Host microecology and human health

Shenderov B.A.

Moscow Research Institute of Epidemiology and Microbiology after G.N. Gabrichevsky

Moscow State University of Food Processing

shenderof@yandex.ru

Composition of Human being Intestinal microbiota

The size of the adult human intestine microbe population contains up to 100 trillion and it is approximately 10 times greater than the total number of somatic and germ cells. More than 99% of the commensal gastrointestinal bacteria are obligate anaerobes and belong to 7000 species (representatives of about 700-1000 species now may only be cultivated);

Species *Ruminococcus obeum, Eubacterium halii, Fusobacterium prausnitzii*, *Bifidobacterium adolescentis* can be found only in *homo sapiens*

More than 1200 virus species are present in the colon

Human being genome contains 35000-60000 different genes; gut microbiome contains 400000-600000. The vast majority of human being eukaryotic cells genes has microbe (including virus) origin.

*Bacterium genera and species more often determined in human being feces

Dominated resident microflora (10^{10}-10^{11} cfu/g), determined in 80-100% individuals

Bacteroides

Clostridium coccoides

Eubacterim

Bifidobacterium u anaerobic Lactobacillus

Peptostreptococcus

Ruminococcus

Fusobacterium

Subdominated microflora (10^{5}-10^{8} cfu/g), determined in 40-80% individuals

Lactobacillus

Clostridium

Peptococcus

Enterococcus

Enterobacteria

Veillonella

Bacillus

FUNCTIONS OF HOST MICROFLORA

- **Morphokinetic action**
- **Regulation of gas composition, pH, water-salt metabolism**
- **Processing of foods (formation of the first immune tolerance to food antigens)**
- **Participation in metabolism of proteins, carbohydrates, lipids, nucleic acids and other substances**
- **Provision for eukaryotic cells by energy including regulation of keeping body's temperature in due**
- **Participation in recirculation of bile acids, steroid hormones and other macromolecules**
- **Production and modulation of production of biologically and pharmacologically active compounds)**
- **Immunogenic function**
- **Provision of colonization resistance**
- **Stimulation of angiogenesis**
- **Participation in oxidative / antioxidative reactions**
- **Mutagenic / antimutagenic function**
- **Detoxication of exogenic and endogenic compounds and metabolites**
- **Regulation bacterial and eukaryotic cell-to cell signaling (Quorum sensing and Host-Microbial Cross talk)**
- **Regulation of behavior reactions including appetite, sleep, mood, biorhythms and so on**
- **Storage of plasmid and chromosomal genes**
- **Regulation of replication and phenotypic expression of prokaryotic and eukaryotic genes**
- **Regulation of apoptosis**
- **Participation in etiology and pathogenesis of many infectious and somatic diseases**
- **Other functions and reactions**

SOME MECHANISMS OF MORPHOKINETIC EFFECTS OF HOST MICROFLORA TO INTESTINAL TRACT

1. *Production of SCFA that are substrates for energy colonocyte metabolism

2. *Microbial SCFA as growth factors for healthy epithelium

3. *Induction of proliferation at the crypt base enhancing tissue turnover and maintenance in small and large intestines

4.*Stimulation of angiogenesis producing submucosal network of interconnected capillaries

5.*Production of SCFA, γ-amino butyric acid and glutamate, that regulate motility and blood flow of intestines

*SOME MECHANISMS OF PARTICIPATION OF HOST MICROFLORA IN WATER METABOLISM

-water accumulation by intestinal microorganisms

- microbial regulation of quantity and composition of osmotic compounds in intestine (different polysaccharide containing substances of endogenous or exogeneous origin)

-microbial regulation of cation content influencing to water absorption in the intestinal gap

-microbial influence to intestinal mucus space

-microbial production of a number of substances influencing to water balance on the local and systemic level (histamine, glutamate, γ-amine butiric acid, SCFA and others)

Some mechanisms of microelement homeostasis regulation by intestinal microflora

-modification of chemical elements into forms specific for determined species of living being and possibly for certain tissues and organs

-carrying out oxidize-reduction reactions; production of organic acids, chelate, complex forming and other compounds altering bio

assimilation and toxicity of macro- and micro - elements

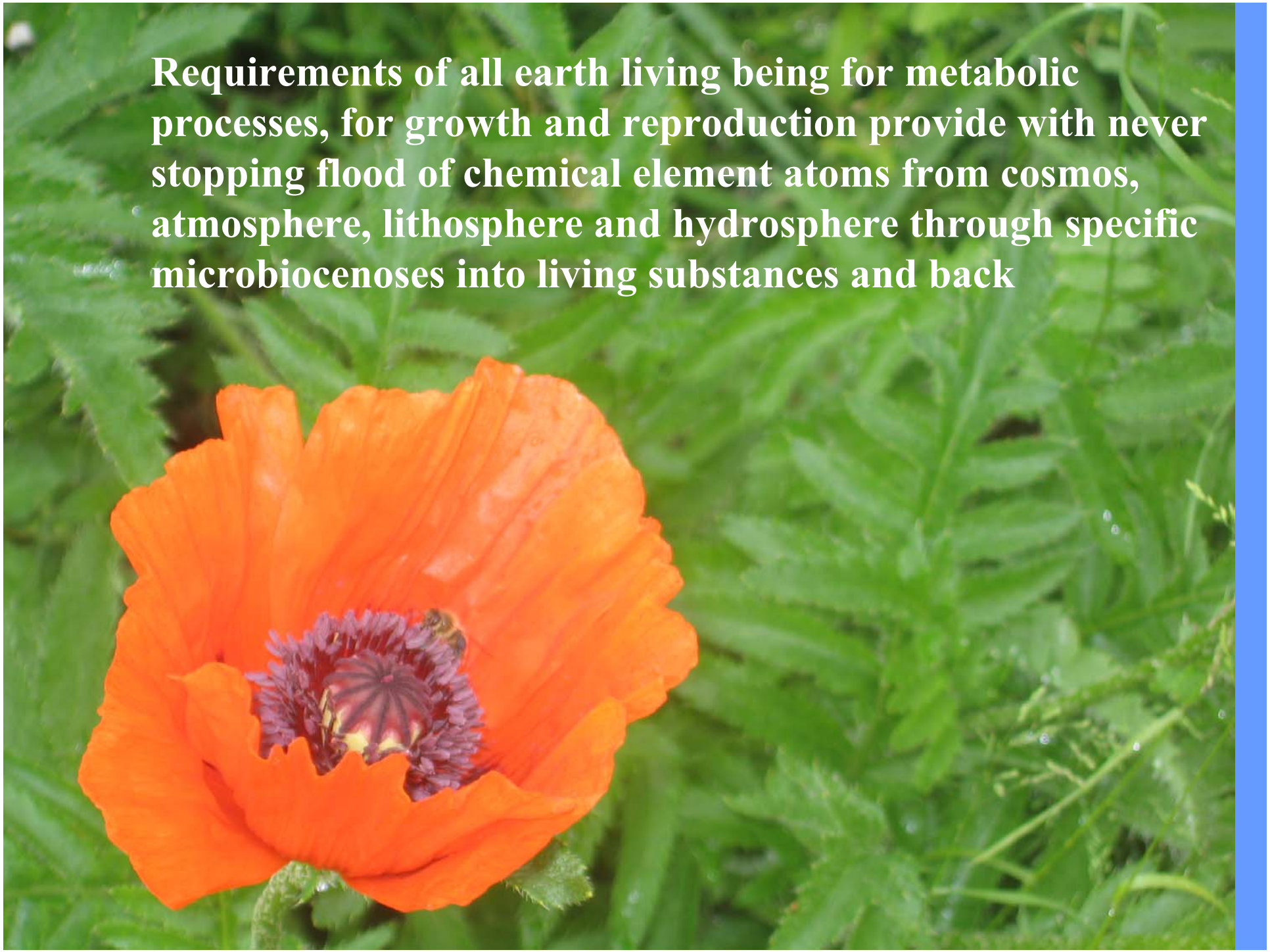
-chemical element restoration from complex compounds to element or gas condition

-mineralization, absorption, deposit of chemical elements on surface, in cell citoplasme, or in various microbial cell structures

-isotopes selection, their accumulation and microbial synthesis on their base of new nutrient and regulator compounds

-increasing or decreasing translocation of chemical elements through mucus thanks to transport discrimination of anions and cations

-indirect regulation of chemical element number in intestinal content and in the biological fluids through changing speed movement of nutrient lump along intestine; host microflora influence to other physiological functions and biochemical reactions associated with chemical elements metabolism


Requirements of all earth living being for metabolic processes, for growth and reproduction provide with never stopping flood of chemical element atoms from cosmos, atmosphere, lithosphere and hydrosphere through specific microbiocenoses into living substances and back

Substrates metabolized by host microflora in large intestines

Substrates	**Quantity (g/day)**
Fibre:	**27-85**
Resistance starch	**8-40**
Cellulose; hemicellulose	**8-18**
Ingestible sugars and alcohols	**2-10**
Chitins, aminosugars	**1-2**
Oligo- and Polysaccharides (galactooligosaccharides, soya-bean oligosaccharides, inulin, pectins, β-glucans and others)	**8-15**
Glycosides, phytosterols, phytohormons	**?**
Organic acids (oxalate and others)	**?**
L-sugars	**?**
Nitrogen-containing compounds:	**7-20**
Food protein	**3-12**
Enzymes of saliva, digestive juices	**4-6**
Carbamide, nitrates and others	**0.5-2**
D-amino acids	**?**
Lipids	**3,5**
Others:	**25-30**
Mucus	**2-3**
Bacterial fragments	**?**
Desquamated intestinal epithelium cells	**?**

CHOLESTEROL MODYFYING ACTIVITY OF LACTOBACILLI

Lactobacillus species	Number of strains investigated	Results	
		% increase of cholesterol level in medium in vitro (initial concentration 1.5 mMol/l	% decrease
L. plantarum	11	9-47	13-46
L. acidophilus	9		15-77
L.casei	4	47-220	
L.delbrueckii	5		14-63
L. helveticus	2		46; 54
L. fermentum	1		22
L. oris	1		23

Lactobacillus species	Number of strains investigated	Results % increase of oxalate level in medium in vitro (initial concentration 1.5 mMol/l	% decrease
L. plantarum	14	10-41	13-69
L. acidophilus	4		13-24
L.casei	2		0-17
L.delbrueckii	5	0-15	7-34
L. helveticus	1		
L. fermentum	1		13
L. oris	1		

MAIN CATEGORIES OF FUNCTIONAL NUTRIENTS

- Microbioelements
-Lactic acid bacteria, bifidumbacteria
-Oligosaccharides
-Sugars, alcohols
-Fiber
-Isoprenoides, Vitamins
-Amino acids, peptides, proteins, nucleotides, nucleic acids
-Glycosides
-Nonsaturated fatty acids, other antioxidants
-Phospholipids
-Organic acids
-Citoamines
-Some plant enzymes
-Lectins

Low-molecular regulator metabolites produces by host intestinal microflora

*SCFA (butiric, propionic, acetic and other acids)
*Lactic, formic, gamma-amino butiric and other organic acids
*Various biologically active peptides
* Amino acids (glutamate, beta - alanine and others)
* Amines (histamine, serotonine and others)
*Estrogen-similar substances
*Neoropeptides
*Hormone-similar substances
*Different polysaccharides, oligosaccharides, muramil-dipeptides
*Endotoxins
*Exotoxins
*Antibiotics, bacteriocins, hydrogen peroxide, nitrogen oxide
*Lactons
*Lectins

Factors and agents are able to produce host microbial ecology disorders

-antibiotics and antiseptic agents
-antitumor medicines
-antihistamine medicines
-some antidepressant drugs
-other medicines
-technological nutrient additives
-heavy metal salts
-some industrial pollutions
-pesticides
-radiation
-other chemical, physical, biological stress agents and their complexes

Some ecological and social consequences of host microbial ecology disorders

-distribution of drug resistance microorganisms
-decreasing effectiveness of chemotherapy and chemoprophylaxis; raising price of disease treatment
-selection of strains with atypical biological characteristics
-formation of new uncommon microbial associations
-changing pharmacokinetic and biotransformation of medicines and nutrients
-changing etiological structure of infectious diseases
-broadening of disease spectrum associated with host microecology disorders
-increasing a number of individuals with decreased resistance to infection
-changing behaviour reactions of human being

Clinical Conditions whose Pathogenesis may Be Associated with Changes in Human being Microbial Ecology

- Diarrhea, constipation, colitis, low absorption syndrome
- Gastritis, duodenitis, peptic ulcer
- Hypo- and hypertension
- Insulin-independent diabetes
- Obesity
- Hypo- and hypercholesterinemia
- Acute mesenteric ischaemia
- Disorders of blood coagulation
- Rheumatoid arthritis, other affections of the connective tissue
- Diseases connected with impairment of water and salt metabolism
- Malignant neoplasms of the colon, breast and so on
- Caries, periodontal disease
- Urolithiasis
- Bronchial asthma, atopic dermatitis, other allergic conditions
- Psoriasis
- Portal systemic encephalopathy, other liver affections
- Opportunistic endo- and superinfections of various localization
- Graft-versus-Host disease
- Impairments in menstrual cycle
- Infertility, premature birth
- Decrease in efficacy of hormonal contraceptives
- Neonatal anaemia, cachexia

Methods used for formation, preservation and correction of Host Microflora

- Probiotics, including autoprobiotics
- Prebiotics
- Synbiotics
- Symbiotic bacteria metabolites
- Structural components of symbiotic bacterium cells
- Microecological engineering

Microbial species, used for probiotic manufacture

*Bifidobacterium adolescentis, B. bifidum, B. longum,
B. breve, B. infantis,
*Lactobacillus acidophilus. L. casei, L. delbrueckii subsp. bulgaricus, L. helveticus, L. fermentum, L. lactis,
L. rhamnosus, L. salivarius, L. plantarum, L. johnsonii, L.reuteri
*Bacillus subtilis
*Streptococcus cremoris, S. lactis, S. salivarius subsp. thermophilus
*Enterococcus faecalis, E. faecium
*Lactococcus spp.
*Leuconostoc spp.
*Pediococcus spp.
*Propionibacterium acnes
*Saccharomyces boulardii
*Clostridium butiricum
*Escherichia coli

The most known foreign strains of lactobacilli and bifidobacteria used for probiotic manufacture [Holm F., 2003]

Strains	*Property*
L.acidophilus NCFM	Rhodia Inc.
L.acidophilus DDS-1	Nebraska Cultures
L.acidophilus SBT-2062	Snow Brand Milk Products
L.acidophilus LA-1/ LA-5	Chr. Hansen
L.casei Shirota	Yakult
L.casei Immunitas	Danone
L.fermentum RC-14	Urex Biotech
L. johnsonii La 1/Lj1	Nestle
L.paracasei CRL 431	Chr.Hansen
L.plantarum	Probi AB
L.reuteri SD 2112/MM2	Biogai
L.rhamnosus GG	Valio
L.rhamnosus GR-1	Urex Biotech
L.rhamnosus 271	Probi AB
L.rhamnosus LB21	Essum AB
L.salivarius UCC 118	University College Cork
L.lactis L 1A	Probi AB
B.animalis	Danone
B.lactis B6-12	Chr. Hansen
B.longum BB 536	Morinaga Milk Industry
B.longum SBT- 2928	Snow Brand Milk Products
B.breve	Yakult

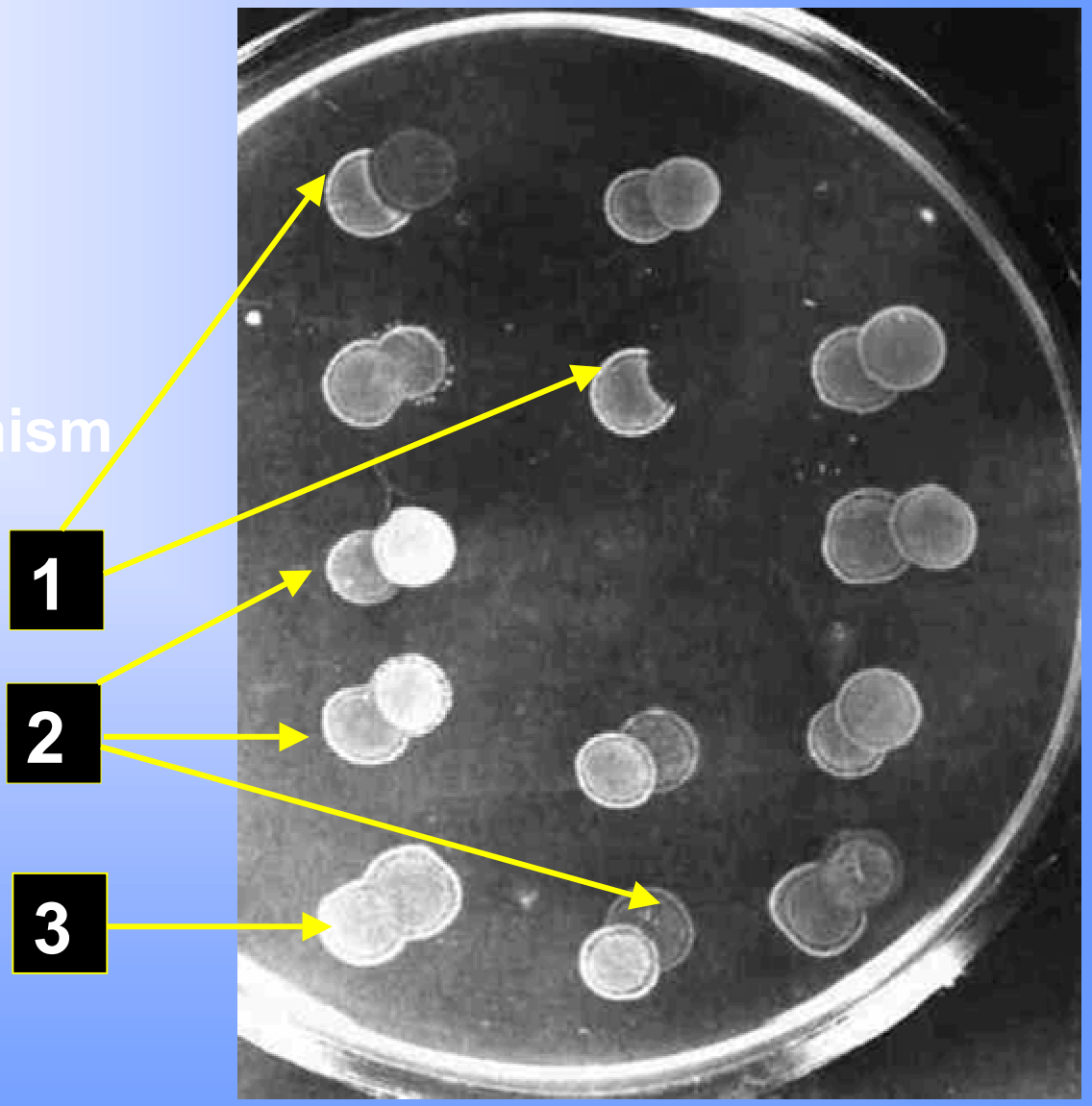
The most known strains of lactobacilli and bifidobacteria used for probiotic manufacture in Russia

- Lactobacillus acidophilus 100аш;
- L. acidophilus NK1;
- L. acidophilus К3Ш24;
- L. acidophilus Ep317/402
- Lactobacillus fermentum 90-ТС-4
- Lactobacillus plantarum 8RA-3
- Bifidobacterium bifidum 1;
- B. bifidum 791;
- B. bifidum ЛВА-3
- Bifidobacterium longum B379M
- Bifidobacterium breve 79119;
- B. breve 79-88
- Bifidobacterium infantis Г 73-15;
- B. infantis 79-43
- Bifidobacterium adolescentis 7513;
- B. adolescentis МС-42;
- B. adolescentis Г013

1. Pronounced antagonism

2. Slight antagonism

3. Compatibility

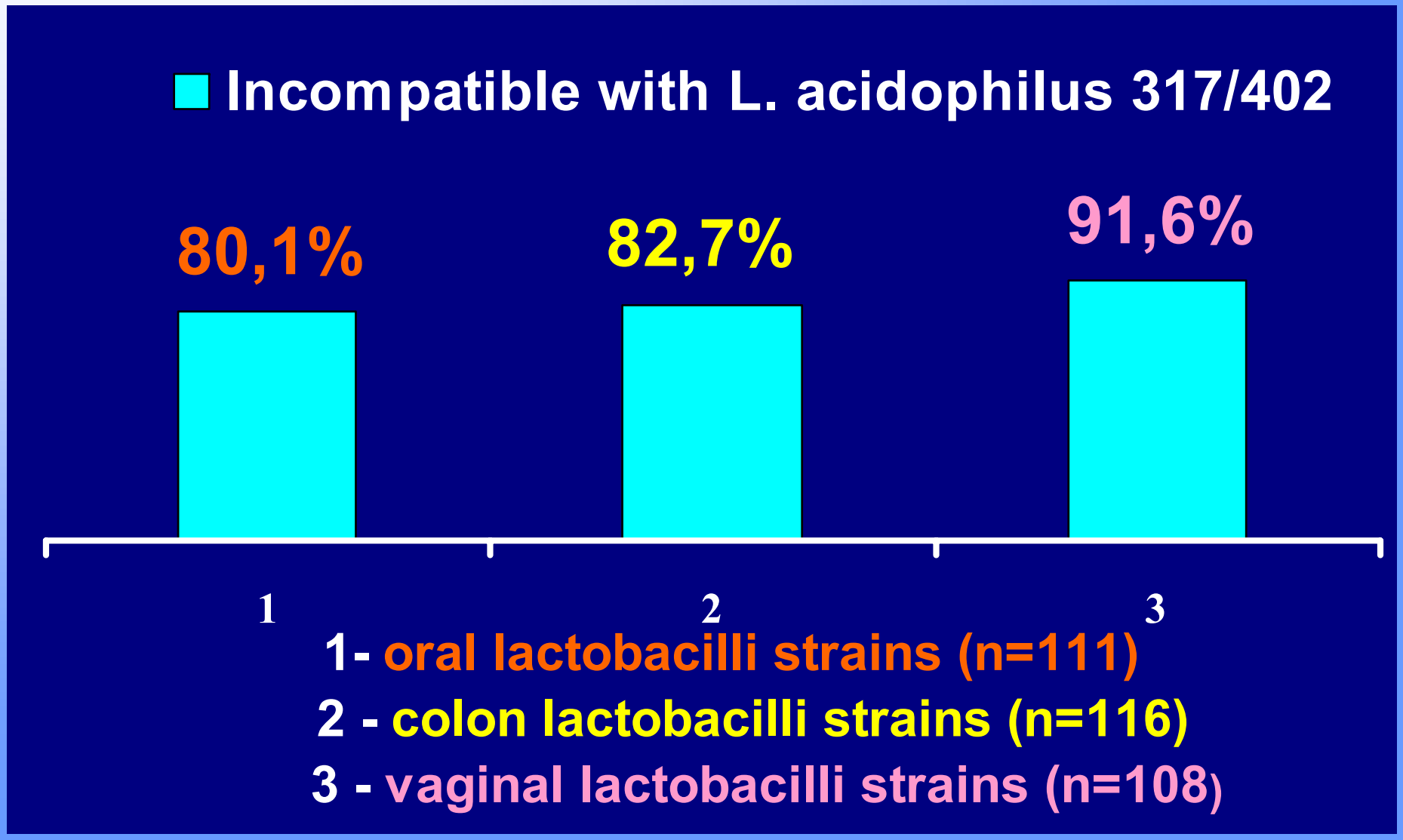


Examples of interstrain interactions during joint pair cultivation of lactobacilli strains on the solid medium

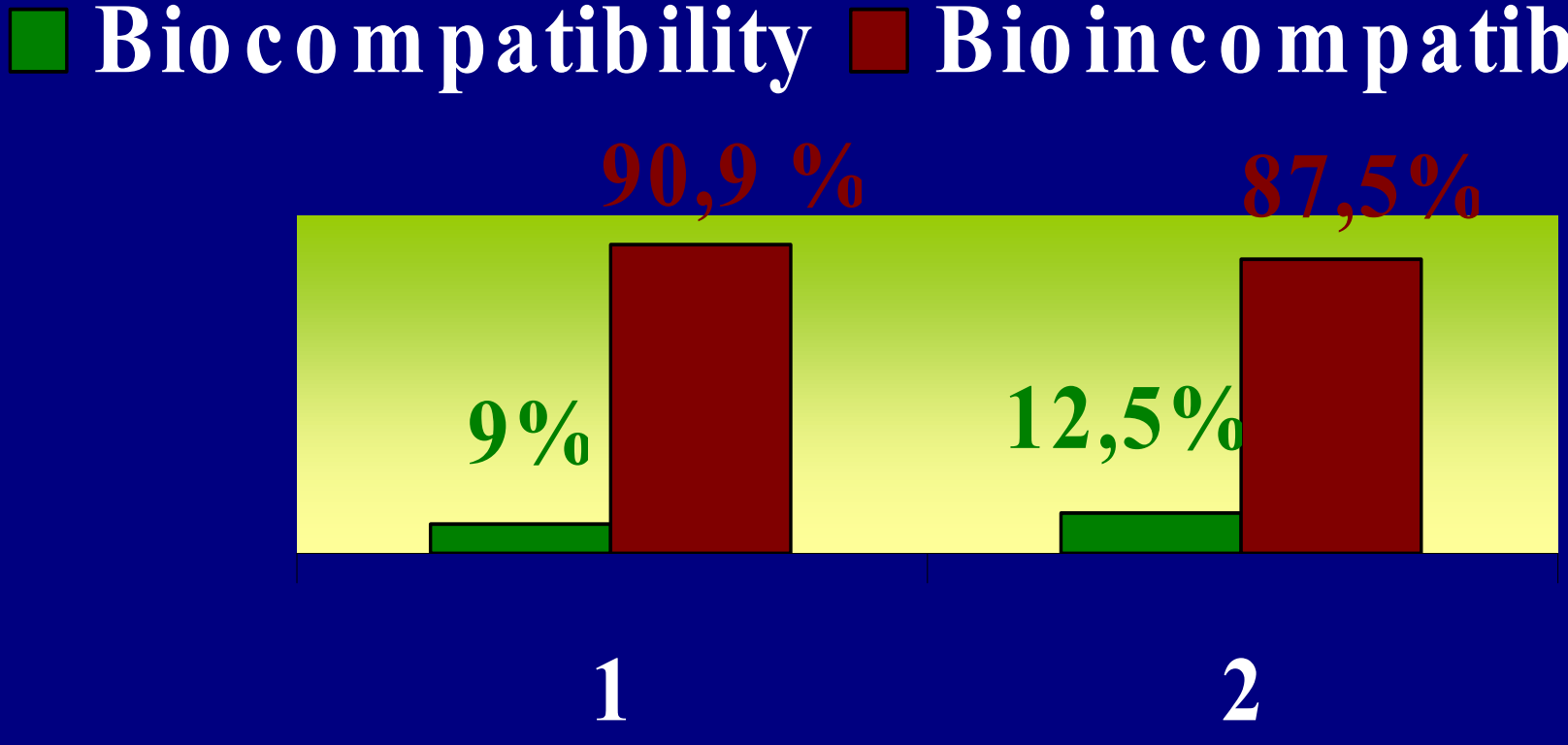
Fresh isolated Lactobacilli strains may be divided to:

1. **Compatible**
2. **Incompatible**
3. **Sinergistic**

Interactions of indigenous lactobacilli strains with probiotic strain (Lactobacillus acidophilus 317/402) during pair cultivation on the solid medium



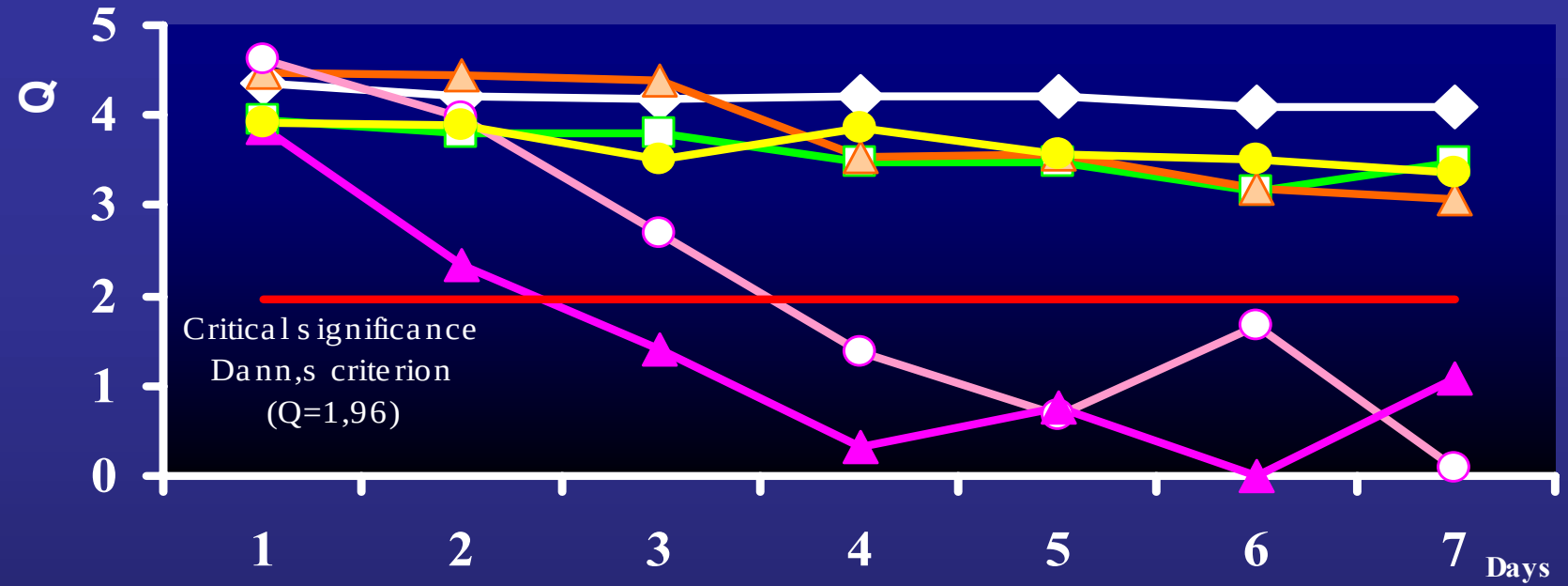
Biocompatibility of lactobacilli strains isolated from different biotopes of the same human being



1 - Colon and vaginal strains

2 - Colon and oral strains

Probiotic strain colonization of mice, intestinal lactoflora of that were before eliminated with antibiotics



Group №1 Control

Group №2 Homoprobiotic incompatible strain L. fermntum VM, isolate from mouse vagina cavity

Group №3 Homoprobiotic incompatible strain L. plantarum KM, isolated from mouse excrement

Group №4 Homoprobiotic compatible strain L. cellobiosus KM2D, isolated from mause excrement

Group №5 Autoprobiotic strain L. cellobiosus, isolated from mouse excrement

Group №6 Industrial probiotic strain (L. acidophilus 317/402)

To receive fast, stable positive probiotic effect and to prevent undesirable aside consequences it is necessary to individualize selection of probiotics for each recipient using specific *in vitro* laboratory tests.

New generations of probiotics and functional food products have to be based on the strains of microorganisms with clinically proved specific physiological and pharmacological activities (must have the concrete targets: e.g. to increase colonizing resistance, stimulate immunity, modify the pool cholesterol, histamine et so on).

For effective probiotocotherapy and decreasing of risk of microecology disbalance arising it is necessary preliminary in vitro to determine the biocompatibility of probiotic lactobacilli strains with host resident lactoflora .

It is necessary to use homoprobiotics prepared on the base of resident strains isolated from defined biotopes. These strains have to be biocompatible with indigenous strains colonizing the same biotope.

Autoprobiotics prepared on the base of autostrains are the most optimal variants of probiotics for supporting and correction of microecology in any living being

It is necessary to organize the national microbiocenoses cryobanks as constant sources of autostrains for creation of simple and complex autoprobiotics for supporting host microflora at the optimal level