

Probiotics Prebiotics and Synbiotics

Clinical effects

Luc Delmulle
Consuelo Gandino

PRO- and PREBIOTICS

Antibiotics:

- ◆ To kill a maximum of bacteria, if possible the bad ones

Probiotics:

- ◆ To help develop a maximum of good bacteria to control the growth and negative influences of the bad ones

Prebiotics:

- ◆ Specific food for bacteria, if possible just for the good ones

SYNBIOTIC

Probiotics

Prebiotics

Bacteria

Nutrients

Health effects

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Probiotics

- Elie Metchnikoff in 1907:
Relation between long life and
consumption of fermented milk



Intestinal system

- Complex system
 - ◆ 1 g of faeces contains 10^{12} bacteria
- 400 - 500 different species in the intestines
 - ◆ huge interactions
 - ◆ soup of chemicals, enzymes, toxins, bactericins,...
- Permanent war to occupy a max of space
- Strong interactions in between bact. species
- Strong interactions in between host's immune system and bacteria

Evolution of the intestinal flora

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Flora as a function of the age

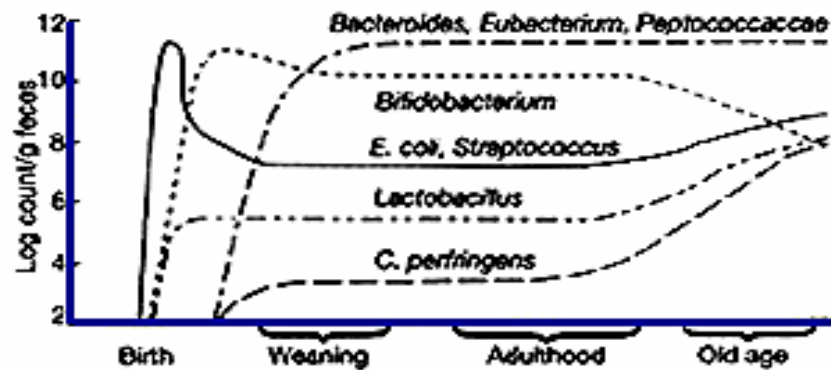
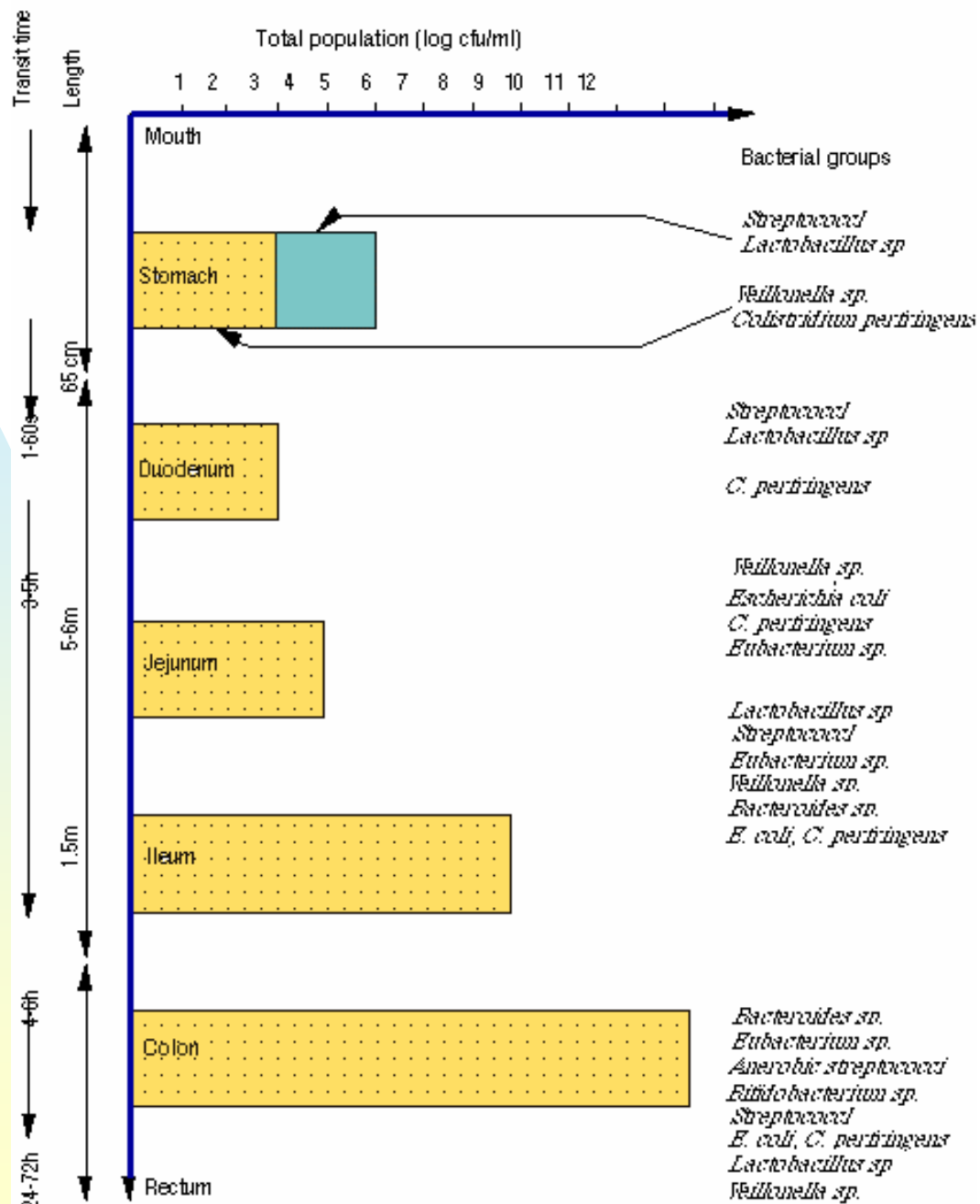
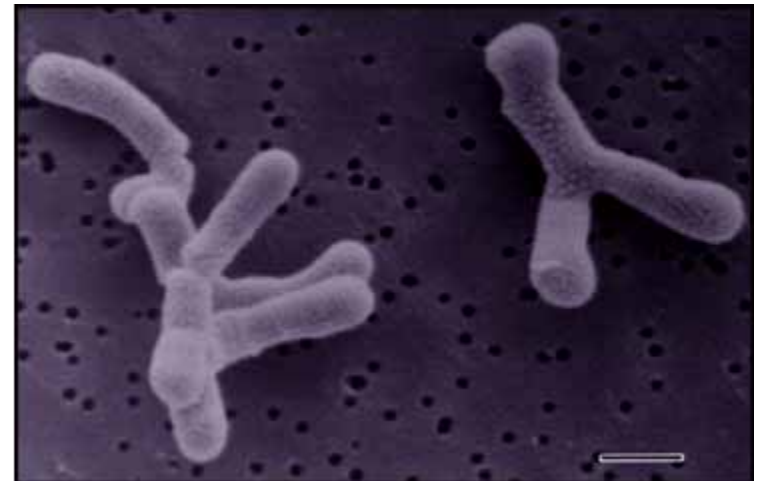
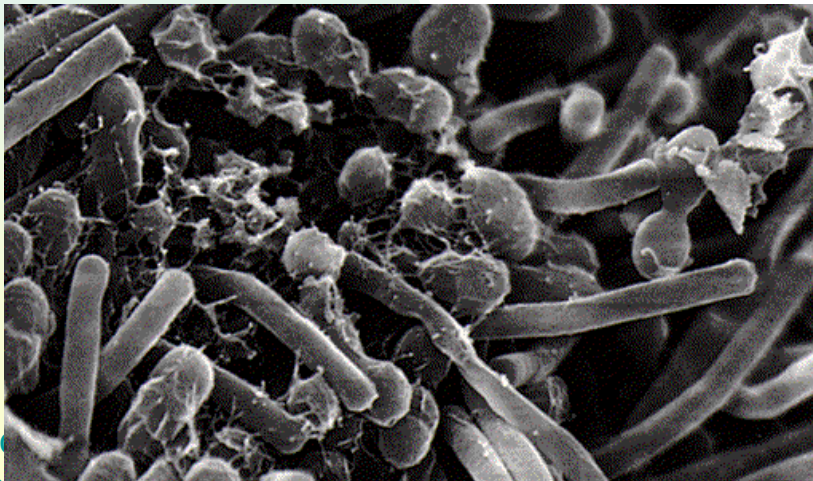
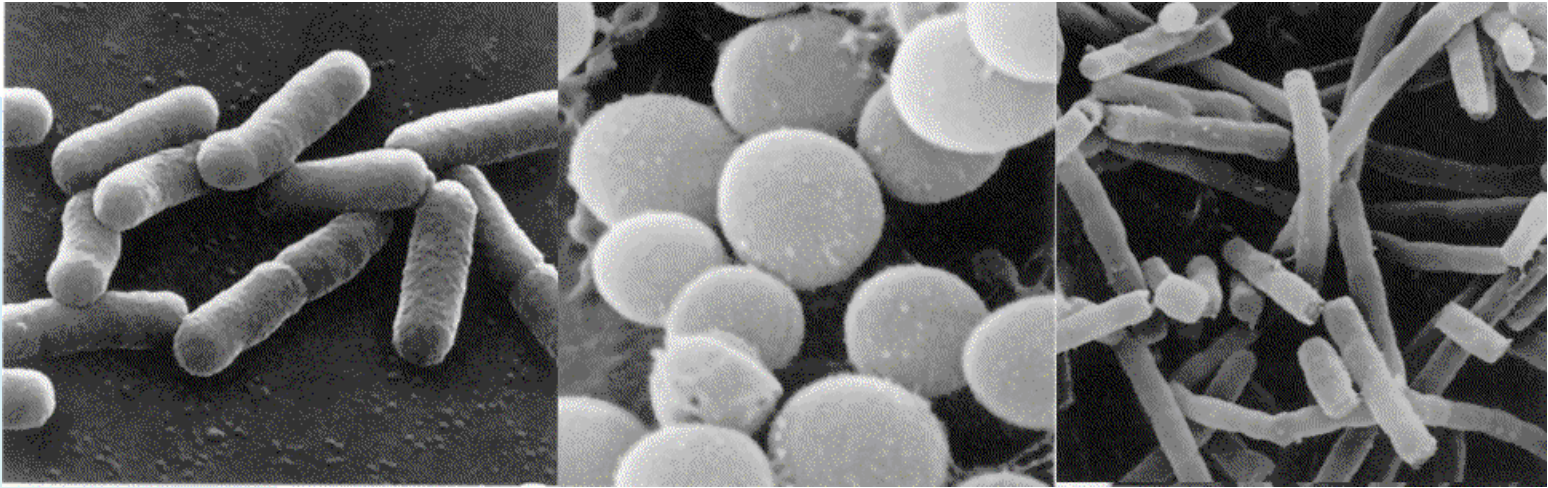


Fig. 1. Difference in species of bacteria in human feces of different ages (from 3).



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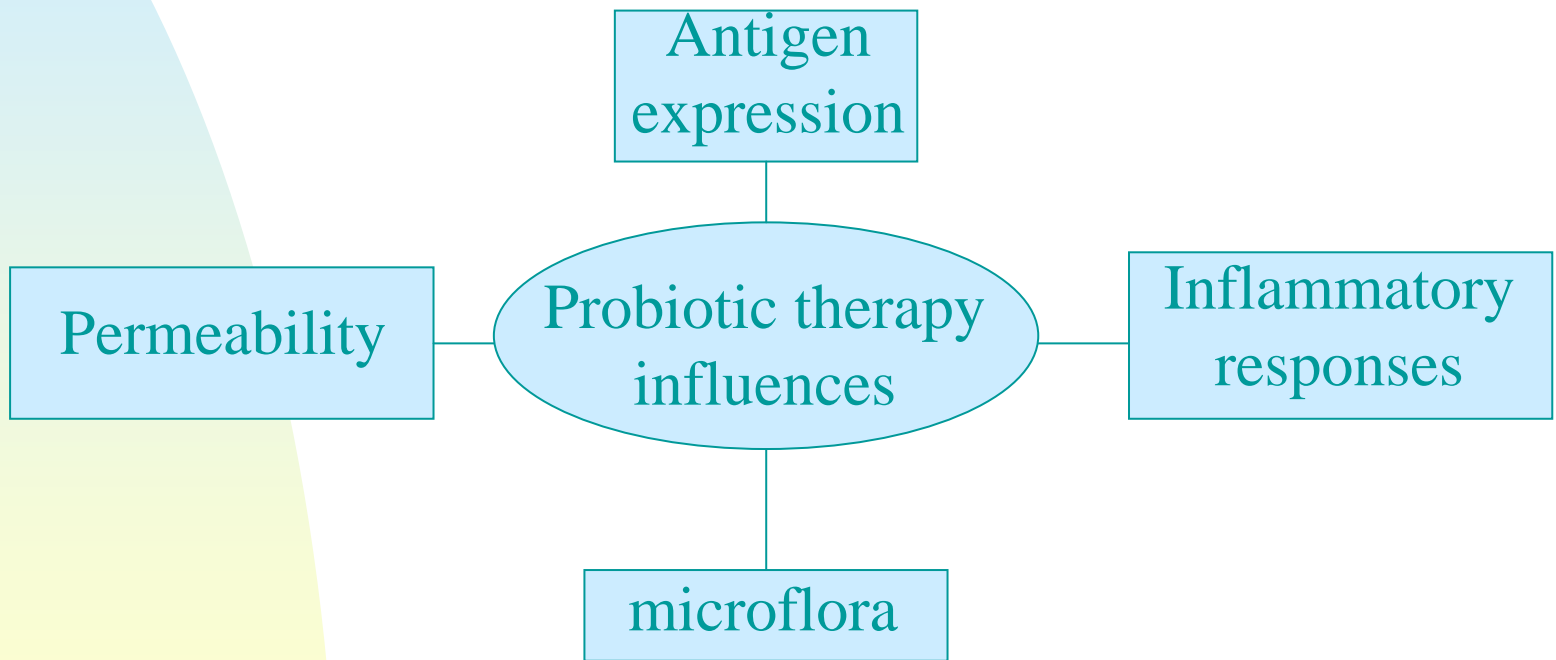
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Probiotic effects

The GNOTOBIOLGY

Study of the influence
of different bacteria
in germ free mice

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Microflora



- Intestine is a bioreactor
 - ◆ Place for X bacteria
 - ☞ If Y added then same amount to be dropped out
 - ◆ Effect of changed flora can be measured in faecal analyses
 - ◆ As only 1% of the flora is dominant, changes can at least temporarily be induced
 - ☞ Important consequences on health of flora
- Good bacteria can drop out the bad ones
 - ◆ Also true for yeasts (Candida !)

Microflora improves the barrier

- Barrier effect is more than just a barrier
 - ◆ There are messengers between bacteria–body-bacteria
 - ◆ Colonisation by exogenous bacteria is limited by 2 factors :
 - ☞ direct:
 - Competition for substrates, receptors, bacteriocin production
 - ☞ indirect:
 - Change of bile and mucus secretion production of defensines, increase or induction of peristaltism
 - If the resident flora cannot handle and control the invasion, the immune system will help

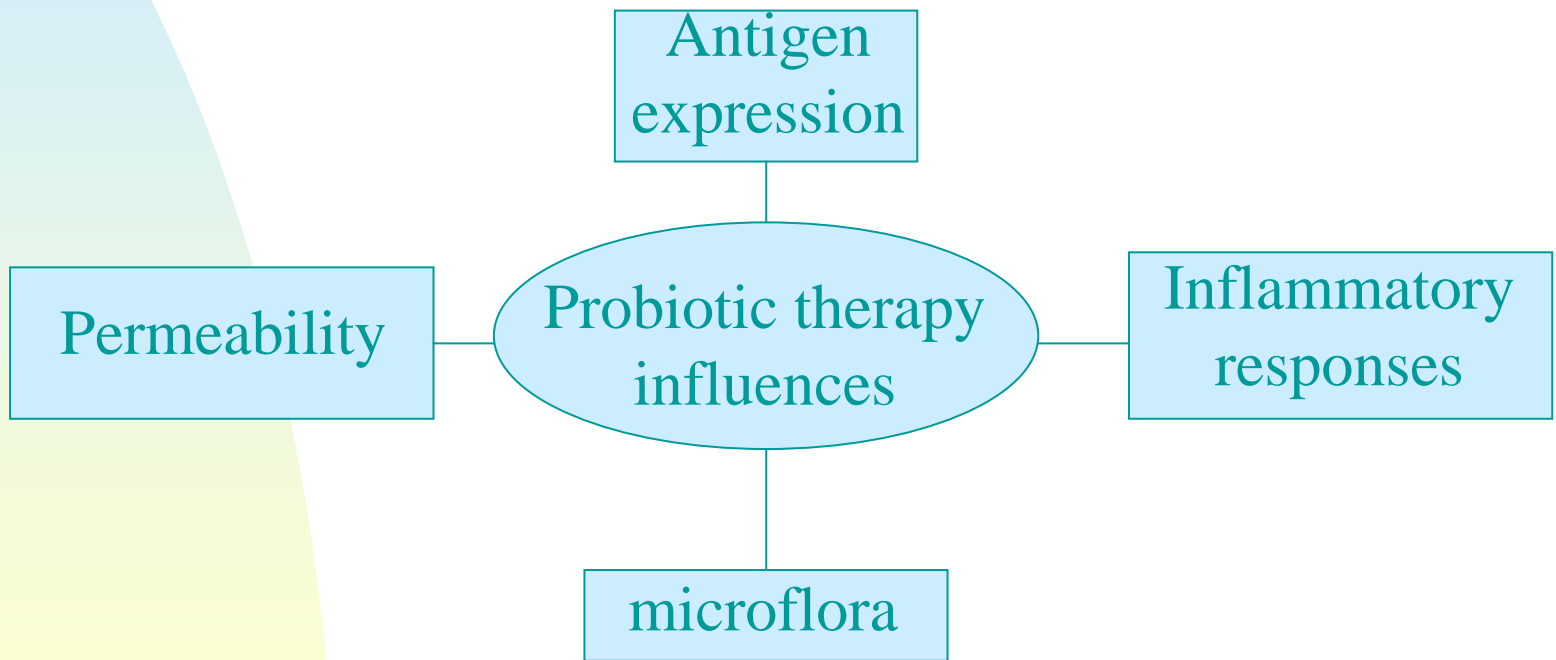


Competitive exclusion

- Barrier effect is important but not the only effect
 - ◆ Adhesive strains = barrier
 - ◆ Non adhesive strains = barrier
 - ☞ Signals by bacteria?
 - ☞ Other molecules involved?

HOWEVER

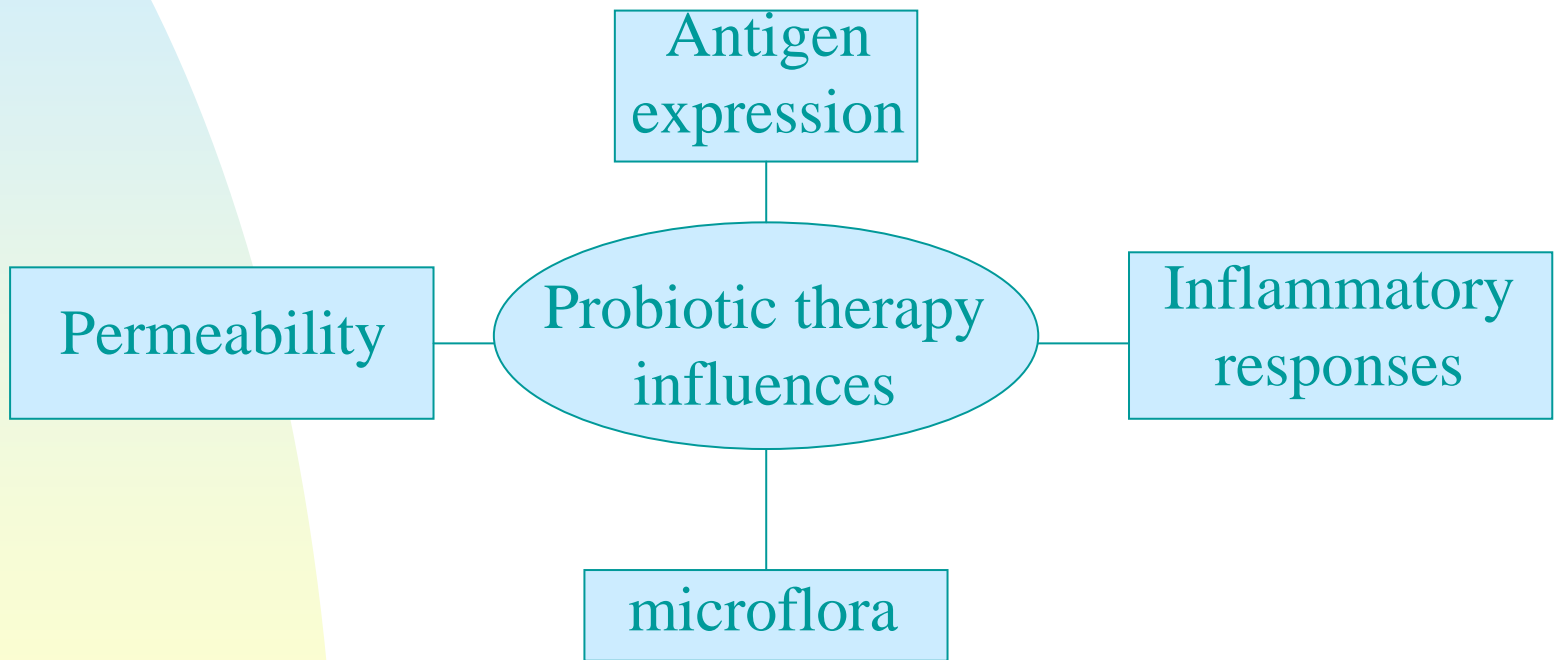
There is much more than
just the barrier effect



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Permeability

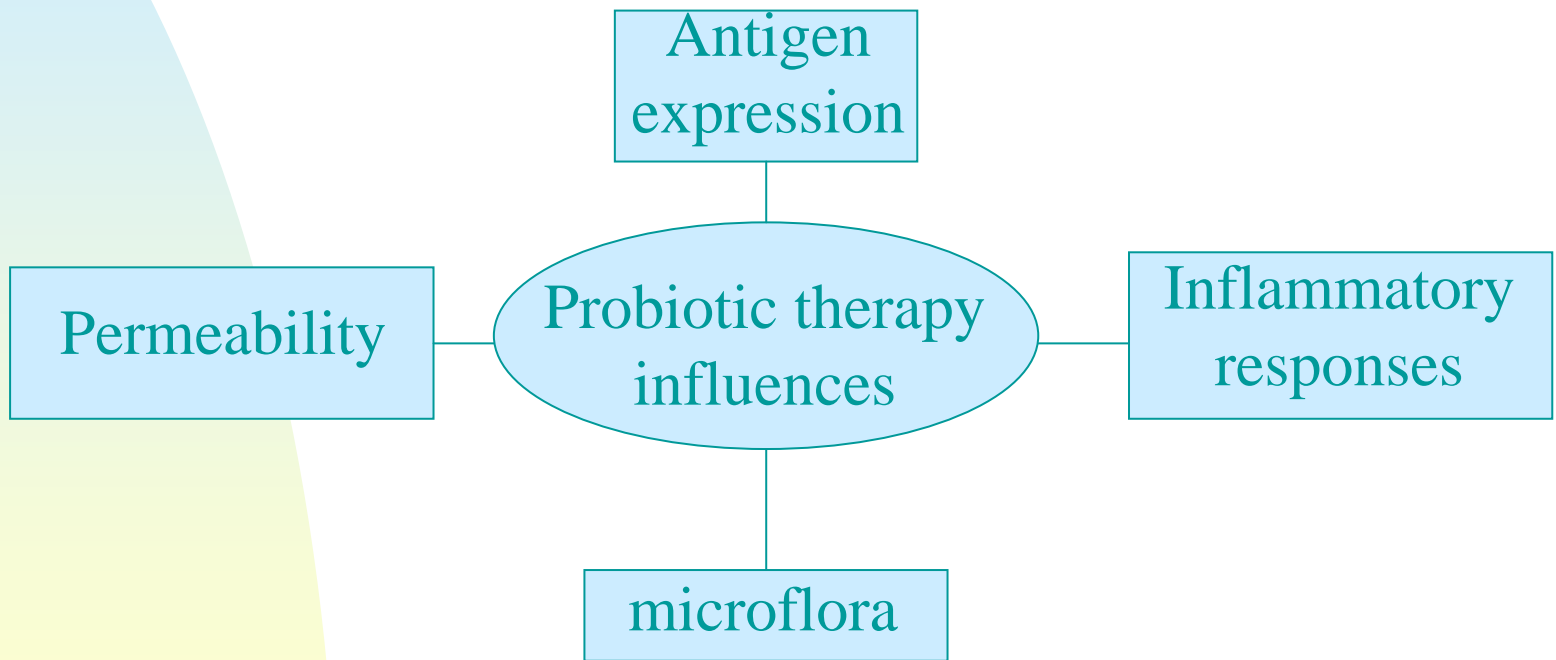
- Leaky gut syndrome is thought to be the result of an unbalanced flora
 - ◆ Consequence : too high permeability
 - ☞ Food born allergies
 - ☞ Some eczemas
 - ☞ Some cases of asthma(?)
- Positive outcome with probiotics



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Antigen expression

- Stimulation of innate and acquired immunity
 - ◆ Innate : macrophage activity increases
 - ◆ Acquired : Increase of sIgA
 - ☞ Also transferred in breast milk
- Consequences
 - ◆ Strong defence against pathogens
 - ☞ Bacterial
 - ☞ Yeasts



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Inflammatory responses

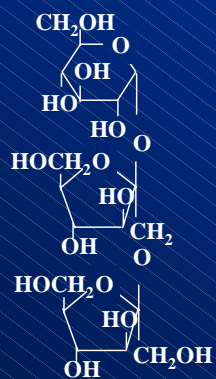
- A healthy flora helps to keep cytokines under control
 - ◆ Decrease of inflammatory bowel problems
 - ◆ Drop in premature delivery by 30%
 - ☞ Heals vaginal inflammatory problems often undiagnosed because subinflammatory state

Probiotics summary

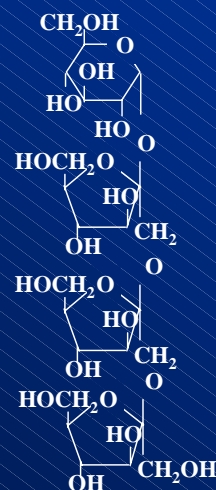
- Positive effects on different important problems
 - ◆ However : not all patients experience these effects to the same extent
 - ☞ It depends of the initial flora
 - ☞ It depends of the strains used
 - ☞ ...

The prebiotics

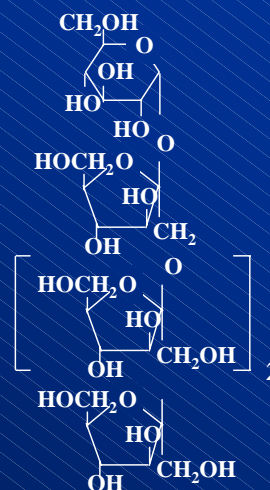
STRUTTURA CHIMICA DEI FRUTTOOLIGOSACCARIDI (FOS)



n 2
1-kestoso



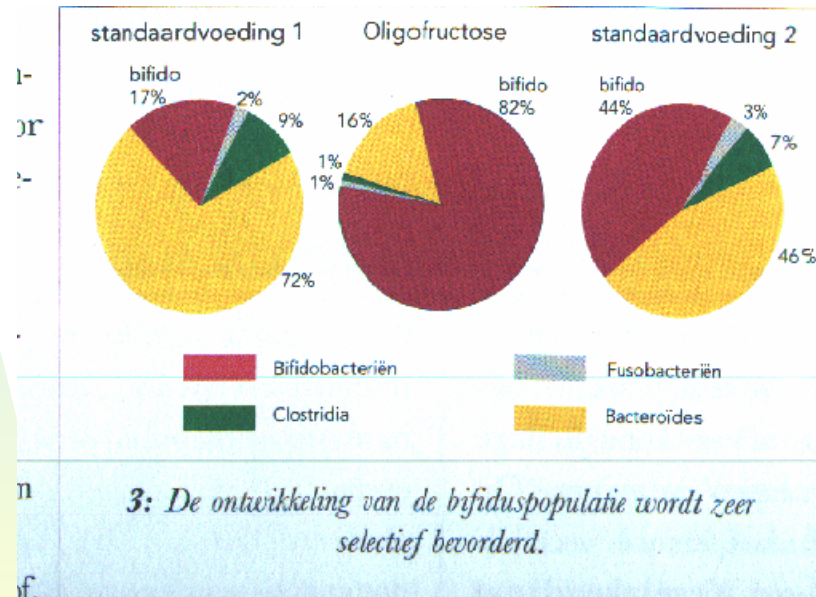
n 3
nistoso



n 3
fruttofuranosilnistoso

- inuline
- fructo-oligosaccharide (FOS)
- galacto-oligosaccharide (GOS)
- lactulose
- isomalto-oligosaccharide (IOS)
- soybean-oligosaccharides (SOS)
- gentio-oligosaccharides
- xylo-oligosaccharides
- lactosucrose
- palatinose-oligosaccharides
- malto-oligosaccharides (MOS)

Bifidogenic effect



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Consuelo Gandino

No doubt about the positive effects of oligosaccharides

	% incidence bottle-fed infants	% incidence bottle-fed + OS
Diarrhoea + fever	21.4	8.25
D + medical attention	24.3	16.13
Vomiting	4.5	2.9
Discomfort	6.7	3.95
Regurgitation	4.8	2.1
Fever + cold symptoms	17.2	11.4
Antibiotic use	12.2	8.2
Day-care absenteeism	0.79	0.31

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Prebiotics and bifidogenic effect

- Prebiotics are fermented by different strains

Drop in culture pH due to fermentation of selected fructo-oligosaccharides by different bacterial species^{1,2}

Group of bacteria (n) ³	Synthetic fructo-oligo-saccharides (Δ pH) ⁴	Chicory oligofructose (Δ pH)	Chicory inulin (Δ pH)	Glucose (Δ pH)
Bacteroides spp. (16)	-0.8 ^a	-0.9 ^a	-0.6 ^a	-1.1 ^b
Clostridium spp. (26)	-0.4 ^b	-0.4 ^b	-0.2 ^a	-1.4 ^c
Enterococcus faecalis (3)	-0.4 ^a	-0.6 ^b	-0.4 ^a	-1.9 ^c
Klebsiella spp. (2) (insufficient data for adequate statistical analysis)	-1.3	-1.3	-0.4	-1.9
Lactobacillus spp. (9)	-0.8 ^b	-1.0 ^b	-0.5 ^a	-2.2 ^c
Proteus spp. (2)	-1.2 ^b	-1.2 ^b	-0.3 ^a	-2.0 ^c
Staphylococcus spp. (3)	-0.4 ^a	-0.7 ^a	-0.3 ^a	-1.9 ^b

Prebiotic fermentation

- FOS is rapidly fermented already in the ileum and in ascending colon
- Inuline is 50% slower fermented than FOS but is unlikely to be available up to distal colon
- How is the protective effect against colon carcinogenesis to explain?
 - ◆ (Syncan cancer study, a synbiotic)

Prebiotics

- Short term use:
 - ◆ Strong bifidogenic effect
- Long term use (3-4 weeks or more)
 - ◆ Bifidogenic effect disappears totally
 - ◆ SCFA production continues more or less
- What is the influence on other strains if long term use?

Prebiotics

- New application field : obesity
 - ◆ Increases production in GPL1
 - ☞ = satiety inducing
 - ◆ Promising results
 - ☞ However:
 - just tested on animals at this stage
 - High amounts needed
 - Impact of long term use
 - Intestinal acidification??
 - Efficacy??

Summary of health effects

Luc Delmulle
Consuelo Gandino

Health effects of pro and prebiotics

- Clinical evidence :
 - ◆ Lactose digestion and improvement of lactose intolerance
 - ◆ Significant shortening of rotavirus induced diarrhoea
 - ◆ Increased calcium absorption (15%)

Health effects of pro and prebiotics

- Positive outcome, further controlled studies ongoing
 - ◆ Inflammatory bowel disease
 - ◆ Antibiotic related diarrhoea
 - ◆ Chron's
 - ◆ Food born allergies,eczema, asthma
 - ◆ Preterm delivery
 - ◆ Urogenital infections
- Inconclusive results
 - ◆ Traveller's diarrhoea
 - ◆ Serum cholesterol reduction
 - ◆ Cancer reduction

Synbiotics

Luc Delmulle
Consuelo Gandino

Probiotics & Prebiotics

- Several studies revealed the synbiotic effect to give better results than a single component
 - ◆ Mixture of different strains
 - ☞ Mixture of Lactobacilli and Bifidobacteria
 - Mixture of different Lacto and Bifido
 - ◆ Mixture of prebiotics
 - ☞ Mixture of FOS and inuline or cellulose/pectine/...
- Observational studies have been made in Cyprus with a commercially available synbiotic by 45 medical doctors
 - ◆ Positive outcome on
 - ☞ Diarrhoea (viral, bacterial), lactose maldigestion, colitis, Chron's

Are all probiotics safe?

Luc Delmulle
Consuelo Gandino

Safety aspects

- Theoretical problems
 - ◆ Systemic infections
 - ◆ Deleterious metabolic activities
 - ◆ Excessive immune stimulation
 - ◆ Gene transfer

Systemic infections

- Rare cases (7) of endocarditis are reported after dental surgery
 - ◆ Analysis of the strains :
 - ☞ No dairy strains but own flora
- Dr. Saxelin :4 and 6 year study in Finland
 - ◆ 4 year period:
 - ☞ Lactobacillus identified in 8 out of 3317 blood cultures
 - ◆ 6 year period
 - ☞ Lactobacillus isolated in 12 out of 5912 blood cultures
 - No one strain of commercial Lactobacillus
- Risk is not zero but extremely low

Metabolic effect

- Is there bile salt deconjugation and decarboxylation inducing toxic secondary bile products?
 - ◆ In vitro results show the possibility
 - ☞ Strain dependent
 - ☞ Dosage dependent
 - ☞ Conversion is very low
- Is there degradation of intestinal mucus possible?
 - ◆ In vitro showed negative results for Lactobacillus acidophilus and Bifidobacteria

Immunological adverse events

- Parenteral administration of bacterial cell wall from gram positive bacteria
 - ◆ Induce fever, arthritis or auto-immune disease
- Oral administration of very high doses of LAB
 - ◆ No immunological side effects
- In rats with colonic injury
 - ◆ Uptake of cell debris through intestinal wall has been observed

Gene transfer

- Lactobacillus, leuconostocs and pediococci
 - ◆ Natural intrinsic antibiotic resistance, chromosomally encoded
 - ☞ No gene transfer inducible or transferable
- Enterococcus faecium
 - ◆ Different situation, gene transfer observed
 - ◆ Warning!

The use of safe strains

- Intrinsic properties
 - ◆ No excessive deconjugation of bile salts
 - ◆ No mucus degradation
- Pharmacokinetics studied
 - ◆ Survival of acid and bile barrier
- Adverse interactions
 - ◆ No acute toxicity observed in animal studies
 - ◆ No alteration on jejunal permeability for proteins
 - ◆ Available data on strains do not show higher risk in immuno compromised subjects

Summary

- Health effects of synbiotics:
 - ◆ Strong positive outcome
- Synergy in horizontal and vertical direction necessary:
 - ◆ Horizontal: pro- and prebiotics
 - ◆ Vertical: mixture of pro- and mixture of prebiotics
- Quality control of strains absolutely necessary

Questions & Answers

- Synbiotics and pregnancy or breast feeding
 - ◆ Clinical tests have proven a better resistance of children and less allergies
- After and during a course of antibiotics:
 - ◆ Clinical tests : shortens the diarrhoea period (certainly with *Clostridium difficile*)
 - ◆ a must to restore the flora

Questions & Answers

- Candida infections?
 - ◆ In case of intestinal Candida overgrowth, synbiotic a must
 - ◆ Even with oral intake, Lb has a strong positive effect in case of vaginal infection
 - ◆ Clinical tests proved that Lb acidophilus decreases the reinfection with a factor of 3

Questions & Answers

- Children
 - ◆ New born children don't have a well established barrier (!). This can take 2-3 years
 - ◆ After taking antibiotics a course can be necessary
 - ◆ Always start with small amount of synbiotic and gradually increase the dosage over 3-4 days to arrive at the full dosage

Questions & Answers

- In case of allergy and atopic eczema
 - ◆ More and more clinical proof of efficacy
 - ◆ Long term treatment (6-8 months) and daily intake without interruption

Questions & Answers

- Preterm delivery
 - ◆ Up to 30 % reduction of preterm delivery if intake during pregnancy period
 - ◆ No translocation of dairy strains has been observed = safe

Questions & Answers

- the elderly
 - ◆ a MUST
 - ☞ protection
 - ☞ absorption of minerals (Ca, Fe, Mg)
 - ☞ Helps to regulate the bowel function
 - ☞ Delayed unbalance in flora typical of elderly

Questions & Answers

- During pregnancy
 - ◆ Strong evidence of reduction in preterm delivery
 - ◆ Influence on inoculation of infant during delivery?
 - ◆ Improvement of sIgA in breast milk