



No Guts, No Glory: Mystery of the Microbiome

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Disclosure

Speakers Bureau: Allergan, Amgen, Lilly Pharmaceuticals

Any unlabeled/unapproved uses of drugs or products referenced will be disclosed.



Learning Objectives

- Define the microbiome
- Discuss the gut-brain axis
- Explore the importance of the microbiome in pain modulation



The Microbiome: A Community of Life FUN FACTS

- Collection of microorganisms (protozoans, bacteria, fungi, and viruses) that inhabit the alimentary canal
- Over 100 trillion microbes; more DNA than the human genome
- Whole microbiome weighs appx 3-5 lbs, about that of the human brain
- The microbiome is essential for human development, immunity, and physical and mental wellness
- Change your microbiome with each meal

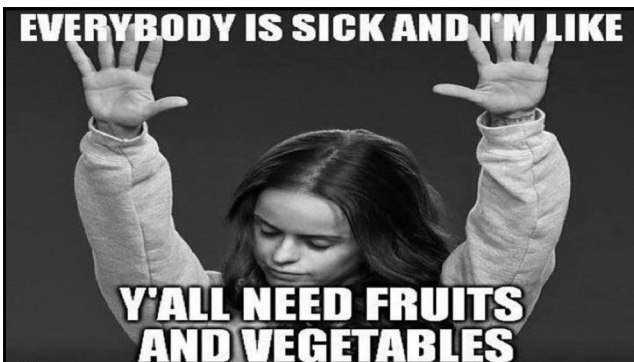


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The Microbiome: A Community of Life

- The microbiome was not generally recognized to exist until the late 1990s
- Most of the science published is <5 years old: new science
- Autoimmune diseases such as diabetes, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, and fibromyalgia are associated with dysfunction in the microbiome
- Relationship of dysbiosis & stress/anxiety/depression/pain

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Basic Principles

- Low inflammatory, low allergenic, high fiber
- Balance of good bacteria & pathogenic bacteria
- Overuse of antibiotics alter the balance and result in overgrowth of pathogenic bacteria, yeast, etc
- Importance of breastfeeding for infant immunity
- Dysbiosis
- Gut – brain axis: simplistic understanding



Newer Principles

- Immune system & pain, stool & serotonin, glial cells & gut
- The enteric nervous system: aka “second brain”
- Any use of antibiotics alters the health of the microbiome
- Infant development of a healthy microbiome dependent on vaginal
- Prebiotics, probiotics & psychobiotics
- Gut – brain axis: advanced understanding of neurobiology



Tick H. Microbiome: The link between nutrition and pain.
Pain Week 2017; September 5-9, 2017; Las Vegas, NV.

"Whenever we eat a meal, we either increase or decrease our inflammation."

She continued, "and increased inflammation leads to increased pain."

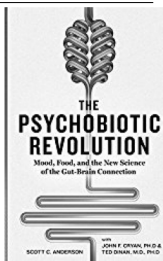


The Psychobiotic Revolution (2017) SC Anderson, JF Cryan & T Dinan

Are bacteria controlling your brain?

- Microbes improve mood – psychobiotics
- Psychobiotics major players in gut-brain axis
- Importance of gut function and the food we eat on mental well-being
- Bacteria in you gut secrete & respond to dopamine, serotonin & GABA
- Every cell of the GI tract can trigger an immune response → release cytokines → activates microglia
- Science gut-brain axis

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How are the gut and brain connected?

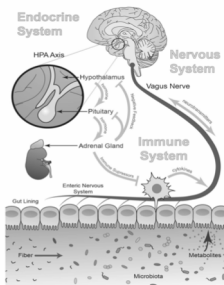
The gut microbiota communicates with the central nervous system (brain):

Nervous system – using neurotransmitters via the vagus nerve

Immune system – using cytokines via the blood stream

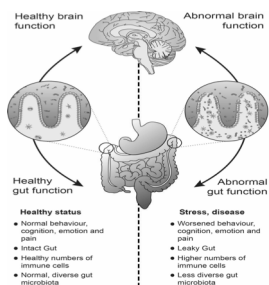
Endocrine system – using hormones (such as cortisol) via the blood stream

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Gut-Brain Axis is regulated through bi-directional mechanisms

- A healthy gut (left) maintains homeostasis
- A dysbiotic gut (right) lets pathogens through, resulting in inflammation in the brain and in the gut



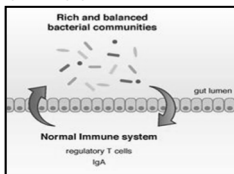
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What is a Healthy Gut

- Intestinal lining = mucus layer, epithelial layer, lamina propria layer
- Maintenance of intestinal lining integrity
- Prevents the loss of water, electrolytes, nutrients
- Prevents the entry of antigens, toxins and pathogenic microorganisms

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- Bacteria in the gut also play a role in preventing a leaky gut (dysbiosis). Clostridia, aids in regulating gut permeability



Factors that enhance tight-junction (TJ) integrity & regulate intestinal permeability

Categories	Names
Prebiotic nutrients	Galacto-oligo & fructo-oligo-saccharides
SCFA, polyunsaturated fatty acids, nutrients	Butyrate, glutamine, zinc
Plant-derived flavonoids	Quercetin, propolis, green tea, coffee, berries, other fruits/veggies
Vitamins, probiotics	Vit A&D, lactobacillus, bifidobacterium
Microbial enzymes	Proteases
Chemical compounds	Gelatin tannate

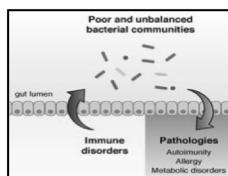
(Lerner, et al., 2017)

What is Dysbiosis: aka Leaky Gut

- A microbiota this is unbalanced = ↑ intestinal permeability
- ↑ immune response/autoimmune cascade
- ↑ immune response to food particles in the bloodstream = ↑ food allergies
- Depression/anxiety dysbiosis reinforcing feedback loop through gut-brain axis

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- Role in neurodegenerative & neuroinflammatory diseases



Factors that increase intestinal permeability			
Pathogens	Nutrients	Drugs	Toxins
H. pylori Salmonella C. difficile Rotavirus Shigella	High fat/carbohydrate diet Fructose, gluten, processed food, additives, Vit A&D deprivation	PPIs, NSAIDs	Clostridium/Botulinum toxins, EDTA
Lifestyle & Behavioral factors	Gut perfusion	Allergens	Carcinogens
Western diet Chronic stress	Obesity	Peanuts, soy beans, wheat, milk proteins, nuts, sesame	Phenols, mercury, arsenic (Lerner, et al., 2017)

Some Basic Chemistry/Microbiology of Nutrition for the Nonscientist

Diets rich in fiber from fruits/vegetables/plants contain more short-chain fatty acid (SCFA)-producing bacteria, long chain fatty acids, flavonoids & carotenoids

SCFAs

- > have an anti-inflammatory effect on the gut
- > vital for gut-brain communication
- > regulate immune function

LCFAs/flavonoids/carotenoids

- > reduce oxidative stress
- > suppress inflammatory mediators
- > modulate gene expression

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Microbiome - The Immune System - Inflammation

• Dysbiosis (↑ permeability intestinal wall) commonly seen in autoimmune diseases:

- Rheumatoid arthritis
- Ankylosing spondylitis
- Inflammatory joint disease
- Psoriatic arthritis
- Ulcerative colitis
- Crohn's disease
- Fibromyalgia, lupus, multiple sclerosis?

At the Mayo Clinic, researchers found that a species of Prevotella bacteria (p. histicola), can prevent or halt mouse versions of both rheumatoid arthritis & multiple sclerosis (Marietta, et al., 2016)

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Microbiome – The Immune System – Allergies - Inflammation

Foods & nutrients thought to have anti-inflammatory effects:

- Fish & primrose oils
- Black cumin, fenugreek, licorice, coriander, rosemary
- Tomato, carrot, sweet potato, broccoli, dates
- Walnut, hazelnut, wheat germ
- Green tea
- Apple cider vinegar

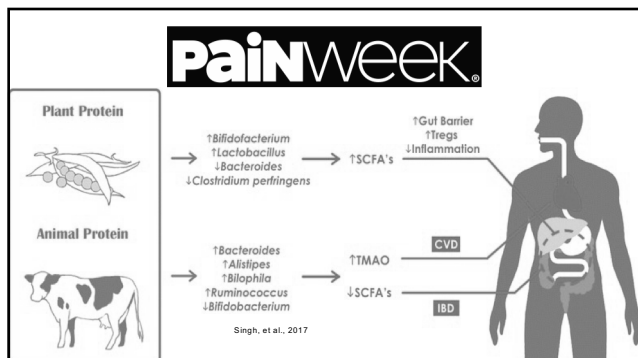


Microbiome – The Immune System – Allergies – Inflammation (cont'd)

Foods & nutrients thought to have pro-inflammatory effects:

- Gluten
 - Immunogenic, cytotoxic, pro-inflammatory
 - Augments apoptosis & effects epigenetic pathways
- Dairy
 - Pro-inflammatory activity seen in individuals with identified milk allergy. (Bordoni, et al. 2017)
- Saturated fats, refined carbohydrates, simple sugars





The Mighty Glia Cell

- Microglia (immune-like cells of the CNS) release:
 - ✓ Cytokines & other proinflammatory molecules
 - ✓ Communicate w/peripheral immune cells
 - ✓ ↑ release of excitatory neurotransmitters & neuronal firing from pain-transmitting neurons.
- In persistent pain, these cells contain fewer of the molecular transporters responsible for this neurotransmitter removal

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Glial Cells and Pain

The Intestinal Glial Neuronal Bouncer (Microglial Network)

- 7x more glial cells in the gut than neurons
 - Intro-ganglionic glial
 - Intra-muscular glial
 - Mucosal glial
- The glial cell's homeostasis is regulated by the microbiome
- The health of the microbiome relies on proper functioning of intestinal microglial network

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Glial Cells and Pain (cont'd)

The Intestinal Glial Neuronal Bouncer (Microglial Network)

Functions of the intestinal microglial network:

- Maintenance of barrier integrity (protective)
 - Regulates neuronal activity, mucosal secretion & immunity, GI motility
 - Defend intestinal mucosa against pathogens
 - Glial cells respond to & produce cytokines and chemokines
- Dysbiosis gut → overactivation of microglial network → overactivation (sensitization) glial cells → prolongation/persistence pain

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Microbiome & central stress effects

Neuroplasticity & microglia activation have been shown to be regulated by the microbiota. (Ogbonnaya, et al., 2015; Erny, et al., 2015).

Microbiome has effects on the amygdala (another key stress & pain related region of the brain):

- emotional learning & social behavior
- gating region of behavioral & physiological responses
- modulates experience of anxiety, fear, learned behavior



Microbiome & central stress effects

In 2004, Sudo, et al., germ free mice who showed an exaggerated stress response, could be reversed with colonization with bifidobacterial.

In 2016, Liu, et al., germ free mice colonized with lactobacillus, showed increased locomotor activity (↑dopamine ↑serotonin).



Microbiome & Visceral Pain

Visceral pain is pain that results from the activation of nociceptors of the thoracic, pelvic, or abdominal *viscera* (organs).

Visceral structures are highly sensitive to distension (stretch), ischemia & inflammation.

Altered Microbiome During Early Life - Critical Sensitive Periods Impacts Visceral Pain in Adulthood.

- Is it possible that better management of dysbiosis during early life may prevent the development of life long changes in pain responsiveness.



Microbiome & Visceral Pain

Alterations of the Microbiome in Visceral Pain Disorders.

- IBS is characterized by chronic abdominal pain and discomfort.
- Growing evidences suggest that IBS patients have a dysbiotic intestinal microbiota.

Alterations in the Microbiome & Visceral Pain Responses in Animal Models.



Microbiome & Visceral Pain – Kamiya, et al., 2006

Does probiotic bacteria influenced the pain perception during colorectal distension in healthy rats?

Lactobacillus reuteri was given by gavage for nine days.

- >Colorectal distension (80 mm Hg) under anesthesia
- >Heart rate was measured
- >Dorsal root ganglion discharge



Microbiome & Visceral Pain – Kamiya, et al., 2006

Results/Conclusions:

- >Mice given the bacteria had significantly decreased dorsal root ganglion single unit activity to distension.
- >Oral administration of either live or killed probiotic bacteria inhibited the constitutive cardio-autonomic response to colorectal distension in rats through effects on enteric nerves.
- >These data may provide a novel explanation for beneficial probiotic effects on visceral pain.



Microbiome & Visceral Pain – Ma, et al., 2009

Does probiotic bacteria influenced the pain perception during colorectal distension?

Lactobacillus species ingestion can decrease autonomic responses and spinal fiber discharge to nociceptive colorectal distension (CRD), even in the absence of inflammation.

Methods: Healthy rats were fed with Lactobacillus reuteri or placebo control for 9 days. They were anesthetized, and intermittent distal colonic CRD at 80 mmHg distension was performed.



Microbiome & Visceral Pain – Ma, et al., 2009

Results/Conclusions: CRD decreased the threshold for action potential generation & increased the number of spikes discharged during a standard depolarizing test stimulus, and this effect was blocked by prior probiotic ingestion.

- We suggest that the effects of CRD may have been caused by activity-dependent neurotransmission between DRG somas.
- Probiotic ingestion may have interfered with this hypothetical mechanism since it blocked the effect of CRD on the action potential.



DOES STOOL CONSISTENCY PREDICT PAIN PERCEPTION? Shiro, et al, 2017

38 healthy volunteers: 24 male:14 female; early 20's

- > Typical stool form [Bristol Stool Form Scale – BSFS]
- > Body Mass Index measurements [BMI]
- > Constipation [Cleveland Clinic Constipation score – CCS]
- > Pain sensation by mechanical stimulus [von Frey mono-filament – VFM & Visual-analogue scale - VAS]
- > Cold pain threshold [CPT]
- > Psychological states [Hospital Anxiety & Depression Scale – HADS; Pain Catastrophizing Scale – PCS; State-Trait Anxiety Inventory Questionnaire - STAI]



DOES STOOL CONSISTENCY PREDICT PAIN PERCEPTION? Shiro, et al, 2017

- Higher pain sensitivity & anxiety correlated with looser & more watery stools.
- Higher BMI = Higher anxiety/depression/catastrophizing.
- Higher VAS scores = anxiety/depression/catastrophizing.

Additional discussion:

- BSFS score is correlated with dysbiosis & a lack of a healthy microbiome (richness of gut bacteria).
- Higher BMI association with lack of healthy & diverse microbiome.
- Obesity is a risk factor for pain & relationship between obesity: ↑ pain intensity

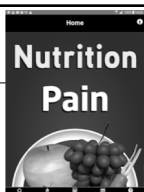


(Eslami, et al. 2017)

NUTRITION & PAIN

Fundamentals:

- Health weight
- Low-inflammatory
- Low-allergenic
- Plant based
- Stress reduction
- Healthy Microbiome
- Use of probiotics?



AAN 70th Annual Meeting Abstract: Gluten-Free Diet May Help People with Neuropathic Pain

Gluten neuropathy (GN) is the second most common neurological manifestation of gluten sensitivity, after cerebellar ataxia.

60 patients with gluten neuropathy were recruited. Pain was present in 33 patients (55.0%).

Design/Methods:

- Pain was assessed via the DN4 questionnaire and the visual analogue scale (VAS).
- Neuropathy Limitations Scale (ONLS) was used to assess the severity of neuropathy.
- The Mental Health Index (MHI-5) was used to measure participants' general



AAN 70th Annual Meeting Abstract: Gluten-Free Diet May Help People with Neuropathic Pain

- Patients w/ painless GN were more likely to be on a strict gluten-free diet.
- Patients w/ painful GN presented with significantly worse MHI-5 scores.
- Multivariate analysis showed that strict gluten-free diet was associated with lowering the odds of peripheral neuropathic pain by 88.7%.

Conclusions:

Pain is very prevalent in GN and is associated with poorer mental health status. A strict gluten-free diet might be protective as it is associated with a significant reduction of the odds of peripheral neuropathic pain associated to GN.



Somatic Pain – Arthritis – Kuptniratsaikul, et al., 2014

To determine the efficacy & safety of Curcuma domestica extracts in pain reduction and functional improvement.

367 primary knee osteoarthritis patients with a pain score of 5 or higher were randomized to receive:

- ibuprofen 1,200 mg/day
- C. domestica extracts 1,500 mg/day for 4 weeks

The main outcomes were:

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) total: pain, stiffness & function scores.
- Adverse events (AEs) were also recorded.



Somatic Pain – Arthritis – Kuptniratsaikul, et al., 2014

➤ The mean of all WOMAC scores at weeks 0, 2, & 4 showed significant improvement when compared with the baseline in both groups.

➤ The number of patients who developed AEs was no different between groups.

However, the number of events of abdominal pain/discomfort was significantly higher in the ibuprofen group.



Somatic Pain - Arthritis

Boer CG, et al. Paper #4. Presented at: Osteoarthritis Research Society International World Congress: April 27-30, 2017: Las Vegas.

Using genetic sequencing, assessed the gut microbial composition of 1,444 study participants.

- They found no association between overall variation of the gut microbiome & osteoarthritis (OA).
- However, among single microbial taxonomies, there were six significant associations with OA after adjustment for BMI, age and gender.
 - Clostridiales - hip WOMAC & Kellgren-Lawrence scores.
 - Streptococcus - knee WOMAC scores.



Somatic Pain - Arthritis

“Our hypothesis is that these species can activate our immune system and cause low-grade systemic inflammation within the joint that will cause inflammation & joint damage that will lead to pain.”

These microbial taxonomies, similar in all 1,444 study participants, in a gut with dysbiosis, can lead to a more systemic inflammation, putting individuals at risk for DJD.



Somatic Pain – Arthritis – Scher, et al., 2013

Rheumatoid arthritis (RA) is a prevalent systemic autoimmune disease, caused by a combination of genetic and environmental factors.

Genetic sequencing on 114 stool samples from rheumatoid arthritis patients & controls.

- We identified the presence of Prevotella copri as strongly correlated with disease in new-onset untreated rheumatoid arthritis patients.
- Increases in P. copri abundance correlated with a reduction in beneficial microbes in subjects.
- This work identifies a potential role for P. copri in the pathogenesis of RA.



America Microbiome Institute & The International Human Microbiome Consortium

<http://www.microbiomeinstitute.org/>

The American Microbiome Institute is a non-profit organization, established in 2013, dedicated to advancing microbiome science and education.

<http://www.human-microbiome.org/>

The International Human Microbiome Consortium - The goal of the IMHC is to work under a common set of principles and policies to study and understand the role of the human microbiome in the maintenance of health and causation of disease and to use that knowledge to improve the ability to prevent and treat disease.



Making Heads/Tails of the Hype



<https://isappscience.org/>

- Resources for patients and clinicians
- Clinical guide to pre & probiotics
- Which pre & probiotics are useful for what indications
- Product watch
- Continuing education related to microbiomes
- And much, much more ...



The world's first sequencing-based clinical microbiome test



https://ubiome.com/clinical/smartgut/?utm_source=google&utm_medium=cpc&utm_campaign=Search-Brand-SG-Broad-GP&qclid=FA1ajQobChMI3u2Fgt242qIVPhkCh1o2w1QFAAYASAAEgKqj_D_BwE

SmartGut is the world's first sequencing-based clinical microbiome screening test based on our patented technology and extensive peer-reviewed research. The test detects beneficial and pathogenic microorganisms associated with gut conditions like irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD), including ulcerative colitis & Crohn's Disease.



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Take Home Points



- Microbiota is diverse and has a definite effect on health, wellness & **pain**.
- Bidirectional interactions between the microbiome, gut and brain.
- Recommendation is to use diet to modulate microbiota, jury is still out on use of probiotic supplements.
- Our microbiota is constantly changing, relies on being replenished, today's antibiotics (broad-spectrum) devastating to the microbiota.
- Practical ways of modulating the microbiota:
 - Consuming low-allergenic, low-inflammatory diets.
 - Rich fiber and diverse diet, low-fat, whole grains



Thank You

Why do you think that the Energizer Bunny, keeps on going?
Because she has a diet rich in carrots.



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