Brain, Body and Environment in Autism: From a collection of fixed genetic deficits to an interactive web of functional challenges

Evolutionarily unprecedented stressors are overwhelming brain and body systems and require unprecedented types of partnerships to respond effectively to the impacts on children, adults, their families, schools, community and culture.

With rising numbers of people with autism and other chronic illnesses, and with global environmental changes that are harder than ever to deny, are we looking at a situation where the bodies and brains of the more vulnerable among us are being pushed beyond a point of tolerance? And where every less vulnerability is needed to get hurt? Is autism the tip of the iceberg in a much larger health crisis? Looking at environmental challenges to physiological function helps both to understand the damage and to find practical approaches to respond, personally and socially.

Autism: A *Behaviorally Defined* Syndrome

DSM-IV Criteria for Autistic Disorder (299.0)

1. Impaired social interaction
2. Delayed and disordered communication
3. Markedly restricted repertoire of activities and interests

Secondary Features of Autism

Seizures (~30%+), cognitive deficits, sensorimotor abnormalities, savant skills, immune impairments, GI distress(50-75%), food allergies (~50+%)

Autism: A *Behaviorally Defined* Syndrome

Biology is not part of the definition (and neither is prognosis)

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Secondary Features of Autism

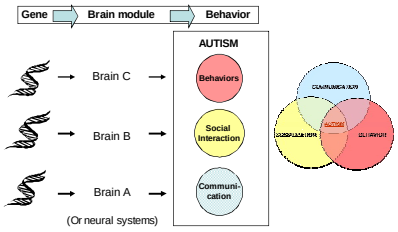
Seizures (~30%+), cognitive deficits, sensorimotor abnormalities, savant skills, immune impairments, GI distress(50-75%), food allergies (~50+%)

No biological markers exist to identify autism at this time

Autism is presumably *Heterogeneous biologically*

But **autism is *biological***

From Definition to Model of Autism: A Common Modular Framework



Things we measure or observe that don't fit the genes→brain→behavior model

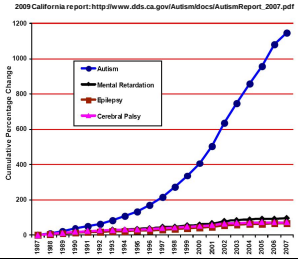
1. **More than genes**
   a) **Rates going up**
   b) **Evidence for environmental contributors**
2. **More than brain: Whole Body Systems**
3. **More than brain wiring diagram**
   a) **Brain tissue**
   b) **Plasticity**
4. **More than prenatal**
   a) **Lifeling impacts**
   b) **Lifelong opportunities**

Core argument

- **What we see in autism is what we would expect to see in a condition heavily modulated by environment**
- **This modulation takes place not only prenatally but throughout the lifespan**
- **We can improve our environment at many levels, personally and for our communities and the world, and this can help health.**

Cumulative Percentage Change of Autism, Cerebral Palsy, Epilepsy, and Mental Retardation over Two Decades

AUTISM UP 1200%

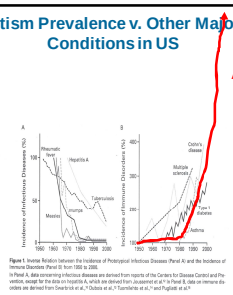


No proof that these arguments explain away ALL the increase

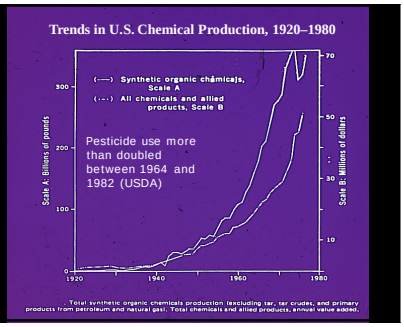
New paper from UC Davis (*Epidemiology*, Hertz-Picciotto and Delwiche, 2009)

- **600% increase in reported cases 1990 → 2001**
  - **200% can be explained by non-environmental factors:**
    - **24%: age at diagnosis**
    - **56%: inclusion of milder cases**
    - **120%: Change in DSM diagnostic criteria (DSM-III to DSM-IV)**
  - **The rest of the increase (400%) may have been from environmental contributors**
  - **Even some of the earlier cases could have been "environmental"**

Rise in Autism Prevalence v. Other Major Chronic Conditions in US

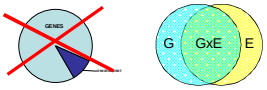


Trends in U.S. Chemical Production, 1920–1980

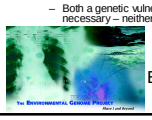


Total synthetic organic chemicals production (excluding tar, tar crudes, and primary products from petroleum and natural gas). Total chemicals and allied products, annual value added.

Gene-Environment Interactions: Not Either-Or but Both-And



- G *and* E probably affect most cases; they don't have to add up to 100%
  - Population-attributable fraction – the number of cases that would not exist if a risk factor were absent
  - Both a genetic vulnerability and an environmental trigger could be necessary – neither alone might be sufficient



AUTISM AND ENVIRONMENTAL GENOMICS

Herbert MR, Russo JP, Yang S, Roohi J, Blaxill M, Kahler SG, McCoy L, Ziegler DA, Hatchwell E

Neurotoxicology, 2006

Of the 287 chemicals detected in umbilical cord blood:

- **180 cause cancer in humans or animals**
- **217 are toxic to the brain and nervous system**
- **208 cause birth defects or abnormal development in animal tests**
- **Nearly 200 have been banned from the market for years**

www.bodyburden.org

EHP Vol 6, 2006: Online 21 June 2006

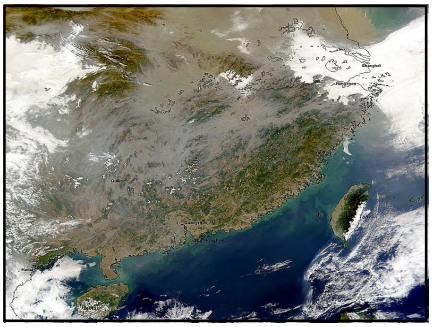
ehp Environmental Health PERSPECTIVES

ehponline.org

Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area (Windham et al., 2006)

Results: The adjusted odds ratios (AOR) were elevated by 50% in the top quartile of chlorinated solvents and heavy metals (95% Confidence Intervals (CIs) = 1.1-2.1), but not for aromatic solvents. Adjusting for these three groups simultaneously led to decreased risks for the solvents and increased risk for metals (AORs for metals: fourth quartile 1.7, 95% CI 1.0-3.0; third quartile 1.95, 95% CI 1.2-3.1). The individual compounds that contributed most to these associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride.

Conclusions: Our results suggest a potential association between autism and estimated metal concentrations, and possibly solvents, in ambient air around the birth residence, requiring confirmation and more refined exposure assessment in future studies.



Some of the possible environmental contributors to autism being studied

- Pesticides
  - Organophosphates
  - Others
- Heavy metals
  - Lead
  - Mercury
  - Cadmium
- Solvents
  - Triethylbenzene
  - Xylene
  - Trimethylbenzene
  - Others
- PCBs (polychlorinated biphenyls)
- Vaccines
- Flame retardants
- Antimicrobial ingredient in hand soaps
- Vitamin D deficiency
- Antibiotic overexposure and injury to intestinal "good bacteria"
- Essential fatty acid deficiency
- Greater genetic need combined with relative dietary deficiency of certain nutrients
  - Folic acid
  - Vitamin B12
  - Magnesium
- Valproic acid (depakote)
- Thalidomide
- Rubella and other infections during pregnancy
- In vitro fertilization

The planet is not stable.

UN Report by 1360 scientists :

Ecosystem damage is so severe that we can no longer be confident that the Planet Earth can support human life for more than two generations.

http://www.millenniumassessment.org

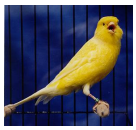
the ONION

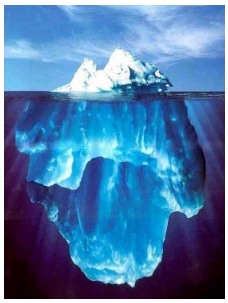
Al Gore Places Infant Son In Rocket To Escape Dying Planet

The Onion, July 30, 2008

A Perspective on the Autism Spectrum:

Tip of the Iceberg, Canary in the Coal Mine



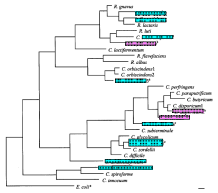


More than Brain: Chronic Body Problems

Multi-system from the start?
Kanner 1943 on *body* symptoms

Case 1: "Eating has always been a problem ….." for him. He has never shown a normal appetite."
Case 2: "…large and ragged tonsils."
Case 3: diarrhea and fever following smallpox vaccination …. healthy except for large tonsils and adenoids.
Case 4: vomited a great deal during his first year… feeding formulas were changed frequently … tonsils were removed…
Case 5: nursed very poorly … quit taking any kind of nourishment at three months… tube-fed five times daily up to one year of age…At camp she slid into avitaminosis and malnutrition but offered almost no verbal complaints."
Case 7: vomited all food from birth through the third month….
Case 8: feeding formula caused …concern. … colds, bronchitis, streptococcus infection, impetigo…
Case 9: none of the usual children's diseases." [? Overactive immune system?]
Case 10: frequent hospitalizations because the feeding problem … repeated colds and otitis media
Case 11: was given anterior pituitary and thyroid preparations for 18 months
Kanner's original paper, discussed in **Jepson 2007**

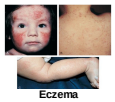
GI problems including Abnormal gut bacteria



Finegold S, 2002

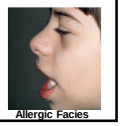
Immune signs and symptoms and measures in autism

- Recurrent infections
- Autoantibodies
- Family history of autoimmune disease
- Autoimmune features
- Food allergies and sensitivities
- Atypical cytokine and chemokine levels
- Abnormal immunoglobulin levels



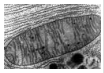
Eczema

Onychomycosis



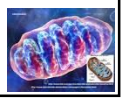
Allergic Facies

Energy metabolism: Mitochondria

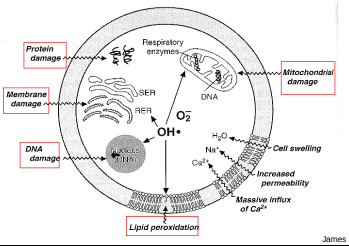


- Mitochondria handle energy metabolism

- Children with mitochondrial disorders frequently have autistic behaviors
  - Sometimes only intermittently, when they are "low-energy"
- Neurons with weaker energy metabolism will act differently



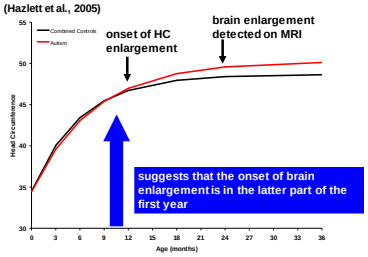
Injury at the cellular level throughout the body



James

Maybe not (just) prenatal brain wiring alterations: Chronic Brain Tissue Problems

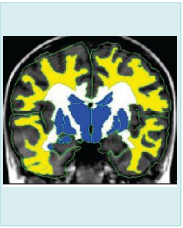
The Timing of Brain Enlargement: Clues from Head Circumference
(Hazlett et al., 2005)



Some characteristics of large brains in autism

Disproportionate increase of white matter

White matter increase localizes to outer ("radiate") white matter

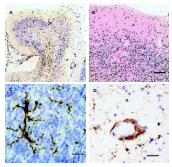


Herbert M. 2003, 2004, 2005

Brain tissue shows signs of immune activation or "neuroinflammation."

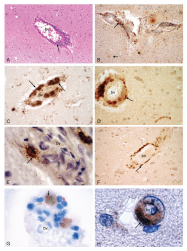
Neuroglial activation and neuroinflammation in the brain of patients with autism
Vargas et al, 2005, Annals of Neurology

Oxidative stress in brain tissues from autistic patients
Vargas et al, 2005, Annals of Neurology



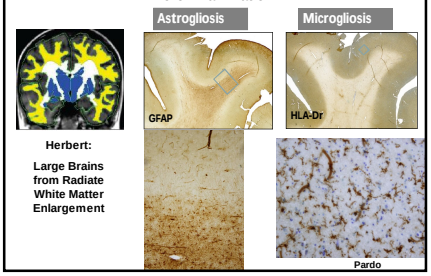
Air pollution and brain inflammation

Air pollution leads to brain inflammation much like what we see in autism.



Long-term Air Pollution Exposure Is Associated with Neuroinflammation, an Altered Innate Immune Response, Disruption of the Blood-Brain Barrier, Ultrafine Particulate Deposition, and Accumulation of Amyloid β-42 and α-Synuclein in Children and Young Adults

The white matter areas that are larger appear to have more inflammation.

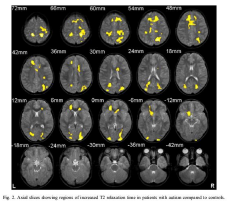


Herbert:

Large Brains from Radiate White Matter Enlargement

Pardo

Brain imaging suggests that areas that are larger might have more water, not more axons



May be a reflection of altered tissue water properties

White matter abnormalities in autism detected through transverse relaxation time imaging. Hendry et al., Neuroimage, 2005.

Rubenstein & Merzenich, *Genes, Brain and Behavior (2003) 2: 255-267*

Model of autism: increased ratio of excitation/ inhibition in key neural systems

Too Much Excitation

Not Enough Inhibition

=

More: irritability, hypersensitivity, overload

Comments:

Increased excitation/inhibition ratio may explain many features of autism, such as:

a) Sensory sensitivities

b) Sleep disturbances

c) Seizures, epilepsy

AND – inflammation and oxidative stress increase this E/I ratio!

Excitotoxicity is a *process* of cumulative impact on cells

Cell Death, Cell loss

Cell stress

Oxidative Stress

Amount of free radicals exceeds ability to handle them

Excessive excitatory neurotransmitters

Excessive excitatory receptor responsiveness

Insufficient inhibitory neurotransmitters or receptor function

While it is a process, when cells are dysfunctional but not dead, there are things you can do.

FINAL COMMON PATHWAYS

Overflowing the Levees

Environmental Inputs:

CHEMICALS · ALLERGENS · HEAVY METALS · RADIATION · INFECTIONS · DRUGS · TOXINS · STRESS · NOISE

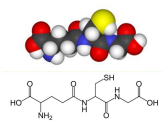
The body's core functions:
Energy, Metabolism, Defense, Structure, Communication, Detox etc.

Genes · Timing · Specific agents

Specific diseases

The body's generic reactions:
Inflammation
Oxidative Stress
Impaired function

GLUTATHIONE is low in many with ASD



- Important for protection of cells from damage
- Important for detoxification
- The body's most potent anti-oxidant

Not static / hardwired, but dynamic: Improvement, Learning, Plasticity

Improvement in core autism behaviors in setting of fever: not consistent with "hard-wired" cause

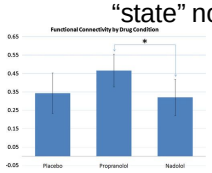
PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Behaviors Associated with Fever in Children with Autism Spectrum Disorders.
Curran et al. Pediatrics 2007

Challenges posed by this study:

- This is not consistent with "static encephalopathy"
- What mechanisms might be consistent with this?
  - Proposed so far: locus ceruleus, environmental impact on glial gap junctions, cytokines, membrane lipids, dysfunctional electrophysiological oscillations
- Additional pertinent citations: Heft / Fein et al, Neuropsychology Review, 2007; Herbert in Chauhan et al CRC Press late 2009, Mehler & Purpura 2009

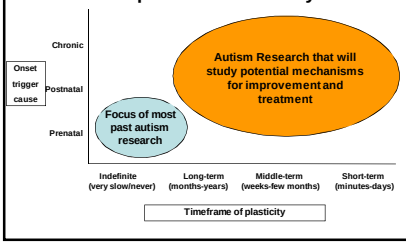
Rapid change in brain connectivity suggests "state" not "trait"



Effect of Propranolol on Functional Connectivity in Autism Spectrum Disorder—A Pilot Study
Narayanan et al. (Beversdorf lab)
Brain Imaging and Behavior. 2010

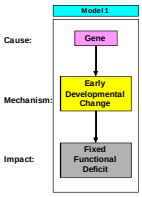
- Functional connectivity, assumed to be a fixed trait, changed rapidly with drug that impacts brain stress level (propranolol)

Implications of clinical observations of good days/bad days and improvement/recovery



Expanding the Spectrum of Autism Mechanisms :

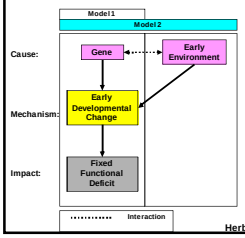
1. Genetically caused static encephalopathy



Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms :

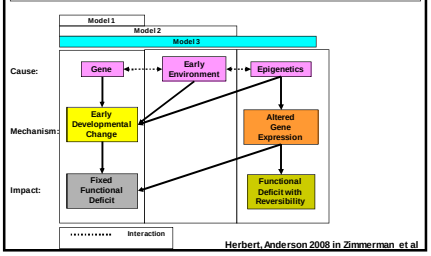
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy



Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms :

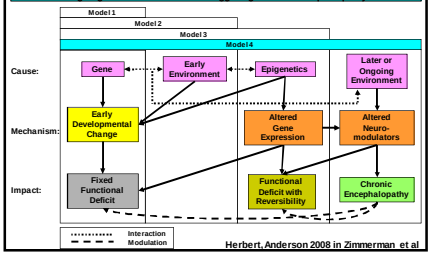
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy
3. Epigenetically altered gene expression



Herbert, Anderson 2008 in Zimmerman et al

Expanding the Spectrum of Autism Mechanisms:

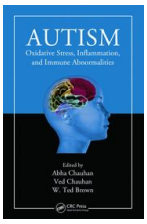
1. Genetically caused static encephalopathy
2. Gene-environment caused static encephalopathy
3. Epigenetically altered gene expression
4. Later or ongoing environmental factors triggering chronic encephalopathy



Herbert, Anderson 2008 in Zimmerman et al

Article detailing much content for this talk:

Autism: The Centrality of Active Pathophysiology and the Shift from Static to Chronic Dynamic Encephalopathy



By Martha R. Herbert, MD, PhD
2009

Autism: Oxidative stress, inflammation and immune abnormalities
Chauhan A, Chauhan V, Brown T, eds., 2009, Taylor & Francis/CRC Press.

Current Opinion in Neurology, April, 2010

Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders
Martha R. Herbert

TRANSCEND Research Program, Pediatric Neurology, Massachusetts General Hospital, Charlestown, Massachusetts, USA

Correspondence to Martha R. Herbert, TRANSCEND Research Program, Pediatric Neurology, Massachusetts General Hospital, 149 13th Street, Room 10.018, Charlestown, MA 02129, USA
Tel: +1 617 724 5920;
e-mail: mherbert1@partners.org

Current Opinion in Neurology 2010, 23:000–000

Purpose of review
To present a rationale and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASDs).
Recent findings
Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150 only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also suggest a role for environment. Systemic and central nervous system pathophysiology, including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be consistent with a role for environmental influence (e.g. from air pollution, organophosphates, heavy metals) in ASD, and some of the underlying biochemical disturbances (such as abnormalities in glutathione, a critical antioxidant and detoxifier) can be reversed by targeted nutritional interventions. Dietary factors and food contaminants may contribute risk. Improvement and loss of diagnosis in some with ASD suggest brain circuitry amenable to environmental modulation.
Summary
Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

A Different Model of Autism

- **Autism could be a consequence of *challenges to cellular function throughout the body, including the brain***
- ***These cellular changes may be related to environmental insults***
- **Altered cellular response could be at the root of brain and body problems**
- ***Many cellular problems can be treated***

TEXTBOOK OF FUNCTIONAL MEDICINE

Principles of a science-based, systems-biology approach to chronic, environmentally modulated illness

www.functionalmedicine.org

What is Functional Medicine?

http://www.functionalmedicine.org/about/whatis.asp

- **Biochemical individuality** describes the importance of **individual variations in metabolic function that derive from genetic and environmental differences** among individuals.
- **Patient-centered** medicine emphasizes "patient care" rather than "disease care," following Sir William Osler's admonition that **"It is more important to know what patient has the disease than to know what disease the patient has."**
- **Dynamic balance** of internal and external factors.
- **Web-like interconnections** of physiological factors – an abundance of research now supports the view that **the human body functions as an orchestrated network of interconnected systems, rather than individual systems functioning autonomously and without effect on each other.** For example, we now know that immunological dysfunctions can promote cardiovascular disease, that dietary imbalances can cause hormonal disturbances, and that **environmental exposures can precipitate neurologic syndromes** such as Parkinson's disease.
- **Health as a positive vitality –** not merely the absence of disease.
- **Promotion of organ reserve** as the means to enhance health span

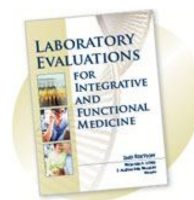
www.functionalmedicine.org

Classes of Functional Imbalances

All of these functions can be imbalanced by ENVIRONMENTAL FACTORS

- **Oxidation-reduction imbalances and mitochondropathy**
  - *Bioenergetics*
- **Detoxification and biotransformational imbalances**
  - *Elimination of waste*
- **Immune imbalances**
- **Inflammatory imbalances**
  - *Protection and defense, repair*
- **Microbiological imbalances**
  - *Protection and defense*
  - *Biotransformation*
- **Digestive, absorptive, eliminative**
  - *Biotransformation, transport, circulation, elimination of waste*
- **Hormonal and neurotransmitter imbalances**
  - *Communication, both inside and outside the cell*
- **Structural** (from cellular to connective tissue and musculoskeletal)
  - *Structural integrity*
  - *Transport and circulation*

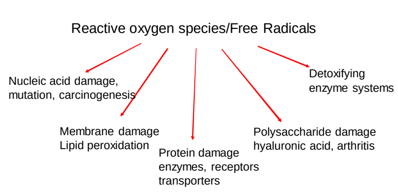
Textbook of laboratory assessments



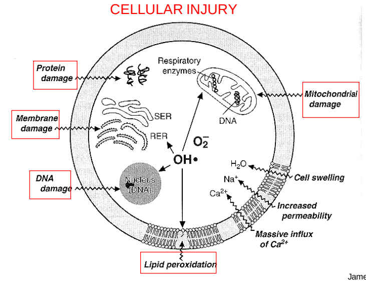
Oxidation-reduction imbalances and mitochondropathy - *Bioenergetics*

- Oxidative Stress
  - Buildup of "free radicals" (reactive oxygen) when there are insufficient antioxidants to quench these products of metabolism
  - Reactive oxygen species have constructive uses; the imbalance is the problem.
- Oxidative stress increases risk for many diseases, including cardiac, cancer, neurodegeneration, obesity, arthritis, and apparently autism

Oxidative stress results in injury to macromolecules



MECHANISMS OF FREE RADICAL-MEDIATED CELLULAR INJURY



James

Many environmental toxicants are potent pro-oxidants

Environmentally relevant levels of toxicants make cells more oxidized in precisely the range that alters the response to the environmental signals, with variable consequences:

- Cell division is suppressed
- Cells are made more vulnerable to inducers of cell death
- Cell regulation is altered

Mark Noble, University of Rochester Medical Center Used with Permission 55

Oxidation-reduction imbalances and mitochondropathy - *Bioenergetics*

- Oxidative Stress
  - Buildup of "free radicals" when there are insufficient antioxidants to quench these products of metabolism
- Mitochondrial disorders
- Mitochondrial injury by xenobiotics/toxins

56

Mitochondrial dysfunction may be a common metabolic cause of or contributor to autism

Mitochondrial evidence

- **Multiple blood markers**
- **Disturbed brain energy metabolism**
- **Elevated brain lactate**
- **Abnormal fatty acid oxidation; reduced carnitine**
- **Autism associated with some mitochondrial SNPs**
- ***Dysfunction can be subtle***

Potential impacts

- **Brain dysfunction – reduced energy for signaling and coordination**
- **Hypotonia**
- **Gut dysfunction**

Potential causes

- **Genetic**
- **Environmental**
- **Gene-environment**

57

Exquisite environmental sensitivity of mitochondria

Annu. Rev. Pharmacol. Toxicol. 2000. 40:353–88

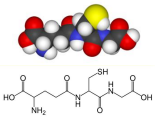
MITOCHONDRIAL TARGETS OF DRUG TOXICITY

K. B. Wallace and A. A. Starkov
Department of Biochemistry and Molecular Biology, University of Minnesota School of Medicine, Duluth, Minnesota 55812; e-mail: kwallace@d.umn.edu, astarkov@d.umn.edu

Key Words oxidative phosphorylation, uncouplers, bioenergetics, permeability transition, redox cycling

58

GLUTATHIONE



Glutathione is synthesized from the amino acids L-cysteine, L-glutamate and glycine.

Excess glutamate at synapses, which may be released in conditions of brain stress, illness or injury, can prevent the uptake of cysteine, a necessary building block of glutathione.

Without the protection from oxidative injury afforded by glutathione, cells may be damaged or killed.

59

Glutathione and Mitochondria

- The most important source of reactive oxygen under normal conditions in aerobic organisms is probably the leakage of activated oxygen from mitochondria during normal oxidative respiration.
- Dysfunction of mitochondria will increase the demand for glutathione and raise the risk of not keeping up with this demand.

60

Many roles of glutathione

- Glutathione plays important roles in antioxidant defense, nutrient metabolism, and regulation of cellular events (including gene expression, DNA and protein synthesis, cell proliferation and apoptosis, signal transduction, cytokine production and immune response, and protein glutathionylation).
- Glutathione deficiency contributes to oxidative stress, which plays a key role in aging and the pathogenesis of many diseases (including kwashiorkor, seizure, Alzheimer's disease, Parkinson's disease, liver disease, cystic fibrosis, sickle cell anemia, HIV, AIDS, cancer, heart attack, stroke, and diabetes).
- New knowledge of the nutritional regulation of GSH metabolism is critical for the development of effective strategies to improve health and to treat these diseases.

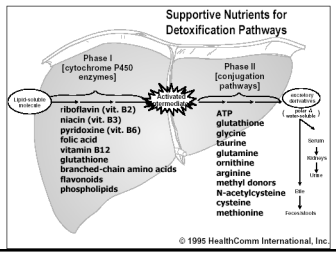
61

Detoxification and biotransformational imbalances - *Elimination of waste*

- Cellular: methylation and transsulfuration
- Organ-metabolic: liver detoxification
  - Requires good phase I and phase II liver detoxification
- Organ-GI: elimination through stool
  - Requires good digestion, good bile
- Organ-kidney: elimination through urine
  - Requires good renal transport
- Organ-skin: elimination through perspiration

62

Interactions between systems: *Nutrients supporting detoxification*



63

Immune imbalances and Inflammatory imbalances – *Protection and defense, Repair*

Specific immune abnormalities have been found in 30-70% of patients with autism (Zimmerman 1999 and Heijnen 1997)

- Shift from TH1 (viral/fungal killing) to TH2 (allergy)
  - » predisposition to infections and autoimmunity/allergy
- Altered immune components
  - » Reduced CD4+ Tcells (Warren 86,90; Younk 90, Gupta 96)
  - » Decreased NK cell activity (Warren 87)
  - » Increased DR+ (activated) Tcells (Plioplys 94, Warren 95)
- Anti-self antibodies
  - » Anti-MBP (Weizman 82; Singh 93, 98)
  - » Anti-NAFP and GFAP (Singh 97, Plioplys 89)
  - » Anti-temporal lobe IgM and IgG (Connolly 99)
  - » Anti-serotonin receptor (Singh 97)
  - » Anti-NGF (Koskovskaia 2000)
  - » Anti-neurofilament protein (Plioplys 94)
- Autoimmunity
  - » FH autoimmune disease (RA, lupus, IDDM), esp. mother (Cemi 99)
  - » MHC types predisposing to autoimmunity overrepresented (Warren 96, 98)

64

RELATONSHIP

Benasich, A. A.. 2002
Biederman, J. et al.,1995
Crawford, S. G. et al.,Cortex. 1994
Dalton, P., et al., 2003.
Galaburda, A. M., 1994 Apr-1994
Kaplan, B. J. and Crawford, S. G. 1994 Nov
Vincent, A. et al., 2002

NO RELATIONSHIP

Berenbaum, S. A. and Denburg, S. D. 1995
Biederman, J.; 1995
Bryden, M. P., 1994
Tonnessen, F. E. 1997

Immune abnormalities and language disorders

Maternal Neuronal Antibodies Associated with Autism and a Language Disorder

Paola Dalton, DPhil,[1] Robert Deacon, DPhil,[2] Andy Blamire, PhD,[3] Michael Pike, FRCPCH,[4] Ian McKinlay, FRCPCH,[5] John Stein, FRCP,[6] Peter Styles, DPhil,[3] and Angela Vincent, FRCPath[1]

Impaired Processing of Brief, Rapidly Presented Auditory Cues in Infants With a Family History of Autoimmune Disorder

April Ann Benasich

Center for Molecular and Behavioral Neuroscience Rutgers, the State University of New Jersey

Glial Cells in the Gut: Immune, Signaling and Barrier Functions

Neurogastroenterol Motil (2005) 17, 777–790 doi: 10.1111/j.1365-2982.2005.00687.x

Glial cells in the gut

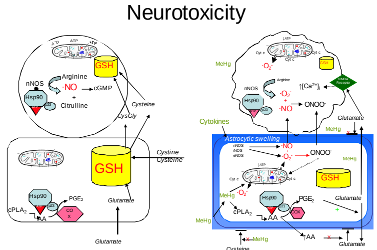
A. RÜHL

Department of Human Biology, Technical University of Munich, Germany

Abstract: The enteric nervous system is composed of both neurons and glia. Recent evidence indicates that enteric glia–which vastly outnumber enteric neurons–are actively involved in the control of gastrointestinal functions: they contain neurotransmitter precursors, have the machinery for uptake and degradation of neuroligands, and express neurotransmitter- receptors which makes them well suited as intermediaries in enteric neurotransmission and information processing in the ENS. Novel data further suggest that enteric glia have an important role in maintaining the integrity of the mucosal barrier of the gut. Finally, enteric glia may also serve as a *link between the nervous and immune systems of the gut* as indicated by their potential to synthesize cytokines, present antigen and respond to inflammatory insults. The role of enteric glia in human disease has not yet been systematically studied, but based on the available evidence it is predictable that enteric glia are involved in the etiopathogenesis of various pathological processes in the gut, particularly such with *neuroinflammatory or neurodegenerative* components.

66

Cartoon Illustrating the Alterations in Cell Signaling that Mediate MeHg-induced Neurotoxicity



M. Aschner

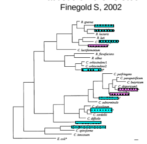
Microbiological imbalances
Protection and defense, Biotransformation

- **Gut flora have many functions, including:**
  - **Metabolism of nutrients, hormones, and potential toxins**
  - **Immune function**
  - **Production of substances necessary for health (e.g. Vitamin B12)**
- **Abnormal gut flora *species* and their *metabolic processes* can:**
  - **Deplete vital nutrients**
  - **Alter metabolism of xenobiotics**
  - **Alter immune function**
  - **Produce unwanted toxic and neuroactive byproducts**
  - **Injure the gut**
- **This can cause or worsen metabolic stress.**

68

Not just human metabolism

Abnormal Clostridial bacterial species in autistic children's stool.
Finegold S, 2002



Extended Genome: Host and gut-microbial co-metabolome interaction
J Nicholson, Nature Review Microbiology, 2005

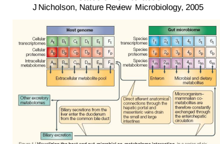


Figure 1 | **Visualizing the host and gut-microbial co-metabolome interaction.** In a series of six

Abnormal gut flora *metabolism* can:
- deplete vital nutrients
- alter metabolism of xenobiotics
- Alter immune function

This can cause or worsen metabolic stress.

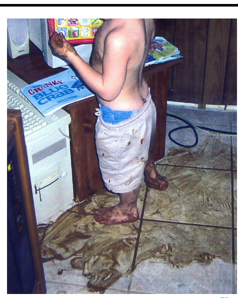
Published:

Transient improvement in core symptoms with antibiotic Rx. (Finegold)

Gut flora can be altered by environment:
- Diet, antibiotics, pesticides, other exposures, etc.

69

The Every Day of Some Autisms



What we need: Clinical labs that will detect and report pertinent gut pathogens

70

Laboratory challenges in working up intestinal abnormalities

- Labs may consider some bacterial species "normal" because in an immune-intact healthy person they rarely cause problems
  - In a medically and immune challenged child with autism (as in individuals with HIV), bacteria with only mild pathogenicity may cause real problems
- Standard laboratory techniques will not be sensitive to anaerobic bacteria or many other species
- Length of time of culture matters for low-grade chronic infections (these may be missed with standard procedures)

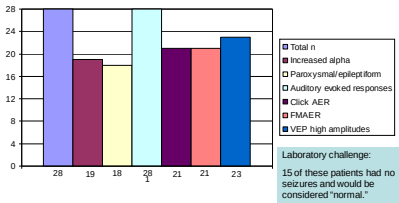
71

Nutritional *deficiencies* and Nutritional *insufficiencies*

- **RDA**
  - The **Recommended Dietary Allowance** or **RDA** (sometimes referred to as *Recommended Daily Allowance*) is defined as "the ***average*** daily dietary intake level that is sufficient to meet the nutrient requirements of nearly all (approximately 98 percent) healthy individuals".
- **Nutrigenomics**
  - Study of how nutrition modulates genes and how genes affect nutritional needs. It is a very new field that in the long run may contribute to ***individualized*** diet and medicine.
- **Deficiency**: Low level by population standard
- **Insufficiency**: Low level by individual genetic or state/stress/illness-related need

72

Autism Electrophysiological Abnormalities (n=28)



Laboratory challenge:

15 of these patients had no seizures and would be considered "normal."

Increased VEP amplitude standard deviation was 2.42-8.92 SD (average 5.4 SD)

Martien & Duffy

Autism and Autonomic Nervous System (ANS)

- High variability in arousal – both high and low
  - Not well studied over long time intervals
  - May be high and low in the same individual at different times
- Additional autonomic abnormalities that have been reported:
  - abnormal skin conductance
  - blunted autonomic arousal to social stimuli
  - increased tonic electrodermal activity

MEDICAL PROBLEMS THAT MAY BE RELATED TO ANS

- Sleep disorders are found in a large majority of children (up to 80%)
- GI symptoms (e.g. chronic constipation or diarrhea)
- Oxidative stress (altered hypothalamic-pituitary-adrenal axis related to ANS and impacting metabolism)

Structural (from cellular to connective tissue and musculoskeletal) - *Structural integrity, Transport and circulation*

IMPACTS OF METABOLIC, IMMUNE AND TOXIC ISSUES ON STRUCTURE

- Osteoporosis
- Endovascular abnormalities (Pratico)
- Glia as "connective tissue" of brain
- Bone and connective tissue as depot for toxic body burden

To climb
To surmount
To exist above and independent of
To be transcendent
To excel

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