Welcome to the SRA Webinar Series

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Protecting the Human Superorganism

SRA Webinar
January 24, 2017

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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

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• Dr. Ellen Silbergeld, Johns Hopkins School of Public Health
• Peg Coleman, Coleman Scientific Consulting
• Janice Dietert, Performance Plus Consulting
OUTLINE

1. Introduction
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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

OFFICIAL SELECTION
LIFE SCIENCES
FILM FESTIVAL
PRAGUE
2014

“WE ARE IN THE MIDST OF THE LARGEST
EXPERIMENT IN HUMAN HISTORY.”
Prof. Sue Carter
Biologist & Behavioural Neurobiologist

MICROBIRTH

Revealing the microscopic events during childbirth
that could hold the key to the future of humanity

“MICROBIRTH” an ALTO FILMS production with ONE WORLD BIRTH
Music composed by KIM HALIDAY produced & directed by TONI HARMAN and ALEX WAKEFORD
MICROBIRTH.COM
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)
A Pattern of 32 Interlinked NCDs for Obesity

Cancer (12 different types)

Psoriasis

Heart disease

Asthma

Depression

Fatty liver disease

Rheumatoid arthritis

Deep vein thrombosis

Hearing loss

Gout

Chronic kidney disease

Chronic obstructive pulmonary disease

Polycystic ovarian syndrome

Multiple sclerosis

Alzheimer’s disease

Hypertension

Infertility

Sleep disorders

Stroke

Gastroesophageal reflux disease

Attention-deficit hyperactivity disorder

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.

The Hidden Cost of Microbiome and Immune Dysbiosis Driven NCDs

Societal change - Isolation
Leaving on a Jet Plane

Leaving on a Jet Plane

*Diabetic adult advised to consume peanut products

Leaving on a Jet Plane

Diabetic adult advised to consume peanut products

*Peanut-allergic child

Leaving on a Jet Plane

Diabetic adult advised to consume peanut products

Peanut-allergic child

*Person with celiac sensitive to pretzels

Leaving on a Jet Plane

*Asthmatic child - dog allergy

Diabetic adult advised to consume peanut products

Peanut-allergic child

Person with celiac sensitive to pretzels

Leaving on a Jet Plane

Asthmatic child - dog allergy

Diabetic adult advised to consume peanut products

Peanut-allergic child

Person with celiac sensitive to pretzels

*MS patient with service dog

Leaving on a Jet Plane

Asthmatic child - dog allergy
*Fragrance-sensitive passenger
*MS patient with service dog
Diabetic adult advised to consume peanut products
Peanut-allergic child
Person with celiac sensitive to pretzels

Leaving on a Jet Plane

3. Superorganism Ecology and The Completed Self Hypothesis
Multiple Microbial Bubbles and Filters

Microbial layer in upper atmosphere

Personal microbial bubble

Image from NASA.gov

Archaea – also in your gut
The Complete Human: Three Domains of Life

Domains of Life
- Eukaryota
  - Mammalian
  - Microbial Eukaryotes
- Bacteria
- Archaea

Genomes
- First
  - ~ 25,000 genes
- Second
  - ~ 10 million genes

Superorganism
- Majority-Microbial Humans
  (based on cell and gene numbers)

Composition
- Approximately 57%-90% microbial by cell number

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

Host-specific, Family-sourced microbiota

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 al.,
Minireview: Gut microbiota: the neglected endocrine organ.

Brown JM, Hazen SL. The gut microbial endocrine organ: bacterially derived signals driving cardiometabolic diseases.

Evans et al. The gut microbiome: the role of a virtual organ in the endocrinology of the host.
**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)

Brain – Who’s Running the Show?

Neurobehavior
Kin recognition
Mating behavior

Food preferences and cravings

See:
<table>
<thead>
<tr>
<th>Type of bacteria</th>
<th>Neural messengers</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacillus</em></td>
<td>Dopamine, norepinephrine</td>
</tr>
<tr>
<td><em>Bifido-bacterium</em></td>
<td>Gamma-aminobutyric acid (GABA)</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Serotonin</td>
</tr>
<tr>
<td><em>Escherichia</em></td>
<td>Norepinephrine, serotonin</td>
</tr>
<tr>
<td><em>Lactobacillus</em></td>
<td>Acetylcholine, GABA</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>Serotonin</td>
</tr>
</tbody>
</table>

Sources: T.G. Dinan et al, J. Psych. Res. 2015;63:1–9
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

- Prenatal Exposure to Environmental Chemicals and Drugs (disrupted maturation)
- Environmentally-Induced Epigenetic Alterations
- Maternal Nutrition and Infant Feeding
- Maternal Stress
- Infant Exposure to Environmental Chemicals and Drugs (disrupted maturation)
- Birth Delivery Mode
- Maternal and Infant Infections
- Childhood Stress/Abuse

Developing Immune System ↔ Infant Microbiome

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

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
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

Skin, gastrointestinal, urogenital, and respiratory tracts

Internal Component of the Exposome

Risk of infections and illness

Risk of NCDs

Neurological and behavioral conditions

Metabolic diseases

Allergic and autoimmune conditions

Tissue-specific cancers

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
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.

Environmental Chemicals (2): Cadmium

Cadmium (as Cl in drinking water)

- 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.
- Decreased thickness of inner mucus layer
- Reduced genes/capacity to produce SCFAs

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

Drugs: NSAIDs

Different NSAIDs Produce Different Types of Microbiome Disruption

Drugs: Chemotherapeutics

Cyclophosphamide or Platinum salts

No Antibiotics


Immune Modulation
Tumor Death

Antibiotics

No Immune Modulation
Tumor Growth
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

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.

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

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.

Using microbiota to block pathogens and reduce the risk of infections.
Perinatal Period

Diabetes, Obesity, Colitis, Asthma, Celiac disease

Birth: Vaginal vs. Cesarean

Vaginal

Cesarean

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

Risk of future generations for various immune dysfunction-promoted NCDs

From: Dietert and Dietert, Healthcare 2015, 3(1), 100-129.
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.
You can check out Alexander Fleming’s Microbial Art at the link below

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)


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).