Gut – microbiome interactions; implications for human health

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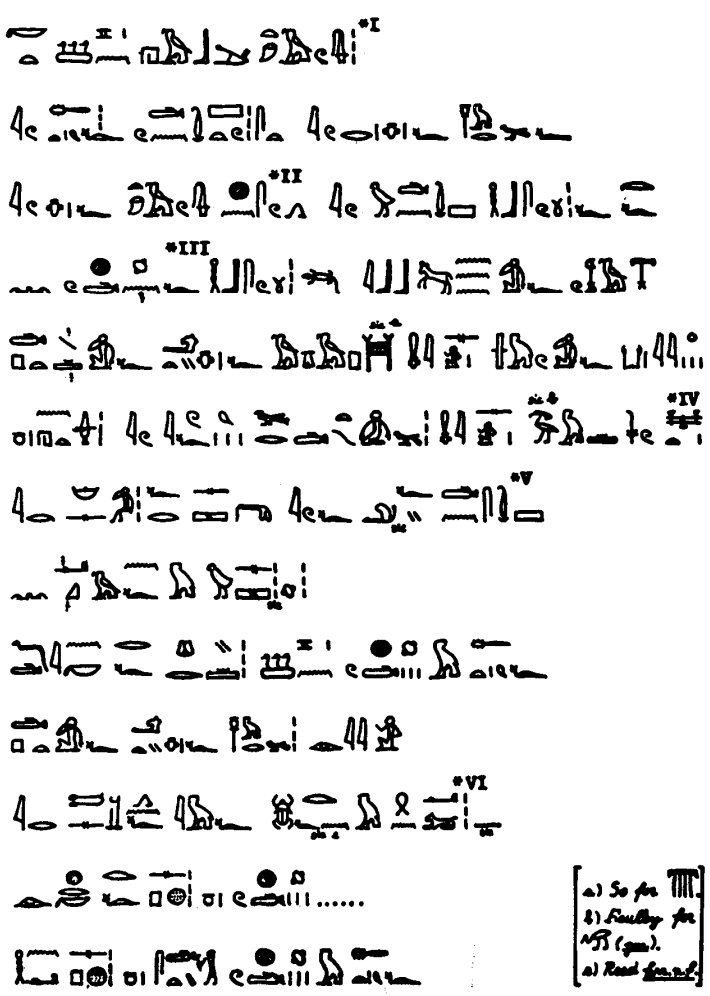
Some key elements

- Textbooks
  - Colon absorbs water and propels feces
- Historical aspects
  - Ancient Egypt
  - Methnickoff and Arbuthnot-Lane
  - Hurst
- Today´s understanding
  - Microbiome
  - Development of immune system
  - Implications for human health

The systemic effect of whdw – the putrefactive priciple of faeces

PAPYRUS BERLIN, XIII, 3-7:



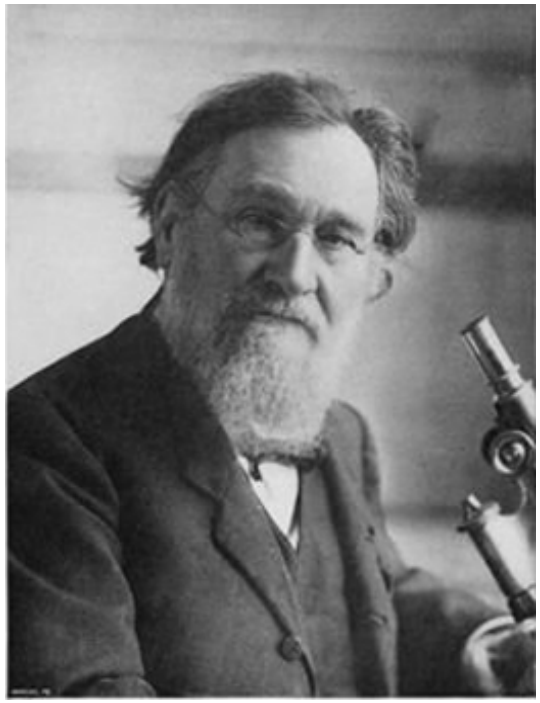
Another [*prescription*] *against a pool* [*of* whdw] *generating fever;*
his [*the patient's*] *body is heavy, his* r3 lb (*cardia? pylorus?*) *is sick;*
his heart is hot, it pulsates;
his covers are heavy on him;
he cannot stand many covers;
he suffers thirst at night
and he tastes [*feels*] *his heart oppressed*
like [*that of*] *a man who has eaten fruits of the sycamore*(?) *tree;*
his flesh is weak like [*that of*] *a man whom the road has found.*
If he crouches in order to evacuate
(*then*) *his intestines are under pressure*
(*but*) *he is not getting along with the evacuation.*
Thou shouldst say to him [*i.e., concerning such a case*];
This is one who is under a pool of whdw *in his body;*
he tastes [*feels*] *his heart;*
he is sick [*and*] *I shall act* (*on his behalf*).
Should it rise in him and become an occlusion
you will have to apply [*to him*]
remedies against whdw, *together with remedies to destroy* whdw.[29]

"The bird which is called the ibis and wich is a native of Egypt, by means of its hooked beak, laves the inside of its body by introducing water into the channel by which it is specially necessary for health that the residuous food shoold be discharged"

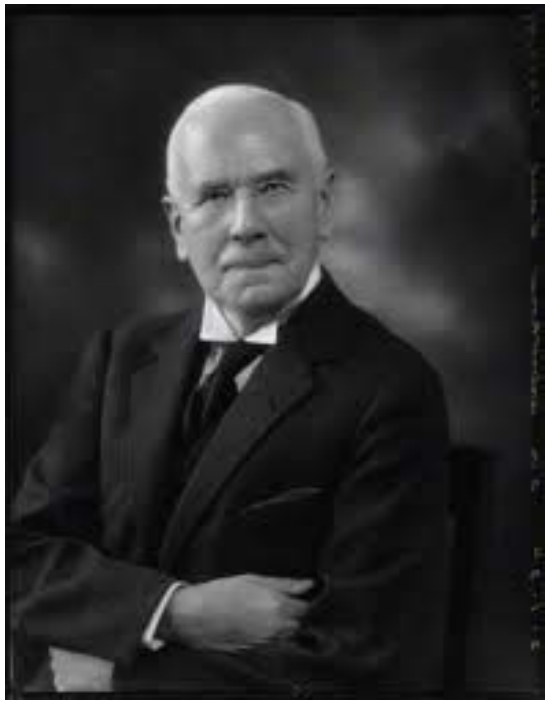
Plinius (23-79 A.D.)

Intestinal intoxication

Elie Methnikoff (1845-1916)



Sir William Arbuthnot-Lane (1856-1943)



Methnikoff: Bacterial toxins from colon responsible for ageing. The colon is a redundant organ and will soon disappear.
Lane: I can take it out!

ADDRESSES AND O

THE UNHAPPY COLON *

By Arthur F. Hurst, D.M. Oxon., F.R.C.P. Lond.
SENIOR PHYSICIAN TO GUY'S HOSPITAL, LONDON

No organ of the body is so misunderstood, so slandered, and so maltreated as the colon. Text-books of anatomy are apt to describe it as it is found in the dissecting-room, not as it occurs in a living man. Text-books of physiology describe its motor functions as seen under experimental conditions in animals, and rarely pay sufficient attention to the results of observations made on healthy human beings, and they ignore more or less completely its secretory functions. The colon is slandered every day in the advertising columns of the popular press, which accuse it of sins it never commits, and the mass suggestion which results from constantly reading about the disastrous effects of intestinal intoxication results in most of the lay public and many of the medical profession joining in these slanders. By promoting the sale of purgatives and encouraging the use of various other methods of irritating the colon, these slanders result in maltreatment. No wonder that the colon is unhappy.

Intestinal autointoxification

Many physicians will today laugh of these old theories – but are they completely to be rejected?

The changing pattern of diseases

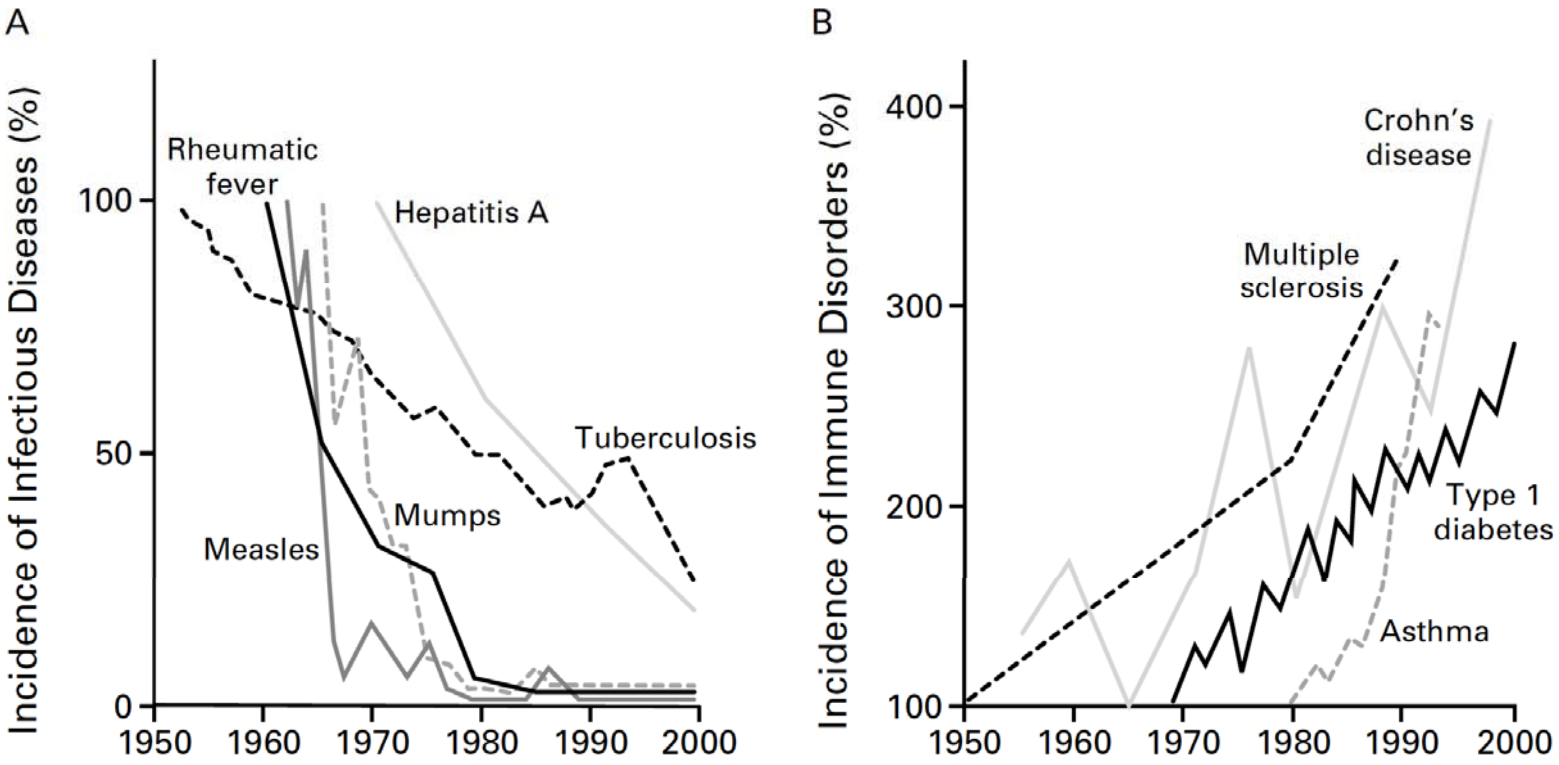


Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.

Bach JF. NEJM 2002

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Anatomy of mucosal surfaces

- Skin 1 ½ - 2 m^2.
- Airway mucosa 100 m^2.
- Intestinal mucosa 3-400 m^2.

- The mucosal immune system by far the largest compartment.

- 2000 + bacterial species
- Outnumbers own cells by 100
- Large interindividual differences
- 6-7000 kg faeces in a lifetime
- Digests carbohydrates

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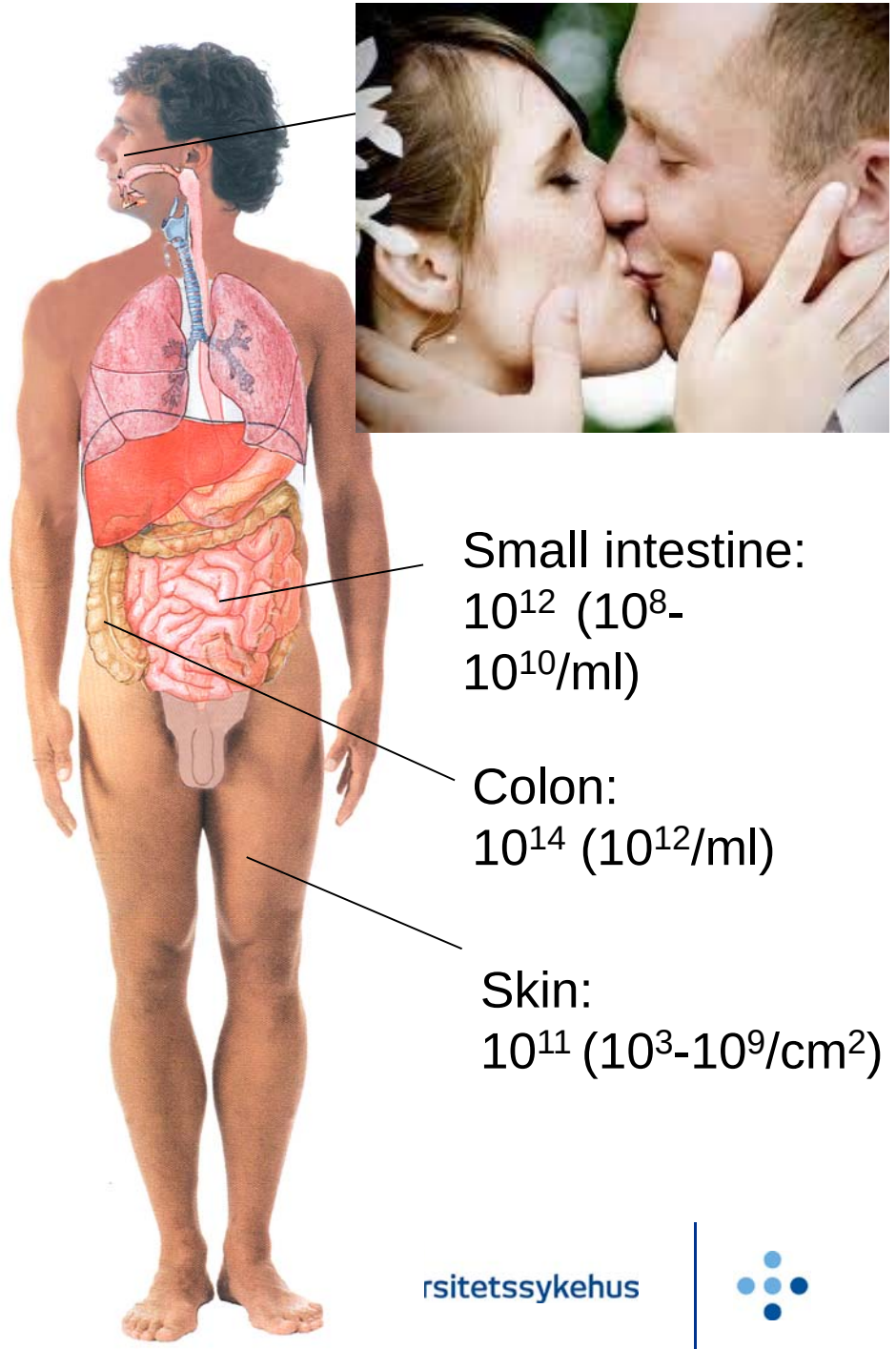
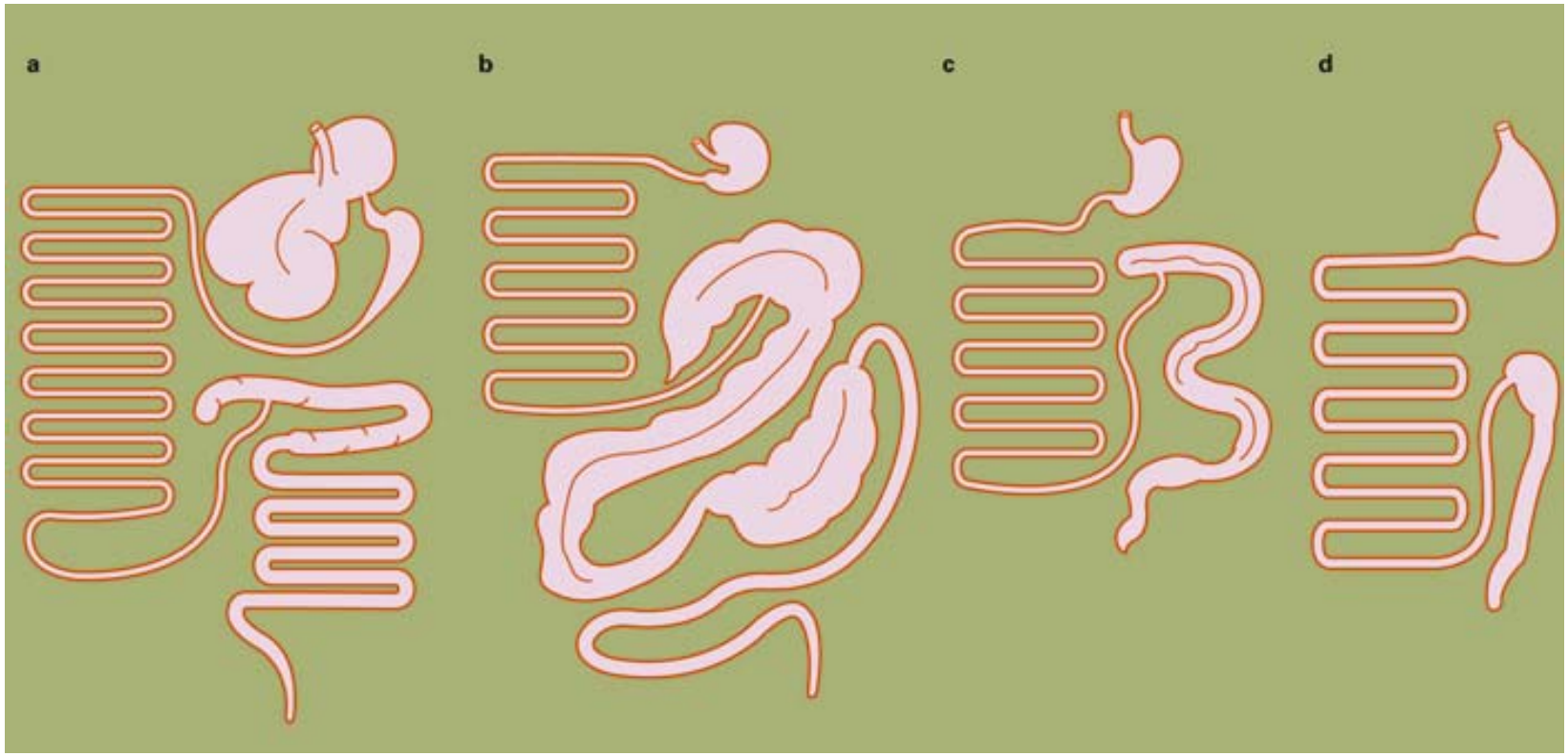
Human organisms is the home of billions and billions of bacteria, in total one hundred tousand billions (10^{14})

(Norways Oil Fortune (which is saved) is now NOK 4000 billions)



Mammalian digestive system



Valeur and Berstad 2008

Ruminating herbivores (sheep)

Non-ruminating herbivores (horse)

Omnivores (humans)

Carnivores (dog)

tidsskriftet.no

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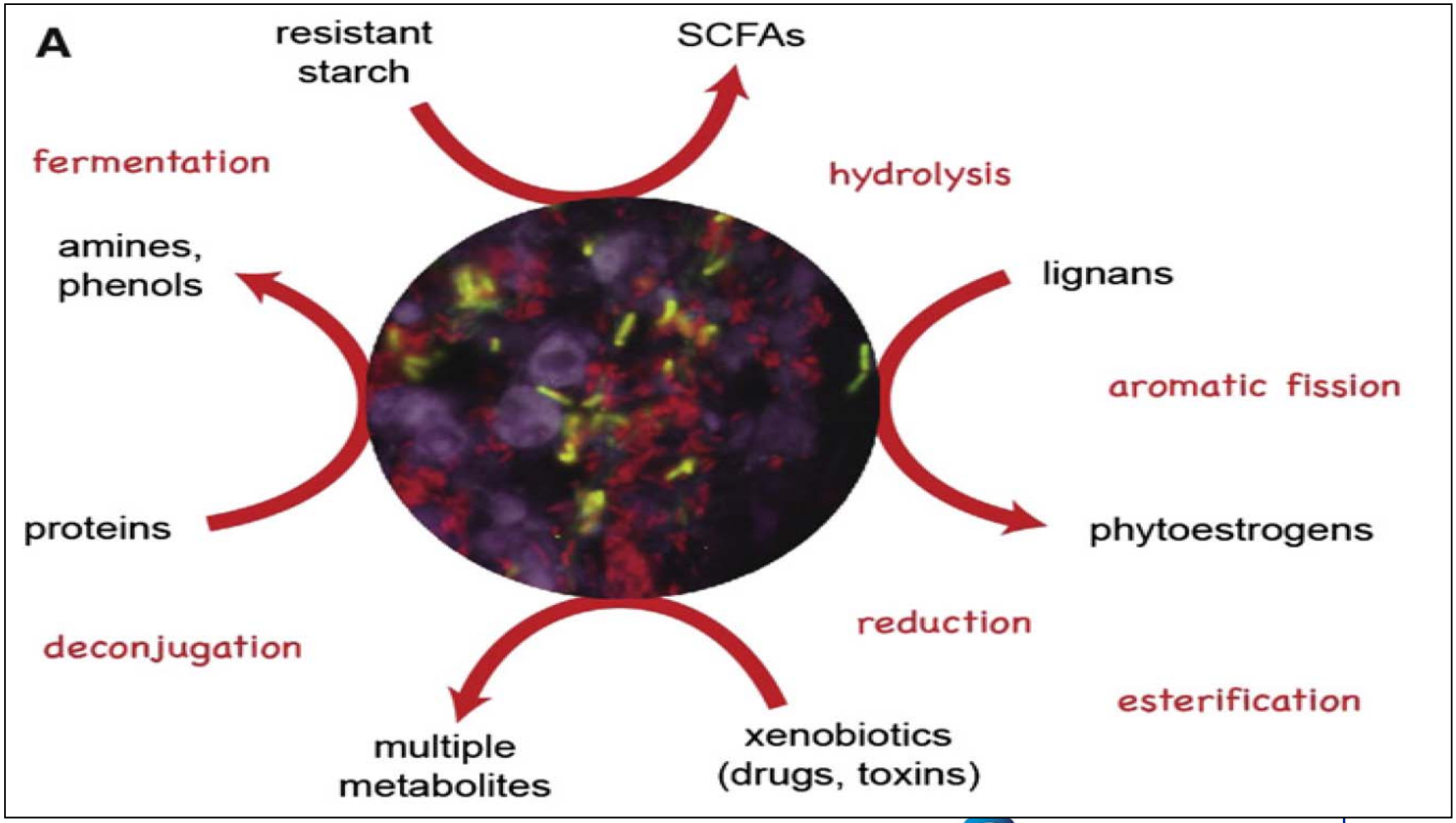
Why do we have a colon?

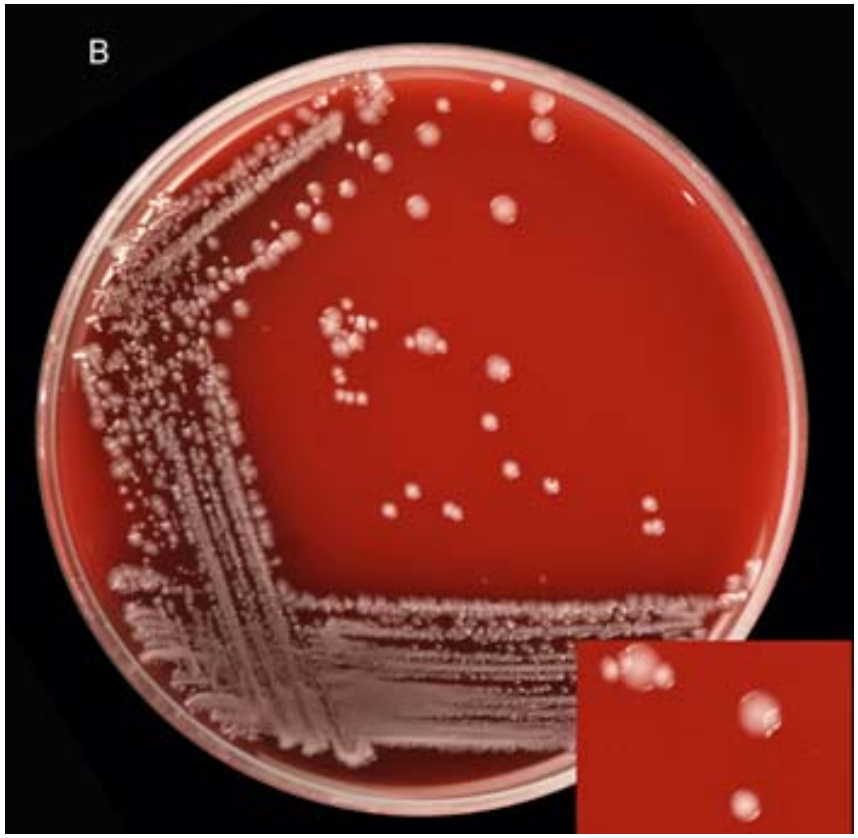
- Proteins, fat and mono- and disaccharides readily absorbed (ex lactase-deficiency)
- Complex carbohydrates passes to colon
  - Structural fibre are not fermented
  - Water soluble fibre fermented giving gases (H_2, CO_2, CH_4) and short-chain fatty acids (SCFA)
- Bacterial fermentation gives
  - 5-10 % of human calories, 30-40 % in non-ruminating herbivores and 60-90 % in ruminating

Most metabolites in human plasma is derived from gut bacteria!



Mikrobiology

Classic culture



<30% of the bacteria in the intestines are cultivable

Microbiomics

- "Genomics" studies of mikrobiology, primarily by means of sequencing (of bakterial-DNA)
- Microbiota: Totality of microbes in a milieu (e.g. intestine)
- Microbiome: Totality of genes in the mikrobiota

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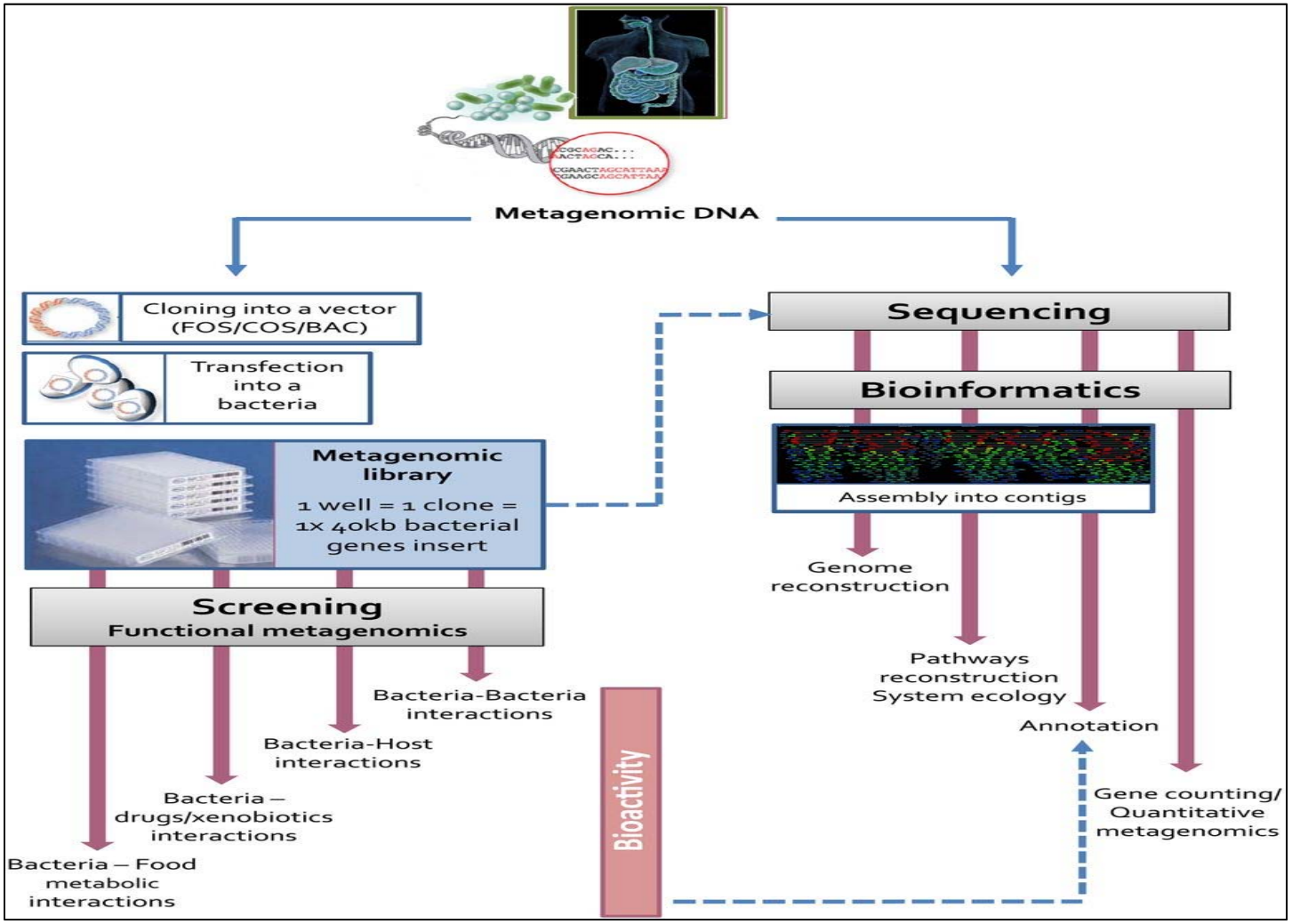
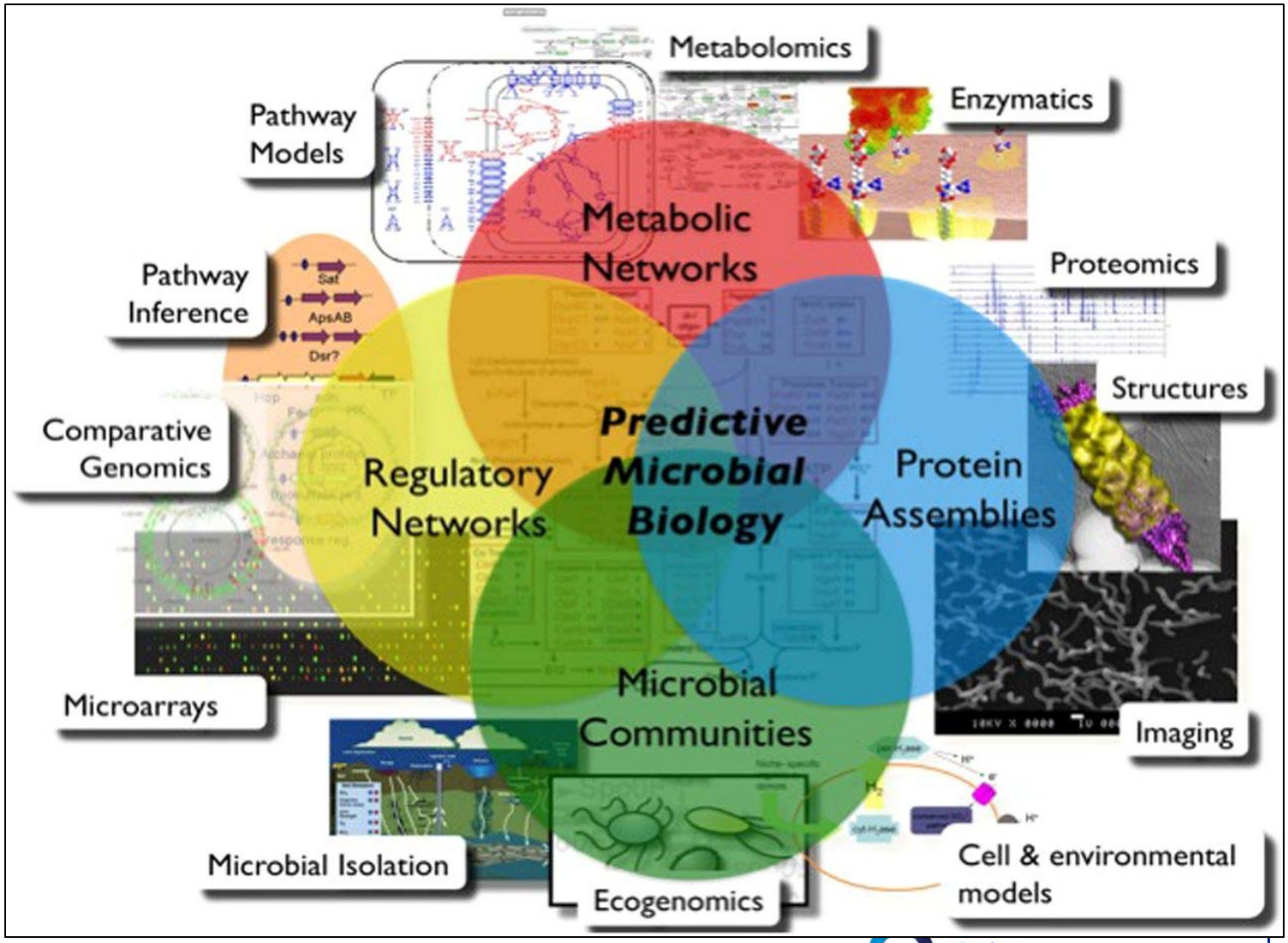
Main metagenomics applications, from the metagenomic libraries construction and screening, until next generation sequencing, gene count and genome reconstruction.



Lepage P et al. Gut 2013;62:146-158

An integrative approach to study microbial



Lepage P et al. Gut 2013;62:146-158

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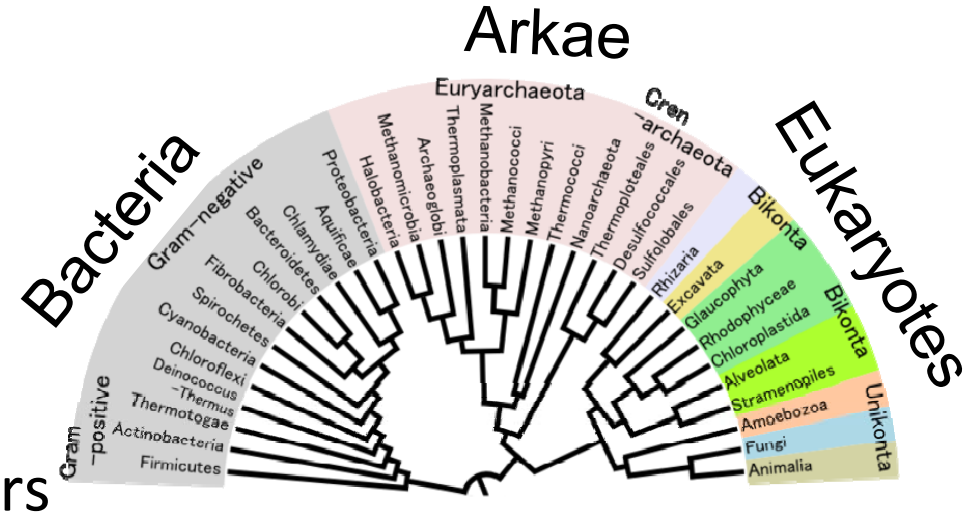
GUT

The diverse forms of life

- Life on earth impossible without bacteria
- Bacteria has been around for 2,5 billion years
- All multicellular organisms live in close collaboration with bacteria
- The modern humans developed for approximately 200 000 years ago
- Co-evolved with bacteria



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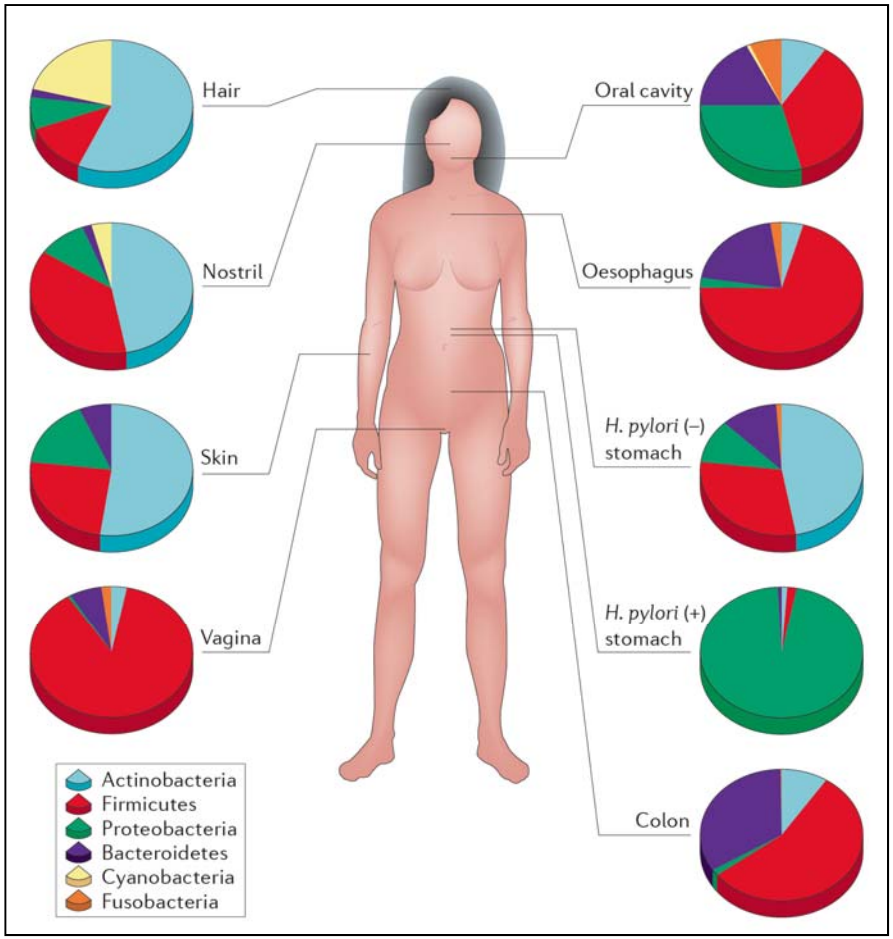
Microbiota = “Normal flora”

- 10^{14} bacterier – 10x more than human cells

- J.Lederberg:
  - “…think of each host and its parasites as a superorganism… “
  - “Teach war no more”

  (Science 2000)



Cho and Blaser 2012

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Human intestinal microbiome

Nature 2010, 464:59-65

A human gut microbial gene catalogue established by metagenomic sequencing

Qin, Li, Raes, et al (MetaHIT consortium)

- Metagenome
  - 2000 different species, each with 4000 genes
  - Equals ~ 8 millioner gener, that means more than 400 times no of genes in human genome
  - Microbiome large inter-indvidual differences
- Recently shown 3 stable enterotypes
  - Prevotella
  - Bacteroides
  - Ruminococcus
- Influenced by food
- Enterotypes assosiated with lean body and with obesity

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Table 1. Dysbiosis Associated with Intestinal and Systemic Diseases

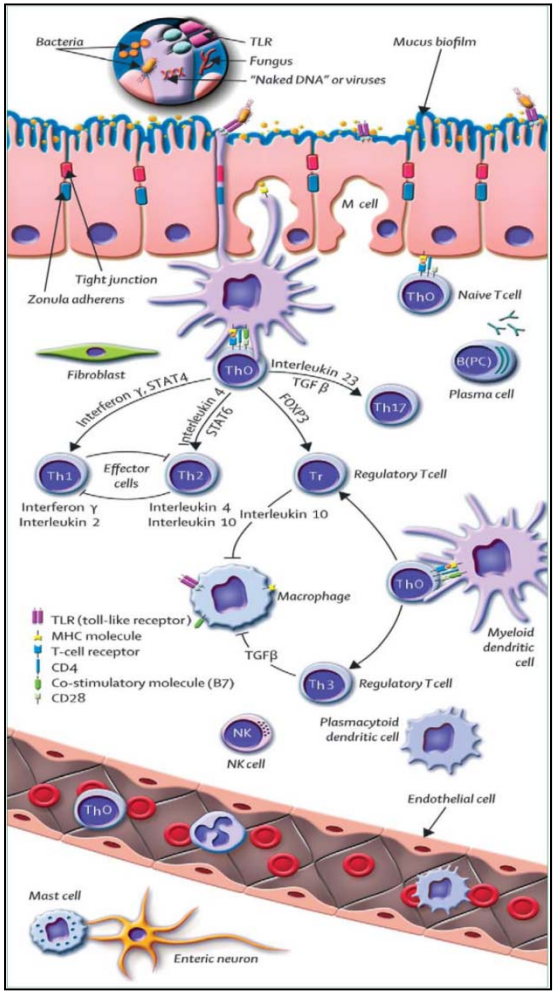
Dysbiosis-Associated Diseases or Conditions
Obesity
Metabolic syndrome
Nonalcoholic steatohepatitis
Inflammatory bowel diseases (Crohn's disease, ulcerative colitis, pouchitis)
Irritable bowel syndrome, functional bowel disorders
Atherosclerosis
Type 1 diabetes
Autism
Allergy
Asthma
Celiac disease

See reviews by Bäckhed et al. (2005), Honda and Littman (2012), Ringel and Carroll (2009), and Sartor (2008, 2010).

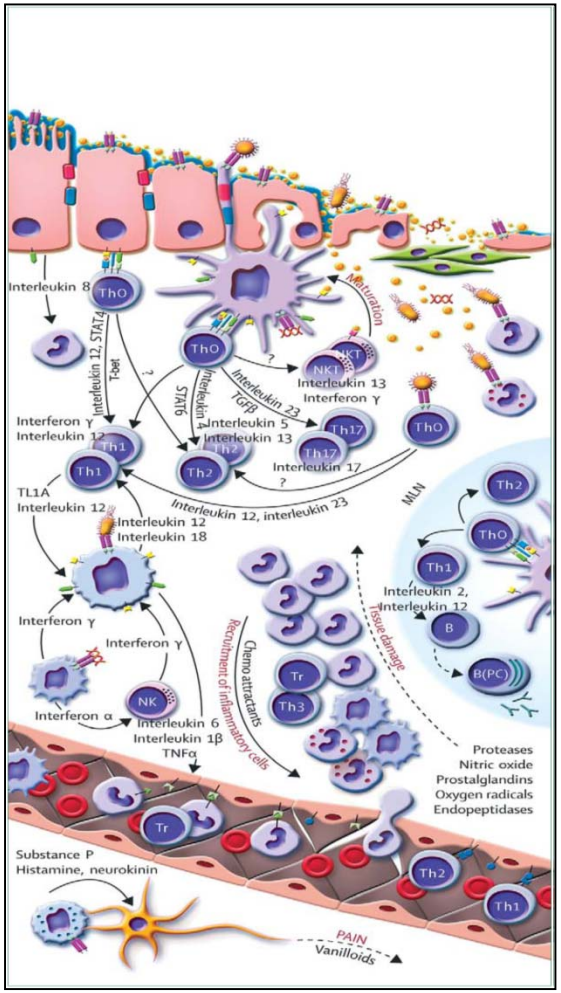
Patogenesis of inflammatory bowel disease

Major differences
- healthy - diseases gut
  - Adaptive immune system
  - Innate immune system

Many possibilities
- for biomarkers (and intervention)



Healthy



Disease

Baumgart and Carding Lancet 2007

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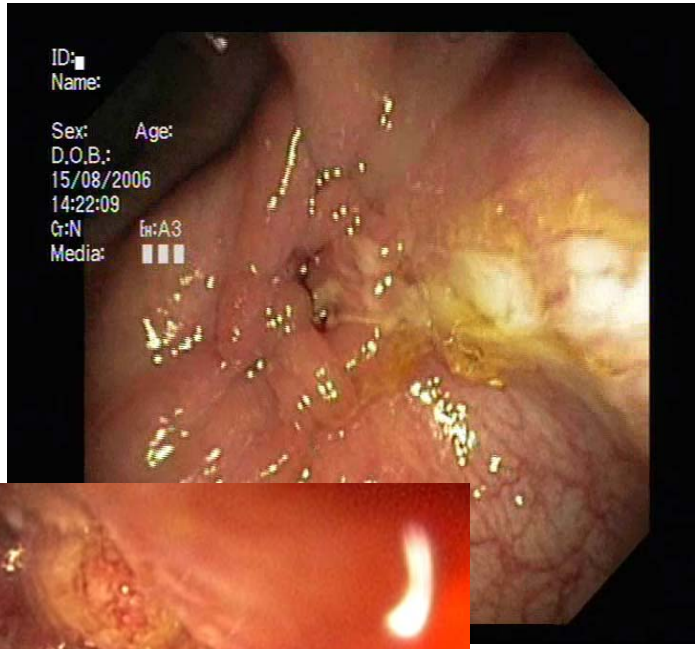
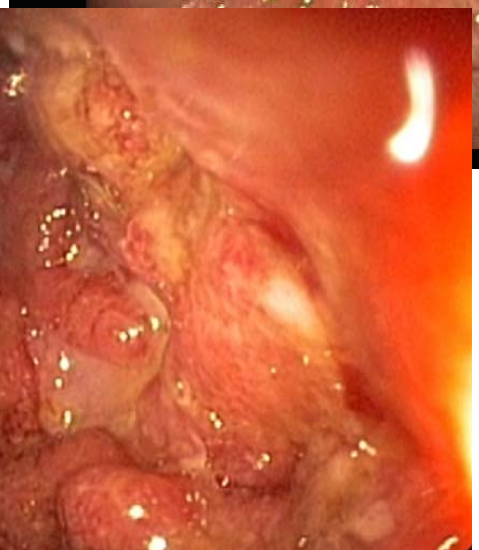
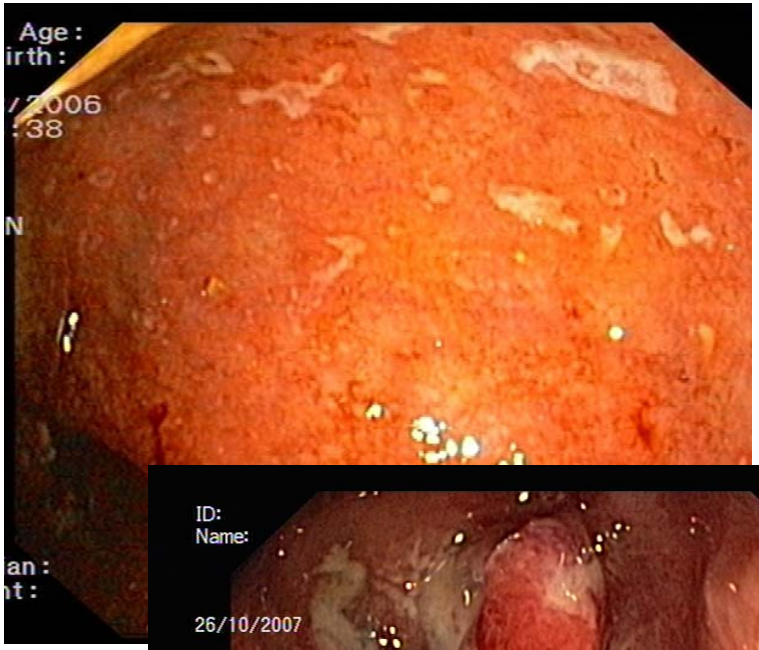
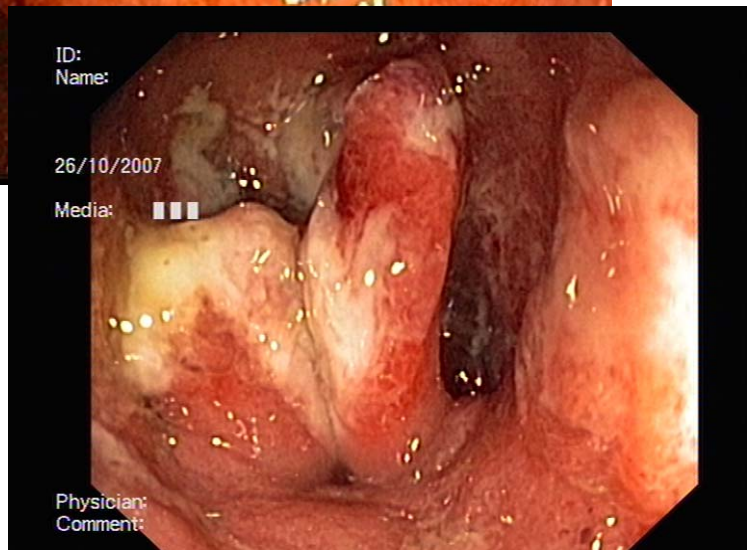
Crohn



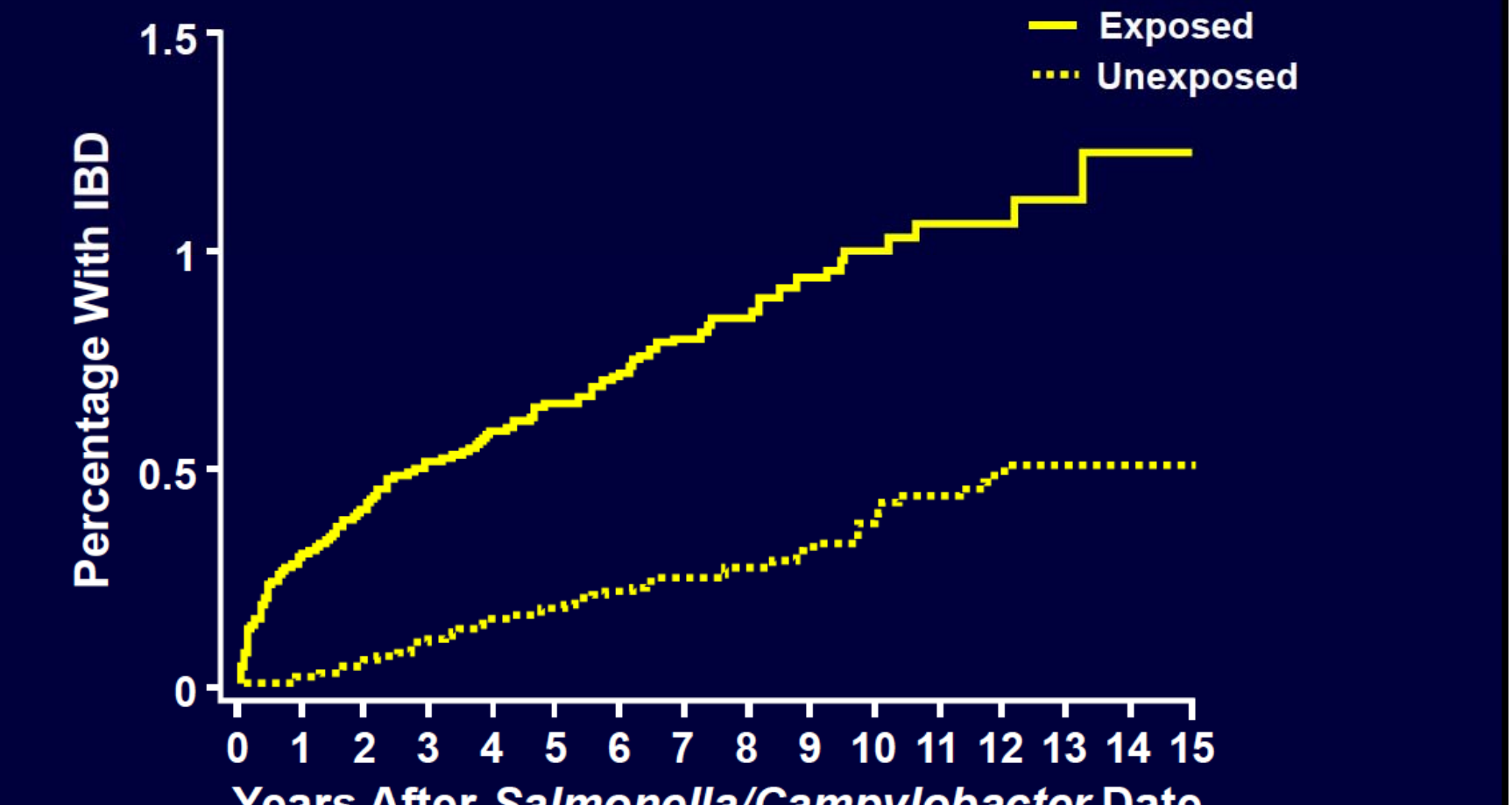


Ulcerative colitis





crease in IBD Incidence for Patients posed to *Salmonella/Campylobacter*



duction of Inflammation Changes the ora: The Chicken-and-Egg Problem

DSS

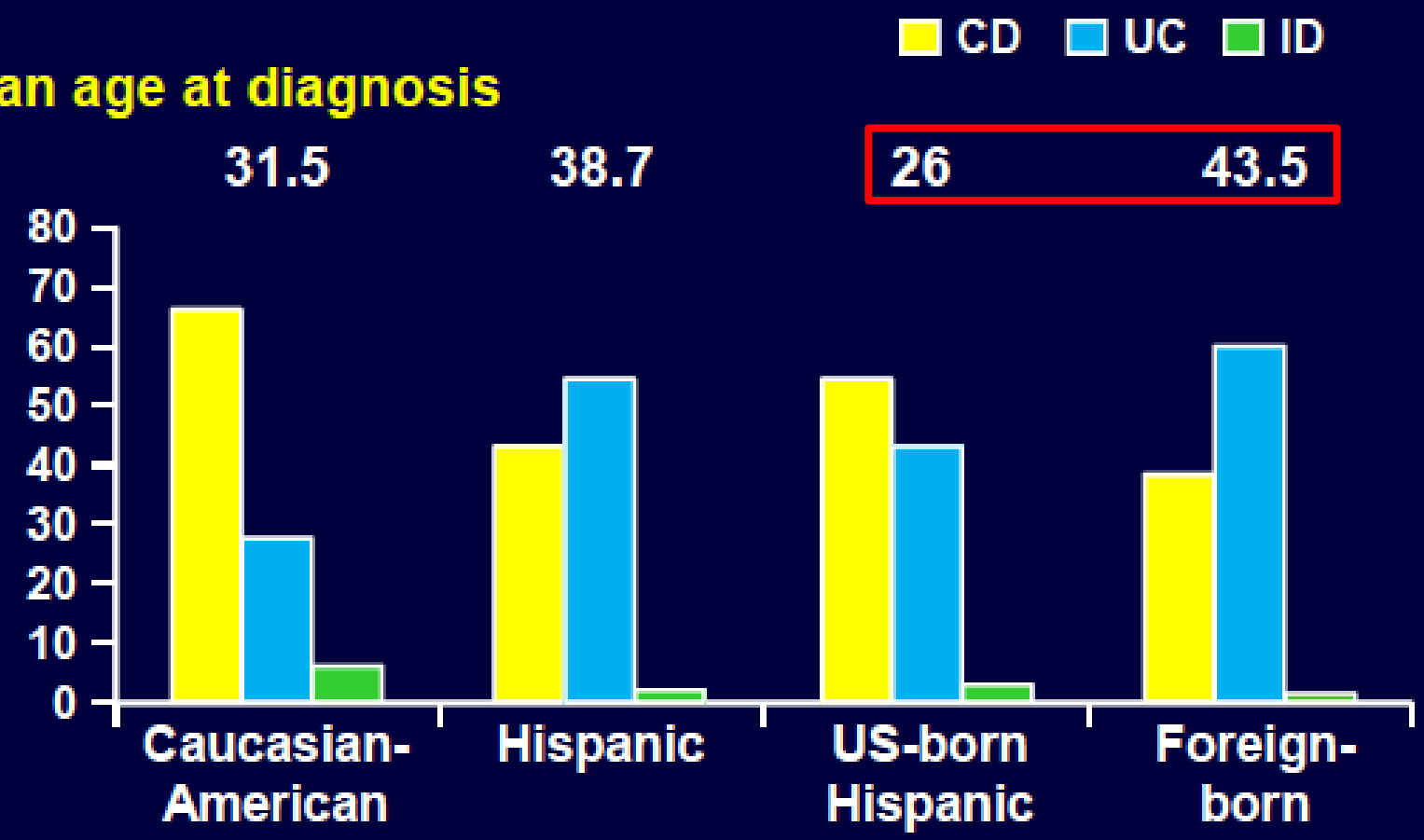
Colitis!!

SS disrupts epithelial barrier

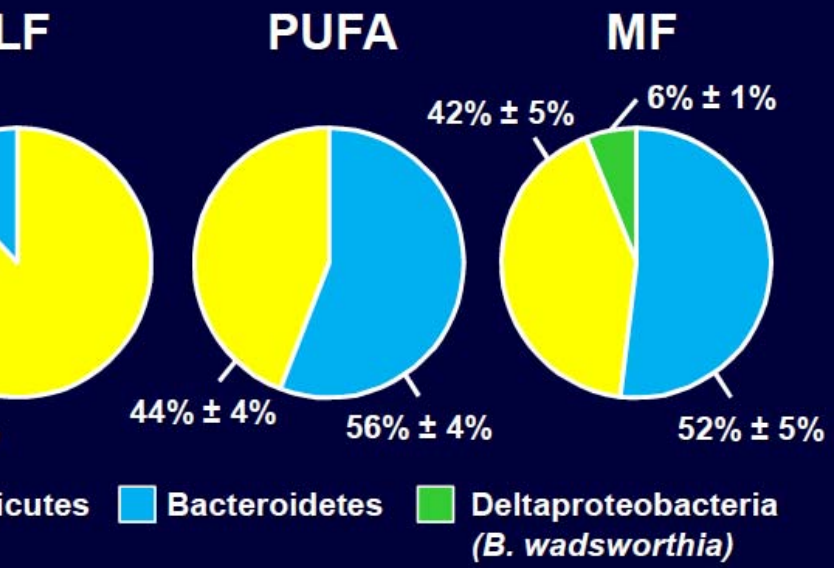
SS-induced colitis causes a shift in the intestinal icroflora towards pro-inflammatory Gram-negative bacteria

uring acute colitis *E. coli* increased in wt and TLR-deficient ice ($P<0.05$)

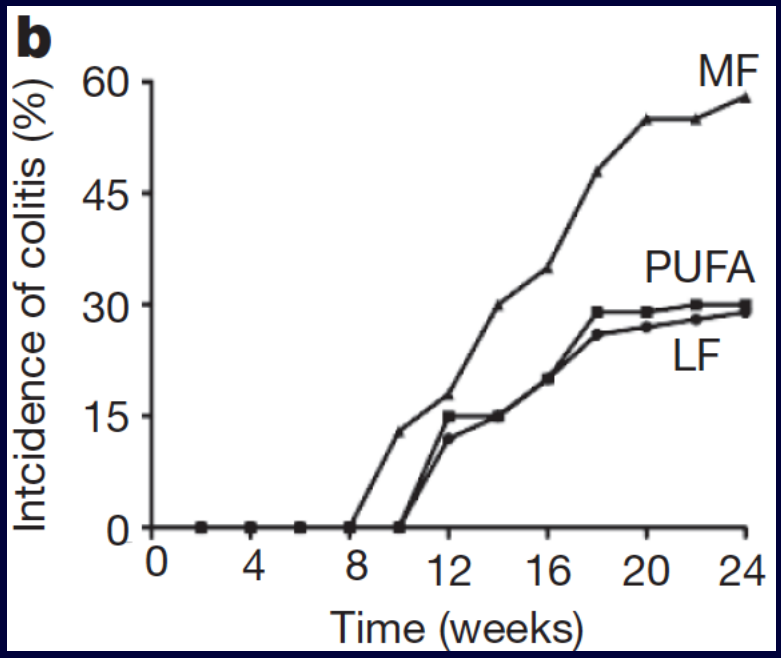
Environmental Factors Determine Disease Expression



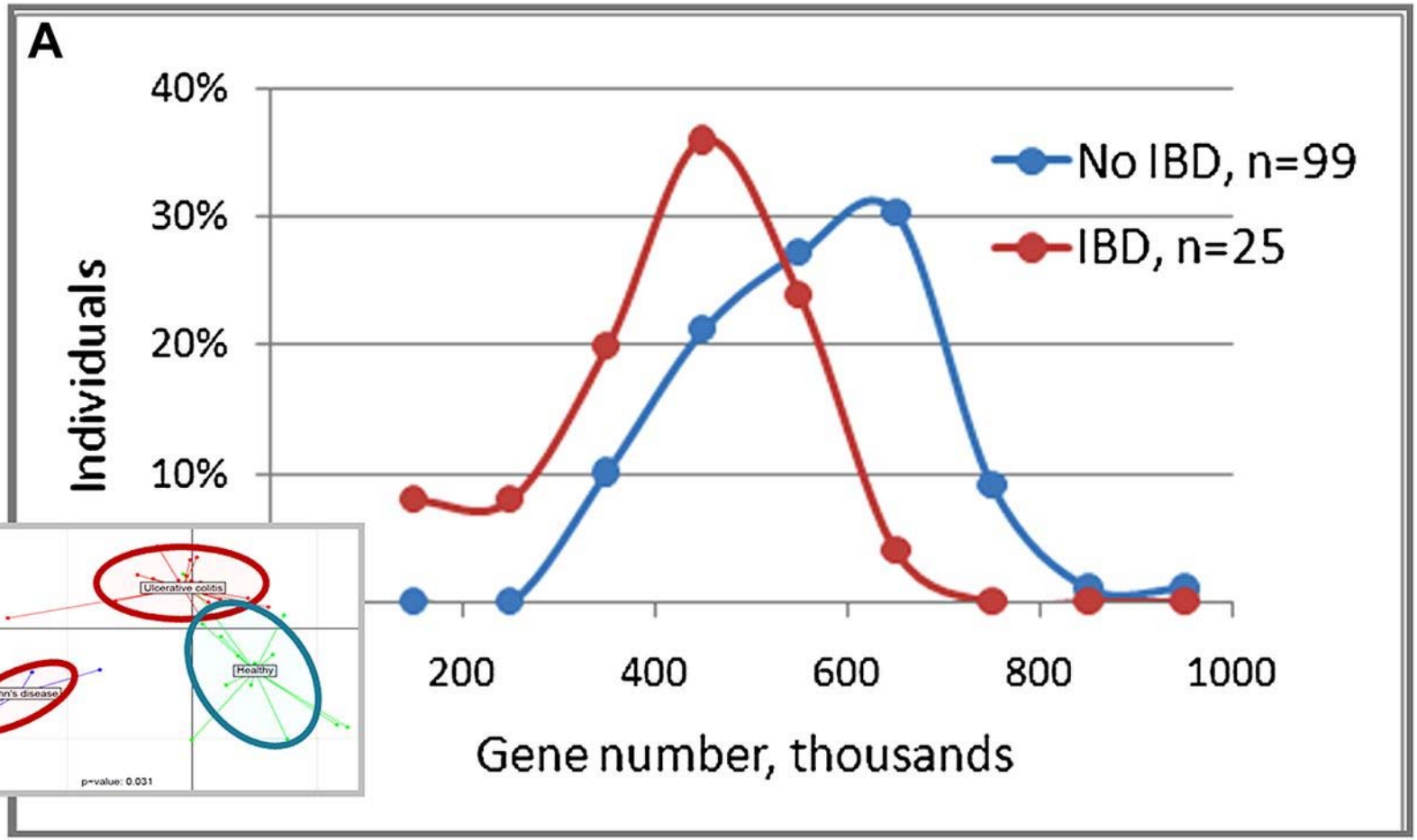
The type of fat intake may increase flammation in the IBD-susceptible host



Saturated high fat diet increased
ılphite-reducing sulphite-reducing
athobiont, ***Bilophila wadsworthia***

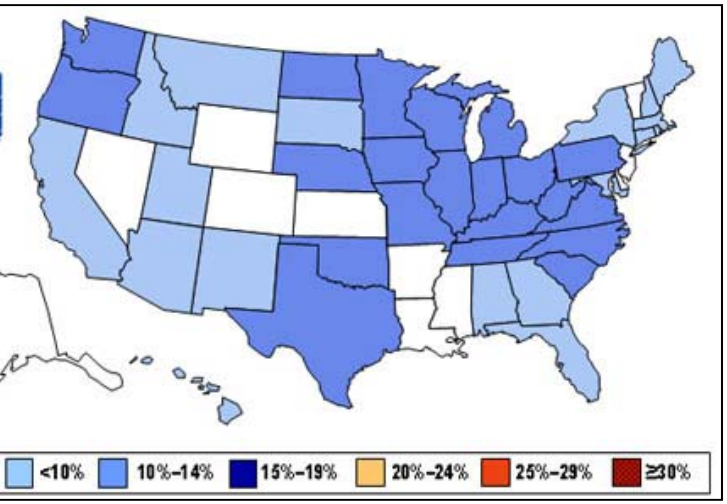


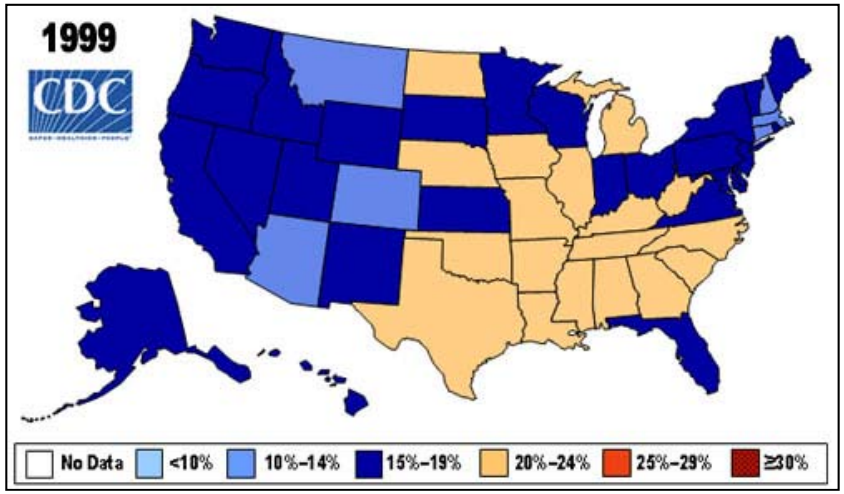
Metagenomic analysis of the human gut microbiota in healthy individuals and IBD

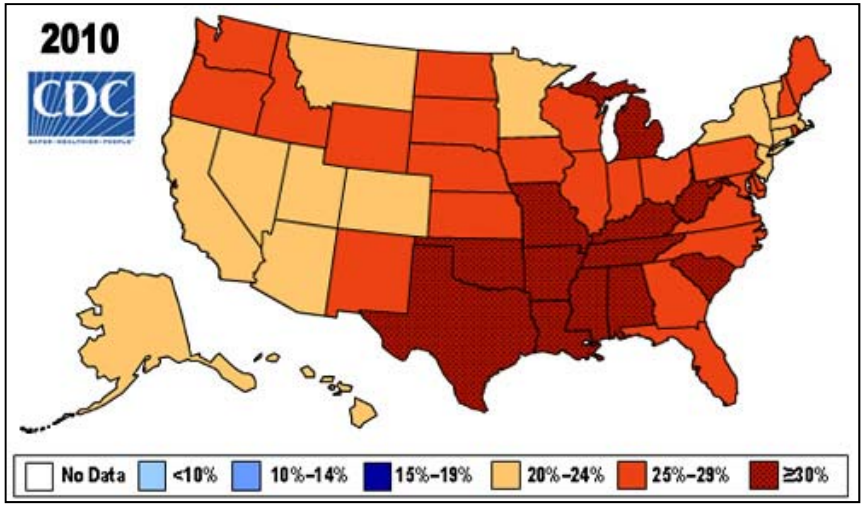


Our new health threat

Obesity epidemic



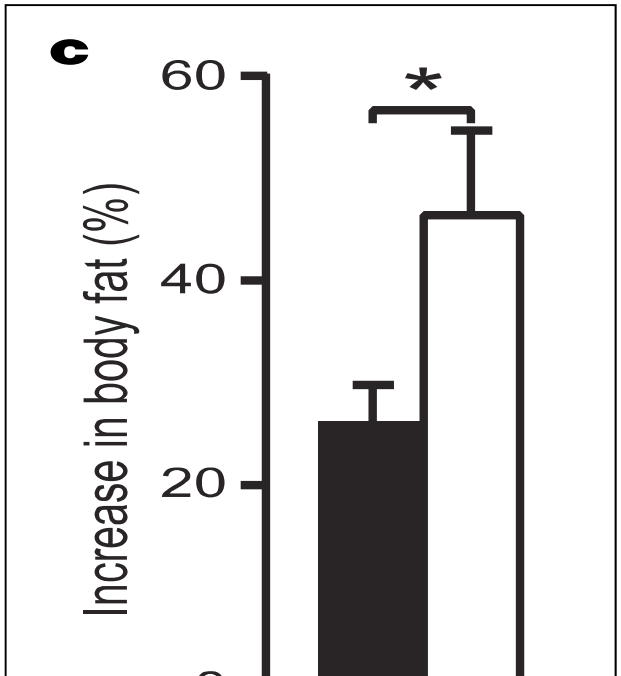




eat nothing but still gain weight”

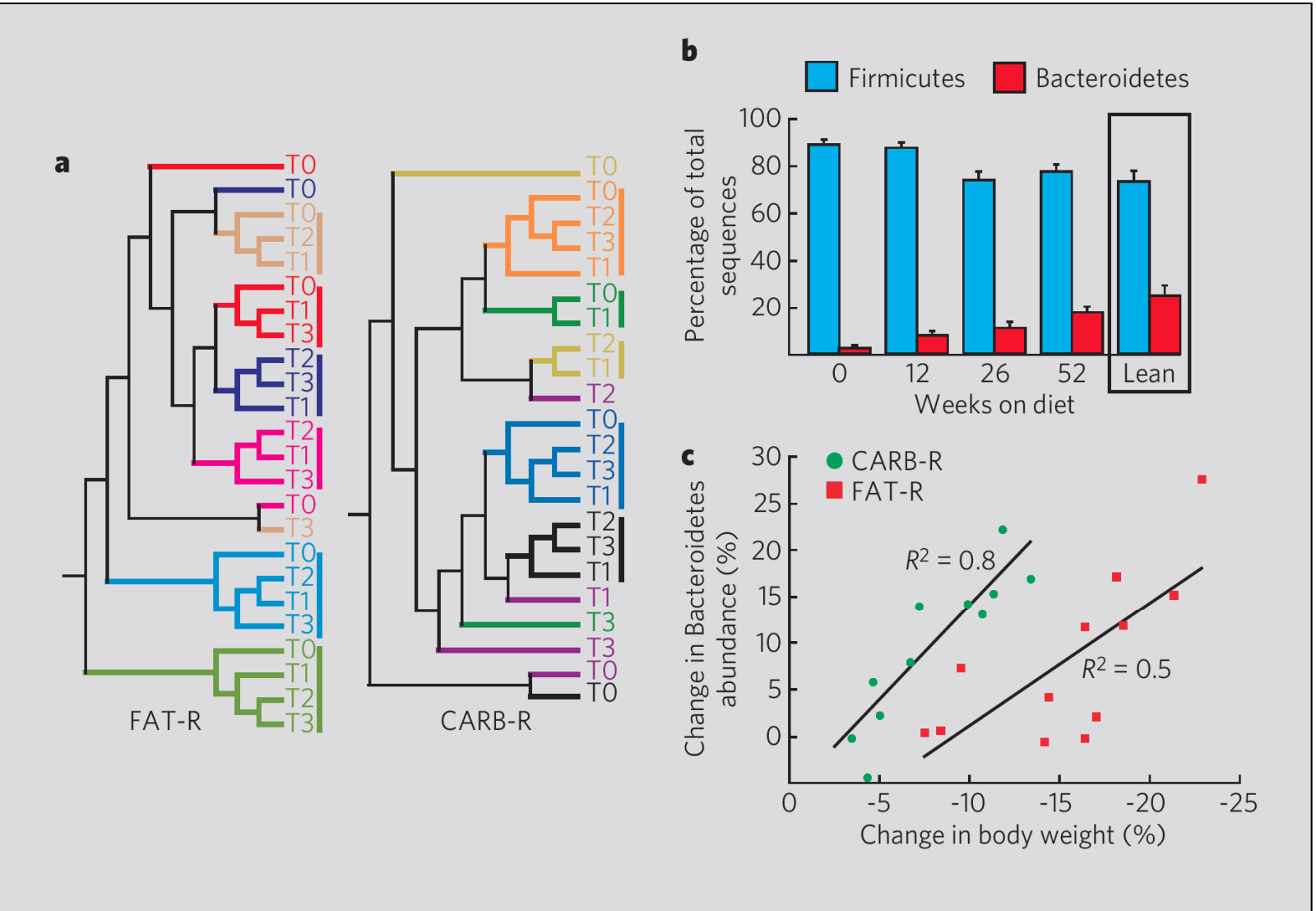
An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh[1], Ruth E. Ley[1], Michael A. Mahowald[1], Vincent Magrini[2], Elaine R. Mardis[1,2] & Jeffrey I. Gordon[1]

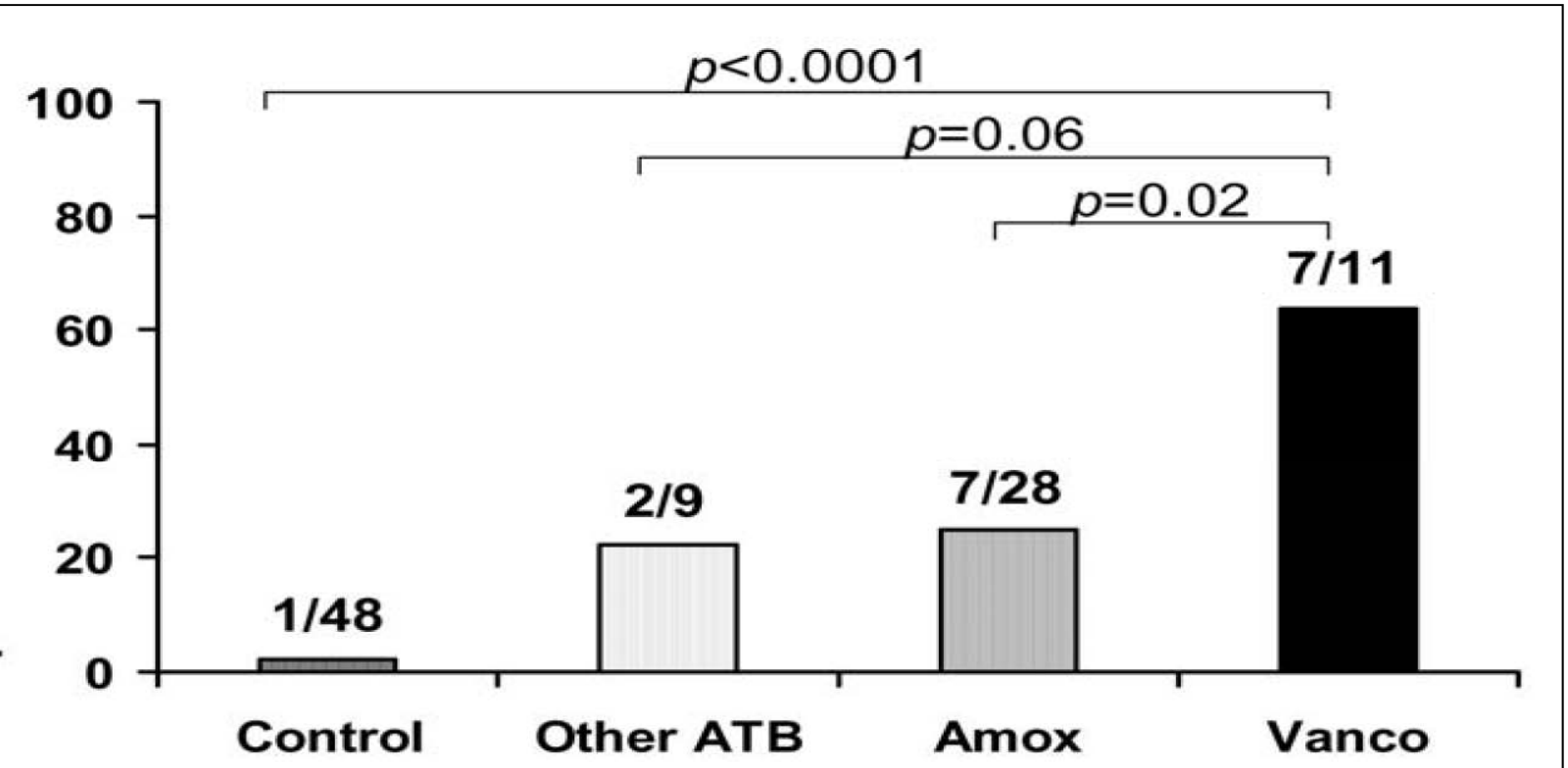


Nature 2006

Manipulation with diet



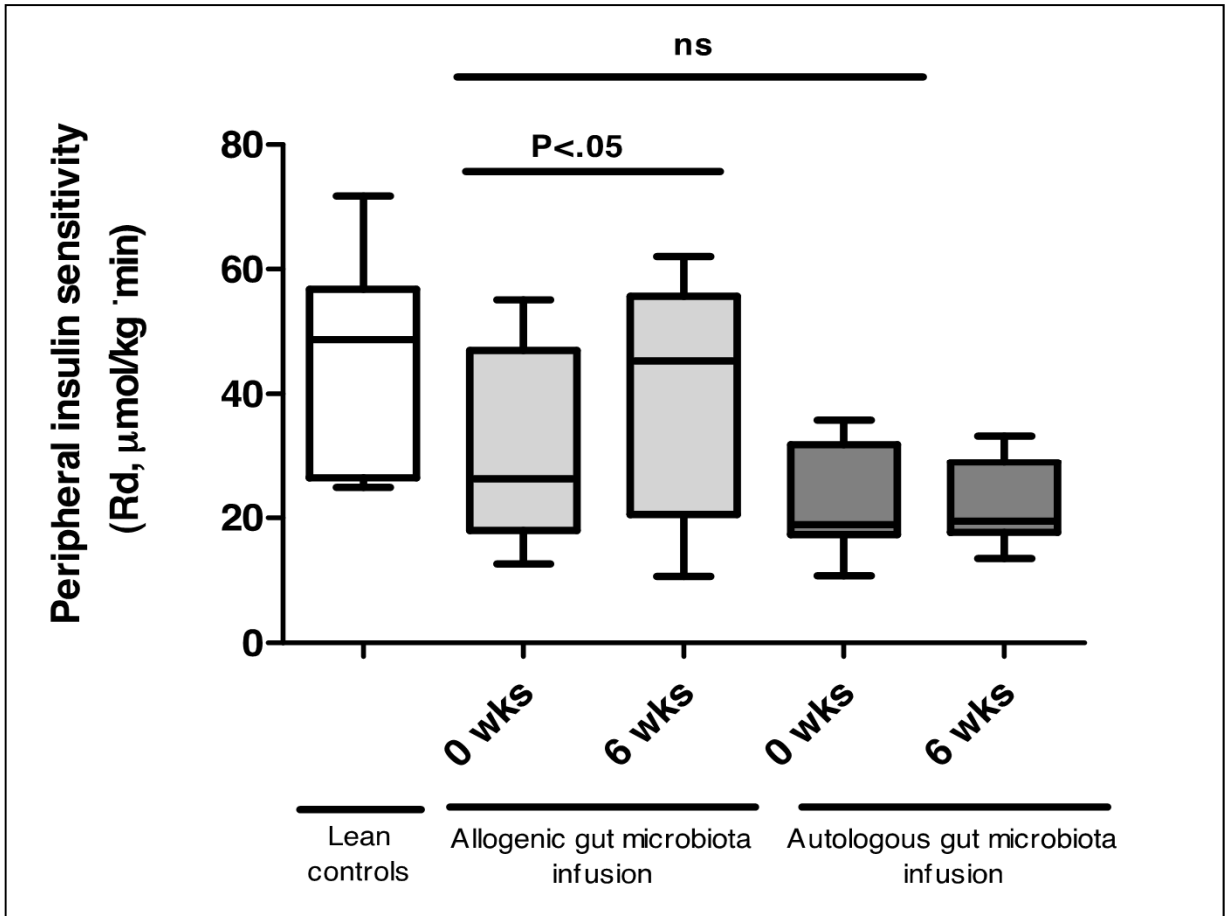
Vancomycin treatment and obesity



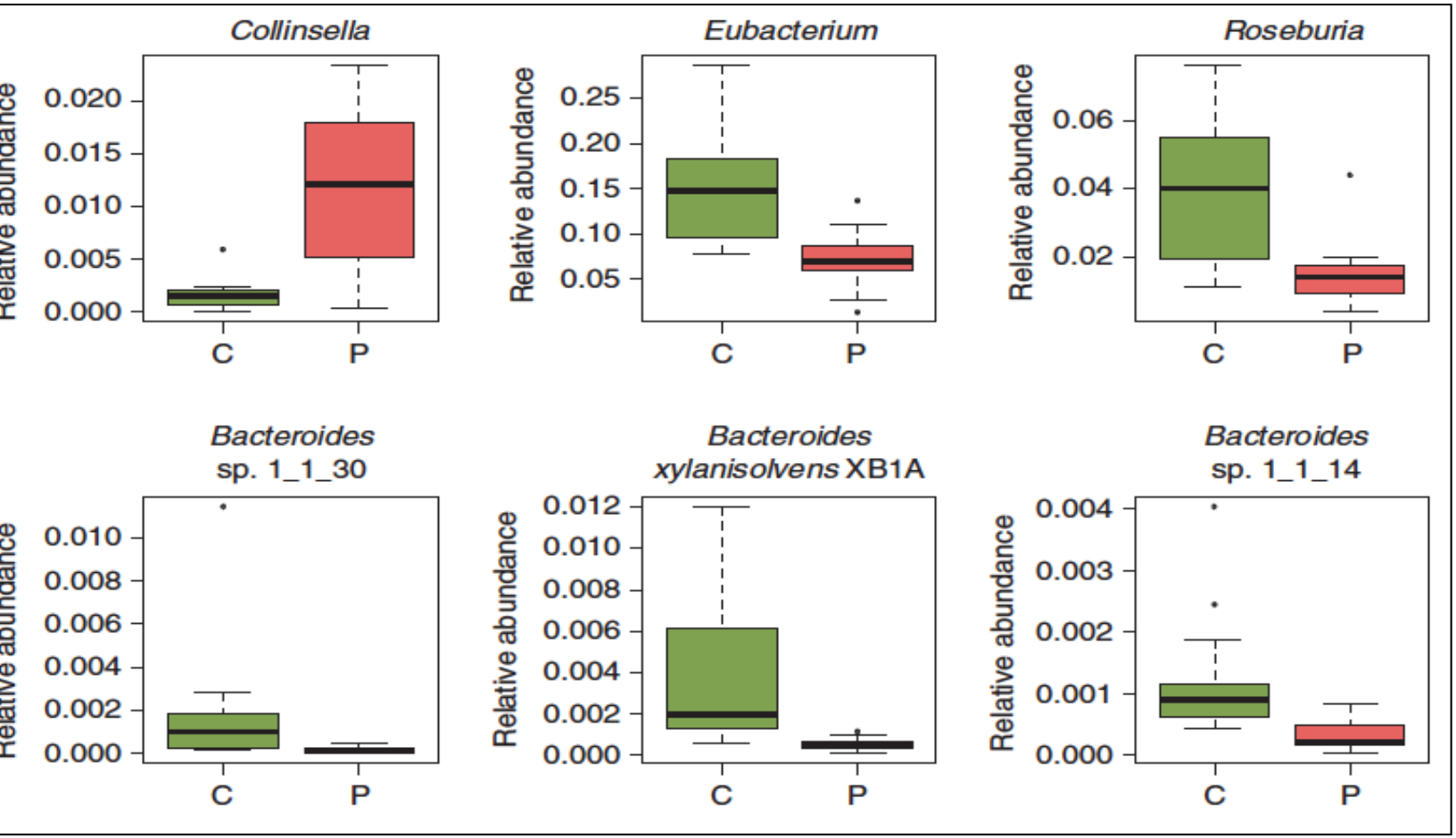
gure 2. Percentage of patients with a major increase (≥10%) body mass index (BMI), defined as an increase.

FATLOSE trial:

Faecal transplantation from lean subjects to cure metabolic syndrome



Gut microbiome and atherosclerosis



Karlsson et al Nature Comm 2012, shotgun sequencing of gut microbes

ell

Leading Edge

Perspective

Metagenomics and Personalized Medicine

Herbert W. Virgin[1,*] and John A. Todd[2,*]

[1]Department of Pathology and Immunology, Department of Molecular Microbiology, and Midwest Regional Center of Excellence for Biodefense and Emerging Infectious Diseases Research, Washington University School of Medicine, St. Louis, MO, 63110, USA

[2]Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory, Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0XY, UK

*Correspondence: virgin@wustl.edu (H.W.V.), john.todd@cimr.cam.ac.uk (J.A.T.)

DOI 10.1016/j.cell.2011.09.009

Genetic studies

rtual explosion in
understanding of
genetics of IBD

VAS and Crohn

- 2001 two loci (NOD2 and 5q31)
- 2006 one locus (IL23R)
- 2007 seven loci (IRGM,ATG16L1 etc)

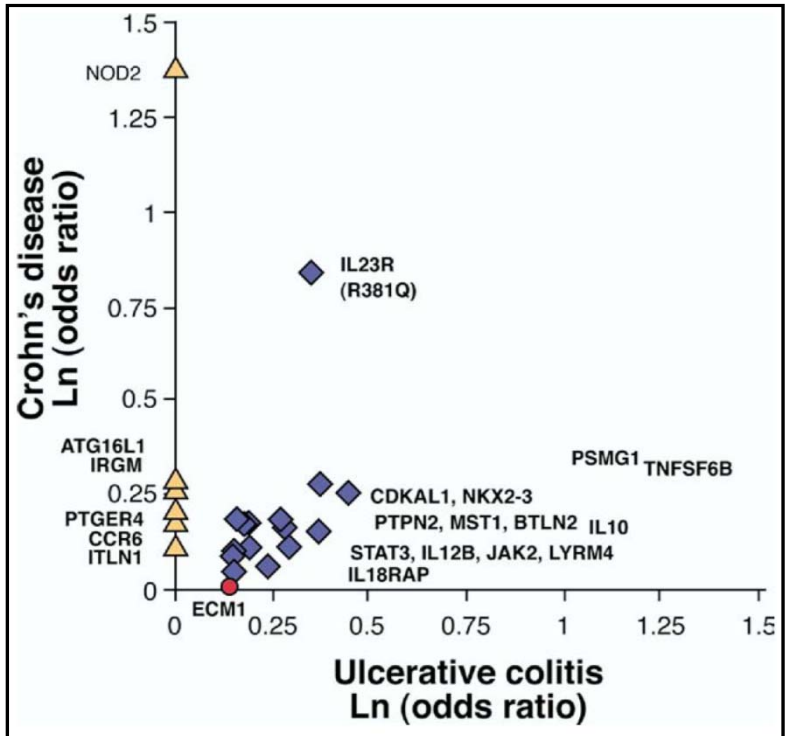


Figure 1. Genes significantly associated with CD (*triangles*), UC (*circles*) or both (*diamonds*) as reported in recent genome wide association, CD meta-analysis and follow up studies plotted by Odds Ratios of risk allele for UC vs. controls as compared to same/equivalent risk allele for CD vs. controls. Genes listed are those with allele frequencies reported for CD and UC. Data preferentially from largest studies. Gene symbols *outside axes lines* have significant evidence for UC only or CD only.

GWAS studies complicate previous thoughts on diseases as ”single diseases”

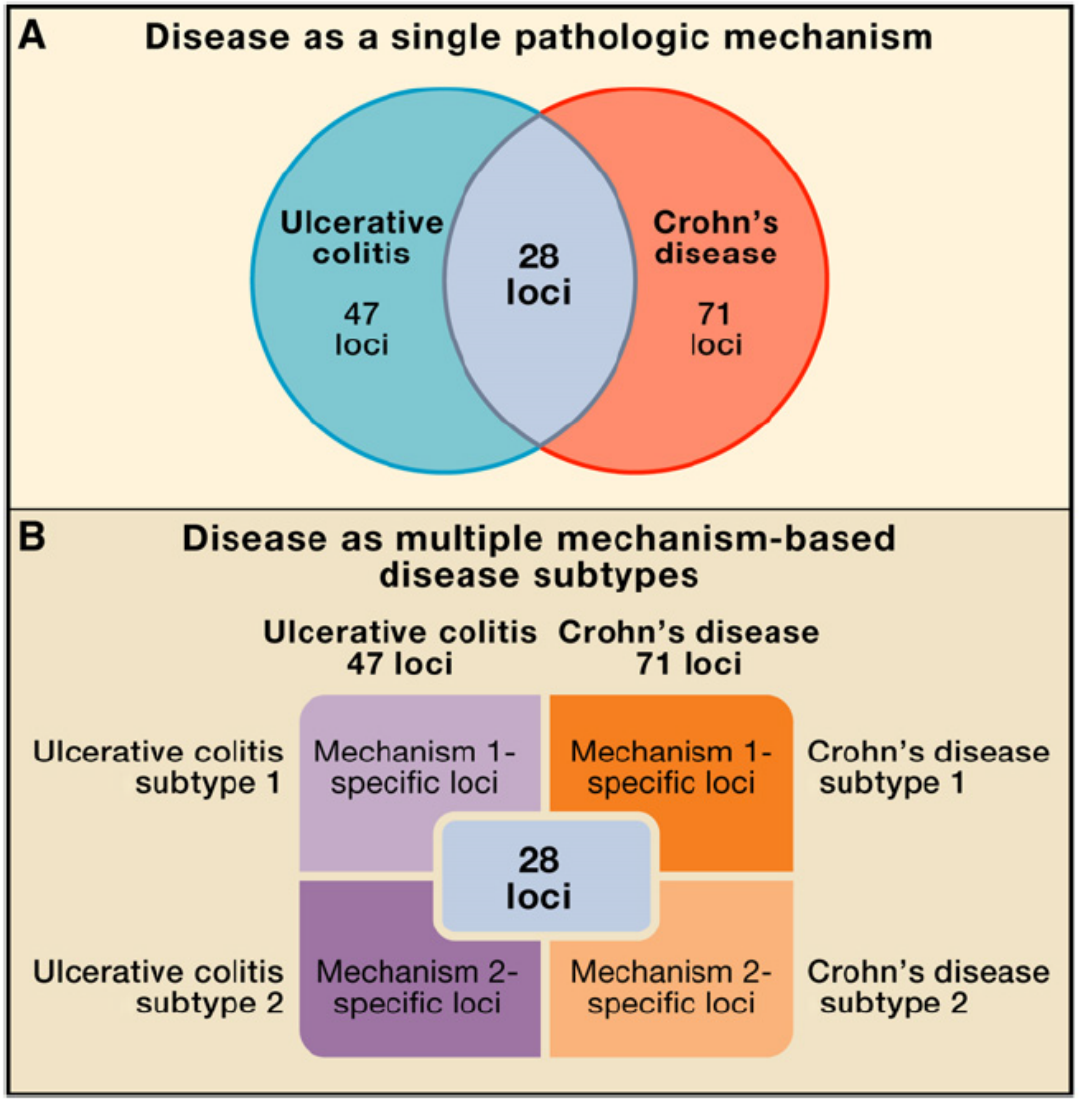
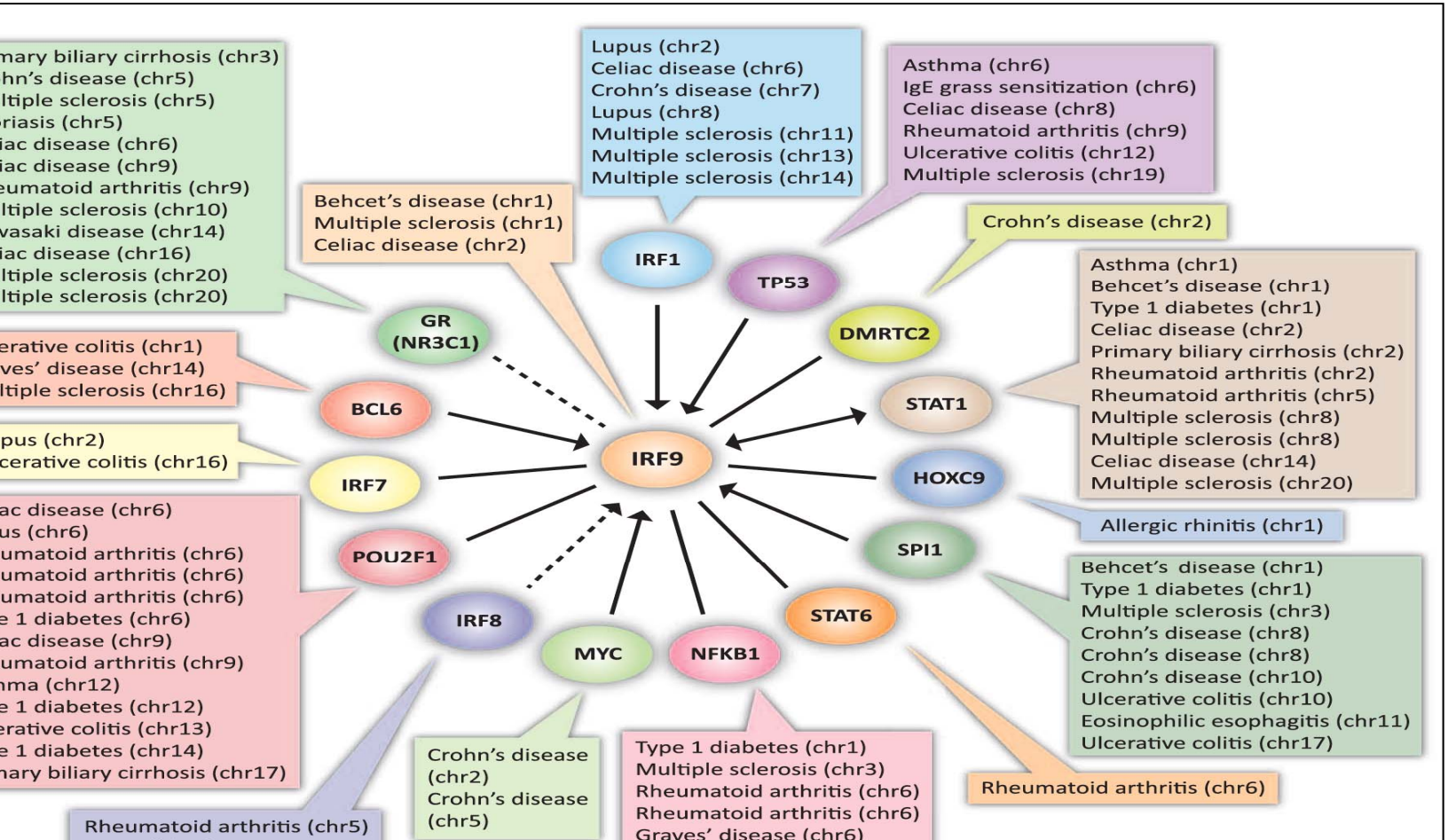
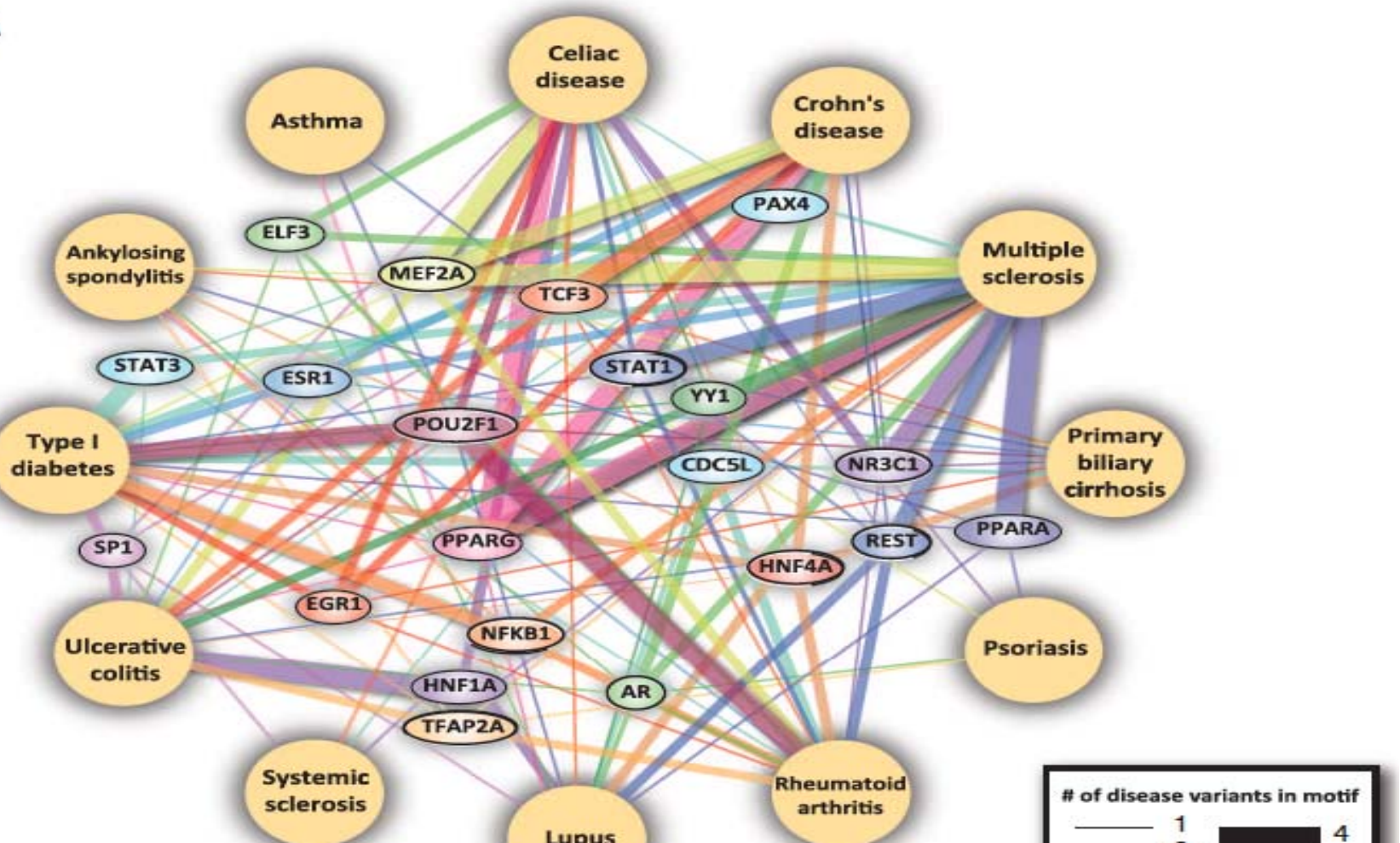


Figure 2. Refining the Relationship between Genotype and Pheno-
type in Complex Inflammatory Diseases

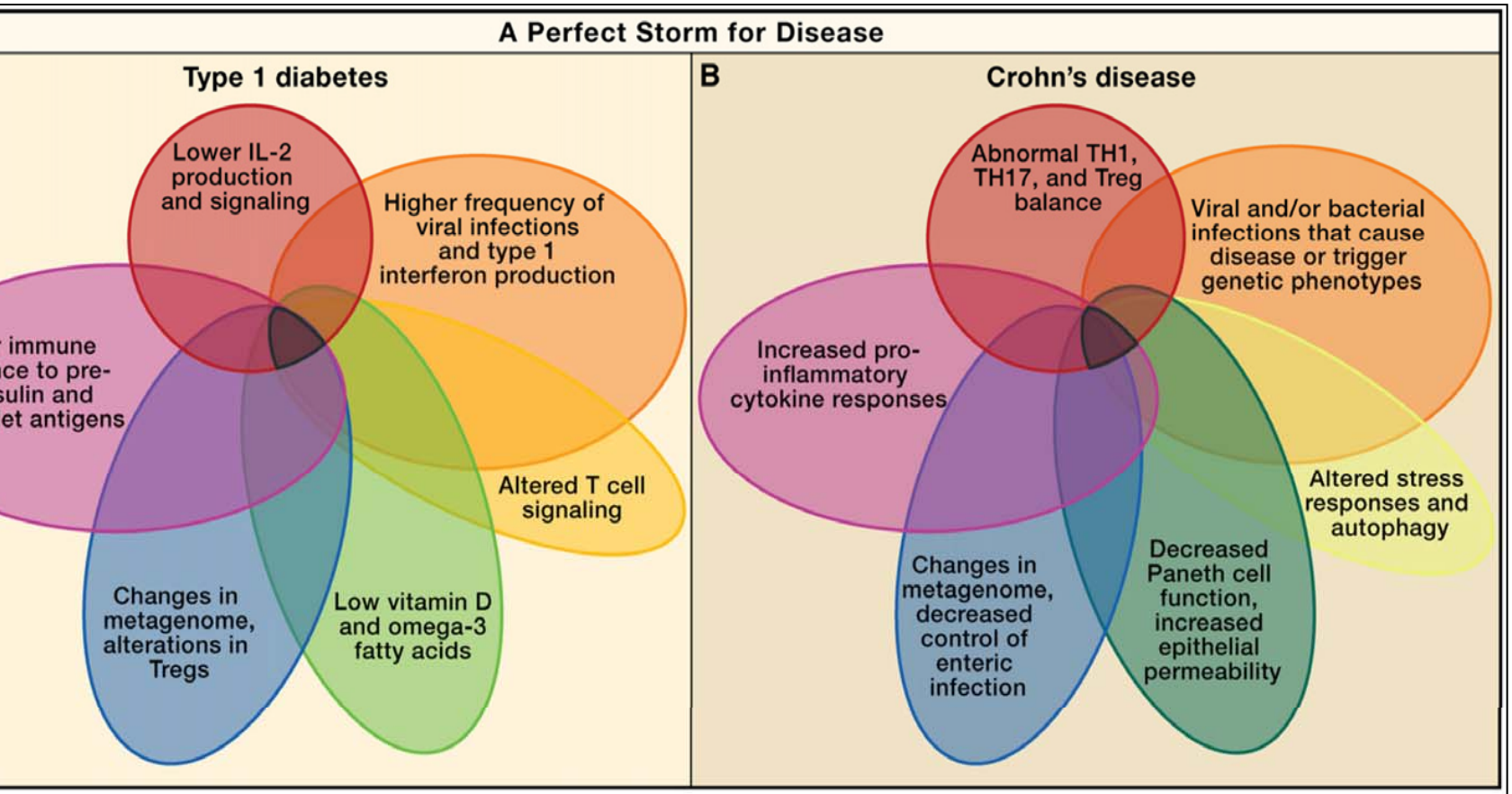
Common disease-associated variants cluster in pathways



Common disease networks

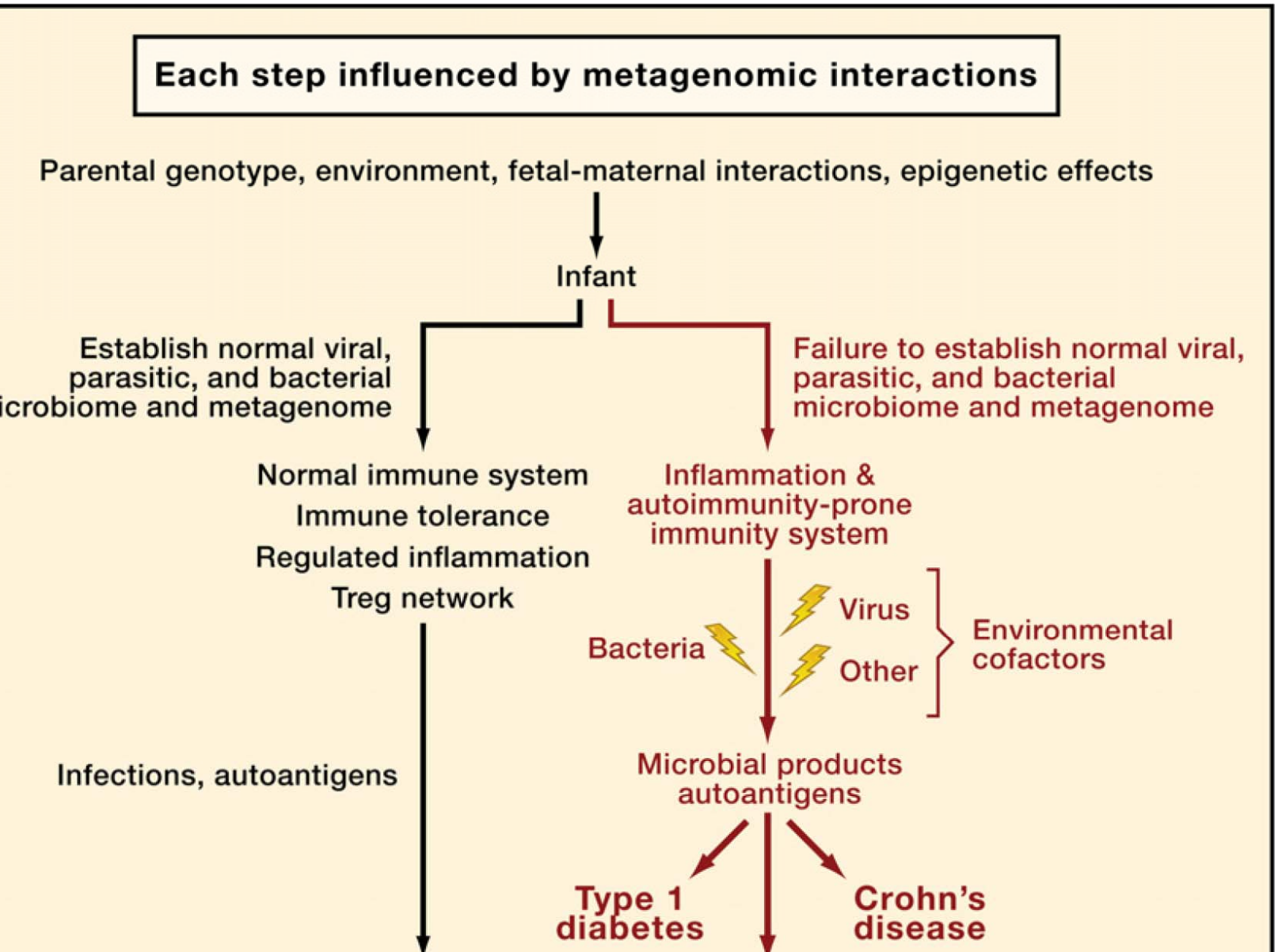


A perfect storm for disease

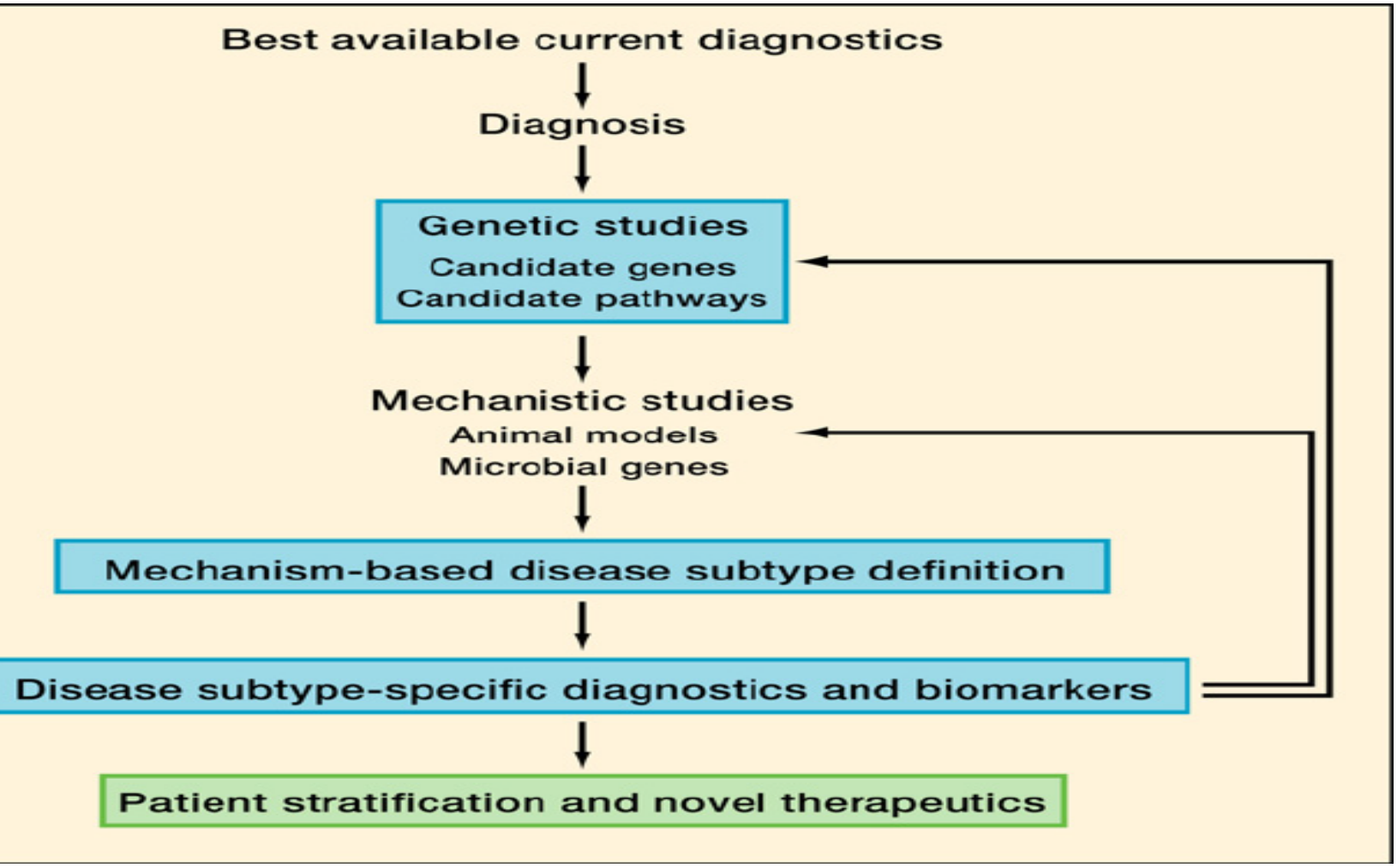


Perfect Storms for Developing Crohn's Disease and Type 1 Diabetes

overlapping events and phenotypes driven by metagenetic and environmental processes that, in sum, contribute to the development and patho-
ype 1 diabetes (A) and Crohn's disease (B).


Each step influenced by metagenomic interactions
Parental genotype, environment, fetal-maternal interactions, epigenetic effects
Infant
Establish normal viral, parasitic, and bacterial microbiome and metagenome
Failure to establish normal viral, parasitic, and bacterial microbiome and metagenome
Normal immune system
Immune tolerance
Regulated inflammation
Treg network
Inflammation & autoimmunity-prone immunity system
Virus
Bacteria
Other
Environmental cofactors
Infections, autoantigens
Microbial products autoantigens
Type 1 diabetes
Crohn's disease

rospect for future personalized medicine



Can something be done?

Prebiotics

- Food and components promoting ”good” intestinal microbiome

Probiotics

- Probiotics are living micro-organisms that, if intake is sufficient, will give a health effect *FAO/WHO*

Postbiotics

- Components produced by intestinal bacteria with possible health effects

A major breakthrough is eagerly awaited!

Recommended reading

Baeckhed et al., Cell Host and Microbe 2012; 12: 611-622.

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