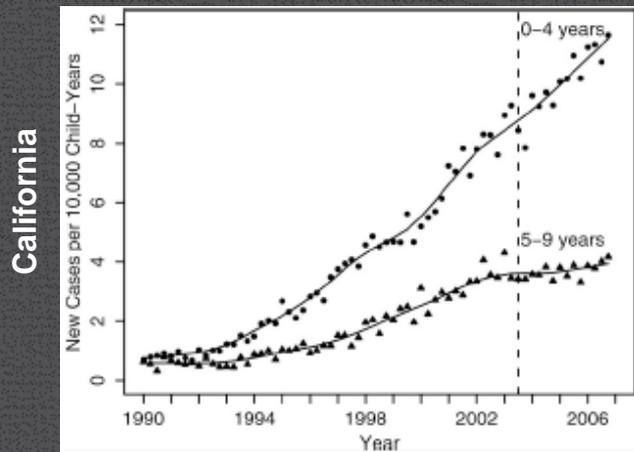


CLINICAL PERSPECTIVES ON THE AUTISM AND ENVIRONMENT CONNECTION

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ARI May 2013

Mounting Evidence of the Autism Environment Connection



Rising rates of autism

Genetic heritability and shared environmental factors among twin pairs with autism.

Association of ASD rates with environmental toxins, including proximity to freeways, hazardous air pollutants, indoor environmental factors, and environmentally released mercury.

I. Basic Principles – Complex, Dynamic, Whole Body Based Condition

- Causes of ASD are complex, individualized, and multifactorial:
 - Environmental toxins
 - Microbes
 - Genetic vulnerabilities
- Epigenetics – interaction of environment and genes.
- ASD are whole body based disorders

I. Basic Principles – Complex, Dynamic, Whole Body Based Condition

ASD as a dynamic and plastic condition

- Some behavioral and associated medical symptoms can fluctuate from day to day.
- At least 10 percent, and possibly as many as 20 percent, of children who receive a diagnosis of autism or autism spectrum disorder can “recover.” (Fein, 2009)

II. Basic Principles – Toxins

- The development of these disorders is likely affected by exposure to multiple toxins over time, not acute poisoning by one toxin.
- These individual toxic exposures may never reach the threshold for acute toxicity.

Small study of 10 newborns done by the
Environmental Working Group in 2004.

A total of 287 toxins were found in the entire group.

BodyBurden

The Pollution in Newborns

A benchmark investigation of industrial
chemicals, pollutants, and pesticides in
human umbilical cord blood

III. Basic Principles - Testing

- We do not have readily available clinical testing for many of the commonly used toxins.
- Most available testing only measures acute or subacute exposure in blood or urine.
- A toxin that was present early in development may have had long lasting impact but may no longer be present.
- Over time, toxins may become deposited into tissues and organs, such as brain, liver, and bone. Once this happens, the toxins may not be readily detected by blood and urine testing.

IV. Basic Principles – Research Findings

- We do not currently have double blind, placebo controlled studies for the majority of the biomedical interventions.
- Most of the studies we rely on are animal studies, laboratory studies or small clinical trials.
- Collective clinical observations are evidence
- Because we do not have conclusive studies, focus on interventions that are non-invasive, well tolerated, safe, and relatively inexpensive.

V. Basic Principles - Treatment

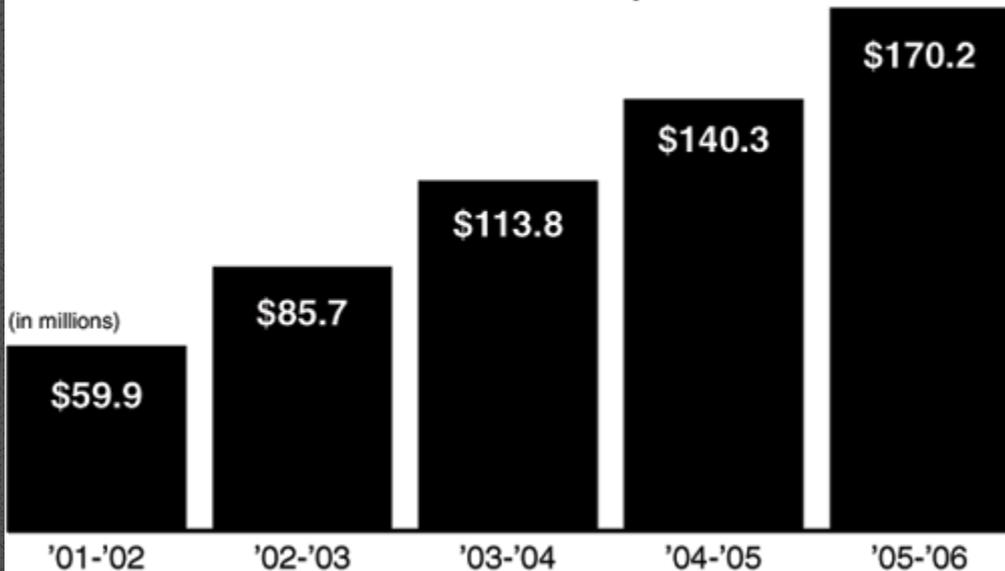
- Best outcomes usually come from working on multiple levels simultaneously.
- Because many interconnected systems usually are involved, ideal interventions will work on many systems.
- Most studies focus on one intervention, one system, and one outcome.
- Ideally, interventions should occur prior to conception with aim of preventing autism.

Price of Inaction

Costs have continued to increase.

Extraordinary spending

Statewide education spending on autistic students whose bills exceed \$40,000 per year – which is about one-third of all autistic students. The other students' costs are not tracked by the state.



Source: State Department of Education, Office of School Funding

R.L. REBACH/STAFF ARTIST

Clinical Approaches

- Reduce or avoid exposure to toxins
- Prevent conversion to more toxic forms in the body
- Support body's ability to eliminate toxins (detoxification)
- Mitigate the harmful effects of toxins
 - Support metabolic pathways
 - promote cell repair and neurogenesis
- Targeted therapy to remove specific toxins

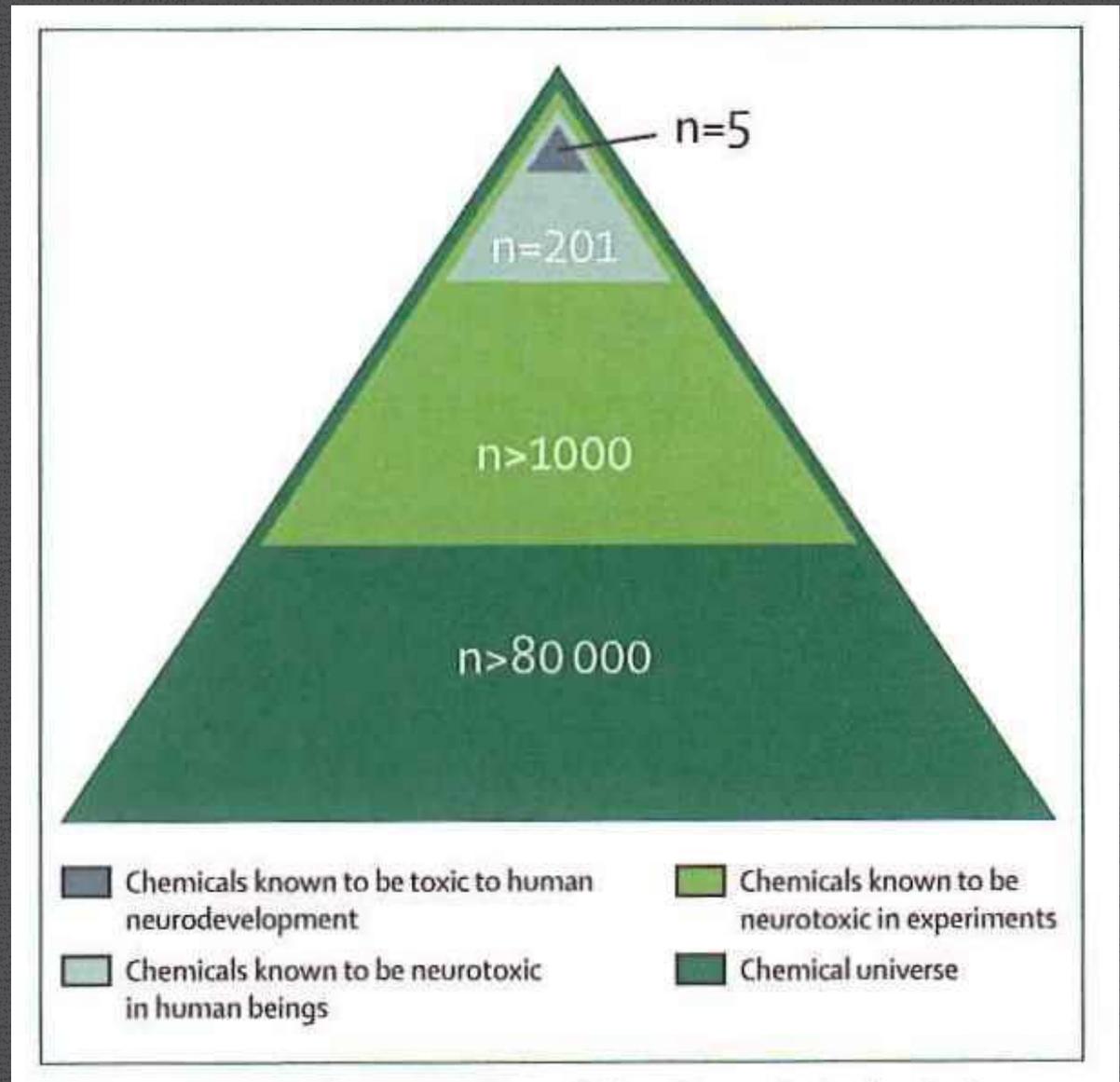
Top Toxins Associated with Autism

1. Lead
2. Methylmercury
3. PCBs
4. Organophosphate pesticides
5. Organochlorine pesticides
6. Endocrine disruptors
7. Automotive exhaust
8. Polycyclic aromatic hydrocarbons
9. Brominated flame retardants
10. Perfluorinated compounds

Inadequate Testing of Toxins on Neurodevelopment

There are more than 80,000 toxins being produced and used

Only 20-30 chemicals have been tested for their impact on neurodevelopment



PEDIATRICS[®]

The Toxic Substance Control Act (TSCA) was passed in 1976. It is widely recognized to have been ineffective in protecting children, pregnant women, and the general population from hazardous chemicals in the marketplace.

It does not take into account the special vulnerabilities of children in attempting to protect the population from chemical hazards.

Our Challenge

How do we make wise choices to protect our children's health in the setting of an epidemic of ASD, insufficient scientific data regarding the impact of environmental toxins on neurodevelopment, and a deeply flawed regulatory system?

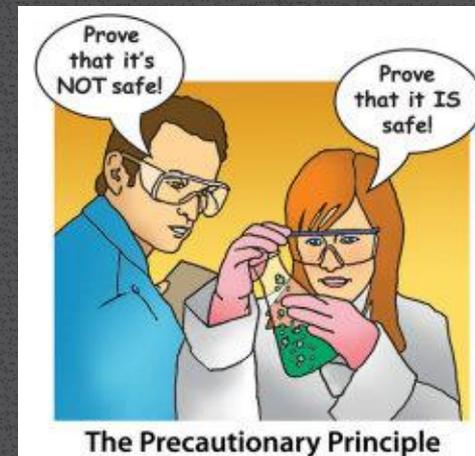
TIPS FOR LOWERING YOUR EXPOSURE TO ENVIRONMENTAL TOXINS

See handout

Precautionary Principle

"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

-The 1998 *Wingspread Statement*



Small Changes Can Make a Big Difference in Toxin Exposure

An organic diet provides a dramatic and immediate protective effect in five days against exposures to organophosphorus pesticides

Environ Health Perspect. 2006 February; 114(2): 260–263

Even a short, five day change in dietary behavior may significantly decrease inadvertent exposure to antibiotics and phthalates and hence may reduce oxidative stress levels.

[Environmental Research Volume 110, Issue 4](#), May 2010, Pages 375–382

Pesticides and ADHD

Pediatrics, May 17, 2010.

Children with higher levels of organophosphate pesticides in the urine were more likely to develop ADHD



Organophosphates are well known to cause damage to the nerve connections in the brain. That is how they work.

Systems involved in ASD

- Neurologic
 - Gastrointestinal
 - Endocrine
 - Immune
-
- These systems are interconnected and effect each other in complex and bidirectional way

The Prevalence of Gastrointestinal Problems in Children Across the United States With Autism Spectrum Disorders From Families With Multiple Affected Members

Parents reported significantly more GI problems in children with ASD compared with their unaffected siblings.

The 2 most common GI problems in children with ASD were constipation (20%) and chronic diarrhea (19%).

Children with ASD have altered gut microbiota

Desulfovibrio species and Bacteroides vulgatus were present in significantly higher numbers in stools of severely autistic children. (Finegold SM, 2010)

Lower relative abundances of Bifidobacteria species and the mucolytic bacterium Akkermansia muciniphila were found in children with autism. (Wang L, 2011)

Sutterella species were found in ileal mucosal biopsy specimens from patients diagnosed with ASD but not in control children with GI symptoms. (Williams BL, 2012)

Fermented Foods Can Degrade Environmental Toxins

- During fermentation of kimchi, four lactic acid bacteria are involved in the degradation of the pesticides chlorpyrifos, coumaphos, diazinon, and parathion. (Cho KM, 2009)
- Novel bisphenol A (BPA)-degrading bacterial strains, identified as *Bacillus pumilus*, were isolated from kimchi. (Yamanaka, 2007)

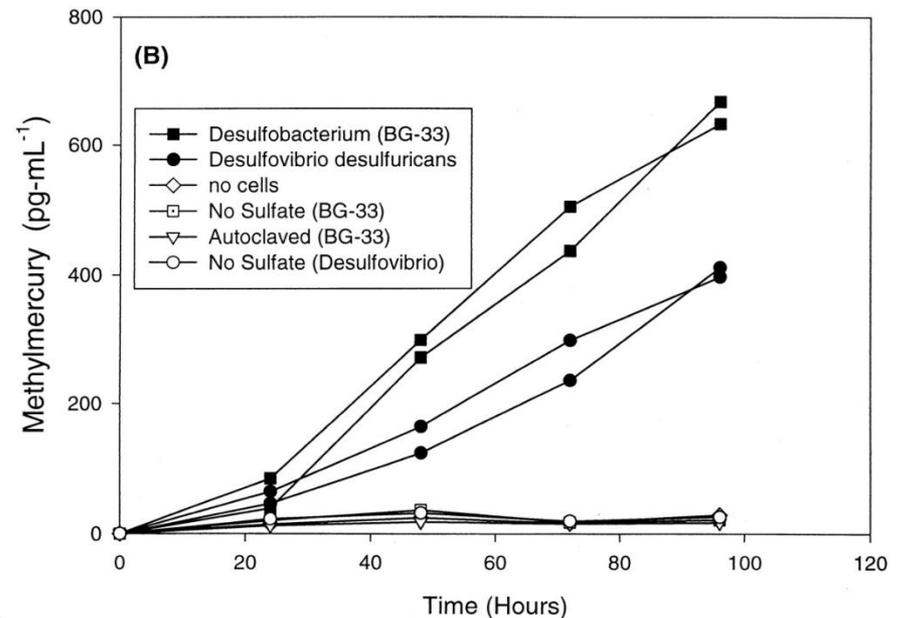
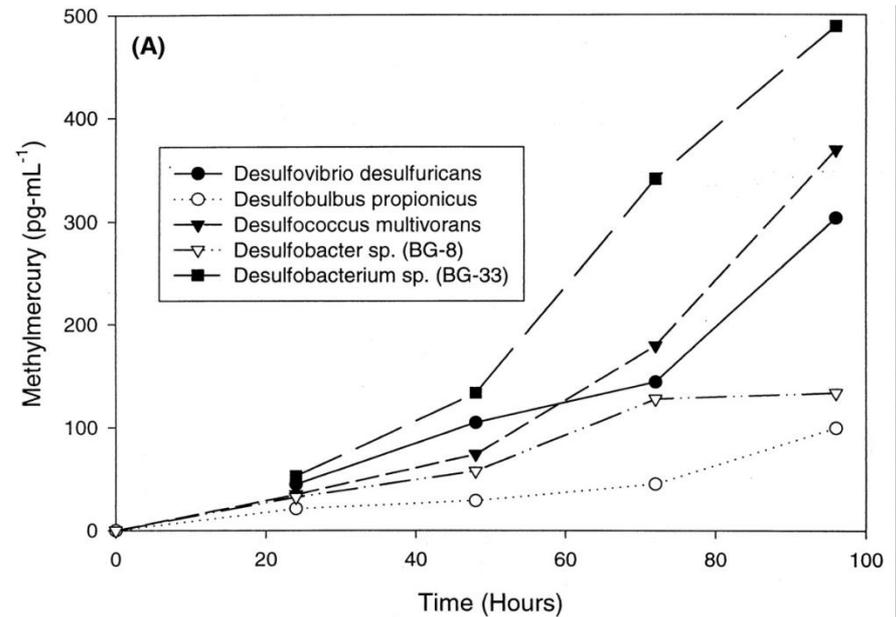
Tissue content of mercury in rats given methylmercuric chloride orally: influence of intestinal flora.

- Antibiotics-treated rats given labeled methylmercuric chloride orally had significantly more mercury in their tissues, especially in kidney, brain, lung, blood, and skeletal muscle, and also excreted less mercury in the feces than conventional rats.
- 4 of the 5 rats given antibiotics developed neurological symptoms of mercury toxicity.
- Only 1 of the 5 conventional rats was affected.
- Reduction of intestinal microorganisms by antibiotics was thought to have caused reduced decomposition of methyl mercury
- [Arch Environ Health](#). 1980 May-Jun;35(3):155-60.

Sulfate-Reducing Bacteria Methylate Mercury in the Environment

Appl. Environ. Microbiol. June 2000. Vol 66.

Desulfovibrio species are sulfate reducing bacteria. Methylmercury is the form most readily incorporated into biological tissues and most toxic to humans.



HYPOTHESIS

Could the alterations seen in GI flora in autism spectrum disorders lead to an increased risk of chemical and/or metal absorption and burden?

Constipation

- Most common GI symptom in ASD
- Slower transit time increases chance of transformation to more toxic forms and absorption of exposures.
- The FDA has approved Miralax use only by adults, and for only seven days at a time.

Treatment:

Magnesium Citrate

Vitamin C

Probiotics

Fibers/prebiotics

Hydration

Movement

Herbs

Fibers and Binders Help Excrete Toxins

- Chlorella accelerates fecal dioxin excretion in rats. (Morita, 1999)
- Dietary function food increases excretion of cadmium and lead (Hong, 2012)
- Chitosan promotes fecal dioxin, bisphenol A and di(2-ethyl)phthalate excretion. (Kohda, 2012)

The Intestinal Barrier in ASD

- Several studies have shown that the integrity of the intestinal mucosal barrier might be compromised in ASD
- Studies have demonstrated enhanced expression of duodenal epithelial tight junction proteins with exposure to *L. plantarum*. (Karczewski, 2010)
- Dietary fiber can alleviate damage to intestinal barrier function (Kou, 2010)

Treatment of Dysbiosis

We are still in the infancy stages of treatment,

Over 1000 human associated microorganisms have been identified in the human microbiota. Probiotics usually contain only a few different species.

- Preserve and restore natural diversity
- Avoid unnecessary antibiotics and antibiotic treated meat
- Probiotics
- Prebiotics/fibers
- Fermented foods
- Reduce Stress
- Dietary Changes
- Target possible pathogenic biofilm formation

Treatment of Dysbiosis

- Possible future treatments:
- Herbs to balance and restore gut microbiota – need studies to better understand and support use.
- Human probiotics
- Fecal transplant
- Identification and targeted treatments for *Desulfovibrio* species

Mitochondrial Dysfunction in Autism

JAMA. 2010;304(21):2389-2396

50-80% of children with autism had one or more biomarkers for mitochondrial dysfunction. Main outcome measure included oxidative phosphorylation capacity, mtDNA copy number and deletions, mitochondrial rate of hydrogen peroxide production, and plasma lactate and pyruvate

The cells of children with autism were exposed to higher levels of oxidative stress.

Half the children had mtDNA over replication, indicating an effort to overcome some form of damage or dysfunction.



Mitochondria and Toxins

- Mitochondria are like canaries in a coalmine: susceptible to early early-stage effects that predict cell and organ toxicity later.
- Mitochondrial DNA is uniquely susceptible to the damaging effects of ROS.
- Mitochondrial DNA generally has less capacity to repair itself, relying on just one enzyme for both replication and repair of DNA

Schmidt CW, 2010 Mito-Conundrum: Unraveling Environmental Effects on Mitochondria. Environ Health Perspect 118(7).

Mitochondria and toxins

Concept of mitochondrial dysfunction secondary to environmental toxins has not been adequately explored in literature

- Heavy metals
- Propionic acid (used as a preservative in food; produced by certain clostridia species)
- Bacterial toxins
- Tobacco smoke
- Rotenone (chemical used in insecticides and pesticides)
- Diesel exhaust
- Fat soluble chemicals with benzene rings such as hair dyes and paint fumes.

Common Symptoms of Mitochondrial Dysfunction

- Fatigue
- Low muscle tone
- Motor delays
- Muscle weakness
- Failure to Thrive
- Developmental delays and neuropsychiatric symptoms

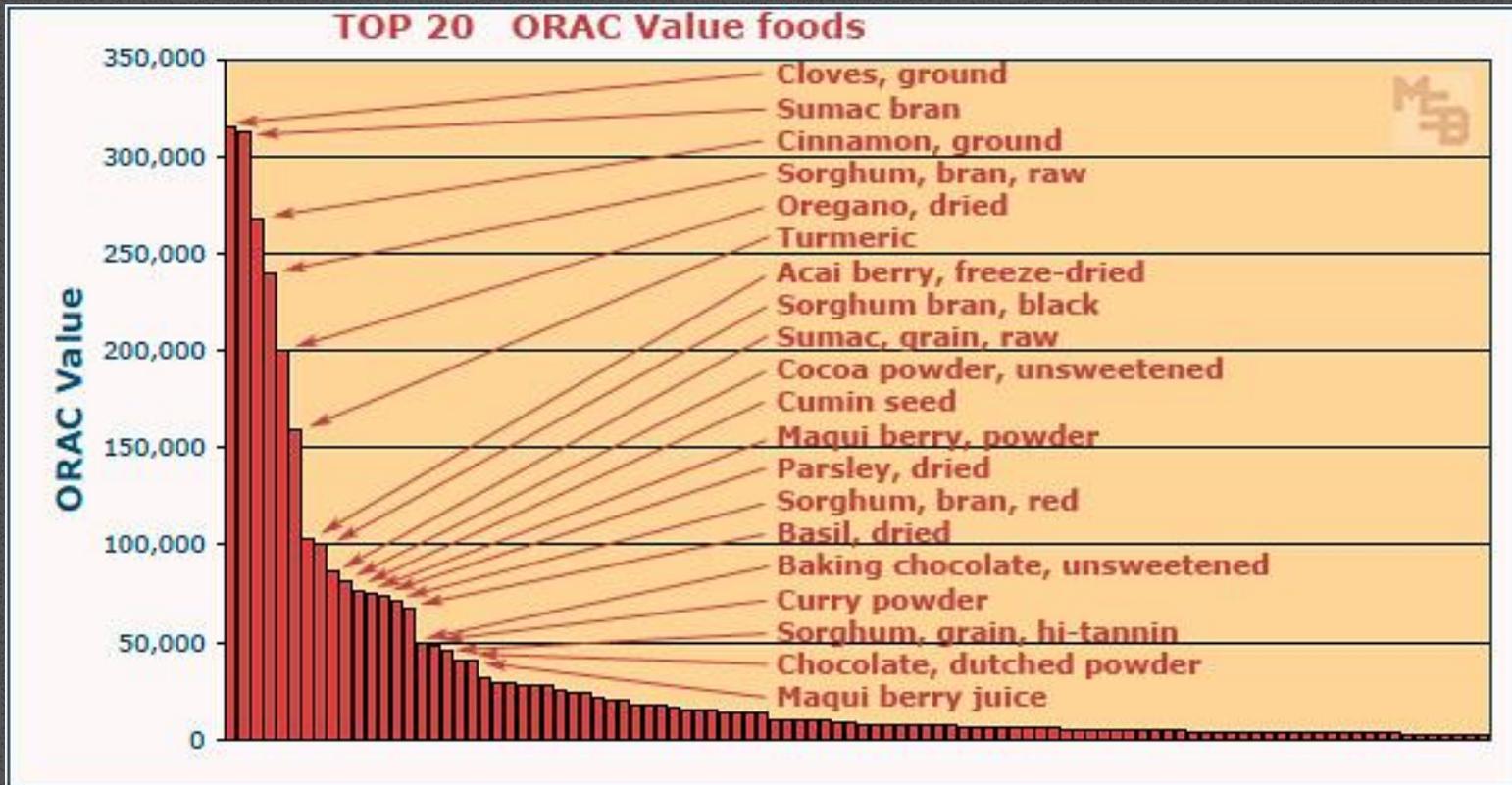
Tests for Mitochondrial Dysfunction

- Ammonia
- Alanine/Lysine ratio (Plasma Amino Acids)
- Lactate
- Pyruvate
- Acylcarnitine levels
- Free and total carnitine levels
- Creatine kinase
- Urine organic acid screening

Mitochondrial Cocktail

- Co-factor for pyruvate carboxylase
 - Biotin
- Precursors for electron acceptors(NAD and NADP)
 - Niacin (B3) or nicotinamide
- Antioxidant support for reactive oxygen species
 - Coenzyme Q10, lipoic acid, vitamin C and vitamin E
- Complex I
 - Carnitine, thiamine (B1), pantothenic acid (B5), and riboflavin (B2)
- Complex IV
 - Copper (only if low)
- Glutathione reductase support
 - Selenium

- ORAC - Oxygen Radical Absorbance Capacity.
- *ORAC units measure the antioxidant capacity of foods.*



Induction of mitochondrial nitrosative damage and cardiac dysfunction by chronic provision of dietary omega-6 polyunsaturated fatty acids

[Free Radic Biol Med.](#) 2006 Nov 1;41(9):1413-24. Epub 2006 Aug 4.

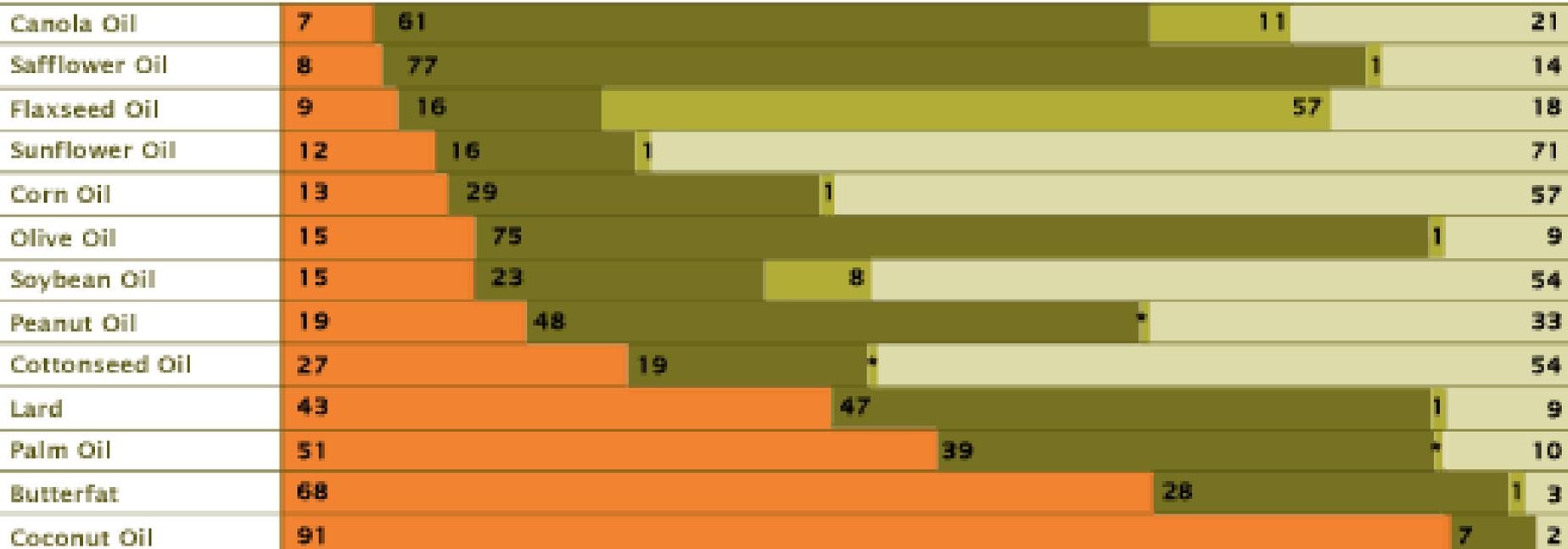
- In the hearts of omega-6 PUFA (HP) fed rats, oxidative damage to mitochondrial DNA (mDNA) was demonstrated by 8-hydroxyguanosine immunopositivity, overexpression of DNA repair enzymes, and a decrease in the mRNA expression of specific respiratory subunits encoded by the mDNA.
- This study demonstrates that consumption of a high fat diet rich in omega-6 PUFA for only 4 weeks instigates mitochondrial nitrosative damage.

Balancing Omega 6/Omega 3 fats: Reduce consumption of processed and foods and polyunsaturated vegetable oils (corn, sunflower, safflower, soy, and cottonseed.)

Comparison of Dietary Fats

DIETARY FAT

Fatty acid content normalized to 100 percent



SATURATED FAT

MONOUNSATURATED FAT

POLYUNSATURATED FAT



Alpha-Linolenic Acid
(an Omega-3 Fatty Acid)



Linoleic Acid
(an Omega-6 Fatty Acid)

*Trace Amount

Source: PDS Pilot Plant Corporation

Holistic Model for Treatment of Mitochondrial Dysfunction

- Avoid toxins that may interfere with function
- Avoid medicines that interfere with mitochondrial function
- Use herbs that protect and support mitochondria
- Individualized mitochondrial cocktail
- High ORAC/antioxidant foods
- Reduce excess consumption of omega 6 oils
- Treat any chronic bacterial issues and infections

Anxiety and Signs of Stress are Common in Children with ASD

Across studies, 39.6% of young people with ASD had at least one comorbid DSM-IV anxiety disorder. (Van Stennsel FJ , 2011)

Prominent stress related symptoms:

- Difficulty with emotion regulation (tantrums)
- Difficulty with flexibility and adaption to change
- Need for consistency
- Withdrawal and avoidance behaviors

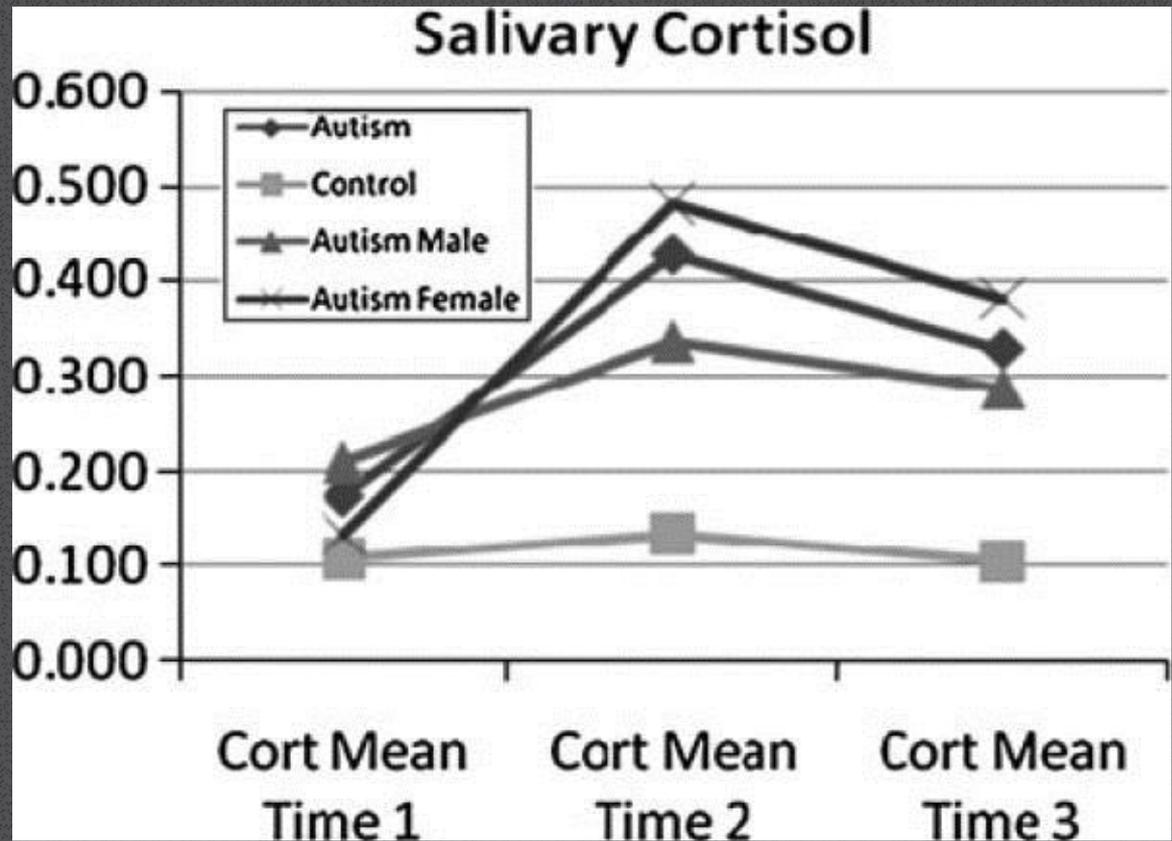
Effects of endocrine-disrupting chemicals on adrenal function

• [J.P. Hinson](#), BSc, PhD, DSc (Reader in Molecular and Cellular Endocrinology)

The chemical nature of adrenal disruptors is highly varied, and there are features of the adrenal structure and function, which render it particularly vulnerable to toxic attack. However, the homeostatic mechanisms inherent in the hypothalamus-pituitary-adrenal axis mean that only the most catastrophic effects are recognized as adrenal disruption, such as in the case of etomidate. In order to detect potentially significant but milder forms of toxic disruption of adrenal function a new approach is needed; this requires the use of more sophisticated approaches than simply measuring one hormone at one time point.

Mean salivary cortisol levels in response to a blood draw stressor

Measurements at Time 1 were taken 10 min prior to a blood draw. Times 2 and 3 refer to measurements at 20 and 40 min post-draw, respectively. Subjects with autism display a higher peak response as well as a prolonged duration.



Effect of toxins and microbes on adrenals

- May be direct effect of endocrine disrupting toxins and chronic infections
- May be secondary effects due to stress from another system
 - Purinergic
 - Immune/infections
 - Increased excitotoxicity

Tests for Acute Exposure to Toxins

- Heavy metal panel, blood
 - Heavy metal panel, urine
 - Hair metals – interpret with caution
 - Solvents, blood or plasma
 - Urine, pesticides
-
- All of these tests represent mainly acute or subacute exposure

Biomarker Testing

- Indirect evidence of toxin involvement
- None are specific to environmental toxins, may reflect exposure to other insults, including infection, stress, and trauma.

- Mitochondrial markers
- Oxidative Stress Markers
 - 8-OHdG
 - Urine Lipid peroxidation marker
 - Isoprostane F2 alpha (lipid oxidation)
 - Reduced Glutathione
 - Malondialdehyde, serum

- Immune Markers

GI Evaluation

- History of constipation, diarrhea, posturing, etc.
- Stool microbiology
- Urine Organic Acids Test (OATS, MAP)
- IgG food panel

TREATMENTS

Magnesium

- Mg²⁺ ions reduce microglial and THP-1 cell neurotoxicity by inhibiting Ca²⁺ entry through purinergic channels. (Lee M, 2011)
- Children with autistic spectrum disorders had significantly lower plasma concentrations of Mg than normal subjects (Strambi M, 2006)

Neuroprotective Effects of Creatine

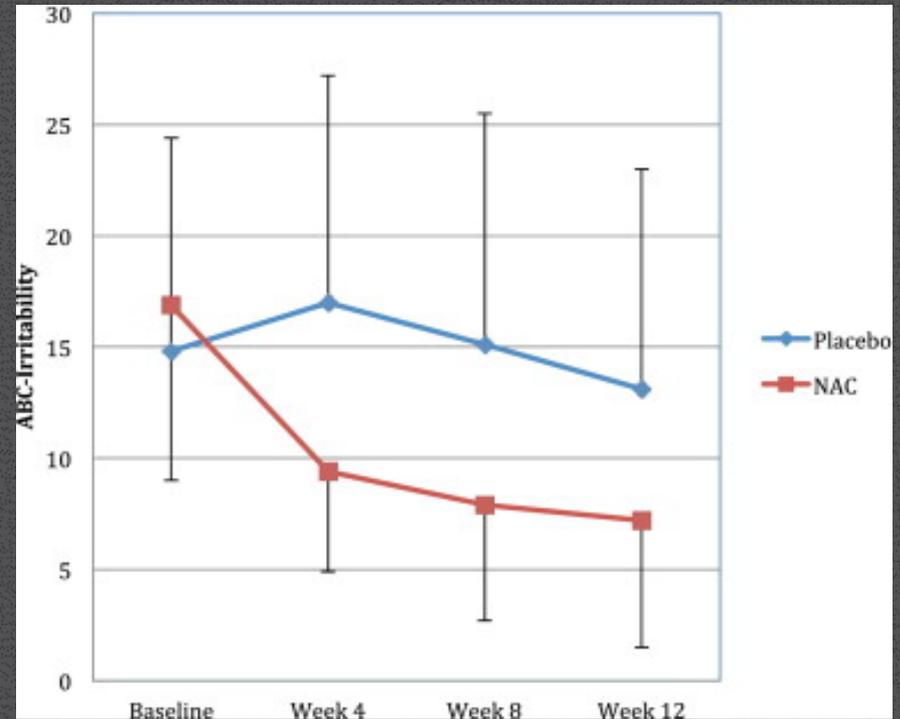
Neuroprotective effects are due to:

- Protective effects on ATP and cellular energy metabolism
- Inhibition of the NMDA receptor-mediated calcium response, which results in:
 - Reduced glutamate spillover
 - Reduced oxidative stress
 - Decreased excitotoxicity

A Randomized Controlled Pilot Trial of Oral N-Acetylcysteine in Children with Autism

The goal of study was to assess the feasibility of using NAC, a glutaminergic modulator and an antioxidant.

Oral NAC was well tolerated with limited side effects. Compared with placebo, NAC resulted in significant improvements on ABC irritability subscale.



[Biol Psychiatry](#). 2012 Jun 1;71(11):956-61.
Epub 2012 Feb 18.

- N-acetyl cysteine treatment was found to be effective in reversing 3-nitropropionic acid induced mitochondrial dysfunction in rats, (Sandhog R, 2012)
- N-acetyl cysteine was protective against synergistic loss of viability as well as of glutathione following unremitting sequential hits of proteotoxic stress as may occur in the diseased brain (Unnithan AS, 2012)

- N-acetyl cysteine significantly increases the extent of peripheral nerve regeneration (Karlidag T, 2012)
- Gastrointestinal side effects with oral NAC are common in children with ASD. Transdermal creams may be better tolerated in children with significant dysbiosis.

Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress

Treatment with 400 mg PAS resulted in a pronounced blunting of both serum ACTH and cortisol, and salivary cortisol responses to the TSST (Trier Social Stress Test).

With regard to the psychological response, 400 mg PAS seemed to exert a specific positive effect on emotional responses to the TSST.

- [Stress](#). 2004 Jun;7(2):119-26.

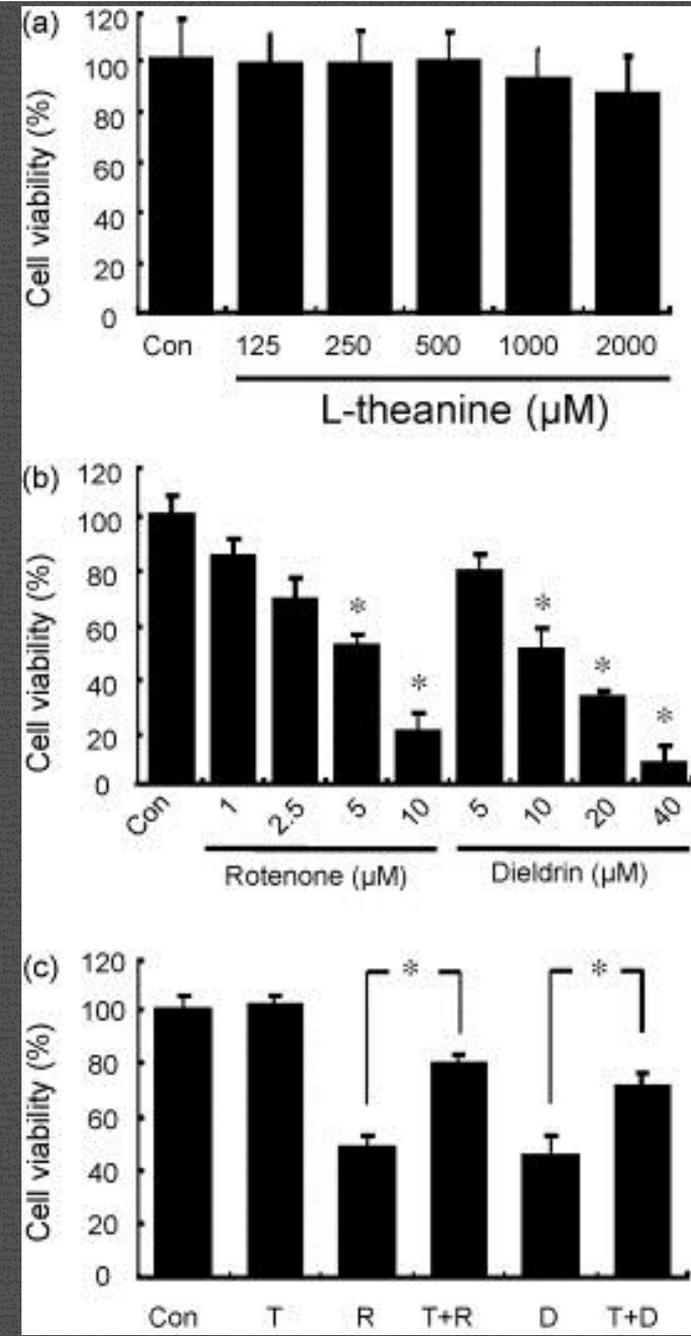
Advantages of Botanical Herbs

- Herbs are complex and often have multiple bioactive compounds.
- These compounds may work on multiple systems – immune, oxidative stress, mitochondria, etc.
- In general, herbs are better tolerated by sensitive children.
- Know your sources for herbs.
- Utilizing herbs may allow you to reduce the dosage of or avoid drugs.

Protective effect of the green tea component, L-theanine on environmental toxins-induced neuronal cell death

- Abbreviations used: Con, Control; T, L-theanine treatment; R, rotenone treatment; T + R, L-theanine plus rotenone treatment; D, dieldrin treatment; T + D, L-theanine plus dieldrin treatment

[NeuroToxicology](#)
[Volume 29, Issue 4](#), July 2008, Pages 656–662





Bacopa monniera (L.) Wettst ameliorates behavioral alterations and oxidative markers in sodium valproate induced autism in rats.

- Early prenatal or post natal exposure to environmental insults such as valproic acid (VPA), thalidomide and ethanol could induce behavioral alterations similar to autistic symptoms.
- Treatment with *B. monniera* significantly improved behavioral alterations, decreased oxidative stress markers and restored histoarchitecture of cerebellum.



- Standardized extracts of *Bacopa monniera* protect against MPP+ and paraquat-induced toxicity by modulating mitochondrial activities, proteasomal functions, and redox pathways. (Singh M, 2012)
- Pretreatment with *Bacopa monnieri* extract offsets 3-nitropropionic acid induced mitochondrial oxidative stress and dysfunction in the striatum of prepubertal mouse brain. (Shinomol GK, 2012)
- Protective effect of *Bacopa monniera* on methyl mercury induced oxidative stress in cerebellum of rats. (Sumathi T, 2012)



Adaptogens

- Are plant derivatives
- Modulate the immune, antioxidant, hormonal, and nervous systems
- Are believed to normalize bodily responses to stress and to help maintain homeostasis
- Many have been used in traditional medical systems for centuries to deal with stress, fatigue, or trauma.
- May help with modern day toxicant induced stress.



Plant Adaptogens

- Asian ginseng (*Panax ginseng*)
- American ginseng (*Panax quinquefolius*)
- Siberian ginseng (*Eleutherococcus senticosus*)
- Georgian Snow Rose (*Rhododendron Caucasicum*)
- Maca (*Lepidium meyenii*)



Plant Adaptogens

- Summa (*Pfaffia paniculata*)
- Golden Artic Root (*Rhoiola rosea*)
- Astragalus (*Astragalus membranaceus*)
- Tulsi or Holy Basil (*Ocimum sanctum*)
- Schisandra (*Schisandra chinensis*)
- Aswhaganda (*Withania somnifera*)
- Licorice (*Glycyrrhiza glabra* and *G. uralensis*)



Rhodiola rosea

- Rhodiola rosea activates the synthesis or resynthesis of ATP in the mitochondria in rats. (Abidov, 2003)
- Rhodiola enhances superoxide levels and protects against the toxic effects of paraquat (herbicide) in Drosophila (Schriner, 2009)
- Rhodiola rosea extract protects human cortical neurons against glutamate and hydrogen peroxide-induced cell death through reduction in the accumulation of intracellular calcium. (Palumbo, 2012)

Rhodiola rosea



- In rats exposed to cold and hypoxia, Rhodiola root extract increased blood reduced glutathione and SOD activity and maintained cell membrane permeability. (Gupta, 2010)
- In depressive rats, Rhodiola rosea improved serotonin levels in the hippocampus and induced neural stem cell proliferation. (Chen, 2009)

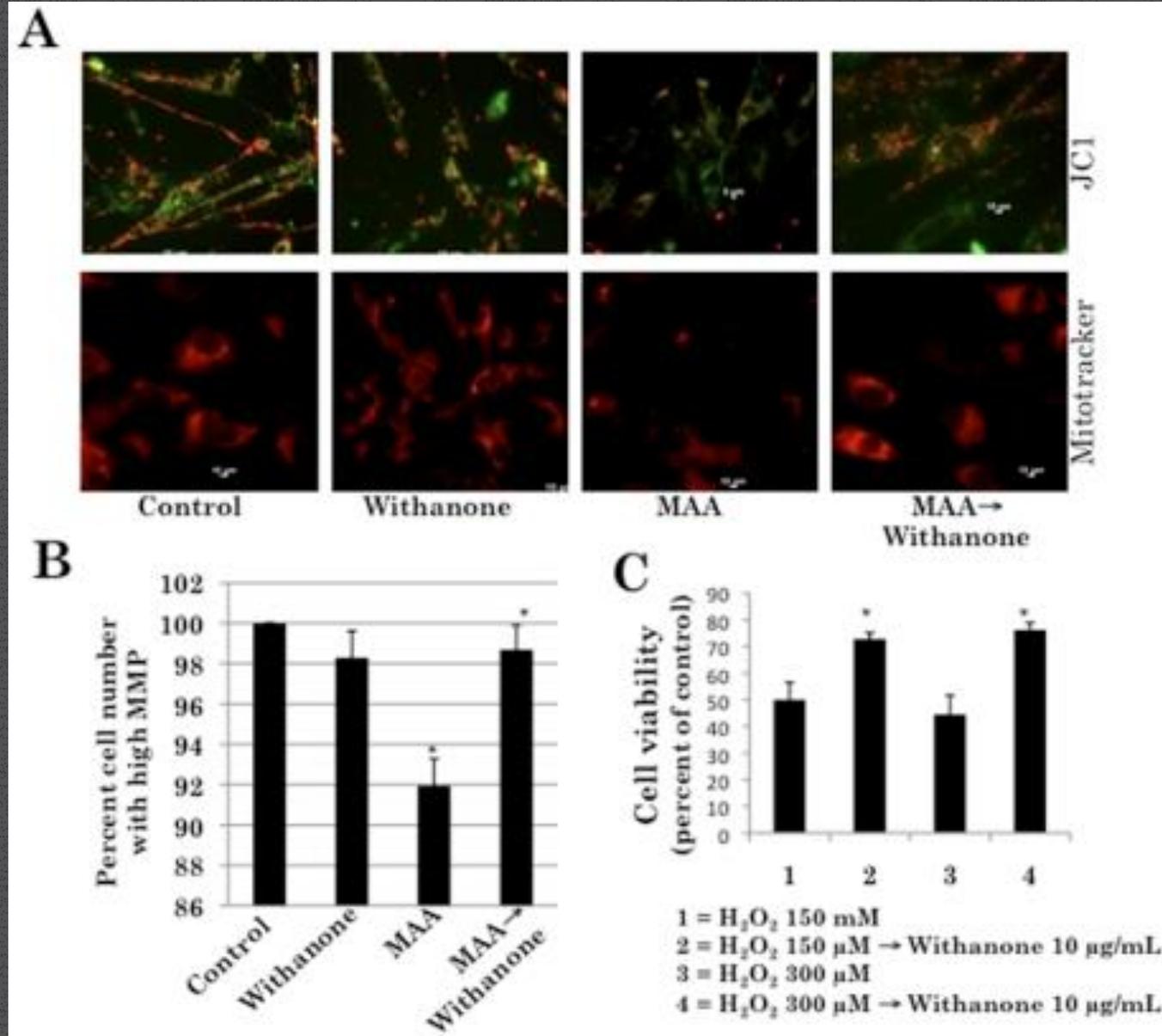
Rhodiola rosea



- Rhodiola rosea was found to normalize immune, hormonal, and antioxidant parameters in patients with Parkinson's disease. (Bocharov, 2010)
- In a small pilot study, Rhodiola rosea significantly improved generalized anxiety disorder symptoms, with a in HARS scores similar to that found in clinical trials. (Byrtistisky, 2008)

Ashwagandha leaf derived withanone protects normal human cells against the toxicity of methoxyacetic acid, a major industrial metabolite.

Withanone protects cells from MAA-induced toxicity by suppressing the ROS levels, DNA and mitochondrial damage, and induction of cell defense signaling pathways





- Selective Th1 up-regulating activity of Withania somnifera aqueous extract in an experimental system using flow cytometry. (Bani S, 2006)
- Withania somnifera was found to have potent inhibitory effect on proteinuria, nephritis and other inflammatory markers in pristane-induced model of SLE. (Minhaus U, 2012)
- Possible neuroprotective effect of Withania somnifera root extract against 3-nitropropionic acid-induced behavioral, biochemical, and mitochondrial dysfunction in an animal model of Huntington's disease. (Kumar P 2009)

Possible Sources of Arsenic Exposure

- Rice
- Organic rice syrup
- Chicken
- Apple juice
- Water
- Pressure treated wood



Testing for Arsenic Exposure

- Arsenic, 24 Hour, Urine (preferred test)
- Arsenic, blood

These tests detect acute or subacute exposure and toxicity, not chronic body burden.

- Arsenic, Hair

Detection of nonacute arsenic exposure. Hair grows at a rate of approximately 0.5 inch/month. 1 inch distally from the skin represents exposure 2 months ago.

Consequences of Arsenic Exposure

- Human gut bacteria are involved in methylation and transformation of arsenic into forms, including the highly toxic MMA(III)
- Both inorganic arsenic and its methylated metabolites easily pass the placenta

Early arsenic exposure is associated with:

- Epigenetic effects, mainly via DNA hypomethylation
- Reactive oxygen species induced mitochondrial dysfunction
- Immune disruption in human placenta and cord blood.
- Altered adrenal genetic programming during critical periods of fetal development.

Treatment of arsenic induced dysfunction

May include evaluation and treatment of:

Current exposures

GI microbiota

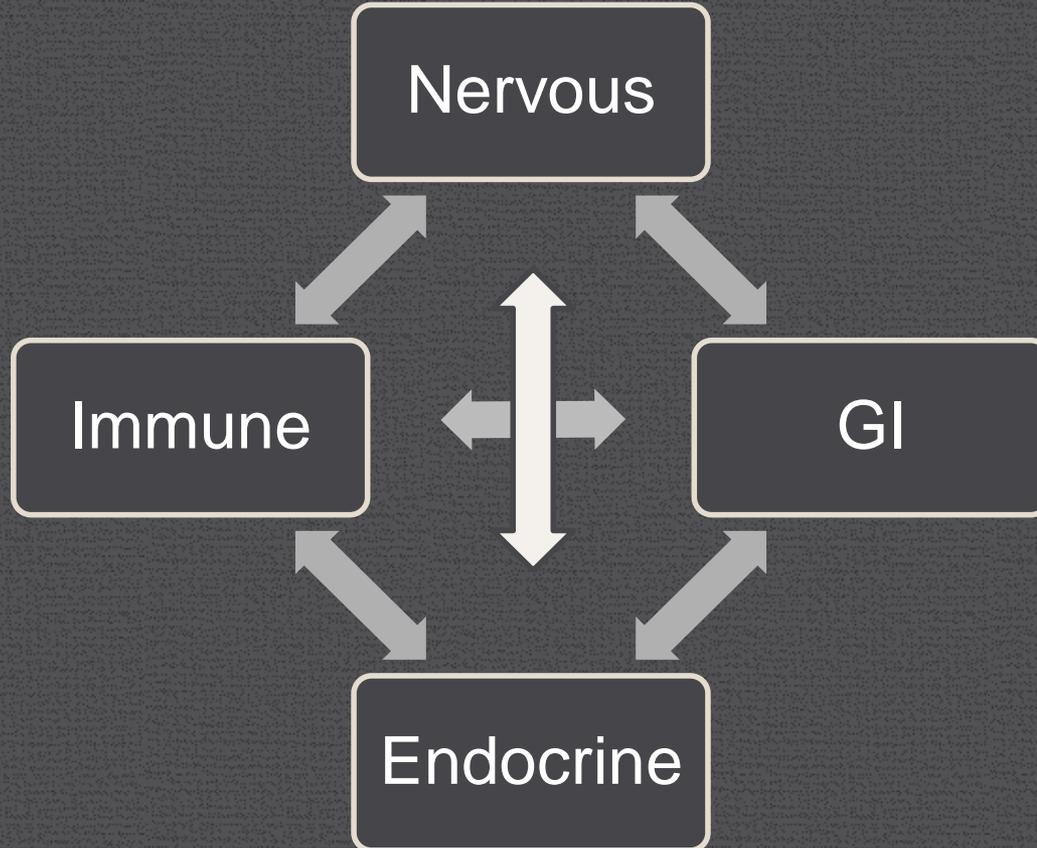
Mitochondria function

Methylation status. Vitamin B12 and folic acid protect against arsenic induced mitochondrial dysfunction and oxidative stress (Majumdar S, 2012)

HPA function

Evaluation and treatment of immune dysfunction

- Disruption in one organ system can have downstream consequences on multiple systems
- Supporting one organ system may benefit other systems
- This is also true at the cellular and metabolic levels



Conclusion

- Identify possible sources of exposure
- Identify which systems seem most affected
- Remove sources of toxin exposure early on in treatment
- For optimal outcomes, treat more than one system at a time
- Ideally, treat parents before conception with aim of preventing autism
- This approach requires dedication and a considerable investment in effort and time

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