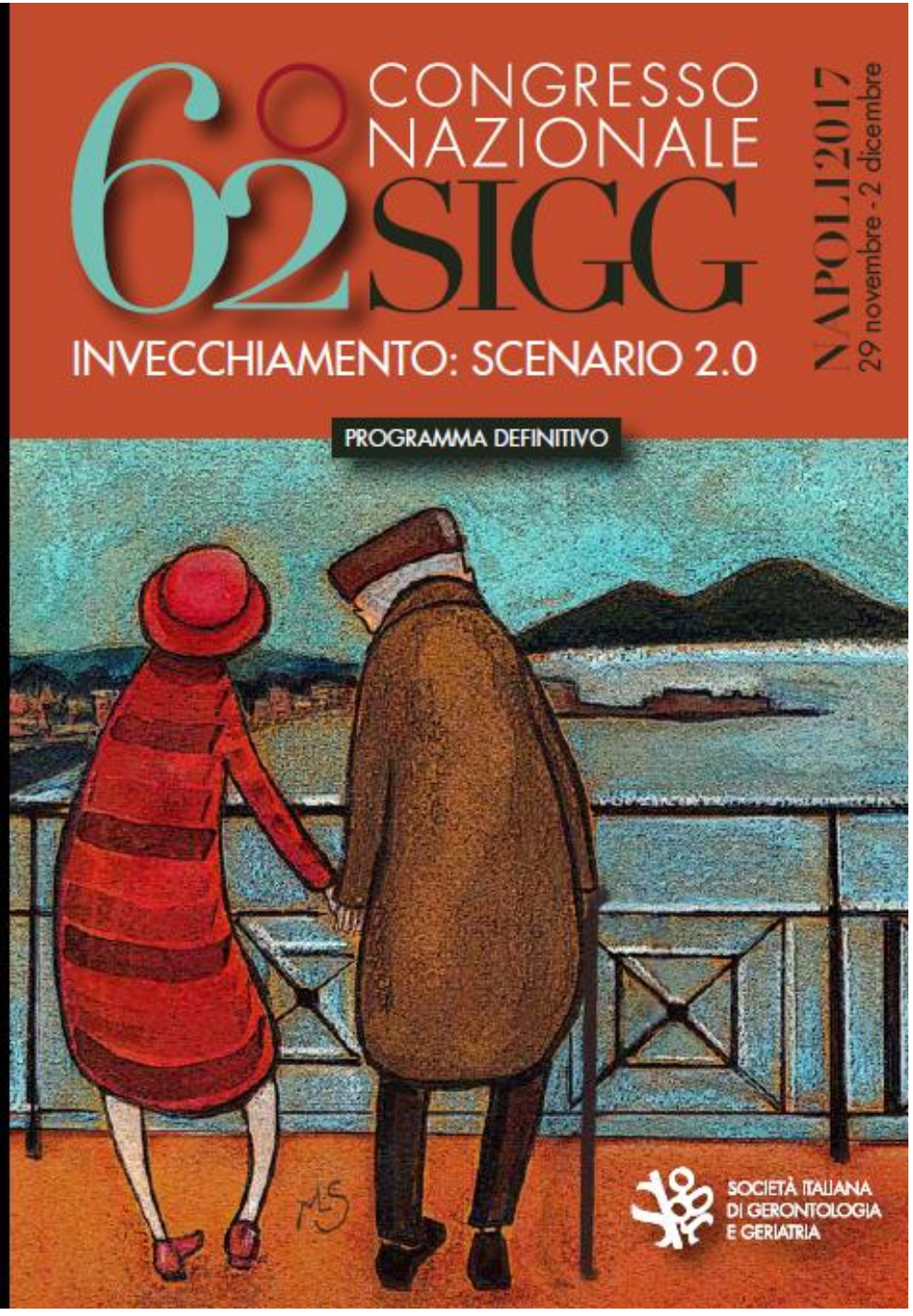


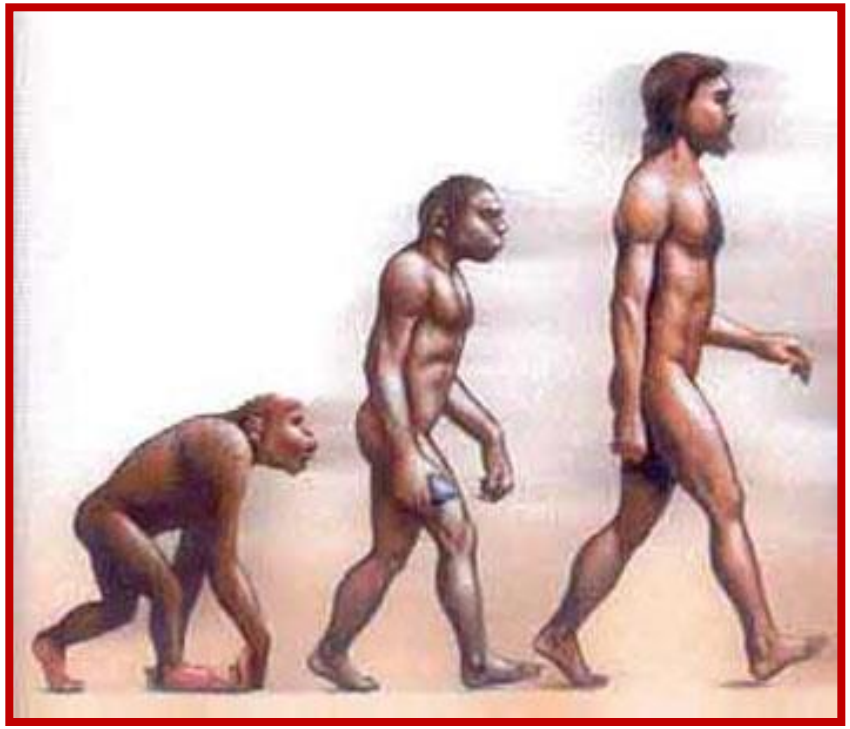
Il microbiota intestinale: come regola la riserva e la spesa energetica?

Gerardo Nardone

nardone@unina.it

Department of Medicine and Surgery
Gastroenterology Unit
University "Federico II", of Naples, Italy

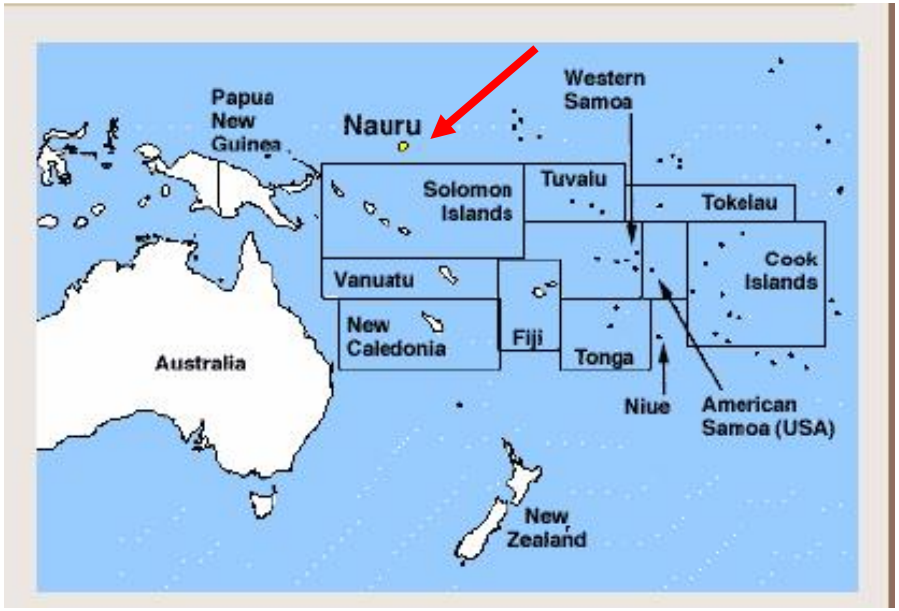
Homo Sapiens



"Thrifty Gene Hypothesis"

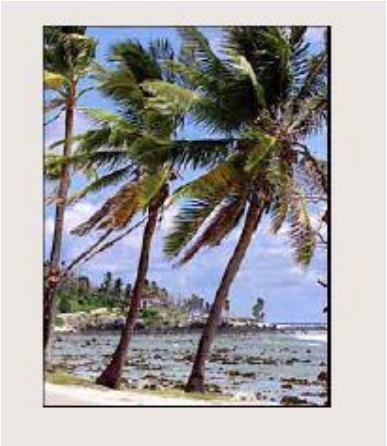
In the past, starvation caused diseases and death thus, the biological systems selected mechanisms, to increase food derided energy and, better protect against weight loss than weight gain

NAURU



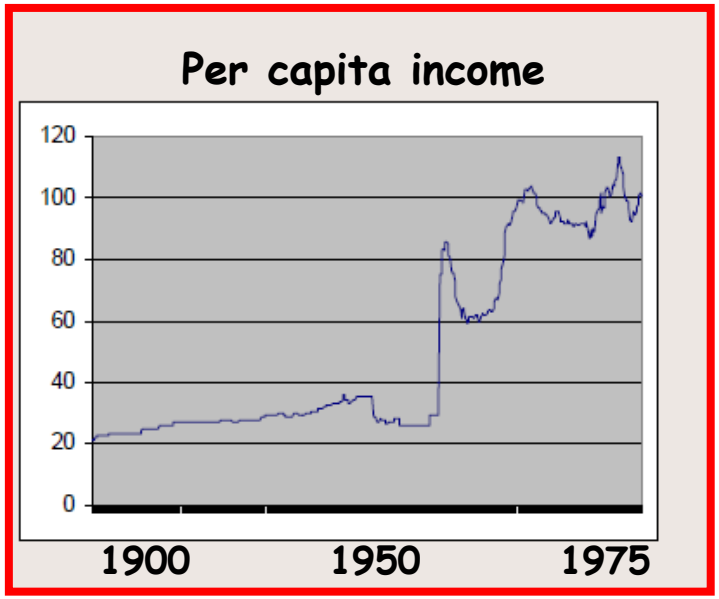
A small island in the Pacific Ocean

A frugal lifestyle based on hunting and fishing

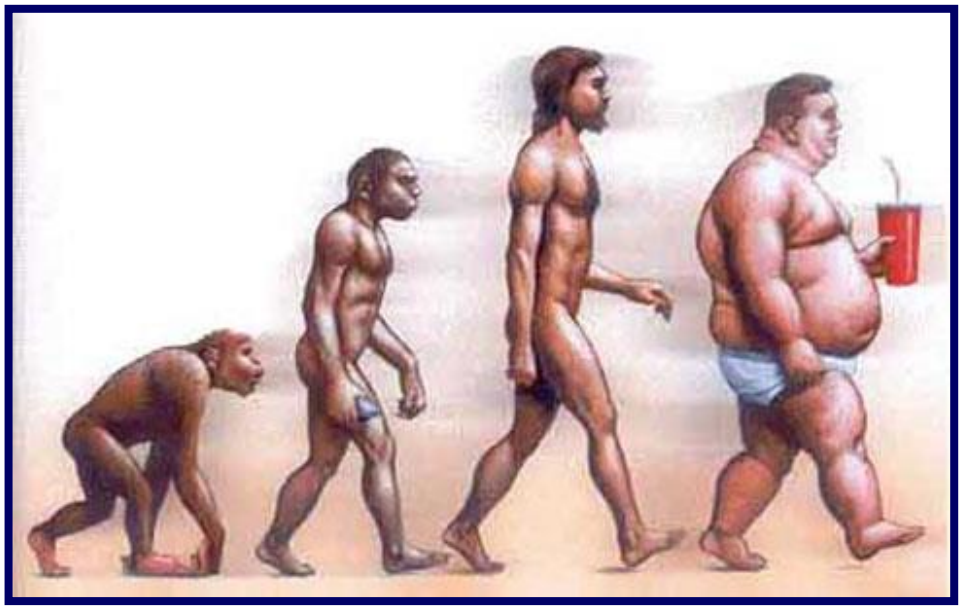


NAURU

In the middle of XX century, the discovery of deposits of phosphates, changed the Nauru residents in **one of the most rich population in the world**



The rapid increase of pro capita income improved the food availability and in few years …

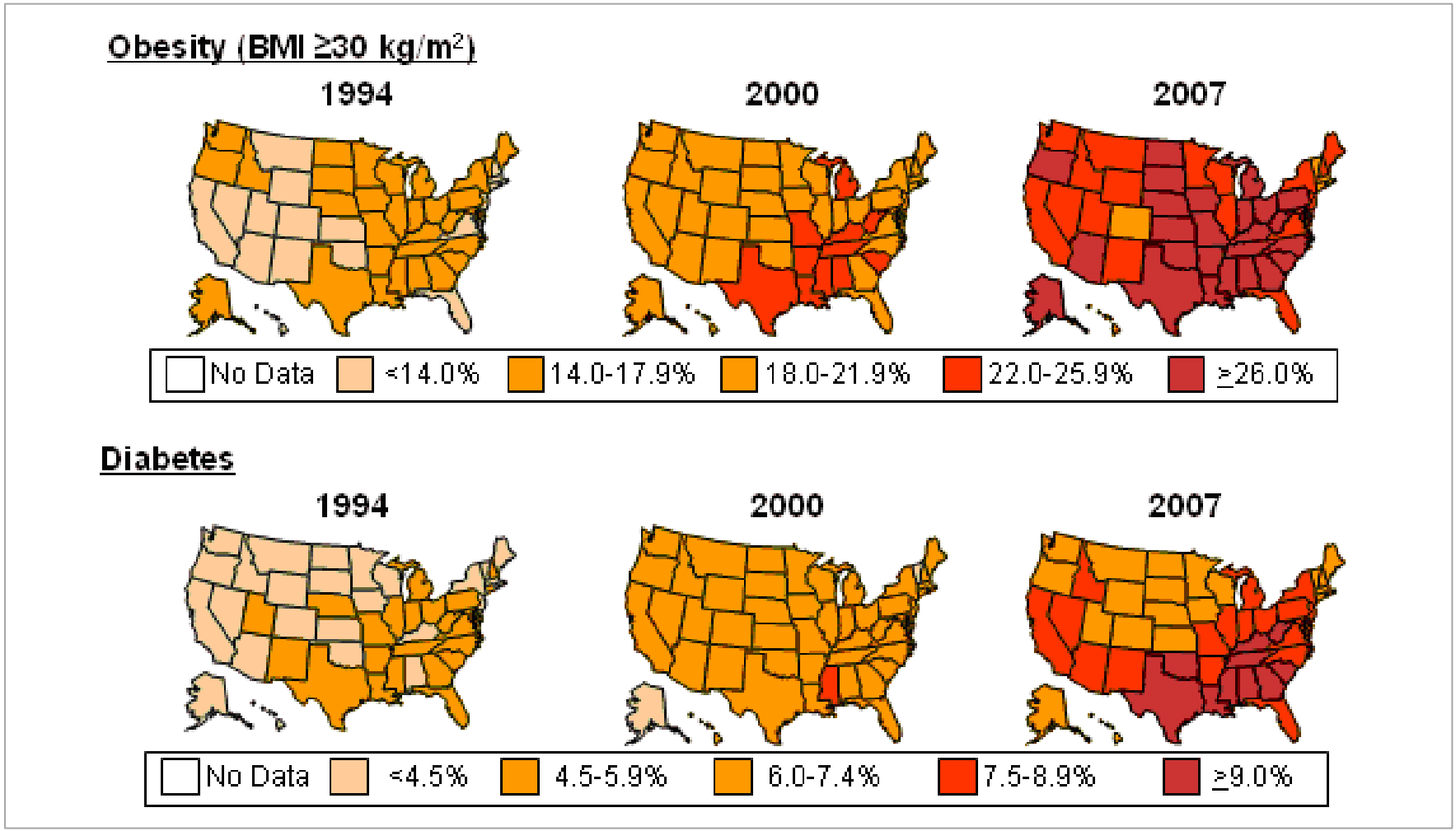


1/3 of people
old more than 20 years

2/3 of people
old more than 55 years

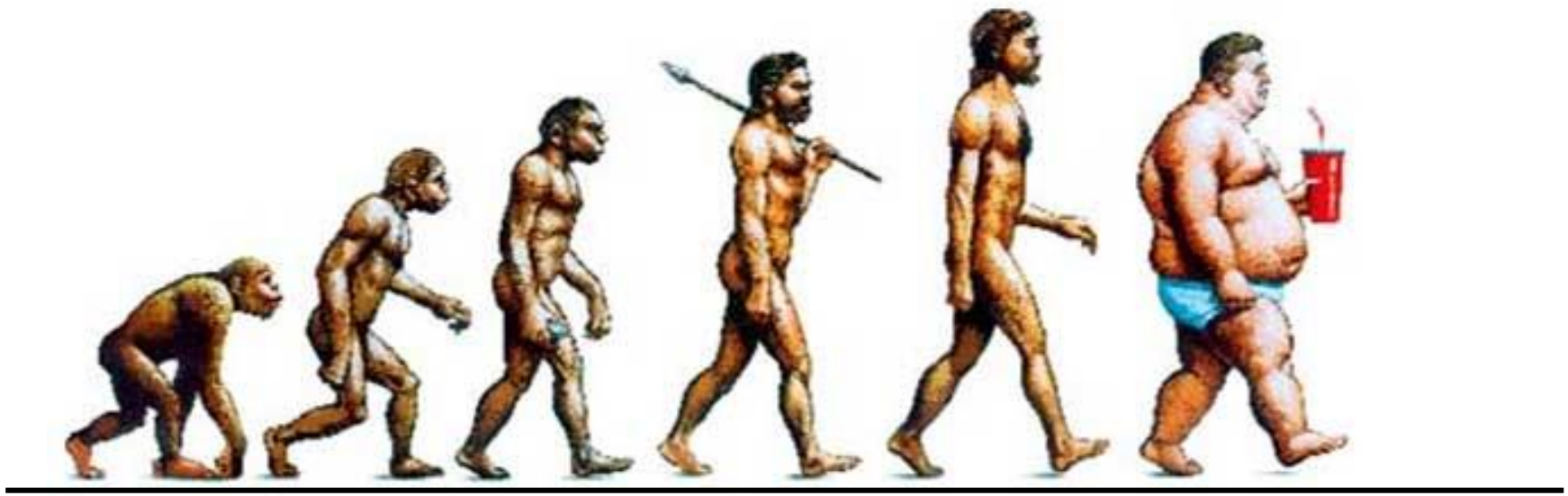
Suffer from diabetes and obesity

Prevalence of Obesity and Diabetes



1980-2008: from 153 to 347 million of people

The increase of obesity and diabetes over the past three decades cannot be explained by genetic factors …
the eukaryotic genome is changed of 0.3% in 1 million years



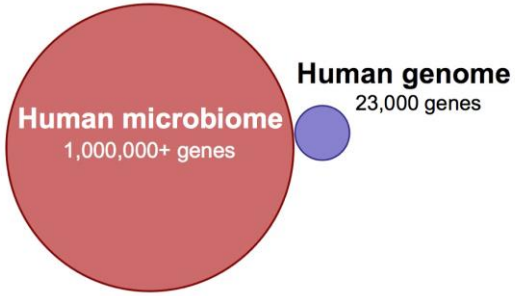
… as well as cannot be attributed solely to changes in nutritional habits, or the reduction of daily physical activity

Accumulating evidence indicates that GUT MICROBIOTA is involved in the control of host energy metabolism

Gut Microbiota is a community of living microorganisms (symbionts, pathobionts) assembled in a niche of the individual however, …

Number of microbes that colonizes the human body is **10 times greater** than that of human body cells

Number of microbial genes **is 150 times higher** than that expressed in the human body

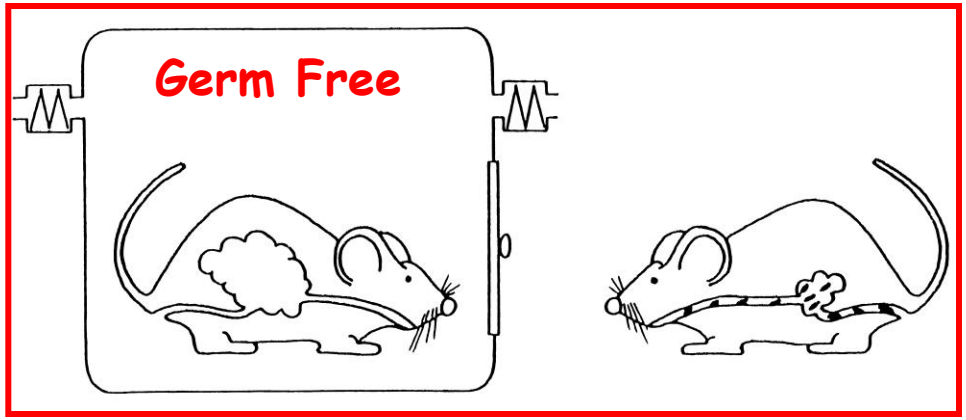


Gut microbiota is an **organ** that, together with the genome and immune system, constitutes 1 of the 3 pillars that **support the development & human health** since the first months of life

GERM FREE ANIMALS

Villi longer
Crypts shorter
Mucosa thinner
Cell turnover rate lower

Digestive Enzyme Activity ↓↓
Cytokine production ↓↓
Lymphoid tissues GALT ↓↓



Mucosal vascularity ↓↓
Migrating Motor Complex ↓↓
Intestinal Transit Times ↑↑
Cecum distended

Louis Pasteur

1822-1895

Life without bacteria would be impossible

GUT MICROBIOTA FUNCTION

Trophic

Control of epithelial cell proliferation
Control of epithelial cell differentiation
Tight junction and Permeability

Immune modulation

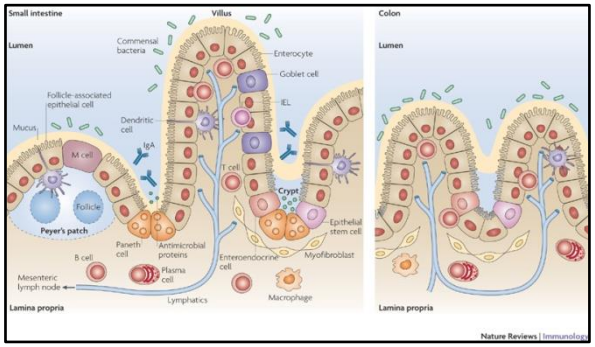
Immune-response
Protection against pathogens
Bacterial growth and proliferation

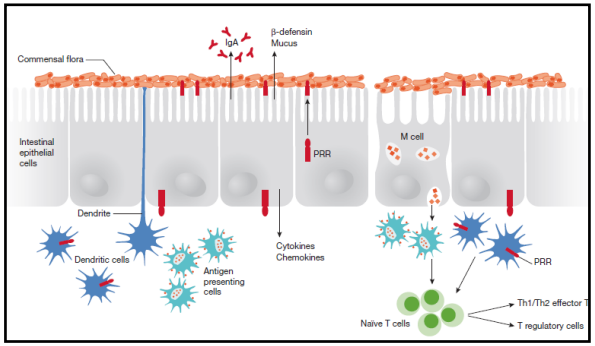
GI motility control

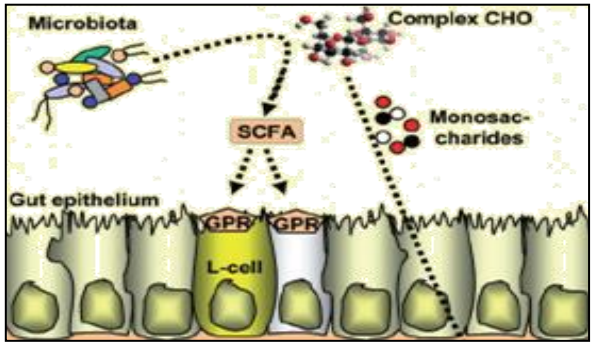
Oro-cecal transit

Metabolic

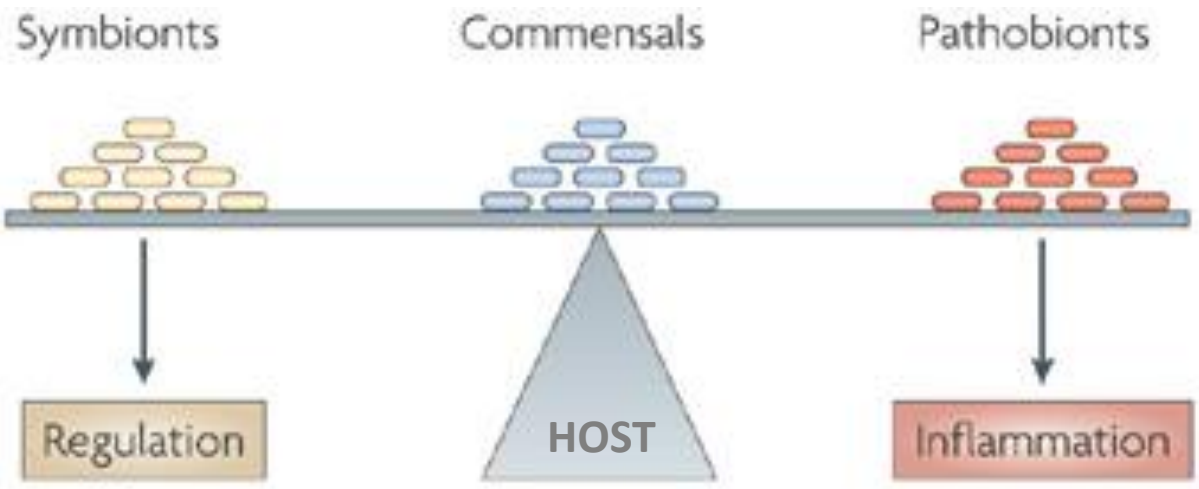
Fermentation of indigestible complex carbohydrates and dietary residue







GUT MICROBIOTA



Equilibrium

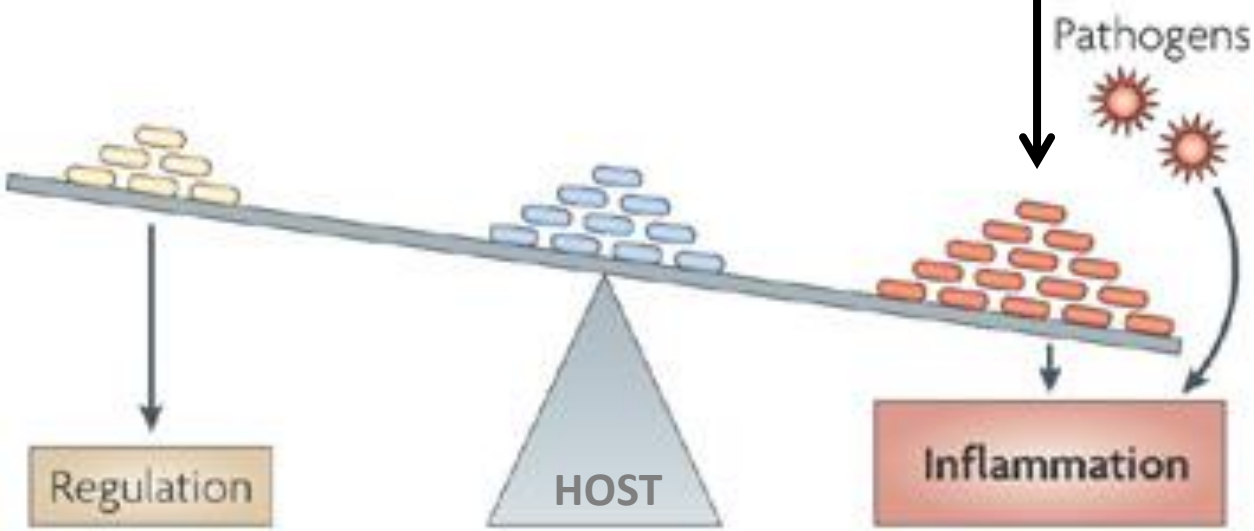
↓

HEALTH

GUT MICROBIOTA

Agents affecting the composition of Gut Microbiota

- Drug
- Diet
- Peristalsis
- Immune system
- Daily exercise
- Smoking

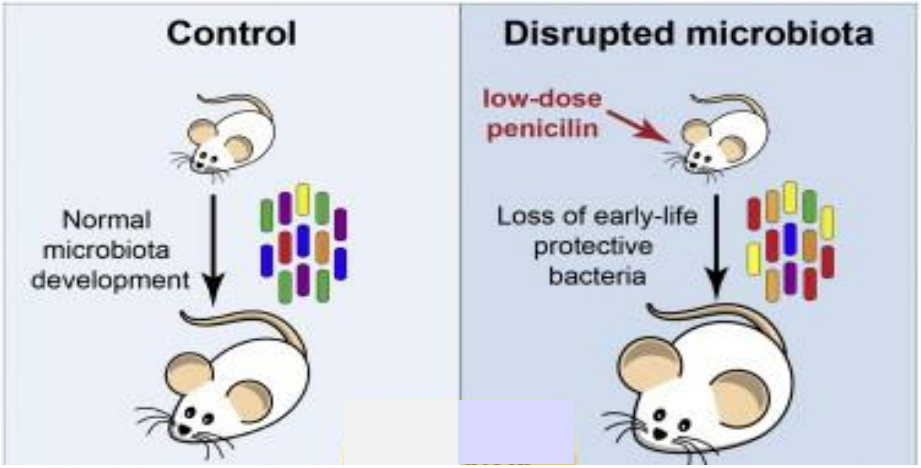


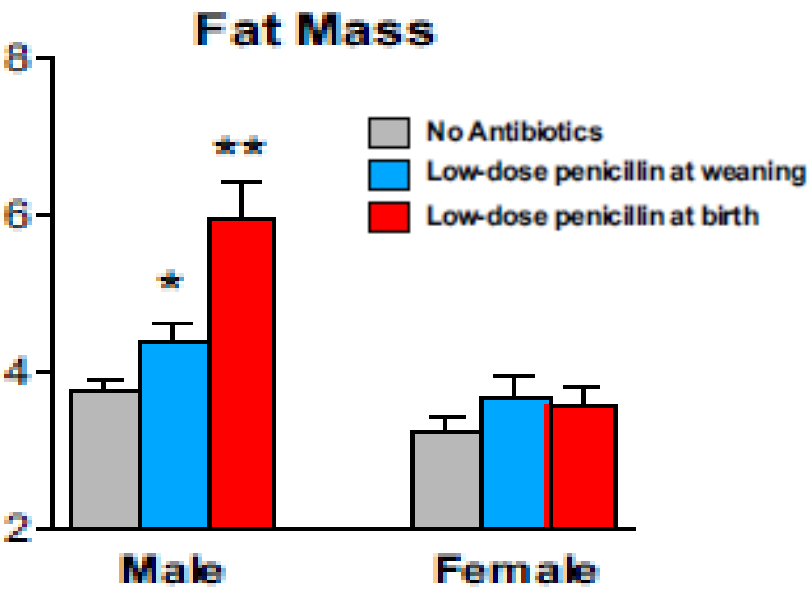
Unbalance

DISEASE

Altering the Intestinal Microbiota during a Critical Developmental Window Has Lasting Metabolic Consequences

2014
Cell





Low-dose of penicillin at birth alters gut microbiota that in turn increases host metabolism and adiposity

Laura M. Cox,

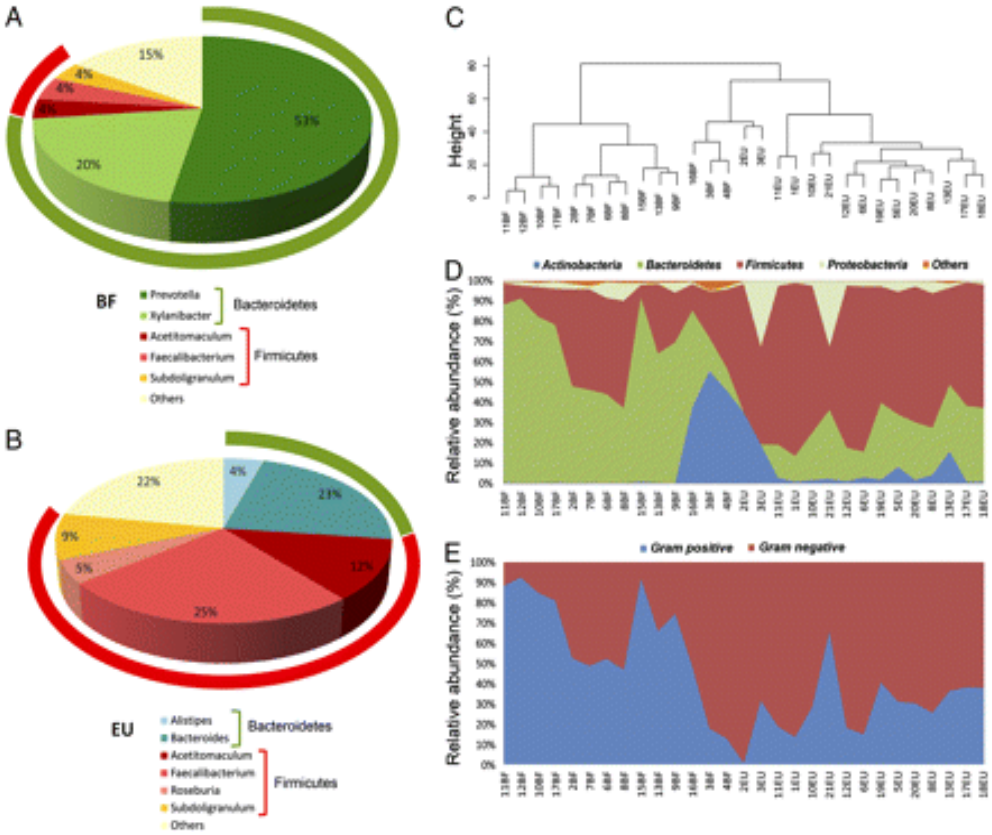
Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

2010

African Children

European Children



African Rural Diet = ↑ vegetable fibre: ↑ Bacteroidetes ↑ Prevotella

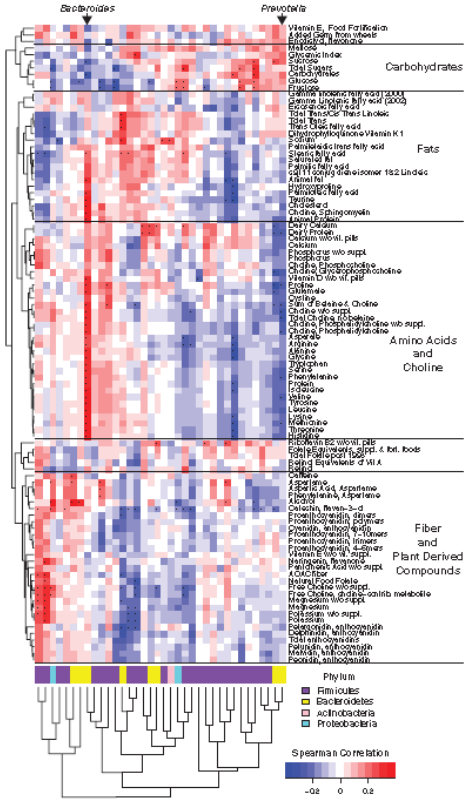
European Western diet = ↑ starch-protein: ↑ Firmicutes ↑ Proteobacteria

Science AAAS

2011

Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes

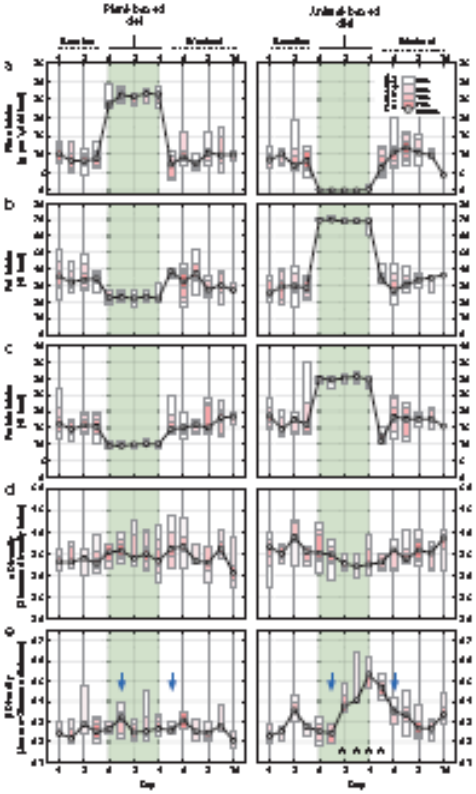
Gary D. Wu



LETTER nature 2014

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David



Diet changes gut microbiota and is associated with specific enterotype

Protein-and animal fat — Bacteroides

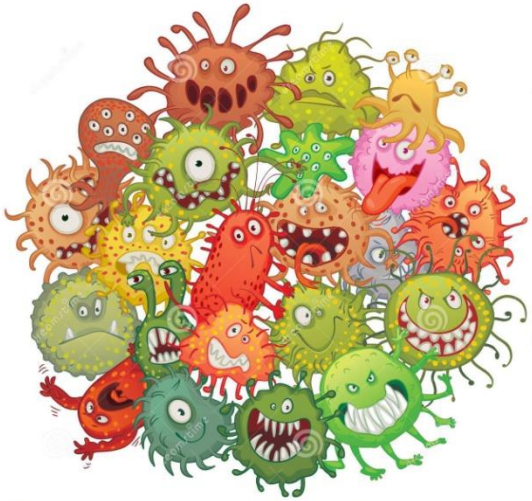
Carbohydrates — Prevotella

Animal-fat diet is characterized by

↑↑ Alistipes, Bilophila and Bacteroides

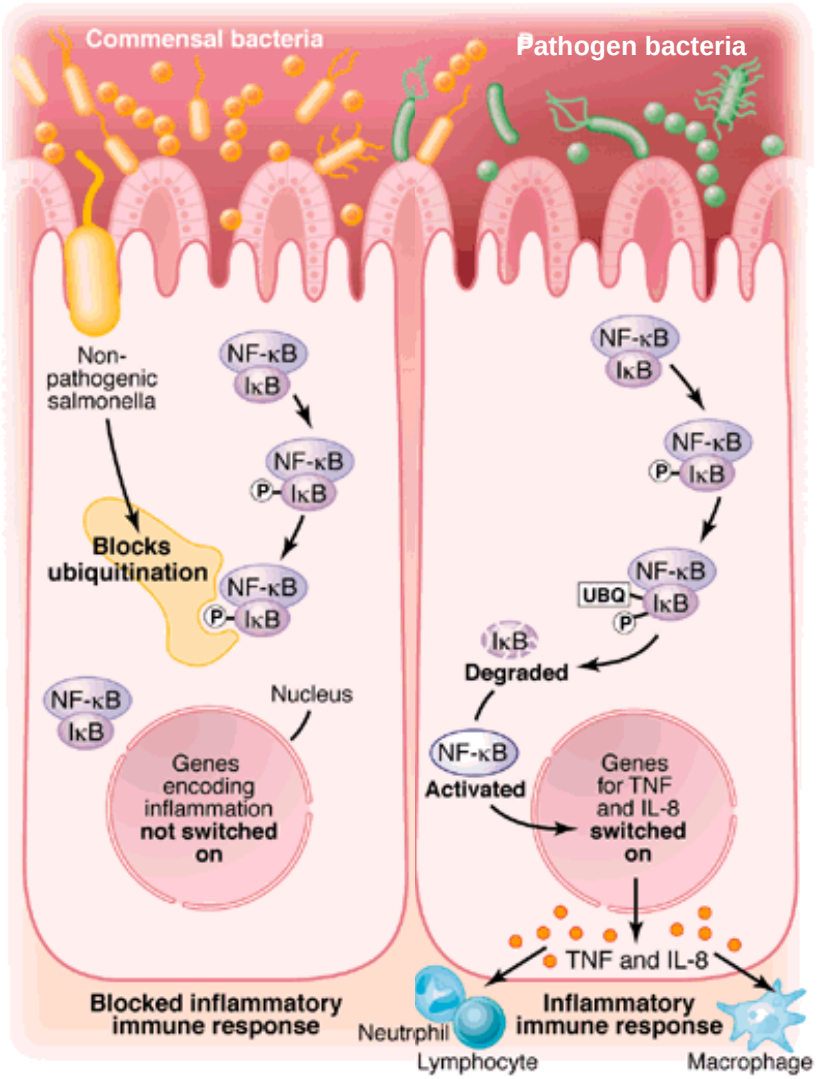
↓↓ Firmicutes Eubacterium rectale Ruminococcus Roseburia,

How Gut Microbiota may modulate Energy Homeostasis ?

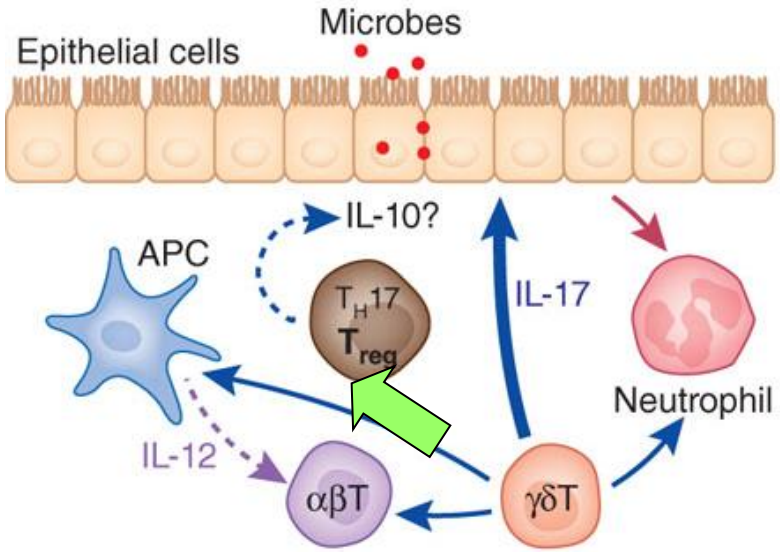


1. Inflammatory immune response
2. Intestinal permeability
3. Metabolism

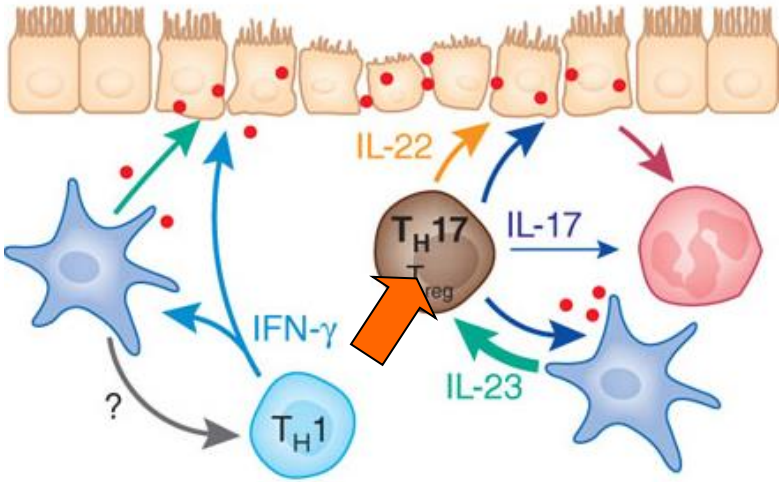
Inflammatory-Immune Response



NF-kB is the masterplayer of inflammatory immune response to pathogenetic bacteria



Physiological Inflammation

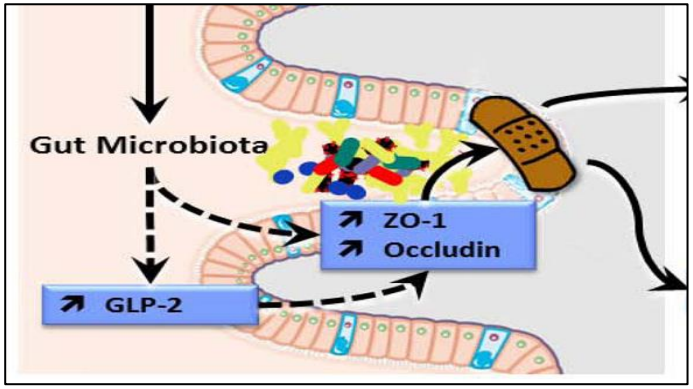


Pathological Inflammation

GUT MICROBIOTA-RELATED PERMEABILITY IMPAIREMENT

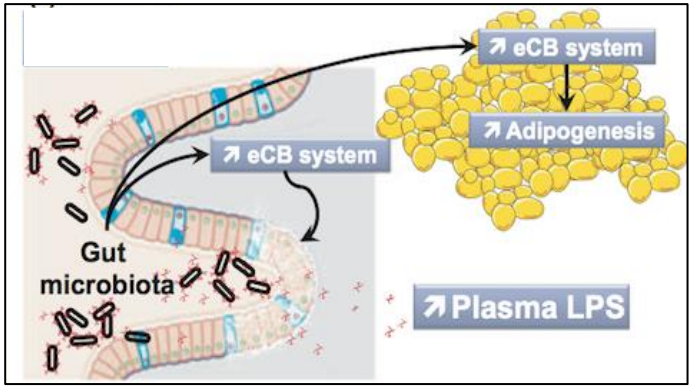
↓↓ **Zonulina-1 and Occludin**
↓↓ **Glucagon-like peptide (GLP) 2**

Cani PD, Gut 2009



↑↑ **Cannabinoid receptors (CB)**
The endocannabinoid system controls gut permeability through CB receptors

Muccioli GG, Mol Sist Biol 2010



DISBYOSIS

↓

Inflammation

↓

LEAKY GUT

↓

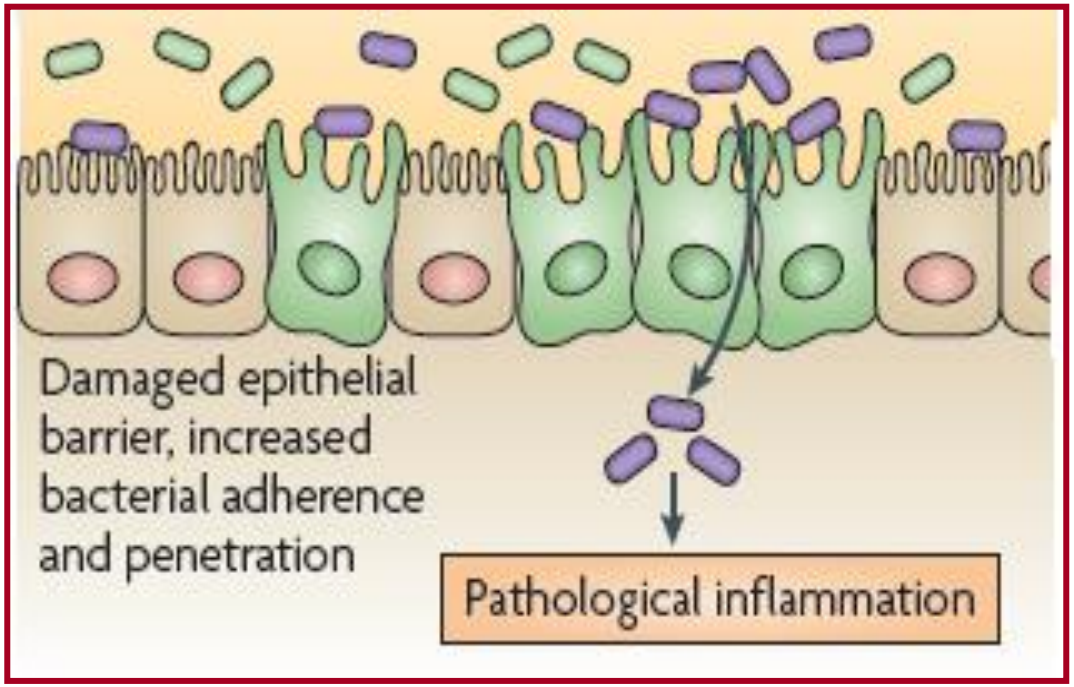
Bacterial translocation

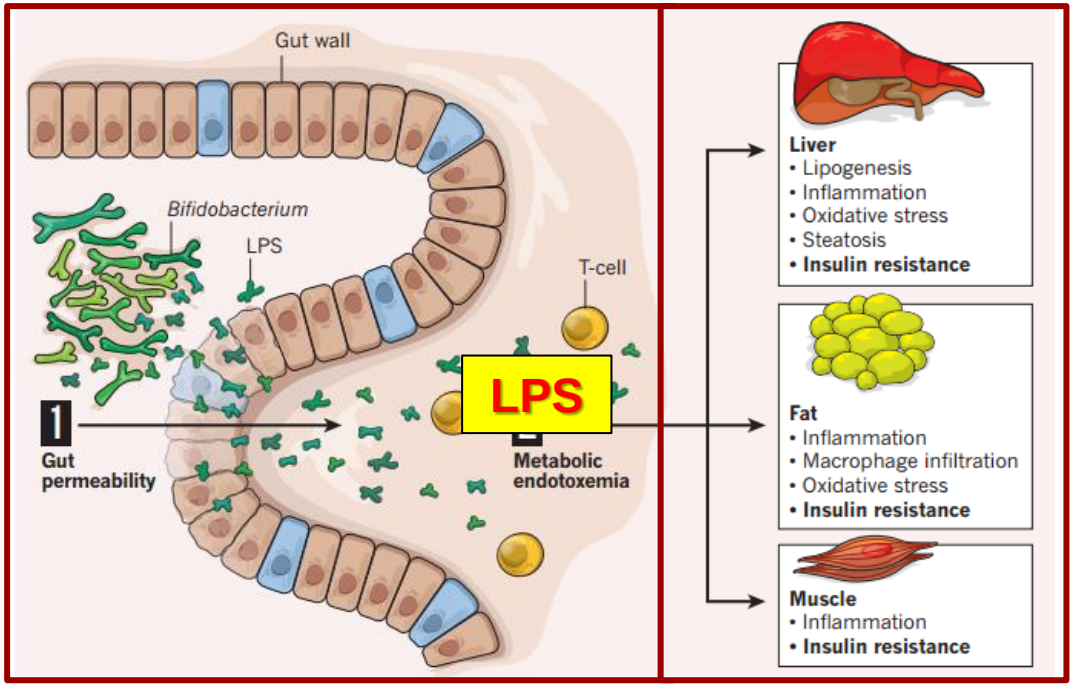
↓

LPS

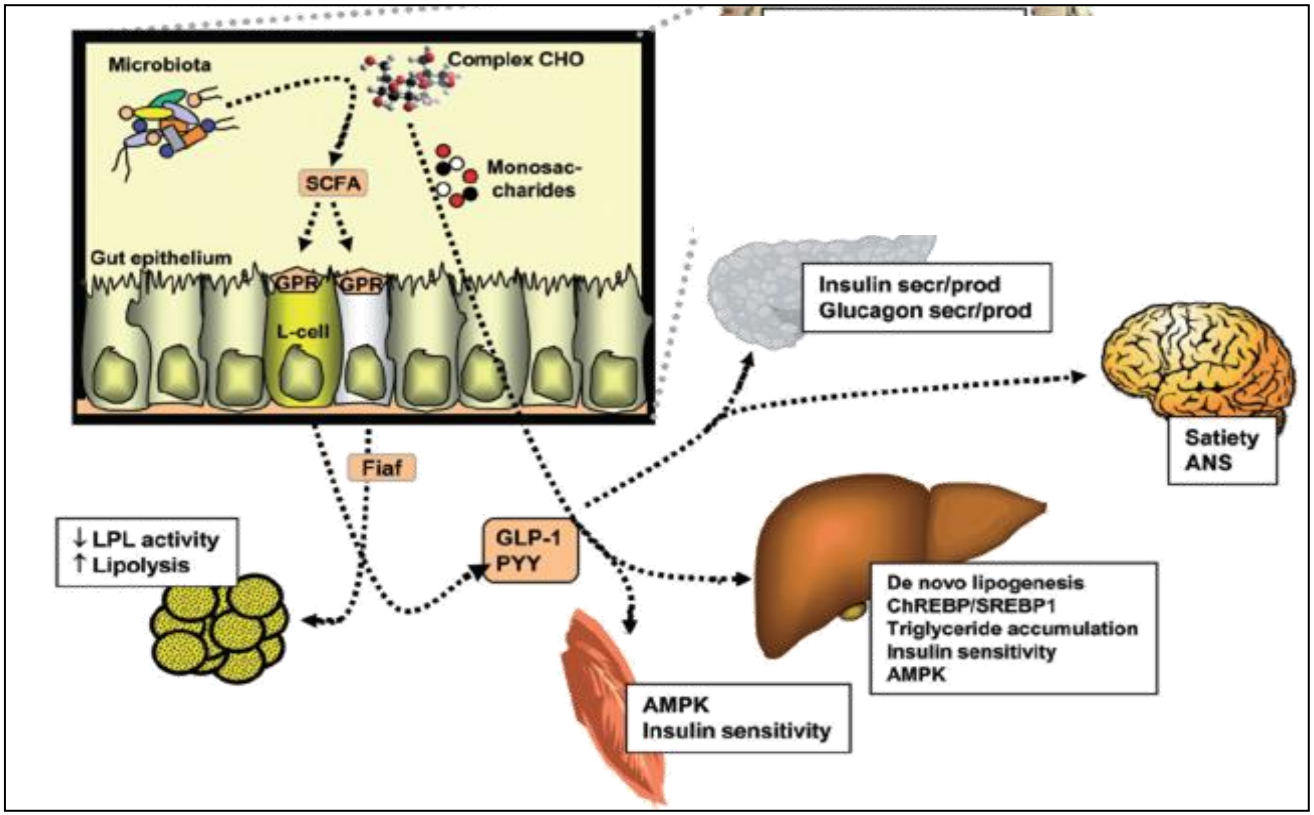
↓

Metabolic Endotoxemia





Gut Microbiota & Metabolic Endotoxemia



↓ intestinal Fiaf
↑ lipoprotein lipase activity

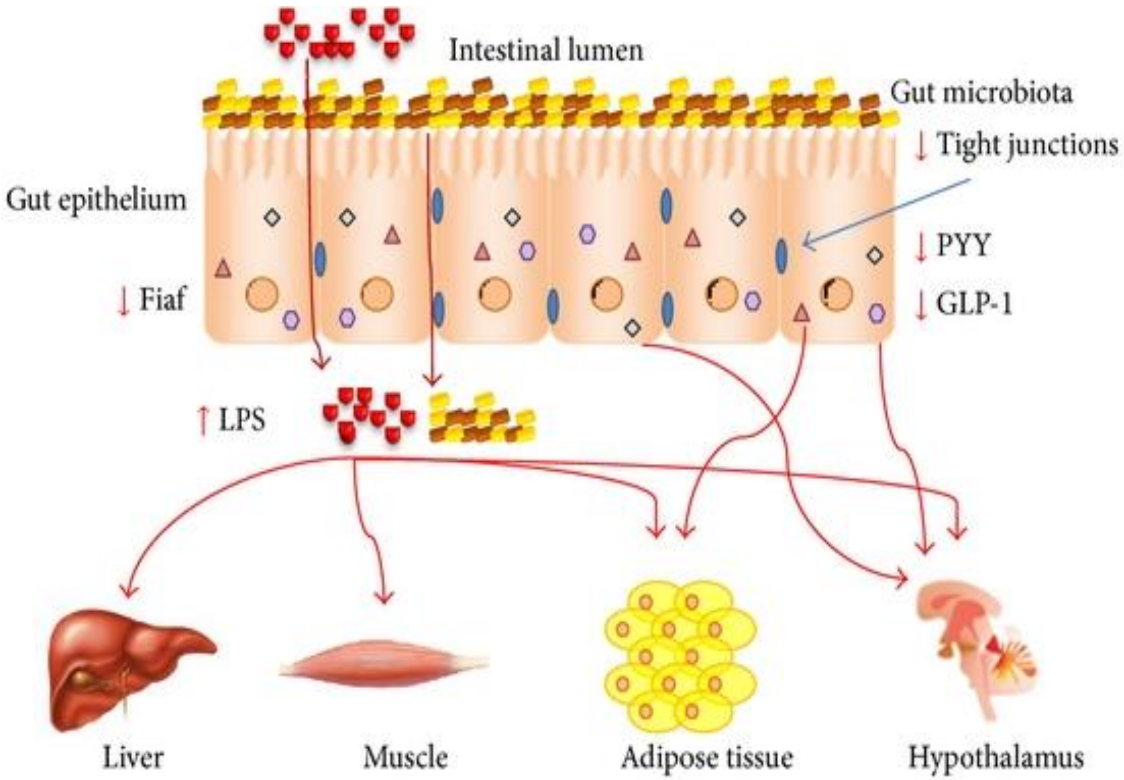
↓ GLP-1 Glucagon like peptite
↑ Grelin ↑ PYY

↓ intestinal AMPK
↓ FA oxidation
↓ Insulin sensitivity

↓ Intestinal alkaline phosphatase (IAP)
↓ breakdown of dietary lipids
↓ LPS detoxification

Tilg H JCI 2013

DYSBIOSIS



↑ GUT HORMONES SECRETION

↑ GLUCONEOGENESIS

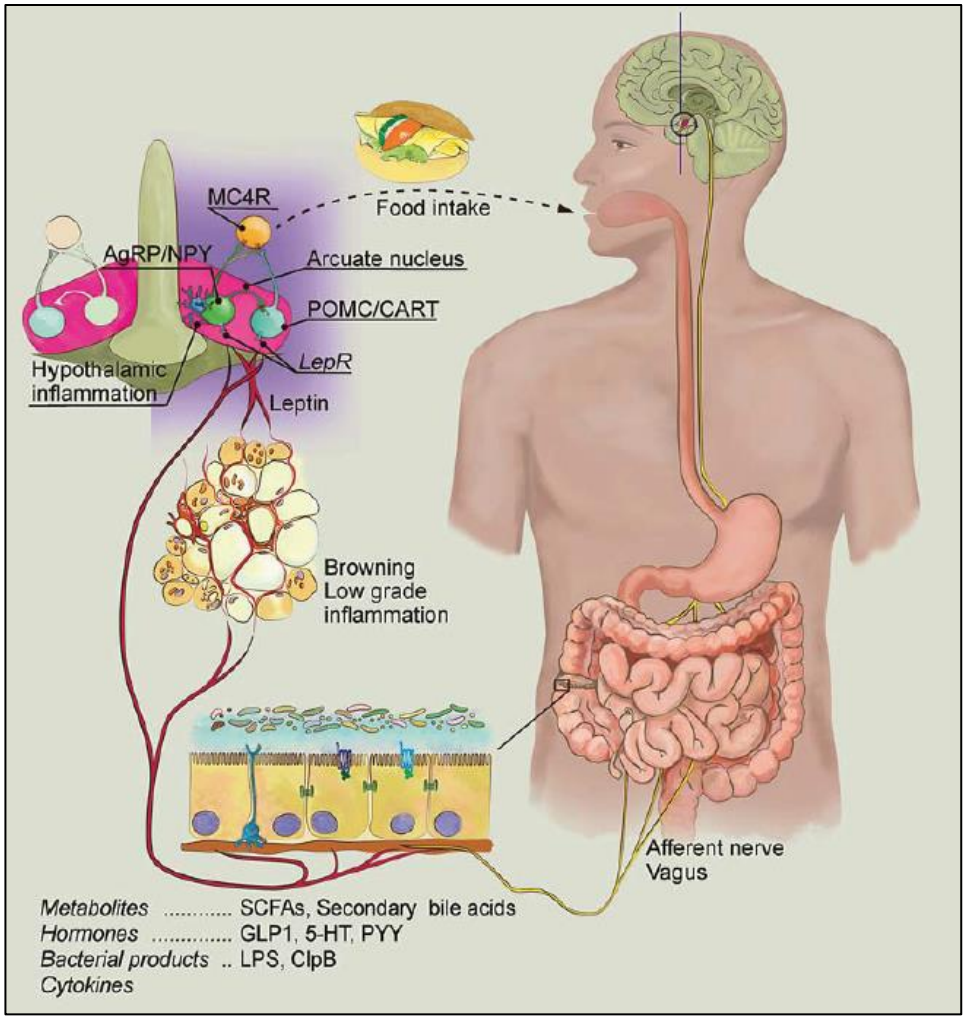
↓ LIPOLYSIS

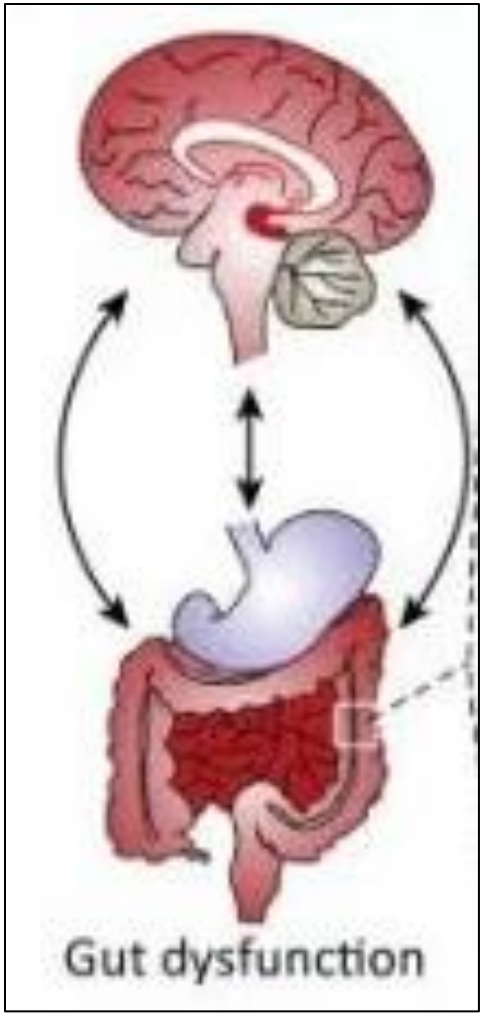
↓ INSULIN SENSITIVITY

↑ FOOD INTAKE ↑ hunger ↓ satiety

Tilg H., 2014 Carvalho BM, 2013

GUT - BRAIN AXIS





The brain receives information from the GUT MICROBIOTA and uses this information to regulate the Hypothalamic energy balance

Metabolic function of Gut Microbiota

Fermentation of indigestible carbohydrates, dietary residue and mucus

Saccharolytic Fermentation

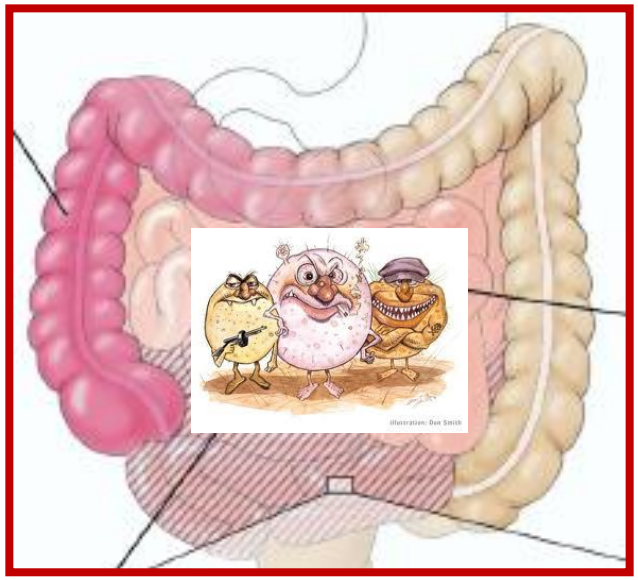
↓

Short Chain Fatty Acid

↓

The increase of SCFA induces

- ↑ Caloric production
- ↑ Lipogenesis
- ↑ Insulin resistance



The organisms most efficient are Firmicutes (clostridium)

Saccharolytic Fermentation

↓

Acetic acid
Propionic acid

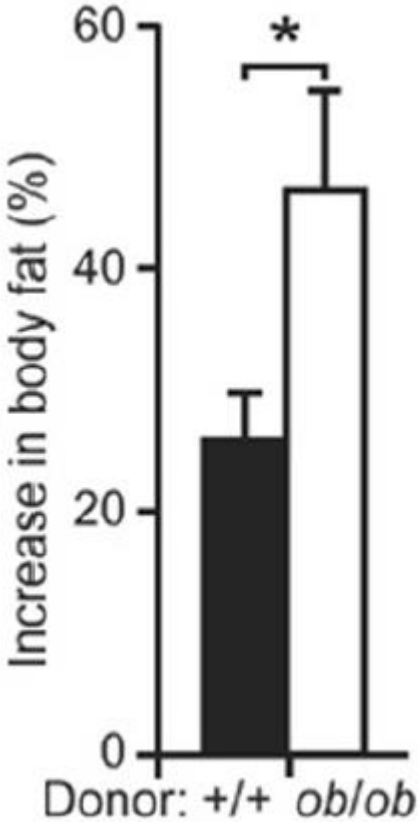
↓

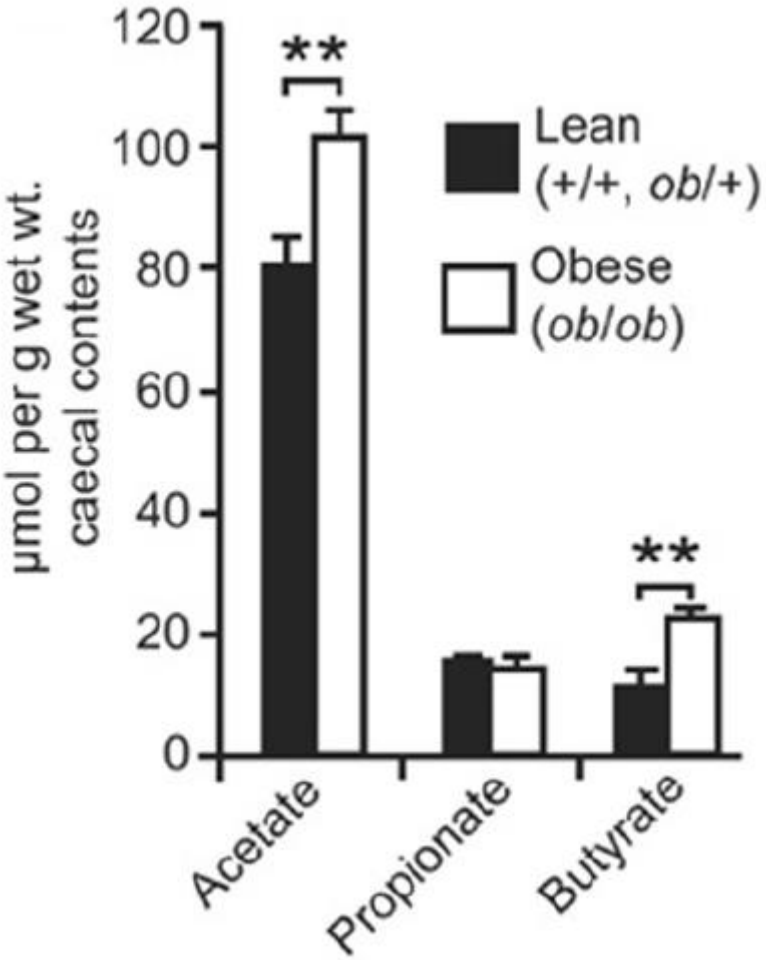
Propionate:
Lipogenesis
Gluconeogenesis

Acetate:
Cholesterol synthesis

The products of fermentation are an important energy source for microbiota and Host (5-15% of human energy requirements)

The *ob/ob* microbiota has an increased capacity for dietary energy harvest





Tumbaugh Nature 2006

Methanogenic Flora and Obesity

METHANOBREVIBACTERS TRANSFORM HYDROGEN IN METHANE AND INCRESE ENERGY HAVEST

Gastroenterology & Hepatology Volume 8, Issue 1 January 2012

Intestinal Methane Production in Obese Individuals Is Associated with a Higher Body Mass Index

Basseri R

BMI is significantly higher in methane-positive subjects (p 0 .001)

(*J Clin Endocrinol Metab* 98: E698–E702, 2013)

Brief Report—Endocrine Research

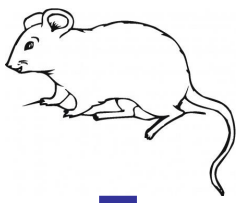
Methane and Hydrogen Positivity on Breath Test Is Associated With Greater Body Mass Index and Body Fat

R. Mathur, M. Amichai, K. S. Chua, J. Mirocha, G. M. Barlow, and M. Pimentel

Methane producer subjects had higher BMI and body fat

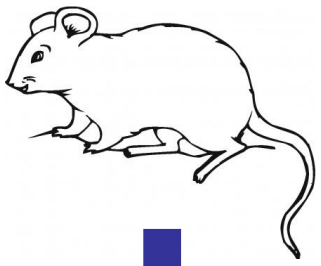
Methanogenic Flora and Obesity

GERM FREE



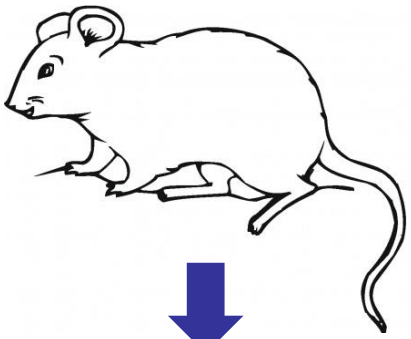
Underweight

Bacteroides thetaiotaomicron
+
Desulfovibrio piger



Normal weight

Bacteroides thetaiotaomicron
+
Methanobrevibacter smithii



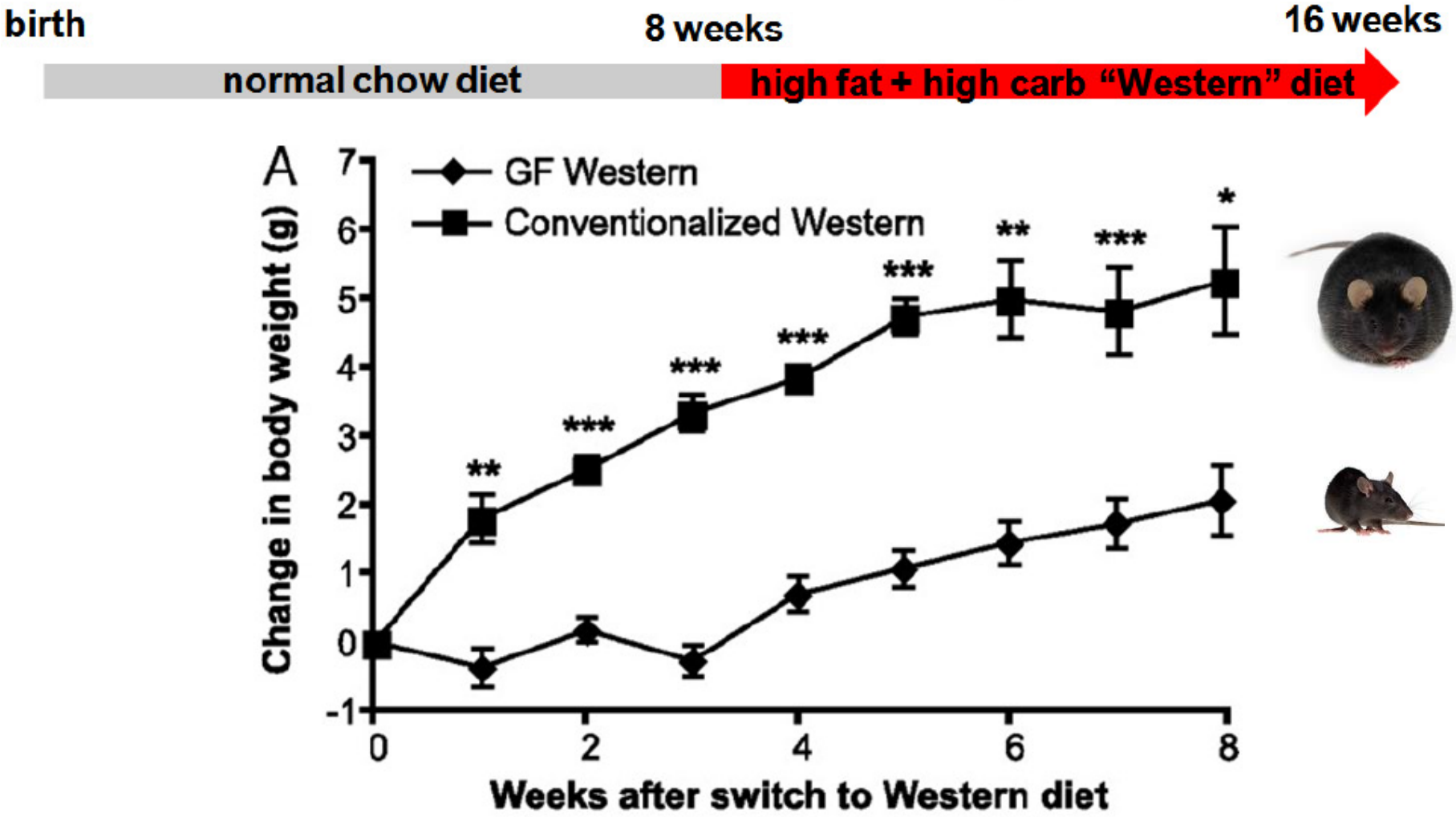
Overweight

Methanogenic Flora may act as the "power brokers" in gut community, regulating energy harvest from dietary glycans and host energy storage

Methanogenic flora represents a promising target to control obesity

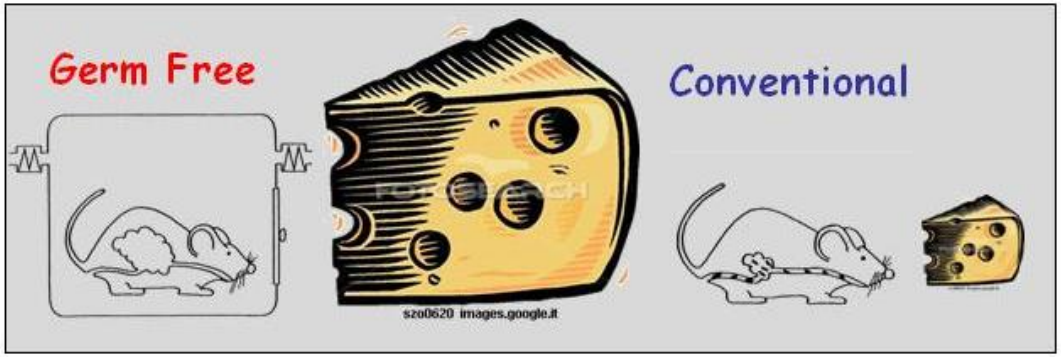
Samuel BS, PNAS 2006

Germ-free mice are protected against diet-induced obesity

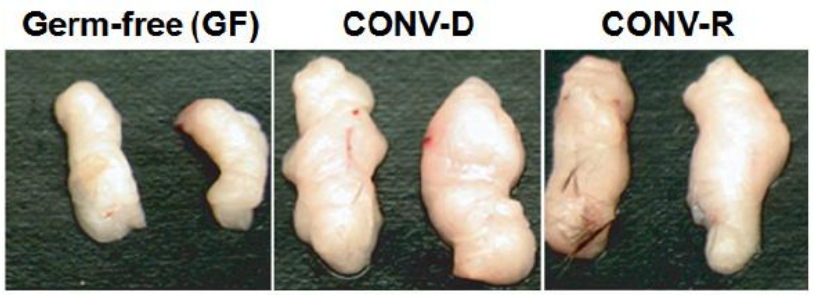


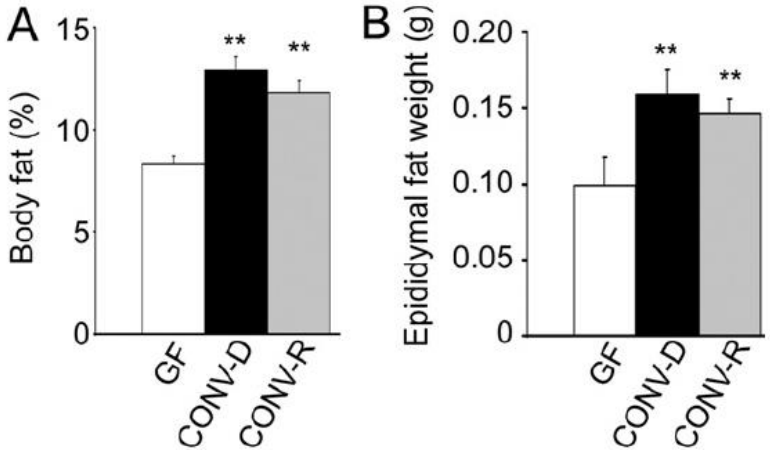
Bäckhed, F. *et al.* (2007) *PNAS*

GERM FREE ANIMALS



The caloric intake required to sustain body weight is 27% greater in germ-free mice





Conventionalization promotes body fat increase

The effect is rapid (<10 dys), and independent of sex, mouse strain and diet

Bäckhed, F. *et al.* (2004) *PNAS*

I do not eat anything but I gain weight

Mice genetically obese (ob/ob) have
50% fewer Bacteroidetes ↓
50% more Firmicutes ↑
than their lean siblings

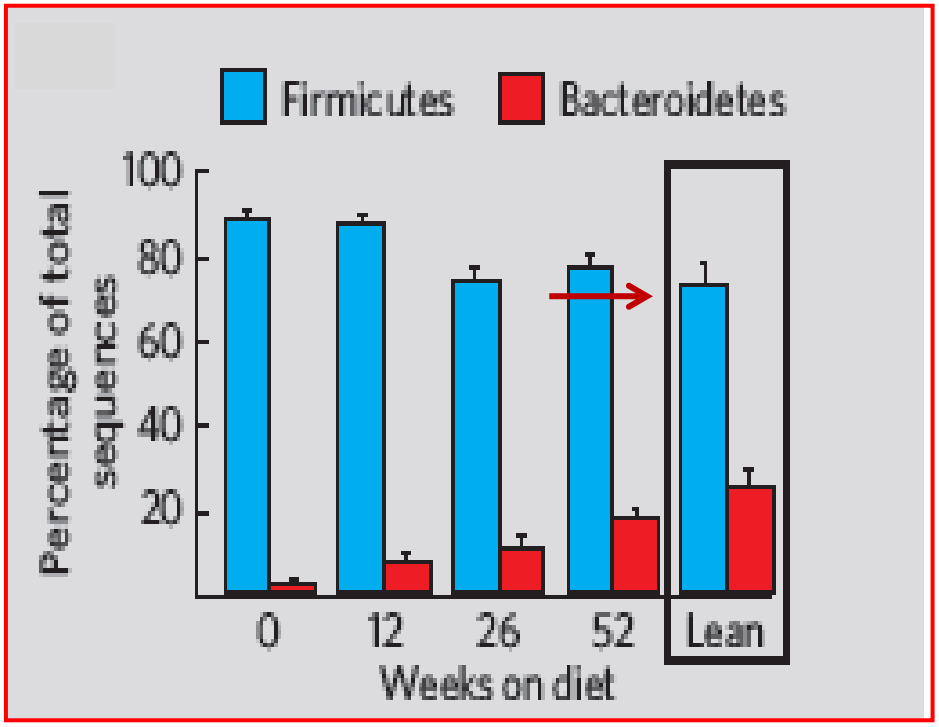
Obese humans exhibit a shift in the microbial composition similar to that found in obese mice

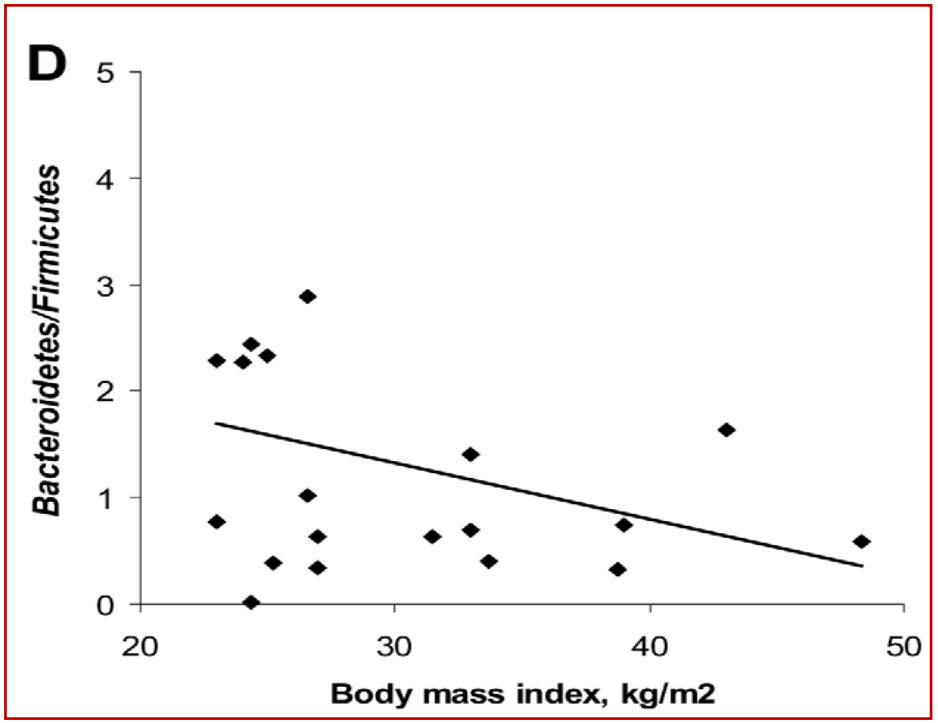
In children from birth to 7 years old the alterations of the gut microbiota precede overweight-obesity
(stool samples every 6 mths)

Ley PNAS 2005; Ley Nature 2006, Backhed 2009

Human gut microbes associated with obesity

↑ Firmicutes 85% in obese people's 70% in the lean subjects
↓ Bacteroidetes 5% in obese people's 20% in the lean subjects





After one year of restricted diet, the ratio Bacteroidetes/Firmicutes shifted towards that of lean subjects and the obese patients lost weight

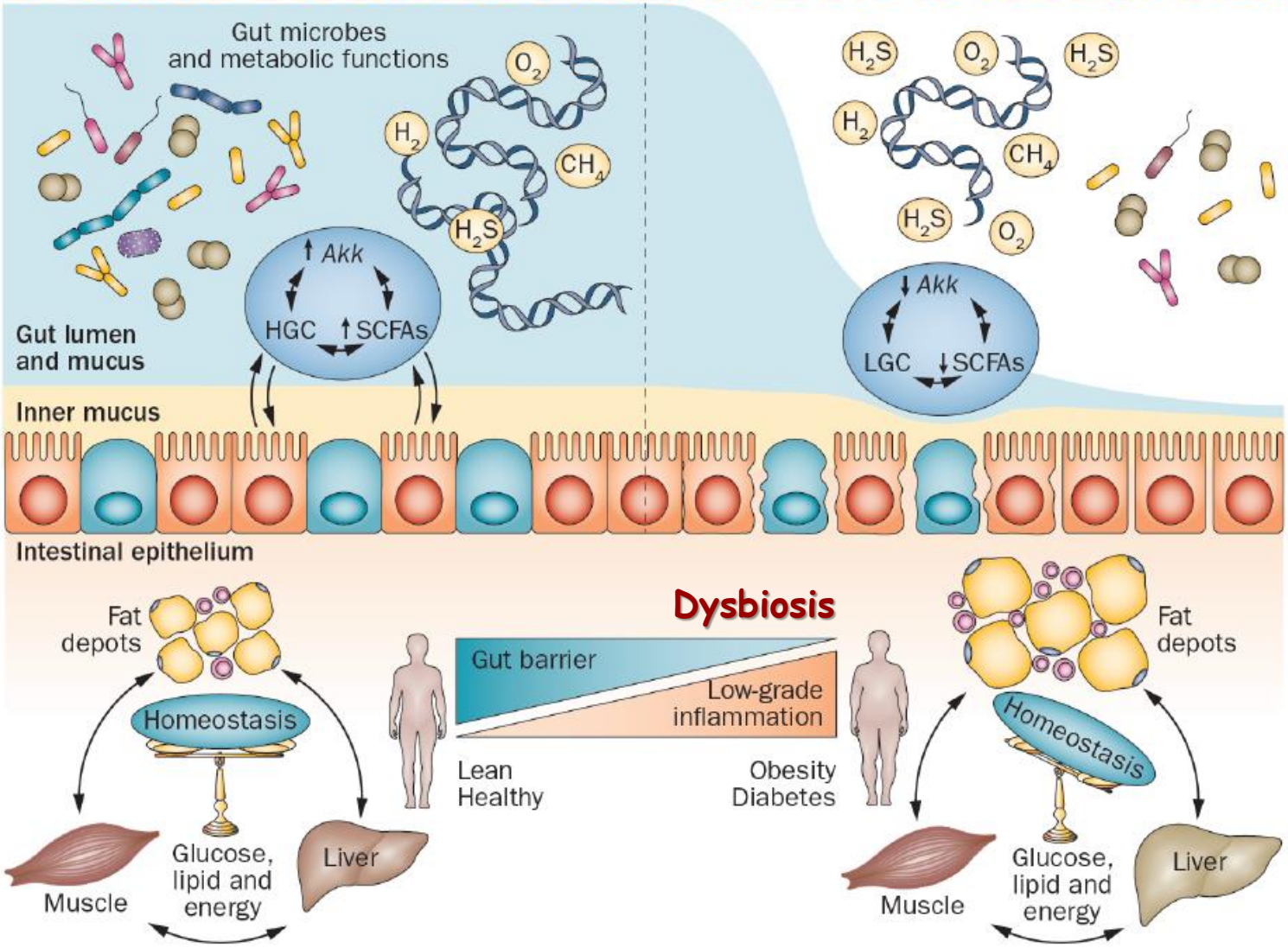
Bacteroidetes/Firmicutes ratio

NEGATIVE correlates with BMI

Ley RE Nature 2006

Larsen N, PlosOne 2013

Gut Microbiata and Energy Homeostasis and Metabolic Diseases



Cani PD 2014

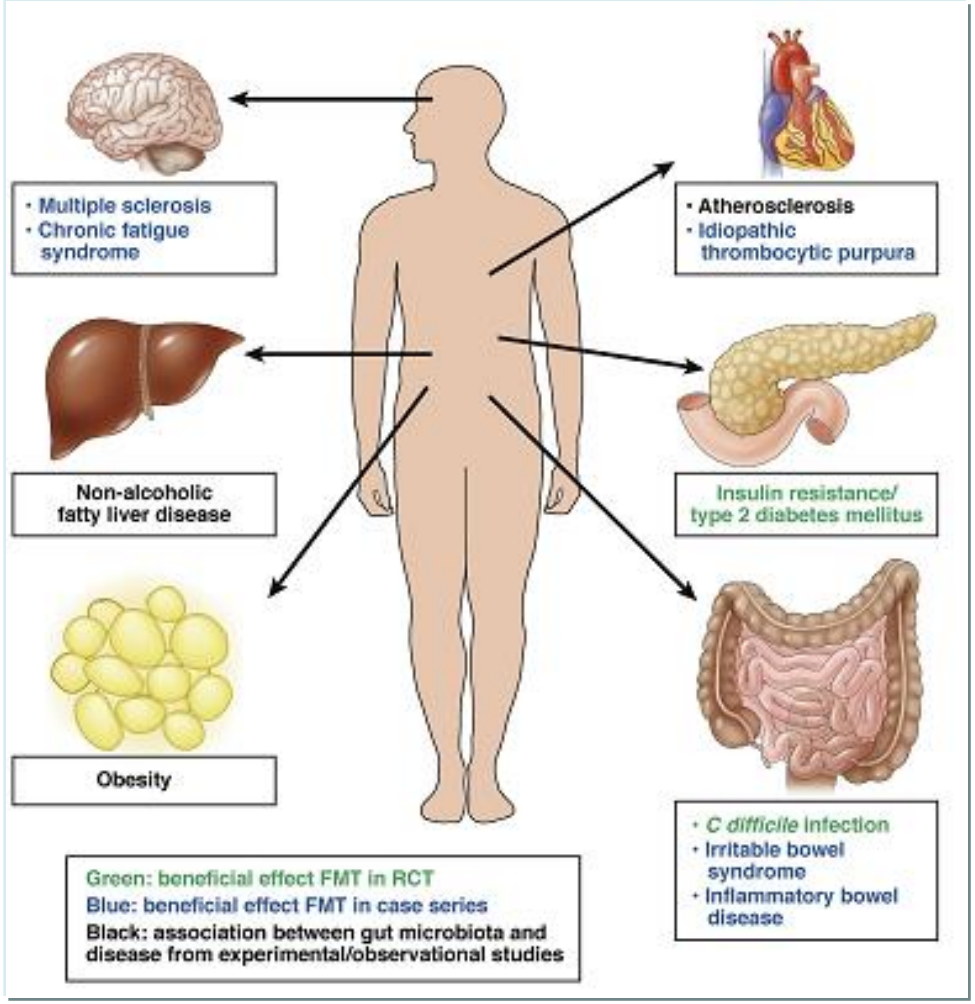
BRIEF REVIEW

GASTROENTEROLOGY 2013;145:946–953

Robert F. Schwabe and John W. Wiley, Section Editors

Therapeutic Potential of Fecal Microbiota Transplantation

LOEK P. SMITS,[1] KRISTIEN E. C. BOUTER,[1] WILLEM M. DE VOS,[2,3] THOMAS J. BORODY,[4] and MAX NIEUWDORP[1]



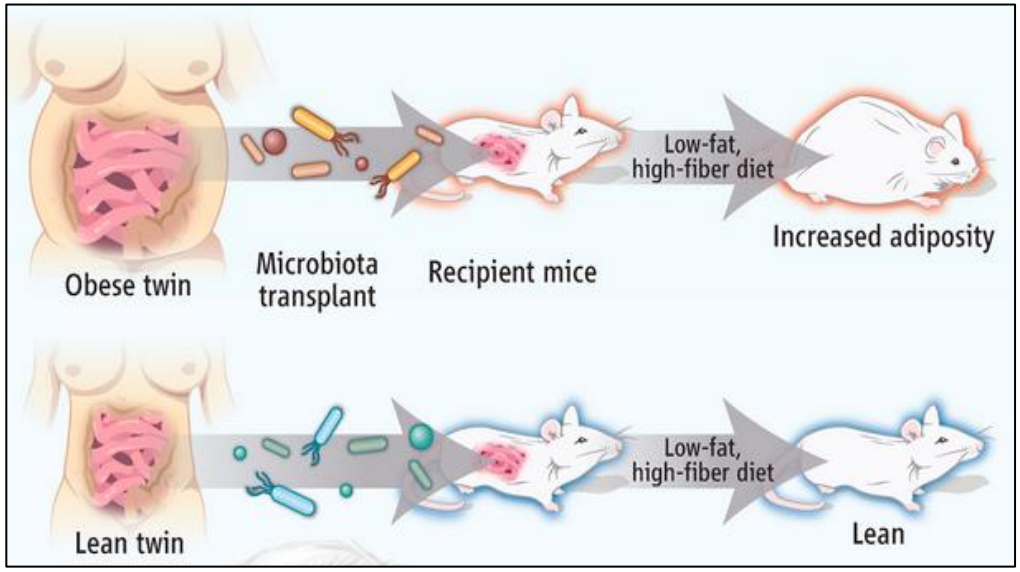
Gut microbiota may represent a **NEW TARGET** to treat or prevent a variety of diseases

Science AAAS

Fighting Obesity with Bacteria

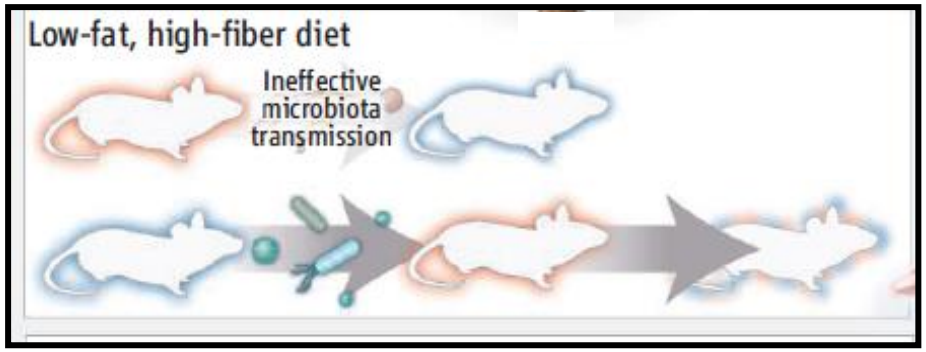
Alan W. Walker and Julian Parkhill

2013



Mice receiving a transplant from the Obese twin donors developed increased adiposity compared to those receiving transplants from Lean twin donors

Cohousing Ln and Ob mice prevented the development of adiposity in Ob mice suggesting that the lean microbiota was predominant

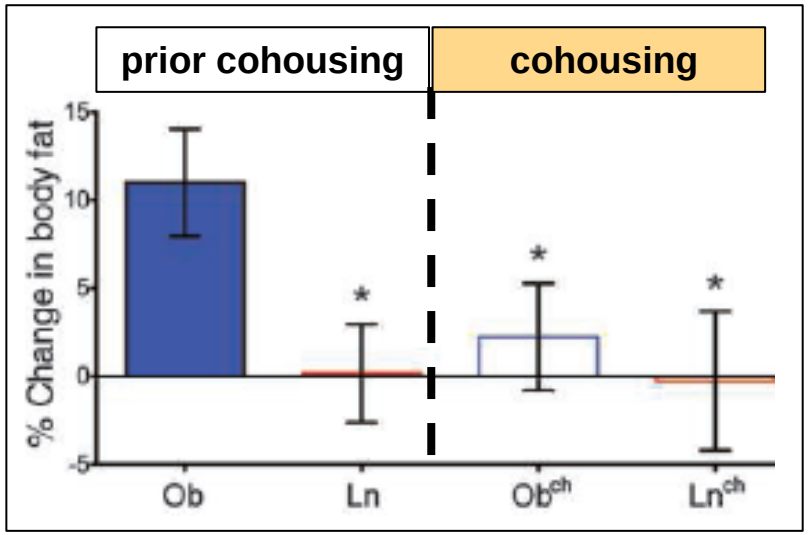


Science AAAS

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

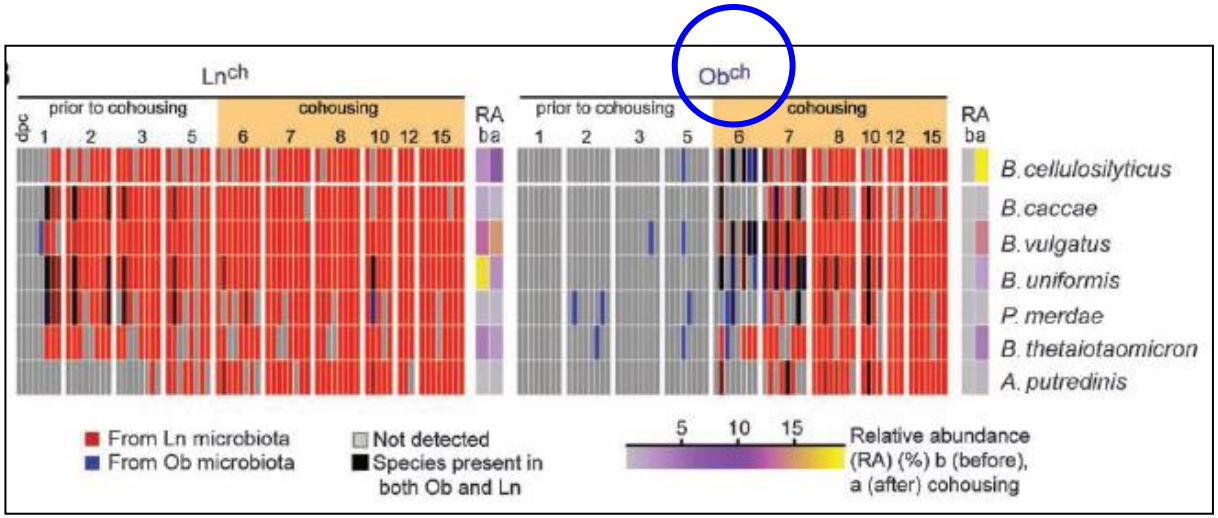
Vanessa K. Ridaura *et al.*

2013



Cohousing Ln and Ob mice decreased body weight and adiposity in Ob mice…….

……and transformed their microbiota's to a leanlike state, that is invasion of Bacteroidales from Ln into Ob microbiota



CONCLUSIONS

Gut microbiota has been identified as a fascinating 'new organ' which affects many biological systems throughout the body

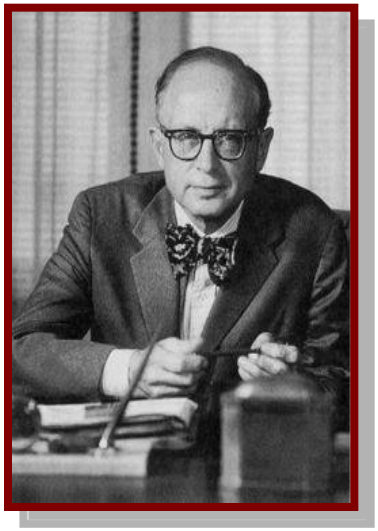
The dysbiosis produces metabolites and bacterial products acting as systemic signalling molecules. The end result of this process is energy harvest and weight gain

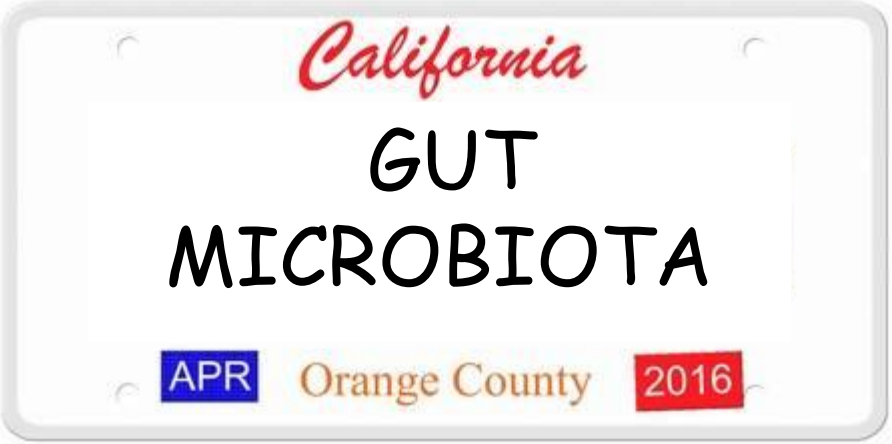
The transplantation of obese humans and rodents fecal microbiota transfers the obese phenotype in recipients

The transplantation of lean microbiota to the mice colonized with the obese microbiota was associated with the rescue of the obese phenotype.

The greatest obstacle to the knowledge is not ignorance, it is the illusion of knowledge

Daniel Joseph Boorstin, Historian [1914-2004]





Merry Christmas

Thank You for the kind attention