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, communities 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

From Definition to Model of Autism: A Common Modular Framework

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.

No proof that these arguments explain away ALL the increase

New paper from UC Davis (Streissguth, et al. Placental and Birth 2006)
- 600% increase in reported cases 1990 - 2001
  - 200% can be explained by non-environmental factors:
    - 4x age of diagnosis
    - 5x: Inclusion of milder cases
    - 12x: 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

- Autism
- Pesticide use more than doubled between 1964 and 1982 (USDA)

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

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%
- Both a genetic vulnerability and an environmental trigger could be necessary - neither alone might be sufficient

AUTISM AND ENVIRONMENTAL GENOMICS


Neurotoxicology, 2006

GENES
ENVIRONMENT

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

Some of the possible environmental contributors to autism being studied

- Pesticides
- Organophosphates
- Heavy metals
  - Lead
  - Mercury
  - Cadmium
- Solvents
  - Trichlorobenzene
  - Xylene
  - Toluene
  - Other
- PCBs (polychlorinated biphenyls)
- Vaccines
- Flame retardants
- Antimicrobial ingredient in hand soaps

- Vitamin D deficiency
- Antibiotic overexposure and disruption of “good bacteria”
- Essential fatty acid deficiency
- Greater genetic need combined with relative dietary deficiency of certain nutrients
  - Folic acid
  - Vitamin B12
  - Magnesium
  - Iodine
  - Other
- Rubella and other infections during pregnancy
- In vitro fertilization

The planet is not stable.

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

Al Gore Places Infant Son In Rocket To Escape Dying Planet

The Onion, July 31, 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 .... 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 tonsil and adenoids

Case 4: vomiting a great deal during his first year ... feeding formulas were changed frequently ... tonsils were removed.

Case 5: entered very poorly ... eating any kind of nourishment of three months ... took the five times daily up to one year of age. At the end of the second year ... had fever almost no verbal complaints.

Case 7: vomiting all food from birth through the third month...

Case 8: feeding formula caused ... concern. ... repeated 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 ear infections.

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

Immune signs and symptoms and measures in autism

• Recurrent infections
• Autoantibodies
• Family history of autoimmune disease
• Autoimmune features
• Food allergies and sensitivities
• Hypothalamic and cerebellar 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

Injury at the cellular level throughout the body

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

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

suggests that the onset of brain enlargement is in the latter part of the first year.
Some characteristics of large brains in autism:

- Disproportionate increase of white matter
- White matter increase localizes to outer ('radiate') white matter

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

- Neuronal activation and neuroinflammation in the brains of patients with autism
- Oxidative stress in brain tissues from autistic patients

Air pollution and brain inflammation:

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

- Oxidative stress in brain tissues from autistic patients

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

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

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

- May be a reflection of altered tissue water properties


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

- Too Much Excitation
- Not Enough Inhibition

Comments:
- Increased excitation/inhibition ratio may explain many features of autism, such as:
  a) Sensory sensitivities
  b) Sleep disturbances
  c) Tics, epilepsy

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

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

Challenges posed by this study:
- This is not consistent with “static encephalopathy”
- Proposed so far: fever ontogeny, environmental impact on glial gap junctions, cytokines, membrane lipids, dopaminergic and/or serotonergic mechanisms

Additional pertinent citations:
- Herbert in Chauhan et al CRC Press late 2009
- Mehler & Purpura 2009

Rapid change in brain connectivity suggests “state” not “trait”

- 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

Autism Research that will study potential mechanisms for improvement and treatment

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

Causes:
- Genetically caused static encephalopathy
- Gene-environment caused static encephalopathy
- Epigenetically altered gene expression
- Later or ongoing environmental factors triggering chronic encephalopathy

Mechanisms:
- Early Environment Interaction
- Early Developmental Change
- Gene
- Functional Deficit with Reversibility

Impact:
- Chronic Encephalopathy
- Modulation
- Altered Neuro-modulators
- Altered Gene Expression

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
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
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

Oxidation-reduction imbalances and mitochondriopathy - 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

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
- Potential causes
  - Genetic
  - Environmental
  - Gene-environment

Exquisite environmental sensitivity of mitochondria

- 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 neoplastic, artherosclerotic, 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.

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.

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

Interactions between systems: Nutrients supporting detoxification
Immune imbalances and Inflammatory imbalances –
Protection and defense, Repair
Specific immune abnormalities have been found in 30-70% of patients with autism (Broderick, 1998 and Harper, 1981).
- Shift from TH1 (viral/fungal killing) to TH2 (allergy)
- Altered immune components: lymphocytes, antibodies, cytokines, interferons, etc.
- Anti-self antibodies
- Autoreactivity
- Immune function
- Inflammatory
- Reduced CD4+ T cells

Clinical lab tests that will detect and report gut pathogens

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 D2)
- 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.

Glia in the Gut: Immune, Signaling and Barrier Functions
Abnormalities
- Morphological
- Functional
- Neurochemical

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)

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."
- Nutritional genomics: 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 personalized diet and medicine.
- Deficiency: Low level by population standard
- Insufficiency: Low level by individual genetic or state/stress/illness-related need
Autism Electrophysiological Abnormalities (n=28)

- Increased VEP amplitudes (standard deviation was 2.42-8.92 SD (average 5.4 SD)
- Laboratory challenge: 15 of these patients had no seizures and would be considered "normal."

Autism and Autonomic Nervous System (ANS)

- High variability in arousal – both high and low
- May be high and low in the same individual at different times
- Additional autonomic abnormalities that have been reported:
  - Diminished autonomic correlates
  - Increased 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

Grateful acknowledgement of support from:

- NIH/NINDS
- Autism Speaks/CAN/NAAR
- Nancy Lurie Marks Family Foundation
- Dept of Defense Autism Research Program
- Autism Society
- Bernard Fund for Autism Research
- Commonwealth Fund
- Jane Botsford Johnson Foundation
- Autism Research Institute
- Aufhebung Foundation

Affiliates/Collaborators:

- Matthew Belmonte PhD
- Matthew Goodwin PhD
- Philip Grieve PhD
- Joseph Isler, PhD
- Rosalind Picard ScD
- Eva-Marie Ratai PhD
- Jung Suh, PhD
- Lorin Wilde PhD
- David Holtzman MD PhD

And many volunteers
And many precious friends

www.transcendresearch.org