FUNCTIONAL MEDICINE
Continuing Education

The Effects of Common Prescription Medications on the GI System – Counseling Patients on Drug-Induced Microbiome Disruption (DIMD)

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Founder Metabolic Code Enterprises, LLC
Education CoChair A4M/MMI

Drug Induced Microbioime Disruption (DIMD)

- Prescription and non-prescription drugs can alter the microbiome

- Potentially disrupting metabolic pathways

- Affects all facets of metabolism
  - Nutrient absorption
  - GUT-IMMUNE-BRAIN axis
  - Blood glucose balance/insulin resistance
  - Hormonal balance – sex / thyroid / appetite
  - Sleep
  - Detoxification

What Drugs Commonly Affect the Microbiome

- Antibiotics
- NSAIDs
- Corticosteroids
- OCs/HRT
- PPIs / H2 blockers
- Metformin
- Statins
- Antisychotics
- Opioids

Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther. 2018;47(3):332-45.

Why Drugs and Microbiome Effects Are Important

- Almost 60% of the population takes at least 1 prescription daily
  - In 2014 it was 46.9%
  - In 1994 it was 39.1%

- These prescriptions can lead to DIND and DIMD

- Studies reporting over ¼ drugs affect microbiome populations

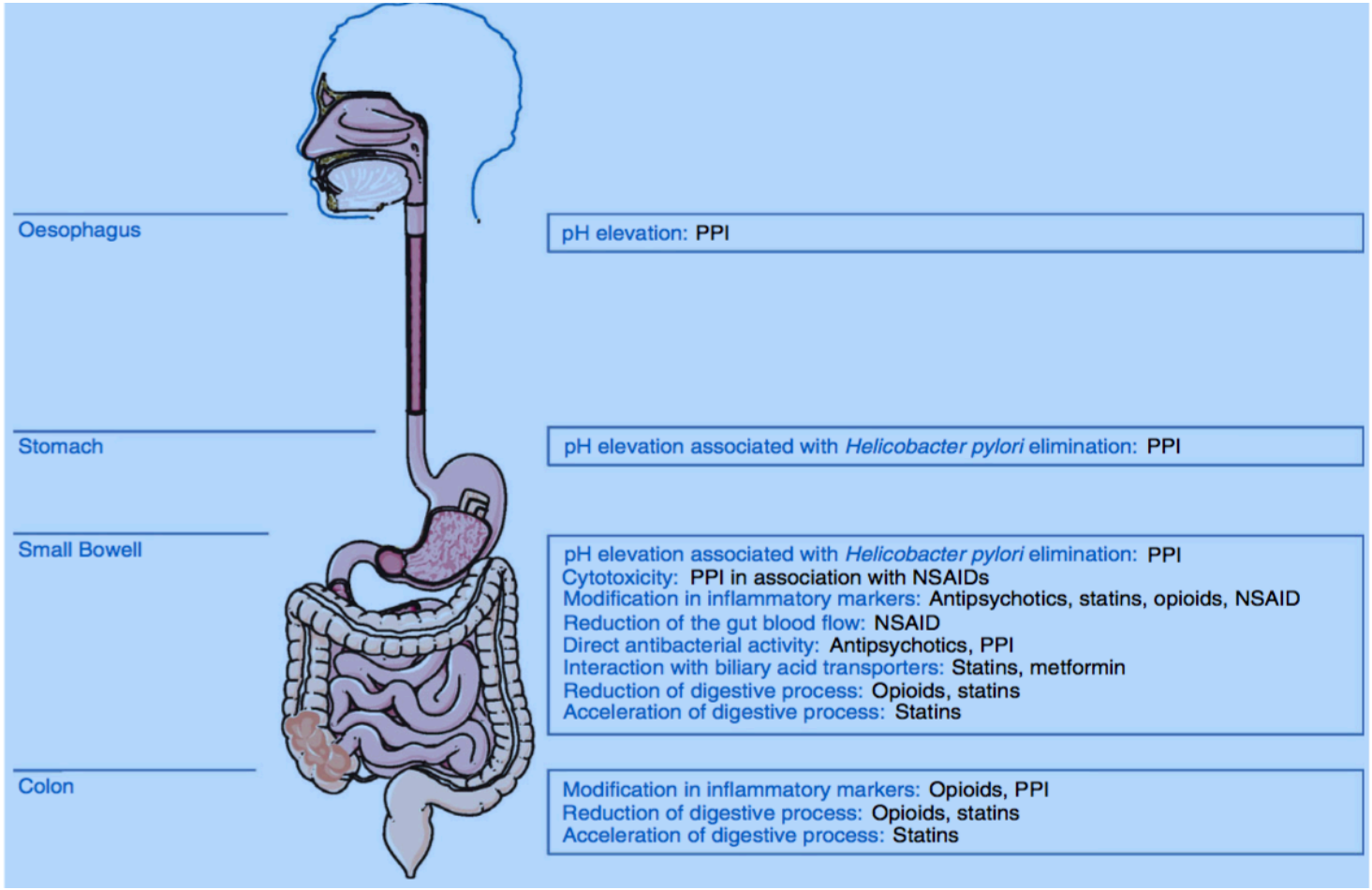
Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther. 2018;47(3):332-45.

Why Drugs and Microbiome Effects Are Important

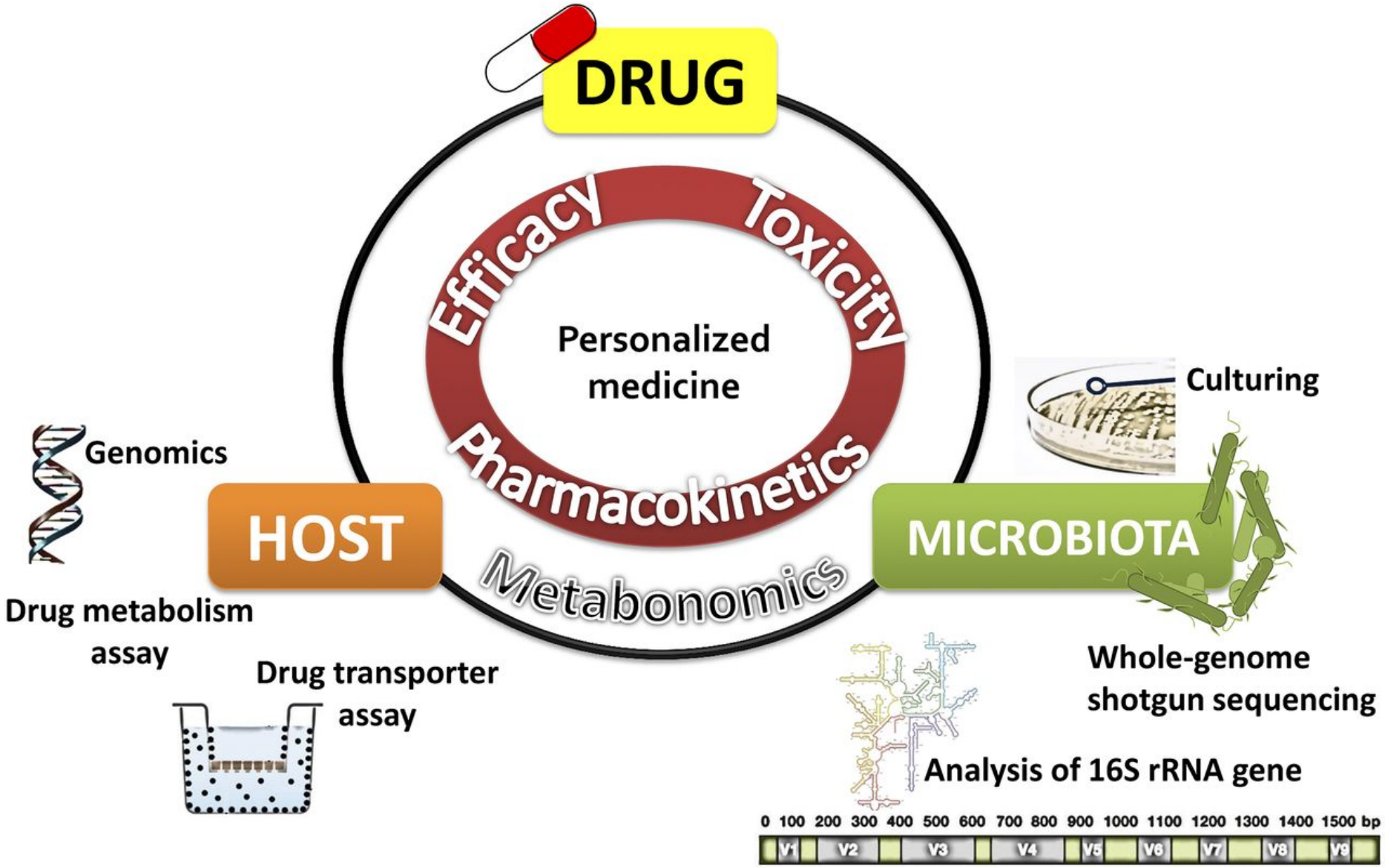
- Study tested 1,100 drugs on 40 representative GUT bacterial strains
- 25% of drugs affected bacterial growth *in vitro*
- Possible new source of antibiotic resistance

Maier L, et al. Extensive impact of non-antibiotic drugs on human gut bacteria. Nature. 2018;555:623-28.

Some Proposed Mechanisms of DIMD



Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther. 2018;47(3):332-45.



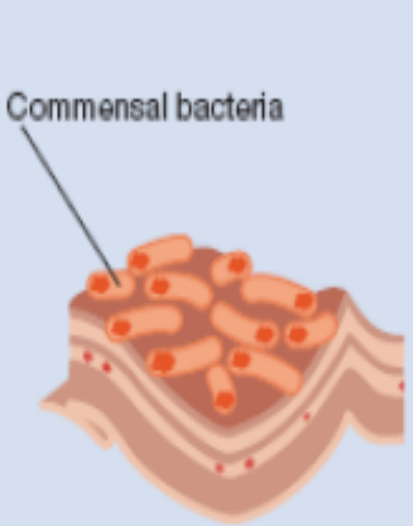
Yip LY, et al. Investigation of host-gut microbiota modulation of therapeutic outcome.

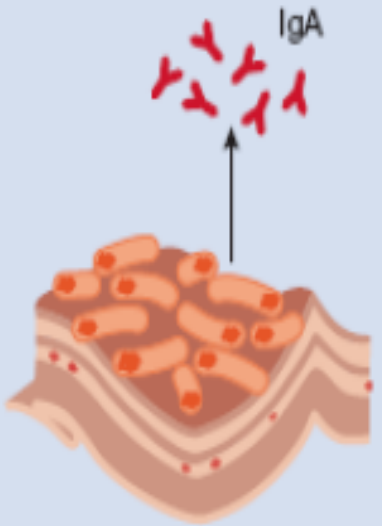
Background - GUT and Microfloral Balance

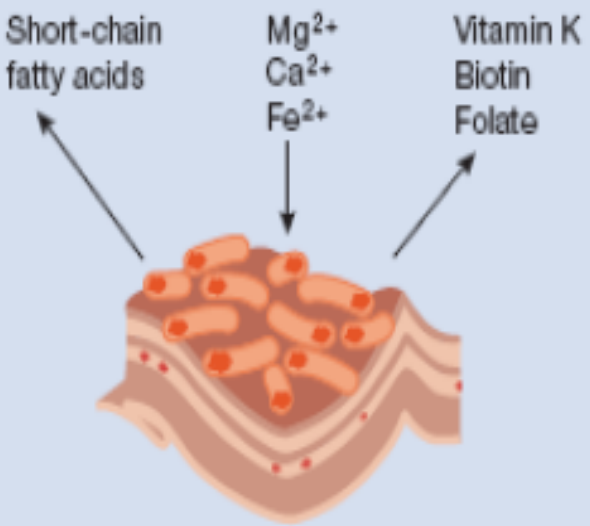
- Important in:
  - GI health
  - Nutrient absorption
  - Immunity
  - Sleep
  - Neurochemical balance
  - Cognition
  - Brain inflammation
  - Overall systemic inflammation
  - Joint/muscle aches/pains
  - Food craving issues – serotonin

Role of commensal bacteria

Protective functions	Structural functions	Metabolic functions	
Pathogen displacement	Barrier fortification	Control IEC differentiation and proliferation	Ferment non-digestible dietary residue and endogenous epithelial-derived mucus
Nutrient competition	Induction of IgA	Metabolize dietary carcinogens	Ion absorption
Receptor competition	Apical tightening of tight junctions	Synthesize vitamins e.g., biotin, folate	Salvage of energy
Production of anti-microbial factors e.g., bacteriocins, lactic acids	Immune system development		







Gut Microbiome: Think of the Flora as…

A Metabolic Organ

- Influences nutrient utilization
- Intestinal permeability
- Immune Modulation
- Hormone metabolism

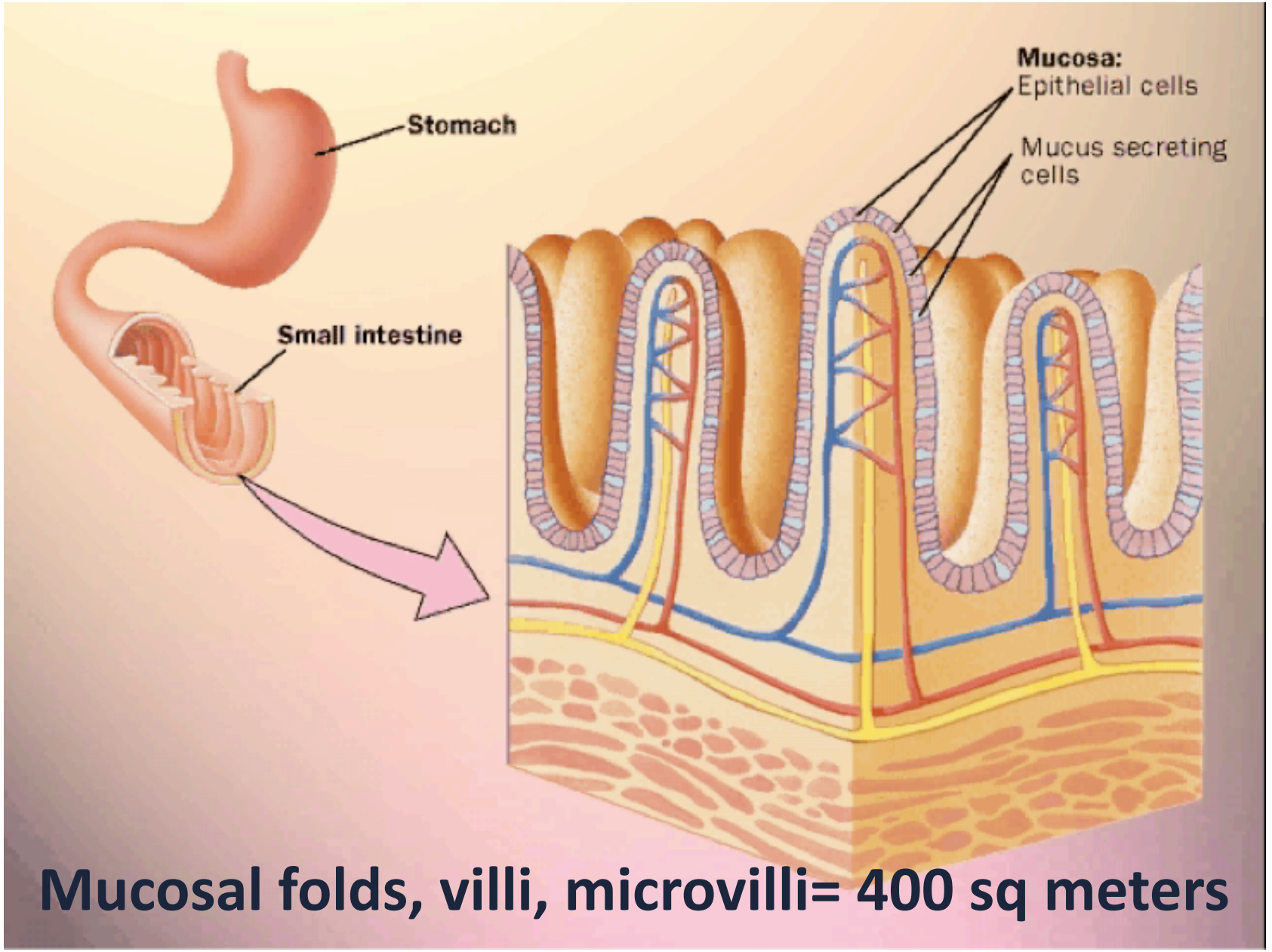
Factors Influencing Microflora

- Antibiotics
- OC's/HRT
- Radiation/chemo
- Corticosteroids
- Statins
- Metformin
- NSAID's
- PPI's
- Antisychotics
- Opioids
- Sugar intake
- Bactericidal chemicals in drinking water
- Pesticides
- Alcohol
- Heavy metals
- H. pylori
- Gastrointestinal pH
- Stress
- Bowel transit time
- Allergies
- Intense Exercise

Microflora Disruption Leads To…

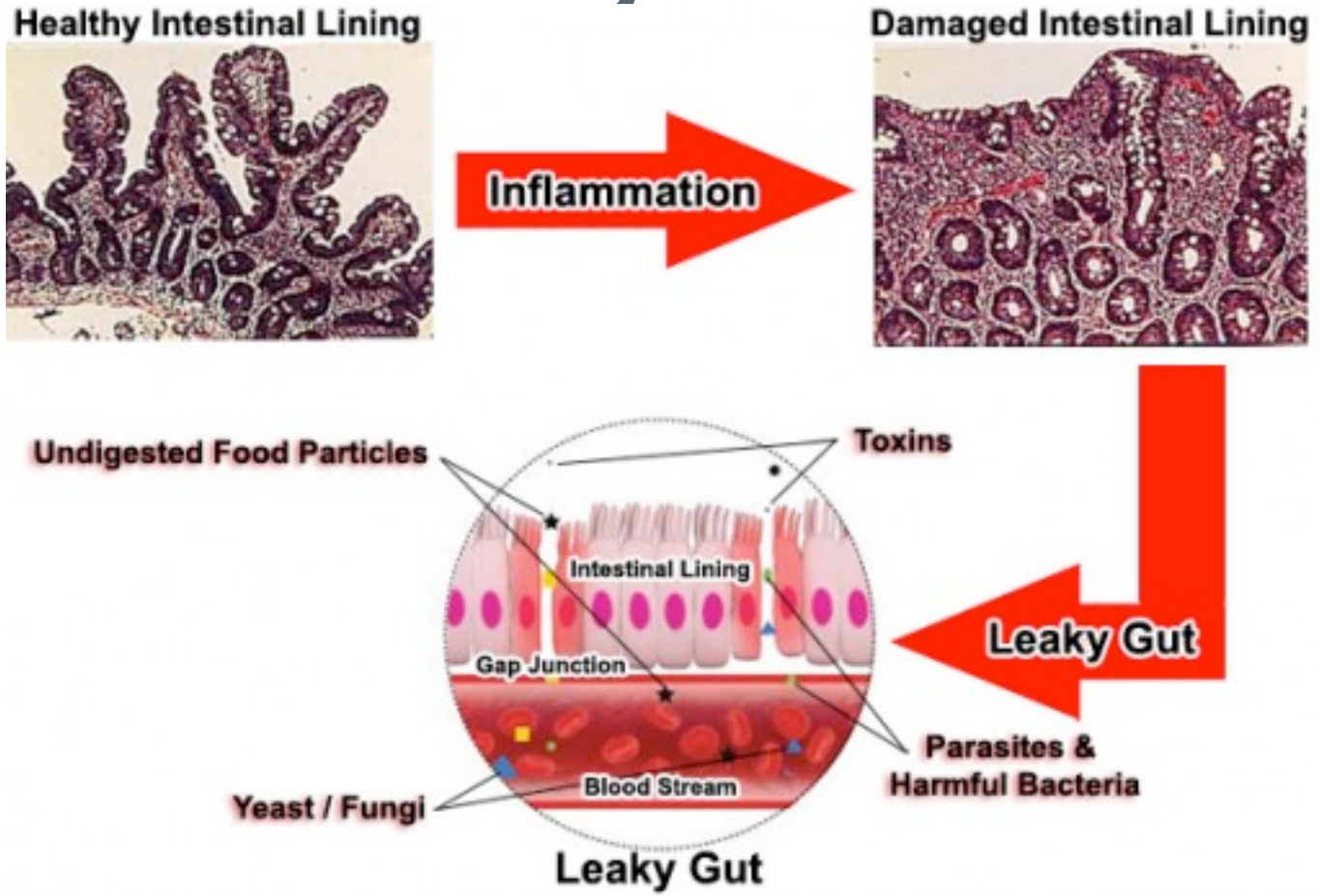
- Leaky Gut and Intestinal Permeability
- Low grade endotoxemia
- Non Alcoholic Fatty Liver
- Enteric nervous system imbalance
- Hormonal imbalances
- Systemic inflammation signaling
- Weight management issues
- Cancers

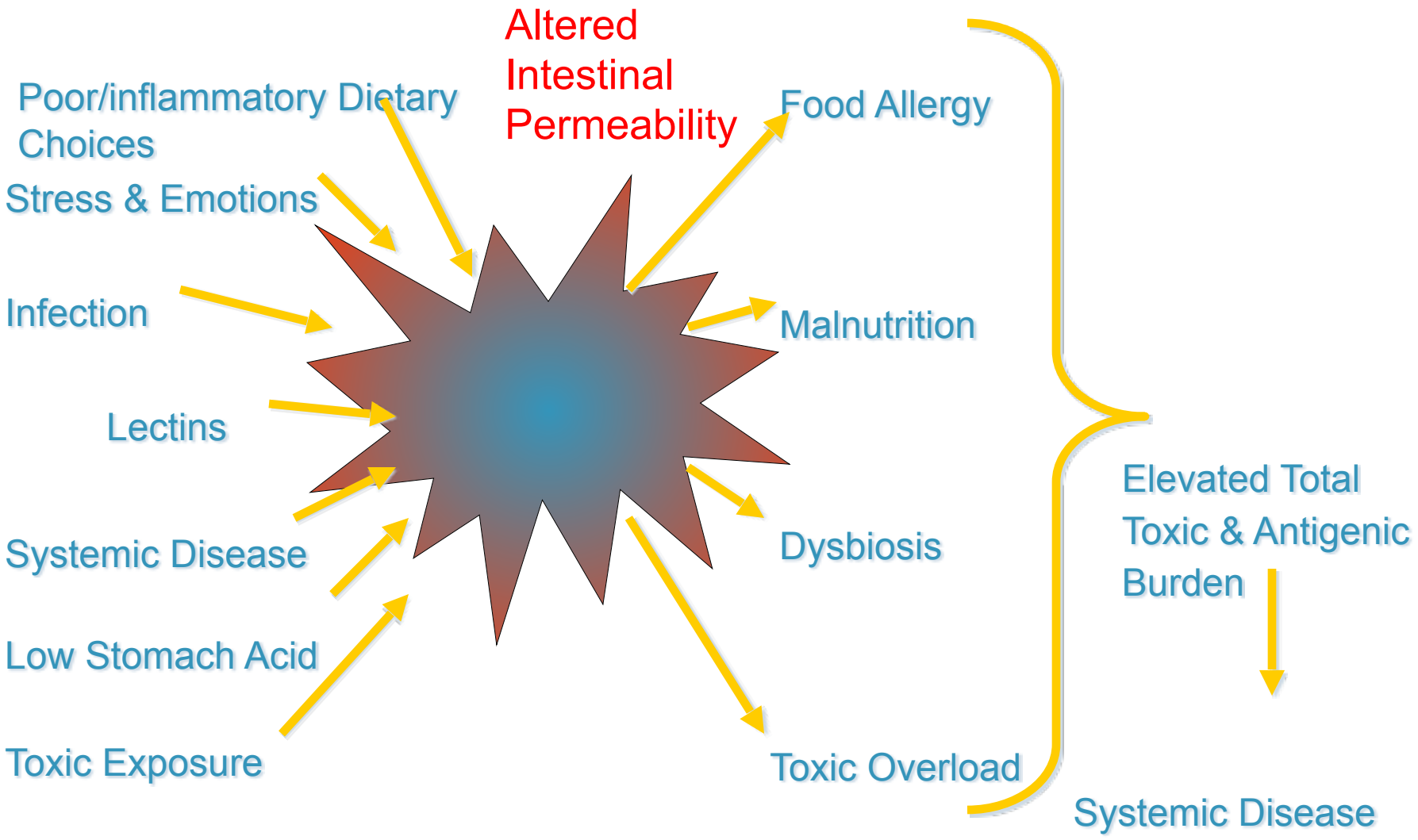
Frazieret al., Gut Microbiota, intestinal permeability , obesity-induced inflammation , and Liver Injury J Parenter Enteral Nutr **September 2011** vol. 35 no. 5 suppl **14S-20S**



Mucosal folds, villi, microvilli= 400 sq meters

Intestinal Permeability




Altered Intestinal Permeability
Poor/inflammatory Dietary Choices
Stress & Emotions
Infection
Lectins
Systemic Disease
Low Stomach Acid
Toxic Exposure
Food Allergy
Malnutrition
Dysbiosis
Toxic Overload
Elevated Total Toxic & Antigenic Burden
Systemic Disease

Gut as a Source of Inflammation

- Over-activation of immunity in gut leads to increased production of inflammatory cytokines

Result of an Inflammed GUT

- Increased food allergies/intolerances
- Digestive problems like IBDs, IBS, Crohn's, colitis
- Increased sleep and mood disturbances
- Fatigue
- Increased time to recovery
- Increased joint and connective tissue issues
- Decreased performance and exercise ability
- Memory and cognitive decline
- Sex hormone issues – testosterone, estrogen
- Thyroid imbalance
- Nutrient deficiencies – vitamin D, B vits
- Food cravings
- Immune problems
- Cardiovascular problems
- Chronic Inflammation
- Weight gain

Examples of DIMD Drugs

PPIs and Microbiome

- PPIs among top selling prescription and non-prescription drugs
- Not only affects H. pylori, also commensal bacteria in GUT
  - Directly target bacterial and fungal proton pumps
  - Disrupt normal gastric microenvironment by ↑ gastric pH
- Increases in Streptococcus sp. in PPI patients
- Also reported increase in Salmonella, campylobacter and other enteric infections

Minalayan A, et al. The gastric and intestinal microbiome: role of proton pump inhibitors. Curr Gastro Reports. 2017;19:42.
Leonard J, et al. Systematic review of the risk of enteric infection in patients taking acid suppression. Am J Gastroenterol. 2007;102(9):2047-56.

PPIs and Microbiome

- 2015 study; fecal samples in 1827 healthy volunteers collected
- Using 16S rRNA amplification studied effects of PPI on composition of gut microbiota
- PPI users had significantly lower numbers of commensal organisms and lower bacterial diversity
- PPI use also increased pharyngeal commensals in GUT
- Conclusion: PPIs consistently shift toward less “healthy” microbiome = DIMD

Jackson MA, Goodrich JK, Maxan M-E, et al. Proton pump inhibitors alter the composition of the gut microbiota. Gut. 2016;65(5):749–56.

PPIs and Microbiome

- PPI use + NSAID compounds DIMD
- Produces 2^0 dysbiosis
- Also reported to increase risk of GI bleeding using both drugs

Fujnimori S. What are the effects of proton pump inhibitors on the small intestine? World J Gastroenterol. WJG. 2015;21(22):6817-9.

Lue A, et al. Proton pump inhibitor treatment and lower gastrointestinal bleeding: balancing risks and benefits. World J Gastroenterol. 2016;22(48):10477-81.

PPIs and Microbiome

- Other studies suggest DIMD caused by PPIs can increase gastric and esophageal cancer risks

Amir I, et al. Gastric microbiota is altered in ersophagitis and Barrett's esophagitis and further modified by proton pump inhibitors. Environ Microbiol. 2014;16(9):2905-14.
Alsalahi O et al. Proton pump inhibitors: the culprit for Barrett's esophagitis. Front Oncol. 2015;

Metformin and DIMD

- 30% metformin users report GI side effects
  - Abdominal pain, diarrhea
  - Linked to DIMD

- Gut microbiome shifts to butyrate-producing taxa in Type 2 diabetes

Karlsson, F. H. et al. Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature 498, 99–103 (2013).
Carpio GRA, Fonseca VA. Update on safety issues related to anti- hyperglycemic therapy. Diabetes Spectr Publ Am Diabetes Assoc. 2014;27:92-100.

Metformin and Microbiome

- Several studies report lack of microbiome diversity in meformin users

Forslund K, Hildebrand F, Nielsen T, et al. Disentangling type 2 dia- betes and metformin treatment signatures in the human gut micro- biota. Nature. 2015;528:262-266.

e la Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, et al. Met- formin is associated with higher relative abundance of mucin- degrading Akkermansia muciniphila and several short-chain fatty acid-producing microbiota in the gut. Diabetes Care. 2017;40:54-62.

Zhernakova A, Kurilshikov A, Bonder MJ, et al. Population-based metagenomics analysis reveals markers for gut microbiome compo- sition and diversity. Science. 2016;352:565-569.

NSAIDs and DIMD

- Microbiome changes when using NSAIDs
- Bacterial composition depends on which NSAID
- Long term NSAID use leads to hyper-permeation of small intestinal mucosa
  - NSAID-induced inhibition of prostaglandin synthesis = decreased blood flow

Rogers MAM, et al. The influence of non-steroidal antiinflammatory drugs on the gut microbiome. Clin Microbiol Infect. 2016;22(2):178.

OC and HRT DIMD

- Reported to increase Crohn's and Ulcerative colitis risk
  - Estrogen reported to modify intestinal permeability
  - Exogenous hormone use enhances development of Th1 and Th2 mediated inflammatory diseases
  - Increased autoimmunity
  - Also alters androgenic hormone levels

Khalili H. Risk of inflammaotry bowel disease with oral contraceptives
And menopausal hormonal therapy: current evidence and future direction. Drug Saf. 2016;39(3):193-7.

OC and HRT DIMD

- 2008 meta analysis
- 14 studies with 75,815 patients
  - 36,797 patients exposed to OCs
  - 39,018 as control (no exposure)
- Reported use of OCs associated with increase development of IBD, particularly Crohn's disease
- Relative risk (RR) no longer significant when OCs stopped

Cornish JA, et al. The risk of oral contraceptives in the etiology of Inflammatory bowel disease: a meta-analysis. Am J Gastroenterol. 2008;103(9):2394-400.

Other Drugs DIMD

- Corticosteroids
  - Imbalance microbiome
  - Alter mucin content of GUT
  - Side effects of constipation/diarrhea, abdominal pain, weight gain, immune problems

- Statins
  - Interactions between bile acids and statins leads to DIMD
  - Statins have direct antibacterial activity in GUT
  - Side effects of constipation/diarrhea, bloating, abdominal pain

Huang EY, et al. Using corticosteroids to reshape the GUT microbiome: implications for inflammaotry bowel disases. Inflam Bowel Dis. 2015;21(5):963-72.
Masadeh M, Mhaidat N, Alzoubi K, Al-Azzam S, Alnasser Z. Antibacterial activity of statins: a comparative study of atorvastatin, simvastatin, and rosuvastatin. Ann Clin Microbiol Antimicrob. 2012;11:13.

Other Drugs DIMD

- Opioids
  - Morphine-mediated immune changes = toll-like receptor changes
  - Overexpressin of IL-17A
  - Results in dysbiosis
  - Epithelial barrier destruction
  - Opioids also reduce digestive processes
  - Side effect of constipation

Banerjee S, Sindberg G, Wang F, et al. Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compro- mise and sustained systemic inflammation. Mucosal Immunol. 2016;9:1418- 1428.
Huang EY, et al. Using corticosteroids to reshape the GUT microbiome: implications for inflammaotry bowel disases. Inflam Bowel Dis. 2015;21(5):963-72.

Other Drugs DIMD

- Antisychotics
  - Frequent side effects of weight gain – increased visceral fat
  - Directly affects growth of microorganisms in GUT
  - Alters microbiome diversity
  - Alters immune system
    - IL-8 and IL-1 beta
    - Imbalances lead to IR and obesity
    - Altered in lab study w/ olanzapine (Zyprexa)
    - Leptin/Ghrelin ratio impacted

Davey KJ, O'Mahony SM, Schellekens H, et al. Gender-dependent consequences of chronic olanzapine in the rat: effects on body weight, inflammatory, metabolic and microbiota parameters. Psy- chopharmacology. 2012;221:155-169

Antibiotics

- Beneficial bacteria manufacture B vitamins and vitamin K in the GI tract
- Beneficial bacteria produce proteases, lipases, and lactase that aid in digestion of nutrients
- Bifidobacteria produce SCFAs that provide from 5-10% of our daily energy supply

Hill, “Intestinal flora and endogenous vitamin synthesis,” Eur J Cancer Prev. 1997; 6 (suppl 1): S43-5.

Antibiotics

- Dysbiosis further disrupts digestion and absorption of nutrients
- Gut microbiome is altered after bariatric surgery
- Replacement with heat-stable probiotic, 15-20 billion CFU/gm, 1 capsule 1-2 times daily

Zhang H, et al. Human gut microbiotia in obestity and after gastric bypass. PNAS. 2009;106(7):2365-2370 .

Yeast and Antibiotics

- Antibiotics destroy the probiotic organisms
- Allows yeast to flourish in the mucous membranes
- Once established, can be difficult to eradicate (treatment resistant.)
- Candida – makes mycotoxins, damages intestinal cells and interfere with metabolism, ie thyroid hormone competitive inhibitor.
- Yeast fermentation of sugars and starches creates acetaldehyde production.

Frohloch EE, et al. Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. Brain Behav Immun. 2016;56:140-55.

Acetaldehyde Effects on Chemistry

- Reduces microtubules in the liver
- Decreases protein secretion, increases retention in liver
- Engorges of Golgi apparatus with VLDL
- Accumulation of lipids/proteins, increases hepatocyte size
- Depresses glutathione in Liver Phase II
- Stimulates hepatic smooth endoplasmic reticulum, increases rate of conversion to secondary toxic metabolites
- Increases collagen deposition in the liver shrinks
- Shrinks epithelial cells in the intestine

Side Effects of Acetaldehyde

- Acetaldehyde depletes vitamin B1, and B3 (niacin)
- Stops ability of Acetyl Coenzyme A to trigger energy production. Cell energy production falls in dose-dependent fashion with increase of Acetaldehyde
- Reacts ***with dopamine in brain to make a chemical called salsolinol***
- Reacts ***with serotonin to form beta-carboline***
- Addiction profiles (alcoholics-reward cascade issues)

Acetaldehyde, cont'd

- Excesses attach to proteins and red blood cells keep RBC from being able to bend and fold to get through capillaries so compromises 0_2 delivery

- Stops ability of Acetyl Coenzyme A energy production. Cell energy production falls in dose-dependent fashion with increase of acetaldehyde.

Effects of Acetaldehyde

- Chemical sensitivities
- Headaches
- Foggy Head
- Impaired memory
- Stops neurotransmitter production (P5P depletion)
- Mood disorders - depression, anxiety, irritability, paranoia
- Addiction
- Cell damage - brain cell death, liver cell death

Ibuprofen Use in Ultramarathon Competition

- Ibuprofen did not alter muscle damage or soreness
- Elevated endotoxemia and inflammation vs controls
- Elevated C-RP, cytokines (il-6,il 10, il8 iL 1ra, mcp-1

  Nieman,D., et al.,Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competitionBrain behavior and immunity (2006) Volume: 20, Issue: 6, Pages: 578-584
- Also associated with worsened kidney function post race
- McAnulty, et al. (2007). Ibuprofen use during extreme exercise: effects on oxidative stress and PGE2. *Medicine and Science in Sports and Exercise (39)*7.

How The Body Synthesizes Healthy Mucosa

- Vagal stimulation[4]
  - Neuropeptides
  - Beta adrenergic signaling
- Zinc-assisted gene expression[5]
  - IL-1 signals for migration of zinc[6]
  - Zinc carnosine increases mucosa proliferation by a factor of 3 or 4[7]
    - [7] – Fitzgerald, A., et al., *Gastroenterol* 128:2005

Why Learn To Rebuild The Intestinal Mucosa?

- 50% of people over age 60 suffer from gastrointestinal problems, involving the mouth, esophagus, stomach, intestines and colon. These include:
  - Gastric reflux – Food sensitivities
  - Celiac Sprue – Dysbiosis and infection
  - Irritable Bowel Syndrome – Leaky Gut Syndrome
  - Crohn's Disease – Colon Cancer

IMS Health. 2007 www.imshealth.com.

Targets for Gut Strengthening / Rebuilding

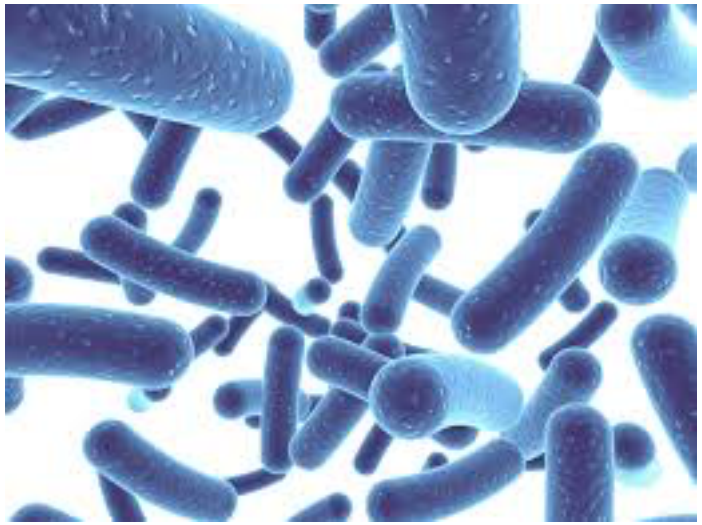
- Maintain Flora
- Proper elimination diet / Antiinflammatory diet
- Tightening of the interepithelial junctions
- Retard propagation of inflammatory and autoimmune signaling pathways via nutritional and pharmacologic means

Alternatives to PPIs and H2 blockers

- Probiotics –10-20 billion CFU/gm 1-2 times daily
- Digestive enzymes – broad pH, 1 tab w/ meals
- Zinc carnosine
  - Chelate of zinc with the dipeptide L-carnosine (beta-alanine-L-histidine)
  - Used as an anti-ulcer/mucosal healing drug in Japan for over a decade
  - In vitro activity against H. pylori
  - Reported to reduce or prevent gastric erosions and also prevents stress-induced ulcers
  - Decreases proinflammatory cytokine-induced interleukin (IL)-8 expression in gastric epithelial cells
  - 37.5mg zinc carnosine (8.5mg elemental zinc), 2 times daily

MahmoodA,FitzGeraldAJ,MarchbankT,etal.Zinc carnosine, a health food supplement that stabilizes small bowel integrity and stimulates gut repair processes. Gut 2007 Feb;56(2):168-175.
Ghoshal UC, Ghoshal U. Gut flora in health and small intestinal bacterial overgrowth syndrome. Trop Gastroenterol. 2007;28(2):43-4.

Probiotics



- Probiotic flora consists of over 400 species of bacteria
- Enhanced immunity
- Interact with mucosal cells of GUT to provide a barrier against pathogens
- Microfloral imbalances
  - Overtraining; intense physical exercise
  - Poor food choices – high sugar, pesticides, additives, preservatives, antibiotics, hormones
  - Chronic stress
  - Impure water
  - Drugs

Functions of Beneficial Flora

- Make vitamin K and biotin via nutrient metabolism
- Functions in digestion of foods, absorption and use of nutrients
- Detoxify compounds from food or created in digestion process (probiotics have been found to decrease colon cancer risk)
- Helps metabolize estrogens in the body via inhibiting beta glucuronide.

Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des. 2009;15(13):1546-58. Review.

Functions of Probiotics

- Synthesize short chain fatty acids (SCFA)
- SCFA a primary source of fuel for intestinal epithelial cells, keeps them from flattening out.
- Butyrate - helps remove lipid soluble toxins
- Butyrate protects intestinal cells from abnormal growth, and may protect against colon cancer
- SCFA's improve acidic environment in the intestines
- Acidic environment decreases pathogenic overgrowth

Cani PD, Delzenne NM. The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des. 2009;15(13):1546-58. Review.

Regulation of Inflammation in the Gut

- Probiotics play an essential role in:
  - Immune modulation
  - Population control of pathogens
  - Nutrient absorption and metabolism
  - Allergies/Intolerances
  - Hormonal Regulation
  - Brain – mood cognition

Park C, et al. Probiotics for the treatment of depressive symptoms: An Antiinflammatory mechanism? Brain Behav Immun. 2018;[Epub ahead Of print].

Probiotic Use Meta-Analysis

- Meta- analysis 1970-2011
- 79 randomized, controlled trials in 10,351 patients comparing probiotic to placebo
- 11 probiotic strains
- The Question - Are probiotics beneficial in treating gastrointestinal diseases, including
  - Infectious diarrhea
  - IBS
  - *H. pylori* infections
  - *C. Difficile*
  - Antibiotic Associated Diarrhea
  - Traveler's Diarrhea
  - Necrotizing entereocolitis
  - Pouchitis
- The results: YES for all (statistically significant positive outcomes over placebo)

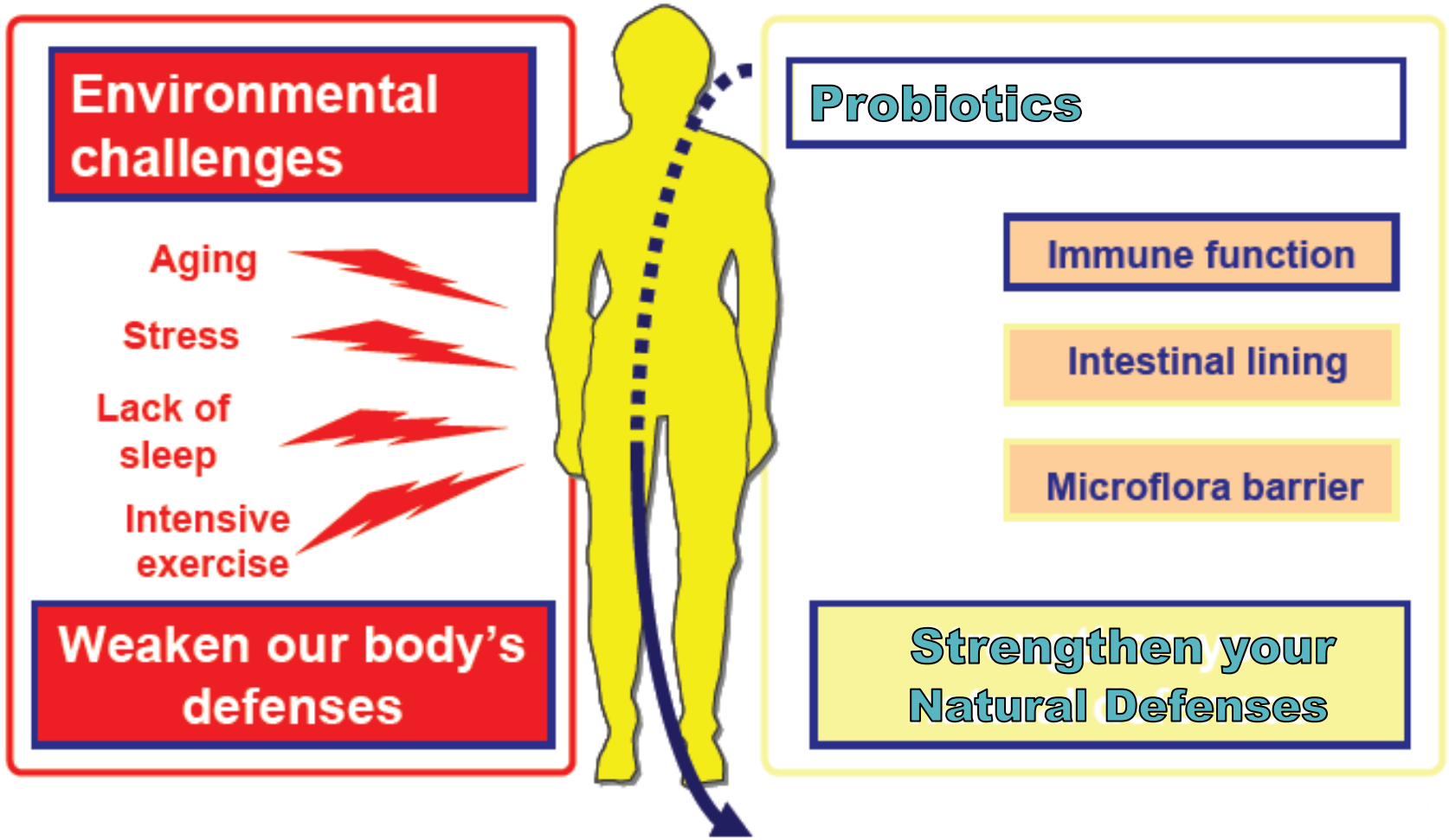
Ritchie ML, et al. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One. 2012;7(4):e34938.

Probiotic Use Cochrane Database Review

- 2018 Cochrane Collaboration Overview of 14 Cochrane Database Systematic Reviews from 2006-2015
- Focused on probiotic supplementation and GI related medical conditions
- RESULTS:
  - Probiotic use does have a beneficial effect on diarrheal conditions and related GI symptoms

Parker EA, et al. Probiotics and gastrointestinal conditions: an overview of Evidence from the Cochrane Collaboration. Nutrition. 2018;45:125-34.

Probiotics Strengthen Your Natural Defenses



Probiotics

- DOSE
  - Use 20 billion CFU 1-2x daily, containing *Lactobacillus , Bifidobacterium*
  - Heat stable product
  - *Saccharomyces (*2 billion CF*U)* species are added to some formulas for additional support

Berberine HCL

- Isolated from Coptis sp. (Chinese goldthread), Hydrastis sp. (Goldenseal) , and Berberis sp. (Oregon grape or barberry)
- Antibacterial/antifungal
- Useful in GUT microbiome imbalances

Yordanov, M., Dimitrova, P. et al. Inhibition of Candida albicans extracellular enzyme activity by selected natural substances and their application in Candida infection. Can Microbiol. 2008; 54(6):435-440.
Jin Y, et al. Pharmacological effects of berberine and its derivatives: a patent update. Expert Opin Ther Pat. 2016;26(2):229-43.

Berberine HCL

- Inhibits Candida from adhering to HT-29 epithelial cells
- Inhibits SAP (secreted aspartyl proteinase) activity by over 70%
- SAP marker of yeast conversion to aggressive form

Yordanov, M., Dimitrova, P. et al. Inhibition of Candida albicans extracellular enzyme activity by selected natural substances and their application in Candida infection. Can Microbiol. 2008; 54(6):435-440.
Jin Y, et al. Pharmacological effects of berberine and its derivatives: a patent update. Expert Opin Ther Pat. 2016;26(2):229-43.

Berberine HCL

- Also reported to help regulate glucose and lipid metabolism
- Helpful in Type 2 diabetics
- Reported to lower HbA1c, fasting and postprandial glucose
- Transient GI side effects
- Dose – 500- 900 mg daily

Yin J, et al. Efficacy of berberine in patients with type 2 diabetes. Metabolism. 2008;57(5):712-17.
Jin Y, et al. Pharmacological effects of berberine and its derivatives: a patent update. Expert Opin Ther Pat. 2016;26(2):229-43.

Caprylic acid

- Fatty acid found in coconuts
- Lab studies report caprylic acid inhibits aerobic and anaerobic growth, including Candida
- Reported to help restore microbiome balance
- Increase telomere size to 750 ng BDORT units

Omura Y, et alAcupunct Electrother Res. 2011;36(1-2):19-64.
Payne WJ, et al. Effects of sodium caprylate on Candida albicans influence of various concentrations on biochemical changes. J Bacterial. 1963;86:548-557.

Caprylic Acid

- Dosage
  - 1,000 – 2,000 mg TID w/ meals
  - Timed release or enteric coated best
  - 3-4 months
  - Monitor for GI upset
  - Can use stable sodium salt of caprylic acid - Sodium caprylate

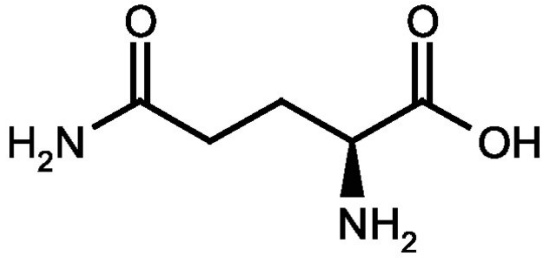
Omura Y, et alAcupunct Electrother Res. 2011;36(1-2):19-64.

Additional Botanical Support

- Oregano extract (*Oreganum vulgare*)
  - Essential oils Antibacterial; antifungal antiviral
  - Oils significantly reduce phospholipase enzyme produced by *Candida sp.*
- Rosemary leaf extract (*Rosmarinus officinale*)
  - Essential oils antibacterial antifungal antiviral
- Pau d'arco (*Tabebuia sp*)
  - Inner bark used for thousands of years by Native South American tribes
  - Antimicrobial
  - Promotes healthy microbiome

Brondani P, et al. Evaluation of anti-enzyme properties of Origanum Vulgare essential oil against oral Candida albicans. J Microl Med. 2018;28(1):94-100.
De Oliveira, et al. Biological activityes of Rosmarinum officinalis L (rosemary) extract as analyzed in microorganisms and cells. Exp Biol Med (Maywood). 2017;24(6):625-34.

L-Glutamine



- Protects GI mucosal barrier
- Skeletal muscle contains 60% of body glutamine
- FUEL
- Involved in glutathione synthesis
- Protects against endotoxemia
- Substrate for Growth hormone release

Agostini F, Biolo G. Effect of physical activity on glutamine metabolism. Curr Opin Clin Nutr Metab Care. 2010;13(1):58-64.
Elwafi F, Curis E, Zerrouk N, et al. Endotoxemia affects citrulline, arginine, and glutamine bioavalability. Eur J Clin Invest. 2012;42(3):282-9.

L-Glutamine

- Most abundant amino acid in plasma & skeletal muscle
- Now conisidered conditionally essential (trauma; surgery, burns)
- Skeletal muscle is key site for synthesis
- <1 hour intense exercise increase
- >1 hour significant decrease

Babij P, Matthews SM, Rennie MJ Changes in blood ammonia, lactate and amino acids in relation to workload during bicycle ergometer exercise in man. *Eur J Appl Physiol Occup Physiol.* 1983;50:405–11.

L-Glutamine

- Strenuous physical exercise as well as exhaustive training programs lead to glutamine depletion
- Over-trained people have a 9% deficit of glutamine in muscle -- affects liver/ immune system
- Physical inactivity also leads to depletion
  - Due to decreased synthesis and enhanced uptake by liver and immune cells
- Moderate exercise leads to improved glutamine availability due to a positive balance between muscle synthesis and peripheral clearance

Agostini F, Bolo G. Effect of physical activity on glutamine metabolism. Curr Opin Clin Nutr Metab Care. 2010;13(1):58-64.

L-Glutamine

- Ideal for metabolically-stressed states including heavy exercise
- Converts glycogen to glucose to convert fats to sugars (as long as nitrogen available)
- Strengthens immune system as fuel for lymphocytes / phagocytic growth
- L-glutamine essential for GUT health

L-glutamine and GUT

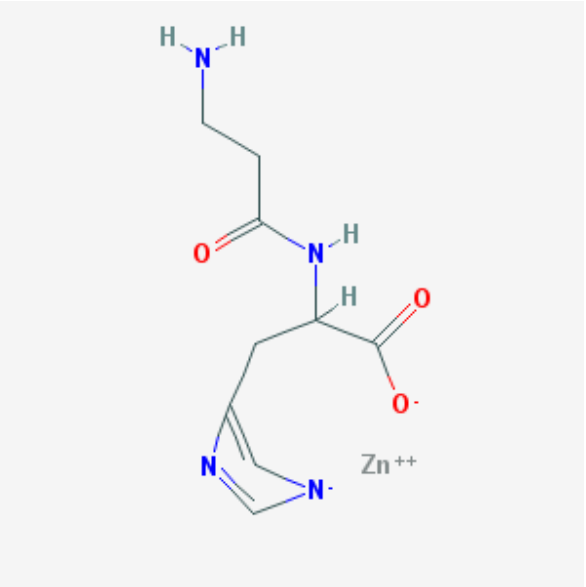
- Supports microfloral health
- Major fuel for enterocytes and colonocytes
  - Maintain integrity and function of mucosal barrier
  - Improves height of villi
  - Reduces villi permeability
  - Reduces leaky gut syndrome symptoms
  - Defends against food allergies and intolerances
  - Protects against injury and inflammation including drug induced (NSAID damage)
  - Helps in chemotherapy induced GUT damage
  - Supports IBD - Crohn's and UC
  - Helps in ulcers – decreases mucosal apoptosis
- Helps maintain secretory IgA
  - Prevents attachment of bacteria (i.e. H pylori) to mucosal cells
  - Inhibits gram-negative translocation of bacteria from colon

Kim M, et al. the roles of glutamine in the intestine and its implication in Intestinal disaeses. Int J Mol Sci. 2017;18(5):1051.

L Glutamine

- Prolonged decreased plasma glutamine can lead to increased risk of infection due to impaired immune function.
- L Glutamine is a substrate for lymphocytes, macrophages and monocytes
- Precursor to cell replication (DNA/RNA)
  - Sports Med 1996 Feb:21(2):80-97
- 500-2,000 mg, 3 times daily

Zinc Carnosine



- Zinc ions bound to L-carnosine

  in a 1:1 ratio
- Advanced gastric cytoprotection
- Helps improve integrity of GI mucosa
- Protects against sensitizing proteins, i.e. gluten or casein
- Helps establish lower pH environment in hospitable to H. pylori
- L-carnosine helps transport zinc to heal tissue

Mahmood A, et al. Zinc carnosine, a health food supplement that stabilizes small bowel integrity and stimulates gut repair processes. Gut. 2007;56(2):168-175.

Zinc Carnosine

- Improves cell migration to wound
- Increases cell proliferation and tissue repair
- Reported to protect against indomethacin-induced gut pearmeability changes in humans
- 1 cap BID
- Contains/cap:
  - Zinc (as zinc carnosine) 17 mg
  - Zinc-carnosine (chelated) 75 mg

Mahmood A, et al. Zinc carnosine, a health food supplement that stabilizes small bowel integrity and stimulates gut repair processes. Gut. 2007;56(2):168-175.

DGL Licorice

- From *Glycyrrhiza glabra* - used for Centuries in Chinese medicine for adrenal and GI problems
- DGL = deglycyrrhizinated
  - Glycyrrhizin removed
  - Can lead to pseudohyperaldosteronism
- DGL soothing on GI mucosa
- Provides mucosal support
- *H. pylori* activity

Rahnama M, et al. The healing effect of licorice (Glycyrrhiza glabra) on Helicobacter pylori infected peptic ulcer. J Res Med Sci. 2013;18(6):532-33.

DGL Licorice

- 800 mg DGL daily
- Chewable available

- Addition of other botanicals for support
  - Marshmallow (*Althaea officinalis*) – mucopolysaccharides
  - Slippery elm (*Ulmus fulva*) – reduces GI inflammation
  - Aloe vera leaf gel – mucopolysaccharides ; emodin free so no laxative effect

Rahnama M, et al. The healing effect of licorice (Glycyrrhiza glabra) on Helicobacter pylori infected peptic ulcer. J Res Med Sci. 2013;18(6):532-33.