“All diseases begin in the gut.”

Hippocrates

The Power of the Microbiome

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We Are More Bacteria Than Human
A Paradigm Shift

• Bacteria cause infection
  – Well known
  – Well accepted
  – And there are known treatments

• Has this mindset possibly “blinded” medical community to richness/relevance of our microbial ecosystems to health and disease?
We Are More Bacteria Than Human

- Healthy adult harbors ~100 trillion bacteria in gut alone
- This is 10X the number of human cells we possess
- Humans possess 23,000 genes
- Microbiome contributes ~3,300,000
- Communal gut microbial genome (microbiome) is ~150 times larger than human genome
Microbiome as “Human Organ”

- Reasonable to view microbiome as an organ
- Weighs ~1kg although is without distinct structure
- Is organized system of cells more akin to immune system than liver
- Is dominated by 4 large groups of bacteria or phyla: *Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria*
Development of the Microbiota
Single Layer of Intestinal Epithelial Cells Separates Trillions of Bacteria from Lamina Propria
Coevolution of Host and Microbiome

• Host and microbiome have evolutionary aligned interests and interplay; neither wishes the other harm
• Resulted in lack of some genes in bacterial symbionts that are critical to other bacteria
• Some genes bacteria retain benefit only the host
• Microbiome provides critical biosynthetic pathways that significantly extend host metabolic and physiologic capacity
Commensal Bacteria Provide Benefits to Host

**Protective Functions**
- Pathogen displacement
- Nutrient competition
- Receptor competition
- Production of anti-microbial factors

**Structural Functions**
- Barrier fortification
- Induction of IgA
- Apical tightening of tight junctions
- Immune system development

**Metabolic Functions**
- Control of epithelial cell differentiation and proliferation
- Metabolism of dietary carcinogens
- Synthesis of vitamins
- Fermentation of non-digestible dietary residue and epithelial-derived mucus
- Ion absorption
- Salvage of energy
Expansion of Host Metabolic Capacity by Microbiome

- Bacteria express glycoside hydrolase which converts glycans into useable sugars
- No enzyme encoded in human genome is capable of digesting glycans—only bacterial enzymes
- Many carbohydrates are digestible only by bacteria and produce SCFAs—primary fuel for colonocytes
- 10-15% of adult energy may be generated by SCFA production or stored as fat
Sensing of Bacteria by Intestinal Epithelial Cells

Nature Reviews Immunology
Abreu MT 10:2010
Axes of Host-Gut Microbiota Metabolic Interactions

Diet, the Gut Microbiome, Metabolome, and Disease

Axes of Host-Gut Microbiota Metabolic Interactions

Importance of Host-Microbiome Alignment

• Microbiome may cause disease, directly or indirectly, when delicate balance is perturbed
Many Diseases May Result from Dysregulated Gut Microbiome

- Diabetes
- Obesity
- Metabolic syndrome
- Stress/anxiety
- Heart disease
- Allergic disorders
- IBD
- Cancer
Evidence for Role of Microbiota in IBD

• Antibiotics improve disease course in some IBD patients
• Animal models of IBD require presence of microbiota for inflammation
• Patients with IBD have less diverse microbiome
Evidence for Role of Microbiota in IBD

• Genetic studies support role of microbial-host interaction in IBD:
  – NOD2 mutation-intracellular host receptor that recognizes bacterial cell wall components
  – NOD2 carriers have 1.75-4-fold increase risk of CD and more likely to undergo surgical resection
  – Disease occurs only in animal models when gut bacteria are present
  – GWAS identified 100 genetic risk loci for UC and CD (28 shared) and many involve pathways for protection of host against gut microbiota- regulation of epithelial barrier, microbial defenses, regulation of innate/adaptive immunity
Evidence for Role of Microbiota in IBD

- Recent increase incidence in IBD is too rapid to be attributed to genetic factors alone
- Westernized diet of increased fat and red meat is associated with increased incidence of IBD
- Increased fiber and fruit decreased CD risk
- Increased vegetable intake decreased UC risk

Hygiene Hypothesis and IBD

• **Hygiene hypothesis** - exposure to fewer microbes and less complex microbial communities at early age may lead to development of immune system less able to “tolerate” exposure to microbial-laden environment later in life leading to inappropriate immune activation

• Increased use of antibiotics at young age may also contribute to reduced microbiota diversity and development of IBD
Evidence for Role of Microbiota in IBD

- *Firmicutes* are decreased in CD, specifically *Faecalibacterium prausnitzii*
- Decreased *F. prausnitzii* is associated with risk of post-op recurrence of ileal CD
- In vitro and animal studies demonstrate anti-inflammatory properties of *F. prausnitzii* and increase in IL-10 and SCFA
Role of Microbiota in IBD

• Together these data support the notion that IBD is due to the inability of the host to protect against microbial invasion and unrestrained immune activation

• Tempting to speculate that altering gut microbiome by consumption of agrarian versus “Westernized” diet could decrease IBD risk and be used as a treatment modality
Antibiotics Promote Fat Gain

• Low-dose antibiotics have been used for decades to enhance growth and feed efficiency in farm animals but mechanism is not known
• Might antibiotic use in children contribute to obesity in humans later in life?
• Using young mice as a model, M. Blaser and colleagues showed that various low-dose antibiotics for 7 wks increased adiposity and changes in hormone levels related to metabolism

Antibiotics Promote Fat Gain

- No difference in caloric intake but caloric output in fecal pellets was lower in Abx-treated mice
- Increased Firmicutes:Bacteroidetes ratio is associated with obesity and was seen in Abx-treated mice
- Substantial increases in SCFA correlated with compositional changes in gut microbiome
  - SCFA provide direct energy to colonocytes and absorption into portal circulation stimulates adipogenesis
Antibiotics Promote Fat Gain

• This study supports the possibility that modulation of the infant human gut microbiome by antibiotics could have long-term metabolic consequences on the development of adiposity
Role of Gut Microbiome in Non-GI Diseases

• Production of specific metabolites by gut microbiota has the power to affect distant organs
• Is evidence that gut microbiota contributes to atherosclerosis via metabolism of dietary lipid phosphatidylcholine
• Foods rich in phosphatidylcholine are major source of choline; choline breakdown by intestinal microbiota forms trimethylamine that is metabolized by liver to trimethylamine oxide which promotes development of atherosclerosis
• Consumption of choline correlates positively with Bacteroides enterotype that is associated with a ‘Westernized’ diet

Gut Microbiota Can Accelerate Atherosclerosis

Gut Microbiota Can Modulate Gut-Brain Axis

Human microbiome ecosystems differ from place to place much like forests or coral reefs.
Diet Influences Microbiome Composition

• Long-term diet is associated with development of specific enterotypes
  – Diets high in animal protein and fat with high levels of *Bacteroides* and low levels of *Prevotella*
  – Diets high in carbohydrates but low in animal protein and fat with higher levels of *Prevotella* but lower levels of *Bacteroides*

• Japanese harbor organisms that produce enzyme that aids in seaweed digestion

• Microbiota of African children enriched in *Bacteroidetes* and depleted in *Firmicutes* to maximize energy uptake from fiber-rich diet
Impact of Short-Term Dietary Changes on Gut Microbiota

• Are significant and rapid changes in microbiota within 24 hrs of initiation of high fat/low fiber or low fat/high fiber diet but magnitude is modest as enterotype remains stable for at least 10 days

• Enterotype therefore is strongly associated with long-term diet

• If a specific enterotype is shown to be causally related to disease, long-term dietary interventions may allow microbiota modulation to improve health

Gut Microbiota Composition Correlates with Diet and Health in Elderly

- Intestinal microbiota of older people (>65) is extremely variable and differs from microbiota and diversity levels of younger adults.
- Aging is associated with inflammation.
- Recent study demonstrated links between diet, microbiota composition, and health.
- Compared community dwelling, out patient day hospital, short-term rehab (<6 wks) and long-term residential care.

Gut Microbiota Composition Correlates with Diet and Health in Elderly

• 98% of community and day hospital dwellers had low-moderate fat/high fiber diets while 83% of long-term stay subjects had moderate-high fat/low fiber diets

• Intestinal microbiota of those in long-term care facilities was less diverse than that of community dwellers

• Loss of community-associated microbiota correlated with increased fragility, increased inflammatory markers, sarcopenia, poor scores on geriatric depression test, functional independence measures, mental state exam, and nutritional assessment
Gut Microbiota Composition Correlates with Diet and Health in Elderly

• Major trends in microbiota that separated healthy community subjects from less healthy long-stay subjects were increased fragility and poorer health, having adjusted for gender, age and location.

• Supports a case for microbiota-related acceleration of aging-related health deterioration arguing for modulation of microbiota with dietary intervention designed to promote healthier aging.
But......it’s more complicated than that!!

- It’s not just about long-term dietary changes and shifts in enterotypes
- Consider IBD - a disease stemming from environmental and microbial factors on a background of genetic susceptibility
- Intestinal microbes metabolize and react to dietary components that in turn can alter microbial populations
Might Diet Alter Intestinal Microbiota and Enhance Inflammation?

• Chang and colleagues asked if certain dietary fats prevalent in Western diets precipitate colonic inflammation via actions on gut microbiota

• Compared impact of high fat diet derived from different sources (milk fat-based saturated fat, lard, and polyunsaturated fat (safflower oil) on development of colitis in genetically susceptible host

Might Diet Alter Intestinal Microbiota and Enhance Inflammation?

- Milk fat has high levels of hydrophobic stearate demanding emulsification by bile salts.
- High milk fat-based diet increased taurocholate:glycocholate ratio as taurocholate more efficiently emulsifies hydrophobic fats.
- Increased taurocholate (80%:20%) in bile results in bloom of *Bilophilia wadsworthia* in gut.
- At low-saturated fat levels, ratio is 50%:50% and *B. wadsworthia* is undetectable.
Might Diet Alter Intestinal Microbiota and Enhance Inflammation?

• Mice on low fat diet gavaged with TC, GC or buffer; only those receiving TC had *B. wadsworthia* bloom

• These data emphasize two things:
  – Profound impact of a single dietary factor on our bodies and not just at macronutrient level
  – Observed microbial change may be secondary effect of altered host physiology
Might Diet Alter Intestinal Microbiota and Enhance Inflammation?

- High milk fat diet had no impact on intestine of wild-type mice
- However, in colitis prone IL-10⁻/⁻ mice, spontaneous rate of colitis increased from 25% to >60% and was more severe and extensive
- Colitis incidence in IL-10⁻/⁻ mice fed PUFA was not changed
- No inflammation in germ-free mice on milk fat diet or gavaged with TC in absence of *B. wadsworthia*
Might Diet Alter Intestinal Microbiota and Enhance Inflammation?

• *B. wadsworthia* antigen specifically induces $T_{H1}$ response
  – Increased IFN-$\gamma$, IL-12p40, and low IL-6, IL-17, IL-23 in colonic mucosa
  – Increased CD4$^+$ IFN-$\gamma^+$ cells in MLNs
  – Inflammation was result of activation of dendritic cells presenting *B. wadsworthia* Ag to naïve T cells
Dietary Fat-Induced Taurocholic Acid Promotes Pathobiont Expansion and Colitis in IL-10 KO Mice

Devkota et al. Nature 2012;487:104
Exciting Opportunities for the Future

• Finding that high milk fat diet resulted in *B. wadsworthia* bloom in wild-type mice with intact immune system but had no impact on intestinal health highlights the necessity of a genetic predisposition to disease

• This provides rationale for tailored interventions and a move toward personalized medicine
Gut Microbiota as Therapy

• Several chronic diseases are associated with intestinal dysbiosis
• In general, microbiota diversity is lacking
• It is intriguing to contemplate the use of bacteriotherapy in the treatment of such diseases
• Most is know about this process with regard to recurrent *C. difficile* infection and there is strong evidence supporting fecal transplantation for its cure
Proposed Model for Establishment of *C. difficile*-Mediated Dysbiosis and Successful Bacteriotherapy

Intestinal Microbiota Transplantation for Recurrent *C. difficile* Infection

- First performed in 1958 for fulminant pseudomembranes
- Now accepted as effective for recurrent *C. difficile*
- 92% effective when standard therapy failed
- Administered by NG, NJ, enema, or colonoscopy
- Efficacy slightly improved with Abx before IMT
Intestinal Microbiota Transplantation for Recurrent C. difficile Infection

- Recent study in mice identified a mixture of 6 phylogenetically diverse intestinal bacteria (*Staphylococcus warneri, Enterococcus hirae, Lactobacillus reuteri*, and three novel species from *Anaerostipes, Bacteroidetes* and *Enterorhhabdus*) that reestablish a “healthy” microbiota and clear *C. difficile* infection from mice.

- This diverse mixture of defined bacteria appears to trigger major shifts in intestinal microbial community structure thus displacing *C. difficile* and resolving disease.

Intestinal Microbiota Transplantation for Other Chronic Diseases

• In 1989, an author reported successful self treatment of his UC with fecal microbiota transplantation

• In 2003, 6 patients with moderate-severe UC received fecal microbiota transplantation; all responded and remained in remission for 6 mos-13 yrs with mucosal healing at endoscopy
Links Between Gut Microbiota and Metabolism

Fig 2: Possible links between the gut microbiota and metabolism
straight lines: likely pathways
dotted lines: putatively pathways

FATLOSE trial
(Fecal Administration To LOSE metabolic syndrome)

• Study design: double blind RCT
• Inclusion criteria:
  – male subjects
    • BMI ≥ 30 kg/m²
    • FPG ≥ 5.6 mmol/l
    • Age 21-65 years
    • No medication use
• Randomization:
  – allogenic FT (from lean male volunteers), n=9 subjects
  – autologic FT (own feces), n=9 subjects
Intestinal Microbiota Transplantation for Other Chronic Diseases

• Lean donor fecal infusion in males with metabolic syndrome:
  – Improved peripheral insulin sensitivity
  – Increased microbial diversity
  – Increased levels of butyrate producing microbiota in small and large intestine
    • Butyrate has a direct effect on glucose metabolism

• No adverse events

• Current goal is to identify microbiota that when administered orally result in comparable effects on glucose metabolism

Cautions?

• Recognition of the vast therapeutic capacity of the intestinal microbiota is exciting but with recognition comes responsibility.
  – What level of detail should be included in informed consent?
  – How do we convey potential risks that evolve from complex science to patients?
  – Follow up studies are needed to determine if there are long term health risks associated with fecal transplantation.
Exciting Opportunities for the Future

• Future studies will likely identify interventions that specifically suppress, eliminate, or enhance the presence of key microbes by manipulating the enteric environment of the host

• Targeted pharmacotherapy that acts synergistically with dietary manipulations or the provision of defined cocktails of intestinal microbiota may well be the way of the future
Therapeutic Modulation of Gut Microbiota From Cradle to Grave
Conclusions

• Gut microbiome functions as a virtual organ and significantly extends metabolic capacity of the host
• Combining microbial phenotyping, metabolic profiling and clinical expertise will drive our understanding of the metabolic language of mammalian-microbial communication
• This provides a new paradigm for developing new therapies for a range of acute and chronic pathologies
The Roux-en-Y Gastric Bypass in Relation to Physiological and Microbial Activities

1. **Protein putrefaction**
   1. **Fibre fermentation**
   1. **Fecal putrescine, (distal colon) dianmoethane**
   1. **Fecal tyrosine**
   1. **Urinary cresols, amines, indoxyl sulfate**

2. **Intestinal motility**
   1. **Neuroactive chemicals (Fecal GABA)**

3. **Proteins increasingly used as secondary energy resource**
   1. **Microbial or Gut Omithine decarboxylase**
   1. **Enterobacter hormoche**

4. **Enteric ph**
   1. **Enteric Bifidobacteria**

5. **Direct correlation observed between Enterobacter, hormoche & Urinary Cresols**

**COLOR CODE KEY FOR BRAVE EFFECTS (Box outline)**
- **Purple**: Bile Flow alteration
- **Yellow**: Reduction of gastric size
- **Blue**: Anatomical gut rearrangement and altered flow of nutrients
- **Gray**: Vagal manipulation
- **Pink**: Enteric gut hormone modulation

**LABEL KEY**
- 1. Direct observation
- 2. Literature
- 3. Hypothesis

**TEXT COLOR KEY**
- Physiology
- Biochemistry
- Microbiology
Intestinal Microbiota Protects Against Allergic Inflammation