PAINWEEK

No Guts, No Glory: Mystery of the Microbiome

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Disclosure

Consultant/Independent Contractor; Speakers Bureau; Honoraria: Allergan, Amgen, Lilly Pharmaceuticals

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

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Learning Objectives

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

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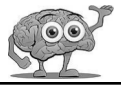
The Microbiome— A Community of Life: Fun Facts

- Collection of microorganisms (protozoans, bacteria, fungi & viruses) that inhabit the alimentary canal
- Over 100 trillion microbes, outnumbering our human cells 10:1. 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 & nutrition
- 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 less than 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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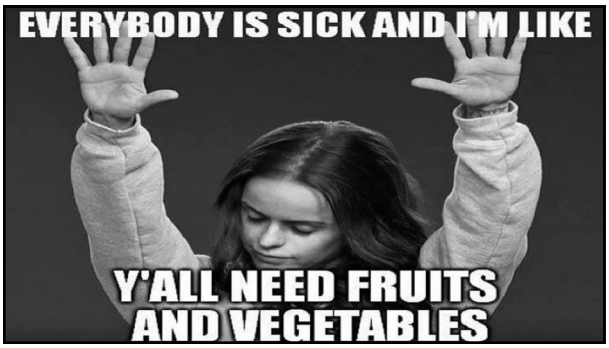

Basic Principles

- 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

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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 delivery
- Prebiotics, probiotics, & psychobiotics
- Gut-brain axis: advanced understanding of neurobiology

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Tick H. Microbiome: The link between nutrition and pain. PAINWeek 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."

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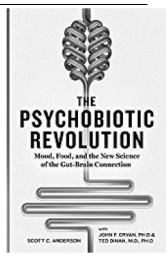
The Psychobiotic Revolution (2017) SC Anderson, JF Cryan, & Dinan T

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 your 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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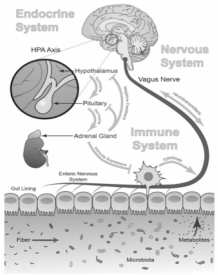
How are the gut and brain connected?

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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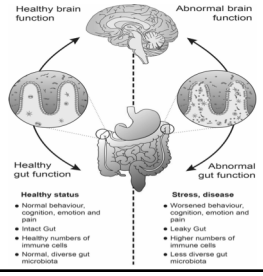
Gut-Brain Axis Regulated Through Bi-Directional Mechanisms

- 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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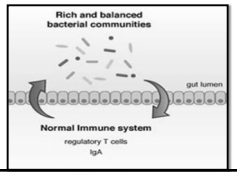
What is a Healthy Gut

- 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

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



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

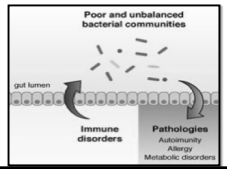
Categories	Names
Prebiotic nutrients	Galacto-oligo & fructo-oligo-saccharides
SCFA, polyunsaturated fatty acids, nutrients	Butyrate, glutamine, zinc
Plant-derived flavonoids	Quercetin, propolis, green tea, coffee, berries, other fruits/veggies
Vitamins, probiotics, VSL#3	Vitamins A&D, lactobacillis, 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
- Role in neurodegenerative & neuroinflammatory diseases
- ↑ immune response to food particles in the bloodstream = ↑ food allergies

- Depression/anxiety dysbiosis reinforcing feedback loop through gut-brain axis



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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, vitamin 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

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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

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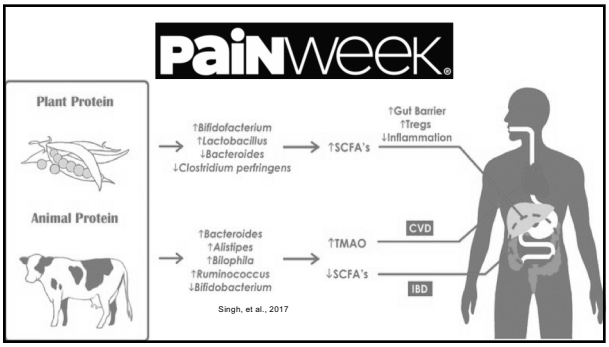

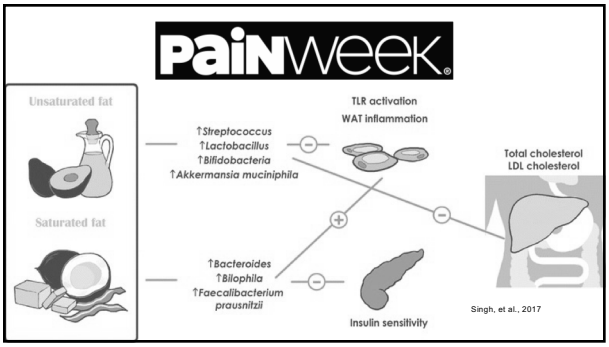

The Mighty Glia Cell

- 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
- Glial cytokines & chemokines = ↑ numbers of receptors to be displayed on the postsynaptic terminal neurons → further promoting neuroexcitability

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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)
- 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 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

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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
  - –It is possible that better management of dysbiosis during early life may prevent the development of life long changes in pain responsiveness

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Microbiome & Visceral Pain (cont'd)

- Alterations in the Microbiome & visceral pain responses in animal models
- 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

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Microbiome & Visceral Pain
Kamiya et al, 2006

Does probiotic bacteria influenced the pain perception during colorectal distension?

Explore the effects of Lactobacillus reuteri on cardio-autonomic response & single fibre unit discharge in dorsal root ganglia to colorectal distension in healthy rats.

Methods: Bacteria were given by gavage for nine days.
Colorectal distension occurred under anesthesia. Heart rate was measured. Single fibre unit discharge was recorded from dorsal root ganglion.

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Microbiome & Visceral Pain
Kamiya et al, 2006 (cont'd)

Results: Treatment with bacteria prevented the pain response even during the maximum distension pressure (80 mm Hg). Mice given the bacteria had significantly decreased dorsal root ganglion single unit activity to distension.

Conclusions:

- 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.

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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.

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Microbiome & Visceral Pain
Ma et al, 2009 (cont'd)

Results/Conclusions: CRD decreased the threshold for action potential generation. and 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.

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Does Stool Consistency Predict Pain Perception?
Shiro et al, 2017

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

Assessments:

- 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

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Does Stool Consistency Predict Pain Perception? Shiro et al, 2017 (cont'd)

Findings:

- Higher pain sensitivity & anxiety correlated with looser & more watery stools (higher BSFS scores).
- Higher BMI = higher HADS & STAI
- Higher VAS scores = higher STAI scores
- Constipation had no predictability to pain perception or psychological status

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)

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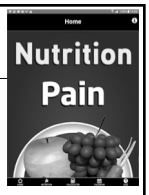
Nutrition & Pain

Fundamentals:

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



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

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

- Idiopathic neuropathy
- Serological evidence of gluten sensitivity (IgA and/or IgG antibodies)

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 mental health status

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

Results: 60 patients (76.7% males, mean age 69.9±10.1 years) with gluten neuropathy were recruited. Pain was present in 33 patients (55.0%).

- Patients with painless GN were more likely to be on a strict gluten-free diet (55.6% vs 21.2%, p=0.006)
- Patients with painful GN presented with significantly worse MHI-5 score (75.9±13.8 vs 87.4±8.1, p<0.001)
- 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.

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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

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Somatic Pain—Arthritis Kuptniratsaikul et al, 2014 (cont'd)

- The mean of all WOMAC scores at weeks 0, 2, and 4 showed significant improvement when compared with the baseline in both groups
- C. domestica extracts were noninferior to those for the ibuprofen group (P=0.010, P=0.018, and P=0.010, respectively), except for the WOMAC stiffness subscale, which showed a trend toward significance (P=0.060)
- 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 than that in the C. domestica extracts group (P=0.046)
- Most subjects (96%-97%) were satisfied with the treatment, and two-thirds rated themselves as improved in a global assessment

CONCLUSION: C. domestica extracts are as effective as ibuprofen for the treatment of knee osteoarthritis. The side effect profile was similar but with fewer gastrointestinal AE reports in the C. domestica extracts group.

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Somatic Pain—Arthritis

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

Using 16S ribosomal RNA-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
  - Two families from the Clostridiales order were associated with both hip WOMAC & Kellgren-Lawrence scores
  - The only species with an association with OA was Streptococcus, which was associated with knee WOMAC scores

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Somatic Pain—Arthritis (cont'd)

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

- "Our hypothesis is that these species can activate our immune system and cause low-grade systemic inflammation within the joint that will cause inflammation and joint damage that will lead to pain."
- Take away: 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

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Somatic Pain—Arthritis
Scher et al, 2013

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

Here we performed 16S sequencing on 114 stool samples from rheumatoid arthritis patients and controls.

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

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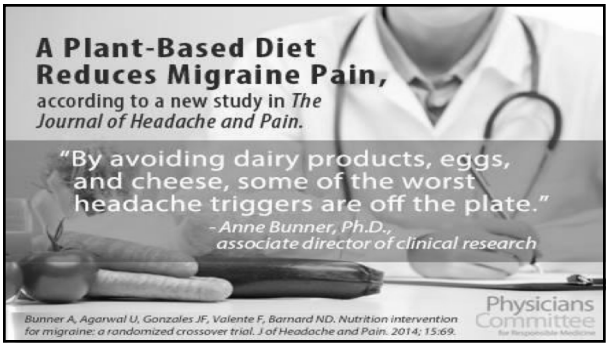

Bunner et al, 2014
Journal of Headaches and Pain

The effects of a low-fat plant-based diet intervention on migraine severity and frequency.

Methods: 42 adult migraine sufferers were recruited. This 36-week crossover study included two treatments:

- ➢Dietary instruction
- ➢Placebo supplement

- ✓Each treatment period was 16 weeks, with a 4-week washout between
- ✓During the diet period, a low-fat vegan diet was prescribed for 4 weeks, after which an elimination diet was used
- ✓Participants were assessed at the beginning, midpoint, and end of each period

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Bunner et al, 2014
Journal of Headaches and Pain (cont'd)

- ➢↓ 20% during the diet period & ↓7% during placebo period (p=0.03).

Average headache intensity (0-10 scale) was initially 4.2 (SD 1.4) per week.

- ➢↓ 3.2 during the diet period & ↓ 3.7 during the supplement period (p=0.20).

Average headache frequency was initially 2.3 (SD 1.8) per week.

- ➢↓ by 0.3 during the diet period & by 0.4 during the supplement period (p=0.61).

The Patient's Global Impression of Change showed greater improvement in pain during the diet period (p<0.001).

Conclusions: These results suggest that a nutritional approach may be a useful part of migraine treatment.

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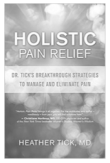
Heather Tick, MD

Gunn-Loke Professor of Integrative Pain Medicine, Clinical Associate Professor of Family Medicine, Anesthesiology & Pain Medicine
Integrative Pain Management and the Role of Nutrition
http://heathertickmd.com/



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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.

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Making Heads/Tails of the Hype

ISAPP INTERNATIONAL SCIENTIFIC ASSOCIATION OF PROBIOTICS AND PREBIOTICS™

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 …

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The world's first sequencing-based clinical microbiome test

SmartGut™

https://ubiome.com/clinical/smartgut/?utm_source=google&utm_medium=cpc&utm_campaign=Search-Brand-SG-Broad-GP&gclid=EAIaIQobChMI3u2Fqt242gIViPhkCh1o2w1OEAAYASAAEgKqi_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, and **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

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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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