A Unified Theory of Disease

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Disclosure

Joe Pizzorno, ND disclosed he was on the advisory board for Bioclinic Naturals and his spouse is a consultant for AlgaeCal.
Outline

• Humans are Complex, Synchronous Enzyme Machines
• Themes
  1. Nutrient Deficiencies Rampant
  2. High Body Load of Toxic Metals and Chemicals
  3. Deficiencies + Toxins Synergistically Increase Damage
  4. Human Physiology Massively Parallel—Few Single Pathways
  5. Modern Agriculture Dangerously Distorts Food Supply
  7. Loss of Synchronization with the Environment
• Putting It All Together
• Take Home Message
HUMANS ARE COMPLEX,
SYNCHRONOUS ENZYME MACHINES
Theme 1

NUTRIENT DEFICIENCIES RAMPANT
Decreasing Nutrient Density (1950-1999)

- 43 foods (mainly vegetables)
- 13 nutrients measured
- 6 significantly low
  - Biggest drop 37% in riboflavin
- Did not measure trace minerals!

“Changes in seed types …not fertilizer.”

Chemical Fertilizers Decrease Minerals (1940-1991)

Commonly eaten foods
- Vegetables – 27
- Fruits – 17
- Meats – 10
- Dairy – 2
- Fish – no data

Every mineral, except phosphorus in fruits and vegetables (fertilizer) and sodium in dairy decreased significantly
- Trace minerals worst
- Cu down 77% in vegetables

Fertilizers Decrease Nutrient Density

- Fertilizers make plants grow bigger causing “dilution effect”
- Red raspberry nutrient content decreases in proportion to use of high-phosphate fertilizers

122 Years of Data!

- 14 varieties of hard red winter wheat
- 20-33% drop in minerals/100 years
- Strong inverse correlation with mineral content and size

Wallace TC, McBurney M, Fulgoni VL 3rd. Multivitamin/mineral supplement contribution to micronutrient intakes in the United States, 2007-2010
Theme 2

HIGH BODY LOAD OF TOXICANTS
# Lead: Increases All-Cause Mortality & Death From Cardiovascular Disease


## Table 2: Adjusted HRs, population attributable fractions, and avoidable deaths from all causes, cardiovascular disease, and ischaemic heart disease in the NHANES-III mortality follow-up study (n=14 289)

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR (95% CI)</th>
<th>HR (95% CI)</th>
<th>Population attributable fraction (95% CI)</th>
<th>Avoidable deaths (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>3.79 (3.18-4.50)</td>
<td>1.37 (1.37-1.60)</td>
<td>18.0% (10.9-26.1)</td>
<td>412 000 (250 000-598 000)</td>
</tr>
<tr>
<td>Cardiovascular disease mortality</td>
<td>4.44 (3.47-5.68)</td>
<td>1.70 (1.30-2.22)</td>
<td>28.7% (15.5-39.5)</td>
<td>256 000 (138 000-352 000)</td>
</tr>
<tr>
<td>Ischaemic heart disease mortality</td>
<td>5.31 (4.06-6.93)</td>
<td>2.08 (1.52-2.85)</td>
<td>37.4% (23.4-48.8)</td>
<td>185 000 (116 000-241 000)</td>
</tr>
</tbody>
</table>

All models are adjusted for age (continuous and age-squared), sex, household income (≤US$20 000 or ≥$20 000 per year), ethnic origin (white, black, or Mexican-American), body mass index (normal [<25.0 kg/m²], overweight [25.0-29.9 kg/m²], or obese [≥30.0 kg/m²]), smoking status (never, current, or former), hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), urinary cadmium (tertiles [µg/g]), alcohol consumption (four or fewer or more than four drinks per month), physical activity in previous month (none, one to 14 times, 15 or more times), healthy eating index (tertiles), serum cholesterol (continuous), and glycated haemoglobin (continuous). Hazard ratios (HRs) for continuous concentrations of lead in blood represent the risk for an increase in log-transformed concentrations of lead in blood from 1.0 µg/dl to 6.7 µg/dl (0.048 µmol/L to 0.324 µmol/L, tenth to 90th percentiles).
Arsenic: Major Factor in Many Cancers

- 3,932 American Indians
- Dose-dependent carcinogen
- Arseic dose-dependent correlation with:
  - Overall cancer risk
  - Cancers of lung, prostate, pancreas, liver
- Arsenic not associated with cancers of:
  - Esophagus, stomach, colon, rectum, breast
- Protective for blood cancers?
- Adjusted for age, sex, smoking status, BMI (kg/m2)

Arsenic Contamination of US Water Supplies

- Only 50% of US public water supplies have reported their arsenic levels!
Arsenic Contamination of US Private Wells

Estimated Population with Arsenic > 10 μg/L
- 0 - 50
- 50 - 500
- 500 - 5,000
- > 5,000

Arsenic Contamination of US Soil

[Map of arsenic contamination in US soil]

Portland Industrial Example

- Arsenic from colored glass manufacturing
- (Also releases a lot of cadmium into environment)
Primary sources: water, chicken, rice
Threshold for increased disease risk: 10.0 ug/L urine
⇒ >35% of US population exceeds threshold

# Toxicity of Common Forms of Arsenic in Humans

<table>
<thead>
<tr>
<th>Species</th>
<th>Type</th>
<th>Half-Life</th>
<th>Primary Source</th>
<th>LD50</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMA</td>
<td>Organic</td>
<td>10-20 hrs</td>
<td>Food</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Arsenate (V)</td>
<td>Inorganic</td>
<td>2-4 days</td>
<td>Water</td>
<td>8 mg/kg</td>
</tr>
<tr>
<td>Arsenite (III)</td>
<td>Inorganic</td>
<td>2–4 days</td>
<td>Water</td>
<td>26 mg/kg</td>
</tr>
<tr>
<td>DMA</td>
<td>Organic</td>
<td>10-20 hrs</td>
<td>Food</td>
<td>648 mg/kg</td>
</tr>
<tr>
<td>Arsenobetaine</td>
<td>Organic</td>
<td>4-6 hrs</td>
<td>Seafood</td>
<td>&gt;4,000 mg/kg</td>
</tr>
</tbody>
</table>
Arsenic Metabolism - Multiple Key Enzymes

- MMA 8x **MORE** toxic than inorganic arsenic
- DMA 400x **LESS** toxic than inorganic arsenic
- Blood GSH inversely associated with arsenic in urine and blood
Genetics Hugely Important

- C allele of AS3MT 14458 (rs11191439) higher 1st methylation capacity than T
- C allele of AS3MT 12390 (rs3740393) higher 2nd methylation capacity than G

- Fast 1st methylation + Slow 2nd methylation = **Greatly increased arsenic toxicity**

- 21% of population poorly detoxifies arsenic

- 1% of population especially susceptible to arsenic damage

Inorganic Arsenic → MMA (MORE TOXIC) → DMA (LESS TOXIC)

1\(^{st}\) methylation

\[\text{AS3MTT14458C rs11191439} \quad (\text{C allele = higher methylation capacity})\]

\[\text{AS3MTT14458C rs3740393} \quad (\text{T allele = lower methylation capacity})\]

2\(^{nd}\) methylation

\[\text{AS3MTC12390G rs11191439} \quad (\text{C allele = higher methylation capacity})\]

\[\text{AS3MTC12390G rs3740393} \quad (\text{G allele = lower methylation capacity})\]

rs11191439 prevalence
CC: 0.013
CT: 0.181
TT: 0.805
Reduced Glutathione Especially Important When Folate Deficient

Huge Variability Detoxification Function

- **CYP2D6**
  - Metabolizes ~25% of common prescription drugs
  - 7% of Caucasians poor metabolizers
  - ~30% ultra rapid metabolizers in Arabian and Eastern African populations
  - More adverse effects in poor metabolizers, and ineffective dosing in ultra-rapid metabolizers
  - Inhibited by ginger

Figure 1. Pharmacogenetics of CYP2D6. Urinary metabolic ratios of debrisoquin to its metabolite, 4-hydroxydebrisoquin, are shown for 1011 Swedish subjects. The Cutoff box indicates the cutoff point between subjects with poor metabolism as a result of decreased or absent CYP2D6 activity and subjects with extensive metabolism. Modified from Bertilsson et al. with the permission of the publisher.

Kirchheiner J, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J. 2007
Theme 3

TOXINS AND NUTRIENT DEFICIENCIES SYNERGISTICALLY INCREASE DAMAGE
LEAD INCREASES NEED FOR B-VITAMINS: HYPERHOMOCYSTEINEMIA

Deficiencies in folate, B6 or B12 make lead more toxic!
Lead aggravates damage from low B-vitamins

NUTRIENT DEFICIENCY AGGRAVATES LEAD TOXICITY

Supplement users more protected from lead
Best protection when both nutrient-rich diet AND supplements—BUT dietary more effective

TOXINS IN SOIL DECREASE MINERALS AND VITAMINS IN FOOD

Arsenic: ↓ Mn, Fe, Mg, K, P
Cadmium: ↓ 62% vitamin A; ↓ 75% vitamin C; ↓ Zn
Glyphosate: ↓ Mn


Endocrine Disrupting Chemicals, Toxic Metals, Air Pollutants Decrease Vitamin D

- Pesticides, BPA, phthalates, polyhalogenated compounds
- Cadmium, lead
- Ozone, tobacco, polycyclic aromatic hydrocarbons (PAHs)

Toxins Impair Detoxification Systems

- Animal study (goldfish)
- Heme is core of CYPs
- Lead (Pb) and paraquat (PQ) decrease both Phase I and Phase II detoxification enzymes
- Worse when also iron deficient

Arsenic Decreases CYP Induction

- Human cell culture
- Arsenic blocks enzyme induction
- Note that MMA much more damaging than elemental arsenic

Theme 4

HUMAN PHYSIOLOGY IS A MASSIVELY PARALLEL MATRIX, NOT SIMPLY SINGLE PATHWAYS
Detoxification of Acetaminophen
Clear Example of Multiple Pathways
Reductionistic View of Biochemistry Misses A Lot

- MANY plant molecules are now shown to have substantial physiological effects independent of previously discovered biochemistry
- Cannabinoid pathway classic example

Theme 5

MODERN AGRICULTURE DANGEROUSLY DISTORTS THE FOOD SUPPLY
WHAT ABOUT ALL THOSE OTHER MOLECULES?
Subtle and Often Unexpected Impact of “Unimportant” Constituents

• **Concept**: when plants are hybridized to increase one class of molecules, then there is decreased production of the others

• **Concept**: When foods are refined, the levels of many “unimportant” constituents decline
How Many Molecules in Food?

• Humans consume many grams everyday of molecules in food not considered “important”

• Many of these phytochemicals are bioactive beyond our current understanding because they act through weak biological feedback mechanisms, difficult to detect in vitro or considered involved in minor unimportant pathways

• 50,000 molecules identified; 200,000 projected

The Food Supply has Changed Dramatically

- Hybridization
- GMO
- Growth induced with chemicals
- Plants are now so weak they need toxic chemicals to protect from insects, viruses, mold, etc.
- Farming costs decreased by spraying fields with herbicides to control weeds and pesticides to protect against organisms the foods have lost the ability to resist
Plant Molecules

- Anti-bacterial, anti-fungal, anti-viral
- Anti-insect
- Anti-herbivore
- Anti-oxidant
- Etc.

⇒ Organically-grown, heirloom plants are more resilient and need less help against pests

⇒ Humans eating these plant molecules are more resilient and less susceptible to pests

PMID: 30145251
Ancient Kamut Compared to Current Wheat

- Crossover clinical study
- Much higher mineral levels:
  - Zinc: 64.7% higher
- Much lower inflammation:
  - TNF-alpha 49.7% lower
- Also lower cholesterol, LDL, blood sugar, etc.

Ancient Wheat Healthier than Modern Wheat

- Emmer, einkorn, spelt, khorasan and various regional Italian varieties
- Higher in multiple nutrients: phytosterols, alkylresorcinols, minerals, etc.
- Real clinical impact (many human studies)

⇒ Heirloom seeds

# Example Plant Metabolites Important to Human Health

List of plant secondary metabolites against Insects. Listed secondary metabolites are shown their linked to a specific category and their target insect in specific plan.

<table>
<thead>
<tr>
<th>Secondary Metabolites</th>
<th>Plants</th>
<th>Categories</th>
<th>Resistance against</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terpenoids</td>
<td>Citrus</td>
<td>Terpenoid Limonene</td>
<td><em>Auta cephalotes</em></td>
<td>[57]</td>
</tr>
<tr>
<td>Steroids</td>
<td>Pine and fir</td>
<td>Monoterpenes</td>
<td><em>bark beetle</em></td>
<td>[58]</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>Common fern</td>
<td>Phytoecdysones</td>
<td><em>Insect</em></td>
<td>[59]</td>
</tr>
<tr>
<td>Terpenoids</td>
<td>Tobbaco</td>
<td>Trans-anethole and thymol, citronellal,</td>
<td><em>Spodoptera litura</em></td>
<td>[60]</td>
</tr>
<tr>
<td>Phenolics</td>
<td>Wheat</td>
<td>Phenolics</td>
<td><em>Rhopalosiphum padi</em></td>
<td>[61]</td>
</tr>
<tr>
<td>Phenolics</td>
<td>Willow plant</td>
<td>Phenolics</td>
<td><em>Galerucella lineola</em></td>
<td>[62]</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>Salix</td>
<td>Benzoic acid</td>
<td><em>Operophthora brumata</em></td>
<td>[63]</td>
</tr>
<tr>
<td>Phenolics</td>
<td>Strawberry</td>
<td>Phenolics</td>
<td><em>Tetramythus urticae</em></td>
<td>[64]</td>
</tr>
<tr>
<td>Phenolics</td>
<td>Cotton</td>
<td>Gossypol</td>
<td><em>Heliothis virescens, Heliothis zeas</em></td>
<td>[65]</td>
</tr>
<tr>
<td>Alkaloids</td>
<td>Nightshade potato</td>
<td>Alkaloid dissimine</td>
<td><em>Leptinotarsa decemlineata</em></td>
<td>[66]</td>
</tr>
<tr>
<td>Benzoxazinoids</td>
<td>Gramineae</td>
<td>DIMBOA</td>
<td><em>Ostrinia nubilalis</em></td>
<td>[67]</td>
</tr>
<tr>
<td>Cyanogenic Glucosides</td>
<td>Cassava</td>
<td>CNgles</td>
<td><em>Cyrtothrips magnostus</em></td>
<td>[68]</td>
</tr>
<tr>
<td>Cyanogenic Glucosides</td>
<td>Bitter almond plants</td>
<td>Amygdalin and prunasin</td>
<td><em>Capnodius tenebrionis</em></td>
<td>[69]</td>
</tr>
<tr>
<td>Cyanogenic Glucosides</td>
<td>Trifolium repens</td>
<td>Amygdalin and prunasin</td>
<td><em>Hypora postica</em></td>
<td>[70]</td>
</tr>
<tr>
<td>Cyanogenic Glucosides</td>
<td>Lotus</td>
<td>Cyanogenic glucosides</td>
<td><em>Zyganga filipendulae</em></td>
<td>[71]</td>
</tr>
<tr>
<td>Cyanogenic Glucosides</td>
<td>P.Lunatus</td>
<td>CNgles</td>
<td><em>Spodoptera eridania</em></td>
<td>[73]</td>
</tr>
</tbody>
</table>

PMID: 30145251
Terpenoids

- Carvacrol, linalool, and limonene
- Limonene most common terpenoid
- MANY beneficial physiological effects
- Terpenes active constituents in many herbal medicines

Limonene

- Anticancer
- Multiple patents on limonene-derived chemotherapy agents

Peak Sugar Levels Much More Damaging than Average Blood Sugar

- Polyol and glycation activation greatly increased at higher glucose levels which results in the sequelae of diabetes
- MANY “Unimportant” plant constituents:
  - Decrease peak sugar
  - Inhibit polyol pathway
  - Inhibit glycation of proteins, enzymes, etc.
Hemoglobin A1c

- HbA1c is the standard, but:
- Not just average—the peaks are what cause the damage!
- However, misses daily fluctuations such as postprandial hyperglycemia, which can be detected with continuous glucose monitoring
- Patient 1 far more diabetes sequelae

PMID: 19027978
24-Hour Blood Sugar Monitor of Obese Diabetic

Standard diet

Standard diet + fiber

Personal communications Michael Lyon, MD


Chlorophyll

- **Concept**: Whole foods, plant-based diet has many constituents with unexpected health benefits

- Remember: glucose spikes cause the most damage

Blue dots: 75g glucose only  
Green dots: Plus 1g chlorophyll

Theme 6

ORGANICALLY-GROWN FOODS MORE HEALTHFUL THAN CHEMICALLY-GROWN FOODS
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Food produce</th>
<th>Organic versus conventional</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins: e.g., vitamin C, vitamin E, and carotenoids</td>
<td>Fruit, vegetables</td>
<td>Higher (most studies)</td>
<td>7, 11, 17, 49, 115</td>
</tr>
<tr>
<td>Minerals: calcium, potassium, phosphorous, magnesium, iron</td>
<td>Fruit, vegetables, cereals</td>
<td>Higher</td>
<td>11, 14, 28, 49, 93, 99, 118</td>
</tr>
<tr>
<td>Nitrate</td>
<td>Fruit, vegetables, cereals</td>
<td>Lower</td>
<td>7, 17, 61, 69, 115, 118</td>
</tr>
<tr>
<td>Antioxidant activity</td>
<td>Fruit, vegetables, cereals</td>
<td>Higher</td>
<td>7, 11, 17, 49, 61, 93</td>
</tr>
<tr>
<td>Phenolic compounds (total)</td>
<td>Fruit, vegetables, cereals</td>
<td>Higher</td>
<td>7, 18, 99</td>
</tr>
<tr>
<td>Protein, amino acids, nitrogen</td>
<td>Fruit, vegetables, cereals</td>
<td>Lower</td>
<td>7, 28</td>
</tr>
<tr>
<td>Beneficial fatty acids, i.e., eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid, α-linolenic acid, and conjugated linoleic acid</td>
<td>Milk, meat</td>
<td>Higher</td>
<td>61, 87, 102, 103</td>
</tr>
<tr>
<td>Iodine and selenium</td>
<td>Milk</td>
<td>Lower</td>
<td>102, 103</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Fruit, vegetables, cereals</td>
<td>Lower in cereals</td>
<td>7</td>
</tr>
<tr>
<td>Pesticide residues</td>
<td>Fruits, vegetables, and grains</td>
<td>Lower risk for contamination</td>
<td>6, 14, 61, 69, 99</td>
</tr>
<tr>
<td>Fusarium toxins</td>
<td>Cereals</td>
<td>Similar or lower in organic</td>
<td>99</td>
</tr>
<tr>
<td>Microorganisms, antibiotic-resistant bacteria</td>
<td>Chicken and pork</td>
<td></td>
<td>99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>End point</th>
<th>Study population and design</th>
<th>Exposure</th>
<th>Result</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>Cross-sectional study in 295 children from families with anthroposophic lifestyle and 380 children from control families in Sweden</td>
<td>Organic food consumption as part of an anthroposophic lifestyle</td>
<td>Fewer anemia in the children coming from anthroposophic families</td>
<td>3</td>
</tr>
<tr>
<td>Allergies and anaphylactic sensitization</td>
<td>Cross-sectional study including 14,893 children aged 5–13 years from anthroposophic families and reference children from five European countries (Austria, Germany, the Netherlands, Sweden, and Switzerland)</td>
<td>Organic food consumption as part of an anthroposophic lifestyle</td>
<td>Lower prevalence of anaphylactic sensitization in children with anthroposophic lifestyle</td>
<td>98</td>
</tr>
<tr>
<td>Hay fever and asthma-like symptoms</td>
<td>Cross-sectional study in 393 organic and 1,209 conventional farmers in the Netherlands</td>
<td>Organic vs. conventional farming practice</td>
<td>No difference in respiratory disease associated with farming practice/organic consumption</td>
<td>807</td>
</tr>
<tr>
<td>Recurrent wheeze occurrence</td>
<td>Prospective follow-up of 2,700 children in the KOALA birth cohort in the Netherlands. Blood samples from 815 infants at 2 years of age were analyzed for total and specific immunoglobulin E</td>
<td>Organic consumption in five food groups and proportion of organic within the diet</td>
<td>Lower prevalence of recurrent wheeze with consumption of organic dairy products but not with other organic foods or proportion of organic food</td>
<td>807</td>
</tr>
<tr>
<td>Allergic sensitization</td>
<td>Prospective study of 330 children from families with anthroposophic, partly anthroposophic, or non-anthroposophic lifestyle in Sweden. Allergy-specific immunoglobulin E sensitization measured in blood</td>
<td>Organic food consumption as part of an anthroposophic lifestyle</td>
<td>Lower prevalence of allergic sensitization in children with anthroposophic lifestyle</td>
<td>108</td>
</tr>
<tr>
<td>Hypoplasia</td>
<td>Case-control study in mothers of 306 boys who were operated on for hypoplasia and 306 mothers of healthy boys</td>
<td>Retrospective recall of organic consumption in five food groups during pregnancy</td>
<td>No difference with any organic consumption but higher prevalence with non-organic milk/dairy combined with frequent consumption of high fat dairy products</td>
<td>23</td>
</tr>
<tr>
<td>Hypoplasia and cryptorchidism</td>
<td>Prospective study in 351,079 mothers of singleton male infants in Norway 2002–2008</td>
<td>Organic food in six food groups assessed by FFQ grouped into frequent versus sometimes</td>
<td>Lower prevalence of hypoplasia with organic consumption, and in particular organic vegetables. No difference for cryptorchidism</td>
<td>19</td>
</tr>
</tbody>
</table>

References:
Dramatic Difference Between Organic- and Chemically-Grown Foods

- Tomatoes
- Highly controlled greenhouse
- Shows variation over normal growth cycle
- Dramatic decrease in “unimportant” molecules
- Note: the coloring molecule echinenone (beta-carotene variant) is least reduced

Tomatine

- The major saponin in tomatoes
- Antitumor, antioxidant, anti-inflammatory
- Suppresses production of pro-inflammatory cytokines in lipopolysaccharide (LPS)-induced macrophages
- Human prostate cancer cells

Note synergistic effects

Tomatine, etc. Clinically Significant

- Virtually no direct clinical research on tomatine in humans
- Implied research comparing vegans to other eating patterns
- Research inconsistent ranging from no statistical difference to substantial protection
- Probable cause is uncontrolled variance in genomics of test populations and quality of food

More Vegetables, Less Prostate Cancer

The “Unimportant” Molecules Greatly Impact “Important” Nutrients

• Zinc critical for metabolism—but only if in cells
• Bioflavonoids increase zinc transport into cells
• Foods depleted in zinc and also depleted in bioflavonoids have even lower cellular zinc
• Foods grown with high phosphates typically have higher levels of zinc-antagonist cadmium
Favonoids Critical to Transport of Zinc Into Cells

- Cell study
- Dietary plant polyphenols such as flavonoids quercetin and epigallocatechin-gallate are zinc ionophores
  - Transport zinc cations through the plasma membrane
- Numerous enzymes dependent on zinc are activated by polyphenols
- Combination of zinc and flavonoids dramatically increase zinc levels in cells and metabolic activity of Zn-dependent enzymes

Flavonoids
Critical For Health

Preserving Our Brains

- Flavonoids enhance glyoxalase pathway
- Detoxifies reactive dicarbonyl compounds, esp. methylglyoxal
- Critical antioxidant neuron protection
- Decreases risk for:
  - Alzheimer’s
  - Parkinson’s
  - Aging
  - Autism Spectrum Disorder

PMID: 29080525
The Higher Level of “Unimportant” Molecules in Organically-Grown Foods Has Huge Clinical Implications

- Lower risk of cancer: OR 0.75 (0.23 for lymphomas!)
- Not just lower pesticide levels

Why Do Organic Foods Taste Better?

- Three strawberry cultivars grown both chemically and organically
- 79% variation in metabolome explained 88% of variation in sensory profiles
- Sensory variations due to flavonoids, tannins, and fatty acids
- Organic farming practices enhance accumulation of sensory plant metabolites

⇒ Full taste, not overstimulation of 1 or 2 sensors = health

Many Studies Show Organic Foods Higher in Nutrients

- Onions: phenolics, total flavonoids and antioxidant activity
- Broccoli: indolyl glucosinolates (precursors of I3C)
Why Disconnect Between Nutrient Levels and Metabolites?

- Blood levels of nutrients poorly predict metabolite levels
- Why?
  - Methylation polymorphisms only partial explanation
  - Virtually all B12 measurements do not differentiate between cyano-cobalamin, methyl-cobalamin and adenosyl-cobalamin
  - Rarely measure holo-cobalamin—the key transport molecule into cells

Figure H.1.d. Prevalence estimates of low serum vitamin B12 (B12), high plasma methylmalonic acid (MMA), and high plasma total homocysteine (tHcy) concentrations in U.S. persons 60 years and older, National Health and Nutrition Examination Survey, 2003–2006.

Data shown for plasma MMA are from NHANES 2003–2004 only. Error bars represent 95% confidence intervals.
Theme 7

LOSS OF SYNCHRONIZATION WITH ENVIRONMENT
Circadian Rhythms and Epigenetics Highly Impacted by Environment

- The Circadian Clock is an endogenous timekeeping system that synchronizes physiology and behavior to day/night cycles
- Circadian clocks exist in nearly every cell, tissue, and organ system
- Virtually every cell has sensors sampling environmental signals


Aryl Hydrocarbon Receptor (AhR)

- Ligand-activated transcription factor that regulates gene expression

- Originally considered a sensor of xenobiotic chemicals and as the regulator of the cytochrome P450s that metabolize these toxic chemicals.

- Now known to:
  - Respond to many endogenous and exogenous molecules
  - Plays a major role in circadian clockwork

AhR Ligands

<table>
<thead>
<tr>
<th>Endogenous Ligands</th>
<th>Natural Compounds</th>
<th>Exogenous Ligands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigoids</td>
<td>Flavonoids</td>
<td>Halogenated dioxins</td>
</tr>
<tr>
<td>Equilenin</td>
<td>Carotenoids</td>
<td>Polychlorinated biphenyls</td>
</tr>
<tr>
<td>Arachidonic acid metabolites</td>
<td>Berberine</td>
<td>Polycyclic aromatic hydrocarbons</td>
</tr>
<tr>
<td>Heme metabolites</td>
<td></td>
<td>Pesticides</td>
</tr>
<tr>
<td>Tryptophan metabolites</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Circadian gene</th>
<th>Toxin</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMal1</td>
<td>WY14643</td>
<td>PPARα</td>
</tr>
<tr>
<td></td>
<td>TCDD</td>
<td>AhR</td>
</tr>
<tr>
<td>Per1</td>
<td>FICZ</td>
<td>AhR</td>
</tr>
<tr>
<td></td>
<td>TCDD</td>
<td>AhR</td>
</tr>
<tr>
<td>Per2</td>
<td>TCDD</td>
<td>AhR</td>
</tr>
<tr>
<td>Per3</td>
<td>DEHP</td>
<td>PPARα</td>
</tr>
<tr>
<td>Cry1</td>
<td>FICZ</td>
<td>AhR</td>
</tr>
<tr>
<td></td>
<td>DEHP</td>
<td>PPARα</td>
</tr>
<tr>
<td>Cry2</td>
<td>FICZ</td>
<td>AhR</td>
</tr>
<tr>
<td>Dbp</td>
<td>DEHP</td>
<td>PPARα</td>
</tr>
</tbody>
</table>
DEHP (Bis(2-ethylhexyl) phthalate)
DHEP (Di(2-Ethylhexyl) phthalate)

• Used to soften PVC plastic products such as:
  ▪ Wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, some toys, shoes, automobile upholstery and tops
  ▪ Food packaging films
  ▪ Sheathing for wire and cable
  ▪ Medical tubing and blood storage bags
• Contaminant in many water supplies

⇒ DHEP/DEHP constantly disrupt Circadian Rhythm and dis-integrates epigenetics from environment
PUTTING IT ALL TOGETHER
WE’VE MOVED FROM LIVING IN A MATRIX OF HEALTH-PROMOTING MOLECULES IN SYNCHRONY WITH THE ENVIRONMENT to A MIASMA OF TOXINS, DEFICIENCIES AND ISOLATION RESULTING IN HIGH DISEASE BURDEN
CONVERTING DISEASE RISK TO % OF DISEASE DUE TO TOXINS
Converting Disease Risk to % Caused: Attributable Fraction (AF) Calculation

\[
AF = \frac{p(\text{rr}-1)}{p(\text{rr}-1) + 1}
\]

\(p\) = underlying prevalence of risk factor in the population

\(\text{rr}\) = relative risk (risk of contracting a disease in an exposed population divided by the risk of contracting the disease in an unexposed population)

\(AF\) = % of disease due to the toxin

## Arsenic and Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Threshold</th>
<th>% Above Threshold</th>
<th>Odds Ratio</th>
<th>% of Disease</th>
<th>Example PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gout</td>
<td>12.5 ug/L</td>
<td>25%</td>
<td>5.5</td>
<td>52%</td>
<td>25499256</td>
</tr>
<tr>
<td>Cancer, prostate</td>
<td>13.3 ug/g</td>
<td>20%</td>
<td>3.3</td>
<td>32%</td>
<td>23800676</td>
</tr>
<tr>
<td>Cancer, pancreatic</td>
<td>13.3 ug/g</td>
<td>20%</td>
<td>2.5</td>
<td>23%</td>
<td>23800676</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16.5 ug/L</td>
<td>20%</td>
<td>2.1</td>
<td>18%</td>
<td>18714061</td>
</tr>
<tr>
<td>Cancer, bladder</td>
<td>10.0 ug/L</td>
<td>10%</td>
<td>2.7</td>
<td>14%</td>
<td>24889821</td>
</tr>
</tbody>
</table>
Arsenic in Water

\[4-6 \text{ ug/L} (25\%)\]
\[7-10 \text{ ug/L} (20\%)\]
\[11-19 \text{ ug/L} (15\%)\]
\[>20 \text{ ug/L} (20\%)\]

↑ Disease: If folate deficient (17%)
↑ Disease: If 2 AS3MT SNPs (1%)
↑ Disease: If 1 AS3MT SNP (20%)
↑ Disease: Almost everyone

(Prevalence from research; thresholds only estimated at this time; water estimated from urine)
Clinical Application

1. Arsenic in water >20.0 ug/L is toxic for everyone (2% of reported US public water supplies, higher in private wells)

2. Arsenic in water >10.0 ug/L is toxic for everyone, if also another exposure such as regularly eating chicken or rice (10% of reported US public water supplies, higher in private wells)

3. If 1 of 2 AS3MT SNPs, toxic effects >11.0 ug/L of water or significant other arsenic sources (regularly eating rice or chicken)
   - Incidence of SNPs 8% and 14% ⇒ 21% experience toxicity at “safe” levels

4. If both AS3MT SNPs, toxic effects >7.0 ug/L or significant other arsenic exposures
   - 1% likely to suffer arsenic toxicity if regularly eating rice and chicken, even if water arsenic not high. Deadly if also As in water.

5. B-vitamin supplementation if homocysteine > 8.0

6. Glutathione support (NAC: 500 bg bid)

7. Treat water if above 5.0 ug/L
High Toxicant Load Causes Disease

- Minamata disease (Hg)
- Gout (Pb, As)
Gross Nutritional Deficiencies Cause Disease

Ricketts (Vitamin D)
Scurvy (Vitamin C)
Some Diseases Really Are Caused by Genetics

- Inborn Errors of Metabolism
  - Cystic fibrosis
  - Sickle cell anemia
Unified Theory of Disease

- Chronic low-level exposures in air, food, water, cosmetics
- Chronic deficiencies of vitamins, minerals and "unimportant" molecules
- Genetic susceptibilities

Disease
Any Wonder Why Chronic Disease is Epidemic?

• We transformed the food supply to be deficient not just in nutrients known to be required for metabolism but also “unimportant” molecules that hugely impact health.

• Then we create drugs that are patentable modifications of some of these “unimportant” molecules and prescribe them to the population for the diseases caused by a depleted food supply.

• Now add toxins and toxicants to further poison metabolism…
Bottom Line

• There is no substitute for a whole foods diet
  ▪ Primarily plant based
  ▪ Organically grown
  ▪ Heirloom seeds
  ▪ Uncontaminated during growing, transport, processing, storage and cooking

• Nutritional supplements are not a substitute for a whole foods diet
  ▪ Most valid use of supplements are for addressing genomic susceptibilities, protecting from toxic world, enhancing function when needed (e.g. antiaging)

Substituting drugs for natural food molecules will never be an effective strategy
Mom Was Right! Eat your vegetables!

Eat your organically grown, heirloom vegetables!