Microbiome (The Second Human Genome)

What Shapes it and How it Shapes Us

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Hepatology Section Up to Date

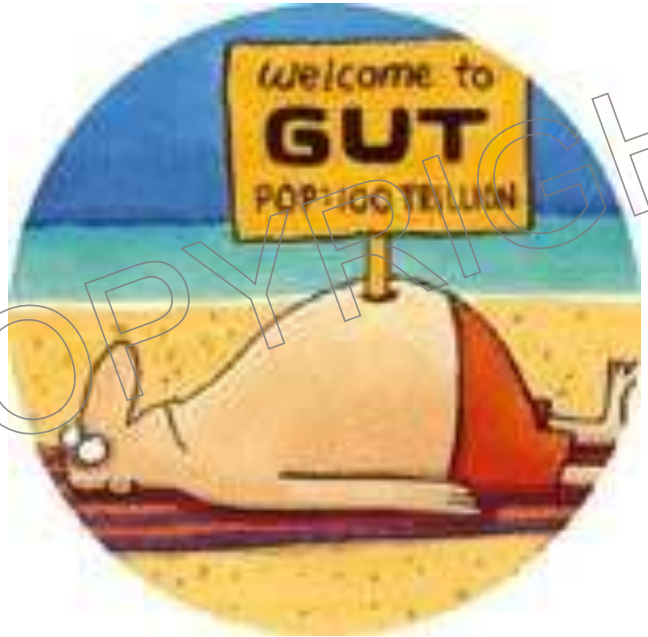
Disclosure Statement

The commercial entities with which I, Sanjiv Chopra, MD, MACP have relationships do not produce healthcare-related products or services relevant to the content I am planning, developing, or presenting for this activity.

Definition

The concept of the human microbiome was first suggested by Joshua Lederberg, who coined the term “microbiome, to signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space”.

Microbiome = the community of microorganisms that shares our body space



Population 100 Trillion: Microbes outnumber human cells 1.1:1

Humans have 23,000 genes. Microbiome has 8 million genes.

Microbiome

"2nd human genome"

"Newly discovered organ"

"Bacterial inner rainforest"

Weight of Gut Microbiome

3 LBS!

What shapes our microbiome?

Birth

Antibiotics

Probiotics

Where we live

Travel

Diet (vegetarian, fiber)

Exercise

PPIs

Malnutrition

Coffee

Laughter

Weight loss drugs

Worst and Best Foods for Gut Health

Worst:

1. Refine Sugar
2. Factory Farmed Meat
3. Refined Grains
4. Artificial Sweetners
5. Saturated Fat
6. Fried Foods

Best:

1. Plant Based
2. High Fiber
3. Seafood
4. Fermented Foods
5. Polyphenol Containing
6. Vitamin D Foods

Ultra Processed Foods Are Unhealthy

- Percentage of energy intake from ultra processed foods:

  29% in France

  42% in Australia

  58% in USA

- Ultra processed foods can change the gut microbiota and lead to inflammation.

Zinocker M. Lindseth I. PubMed. 2018

Diet – Gut Microbiome Interactions Influence Human Energy Balance

- A Microbiome Enhancer Diet (MBD) compared to the Western Diet (WD) resulted in additional in feces daily. calories lost

- In the Feces there was an **additional loss of** 116 Kcal/D or equivalent of 2 lbs/month

- Microbial 16s, r RNA gene copy number (surrogate of biomass) and fermentation products increased in MBD compared to WD. Significant changes noted in host entroendocrine system as well.

Corbin KD. Et al. *Nature Communications* May 2023.

Obesity: Twin Studies Shed Light

- Four pairs of identical twins. One lean and the other obese in each pair.
- Genetically identical baby mice had their guts populated with intestinal microbes from either obese women or their lean twin sister.
- Mice that received bacteria from obese twin gained weight and had more body fat. They also had a less diverse community of gut microbes.

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice
Ridaura, VK *et al. Science*, 6 September 2013: Vol. 341 no. 6150

Diets Modulate Gut Microbiome and Improve Insulin Sensitivity

- 20 obese men with CAD. Randomized to Mediterranean diet (Med) or low-fat, high-complex carbohydrate diet (LFHCC) for one year
- Bacterial composition and relationship with fecal and plasma metabolome evaluated
- Both diets shown to exert a protective effect on the development of T2DM. Med diet increased *Roseburia* genus and LFHCC diet increased *F. prausnitizii*.

Haro, C *et al*. *Endocrinol Metab* 101:233-242, 2016

Bariatric Surgery Affects Gut Microbiome Composition

- Gut microbiomes different in patients after gastric bypass surgery compared to obese controls
- E. coli, Klebsiella, Pseudomonas, all more common
- Stool from gastric bypass patients transferred to germ free mice:
  - Mice had improved fat oxidation
  - Microbe trasplanted mice gained 43% less body fat compared to mice that received stool from gastroplasty patients

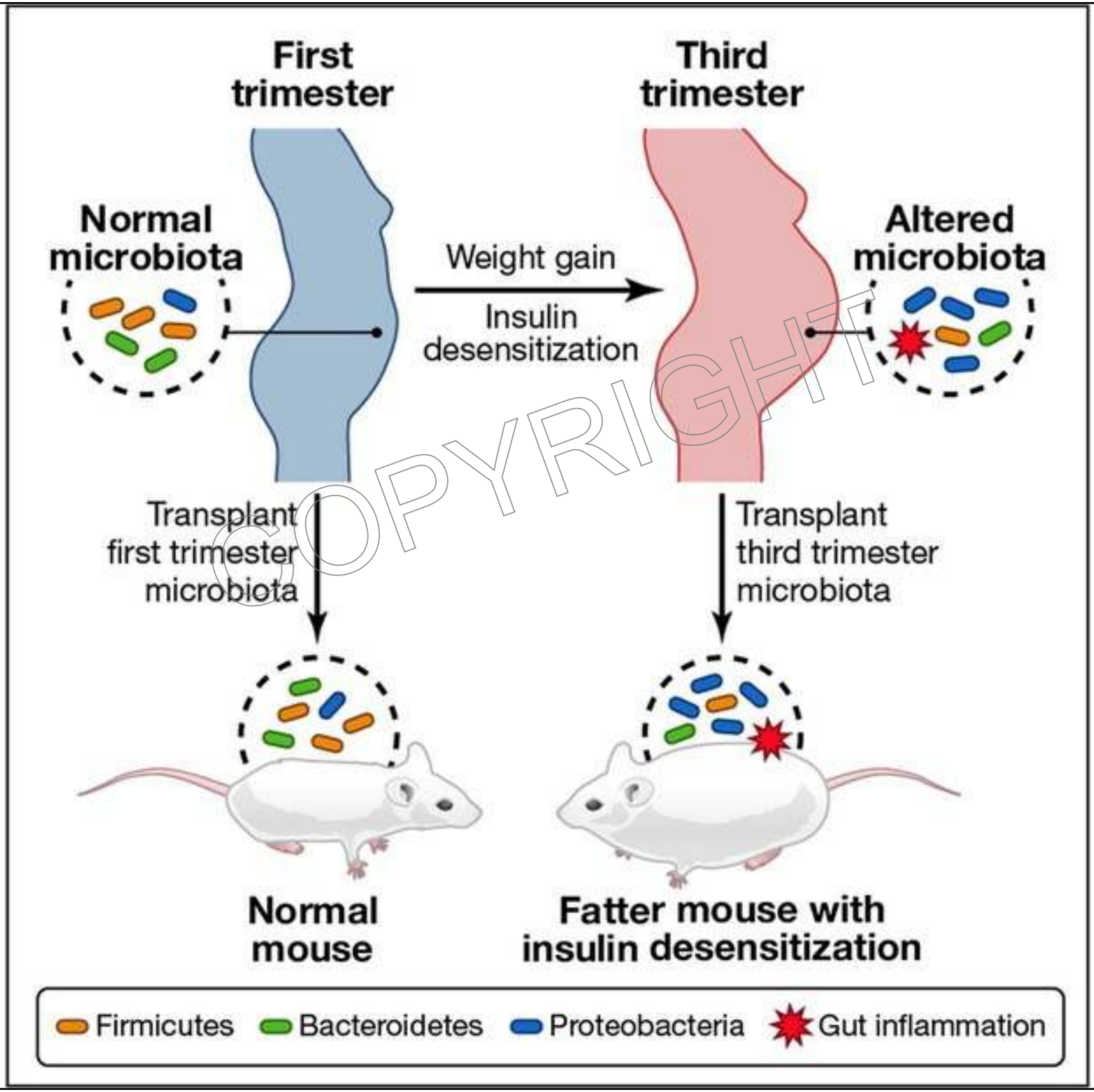
Tremaroli, V. et al. Cell Metabolism, 22, 2015.

Pregnancy, Weight Gain, and Altered Microbiota

- Gut microbiota changed dramatically from first to third trimesters, with vast expansion of diversity between mothers, an overall increase in Proteobacteria and Actinobacteria, and reduced richness.

- When transferred to germ-free mice, third trimester microbiota induced greater adiposity and insulin insensitivity compared to first trimester.

Host remodeling of the gut microbiome and metabolic changes during pregnancy
Koren *et al.*, *Cell*, 2012



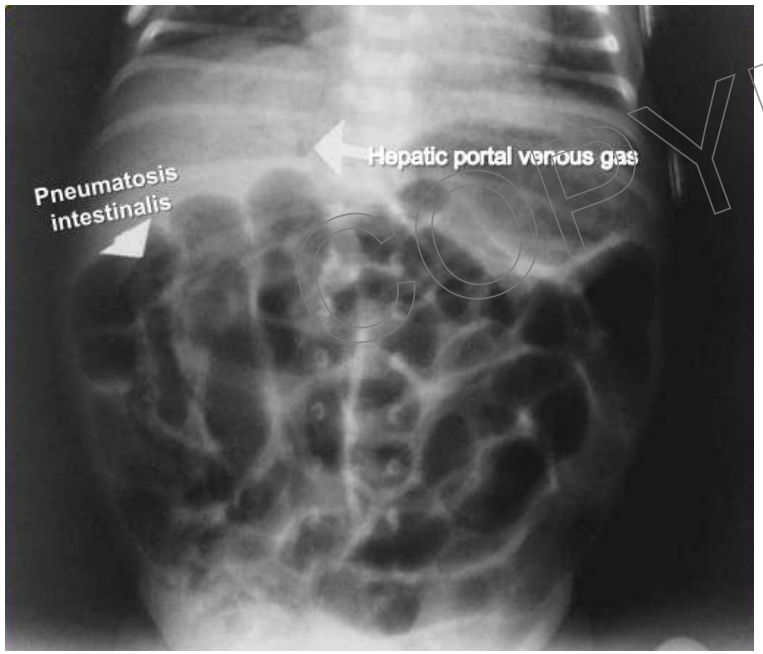
Koren et al, 2012

Long Term Infant Outcomes are Influenced by Mode of Delivery

- Children born by Cesarean section are more likely to develop:
  - Type 1 Diabetes
  - Celiac disease
  - Hospitalization for Gastroenteritis
  - Asthma
  - Allergic rhinitis

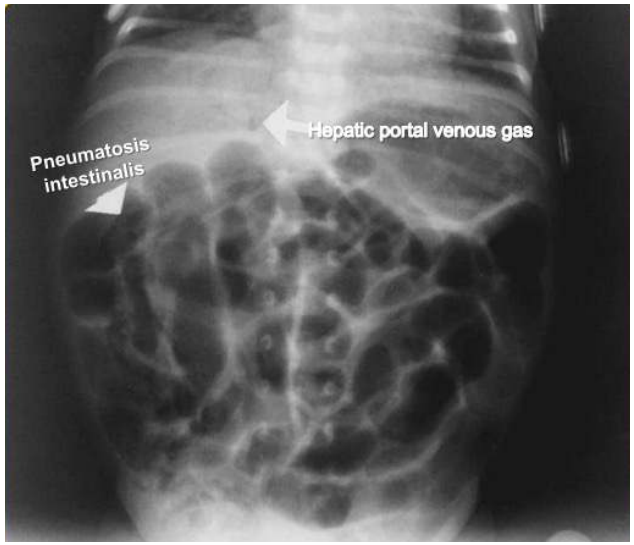
Neu, J and J Rushing. Cesarean versus Vaginal Delivery: Long term infant outcomes and the Hygiene Hypothesis. *Clin Perinatol*. 2001 June: 38(2): 321-331.

What is this condition?



Necrotizing Enterocolitis

- A study of 1000 premature newborns
- Up to 6% incidence in premature newborns
- 36% mortality rate



Gut Microbes Linked to Necrotizing Enterocolitis in Premature Newborns

- Premature newborns who survive the first two weeks have a much higher risk of dying from Necrotizing Enterocolitis
- Gut microbiota in these newborns are different - more Gram negative, less anaerobes
- This dysbiosis observed before any clinical event
- Potential window for intervention

Warner, B.B. *et al*. Gut bacterial dysbiosis and necrotizing enterocolitis in very low birth weight infants: a prospective case control study. Lancet, March 2016.

Administration of Bifidobacterium Infantis EVC001 Led To…

- 73% reduction in risk of necrotizing enterocolitis (NEC) in very low birth weight infants.

- NEC mortality 2.7 in the no-treatment group versus 0% in the EVC001 group.

- *B. infantis* administration safe and effective for reducing morbidity and mortality.

Tobias J. et al. Journal Pediatrics. 2022

Predictive Signature of Gut Microbiota Prior to Onset of Crohn's Disease

- Gut bacterial composition in treatment naïve IBD patients differ from those with controls.

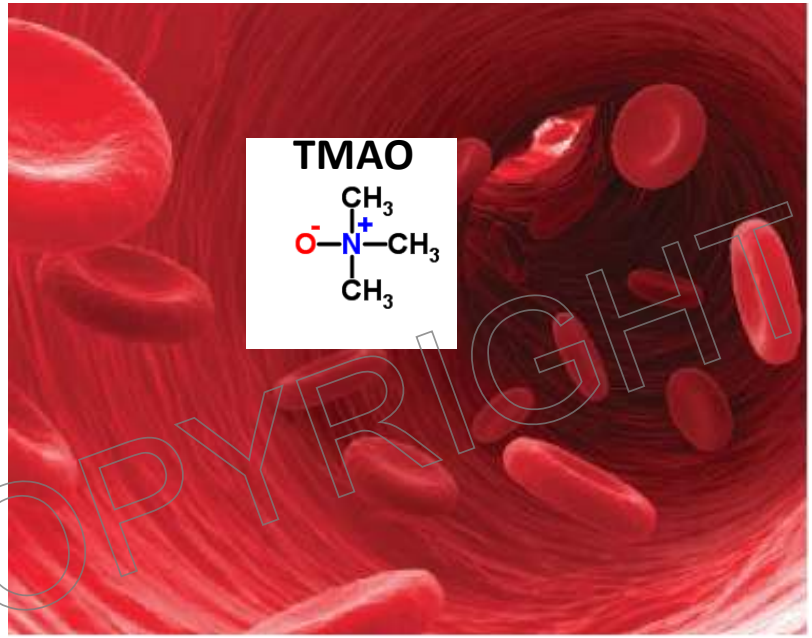
- In a multi country set of first degree relatives of Crohn's disease patients a predictive signature was present up to 5 years before Crohn's disease became clinically apparent.

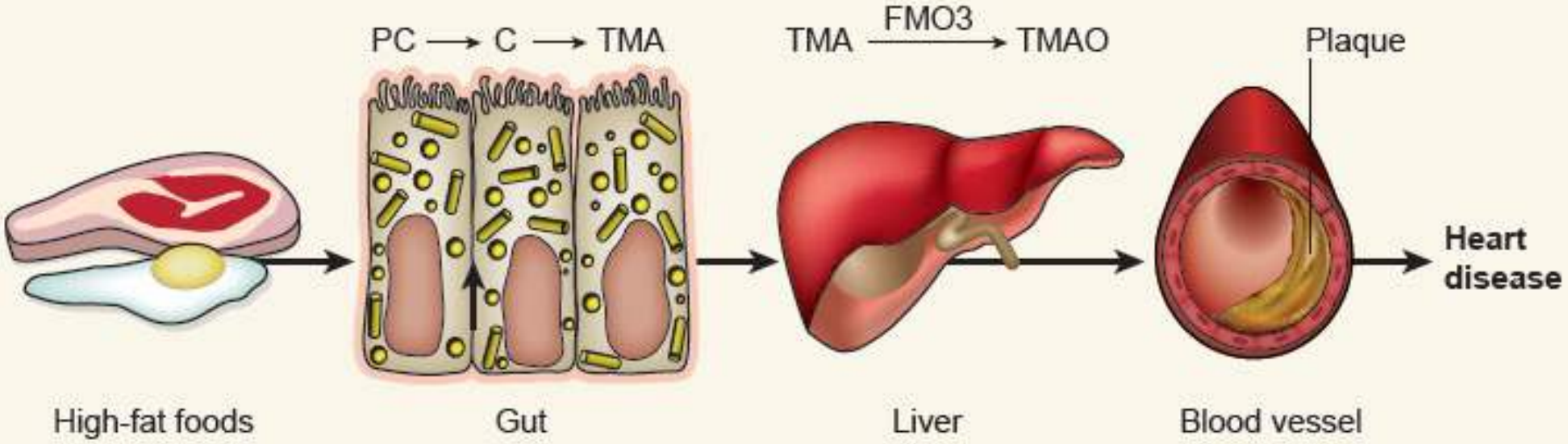
Garay JA. Et al. Gastroenterology May 2023.

nature

The diet–microbe morbid union

Tri-
Methyl-
Amine N-
Oxide

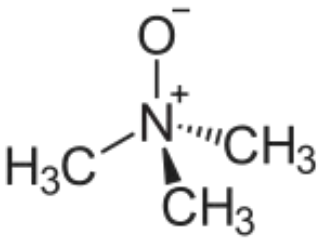


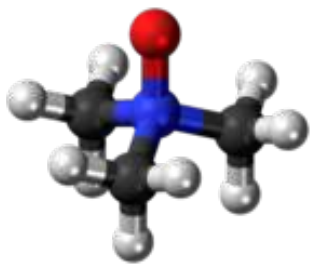


Nature, 2011

TMAO, Microbiome, and CAD/Stroke!

- TMAO is produced when intestinal bacteria digest the nutrient Lecithin.
- Human subjects, after eating two hard-boiled eggs and a capsule of labelled Lecithin, have an increase in TMAO levels.
- However, when subjects are given broad-spectrum antibiotics, their TMAO levels are suppressed.
- High TMAO blood levels are associated with higher risk of heart attack or stroke, independent of other risk factors and other blood test results.





TMAO Important Predictor of Atherosclerosis

- Dietary meat is a major source of TMAO in humans
- TMAO levels independent risk factor for atherosclerosis in humans
- In Apo E deficient mice, TMAO levels correlate with atheroma burden
- When Apo E deficient mice are treated with antibiotics, there is a significant decrease in atheroma burden

An Important Reference

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk.
Wilson Tang *et al*., *NEJM* 2013, 368.

Association of Gut Microbiota Composition with Coronary Atherosclerosis

- 8973 participants without overt Atherosclerotic Disease studied using Coronary Artery Calcium Score and CT Angiography.

- Streptococcus Species (Strep Anginosis and Strep Subsp Oralis) Abundance in the Gut linked to sub-clinical Coronary Atherosclerosis.

Sayols-Baixeras S. et al. Circulation 2023.

Gut Microbiome Composition Influences Risk of Ischemic Stroke

- There appears to be a causal effect of specific bacterial composition on the risk of Ischemic Stroke – cardio metabolic stroke, small vessel stroke, and larger artery stroke.
- genus_Intesinimonas and genus_LachnospiraceaeNK4A136group

  Displayed significant protection against more than one Ischemic Stroke Subtype.

Meng C. et al. European Journal of Preventive Cardiology 2023

Gut Microbiome Dysbiosis Occurs Early in Parkinson's Disease

- The gut microbiota brain axis likely plays an important role in Parkinson's Disease. (PD)

- In a study it was shown the gut microbiota compositions are significantly altered in early PD.

Huang. B. et al. Gut microbiome dysbiosis across early Parkinson's disease, REM sleep behavior disorder and their first-degree relatives. Nature Communications 14 2023.

Is There A Link Between The Gut Microbiota And Alzheimer's?

- In a excellent article the authors discuss the potential role of gut microbiota in Alzheimer's disease from diagnosis to treatment.
- They explore the potential role of pre-biotics, pro-biotics, FMT, and diets as complimentary therapeutic interventions on disease pathogenesis and progression.

Varesi A. et al. Nutrients 2022.

Diet – Gut Microbiome Interactions Influence Human Energy Balance

- A Microbiome Enhancer Diet (MBD) compared to the Western Diet (WD) resulted in additional calories lost in feces daily.
- Microbial 16s, r RNA gene copy number (surrogate of biomass) and fermentation products increased on MBD compared to WD. Significant changes noted in host entroendocrine system as well.

Corbin KD. Et al. *Nature Communications* May 2023.

Diet is destiny!

Fate is shaped by

genome and microbiome.

Our Diet Effects the Gut Microbiome

… And in turn our mood, **happiness** and mental health.

Martin SE. et al. The Role of Diet on the Gut Microbiome, Mood and Happiness.

medRxiv 2023 March.

Is this person trying to lose weight?

430 calories

510 calories

500 calories

Total: 1440 calories

New total: 1441 calories!

Gut Microbiome Influences Response to Chemotherapy

- **Side effects** of chemotherapy dictated by gut microbiome composition.

Erica Hartmann et al. Journal mSphere May 2021.

- **Efficacy** of chemotherapy dictated by gut microbiome composition.

Preliminary but Exciting Study

- Fecal microbiota transplantation (FMT) and re-induction of anti-PD-1 immunotherapy in 10 patients with anti-PD-1 refractory metastatic melanoma.

- Clinical response seen in 3 patients.

- Treatment associated with favorable changes in immune cell infiltrates and gene expression in gut lamina propria and tumor microenvironment.

Baruch EN. Et al. Science 2020.

Preliminary work shows…

- Vegan diet
- High fiber diet
- Highly fermented foods (Kimchi)
- Breast milk
- Coffee

All have a favorable influence on the composition of the gut microbiome.

Exercise might improve health by changing the Microbiome

- A growing body of evidence shows that greater gut microbiota diversity is related to greater health

- The efficiency with which we transport oxygen to our tissues (cardiorespiratory fitness) is a far greater predictor of gut microbiota diversity than either body fat percentage or general physical activity

Carter SJ. et al. Experimental Physiology 2019.

Gut Microbiota and Autism Spectrum Disorder

- Pregnant mice injected with artificially created virus-like DNA
- Offspring display less socialization, greater sense of being startled by sounds, fewer vocalizations
- Serum of ASD mice contain more than 45x the amount of 4-ethylphenyl sulfate (4-EPS) (a metabolite of gut bacteria)

Gut Microbiota and Autism Spectrum Disorder

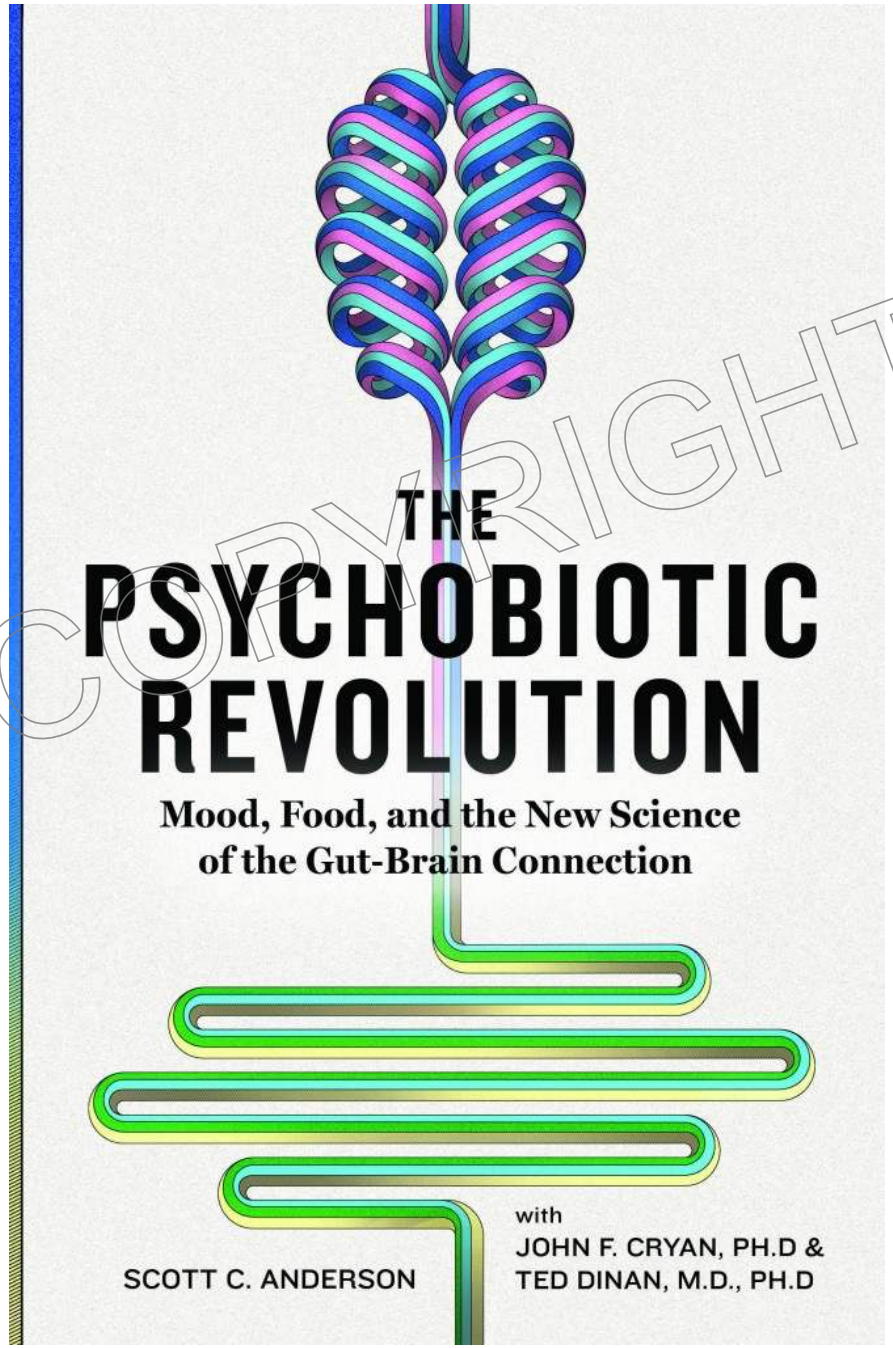
- Children with ASD have high concentrations of a similar compound p-cresol in their urine
- Healthy mice injected with 4-EPS have a leaky gut and display ASD symptoms
- Probiotic treatment with *B. fragilis* in ASD mice restored intestinal permeability and 4-EPS levels returned to normal

Hsiao, E.Y. *et al.*, Presentation at Gut Microbiota for Health. World Summit. Barcelona, Spain. 2015.

Tantalizing Study Regarding Long-Term Benefit of Microbiota Transfer Therapy on Autism Symptoms

- Follow up of 18 participants two years after Rx
- Most Improvements in GI Sx maintained
- Autism related Sx improved even more
- Changes in Gut Microbiota were maintained two years later
- A randomized placebo-controlled trial is warranted

Kang D-W. et al. Nature.com/Scientific Reports. April 2019.


THE
PSYCHOBIOTIC
REVOLUTION
Mood, Food, and the New Science
of the Gut-Brain Connection
SCOTT C. ANDERSON
with
JOHN F. CRYAN, PH.D &
TED DINAN, M.D., PH.D

Gut Microbiome Determines Vaccine Responsiveness

- *Bifidobacterium* and *Bacteroides* influence immunity and individual vaccine response.

- These two genera are important constituents of the developing healthy infant gut microbiota and are susceptible to C-section birth, formula milk versus breast milk and early antibiotic use.

Jordan A. et al. TheLancet.com/Microbe
October 2022

Gut Microbes Are Essential

- Not free-loaders
- Digest food
- Produce anti-inflammatory chemicals and compounds
- Guide the Immune System to distinguish friend from foe

Basic Definitions

- **Prebiotics** are selectively fermented products that confer changes in the composition and/or activity of the GI tract microflora and confer health benefits

- **Probiotics** are ingested microorganisms that are associated with health benefits

Global sales of probiotics exceeded

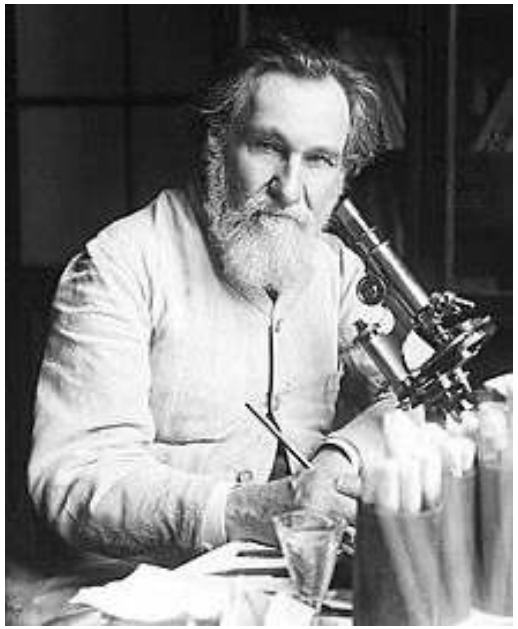
$40 Billion in 2018

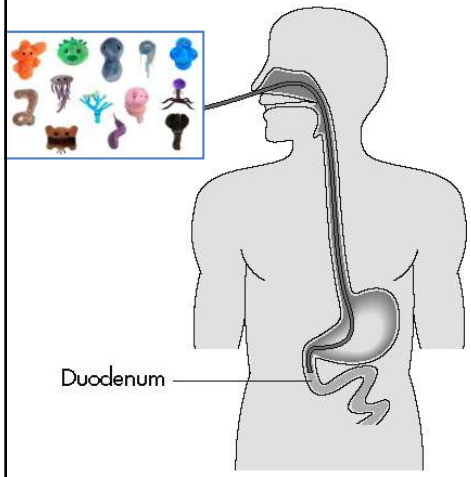
Estimated to exceed **$64 Billion** in 2020

More than a Century ago…

"The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes."

Elie Metchnikoff (1907)
Nobel Laureate





The NEW ENGLAND JOURNAL of MEDICINE

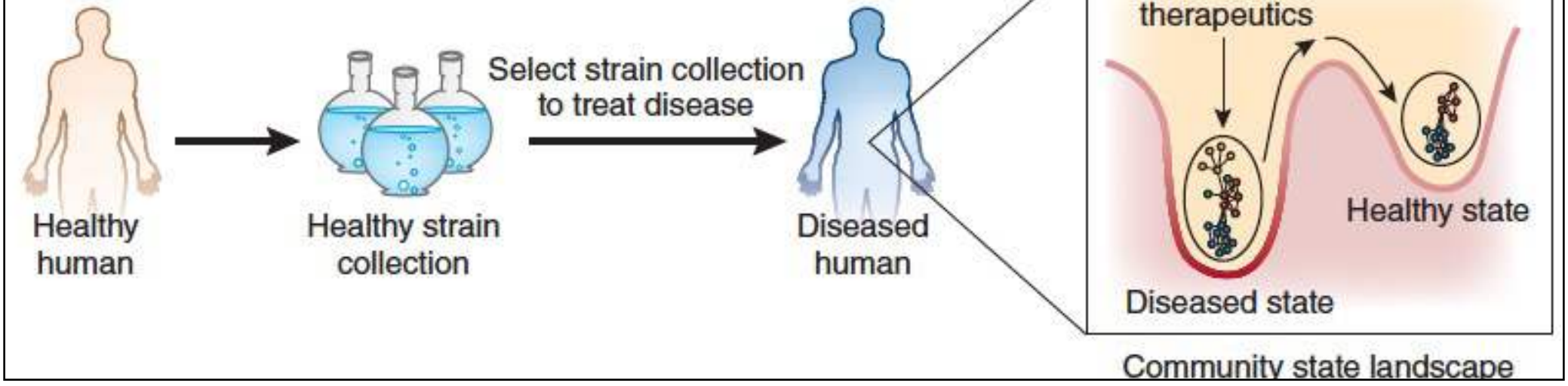
ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Restoration of the gut microbial habitat as a disease therapy

David A Relman



Frozen Poopsicle!

- 14 of 20 with recurrent *C. diff* diarrhea resolved
- 4 of 6 non-responders' diarrhea resolved with retreatment
- No adverse effects noted in this small study

Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing *Clostridium difficile* Infection. Youngster *et al., JAMA,* 2014, 312(17).

Probiotics Beneficial in Hepatic Encephalopathy (HE)

- Daily intake of a probiotic, VSL #3, over 6 months significantly reduced the risk of hospitalization for HE in cirrhotics

- Patients given VSL #3 had improvement in Childs Pugh and MELD scores

R.K. Dhiman *et al*., Gastroenterology 2014; 147: 1327-1337.

Bacterial Baptism!

- Sharp rise in rate of C-Section in recent years.
- Accompanying increase of Asthma, Allergies, Eczema, Obesity etc. in offspring.
- Is the Microbiome to blame?
- In addition to different Microbiome with C-Section other factors may play a role…Mother's who get C-Section receive anti-biotics, greater prevalence of obesity and lower rates of breast milk feeding.
- FDA approved studies being conducted in Virginia and New York City.

Early Onset Colocrectal Cancer (CRC)

- CRC incidence rising in younger adults.
- Significant difference in species enrichment noted in patients with CRC below 50 versus >65 years.
- Gene expression data- a stronger microbe-host interaction in early CRC noted.

Adnan D. et al. Cancer Prev Res (Phila) 2024.

Link between Microbiome and Longevity

The Fruit Fly remarkably similar to mammals in terms of biochemical pathways.

Fruit Flies fed with a synbiotic (probiotics combined with a herbal supplement)

Had reduced inflammation, oxidative stress and a 60% increase in Longevity.

Probiotics dramatically change gut microbiota – composition and in respect to how food is metabolized.

Susan Westfall et al. Longevity extension in Drosphilia through gut brain communication. *Scientific Reports, 2018.*

Certain Gut Microbiota Profile Can Predict Mortality!

- Largest population level study in the world.
- Based on sample of over 7,000 Finnish Adults.
- Study of the composition of gut microbiota improved mortality prediction even while taking into account smoking and obesity.

The microbes in your gut could predict whether you're likely to die in the next 15 years

Rodrigo Perez Ortega

https://www.sciencemag.org/news/2020

A Few Notable Stool Banks

OpenBiome is a nonprofit stool bank. Rigorously tested stool preparations are provided to clinicians and researchers for fecal microbiota transplantation. *https://www.openbiome.org/*

Five years later celebrated their 40,000th FMT RX.

Viome is a commercial enterprise that tests stool, saliva, and a drop of blood uses AI and recommends specific probiotics and supplements. Research in progress.

AMILI Advancing Human Health through Microbiome Science. First precision gut microbiome company launched in Singapore 2019.

Forget Superman
We have Super Pooper!

FMT Effective in IBS 3 Years After Transplantation

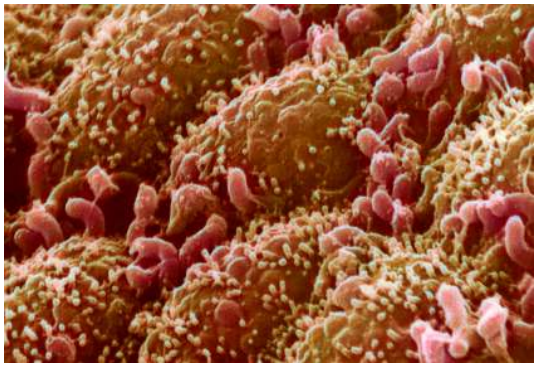
125 Patients. 33 Placebo Group. 42 Received 30g of donor stool and 45 who received 60g of stool.

Response rate 26%, 69% and 78% in the placebo, 30 g, and 60 g groups.

El-Salhy M. et al. Gastroenterology June 2022.

Microbiome Disease Architectures

- More than 2,500 samples from patients linked to 1 million microbial features
- CAD, IBD and Cirrhosis share gene level signatures ascribed to streptococcus genus



Patel C. et al. Nature Communications. 2021

Potential Clinical Applications of FMT

- FMT Safe and Associated with Short Term Reduction in **Alcohol Craving and Consumption** with Favorable Microbial Changes.

Bajaj JS. et al. Hepatology 2020.

- Two patients with co-morbidities and immunosuppression had both C.diff and COVID-19, received FMT. **Treatment effective for C.diff and appears to have mitigated COVID-19**.

Fecal Microbiota Transplant (FMT) Benefits in Severe Alcoholic Hepatitis May Last A Few Years

- Patients with severe Alcoholic Hepatitis who underwent FMT had lower rates of:

1. Alcohol Relapse
2. Complications
3. Trend towards improved survival

Philips CA. AASLD 2021

FMT vs Prednisolone in Severe Alcoholic Hepatitis

- 120 patients with severe alcoholic hepatitis were enrolled and 112 completed the trial.

- 90 day survival, 56.6% in Prednisolone group.
  75% in FMT group

Pande A. et al. Hepatology International 2023.

COVID-19 Disrupts Gut Microbiome

- COVID-19 by disrupting the gut microbiome allows pathogenic bacteria to thrive.

- It also affects the lining of the gut, allowing these pathogenic bacteria to enter the bloodstream and lead to dangerous secondary infections.

Cadwell K., Schluter J.

Nature Communications November 2022

Novel Microbiome Targeted Treatments Offer Hope for Obesity?

- Potential Mechanisms Include:

Production of Short Chain Fatty Acids, Tryptophan Metabolites, Bile Acids, and Endocannabinoids.

- For example both Butyrate and Propionate stimulate secretion of gut peptides such as GLP-1.

Van Hul M., Cani PD. The gut microbiota in obesity and weight management: microbes as friends or foe? Nat Rev Endocrinol. 2023.

Let's Summarize

1. Microbes appeared 3.5 billion years ago.

2. There's a cross talk! They've been doing it for billions of years. Yet to be silent!

Lets Summarize (continued)

3. Gut microbiota affect:

Obesity	Diabetes
Cardiovascular Disease	Colon Cancer
Stroke	IBD
Autism	Arthritis
Parkinson's Disease	IBS
Necrotizing Enterocolitis	Pregnancy Outcomes

Longevity and more…

Let's Summarize (continued)

4. Composition of the microbiota is in flux and altered by a diverse array of factors

5. Microbiota-directed therapies include:
   - *Fecal transplants* (*C. difficile* colitis)
   - Hepatic Encephalopathy
   - Autism
   - Alcohol use disorder
   - Bolstering Cancer Treatment Efficacy

Have you heard of Biological Dark Matter?

- It is uncategorized genetic material found in humans that does not fall under the three existing domains of life: bacteria, archaea, and eukaryotes.
- It may well be a fourth domain of life yet to be discovered.
- Biological dark matter accounts for:
  - 40-50% of the genetic material in the human gut
  - 20% of the genetic material in the nose
  - 1% of genetic material in sterile blood

Worth listening to…

“What’s left to explore?”

Nathan Wolfe, biologist and explorer gave a terrific TED talk in 2015 about biological dark matter.

http://www.ted.com/talks/nathan_wolfe_what_s_left_to_explore

Two TEDTalks Worth Watching…

1. Feed Your Microbes – Nurture Your Mind

John Cryan

TEDxHa'pennyBridge 2017

2. Your Gut Microbiome: The Most Important Organ You've Never Heard Of

Erika Ebbel Angle

TEDxFargo 2019

An Excellent Review

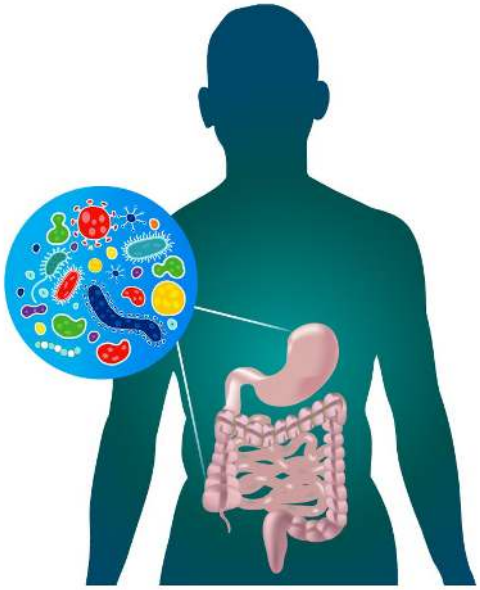
Gut microbiome-brain-cirrhosis axis

Smith ML. Wade JB Wolstenholme. Bajaj JS.

Hepatology 80 2024

I have a gut feeling!

Who is doing the talking?



Research and Clinical Applications are at an Early Stage

- Large scale studies needed.
- Studies looking at the microbiome outside the gut will likely shed insights.
- In addition to bacteria, viruses and fungi likely play an important role (Virome, Fungiome).

Nothing new under the Sun!

"All disease begins in the gut"

Hippocrates
460 BC to 370 BC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An African Proverb

We have only seen the head of the hippo.