Autism & Environmental Vulnerability: Whole Brain, Whole Body, Whole Planet

Overview:
Autism as a Warning for All of Us
• Autism has been defined behaviorally
• But it is a whole-body condition
• Many of its core biological features are found in a wide range of other chronic childhood and adult illnesses
• Many of its features strongly suggest environmental insults
• Many of its features are treatable through easily available environmental changes, i.e. diet and nutrition
• Preventing and treating autism open doors to helping many millions of others as well

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 as a Warning for All of Us
Biology is not part of the definition
(and neither is prognosis)

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

Gene → Brain module → Behavior

AUTISM

• Not just genetic:
  ➢ Numbers going up
  ➢ This suggests environment

• Not just brain modules:
  ➢ Whole brain involvement
  ➢ Brain tissue changes

• Not just brain:
  ➢ Systemic features – Whole Body

• Not necessarily hardwired:
  ➢ Plasticity and recovery
  ➢ Treating body with diet and nutrition can help brain

Mindd Regional Seminars, Sydney, 2010
www.mindd.org
What could make numbers go up?

- Factors in the environment
- Differences in vulnerability

Or both:

- Things in the environment that make vulnerability worse

No proof that these arguments explain away ALL the increase

New paper from UC Davis (Epidemiology, Herjog-Picciotto and Dohmche, 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”

Is autism really “all” genetic?

- Twin studies and high recurrence support genetic influence, not genetic determination.
  - More identical than fraternal twin pairs are concordant (share an autism diagnosis)
  - But concordance is only 60% for full autism
  - 90% concordance is for broad autistic spectrum (i.e., milder) in one of the twins

- Swedish study of schizophrenic identical twins
  - Probable same placenta: 60% concordance
  - Different Placentas: 11% concordance

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

- “G and E probably affect most cases
  - ASD can be 80% genetic AND 80% environment
  - Population attributable Fraction does not have to add up to 100%
  - Example: if everyone smoked, then who gets cancer is “genetic”

Rise in Autism Prevalence v. Other Major Chronic Conditions in US
Pesticide use more than doubled between 1964 and 1982 (USDA)

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

Texas autism rates, by school districts

Status of Developmental Toxicity Testing for the 2,863 Chemicals
Produced Above 1 million pounds/year

Proximity to point sources of environmental mercury release as a predictor of autism prevalence.

www.bodyburden.org

20-30 Tested for Neurodevelopmental Toxicity

According to EPA Guidelines

This testing is NOT REQUIRED.

In Harm’s Way, www.preventingharm.org

Autism & Environmental Vulnerability
Martha Herbert, MD, PhD
Flame retardant found in peregrine falcon eggs

The eggs of peregrine falcons living in California's big cities contain some of the highest levels ever found in wildlife of a flame retardant used in consumer products, a new study has found. Urban wildlife are the sentinel species that can tell us about chemicals of emerging concern from city exposures. Information from these species can be useful to us in protecting the sensitive members of our population like infants, children and pregnant women.

Several studies suggest that girls whose mothers were exposed to high levels of pesticides, particularly the banned pesticide DDT, show signs of accelerated puberty. Recent research shows early puberty associated with increased risk for breast cancer.

Bisphenol A Causes Chromosomes to Sort Incorrectly During the Development of Egg Cells


Several studies suggest that girls whose mothers were exposed to high levels of pesticides, particularly the banned pesticide DDT, show signs of accelerated puberty.

Recent research shows early puberty associated with increased risk for breast cancer.
PUBLIC HEALTH ASSESSMENT: BRICK TOWNSHIP AUTISM INVESTIGATION

OCEAN COUNTY, NJ
EPA FACILITY ID: NJUCCA45550
November 29, 2000
Superfund Site Assessment Branch
Division of Health Assessment and Consultation Agency for Toxic Substances and Disease Registry.

APPENDIX A: Contaminants of Concern in Brick Township
Screening exposures for risk

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Concentration (ppb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>1,000</td>
</tr>
<tr>
<td>Anthracene</td>
<td>3,000</td>
</tr>
<tr>
<td>Arsenic</td>
<td>3</td>
</tr>
<tr>
<td>Benzene</td>
<td>1</td>
</tr>
<tr>
<td>Benzo(b)fluoranthene (PAH)</td>
<td>0.2</td>
</tr>
<tr>
<td>Benzo(a)pyrene (PAH)</td>
<td>0.005</td>
</tr>
<tr>
<td>Benz(a)anthracene (PAH)</td>
<td>2,800</td>
</tr>
<tr>
<td>Bis-phthalate</td>
<td>6,000</td>
</tr>
<tr>
<td>Bromoform</td>
<td>4</td>
</tr>
<tr>
<td>Butyl benzyl phthalate</td>
<td>2,000</td>
</tr>
<tr>
<td>Cadmium</td>
<td>5</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td></td>
</tr>
<tr>
<td>Chlordane</td>
<td>0.6</td>
</tr>
<tr>
<td>Chlorobenzenes</td>
<td>100</td>
</tr>
<tr>
<td>Chloroform</td>
<td>6</td>
</tr>
<tr>
<td>Chromium</td>
<td>100</td>
</tr>
<tr>
<td>Copper</td>
<td>100</td>
</tr>
<tr>
<td>DDT</td>
<td>5</td>
</tr>
<tr>
<td>Dieldrin</td>
<td></td>
</tr>
<tr>
<td>1,2-Dichlorobenzene</td>
<td>600</td>
</tr>
<tr>
<td>1,4-Dichlorobenzene</td>
<td>75</td>
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<tr>
<td>Dichloroethanes</td>
<td></td>
</tr>
<tr>
<td>1,1-Dichloroethene</td>
<td>0.06</td>
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<tr>
<td>Dieldrin</td>
<td></td>
</tr>
<tr>
<td>Chlorinated Hydrocarbons</td>
<td>280ppb</td>
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<tr>
<td>Vinyl Chloride</td>
<td>0.2</td>
</tr>
<tr>
<td>Xylene</td>
<td>2,000</td>
</tr>
<tr>
<td>Zinc</td>
<td>3,000</td>
</tr>
</tbody>
</table>

The CDC looked at these one at a time, and used adult toxicity levels to evaluate impacts on infants.

Pyrethrin Pet Shampoos and Autism

Anti-flea Pet Shampoos with Pyrethrin May Play a Role in Autism

mothers of children with autism spectrum disorders were twice as likely to report that they had shampooed their pets with pyrethrin-containing anti-flea/anti-tick shampoos around the time of their pregnancy.

Hertz-Picciotto, UC Davis MIND Institute; presented at 7th Annual International Meeting for Autism Research May 15-17, 2008.

Research 1 Children’s Health

Maternal Residence Near Agricultural Pesticide Applications and Autism Spectrum Disorders among Children in the California Central Valley

Risk of exposed mother having child develop autism increased with the poundage of organochlorine applied and decreased with distance from field sites.

(Odds ratio 6.1)

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

Brains are on average unusually large in autism, and they grow larger than average after birth, not before.

The Timing of Brain Enlargement: Clues from Head Circumference

Brain enlargement is due more to white matter getting bigger than to gray matter getting bigger.
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

To understand the impact of brain enlargement, we need to learn what cellular changes are causing the size increase.

But it does not look like the brain enlargement is due to an increase in axon density.

Brain magnetic resonance spectroscopy summary of findings in literature to date:
- Mostly lower density of metabolites
- Mostly reduced or no change; few reports of increase
- Most studies done on 1.5T which has poor signal to noise ratio (only 1 of 22 done on 3T) and could miss differences

Metabolites
- NAA, Cho, mI, Cr+PCr, Glx, Lac

Shetty, Raisi, Ringer, Herbert, 2009

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

May be a reflection of altered tissue water properties

Shetty, Raisi, Ringer, Herbert, 2009
Reduced FA and Increased Diffusivity in Short-Range Fibers:
Less fiber integrity, more disorganization
FA = Fractional Anisotropy: measure of white matter integrity. Lower is “worse”.

- Short-range and long-range association fibers of frontal lobe – separated without arbitrary demarcation
- Fractional Anisotropy (FA):
  - Short-range fibers: Autism less (less white matter integrity) bilat
  - Long-range fibers: no difference
- Apparent Diffusion Coefficient (ADC):
  - Long range greater (more white matter disorganization) bilat, p < 0.001
  - Short range fibers: autism more disorganized bilaterally

More than Brain Circuits: Brain tissue
- Could brain enlargement come from inflammation?

Brain tissue shows signs of immune activation or “neuroinflammation.”

Brain tissue shows signs of immune activation or “neuroinflammation.”

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

Environment and Brain tissue vulnerability
- Many environmental exposures can contribute to
  - Inflammation
  - Reduction in brain perfusion
  - Compromise of the blood-brain barrier

Air pollution and brain inflammation
- Air pollution leads to brain inflammation much like what we see in autism.
Factors documented in autism increasing blood viscosity and reducing perfusion

- decreased red-cell membrane fluidity
- increased urinary marker for thromboxane which activates and aggregates platelets,
- increased signs of oxidative stress in red blood cells in ASD, including increased NO
- increased xanthine oxidase
- depressed glutathione peroxidase (GSHPX)
- depressed SOD
- depressed catalase
- increased lipid peroxides

The “Blood-Brain Barrier” is not an absolute barrier

Things that can open the BBB

- Hypertension (high blood pressure)
- Hyperosmolality (a high concentration of a substance in the blood)
- Microwaves
- Radiation
- Infection
- Inflammation
- Ischemia (insufficient oxygen)
- Injury, Trauma, Pressure
- Deficient Vitamin C or flavonoids

Astrocyte activation can impair perfusion by constricting small vessels

- Astroglia are part of the blood-brain barrier and the swelling they undergo with activation can reduce capillary lumen by as much as 50%, reducing perfusion

Lower perfusion in ASD brains has been abundantly documented but remains marginal to most brain research. The surface has barely been scratched in researching the physical reasons for this.

- 17 of 19 PET and SPECT autism studies showed low perfusion
- Those that showed areas of high perfusion still showed lower perfusion more than higher
- Almost all studies analyzed this psychologically, not medically:
  - discussed only implications of location of low perfusion in brain
  - Did not ask what physically what might be causing this
  - Seemed to assume that this low perfusion was permanent

What’s wrong with this statement?

“Nevertheless, cerebral hypoperfusion remains out of the mainstream of scientific thought on the source of autism, which is now focused on variant genes and environmental factors that combine to impair development in early childhood.”

— From news report
More than Brain: Body Problems

Autism is a Whole-Body, Whole-System Condition

- Seizures (~30%+)
- Cognitive deficits
- Sensorimotor abnormalities
- Disordered sleep
- Immune impairments
- GI distress
- Food allergies
- Systemic metabolic disturbances

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 6: Taken to doctor because of….
Case 7: Vomited all food from birth through the third month... repeated colds and otitis media

Case 8: 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

Gi problems including Abnormal gut bacteria

Microbiome problems may underlie many health issues.

Microbiome problems may underlie many health issues.
Diet and Nutrition for Gut Health

- Fermented foods were part of traditional diets
  - Include them again – can buy or make at home
- Probiotics
  - Finally an active area of research
- Avoid foods that make gut problems worse
  - Especially avoid simple sugars

Elimination diets and gut health

- Many benefit from elimination diets
  - Gluten free, casein free
  - Specific carbohydrate diet: eliminates all grains and more
- Some of these diets are almost opposite of self-imposed restriction to gluten and casein
- Possible mechanisms
  - Reduction of immune challenges
  - Improvement of gut flora
  - Elimination of psychoactive byproducts of inadequate gluten and casein digestion

Gluten and casein problems

- Evidence for gluten problems in schizophrenia
- Early evidence in ADHD
- Recent strong study in autism:
- Strong anecdotal support for casein elimination in some cases of autism, asthma, ADHD
- More research is needed

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

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 neurotransmitters, 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.

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

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
Classes of Core Functions
Abnormalities at all of these levels in autism—and many other major chronic diseases as well

- Bioenergetics
  - Mitochondrial dysfunction
- Biotransformation
  - Metabolic dysfunction
- Transport, circulation
  - Cerebral hypoperfusion
- Communication, inside and outside the cell
  - Immune dysregulation
  - Neurotransmitters, hormones
- Structural integrity
  - Hypotonia
- Protection and defense
  - Autoimmune problems
- Elimination of waste
  - Impaired intestinal function
  - Impaired detoxification

Systems are Deeply Interconnected:
Immune and Nervous system cross-talk

TEXTBOOK OF FUNCTIONAL MEDICINE
“Principles of a science-based, systems-biology approach to chronic, environmentally modulated illness”

Going for the ROOTS
- Go to and treat the roots of the problems
- Identify and treat problems early before they become catastrophic

Injury at the cellular level throughout the body

Influencing Vulnerability
- Things can increase vulnerability
  - Or
- Decrease vulnerability
GLUTATHIONE is low in many with ASD

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

Abnormal metabolic-chemical processes create many vulnerabilities

Vulnerability with low GSH

Impact on Brain function

Neurometabolic Disorders and Dysfunction in Autism Spectrum Disorders

The cause of autism remains largely unknown because it is likely multifactorial, arising from the interaction of biologic, genetic, and environmental factors.

Current research may provide insight into the pathophysiologic underpinnings of autism, at least in some patients.

Some known neurometabolic disorders have an autistic phenotype.

Possible involvement of mitochondrial disorders and dysfunction.

Increased vulnerability to oxidative stress may be the route by which various environmental toxins produce metabolic alterations that impair normal cellular function.

Emergence of a broader understanding of underlying metabolic disturbance even in the absence of known disease.
Rubenstein & Merzenich, 

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

**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.

Autism Electrophysiological Abnormalities

Something in everyone, much in some

![Graph showing increased VEP amplitude standard deviation](graph.png)

- Total n
- Increased alpha
- Paroxysmal epileptiform
- Auditory evoked responses
- Click AER
- FMAER
- VEP high amplitudes

1/5 of these patients had no seizure history.

Martien & Duffy

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Chronic mechanisms can impact brain FUNCTION

**Functional Vulnerabilities**

- **Free Radicals**
  - Energy Production
- **Calcium Uptregulation**
  - NMDA plasticity
- **Peroxidation**
  - Lipid Membranes
- **Toxic Mediators**
  - Transmitter Specificity
- **Chronic Inflammation**
  - Glial Support

These are:

- Cellular
- Widespread

- Impact timing, signal intensity, coordination

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Excitotoxicity is a process

- Cell death, cell loss
- Cell stress
- Oxidative stress

When it is in process there are things you can do.

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Autism Nervous System Electrical Abnormalities:

Sensitive Brains

- Stress
- Sensory
- Sleep
- Seizures

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What’s wrong with this statement?

- “You can treat the gut if you want, but that won’t affect the autism because the autism is caused by structural changes in the brain.”

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Researcher with finding about a gene that affects multiple systems beyond brain

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Minddd Regional Seminars, Sydney, 2010

www.minddd.org
**Vicious Circles:**
Each thing makes the next thing worse

- Genes
- Toxics
- Infection/Immune
- Increased Excitation / Inhibition Ratio
- Sensory/Sleep
- Stress

**Rabbit or duck?**
Is autism a **BRAIN DISORDER**
or a **DISORDER THAT AFFECTS THE BRAIN?**

**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.

**Rabbit or duck?**
Is autism a **BRAIN DISORDER** or a **DISORDER THAT AFFECTS THE BRAIN?**
Overflowing the Leves

The body’s core functions:
- Energy
- Metabolism
- Defense
- Structure
- Communication
- Detox etc.

The body’s generic reactions:
- Inflammation
- Oxidative Stress
- Impaired function

Specific diseases

Environmental Inputs:
- CHEMICALS
- ALLERGENS
- HEAVY METALS
- RADIATION
- INFECTIONS
- DRUGS
- TOXINS
- STRESS
- NOISE

Current Opinion in Neurology, April, 2010

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

Purpose of review: To present a review and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASD).

Recent findings: Recent studies suggest a substantial increase in ASD prevalence above national Centers for Disease Control figures of one in 150 only replicable by data artifacts, reviewing the diversity of environmental conditions to increased prevalence or exposure. Decreased inflammation and advanced paternal age as a risk factor for ASD also suggest a role for environmental factors. Systemic and central nervous system pathophysiology including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be correlated with a variety of environmental factors, including air quality, diet, and dust. Although the role of environmental factors in ASD is not established, environmental influences on brain development are recognized as an essential risk factor and some can be modulated by lifestyle factors, such as breastfeeding, additional maternal health and nutrition, or other environmental factors. In addition, the increased prevalence of ASD is likely at least in part related to increased factors associated with environmental exposures.

Conclusion: Environmental factors that may play a role in the increased prevalence of ASD are likely to have a role in the development of ASD, and should be considered in the diagnosis and treatment of ASD.

Another book recommended: The Music of Life: Biology Beyond the Genome

Beautiful readable book

Discusses physiology and the “middle-out” approach

http://www.musicoflife.co.uk/
Autism & Environmental Vulnerability
Martha Herbert, MD, PhD

From a unique behavioral syndrome
- Communication
- Socialization
- Autism
- Behavior

To a developmental outcome of a widespread systemic metabolic injury
- Detoxification
- Oxidative stress
- Inflammation

GSH = Glutathione, prime anti-oxidant and detoxifier in the body

Genes that had biggest impact and/or occurred most commonly across 9 comorbid conditions largely had immune function

Autism comorbidities
Rzhetsky, 2007, PNAS
- PDD, Fragile X
- Neurological disorders
- Attention deficit, epilepsy, cerebral palsy, schizophrenia, bipolar disorder, neural dysfunctions, Parkinson’s Disease, Migraine
- Bacterial, viral, protozoan
- Viral infections of CNS, tuberculosis, viral infections of other systems, staphylococcal and Helicobacter pylori infections
- Allergies, Autoimmune disorders
- Allergic rhinitis, eczema, psoriasis
- Benign and Malignant Neoplasms
- Other
- Kawasaki’s disease, acanthosis nigricans, aberrations of carbohydrate metabolism

Genetic overlaps between multiple conditions
- Genes affecting synapses
- Genes affecting immune functions
- Genes affecting environmental responses
- CNVs (copy number variants)
  - Often predispose to more than one condition
    - e.g. Guilmatre, Archives Gen Psychiatry 2008
- Genes affecting core cellular functions
Disorders without Borders

CTLA4 Rheumatoid arthritis, Graves Disease, MS, Hashimoto’s thyroiditis, Diabetes mellitus type 1
TNFα Asthma, primary biliary cirrhosis, sepsis, plantaritis, lupus, GORD, ulcerative, ILE, Celias, chronic bronchitis, Graves disease

All the components of this injury have treatable features

Detoxification
Oxidative stress
GSH
Inflammation

GSH = Glutathione, prime anti-oxidant and detoxifier in the body

Brain changes do not just happen before birth but also after birth and into the lifespan.

BRAIN CHANGES AFTER BIRTH

Early Rapid Brain Growth

Ongoing cellular changes into the lifespan

Neuroinflammation continues far into the lifespan

- These changes were found at similar intensities in brain aged 5-44 years
- Greater intensity of inflammation in a 3 year old’s brain

More than Prenatal

Brain changes do not just happen before birth but also after birth and into the lifespan.
Not static but dynamic: Plasticity

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

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

Other improvement in autism
• Short-term, transient
  – Improvement in core features
    • During antibiotic treatment
    • During ‘clear fluids only’ prep for colonoscopy
    • Postoperatively after anesthesia
    • During times of emotional intensity
  • Longer term
  – Improvement in some core features with anti-epileptic meds in some
  – Loss of diagnosis
    • After intensive therapy
    • Goes away by itself in some?

How can autism be purely a hard-wired brain structure disorder, a “static” encephalopathy, if things change?

Reversal in Mouse Models

Inhibition of p21-activated kinase rescues symptoms of fragile X syndrome in mice

Reversal of learning deficits in a Tbx2+ mouse model of tuberculous sclerosis

Mindd Regional Seminars, Sydney, 2010
www.mindd.org
Rapid reversal of Alzheimer’s symptoms by drug that inhibits TNF-α and therefore inhibits inflammation

**Journal of Neuroinflammation**

Case report
Rapid cognitive improvement in Alzheimer’s disease following peripinal etanercept administration
Edward J Tobinick and Hyman Care

**BMC Neurology**

Research article
Rapid improvement in verbal fluency and aphasia following peripinal etanercept in Alzheimer’s disease
Edward J Tobinick and Hyman Care

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Short-term immune triggers cause long-term brain inflammation

- TNF-α increases are triggered by bacterial and other exposures.
  - In the bloodstream this increase lasts 9 hours
  - In the liver it lasts 1 week
  - IN THE BRAIN IT LASTS 10 MONTHS!!!

This means that someone who gets exposed to a trigger of TNF-α every now and then could look like they have a chronic and untreatable brain problem.

Qin, GLIA, 2007 116

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Improvement in brain function after treatment

Example:
- Depakote was given for spike-waves during sleep that did not meet criteria for CSWS (continuous spike-wave during sleep)
- Substantial improvement resulted in speech and cognition
- This was measurable in brain by techniques not in standard use
- Where does this leave us?

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

Autism Research that will study potential mechanisms for improvement and treatment

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Expanding the Spectrum of Autism Mechanisms:

1. Genetically caused static encephalopathy
   - Gene
   - Early Developmental Change
   - Fixed Functional Deficit
   - Cause:
   - Mechanism:
   - Impact:

   Herbert, Anderson 2008 in Zimmerman et al 119

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Expanding the Spectrum of Autism Mechanisms:

1. Gene-environment caused static encephalopathy
   - Gene
   - Early Environment
   - Early Developmental Change
   - Fixed Functional Deficit
   - Cause:
   - Mechanism:
   - Impact:

   Herbert, Anderson 2008 in Zimmerman et al 120
Realize that practical day-to-day things may be of some help

Self-reinforcing or “vicious” circles
- Genes modulate vulnerability to toxic, immune and infectious stress
- Toxics impair immunity
- Infection and immune stress alter gene expression
- Increased excitation/inhibition contributes to sensory overload and sleep disruption
- These contribute to stress
- Stress worsens the HPA axis contribution to biological factors increasing the I/E ratio (HPA = hypothalamo-pituitary-adrenal)

Chilling out “vicious” circles and allowing adaptive self-re-regulation
- Less toxic exposure
- Better ability to detoxify
- Improved nutritional status
- Immune support
- Reduce/avoid infection
- Behavioral organization and stress reduction

Autism research has been focused on describing a “broken brain” and looking for genes that broke it

But new science is suggesting the brain in autism and other neurodevelopmental disorders may not be “broken” so much as heavily challenged.

We need a fresh approach to brain research that focuses on avoiding harm and optimizing potential.
Can Children with Autism Recover? If So, How?

Martha Herbert, MD, PhD

Mindd Regional Seminars, Sydney, 2010

If recovery is possible, then we need to take a fresh look.

Brain “plasticity” is in the air

If Brain Change is Possible, We need careful documentation and study

• Rigorous tracking of change

• Sophisticated measures of change

A Whole-Body Approach to Brain Research

Findings that inspired TRANSCEND to go beyond (to transcend)

• Widespread brain enlargement after birth

• Inflammation in the brain

• Many with autism spectrum have medical problems (gut, immune, etc.)

• EEG is abnormal even without seizures

• More and more children with autism spectrum

• Documented improvements in core autism features
TRANSCEND Middle-Out approach: Mechanism-based disease model

BRAIN

BODY

UNDERLYING FUNCTIONAL MECHANISMS

Genes

Environment

BEHAVIOR

Treatment targets!

EEG and MEG: Brain Signaling Networks

MRI: Brain Structure, Wiring and Chemistry

Biomarkers

- Connecting brain and body through molecular and physiological science

TRANSCEND is a Verb

transcendere
trans- + -scendere,

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

www.transcendresearch.org

www.mindd.org
Example of TRANSCEND Work
Infants at Risk

- Baby Sibs ➔ it’s the whole body!

* A Multisystem Evaluation of Infants At Risk for Autism

- The first study to look at MEDICAL development alongside behavioral and brain development

- New functional measures:
  - EEG
  - Metabolic, Immune, Toxics, Nutrition
  - Autonomic nervous system (stress measure)

Example of TRANSCEND Work
Infants at Risk -- Continued

QUESTIONS:
- Do biological abnormalities precede behavioral abnormalities?
- Are there biological predictors?
- Are there things we could treat very early that might reduce severity or prevent autism altogether?

Discussion of Whole Baby Sibs and TRANSCEND intellectual framework is in press

Chapter 25
*A Whole Body Approach to ASD*
By Martha R. Herbert

In
*The Neuropsychology of Autism*
Edited by Deborah A. Fein, PhD
Oxford University Press, 2011

Crisis means Danger + Opportunity

- DANGER:
  - Suffering and damage to more and more
  - Children
  - People of all ages
  - All life and our planet

- OPPORTUNITY:
  - Get a grip
  - Create better, healthier lives for everyone

A Perspective on the Autism Spectrum:
Tip of the Iceberg, Canary in the Coal Mine

Photos used with permission
Our national faith so far has always been “There’s always more.” Our true religion is a sort of autistic industrialism. -Wendell Berry, Harper’s, May 2008

For further details: THE SHOCK DOCTRINE by Naomi Klein

Manufacturing Uncertainty

We all live downstream Everyone, Everywhere

Autism: Thinking the unthinkable

To cling to a purely genetic explanation of autism is a desperate attempt to maintain the illusion that one lives in a comfortable and rational world where new chemicals and technologies always mean progress, experts are always objective and thorough, corporations are honest, and authorities can be trusted. That human actions, rather than genetics, might be responsible for compromising the health of a significant proportion of a whole generation is so painful as to be, for many unthinkable.
Will Women Lead the Environmental Health Movement?

How can we imagine that ordinary people might be able successfully to challenge the overwhelming internal logic of the global economic system because of concern over environmental health?

There is an Ethiopian proverb that when spider webs unite they can tie up a lion. The lion of the globally destructive patterns of production and consumption may one day be ensnared and ultimately domesticated by the gossamer webs of human consciousness and community action. What will happen when ordinary people, whose lives are often mortally wounded by the destruction of the biosphere, come to understand that their wounds are so often intimately related to the wounds of the earth?

What will happen when a working woman comes to a realization that her own breast cancer, her husband's lymphoma, her brother's melanoma, her son's learning disability, her husband's autism, her neighbor's infertility, her brother's testicular cancer, and her best friend's severe chemical sensitivity, her best friend's daughter's asthma, her uncle's infertility, her cousin's chronic anxiety and panic disorder, her best friend's daughter's childhood leukemia, may form a pattern?

What will happen when this working woman begins to understand that these new human pandemics, that affect her family and her community directly, may be profoundly connected to what is happening to the fish in the sea, the birds in the sky, and the animals of the earth?

I believe this working woman will understand that the cancers and infertility of the fish, the disappearance of the frogs, the cleft palates of the mice, the shifts in gender orientation of the birds, the susceptibility to viruses and infections of the seals, the disappearance of the songbirds, — that all this and much, much more may be telling us a story that is also our story.

The story that the birds and the fish and the mice are telling us is the story of InterBeing — the story that all life on earth is truly, breathtakingly, concretely connected right now, and that what we do to the mice of the field and the birds of the forest, we also ultimately do also to ourselves and our families right now.

I do not believe that we can hide from this story much longer. It is among the great stories of our time.

Making our own hope

continued from Lerner, Age of Extinctions

This very human protest against a massive entrenched and toxic global system of production and consumption may seem unrealistic economically and politically. But is it any less realistic than the Quaker protests in Europe and the United States that played such a key role in ending the 350-year-old slave trade? I do not invoke the parallel to ending the slave trade lightly. For we are as enchained by toxic chemicals and ozone depletion and climate change and the destruction of nature as we were once enchained by slavery. I believe environmental health may be one of the greatest human rights issues of the millennium. That is our best hope.

Chief Seattle

We are part of the earth and it is part of us.
We do not weave the web of life, we are merely a strand in it.
Whatever we do to the web, we do to ourselves.

Canary

in a Coal Mine

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

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