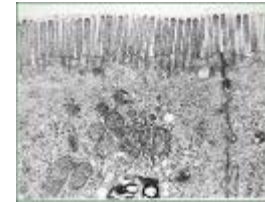
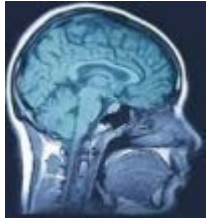
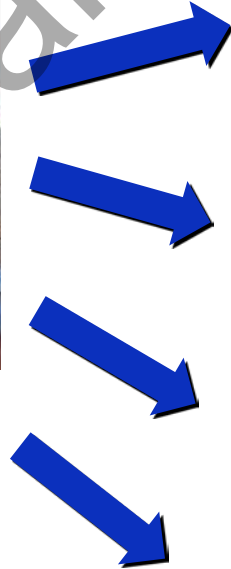


Gut Microbiome: The Mechanisms Behind the Magic of Staying Healthy !



**8th Annual Nutrition Day
“When is Food Medicine”**

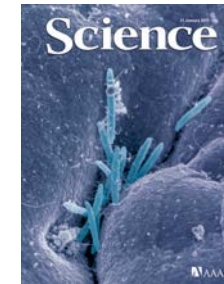
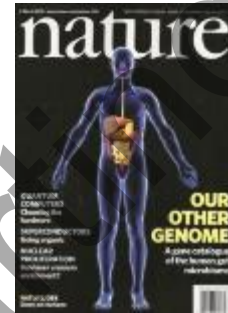
**Bob and Charlee Moore Institute for Nutrition and Wellness
April 27, 2023**

Robert Martindale MD, PhD
Professor of Surgery
General and Gastrointestinal Surgery
Oregon Health and Sciences University
Portland, Oregon

Microbiome literature: Science or Quackery?

- Recent lead articles:

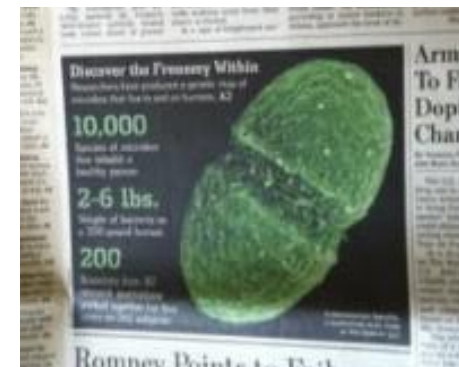
- All major medical journals 2018-2023
- JAMA 2017, Nature 2017, Ann Surg 2017
- PNAS 2016
- Nature 2015
- Science 2014
- NY Times 2013
- Wall Street Journal 2012
- Scientific American 2012
- Economist 2012



New York Times 2013



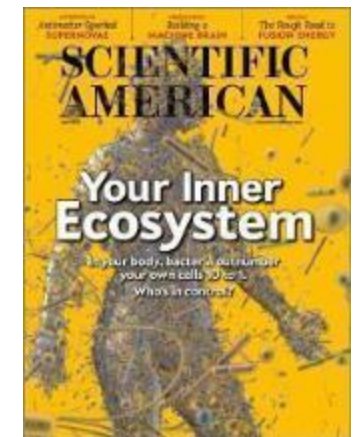
2012



Wall Street Journal 2012



SUPPORT BACTERIA!
it's the only culture some people have



Searching for the link between microbiome and human maladies

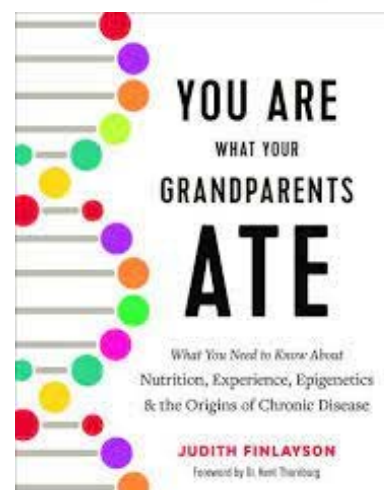
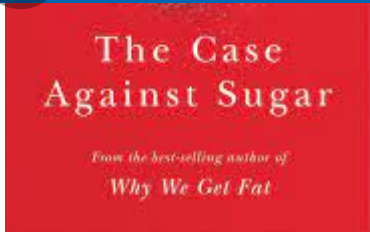
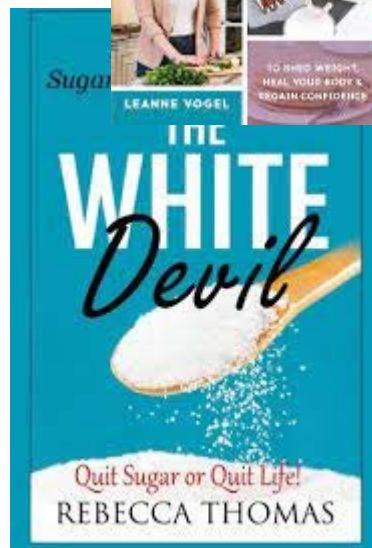
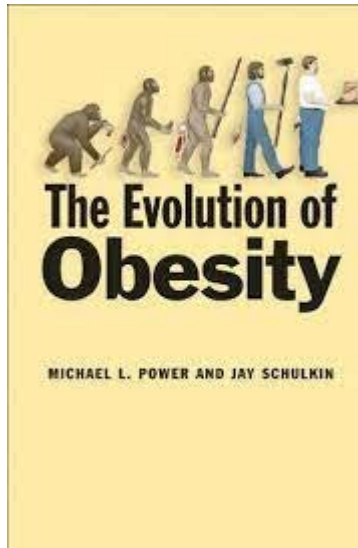
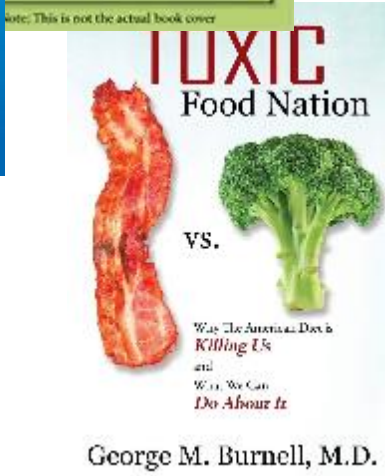
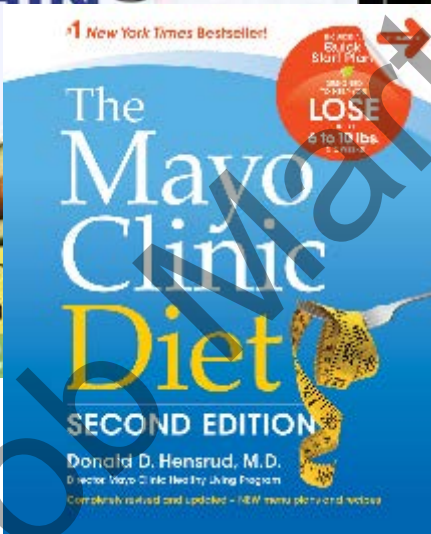
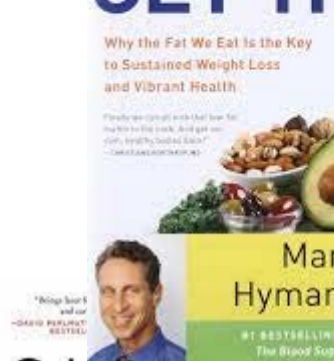
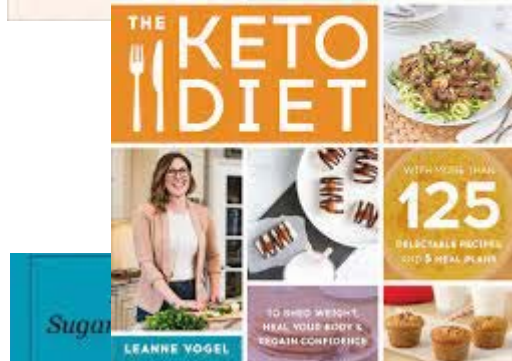
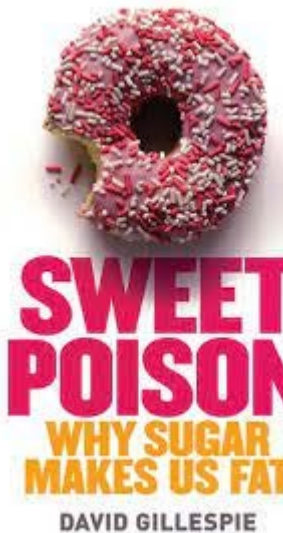
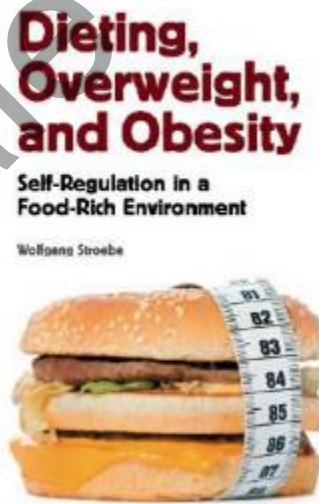
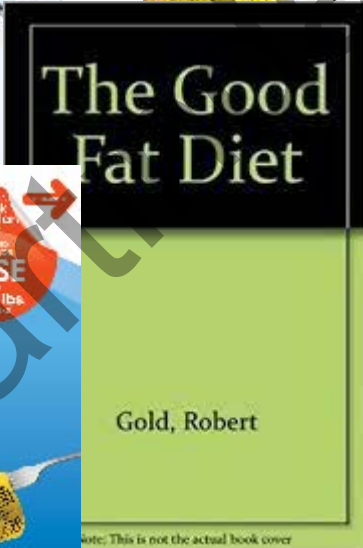
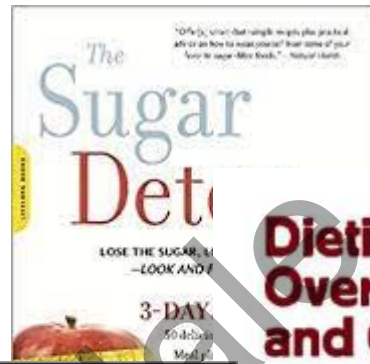
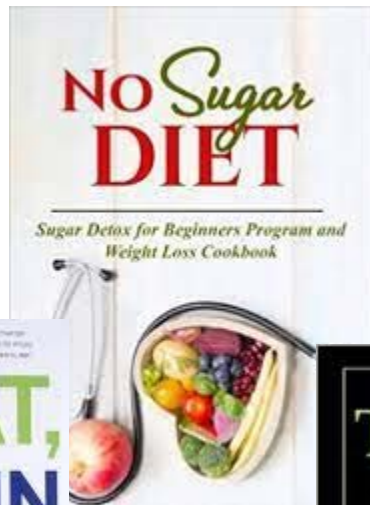
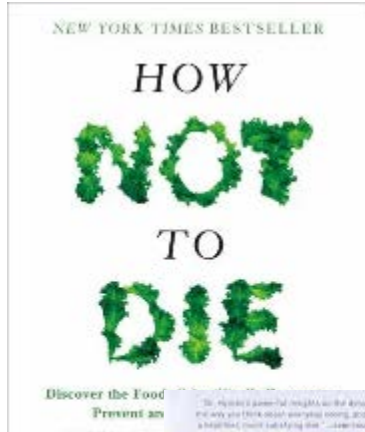
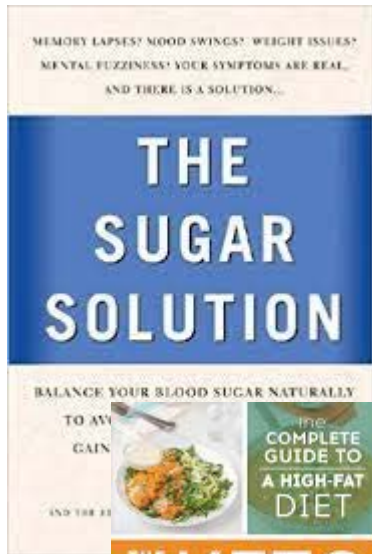
- Diseases commonly accepted to be associated with alterations in microbiome: **obesity, inflammatory bowel, arthritis, autism, colon cancer, depression, type 2 DM, autoimmune diseases, etc etc etc**
- Rapid DNA sequencing has led to the explosion of knowledge
- **The challenge now is attempting to understanding all the data**
 - “...strategies that leverage the existing knowledge from correlation to causation and ultimately to transition into therapies.”

We are at a critical inflection point – transitioning from description to developing disease specific treatment strategies

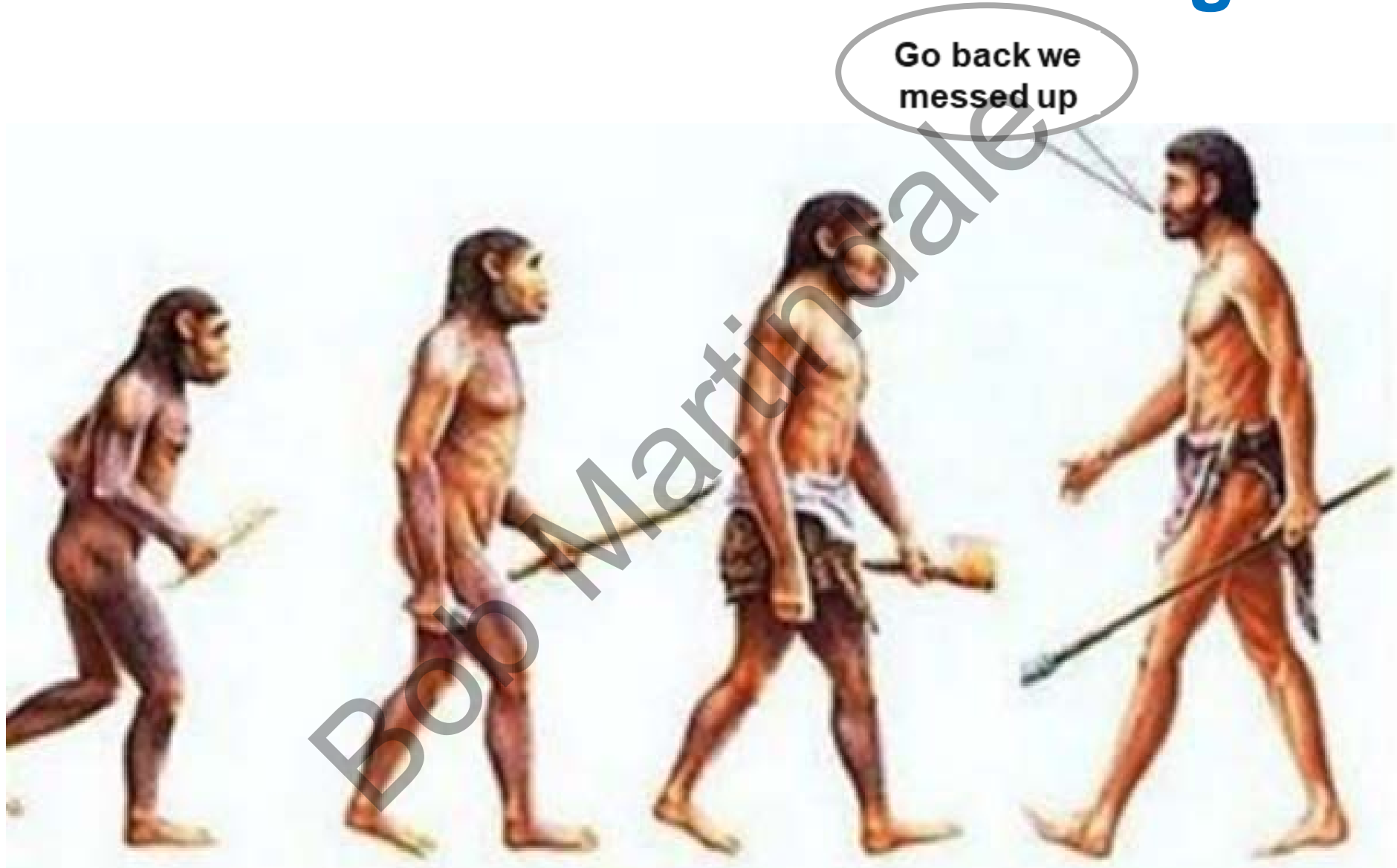
**Healthy
Microbiome**



**Maintains
health and
cures
everything**

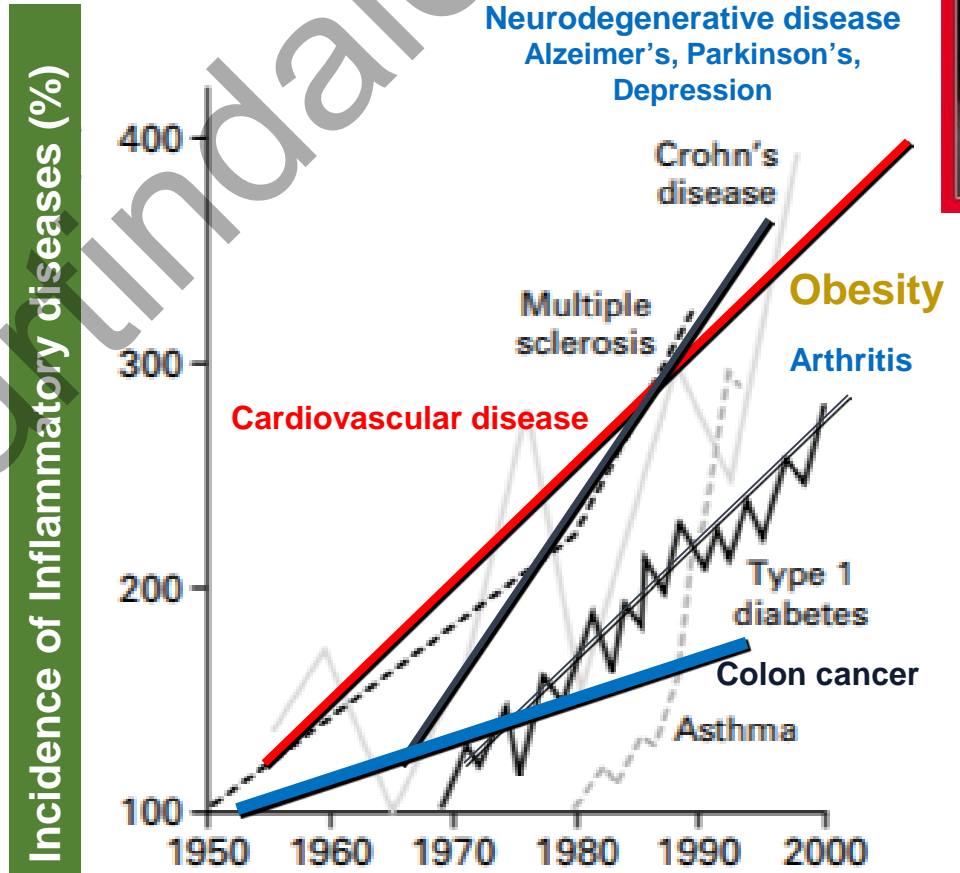
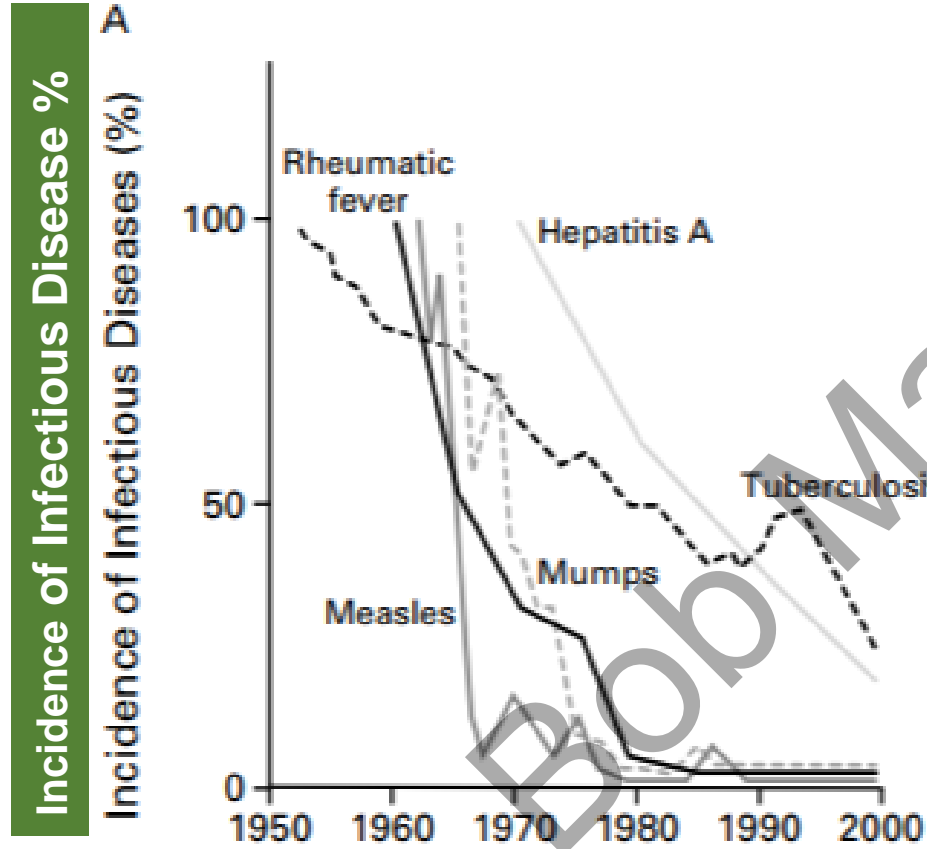


Our current “Western” Diet is killing us ?



Inflammatory Diseases have Replaced Infectious Diseases:

Is Diet the Driving Force of Systemic Inflammation ?



Diseases where Inflammation is thought to be a major part or all of the etiology of the disease !

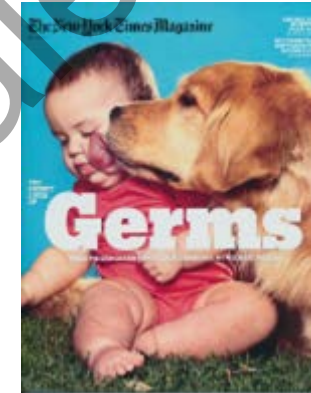


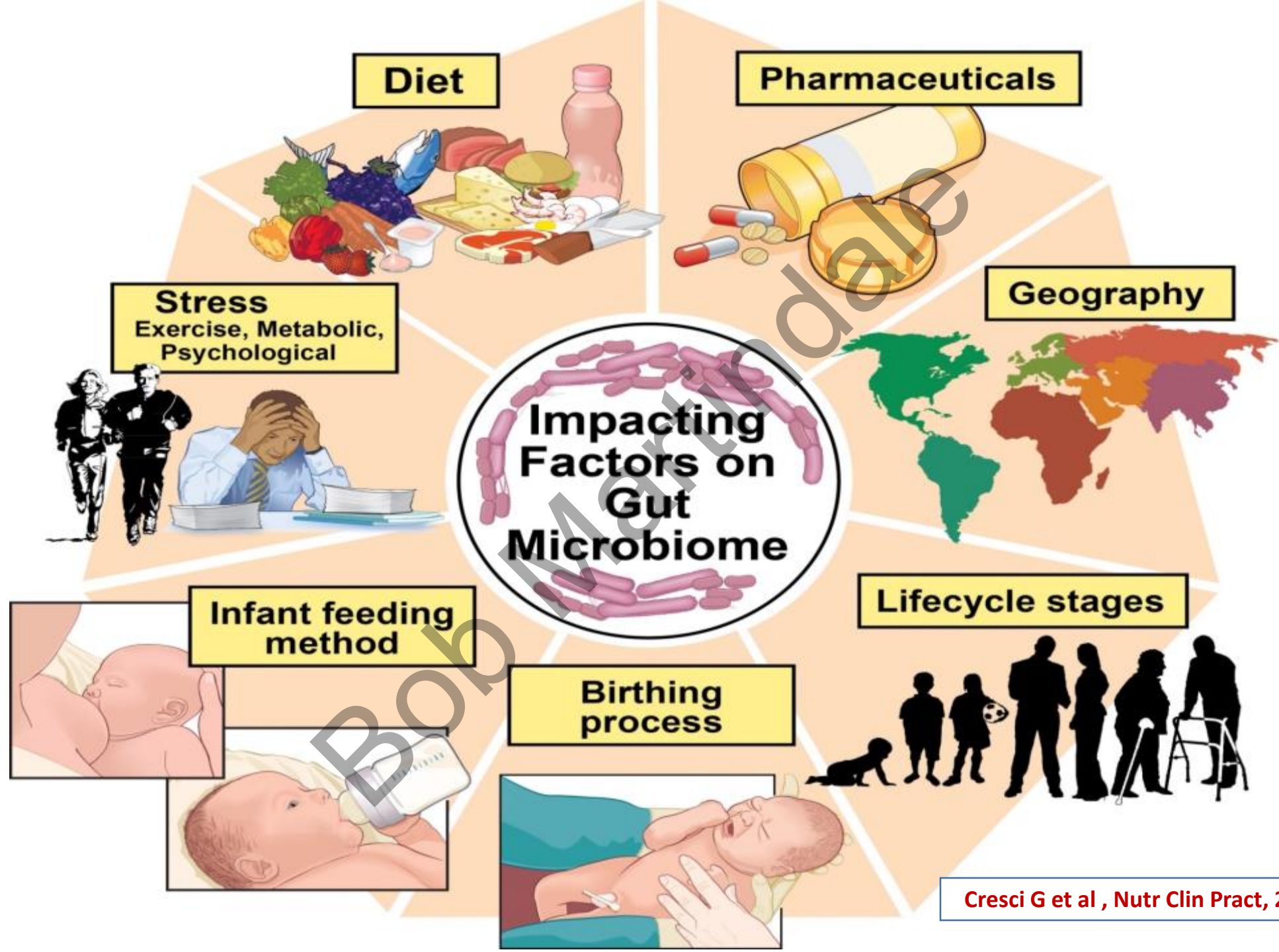
- Diabetes
- Obesity
- Metabolic syndrome
- Heart disease
 - atherosclerosis
- Neuropsychiatric
 - Depression
 - Anorexia nervosa
 - Alzheimer's
 - Parkinson's
- Hepatic diseases
 - Non-alcoholic fatty liver
 - cirrhosis
- Infectious disease
 - General, TB, Malaria
- Asthma
- Allergy
- Inflammatory Bowel Disease
- Autoimmune diseases
- Peptic ulcer disease
- HIV / AIDS
- Cancer
 - Carcinogenic diets
 - Metabolic effects (cachexia)
 - Metastasis
- Critical Care / Surgery
 - Trauma
 - Pancreatitis
 - Sepsis
 - ARDS / ALI
 - COVID
- Aging
- etc etc etc

The “Western” Diet and Lifestyle

Have we evolved fast enough ?

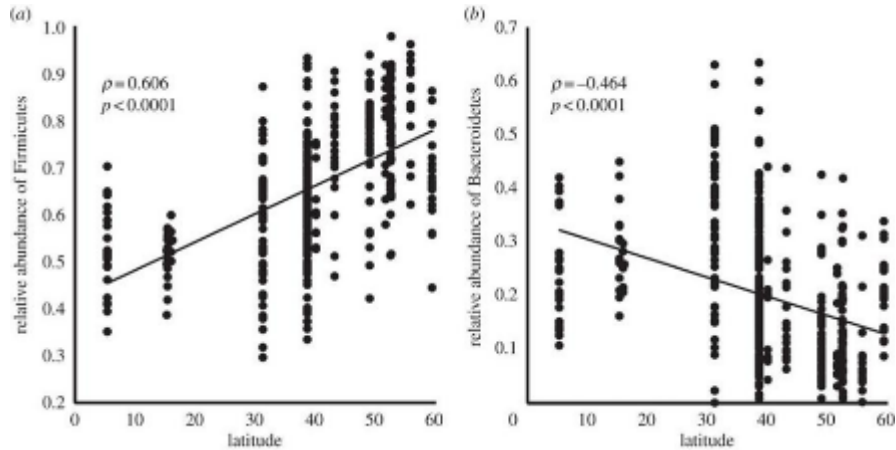
- Sedentary lifestyles
- Newborns in USA
 - 32.1% of live birth 2021 were via cesarean section
- Immunizations
- Domestic pets
- Decrease in parasitic infection
- Refrigeration
- Sanitation and hygiene standards
- Urban life in cities and concrete
- Increased use of antibiotics
 - Indicated or not !
 - Now beginning to understand “collateral damage” of antibiotics – mitochondrial toxin
- Dramatic changes in the way we feed our sick in patients
 - Processed foods to our sickest patients ?
- **Major dietary changes**
 - **Fats, protein, sugar, fiber, additives, emulsifiers, sweeteners, anti-oxidants, preservatives, refining grains, de-germination of grains**
 - “essentially processed energy dense foods”





It takes very little to rapidly change our microbiome

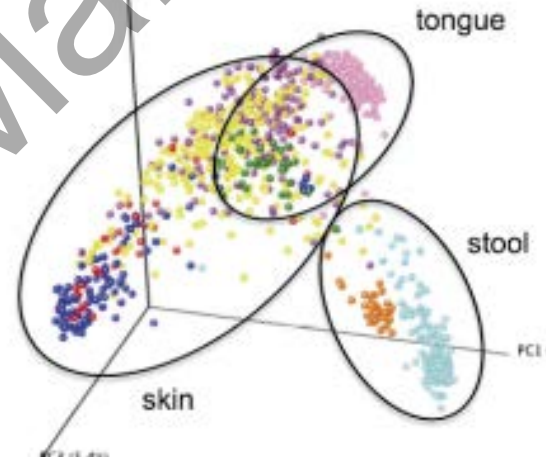
- International travel



- Cohabiting with pets

Cohabiting family members share microbiota with one another and with their dogs

Se Jin Song¹, Christian Lauber², Elizabeth K Costello³, Catherine A Lozupone^{4†b}, Gregory Humphrey², Donna Berg-Lyons², J Gregory Caporaso^{5,6}, Dan Knights^{7,8}, Jose C Clemente^{4†a}, Sara Nakielny⁹, Jeffrey I Gordon¹⁰, Noah Fierer^{1,2}, Rob Knight^{11,12*}





Can Whole Grains Really Decrease All Cause Mortality?

- **Aune D et al BMJ 2016**
 - 45 studies
 - **Decrease in all cause mortality (CVD, Ca etc)**
 - Modest amounts of fiber
 - 3 serving per day
- **Zong G et al Circulation 2016**
 - Prospective cohort studies **786,076 participants**
 - Whole grains
 - **Decrease all cause mortality**
 - **CVD, Cancer, etc**
- **Reynolds A et al Lancet 2019**
 - Series of systematic reviews and meta-analyses
 - 185 prospective trials, 58 clinical trials
 - 15 to 30% in cardiac disease, stroke, DM2, GI cancer----
 - appears to be a dose response
 - **Decrease all cause mortality**
- **Kwok SS et al European J Preventative Cardiology 2019**
 - Whole grains, fish, nuts, vegetables associated with **decrease all cause mortality**
- **English LK et al JAMA 2021**
 - 1 RCT, 152 observational studies.
 - Highly consistent – dietary patterns consuming:
 - Vegetables, fruits, legumes, nuts, whole grains, minimal meats
 - **Decrease all cause mortality**
- **Reynolds AN et al PLOS Medicine 2020**
 - Diabetes – Systematic review and meta-analysis
 - Improved glycemic control, blood lipids, inflammation markers
 - 15 to 35 gm fiber per day

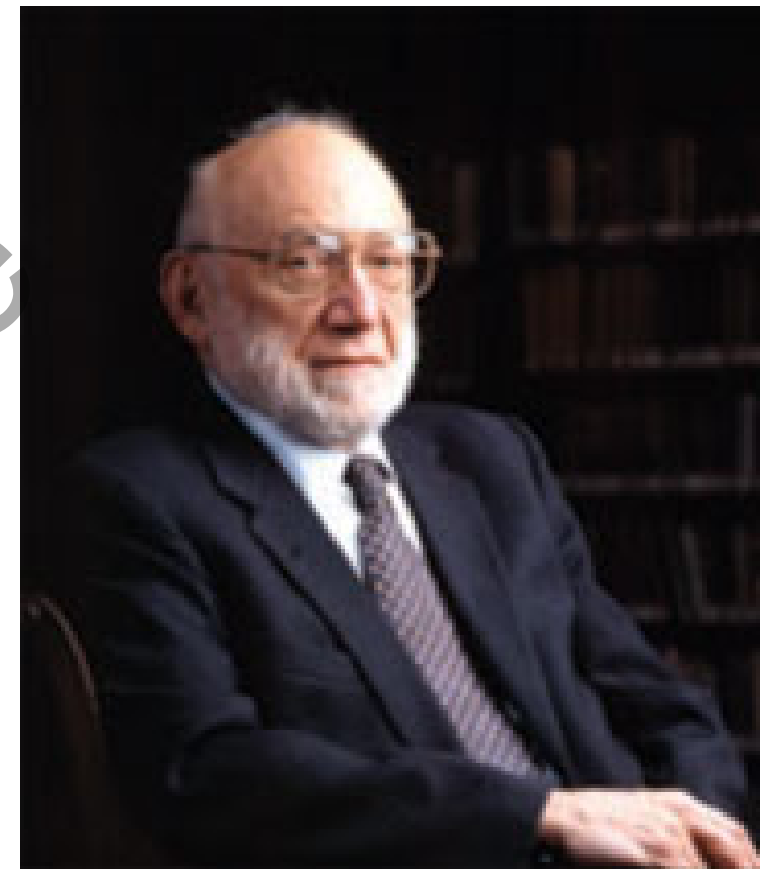


Human Microbiome

- Term suggested by Nobel Prize Winner Dr. Joshua Lederberg
- Described the collective genome of our indigenous microbes (microflora), the idea that a comprehensive genetic view of *homo sapiens* as a life form should include the genes of our microbiome
- Includes bacteria, fungi, archaea



99% of our total genome is absent at birth

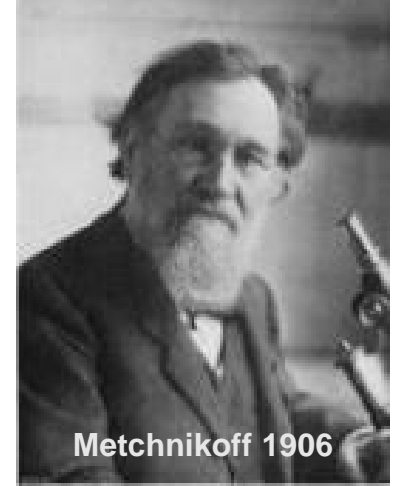


Joshua Lederberg, PhD
1925-2008

Where “man meets microbe” dynamic mutualism

- **Concepts are not new**

- Referenced in Bible, Koran and in ancient Hindu text
- Metchnikoff “father” of modern probiotic concepts



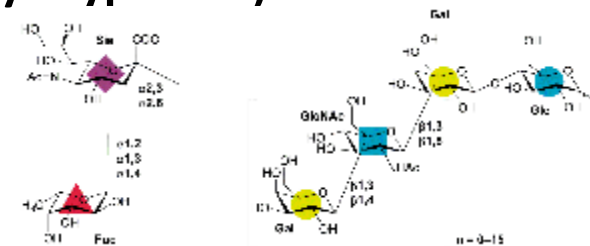
- **Surface area of GI tract 50 to 100 sq meters**

- **2 million genes in the bacterial genome vs 20,000 in the human**

- approximately 1.3 bacterial cell to 1.0 human cells
- Several thousand species in human colon, many non-culturable
- Extensive # of microenvironments (skin, R v L hand only have shared 17% phylotypes etc)
- Metagenomics is exploding now that it is cost effective

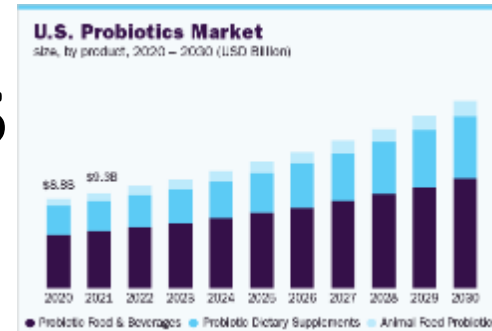
- **Exposed to “pro and prebiotics” from day one of life**

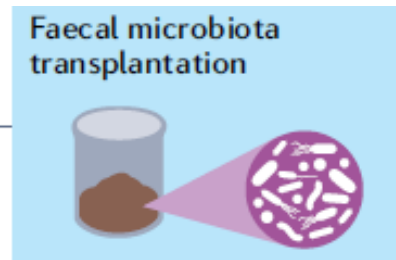
- 13 to 15% of CHO in breast milk not absorbed by infant



- **Probiotics expected to be >100 Billion \$ industry by 2025**

- Difficult to short reality from quackery





Faecal microbiota transplantation

- Transfer of faeces or complex communities derived by in vitro culture or purification of spores
 - Demonstrated efficacy for treatment of recurrent *Clostridioides difficile* infections
- Advantages: transfer of intact community, proven efficacy in clinic
 - Challenges: screening of donor samples, scalability, potential variability in efficacy depending on donor

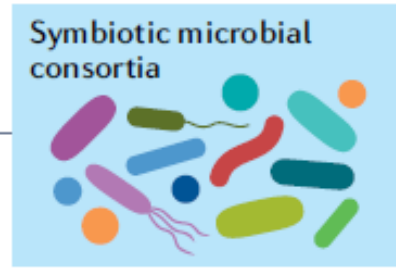
FMT



Diet and prebiotics

- Supplementation of microbiota-targeted substrates, such as specific dietary fibres to promote a desired compositional changes in the microbiota, or production of a desired metabolite
- Advantages: relatively easy to prepare, safety
 - Challenges: predicting outcomes of supplementation across different microbiota compositions, length of impact following supplementation, targeted species or activities must be present

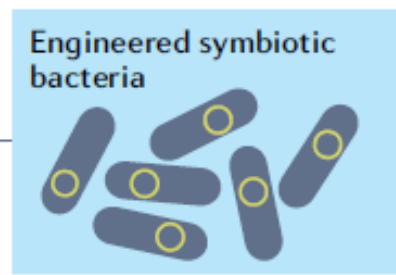
Prebiotics



Symbiotic microbial consortia

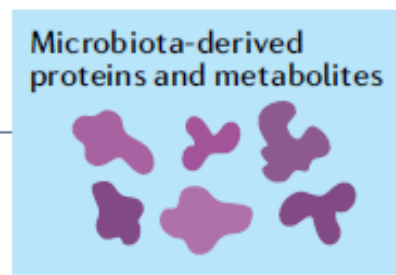
- Transfer of a group of isolates, selected or designed to promote specific microbiota functions
- Advantages: known composition of consortia, individual isolates and potentially self-sustaining community can be screened for safety
 - Challenges: isolate selection, replicating phenotypes emerging from complex bacterial interactions, growing desired isolates in culture

Synbiotics



Engineered symbiotic bacteria

- Transfer of bacteria that colonize the targeted site and are engineered to have a desired function or deliver a desired product or metabolite
- Advantages: potential for producing desired metabolites or compounds in the correct location using a platform strain background that could be engineered for multiple purposes
 - Challenges: limited ability to manipulate many species of the microbiota, have to demonstrate safety of modifications



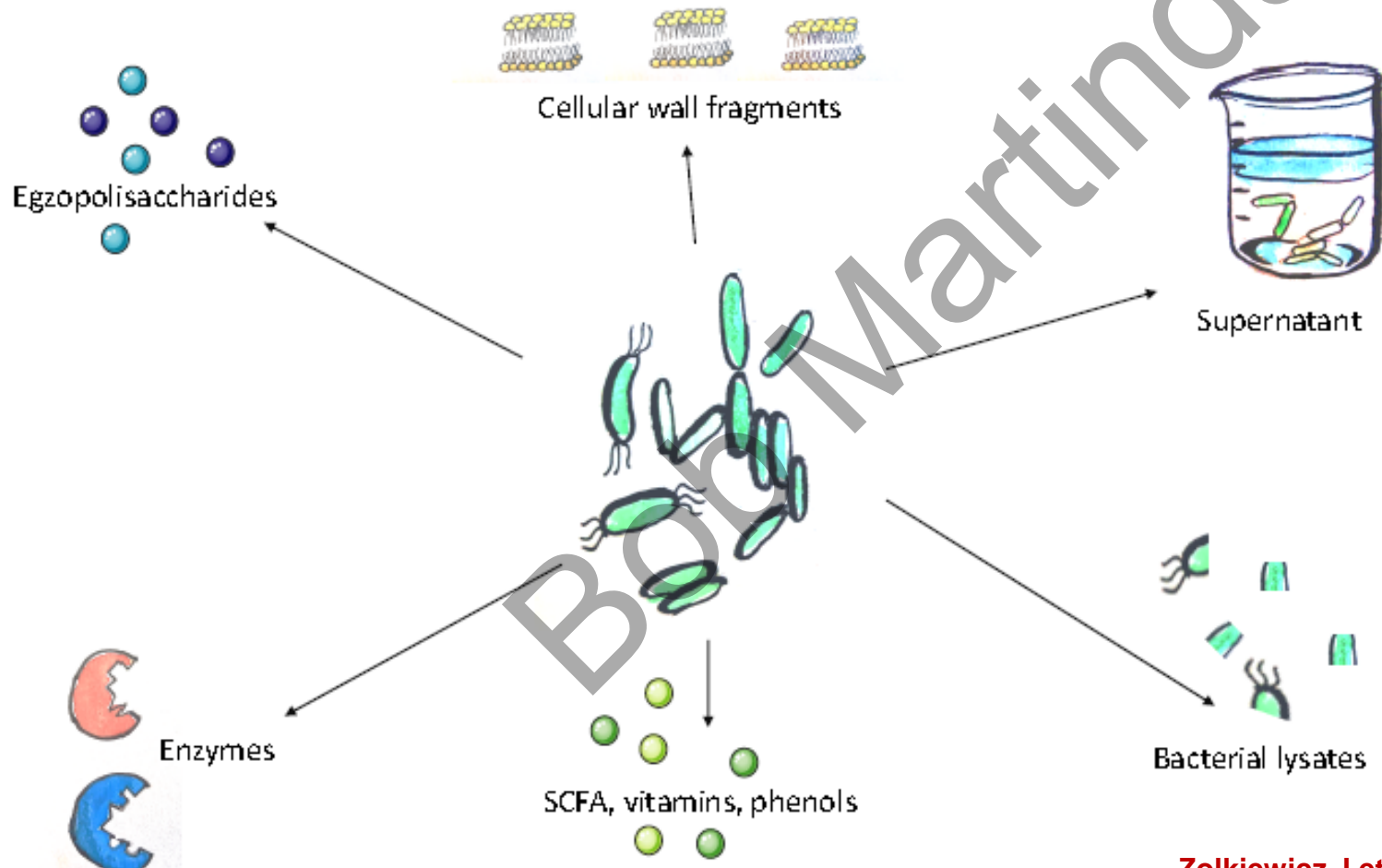
Microbiota-derived proteins and metabolites

- Direct supplementation with beneficial proteins or metabolites
- Advantages: relatively easy to prepare, assess safety, likely to follow conventional pharmaceutical development pathways
 - Challenges: determining and delivering adequate concentrations to desired site

Postbiotics

Postbiotics – can this answer some of the questions without the risk ?

- **Postbiotics** - are soluble factors (metabolites), secreted or generated by live bacteria during fermentation, or released after bacterial lysis providing physiological benefits to the host.

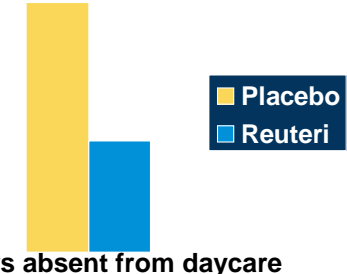
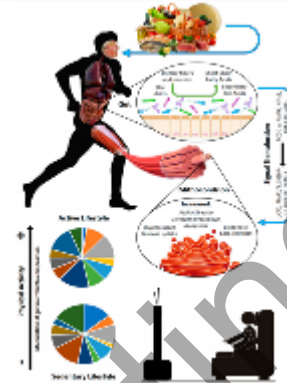


Note: NO live bacterial needed

Does Modulating the Microbiome Really Have Clinically Relevant Data to Support the Claims ?





- Enhancing immune response to viral challenge¹
- Short chain fatty production^{2,3,4}
 - Anti-inflammatory (local and systemic)
 - Enhance WBC function
 - Decrease insulin resistance
 - Decrease cancer development
 - Enhanced muscle function
 - Enhanced mitochondrial biogenesis
- Decrease sick days from work⁵
- Decrease duration of URI symptoms⁶
- Decrease antibiotics, MD visits, missed preschool⁷
- Decrease gestational DM⁸
- Decrease necrotizing enterocolitis
- C. difficile (preventative > treatment)
- VAP +/- (majority of data +)
- Post op surgical infections¹⁰
- Prevention of pediatric sepsis¹¹



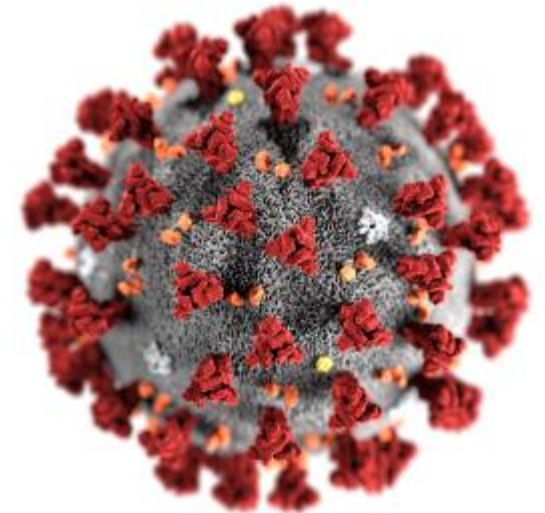
1. Razzardini G et al Br J Nutrition 2012
2. Bhat M et al Nutrition Reviews 2017
3. Scheiman J et al Nature Medicine 2019
4. Tecinesi A et al Nutrients 2017
5. Tubeilus P et al Environ Health 2005
6. Hao Q et al Cochrane 2015
7. Weizman et al Pediatrics 2005
8. Lindsay KL et al J Maternal-Fetal Med 2013
9. Janviar A et al J Pediatrics 2014
10. Martindale R et al Surgical Infections 2018
11. Panigraphi P et al Nature 2017

Probiotic improves symptomatic and viral clearance in Covid19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial

Pedro Gutiérrez-Castrellón ^{a,b}, Tania Gandara-Martí^a, Ana T. Abreu Y Abreu^c, Cesar D. Nieto-Rufino^a,
Eduardo López-Orduña^d, Irma Jiménez-Escobar^a, Carlos Jiménez-Gutiérrez^a, Gabriel López-Velazquez^b,
and Jordi Espadaler-Mazo ^e

Gut Microbes
2022

- n = 300 probiotics vs placebo
- Endpoints followed
 - Complete viral remission
 - % progressing to moderate of severe disease and/or death
 - Days required in ICU
- Probiotics
 - Increases IgM, IgG against SARS-CoV2
 - Reduced nasopharyngeal and lung viral load
 - Reduced symptoms



A randomized synbiotic trial to prevent sepsis among infants in rural India

Pinaki Panigrahi^{1,2}, Sailajanandan Parida³, Nimai C. Nanda⁴, Radhanath Satpathy⁵, Lingaraj Pradhan⁶, Dinesh S. Chandel⁷, Lorena Baccaglini¹, Arjit Mohapatra⁵, Subhranshu S. Mohapatra⁵, Pravas R. Misra⁵, Rama Chaudhry⁸, Hegang H. Chen⁹, Judith A. Johnson¹⁰, J. Glenn Morris Jr¹⁰, Nigel Paneth¹¹ & Ira H. Gewolb¹²

- **RDBPCT of *L. plantarum* + FOS** n=4,556 infants >2,000gm, 35wk gestation
- **WHO criteria for sepsis, NIH funded** 42% reduction in sepsis 1 week of tx \$1

Table 2 | Effect of synbiotic treatment on sepsis and other morbidities in the first 60 days of life

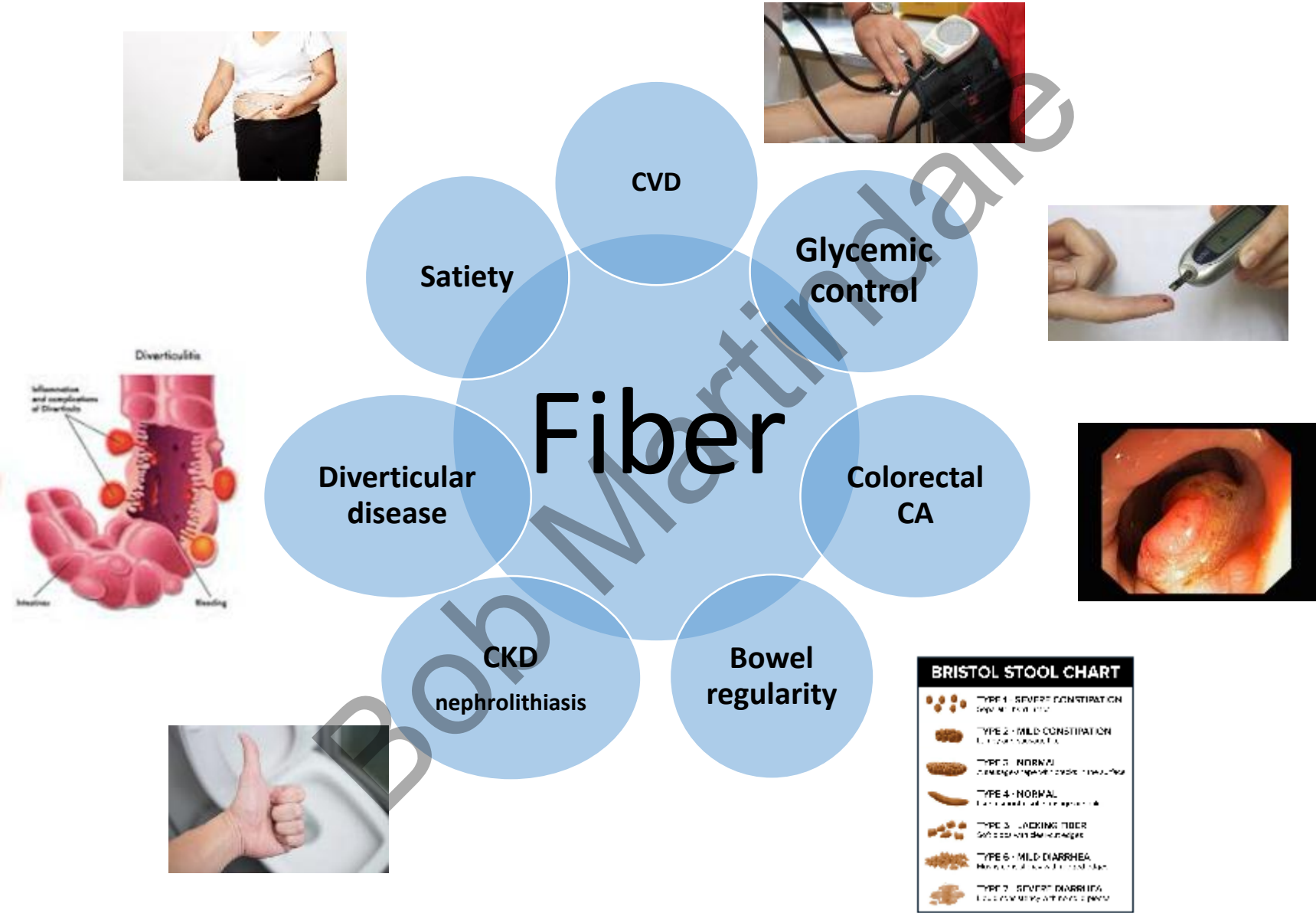
Outcome variables	Control n= 2,278 (%)	Synbiotic n= 2,278 (%)	RR (95% CI)	NNT (95% CI)	P value
Death and sepsis (primary outcome)	206 (9.0)	123 (5.4)	0.60 (0.48, 0.74)	27 (19, 47)	<0.001
Deaths	4 (0.2)	6 (0.3)	1.50 (0.42, 5.31)	NA*	0.526†
Sepsis (A + B + C)	202 (8.9)	117 (5.1)	0.58 (0.46, 0.72)	27 (19, 44)	<0.001
A. Sepsis/pSBI—culture-positive septicaemia	27 (1.2)	6 (0.3)	0.22 (0.09, 0.53)	108 (71, 232)	<0.001
Gram-negative sepsis	16 (0.7)	4 (0.2)	0.25 (0.08, 0.75)	190 (110, 699)	0.007
Gram-positive sepsis	11 (0.5)	2 (0.1)	0.18 (0.04, 0.82)	253 (142, 1,169)	0.012
B. Sepsis/pSBI— culture-negative sepsis (Culture-negative clinical sepsis warranting hospitalization and IV antibiotics)	36 (1.6)	19 (0.8)	0.53 (0.30, 0.92)	134 (72, 890)	0.021
C. Sepsis/pSBI—LRTI (LRTIs requiring antibiotic therapy)	139 (6.1)	92 (4.0)	0.66 (0.51, 0.88)	48 (30, 126)	0.002
Diarrhoea	59 (2.6)	12 (0.5)	0.20 (0.11, 0.38)	48 (36, 74)	<0.001
Local infections (including >10 pustules, oral thrush, conjunctivitis)	33 (1.5)	16 (0.7)	0.48 (0.27, 0.88)	134 (74, 677)	0.015
Abscess/ otitis media	11 (0.5)	5 (0.2)	0.45 (0.16, 1.33)	NA*	0.133*
Omphalitis	13 (0.6)	3 (0.1)	0.23 (0.07, 0.81)	228 (128, 1,045)	0.014

Prebiotics in microbiome manipulation:

- **Prebiotics – manipulation of the gut lumen environment**
 - Minimizing conversion of microbiome to pathobiome and decreasing colonization pathogens
 - Metabolite products
 - Butyrate – pleomorphic benefits: local and systemic
 - Milk sugars -Selectively enhance desired bacteria
 - Breast milk contains 15% non absorbable CHO
 - Fermented products provides optimal pH preventing dysbiosis
 - Alters glycosylation of epithelial cells limiting infections/pathogen binding
 - Stimulates mucous synthesis and secretion
 - Helps preserve barrier function
 - Example: *L. salivarius* increases tight junction proteins



Benefits of fiber (prebiotics) in healthy and patients



Processed foods and then hospitalization is a two hit model for trouble !

Mice Fed an Obesogenic Western Diet, Administered Antibiotics, and Subjected to a Sterile Surgical Procedure Develop Lethal Septicemia with Multidrug-Resistant Pathobionts

mBIO 2020

Sanjiv K. Hyoju,^a Alexander Zaborin,^a Robert Keskey,^a Anukriti Sharma,^{a*} Wyatt Arnold,^{a*} Fons van den Berg,^{a,b} Sangman M. Kim,^c Neil Gottel,^{a*} Cindy Bethel,^d Angella Charnot-Katsikas,^d Peng Jianxin,^{a,e} Carleen Adriaansens,^{a,f} Emily Papazian,^a Jack A. Gilbert,^{a*} Olga Zaborina,^a John C. Alverdy^a



Dietary supplementation with non-fermentable fiber alters the gut microbiota and confers protection in a murine model of sepsis

Michael Morowitz, MD^{1,2}, Valentina Di Caro, PhD³, Diana Pang, MD^{3,4}, Jessica Cummings³, Brian Firek, MS¹, Matthew B. Rogers, PhD¹, Sarangarajan Ranganathan, MD⁵, Robert S. B. Clark, MD^{3,4}, and Rajesh K. Aneja, M.D.^{3,4}

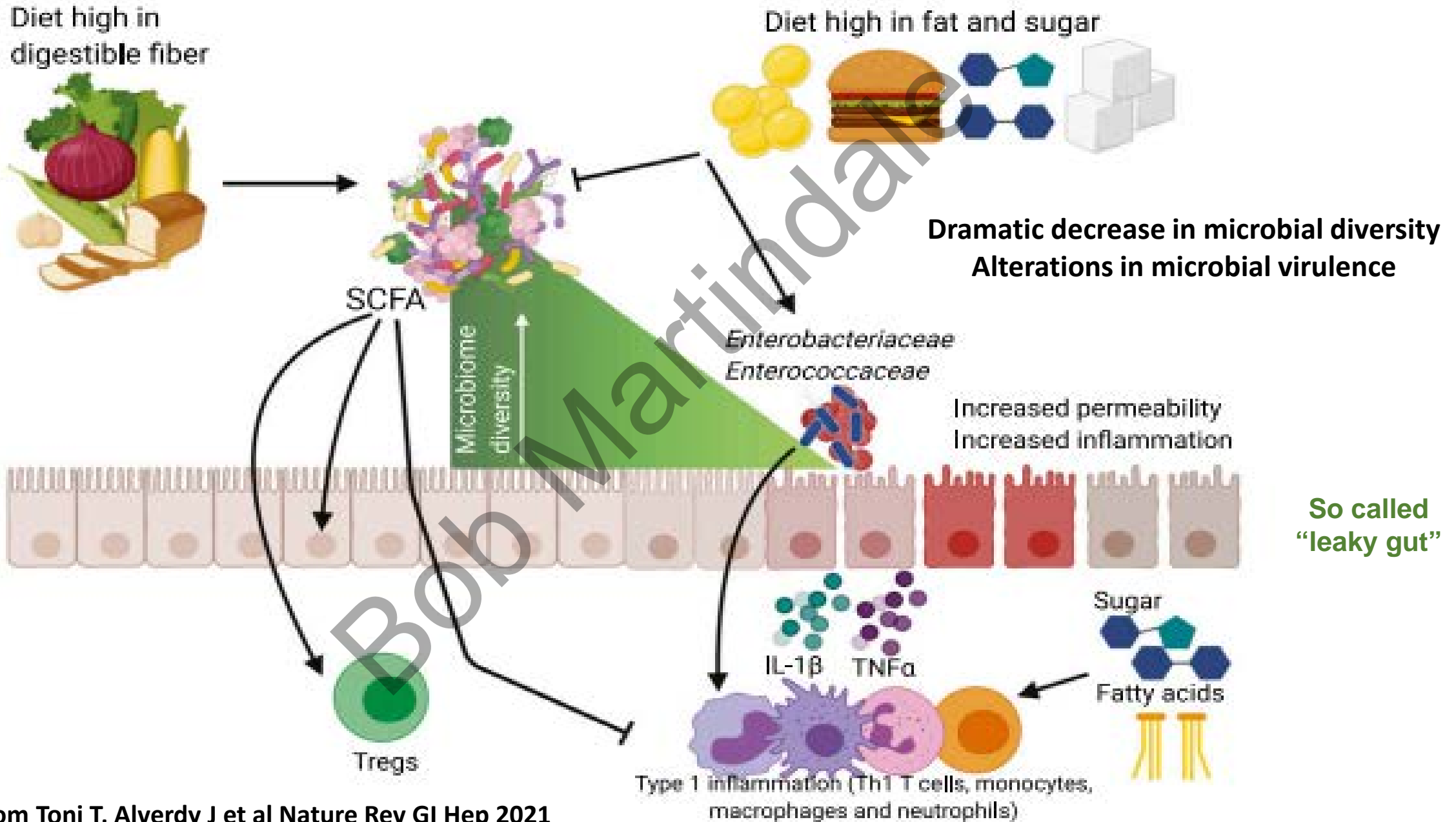
Critical Care Medicine 2017

The non-fermentable fibers are also beneficial !



- Murine model: 3 groups, 2 sepsis models (CLP, Endotoxin)
 - High fiber vs normal fiber vs no fiber , +/- antibiotics
- **Conclusions:**
 - High fiber increased survival, decrease inflammation etc
 - High fiber increased Akkermansia and Lachnospiraceae
 - Antibiotics negated benefits of fiber



Are our diets setting us up for gut derived excessive inflammatory response ?



Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model

S. K. Hyoju¹, C. Adriaansens^{1,2}, K. Wienholts^{1,2}, A. Sharma¹, R. Keskey¹, W. Arnold¹, D. van Dalen^{1,2}, N. Gottel¹, N. Hyman¹, A. Zaborin¹, J. Gilbert¹, H. van Goor², O. Zaborina¹  and J. C. Alverdy¹ 

Departments of Surgery, ¹University of Chicago, Chicago, Illinois, USA, and ²Radboud University Medical Centre, Nijmegen, the Netherlands

Correspondence to: Professor J. C. Alverdy, Department of Surgery, University of Chicago, 5841 S Maryland MC6090, Chicago, Illinois 60625, USA (e-mail: jalverdy@surgery.bsdu.uchicago.edu)

Short course (2 days) of high fiber diet prevented anastomotic leaks in colorectal anastomosis

British J Surg 2020



Low-fat/high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model

S. K. Hyoju¹, C. Adriaansens^{1,2}, K. Wienholts^{1,2}, A. Sharma¹, R. Keskey¹, W. N. Gittel¹, N. Hyman¹, A. Zaborin¹, J. Gilbert¹, H. van Goor², O. Zaborin¹

Departments of Surgery, ¹University of Chicago, Chicago, Illinois, USA, and ²Radboud University Medical Center, Nijmegen, The Netherlands
Correspondence to: Professor J. C. Alverdy, Department of Surgery, University of Chicago (e-mail: jalverdy@surgery.bsduchicago.edu)

JAMA Surgery | Original Investigation

Association of Habitual Preoperative Dietary Fiber Intake With Complications After Colorectal Cancer Surgery

Dieuwertje E. Kok, PhD; Melissa N. N. Arron, MD; Tess Huibregtse, BSc; Flip M. Kroyt, MD; Dirk Jan Bac, MD, PhD; Henk K. van Halteren, MD, PhD; Ewout A. Kouwenhoven, MD, PhD; Evertine Wesselink, MSc; Renate M. Winkels, PhD; Moniek van Zutphen, MSc; Fränzel J. B. van Duijnhoven, PhD; Johannes H. W. de Wilt, MD, PhD; Ellen Kampman, PhD

JAMA Surgery 2021

British J Surg 2020



Perioperative Probiotics or Synbiotics in Adults Undergoing Elective Abdominal Surgery

A Systematic Review and Meta-analysis of Randomized Controlled Trials

Abeed H. Chowdhury, PhD, FRCS, Alfred Adiamah, MRCS,* Anisa Kushairi, BMedSci, BM BS,*
Krishna K. Varadhan, PhD, MRCS,* Zeljko Krznaric, MD, PhD,† Anil D. Kulkarni, MSc, PhD,‡
Keith R. Neal, DM, FRCP,§ and Dileep N. Lobo, DM, FRCS, FACS, FRCPE* ¶✉*

34 RCT n=2753

1354 treated with Synbiotics or Probiotics

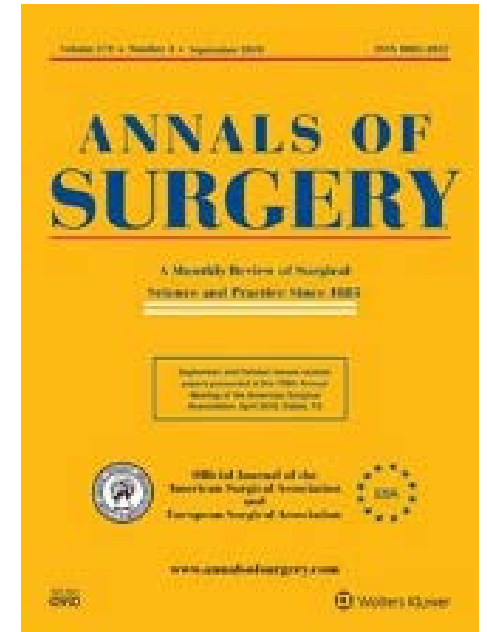
1369 control

Synbiotics and Probiotics decrease risk of infections 56% $p < 0.00001$

Synbiotics > than probiotics alone $p < 0.00001$

Conclusions:

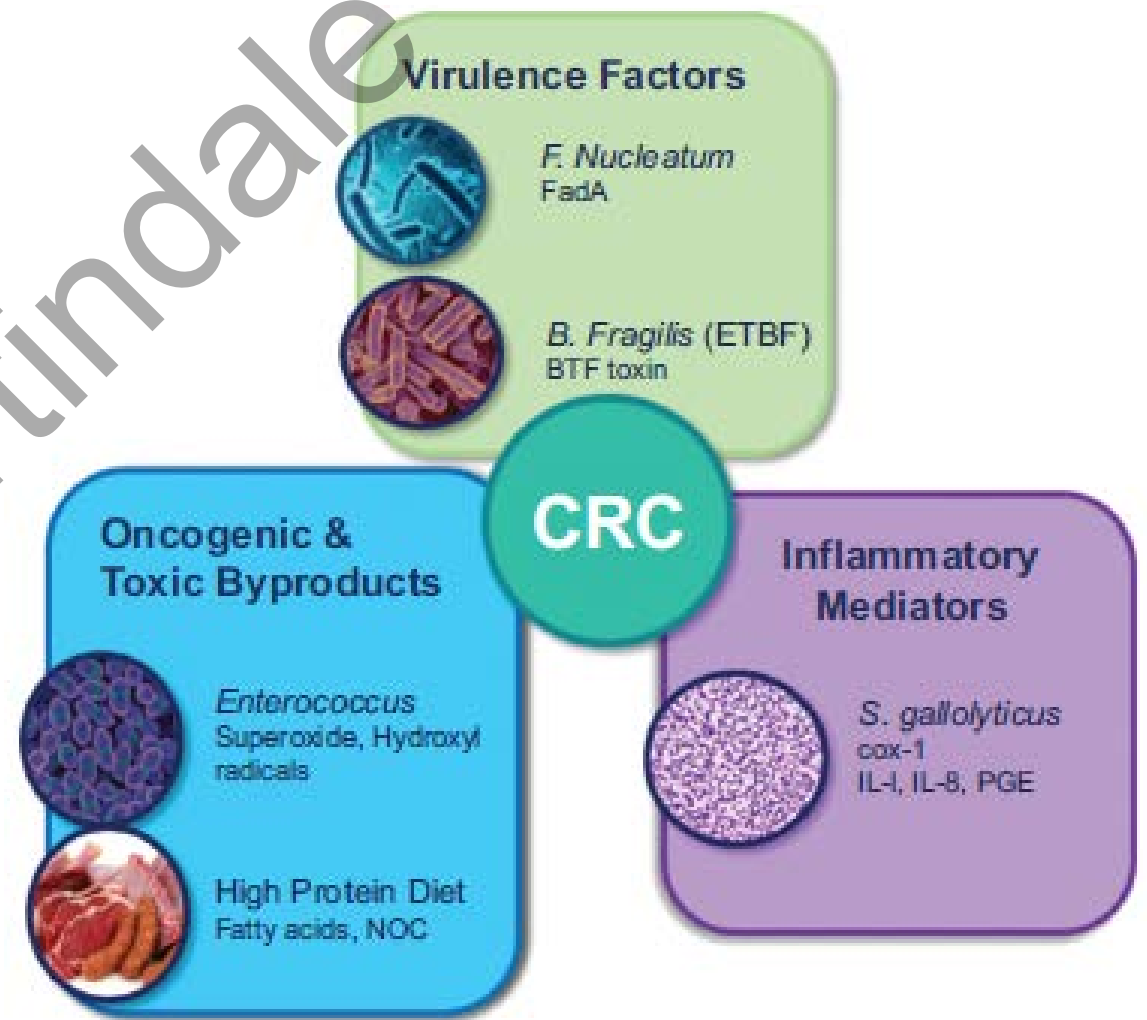
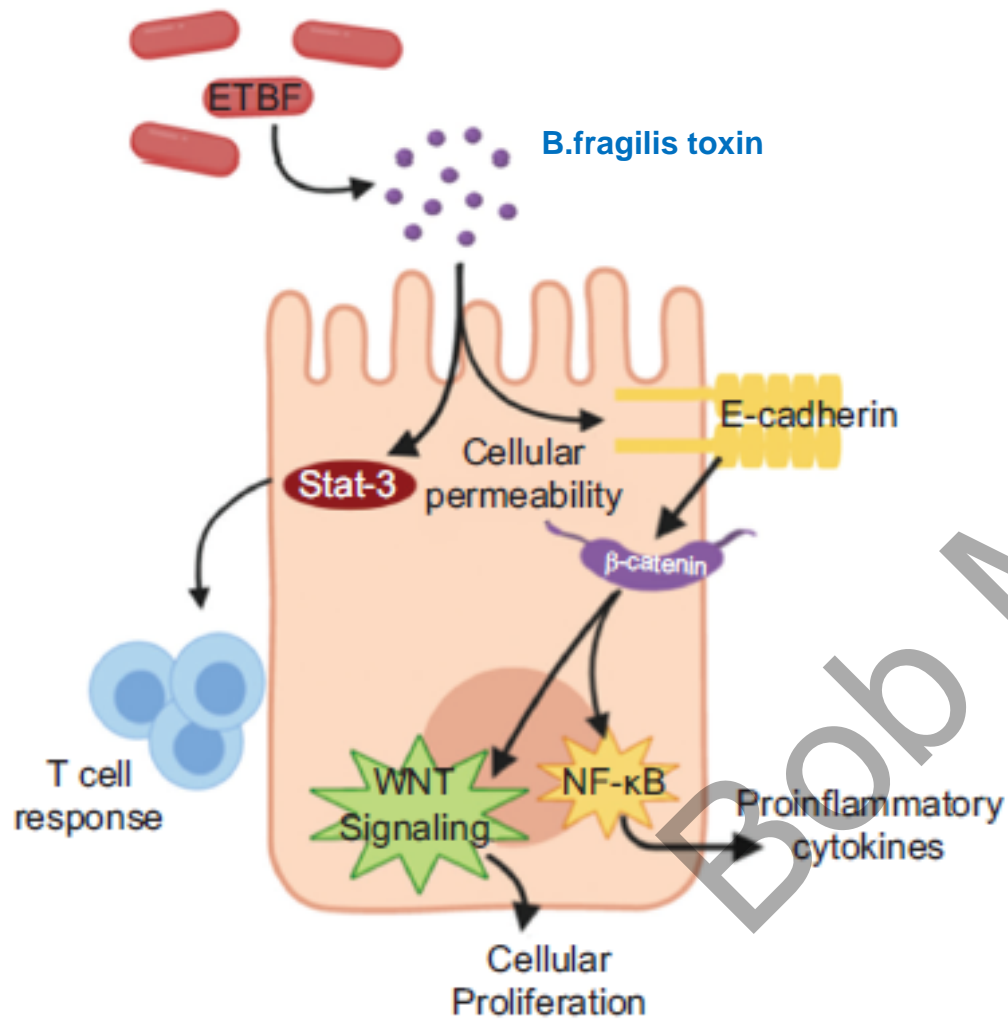
- 1) Synbiotics and Probiotics decrease infections, LOS**
 - No adverse effects reported**
- 2) No change in mortality**



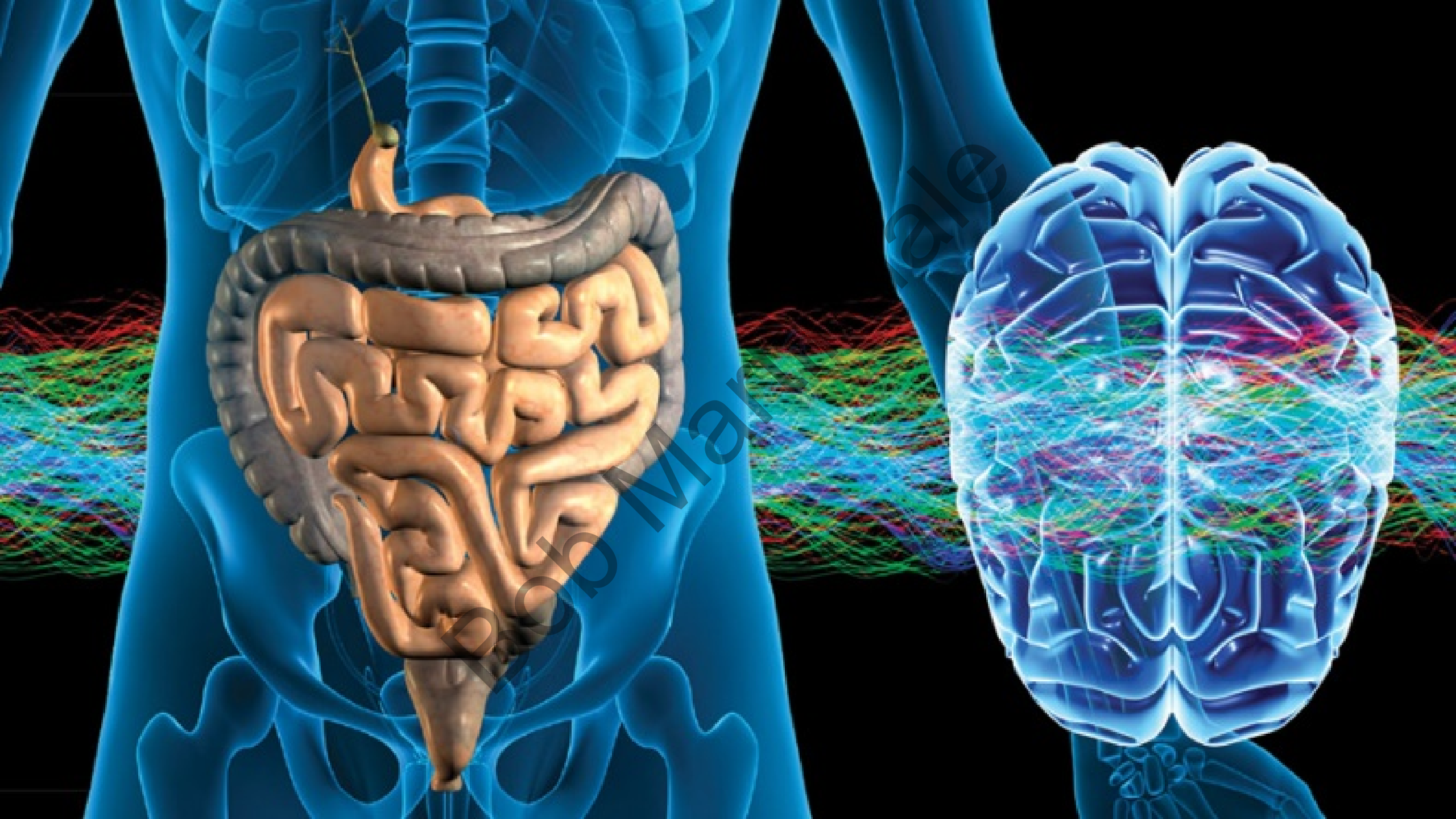
2020

Understanding the microbiome: a primer on the role of the microbiome in colorectal neoplasia

Annals of Gastroenterology 2020



ETBF- enterotoxigenic Bacteroides fragilis
 STAT3 – signal transduce and activator of transcription 3



THE PSYCHIC LIFE
OF
MICRO-ORGANISMS

A STUDY IN EXPERIMENTAL PSYCHOLOGY

BY
ALFRED BINET

PROPERTY OF
RUPERT

CHICAGO
THE OPEN COURT PUBLISHING COMPANY
(London: 27 John Street, Fleet St., E.C.)

1911

- **The Gut Brain connection is not new !**

- From 1914: "The control of man's diet is readily accomplished, but mastery over his intestinal bacterial flora is not... They are the cases that present...malaise, total lack of ambition so that every effort in life is a burden, mental depression often bordering upon melancholia...A battle royal must be fought and when this first great struggle ends in victory for the *Bacillus bulgaricus* it must be kept on the field of battle forever at guard..."

- Stow, Medical Record Journal of Medicine and Surgery, 1914

“on autointoxication and *Lactobacillus bulgaricus*”

Bond Stow 1914

Microbiome and Brain Function

“Gut-Microbiota-Brain Axis”



Recently shown to alter:

- **Behavior**
 - Anxiety, depression
 - Learning, memory
- Neurogenesis
- Neuroplasticity
- Microglial activity
- Blood Brain Barrier integrity
- Attention deficit hyperactivity disorder
- Parkinson's
- Epilepsy (seizure control)
- Social anxiety disorder



High Quality Human data
currently available for:

Anxiety / stress
Depression
OCD / ADHD

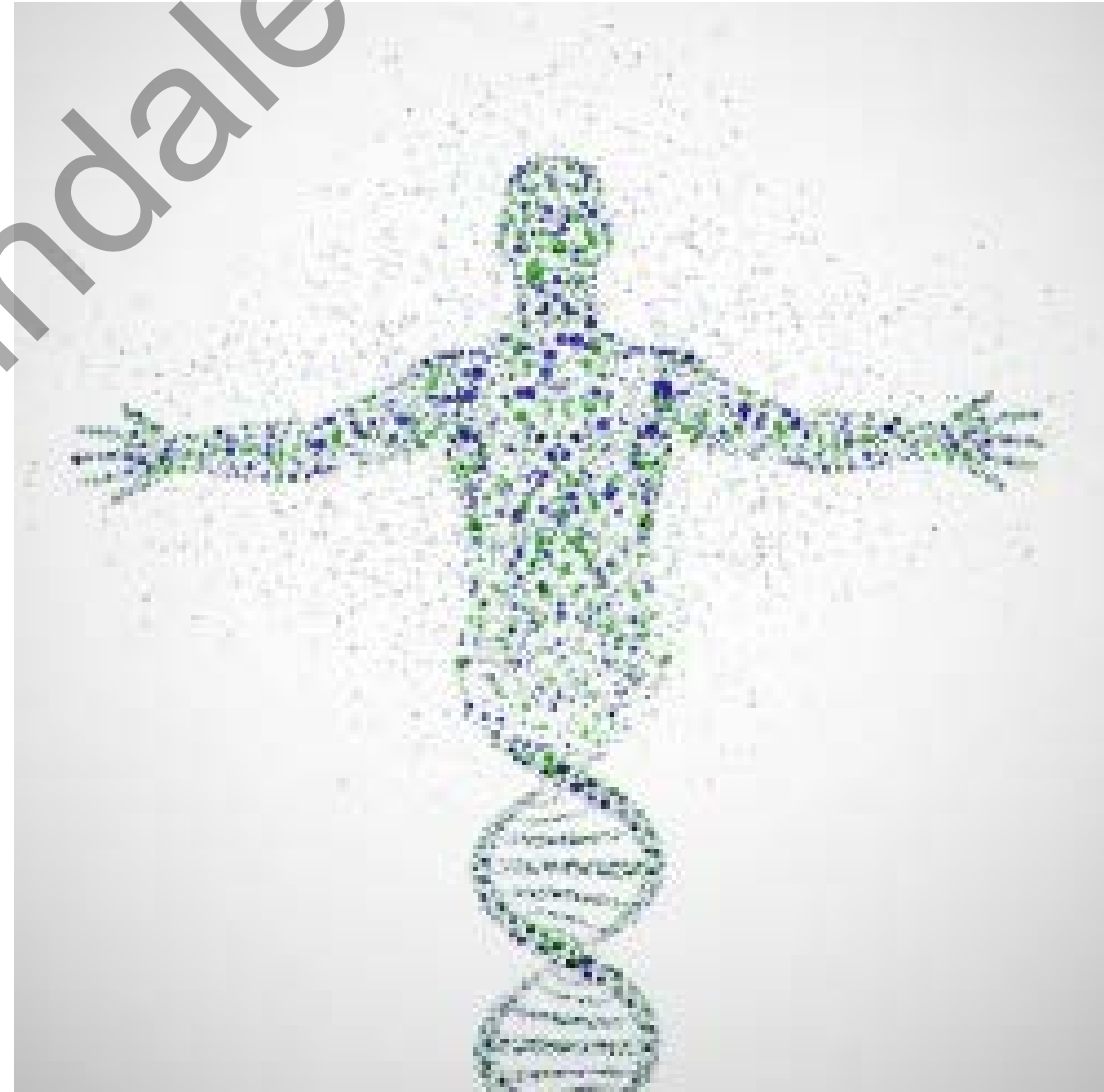
Growing quantity and
quality of data for:

Autism
Social anxiety disorder

Cryan FJ et al Nature Rev Neuroscience 2012
Minter MR et al Sci Rep 2016
Mayer EA et al Ann Rev Med 2022
Keefer L et al Gastroenterology 2022
Nandwana V et al Nutrients 2022
Butler MI et al Translational Psychiatry 2023

In 2023 we need to think of the microbiome as another organ: A stable microbiome is critical in maintaining the local and systemic immune system as well as controlling systemic inflammation !

- **Functions of microbiome:**
 - Metabolizes drugs
 - Produces and metabolizes nutrients
 - Vitamins (folate, vitamin K)
 - SCFA-multiple metabolic effects
 - Amino acids
 - Provides up to 10% of daily calories from SCFA
 - Stimulation of hormone secretion
 - Modulates immune function
 - Maintains mucosal barrier function
 - Modulates systemic inflammation
- **If microbiome not maintained:**
 - Dramatic **decrease** in microbial diversity
 - Alterations in microbial virulence
 - Phenotypic switch in microbiome to **“pathobiome”**

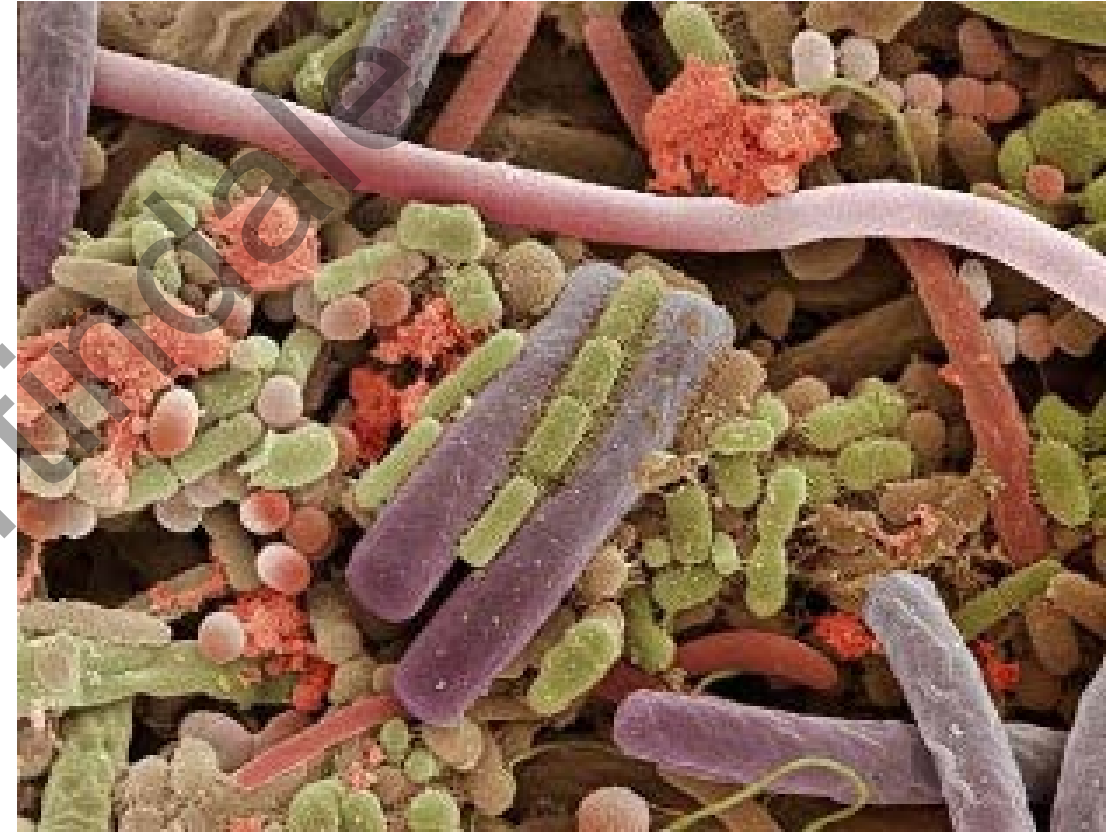


Bacterial (probiotic) Strains with Significant #s of Supportive Clinical Published Data in Clinical Populations

- Lactobacillus rhamnosus
- Bifidobacterium lactis BB-12
- L. casei 431
- L. acidophilus LA-5
- L. salivarius UC118
- L. plantarum
- B. animalis lactis
- L. reuteri
- Akkermansia mucinophilia

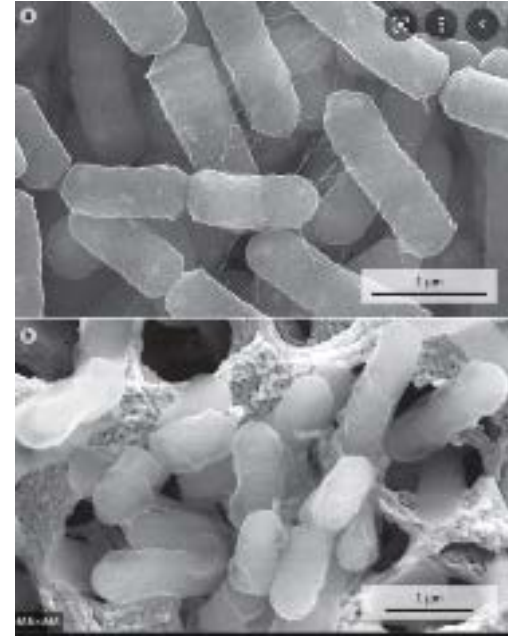
- Disclaimer:

- many other probiotic have published data to support in specific disease and health states
- Some effects are strain specific effects
- Strain “drift” is real



Limitations of Viable Probiotics

- **Probiotics must survive the GI tract**
 - Survival to IC valve 1% to 90% depending on species
- **Colonization resistance**
 - Host factors and compositional patterns of baseline microbiota
 - Example: *L. rhamnosus* GG of human origin with marginal data that it can permanently colonize
 - Processing for “packaging and distribution” alter viability of bacteria
- **What about safety**



It is all about “Risk vs. Benefit”



Safety of Probiotics



- > 750 human clinical trials from the last 14 years (2008-2022)
- Quantity and nature of the reported adverse events (AEs)
 - AE= occurrence of a complication or illness, or worsening of the condition throughout the study
- Examined 60> different strains of bacteria
- Virtually no significant attributable morbidity or mortality
- Conclusion (2)
 - The use of probiotics seems to play a role in decreasing the incidence of ICU-acquired infections. Also, a potential reduction in terms of the incidence of diarrhea has been reported, with no examples of adverse incidents, **suggesting probiotics are safe**

• 1) Van den Nieuwboer M et al, *Benef Microbes*, 2015

• 2) Alsuwaylihi AS et al *Nutrition Reviews* 2022

Strains

L. plantarum [CGMCC no.125]
L. acidophilus-1
B. longum-8
B. longum (unspecifie
L. rhamnosus GR
L. plantarum 299 (Lp299) (DSM 659
L. casei LBC80F
L. acidophilus CL128
Pediococcus pentosaceus 533
Leuconostoc mesenteroides 327
L. plantarum 236
L. paracasei 1
B. breve (unspecifie
L. rhamnosus G
S. thermophilus (unspecifie
L. bulgaricus (unspecifie
Saccharomyces boulardii
L. acidophilus (unspecifie
B. bifidum (unspecifie
L. casei (unspecifie
L. casei Shiro
L. rhamnosus R001
L. acidophilus R005
E. coli Nissle 1917
L. johnsonii La
Bacillus coagulans GBI-30, 608
L. reuteri C-1
B. longum BB536
Streptococcus faecalis
B. breve Yakult
L. plantarum 8PA
L. acidophilus L1
B. lactis B5
L. reuteri ATCC 5573
Enterococcus faecalis
Streptococcus salivarius K1
Trichuris suis O1
S. thermophilus KB2
Lactococcus lactis W5
L. salivarius W2
L. rhamnosus HN001
L. rhamnosus CAN
L. plantarum ATCC 10299
L. plantarum (unspecifie
L. paracasei (unspecifie
L. casei W5
L. acidophilus W7
L. acidophilus KB3
Bifidobacterium (unspecifie
B. longum KB3
B. lactis Bi-07
B. infantis W5
B. infantis (unspecifie
B. bifidum W2

Recently presented paper at American College of Chest Physicians Nashville Tennessee October 19, 2022

Presentor S. Mayer MD

- **Press release “Probiotics increase bacteremia in ICU populations”**
- **All from large administrative database, No SOFA, APACHE, NUTRIC, or other indicators of severity of ICU illness**
 - N=25,533 over 5 years
- **Deep dive into cases:**
 - Only noted in those receiving powdered product
 - Did not differentiate by species of which bacteria involved in bacteremia
 - *Sarcomyces bulardii* – not a true probiotic know to increase risk (CDC black box warning)
 - Spore forming organism

Harms Reporting in Randomized Controlled Trials of Interventions Aimed at Modifying Microbiota

A Systematic Review

Aïda Bafeta, PhD; Mitsuki Koh, MPH; Carolina Riveros, MSc; and Philippe Ravaud, MD, PhD

- **Evaluated 384 trials**
 - Combined ICU, inpatient and outpatient
- **Conclusion:** Harms reporting in published reports of RCTs assessing probiotics, prebiotics, and synbiotics often is lacking or inadequate. We cannot broadly conclude that these interventions are safe without reporting safety data

Few trials collect or report adverse events well !!

To summarize the limitations with the probiotic literature in the hospitalized patients:

Lots of room for improvement

- **Efficacy**- most studies report positive results, VAP widely variable
- **Safety**- lack of consistent reporting of adverse events
- **Mechanisms** – animal models excellent with proof of concept, humans difficult to show causal link between intervention and improved outcome
- **Heterogeneity**- of microbes and patients
 - Wide variability in the composition (strain drift)
 - Viability and function of specific bacteria not universal
 - Probiotic delivery with or without prebiotics
- **Dosing** - probiotic preparations widely variable
- **Small study sizes** - most studies
- **Failure to overcome confounding factors** –
 - Concomitant medications, comorbidities, treatments, during ICU stay etc

Vehicle for Delivery:

(Tablets, capsules, sachets, wafers, fermented milks or drinks, in yogurts, cheese, even chocolates)



Yogurt	Pills or Capsules
<ul style="list-style-type: none">• Contains nutrients that may protect the viability of the probiotic (protein, prebiotic)• Contains additional nutrients that are beneficial to the patient (protein, prebiotic, calcium, vitamin D etc.)• Perceived benefit by family and/or patient for receiving “real food”• No AEs associated with food source probiotic	<ul style="list-style-type: none">• Reliable CFU count (reputable brand)• Targeted and selective therapy• Can still be given if patient is NPO• May be an alternative for patients with food allergies or intolerances

Recent OHSU data showing more viable probiotic when taken with yogurt

Gutgsell J, Warren M , Gillingham M, Lasarev M, Martindale R 2021 in review

Clinical modifiers of the microbiome in 2023



- **We do not understand the microbiome well enough to manipulate all hospitalized populations**
 - Need more information on functionality down to the strain level
 - Caution with microbiome literature as heterogeneity is widely variable
- **We have not yet been able to define the ideal community of microbes**
 - **We can define a healthy set of metabolic functions**
 - **We can say that increased microbial diversity is associated with better outcomes**
 - **We cannot extrapolate one probiotic strain to another**
 - **Many mechanisms are strain or metabolite specific**
 - It appears that probiotics, prebiotics and postbiotics are **relatively safe**
- **Probiotics as preventative treatment in high risk patients appears to yield the best current applications**

Microbiome interventions on the horizon

- **Attempt to minimize or control the release of “cues” from the stressed host to the microbiota**
 - Minimize opioids to decrease conversion to pathobiome
 - Minimize antibiotic to prevent colony destruction
 - Maintain gut perfusion
 - Provide enteral nutrients that support a healthy microbiome – prebiotics ---- butyrate
- **Novel approaches to maintain “healthy” microbiome**
 - Maintaining colonic lumen phosphate levels (peg conjugated -phosphate)
 - Tributyrin supplementation
 - IV butyrate
 - Blenderized “food based” formulations in the to support healthy microbiome
- **The future looks promising with microbiome- based therapeutics. As the science progresses from FMT to the delivery of precisely defined and clinically validated synbiotic microbial / fermentable substrate that optimize disease prevention and resistance**

Why do current strategies for optimal nutritional therapy neglect the microbiome?

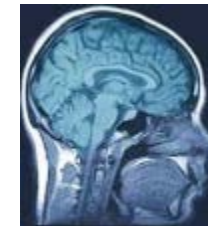
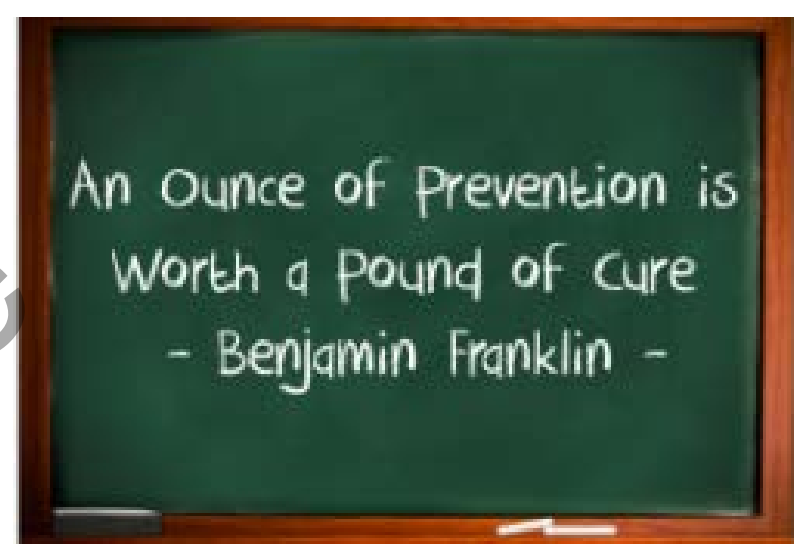
Stephen A. McClave M.D.^{a,*}, Robert G. Martindale M.D., Ph.D.^b **Nutrition 60:100-105, 2019**

- Current ICU **enteral and parenteral nutrition** therapy does not specifically address evolutionary interaction and mutualism between host and luminal bacteria
 - Current dogma has primary concern for:
 - Macronutrients (fat, CHO, protein), micronutrients (vitamins and trace minerals)
 - Starting to consider gut derived metabolites which can signal cellular responses both locally and systemically (example - butyrate)
 - **Amount of interactions and crosstalk between microbiome, metabolic end products, host local and systemic immune system, gut epithelial is currently too complex**

Gut Health:

Practical Applications for Everyday Life !

- **Eat a wide variety of foods**
 - Try to add fermented foods and prebiotics when possible
 - Minimize food additives (sweeteners, emulsifiers, etc)
 - Consider blenderized diets for pts needing formulas
- Locate a good local source of probiotic that has strains of bacteria that have data to support benefit
- Do not spend a lot of money
- **Daily intake with a good source of prebiotics (whole grains) is beneficial**
- More bacteria #'s does not automatically mean better



Dietary Production a Healthy Microbiome: Practical Applications for Everyday Life !

- **Be cautious of overstatement and or extrapolation of claims of benefit**

- Association does NOT equal causation
- Animal models do not equal human models
- Anecdotes does no equal data



Wall Street Journal June 2019

- **The therapeutic potential of diet modulating the gut microbiota is considerable but remains to be fully realized**



Acknowledgements

- **Bob's Red Mill**

- Bob Moore



- **Springfield Creamery**

- Nancy's yogurt
- Sheryl Kesey, Blake Thompson
- "Nancy"

- **Stephen McClave MD**

- University of Louisville

- **Ryan Hurt and Manpreet Mundi**

- Mayo Clinic (Rochester)

- **OHSU**

- My patients
- Malissa Warren RD
- Mary Weinberg RD
- Lindsay Keeney RD
- Sherry Garrelts
- Surgical residents
- Nutrition fellows
- Charlie Borzy