



Mikrobiotanın Önemi ve Rolü

Dr. Ateş Kara

Hacettepe Üniversitesi

Tıp Fakültesi

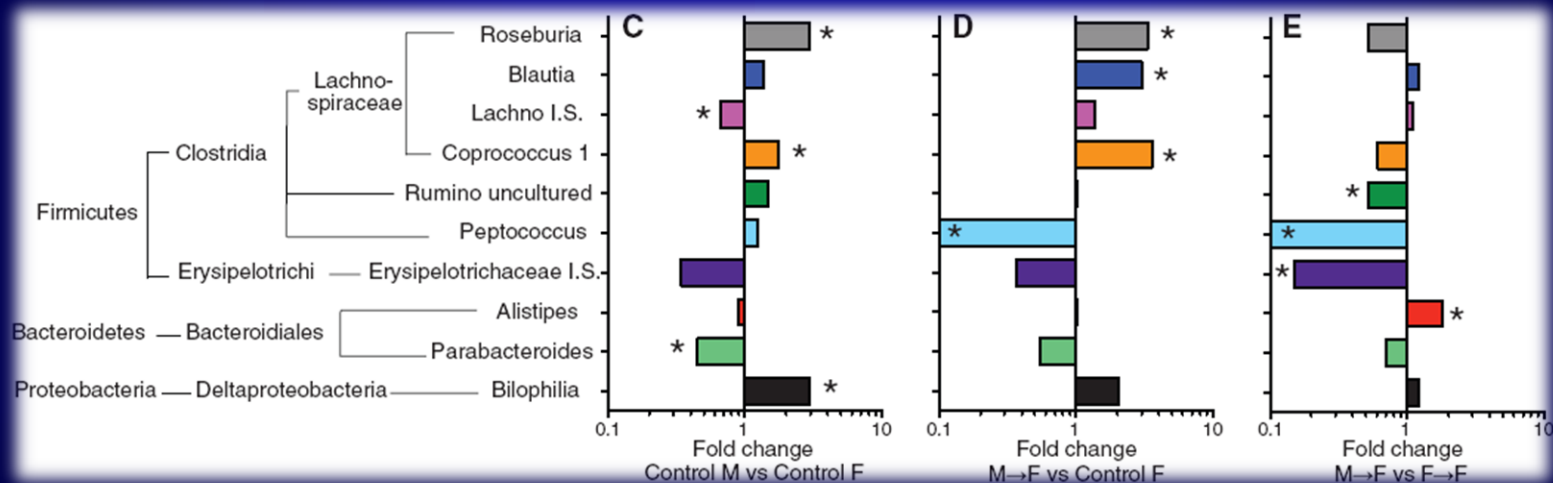
Çocuk Sağlığı ve Hastalıkları Anabilim Dalı

Enfeksiyon Hastalıkları Ünitesi

Sex Differences in the Gut Microbiome Drive Hormone-Dependent Regulation of Autoimmunity

Janet G. M. Markle,^{1,2} Daniel N. Frank,³ Steven Mortin-Toth,¹ Charles E. Robertson,⁴ Leah M. Feazel,³ Ulrike Rolle-Kampczyk,⁵ Martin von Bergen,^{5,6,7} Kathy D. McCoy,⁸ Andrew J. Macpherson,⁸ Jayne S. Danska^{1,2,9*}

- Otoimmün hastalıklara yatkınlıkta mikrobiotanın rolü var
- Komensal bakteriler seks hormonlarının düzeyini deęiřtiriyor
- Cinsiyete baęlı tip 1 DM duyarlıęının kaynaęı mikrobiyota
- Eriřkin erkek farelerden, olgunlařmamıř diři farelere mikrobiota aktarımı testosteron artıřına ve otoimmün hastalıklara dirence yol aęıyor



Sex Differences in the Gut Microbiome Drive Hormone-Dependent Development of Autoimmunity

Michael N. Frank,³ Steven Martin-Toth,¹ Charles E. Robertson,⁴ Andrzej Karpczyk,⁵ Martin von Bergen,^{5,6,7} Kathy D. McCoy,⁸ and S. Danka^{1,2,9*}



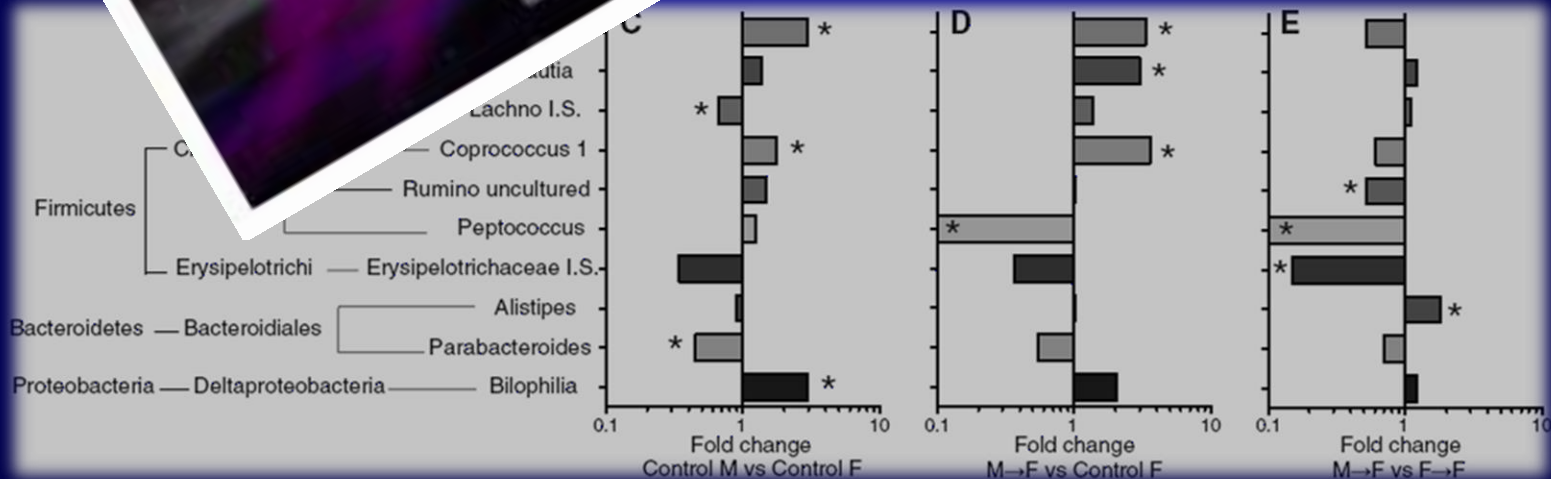
1. Hastalıkta mikrobiotanın rolü var

2. Hastalıkların düzeyini deęiřtiriyor

3. Hastalıkların kaynaęı mikrobiyota

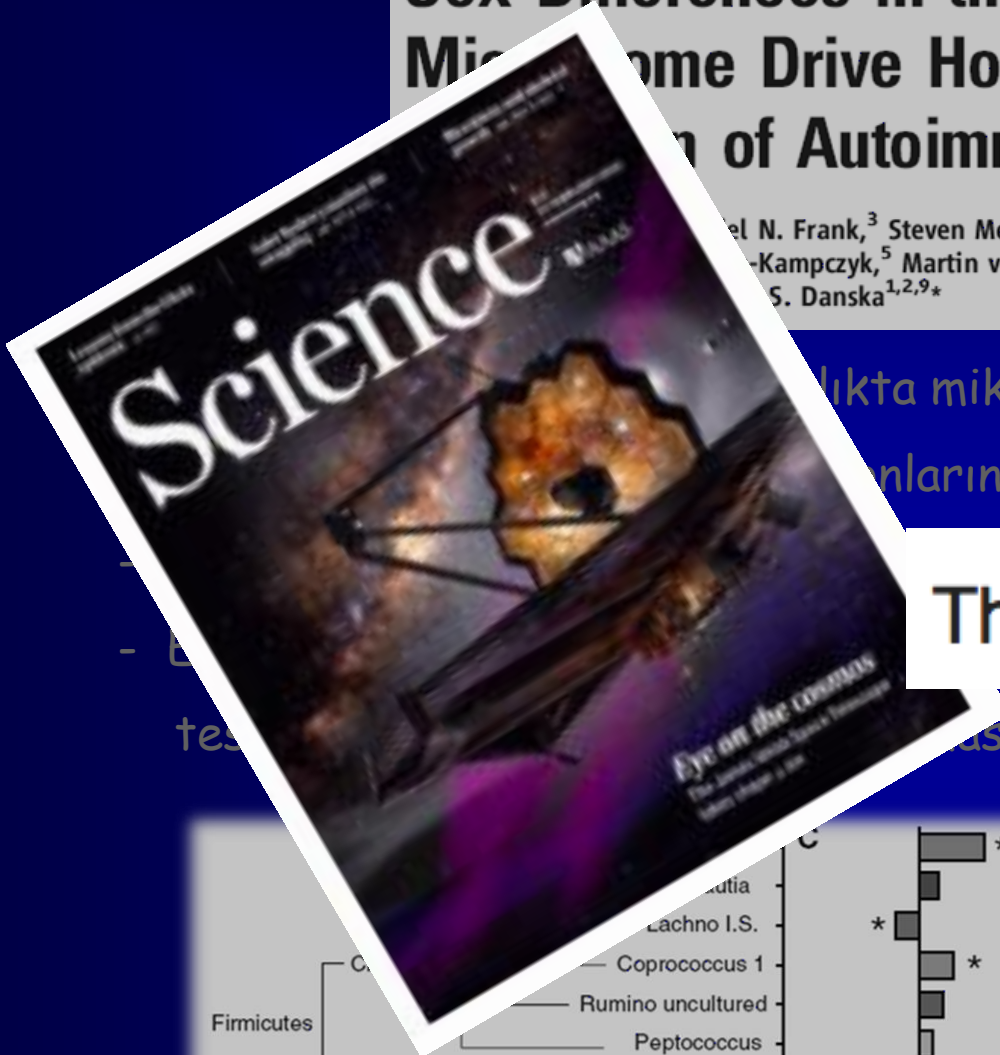
4. Hastalıklardan korunmuş diři farelere mikrobiota aktarımı

5. Hastalıklara dirence yol açıyor



Sex Differences in the Gut Microbiome Drive Hormone-Dependent Development of Autoimmunity

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İmmünitekte mikrobiotanın rolü var

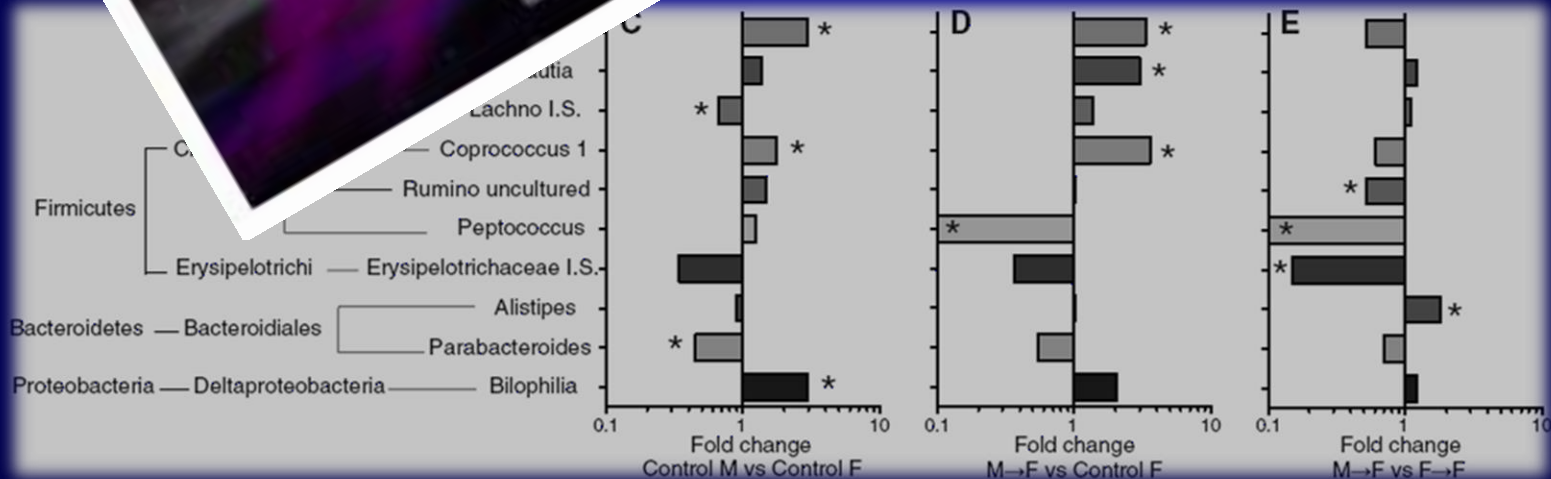
İmmünitezin düzeyini deęiřtiriyor

The top 100 papers

İmmünitez faktörlerini

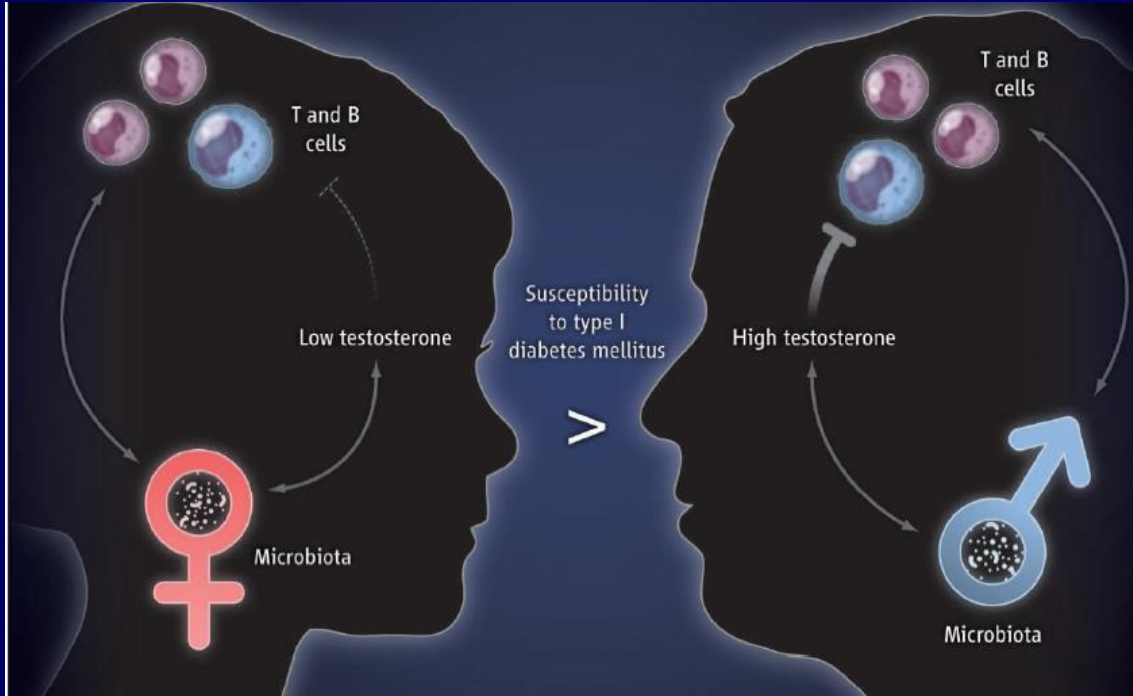
tes

İmmünitez hastalıklarına dirence yol aęıyor



Welcome to the Microgenderome

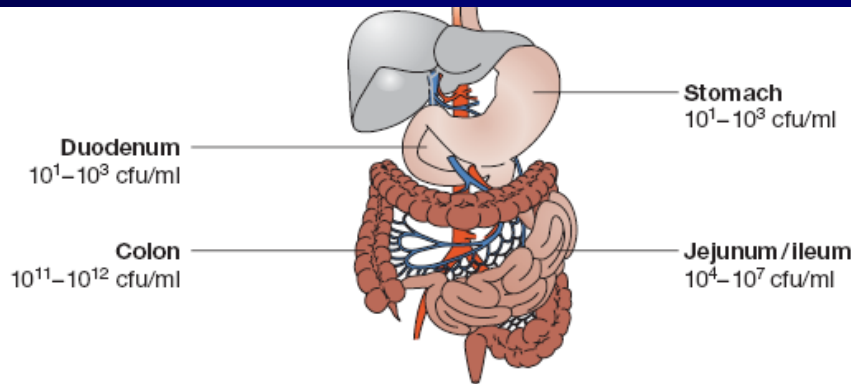
Magdalena B. Flak, Joana F. Neves, Richard S. Blumberg



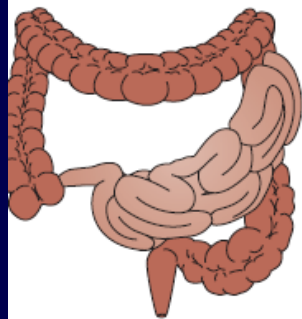
- Erkeklerde püberte döneminde barsak MİKROBİYOTASI deęiřiyor
- Testosteron üretimi artıyor
- Bu durum B ve T hücre fonksiyonlarını güçlendiriyor

The gut flora as a forgotten organ

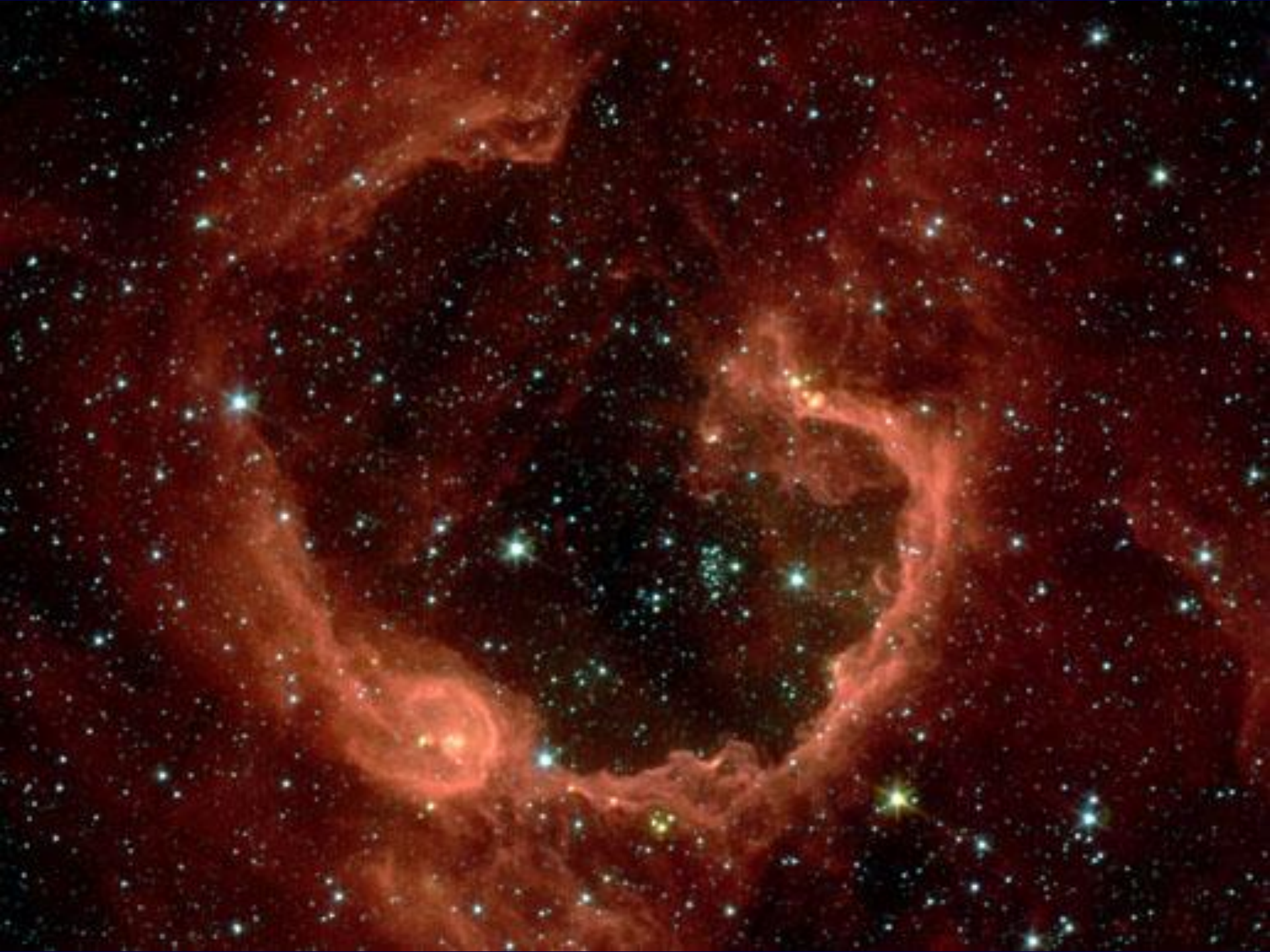
Ann M. O'Hara¹ & Fergus Shanahan^{1,2+}



Anaerobic genera	Aerobic genera
<i>Bifidobacterium</i>	<i>Escherichia</i>
<i>Clostridium</i>	<i>Enterococcus</i>
<i>Bacteroides</i>	<i>Streptococcus</i>
<i>Eubacterium</i>	<i>Klebsiella</i>



Protective functions	Structural functions	Metabolic functions	
Pathogen displacement Nutrient competition Receptor competition Production of anti-microbial factors e.g., bacteriocins, lactic acids	Barrier fortification Induction of IgA Apical tightening of tight junctions Immune system development	Control IEC differentiation and proliferation Metabolize dietary carcinogens Synthesize vitamins e.g., biotin, folate	Ferment non-digestible dietary residue and endogenous epithelial-derived mucus Ion absorption Salvage of energy
<p>Commensal bacteria</p>	<p>IgA</p>	<p>Short-chain fatty acids</p> <p>Mg²⁺ Ca²⁺ Fe²⁺</p> <p>Vitamin K Biotin Folate</p>	





**Bakteri:
3.5 milyar yıl**



**İnsan:
195.000 yıl**



4.5 Milyar yıl



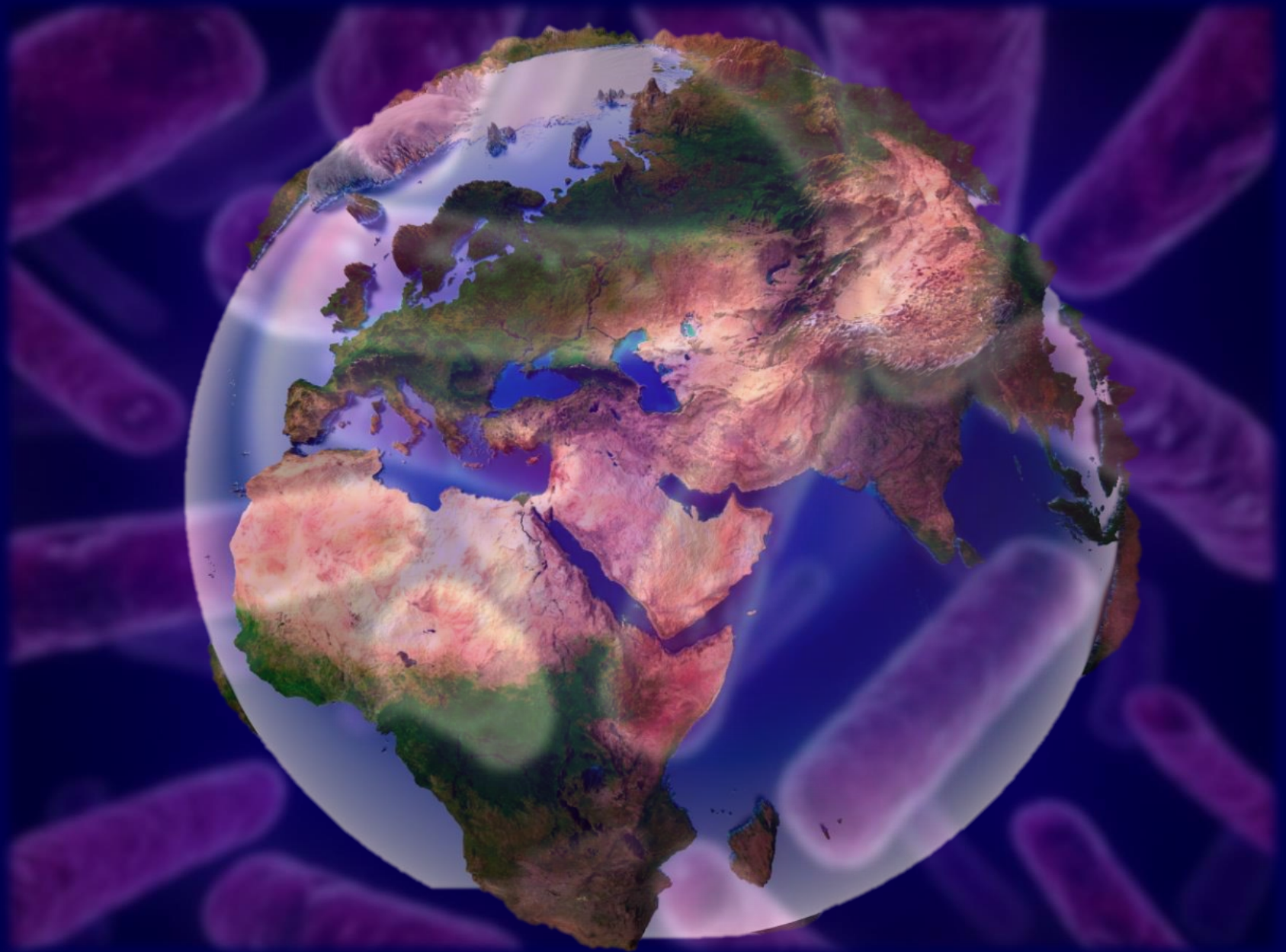
24 saat üzerinden değerlendirildiğinde bakteriler 1 gündür, biz bugün saat 12 ise, 11.59.58'den itibaren varız

3.5 milyar yıl

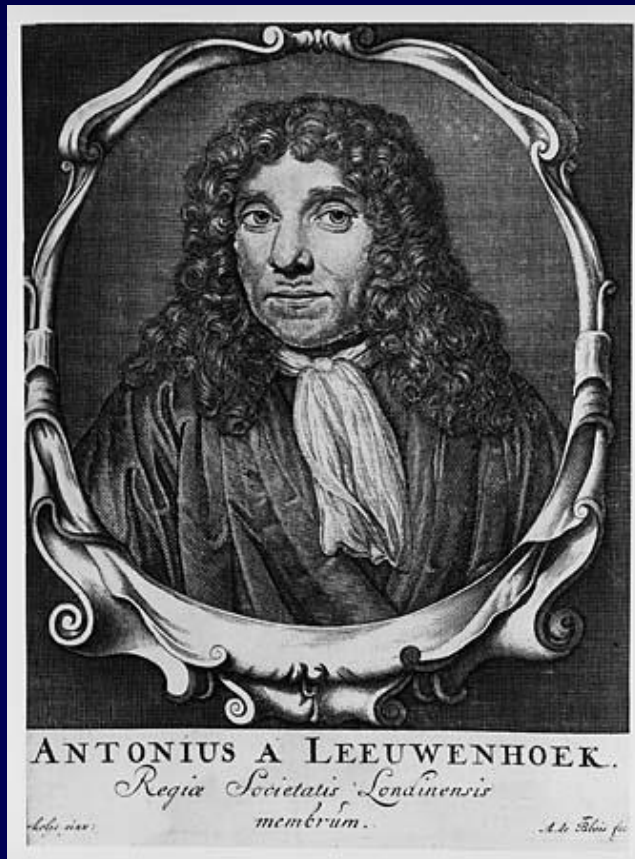
İnsan:
195.000 yıl

4.5 Milyar yıl

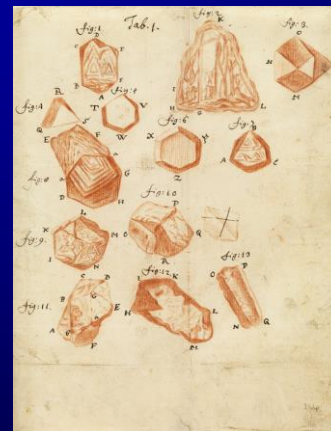
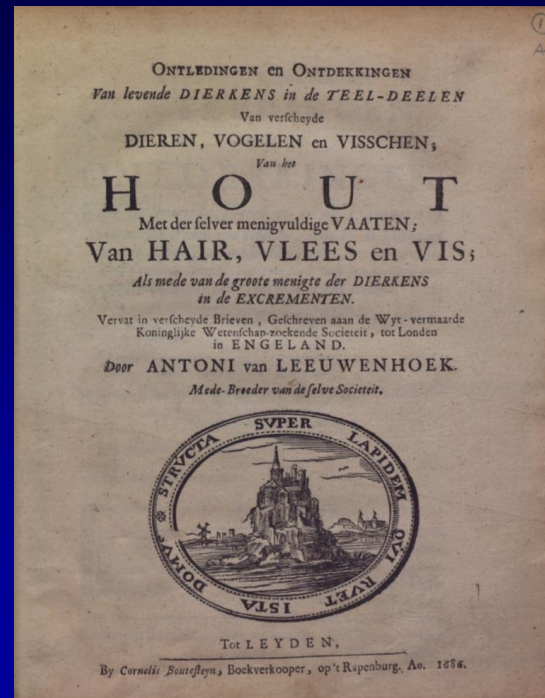








Antonie van Leeuwenhoek
(1632-1723)



Animalcules

Benzer olmayan organizmaların birlikte yařamı



Anton de Bary

geb. 26. Januar 1831, gest. 19. Januar 1888.

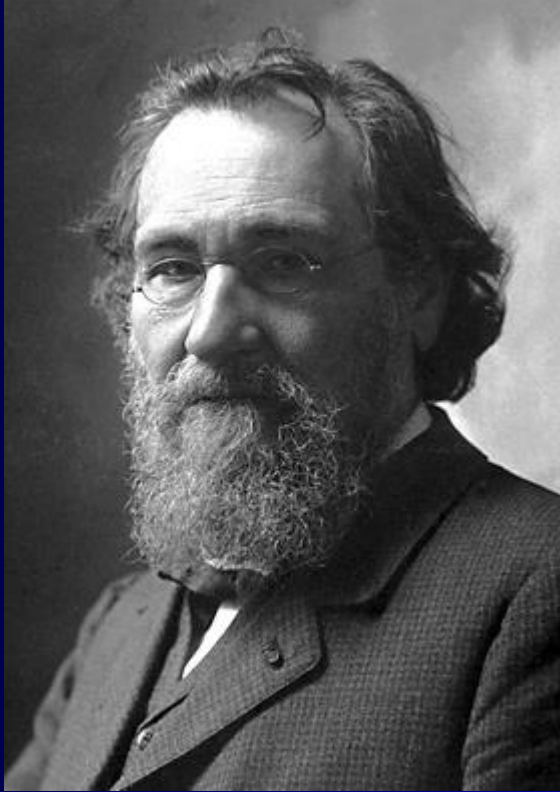
- Sembioz çeřitleri: mutualizm, komensalizm, parazitizm
- Mikroorganizmalarla aramızda hem yarış, hem işbirliđi var
- SAVAŐ ve BARIŐ deđil, ortak yařam...

Benzer olmayan organizmaların birlikte yařamı

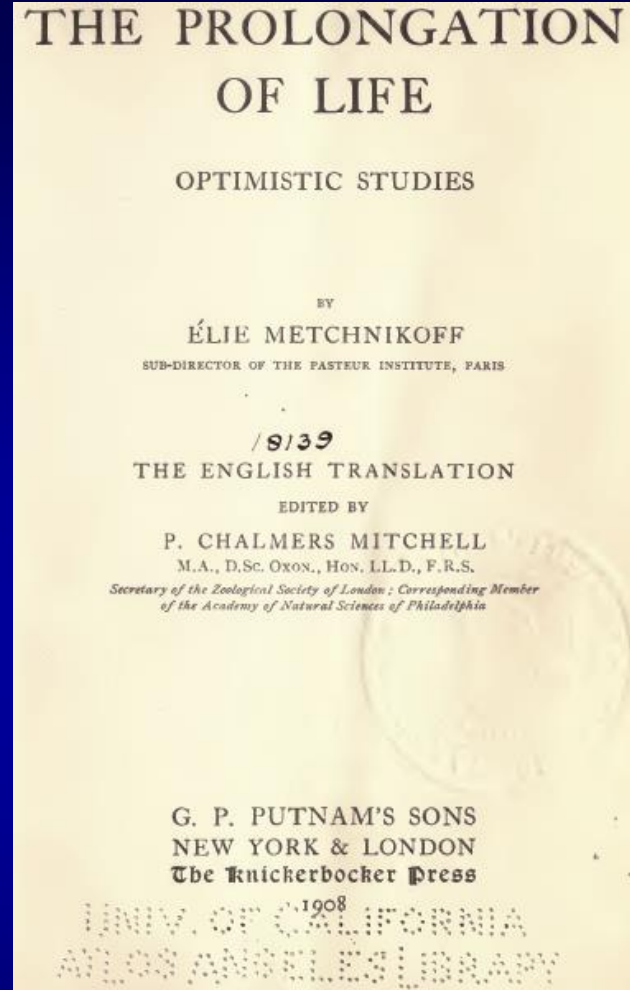
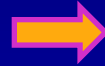


- Sem
- Mik
- SA

izm
đi var



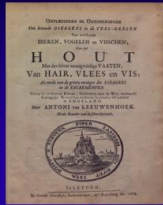
Elie Metchnikoff
(1845-1916)



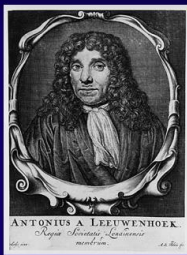
- Disbiozis (*Disbacteriosis*): sembiozisin karşıtı
- Barsak mikrobiotasında kalitatif / kantitatif değişim
- Disbiozis bir dizi hastalığa yol açar: diyare, IBH, obezite, DM, alerji vb....
- Çoğunda barsak bakterilerine karşı immün yanıtta değişim söz konusu



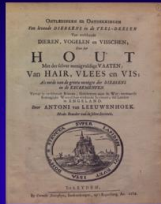
Antonie van Leeuwenhoek
(1632-1723)



«Animalcules»



Antonie van Leeuwenhoek (1632-1723)



<Animalcules>

Pharynx, Respiratory System

Click on a label for more information

Ağız içinde bulunan mikroorganizma çeşidi 600'ün üzerinde

JOURNAL OF BACTERIOLOGY, Oct. 2010, p. 5002-5017

0021-9193/10\$12.00 doi:10.1128/JB.00542-10

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Vol. 192, No. 19

The Human Oral Microbiome[†]

Floyd E. Dewhirst,^{1,2*} Tuste Chen,¹ Jacques Izard,^{1,2} Bruce J. Paster,^{1,2} Anne C. R. Tanner,^{1,2} Wen-Han Yu,¹ Abirami Lakshmanan,¹ and William G. Wade^{1,3}

Department of Molecular Genetics, The Forsyth Institute, Cambridge, Massachusetts 02142¹; Department of Oral Medicine, Infection and Immunology, Harvard School of Dental Medicine, Boston, Massachusetts 02115²; and King's College London Dental Institute at Guy's, King's College and St. Thomas' Hospitals, Infection Research Group, Guy's Campus, London SE1 9RT, United Kingdom³

Received 11 May 2010/Accepted 10 July 2010

The human oral cavity contains a number of different habitats, including the teeth, gingival sulcus, tongue, cheeks, hard and soft palates, and tonsils, which are colonized by bacteria. The oral microbiome is comprised of over 600 prevalent taxa at the species level, with distinct subsets predominating at different habitats. The oral microbiome has been extensively characterized by cultivation and culture-independent molecular methods such as 16S rRNA cloning. Unfortunately, the vast majority of unnamed oral taxa are referenced by clone numbers or 16S rRNA GenBank accession numbers, often without taxonomic anchors. The first aim of this research was to collect 16S rRNA gene sequences into a curated phylogeny-based database, the Human Oral Microbiome Database (HOMD), and make it web accessible (www.homd.org). The HOMD includes 619 taxa in 13 phyla, as follows: Actinobacteria, Bacteroidetes, Chlamydiae, Chloroflexi, Euryarchaeota, Firmicutes, Fusobacteria, Proteobacteria, Spirochaetes, SR1, Synergistetes, Tenericutes, and TM7. The second aim was to analyze 36,043 16S rRNA gene clones isolated from studies of the oral microbiota to determine the relative abundance of taxa and identify novel candidate taxa. The analysis identified 1,179 taxa, of which 24% were named, 8% were cultivated but unnamed, and 68% were uncultivated phylogenies. Upon validation, 434 novel, nonsingleton taxa will be added to the HOMD. The number of taxa needed to account for 90%, 95%, or 99% of the clones examined is 259, 413, and 875, respectively. The HOMD is the first curated description of a human-associated microbiome and provides tools for use in understanding the role of the microbiome in health and disease.



Süperorganizma = Konak + Mikrobiotası

(100 trilyon mikrobiota + 10 trilyon «self» + 1 trilyon immün hücre)

İnsan vücudunda
hücre sayısı



~10¹² cells

~ 10⁴ genes

The mammalian metabolome



~10¹⁴ Bacteria
+ Archea
+ Fungi
+ Viruses

> 10⁶ genes

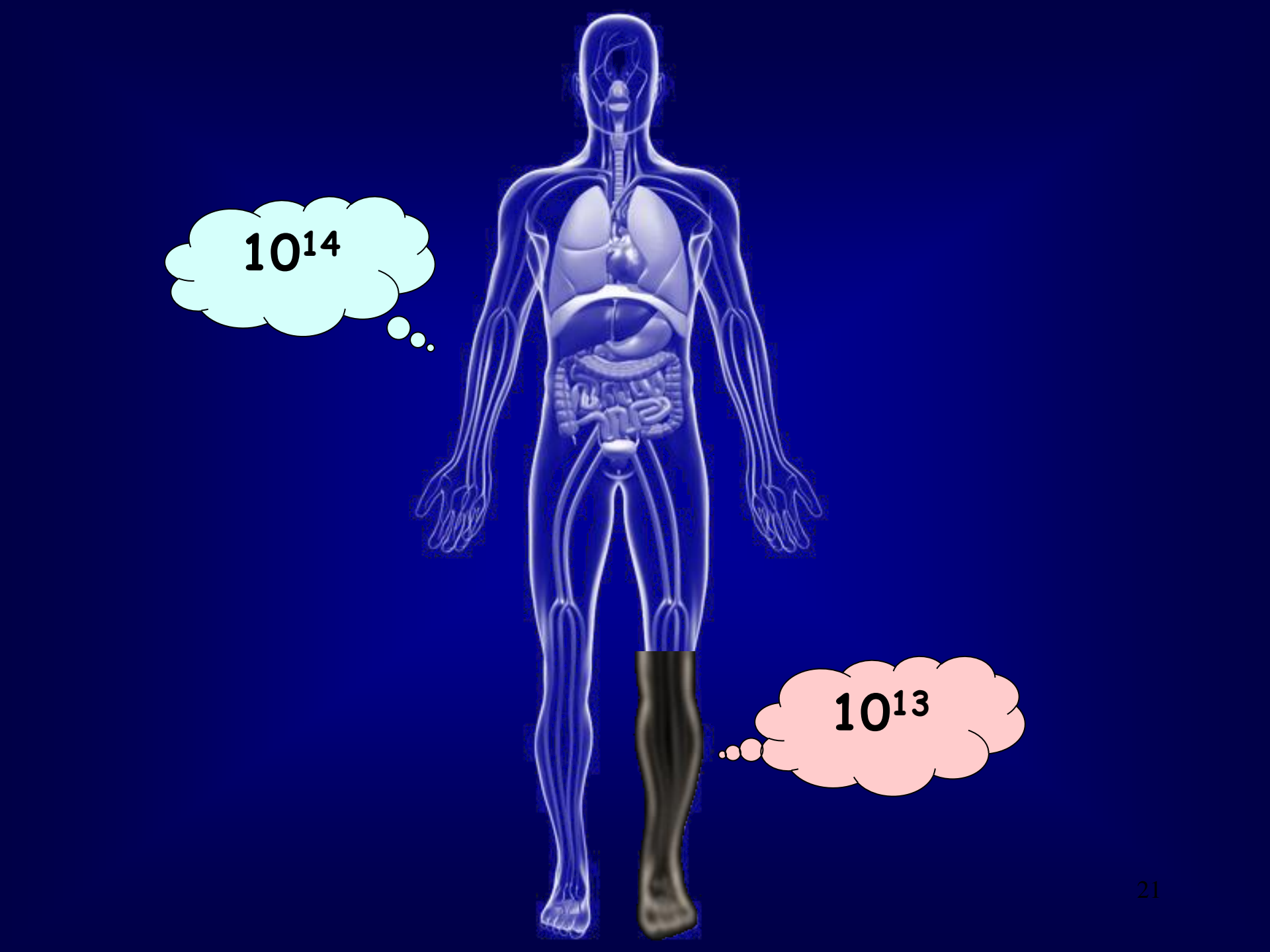
The microbial metabolome

İnsan barsağında
mikroorganizma
sayısı
(> 1000 tür)

The mammalian metabolome +
– Processing of nutrients
– Degradation of xenobiotics
– Protection from new microbes
– Regulation of epithelial homeostasis

Optimal
fitness





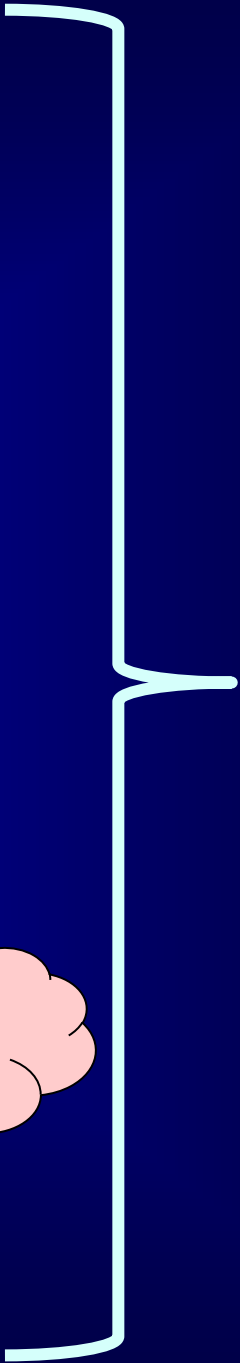
10^{14}

10^{13}

10^{14}



10^{13}



M
i
k
r
o
b
a

8.000.000



23.000

8.000.000



23.000

M
i
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r
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b
m

10^{14}

8.000.000

Fonksiyonel bir
organımız



10^{13}

23.000

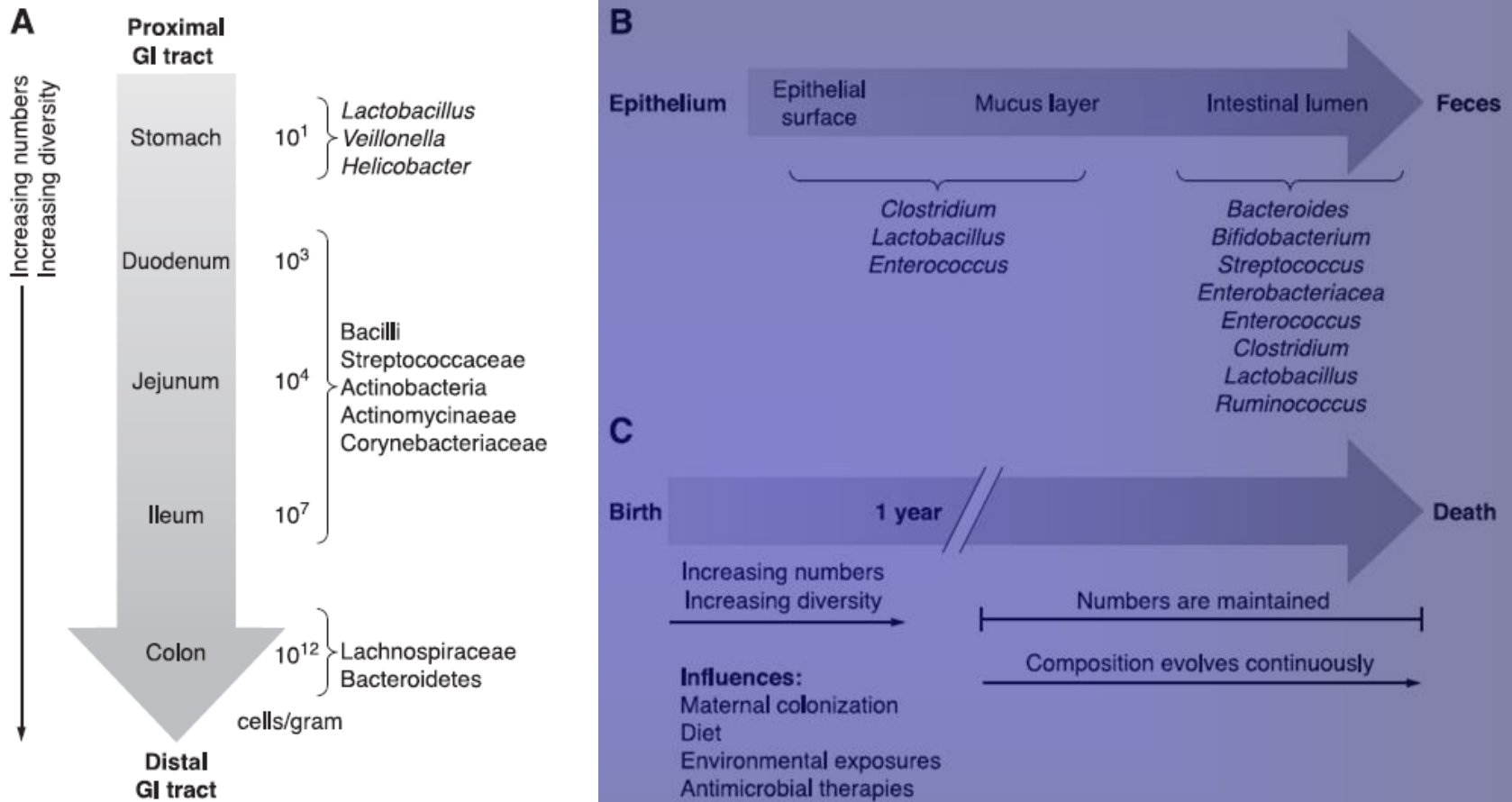


FIG. 2. Spatial and temporal aspects of intestinal microbiota composition. *A*: variations in microbial numbers and composition across the length of the gastrointestinal tract. *B*: longitudinal variations in microbial composition in the intestine. *C*: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition.

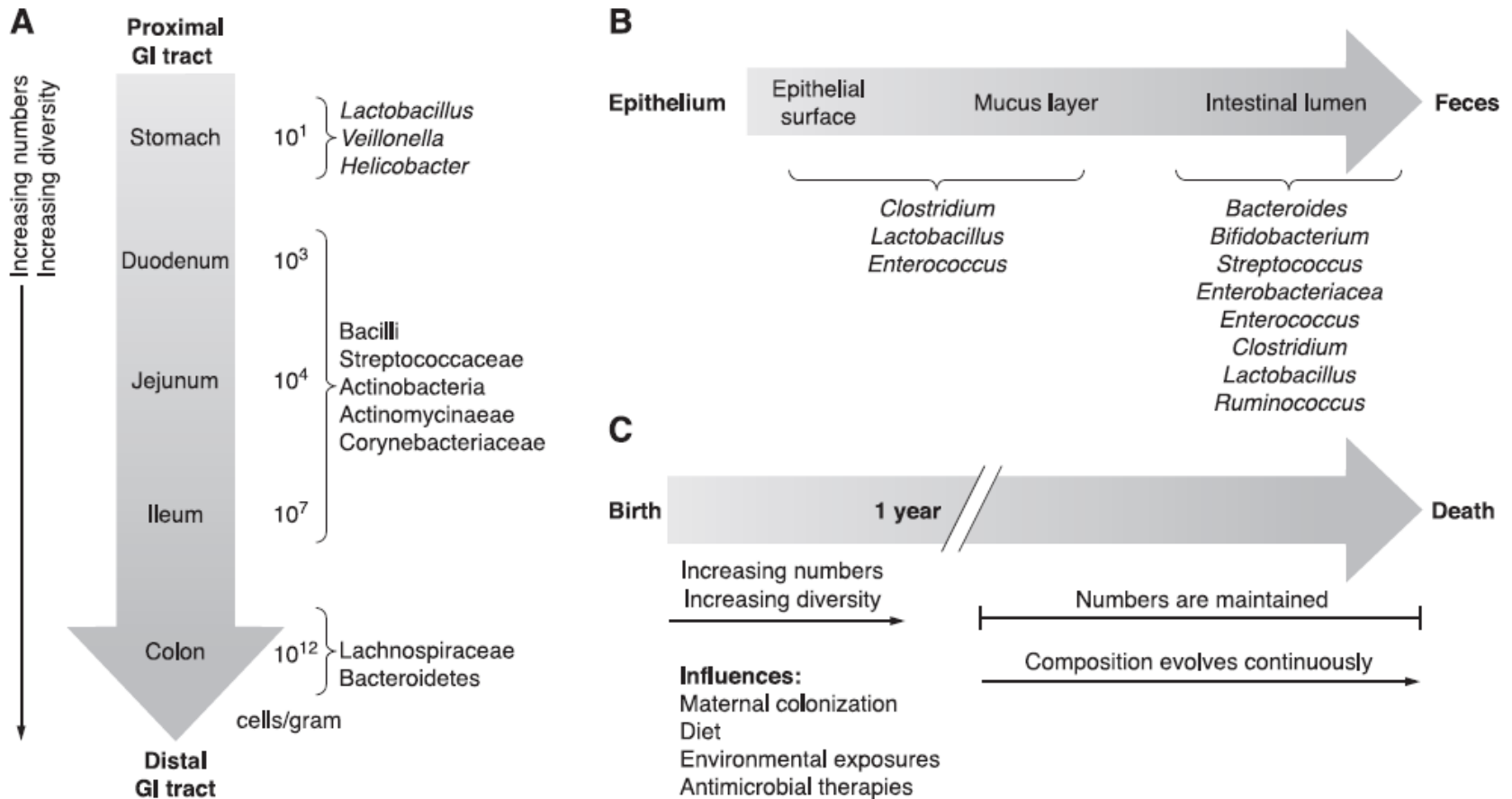
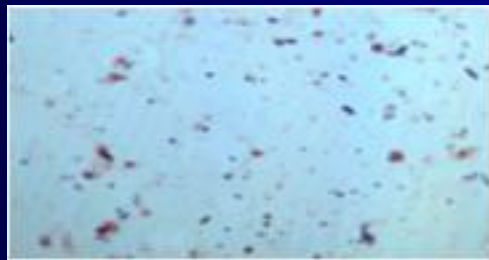
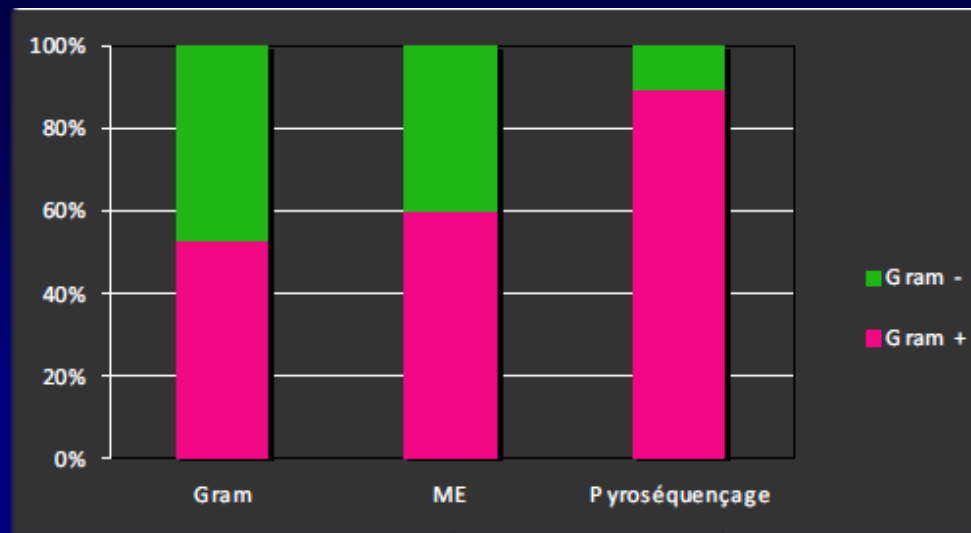
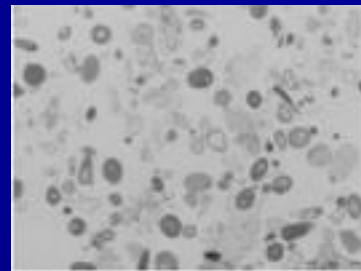


FIG. 2. Spatial and temporal aspects of intestinal microbiota composition. *A*: variations in microbial numbers and composition across the length of the gastrointestinal tract. *B*: longitudinal variations in microbial composition in the intestine. *C*: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition.



Gram staining (x100 oil immersion)
 53% bacteria Gram-positive
 47% bacteria Gram-negative



Electron microscopy (x7100)
 60% bacteria Gram-positive
 40% bacteria Gram-negative

Phylum	Reads	%
<i>Firmicutes</i>	44769	71.12
<i>Actinobacteria</i>	5797	9.21
<i>Other</i>	6627	10.53
<i>Bacteroidetes</i>	3983	6.33
<i>Proteobacteria</i>	1747	2.78
<i>Cyanobacteria</i>	21	0.03
<i>Verrucomicrobia</i>	4	0.01
<i>Total</i>	62948	100

A comparison of Gram staining, electron microscopy, and pyrosequencing to determine the proportion of Gram-positive/Gram-negative bacteria in the same stool sample.

The NIH Human Microbiome Project

The NIH HMP Working Group¹

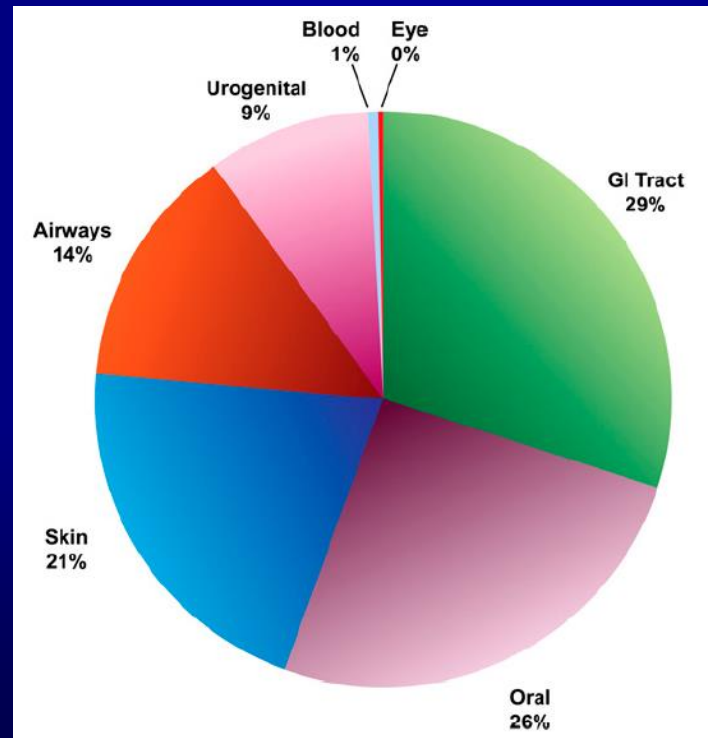
The Human Microbiome Project (HMP), funded as an initiative of the NIH Roadmap for Biomedical Research (<http://nihroadmap.nih.gov>), is a multi-component community resource. The goals of the HMP are: (1) to take advantage of new, high-throughput technologies to characterize the human microbiome more fully by studying samples from multiple body sites from each of at least 250 "normal" volunteers; (2) to determine whether there are associations between changes in the microbiome and health / disease by studying several different medical conditions; and (3) to provide both a standardized data resource and new technological approaches to enable such studies to be undertaken broadly in the scientific community. The ethical, legal, and social implications of such research are being systematically studied as well. The ultimate

NIH Jumpstart Program USA

MetaHIT, Metagenomics of the Human Intestinal Tract EU

MicroObes, Human Intestinal Microbiome in Obesity and Nutritional Transition France

DACC, Data Analysis and Coordination Center USA



CMI, Canadian Human Microbiome Initiative Canada

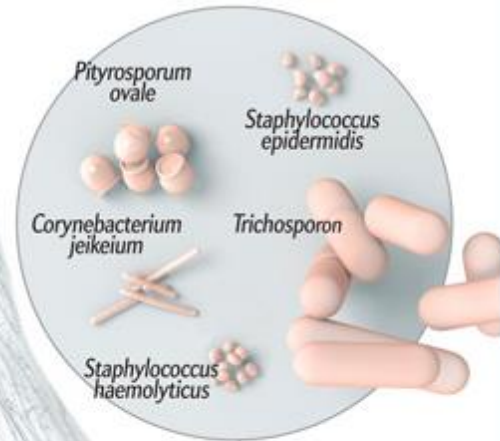
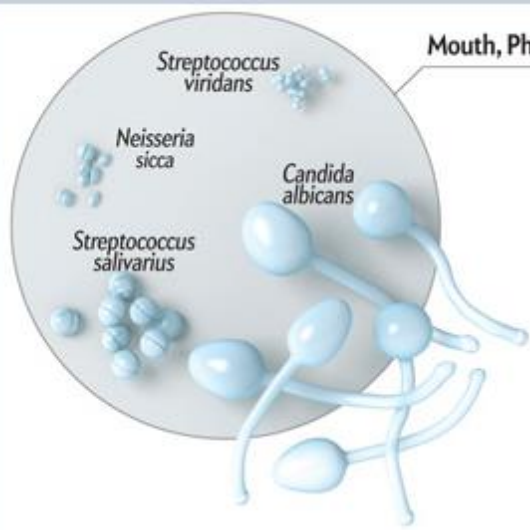
The Australian Jumpstart Human Microbiome Project AU

HMP, NIH Human Microbiome Project USA

Korean Microbiome Diversity, using Korean Twin Cohort Project Korea

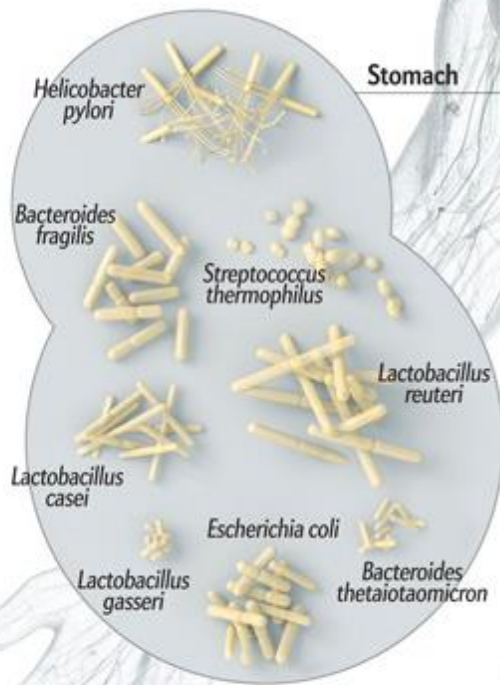
Click on a label for more information

Mouth, Pharynx, Respiratory System



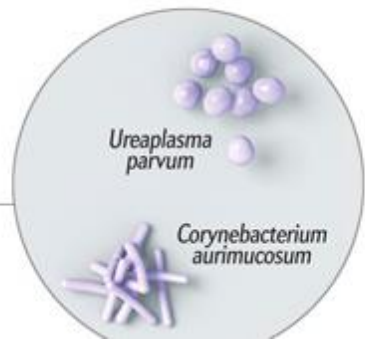
Skin

Stomach



Intestines

Urogenital tract

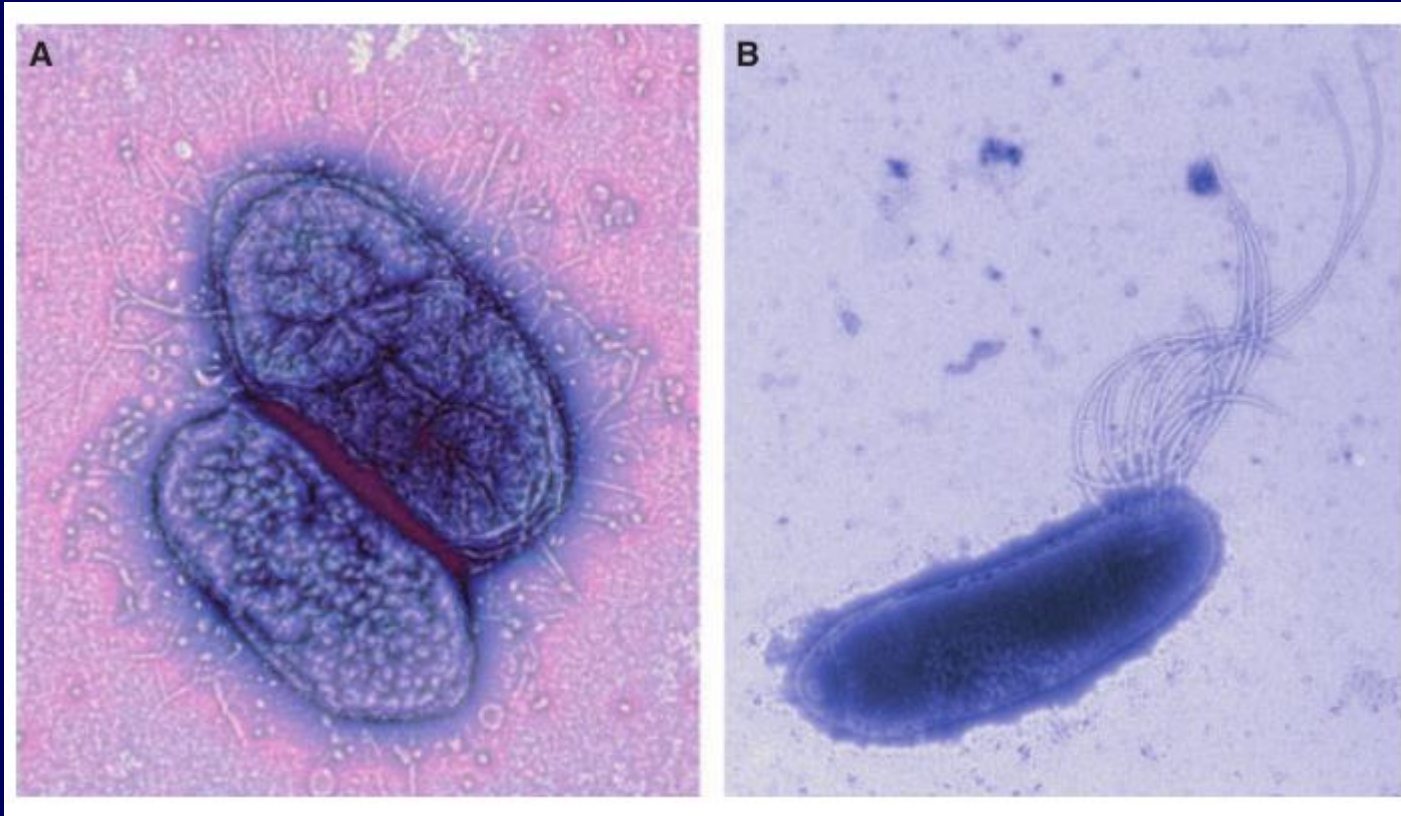


İnsan barsak mikrobiyotası bakteriyel bileşenleri

Filum	Kısa tanım	Bileşenler
Firmicutes	G (+); zorunlu anaerop; ileri derecede çeşitli; çoğu üretilemiyor; sıklıkla bol miktarda	Lachnospiraceae Ruminococcaceae Öteki Firmikütler Segmentli filamentöz bakteriler(?)
Bacteroidetes	G (-); zorunlu anaerop; sıklıkla bol miktarda	Alistipes, Bacteroides, Barnesiella, Prevotella, Parabacteroides
Actinobacteria	G (+); zorunlu anaerop ya da mikroaerofil; kimi cinsleri infantlarda bol	Atopobium, Bifidobacterium, Collinsella, Eggerthella
Proteobacteria	G (-); başlıca fakültatif anaerop ; birçok patojen türü içerir	Alcaligenes, Bilophila, Campylobacter, Escherichia, Enterobacter, Desulfovibrio, Hafnia, Helicobacter,
Proteus,		
Diğerleri	Genellikle az sayıdadırlar	Klebsiella, Sutterella vb. Akkermansia, Fusobacterium, Victivallis

Bacteroidetes

Firmicutes



Bacteroides thetaiotaomicron

Roseburia intestinalis

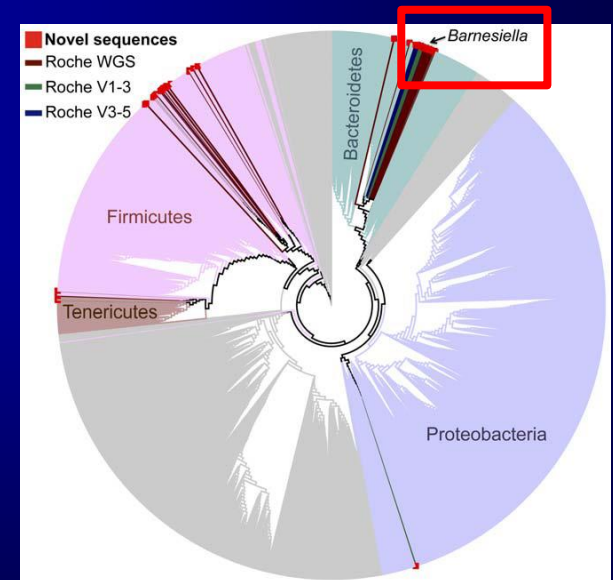
Bacteroides uniformis
Alistipes putredinis
Parabacteroides merdae
Dorea longicatena
Ruminococcus bromii L2-63
Bacteroides caccae
Clostridium sp. SS2-1
Bacteroides thetaiotaomicron VPI-5482
Eubacterium hallii
Ruminococcus torques L2-14
 Unknown sp. SS3 4
Ruminococcus sp. SR1 5
Faecalibacterium prausnitzii SL3 3
Ruminococcus lactaris
Collinsella aerofaciens
Dorea formicigenerans
Bacteroides vulgatus ATCC 8482
Roseburia intestinalis M50 1
Bacteroides sp. 2_1_7
Eubacterium siraeum 70 3
Parabacteroides distasonis ATCC 8503
Bacteroides sp. 9_1_42FAA
Bacteroides ovatus
Bacteroides sp. 4_3_47FAA
Bacteroides sp. 2_2_4
Eubacterium rectale M104 1
Bacteroides xylanisolvens XB1A
Coprococcus comes SL7 1
Bacteroides sp. D1
Bacteroides sp. D4
Eubacterium ventriosum
Bacteroides dorei
Ruminococcus obeum A2-162
Subdoligranulum variabile
Bacteroides capillosus
Streptococcus thermophilus LMD-9
Clostridium leptum
Holdemania filiformis
Bacteroides stercoris
Coprococcus eutactus
Clostridium sp. M62 1
Bacteroides eggerthii
Butyrivibrio crossotus
Bacteroides fingoldii
Parabacteroides johnsonii
Clostridium sp. L2-50
Clostridium nexile
Bacteroides pectinophilus
Anaerotruncus colihominis
Ruminococcus gnavus
Bacteroides intestinalis
Bacteroides fragilis 3_1_12
Clostridium asparagiforme
Enterococcus faecalis TX0104



A human gut microbial gene catalogue established by metagenomic sequencing

Junjie Qin^{1*}, Ruiqiang Li^{1*}, Jeroen Raes^{2,3}, Manimozhayan Arumugam², Kristoffer Solvsten Burgdorf⁴, Chaysavanh Manichanh⁵, Trine Nielsen¹, Nicolas Pons⁶, Florence Levenez⁶, Takuji Yamada⁷, Daniel R. Mende², Junhua Li^{1,7}, Junming Xu¹, Shaochuan Li¹, Dongfang Li^{1,8}, Jianjun Cao¹, Bo Wang¹, Huiqing Liang¹, Huisong Zheng¹, Yinlong Xie^{1,7}, Julien Tap⁶, Patricia Lepage⁶, Marcelo Bertalan⁹, Jean-Michel Batto⁶, Torben Hansen¹, Denis Le Paslier¹⁰, Allan Linneberg¹¹, H. Bjørn Nielsen⁹, Eric Pelletier¹⁰, Pierre Renault⁶, Thomas Sicheritz-Ponten⁹, Keith Turner¹², Hongmei Zhu¹, Chang Yu¹, Shengting Li¹, Min Jian¹, Yan Zhou¹, Yingrui Li¹, Xiuding Zhang¹, Songgang Li¹, Nan Qin¹, Huanming Yang¹, Jian Wang¹, Søren Brunak⁹, Joel Doré⁶, Francisco Guarner³, Karsten Kristiansen¹³, Oluf Pedersen^{4,14}, Julian Parkhill¹², Jean Weissenbach¹⁰, MetaHIT Consortium†, Peer Bork², S. Dusko Ehrlich¹ & Jun Wang^{1,15}

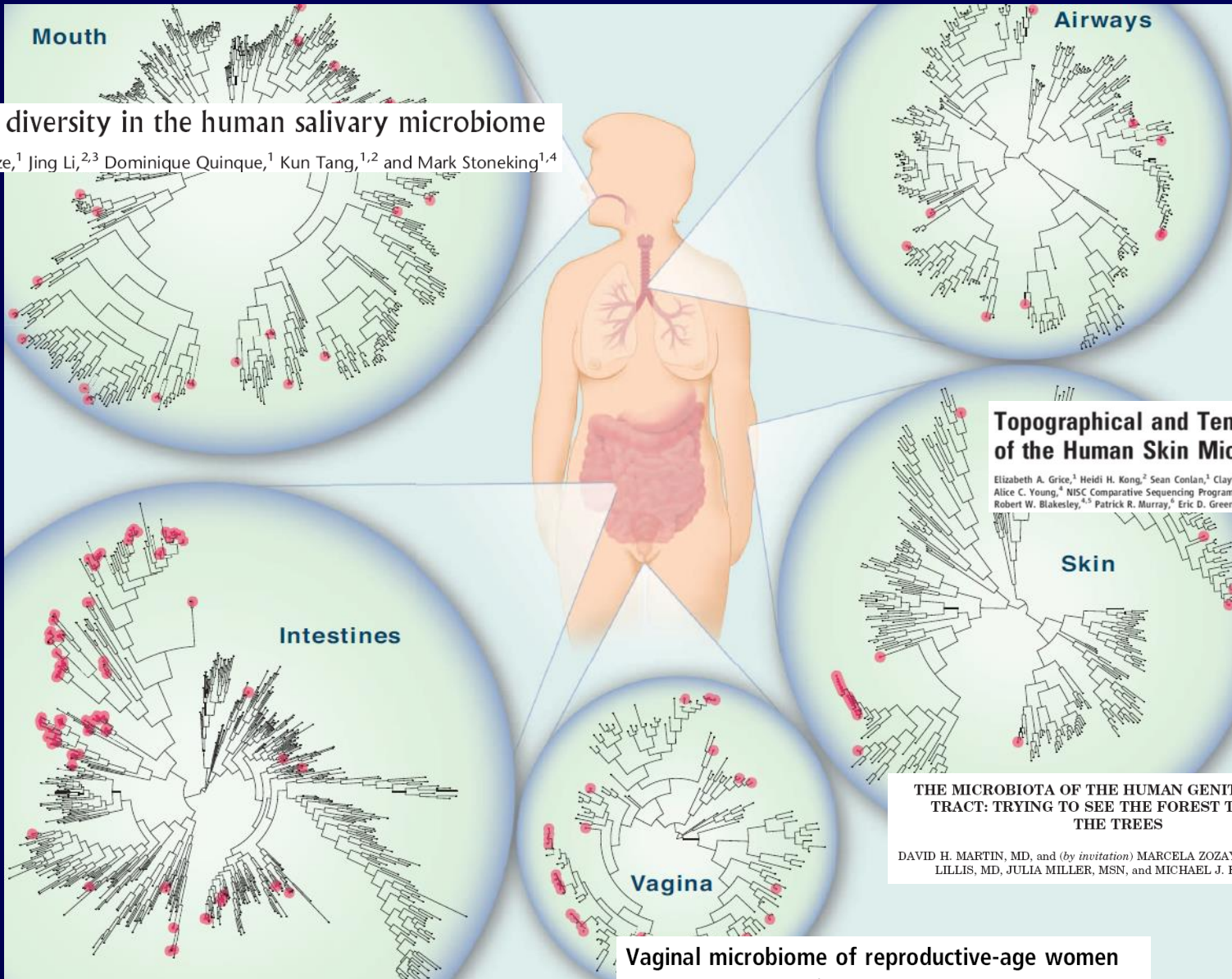
Nature 2010;464: 59



Mikrobiota Sadece Barsakta Değil...

Global diversity in the human salivary microbiome

Ivan Nasidze,¹ Jing Li,^{2,3} Dominique Quinque,¹ Kun Tang,^{1,2} and Mark Stoneking^{1,4}



Topographical and Temporal Diversity of the Human Skin Microbiome

Elizabeth A. Grice,¹ Heidi H. Kong,² Sean Conlan,¹ Clayton B. Deming,¹ Joie Davis,¹ Alice C. Young,¹ NISC Comparative Sequencing Program,⁴ Gerard G. Bouffard,^{4,5} Robert W. Blakesley,^{4,5} Patrick R. Murray,² Eric D. Green,^{4,5} Maria L. Turner,² Julia A. Segre^{1,6}

THE MICROBIOTA OF THE HUMAN GENITOURINARY TRACT: TRYING TO SEE THE FOREST THROUGH THE TREES

DAVID H. MARTIN, MD, and (by invitation) MARCELA ZOZAYA, PhD, REBECCA LILLIS, MD, JULIA MILLER, MSN, and MICHAEL J. FERRIS, PhD

Vaginal microbiome of reproductive-age women

Jacques Ravel^{a,1}, Pawel Gajer^a, Zaid Abdo^b, G. Maria Schneider^c, Sara S. K. Koenig^d, Stacey L. McCulle^e, Shara Karlebach^f, Reshma Gorle^g, Jennifer Russell^h, Carol O. Tacketⁱ, Rebecca M. Brotman^j, Catherine C. Davis^g, Kevin Ault^g, Ligia Peralta^a, and Larry J. Forney^{c,1}

Mikrobiota da Sadece Bakteriler Yer Almaz...

The human gut virome: Inter-individual variation and dynamic response to diet

Samuel Minot,¹ Rohini Sinha,¹ Jun Chen,² Hongzhe Li,² Sue A. Keilbaugh,³ Gary D. Wu,³ James D. Lewis,² and Frederic D. Bushman^{1,4}

Genome Res 2011;21: 1616

Immense populations of viruses are present in the human gut and other body sites. Understanding the role of these populations (the human “virome”) in health and disease requires a much deeper understanding of their composition and dynamics in the face of environmental perturbation. Here, we investigate viromes from human subjects on a controlled

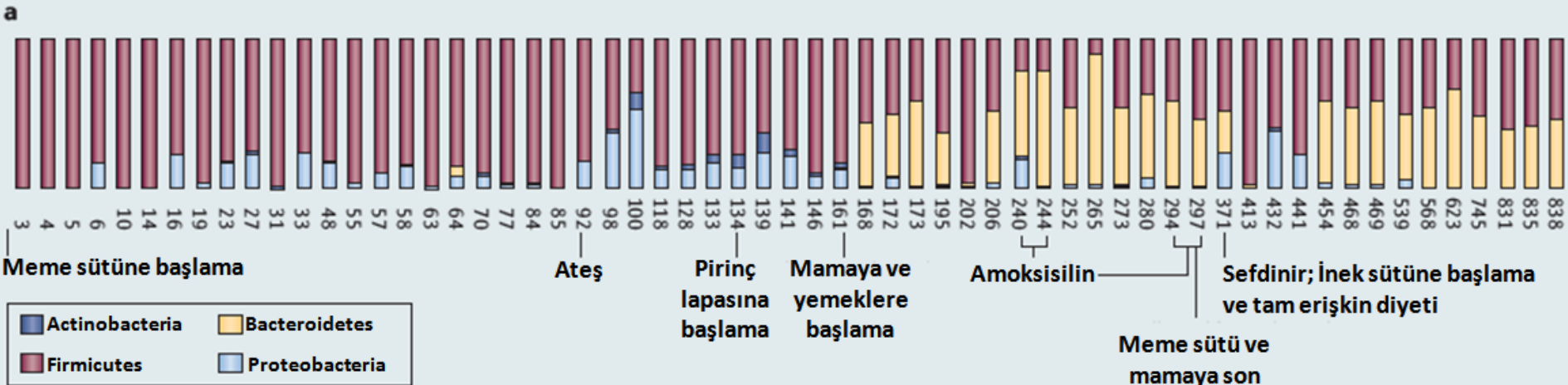
Archaea as emerging organisms in complex human microbiomes

Bédis Dridi, Didier Raoult, Michel Drancourt*

Anaerobe 2011;17:56

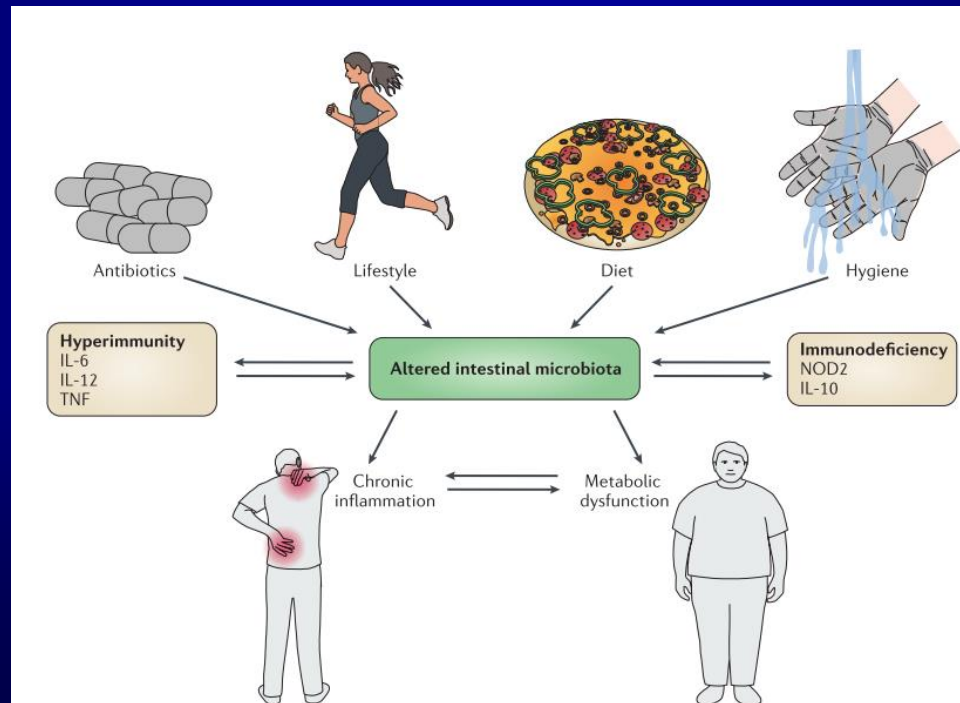
In this work, we review the state of knowledge of Archaea associated with the human microbiome. These prokaryotes, initially discovered in extreme environments, were named Archaea because these environments were thought to be the most primitive on Earth. Further research revealed that this terminology is misleading because these organisms were later found in various non-extreme environments, including the human host. Further examination of the human microbiome has enabled the isolation of

Mikrobiyotanın Gelişimi ve Barsak Mikrobiyomunu Yaşam Boyu Etkileyen Çevresel Faktörler



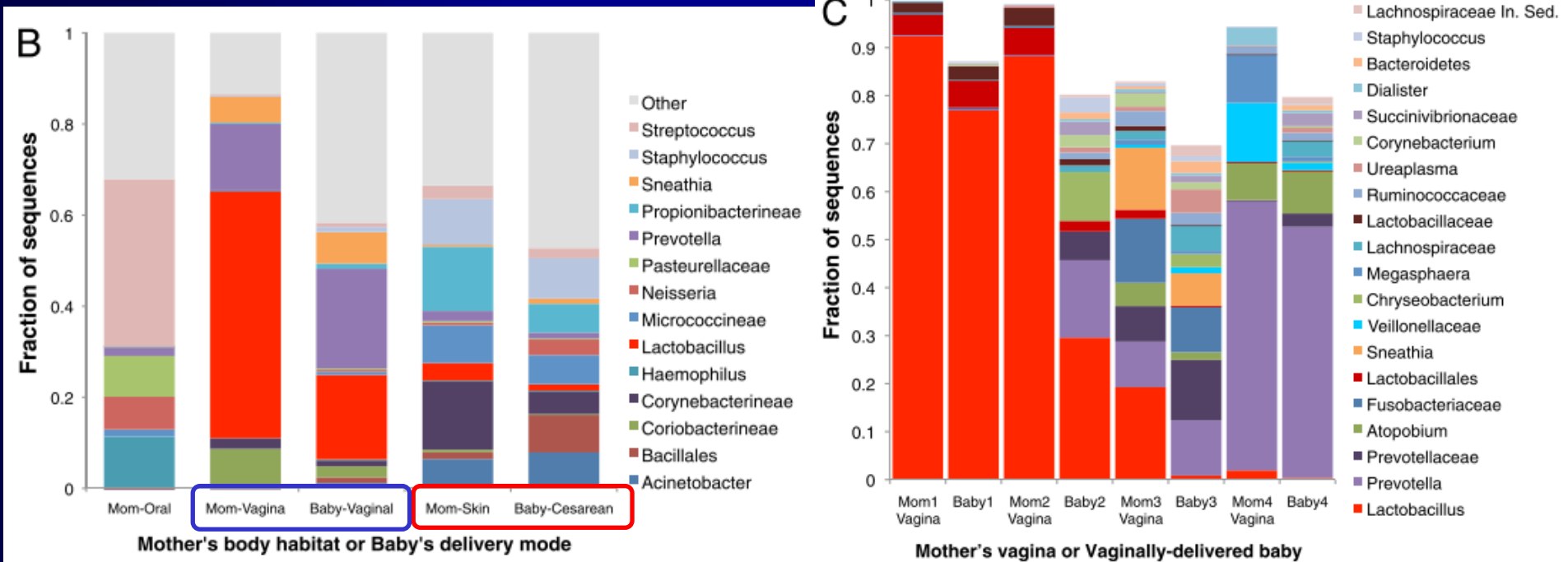
Mikrobiota İçeriğini Etkileyen Faktörler:

- * Maternal kolonizasyon
- * Yaş
- * Diyet
- * Çevresel temaslar
- * Antimikrobiyal tedaviler

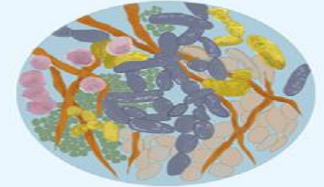
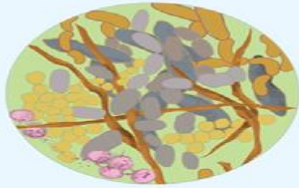


Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns

Maria G. Dominguez-Bello^{a,1,2}, Elizabeth K. Costello^{b,1,3}, Monica Contreras^c, Magda Magris^d, Glida Hidalgo^d, Noah Fierer^{e,f}, and Rob Knight^{b,g}



Mother



Vaginally born/Breast feed

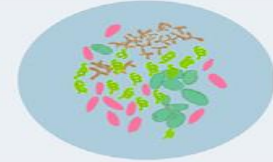


Vaginally born/Bottle feed

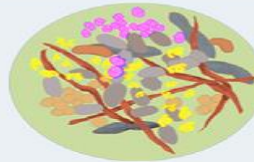
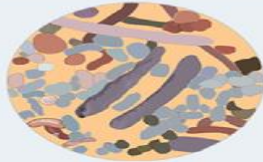


C-section

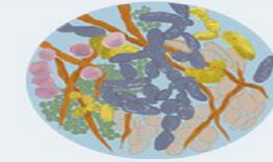
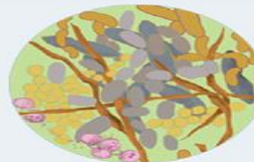
4 days



4 month



12 month



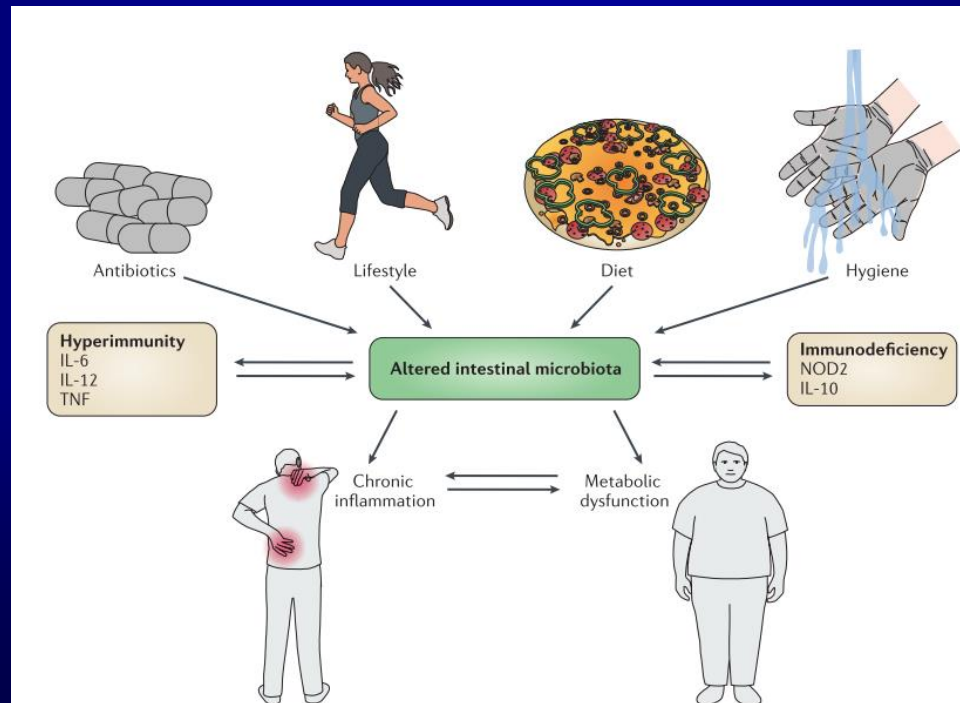
Intestinal Microbiota Development in Preterm Neonates and Effect of Perinatal Antibiotics

Silvia Arboleya, MSc¹, Borja Sánchez, PhD^{1,*}, Christian Milani, MSc², Sabrina Duranti, MSc², Gonzalo Solís, PhD³, Nuria Fernández, PhD⁴, Clara G. de los Reyes-Gavilán, PhD¹, Marco Ventura, PhD², Abelardo Margolles, PhD¹, and Miguel Gueimonde, PhD¹

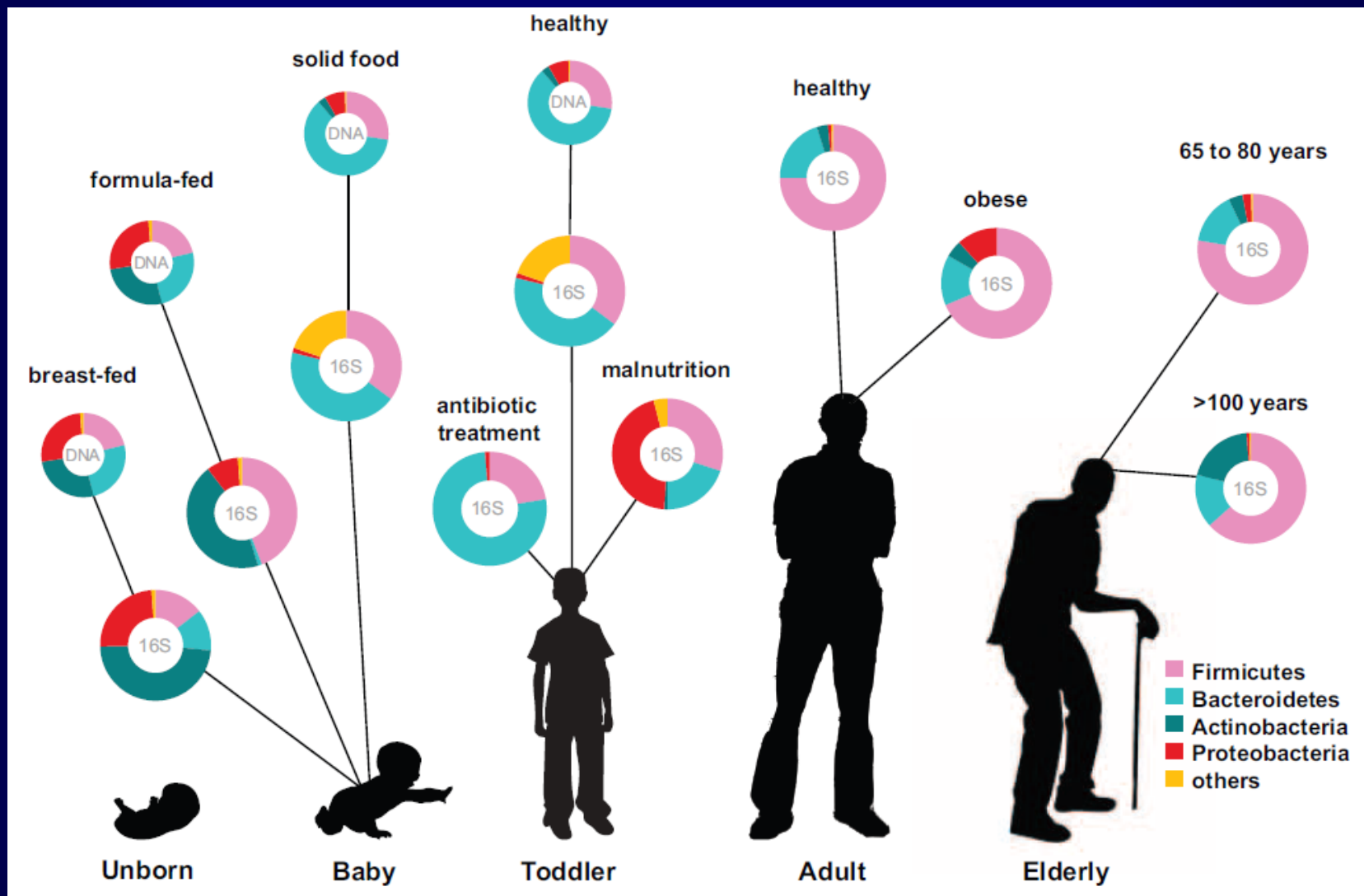
Results Immaturity affects the microbiota as indicated by a reduced percentage of the family *Bacteroidaceae* during the first months of life and by a higher initial percentage of *Lactobacillaceae* in preterm infants compared with full term infants. Perinatal antibiotics, including intrapartum antimicrobial prophylaxis, affects the gut microbiota, as indicated by increased *Enterobacteriaceae* family organisms in the infants.

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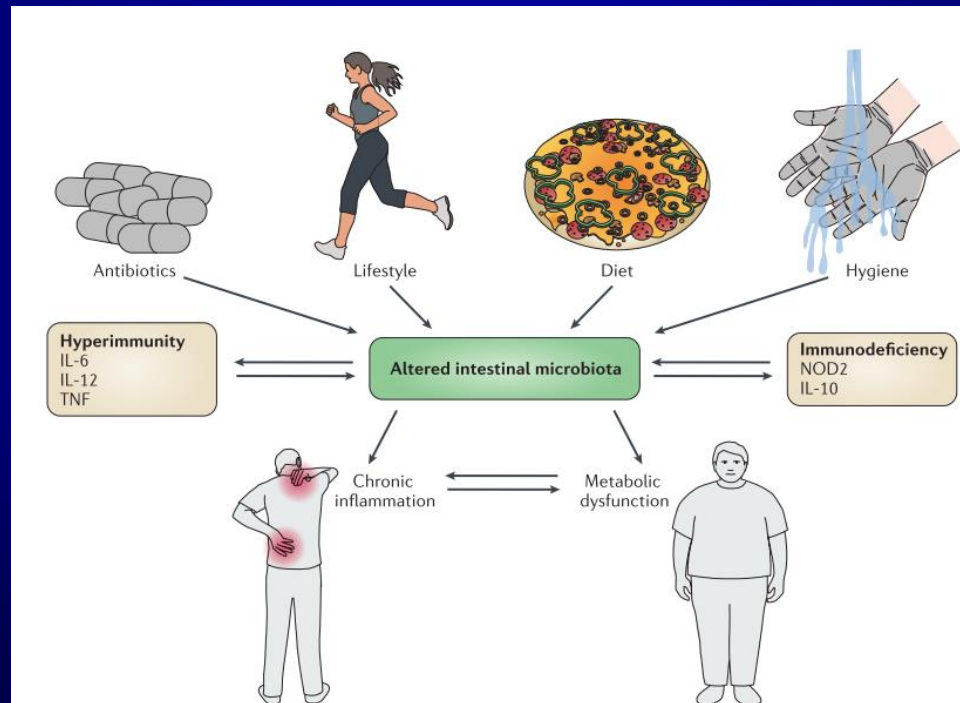


İnsan Mikrobiotası: Farklı Yaş dönemlerinde Değişimler



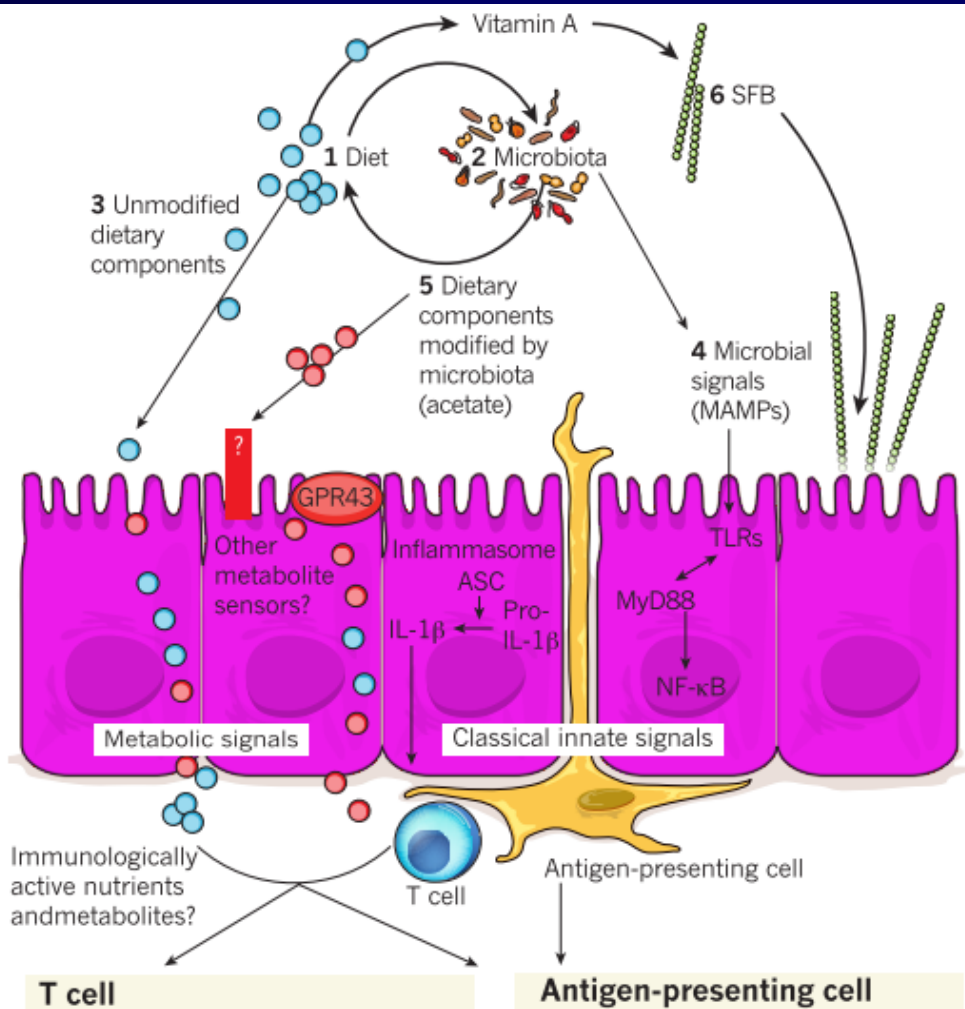
Mikrobiota İçeriğini Etkileyen Faktörler:

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Human nutrition, the gut microbiome and the immune system

Andrew L. Kau¹*, Philip P. Ahern¹*, Nicholas W. Griffin¹, Andrew L. Goodman¹† & Jeffrey I. Gordon¹



T cell

mTOR

Promotes T_H1, T_H2, T_H17 cell differentiation; inhibits T_{reg} cell differentiation

RAR-RXR

Promotes intestinal T-cell homing; promotes T_H2 and T_{reg} cell differentiation

VDR-RXR

Promotes T_{reg} cell differentiation; inhibits T_H1 and T_H17 cell differentiation

AHR

Promotes T_H17 and T_{reg} cell differentiation

LXR and PPAR

Control T-cell differentiation

Antigen-presenting cell

TLRs

Inflammasomes

mTOR

Modulates DC function and differentiation

RAR-RXR and VDR-RXR

AHR

Modulates DC differentiation

PKR

Regulates inflammatory responses

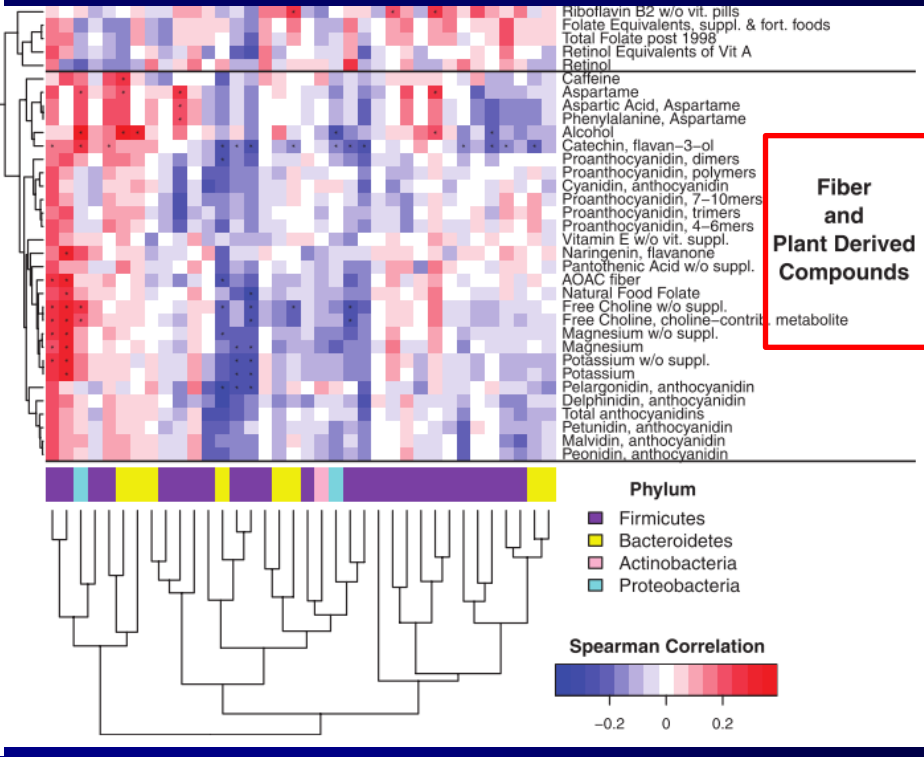
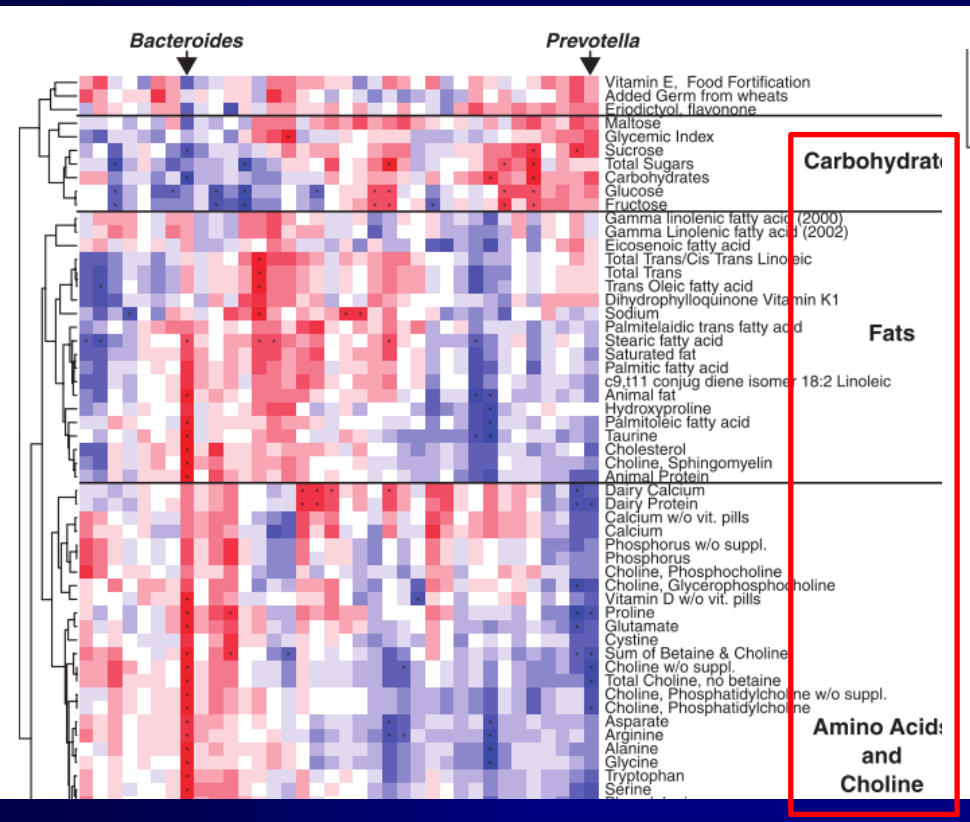
GPR120

Inhibits inflammatory responses in macrophages

Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes

Gary D. Wu,^{1*} Jun Chen,^{2,3} Christian Hoffmann,^{4,5} Kyle Bittinger,⁴ Ying-Yu Chen,¹ Sue A. Keilbaugh,¹ Meenakshi Bewtra,^{1,2} Dan Knights,⁶ William A. Walters,⁷ Rob Knight,^{8,9} Rohini Sinha,⁴ Erin Gilroy,² Kernika Gupta,¹⁰ Robert Baldassano,¹⁰ Lisa Nessel,² Hongzhe Li,^{2,3} Frederic D. Bushman,^{4*} James D. Lewis^{1,2,3*}

Diet strongly affects human health, partly by modulating gut microbiome composition. We used diet inventories and 16S rDNA sequencing to characterize fecal samples from 98 individuals. Fecal communities clustered into enterotypes distinguished primarily by levels of *Bacteroides* and *Prevotella*. Enterotypes were strongly associated with long-term diets, particularly protein and animal fat (*Bacteroides*) versus carbohydrates (*Prevotella*). A controlled-feeding study of 10 subjects showed that microbiome composition changed detectably within 24 hours of initiating a high-fat/low-fiber or low-fat/high-fiber diet, but that enterotype identity remained stable during the 10-day study. Thus, alternative enterotype states are associated with long-term diet.

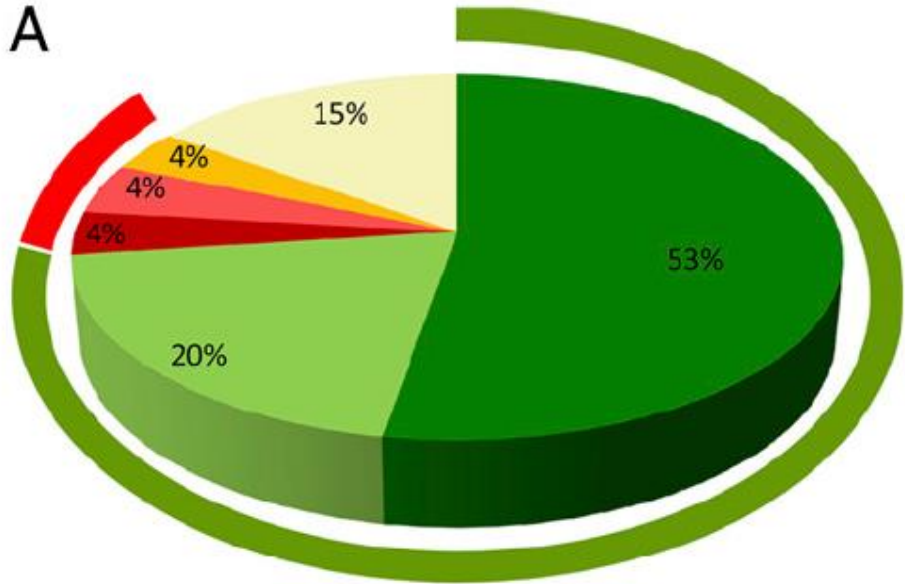


Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

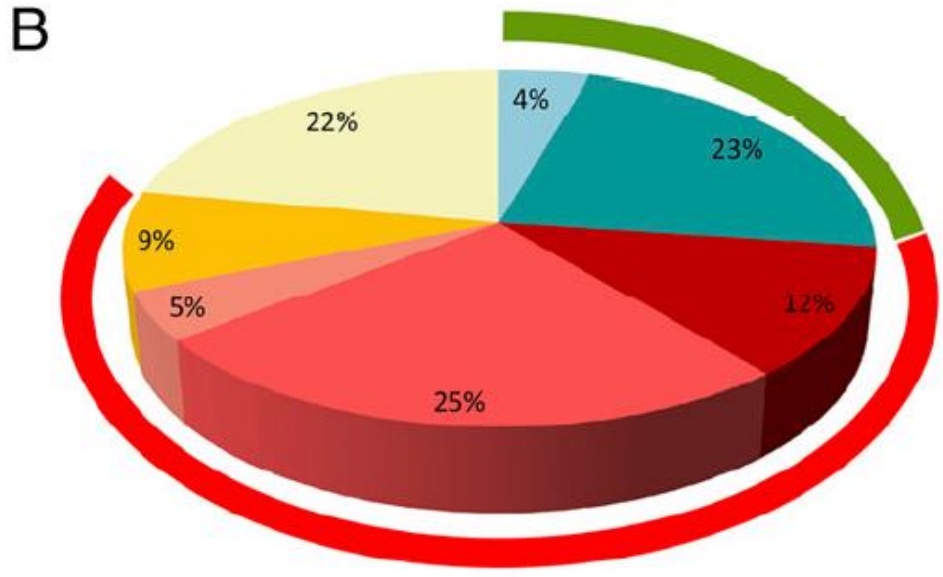
Carlotta De Filippo^a, Duccio Cavalieri^a, Monica Di Paola^b, Matteo Ramazzotti^c, Jean Baptiste Poulet^d, Sebastien Massart^d, Silvia Collini^b, Giuseppe Pieraccini^e, and Paolo Lionetti^{b,1}

Gut microbial composition depends on different dietary habits just as health depends on microbial metabolism, but the association of microbiota with different diets in human populations has not yet been shown. In this work, we compared the fecal microbiota of European children (EU) and that of children from a rural African village of Burkina Faso (BF), where the diet, high in fiber content, is similar to that of early human settlements at the time of the birth of agriculture. By using high-throughput 16S rDNA sequencing and biochemical analyses, we found significant differences in gut microbiota between the two groups. BF children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes ($P < 0.001$), with a unique abundance of bacteria from the genus *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis, completely lacking in the EU children. In addition, we found significantly more short-chain fatty acids ($P < 0.001$) in BF than in EU children. Also, *Enterobacteriaceae* (*Shigella* and *Escherichia*) were significantly underrepresented in BF than in EU children ($P < 0.05$). We hypothesize that gut microbiota coevolved with the polysaccharide-rich diet of BF individuals, allowing them to maximize energy intake from fibers while also protecting them from inflammations and noninfectious colonic diseases. This study investigates and compares human intestinal microbiota from children characterized by a modern western diet and a rural diet, indicating the importance of preserving this treasure of microbial diversity from ancient rural communities worldwide.





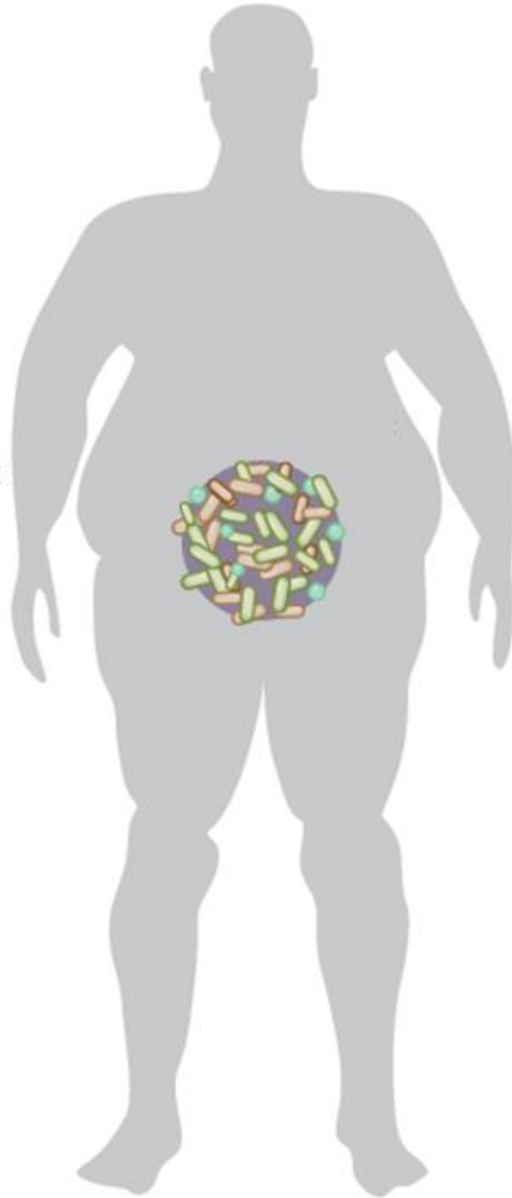
- BF**
- Prevotella } Bacteroidetes
 - Xylanibacter }
 - Acetitomaculum } Firmicutes
 - Faecalibacterium }
 - Subdoligranulum }
 - Others



- EU**
- Alistipes } Bacteroidetes
 - Bacteroides }
 - Acetitomaculum } Firmicutes
 - Faecalibacterium }
 - Roseburia }
 - Subdoligranulum }
 - Others

Barsak mikrobiyotası

- Değişmiş içerik
- Değişmiş fermentasyon
- Artmış enerji hasadı

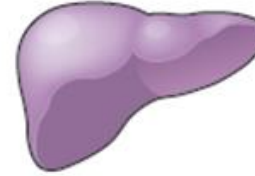


Beyin



↓ Tokluk duygusu

Karaciğer



↑ Kısa zincirli yağ asitleri
↑ İnflamasyon

Yağ dokusu



↑ Trigliserit katılımı
↑ İnflamasyon

Kas



↓ Yağ asidi oksidasyonu

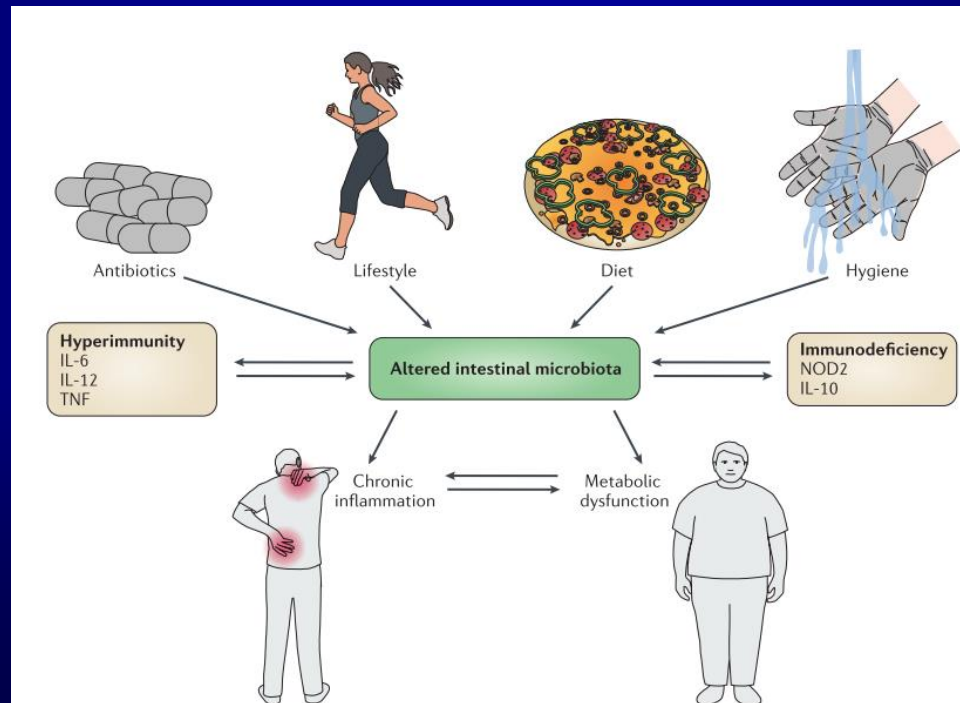
Epitel



↑ Epitel permeabilitesi
↓ L hücrelerden PYY/GLP-1

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Differences in Fecal Microbiota in Different European Study Populations in Relation to Age, Gender, and Country: a Cross-Sectional Study

Susanne Mueller,^{1†} Katiana Saunier,^{2†} Christiana Hanisch,³ Elisabeth Norin,⁴ Livia Alm,⁴ Tore Midtvedt,⁴ Alberto Cresci,⁵ Stefania Silvi,⁵ Carla Orpianesi,⁵ Maria Cristina Verdenelli,⁵ Thomas Clavel,^{1,2} Corinna Koebnick,³ Hans-Joachim Franz Zunft,³ Joël Doré,² and Michael Blaut^{1*}

A cross-sectional study on intestinal microbiota composition was performed on 230 healthy subjects at four European locations in France, Germany, Italy, and Sweden. The study participants were assigned to two age groups: 20 to 50 years (mean age, 35 years; $n = 85$) and >60 years (mean age, 75 years; $n = 145$). A set of 14 group- and species-specific 16S rRNA-targeted oligonucleotide probes was applied to the analysis of fecal samples by fluorescence in situ hybridization coupled with flow cytometry. Marked country-age interactions were observed for the German and Italian study groups. These interactions were inverse for the predominant bacterial groups *Eubacterium rectale*-*Clostridium coccoides* and *Bacteroides-Prevotella*. Differences between European populations were observed for the *Bifidobacterium* group only. Proportions of bifidobacteria were two- to threefold higher in the Italian study population than in any other study group, and this effect was independent of age. Higher proportions of enterobacteria were found in all elderly volunteers independent of the location. Gender effects were observed for the *Bacteroides-Prevotella* group, with higher levels in males than in females. In summary, age-related differences in the microbiota makeup were detected but differed between the study populations from the four countries, each showing a characteristic colonization pattern.

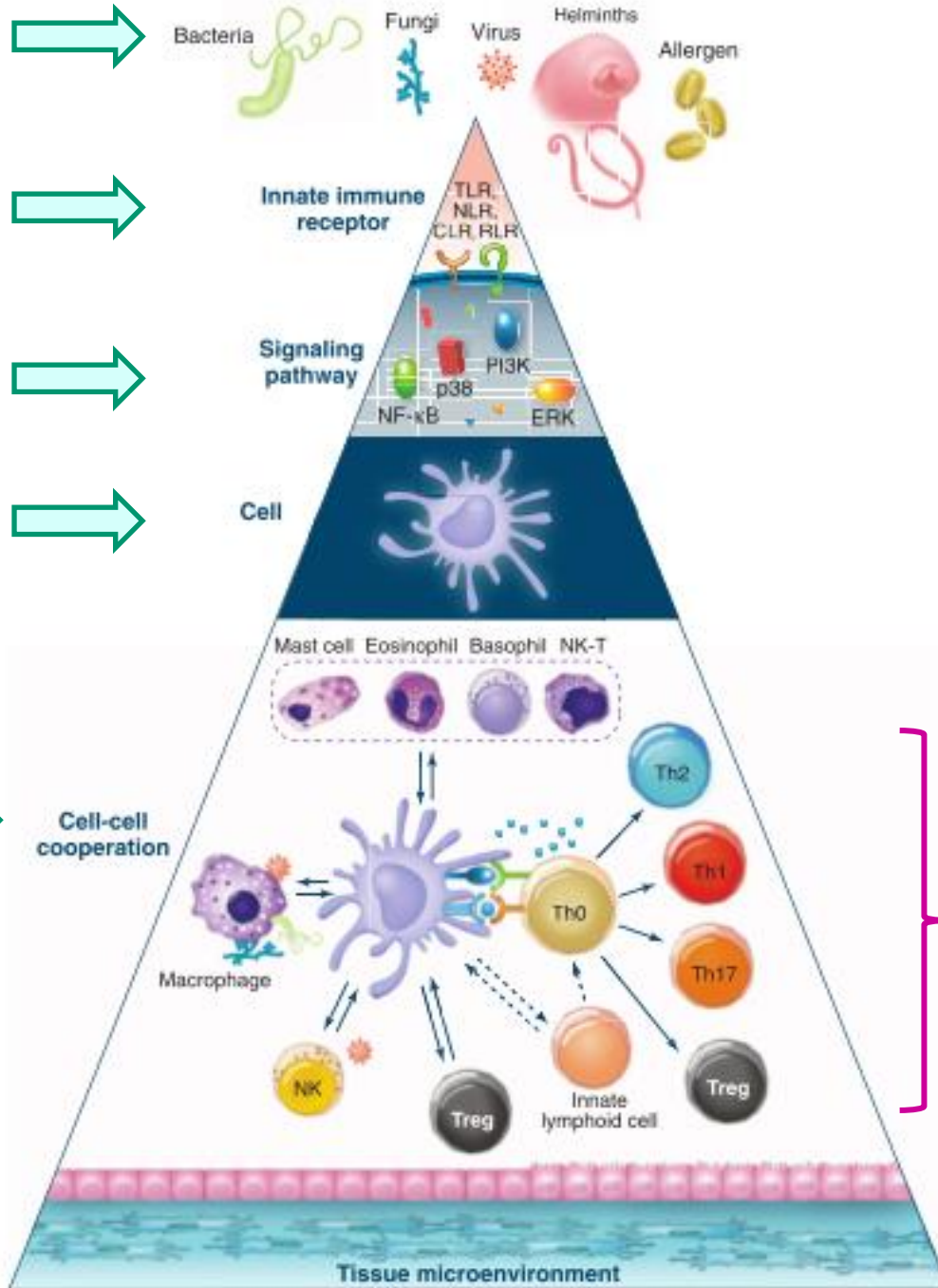
Yabancı Mikroorganizma

Reseptör

Sinyal iletisi

Doğal Bağışıklık Hücresi

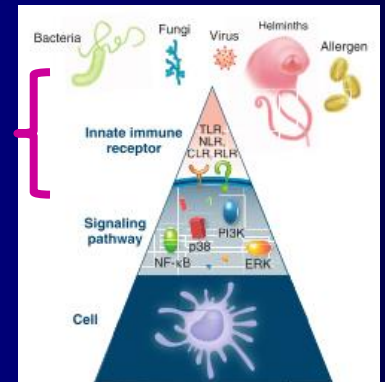
Hücreler arası ilişki



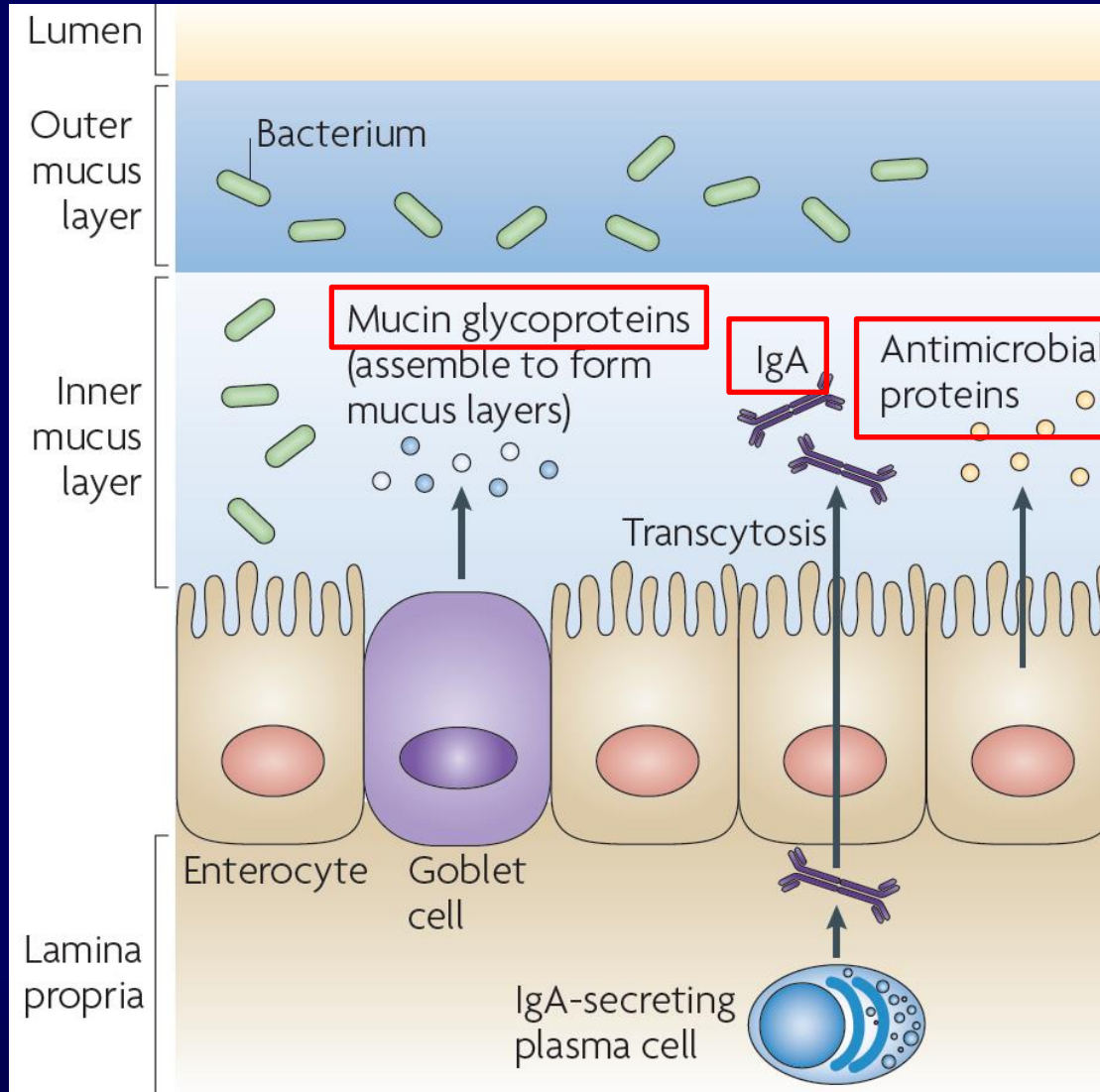
Naif CD4⁺ T hücrelerinin Farklılaşması



Tanima



Bakteri-Epitel Hücre Direkt Temasını Sınırlayan/Engelleyen Yapılar



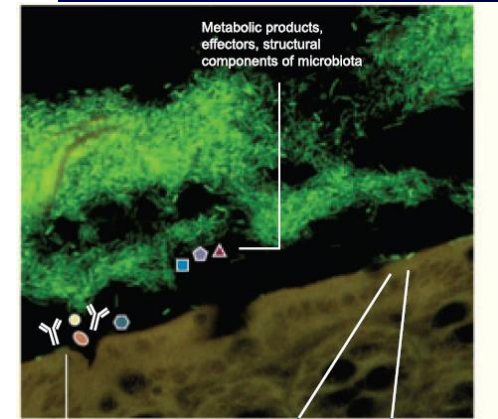
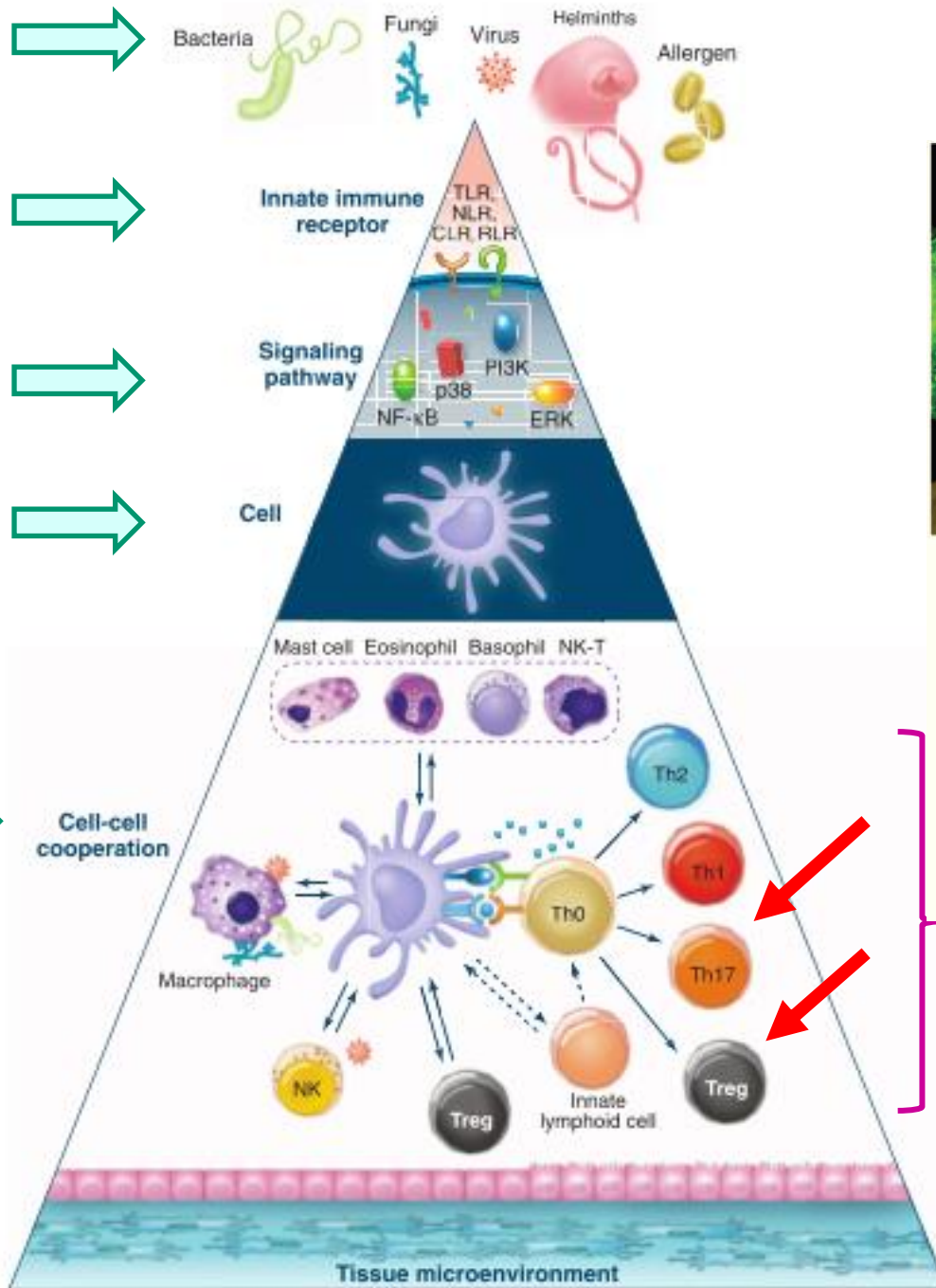
Yabancı Mikroorganizma

Reseptör

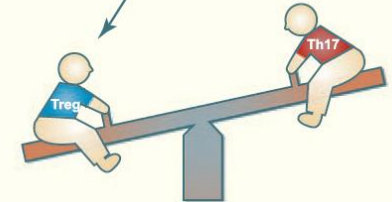
Sinyal iletisi

Doğal Bağışıklık Hücresi

Hücreler arası ilişki



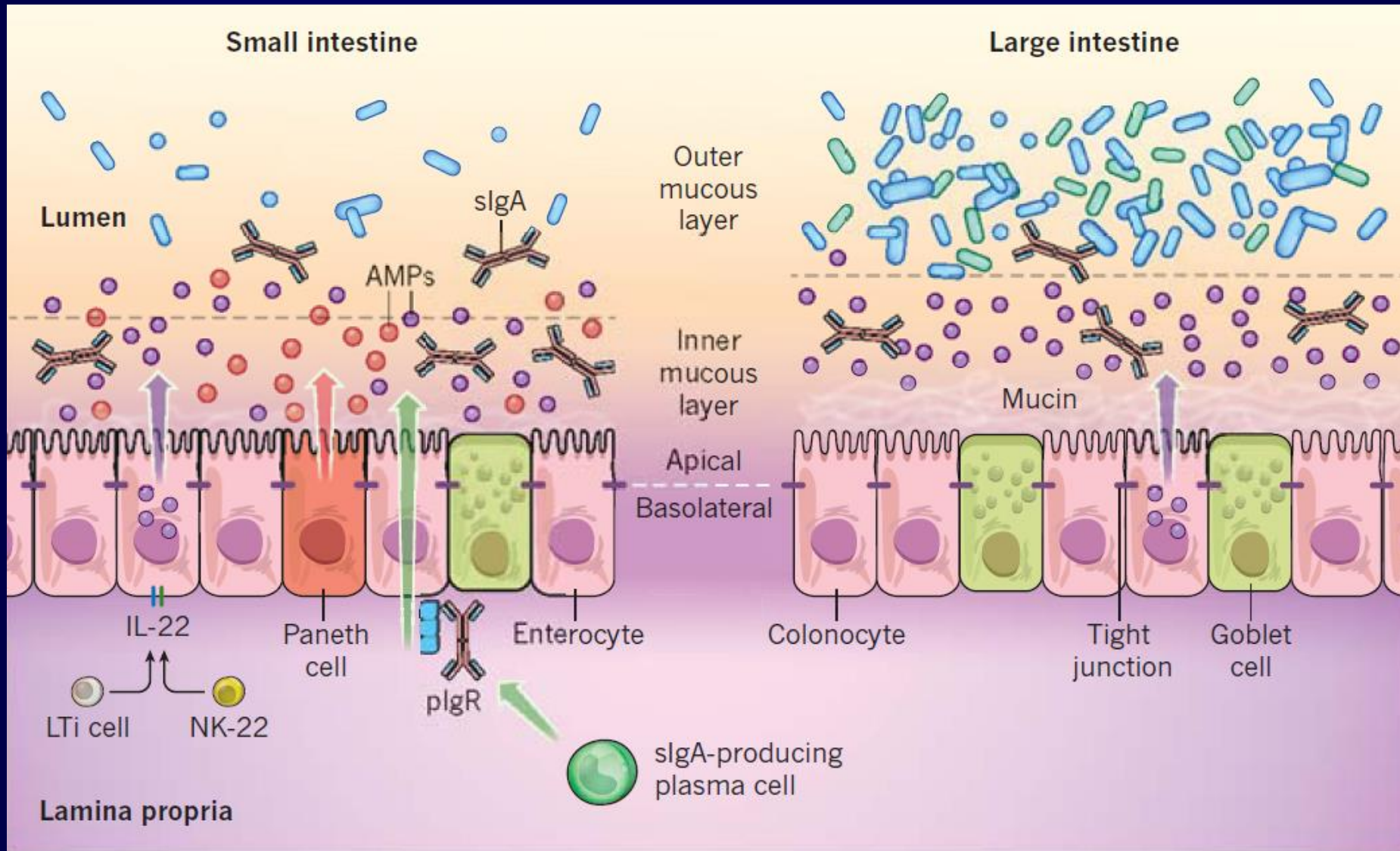
Anti-microbial effectors; IgA



Immunol Rev 2012;245: 7

Science 2012;337: 431
Science 2012;337: 431

Barsak Epitel tabakasının Bariyer İşlevi



Healthy Microbiota

Depleted Microbiota

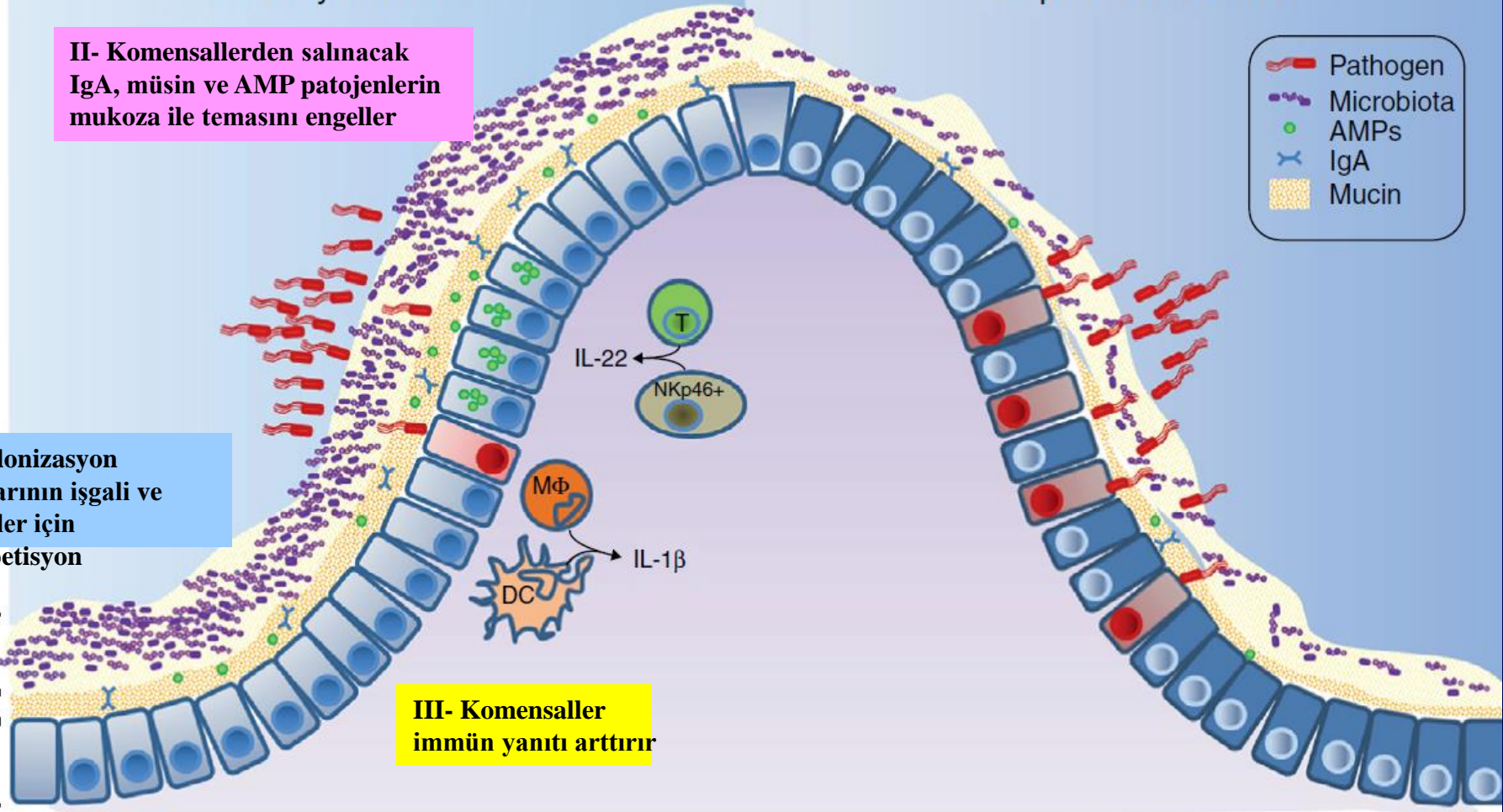
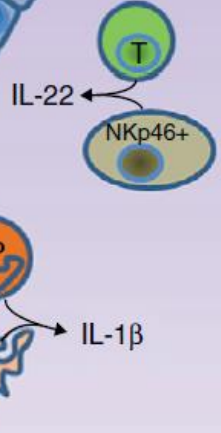
II- Komensallerden salınacak IgA, müsin ve AMP patojenlerin mukoza ile temasını engeller

- Pathogen
- Microbiota
- AMPs
- IgA
- Mucin

I- Kolonizasyon alanlarının işgali ve besinler için kompetisyon

III- Komensaller immün yanıtı arttırır

I
II
III





1850

2010

Her dört bebekte
Birisi ölüyor

Bir yaşından önce
1000'de 6



1850

2010

Her dört bebekte
Birisi ölüyor

Bir yaşından önce
1000'de 6

1990

2010

Obez oranı %12

Obez oranı %30

Dünya genelinde 1.5 milyar insan kilolu, 200 milyon erkek ve 300 milyon kadın obez





Tip I DM, her 20
yilda yeni sayısı iki
katına çıkmakta,



Tip I DM, her 20
yilda yeni sayısı iki
katına çıkmakta,

Finlandiya'da 1950
- 2010,
İnsidansda %550
artış

Tip I DM, her 20
yılıda yeni sayısı iki
katına çıkmakta,

Finlandiya'da 1950
- 2010,
İnsidansda %550
artış

1990

2010

Ortalama yaş
9

Ortalama yaş
64

64



Amerika Birleşik
Devletleri'nde
astım



Amerika Birleşik
Devletleri'nde
astım

2001'de 14 çocukta
1,
2009'da 12 çocukta
1

Amerika Birleşik Devletleri'nde astım

2001'de 14 çocukta
1,
2009'da 12 çocukta
1

1900

1990

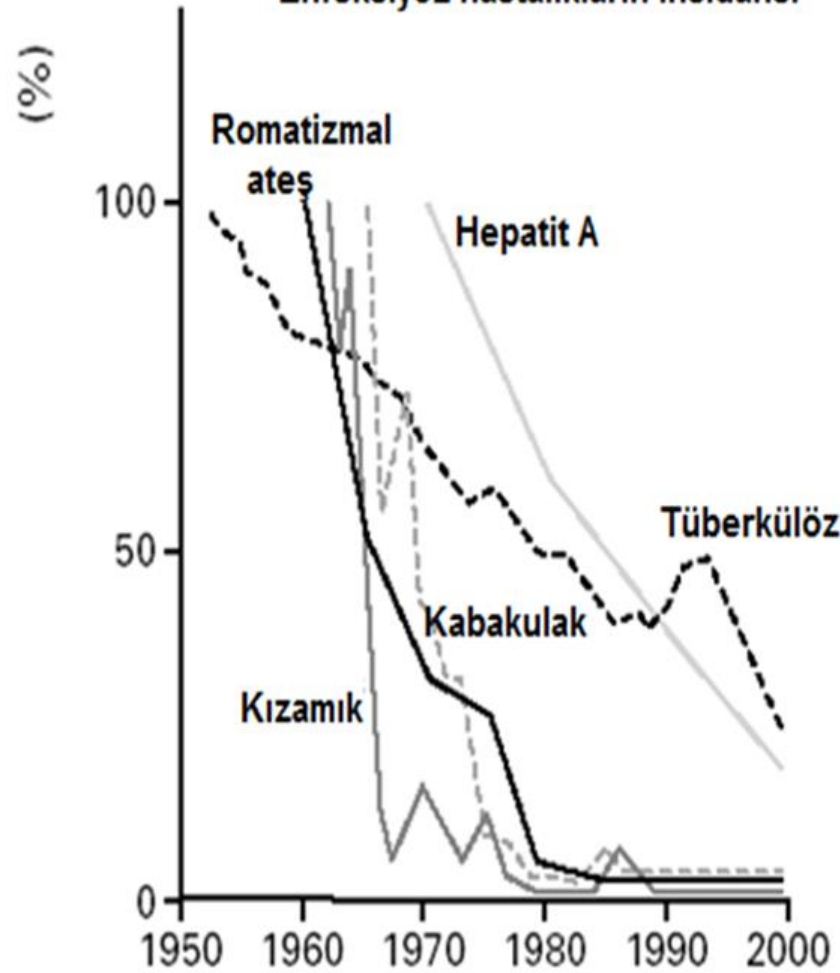
2010

Gıda allerjileri
Egzema

İnflamatuvar barsak hastalıkları

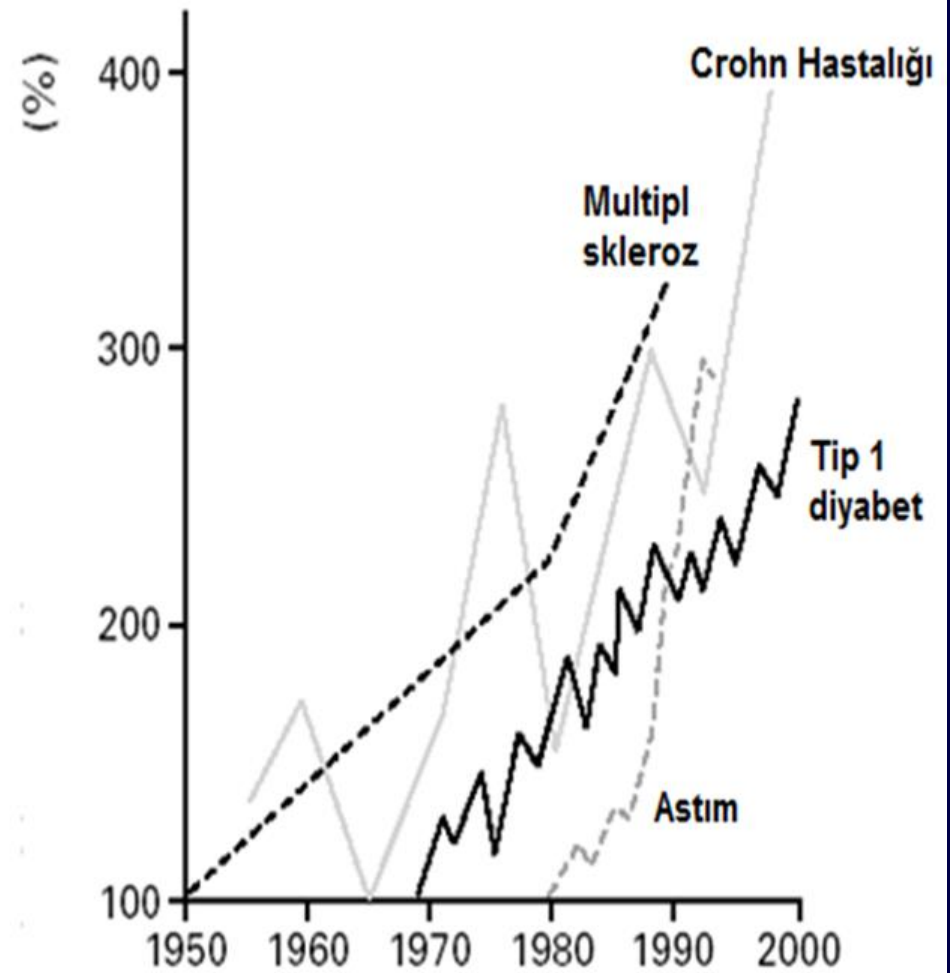
A

Enfeksiyöz hastalıkların insidansı



B

İmmün hastalıkların insidansı



Clinical Microbiology

N E W S L E T T E R

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Vol. 35, No. 20

October 15, 2013

www.cmnewsletter.com

The Oral Microbiome: Its Role in Health and in Oral and Systemic Infections

*Frank A. Scannapieco, D.M.D., Ph.D., Professor and Chair, Department of Oral Biology, School of Dental
Medicine, University at Buffalo, State University of New York, Foster Hall, Buffalo, New York*

Pristine Gingiva



Early Gingivitis



Established Gingivitis



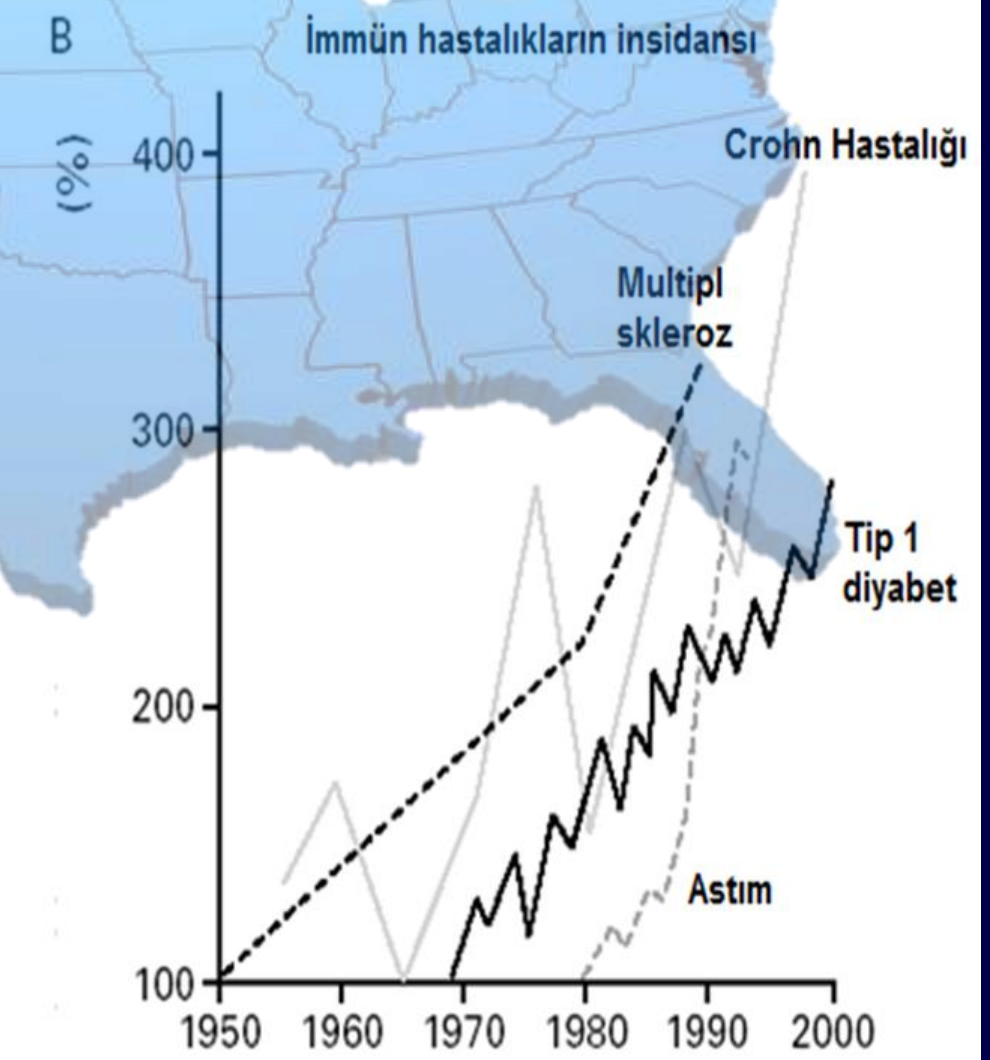
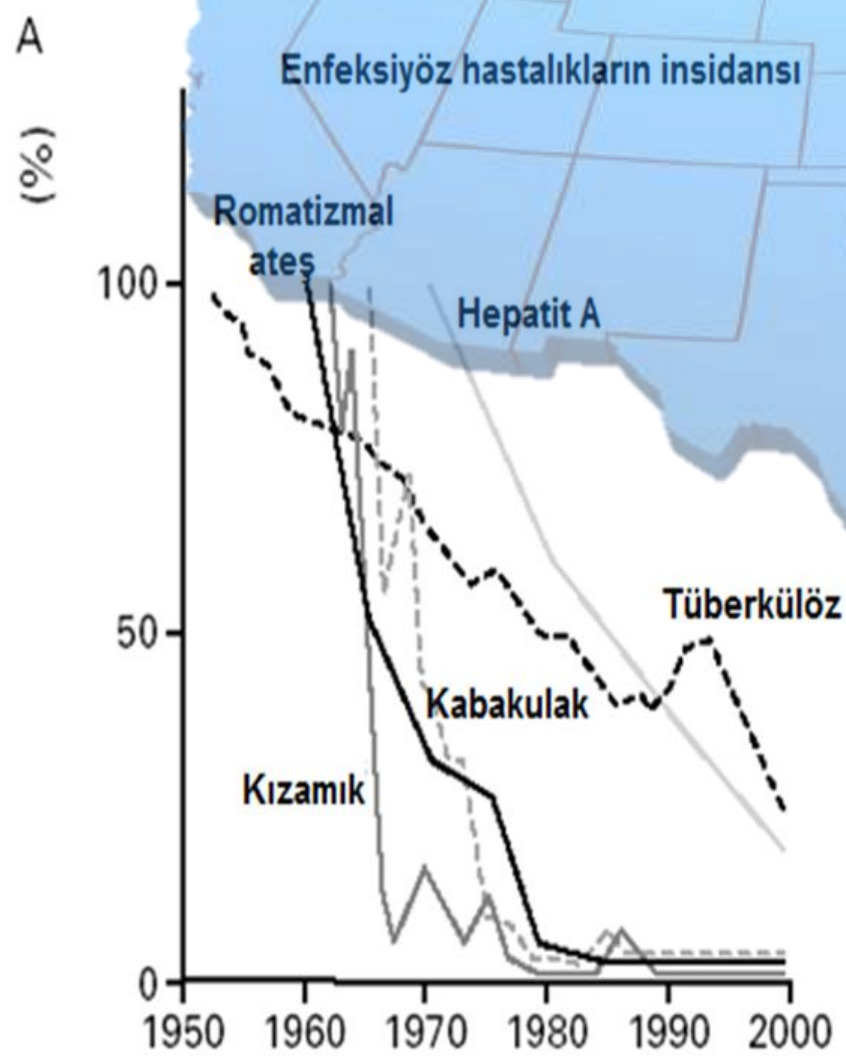
Periodontitis



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Health and

*Oral Biology, School of Dental
Buffalo, New York*





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International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl



Chorda tympani nerve function in children: Relationship to otitis media and body mass index[☆]

Raewyn M. Seaberg^{a,*}, Neil K. Chadha^b, Bradley J. Hubbard^a, Karen A. Gordon^a, Brooke A. Allemang^a,
Brittany J. Harrison^a, Blake C. Papsin^a

^a Department of Otolaryngology – Head and Neck Surgery, Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

^b Division of Pediatric Otolaryngology, BC Children's Hospital, University of British Columbia, Vancouver, Canada



Changes in Taste Function Related to Obesity and Chronic Otitis Media With Effusion

Il Ho Shin, MD; Dong Choon Park, MD; Chul Kwon, MD; Seung Geun Yeo, MD, PhD

Objective: To evaluate changes in taste threshold in patients with chronic otitis media with effusion (COME) and their relationship with body mass index. A relationship has been suggested between pediatric obesity and COME, and we hypothesized that changes in taste function may occur in children with COME and that such changes may be associated with changes in body weight.

Design: A prospective, nonrandomized, case-control study.

Setting: A university tertiary care center.

Subjects: The experimental group comprised 42 children with COME who underwent tympanostomy tube insertion, and the control group, 42 children without otitis media with effusion. Patients were enrolled between September 2007 and August 2009.

Main Outcome Measure: Taste threshold was measured by electrogustometry, and 4 standard taste solutions (sucrose, sodium chloride, citric acid, and quinine hydrochloride) were used in chemical taste tests.

Results: Body mass index was significantly higher in the COME than in the control group ($P=.02$). Electrogustometry showed that the anterior part of the tongue had a significantly higher taste threshold in the COME than in the control group (anterior right, $P=.03$; anterior left, $P=.04$), and chemical taste test results showed that sweet and salty tastes were significantly lower in the COME group (sweet, $P=.02$; salty, $P=.04$).

Conclusion: These results showed that COME can cause changes in taste and that these changes may be related to pediatric obesity.

Arch Otolaryngol Head Neck Surg. 2011;137(3):242-246

Relationship Between Pediatric Obesity and Otitis Media With Effusion

Jong Bin Kim, MD; Dong Choon Park, MD, PhD; Chang Il Cha, MD, PhD; Seung Geun Yeo, MD, PhD

Objective: To investigate the relationship between pediatric otitis media with effusion and obesity, as determined by body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) and serum triglyceride (TG) and total cholesterol (TC) concentrations.

Design: A prospective, nonrandomized, case-control study.

Setting: University-affiliated hospital.

Subjects: The experimental group comprised 155 children aged 2 to 7 years, who received unilateral or bilateral ventilation tube insertion for the treatment of otitis media with effusion. The control group comprised 118 children with no history of otitis media with effusion, who underwent operations for conditions other than ear diseases. Based on BMI and serum TG and TC concentrations, we divided the experimental group into 2 subgroups, those who were and were not obese.

Main Outcome Measures: We determined the difference between the experimental and control groups in BMI and serum TG and TC concentrations and the difference between the obese and nonobese subgroups in frequency of ventilation tube insertion.

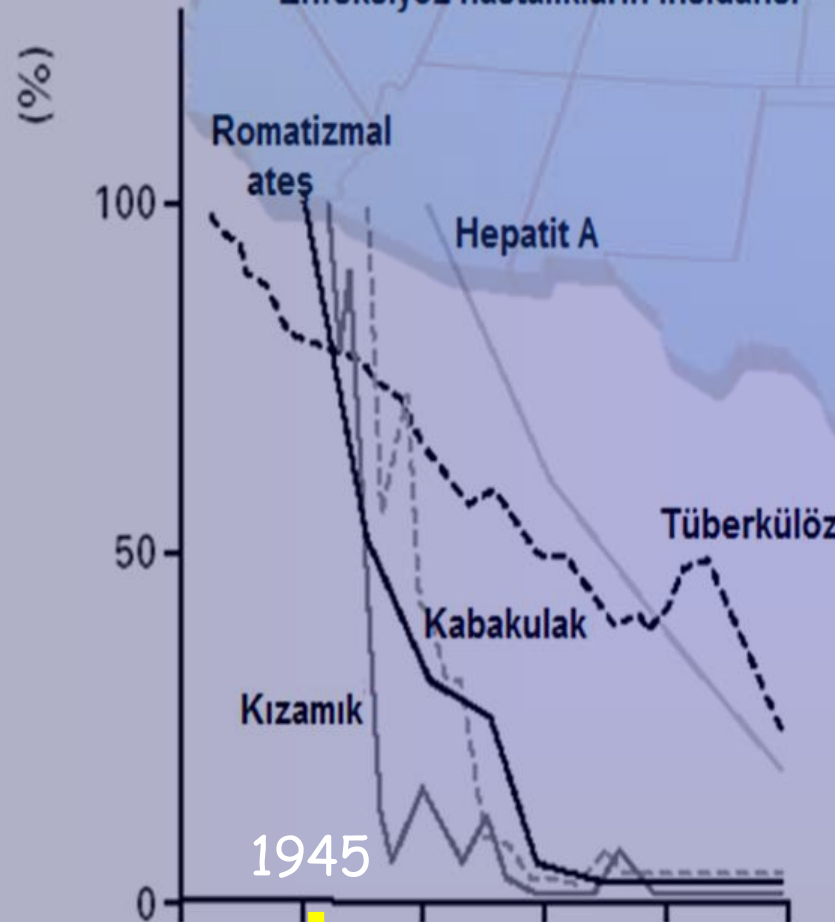
Results: Mean \pm SD BMI (22.0 ± 3.4 vs 16.3 ± 2.4) ($P=.01$) and mean \pm SD TC level (195.0 ± 31.0 mg/dL vs 159.3 ± 26.9 mg/dL [5.05 ± 0.80 mmol/L vs 4.13 ± 0.70 mmol/L]) ($P=.04$), but not mean serum TG level (109.4 ± 40.4 mg/dL vs 90.0 ± 52.3 mg/dL [1.24 ± 0.46 mmol/L vs 1.02 ± 0.59 mmol/L]) ($P=.13$), were significantly higher in the experimental group than in the control group. Frequency of ventilation tube insertion, however, did not differ significantly between the obese and nonobese subgroups, whether divided by BMI ($P=.10$) or serum TG ($P=.12$) or TC ($P=.07$) concentration.

Conclusion: Childhood obesity may be associated with the occurrence of otitis media with effusion.

Arch Otolaryngol Head Neck Surg. 2007;133:379-382

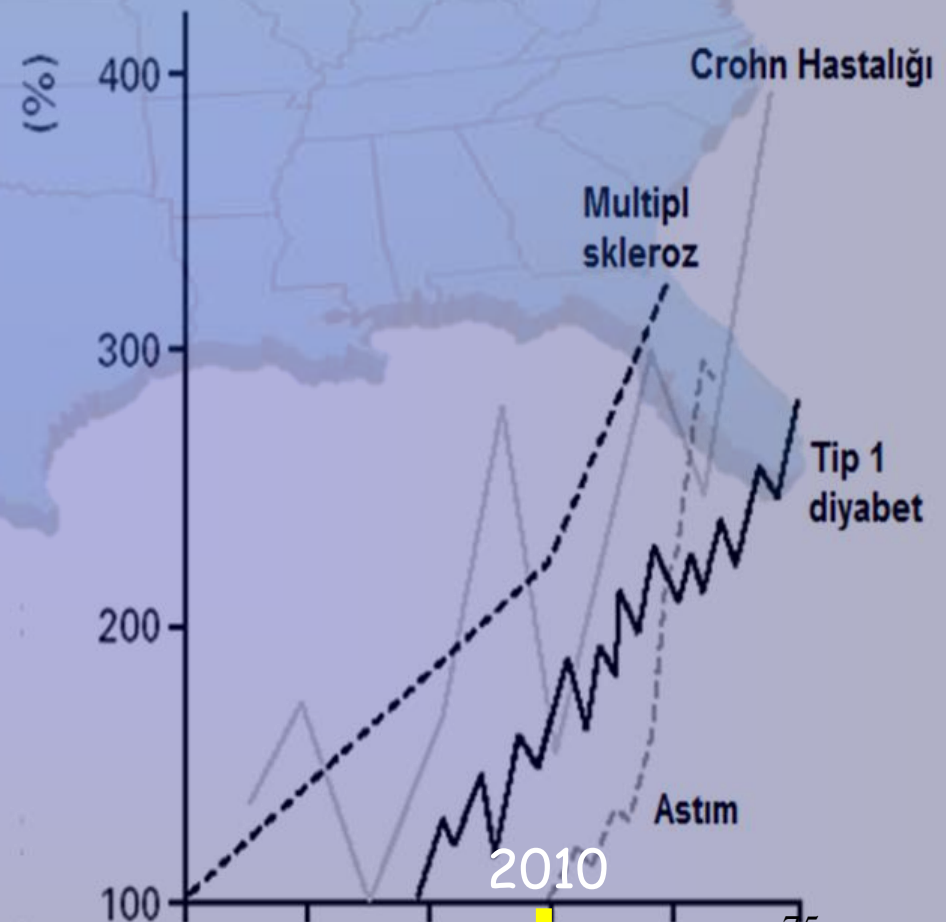
A

Enfeksiyöz hastalıkların insidansı



B

İmmün hastalıkların insidansı



64 hasta penisilin ile
Tedavi edildi

250 milyon antibiyotik kürü

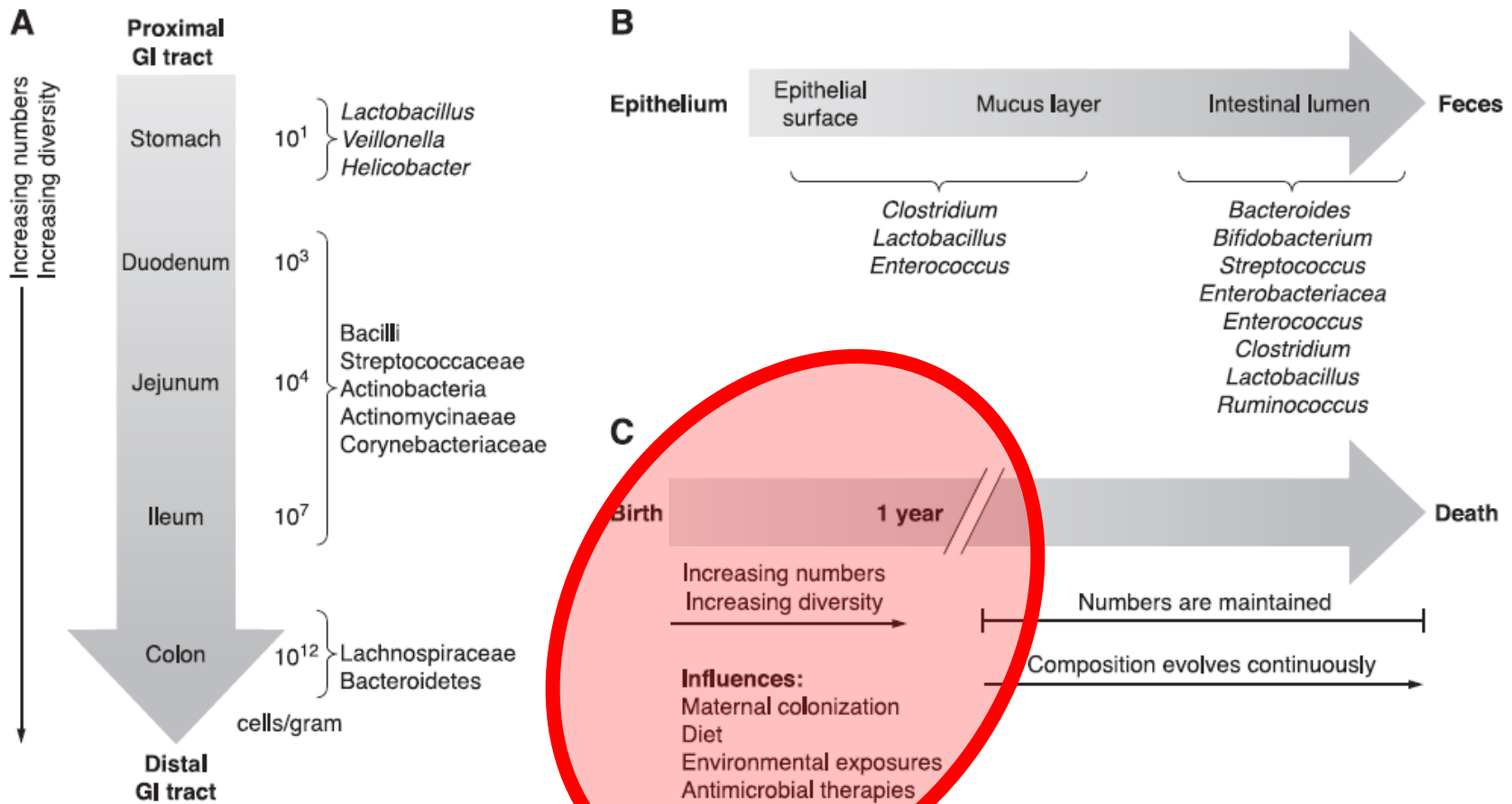


FIG. 2. Spatial and temporal aspects of intestinal microbiota composition. *A*: variations in microbial numbers and composition across the length of the gastrointestinal tract. *B*: longitudinal variations in microbial composition in the intestine. *C*: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition.

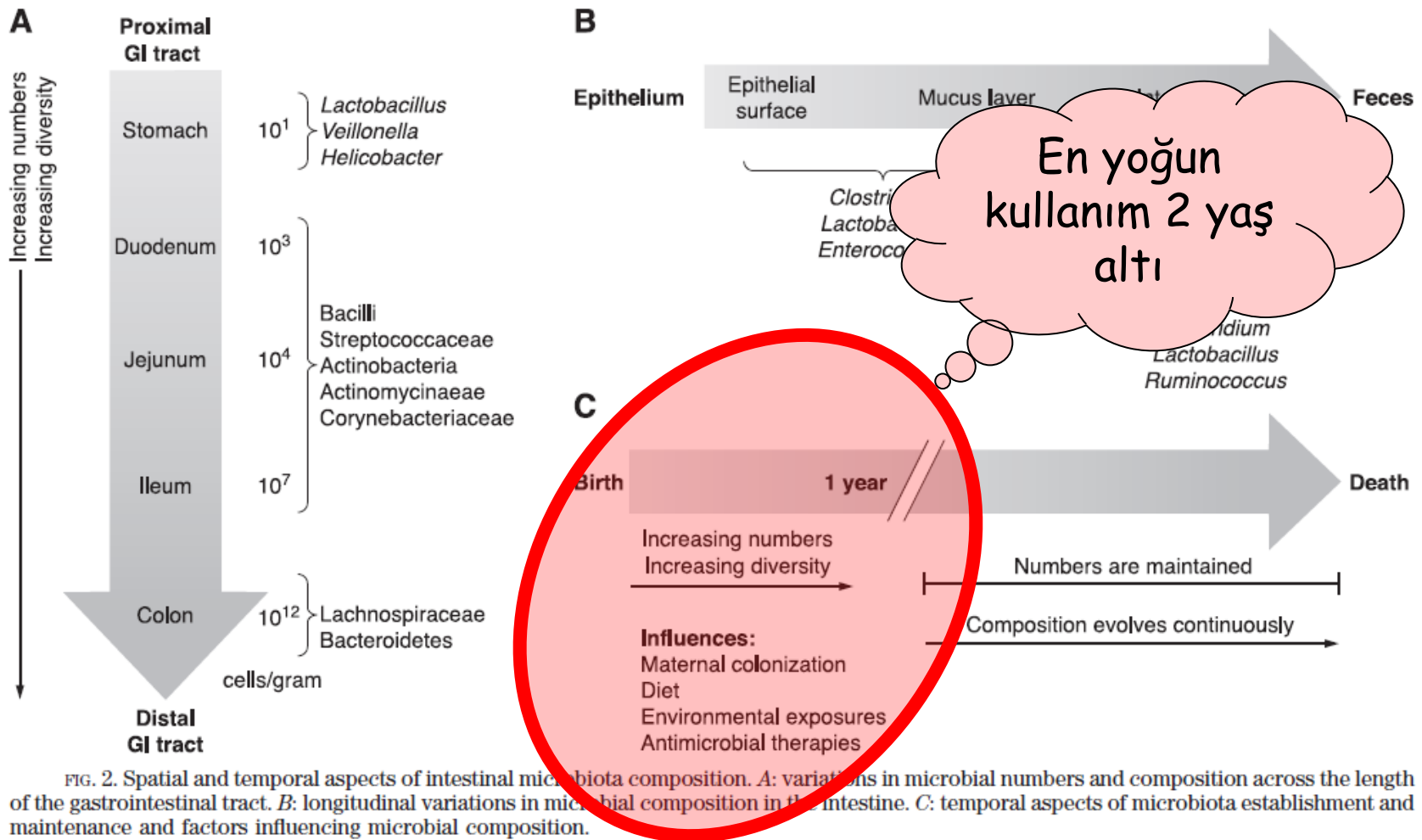


FIG. 2. Spatial and temporal aspects of intestinal microbiota composition. *A*: variations in microbial numbers and composition across the length of the gastrointestinal tract. *B*: longitudinal variations in microbial composition in the intestine. *C*: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition.

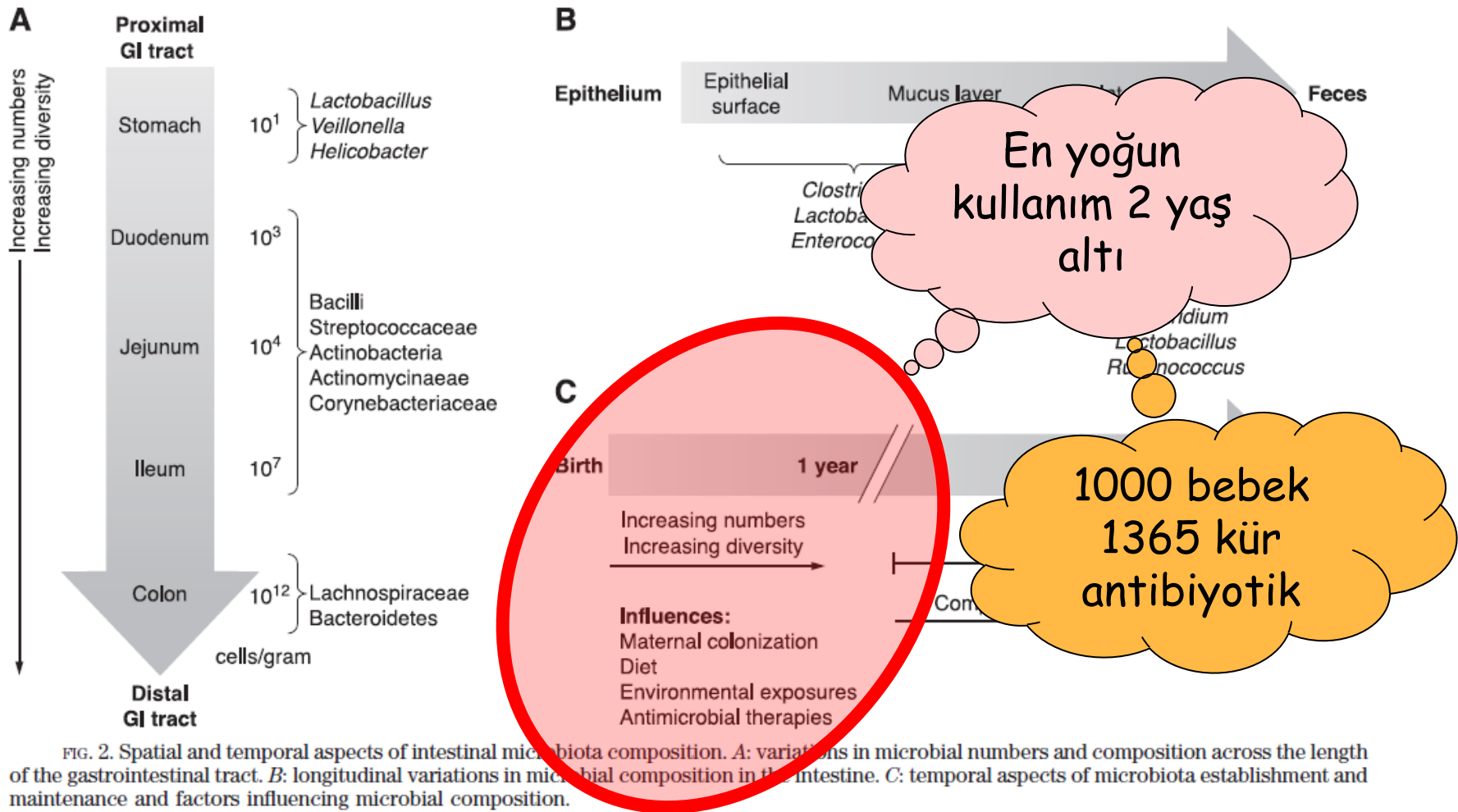


FIG. 2. Spatial and temporal aspects of intestinal microbiota composition. *A*: variations in microbial numbers and composition across the length of the gastrointestinal tract. *B*: longitudinal variations in microbial composition in the intestine. *C*: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition.

DIBNER AND RICHARDS

TABLE 1. Trends in the Therapeutic use of antimicrobial compounds¹ in food animals in Denmark (WHO, 2000)

Compound	1994	1996	1998	2000	2002	2004	2006
Tetracyclines	36,500	12,900	12,100	12,100	12,100	12,100	12,100
Penicillins, β -lactamase sensitive	9,400	7,200	14,300	14,300	14,300	14,300	14,300
Other penicillins, cephalosporins	4,400	5,800	6,700	6,700	6,700	6,700	6,700
Sulfonamides and trimethoprim	9,500	4,800	7,700	7,700	7,700	7,700	7,700
Sulfonamides	5,600	2,100	1,000	1,000	1,000	1,000	1,000
Macrolides, lincosamides, tiamulin	11,400	7,600	7,100	8,700	15,600	19,900	21,200
Aminoglycosides	8,600	7,100	7,800	7,500	10,400	10,400	10,400
Others	1,000	1,000	650	350	350	350	350
Total	61,900	61,900	61,900	61,900	61,900	61,900	61,900

1950'li yıllarda ilk kullanım

Aralık 2008, Amerikan Kongresi tarafından ret ediliyor

%5 -%10 -%15 ekstra kilo kazanımı

Amerika Birleşik Devletleri'nde kullanılan antibiyotiklerin %70-80'ı

BUILD ONE-TUBE ALL-WAVE RECEIVER

POPULAR ELECTRONICS

JANUARY
1963

35
CENTS

Transistor Testing Explained

Small Fry Stereo

RF Flash Gun Goes A.C.

Rewire to Instant Sound

Variable Bench Supply

Use Dynamic Earpieces

The AMVER Story

CB, Hi-Fi, SWL and

Ham Radio Reports

PLUS:
Science Fair Project
(see page 51)



Normal beslenme



Germ free



Germ free + Antibiyotik



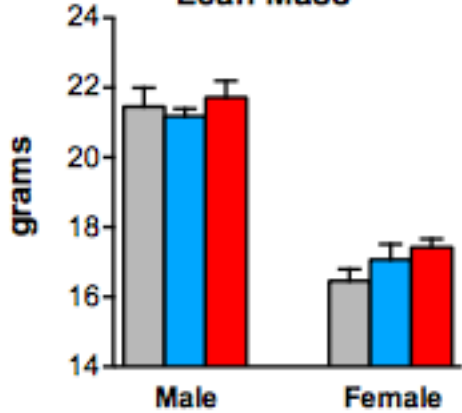
Antibiyotik



Age (weeks)

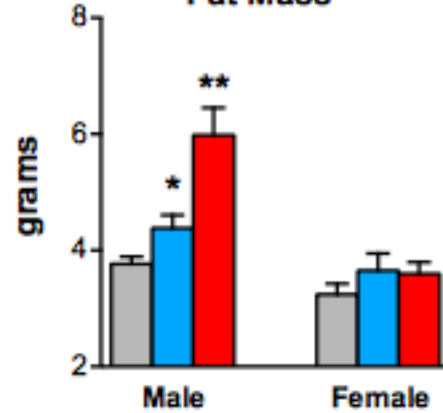
E

Lean Mass



F

Fat Mass



Normal beslenme



Yüksek kalorili yağlı beslenme



Yüksek kalorili yağlı + Antibiyotik



Antibiyotik



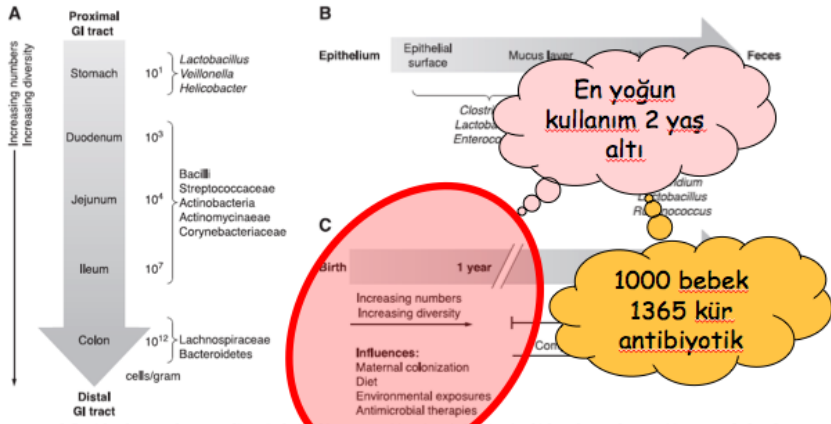


FIG. 2. Spatial and temporal aspects of intestinal microbiota composition. A: variations in microbial numbers and composition across the length of the gastrointestinal tract. B: longitudinal variations in microbial composition in the intestine. C: temporal aspects of microbiota establishment and maintenance and factors influencing microbial composition.

4 hafta

12 - 20 hafta

Normal beslenme



Normal beslenme



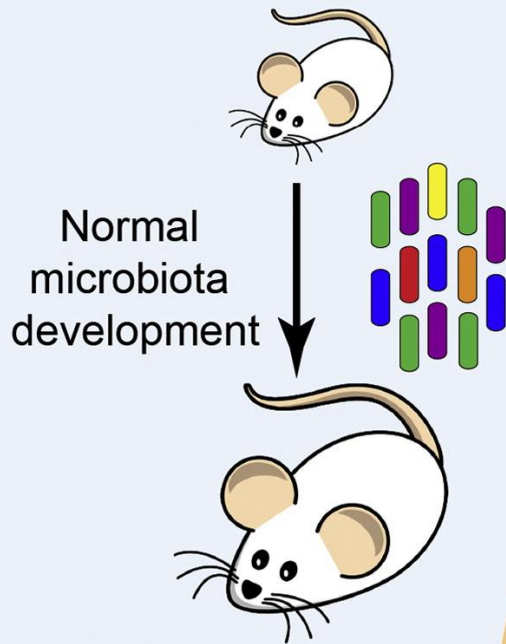
Antibiyotik



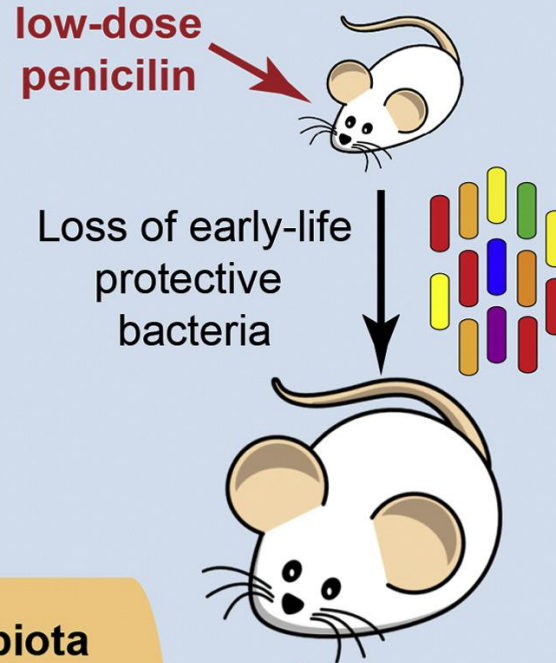
Antibiyotik



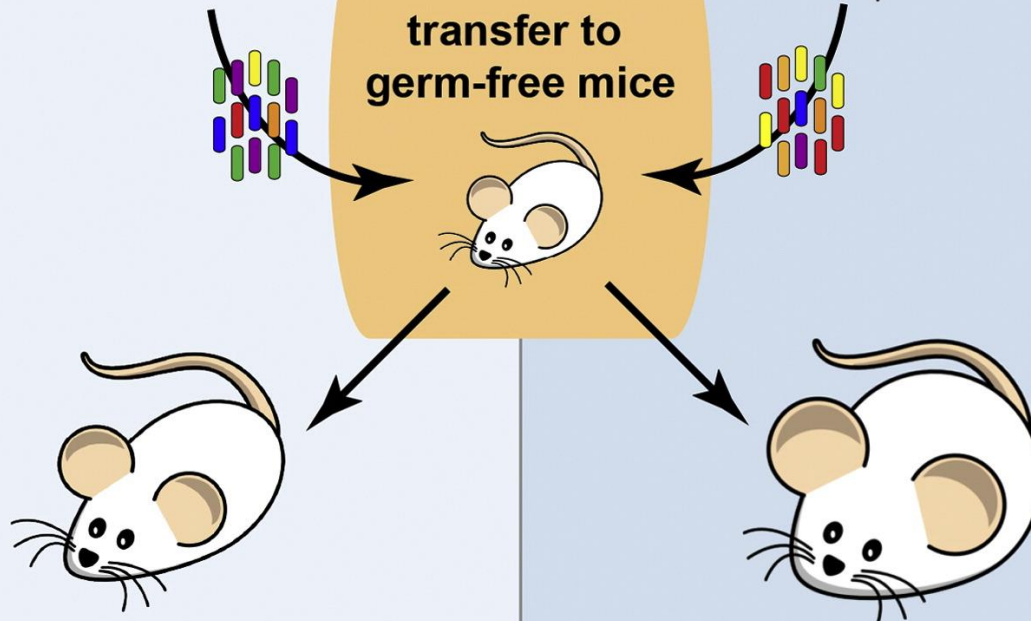
Control



Disrupted microbiota



Microbiota transfer to germ-free mice



Low-Dose Penicillin Exposure

Control



Normal microbiota



After weaning



Mother exposed and throughout weaning



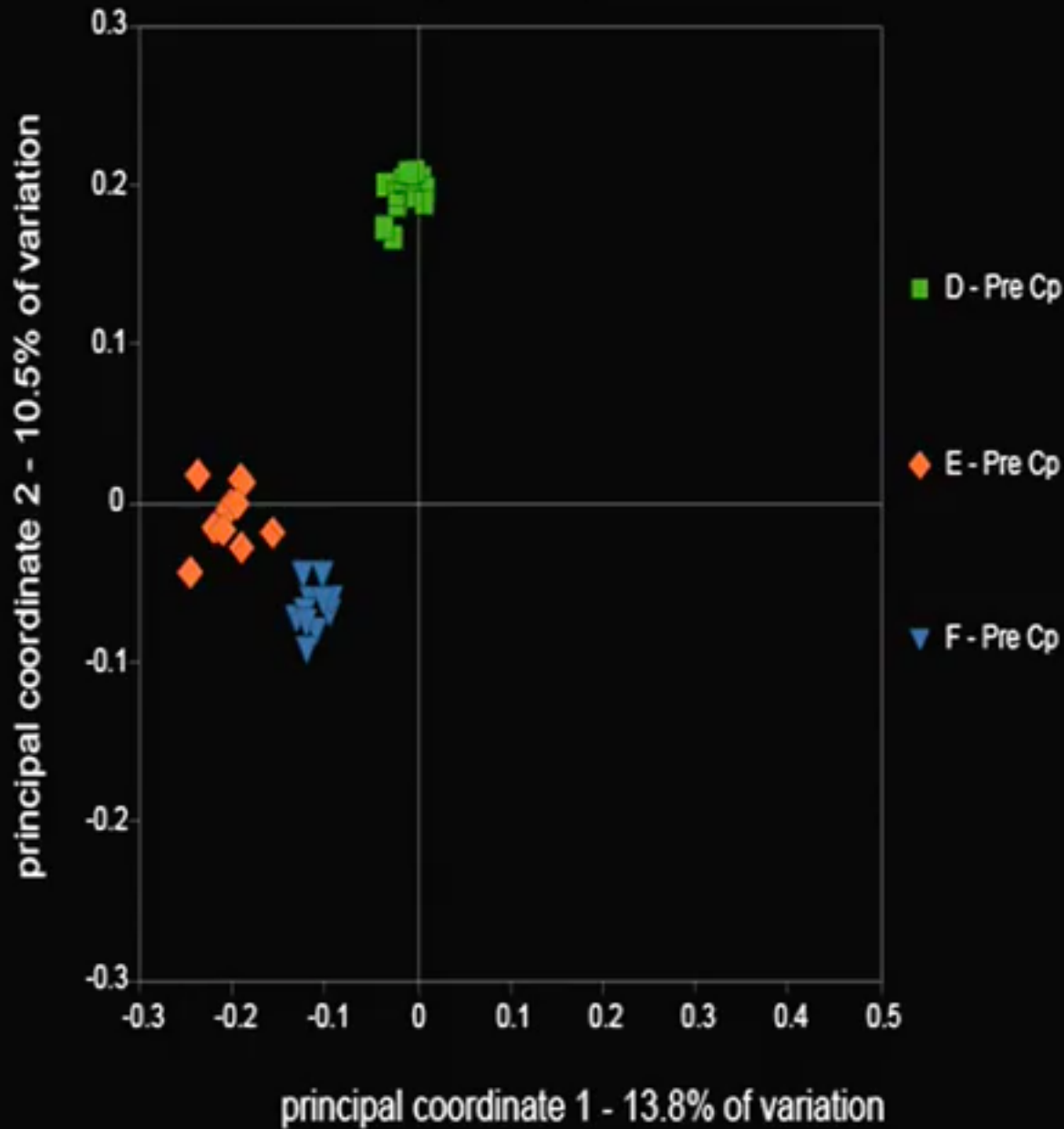
Microbiota transfer to germ-free mice



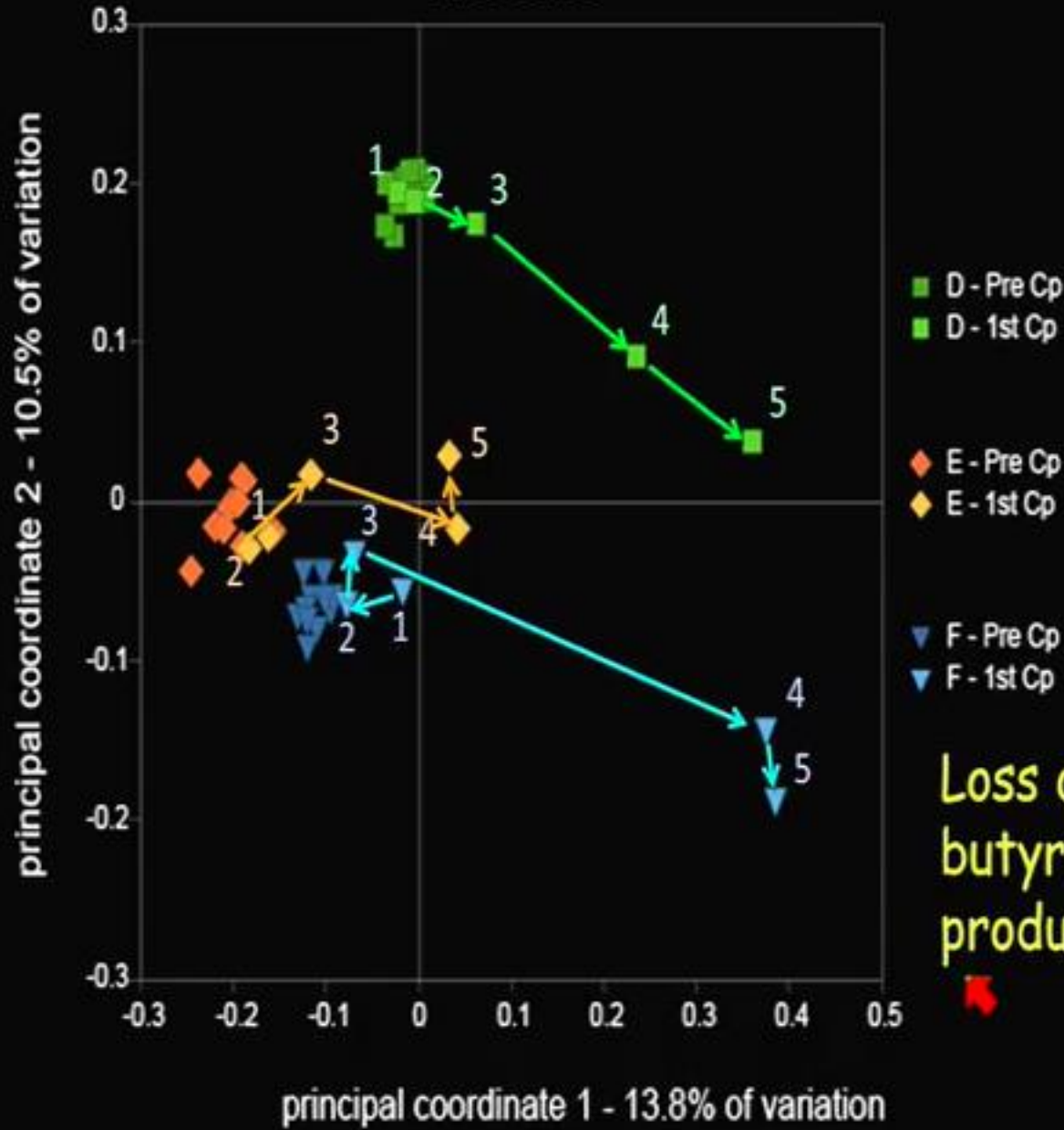
Mice receiving altered microbiota gained total mass and fat mass at a significantly faster rate than mice receiving normal microbiota



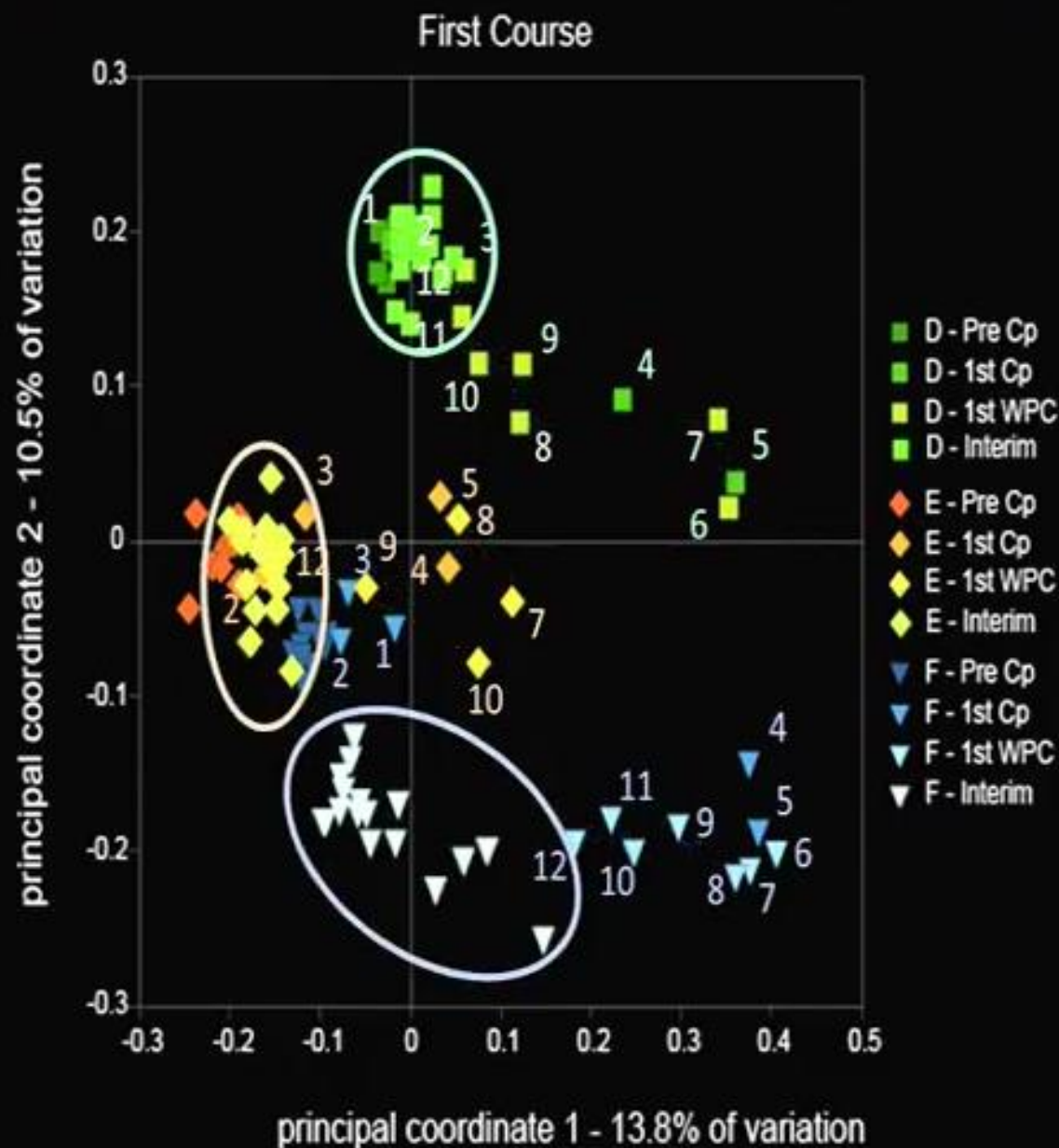
First Course



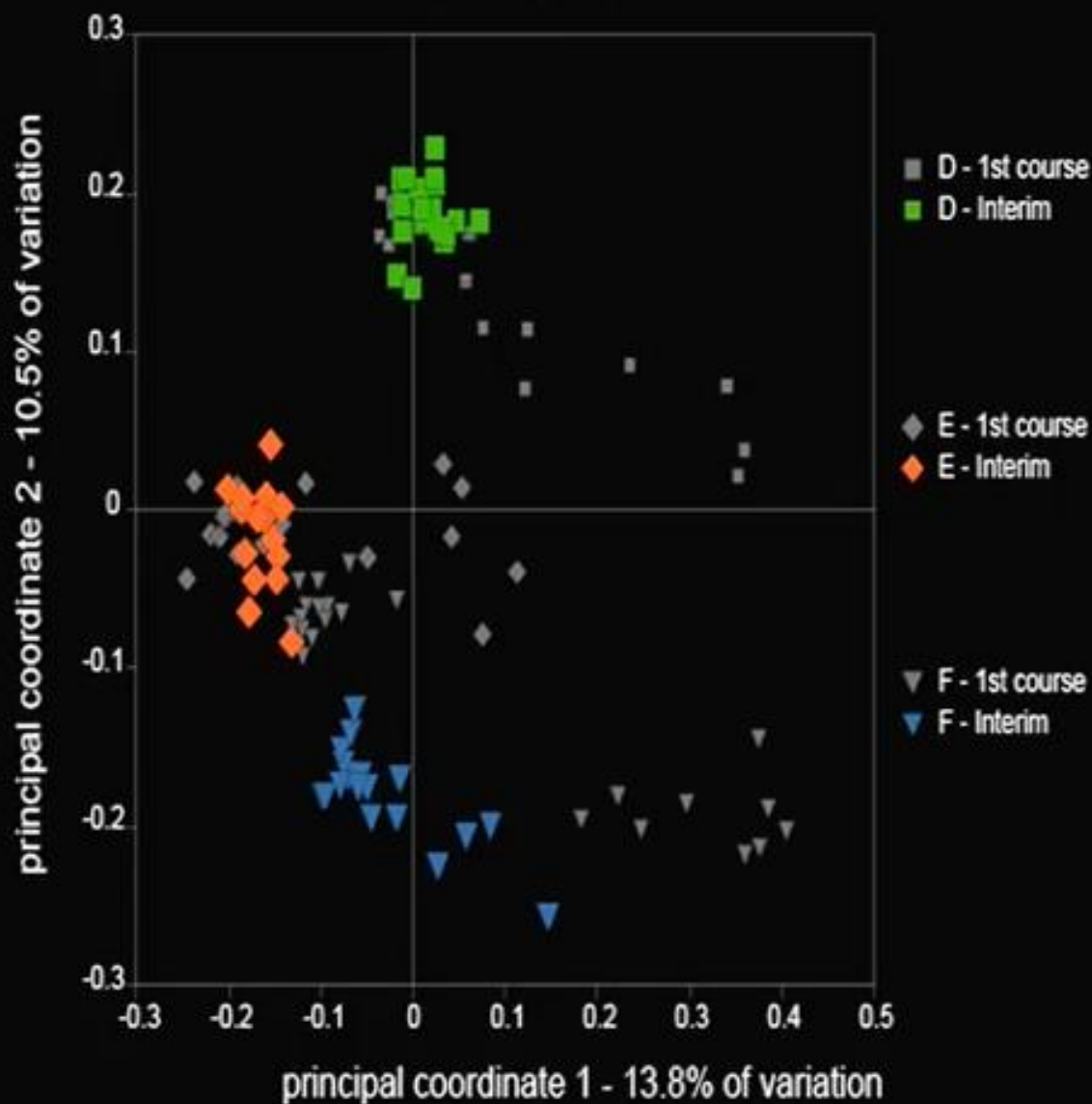
First Course

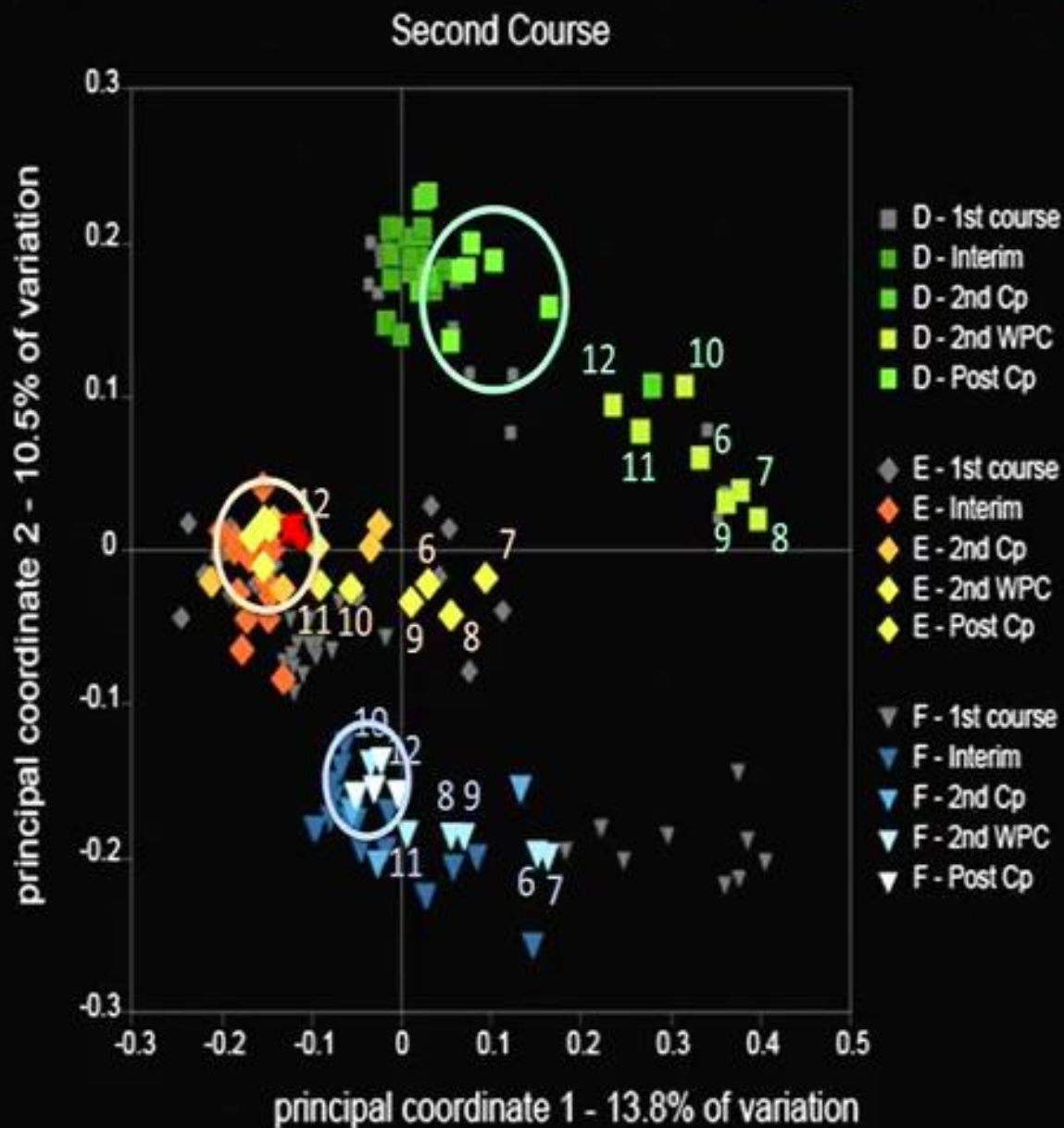


Loss of butyrate producers



Second Course





Original Article

International Journal of Obesity , (21 August 2012) | doi:10.1038/ijo.2012

Infant antibiotic exposures and early-life body mass

L Trasande, J Blustein, M Liu, E Corwin, L M Cox and M J Blaser

Objectives:

To examine the associations of antibiotic exposures during the first 2 years of life and the development of body mass over the first 7 years of life.

Design:

Longitudinal birth cohort study.

Subjects:

A total of 11 532 children born at ≥ 2500 g in the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based study of children born in Avon, UK in 1991–1992.

Yaşamın ilk
6 ayında

ARCHIVIST

Do antibiotics make children grow?

Accepted 3 May 2014

Arch Dis Child 2014;**0**:1. doi:10.1136/archdischild-2014-306698

ARCHIVIST

Do antibiotics make children grow?

promote growth and increase profits. Could the same principle apply to humans? An international team of authors, acknowledging the important link between sustained growth and favourable health outcomes, examined the evidence for whether this principle could apply to children in developing countries (Gough EK and colleagues. *BMJ* 2014;348:g2267). Perhaps surprisingly, they found 10 trials of sufficient quality, spanning 6 decades, to be included in their meta-analysis. There was a wide variety of inclusion criteria and antibiotics used. Nine studies compared to placebo, and one to nothing. Treatment and follow-up periods varied enormously. Only one involved HIV-positive children. The net cumulative beneficial effects on height amounted to 0.04 cm/month, and on weight to 23.8g/month. The effect seemed greater for weight than for height, for younger children, and for studies done in Africa. If this effect was sustained over a whole 15 years of growth, antibiotics could, in theory, make children 7.2 cm taller and 4.3 kg heavier.

A recent randomised controlled trial not included in this meta-analysis came from Malawi, where researchers added antibiotics (amoxicillin or cefdinir) or placebo to their existing severe acute malnutrition treatment regime (Trehan I and colleagues. *N Engl J Med* 2013;368:425–35). The study involved over 2750 children less than 3 years of age. Antibiotics produced a significant improvement in mortality (RR of death for placebo vs. cefdinir 1.8; 95% CI 1.22–2.64), and improved recovery rates. Weight gain was modestly but significantly superior for the antibiotic-treated groups.

Antibiotic Exposure in Infancy and Risk of Being Overweight in the First 24 Months of Life

Antti Saari, MD^{a,b}, Lauri J. Virta MD, PhD^c, Ulla Sankilampi MD, PhD^b, Leo Dunkel MD, PhD^d, Harri Saxen MD, PhD^e

PEDIATRICS Volume 135, number 4, April 2015

WHAT THIS STUDY ADDS: The weight-promoting effect of antibiotics is most pronounced when the exposure occurs at <6 months of age or repeatedly during infancy. Increased body mass is distinctly associated with exposure to cephalosporins and macrolides, especially in boys.

İNTESTİNAL MİKROBİYOTA

Obesite-Diabetes 2015

Mezenterik viseral yağ dokuda bakteri

DNA örnekleri saptanmış

(omentum ve diğer viseral adipoz doku örneklerinde yok)

RALSTONIA PICKETTI

Gram negatif çomak, proteobakter

İNTESTİNAL MİKROBİYOTA

Obesite-Diabetes 2015

RALSTONIA PICKETTI

- 1- Viseral dokuda *R. picketti* yükü ile sistemik inflamasyon arasında pozitif korelasyon mevcut
- 2- Fecal *R. picketti* düzeyi ile insülin rezistansı olduğu gösterilmiş.
- 3- Deneysel çalışmada 4 hafta süre ile oral *R. picketti* içeren gavaj alan ratlarda kilo alımının olduğu, OGTT'nin bozulduğu gösterilmiş.
- 4- *R. picketti* için geliştirilmiş AŞI uygulanan ratlarda insülin rezistansı gelişiminde azalma!!

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Comm

Pediatrics 2012;130:e794; originally published online September 24, 2012;
DOI: 10.1542/peds.2011-3886

Antibiotic Exposure and IBD Development Among Children: A Population-Based Cohort Study



WHAT'S KNOWN ON THIS SUBJECT: Inflammatory bowel disease pathogenesis is incompletely understood. Previous pediatric studies suggested associations between antibiotic use and inflammatory bowel disease development but were limited by recall bias, lack of controls, incomplete antibiotic capture, or included exposures between symptom onset and diagnosis.



WHAT THIS STUDY ADDS: Our population-based cohort study suggests that certain childhood antibiotic exposures are associated with an increased risk of developing inflammatory bowel disease. Our findings have implications for understanding the condition's pathogenesis and provide additional stimulus for reducing unnecessary childhood antibiotic use.

AUTHORS: Matthew P. Kronman, MD, MSCE,^a Theoklis E. Zaoutis, MD, MSCE,^{b,c} Kevin Haynes, PharmD, MSCE,^c Rui Feng, PhD,^c and Susan E. Coffin, MD, MPH^{a,c}

^aDivision of Infectious Diseases, Seattle Children's Hospital, University of Washington, Seattle, Washington; ^bDivision of Infectious Diseases, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; and ^cDepartment of Biostatistics and Epidemiology, the Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania

KEY WORDS

antimicrobials, epidemiology, inflammatory bowel disease, pediatric, population-based studies

ABBREVIATIONS

aHR—adjusted hazard ratio
CI—confidence interval

DOI: 10.1572/peds.2014.13600

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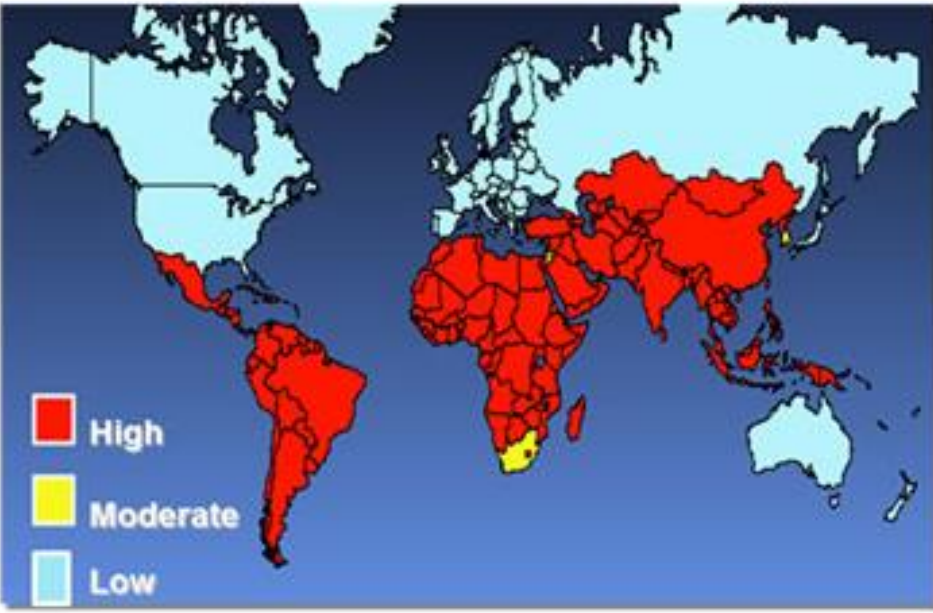


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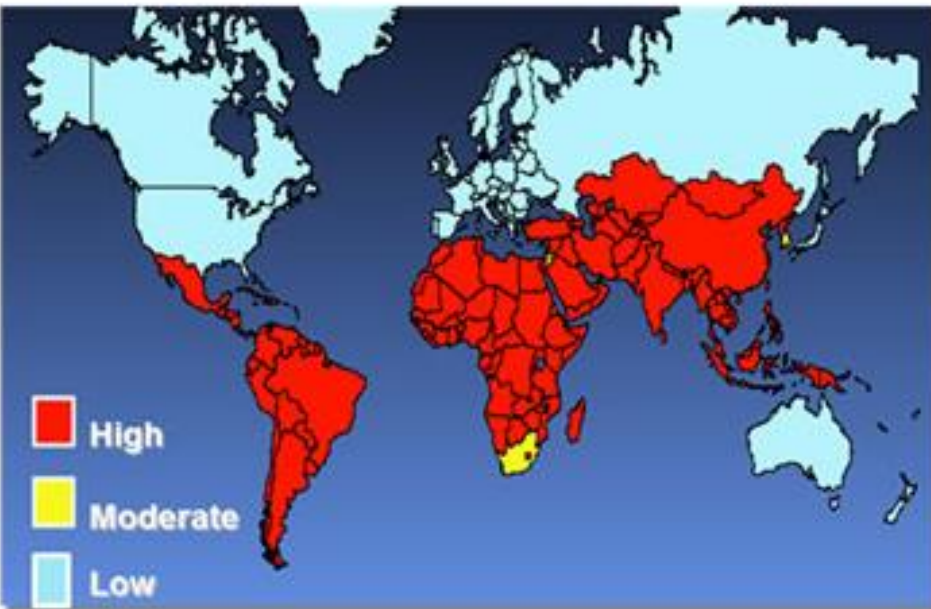


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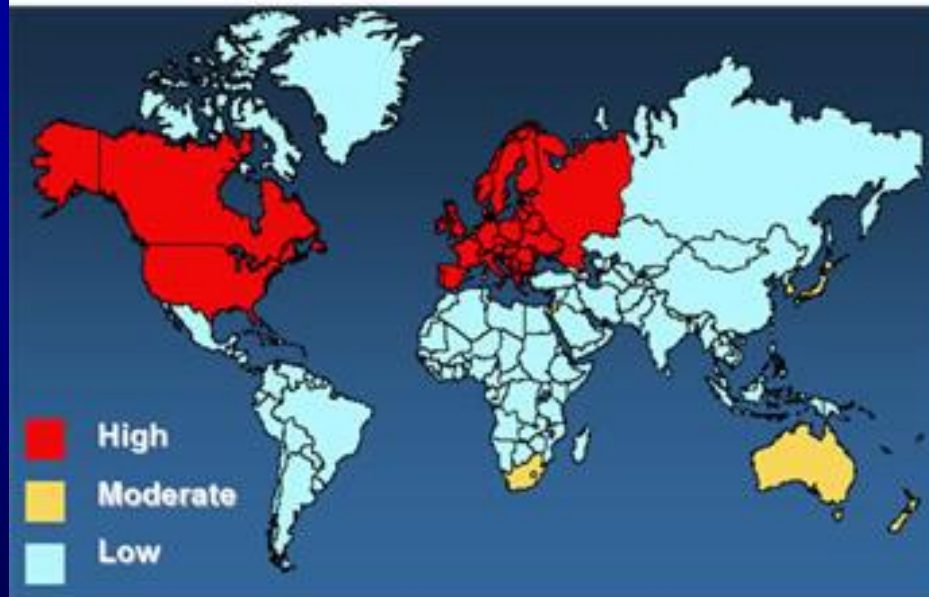
Helminths infestation incidence



Helminths infestation incidence



Autoimmune disorders incidence



Personal communication from Dr. Joel Weinstock

For a better start in life
start **COLA** earlier!



- Promotes Active
Lifestyles!
- Boosts Personality!
- Gives body essential
sugars!

How soon is too soon?

Not soon enough. Laboratory tests over the last few years have proven that babies who start drinking soda during that early formative period have a much higher chance of gaining acceptance and "fitting in" during those awkward pre-teen and teen years. So, do yourself a favor. Do your child a favor. Start them on a strict regimen of sodas and other sugary carbonated beverages right now, for a lifetime of guaranteed happiness.

The Soda Pop Board of America
1515 W. Hart Ave. - Chicago, ILL.

ALO 171 SİGARA
BIRAKMA HATTI MI ?

EVET
BUYRUN...

ADRESİ VERİYORUM
2 PAKET BIRAKIRSINIZ

DÜLÜTT.....



Unraveling the Influence of Gut Microbes on the Mind

5 May 2015

M. J. Friedrich

JAMA[®]
The Journal of the American Medical Association



THE DAILY BEAST



The Cure for Brain Diseases Is in Your Gut

28 April 2015

Melancholic microbes or how the microbiota can affect our mood

January 27, 2014, 13:52



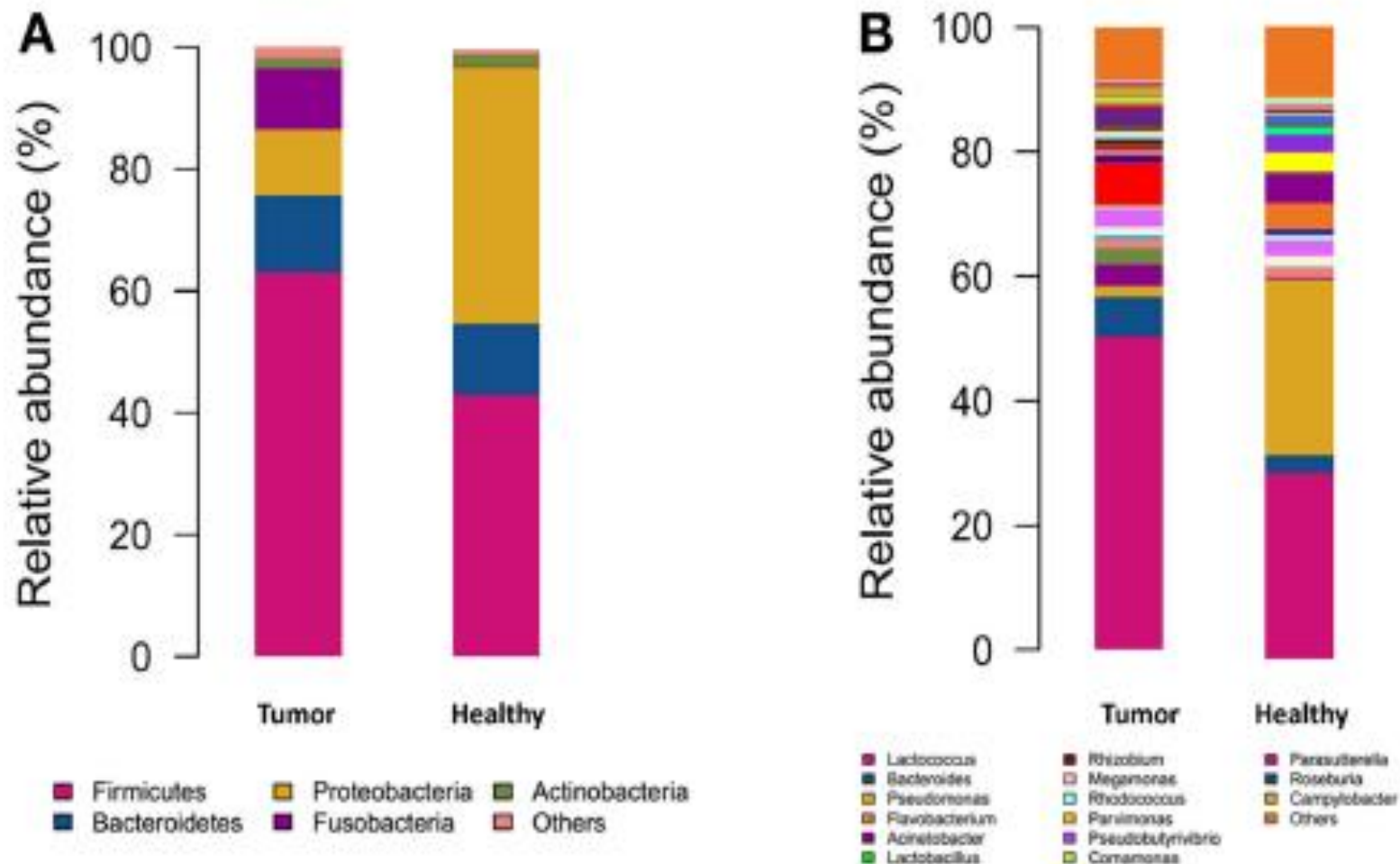
- Dinan et al.
- University College Cork
- Deneysel alıřmalarda intestinal mikrobiyota kompozisyonunda deęiřiklięin depresyon ve anksiyete arasında iliřki olduęu gsterilmiřtir.
- Bazı bakterilerin bulunmamasının serotonin baęırsak ve beyinde yeterli dzeyde retilmedięi gsterilmiř (mutluluk?)
- Tedavide probiyotikle



Microbiota disbiosis is associated with colorectal cancer

Zhiguang Gao[†], Bomin Guo[†], Renyuan Gao[†], Qingchao Zhu and Huanlong Qin^{*}

Department of General Surgery, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China

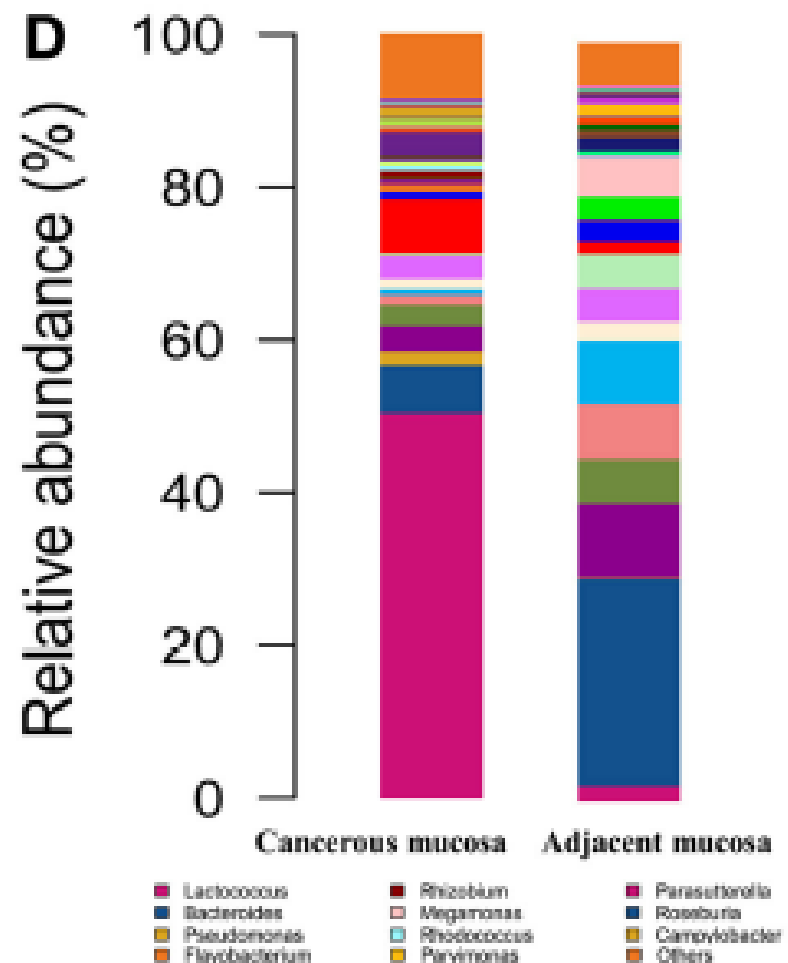
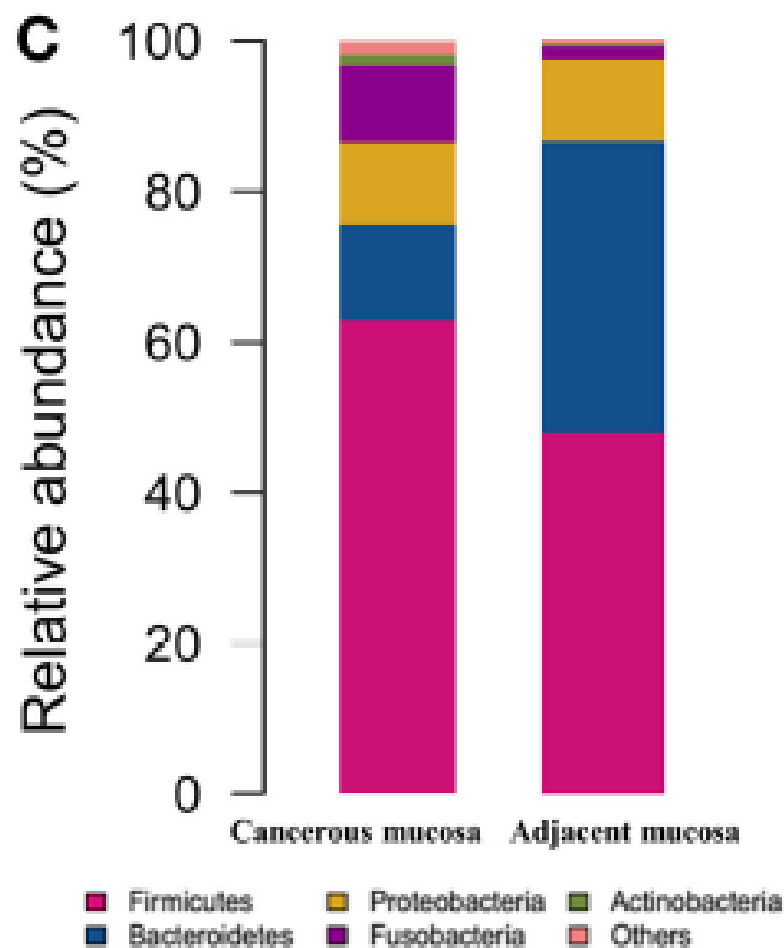




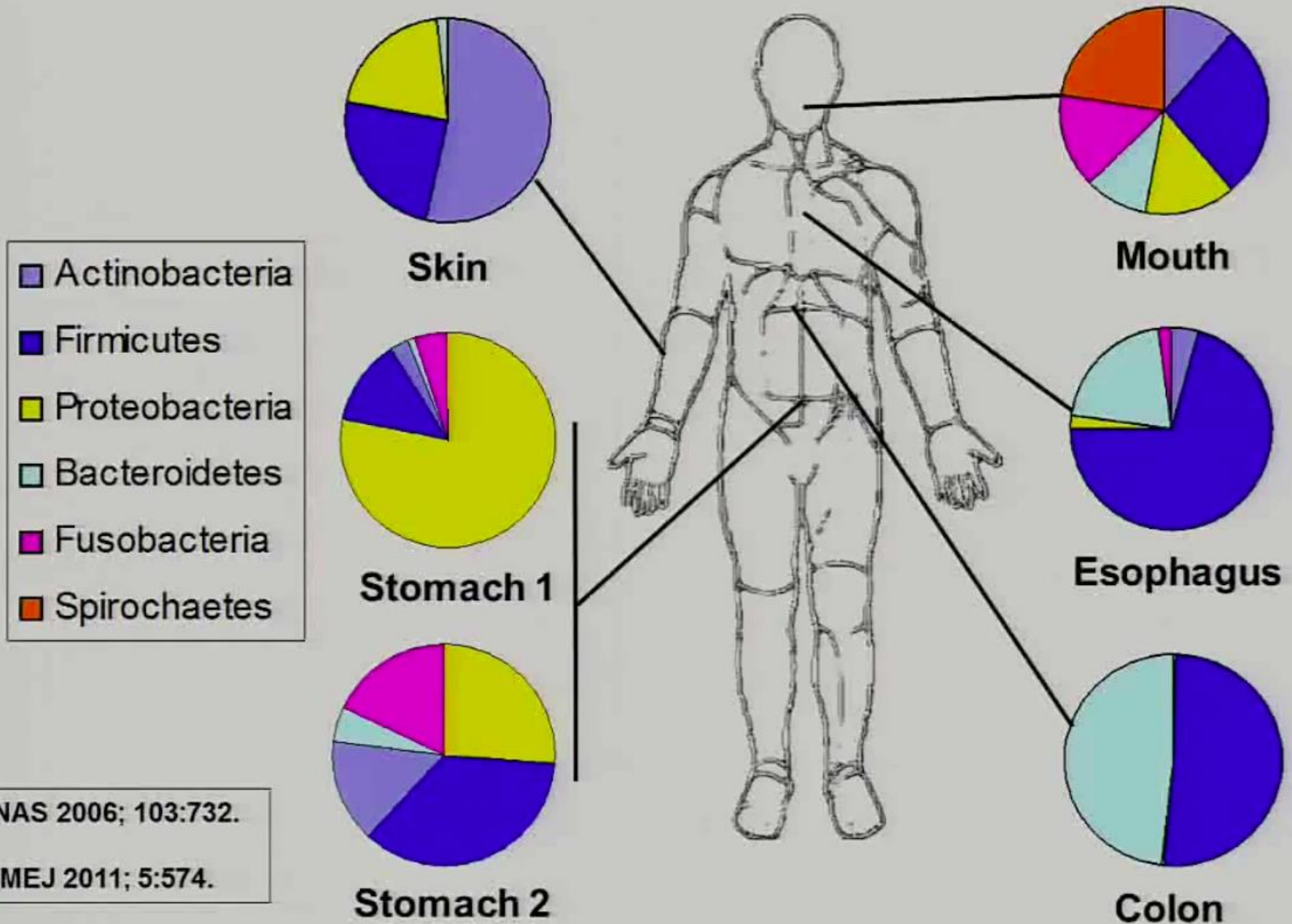
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Effects of *H. pylori* loss on gastric microbiome



PNAS 2006; 103:732.

ISMEJ 2011; 5:574.

