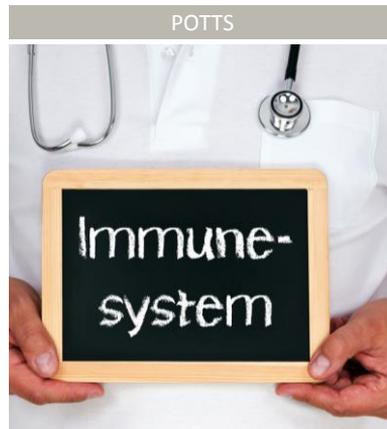




**GUTS, INFLAMMATION, & OUR CHILDREN'S HEALTH:  
THEIR FUTURE IS IN OUR HANDS**

AVIVA ROMM, MD

WHAT ROOTS DO THESE CONDITIONS  
SHARE?



CHRONIC ABDOMINAL PAIN, IBD



ALLERGIES & ASTHMA



CHRONIC INFECTIONS



DIABESITY



## SARAH: A 2 year old girl old w/JRA

- 2 yo girl old, dg with polyarticular JRA
- Fever x 1 week, ATC tylenol and ibuprofen
- → Gastritis, PPI x 8 months
- Developed polyarticular pain and swelling
- Diagnosed clinically by rheumatologist age 18 mo
- Chronic limp, pain → chronic NSAID use
- Born by NSVD, mother on insulin for poorly controlled GDM
- Live rurally, ? pesticide exposure, heavy metal contamination of water, ? arsenic exposure
- Rheumatologist ready to start S. on methotrexate

**SARAH IS REPRESENTATIVE OF INCREASING  
CHRONIC DISEASE SPECTRUM  
from ALLERGIES TO AUTOIMMUNITY!**

## Additional Assessments & Diagnoses for Sarah

- Eczema
- Digestive symptoms, especially bloating, belly aches
- Antibiotic Use
- Gluten Intolerant
- Iron deficiency anemia
- Lead - Elevated Body Burden
- MTHFR +/-

## THE NEW NORMAL or THE MODERN PLAGUE?

### Asthma

The most prevalent chronic disease affecting American children, leading to 15 million missed days of school per year. Increased From 3.6% to 9.4% between 1980 to 2008.

### Allergies

From 1997 to 2007, the prevalence of reported food allergy increased 18% among children under age 18 years. Doubling of peanut allergies in US and UK. Allergic rhinitis similarly increased in recent decade.

### Eczema

Increasing rates, now affects 15% of children and 2% of adults, Has tripled in industrialized countries in the past 30 years.

### Obesity

1 in 3 children is overweight or obese; diabetes in kids is increasing In the past 20 years, the prevalence of obesity among children aged 6-11 has more than doubled, and more than tripled for 12-19 year olds. Inflammation, toxins, nutrition.

### Diabetes

Affects one in 400-500 children. Approximately 15,000 youth (under age 20) in the United States are newly diagnosed with type 1 diabetes annually, and about 3,700 youth are newly diagnosed with type 2 diabetes annually.

### Mental Health

1 in 10 children and young people aged 5 - 16 suffer from a diagnosable mental health disorder - double the rate seen in the 1980s. One in 12 children is diagnosed with ADHD and 1/88 with ASD.

### Autism

1 in 68 kids is now on the autistic spectrum. Most with gut symptoms.

### Early Puberty

Girls as young as 8 years old are going through = increased susceptibility to immunologic problems due to toxin exposure.

### Cancer

The leading cause of death by disease among U.S. children between infancy and age 15. More than 10,000 new cases are expected to be diagnosed annually.



For the first time in modern history life expectancy in our kids is predicted to be shorter than our own.

THE CONVENTIONAL RESPONSE?



## Benign Conditions or Canaries in the Coalmine?

*And is this merely a  
rhetorical question?*

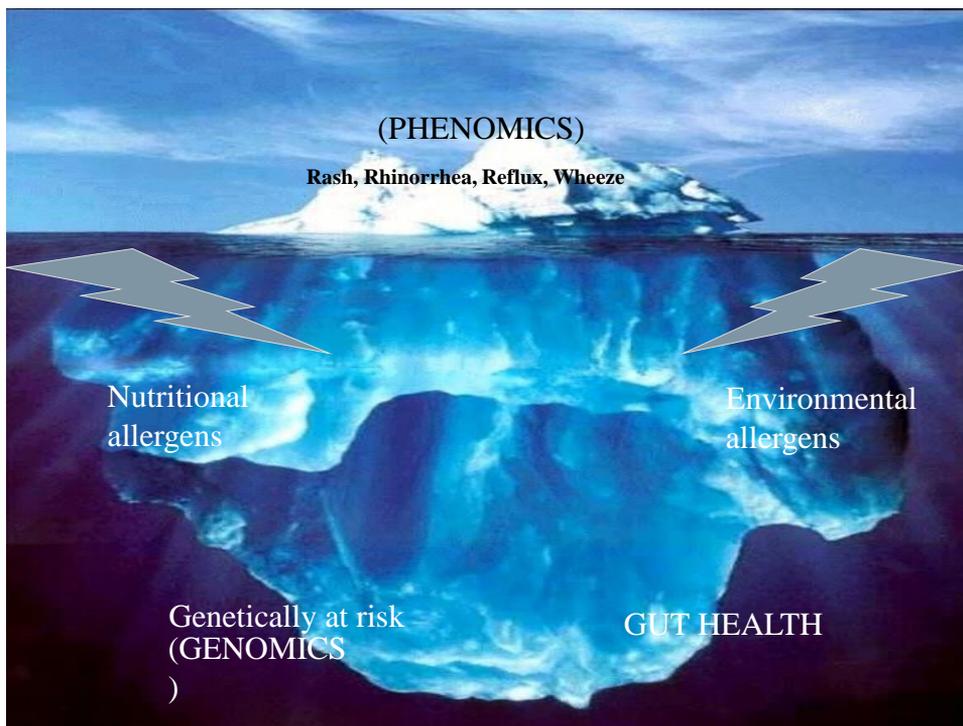
### The New Pediatric Morbidity or The Modern Plagues

Today the most serious diseases confronting children in the United States and in other industrially developed nations are a group of chronic conditions of multifactorial origin that have been termed the "new pediatric morbidity."

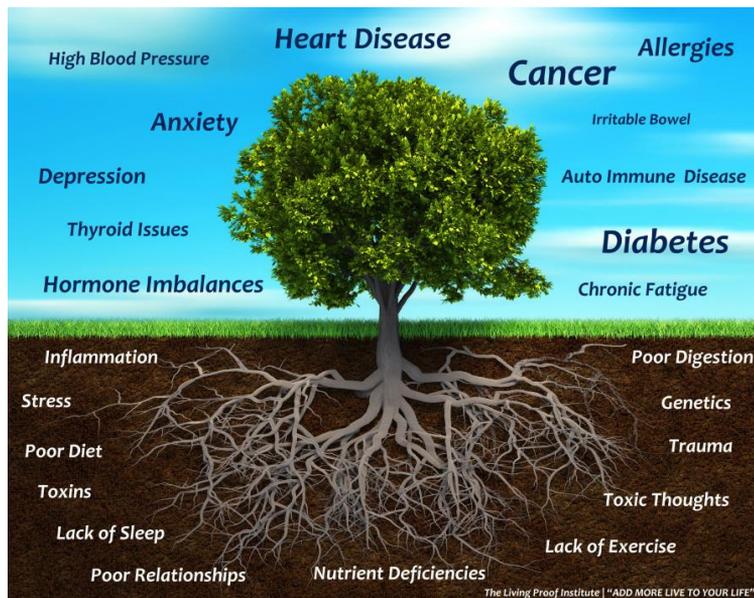
Examples include asthma, food allergies, diabetes, asthma, and obesity, in addition to childhood cancers, neurodevelopmental problems, and mood and behavioral issues.

Landrigan, P et al. Environmental pollutants and disease in American children: Estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environmental Health Perspectives* Jul 2002; 110:7, 721-28.

Blaser, M. *Missing Microbes*. Henry Holt and Company, NY, 2014.



## Roots Causes



## THE GUT CONNECTION

- Immunological dysregulation is the cause of many non-infectious human diseases such as autoimmunity, allergy and cancer.
- The gastrointestinal tract is the primary site of interaction between the host immune system and microorganisms, both symbiotic and pathogenic.
- Disturbances in the healthy bacterial microbiota of the human gut during critical windows, and generally, results in dysregulation of adaptive immune cell development and response.
- Increased intestinal permeability leads to sensitization of the immune system due to breach of barrier between response to "self" and "other."

## Commensal Bacteria and Immune Development

Inhibits epithelial NF- $\kappa$ B activation and inflammatory gene expression

Activates CD4 cells in Peyer's patches

Activates CD8 or natural killer cells in intraepithelial leukocyte spaces

Increases numbers of T and B cells, including CD86-positive cells

Organizes the special relationships between T, B, and dendritic cells in the Peyer's patches

Increases the numbers of microfold cells

Increases IgA producing B cells

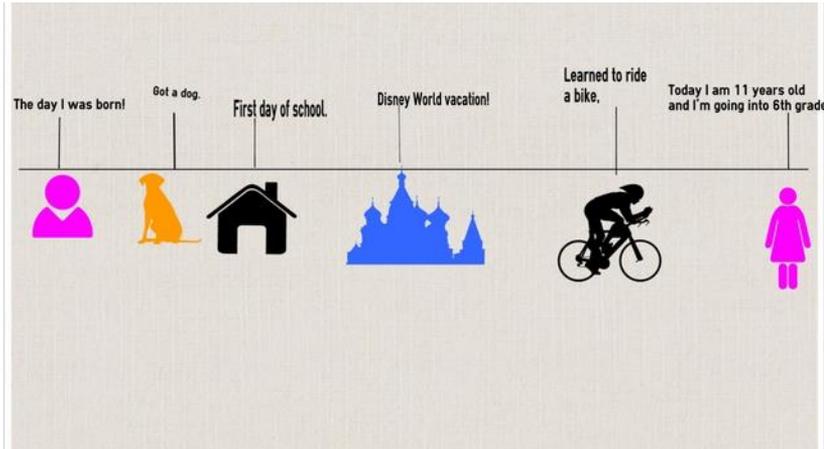
Hypertrophies Peyer's patches and the development of germinal centers

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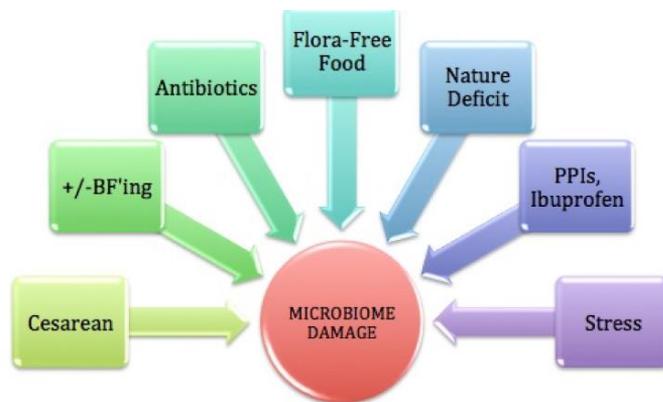
## GOALS FOR TODAY

- Learn how cesarean sections, urban living, antibiotics, ibuprofen, and PPI overuse are leading to dysbiosis and leaky gut in kids
- Understand the connection between leaky gut, dysbiosis, and pediatric inflammatory conditions – including atopy, food allergies, “diabetes,” and autoimmunity
- Learn why antibiotics and other medications are overprescribed, and some of the global problems behind antibiotic overuse
- Learn how to apply the 4R program at home with your children or in clinical practice with your patients
- Learn which lifestyle changes, supplements and botanicals heal leaky gut and inflammation, and can be used safely in children.

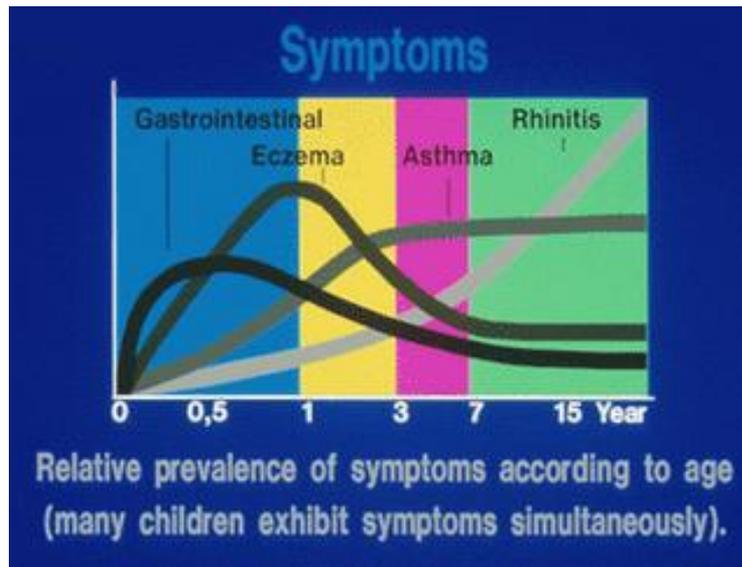
## The Timeline



## THE MODERN TIMELINE



## The Atopic March



Weinberg EG: The atopic march. *Current Allergy & Clinical Immunology*, 18: 4-5, 2005

## Sample Trigger Data

- Infantile colic a harbinger of atopy in children.
- Positive association between the lactulose to mannitol ratio and the severity of the eczema after active treatment with probiotics. Impairment of the intestinal mucosal barrier appears to be involved in the pathogenesis of atopic dermatitis.
- Meta-analysis of 8 studies examining relationship between exposure to antibiotics and development of childhood asthma compared exposure to at least one course of antibiotics in first year vs. no exposure (12,082 children, 1,817 asthma cases). Risk of asthma was significantly increased in children receiving one or more courses of antibiotics during first year of life: OR was 2.05 (95% CI 1.41-2.99). Dose-response analysis showed increase in OR of 1.16(95% CI 1.05-1.28) for each additional course of antibiotics.
- Cesarean section positively correlated with development of obesity and autoimmunity in children.

Savino, F. A prospective 10-year study on children who had severe infantile colic Colicky infants 10 years later. *Acta Paediatrica Suppl.* 94(s449): 129 - 132. 2005.

Marra C, et al. Does Antibiotic exposure During Infancy lead to Development of Asthma. *Chest* 2006.

J. L. Round and S. K. Mazmanian, The gut microbiota shapes intestinal immune responses during health and disease. *Nature Reviews Immunology*, vol. 9, no. 5, pp. 313–323, 2009.

Comito, D and C. Romano. Dysbiosis in the pathogenesis of pediatric inflammatory bowel diseases. *International Journal of Inflammation* Volume 2012 (2012),

## 3 KEY AREAS OF GUT PERTURBATION



- Dysbiosis
- Hyperpermeability
- Chronic inflammation

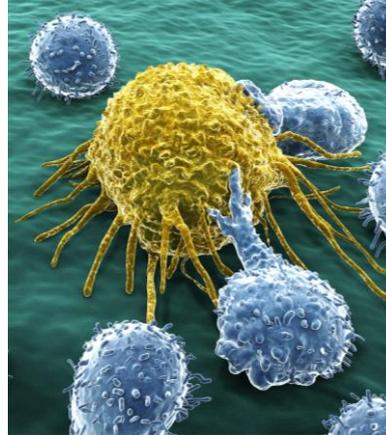
## The Microbiome



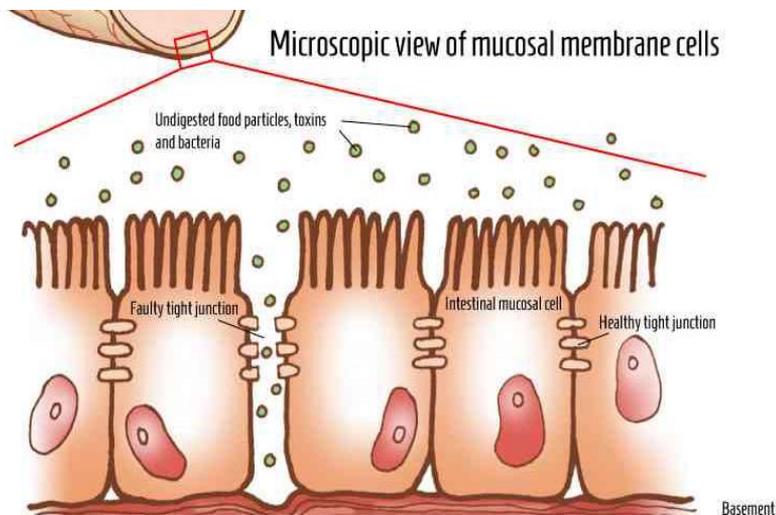
- The human gut is sterile at birth, but colonization with numerous bacterial species starts immediately after birth, generating a resident microbiota characterized by unique bacterial profiles and high interindividual and environmental variation.
- Adult microbiome usually established by age 3.
- The adult human microbiota consist of over a trillion bacterial cells and up to an estimated 1,000 different bacterial species.
- The predominant organisms found in healthy human large intestine are Gram-negative Bacteroidetes and Gram-positive low-GC Firmicutes.
- Microbiota composition varies greatly between individuals, with each individuals and is highly stable over time.
- The immune regulatory function of the intestinal microbiota consists of priming the mucosal immune system and maintenance of intestinal epithelium homeostasis.
- Microbiome also essential for healthy gut endothelium, nutrient production and metabolism, and detoxification.

## What is DYSBIOSIS?

- Dysbiosis is loss of biodiversity, species, and reserves, "Loss of ancestral defenses."
- Changes in species dominance from physiologic to pathologic
- Bacterial resistance of pathogenic species and even commensal species
- Lack of proper immunologic development and response



## What is LEAKY GUT?



## Barrier Protection



- An extremely important function of the intestine is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism.
- Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens.
- Zonulin is the physiological modulator of intercellular tight junctions involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance.
- Gluten is a known up-regulator of zonulin activity which leads to down-regulation of the protein occludin and results in increased gut permeability.

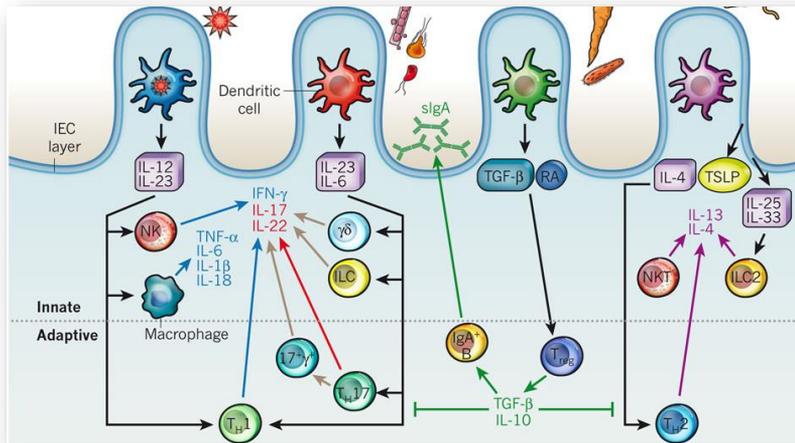
Fashion, A. Zonulin and Its Regulation of Intestinal Barrier Function: The Biological Door to Inflammation, Autoimmunity, and Cancer. *Physiological Reviews* Published 1 January 2011 Vol. 91 no. 1, 151-175

## The Healthy Epithelium



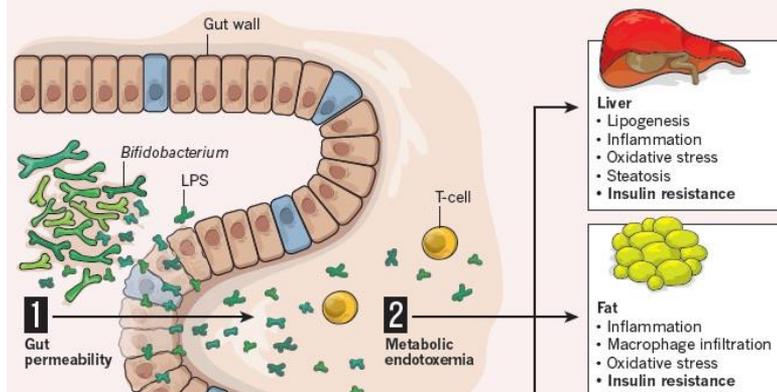
- Commensal bacteria play a role in maintaining the integrity of the intestinal epithelium.
- Intestinal epithelial cells (IECs) provide a physical barrier between luminal microbes and underlying intestinal tissues to control defense and tolerance.
- IECs express pattern recognition receptors (PRRs) and can recognize microbial pathogen-associated molecular patterns (PAMPs) and respond to intestinal microbes through secretion of cytokines and antimicrobial proteins and up-regulation of surface molecules that mediate intercellular interactions.
- Secretory IgA reduces intestinal proinflammatory signals and drives diversity in gut microbiota. Stress reduces SIgA.
- A defective barrier allows translocation of foreign proteins, LPSs, and can lead to endotoxemia, antibody formation and food sensitivities, allergic, and autoimmune responses. In a vicious cycle it also perpetuates disordered gut flora.
- Disruptions lead to disruptions in nutrition – many children end up anemic, low in vitamin D, depleted antioxidant status (ie glutathione).
- Endothelium also important for production of systemically important antioxidants reduction of which increases oxidative stress, as does the chronic gut inflammation so overall burden of oxidative stress increases.

## LEAKY GUT & IMMUNE DYSREGULATION



## Intestinal Permeability, Dysbiosis, and Obesity

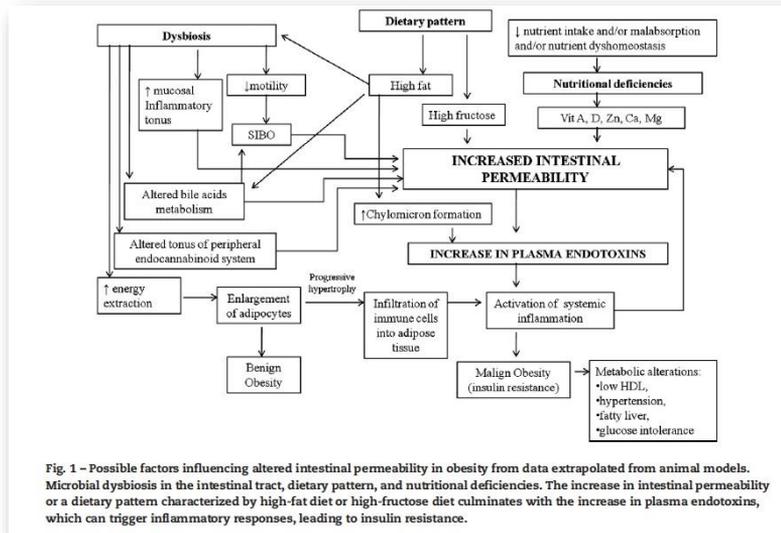
wall. The resulting metabolic endotoxaemia causes a low-grade inflammation and can induce a number of metabolic disorders – including the insulin resistance that characterizes T2D.



Gravitz, L. The critters within. *Nature*: 485; S12-13. 2012.

Teixeira, T. et al. *Nutrition Research*, Volume 32, Issue 9, September 2012, Pages 637–647

## Dysbiosis, Permeability, Obesity, and Inflammation



## OBESITY & GUT FLORA

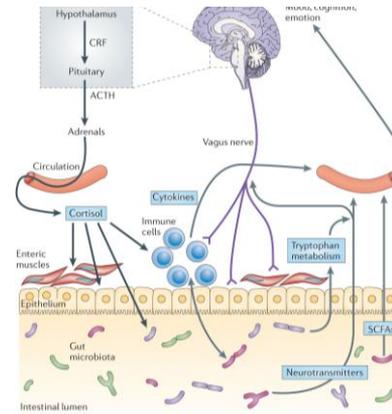
- 1990: 12% Americans obese
- 2010: 30%
- 2020 prediction: 50% obese with 1 in 2-3 with diabetes!
- Global fat accumulation has occurred in just 2 decades.
- Not just dietary changes but dietary changes in conjunction with losses in ancestral microbiome → changes in calorie extraction and fat metabolism
- Up to 15% of calories extracted by normal resident gut flora
- Cesarean section: 284 children (22.6%) were delivered by caesarean section. At age 3, 15.7% of children delivered by caesarean section were obese compared with 7.5% of children born vaginally. In multivariable logistic and linear regression models adjusting for maternal prepregnancy BMI, birth weight, and other covariates, birth by caesarean section was associated with a higher odds of obesity at age 3 (OR 2.10, 95% CI 1.36 to 3.23), higher mean BMI z-score (0.20 units, 95% CI 0.07 to 0.33), and higher sum of triceps plus subscapular skinfold thicknesses (0.94 mm, 95% CI 0.36 to 1.51).

Huh, S. et al. Delivery by caesarean section and risk of obesity in preschool age children: a prospective cohort study.

Arch Dis Child doi:10.1136/archdischild-2011-301141

M. G. Domínguez-Bello, E. K. Costello, M. Contreras et al., "Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns," Proceedings of the National Academy of Sciences of the United States of America, vol. 107, no. 26, pp. 11971–11975, 2010.

## PSYCHOBIOSIS & GUT-BRAIN SYNDROME

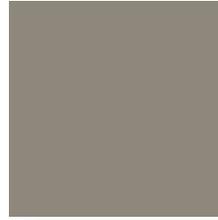


## FOOD INTOLERANCES & GLUTEN INTOLERANCE: WHAT'S REALLY GOING ON?

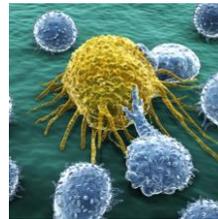
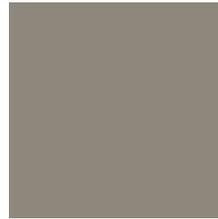
- Rates of food sensitivities and true food allergies sky-rocketing. “Biba I can’t have peanuts because they might make my friends sick.”
- Much more prevalent than previously thought; often still dismissed by conventional medicine but a growing body of evidence supports a range from GS to celiac disease.
- Multifactorial from possibility of GMO to changes in grain.
- Most likely underlying these are dysbiosis, gut inflammation and hyperpermeability a common underlying factor leading to translocation of proteins into circulation and triggering antibody formation, histamine reactions, and other allergic and inflammatory responses.
- Once triggered on “red alert.”

## What do 34% AND 40% Represent?

Loss of gut and skin flora during critical windows of immunologic development.



## How about 10-20? And 13?



## CESAREAN SECTION & MICROBIOME DISRUPTION EFFECTS ON HEALTH



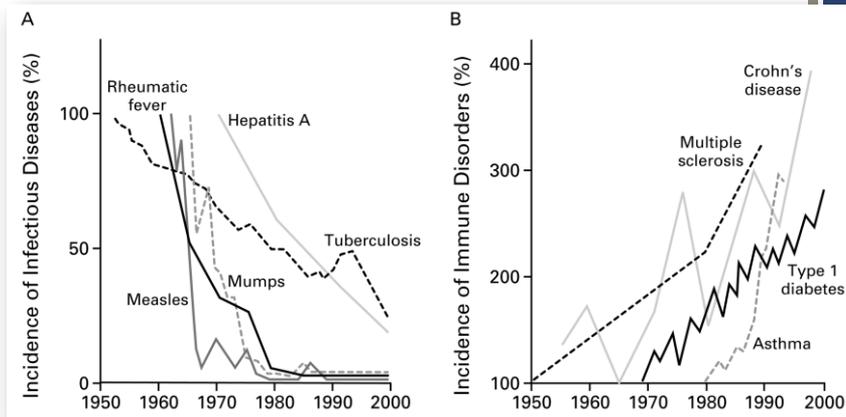
- Gut, oral, dermal colonization affected by change in mode of birth.
- Most adult flora determined by early inoculation and established by age 3.
- Affects immune development via altered signaling mechanisms affecting Th2 differentiation and/or tolerance induction and leading to Th1 dominance with increased respiratory reactivity.
- Cesarean section increases the risks of
  - Allergic rhinitis
  - Asthma
  - Celiac disease
  - Type I Diabetes
  - Obesity
  - IBD

## WHY THE ANTIBIOTICS OVERUSE?



- Practitioners afraid not to rx antibiotics for fear of legal repercussions
- Practitioner perception that patients want/expect an antibiotic prescription
- Lack of time to discuss alternatives in the context of conventional medical care
- Lack of knowledge of alternatives to conventional interventions; especially notable is a lack of knowledge of botanicals

## Hygiene Hypothesis & Gut microbial deprivation hypothesis



Bach JF. 2002. N Engl J Med. 347:911.

## Nature Deficit Disorder: Let Them Get Dirty & Play with Animals

Soil microbiota a missing link?



Benefits of play & dirt!



## STRESS & THE GUT

- “I feel it in my gut,” “I can’t stomach this,” “This makes me sick to my stomach”...
- Stress reduces SIgA
- Stress diverts blood flow from away from the gut
- Known impact on predominant species with changes seen in reduction in *Lactobacillus* and *Bifidobacterium* spp toward *Coliform* and *E coli*.
- Stress changes the chemical milieu which changes the food resources available for gut flora.
- Changes in neuro-immune system now known to be ubiquitous and completely interconnected and not really separate systems.

## THE LONG AND SHORT TERM SOLUTIONS

### IN PREGNANCY

- NON-restrictive maternal diet
- Maternal probiotic use to ensure healthy vaginal and GI flora
- Maternal optimized nutrition
- Reduce maternal morbidity that can have an impact: preterm labor risks, gestational diabetes (inflammation, dysglycemia, and increased cesarean risk), reduce maternal prenatal use of antibiotics (i.e, chronic UTI ppx).

### PERINATALLY

- Change priorities to reduce cesarean section rate (midwives, doulas, evidence-based obstetrics practices)
- Reduce intrapartum and immediate postnatal maternal antibiotic use
- Consider methods of reinoculating newborns:
  - BF’ing
  - “Gauze in the vagina”
  - Probiotics

## ANTIBIOTIC STEWARDSHIP: A NEW APPROACH TO ILLNESS PPX and TX

### INFECTION PREVENTION

- Healthy lifestyle, optimal nutrition
- Probiotics
- Saline nasal washes
- Echinacea, Zinc, Vitamin C
- Xylitol
- Avoid sanitizers

### NATURAL INFECTION TREATMENT

- EDUCATE PEDIATRICIANS AND FPS, change reimbursement priorities to allow time for physicians to talk with parents
- EDUCATE PARENTS
- AVOID UNNECESSARY ABX: Sweden vs US 388: 833/1000 people, no change in infx dx outcomes; France 2006-07 32% reduction in pediatric abx rx to achieve overall national abx efficacy
- AVOID IBUPROFEN, NSAIDS
- AVOID PPIs
- BOTANICALS FOR COMMON CHILDHOOD ILLNESSES AS NEEDED
- ZINC, VITAMIN C, PROBIOTICS, ETC

## GUT HEALTHY DIET

- Smart start to solids; no food avoidance unless necessary +/- dairy products
- Food diversity
- REAL food
- Fiber
- Fermented foods
- Low sugar
- Avoid antibiotic exposures in foods
- Healthy daily (or age appropriate) evacuation

Silano M, Agostoni C, Guandalini S. Effect of the timing of gluten introduction on the development of celiac disease. *World J Gastroenterol.* 2010 April 28; 16(16): 1939-1942  
 Greer F, Sicherer SH, Burks AW. Effects of Early Nutritional Interventions on the Development of Atopic Disease in Infants and Children: The Role of Maternal Dietary Restriction, Breastfeeding, Timing of Introduction of Complementary Foods, and Hydrolyzed Formulas. *Pediatrics.* Vol. 121 No. 1 January 2008, pp. 183-191

## (Breast) Food as Medicine

- Lower incidence of atopy disease and autoimmunity in BF children.
- No clear evidence that maternal dietary restrictions during pregnancy or lactation play a significant role in the prevention of atopic disease in infants; possible exception of eczema in some cases (lactation)
- For infants at high risk of developing atopic disease, there is evidence that exclusive breastfeeding for at least 4 months compared with feeding intact cow milk protein formula decreases the cumulative incidence of atopic dermatitis and cow milk allergy in the first 2 years of life.

## THE 4R PROGRAM



- **Remove:** Triggers and irritants
- **Replace:** Digestive enzymes and hydrochloric acid, for example, are replaced in this phase. Low B complex associated with low stomach HCL.
- **Repair:** Provide nutrients that nourish and heal the intestinal membranes and healthy flora. Consider L-glutamine, turmeric, licorice root extract (or DGL), marshmallow root, zinc, quercetin, and larch-arabinogalactans.
- **Reinoculate:** Prebiotics and probiotics, along with good quality fiber

## REMOVE: THE ELIMINATION DIET

- Elimination phase: “classical approach” and “gold standard”
  - 2-6 weeks
  - Highly simplified diet
  - Avoiding common causes of food sensitivity
  - Daily symptom monitoring
  - Screen for eating disorder
  - Pros and cons of “all-in” vs. staged elimination
- Study findings are equivocal but some studies find definite improvement with use of elimination diet
- Most common foods in producing allergy symptoms are milk, eggs, chocolate, soy, citrus, nuts, wheat and corn
- Skin testing for allergens does not usually correlate with clinical symptoms

Oehling A, Garcia B, Santos F, et al. Food allergy as a cause of rhinitis and/or asthma. *J Investig Allergol Clin Immunol.* 2:78-83, 1992.

Onorato J, Merland N, Terral C, Michel FB, Bousquet J. Placebo-controlled double-blind food challenge in asthma. *J Allergy Clin Immunol.* 78:1139-1146, 1986.

James JM, Bernhisel-Broadbent J, Sampson HA. Respiratory reactions provoked by double-blind food challenges in children. *Am J Respir Crit Care Med.* 149:59-64, 1994.

Pelikan Z, Pelikan-Filipek M. Bronchial response to the food ingestion challenge. *Ann Allergy.* 58:164-172, 1987.

## Elimination Diet

- Provocation/ “Testing” phase
  - Add one new food every 3-5 days
  - Start with foods eaten most frequently
  - Continue daily symptom monitoring
  - If no change in symptoms, food can stay in diet; if symptoms worse, food should be avoided as a possible cause
  - Use of “rotation diet” concept

## REPLACE

- Nutrients – gut permeability reduces nutrition
- Enzymes
- Betaine HCL
- B-6

## REINOCULATE

- Probiotics, prebiotics, symbiotics
  - S. Boulaardi
  - Bifido spp, Lactobacillus spp.
  - VSL#3 (Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus and Streptococcus thermophilus)
  - Klare Therbiotic Infant

## Probiotic Benefits



- Double-blinded, placebo-controlled, cross-over study, probiotic lactobacilli (Lactobacillus rhamnosus 19070-2 and L reuteri DSM 12246) were administered for 6 weeks to 41 children with moderate and **severe atopic dermatitis**. **Significant decrease in the frequency of gastrointestinal symptoms** during active treatment (39% during the placebo period versus 10% during active treatment, P=.002).

Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *Journal of Pediatrics*. 145(5):612-6, 2004

## Prevention of Atopic Disease with Probiotics



- Double blind randomized placebo-controlled trial (n=132) of children with a strong family history of atopic disease
- Lactobacillus GG (1X 10<sup>10</sup> CFUs) to mothers for 2-4 weeks prenatally and then to infants postnatally for six months
- **Atopic eczema dx by age 2 in 23% (15/64) of probiotic group vs. 46% (31/68) in placebo group (RR 0.51 95% CI 0.32-0.84)**
- Number needed to treat 4.5

Kalliomaki M et al. Probiotics in primary prevention of atopic disease: A randomised placebo-controlled trial. *Lancet*. 2001; 357:1076-79

## Reduction in Allergic Rhinitis with Probiotic Treatment

- Nine of 12 RCTs reviewed by Cochrane that evaluated clinical outcomes **in AR showed an improvement** (lower reported AR scores and less medication use) due to the use of probiotics. compared with placebo.
- Also, 5 of the 8 RCTs that referred to seasonal AR suggested an improvement in clinical outcomes.
- Nine RCTs that reported various immunologic measurements of allergy found no significant probiotic effects and no clear improvement in asthma.

Vliagoftis V, Kouranos V, Betsi G, Falagas M. Probiotics for the treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials. *Annals of Allergy, Asthma & Immunology* 101:6, 200

## Prevention of Atopic Disease with Probiotics

- **Perinatal administration of the probiotic *Lactobacillus rhamnosus* strain GG (ATCC 53103), reduces incidence of atopic eczema in at-risk children during the first 2 years of life (infancy).**
- At age 4, 14 of 53 children receiving *Lactobacillus* had developed atopic eczema, compared with 25 of 54 receiving placebo (relative risk 0.57, 95% CI 0.33-0.97).
- Skin prick test reactivity was the same in both groups: ten of 50 children previously given *Lactobacillus* compared with nine of 50 given placebo tested positive.

Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet*. 2003 May 31;361(9372):1869-71

## Prevention of Atopic Disease with Probiotics



- 7-year follow-up confirmed that the cumulative risk of developing eczema during the first 7 years of life was significantly lower in the probiotic group than in the placebo group.
- However, atopic sensitization was similar between the groups, suggesting that the preventive effect on eczema was not IgE-mediated.

Kalliomaki M, Salminen S, Poussa T, et al. Probiotics during the first 7 years of life: a cumulative risk reduction of eczema in a randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2007;119:9–21.

## Prevention of Atopic Disease with Probiotics



- Abrahamsson: cumulative incidence of eczema was similar in babies receiving *Lactobacillus reuteri* before delivery and up to 12 months old and the control group. The *L. reuteri* group did have lesser IgE-associated eczema during the second year
- Kuitunen: 1223 mothers with infants at high risk for allergy were randomized to receive probiotic or placebo during the last month of pregnancy and their infants to additionally receive prebiotic galactoligosaccharide from birth until 6 months. No differences in the frequency of allergic diseases and sensitization after 5 years of follow-up.
- BUT...Less IgE-associated allergic disease occurred in cesarean-delivered children receiving a probiotics mixture.

Abrahamsson TR, Jakobsson T, Bottcher MF, et al. Probiotics in prevention of IgE-associated eczema: a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 2007;119:1174–1180.

Kuitunen M, Kukkonen K, Juntunen-Backman K, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol.* 2009;123:335–341.

## Altered States



- Gut microbiota of children with atopy characterized by a predominance in *C. difficile*, *Coliform* species, and *S. aureus* compared with non-allergic children

Bereltsen RJ et al. Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. *J Allerg Clin Immunol.* 2014 ; 133, 165-171.

## Physiologic mechanisms for probiotics in atopic disorders



- TH1 vs. TH2 regulation: may help downgrade TH2 responses which lead to atopy (hygiene hypothesis)
- Systemic down-regulation of inflammatory processes by balancing the generation of pro and anti-inflammatory cytokines
- Capacity to reduce the dietary antigen load by degrading and modifying macromolecules in the gut
- Reverse the increased intestinal permeability characteristic of children with food allergy
- Enhance specific IgA responses frequently defective in children with food allergy

## REPAIR



- Reduce inflammation from diet to allow healing diet
- Appropriate supplements especially zinc and L-glutamine.
- Botanicals

## L-glutamine



- Amino acid
- Stimulates enterocyte repair and proliferation.
- Increases intestinal villous height, stimulates gut mucosal cellular proliferation, and maintains mucosal integrity.
- Prevents intestinal hyperpermeability and bacterial translocation.
- In inflammatory conditions, the availability of glutamine as an enterocyte fuel substrate is essential for the preservation of a functional barrier to microorganisms.

Rhoads, J et al. L-glutamine stimulates intestinal cell proliferation and activates mitogen-activated protein kinases. *Amer J Phys*.1997 Vol. 272 no. 5, G943-G953  
Miller AL. Therapeutic considerations of L-glutamine: a review of the literature. *Alternative Medicine Review: a Journal of Clinical Therapeutic* [1999, 4(4):239-248]  
Clark, EC. et. al. Glutamine deprivation facilitates tumour necrosis factor induced bacterial translocation in Caco-2 cells by depletion of enterocyte fuel substrate. *Gut* 2003;52:224-230

## Zinc

- Considered to be a key factor for the preservation of structural integrity of the intestinal barrier
- Improves enterocyte repair, aids in repair of cells with rapid turnover – esp mucosa and immune system.
- Correction of zinc deficiency leads to a faster regeneration of the gut epithelium and increases the levels of enterocyte brush-border enzymes
- Also antioxidant
- Zinc absorption is inhibited by some non-digestible plant ligands, such as contained in corn, cereals, rice, legumes, which form insoluble complexes with zinc ions that are excreted in the stool.
- The amount of proteins is positively correlated with zinc bioavailability.
- Some proteins, such as casein in milk and soy protein, have been reported to have an inhibitory effect on zinc absorption

Faa et al. Zinc in gastrointestinal and liver disease. *Coordination Chemistry Reviews*. Volume 252, Issues 10–11, May 2008, Pages 1257–1269  
 Prasad, A. Zinc: role in immunity, oxidative stress and chronic inflammation *Current Opinion in Clinical Nutrition and Metabolic Care*. Issue: Volume 12(6), November 2009, p 646–652

## IgG Antibodies

- Bovine or serum derived
- Colostrum is the first natural food produced by female mammals during the first 24–36h directly after giving birth.
- Chemically, colostrum is a very complex fluid rich in nutrients, antibodies and growth factors. In cows the antibodies provide passive immunity to the new born calf, whereas the growth factors especially stimulate the growth of the gut.
- The other antimicrobial components of colostrum include lactoferrin, lysozyme and lactoperoxidase.
- Bovine colostrum has also been used as a raw material for immunoglobulin-rich commercial products (immune milk preparations).
- These products can be given orally to patients who are suffering infections of the gastrointestinal tract or in order to prevent these infections.
- Several animal studies have shown that the growth factors in bovine colostrum, especially insulin-like growth factors, stimulate cell growth in the gut.

Stewagen, K et al. Immune components of bovine colostrum and milk. *Journal of Animal Science* [2009, 87(13 Suppl):3-9]  
 Playforda, R.J. Bovine colostrum is a health food supplement which prevents NSAID induced gut damage. *Gut* 1999;44:653-658.

## Quercetin



- Flavonoid in red wine, tea, onions, kale, tomatoes, broccoli, green beans, asparagus, apples, and berries
- Anti-inflammatory
- May influence immune system function
- Demonstrates activity against retroviruses, parainfluenza, and respiratory syncytial viruses.

**Dose:** Typical dietary intakes are between 5 mg and 40 mg/day -- 250-500 mg/day with high consumption of fruits and vegetables, especially if eating peel. Supplement 250-500 mg 1-2x daily. (Question of nephrotoxicity > 722 mg/day)

Stoner, G, Wang, LS. (2013). Natural Products as Anti-inflammatory Agents. In *Obesity, Inflammation and Cancer* (pp. 341-361). Springer New York.

## Turmeric



### What the Science Says

- NIH: positive studies for UC, Crohn's, rheumatoid d/o
- In vitro and animal studies show it increases phase II enzymes and inhibits phase I CYP1A
- Antioxidant effects: Down regulates COX2, LOX, NFkB, AP-1, TNF

### Safety

- Warfarin interaction, bleeding risk at high doses

### Dose (Adult)

- 1200-2400 mg/d curcumin for IBD
- India: average daily intake = 60 mg curcumin (2.5 gm/d of turmeric)
- 20 mg black pepper/1 kg curcumin -> approx 2000% absorption increase

Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res* 2012;26:1719-25.

Taylor RA, Leonard MC. Curcumin for inflammatory bowel disease: a review of human studies. *Altern Med Rev*. 2011 Jun;16(2):152-6.

## Chamomile



- Traditionally widely used
- Evidence based uses included
  - Anxiety/GAD
  - Colic (w/fennel, lemon balm)
  - Pediatric “stomach aches”
  - Diarrhea (w/apple pectin)
  - Dyspepsia (in Iberogast)
  - Oral mucositis

**Dose:** 1 ml TID

### Safety

- May cause allergic reaction in some individuals (rare).

McKay DL, Blumberg JB. A review of the bioactivity and potential health benefits of chamomile tea (*Matricaria recutita* L.). *Phytother Res.* 2006 Jul;20(7):519-30.  
 Ross SM. Generalized anxiety disorder (GAD): efficacy of standardized *Matricaria recutita* (German chamomile) extract in the treatment of generalized anxiety disorder. *Holist Nurs Pract.* 2013 Nov-Dec;27(6):366-8.

## Ginger



### What the Science Says

- Clinical research shows that taking ginger extracts can modestly improve pain in some patients with osteoarthritis
- May be comparable to ibuprofen in a dose of 500 mg twice daily
- Also compared favorably to diclofenac + glucosamine sulfate
- There is some preliminary evidence that ginger might be helpful for decreasing joint pain in patients with RA

**Dose (Adult):** 250 mg ginger extract four times daily, dosing may vary according to the preparation

Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum.* 2001 Nov;44(11):2531-8.  
 Srivastava K. C, Mustafa T. Ginger (*Zingiber officinale*) in rheumatism and musculoskeletal disorders. *Med Hypotheses.* 1992;39(4):342-8

## Licorice



- Traditional uses: cough, colds, sore throat, GERD, gastritis
- Compounds in licorice increase local prostaglandin levels that promote mucus secretion and cell proliferation in the stomach
- Preparations without glycyrrhizin are called DGL

### Dose

- 700-800 mg (760 mg)
- Chewable tablets

**Safety:** Avoid in pts with HTN, hyperaldo, on steroid. Likely safe in healthy adults when used at doses not exceeding 3 grams/d for periods up to 3-4 weeks.

## Sarah's Supplements

- Multivitamin
- Proprietary licorice blend containing licorice, ashwagandha, rehmannia, and wild yam.
- Chamomile tea
- Pro EFA Jr- Nordic Naturals, 1, twice daily
- Vitamin D3
- Curcumin concentrate with ginger and boswellia
- L-Glutamine
- Zinc
- Probiotic containing Lactobacillus and Bifido strains

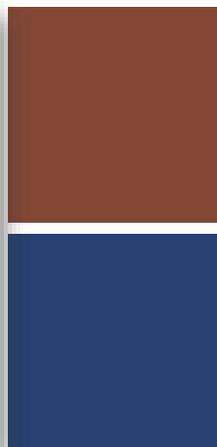
## Evaluation & Testing

- History reveals the cure
- Diet & nutrition review
- Digestion evaluation
- (Known) toxic or infectious exposures
- CBC, iron studies, ANA, ESR Lyme (WB)
- Celiac HLA, Gluten Abs
- EFA testing (omega 3, 6)
- Leaky gut via lactulose: mannitol
- Stool testing
- Detox studies
- Can consider IgG and IgM testing thru specialty labs

## Sarah Gets Her Life Back!



- 8 months no need for NSAIDs, methotrexate no longer indicated
- Has had 1 (prescheduled) joint injection
- Per rheumatologist, only 1 joint (index finger) remains slightly swollen compared to 8 joints before starting care
- Able to run, play, dance without pain, just like other kids in family!



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