Mark Cannon DDS MS
FAAPD, FADM, FICD, FAAOSH, etc.

Let’s start at the “Beginning” Evolution than Prevention

- Chicago, IL USA
- Full time practice
The “Gateway” Microbiomes

“Nothing in biology makes sense except in the light of evolution.”

—Theodosius Dobzhansky

Sequencing ancient calcified dental plaque shows changes in oral microbiota with dietary shifts of the Neolithic and Industrial revolutions

Christina J Adler, Keith Dobney, Laura S Weyrich, John Kaidonis, Alan W Walker, Wolfgang Haak, Corey J A Bradshaw, Grant Townsend, Arkadiusz Sołtysiak, Kurt W Alt, Julian Parkhill & Alan Cooper
The importance of commensal microbes for human health is increasingly recognized yet the impacts of evolutionary changes in human diet and culture on commensal microbiota remain almost unknown. Two of the greatest dietary shifts in human evolution involved the adoption of carbohydrate-rich Neolithic (farming) diets beginning ~10,000 years before the present and the more recent advent of industrially processed flour and sugar (in ~1850). The Industrial Revolution. Modern oral microbiotic ecosystems are markedly less diverse than historic populations, which might be contributing to chronic oral (and other) disease in postindustrial lifestyles.
From pilfered-from-predators to processed-and-packaged, animals have been part of human diets for more than 3 million years. Cooking was unquestionably a revolution in our dietary history. Cooking makes food both physically and chemically easier to chew and digest, enabling the extraction of more energy from the same amount of food. The biggest increase in brain size in our evolutionary history happened right after we see the earliest evidence for cooking.
Fig. 2. Caries trends in the Old World across time. a) Indus valley civilization sequence, caries frequency versus corrected frequency (Lukacs, 1996). b) Britain sequence, caries frequency versus prevalence (Roberts & Cox, 2007).
What Do Mummies Tell Us?

**Porphyromonas gingivalis** became much more common when our Neolithic ancestors began farming.

**Streptococcus mutans** proliferated when the industrial revolution brought refined sugars to the table.

- Mesolithic
- Neolithic
- Bronze age
- Medieval
- Modern

Percentage of microbe DNA found on teeth.

Although commonly assumed to be a modern disease, the presence of atherosclerosis in premodern human beings raises the possibility of a more basic predisposition to the disease.
Children and Atherosclerosis


- Performed autopsies on 204 young persons 2 to 39 years of age, who had died from various causes, principally trauma.
These results suggest that commensal Bacteriodetes bacteria of the gut and the oral cavity may contribute to the pathogenesis of TLR2-dependent atherosclerosis through serine dipeptide lipid deposition and metabolism in artery walls.
8 years ago - it was missed

Phosphorylated Dihydroceramides from Common Human Bacteria Are Recovered in Human Tissues

Frank C. Nichols, Xudong Yao, Bekim Bajrami, Julia Downes, Sydney M. Finegold, Erica Knee, James J. Gallagher, William J. Housley, Robert B. Clark

Cell Reports

Volume 18, Issue 9, 28 February 2017, Pages 2269-2279

open access

Article

Plasma Dihydroceramides Are Diabetes Susceptibility Biomarker Candidates in Mice and Humans

Leonore Wigger, Céline Cruciani-Guglielmacci, Anthony Nicolas, Jessica Denom, Neiké Fernandez, Frédéric Fumeron, Pedro Marques-Vidal, Alain Ktorza, Werner Kramer, Anke Schulte, Hervé Le Stunff, Robin Liechti, Ioannis Xenarios, Peter Vollenweider, Gérard Waeber, Ingo Uphues, Ronan Roussel, Christophe Magnan, Bernard Thorens
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0016771
These data suggested that specific combinations of periodontal bacteria, even without inducing clinically significant periodontitis, may have a significant impact on human cause-specific death rates. Our findings implied that increased disease and mortality risk could be transmittable via the transfer of oral microbiota, and that developing personalized strategies and maintaining healthy oral microbiota beyond protection against periodontitis would be important to manage the risk.
Pediatric Oral Health and Adult CVD

In this cohort study of 755 participants followed up for 27 years into adulthood, a number of clinical signs of oral infections in childhood were associated with both cumulative exposure to cardiovascular risk factors during the follow-up and subclinical atherosclerosis in adulthood. Childhood oral infections may be a modifiable risk factor for adult cardiovascular disease.

Just have everyone use an anti-microbial mouth rinse???
Mouth rinse is GOOD for you

• Or is it?
• Can we really sterilize the mouth?
• Do we really want to?
• What exactly are we trying to do?
Nitrate Reducing Bacteria

• But if you kill nitrate reducing bacteria?

2004 Article

“Nitrate reducing commensals limit growth of cariogenic bacteria”

Subjects, a significant reduction in caries experience was found in patients with high salivary nitrate and high nitrate-reducing ability. Production of nitrite from salivary nitrate by commensal nitrate-reducing bacteria may limit the growth of cariogenic bacteria as a result of the production of antimicrobial oxides of nitrogen, including nitric oxide.
In various animal models and in humans, dietary nitrate supplementation has shown numerous beneficial effects, including a **reduction in blood pressure**, **protection against ischemia reperfusion damage**, restoration of NO homeostasis with associated cardioprotection, increased vascular regeneration after chronic ischemia, and a reversal of vascular dysfunction in the elderly.
The San Juan Overweight Adults Longitudinal Study (SOALS) recruited 1206 overweight/obese individuals, aged 40–65, and free of diabetes and major cardiovascular diseases. Frequent regular use of over-the-counter mouthwash was associated with increased risk of developing pre-diabetes/diabetes in this population.
The SBP-lowering effect of exercise was attenuated by 61% at 1 h in the recovery period, and it was fully attenuated 2 h after exercise with antibacterial mouthwash. This was associated with a lack of changes in circulatory nitrite ($P > 0.05$), and impaired microvascular response. These findings show that nitrite synthesis by oral commensal bacteria is a key mechanism to induce the vascular response to exercise over the first period of recovery thereby promoting lower blood pressure and greater muscle oxygenation.
Vegetarian diets are commonly associated with lower blood pressure levels. This has been related to greater consumption of inorganic nitrate, since vegetables are the main source of this anion. Dietary nitrate is reduced to nitrite by commensal bacteria in the mouth, which in turn leads to increased circulatory nitrite availability. Nitrite can form nitric oxide by several pathways promoting a reduction in the vascular tone and lower blood pressure.
Nitrate reducing bacteria - keep!

We identified 14 candidate species, seven of which were not previously believed to contribute to nitrate reduction. We cultivated isolates of four candidate species in single- and mixed-species biofilms, revealing that they have substantial nitrate- and nitrite-reduction capabilities. Colonization by specific oral bacteria may thus contribute to host NO homeostasis by providing nitrite and nitric oxide. These findings may also provide mechanistic evidence for the oral systemic link.
Nitrate reducers and PERFORMANCE

The oral nitrate-reducing capacity correlates with peak power output and peak oxygen uptake in healthy humans.

What influence diet had on early man? The hunter gatherer.
Dental Calculus - Fossils

Average height went down from 5'10" (178 cm) for men and 5'6" (168 cm) for women to 5'5" (165 cm) and 5'1" (155 cm), respectively, and it took until the twentieth century for average human height to come back to the pre-Neolithic Revolution levels. Agriculturalists had more anemias and vitamin deficiencies, more spinal deformations and more dental pathologies.
The Natufian culture is the name given to the sedentary Late Epi-Paleolithic hunter-gatherers living in the Levant region of the Near East between about 12,500 and 10,200 years ago. The Natufians foraged for food such as emmer wheat, barley, and almonds, and hunted gazelle, deer, cattle, horse, and wild boar.
Some fairly rare evidence suggests that the Natufian people may have cultivated barley and wheat. The line between horticulture (tending wild stands of crops) and agriculture (planting new specific stands) is a fuzzy one and difficult to discern in the archaeological record. Most scholars believe that moving to agriculture was not a one-time decision, but rather a series of experiments that may well have taken place during the Natufian or other hunter-gatherer subsistence regimes.
Researchers Hayden et al. (2013) compiled circumstantial evidence that the Natufians brewed beer and used it in the context of feasting. They argue that production of beverages from fermented barley, wheat, and/or rye may well have been an impetus for early agriculture, for assuring that a ready source of barley was available.
Dental calculus preserves DNA of oral microbiome...
Dental Calculus - Fossils

Figure 1. Supra-gingival dental calculus is identifiable in a concave ring on a lower molar from a Medieval specimen, York, UK.

Thank God they didn’t have Dental Hygienists back then!
Dental Calculus- Fossils

- Calcified dental plaque (dental calculus) preserves for millennia and entraps biomolecules from all domains of life and viruses. We characterize (i) the ancient oral microbiome in a diseased state, (ii) 40 opportunistic pathogens, (iii) ancient human–associated putative antibiotic resistance genes, (iv) a genome reconstruction of the periodontal pathogen Tannerella forsythia, (v) 239 bacterial and 43 human proteins, allowing confirmation of a long-term association between host immune factors, 'red complex' pathogens and periodontal disease, and (vi) DNA sequences matching dietary sources.
Tubers are present within the latitudes that hominins have occupied from their inception through the first expansion of Homo out of Africa (O’Connell et al., 1999; Laden and Wrangham, 2005). Some hominins show dental features (e.g., thick enamel) that have been interpreted as adaptations to eating USOs (Hatley and Kappelman, 1980; Teaford and Ungar, 2000; Laden and Wrangham, 2005). Wrangham and Conklin-Brittain (2003) and Wrangham et al. (1999) have argued that tubers are implicated in the transition to Homo and that cooking is also implicated because tubers are usually roasted before eaten.
In the majority of plants, the main glucide transported is saccharose. However in a large number of plants, other compounds, such as polyols, are also transported. Polyols (or sugar alcohols) are like saccharose, primary products of photosynthesis, which include mannitol, sorbitol, dulcitol, galactitol, inositol, myo-inositol, ribitol, xylitol and more.
Cellulose and Xylan Hydrolysis

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

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

• 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.
Life in a rural village of Burkina Faso.

Carlotta De Filippo et al. PNAS 2010;107:14691-14696
Cellulose and Xylan Hydrolysis

• Xylanibacter, Prevotella, Butyrivibrio, and Treponema Genera May Enhance the Ability to Extract Calories from Indigestible Polysaccharides in BF Children. Whole grains are concentrated sources of dietary fiber, resistant starch, and oligosaccharides, as well as carbohydrates that escape digestion in the small intestine and are fermented in the gut, producing short-chain fatty acids (SCFAs).

Xylanibacter, Prevotella, Butyrivibrio, and Treponema are exclusive to the BF children and indicate the presence of a bacterial community using xylane, xylose, and carboxymethylcellulose to produce high levels of SCFAs whose protective role against gut inflammation has been well proven. Increase in acetate, butyrate, and propionate—butyrate is protective...gut AND neuroprotective... Timing sensitive.
16S rRNA gene surveys reveal a clear separation of two children populations investigated.

Carlotta De Filippo et al. PNAS 2010;107:14691-14696
Cellulose and Xylan Hydrolysis

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

Carlotta De Filippo, Duccio Cavalieri, Monica Di Paola, Matteo Ramazzotti, Jean Baptiste Poullet, Sebastien Massart, Silvia Collini, Giuseppe Pieraccini, and Paolo Lionetti.

• The SCFA-producing bacteria that are abundant in the BF children's gut possibly help to prevent the establishment of some potentially pathogenic intestinal microbes causing diarrhea, as seen by the fact that Enterobacteriaceae, such as Shigella and Escherichia, were significantly underrepresented in BF than in EU children. **Increased gut microbial diversity and reduced quantities of potentially pathogenic strains in BF would agree with the “old friend” hypothesis, indicating a role of microbiota in protecting children from pathogens as well as from gastrointestinal diseases.**
The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level.

- Athletes had relative increases in pathways (eg, amino acid and antibiotic biosynthesis and carbohydrate metabolism) and faecal metabolites (eg, microbial produced short-chain fatty acids (SCFAs) acetate, propionate and butyrate) associated with enhanced muscle turnover (fitness) and overall health when compared with control groups. Differences in faecal microbiota between athletes and sedentary controls show even greater separation at the metagenomic and metabolomic than at compositional levels and provide added insight into the diet–exercise–gut microbiota paradigm.
Exercise and associated dietary extremes impact on gut microbial diversity

Siobhan F Clarke1, 2, 3, Eileen F Murphy2, 4, Orla O'Sullivan1, Alice J Lucey5, Margaret Humphreys6, Aileen Hogan2, Paula Hayes2, Maevé O'Reilly2, 4, Ian B Jeffery2, 3, Ruth Wood-Martin7, David M Kerins8, 9, Eamonn Quigley2, R Paul Ross1, 2, Paul W O'Toole3, Michael G Molloy10, Eanna Falvey10, 11, Fergus Shanahan2, 10, 12, Paul D Cotter1, 2

When does the protection start? How do children develop the protective microbiome? Before birth! accompanying dietary extremes.
Pre-natal microbiome

• The Maternal Effect—everyone knows!

How Bacteria in the Placenta Could Help Shape Human Health

The placenta is full of microbes, a new study finds, raising questions about how that ecosystem and mothers' oral health influence the risk of preterm birth
Pre-natal microbiome

• The Maternal Effect

We characterized a unique placental microbiome niche, composed of nonpathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla. In aggregate, the placental microbiome profiles were most akin (Bray-Curtis dissimilarity <0.3) to the human oral microbiome. 16S-based operational taxonomic unit analyses revealed associations of the placental microbiome with a remote history of antenatal infection (permutational multivariate analysis of variance, P = 0.006), such as urinary tract infection in the first trimester, as well as with preterm birth <37 weeks (P = 0.001).
Fig. 1. The placental microbiome has a taxonomic profile that is similar to the oral microbiome.

Kjersti Aagaard et al., Sci Transl Med 2014;6:237ra65
Fig. 2. Comparison of WGS-generated taxa and metabolic capacity among body sites reveals distinct features of the placental microbiome.
Fig. 3. The placental microbiome from pregnancies complicated by a preterm delivery demonstrates discrete taxonomic profiles and variations in metabolic pathways.

Kjersti Aagaard et al., Sci Transl Med 2014;6:237ra65
Antibiotics again!

Kjersti Aagaard et al., Sci Transl Med 2014;6:237ra65

Published by AAAS
In a previous study, lactic acid bacteria were isolated from meconium obtained from healthy neonates born by cesarean section. Such a finding suggested that term fetuses are not completely sterile, and that a mother-to-child efflux of commensal bacteria may exist. Therefore, presence of such bacteria in umbilical cord blood of healthy neonates born by elective cesarean section was investigated. The blood samples were submitted to an enrichment step and then inoculated onto agar plates. All the identified isolates belonged to the genus Enterococcus, Streptococcus, Staphylococcus, or Propionibacterium.

Later, a group of pregnant mice were orally inoculated with a genetically labeled E. faecium strain previously isolated from breast milk of a healthy woman. The labeled strain could be isolated and polymerase chain reaction detected from the amniotic fluid of the inoculated animal.
In rodents, subcutaneous inoculations with periodontal pathogens cause dose-dependent decreases in pup weights, and elicit inflammatory responses that can trigger preterm birth when present in amniotic fluid. Periodontitis (defined as a destructive inflammation of the periodontium) has a prevalence of 30% or greater in women of child bearing age. By definition, it involves microbial infiltration of the periodontium, which stimulates a chronic inflammatory response, recurrent bacteremia, and the production of cytokines and prostaglandins which trigger risk of preterm birth. The investigators' overarching hypothesis is that comprehensive primary preterm birth prevention, inclusive of maternal oral health with xylitol chewing gum (the intervention), will reduce the risk of periodontal disease and caries, preterm birth prevalence, and neonatal mortality.
Prevention:

• Diagnosis
• What is missing?
Prebiotics and Probiotics

Diagnosis:
- Oral CariScreen (Carifree)
- CamX Spectra (Air Tech)
- Alert2 (OralDNA Labs)
- MitoSwab (MitoSwab)
- GenoTek (DNA GenoTek)
- VIOME
- American Gut Project
<table>
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Synergistic interactions between recombinant bacteria and genetically modified plants can further enhance the restoration of environments impacted by organic pollutants.

Nevertheless, releasing genetically modified microbes and plants into the environment does pose potential risks.

- **Organic pollutants e.g.**
  - Xenobiotics, TNT, POPs, PCB, VOCs, Phenols, Dyes, Hydrocarbons, RDX

- **Sequestration, Phytovolatilization, Compartmentalization**
  - After transport in shoot

- **Rhizobacteria and Fungi**
  - Rhizodegradation

- **Genetically modified Bacteria**
  - Endophytic microbes
Prebiotics and Probiotics

**Diagnosis:**
– Salivary- oral microbiome genetic info
Diagnostic tests

- DNA GenoTek – OMNIgene Oral
- OM-501
Microbiome and Mitochondria

Microbiome effects mitochondrial health, and the health of mitochondria reflects changes in the microbiome.

MITOswab test analysis reveals -
- The overall content of mitochondria is significantly higher than 'normal range' as indicated by the citrate synthase activity value (355% of the normal mean activity level) in test buccal sample.
- The activity of Resp range.
- The activity of Resp

MITOSWAB
Interpretation -
- Biochemical analysis of RC-IV.
- Although the RC-I and II suggest a compensatory/mitochondrial process.
- Periodic mitochondrial compensatory/corrective

• Microbiome reflects health
Among the complete mtDNA sequences, a total of 162 variations were spread across the whole mitochondrial genome and present only in the coronary artery and the gingival tissue samples but not in the blood samples. Among the 162 variations, 12 were novel and four of the 12 novel variations were found in mitochondrial NADH dehydrogenase subunit 5 complex I gene (33.3%).
The term can be applied to the total set of transcripts in a given organism, or to the specific subset of transcripts present in a particular cell type. Unlike the genome, which is roughly fixed for a given cell line (excluding mutations), the transcriptome can vary with external environmental conditions. Because it includes all mRNA transcripts in the cell, the transcriptome reflects the genes that are being actively expressed at any given time, with the exception of mRNA degradation phenomena such as transcriptional attenuation.
Prevention:

• Prebiotics
• Probiotics
Dental Disease - Dysbiosis

- Disease, bacterial, fungal, yeast, and probably viral, are due to "dysbiosis".
- Bacteria protect from, and cause dental decay, and periodontal disease.
- Esthetic dentistry may also be needed because of trauma, or genetic causes, or iatrogenic reasons.

Principles of Prevention
Streptococci - Plaque Kingdoms

- Actinomyces species
  - S. mitis
  - S. oralis
  - S. sanguis
  - Streptococcus sp.
    - S. gordonii
    - S. intermedius

- V. parvula
- A. odontolyticus

- S. constellatus
- C. gracilis
- C. rectus
- E. nodatum

- P. intermedia
- P. nigrescens
- P. micros
- F. nuc. vincentii
- F. nuc. nucleatum
- F. nuc. polymorphum
- F. periodonticum

- P. gingivalis
- T. forsythia
- T. denticola

- A. actino. b
- S. noxia

- S. entericus
- S. pluranimilium
- S. mutans
Caries Risk Assessment

CariScreen Caries Susceptibility Test

The CariScreen Caries Susceptibility Test is a quick, 1 minute chair-side test for ATP (adenosine triphosphate) levels on the teeth.

Keep swabs refrigerated until 5 minutes before use.

“There is no reason anyone would want a computer in their home.”
Caries Risk Assessment
Interpreting the Results

Risk Indication Values (RLU’s)
- 0-1500 = low risk
- 1501-3500 = moderate risk
- 3501-9999 = high risk

“And in the end it’s not the years in your life that count. It’s the life in your years.”
Caries Risk Assessment
Interpreting the Results
Probiotics - Replacing Nature

Necessary for today and TOMORROW
Gary B. Huffnagle, Ph.D., is Professor of Internal Medicine, Microbiology, and Immunology, University of Michigan Medical Center. His research on probiotics has appeared in leading scientific journals and has been featured in Newsweek, Forbes, and on BBC News.

"A general belief is that microbes are harmful. This belief is erroneous. There are many useful microbes......"
Pathogen = bacteria in the wrong place at the wrong time
Probiotic = bacteria in the right place at the right time
- Dr. Cannon’s Definition on the host”

The number of published studies investigating probiotics has increased 15 fold in as many years, and 2011 looks set to be a record year with more than 1300 publications anticipated.

An analysis of publications posted to the NIH PubMed database reveals strong growth in the number of publications featuring the keyword 'probiotic'. In 1997 there were roughly 80 publications globally per year referencing probiotics, today that figure is over 1200 per year or 100 publications per month.
How do probiotics work?

- Preventing the growth of pathogens
- Competitive displacement of pathogens
- Regulating gut microbial ecosystems
- Improving gut function/nutritional uptake
- Modulating immune responses to improve health


CONCLUSIONS. Bacterial translocation is a unique physiologic event, which is increased during pregnancy and lactation in rodents. Human breast milk cells contain a limited number of viable bacteria but a range of bacterial DNA signatures, as also found in maternal peripheral blood mononuclear cells. Those peripheral blood mononuclear cells showed greater biodiversity than did peripheral blood mononuclear cells from control women. Intestinally derived bacterial components are transported to the lactating breast within mononuclear cells. We speculate that this programs the neonatal immune system to recognize specific bacterial molecular patterns and to respond appropriately to pathogens and commensal organisms.
Treatment of the Mother Resulted in Less Disease in the Child

- Mothers chewed Xylitol gum for 2 years beginning at 3 months post-partum.
- When the children were 5 years old, the need for treatment was 71-75% lower in the Xylitol group.
- Isokangas et al. JDR 2000

“Is it so confusing -- which nostril do I use? Or should I breathe through my mouth or what?” -- Ed E. Ott

BREATHING FOR DUMMIES

- Respiration for the Compleat Moron
- Actually prolong your life by utilizing proper breathing techniques.
- By Joe Mahmet, Lung Professional

Air and how to use it

Xylitol
Maternal
Discuss with mother xylitol gum or mint use and why, encourage use.
Give copy of maternal use of xylitol/child protection from decay research article. Ask mother to share with pediatrician. Explain probiotic use to mother, give information on Klaire Lab products, and oral probiotics, such as Evora Plus and Spry probiotic.
Twice yearly dental visits stressed for themselves and good home care practices.
Complementation of the fadA mutation in Fusobacterium nucleatum demonstrates that the surface-exposed adhesin promotes cellular invasion and placental colonization.

Ikegami A¹, Chung P, Han YW

Abstract

Fusobacterium nucleatum is a gram-negative oral anaerobe implicated in periodontal disease and adverse pregnancy outcome. The organism colonizes the mouse placenta, causing localized infection and inflammation. The mechanism of placental colonization has not been elucidated. Previous studies identified a novel adhesin from F. nucleatum, FadA, as being involved in the attachment and invasion of host cells. The fadA deletion mutant F. nucleatum 12230 US1 was defective in host cell attachment and invasion in vitro, but it also exhibited pleiotropic effects with altered cell morphology and growth rate. In this study, a fadA-complementing clone, F. nucleatum 12230 USF81, was constructed. The expression of FadA on USF81 was confirmed by Western blotting and immunofluorescent labeling. USF81 restored host cell attachment and invasion activities. The ability of F. nucleatum 12230, US1, and USF81 to colonize the mouse placenta was examined. US1 was severely defective in placental colonization compared to the wild type and USF81. Thus, FadA plays an important role in F. nucleatum colonization in vivo. These results also represent the first complementation studies for F. nucleatum. FadA may be a therapeutic target for preventing F. nucleatum colonization of the host.
Colorectal Cancer - *Fusibacterium nucleatum*

**International Cancer Screening Network**

Sponsored by the National Cancer Institute

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<th>United States</th>
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**Fusobacterium nucleatum** Promotes Colorectal Carcinogenesis by Modulating E-Cadherin/β-Catenin Signaling via its FadA Adhesin

Mara Roxana Rubinstein*, Xiaowei Wang*, Wendy Liu, Yujun Hao, Guifang Cai, Yiping W. Han

**Summary**

*Fusobacterium nucleatum* (Fn) has been associated with colorectal cancer (CRC), but causality and underlying mechanisms remain to be established. We demonstrate that *Fn* adheres to, invades, and induces oncogenic and inflammatory responses to stimulate growth of CRC cells through its unique FadA adhesin. FadA binds to E-cadherin, activates β-catenin signaling, and differentially regulates the inflammatory and oncogenic responses. The FadA-binding site on E-cadherin is mapped to an 11-amino-acid region. A synthetic peptide derived from this region of E-cadherin abolishes FadA-induced CRC cell growth and oncogenic and inflammatory responses. The *fadA* gene levels in the colon tissue from patients with adenomas and adenocarcinomas are >10–100 times higher compared to normal individuals. The increased FadA expression in CRC correlates with increased expression of oncogenic and inflammatory genes. This study unveils a mechanism by which *Fn* can drive CRC and identifies FadA as a potential diagnostic and therapeutic target for CRC.
Xylitol - 5 carbon chain

- From Xylon (wood) and itol (sugar alcohol). Xylitol is found in the fibers of many fruits and vegetables, and can be extracted from various berries, oats, and mushrooms, as well as fibrous material such as corn husks and sugar cane bagasse, and birch.
Xylitol research

Compared with the no-gum group, sucrose gum usage resulted in a marginal increase in the caries index (95% confidence interval, 0.96 to 1.49; p = 0.1128). Sorbitol gum significantly reduced caries rates (relative risk 0.74; 95% confidence interval, 0.57 to 0.96; p = 0.0074). The four xylitol gums were most effective in reducing caries rates, the most effective agent being a 100% xylitol gum (relative risk 0.27; 95% confidence interval, 0.20 to 0.36; p = 0.0001). This gum was superior to any other gum (p < 0.01). The four xylitol gums were more effective than xylitol, but they reduced caries rates significantly compared with the no-gum group. DMFS analyses support these conclusions. The results suggest that systematic usage of polyol-based chewing gums reduces caries rates in young subjects, with xylitol gums being more effective than sorbitol gums.
Influence of maternal xylitol consumption on acquisition of mutans streptococci by infants.
Söderling E, Isokangas P, Piisihäkkinen K, Tenovuo J.
Institute of Dentistry, University of Turku, Finland. eva.soderling@utu.fi

Abstract
Xylitol is effective as a non-cariogenic sugar substitute. Habitual xylitol consumption appears to select for mutans streptococci (MS) with impaired adhesion properties, i.e., they shed easily to saliva from plaque. One hundred sixty-nine mother-child pairs participated in a two-year study exploring whether the mothers’ xylitol consumption could be used to prevent mother-child transmission of mutans streptococci. All mothers showed high salivary levels of mutans streptococci during pregnancy. The mothers in the xylitol group (n = 106) were requested to chew xylitol-sweetened gum (65% w/w) at least 2 or 3 times a day, starting three months after delivery. In the two control groups, the mothers received either chlorhexidine (n = 30) or fluoride (n = 33) varnish treatments at 6, 12, and 18 months after delivery. The children did not chew gum or receive varnish treatments. MS were assessed from the mothers’ saliva at half-year intervals and from the children’s plaque at the one- and two-year examinations. The MS were cultured on Mitis salivarius agar containing bacitracin. The salivary MS levels of the mothers remained high and not significantly different among the three study groups throughout the study. At two years of age, 9.7% of the children in the xylitol, 28.6% in the chlorhexidine, and 48.5% in the fluoride varnish group showed a detectable level of MS. In conclusion, therefore, habitual xylitol consumption by mothers was associated with a statistically significant reduction of the probability of mother-child transmission of MS assessed at two years of age. The effect was superior to that obtained with either chlorhexidine or fluoride varnish treatments performed as single applications at six-month intervals.

Mutans strep detectable-
9.7% of xylitol group
28.6% of chlorhexidine group
48.5% of fluoride varnish group
Table 1. Acid production after exposure to xylitol.

<table>
<thead>
<tr>
<th>Strain</th>
<th>Species</th>
<th>Time of acid production (in M2 medium, days)</th>
<th>Rate of pH change (u per day)</th>
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WHISKEY Tooth Paste!

Genuine 6 Proof Stuff
SCOTCH • BOURBON

Why fight oral hygiene—enjoy it! Here’s real he-man toothpaste, best argument yet for brushing 3 times a day. 2 1/2 oz. tubes flavored with the real thing—Scotch or Bourbon. Night-before feeling on the morning after. Rinse with soda instead of water if you prefer. Per tube ppd. . . . . . . .

$1

Greenland Studios
DEPT. HG-114, MIAMI 47, FLORIDA

• Xlear (Clear)
New Xylitol Products

For Special Needs!

- Children’s Mouthwash- safe for all ages
MRE- xylitol gum- G.I. issue
Abstract: The purpose of this study was to evaluate the effectiveness of xylitol in reducing dental caries in children compared to no treatment, a placebo, or preventive strategies.

Methods: MEDLINE via PubMed, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1, 1995 through Sept. 26, 2016 for randomized and controlled trials on children consuming xylitol for at least 12 months. The primary endpoint was caries reduction measured by mean decayed, missing, and filled primary and permanent surfaces/teeth (dmfs/t, DMFS/T, respectively).


Xylitol and Dentistry

- Only ten studies out of 210. Excluded 190. All basically gum/lozenges except 2 toothpaste and one wipes. Should they be grouped together? And why exclude all with other polyols?
Xylitol and Dentistry

- Toothpaste works, wipes work, but gum had a varied result.
The fluoride content in the pipe drinking water was ≤0.3 p.p.m. !!!

Informed consent, they were randomly assigned into a xylitol and a xylitol-fluoride group. They were instructed to take two tablets three times a day (total xylitol and fluoride dose 2.5 g and 1.5 mg, respectively). The dropout rate was 28%, and 41% exhibited a good compliance with the study protocol. No statistically significant differences in caries incidence could be found between the study groups (P > 0.05). Huge non-compliance rate of 59%! Plus 28% dropout??
Criticism of the Cochrane review and some recent clinical studies

The study by Nakai et al. [2010] showed that significantly more children in the xylitol chewing group remained *S. mutans* free at 9, 12, and 24 months. Furthermore, pre- and perinatal xylitol chewing by mothers delayed *S. mutans* carriage in children. The children’s *S. mutans* acquisition age in the xylitol chewing group was 8.8 months later than that of the control group (mean age 20.8 vs. 12.0 months old).
Cervitec Plus - Ivoclar

- FDA approved in 2008
- Used in Europe for many years
- 1% chlorhexidine and 1% thymol varnish
Cervitec Plus- Ivoclar

- Swollen and inflamed gingival tissues
- Periodontal Classification Type I- gingivitis
Cervitec Plus - Ivoclar

Unit dose and bulk packaging
Cervitec Plus- Ivoclar

• Apply to gingival third of dentition

Inside Dentistry
June 2011, Volume 7, Issue 6
Published by AEGIS Communications

Clinical Application of Probiotic Therapy
New adjunctive therapies offer new alternatives for treatment.
By Mark L. Cannon, DDS, MS

then start a probiotic
THE PRIMARY OBJECTIVE OF THIS CLINICAL STUDY IS TO DETERMINE THE EFFECT, IF ANY, OF “OVER THE COUNTER” PROBIOTIC SUPPLEMENTS ON THE DNA-PCR And CRT ANALYSIS
DNA-PCR and CRT Results in Children After Probiotic use

**Methods**

- 60 patients 6 to 12 years of age - caries prone with 4 or more restorations and/or lesions
- CRT collected before and after probiotic use
- 8 week (60 day) experimental time period - considered optimal to see effect
DNA-PCR and CRT Results in Children After Probiotic use

Two separate statisticians in different institutions
Conclusions:

Effectiveness of CRT at Measuring the Salivary Level of Bacteria in Caries Prone Children

Cannon M* / Trent B** / Vorachek A*** / Kramer S**** / Esterly R*****

Aim: This IRB approved clinical trial was to determine the effect of "over the counter" probiotic supplements on the Caries Risk Test- CRT (Ivoclar) results of the oral microflora in high caries risk children. Study design: Sixty subjects 6 to 12 years old with a caries risk assessment (CAMBRA) of moderate to high (caries prone) were evaluated by an analysis of the difference in the salivary levels of pathogenic bacteria (mutans streptococci and Lactobacilli). The subjects were randomly selected by randomizing software and assigned to two different Groups. Group A used PerioBalance (Lactobacilli reuteri-CFU of 200 million) lozenges for 28 days. Group B used the EvoraKids (Streptococcus uberis KJ2, Streptococcus oralis KJ3, Streptococcus rattus JHH45, ≥ 100 million) probiotics chewable tablets for 30 days. Salivary samples were collected then incubated for 48 hours for colony counting and ranking. Follow up testing with the CRT was performed after 60 days at a follow up visit. Results: There was a statistically significant difference in the CRT results between the pre and post use of the probiotics. PerioBalance: SM results t = -5.762, p < .0001, Lactobacilli results t = -7.33, p < .0001, EvoraKids SM results t = -7.33, p < .0001, Lactobacilli results t = -2.952, p = .0068. Conclusions: The CRT values obtained with caries prone children may be significantly affected by probiotic use. Based on this study’s results the following conclusions can be made: Both EvoraKids and PerioBalance affected the CRT results by significantly decreasing the number of S. mutans and lactobacilli present in the salivary samples.
Retrospective Review of Probiotic Therapy.
ML Cannon DDS MS
A Vorachek DDS
K White DMD
C Le DMD
An IRB Approved Study

Does EvoraKids and PerioBalance affected the caries proneness of the subjects?
Is the reduction in dental caries was statistically significant?
Materials and Methods:
Dental records of 60 patients that were enrolled in the Institutional Review Board approved study, "A clinical trial to evaluate the effectiveness of DNA-PCR and CRT at measuring the salivary level of bacteria in caries prone children with PerioBalance or EvoraKids Plus therapy" were reviewed as to current caries activity status with measurement of the Decay Missing Filled Teeth index and Caries By Risk Assessment (CAMBRA) determination. The current Oral health status was compared to the prior-to-study enrollment status and then analyzed in respect to published national norms.

Results:
Of the 53 subjects available for follow up, only 4 had remained caries active with a grand total of 17 caries lesions being detected and subsequently restored in this group. Of the original total of 60 patients with 292 initial carious lesions, after probiotic therapy and dental restoration, 36 total restorations were place in the subject group over the following three years. Approximately half of these restorations were required in teeth that had initially presented with smaller lesions and had been placed in a “watch” category. Two of the patients that developed further carious lesions had been randomly assigned to the probiotic PerioBalance, what the other two caries active patients were assigned EvoraKids probiotic.
Of the original group of caries active patients, 23 did not present with any further carious involvement. Another 26 could be categorized as Caries static, as the restorations required were substantially less than before probiotic therapy had been begun.
Conclusion:
Within the limitations of this retrospective IRB approved study, the tested probiotic supplements had a statistically significant effect on the caries experience of the enrolled subjects.
The ANOVA table decomposes the variance into two components: a between-group component and a within-group component. The F-ratio, which in this case equals 51.3313, is a ratio of the between-group estimate to the within-group estimate. Since the P-value of the F-test is less than 0.05, there is a statistically significant difference between the means of the 4 variables at the 95.0% confidence level.
Validation Study (I told you so!)

Low caries rate
To begin with!

Results
The groups were balanced at baseline and the attrition rate was 20%. Around 2/3 of the children in both groups reported an acceptable compliance. The caries increment (Δds) was significantly lower in the test group when compared with the placebo group, 0.2 vs. 0.8 (p < 0.05). The risk reduction was 0.47 (95% CI 0.24–0.98) and the number needed to treat close to five. No differences were displayed between the groups concerning presence of visible plaque or bleeding-on-brushing. No side effects were reported.
Oral Health Probiotics - what to use?

- Periobalance
- Probiora
- Biogaia
- ProlacSan
- BLIS K12
- Prodegin
- Gluten metabolizers
ProBioraPro Product Overview

- Distributed exclusively by dental professionals
- Extra-strength blend of ProBiora3® crowds out harmful bacteria
- Use once daily for 90 days after a dental hygiene visit
- Extends the benefits of a dental hygiene visit
The hazy background on these petri dishes is due to the growth of *Aggregatibacter actinomycetemcomitans*, or (Aa). In the petri dish to the right, the clear zone surrounding *S. oralis KJ3 and S. uberis KJ2 colonies* indicate that these beneficial bacteria are producing hydrogen peroxide which inhibits the growth of undesirable bacteria and naturally whitens teeth.
Infant Probiotics- Necessary?

• Depends on the maternal microbiome- probably YES!
Probiotics- Bio-kult for Infants

Probiotic Strains:

- Lactobacillus casei PXN® 37™
- Lactobacillus rhamnosus PXN® 54™
- Streptococcus thermophilus PXN® 66™
- Lactobacillus acidophilus PXN® 35™
- Bifidobacterium breve PXN® 25™
- Lactobacillus delbrueckii ssp. bulgaricus PXN® 39™
- Bifidobacterium infantis PXN® 27™

Each sachet contains:

- Minimum 1 billion microorganisms per sachet \((1 \times 10^9 CFU/g)\), guaranteed throughout the shelf life
Probiotics- BioGaia Protectis

- Establishing a healthy microbiota, filled with protective bacteria, is...
Lifeway Kefir is a tart and tangy cultured milk smoothie that is high in protein, calcium and vitamin D. Due to their exclusive blend of kefir cultures, each cup of kefir contains 12 live and active cultures and 15 to 20 billion beneficial CFUs.
Lifeway Kefir- ProBugs

- Frozen kefir for kids
- Great dessert item or health treat after a lot of outside play
Probiotics? Some caution necessary!

What is changing? What needs to change? Requires understanding.

A Review of Probiotic Therapy in Preventive Dental Practice

Mark L. Cannon
Probiotics often forgotten

Bacillus subtilis

Bacillus Subtilis

Contact details:

wuhan nature.en.alibaba.com
Probiotics and Microbiome

• Autism Spectrum Disorder
Autism is a disorder of neural development characterized by impaired social interaction and communication, and by restricted and repetitive behavior.

Repetitively stacking or lining up objects is a behavior occasionally associated with individuals with autism.

CDC estimate of autism prevalence increases to 15%. Now 1 in 59 children.

Autism Speaks calls on nations' leaders to adequately fund critical research and resources.

NEW YORK (April 26, 2018) The Centers for Disease Control and Prevention (CDC) today released its biennial update of autism’s estimated prevalence among the nation’s children, based on an analysis of 2014 medical and/or school records of 8-year-olds from 11 monitoring sites across the United States. The report demonstrates that while progress has been made on some fronts, there is still critical work to do.
Special Care for Special Patients

- The diagnostic criteria require that symptoms become apparent before a child is three years old.

A young boy with autism who has arranged his toys in order of size.
Here we first summarize previously published data supporting that GI dysfunction is common in individuals with ASD and the role of the microbiota in ASD. Second, by comparing with other publically available microbiome datasets, we provide some evidence that the shifted microbiota can be a result of westernization and that this shift could also be framing an altered immune system. Third, we explore the possibility that gut–brain interactions could also be a direct result of microbially produced metabolites.
Prevotella, is highly enriched in the fecal microbiota in populations in Africa including agrarian societies in Malawi and Burkina Faso, and the Hadza hunter–gatherers in Tanzania intrigued us and inspired us to perform comparative analyses. Since Prevotella is only one genus in the very diverse gut microbiota and has a tendency to co-occur with a complex collection of other bacteria species, we wanted to determine whether Prevotella depletion in children with ASD is an indicator that the gut microbiome of children with ASD who live in the United States differs even more from individuals in the developing world than does the gut microbiome of neurotypical children in the US, providing evidence of the gut microbiota as an environmental factor that may correlate with increased rates of ASD in industrialized countries.
A high rate of GI problems in children with ASD, correlations between symptom severity and GI symptoms within children with ASD, distinctive profiles of gut microbes and their metabolites in children with ASD, and growing appreciation of a link between the gut and other neurological disorders, all point towards the potential role for gut microbiota in the presentation and severity of ASD. Furthermore, our observation of a ‘hyper-Westernization’ of the gut microbiota of children with ASD could indicate that microbiota differences that are driven by unique aspects of the Western lifestyle compared to the developing world lead to the association of unique gut microbiota composition with ASD.
Fig 1. Cerebellar pathology in autism. (A) Normal cerebellar folia in a control brain (H and E staining). (B) Paucity loss of Purkinje cell layer (PCL) and granular cell layer (GCL) neurons (H and E) and (C) marked activation of microglia (immunostained with anti-HLA-DR antibody) are seen in the cerebellar fola of a patient with autism. Bar in A–C = 500 μm. (D) High-magnification detail of a cerebellar region with marked PCL and GCL neuronal loss (H and E). Bar = 50 μm. (E, F) Activated microglia around a Purkinje cell (E) and in the GCL (F), immunostained with anti-HLA-DR. Bars in E and F = 20 μm. (G) Close relationship of...
Valproate Model for Autism - tells all!

Behavior and serotonergic disorders in rats exposed prenatally to valproate: a model for autism.

Dufour-Rainfray D¹, Vourch P, Le Guisquet AM, Garreau L, Ternant D, Bodard S, Jaumain E, Gulhan Z, Baretz C, Andres CR, Chalon S, Guilloteau D.


Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism.

Christensen J¹, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M.


Demethylation of specific Wnt/β-catenin pathway genes and its upregulation in rat brain induced by prenatal valproate exposure.

Wang Z¹, Xu L, Zhu X, Cui W, Sun Y, Nishijo H, Peng Y, Li R.
Valproic and Propionic structures

Autism Spectrum Disorders
Research Article

Assessing autistic traits: cross-cultural validation of the social responsiveness scale (SRS)

Sven Bölte, Fritz Poustka, John N. Constantino

<table>
<thead>
<tr>
<th>TITLE</th>
<th>AUTHOR / YEAR</th>
<th>PMID</th>
<th>MATERIAL</th>
<th>NF PATIENTS / CONTROLS</th>
<th>CONCLUSIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal microbiota studies in late-onset autism</td>
<td>Finegold et al., 2001</td>
<td>121173102</td>
<td>Human (Stools)</td>
<td>13 ASD / 8 controls</td>
<td>Children with autism had nine species of Clostridium not found in controls, with significant alterations in the upper and lower intestinal flora of children with late-onset autism</td>
</tr>
<tr>
<td>Real-time PCR quantification of clostridia in feces of autistic children</td>
<td>Song et al., 2004</td>
<td>15529008</td>
<td>Human (Stools)</td>
<td>13 ASD / 8 controls</td>
<td>Analysis of the real-time PCR data showed cell count differences between autistic and control children for Clostridium boltae and histolyticum.</td>
</tr>
<tr>
<td>Differences in gut microbiota of children with autistic spectrum disorders and that of healthy children</td>
<td>Patradoo et al., 2005</td>
<td>161579505</td>
<td>Human (Stools)</td>
<td>50 ASD / 22 controls (2 groups)</td>
<td>The fecal flora of autistic spectrum disorder (ASD) patients contained a higher incidence of the Clostridium boltae and histolyticum enterotypes compared to healthy children. Elevated level of fecal lactobacilli was demonstrated in 24.4% stools, all from boys (91.2%). No toxins were detected. The boltae and histolyticum spp. were isolated with similar frequency from all samples. It was found that in ASD patients, Clostridium boltae and histolyticum were isolated significantly more often from the autistic stools. The highest microbial diversity was found in ASD children. Based on 16S-RNA and culture-dependent data, Faecalibacterium and Ruminococcus were present at the highest level in fecal samples of pervasive developmental disorder not otherwise specified (PDD-NOS) and healthy children. Faecalibacterium prausnitzii and Ruminococcus genus were the highest in ASD children.</td>
</tr>
<tr>
<td>Fecal lactobacilli and Clostridium spp. in stools of autistic children</td>
<td>Martońko et al., 2011</td>
<td>21167981</td>
<td>Human (Stools)</td>
<td>43 ASD / 10 controls</td>
<td></td>
</tr>
<tr>
<td>Fecal microbiota and metabolome of children with autism and pervasive developmental disorder not otherwise specified</td>
<td>De Angelli et al., 2013</td>
<td>24120622</td>
<td>Human (Stools)</td>
<td>20 ASD / 10 controls</td>
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</tr>
<tr>
<td>Urinary 3-(3-Hydroxyphenyl)-3-hydroxypropionic Acid, 3-Hydroxyphenylacetic Acid, and 3-Hydroxyhippuric Acid Are Elevated in Children with Autism Spectrum Disorders</td>
<td>Xiong et al., 2016</td>
<td>27123488</td>
<td>Human (Urine)</td>
<td>62 ASD / 62 controls</td>
<td>Measurement of these three compounds (aromatic metabolites in autism patients are presumably derived from overgrown Clostridium species in gut) are strong predictors of ASDs and support the potential clinical utility for identifying a subgroup of ASD subjects.</td>
</tr>
<tr>
<td>Intestinal Dysbiosis and Year Isolation in Stool of Subjects with Autism Spectrum Disorders</td>
<td>Jouvene et al., 2017</td>
<td>27655151</td>
<td>Human (Stools)</td>
<td>47 ASD / 33 controls</td>
<td>Significant linear correlation was found between disease severity and calprotectin and Clostridium spp. presence in the stool of subjects with ASD.</td>
</tr>
<tr>
<td>Analysis of the Oral and Microbiome in Autistic Individuals Association with Carbohydrate Digestion</td>
<td>Kuznik et al., 2017</td>
<td>27811633</td>
<td>Human (Intestinal biopsies)</td>
<td>21 ASD / 19 controls</td>
<td></td>
</tr>
<tr>
<td>Detection of Clostridium perfringens toxin genes in the gut microbiota of autistic children</td>
<td>Finegold et al., 2017</td>
<td>28215985</td>
<td>Human (Stools)</td>
<td>33 ASD / 19 controls</td>
<td>The author's results indicate that autistic subjects with gastrointestinal disease harbor significantly lower counts of C. perfringens and C. tertium toxin-producing C. perfringens in their gut when compared to control children. In addition, the incidence of C. tertium toxin-producing C. perfringens is also significantly higher in these autistic subjects.</td>
</tr>
</tbody>
</table>
Results: Eight strains were tested for polyol inhibitory activity: C. histolyticum, B. vulgatis, C. bolteae (x2), C. difficile (x2), Bifidobacterium longham, and Desulfovibrio. All strains grew to variable levels and had results that suggested polyol activity but did not reach a level of discernable growth to be able to assess the assays appropriately. Detailed OD values vs. polyol concentration are plotted as follows with relative inhibition inflection points.
Ann and Robert Lurie Children’s Hospital - Autism Spectrum Disorder Microbiome Research

Erythritol more effective
• Erythritol seems better suited to inhibit Clostridia bolteae
• Xylitol may be better at inhibiting C. difficile
• Perhaps we should think of another C. diff protocol?

CDC puts C difficile burden at 453,000 cases, 29,000 deaths

On the basis of a 2011 study, the Centers for Disease Control and Prevention (CDC) has increased its estimate of the annual burden of *Clostridium difficile* infections in the United States, putting it at 453,000 cases per year, with 29,300 associated deaths.

The agency, which released the findings in the *New England Journal of Medicine (NEJM)*, said they point up the need for better antibiotic stewardship and rigorous infection control in healthcare facilities.

*C diff* infections occur when someone is exposed to the pathogen while receiving antibiotic treatment for some other illness. Antibiotics suppress the normal bacteria in the colon, allowing *C diff* to flourish, producing toxins that cause severe diarrhea. Damage to the colon can cause bacteria to leak into the bloodstream.

The CDC found that about two thirds of the 453,000 cases were related to a stay in a hospital or nursing home and the other third were community-associated cases, involving people with no recent hospital or nursing home exposure. Most of those who died were elderly.
The Gut-Brain Axis: Early life programming of brain function and behavior
The role of epigenetic change in autism spectrum disorders

Yuk Jing Loke, Anthony John Hannan and Jeffrey Mark Craig

1Murdoch Childrens Research Institute, Royal Children’s Hospital and Department of Paediatrics, University of Melbourne, Parkville, VIC, Australia
2Melbourne Brain Centre, Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

**CONCLUSION:** Data reviewed in this article highlight a variety of situations in which epigenetic dysregulation is associated with the development of ASD, thereby supporting a role for epigenetics in the multifactorial etiologies of ASD.
DNA methylation and Autism

DNA methylation (DNAm) in a pilot study of postmortem brain tissue from 19 autism cases and 21 unrelated controls, among three brain regions including dorsolateral prefrontal cortex, temporal cortex and cerebellum.

The DMRs identified in this study represent suggestive evidence for commonly altered methylation sites in ASD and provide several promising new candidate genes.
DNA methylation and Autism

Genome-wide analysis of DNA methylation in a sample of 50 MZ twin pairs (100 individuals) sampled from a representative population cohort that included twins discordant and concordant for ASD, ASD-associated traits and no autistic phenotype.

Significant correlations between DNA methylation and quantitatively measured autistic trait scores across our sample cohort. This study represents the first systematic epigenomic analyses of MZ twins discordant for ASD and implicates a role for altered DNA methylation in autism.
Propionic acid (PPA) is a ubiquitous short-chain fatty acid which is a fermentation product of the enteric microbiome and present or added to many foods. PPA modulates mitochondrial dysfunction differentially in subsets of lymphoblastoid cell lines (LCLs) derived from patients with ASD. Specifically, PPA significantly increases mitochondrial function in LCLs that have mitochondrial dysfunction at baseline [individuals with autistic disorder with atypical mitochondrial function (AD-A) LCLs] as compared to ASD LCLs with normal mitochondrial function [individuals with autistic disorder with normal mitochondrial function (AD-N) LCLs] and control (CNT) LCLs.
In general, these data suggest that **BT can enhance mitochondrial function** in the context of physiological stress and/or mitochondrial dysfunction, and may be an important metabolite that can help **rescue energy metabolism during disease states**. Thus, insight into this metabolic modulator may have wide applications for both health and disease since **BT has been implicated in a wide variety of conditions including ASD**.
Oral Microbiome - Autism

Three-year consumption of erythritol-containing candies by initially 7- to 8-year old children was associated with reduced plaque growth, lower levels of plaque, acetic acid and propionic acid, and reduced oral counts of mutans streptococci compared with the consumption of xylitol or sorbitol candies.
SCFA - microbiome

• Pilot study of the SCFA Headspace Analysis of Bacterial Metabolites in Media with and without Polyols

• MacFabe, D., Habibi, Kabat, B., Cannon, M., Gashkoff, M., Zurek, R.
### Compound List

<table>
<thead>
<tr>
<th>Compound</th>
<th>Retention Time (min)</th>
<th>m/z</th>
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</thead>
<tbody>
<tr>
<td>Methyl Isovalerate</td>
<td>2.4</td>
<td>74</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>4.5</td>
<td>60</td>
</tr>
<tr>
<td>Propionic Acid</td>
<td>4.8</td>
<td>74</td>
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<tr>
<td>Butanoic Acid</td>
<td>5.1</td>
<td>60</td>
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<tr>
<td>Pentanoic Acid</td>
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<tr>
<td>Ethyl Butaric Acid</td>
<td>5.6</td>
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<td>4-Methylvaleric Acid</td>
<td>5.7</td>
<td>57</td>
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<tr>
<td>Hexanoic Acid</td>
<td>5.9</td>
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<tr>
<td>Ethanol</td>
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<td>45</td>
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<tr>
<td>Acetoin</td>
<td>3.8</td>
<td>45</td>
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Sample BK-4: Erythritol-1.25mg

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</table>
Constituents of media effect the bacterial metabolite production, possibly shifting from benign or protective to more pathogenic. Additional laboratory study is required testing other species, specifically the propionic producing *Clostridium histolyticum* and *boltae* plus *Bacteroides vulgatus*. 
Moreover, pathogens such as Haemophilus in saliva and Streptococcus in plaques showed significantly higher abundance in ASD patients, whereas commensals such as Prevotella, Selenomonas, Actinomyces, Porphyromonas, and Fusobacterium were reduced. Specifically, an overt depletion of Prevotellaceae co-occurrence network in ASD patients was obtained in dental plaques. The distinguishable bacteria were also correlated with clinical indices, reflecting disease severity and the oral health status. Finally, diagnostic models based on key microbes were constructed, with 96.3% accuracy in saliva.
Short-chain fatty acids (SCFAs), produced by anaerobic fermentation of mainly indigestible dietary carbohydrates by gut microbiota, have a profound influence on intestinal function and host energy metabolism. The total amount, types and distribution of nearly all fecal SCFAs were significantly altered during the administration and even after withdrawal of the antibiotics in rats.
We determined that short-chain fatty acids (SCFA), microbiota-derived bacterial fermentation products, regulated microglia homeostasis. Accordingly, mice deficient for the SCFA receptor FFAR2 mirrored microglia defects found under GF conditions. These findings suggest that host bacteria vitally regulate microglia maturation and function, whereas microglia impairment can be rectified to some extent by complex microbiota.
We analyzed nine studies, including 254 patients with ASD, and found that children with ASD had lower percentages of *Akkermansia*, *Bacteroides*, *Bifidobacterium*, and *Parabacteroides* and a higher percentage of *Faecalibacterium* in the total detected microflora compared to controls. In contrast, children with ASD had lower abundance of *Enterococcus*, *Escherichia coli*, *Bacteroides*, and *Bifidobacterium* and higher abundance of *Lactobacillus*. This meta-analysis suggests an association between ASD and alteration of microbiota composition and warrants additional prospective cohort studies to evaluate the association of bacterial changes with ASD symptoms, which would provide further evidence for the precise microbiological treatment of ASD.
Autism and microbiome

Important changes in gut microbiota at the end of treatment remained at follow-up, including significant increases in bacterial diversity and relative abundances of *Bifidobacteria* and *Prevotella*. Our observations demonstrate the long-term safety and efficacy of MTT as a potential therapy to treat children with ASD who have GI problems, and warrant a double-blind, placebo-controlled trial in the future.

**Figure 2**

From: Long-term benefit of Microbiota Transfer Therapy on autism symptoms and gut microbiota
Again, the microbiome is recognized as the programmer!
Grandkids!!!!
Erythritol was shown to be an **excellent HO• radical scavenger** and an inhibitor of 2,2′-azobis-2-amidinopropane dihydrochloride–induced hemolysis but inert toward superoxide radicals. The reaction of erythritol with hydroxyl radicals resulted in the formation of **erythrose and erythrulose** by abstraction of a carbon-bound hydrogen atom. Erythritol displayed an **endothelium-protective effect** and, in accordance with the in vitro experiments, erythrose was found in the urine of erythritol-consuming rats.
Dietary low-digestible carbohydrates (LDCs) affect gut microbial metabolism, including the production of short-chain fatty acids. Fecal suspensions from five healthy males were anaerobically incubated with various LDCs. L-Sorbose and xylitol markedly promoted butyrate formation in cultures. Bacterial 16S rRNA gene-based denaturing gradient gel electrophoresis analyses of these fecal cultures revealed a marked increase in the abundance of bacteria closely related to the species Anaerostipes hadrus or A. caccae or both, during enhanced butyrate formation from L-sorbose or xylitol.
Polyols- “Prebiotics”

Confocal microscopic observations showed that the most effective reagent to reduce *P. gingivalis* accumulation onto an *S. gordonii* substratum was erythritol, as compared with xylitol and sorbitol.

Metabolome analyses using capillary electrophoresis time-of-flight mass spectrometry revealed that a number of nucleic intermediates and constituents of the extracellular matrix, such as nucleotide sugars, were decreased by erythritol in a dose-dependent manner.
Polyols- “Prebiotics”

Xylitol, an Anticaries Agent, Exhibits Potent Inhibition of Inflammatory Responses in Human THP-1-Derived Macrophages Infected With Porphyromonas gingivalis

Eunjoo Park, Hee Sam Na, Sheon Min Kim, Shannon Wallet, Seunghee Cha, and Jin Chung

Inhibits cytokine inflammation
Increase nitric oxide production
Inhibits P. gingivalis attachment
Increases phagocytosis of E. coli and P. gingivalis
Polyols are the prebiotics—now for the probiotics for oral disease.
“No research!” Pubmed?
20672 articles on probiotics
The gut microbiota is extremely important for the health of the host across its lifespan. Recent studies have elucidated connections between the gut microbiota and neurological disease and disorders such as depression, anxiety, Alzheimer's disease (AD), autism, and a host of other brain illnesses. Dysbiosis of the normal gut flora can have negative consequences for humans, especially throughout key periods during our lifespan as the gut microbes change with age in both phenotype and number of bacterial species.
Fifteen articles were considered for this review. Of which, 12 were RCTs of good / high quality (Jadad scale), two meta-analysis and one systematic review. The literature reviewed suggests probiotics usage could be beneficial for the maintenance of oral health, due to its ability to decrease the colony forming units (CFU) counts of the oral pathogens. However, randomized clinical trials with long-term follow-up periods are needed to confirm their efficacy in reducing the prevalence/incidence of oral infectious diseases.
Within the limitations of this 18-year retrospective cohort study, our findings provide the first evidence that periodontal disease experience to some extent reflects the host susceptibility to onset of common systemic comorbidities.
Bacteria in Carotid Artery Plaque

Atherosclerosis, a disease condition resulting from the buildup of fatty plaque deposits within arterial walls, is the major underlying cause of ischemia leading to obstruction of peripheral arteries, congestive heart failure, heart attack, and stroke in humans. Emerging research indicates that factors including inflammation and infection may play a key role in the progression of atherosclerosis. In the current work, atherosclerotic carotid artery explants from 15 patients were all shown to test positive for the presence of eubacterial 16S rRNA genes.
Probiotics and *P. gingivalis*

Probiotics alter the immune response of gingival epithelial cells challenged by *Porphyromonas gingivalis*

Emmanuel Albuquerque-Souza, Danilo Balzarini, Ellen S. Ando-Sugulimoto, Karin H. Ishikawa, Maria R. L. Simionato, Marinella Holzhausen, Marcia P. A. Mayer

First published: 04 October 2018 | https://doi.org/10.1111/jre.12608

Probiotics reduce the adherence of *P. gingivalis*, the leakage and the systemic effects of periodontal disease!
The study included 67 salivary and subgingival lactobacilli of 10 species, isolated from healthy humans. The majority of strains suppressed the growth of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, and *Streptococcus mutans*.
All bifidobacteria integrated well into the subgingival biofilms composed of Porphyromonas gingivalis, Actinomyces naeslundii, and Fusobacterium nucleatum and decreased significantly only the number of P. gingivalis in the biofilms. The integration of bifidobacteria into the supragingival biofilms containing Streptococcus mutans and A. naeslundii was less efficient, and bifidobacteria did not affect the number of S. mutans in biofilms.
Oral infections with Porphyromonas gingivalis, or introduction of its lipopolysaccharide (LPS), in various mouse models has demonstrated the development of key neuropathological hallmark lesions defining AD. These are extracellular amyloid-beta plaques, phosphorylated tau, neurofibrillary tangles, widespread acute and chronic inflammation, blood–brain barrier defects together with the clinical phenotype showing impaired learning and spatial memory. Live P. gingivalis and its LPS (commercial or from ‘microbullets’) are powerful peripheral and intracerebral inflammatory signaling initiators, and this has direct implications on memory and lesion development.
Obesity and Cancer

Obesity is a known modifiable risk factor associated with adverse outcomes in children with cancer. We sought to determine whether obesity during childhood cancer treatment increases risk for second malignant neoplasms (SMN).

There was a significantly increased risk for SMN among patients who were obese at both diagnosis and EOT \([aOR, 4.44 (1.37–14.34)]\). This study suggests that obesity during childhood cancer treatment may be associated with increased risk for SMNs, particularly among those obese throughout therapy.
We examined human subjects and mouse models consuming Westernized 'fast food' diet, and found CD4+ Thelper \( \text{Th}^{17} \)-biased immunity and changes in microbial communities and abdominal fat with obesity after eating the Western chow. In striking contrast, eating probiotic yogurt together with Western chow inhibited age-associated weight gain. We went on to test whether a bacteria found in yogurt may serve to lessen fat pathology by using purified Lactobacillus reuteri ATCC 6475 in drinking water. Surprisingly, we discovered that oral L. reuteri therapy alone was sufficient to change the pro-inflammatory immune cell profile and prevent abdominal fat pathology and age-associated weight gain in mice regardless of their baseline diet. These beneficial microbe effects were transferable into naïve recipient animals by purified CD4+ T cells.
Mice topically treated with *L. brevis* CD2 displayed significantly decreased bone loss and lower expression of tumor necrosis factor, and interleukin-1β, -6 and -17A as compared to placebo-treated mice. Moreover, *L. brevis* CD2-treated mice displayed lower counts of anaerobic bacteria but higher counts of aerobic bacteria than placebo-treated mice.
The overuse of antibiotics is currently regarded as the most common reason for disturbance of gut microbiota, and if the disruption reaches a certain level, the host can develop *Clostridium difficile*–associated disease (CDAD). In summary, *B. fragilis* exerted protective effects on a CDI mouse model by modulating gut microbiota and alleviating barrier destruction, thereby relieving epithelial stress and pathogenic colitis triggered by *C. difficile*.

Literally hundreds of studies have demonstrated that probiotics protect all of us from disease! Published in all the top journals!
But then you have this?

• This received a ton of press but also a lot of outraged replies that were NOT covered, Fake News??

30 experimental subjects - sick, 8 controls...

The problems with this paper are first signaled by the very title of the piece where the authors conflate two separate entities, probiotics and small intestinal bacterial overgrowth (SIBO), and, in so doing, give the impression that they are equally culpable in the pathogenesis of their patients’ symptoms. No evidence is provided to support this.

It must be made clear that many lactobacilli and all bifidobacteria only produce L-lactate and do not possess the biochemical machinery to produce D-lactate. Neither, for that matter, do bifidobacterial produce gases. The authors, in contrast, state that ‘Both bacteria (referring to Lactobacillus and Bifidobacterium) produce D-lactic acid’ but provide no source for this statement.
This was a single-blind, randomized control study in which each subject was tested with only one mouthwash regimen. Fifty-two healthy qualified adult patients were selected randomly for the study and were divided into the following groups: group 1 - 10 ml of distilled water, group 2 - 10 ml of 0.2% chlorhexidine mouthwash, group 3 - 10 ml of 500 ppm F/400 ml sodium fluoride mouthwash, and group 4 - 10 ml of probiotic mouthwash.

Chlorhexidine, sodium fluoride, and probiotic mouthwashes reduce plaque S. mutans levels. Probiotic mouthwash is effective and equivalent to chlorhexidine and sodium fluoride mouthwashes. Thus, probiotic mouthwash can also be considered as an effective oral hygiene regimen.
The analysis identified 1,179 taxa, of which 24% were named, 8% were cultivated but unnamed, and 68% were uncultivated phylotypes.
Chris - back home.... Yay!!

Thanks!
Pediatric Oral Systemic Health: From Fetus to Adolescence

Mark Cannon* and John Peldyak

Division of Dentistry, Department of Clinical Otolaryngology, Northwestern University, Chicago, IL, USA

*Corresponding author: Mark Cannon, Division of Dentistry, Department of Clinical Otolaryngology, Northwestern University, Chicago, IL, USA
Review Article

The Prevention and Treatment of Neural Arterial Gingival Simplex

Cannon L Mark¹* and Peldyak N John²

Affiliation

¹Division of Dentistry, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA
²Dentistry practitioner in Mt. Pleasant, Michigan, USA

*Corresponding author: Mark L Cannon, Professor, Division of Dentistry, Department of Otolaryngology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA, Tel: 847-899-6720, E-mail: drmarkcannon@outlook.com

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Volume 3 Issue 1 | PDF 123 | Page 6
Learn more
A Lot More!

AAOSH 2019
Annual Scientific Session
October 17-20, 2019
Gaylord Opryland Resort &
Convention Center
Nashville, Tennessee

Thanks...