Welcome to the SRA Webinar Series

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Protecting the Human Superorganism

SRA Webinar
January 24, 2017

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Cornell University

DISCLOSURE

Present:
Cornell University - Professor (1977 - present)
Dutton Penguin Random House - Author (2015 - present)
The GutBiome Institute -
Microbiome Certificate Program Instructor (2016 - present)

Previous:
Springer - Book Series Editor (2010-2016)
CDC - Tetrachloroethylene (PERC) Peer Review Evaluator (2013-2014)
EPA - Integrative Science Assessment for Lead -
Drafting Consultant (2009-2010)
Burleson Research Technologies (BRT-Labs) - Consultant (2006-2010)

Acknowledgements

Thanks to:

- Society for Risk Analysis
- Dr. Ellen Silbergeld, Johns Hopkins School of Public Health
- Peg Coleman, Coleman Scientific Consulting
- Janice Dietert, Performance Plus Consulting

OUTLINE

1. Introduction
2. The Noncommunicable Disease Epidemic: A Major Target
3. Superorganism Ecology and The Completed Self Hypothesis
4. Microbiome-Immune Co-Maturation
5. The Microbiome as our Gatekeeper
6. Superorganism Safety – Drugs, Chemicals, Food Components, Pathogens
7. Microbial Biomarkers and Rebiosis

Summary

1. Introduction

Scientific Challenge

If you could pick ONE sign that best distinguishes a lifetime of health from one filled with disease ……what would that be????

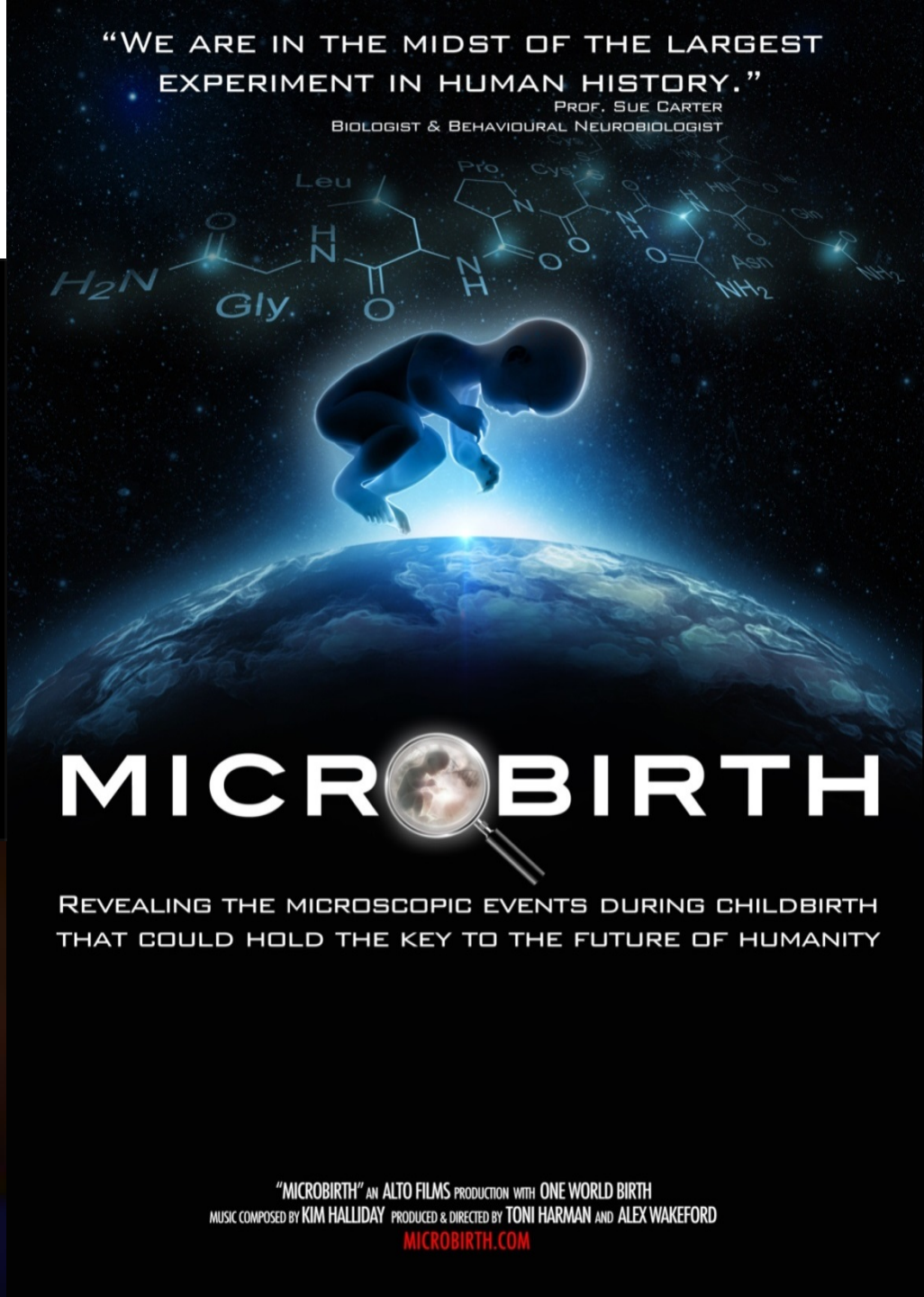
[Challenge was issued for an invited paper for a special issue of the physics journal *ENTROPY]*

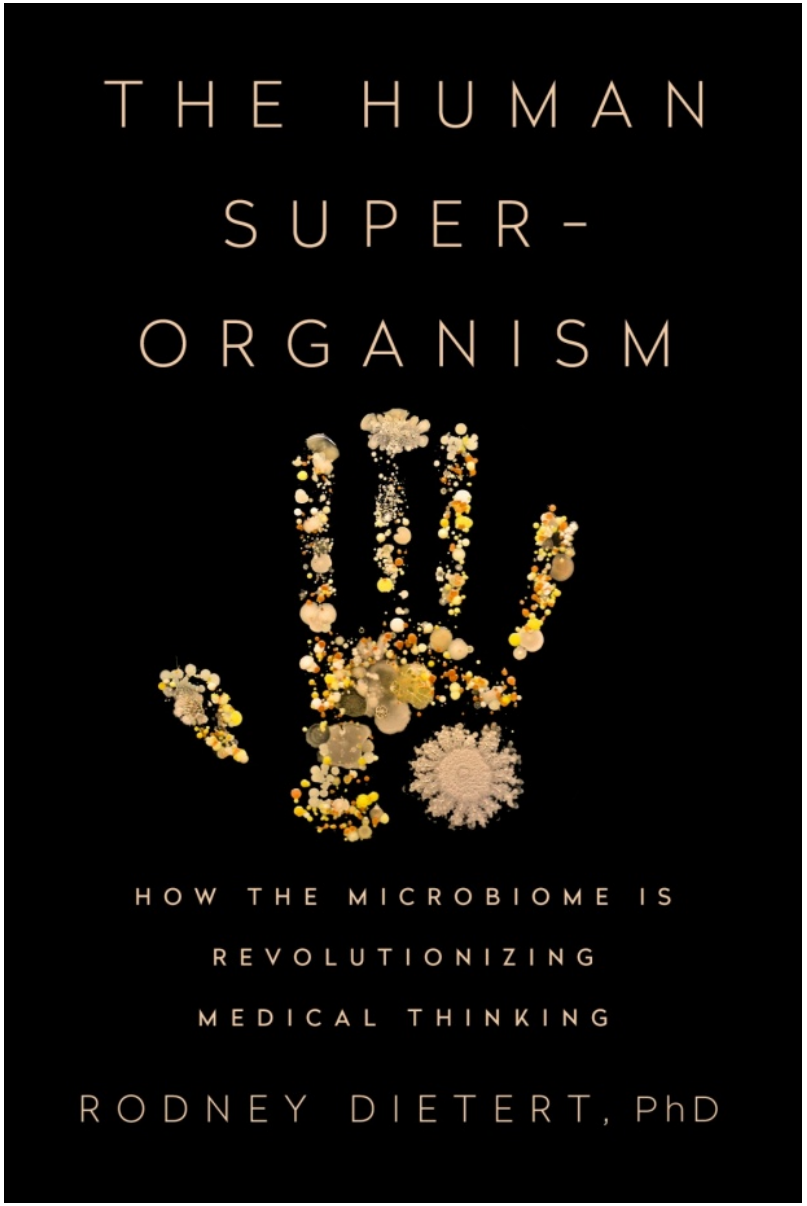
My Answer
(upon waking from a dream)

Self completion of the human-microbial superorganism

2014 documentary film Wellcome Trust screening – Jan. 30, 2015

OFFICIAL SELECTION
LIFE SCIENCES FILM FESTIVAL
PRAGUE
2014





Rodney Dietert: The Human Superorganism

THU, JUL 21, 2016 (00:00)

Rodney Dietert

SHARE

Professor **Rodney Dietert** suggests that the origin of asthma, autism, Alzheimer's, allergies, cancer, heart disease, obesity, and even some kinds of depression may have a lot to do with the microbiome. He reads from his book, *The Human Superorganism: How the Microbiome Is Revolutionizing the Pursuit of a Healthy Life.*

PARTNER

Harvard Book Store

Nature | Books and Arts
(Review Including The Human Superorganism)

- **Microbiology: Mob rule**
- Adrian Woolfson

Nature 536,146–147 (11 August 2016)
doi:10.1038/536146a
Published online 10 August 2016

2. The Noncommunicable Disease Epidemic: A Major Target

Previously called “chronic diseases”
Abbreviation used for noncommunicable diseases and conditions:
NCDs

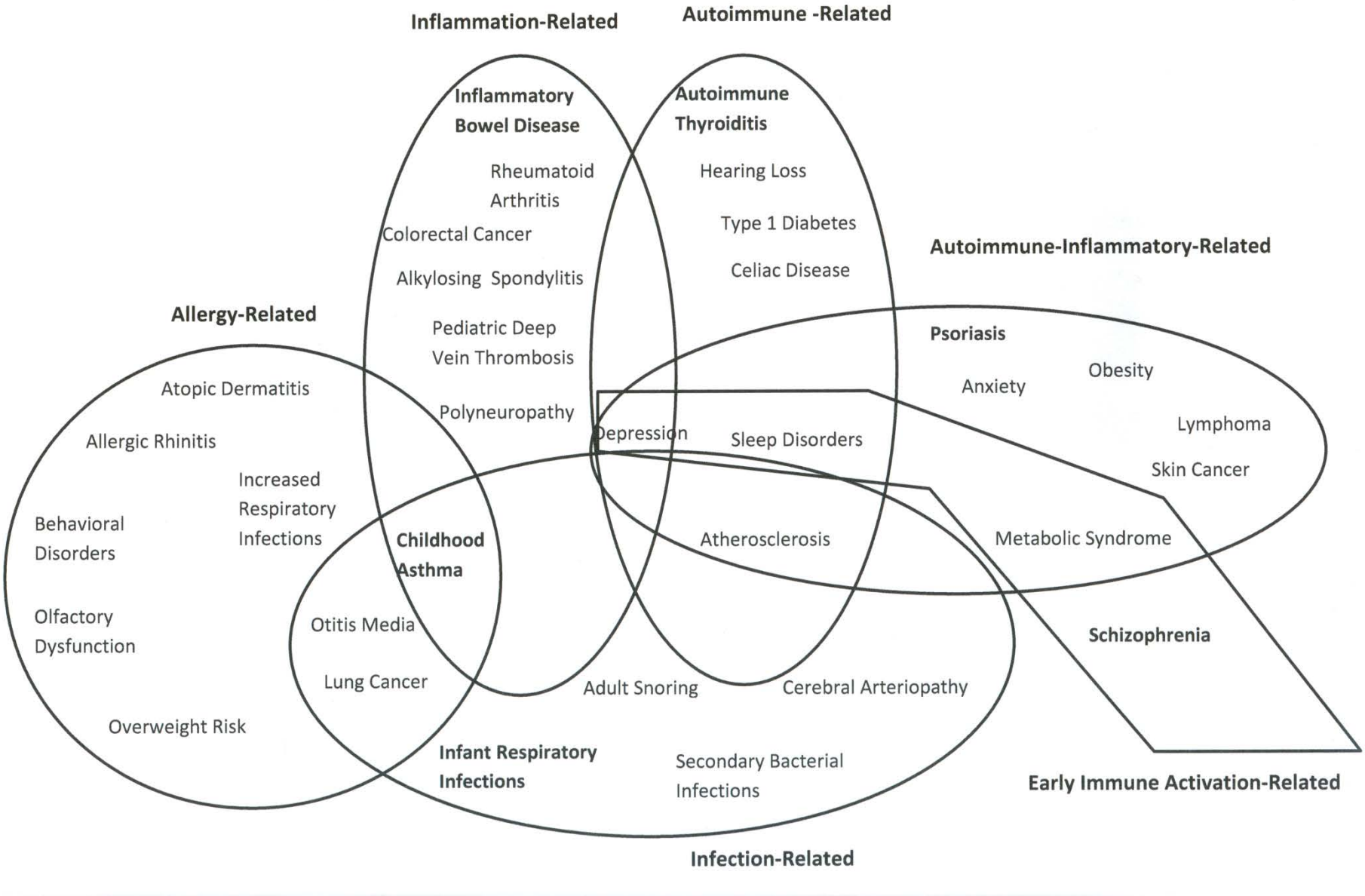
Question?

- Allergies (food/ asthma/rhinitis/dermatitis)
- Cancer
- Obesity
- Diabetes
- Cardiovascular disease
- Arthritis
- Autism spectrum
- ADD/ADHD
- Celiac disease
- IBD (Crohn's, UC)
- Lupus
- Autoimmune thyroiditis
- Depression
- Osteoporosis
- Frailty
- Dementia
- Alzheimer's disease
- Parkinson's disease
- Hypertension
- Sleep disorders
- PCOS
- COPD
- Chronic kidney disease
- Psoriasis
- Multiple sclerosis

2. The Primary Health Target of the 21st Century Reducing the Risk of Noncommunicable Diseases (NCDs)

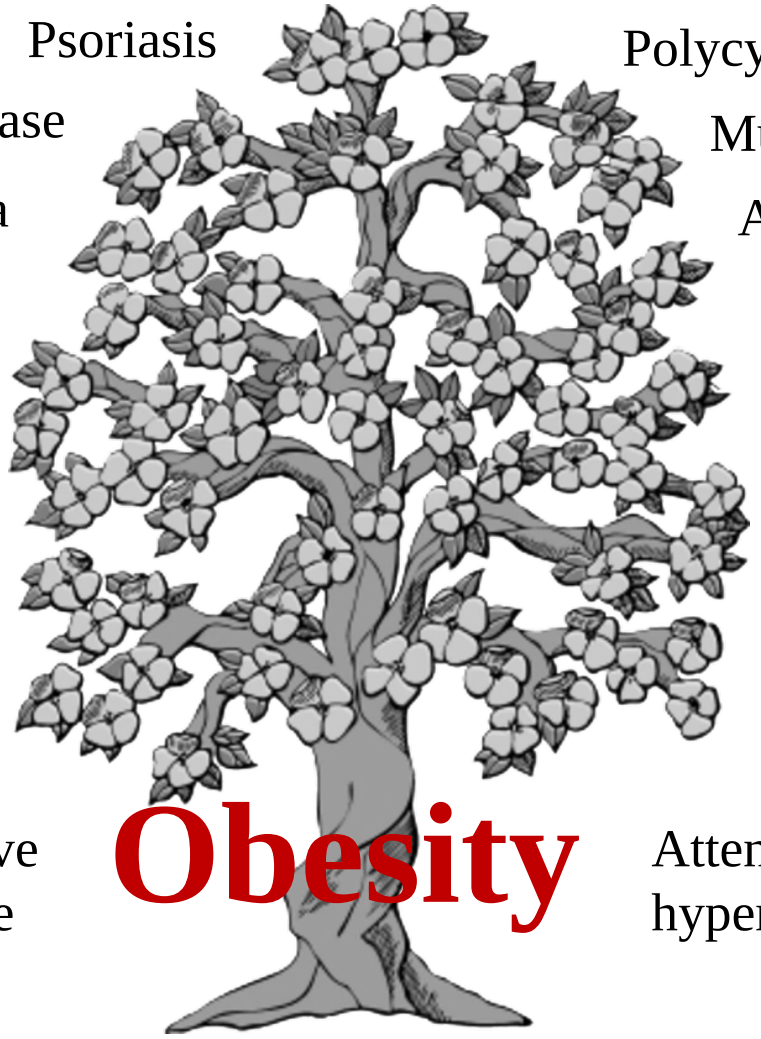
- **NCDs now account for 75% of deaths globally** (CDC, Division of Global Health Protection (DGHP), Feb.4, 2016)
- **Estimated to Cost 48% of Global GDPs by 2030** (WEF-HSPH, 2011)
- **NCD deaths are occurring at earlier ages in developing countries** (Baldwin and Amato, Global burden of NCDs, Population Reference Bureau, 2012)
- **Increased burden of NCDs based on: Years of Life Lost, Years Lost due to Disability, and Disability-Adjusted Life Year (DALY)** (Jakovljevic and Milovanovic, Front. Public Health, 23 April 2015).
- **Adolescence is the last best chance against NCDs** (Baldwin and Amato, Global burden of NCDs, Population Reference Bureau, 2012)
- **Issues of available healthcare and caregivers** (Abuosi et al., BMC Pediatr. 15:185, 2015)
- **45.3% of all US adults age 65 and above have two or more chronic diseases: a 20% increase from the previous decade.** (WEF-Harvard, 2011)

Non-Communicable Diseases Cluster Together



From: Dietert, DeWitt, Germolec and Zelikoff , Environ. Health Perspect. 118:1091-9, 2010

A Pattern of 32 Interlinked NCDs for Obesity



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

Misregulated Inflammation

is

A tie that binds noncommunicable diseases and conditions (NCDs) together

And

A feature of gut microbial dysbiosis

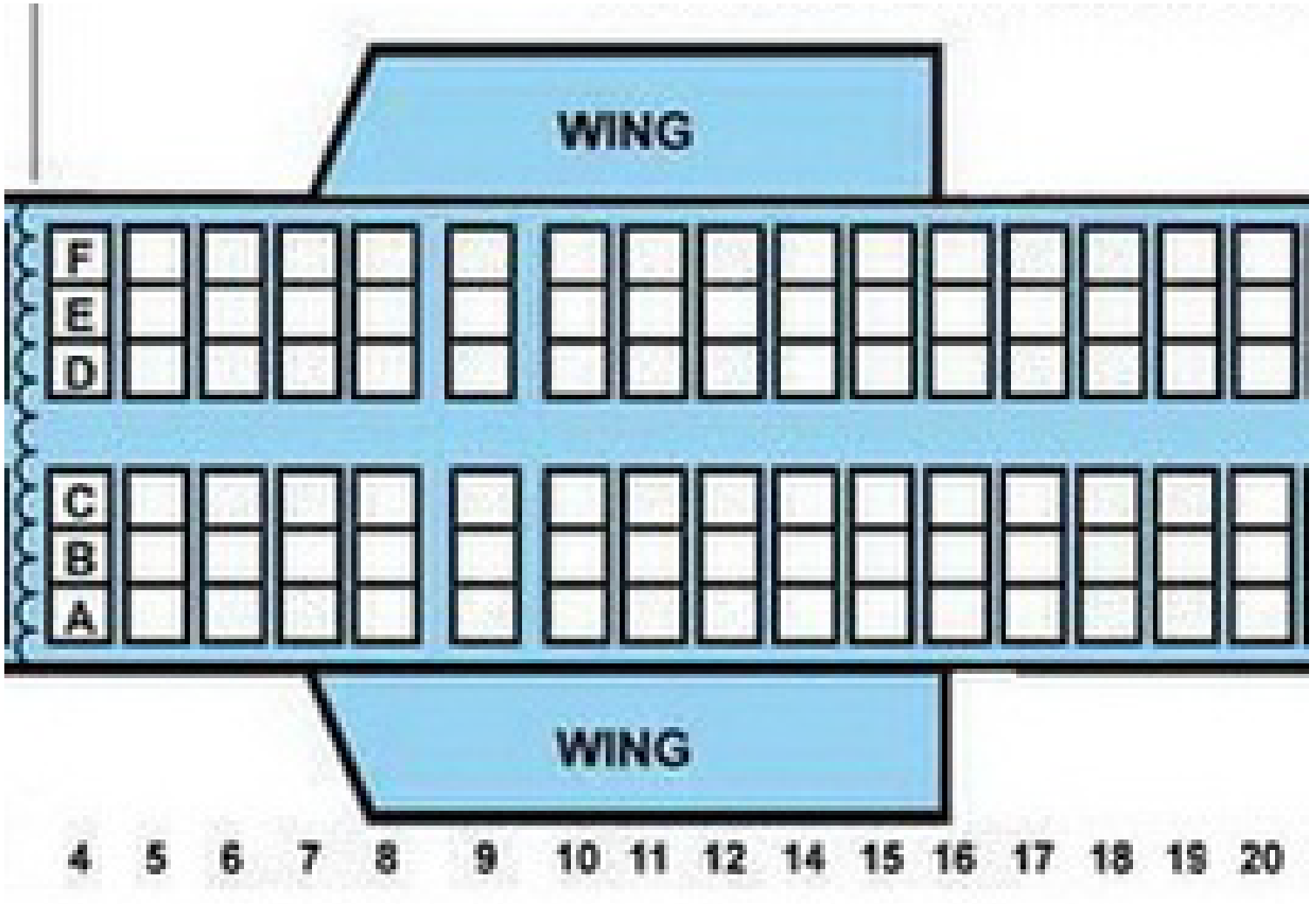
Lipid mediators connected to immune-microbial signaling prove critical in effective control of tissue inflammation.

See: Serhan et al. The resolution code of acute inflammation:
Novel pro-resolving lipid mediators in resolution. Semin Immunol. 2015 Apr 6.
pii: S1044-5323(15)00012-3.

The Hidden Cost of Microbiome and Immune Dysbiosis Driven NCDs

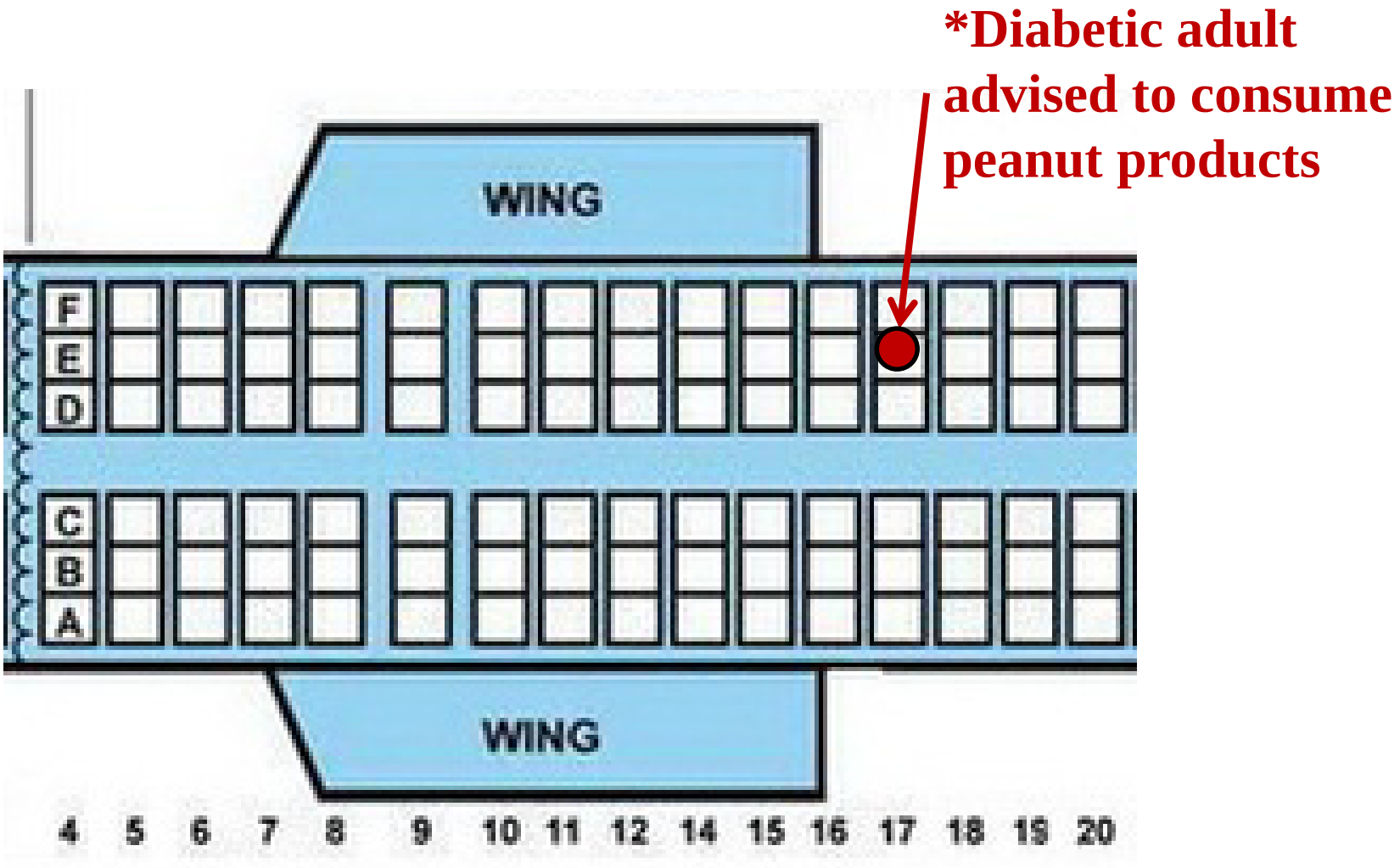
Societal change - Isolation

Leaving on a Jet Plane



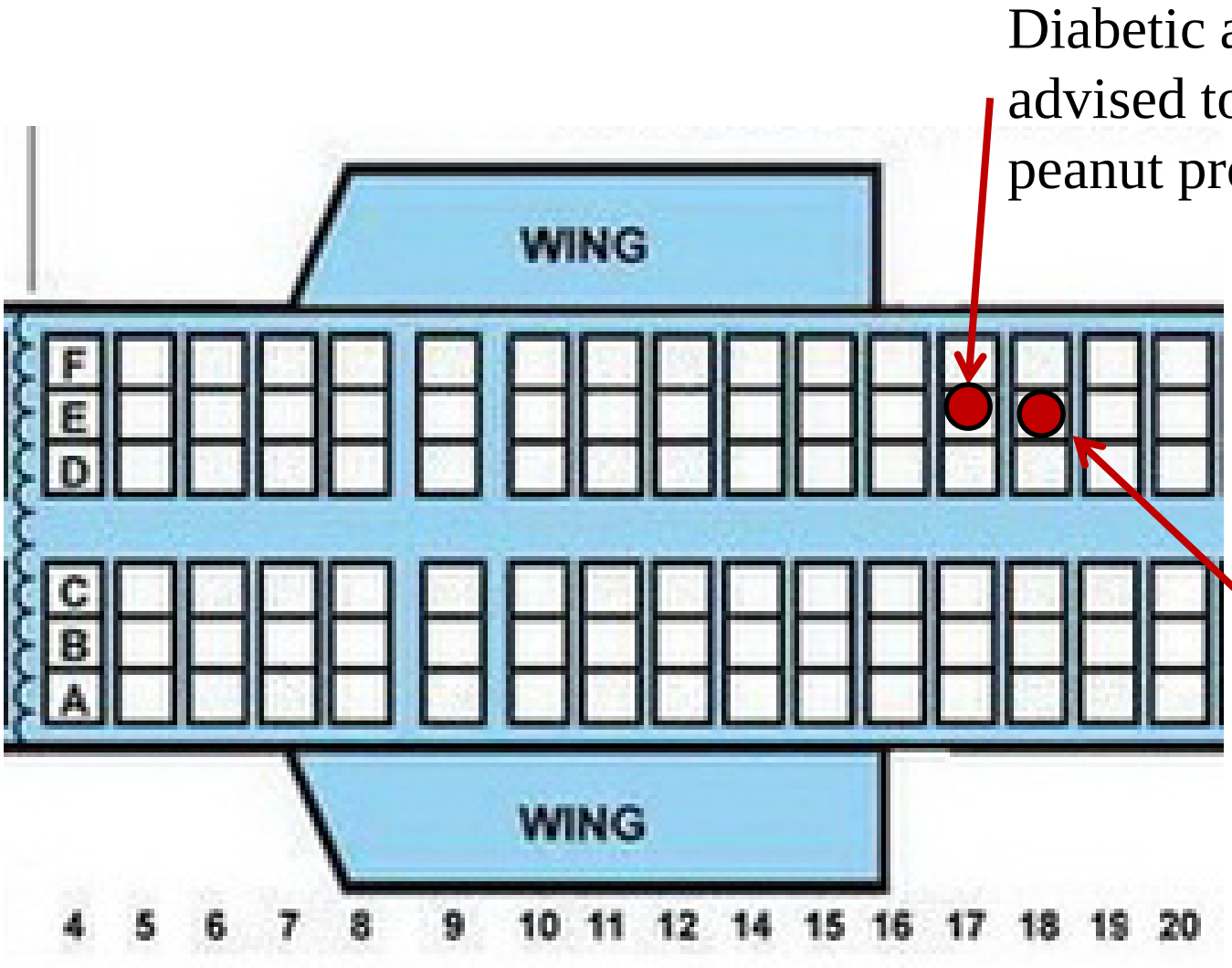
See: Dietert R., *The Human Superorganism,* 2016 (Dutton Penguin Random House)

Leaving on a Jet Plane



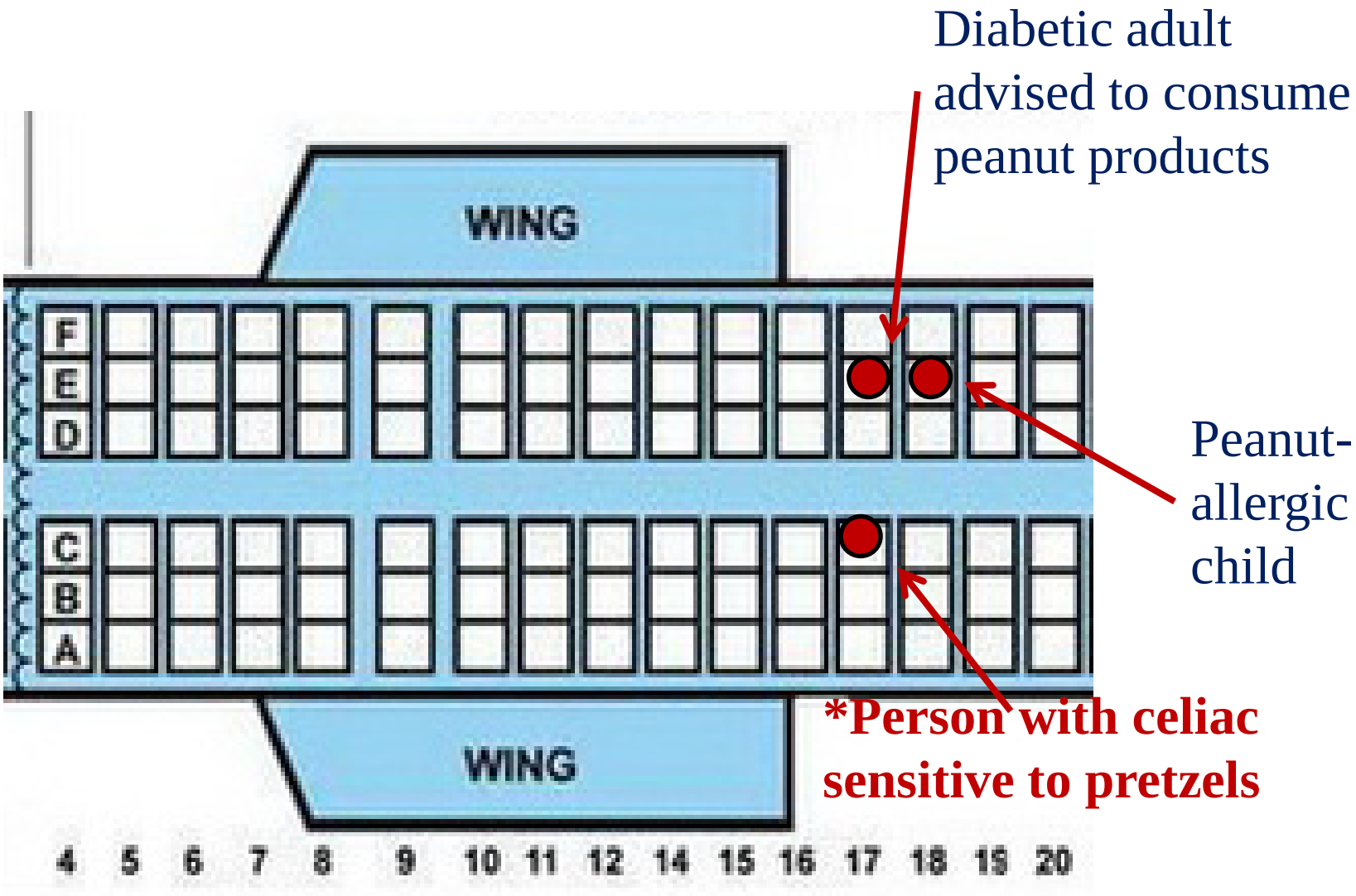
See: Dietert R., *The Human Superorganism,* 2016 (Dutton Penguin Random House)

Leaving on a Jet Plane



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

Leaving on a Jet Plane



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

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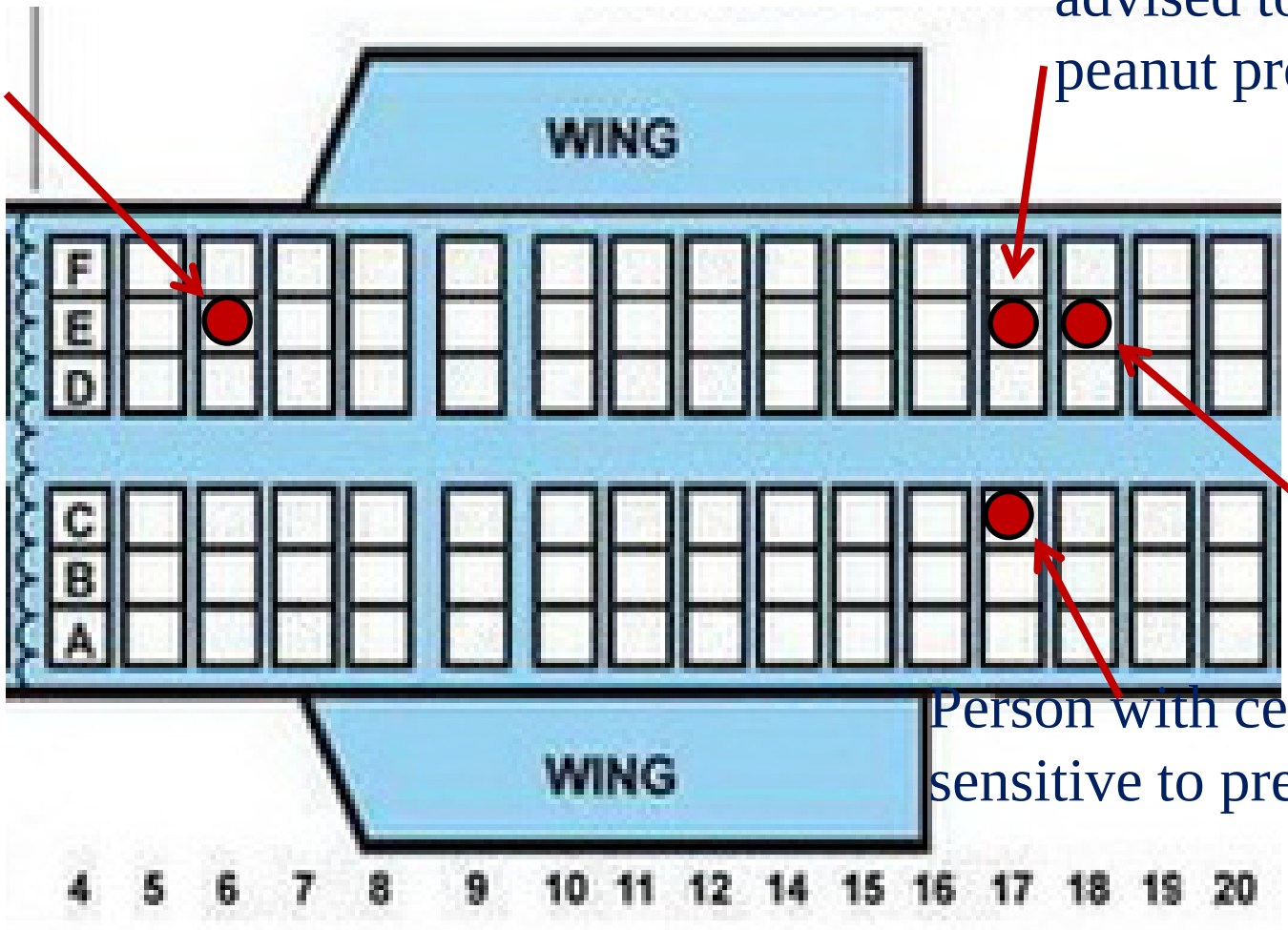
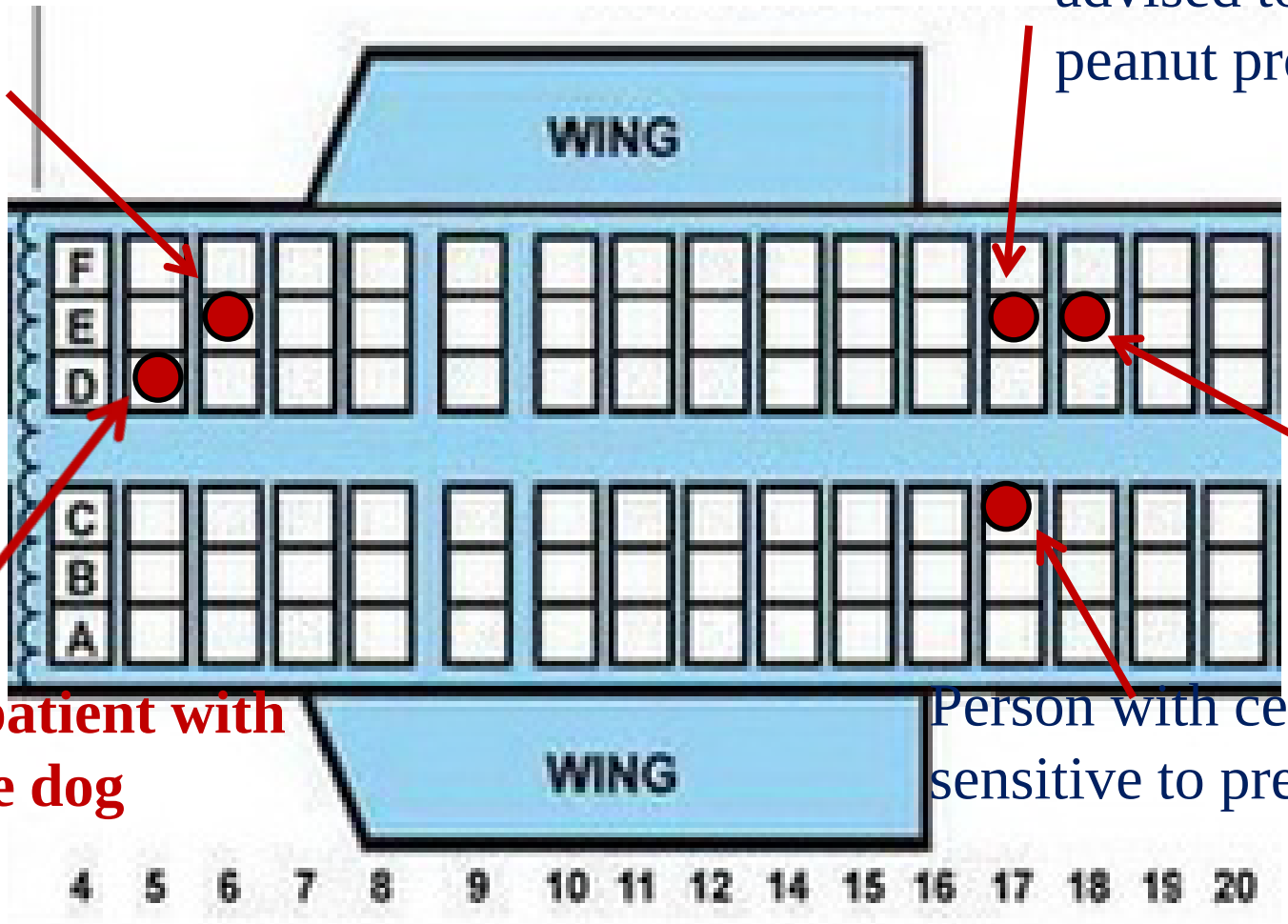


See: Dietert R., *The Human Superorganism,* 2016 (Dutton Penguin Random House)

Leaving on a Jet Plane

Asthmatic child - dog allergy

Diabetic adult advised to consume peanut products



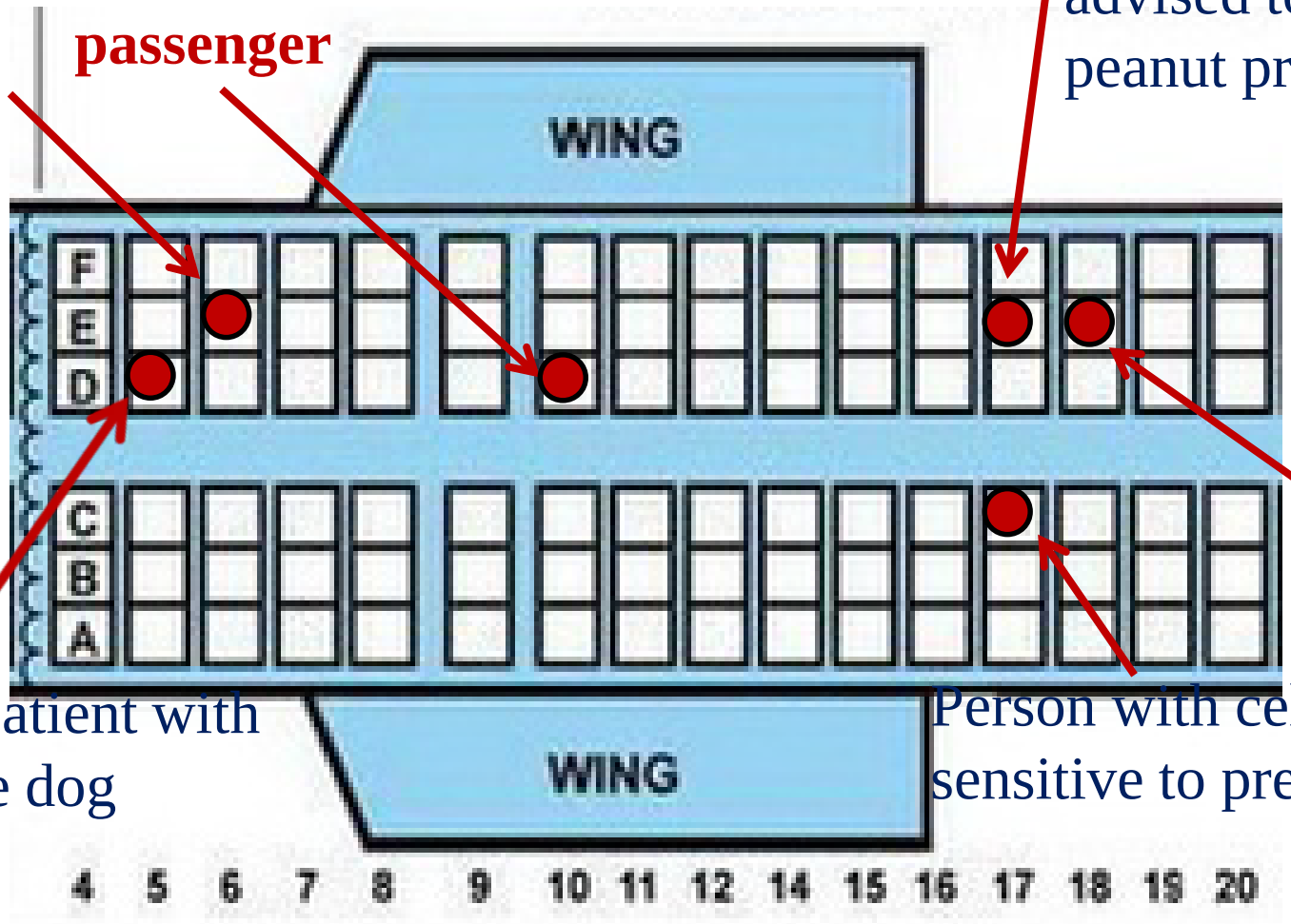
Peanut-allergic child

***MS patient with service dog**

Person with celiac sensitive to pretzels

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

Leaving on a Jet Plane



Asthmatic child - dog allergy

***Fragrance-sensitive passenger**

Diabetic adult advised to consume peanut products

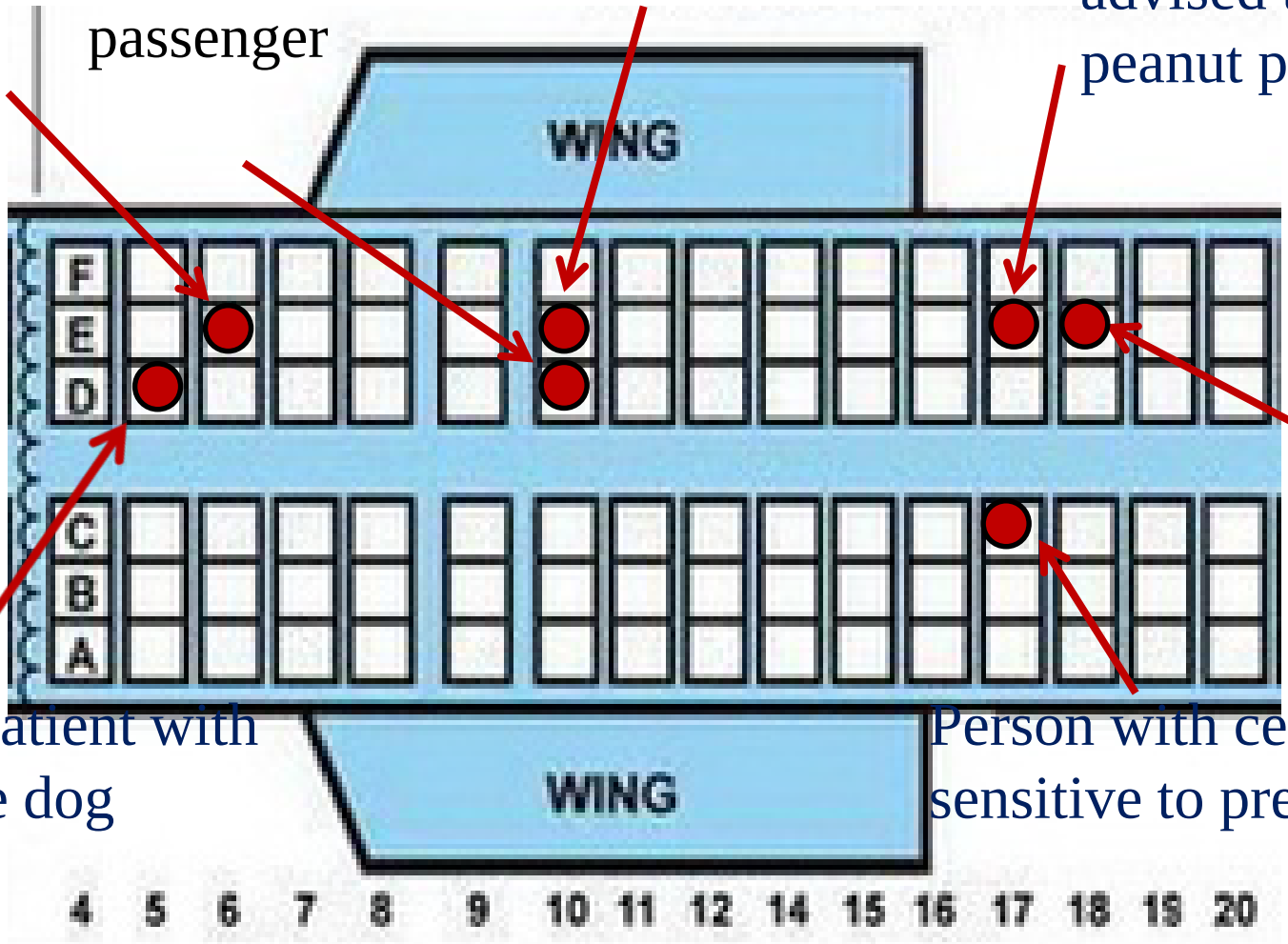
Peanut-allergic child

*MS patient with service dog

Person with celiac sensitive to pretzels

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

Leaving on a Jet Plane



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

3. Superorganism Ecology and The Completed Self Hypothesis

Multiple Microbial Bubbles and Filters

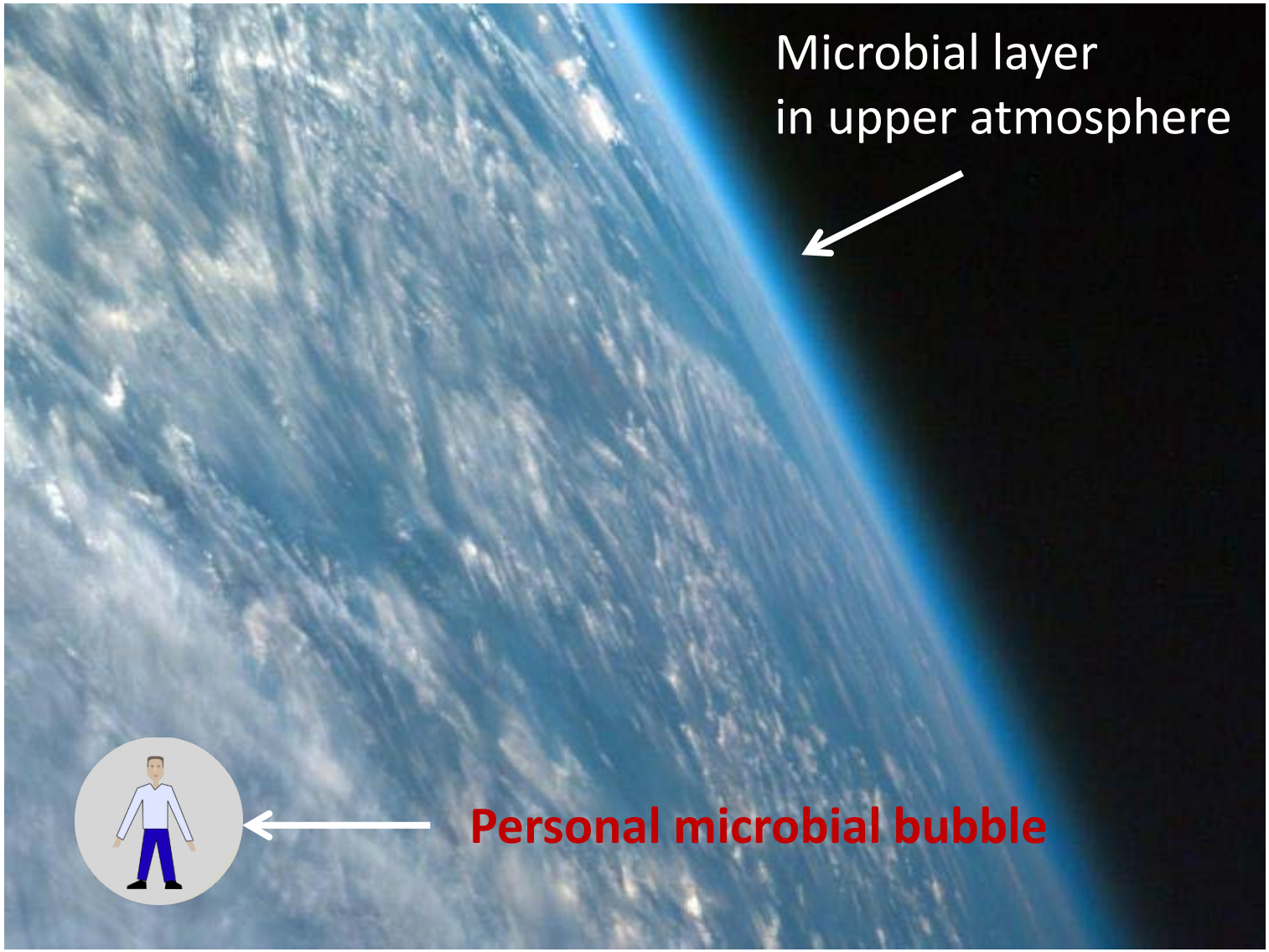
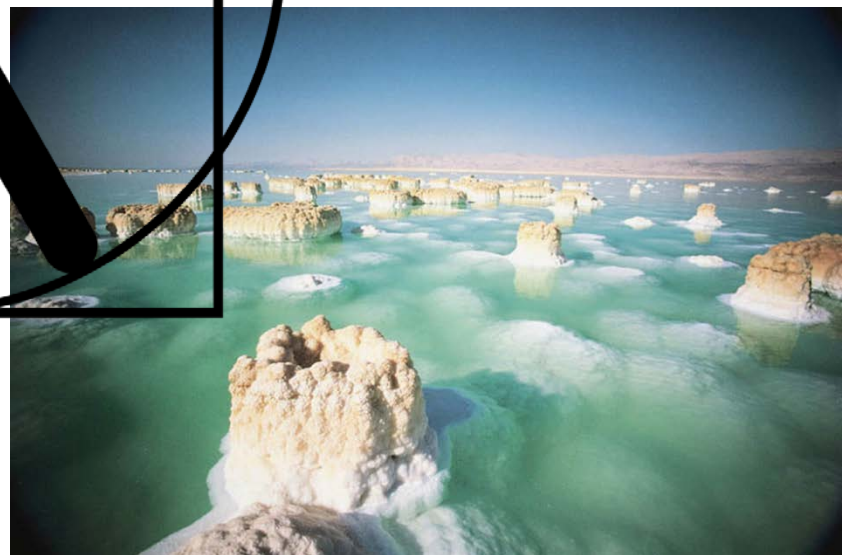


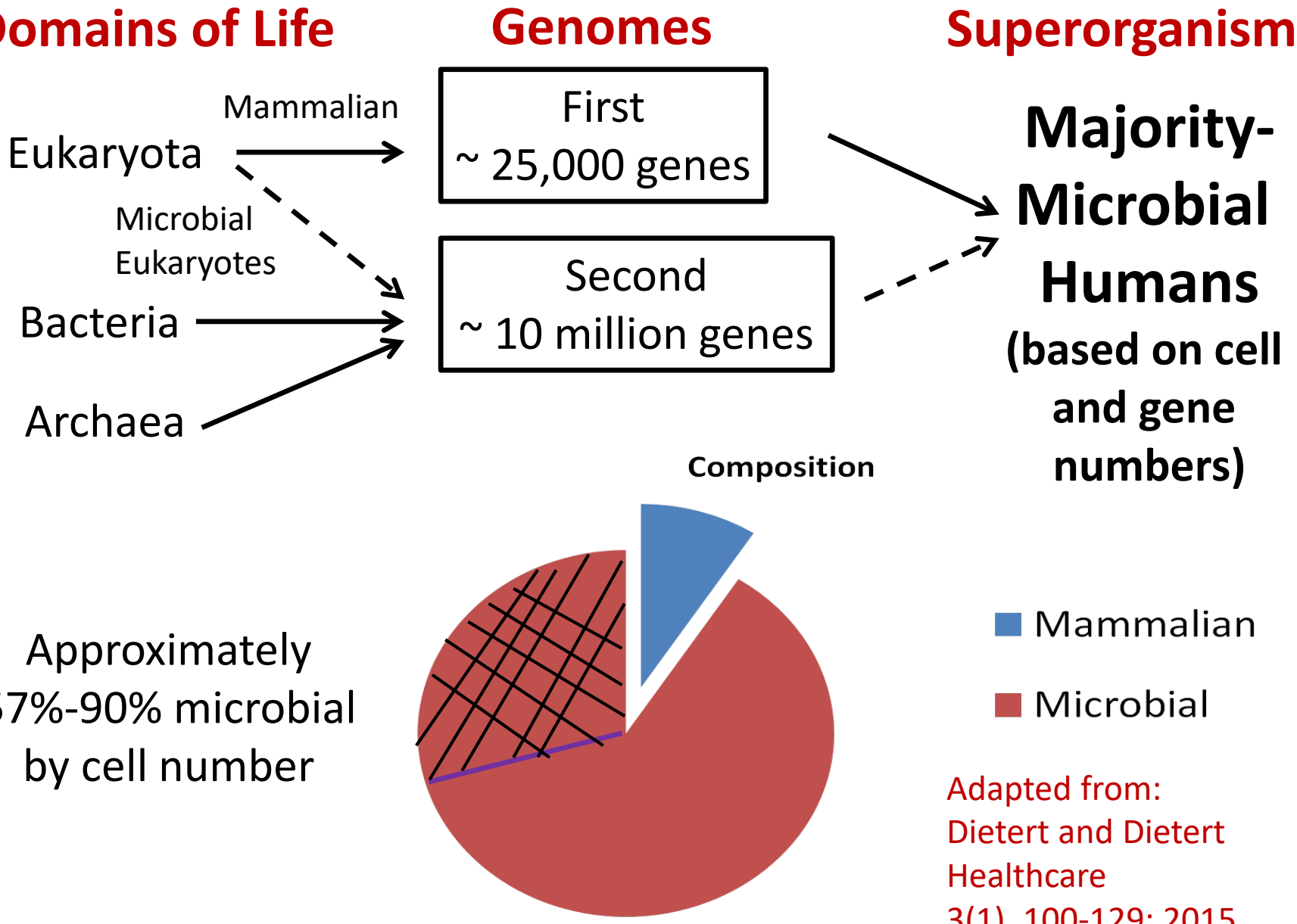
Image from NASA.gov

See: DeLeon-Rodriguez et al. PNAS USA 2013; 110 (7): 2575–2580; Yang et al., Int J Syst Evol Microbiol. 2010 Apr;60(Pt 4):776-9. ;

Archaea – also in your gut



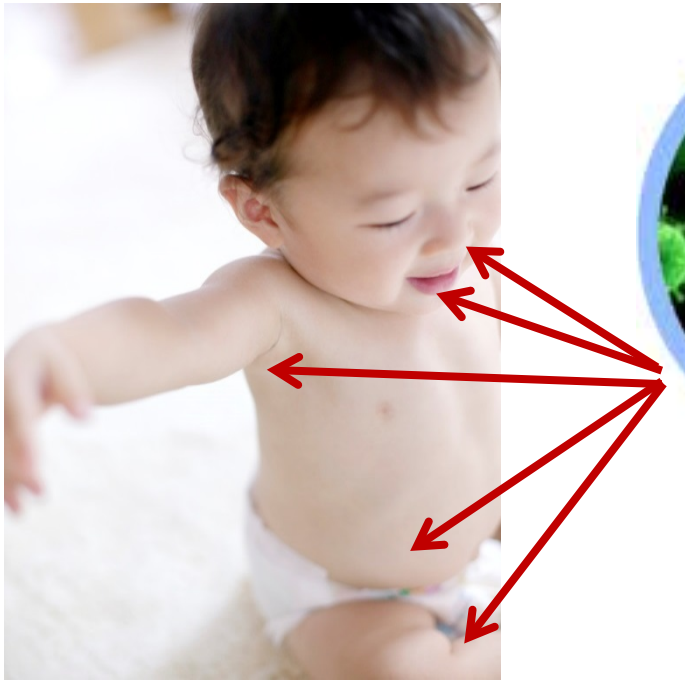
The Complete Human: Three Domains of Life

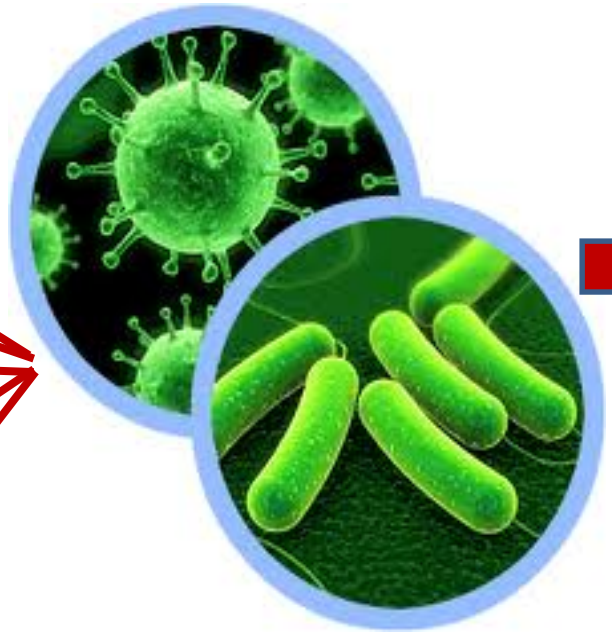


Approximately
57%-90% microbial
by cell number

Adapted from:
Dietert and Dietert
Healthcare
3(1), 100-129; 2015.

Self-Completion - The Completed Self





Self
Completion

Host-specific,
Family-sourced microbiota

See: Dietert and Dietert, Entropy 14(11), 2036-2065, 2012 and
Dietert, Birth Defects Research Part B. 101(4): 333-340, 2014;
Dietert, R. *The Human Superorganism*, Dutton (Penguin Group/Random House), 2016

Ramifications of Self Incompleteness

Microbiota are seen as an "Integral Organ"

If they are missing, it's analogous to a form of birth defect.

e.g., Clarke et el.,
Minireview: Gut microbiota: the neglected endocrine organ.
Mol Endocrinol. 2014 Aug;28(8):1221-38.

Brown JM, Hazen SL. The gut microbial endocrine organ:
bacterially derived signals driving cardiometabolic diseases.
Annu Rev Med. 2015 Jan 14;66:343-59.

Evans et al. The gut microbiome: the role of a virtual organ in the endocrinology of the host.
J Endocrinol. 2013 Aug 28;218(3):R37-47.

Microbiome Activities and Functions

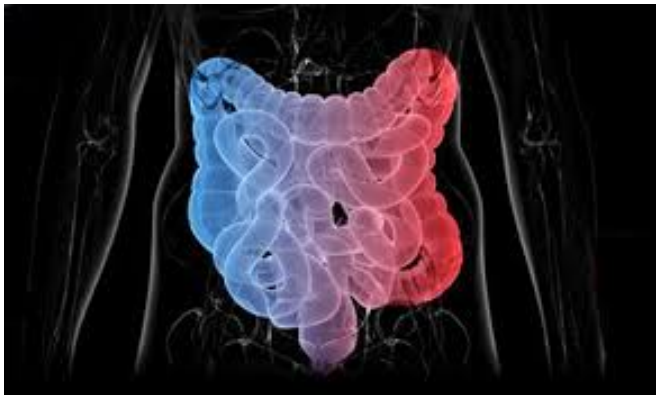
- ***Second brain: serotonin, dopamine, noradrenalin, GABA, catecholamines, acetylcholine***
- ***Regulation of hepatic metabolizing enzymes***
- ***Immune maturation and homeostasis***
- An important endocrine organ
- Bile acid metabolism (affecting lipid metabolism, fat-soluble vitamins, and intestinal barrier function)
- Regulation of HPA axis
- Production of epigenetic regulators (e.g., SCFAs)

Swanson, H.I. Drug Metab Dispos. 2015 Aug 10. pii: dmd.115.065714.
Mayer et al., J Neurosci. 2014 Nov 12; 34(46): 15490–15496. ; Brown and Hazen, Ann Rev Med 2015, 66: 343-359 ; Clarke et al., Mol Endocrinol. 2014 Aug;28(8):1221-38.

Brain – Who's Running the Show?

Neurobehavior
Kin recognition
Mating behavior

Food preferences and cravings



See:
Lize et al.,
Trends Ecol Evol.
2013 Jun;28(6):325-6;
Alcock et al.
Bioessays
36(10):
940-949
2014; Stilling et al.
J Neurovirol. 2016;
22(1):14-21.

Gut Bacteria as a Source of Brain Chemicals

Type of bacteria	Neural messengers
Bacillus	Dopamine, norepinephrine
Bifido-bacterium	Gamma-aminobutyric acid (GABA)
Enterococcus	Serotonin
Escherichia	Norepinephrine, serotonin
Lactobacillus	Acetylcholine, GABA
Streptococcus	Serotonin

Sources: T.G. Dinan et al, J. Psych. Res. 2015;63:1–9
and L. Sanders, Science News 2016; 189(7):23

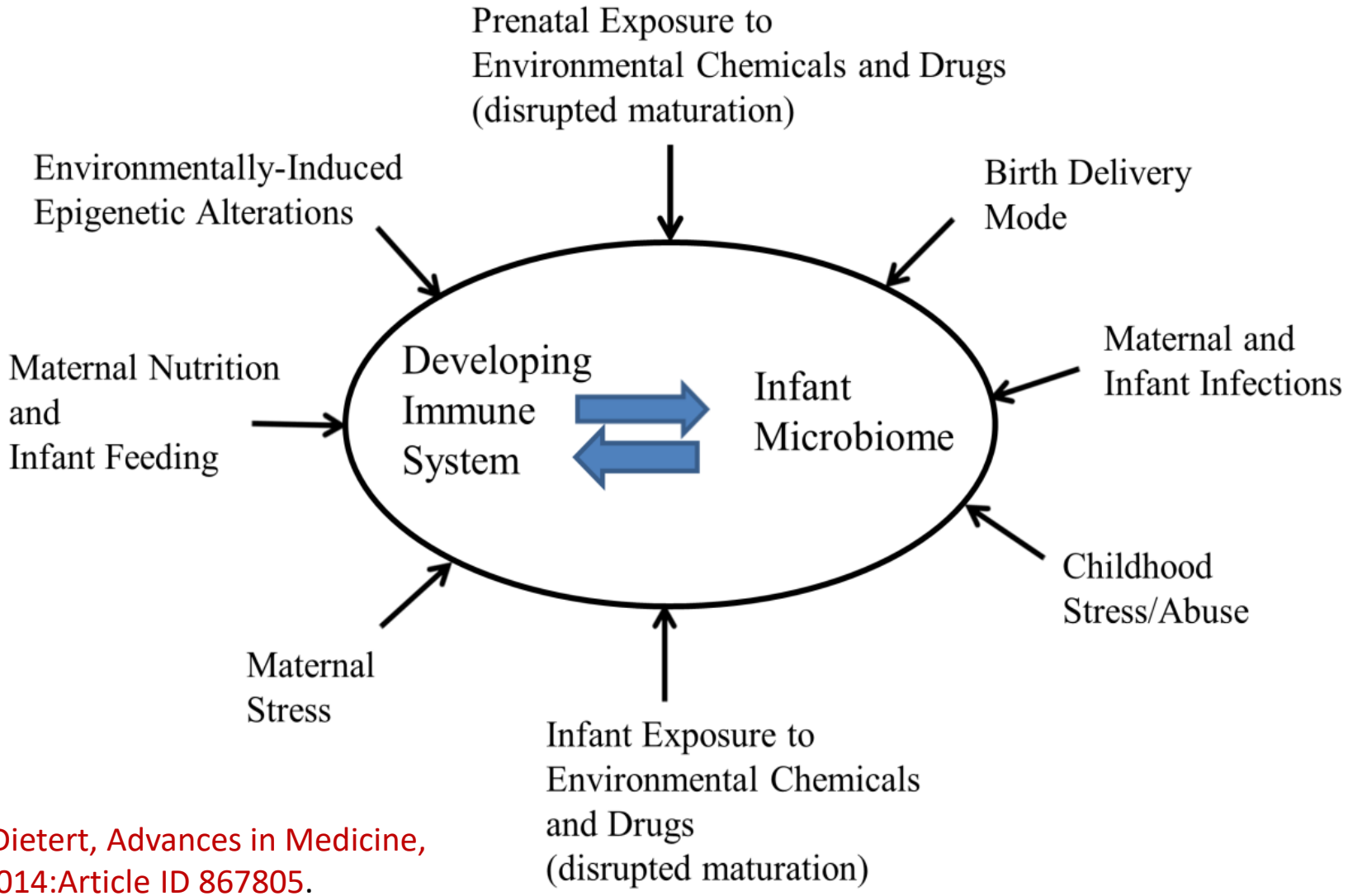
4. Microbiome-Immune Co-existence and Co-maturation

Managing the Human Ecosystem for: Effective Immune Maturation and Tolerance and a Diversified Microbiome

Ineffective Microbiome-Mediated Immune Maturation

Effective Microbiome-Mediated Immune Maturation

Developmental Immunotoxicity (DIT) in the Context of The Completed Self Model for the Human-Microbial Superorganism

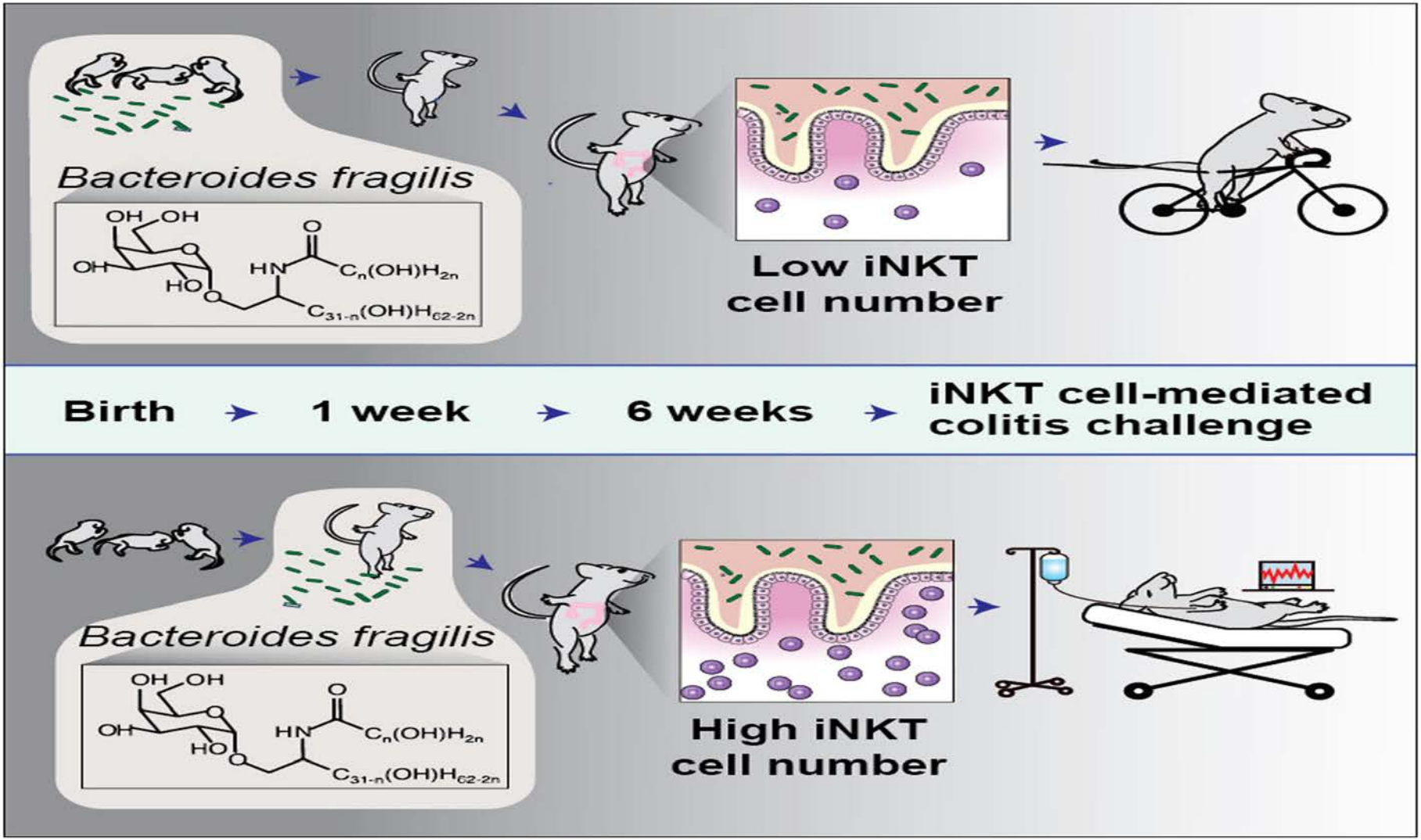


From: Dietert, Advances in Medicine, 2014;2014:Article ID 867805.

Examples of Neonatal "Critical Windows" Involving the microbiome and immune system

- Modulation of proliferative burst of invariant Natural Killer T cells (iNKT cells) in the gut –(determines risk of G.I. inflammatory disease)
- Neonatal timed influx of FoxP3+ T regulatory cells (Tregs) into the skin (determines tolerance to skin commensals)

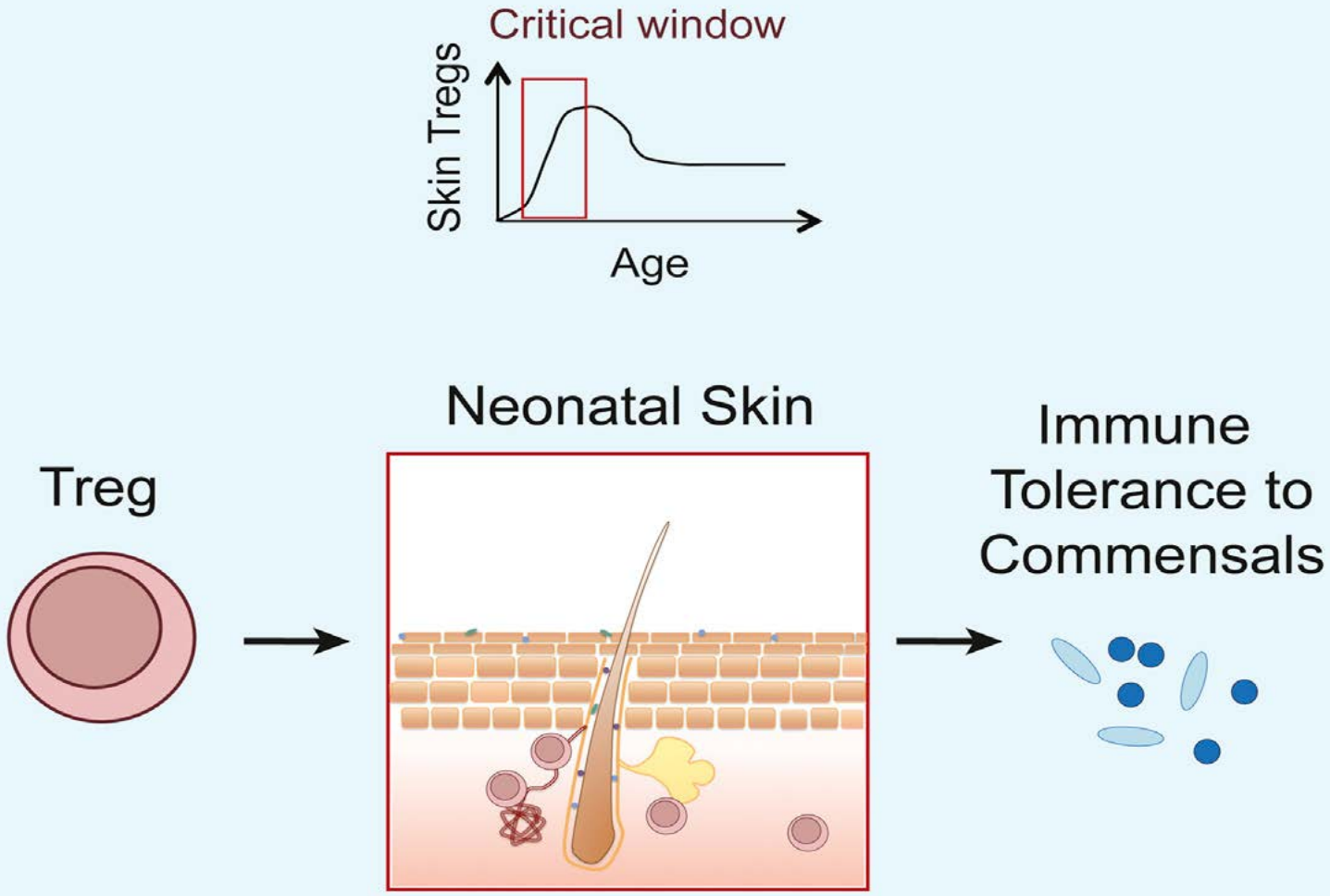
Modulation of colonic iNKT cells by inhibiting cell proliferation during neonatal development.



Dingding An , Sungwhan F. Oh , Torsten Olszak , Joana F. Neves , Fikri Y. Avci , Deniz Erturk-Hasdemir , Xi Lu , ...

Sphingolipids from a Symbiotic Microbe Regulate Homeostasis of Host Intestinal Natural Killer T Cells

Cell, Volume 156, Issues 1–2, 2014, 123 - 133



From: Scharschmidt et al. A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. Immunity 43, 1011–1021, 2015

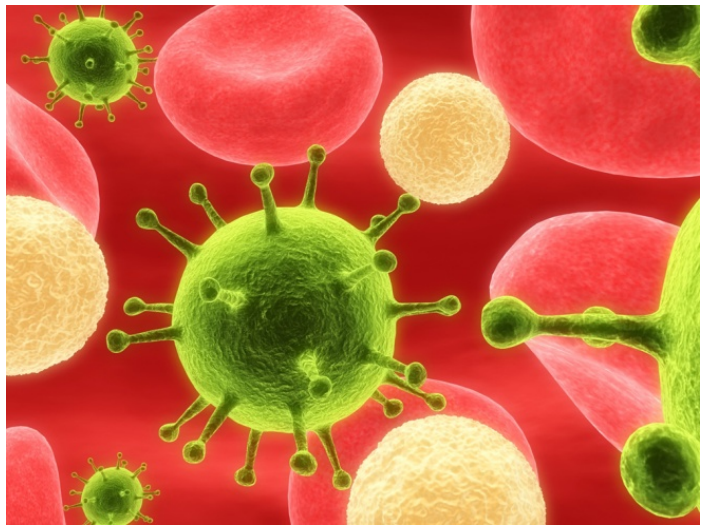
5. The Microbiome as our Gatekeeper

Responses of the Microbiota to Environmental Exposures

Environmental pollutants (*e.g.*, metals, organics)

Diet

Drugs



1. Sequestration
2. Avoidance/Exclusion
3. Metabolism
4. Specific Signaling
5. Selective Microbe Death
6. Selective Microbe Expansion
7. Translocation

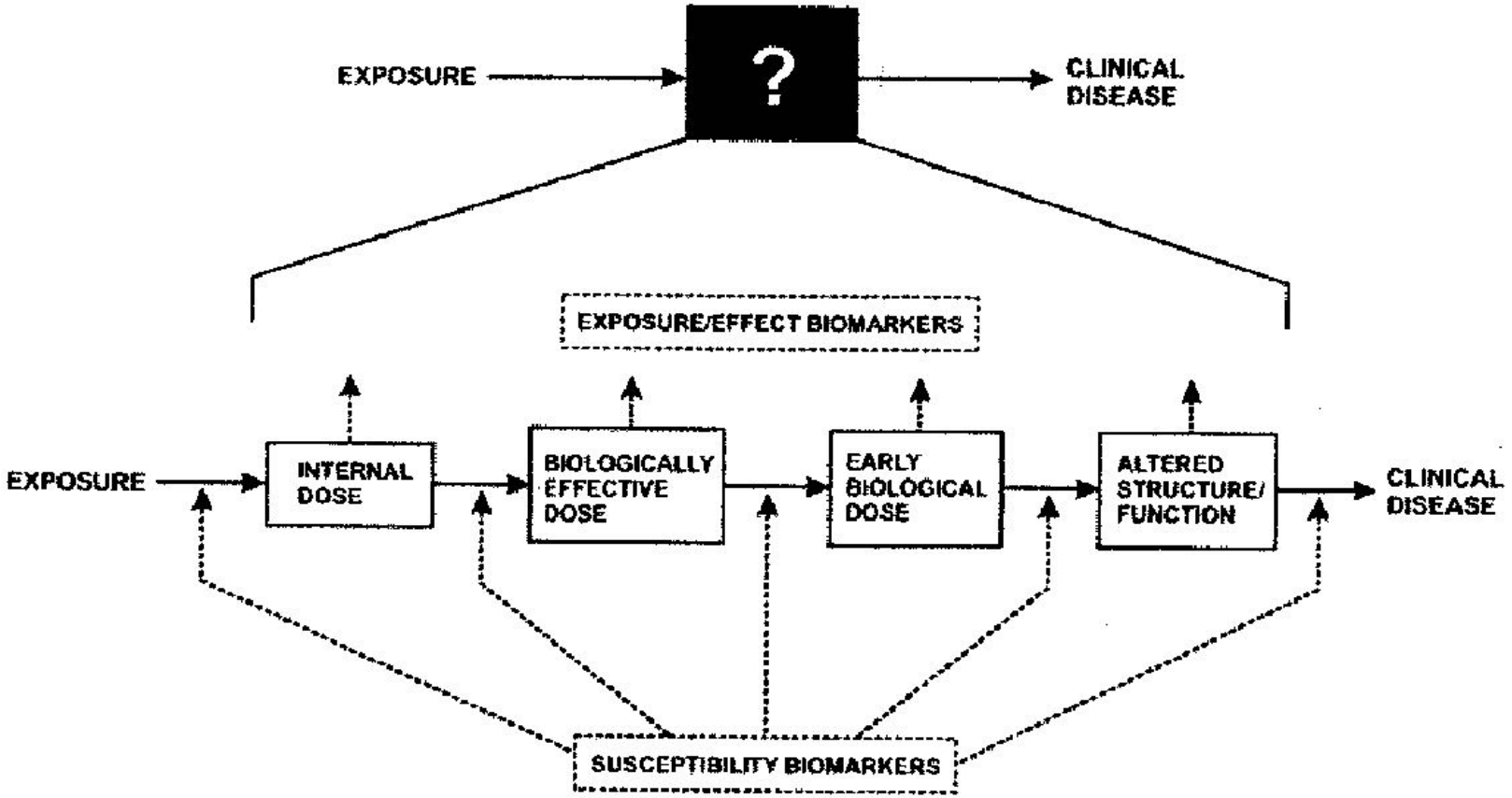
Adapted from: Dietert R. The microbiome in early life: self-completion and microbiota protection as health priorities. Birth Defects Res. Part B. 101(4): 333-340, 2014.

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
- Covert a pro-drug into an active drug
- Respond to one drug/xenobiotic by inactivating host enzymes for an unrelated drug
- Regulate host metabolism

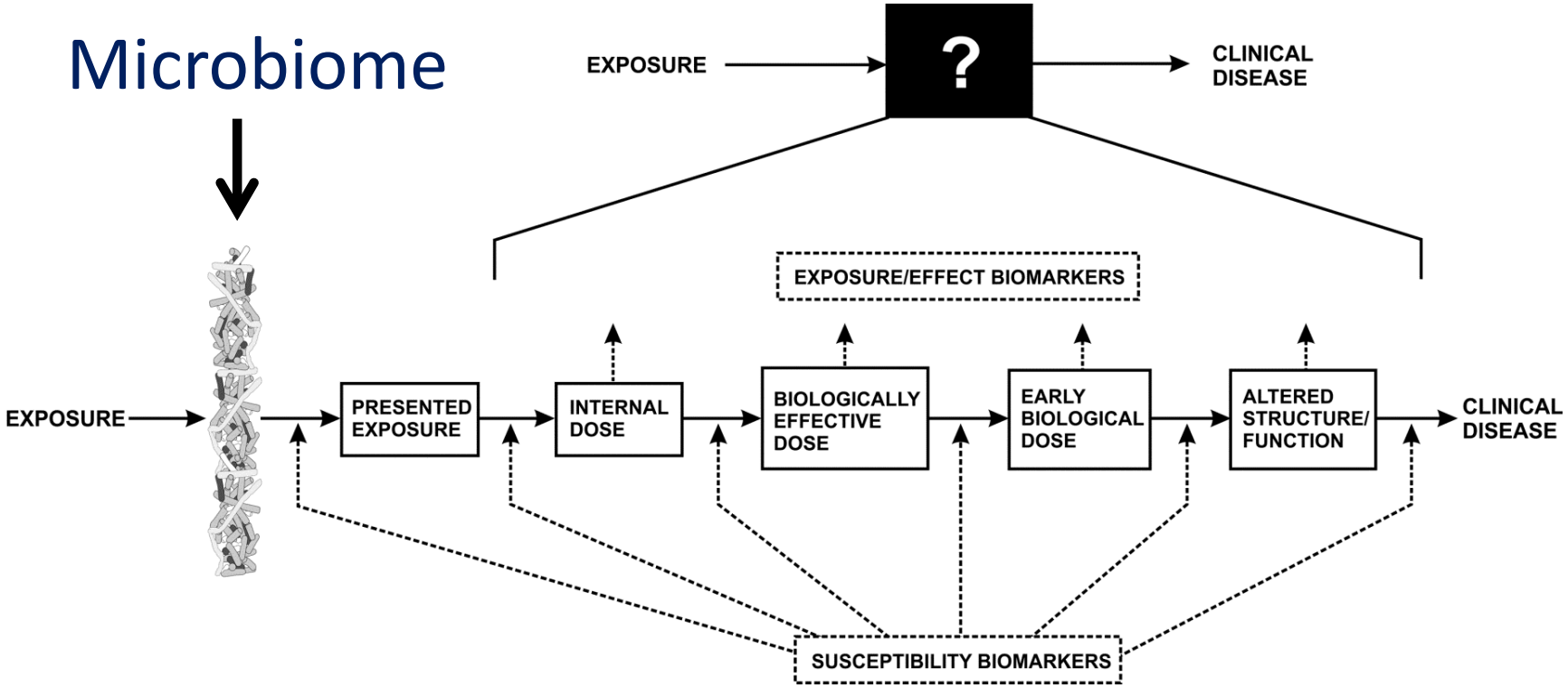
From: Klaassen and Cui, Drug Metab Disp. 2015; 43(10): 1505-1521

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



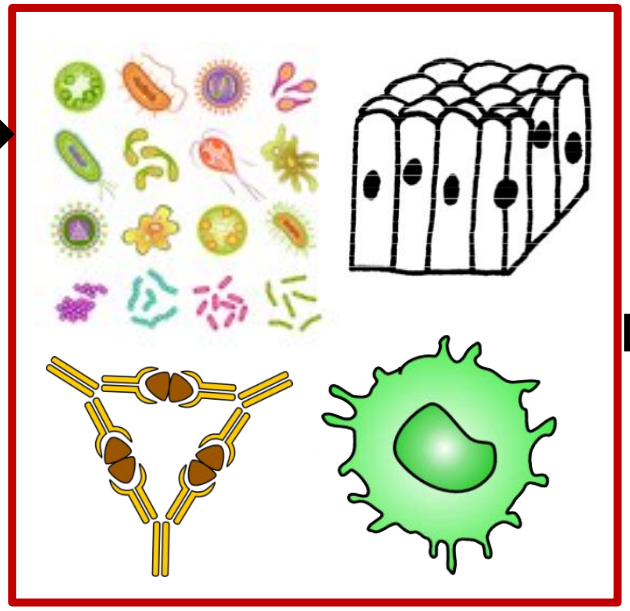
Proposed New Environmental Health Assessment Model

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

The Microimmunosome and the Exposome

External Component of the Exposome

The Microimmunosome



skin, gastrointestinal , urogenital and respiratory tracts

Internal Component of the Exposome

Risk of NCDs

- Neurological and behavioral conditions
- Metabolic diseases
- Allergic and autoimmune conditions
- Tissue-specific cancers

Risk of infections and illness

Modified From Dietert,R. Reprod Toxicol. 2016 May 7. pii: S0890-6238(16)30090-9.

Microbiome Status

- Can make an environmental chemical or drug more toxic or be protective of our cells against toxicity
- Can determine whether a drug has efficacy and/or toxicity in a given patient
- Can determine the physiological response to certain foods
- Can affect vulnerability to certain infections

6. Superorganism Safety

environmental chemicals
drugs
food additives
pathogens

FACTORS

Gut Microbiota Affect Xenobiotic Metabolism and Internal Dose

- Affect host drug metabolism
- Decrease absorption of drug by metabolizing it
- Biotransform xenobiotics
- Convert a prodrug to an active drug
- Increase availability of drug by inhibiting host detoxification
- Biotransform common food constituents
- Generate aryl-hydrocarbon receptor agonists
- Produce a drug metabolite that inactivates a host enzyme
- Increase the duration of drug action
- Increase drug toxicity
- Metabolize a drug to a teratogen
- Decrease and increase the mutagenicity of food-pyrolysis products

From: Klaassen and Cui, Drug Metabolism & Disposition 2015; 43(10): 1505-1521

Environmental Chemicals
Arsenic

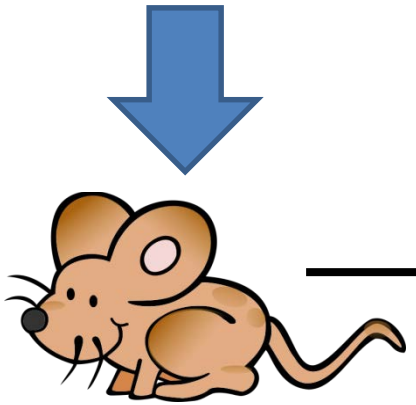
The state of the gut microbiome can determine actual biological impact of arsenic ingestion.

- Sulfur-reducing gut bacteria can convert arsenic into one of its most toxic forms. The amount and balance of microbes affect arsenic metabolism.

See: Rubin et al. Arsenic thiolation and the role of sulfate-reducing bacteria from the human intestinal tract, Environ Health Perspect, 122:817-22, 2014.

Environmental Chemicals (2): Cadmium

Cadmium (as Cl in drinking water)



Decreased thickness of inner mucus layer

Reduced genes/capacity to produce SCFAs

Dispersal to tissues is elevated once gut barrier is compromised

Colonic TNF-α and inflammation elevated

Reduced overall gut bacterial growth. Altered Bacteroidetes to Firmicutes ratio.

Liu et al., PLoS One. 2014 Feb 3;9(2):e85323.

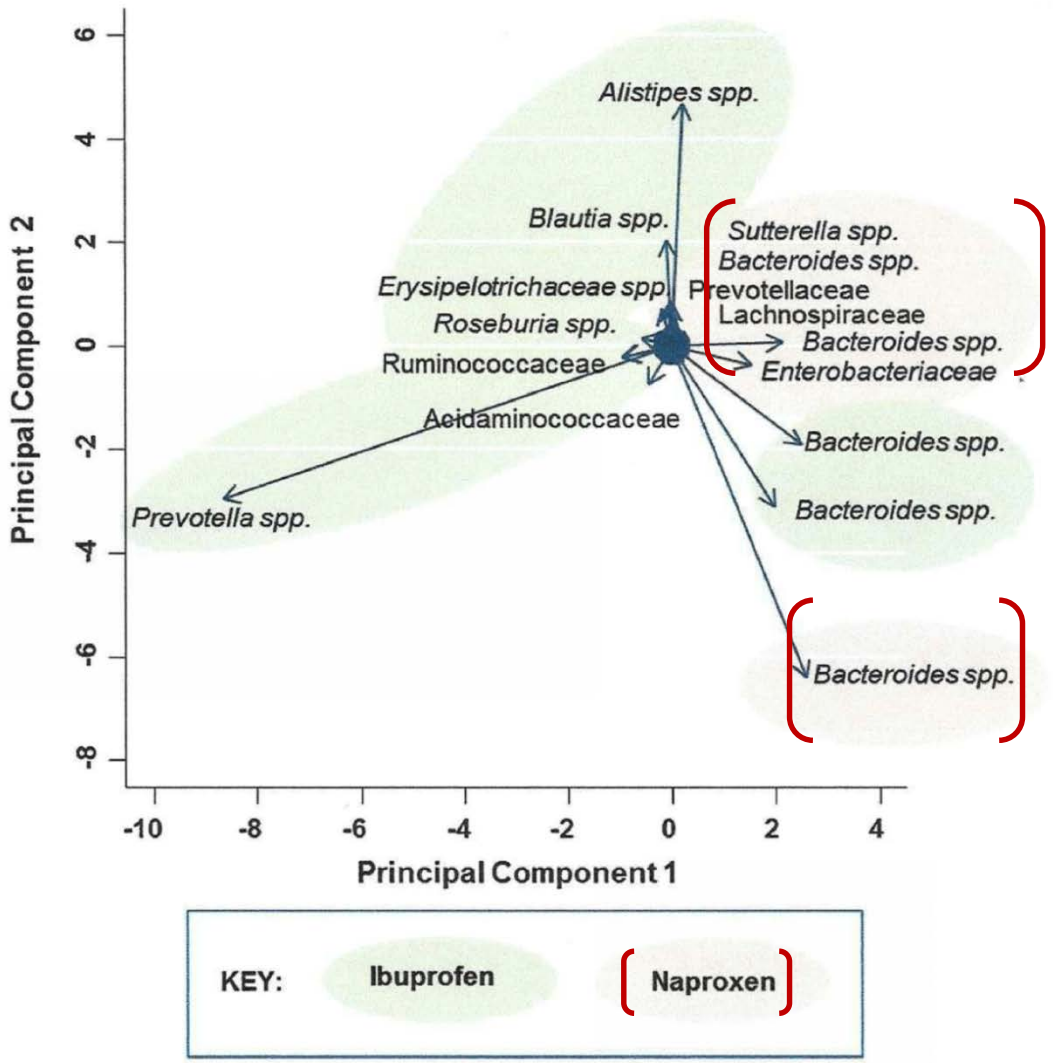
Drugs: Digoxin

- narrow efficacy/toxicity range
- gut microbiota determine actual delivered dose
- adverse outcomes – ineffective drug administration or potentially lethal toxicity
- *Eggerthella lenta* determines outcome

See: Haiser et al. Gut Microbes, 5:233-38, 2014.

Drugs: NSAIDs

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



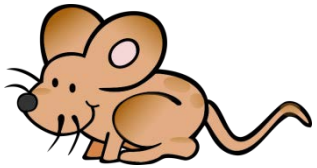
Different NSAIDs Produce Different Types of Microbiome Disruption

Adapted from: Rodgers and Aronoff, Clin. Microbiol. Infect. (Oct. 2015) doi: 10/1016/j.cmi.2015.10.003

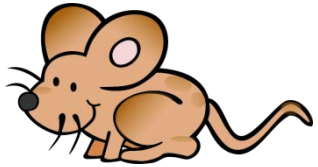
Drugs: Chemotherapeutics

Cyclophosphamide
or Platinum salts

No Antibiotics



Immune Modulation
Tumor Death



Antibiotics

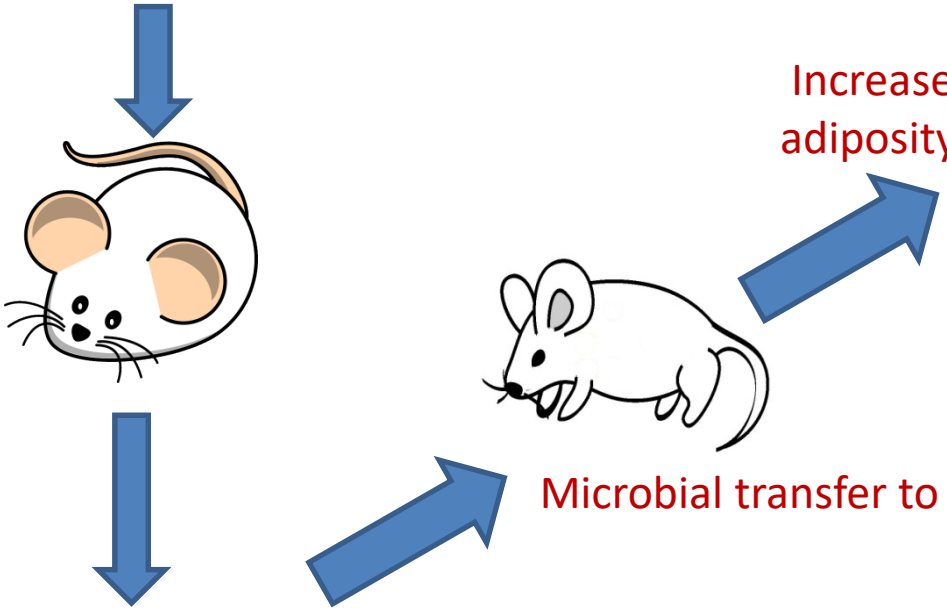
No Immune Modulation
Tumor Growth

Viaud et al., Science. 2013;342:971–6; Iida et al., Science. 2013;342:967–70;;
Viaud et al., Cell Death Differ. 2015 Feb;22(2):199-214.

Food Additives

Food Emulsifiers

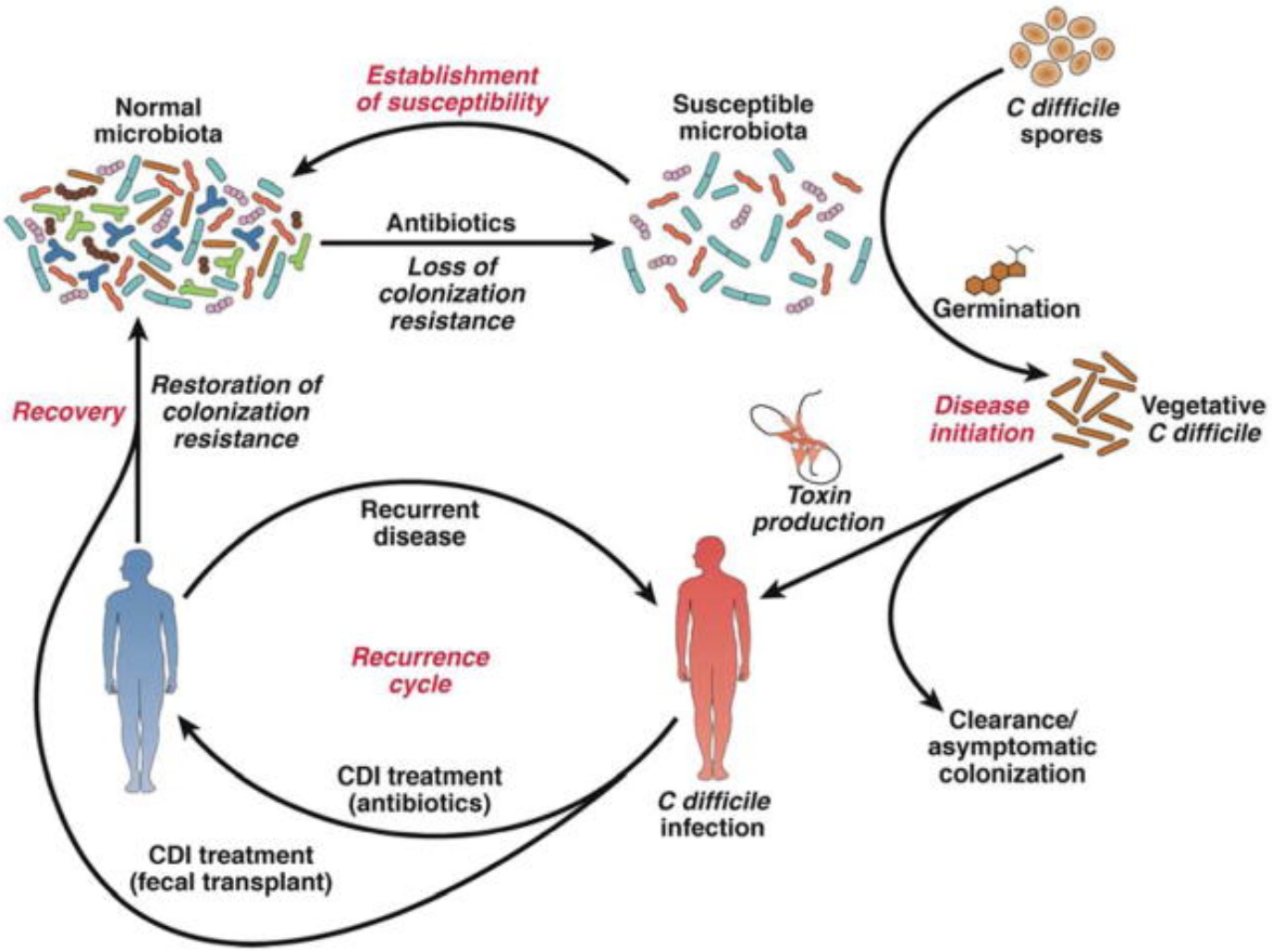
Polysorbate 80 (PS80), Carboxymethylcellulose (CMC)



Blooms in mucolytic *Ruminococcus gnavus* and *Akkermansia muciniphila;*
Decrease butyrate production;
Enrichment mucosa-associated, inflammation-promoting Proteobacteria;
Encroachment of bacteria toward epithelial lining producing leaky gut;
Promotion of metabolic syndrome and colitis

See: Chassaing et al. Nature, 519:92-96, 2015;
Cani PD and Everard A, Trends Endocrinol Metab. 2015 Jun;26(6):273-4.

Pathogens: Colonization Resistance to Protect Against Infections



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

Pathogens: Minimum Microbiota Necessary for Effective Colonization 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.

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

7. Microbial Biomarkers and Rebiosis

Microbial Dysbiosis and Impending *C. Difficile* Outbreaks

Cliff, the original *C. Difficile* detection dog

http://www.dailymail.co.uk/health/article-2247688/Meet-Cliff-remarkable-super-sniffing-dog-detects-hospital-superbugs.html

See: Bomers et al. A detection dog to identify patients with Clostridium difficile infection during a hospital outbreak. J Infect. 2014 Nov;69(5):456-61.

Biomarkers of the Microbiome are Already Being Sampled

Breathalizers Before Prescriptions?

Precision medicine should really focus on personalized patient information beginning with microbiome status.

Dietert, R. EC Pharmacology and Toxicology, 1.S1 (2015): S1-S3.- https://www.ecronicon.com/ecpt/pdf/ECPT-01-000S1.pdf

Rebiosis is Not New

- Competitive exclusion (originally known as the Nurmi Concept) and colonization resistance against pathogens have been well known for decades.

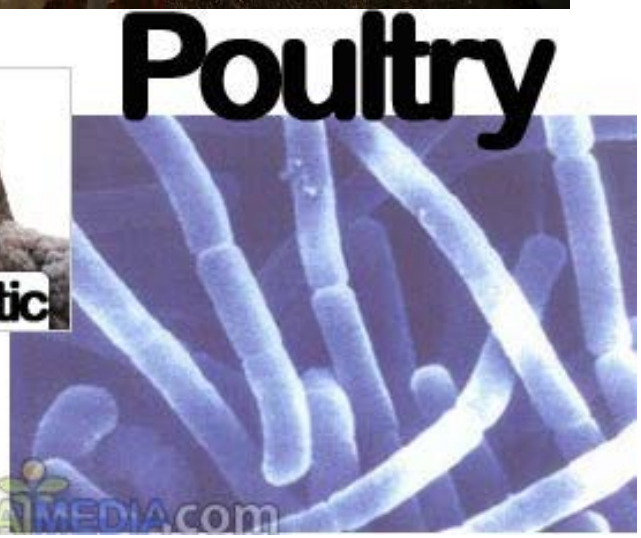
- Used in the poultry industry since the 1970s for risk reduction of salmonellosis and to improve food safety.

- All age groups can benefit from rebiosis.

- It will be a major component of future human health maintenance and treatment of disease.

See: Dietert, R. *The Human Superorganism*, Dutton, 2016

Using microbiota to block pathogens and reduce the risk of infections



Perinatal Period

From:
Dietert and Dietert, *Healthcare* **2015**, *3*(1), 100-129.

Diabetes,
Obesity
Colitis,
Asthma,
Celiac disease

Diabetes, Obesity,
Colitis, Asthma,
Celiac disease

Birth:
Vaginal
vs.
Cesarean

Risk of
future
generations
for
various
immune
dysfunction-
promoted
NCDs

microbiome
adjustment
as part of
adult
disease
management

microbiome
adjustment
for pregnancy
and to
optimize
microbiome
seeding

healthy
microbiome
seeding
plan

feeding
the
microbiota
for optimized
immune and microbial
co-maturation

Summary

- Failure to self-complete in the newborn may be the single greatest health risk across a lifetime. We need microbiome seeding on every birth plan and active management of our "second genome" (*i.e.,* seed, feed, protect).
- The immune system and the microbiome need to co-mature in a narrow window of development or persistent immune dysfunction and elevated risk of NCDs are likely.
- Safety needs to be based on the whole human. It is the superorganism that needs protection.
- Microbiome status is a pivotal factor in environmental health safety.
- Probiotic and prebiotic strategies offer a core component of future personalized healthcare.

QUESTIONS

You can check out
Alexander Fleming's
Microbial Art
at the link below

http://www.smithsonianmag.com/science-nature/painting-with-penicillin-alexander-flemings-germ-art-1761496/

SRA 2017 Advancing the Science Webinar Series Continues:

Microbiota Informing Next-Generation Risks & Benefits

2. Dr. Michelle McGuire (Washington State University), ***Human Milk: Mother Nature's Prototypical Probiotic Food,*** McGuire et al., 2015 (**March,** TBD)

3. Dr. Rodrigo Carvalho Bicalho (Cornell University), ***Bovine Milk Microbiota: Insights and Perspectives from –Omics Studies,*** Addis et al., 2016 (**May,** TBD)

4. Anne Mendelson (Culinary Historians of New York), ***History of the Milk Wars,*** Meldelson, 2011 (**July,** TBD)

A panel of microbial risk assessors will deliberate evidence of microbiota influences on risk & benefit for fresh unprocessed and pasteurized milk (**October,** TBD) prior to **exercises of analytic-deliberative process** at SRA workshop and round table panel symposium (**December 10-14**, Arlington, VA).