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
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)

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Binding to TLR-4

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Activation of NF-kB

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Release of Cytokines

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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-kB
- 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

- 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

Oligo-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
What Is New Is Often Old

“Bad digestion is root of all evil”

-Hippocrates