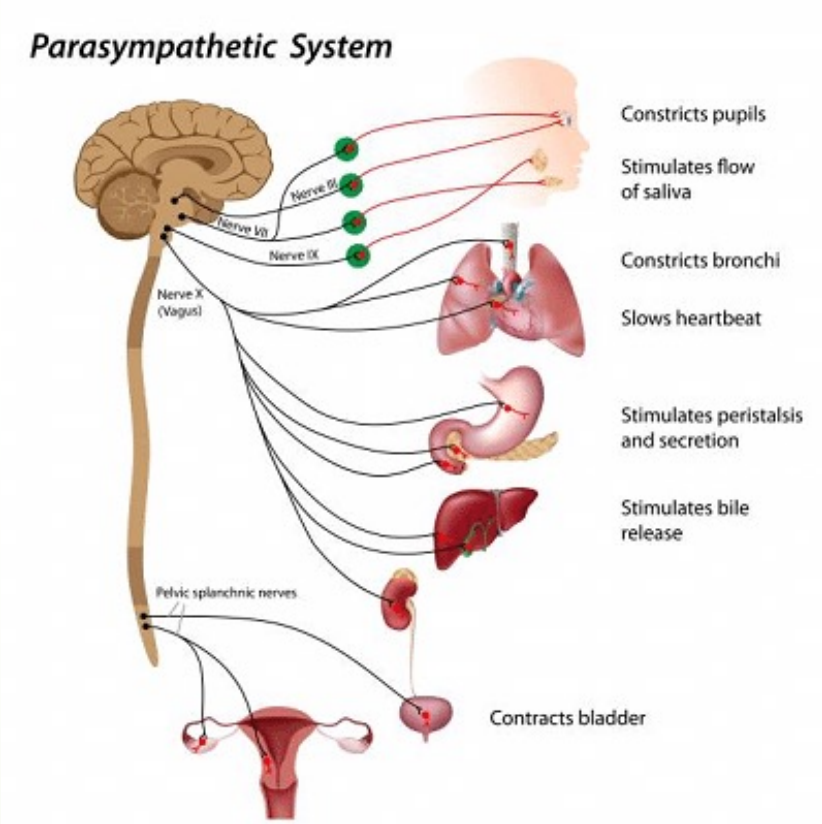
- Most nutrients from food are absorbed in the small intestines
- It has very small amounts of gut flora (10^4)
- Medication absorbed

Large

- Most of our GI microbiome resides in the large intestine, so what the microbiome does/produces starts here!
- Water absorbed
- Stool is bulked

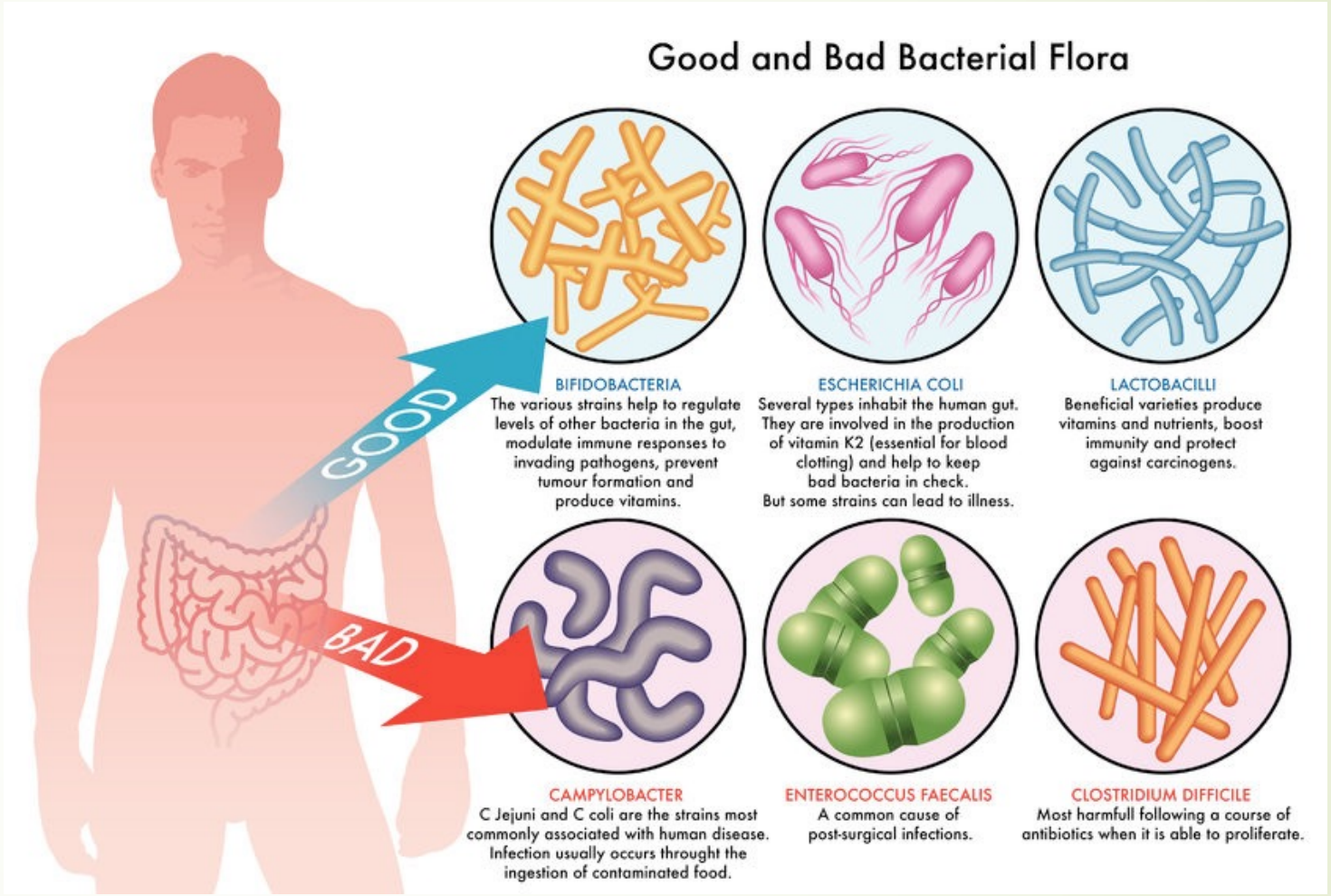
The autonomic nervous system





Microbiome

- Role of the Gastrointestinal Flora:
  - Produce B12, Biotin, Folic Acid, B1, glutathione, etc
  - Ferment dietary fiber to be used for energy
  - Produce Short Chain Fatty Acids
  - More is being learned the more it is being researched



Gastrointestinal disorders in PD

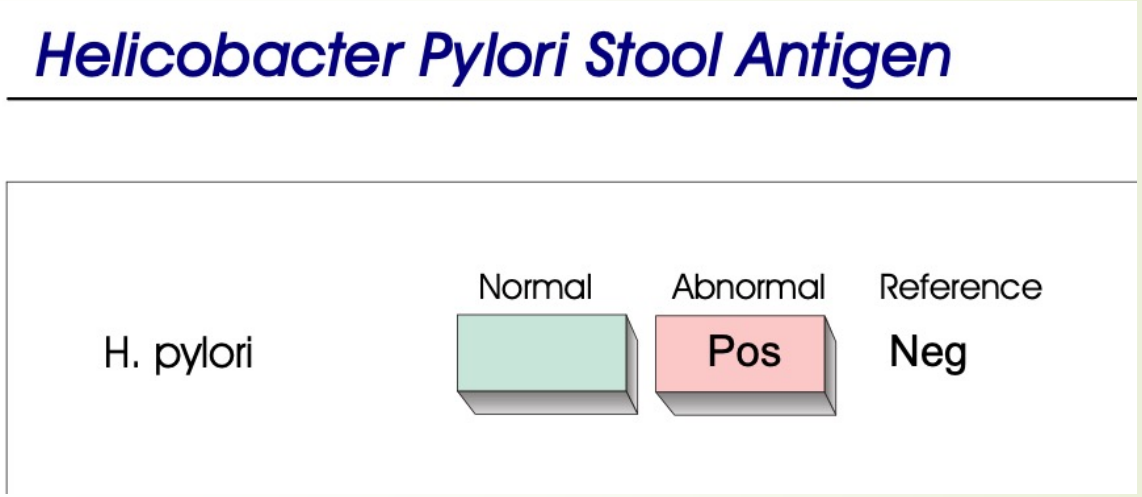
- H Pylori
- Low stomach acid
- Small Intestinal Bacterial Overgrowth
- Intestinal permeability
- Acid reflux
- Dysbiosis
- Inflammatory Bowel Disease*
- Irritable Bowel Syndrome
- Celiac disease
- Food sensitivities
- Low stomach acid
- Candidiasis
- MORE

Helicobacter Pylori

A bacteria infection in your stomach that is associated with the following:

- Peptic Ulcer Disease
- Gastritis
- Iron Deficiency Anemia
- B12 Deficiency
- Migraine
- Bacterial overgrowth
- Alzheimer's disease

  AND
- Parkinson's disease



H. Pylori & PD

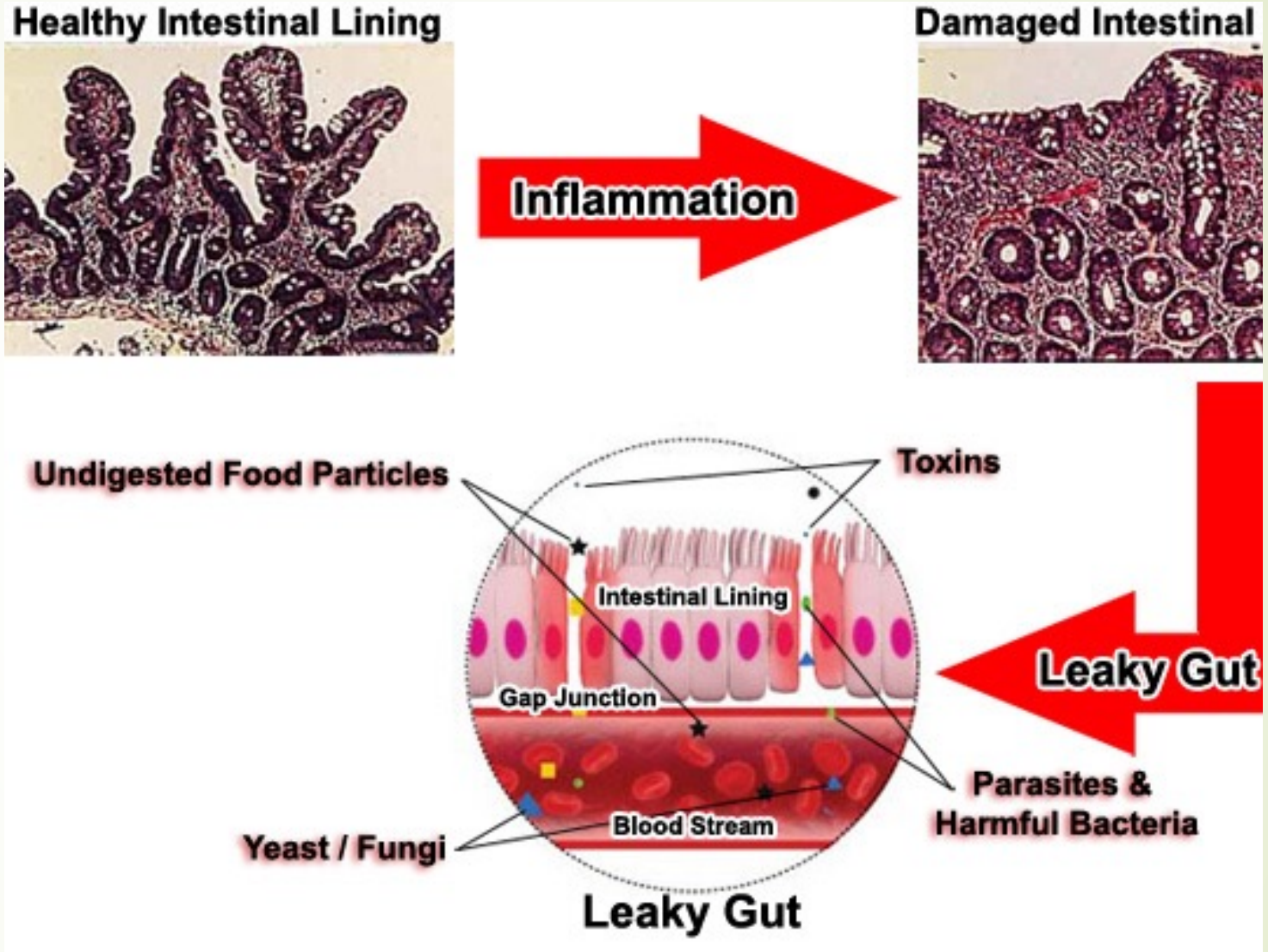
- 2022 study found that people who were H Pylori positive were on more l-dopa and had more motor fluctuations compared to those that were negative(Zhong R, 2022)
- Multiple studies have linked eradication of H. Pylori with improvement in motor/non-motor symptoms and improved medication absorption (Ullah, 2021) (**Nyholm, 2021**)
- Treatments?
  - Antibiotics & acid blockers – Triple therapy
  - Herbal antibiotics – ie GutGard

GASTROINTESTINAL PERMEABILITY

One study tested 12 people with Parkinson's Disease for gastrointestinal permeability

Of the 12 people 4 had intestinal permeability….

Even without gastrointestinal symptoms!!! (Salat-Foix, D 2012)



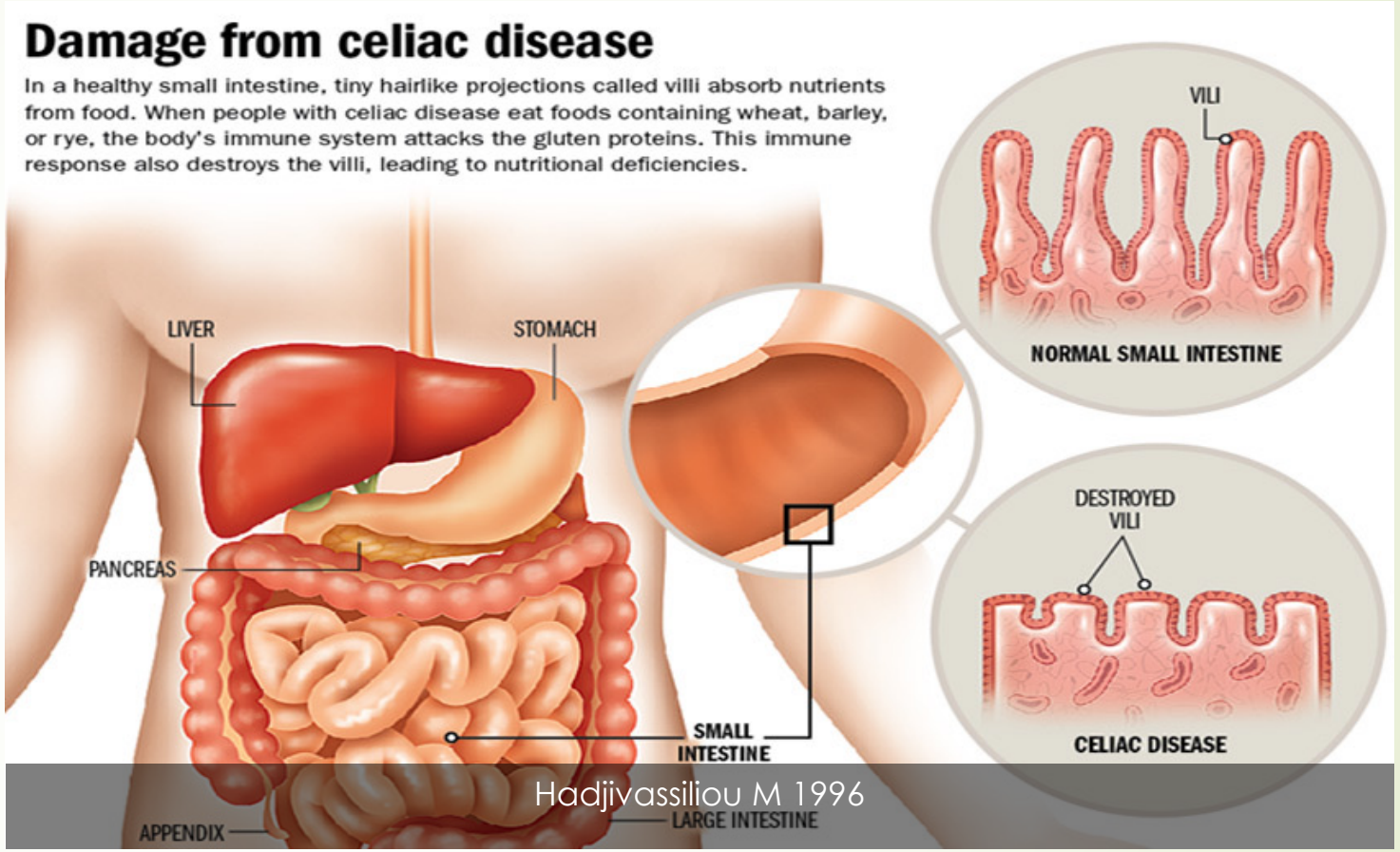
HOW TO TEST FOR IT & WHAT DOES IT MEAN

- Lactulose/mannitol urine Test
- Inflammatory processes are causing you to have leaky gut!

- *Causes of Leaky Gut:*
  - Diet
  - Food Allergens
  - Alcohol
  - Binge Alcohol Drinking
  - Dysbiosis

Celiac Disease

- Allergy to Wheat/Gluten resulting in damage to your small intestines
- Studies are demonstrating an association between CD and Neurological Conditions



Case report:

2014 Case report of a 74yo Man with 1 yr history of:

walking difficulty, instability, increase fatigue, masked face, slowness and postural instability

Labs: elevated homocysteine, low folic acid and + Antibody testing

After treatment with complete elimination of gluten containing products…

What to Expect After Eliminating Gluten

After 3 months of elimination:

- Almost complete resolution of symptoms on exam
- Most improvement seen in rigidity of lower limbs

After 6 months

- Improved Imaging and symptom improvement remained

What to take from this:

- Celiac Disease did not cause the Parkinson's Disease, it likely made the symptoms worse

Lazarro V, 2014

Hypochlorhydria (low stomach acid)

- Testing: Heidelberg test (not commonly used)
- Causes:
  - Autoimmune: anti-parietal cell antibodies
  - Increases sympathetic nervous system activity (fight or flight)
  - Medications
  - Structural
- Needed for:
  - Nutrient absorption
  - Protection against infections
  - Medication absorption

Treatment?

- As always… it depends!

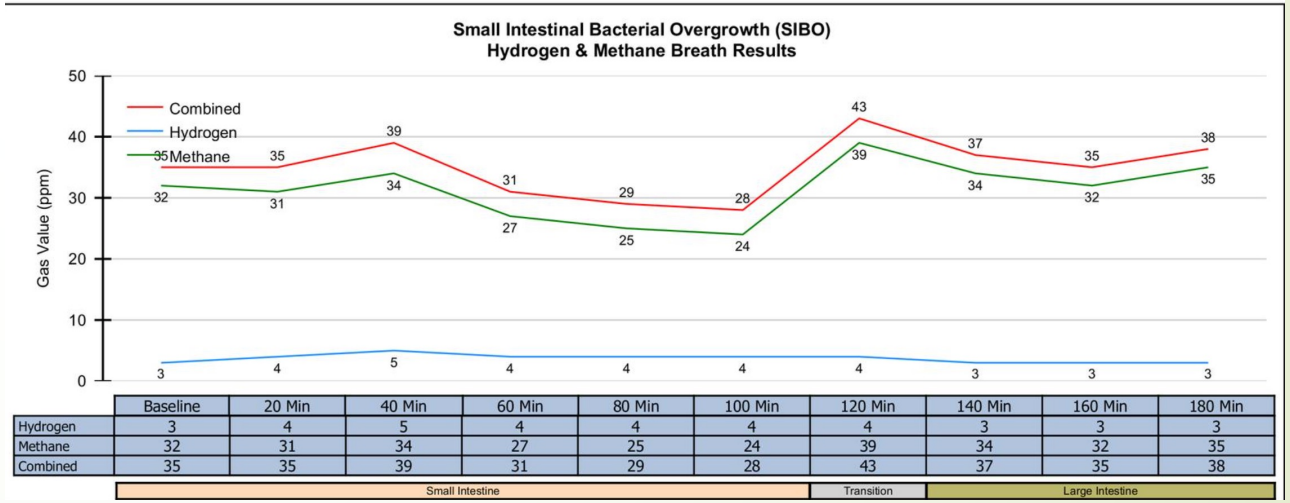
- Anatomical?
  - Injections of B-vitamins
  - Digestive enzymes
- Medication induced?
  - No more PPIs!
  - Deglycyrrhizinated licorice – I like Rhizinate
- Physiological
  - Mindful eating, meditation, lemon water

Small Intestinal Bacterial Overgrowth (SIBO)

Testing: lactulose/glucose breath test

Gasses Analyzed	Patient Result	Expected
Increase in Hydrogen (H_2)	2 ppm (normal)	< 12 ppm
Increase in Methane (CH_4)	15 ppm (high)	< 12 ppm (< 3 ppm[2])
Increase in combined H_2 & CH_4	17 ppm (high)	< 12 ppm[3]
Analysis of the data suggests	Bacterial overgrowth is suspected[2,3,4]	

Number	Expected Location	Collection Interval	ppm H2	ppm CH4	Combined	ppm CO2	fCO2
1	Small Intestine	Baseline	3	32	35	4.0	1.37
2		20 Min.	4	31	35	4.2	1.30
3		40 Min.	5	34	39	4.2	1.30
4		60 Min.	4	27	31	3.8	1.44
5		80 Min.	4	25	29	4.2	1.30
6		100 Min.	4	24	28	3.8	1.44
7	Transition	120 Min.	4	39	43	3.8	1.44
8	Large Intestine	140 Min.	3	34	37	3.9	1.41
9		160 Min.	3	32	35	4.0	1.37
10		180 Min.	3	35	38	4.2	1.30



	Baseline	20 Min	40 Min	60 Min	80 Min	100 Min	120 Min	140 Min	160 Min	180 Min
Hydrogen	3	4	5	4	4	4	4	3	3	3
Methane	32	31	34	27	25	24	39	34	32	35
Combined	35	35	39	31	29	28	43	37	35	38
	Small Intestine						Transition	Large Intestine		

Associated with

- IBD
- H Pylori
- Low stomach acid
- Medication use (ie PPI)
- Gastroparesis
- Leaky gut
- IBS
- Abdominal surgery

- Chicken or the egg?

SIBO & Parkinson's disease

- Increased amounts of *Streptococcus* & *Methanobrevibacter* seen in PD that is commonly found in SIBO
- 2021 meta-analysis of 973 people showed a strong correlation between PD and SIBO with 46% of the PwP having SIBO.
  - Prevalence in western countries higher than in eastern countries

Symptoms of SIBO in PD

- Non-motor symptoms AND motor symptoms
  - Constipation
  - Bloating
  - Abdominal pain
  - Gas
  - More “off” time
  - Increase in motor fluctuations
  - Higher l-dopa doses needed

What more studies are showing

- A study assessed 103 patients with PD via: breath test, UPDRS, quality of life questionnaire and objective measures of bradykinesia. Physicians were blinded to SIBO status
- 25.3% of PD patients were positive for SIBO
- SIBO negative patients were early in their diagnosis and had lower levodopa equivalent dose
- SIBO + had increased abdominal pain, constipation
- Worse motor function

- What I do not like about this study:
  - Did no use standards set forth this year: more strict recently

(Tan AH, 2013)

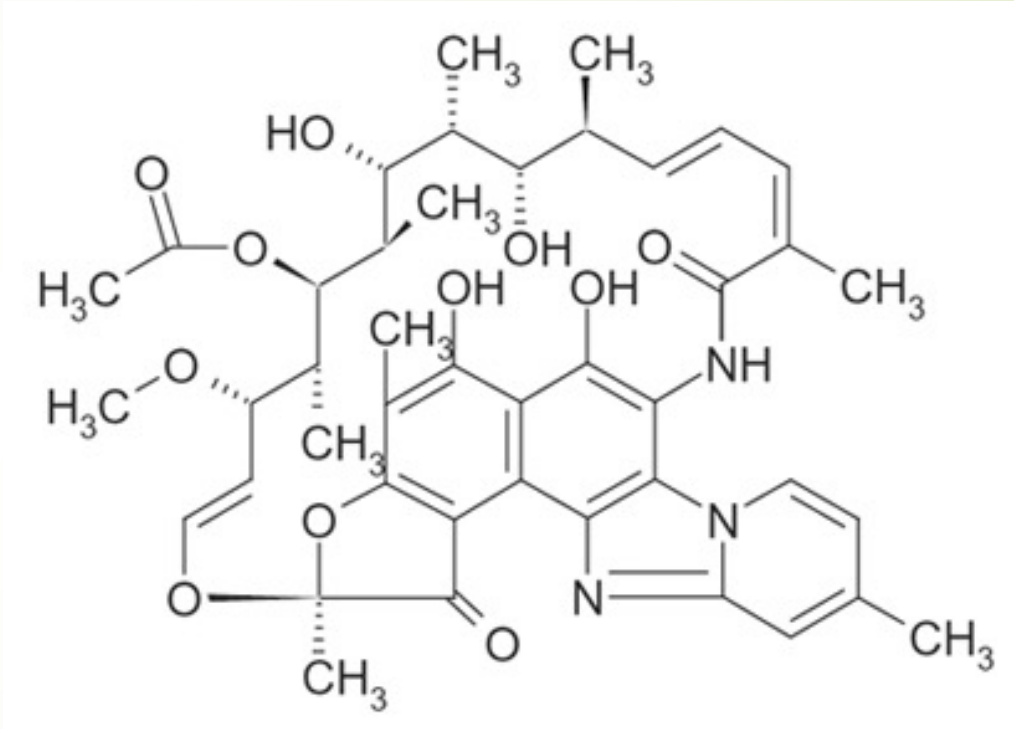
Yes, another study

- 33 patients with PD were compared to 30 controls to assess SIBO & H. Pylori
- SIBO was statistically significantly higher in PD than controls (54.5% vs 20%); H. Pylori was not (33.3% vs 26.7)
- Patients with both SIBO and H. Pylori has significantly higher motor fluctuations than those without (87.5% vs 8.3%)
- SIBO + patients had longer "off" time

- What if you treat….

Treatment in 1 study…

- The SIBO positive individuals in the study were treated with Rifaxamin 400mg three times daily for 7 days showed
- No side effects were reported
- 1 month later 77.8% of the patients were SIBO free & improved motor fluctuations
- However 6 months later 43% were SIBO + again



Fasano A, 2013

What are some of the options to treat?

- Pharmaceutical:
  - Rifaximin with/without Neomycin(Pimentel M, 2011)
  - Statin for methane positive individuals?(Muskal S, 2017)
- Botanical:(Chedid, V 2014)
  - FC-Cidal/Dysbiocide
  - Candibactin-AR/Candibactin-BR
  - Allysin+Berberine+Oregano Oil
- Elemental Diet(Pimentel M, 2004)
  - 14 days – 80% effective
  - 21 days - 85% effective

Patient with PD…. and SIBO

- PROPD prior to treatment: 403
- After treatment: 274
- 5 months later: 169
- Improvement in: orthostatic blood pressure, daytime fatigue, sleep disturbance, constipation, urinary frequency, urgency & incontinence

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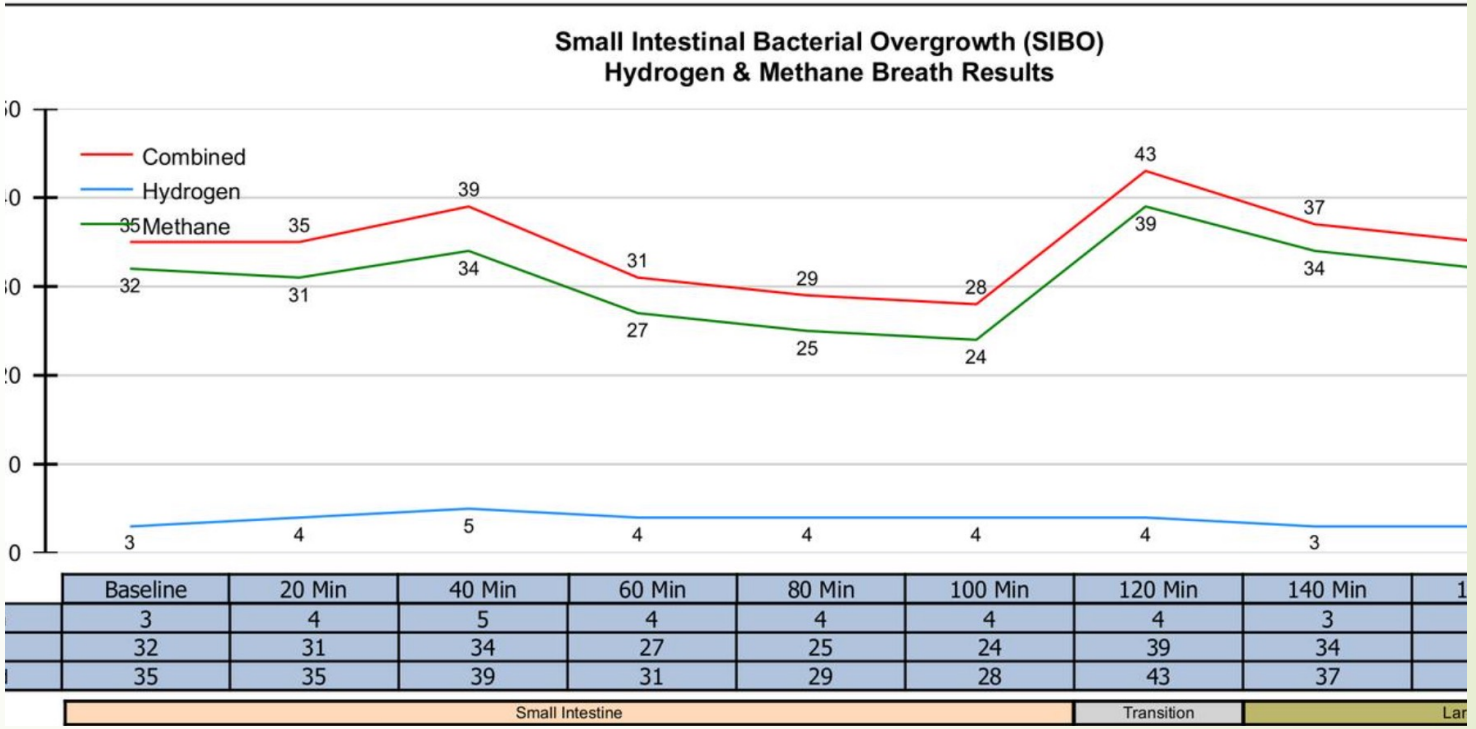


	Baseline	20 Min	40 Min	60 Min	80 Min	100 Min	120 Min	140 Min	1
	3	4	5	4	4	4	4	3	
	32	31	34	27	25	24	39	34	
	35	35	39	31	29	28	43	37	
	Small Intestine						Transition		Lar

Dysbiosis

- What is it?
  - Altered gut flora
  - Too many Bad Bugs and not enough Good Bugs

Multiple studies have linked Dysbiosis and Parkinson's Disease

TABLE 1 | Specific gut microbiota reported in 17 clinical studies.

Family	Genus
Increased in PD	
Lactobacillaceae (Holmqvist et al., 2014; Keshavarzian et al., 2015; Mao et al., 2016; Manfredsson et al., 2018; Lin et al., 2018; Haikal et al., 2019) (6/17)	Lactobacillus (Flavin et al., 2017; Hopfner et al., 2017; Lin et al., 2018; Haikal et al., 2019) (4/17)
Enterobacteriaceae (Keshavarzian et al., 2015; Mao et al., 2016; Manfredsson et al., 2018; Haikal et al., 2019) (4/17)	
Verrucomicrobiaceae (Jangula and Murphy, 2013; Holmqvist et al., 2014; Keshavarzian et al., 2015; Jiang et al., 2017; Hopfner et al., 2017; Lin et al., 2018; Aho et al., 2019; Zhang et al., 2020) (8/17)	Akkermansia (Jangula and Murphy, 2013; Keshavarzian et al., 2015; Jiang et al., 2017; Hopfner et al., 2017; Lin et al., 2018; Barichella et al., 2019; Aho et al., 2019; Zhang et al., 2020) (8/17)
Enterococcaceae (Holmqvist et al., 2014; Hopfner et al., 2017) (2/17)	
Bacteroidaceae (Jiang et al., 2017; Qian et al., 2018) (2/17)	Bacteroides (Jiang et al., 2017) (1/17)
Rikenellaceae (Li et al., 2017; Haikal et al., 2019) (2/17)	
Streptococcaceae (Scheperjans et al., 2015; Qian et al., 2018; Haikal et al., 2019) (3/17)	Streptococcus (1/17)
Clostridiaceae (Jiang et al., 2017) (1/17)	ClostridiumIV (Petrov et al., 2017) (1/17) ClostridiumXVIII (Petrov et al., 2017) (1/17)
Lachnospiraceae (Jiang et al., 2017; Petrov et al., 2017) (2/17)	
Bifidobacteriaceae (Jangula and Murphy, 2013; Scheperjans et al., 2015; Keshavarzian et al., 2015; Lin et al., 2018) (4/17)	Bifidobacterium (Jangula and Murphy, 2013; Flavin et al., 2017; Lin et al., 2018) (3/17)
Ruminococcaceae 57 (1/17)	
Decreased in PD	
Prevotellaceae (Holmqvist et al., 2014; Mao et al., 2016; Flavin et al., 2017; Li et al., 2017; Lin et al., 2018; Aho et al., 2019; Zhang et al., 2020) (7/17)	Prevotella (Holmqvist et al., 2014; Flavin et al., 2017; Hopfner et al., 2017; Li et al., 2017; Lin et al., 2018; Zhang et al., 2020) (6/17)
Lachnospiraceae (Jangula and Murphy, 2013; Scheperjans et al., 2015; Keshavarzian et al., 2015; Li et al., 2017; Manfredsson et al., 2018; Qian et al., 2018; Lin et al., 2018) (7/17)	Roseburia (Jangula and Murphy, 2013; Keshavarzian et al., 2015; Li et al., 2017; Lin et al., 2018) (4/17)
Ruminococcaceae (Jangula and Murphy, 2013; Holmqvist et al., 2014; Li et al., 2017; Lin et al., 2018) (4/17)	Faecalibacterium (Jangula and Murphy, 2013; Flavin et al., 2017; Li et al., 2017; Qian et al., 2018; Lin et al., 2018) (5/17)
Coprobacillaceae (Jiang et al., 2017) (1/17)	Coprococcus (Jiang et al., 2017; Lin et al., 2018) (2/17)

Some Species Specifics

- Enterobacteriaceae
  - Overabundance associated with postural instability and gait difficulty
  - Produce pro-inflammatory cytokines & LPS which can increase inflammation in the CNS.
- Akkermansia
  - Abundance can cause breakdown in intestinal barrier
  - Increases GI inflammation
- One study showed compared the fecal microbiome of 72 patients with Parkinson's Disease to 72 controls
  - Prevotellaceae in feces of PD patients **reduced** by 77.6% compared to controls (another study showed this also decreased intestinal permeability) (Scheperjans F 2015)
- Roseburia
  - "Lower baseline was associated with worse evolution of motor, non-motor and cognitive functions at 3-year follow-up" (Cilia R 2021)
- Ruminococcaceae & Actinobacteria
  - "(Lower) at baseline was associated with faster worsening of global cognitive functions" (Cilia R 2021)

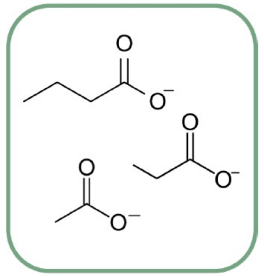
Functional Analysis of Microbiome

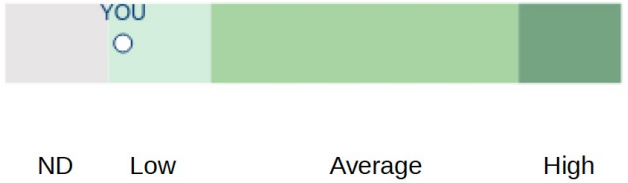
Types of Short Chain Fatty Acids:

- Butyrate
- Acetate
- Proprionate

Short Chain Fatty Acid Production | Summary

Short chain fatty acids are important metabolites in the gut. Bacteria digest unabsorbed and undigested food components, mostly fiber, to produce these small molecules. These SCFAs have many roles in and beyond the gut: they act as signaling molecules that cross through colon cels into various parts of your body, they are involved in immune responses, inflammation, and they may influence psychological functions. The major SCFAs are butyrate, acetate, and propionate.





343.79

Your Gut

535.03 to 1572.59

Healthy Group Range

Short Chain Fatty Acids

Role:

- Decrease full body inflammation
- Increase nerve formation
- Improve memory
- Reduce "leaky" blood brain barrier
- Fuel for gastrointestinal cells to help maintain the GI barrier.
- Decrease growth of harmful bacteria
- MORE

Examples of bacteria that produce SCFA

- *Roseburia spp, Butyricicoccus pullicaecorum, Eubacterium rectale, Bifidobacterium longum, Faecalibacterium prausnitzii, Akkermansia, Prevotella spp.*

Silva YP, et al. 2020

Ways to increase SCFA

- Complex carbohydrates
- Prebiotics - kraut, kimchi
- Probiotics, i.e. ones that contain *Bacillus sp.*
- Improve sleep (this is a two-way street!)
- Increase exercise
- Avoid high sugar and high fat diets

Okay, so now what with the gut?

- Diet
  - Fresh fruits & vegetables, nuts and seeds, fish, etc (sound familiar?)
  - No more artificial sweeteners
  - Hydrate!!
  - Lemon water
- Exercise!
- Probiotics?
  - 2022 meta-analysis showed probiotics can improve cognition & GI symptoms(Xiang S et al, 2022)
- Fecal transplant?
  - We still have a ways to go.

Questions?

Thank You

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