What is an Adverse Effect?

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Disclosure

Current

- Professor: Cornell University(1977-present)
- Author: Dutton Penguin Random House (2015-present
- Consultant: Seed, Head of Translational Science + Education (2017-present)

Previous

Book Series Editor: Springer Science + Business (2009-2016)

Author: World Scientific Publishing (2009-2014).

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- Much appreciation to Janice Dietert for her editorial assistance.

OUTLINE

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2. Why Focus on Gut Microbiota?
    - Epicenter of genes and metabolism
    - Time for a microbiome-inclusive health risk model
2. Adverse Effects and Health Risk Assessment
3. It’s an Ecosystem
    - Similar rules apply (including toxicology)
4. Systems Biology
    - Understanding physiologic conditioning
    - Evaluating the utility of biomarkers
5. Role for Reverse Engineering?

Summary

1. Introduction

Virtually every ingested chemical has some interaction with the gut microbiome.

Some Useful Questions

1. Is the interaction between a xenobiotic and the gut microbiota meaningful?

2. Does the interaction produce an:

Advantageous effect

Neutral effect

Adverse effect (harmful or undesirable biologically or clinically)?

3. What is the adverse effect?

Depriving host cells of a needed xenobiotic (e.g., filter it out)

Producing a toxic metabolite (e.g., arsenic metabolism)

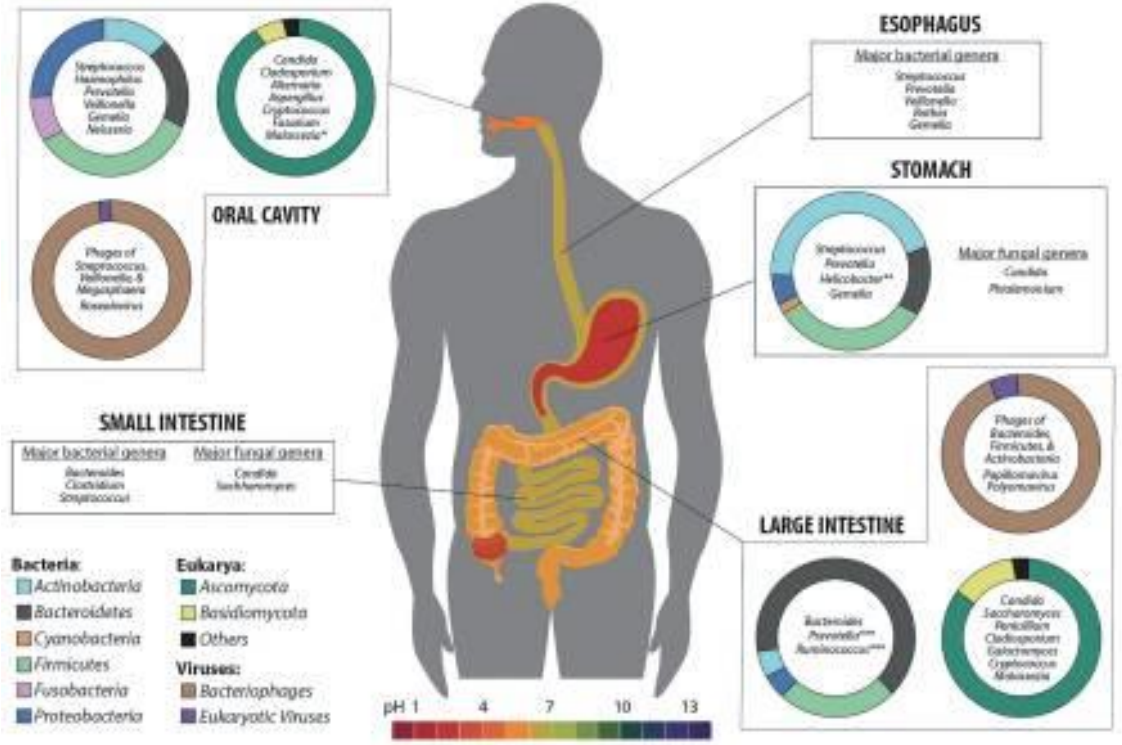
Not producing a needed host co-factor (*e.g.*, vitamin, cancer therapeutic metabolite)

Interactions among microbiota to adversely change the ecosystem (in one or more body sites).

Consider the range of possible adverse effects for the human superorganism.

2. Why Focus on the Gut Microbiome

1. By genes, we are more than 99% microbial.
2. By cells, we are a slight majority microbial.
3. The G.I. tract is a rich source of microbes living in distinct microhabitats.
4. The majority of the immune system is located in the gut in proximity to gut microbiota.

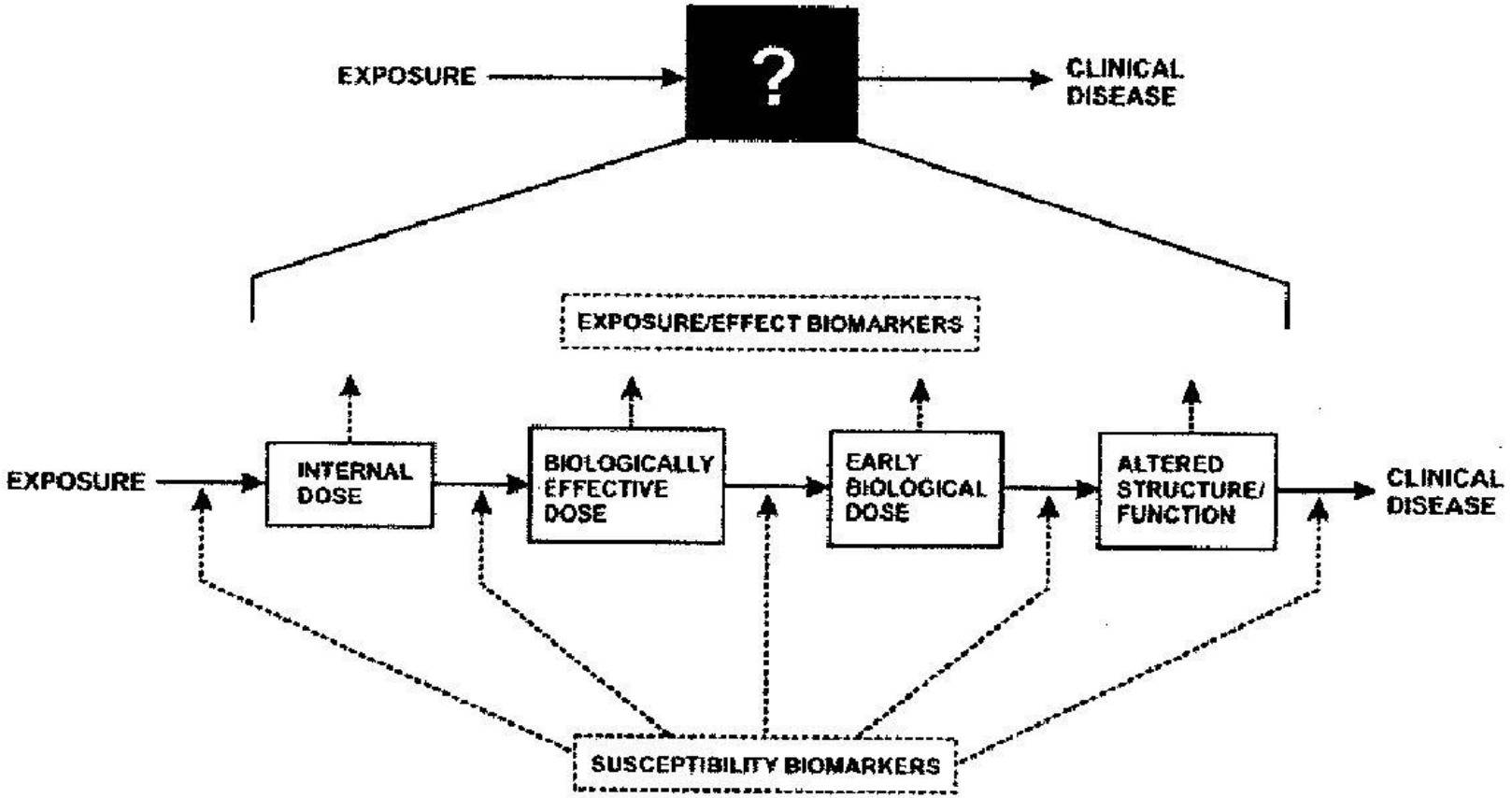


From:
Hillman et al.
Microbes Environ.
2017 Dec; 32(4):
300–313.

See also: Qin et al., Nature. 2010 Mar 4; 464(7285): 59–65;Sender et al. PLoS Biol. 2016 Aug; 14(8): e1002533; Million et al. Hum Microbiom J. 7-8: 23-32. 2018.

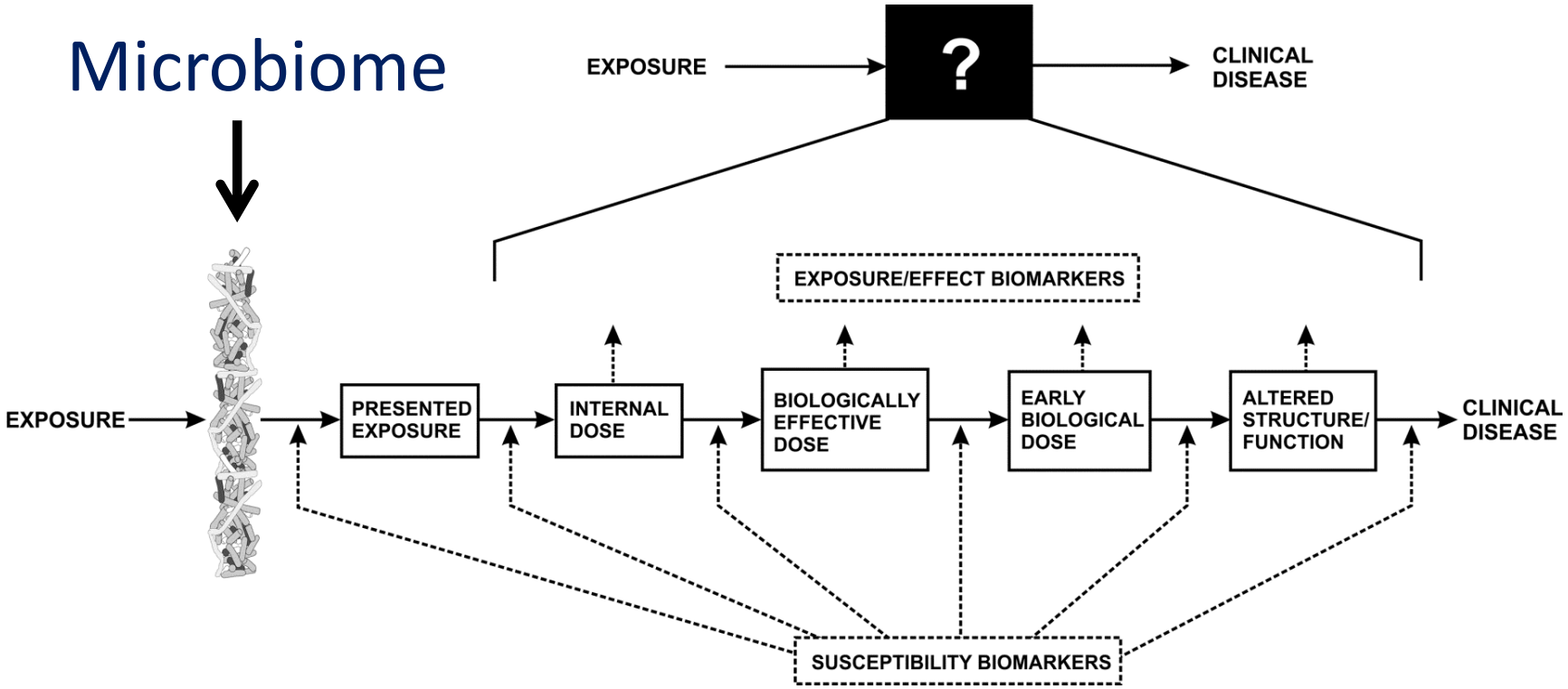
3. Adverse Effects and Health Risk Assessment

Current Biomarkers Model for Health Risk Assessment (1987)



From:
National Research Council,
Environ Health Perspect,
74: 3-9, 1987

The Microbiome Filters Virtually All Exposures and Directly Participates in Epigenetic Alterations



Proposed New Environmental Health Assessment Model

Adapted from: Dietert and Silbergeld, Toxicol. Sci. 2015 Apr;144(2):208-16.

Microbiome Destruction – What happens next?

Elective Cesarean delivery

Altered infant cytokine production

More hospital-associated microbes seeding the neonatal gut

Elevated risk for several diseases associated with the mucosal immune system

Prophylactic use of antibiotics for growth promotion in food-producing animals

Increased antimicrobial resistance and zoonotic risk from *pathogens (e.g., Campylobacter* spp., *Salmonella* spp., *Escherichia coli* and *Staphylococcus aureus)*

Howler monkeys

Captivity

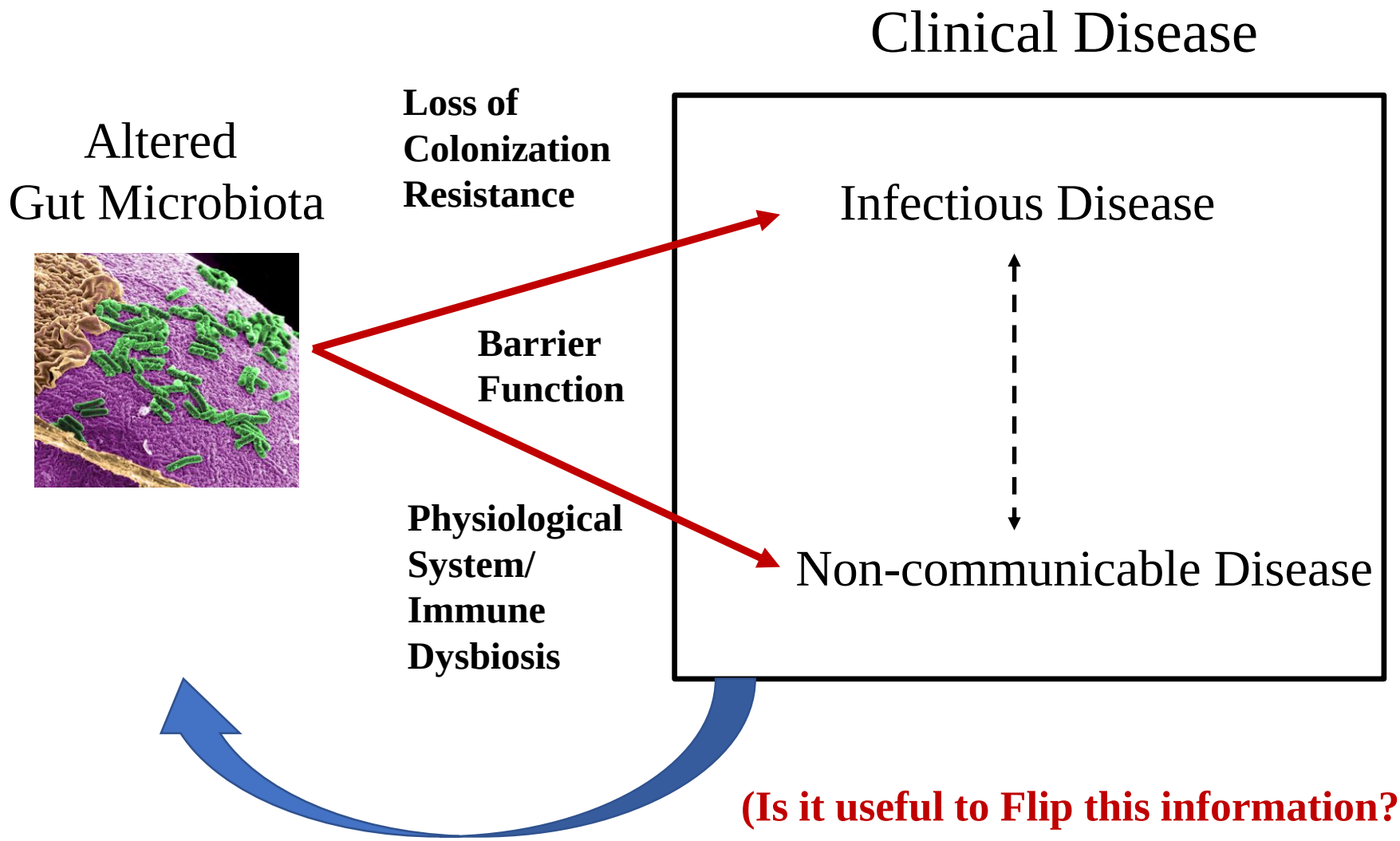
(Food and lifestyle restricted)

Reduced microbiota diversity

Humanized microbiome - from animal handlers

See: Clayton et al. Proc Natl Acad Sci U S A. 2016 Sep 13; 113(37): 10376–10381; Lekshmi et al., Microorganisms 2017, 5, 11; doi:10.3390/microorganisms5010011; Kristensen K1, Henriksen L, J Allergy Clin Immunol. 2016 Feb;137(2):587-90; Kristensen et al. Pediatr Infect Dis J. 2015 Feb;34(2):145-8.

Utility of Biomarkers
From Altered Microbiota to Disease



Adverse Effects for the Microbiome

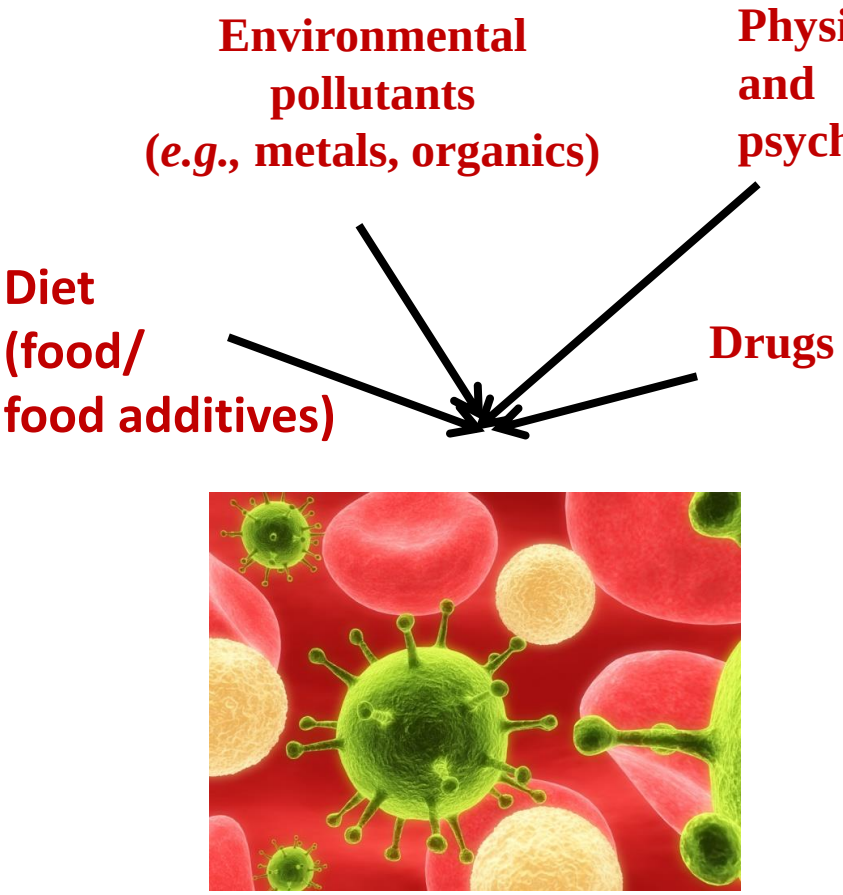
Two Tenets

- Safety has been established only after safety for the microbiome has been established.
- A measured change in a microbiome (biomarker) does not automatically imply biological or clinical significance.

  (If significant, is it adverse? What is the risk? Subpopulation specific?

  What factors could modify the risk for the gut microbiota?)

Responses of the Microbiota to Environmental Changes



1. Sequestration
2. Avoidance/Exclusion
3. Metabolism
4. Specific Signaling
5. Selective Microbe Death
6. Selective Microbe Expansion
7. Translocation
8. Hive Mind Changes (*e.g.*, Biofilms

Modified from: Dietert R. The microbiome in early life: self-completion and microbiota protection as health priorities. Birth Defects Res. Part B. 101(4): 333-340, 2014.

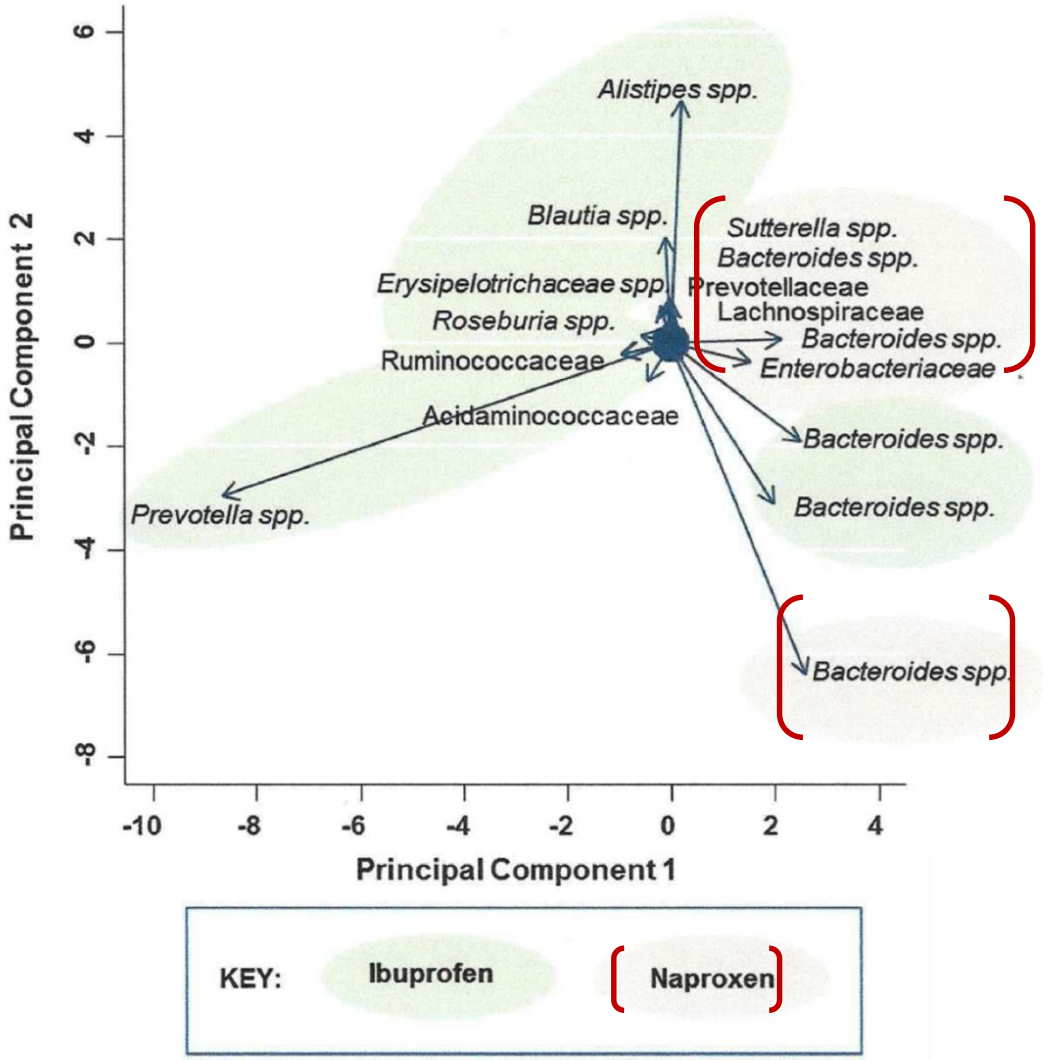
Gut Microbiota and Xenobiotics

- Increase or decrease drug available for absorption
- Directly metabolize drug
- Inhibit detoxification
- Biotransform common food components, drugs, and xenobiotics
- Generate aryl-hydrocarbon receptor agonists
- Convert a pro-drug into an active drug
- Respond to one drug/xenobiotic by inactivating host enzymes for an unrelated drug
- Regulate host metabolism

From: Klaassen and Cui, Drug Metab Disp. 2015; 43(10): 1505-1521

Different NSAIDs Produce Different Types of Microbiome Disruption

FIGURE 5. Principal Component Analysis Biplot of Bacteria to distinguish Ibuprofen Users from Naproxen Users



Adapted from: Rodgers and Aronoff, Clin. Microbiol. Infect. (Oct. 2015) doi: 10/1016/ j.cmi.2015. 10.003

Adverse Effects of NSAIDs

Adverse effect*	Frequency
Increased gut permeability	**44%-70%**
Gut inflammation	**60%-70%**
Blood loss and anemia	30%
Malabsorption	40%-70%
Mucosal ulceration	30%-40%
Protein loss	10%
Mucosal ulceration	30%-40%
Complications requiring hospitalizations	0.3%-0.9%
Diaphragm like strictures of the small bowel	< 1%

*Occurrence of main adverse effects of non-steroidal anti-inflammatory drugs in the lower gastrointestinal tract with non-steroidal anti-inflammatory drug use
Table constructed using data from[2,3,5].

Adapted from: World J Gastroenterol. 2017 Jun 14; 23(22): 3954–3963.

Patterns of Adverse Outcomes for Microbiota

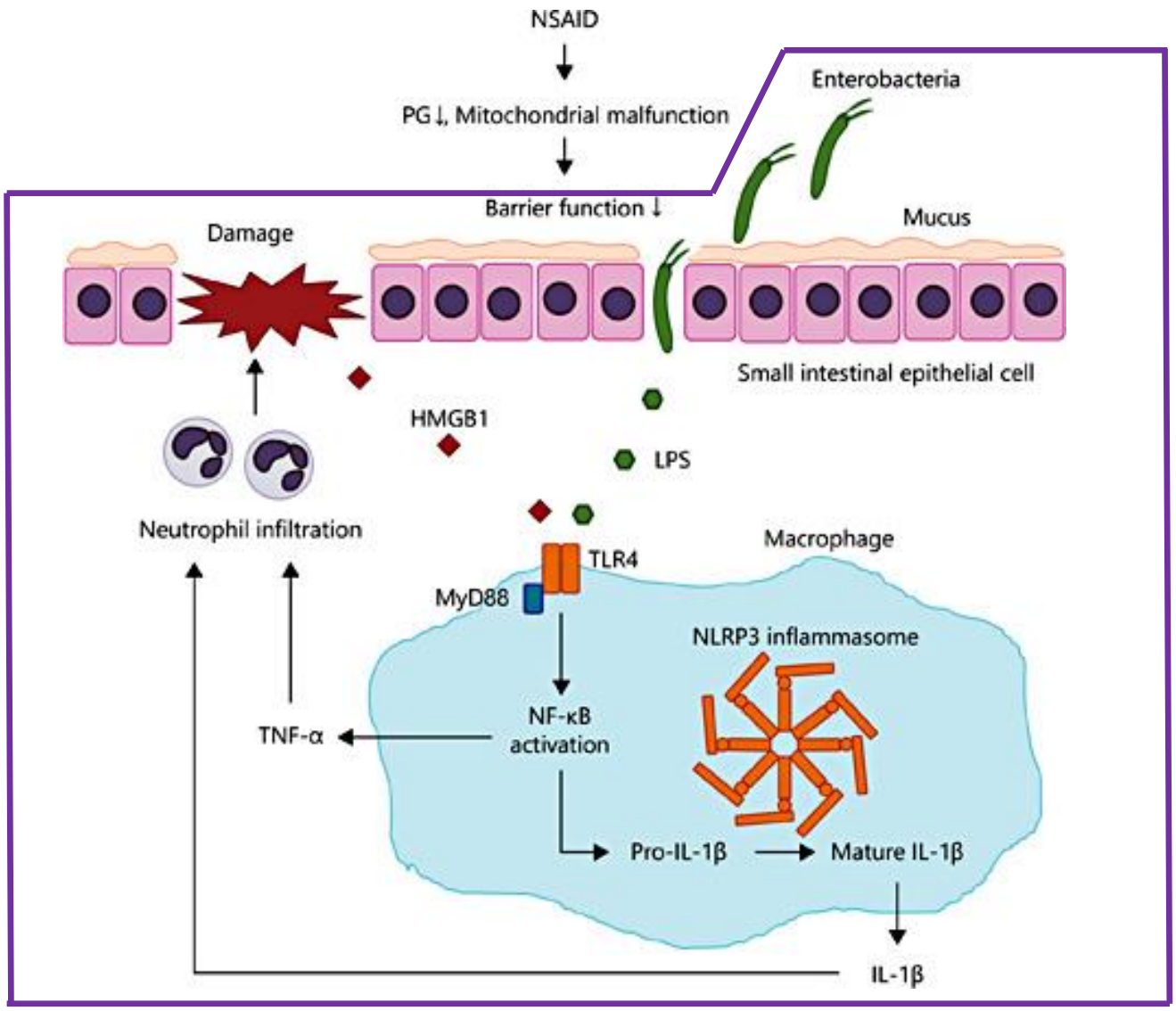
- Transitory (*e.g.*, mac and cheese or ice cream binge)
  - May be as easy to correct as the next meal unless tipping points are reached
- Established (e.g., keystone species destruction – metabolic syndrome)
  - Is likely to require significant host and microbiota changes
- Developmentally programmed (*e.g.*, missed critical window event in host-microbiome co-development)
  - Even minor microbiota perturbations may lead to later-life established problems
- Transgenerationally affected (*e.g.*, vertical inheritance of a diabetic-promoting microbiome, host genome epigenetic regulation?)

Interplay Between Gut Microbiota Status and NSAIDs

- No gut bacteria, no problem (germ-free rodents are protected)
- Installing certain potentially pathogenic bacteria without others is sufficient for NSAID-induced damage
- Gut microbiota depletion with certain antibiotics can predispose for NSAID-induced pathology
- Some mucosal protective agents can protect against NSAID-induced pathology (*e.g.*, Rebamipide)
- Some probiotics offer protection against NSAID-induced pathology

See: Otani et al. Digestion 2017;95:22-28.

Model of NSAIDs Small Intestine Damage

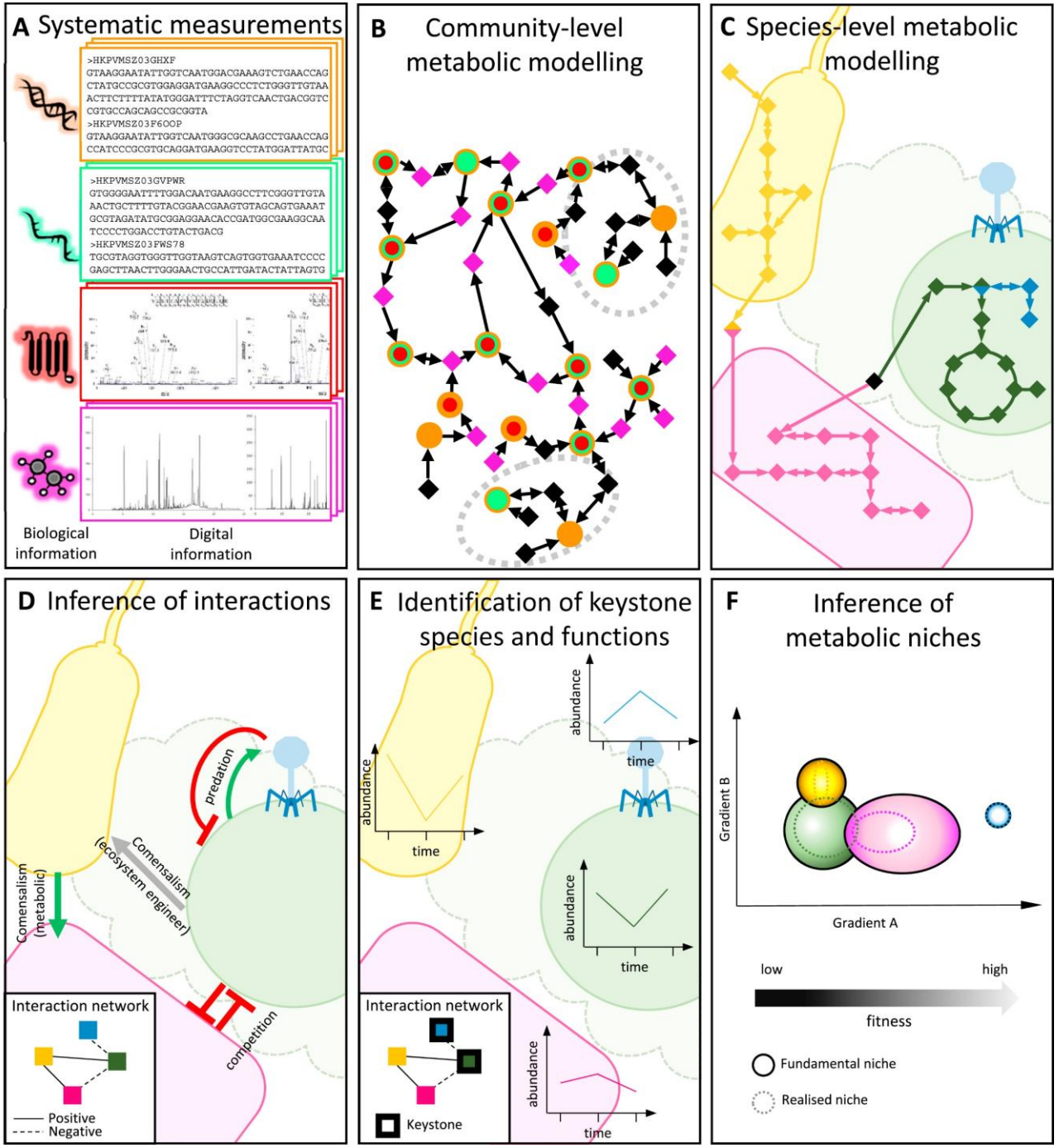


Note:
the box can work for cadmium, fructose, and food emulsifiers as well

Modified from: Otani et al. Digestion 2017;95:22-28.

4. It's an Ecosystem

(we do not have to reinvent the wheel)

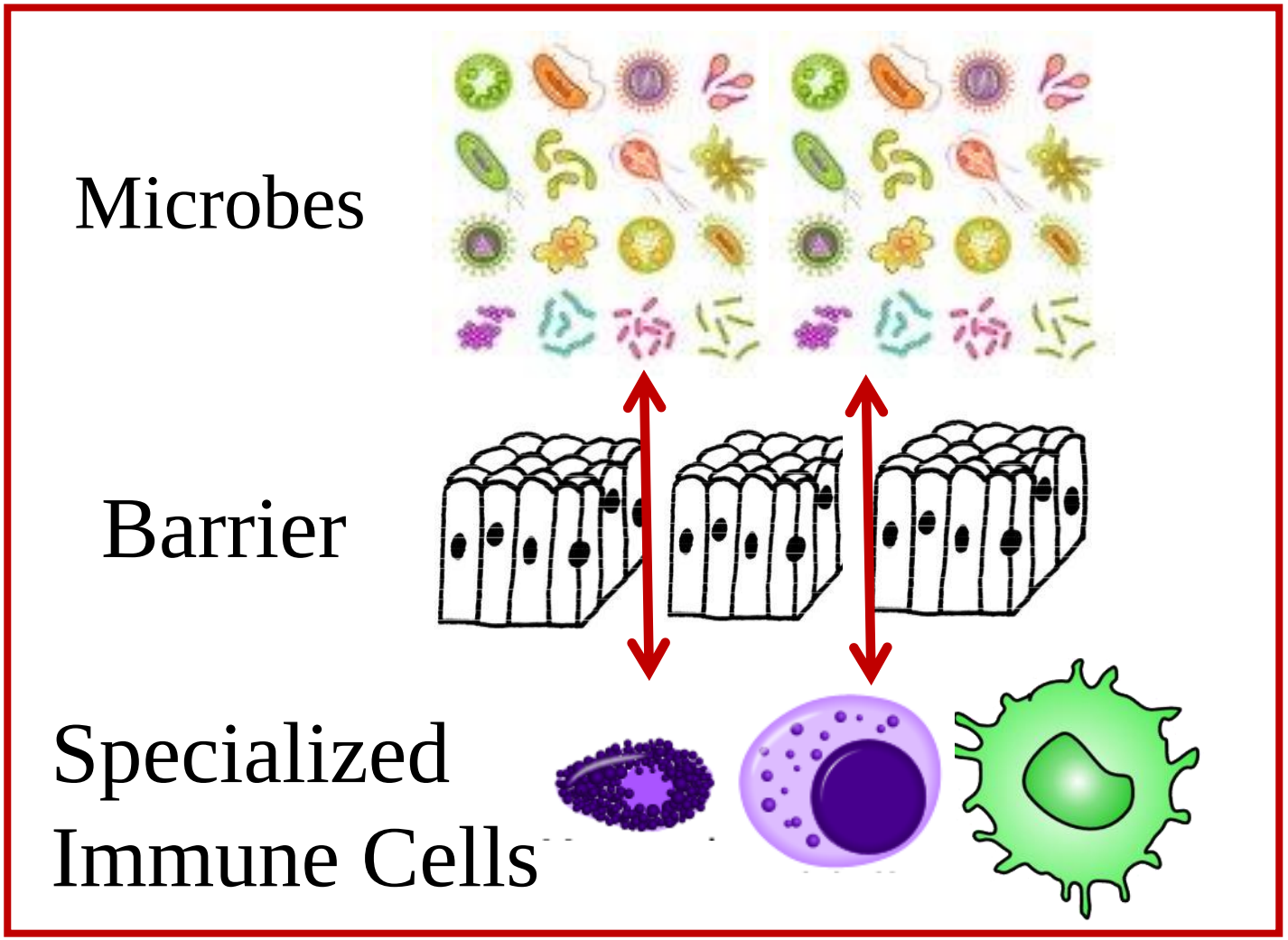


What do you want to measure and compare in an ecological system?

From:
Mueller, E.E.L. et al.
Using metabolic networks to resolve ecological properties of microbiomes.
Curr Opin Syst Biol. 8: 73-80. April 2018.

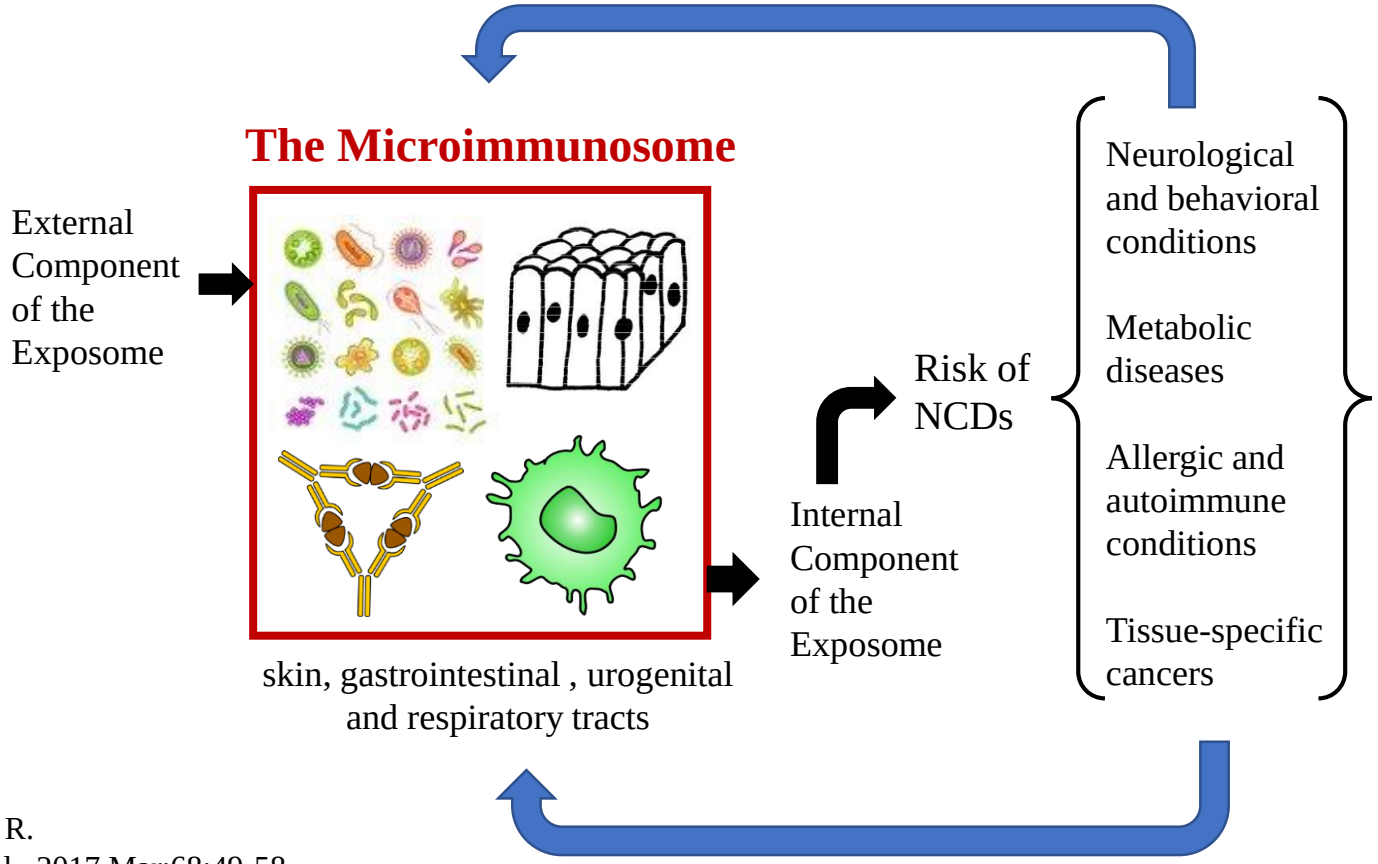
5. Systems Biology

In Skin, Gastrointestinal, Urogenital and Respiratory Tracts



Adapted from Dietert, Reprod. Toxicol. 2016, early view

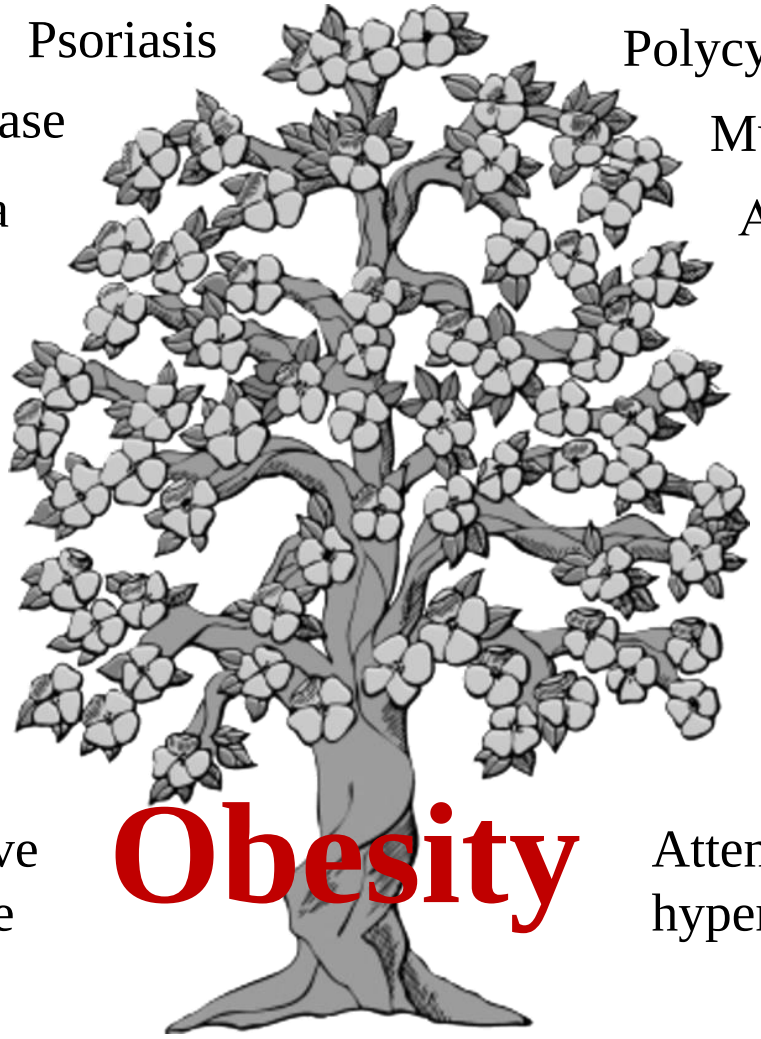
Systems Biology Perspective
The Microimmunosome and the Exposome



From: Dietert, R.
Reprod Toxicol. 2017 Mar;68:49-58.

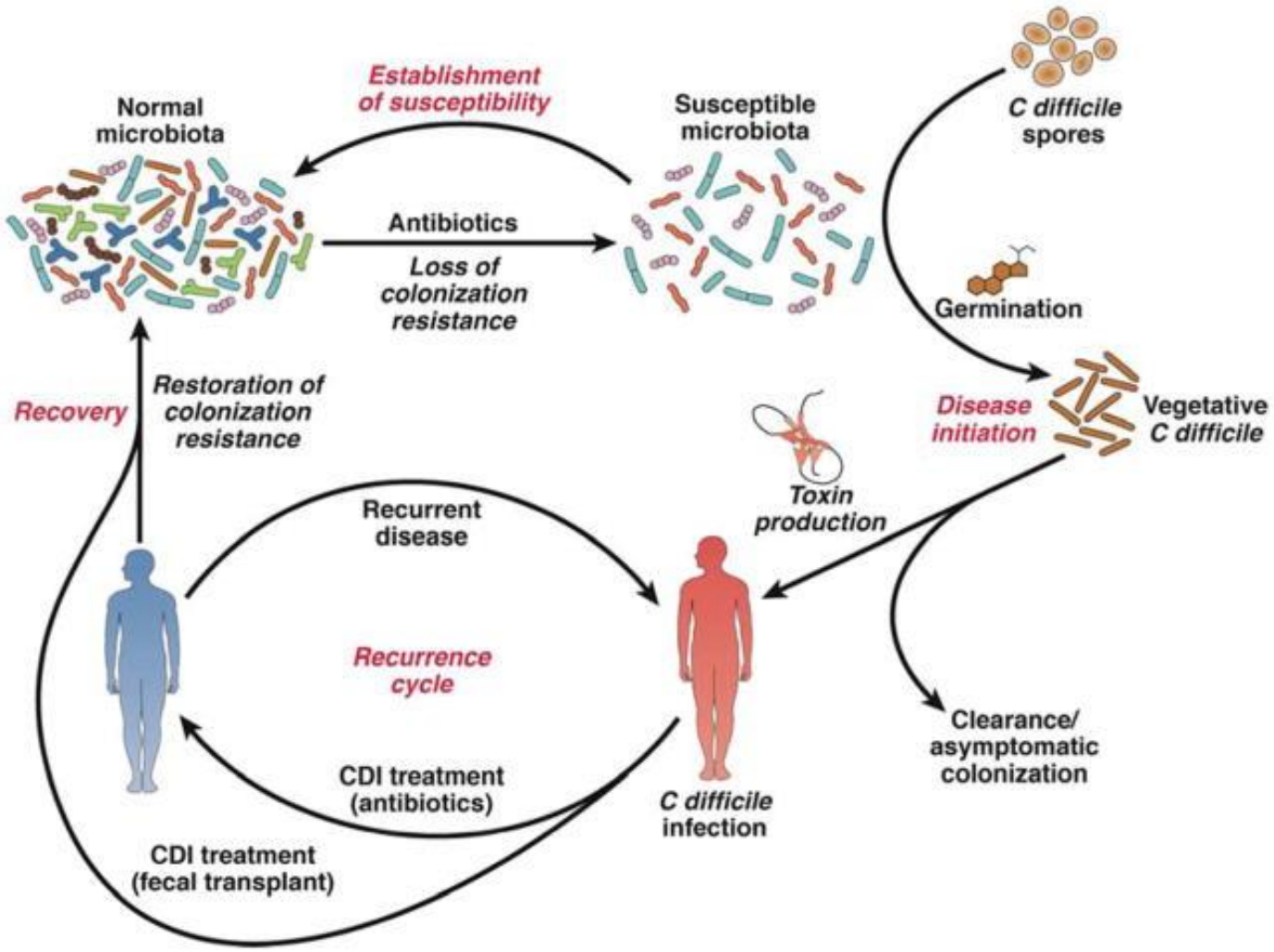
5. Role for Reverse Engineering?

A Pattern of 32 Interlinked NCDs for Obesity



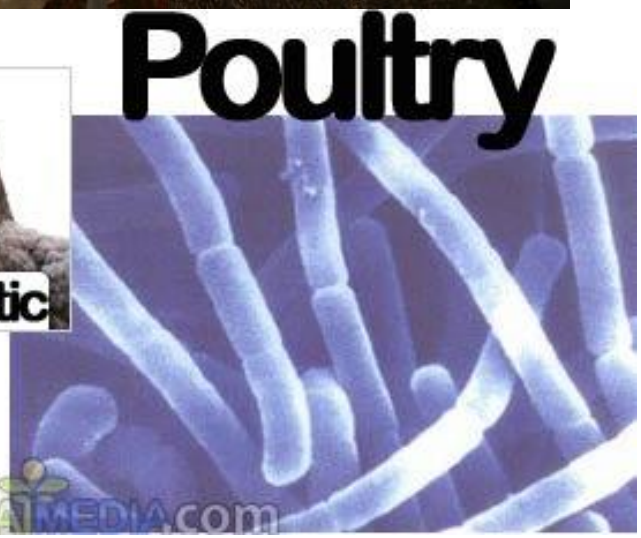
Adapted from: Dietert R., *The Human Superorganism*, 2016 (Dutton Penguin Random House)

Infectious Disease: Colonization Resistance to Protect Against Infections



From: Britton and Young Gastroenterology. 2014 May; 146(6): 1547–1553.

Colonization Resistance in Action



Pathogens: Minimum Microbiota Necessary for Effective Competitive Resistance

- Metagenomic tools were used to construct a minimum consortium of gut microbiota that would protect mice from infection with the human enteric pathogen *Salmonella enterica serovar* Typhimurium (S. Tm).

- An installed combination of 15 specific gut bacterial strains were equivalent to a complete microbiome in effective colonization resistance.

Is it useful to work backwards to harvest potential biomarkers?

From: Brigiroux et al. Nat. Microbiol. 2:16215 · November 2016

SUMMARY

- In future health risk assessments, we must include the microbiome and protection of the microbiome should be a top priority.
- Adverse effects can take many different forms. There are decisions to be made about what to measure.
- We can draw upon prior knowledge of adverse effects and toxicity within complex ecological systems.
- Consideration of adverse effects should also capture the “systems biology” of barrier function and underlying host physiology.
- Reverse engineering of the connection between gut microbiota status and disease may aid the identification of useful biomarkers.