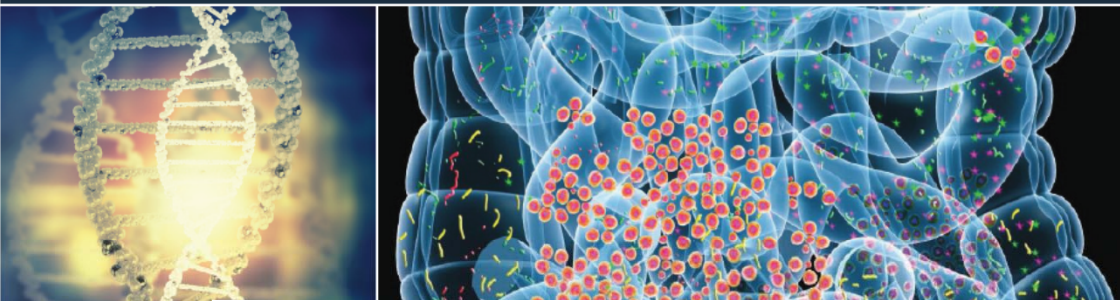


57th annual conference

# Translational Nutrition: The Science of Personalized Nutrition

November 9-11, 2016 • San Diego, California



## THE MICROBIOME & EPIGENOMIC PROGRAMMING



### **Tore Midtvedt**

Professor em, MD, PhD

MTC, Karolinska Institutet, Stockholm, Sweden



# Faculty Disclosure

---

<b>Commercial Interest</b>	<b>Nature of Relevant Financial Relationship (Include all those that apply)</b>	
	<b>What was received</b>	<b>For what role</b>
• None	• N/A	N/A

# Presentation Learning Objectives

After participating in this presentation, learners should be better able to:

- Understand the important roles microbes play in epigenetic programming.
- Understand that microbes begin their role in utero and this continues throughout life

Key words in the title

---

**MICROBIOM**

**EPIGENOMIC**

**PROGRAMMING**

Putting them together in a host in a **personalized way**



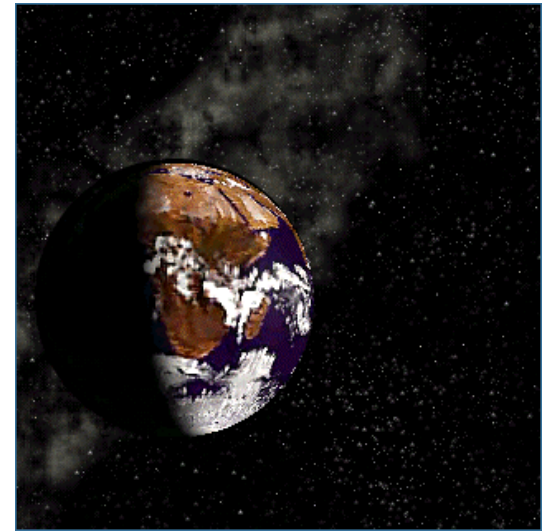
**BIG BANG!**



# To agree upon - I

---

...the Earth was (became) formless and empty.....***Genesis 1.1***





# Then the prokaryotes came – a harsh life

---

- Had to make everything by themselves (autotrophy)
- Had to live without oxygen (anaerobically)
- Had to develop multiplication
- Had to develop communication
- Had to develop co-operation

## **MICROCRATIC RULES**



Please accept:

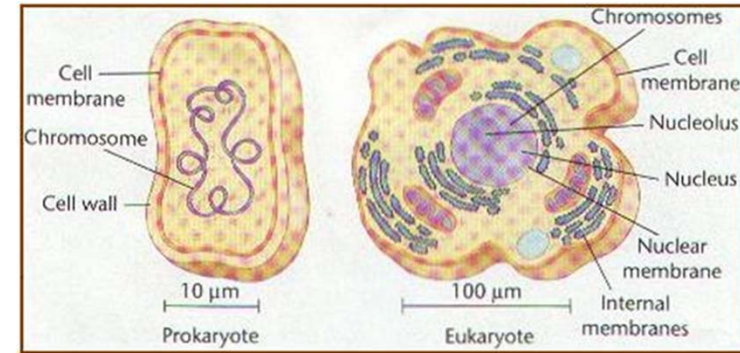
---

WHO'S YOUR PRESIDENT?  
**PROKARYOTES ARE SMARTER  
THAN ME AND YOU!!**



# AT THE END OF THE BEGINNING OF EVERYTHING

---



EUKARYOTE



MR. EUKARYOTE I PRESUME

PROKARYOTE



Mr Eukaryote and Miss Prokaryote talk together:

# The prokaryotes offered the eukaryotes

---

Giving away : Communication molecules (genes)

«Own» genes: Mitochondria (many functions)

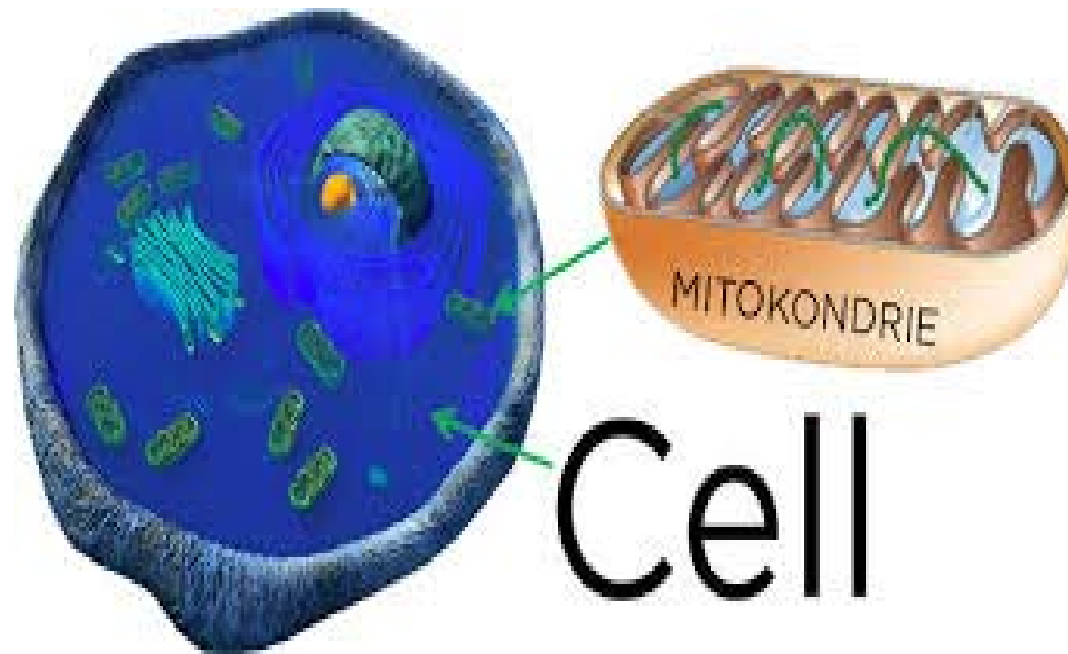
Helping with : Amino acids, vitamins, nucleotides

Promise : if you are kind to us, we will be kind to you

We will keep the secrets how to get nitrogen from the air for ourselves

# MITOCHONDRIA - I

---



# Mitochondria - II

---

1. Own genetics in man mainly (solely?) from mother
2. In man, geographical differences
3. Under epigenetic influences (few studies)

# Dialogue II

---

## **Eukaryotes: We offer you:**

- a. Proper places to live
- b. A certain stability ( in delivery of resources (food, fluid etc)
- c. Possibilities for multiplications

(a - c are basic principles in *Evolutionary Game Theory* = all ecosystems)

If you are peaceful, we will try to be.

Remember: you can live in peace on our surfaces, but we will by many weapons defend ourselves if you try entering inside our body.

However, in the future, there might be species not willing to follow neither our **democratic nor your microcratic rules and our deal**

Additionally, we will keep abstract thinking to ourselves !

🔊 AT THE END OF THE  
BEGINNING OF  
EVERYTHING

---

EUKARYOTE



MR. EUKARYOTE I PRESUME



PROKARYOTE

- Mr Eukaryote sings:



## Teleologically;

---

By recruiting a society of resident microbes with metabolic capabilities to break down a number of dietary substances that are otherwise non-digestible, the host is relieved of the need to evolve such functions

- The host has achieved a high degree of metabolic adaptability that can help him with changes in diet and nutrient availability
- The microflora is given a "protected" nutrient-rich area in which it can multiply and survive

# About man and microbes

---

- **Mankind** > 7,3 billions



- **Microbes in colon: some logs more**



# Mammals are born germ-free

---

*but*

from cradle to grave they are

*out-numbered*

***by their microbes with some log's***

# Born germ free has recently been questioned;

---

## PRO:

- a) Microbial products in uterus, placenta and in the fetus
- b) Mainly products from the oral microbiota
- c) Rare to find living microbes

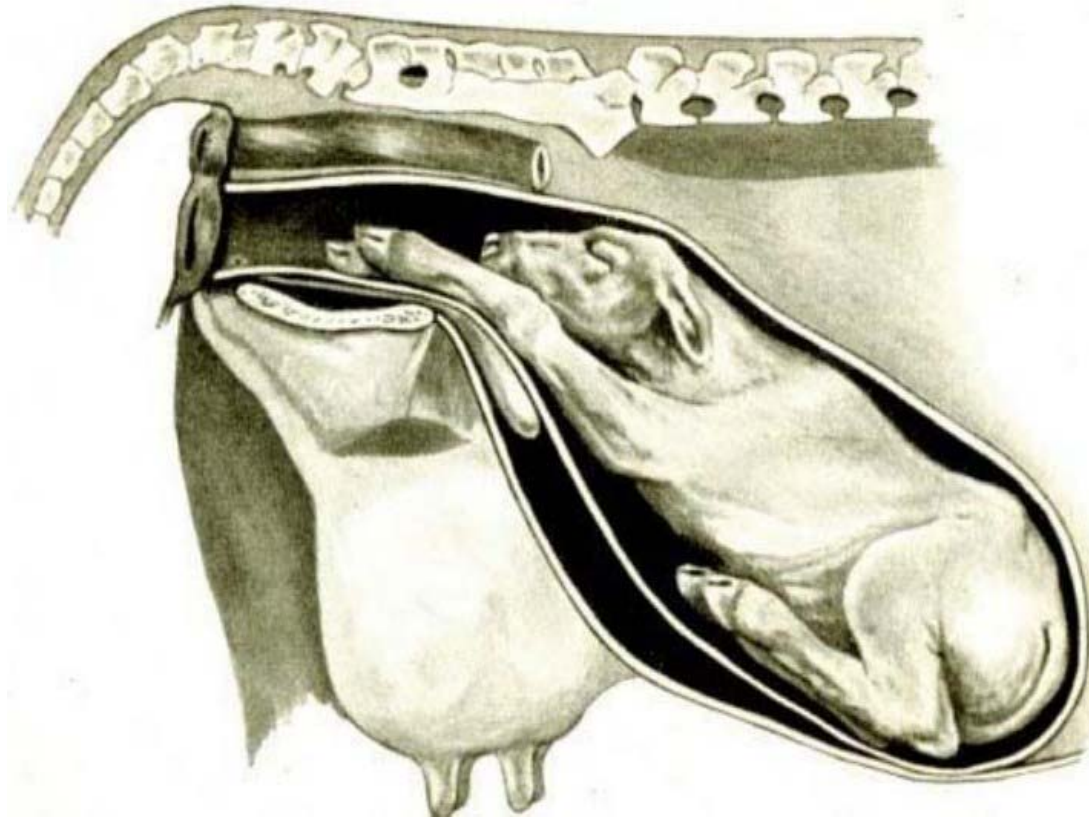
## CON:

- a) 125 years experience with germfree animals
- b) If you are raising GF animals on a microbe-free diet, microbes seen in feces will disappear
- c) To the best of my knowledge, : microbial metabolic products never found
- d) Translocation is a physiological event

**BOTTOM LINE: THE PRODUCTS MAY HAVE EPIGENOMIC EFFECTS**

# Birthday gift from mother

---



# Microbes from mother

---



Benno P et al, *Läkartidningen* 2010

# Rest of life

---

**Every day:**

**You meet some hundreds new strains  
and  
even some new species!**



# You meet new strains every day

---

**He can kill you**     *(very rare - little interest, terrorist)*

**You can kill him** *(more common - some interest, imperialist)*

**You stay together for a while**  
*(most common – great interest, democrats)*

## Important questions to keep in mind when a new microbe is entering :

---

"Windows" for establishment

"Succession" in establishment

Long-term effects of establishment

# Key points in the history of genetics

---

**Heraklitos:** Phanta rhei - Everything floats (500 BC)

*Simplified: one gene*

*- one protein*

*- one enzyme*

*-one function*

ibic

ed the terms «recessiv» and  
monstrating the actions of  
– in providing for visible  
d at the turn of the 20th

**Watson & Crick:** Molecular structures of nucleic acids: a structure for deoxyribose nucleic acid. Nature 1953:171:737-738

**The DNA double helix was born**



# Epigenetics

---



First in use?

Not sure, first in PubMed:

Nanney DL: *Epigenetic factors affecting mating type expression in certain ciliates*. Cold Spring Harbor Symp., Quant Biol 1958

Definition: The study of changes in organisms caused by modification of gene expression rather than alteration of the genetic code itself

Simplified – and from a functionalistic point of view:

**Any alteration in a gene functions without alterations in the gene itself**

# Switch off/switch on dialogue

---

	Fucose
Conv 2 weeks old	+
GF " " "	+
Conv 2 months old	+
GF " " "	-
GF 2 m. monoass 3 d	+
GF 2 m. mono mutant	-

## *Quorum sensing*

***CROSSTALKS, Science 1996;273:1380-1383***

# Is presence of microbes necessary? NO!!!!!!

---

1. Baseline: Conv & GF Mice: Glycosylation pattern:

M. Freitas & al: Microbial host interactions specifically control the glycosylation pattern in intestinal mouse mucosa.

Histochem. Cell Biol 2002;118

**We compared the glycosylation**

«...expression of glycans de

intestine) and on the cell li

**The first report...to directly demonstrate the critical contribution of microflora to intestinal glycosylation, a key characteristic of the gut.**

2. B. the taioamicron –monoassociated (MA) and supernatant (SN)

M.Freitas & al: Indigenous microbes and their soluble factors differentially modulate intestinal glycosylation steps in vivo. Use of a «lectin assay» to survey in vivo glycosylation changes. 2005;124:423-433.

**MA restored a large number,  
SN restored «small but specific number of patterns»**

# Is presence of microbes necessary?

---

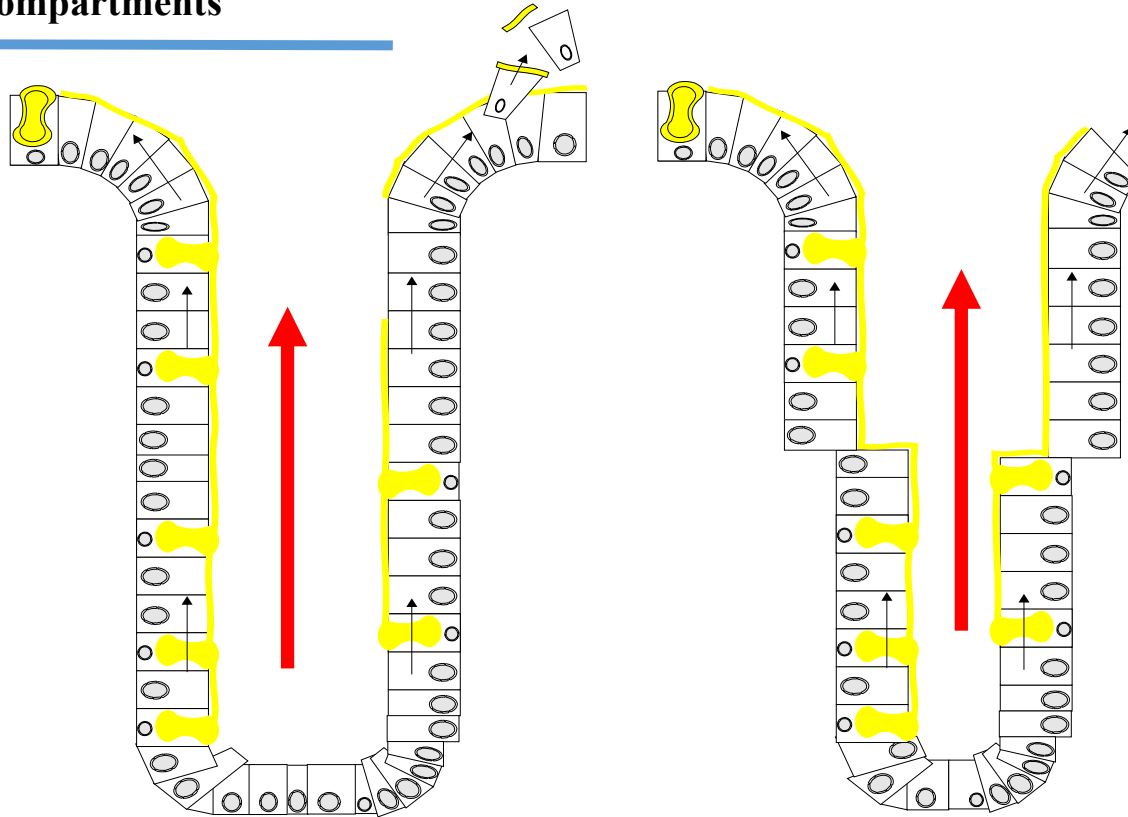
Conclusion article 1 and 2:

*«Generation of diversity and the possibility of modulating this complex pattern by introduction of exogenous bacteria and bacterial products should be considered as a very promising approach towards understanding the molecular basis of host-microbe interactions».*

I think this 11-years old forecast describes the research-front of today!



## Compartments



### Possible consequences:

Microbes may come closer to stem cells

Reduced development of cancer

# PROGRAMMING – A LIFE-LONG EVENT

---

## *In utero:*

First 0-7(?) days: Deprogramming, few human data.

For review, see Shenderov & Midtvedt



Microbial Ecology in Health & Disease 2014, **25**: 24145

REVIEW ARTICLE

## Epigenomic programming: a future way to health?

Boris A. Shenderov<sup>1\*</sup> and Tore Midtvedt<sup>2</sup>

# Window and effects on other organs

Theory: IM may affect development of neural system  
(hypothalamic/pituitary/adrenal axis)

Observation:

A strain of germfree mice was less stress tolerant than their  
conventional counterpart:

Experiment:

Conventionalized at birth: CONV, conventionalized later: GF

Sudo & al: J. Phys 2004;558:263-275)

# DISHARMONY

---

**Burning question:**

Have we – the mankind – kept our promise to  
**leave the gut microbiota in peace?**

**NO!**

It is increasingly under fire

# ECO-SHADOW (antimicrobial)

---

Any alteration in any ecosystem following exposure of the system to any antimicrobials

The alterations can be of variable length and can involve a variable number of species and/or functions

The sum of alterations can be expressed as an

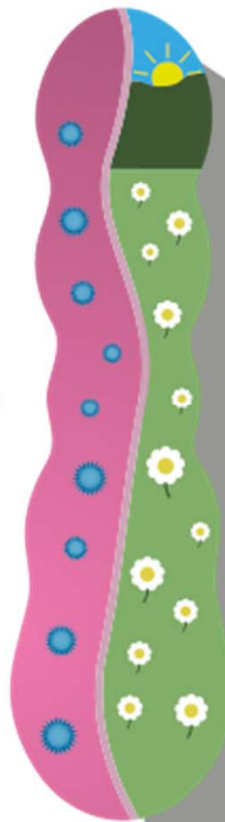
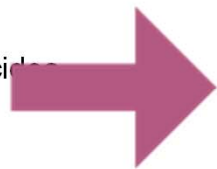
## **ECO-SHADOW INDEX**

- Kümmerer K: Pharmaceuticals in the environment 2001 p232

# ANTIMICROBIAL ECOSHADOW

## EUBIOSIS

1. Antibiotics
2. Disinfectants
3. Herbicides/Pesticides
4. Food Additives
5. Food/GMO
6. Heavy Metals
7. Probiotics



Resistance  
Metabolome Change  
Microbiome Change



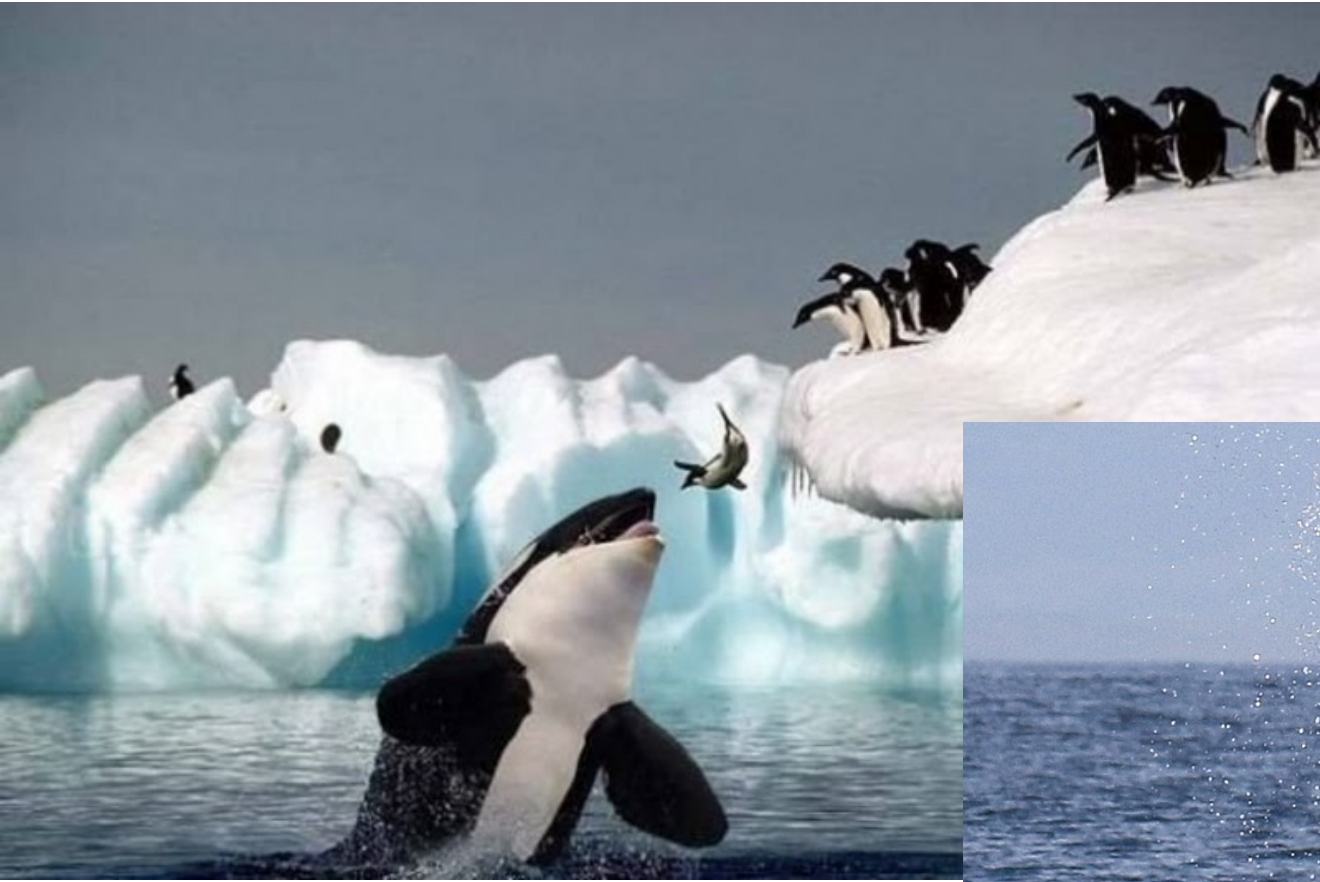
## DYSBIOSIS

1. Antibiotics
2. Disinfectants
3. Herbicides/Pesticides
4. Food Additives
5. Food/GMO
6. Heavy Metals
7. Probiotics

PAST

PRESENT

FUTURE









**May be Bob Dylan has the answer!**

---

**Nobel laureate in 2016.....**

***Where have all the E.coli gone?***

***Long time passing***

***Where have all the E.coli gone?***

***Long time ago***

# Who take the challenge?

---

The answer my friends is – *NOT BLOWING IN THE WIND*-:

**The obese individuals might have a dysbiotic**

***E.coli* microbiota!!**

**Therapy:**

**RESTORATION!!!**

Home of *E.coli*: terminal ileum (C.Rang & al: Can.J.Microb 2001:47:86-90)

Function: signals to the brain: no more food (Fetissov. Nature Rev. 2016, Sept)

# Principles for restoration of dysbiosis

---

1. If microbes are lacking: you have to give microbes
2. If microbial functions are lacking, you may have effects by dietary interventions

**Usually, you don't know!**

## **Restoration by giving microbes:**

- Feces (fresh or stored) FMT = Feces microbiota transplantations
- Selected strains, usually probiotics
- Cultivated feces

Pro's & Con's:

Manipulating the gut microbiota to maintain health and threat diseases (Scott et al: MEHD 2015).

# FINAL QUESTION

---

Will it be possible in the future to create a

***personalized nutrition for establishing a personalized intestinal microbiota***

–optimal for an individual genetic profile?

If so, we will be fulfilling the dream

***«let food be your medicine and medicine your food»***

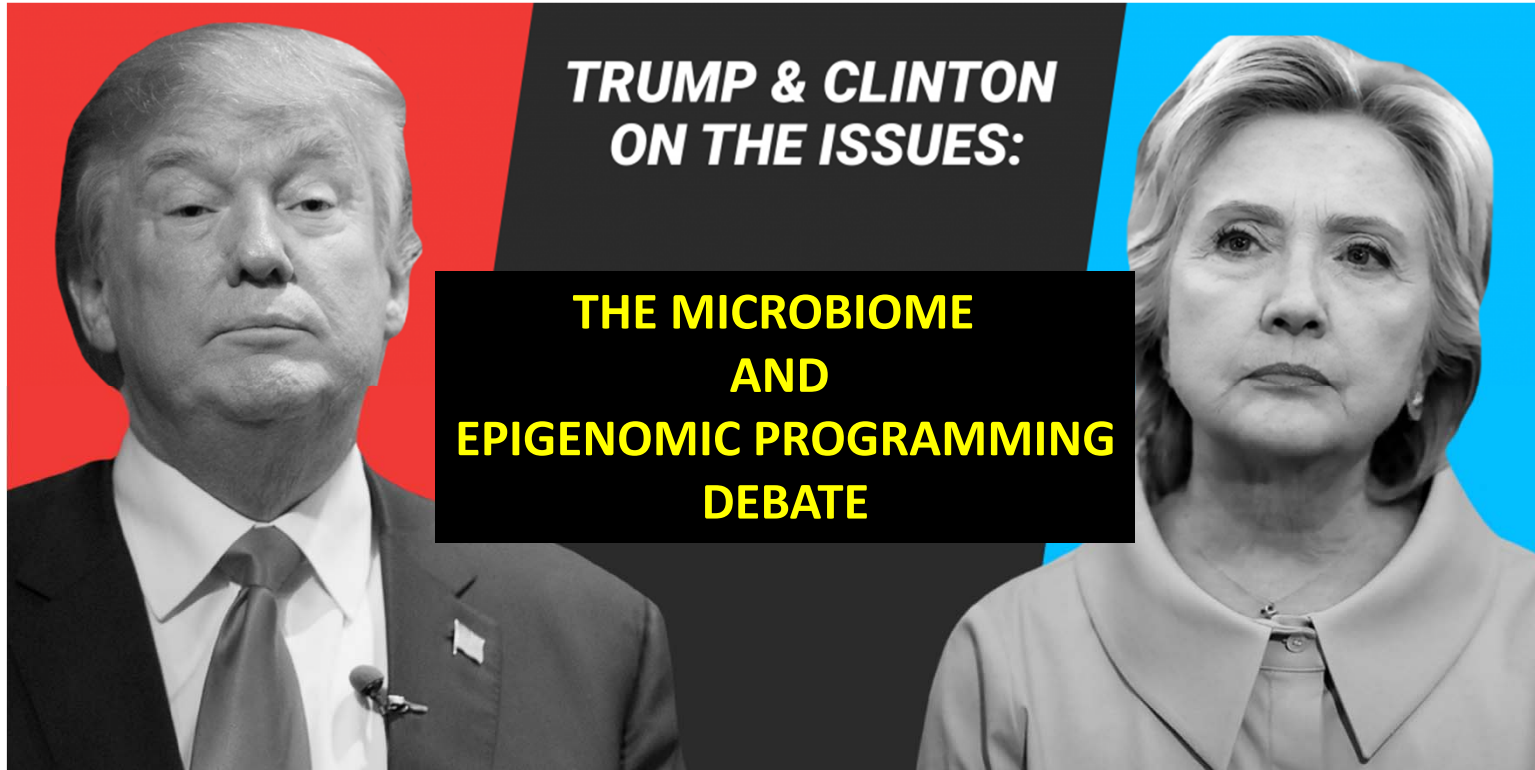
expressed by Hippocrates in 400 BC

**MY answer is; Surely, but it will take some time!**

The key point is that we have to listen, learn and follow the microcratic rules, with their message to us – here given to us by 2 relatively well known Americans:

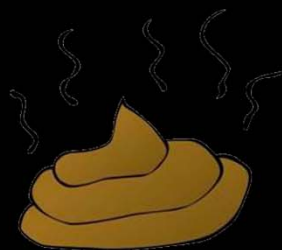
## Some comments:

- Microbiota and communication: B Shenderov et al: Microbiology 2016 and MEHD 2016
- At Karolinska: October 2016: Meeting at Nobel Forum: Science meet Industry: The Food and the Mood! One compound from protein, carbohydrate and fat, respectively. Videotaped and Thematic Cluster in MEHD
- June 1-3, 2017: Nobel Symposium. Free, but you have to register: Working title: Programming in Early Life



**The more we are together the happier we will be.....**

*Thank You for your attention.....*







Clean up  
Your MESS!  
Love Mother

*Stephen [Signature]* 2010

# Presentation Clinical Actions

---

After participating in this presentation, clinicians should be better able to:

- Discuss with patients the importance of maintaining a healthy microbiome.