Welcome!

Disease Begins in the Gut - But Often Doesn't Stay There

NCIMS Grand Rounds, Asheville

March 16, 2024

Welcome!

Disease Begins in the Gut - But Often Doesn't Stay There

Imbalances in the GI Tract can Lead to Systemic Dysfunction and Disease

Defining Functional Interconnectedness

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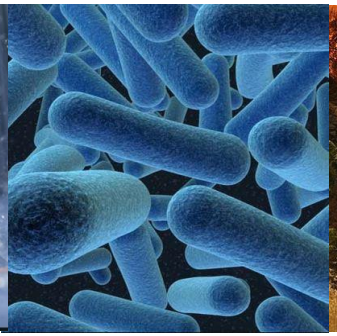

All Things are Interconnected, Uniquely

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- Oxygen Intake and Spiritual Mindset
- Stress and Stress Management
- Toxins and Detoxification Ability
- Sensitivities and Allergies and Immune Health
- Energy Generation and Circulation
- Nourishment and Absorption Ability
- Genetic Predispositions and Infections
- Expectation, Association, History, Belief

Ask what kind of *Person* has this dis-ease vs. what kind of *Disease* does this person have?

A Functional Gut Overview

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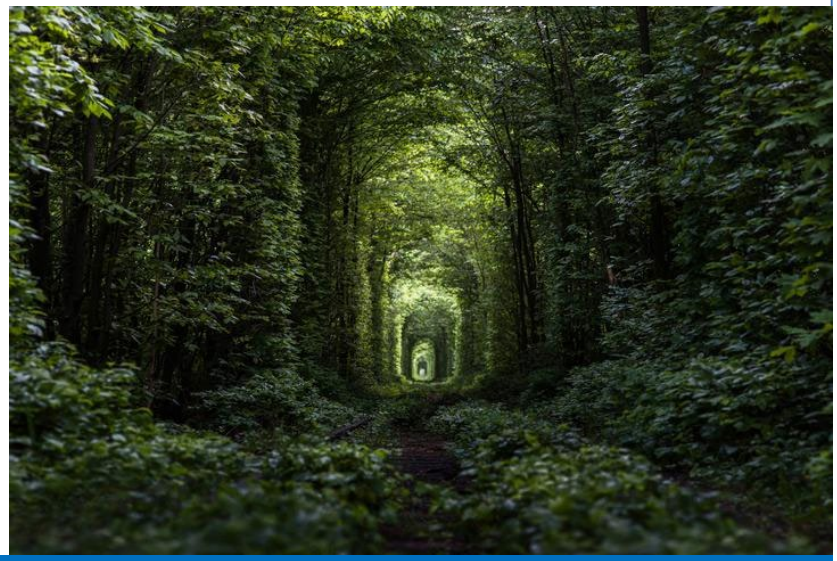
- A weird world.
  Essentially a 25-30 ft. tunnel that is a well-guarded and regulated **exchange corridor** and which is ultimately *outside of the systemic body*.
- The entryway for essential **nutrition to fuel every cell** in the body.
- The exit path for most **toxins and waste** – of exogenous *and* endogenous origin.
  The most toxic place in the body is nearly always the colon.
- Guarded by a planetary level population and **diversity of microbes.** Our biochemistry is regulated by their behavior and DNA (which transfers genes across species and to humans).*
- Home to **2/3+ of the immune system,** surveilling our intake, outflow, and microbial balance to regulate systemic function.
- Exchange controlled by a very complex, one-cell thick **semi-permeable interface.**
- Housing **its own nervous system** which generates neurotransmitters used throughout the body.**
- The gut and brain work as an integrated axis, connected via the **vagus nerve** with 80-90% of the nerve fibers going from the gut *to the brain* (afferent).***



* https://bmcgenomics.biomedcentral.com/articles/10.1186/s12864-017-3649-y and https://www.the-scientist.com/?articles.view/articleNo/47125/title/Bacteria-and-Humans-Have-Been-Swapping-DNA-for-Millennia/
** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5772764/ and https://pharmrev.aspetjournals.org/content/early/2022/12/08/pharmrev.122.000618
*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5808284/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5859128/

Dis-ease and Disease Often Begin in the Gut… and Progress!

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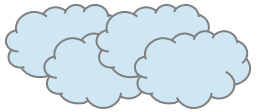
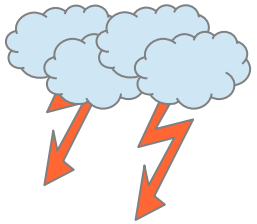
- Deficiency-Driven Dysfunction (digestion, absorption)
  - e.g. anemia, neuropathy, depression, headache

- Gastrointestinal Dis-ease (motility, microbes, hormones)
  - e.g. IBS, constipation, belching, bloating

- GI-origin Inflammation (enhanced gut permeability)
  - e.g. osteoarthritis, asthma, migraine, chronic fatigue, fibromyalgia, eczema, allergy/atopy, anxiety



- Autoimmune Dis-ease (immune dysregulation)
  - Hashimoto's thyroiditis, lupus, multiple sclerosis, Crohn's disease, rheumatoid arthritis



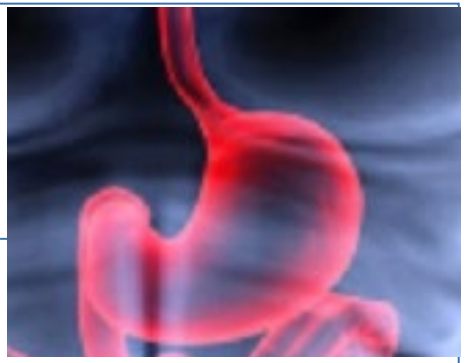
Wellness Must Begin in the Gut - with Nutrients

Not one of the **tens of trillions of cells in the human body can function properly** if nutrient intake is low or if digestion and/or absorption** of nutrients is impaired.

- **In the Brain** (sight, smell, thought of food)
  - The **cephalic phase** of digestion stimulates the brain and then the vagus nerve to trigger ECL cells (to produce histamine for HCl) and G cells (for gastrin). You feel hungry, and your stomach rumbles!
- **In the Mouth**
  - Breaking chunks (bites) of food down into small particles.
    Lingual lipase* begins to act on dietary fats.
    Salivary amylase starts to digest carbohydrates.
    Chewing is essential and often marginalized!
- **In the Stomach**
  - Cleaving polypeptide chains from protein, separating minerals from protein (**Hydrochloric acid and Pepsin**), preparing intestinal uptake of Vitamin B12 (intrinsic factor).
- **In the Small Intestines**
  - Breaking down fats, carbohydrates, and those polypeptides into individual molecules (with **bile** and **digestive enzymes** from both pancreas and "brush border" lining of the villi) and absorption via the enterocytes.

* For a deeper dive: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6356603/
** For an overview of digestion/absorption: https://courses.lumenlearning.com/cuny-csi-ap-1-2/chapter/chemical-digestion-and-absorption-a-closer-look/

Stomach Acid: Digestive Hero!



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- Hydrochloric acid (HCl) is produced by parietal cells in the lining of the stomach (and pepsin from chief cells). Required to denature proteins & isolate/prepare nutrients for absorption.
- **Suboptimal HCl may be caused by many factors*** e.g. poor eating hygiene, sympathetic nervous system state, hypothyroid and/or hypoadrenal state, SIBO or other dysbiosis (antibiotics), chronic use of NSAIDs, *H. pylori* infection, autoimmune antibodies, age, chronically low estrogen***, and/or drugs.
- **Acid-suppressing medication use** is very common in some populations and creates overt hypochlorhydria e.g. PPIs, H2 receptor blockers/antihistamines, NSAIDs.
- Hypochlorhydria may create an opportunity for **microbial overgrowth/pathogens,**** immune hyper-reactivity to maldigested foods (e.g. allergy/sensitivity), or poor nutrient/drug absorption.
- Internal production decays with age, often because of simmering *H. pylori* overgrowth. **30-50% of adults in their 60s and 40-80% of people over age 85 have hypochlorhydria**. Pepsin supply decays with age regardless of *H. pylori* status.*
- **Chronic maldigestion often creates downstream dysfunction!** Hypochlorhydria may promote:
  - **Delayed gastric emptying** that then promotes GERD, bloating, and impaired first-pass insulin response. May also be caused dynamics such as poor vagal tone, low estrogen, or hypothyroid state.#
  - Inhibited pancreatic enzyme and bile release, and thus **impaired downstream digestion**.
  - **Poor denaturation of protein** digestion and absorption (and thus, potentially, sensitivities/allergies).
  - **Nutrient deficiencies**, especially amino acids, vitamin B12, Minerals (e.g. Ca, Fe, Zn, Mg), and Folate.
  - **Many other disease dynamics**! Ulcers, Osteoporosis, Depression, Anemia, Weak immune function, Dysbiosis, Food Sensitivity, Allergy, Autoimmunity, hypertension, Arthritis, Cognitive impairment.

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6502205/ , http://www.ramauniversityjournal.com/medical/pdf_june/16-26.pdf , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5304992/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546438/#R137
** https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2761273 *** https://www.spandidos-publications.com/10.3892/etm.2018.6406
# https://journals.physiology.org/doi/full/10.1152/ajpgi.00144.2019 , https://pubmed.ncbi.nlm.nih.gov/32124195/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6850045/

Hypochlorhydria and Downstream Disease

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Gastrointestinal Tract and the Control of Bone Mass

Thorsten Schinke, Michael Amling, in Translational Endocrinology of Bone, 2013

Hypochlorhydria, a Major Public Health Problem

[redacted] patients with impaired HCl production. In a correlation between eczema and psoriasis and reduced gastric secretions, it was found 8 of 11 patients with eczema and 10 of 19 patients with psoriasis had functional hypoacidity. [redacted] reported

The clinical importance of hypochlorhydria (a consequence of chronic Helicobacter infection): Its possible etiological role in mineral and amino acid malabsorption, depression, and other syndromes

R.E. Cater

30 Nov 1992 - Medical Hypotheses (Med Hypotheses) - Vol. 39, Iss: 4, pp 375-383

TL;DR: Evidence is presented for the clinical relevance of reduced stomach acid secretion and the possible lowering of tryptophan, tyrosine, and phenylalanine in the blood which may be a precipitating factor in depression in hypochlorhydric patients.

Mediators between oral dysbiosis and cardiovascular diseases

Milla Pietiäinen, John M. Liljestrand, Elisa Kopra, Pirkko J. Pussinen

First published: 03 September 2018 | https://doi.org/10.1111/eos.12423 |

In order top-to-bottom as displayed above: https://www.sciencedirect.com/science/article/abs/pii/B9780124157842000063 , https://pubmed.ncbi.nlm.nih.gov/1494327/ Banoo H, et a, RAMA Univ. J. Med Sci 2016;2(2): 16- 26 , https://onlinelibrary.wiley.com/doi/10.1111/eos.12423

Asthma or Allergy May Begin in the Gut

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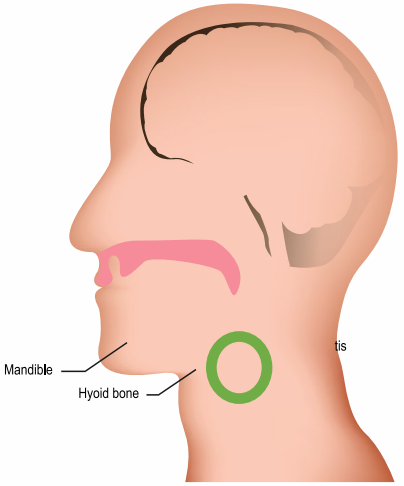


- The majority of **asthmatics also have chronic acid reflux** (GERD), which may promote asthma via acid aspiration and/or vagal stimulation.*
- Stomach acid is key in both **passive immune function** and denaturing proteins. Hypochlorhydria may **increase IgE allergic reactions** by as much as 10X and is more common in asthmatics than the general population.**
- **Allergy can decrease stomach acid production.** "In atopic children, gastric hyposecretion and epithelial degeneration may promote the passage of unhandled food allergens into the mucosa, predisposing them to more severe reactivity." Acid secretion returned to normal for most children on the appropriate elimination diet.***
- **Frequent use of bronchodilators** (weakens the lower esophageal sphincter) and diaphragmatic pressure may predispose those with existing asthma to chronic GERD.#
- **Magnesium insufficiency** is often seen in both acid reflux and asthma re: predisposition to muscle spasm.
- Hypochlorhydria often reduces Vitamin B12 absorption, and **insufficient B12 may promote wheezing.** Wheezing can then trigger acid reflux through compression of the LES.#

Allergy can promote Low stomach acid.
Low stomach acid can promote GERD.
GERD can promote Asthma.
Low stomach acid can then **worsen allergic hypersensitivity**,
Creating a *vicious cycle*.

* https://www.nature.com/articles/s41390-020-0749-1 , https://www.medscape.com/viewarticle/457853
** https://www.e-cep.org/journal/view.php?number=20125555382 , http://qjmed.oxfordjournals.org/content/4/4/397.abstract
*** http://link.springer.com/article/10.1007/BF00441481#page-1 , https://pubmed.ncbi.nlm.nih.gov/574086/ , and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6337651/
Dr. Wright, *Stomach Acid is Good for You*, goes in depth on this topic. # https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4574848/

Essential Digestive Enzymes

- Most carbohydrate and fat digestion (and final protein digestion) occurs in the small intestine thanks to digestive enzymes. Bile secreted from the gallbladder (which is made in the liver) must emulsify fats to allow their full digestion via the action of enzymes (lipases).
- Most digestion in the small intestine occurs in the first portion (12"), the duodenum. Most absorption occurs in the two latter segments, the jejunum and ileum.
- **Digestive enzymes come from both the pancreas and the intestinal brush border.**
- **Brush border enzymes**** include diamine oxidase (DAO) to digest histamine, lactase@ to digest lactose from dairy, sucrase to digest sucrose, and DPP-IV enzymes that are proteases which help to digest various proteins such as gluten, collagen, and casein.
- **Brush border enzyme release** is impaired by various insults to the intestinal villi e.g. chemotherapy, NSAIDs, celiac disease and other IBD, diarrhea, excessive histamine build-up, ongoing dysbiosis. *S. boulardii* probiotic use may increase the synthesis of brush border enzymes (part of why it is often helpful to counter diarrhea).***
- **Pancreatic digestive enzyme** release can be impaired**** by many factors including:
  - Chronic stress, sympathetic nervous system, hyperadrenal state
  - Hypothyroid state, hypoadrenal state
  - Dysbiosis or microbial imbalance#
  - Hypochlorhydria
  - Formula-feeding infants
  - Age @@ (may be 50% reduction or more!)
  - Gastric bypass and related surgeries
  - Celiac disease and other inflammatory bowel diseases
  - Cystic fibrosis, toxicity, pancreatitis/cancer
  - Insulin resistance (all stages!), type 1 diabetes, fatty pancreas

@ Remember that an estimated 2/3 of the human population is lactose intolerant due to innately deficient (low or no) synthesis of lactase, especially as adults.
@@ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4546438/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7099748/ ,
# https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5833470/
** http://www.vivo.colostate.edu/hbooks/pathphys/digestion/smallgut/bbenzymes.html
*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5808955/

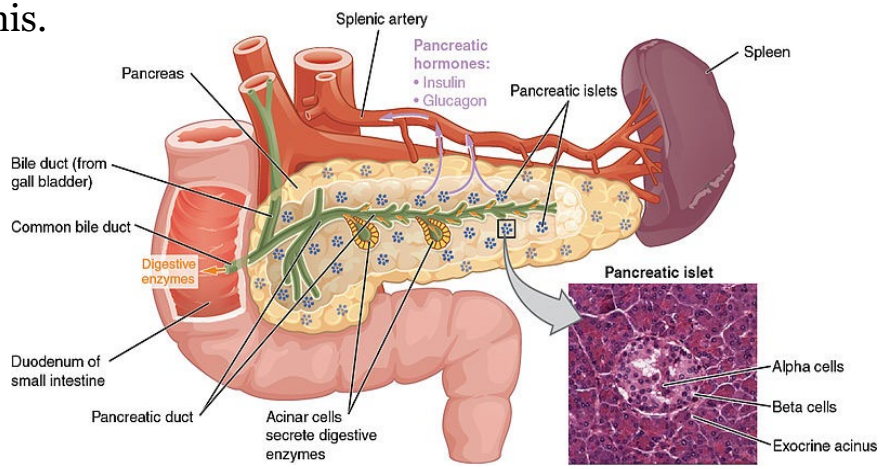
Multifactorial Pancreatic Insufficiency

- Exocrine and endocrine roles.
  Connected to GI tract (via the duodenum) and systemic body (via blood vessels).
  - **Digestive:** producing digestive enzymes and bicarbonate which help to break down foods in the intestines. 99% of pancreatic cells do this. Enzymes are also secreted into the blood.

Exocrine pancreatic insufficiency is common in both insulin and non-insulin dependent diabetes (25-50% T2D patients, even higher in T1D). Disease duration and severity are risk factors. May promote downstream gut dysbiosis and/or nutrient malabsorption. *

  - **Endocrine:** producing **insulin, glucagon**, & other key hormones. ~1% pancreatic cells do this.

- Like any other organ/gland, the **pancreas can become impaired by systemic effects****
  - Damaged from autoimmune activity, high free fatty acids (stress! e.g. high cortisol), or oxidative stress (hyperglycemia).
  - **May become "fatty"** with increased fat deposition (e.g. when the liver is also fatty) and promote **beta islet cell dysfunction**, moving the progression of metabolic dysfunction over time into Type 2 diabetes.



* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4393909/ , https://care.diabetesjournals.org/content/31/Supplement_2/S165
** https://diabetes.diabetesjournals.org/content/51/1/7.long , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3934755/ , https://diabetes.diabetesjournals.org/content/64/6/1886 , https://www.hindawi.com/journals/crie/2018/6147349/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3168743/ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2877635/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6606577/

Celiac-driven & Precious Brush Border Disease*

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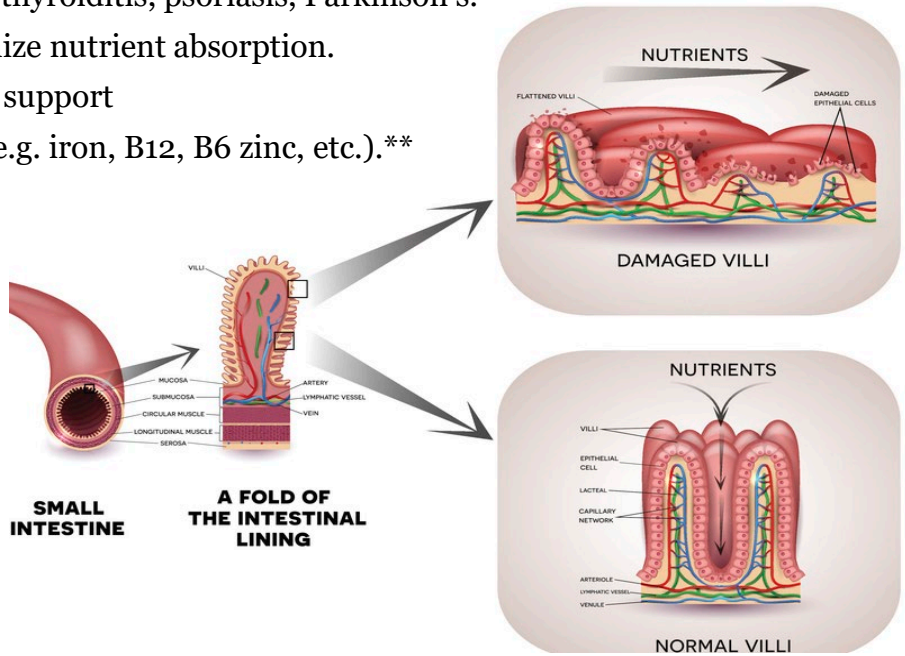
- Chronic autoimmunity (AI) in the small intestinal border can creates **enzyme insufficiency, affecting all nutrients' absorption, including protein and carbohydrates (e.g. lactose, sucrose).**
  - Targeted enzyme supplementation may help sensitive individuals to digest these foods more fully, not only to optimize nutrition but also to avoid ill effects. Maldigestion of gluten and casein can create **gluteo- and caseomorphin compounds which can have opiate-like effects** in sensitive individuals.**
- Tissue transglutaminase antibodies promote damage to intestinal lining. **Antibodies may be cross-reactive to transglutaminase found in other tissues e.g. skin, brain, thyroid.** As a result, celiac disease is often associated with AI dynamics that affect these tissues e.g. Hashimoto's thyroiditis, psoriasis, Parkinson's.
- Nourish enterocytes on an ongoing basis in order to maximize nutrient absorption.
  - Consider ongoing glutamine and mucilaginous herb support
  - Assess and consider key nutrient supplementation (e.g. iron, B12, B6 zinc, etc.).**

Celiac disease creates dramatic brush border enzyme deficiency. However, **low-grade deficiency is much more common (e.g. via dysbiosis, high histamine, NSAIDs)** and is especially detrimental for digesting sugars and proteins e.g. dairy, gluten. Supplementation can help sensitive individuals to digest these more fully .

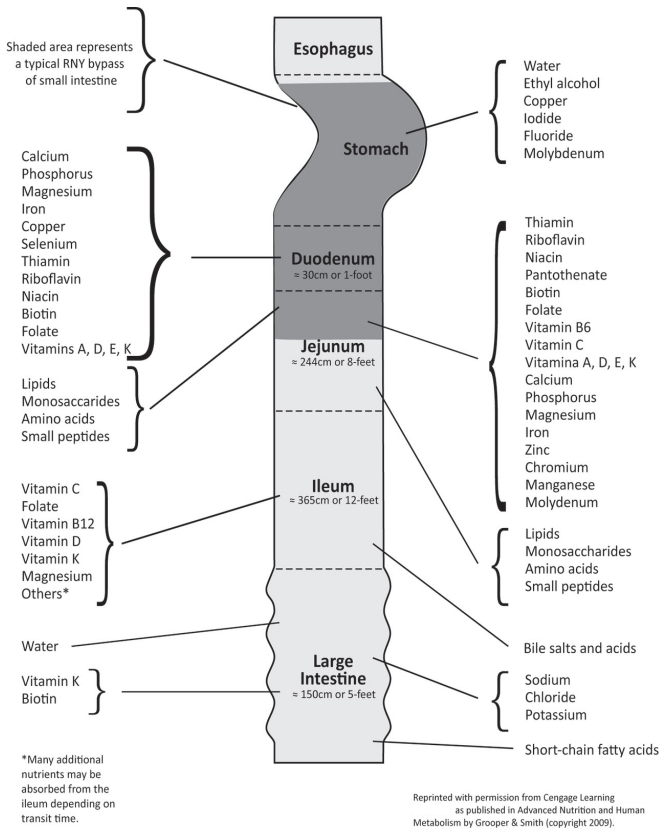


* https://www.ncbi.nlm.nih.gov/pubmed/26345415.
** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7071237/
Remember that an estimated 2/3+ of the world's population is lactose intolerant.

Intestinal Nutrient Absorption

A chronic downward spiral of disease interconnectedness can develop as our poorly digested food then feeds undesirable bacteria and fuels overgrowths, furthering
(1) inflammation,
(2) brush border damage, and thus
(3) further digestive and absorptive dysfunction.

- We don't want nutrients to stay in the gut! They are **transported across the intestinal epithelium** by various transport and diffusion processes. Damage to or removal of that segment overtly impairs absorptive capability.
- Chronic intestinal inflammation injures villi and microvilli and can lead to both **enhanced intestinal permeability** and impaired ability to bring nutrients to systemic circulation. **Wear'n'tear on the gut lining may promote nutrient malabsorption.***
- Microvilli expand the absorptive surface area of the gut exponentially; thus, **nutrient absorption can be damaged significantly by relatively small insults.**
- Damage to the mucosal lining and brush border of the intestines can result in digestive enzyme deficiency due to **impaired hormonal signaling along the GI tract,** and nutrient malabsorption may result, from insults such as:
  - pathogenic microbial infection or overgrowth (e.g. *C. difficile, Salmonella*, parasites)
  - microbial dysbiosis especially due to antibiotic use – worsened by repeated or lengthy courses (e.g. *Candida* overgrowth)
  - medications (e.g. antibiotics, steroids, NSAIDs)
  - toxins in food or water (e.g. chemical colors, too much alcohol, high fructose corn syrup, arsenic, lead)
  - any form of food sensitivity/allergy (IgE, IgG, IgA)



Location of Specific Nutrient Absorption

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4513829/ , https://courses.lumenlearning.com/cuny-csi-ap-1-2/chapter/chemical-digestion-and-absorption-a-closer-look/

Our Microbial Friends: Mutualism at its Best!

- **Comprised of over a thousand different species** – bacteria, archaea, phages, viruses, yeasts & fungi, parasites (protozoa, worms, etc.) – in addition to the biofilms housing these microbes, and all are competing for space, food, and nutrients. **Forming a human organ within the body.**
- The human immune system learns to tolerate commensal microbes (e.g. via secretory IgA*) and respond correctly to pathogens, while **the microbiota also instructs the immune system to work appropriately.** For example:
  - Non-pathogenic *Clostridium* spp. and its butyrate production **induces anti-inflammatory regulatory T cell increases in the colon.****
  - *H. pylori* is implicated in gastritis and gastric/duodenal ulcers, but its induction of T-reg cells seems to be an important mechanism in preventing asthma and Crohn's disease.*****
- **Dysbiosis is an imbalance.** Loss of beneficial bacteria, overgrowth of endemic or opportunistic microbial species, overt pathogen infection, or loss of overall microbial diversity. Dysbiosis promotes immune reactivity to counter the imbalance.

Pathogens and overgrowths of commensals, and well as our immune reaction to them, can damage our mucosal layer, causing (reversible) drops in digestive secretions,****** impaired nutrient absorption in the small intestines, and both **enhanced intestinal permeability and vulnerability to systemic inflammation from translocation of pro-inflammatory debris** (especially endotoxins such as lipopolysaccharides).

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3709412/ ** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4913331/
*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6064966/ **** https://www.hindawi.com/journals/jdr/2015/284680/

Enhanced Intestinal Permeability

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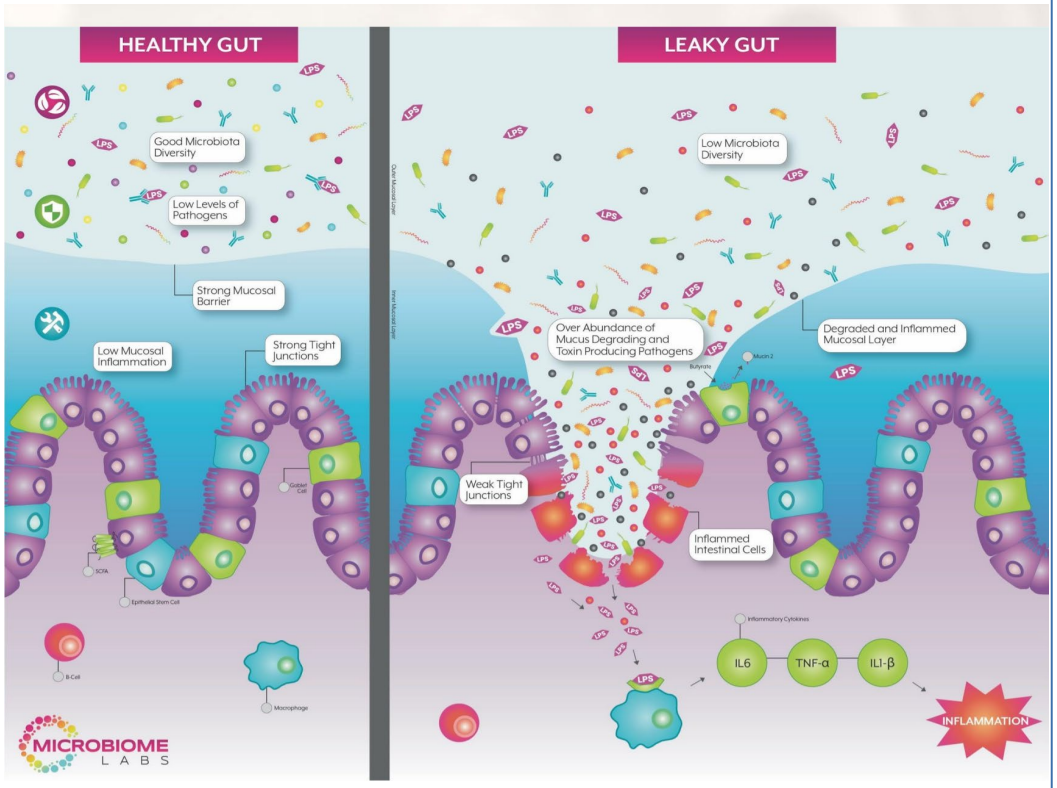
- **Optimal intestinal barrier function** allows the passage/absorption of nutrients, but at the same time, regulates the contact between luminal antigens and the immune system, confining undesirable products to the lumen. It's a delicate balance!

- Common Contributors to **excessive permeability**
  - Insufficient Vitamins D and A and/or zinc[#]
  - High blood sugar[##]
  - NSAID drugs[###]
  - Antibiotics
  - Other drugs (e.g. hormones, birth control pills, chemotherapy)
  - Isolation from "old friend" microbes*
  - Being a newborn**
  - Histamine overload
  - Highly processed foods
  - Chemicals, pesticides, food additives, smoking, glyphosate***
  - Pathogenic microbes
  - Microbial endotoxins (e.g. LPS)
  - Microbial overgrowths (e.g. SIBO/IMO)****
  - Hydrogen sulfide or d-lactate overload
  - Gluten, zonulin
  - **Stress**



Overall overview: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5988153/ Image Credit: Microbiome Labs
* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8007786/ ** https://journals.lww.com/jpgn/fulltext/2005/05000/intestinal_permeability_in_healthy_breast_fed.65.aspx
*** Good overview for practitioner/patient and extensive reference resource: https://chriskresser.com/the-impact-glyphosate-can-have-on-your-health/
**** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7925957/#bibr54-1756284821993586
# https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6431494/ ### https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8290187/
https://www.researchgate.net/publication/328743068_Hyperglycemia_drives_intestinal_barrier_dysfunction_and_risk_for_enteric_infection
The concept of intestinal permeability continues to be debated/disputed amongst some conventional medical practitioners e.g. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3758766/

Immune Disease Begins in the Gut

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- Over 2/3 of our immune cells live in the gut. Just beneath the single-cell-thick epithelial layer in the gut lies the GALT (Gut-Associated Lymphatic Tissue), the immunity "police station."
- Remember: the primary role of a well-balanced immune system is to assess, tolerate, and Not react. **Tolerance requires resilient T-regulatory cell function.** This reactivity is being constantly informed by our environment (especially our microbiome!) throughout life.
  - T-reg cell imbalance may be created by dynamics such as chronic stress, insufficient zinc, isolation from nature (priming by high microbial diversity), and low levels of short chain fatty acids (SCFAs) being produced in the gut.*
- **Both local and systemic immune regulation is sustained (or not) in the gut.**
- **Persistent inflammatory triggers (e.g. bacterial LPS) release potent inflammatory mediators** (e.g. NF-***κβ*** via gut epithelial cells) which increase immune reactivity and intensity.
- **Inflammation often begins (and is sustained chronically!) in the gut**:
  - **Dysbiosis** e.g. parasite, SIBO, *C. difficile,* post-antibiotic decimation of commensal flora.
  - **Food** that looks a little too much like a toxin, allergen, or foreign invader e.g. GMO foods including 90+% of non-organic soy and corn grown in the US.
  - **Toxins** e.g. glyphosate, pesticides, Red #40, birth control pills, artificial sweeteners, toothpaste, mercury, alcohol.
- **Enhanced intestinal permeability** can cause any or all of these things to get deeper into the lymphoid tissue of the gut (and into our blood supply), triggering a stronger immune response.
- With a chronic multifactorial onslaught of All these factors, this inflammation tends Not to stay only in the gut and **will have systemic effects**.

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6419713/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6117408/

Molecular Mimicry Drives Autoimmunity

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Examples of bacterial and viral antigens that can cross-react with self-antigens with potentially resultant diseases.

Pathogen antigen	Cross-reactive self-antigen	Autoimmune disease
Herpes simplex virus	Corneal antigen	Stromal keratitis
Campylobacter jejuni	Ganglioside in peripheral nerve	Guillain-Barré syndrome
Coxsackievirus	Glutamic acid decarboxylase	Type 1 diabetes
Theiler's murine encephalomyelitis virus	Proteolipid protein	Multiple sclerosis
Yersinia enterocolitica	Thyrotropin receptor	Thyroid autoimmunity
Borrelia burgdorferi	Leukocyte function associated antigen	Lyme arthritis
Salmonella typhi and *Yersinia enterocolitica*	HLA-B27	Reactive arthritis
HHV-6, EBV, Rubeolla, influenza virus, and HPV	Myelin basic protein	Multiple sclerosis
Streptococcal M protein	Myosin and other heart valve proteins	Rheumatic fever
Trypanosoma cruzi	Cardiac myosis	Chagas heart disease

While individual cases are leveraged by diverse species, research is increasingly highlighting common patterns of molecular mimicry in various autoimmune diseases .

Table 1. Selected associations of microbial overgrowth and autoimmune disorders [3].

Microbe Species	Disorder
Klebsiella	Ankylosing Spondylitis
Citrobacter, Klebsiella, Proteus, Porphyromonas	Rheumatoid Arthritis
Yersinia	Grave's Disease & Hashimoto's Dz.
S. Pyogenes	Rheumatic Fever
Camphylobacter	Gullian Barre Syndrome
Chlamydia	Multiple Sclerosis
E. coli, Proteus	Autoimmunity in general

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3266166/ In order, tables are found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945069/ and https://www.researchgate.net/publication/261950961_Molecular_Mimicry_the_Hygiene_Hypothesis_Stealth_Infections_and_Other_Examples_of_Disconnect_Between_Medical_Research_and_the_Practice_of_Clinical_Medicine

Permeability Doesn't Stay in the Gut

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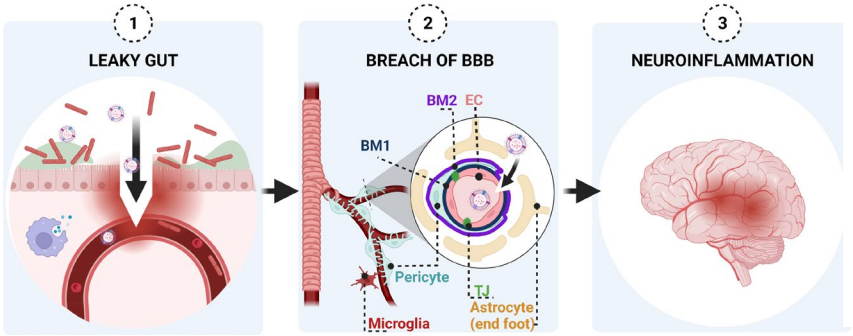
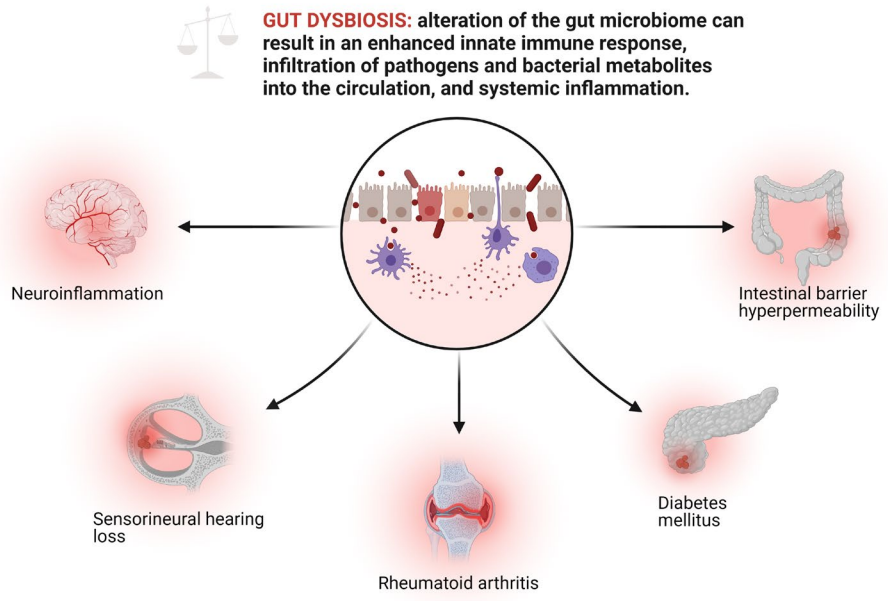
- Enhanced intestinal permeability (EIP) = Systemic Inflammation = **Systemic Epithelial Membrane Dysfunction**.
- In the blood vessels. In the lungs. In the mitochondria. In the brain.**
- Perhaps the ultimate example of "what happens in the gut doesn't stay in the gut".
- The pathogens and their metabolites infiltrate the bloodstream, leading to a spread of inflammation, which can reach remote organs and thus cause extraintestinal manifestations.





Diagrams from https://www.imrpress.com/journal/FBE/14/2/10.31083/j.fbe1402008/htm ; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8657205/
a bit more skeptical view on the concept: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313445/ ** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8391332/

Metabolic Disease May Begin in the Gut

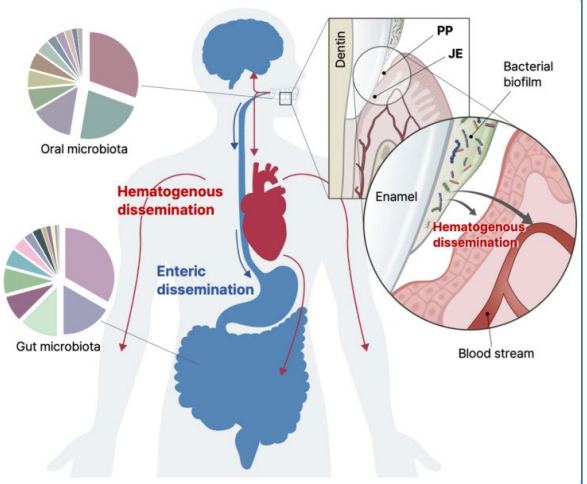
Multiple synergistic avenues whereby the gut imbalances may promote metabolic dysfunction.

- Incretins are gut hormones (e.g. GLP-1, GIP) which trigger 1st phase insulin release. **Incretin secretion is highly affected by gastric emptying** (delayed = less insulin; accelerated = more insulin). Balanced GI motility is key for optimal glucose regulation.
- **Poor 1st phase insulin response** (via gut) can lead to higher blood sugar and progression of fatty infiltration of tissue (e.g. liver, pancreas).
- Insulin release is counter-regulated by **DPP-IV enzymes (in the intestinal brush border!)** which degrade GLP-1. Healthy mucosa and villi are key for metabolic health.*
- Bile acids are signaling molecules (like hormones) that trigger insulin release via FXR receptors. **Bile acid metabolism** is altered in T2D. A healthy microbiome converts primary bile acids into secondary bile acids which appear to affect pancreas and liver metabolism positively. Gallbladders matter! Bile also (along with alkaline phosphatase) helps degrade LPS in the gut.***
- **T2D patients have higher levels of circulating endotoxin from our microbiota.** Pro-inflammatory LPS increases certain cytokines (e.g. IL-6, IL-1) which negatively affect insulin signaling. Appropriate intestinal permeability is important. Chronic higher LPS load can promote amyloid plaque build-up (e.g. pancreas, brain, arteries).**
- **Optimizing SCFA balance** (esp. butyrate) improves metabolic dysfunction and pro/anti-inflammatory balance (by increasing T-regulatory cells). Dietary fiber and polyphenols (prebiotics) helps optimize bacterial production of SCFAs. Modulating the microbiome is a (the?) key mode of action of both metformin and berberine in improving.*

* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6615897/ , https://www.sciencedirect.com/science/article/pii/S1550413113001502
** https://www.nature.com/articles/srep14405 , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5742320/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6470572/
*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5290900/ and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6581552/

The Gut Starts in the Mouth

- **~700 unique microbial species reside in the oral cavity**, with different species (predominantly Firmicutes) occupying different areas (e.g. tongue, plaque, saliva, tonsils, throat, various mucosal surfaces) and creating microenvironments.* What you do to the oral microbiome affects the rest of the body overall!
- In a healthy oral microbiota, commensal bacteria will maintain balance through competition for space/nutrients, diverse bacteriocins, and pH-modulating secretions.
- Oral mucosal barrier function provided by saliva and mucus, containing commensals, lysozyme, antibacterial peptides, and lactoferrin. **Leaky gums can promote systemic inflammation**.**
- **The mouth is the gateway for systemic fecal-oral microbial transmission** (incl. bacteria, virus, parasites) via contaminated foods, pets, fluids, dirty hands, and poor barrier function* as well as local pockets of inflammation (e.g. biofilms harboring LPS producers).***
- **Oral dysbiosis is linked to health throughout the entire body**, e.g. dental caries, periodontitis, intestinal dysbiosis (e.g. SIBO), autoimmunity (e.g. RA), diabetes, atherosclerosis, Alzheimer's progression, colorectal/squamous cell cancers, increased LPS and systemic inflammation (NF-$\kappa\beta$, IL-6), miscarriage, EIP.
- **The oral microbiome has nitric oxide producers** that support healthy blood pressure; antibacterial mouthwash use ≥2x/day may contributes to hypertension and diabetes via reduction of nitrate-reducing bacteria and bioavailability of systemic nitric oxide.****



* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8125773/
** Image from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8997512/ , https://www.jendodon.com/article/S0099-2399(19)30583-7/fulltext
*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8457218 **** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7125030/ , https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3605573/ and https://www.sciencedirect.com/science/article/abs/pii/S1089860317301532 (abstract)

Oral Microbiota Translocation

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- Bacteria found in remote organs have been **traced back to origination in the oral microbiota.**
- **Oral bacteria translocate** via swallowing (and downstream barrier dysfunction), dental cleanings including daily toothbrushing* (bacteria released into bloodstream), and leaky gums.** These dynamics promote **microcolonies of dysbiosis throughout the gastrointestinal tract.**
- **Stomach and small intestinal secretions *should* serve as physical & chemical barriers from the oral cavity.**
  - **Impaired gastric acid and bile release** allow susceptible bacteria to translocate via the GI tract (consider hypothyroid, stress, PPIs, infants/the elderly with reduced digestive capacity).
  - Bacterial translocation occurs in healthy people too; **how does their innate immune system respond**?*
- Examples of places where oral bacteria may translocate and health issues this may contribute to:
  - **Gut**: IBD and colon cancer***
  - **Joints**: Rheumatoid arthritis***
  - **Uterus**: Preeclampsia, preterm delivery+
  - **Biliary & Portal veins**, **Liver**: NAFLD, cirrhosis associated (*Porphyromonas gingivalis*)***
  - **Pancreas**: Pancreatic ductal adenocarcinoma risk and mortality (*P. gingivalis*)***
  - **Brain**: Neurodegeneration and neuroinflammation: e.g. Alzheimer's (*P. gingivalis*)++
  - **Appendix**: Appendicitis (*Fusobacterium* in children)+++
  - **Lungs**: Asthma (lower *Streptococcus*, higher *Veillonella* spp.) ++++

* https://www.ahajournals.org/doi/10.1161/circulationaha.107.758524 ** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8997512/
*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8125773/ + https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8457218
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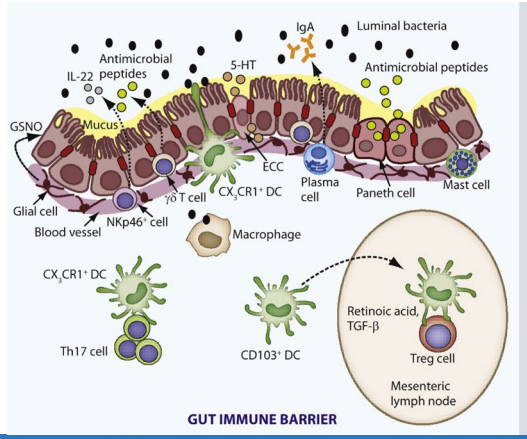
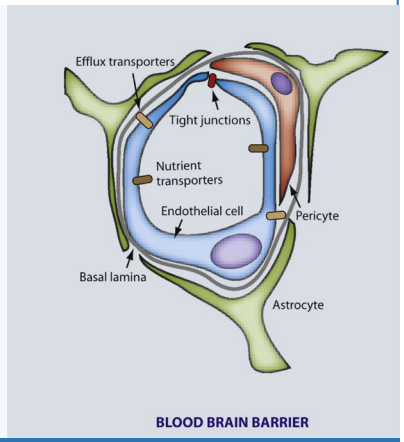
++++ https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9198628/

The Brain-Gut-Microbiota Axis and Leaky BBBs

"The emerging links between our gut microbiome and the central nervous system (CNS) are **a paradigm shift in neuroscience…**
Mounting preclinical evidence broadly suggests that the **gut microbiota can modulate brain development, function and behavior** by immune, endocrine and neural pathways of the brain-gut-microbiota axis…..including deficits in intestinal permeability regulation."

- Increased permeability of the blood-brain barrier (BBB) increases **brain exposure to damaging substances** e.g. inflammatory mediators, toxicity, and free radicals.
- **Low-grade systemic inflammation** substantially affects the BBB, as do many of the same factors that promote EIP in the gut e.g., high zonulin, histamine overload, Vitamin D deficiency, chronic stress.
- In this way, lipopolysaccharides (LPS) and other endotoxins/wastes from gut microbes can directly **promote neurological challenges, neurotoxicity, and mood imbalances**.
- NMDA receptor upregulation (**excitotoxicity**) increases glutamate activation and downstream hypervigilance, anxiety, wakefulness. This dynamic then **worsens BBB permeability**.
- "**Inappropriate antigen trafficking** through an impaired intestinal barrier, followed by passage of these antigens or immune-activated complexes through a permissive blood–brain barrier (BBB), can be part of the chain of events" leading to neurological and mood disorders.





(quotation in call out box) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4359909/ https://journals.sagepub.com/doi/full/10.1177/0004867418796955 , https://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-019-1403-x , https://www.jneurosci.org/content/36/49/12296 , https://molecularautism.biomedcentral.com/articles/10.1186/s13229-016-0110-z , https://www.tandfonline.com/doi/full/10.1080/19490976.2019.1638722 , https://www.ncbi.nlm.nih.gov/pubmed/30449598 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313445/v and https://www.cell.com/fulltext/S1074-7613(09)00424-5 (also diagram)

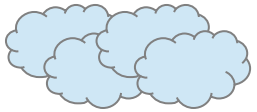
Disease Often Begins in the Gut… and Progresses!

24

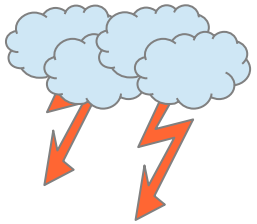
- Deficiency-Driven Dysfunction (digestion, absorption)
  - e.g. anemia, neuropathy, depression, headache

- Gastrointestinal Dis-ease (motility, microbes, hormones)
  - e.g. IBS, constipation, belching, bloating

- GI-origin Inflammation (enhanced gut permeability)
  - e.g. osteoarthritis, asthma, migraine, chronic fatigue, fibromyalgia, eczema, allergy/atopy, anxiety



- Autoimmune Dis-ease (immune dysregulation)
  - Hashimoto's thyroiditis, lupus, multiple sclerosis, Crohn's disease, rheumatoid arthritis



A Perspective Shift on Gut Priorities?

What FM Today Gets Right

- Eat real food.
- Don't eat chemicals.
- Digestion is not a given.
- Arrest overgrowths.
- Leaky gut is real (but not universal).
- NSAIDs erode mucosa.
- Optimize bowel movements.
- The gut is Immune Central.

Just a Few Examples of Where we Need to Focus More!

- **Mouth** (e.g. microbes, mercury (Hg), root canals, secretory IgA, mouth-breathing)
- **Eating Hygiene**, especially Chewing
- **Motility** (e.g. microbial regulation, GB motility, Migrating Motor Complex (MMC), peristalsis, subclinical hypothyroid, stress, gastric emptying effect on Insulin regulation and vice-versa)
- **pH** (e.g. HCl, bicarbonate, bile, enzyme activation, acid-producing microbes)
- **Barrier Integrity** (e.g. LPS, IL-6, COVID, histamine, sIgA, alcohol, SCFAs, BBB impact, H_2S)
- **Epithelial Function** (e.g. brush border enzymes, metformin, MALT, NF-kB, detoxification)
- **Microbial Diversity** (e.g. maximize it, avoid antimicrobials where possible, seeing opportunistic commensal species overgrowth as a "wake up call", avoid a "kill everything questionable" approach)
- **Parasympathetic activation** (e.g. vagal function/tone, breathing, immune brake, sleep)
- **Immunoregulatory balance** (e.g. gut-microbe-brain axis, NF-kB, chronic stress, COVID, O3s, glucocorticoid resistance, hypoadrenal states)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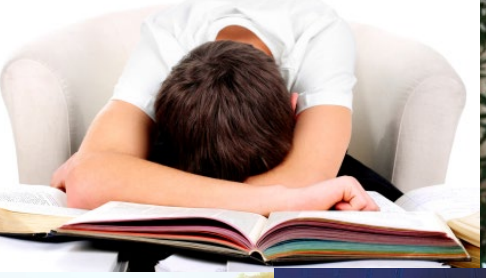
KILLS WEEDS & ROOTS


Mold!

Crest
Crest


Jolly Time
Blast O Butter
ULTIMATE THEATRE STYLE BUTTER











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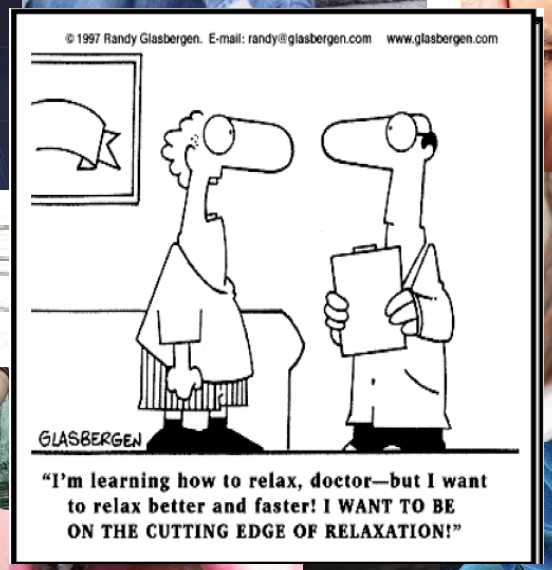
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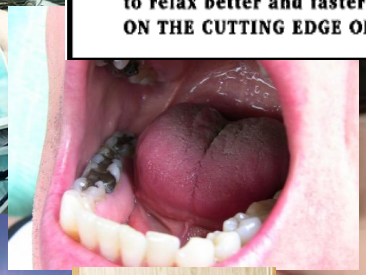
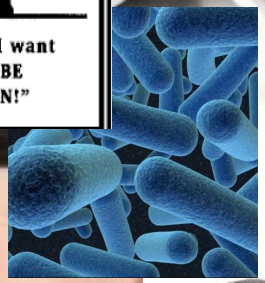
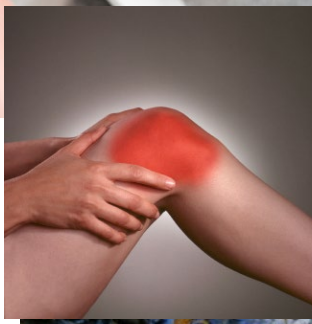
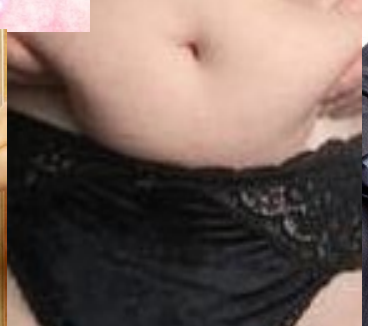
"I'm learning how to relax, doctor—but I want to relax better and faster! I WANT TO BE ON THE CUTTING EDGE OF RELAXATION!"

BUMBLE BEE
Chunk Light Tuna

THE ORIGINAL
Swedish Fish
ASSORTED



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- By honoring and alleviating functional imbalances proactively, we minimize suffering of disease and make health care more affordable and sustainable. More importantly,

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Disease Begins in the Gut - But Often Doesn't Stay There

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