

# The Gut-Brain Axis



# Chronic Disease Burden Kills

- 70% of 65-yr olds have at least two chronic diseases
- Most chronic diseases have common metabolic origins
- Many metabolic diseases may have their start with gut inflammation
- The more chronic diseases you have the faster you die

*Fontana et al Nature 511:405 (2014)*



# Events That Turn On Inflammatory Responses

- Microbial invasion
- Injuries
- Diet
- Aging



# Microbiota Facts

- 10 times more bacteria than human cells in our body
- 100 times more bacterial DNA than human DNA in our body
- We are really composite organisms
  - 90% bacteria, 10% human cells




# Our Bacterial “Organ”

- More complex than we thought
- Diet can determine overall microbe composition
- Composition can change within five days with dietary changes
- Can be source of chronic inflammation via TLR activation



# Our Inner Skin That Allows Us To Live Longer

- Interface at a gigantic immunological load
    - Barbarians at the gate
    - Most dense ecological system in the world
  - Mucus
    - First line of defense
  - Epithelial cells
    - Primary barrier with tight junctions
  - Immune cells
    - 70% of body's immune cells are in the gut
    - Final line of defense against microbial invasion
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# Factors That Cause Leaky Gut

- Diet
  - High-fat diet
  - Alcohol
- Drugs
  - Antibiotics
  - Anti-inflammatory
  - Chemotherapeutic
- Stress
  - Activation of CRH



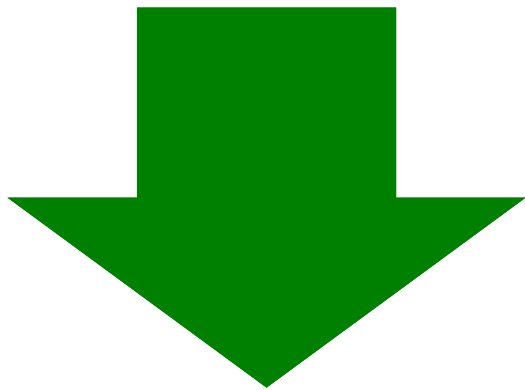
# Factors That Improve Gut Barrier Integrity

- Diet
  - Prebiotics
    - SCFA
  - Omega-3 fatty acids
  - Polyphenols
- Drugs
  - Anti-TNF antibodies





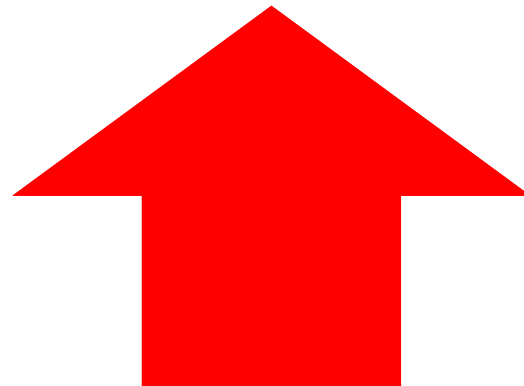
# Dietary Controls On Gut Permeability



High-fat diets,  
Alcohol, Drugs,  
Antibiotics, and  
Stress



Omega-3 Fatty  
Acids,  
Polyphenols,  
and Prebiotics



# Paradoxical Role Of Saturated Fat On Gut Health

- SCFA increase gut integrity
- SCFA promote anti-inflammatory effects
  - Activation of Tregs
- LCFA aid transport of LPS into the blood
- Palmitate-induced inflammation
  - Activation inflammatory cells
  - Inhibition of Tregs



# Many Mind-Body Disorders May Start In The Gut

- Anxiety
- Depression
- Chronic fatigue
- Autism Spectrum Disorders
- Food allergies
- Joint pain
- Auto-immune disorders



# Co-morbidities With GI Dysfunction

- Gastric
  - IBS, Ulcerative colitis, Crohn's disease
- Metabolic
  - Obesity, Metabolic Syndrome, Diabetes
- Neurological
  - Anxiety, Depression, Autism Spectrum Disorder, Alzheimer's
- Immunological
  - Chronic fatigue, fibromyalgia



# Potential Progression of Mind-Body Disorders

Leaky Gut (Endotoxemia)



Binding to TLR-4



Activation of NF-kB



Release of Cytokines



Sickness Response  
(Depression, Lack of Appetite, Fatigue)



# Metabolic Endotoxemia

- Obesity and diabetes are pandemic
- LPS levels increase to activate TLR-4
  - High-fat diet increases LPS blood levels
  - Saturated fats also mimic LPS
- TNF levels increase due to NF- $\kappa$ B
- Insulin resistance develops
  - Hypothalamus, adipose tissue, liver, and muscles



# Microbiota and Obesity In Animal Models

- High-glycemic and high-fat diets can rapidly change gut bacteria composition
- Little relationship of calorie intake and increase in body fat
- 400% difference fat accumulation between 100 different inbred strains
- Most reach upper set point quickly

*Parks et al Cell Metabolism 17:141 (2013)*

# Making Livestock Fat

- Give low levels of antibiotics in their feed
- Change bacterial composition in the gut
- Practiced for more than 50 years in the U.S.
- More than 80% of all antibiotics in U.S. are used in feedlots





# It Is Also True In Humans

- Obese have different gut bacterial composition than lean
  - *Turnbaugh et al. Nature 457:480 (2009)*
- Bacteria from an obese human can be cultured and make germ-free mice obese
  - *Fei and Zhao. ISME Journal doi:10.1038 (2012)*



# Changing Your Microbiota



# 3 Ps of Gut Health

- Probiotics
  - Flowers
- Prebiotics
  - Fertilizer
- Polyphenols
  - Landscaper



# Probiotics

- Target practice for the gut immune system
- Most come from stains in fermented foods
- Do not establish themselves in the gut
- Have limited viability



# Prebiotics

- Fermentable fiber
- Provide energy for the microbes
- Promote probiotic bacteria growth
- Anaerobic fermentation of fiber into short chain fatty acids (SCFA)
  - Nutrition for microbes
  - Prevent degradation of mucus layer
  - Improve gut permeability
  - Reduce inflammation



# What Is Fermentable Fiber?

## Cellulose

- Non-fermentable fiber

## Oligo-galacto polymers (Galactans)

- Breast milk, infant formulas

## Oligio-fructose polymers (Fructans)

- Chicory, onions, asparagus, garlic

## Oligo-glucose polymers (Starches)

- Most starches (bread, pasta, rice, etc.) are quickly degraded in the upper GI
- Resistant starch is not

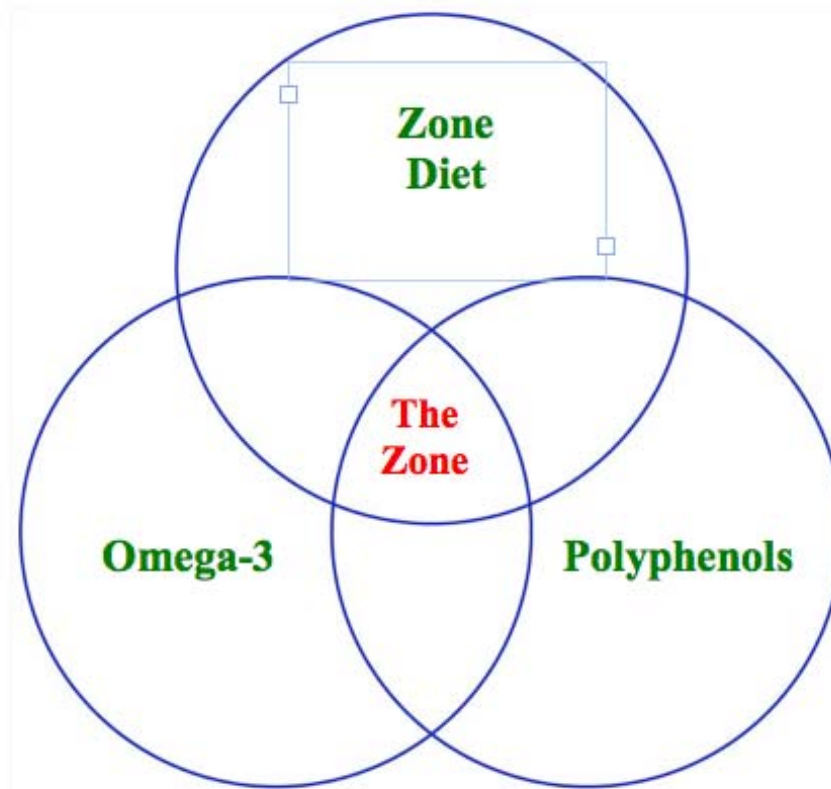


# Polyphenols

- How plants protect themselves
- Promote good microbe growth
- Inhibit pathogens



# Optimal Gut Health Requires Being In The Zone





# Role of Anti-Inflammatory Nutrition In Gut Health

- Zone Diet
  - Low-fat and calorie-restricted diet
  - Rich in fermentable fiber
  - Low in saturated and omega-6 fatty acids
- Omega-3 fatty acids
  - Improve gut barrier
  - Reduce inflammation
- Polyphenols
  - Landscapers of the microbiota




# Dietary Requirements For A Healthy Gut

- Eat small meals
- Have some protein at every meal
- Eat low glycemic load carbohydrates (primarily vegetables with limited fruits)
- Restrict omega-6 and saturated fat intake
- Take adequate levels of supplemental fish oil and polyphenols



# How Does It Work?

- Eat small meals
    - Reduce oxidative and ER stress by reducing calorie intake
  - Have some protein at every meal
    - Increase satiety and stabilize blood glucose so you eat less calories without hunger or fatigue
  - Eat low glycemic load carbohydrates (primarily vegetables with limited fruits)
    - Rich in polyphenols and fermentable fiber to decrease gut inflammation
  - Restrict omega-6 and saturated fat intake
    - Decrease gut inflammation
  - Take adequate levels of supplemental fish oil and polyphenols
    - Decrease gut inflammation
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# What Is New Is Often Old

“Bad digestion is root of all evil”

*-Hippocrates*

