

Principles and long term effects of establishing a normal intestinal microflora

Rikshospitalet 12.september 2009

Oslo

Autisme kan behandles

Tore Midtvedt

MTC – Karolinska Institutet

WHY THIS LONG TITLE?

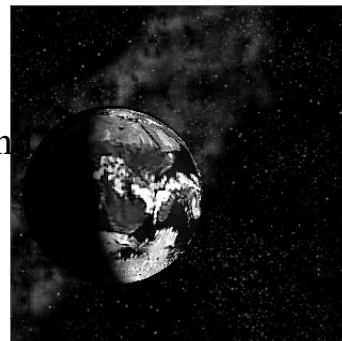
YOU HAVE HEARD ABOUT MANY PROBLEMS AND NOT THAT MANY SOLUTIONS

We need to recognize the problems – and possibilities in influencing upon our microflora

To agree upon - I

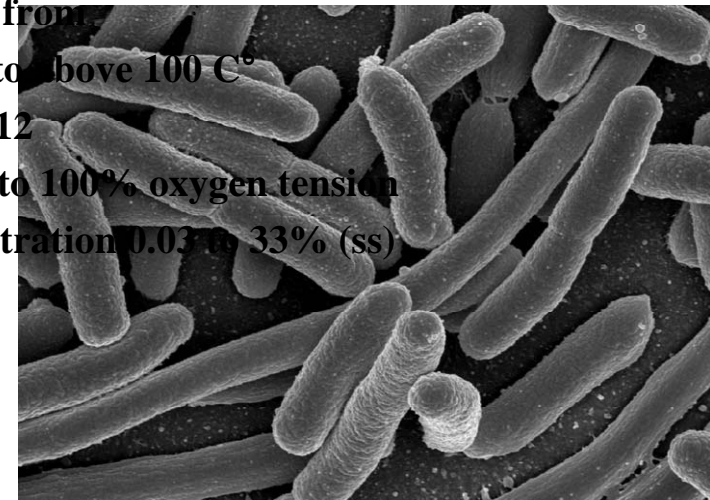
THE START

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



To agree upon II
....then the microbes came....

-and they are still here – **they rule the world!**
- They can grow from
 - a. minus 4 C° to above 100 C°
 - b. pH 1 to pH 12
 - c. zero to close to 100% oxygen tension
 - d. NaCl concentration 0.03 to 33% (ss)
 - e. etc., etc.





L. Pasteur

LIFE IS NOT POSSIBLE WITHOUT BACTERIA

Only microbes can utilize dinitrogen

&

only microbes can get nitrogen back to dinitrogen

Mammals are born germ-free

but

from cradle to grave they are

out-numbered

by their microbes with some log's

TM09

You meet several new strains every day

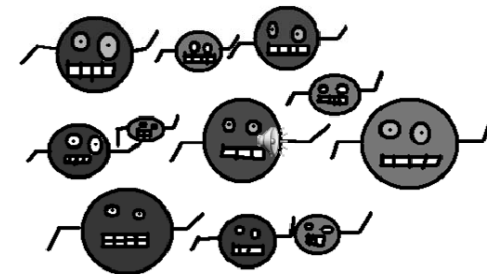
Fate of the new-comer :

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

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

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

Bad bacteria



TM09

A PERSONAL COMMENT

- Today it is 16996 days since I saw the very **first germfree animal**

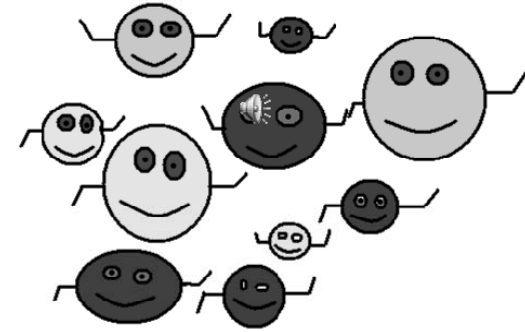
A RAT



At Department of Germfree Research
Karolinska Institute, Stockholm, Sweden

.....possibilities for crosstalk's
microbe/microbe and host/microbe.....

Love bacteria



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

A

B

3. A: Number of microbes B: You / number of cells

YOU: The "road" from 0-24 months

More than 1000 species will be established

Many factors are influencing upon:

Which **microbes can/will/should** be there

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

"Windows" for establishment

"Succession" in establishment

"Long-term" effects of establishment

TM09

The Gastrointestinal Microflora

Never a fixed number of species/strains
or
a fixed number of any strain

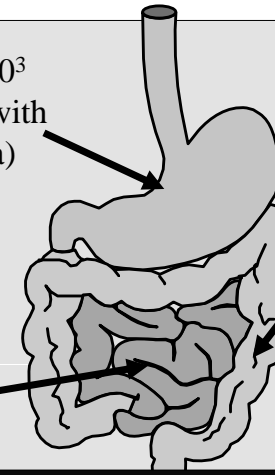
All GI ecosystems are in a balanced unbalance

Stomach: usually $< 10^3$
bacteria/g (increases with
Hypo- or achlorhydria)

Small intestine:
 10^5 - 10^7 bacteria/g
towards distal
ileum.

Colon: climax
microbial
populations $> 10^{11}$
bacteria/g, > 400
different species.

A majority previously
uncultured, many new
to science, many non-



HOST

Compartment

Recirculation

Microclimate

TM09

The gastrointestinal microflora = the Gut flora

METAGENOM

A microbial Empire

1000 species, each 4000 genes/5 mega base pairs =
4 million genes/5 giga base pairs

The gut flora can quickly do the most, 2 limitations:

I: anaerobic conditions

II: low red/ox potential

TM09

3 actors on the stage:

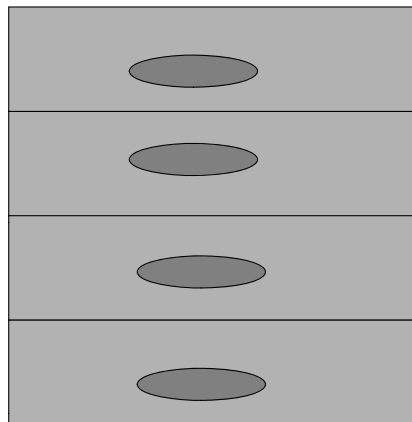
- 1) Microflora
- 2) Food
- 3) Host

1 and 3 have one common interest : ***they need food***

MICROCLIMATE

Tissue

pO₂ : high
pCO₂:low
Rh : high

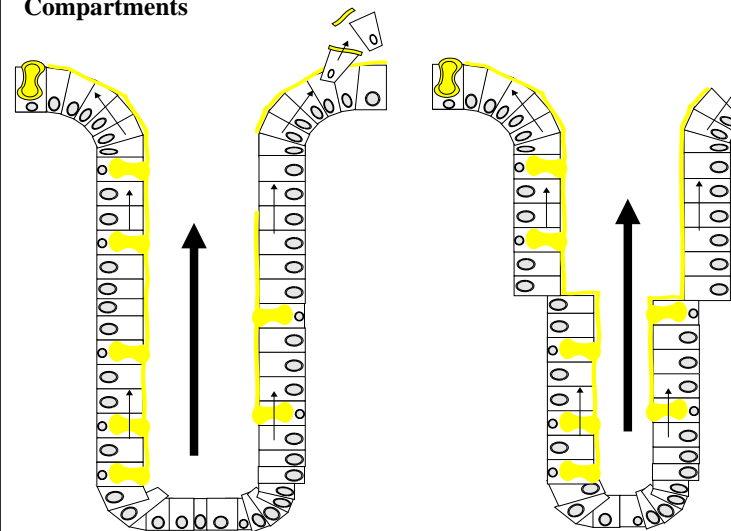


Lumen

Low if microbes are present
High if microbes are present
Low if microbes are present

TM09

Compartments



Possible consequences:

Microbes may come closer to stem cells
Reduced development of cancer

TM09

About mice and men

Mouse : around 1 g of enterocytes in 5 days

Man : around 250 g/day = 50 x 10 mill/enterocytes/min



In both : 90 % is produced in the small intestine

NB: Gender, age and microbial status will influence upon the cell kinetics

Banasaz et al . Microb Ecol Health Disease 2000;13:135
TM09

Host-microbe crosstalk

14 years ago, a young American Ph.D student (Lynn Bry) was in my lab to study development of Paneth cells in conventional (Conv) and germfree (GF) Mice

By serendipidy,
she also stained enterocytes for fucose

TM09

Crosstalks (cont)

	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

TM09

Crosstalks

Microbes like to talk –
to their host and to each other

Mechanisms

- Chemical signalling substances
- Physical signalling conditions

TM09

Microbe-host crosstalks

- Rapid talks, chemical substances as mediators, no "immunology" involved
- The microbes do **not** have to be alive
Histochem Cell Biol 2005, sept issue

TM09

One microbe, i.e. *B. thetaiotamicron*, switches on/off at least 100 genes (400?)

**We have answers to questions
we never have asked!!**

TM09

Mammals, microbes and genes

- In germfree animals:
 - all genes are there, but functions may not be established

TM09



- Da Abraham fikk besøk av Vår Herre, bød han på det beste som fantes, deriblant **surmelk**. (1. Mosebok, Genesis 18:8)



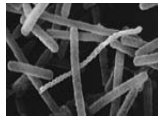
- Begrepet probiotika ble lansert av Lilly & Stillwell (1965):

Probiotics: Growth-Promoting Factor Produced by Microorganisms, **Science** 12 February 1965:
Vol. 147. no. 3659, pp. 747 - 748

- **Probiotika:** (pro; for, bios: liv)
Tilsats av levende mikroorganismer som antas å kunne forbedre helsen hos mottakeren
- **Prebiotika:**
Substanser som man tilsetter maten for å hjelpe vår mikrobiota (eks. kostfiber)
- **Synbiotika:**
Et produkt som inneholder både probiotika og prebiotika

- Vanligste mikroorganismer, brukt som probiotika:

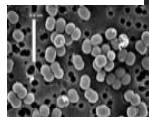
– *Lactobacillus*



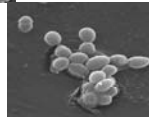
– *Bifidobacterium*



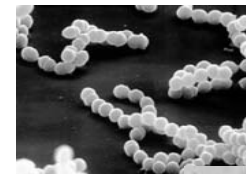
– *Pedioococcus*



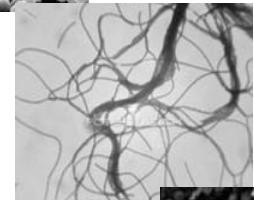
– *Enterococcus*



– *Streptococcus*



– *Bacillus*

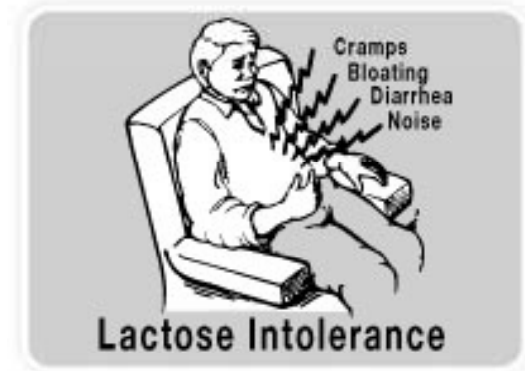


– *Sachromyces* (Gjærsopp)



- Hensikten ved å bruke probiotika
 - Påvirke bakteriene i fordøyelsestraktus
 - Den gode tanken var da at probiotika kunne hjelpe ved at man tilførte bakterier for å "normalisere" floraen hos visse pasienter med ubalanse av mikrobiota i ulike "compartments"

- Laktose-intoleranse



- Ingen faglig begrunnelse
 - Hvorfor akkurat den stammen og den doseringen
 - Mange rapporterer om effekter på produksjon av ulike cytokiner, interleukiner....hvorfor disse parameterene ble fulgt?
 - Hvilke biokjemiske reaksjoner som påvirkes eller om farmakokinetikken endres for de medikamentene pasienter får

- Husk:
 - Probiotika er levende bakterier; kan formere seg og krever næring
 - En normal tarmflora vil kunne virke dempende på "Lebensraum"-tendenser
 - Er tarmfloraen sterkt endret, vil den dempende effekten være svekket
 - Probiotika krever sin rett og tarmen blir ischemisk (akutt pankreatitt), andre bakterier vokser ytterligere til (kritisk syke barn), eller sammensetningen endrer seg ikke (NEC, AAC)

- Konklusjon:
 - De fleste probiotika kan trygt gis til "friske" pasienter
 - Probiotika er ikke ufarlige kosttilskudd som kan gis til alle kritisk syke pasienter
 - Jo sykere pasienten er, jo mer forsiktig bør man være og jo mer må man vite om det probiotiske midlet.

TACK

- för att Du lyssnade
- Hoppast
- att du är eller vil värta
- **VÂN**
- med dine bakterier

To summarize and to REMEMBER

The Empire strikes back

May the force be with you

