THE AUTISM REVOLUTION:
From a Static Brain Defect to a Chronic Systemic Dynamic TREATABLE Encephalopathy

Martha Herbert, MD, PhD
www.marthaherbert.com
TRANSCEND Research Program
Pediatric Neurology
Martinos Center for Biomedical Imaging
Massachusetts General Hospital
Harvard Medical School
www.transcendresearch.org
www.AutismRevolution.org

www.AutismRevolution.org
www.autismWHYandHOW.org
Autism: A *Behaviorally Defined* Syndrome

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

**DSM-IV Criteria for Autistic Disorder (299.0)**

1. Impaired social interaction
2. Impaired social 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+%)  

*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: Classic Modular Framework

Gene → Brain module → Behavior

Gene → Brain C → Behaviors

Gene → Brain B → Social Interaction

Gene → Brain A → Communication

(Or neural systems)
New model – an Autism Revolution: From genetic brain impairment to environmental, medical obstruction of brain function

Not just genetic:
- Hundreds of genes, most modest impact
- Numbers going up
- Evidence for environmental factors

Not just brain:
- Systemic features – Whole Body
- Environmentally vulnerable physiology

Not just brain modules:
- Whole brain involvement
- Brain tissue changes

Not necessarily hardwired:
- Plasticity and recovery
Is autism is really a hard-wired defect?

Research and clinical observations suggest otherwise:

• Published transient improvement with fever
  – Reports of this under various other circumstances
• Documented recovery / remission in some cases
• Reversal of symptoms in autism-relevant animal models

HOW CAN THE BRAIN IMPROVE LIKE THIS?

WHAT IS THIS TELLING US ABOUT AUTISM?

Hypothesis:

⇒ ASD: Not a STATIC but a DYNAMIC encephalopathy
Whole Body Model: Vicious circles in brain and body

Psycho-Social Environment

- Physical environment
- Genetics

Cellular Dysfunction: Energy, Signaling, Metabolism

Brain

Body

Communication
- Social interaction
- Restricted behavior

Sensory
- Sleep
- Seizures

Gastro
- Immune
- Hormones etc.

Frustration

More easily OVERWHELMED

Pain, Poor function
- Sickness

Overload!

STRESS!
An Overview of Biomed

- Improve Cell Health
- Brain Health Improves
- Brain Functions Better
- More Bandwidth, Less Stress
- Better Behavior, More Learning
All the parts really influence each other

Body Cell Health Problems

Challenging Behaviors

Stress and Overwhelm

Brain Cell Health Problems

Brain Function Glitches
Problems in each area make trouble for the other areas

**PHYSIOLOGY:** Vicious Cycles Feed Off of Each Other

- Body Cell Health Problems
- Brain Cell Health Problems
- Challenging Behaviors
- Stress and Overwhelm
- Brain Function Glitches
Dialing back the problems and Moving Toward Whole Body-Brain Health

**PHYSIOLOGY:** Build Resiliency to Stop Vicious Cycles

- Improve Cell Health
- Brain Health Improves
- Less Stress, More Bandwidth
- Brain Functions Better
- Better Learning, Better Behavior
The Music of Life: Biology Beyond the Genome

Beautiful readable book

Discusses physiology and the “middle→out” approach

http://www.musicoflife.co.uk/
Assumption: Autism is a “developmental disorder”

This seems obvious.

But it carries a lot of extra baggage.
Assumption: Autism is a “developmental disorder”

What are the IMPLICATIONS of this assumption?

1. It’s all genetic and predetermined
2. The damage is done really early, probably before you are born
3. The brain is fundamentally and irretrievably differently structured and “broken”
4. Brain changes are the cause of ALL the problems
5. There is nothing you can do about it

LET’S EXAMINE THE EVIDENCE
Not just genetic and predetermined: From Genetic to Gene x Environment, Epigenetics and Gene x Physiology x Environment

1. Are the numbers really going up?
2. Genes, environment and epigenetics can interact
GENETIC EXPLANATIONS
Sense and Nonsense

Edited by SHELDON KRIMSKY and JEREMY GRUBER

Can genes determine which fifty-year-old will succumb to Alzheimer’s, which citizen will turn out on voting day, and which child will be marked for a life of crime? Yes, according to the Internet, a few scientific studies, and some in the biotechnology industry who should know better. Sheldon Krimsy and Jeremy Gruber gather a team of genetic experts to argue that treating genes as the holy grail of our physical being is a patently unscientific endeavor. Genetic Explanations urges us to replace our faith in genetic determinism with scientific knowledge about how DNA actually contributes to human development.

The concept of the gene has been steadily revised since Watson and Crick discovered the structure of the DNA molecule in 1953. No longer viewed by scientists as the cell’s fixed set of master molecules, genes and DNA are seen as a dynamic script that is ad-libbed at each stage of development. Rather than an autonomous predictor of disease, the DNA we inherit interacts continuously with the environment and functions differently as we age. What our parents hand down to us is just the beginning. Emphasizing relatively new understandings of genetic plasticity and epigenetic inheritance, the authors put into a broad developmental context the role genes are known to play in disease, behavior, evolution, and cognition.

Rather than dismissing genetic reductionism out of hand, Krimsy and Gruber ask why it persists despite opposing scientific evidence, how it influences attitudes about human behavior, and how it figures in the politics of research funding.

Sheldon Krimsy is Professor of Urban & Environmental Policy & Planning in the School of Arts and Sciences and Adjunct Professor of Public Health and Community Medicine in the School of Medicine at Tufts University. Jeremy Gruber is President and Executive Director of the Council for Responsible Genetics.

New Book with Critiques of Genetic Overexplanation

Ch.10 on Autism: From Static Genetic Brain Defect to Dynamic Gene-Environment-Modulated Pathophysiology

By Martha Herbert

One-page summary and section headers posted on www.marthaherbert.org under publications – click link for this article
Title: Autism: From Static Genetic Brain Defect to Dynamic Gene-Environment Modulated Pathophysiology

Author: Martha R. Herbert, PhD, MD


Chapter's Section Headers:
- Autism Status Quo: Genes, Brain, Behavior and Hopelessness
- Anomalies Undermining the Genes-Brain-Behavior Model
  - Not a Static Prevalence
  - Not Just Genes: Environmental Contributors.
  - Not Just Inherited Genes: De Novo Mutations.
  - Not Even Mainly Genes: Substantial Environmental Contribution.
  - Not Just Brain Genes
  - Not Just Local, Modular Brain Disturbances: Whole Brain Involvement.
  - Not Just Prenatal
  - Not Necessarily Present at Birth
  - Not Just Behavior
  - Not Just the Brain
  - Not Just Deficit: Giftedness and High Intelligence.
  - Not a Life Sentence: Evidence of Remission and Recovery.
- Dynamical Physiological Processes Implicated In Autism
  - Immune Dysregulation
  - Mitochondrial Dysfunction
  - Oxidative Stress
  - Methylation Disturbance
  - Disturbed Gut Microbial Ecology
  - Hormonal Dysregulation
- Active Pathophysiology, Genes and Environment
  - Active Pathophysiology and the Brain
  - Impact on Synaptic functioning
- Could Active Pathophysiology Be Impairing Connectivity?
- Does Active Pathophysiology Modulate Genetic Substrate Or Could It Be a Primary Cause of Brain Dysfunction?
- From Genes and Neurons to Environment and Glial Cells
- Cause?
- Modulating Severity by Treating Intermediary Metabolism
- Obstructed Rather Than Defective
- Environment: The Gift That Keeps On Giving
  - Hardware or Software?
  - From Developmental To Early Onset Chronic Pathophysiology
- From a Fixed Unitary Phenomenon to Modifiable Manifestations of Complex Interacting Systems Problems
  - Autism as an Epiphenomenon or Emergent Property of a Challenged System
  - Specific Genetic Determinants or Final Common Pathways of Pathophysiology?
- Time to Get a Grip
- Addressing an Apparent Epidemic Through a Praxis of Environmental Pathophysiology
- Beyond Autism

Etiological heterogeneity in autism spectrum disorders: more than 100 genetic and genomic disorders and still counting
C. Betancur, Brain Res 2011 42-77

- An exhaustive review of the clinical genetics and research genetics literature
- 103 disease genes and 44 genomic loci reported in subjects with ASD or autistic behavior.
- Commonalities with intellectual disability and epilepsy.
SHANK3, the Synapse and Autism

- Altered postsynaptic density (PSD) proteins
- Smaller PSD
- Fewer dendritic spines
- More dendritic arborization
- Weaker signaling
- Larger striatum
- Autistic-like behaviors

Lower dendritic spine density

- Spine density in striatal medium spiny neurons (MSNs) from Shank3B$^{-/-}$ mice is lower than that of wild-type MSNs

Peça et al., Nature 2011
Complications

• Well over 100 different genetic disorders involve an autistic phenotype (Betancur, *Brain Res*, 2011)

• These in turn comprise a small minority of cases with autism

• The synapse and PSD are highly complex

• Shank3 is expressed not just in brain but in gut and kidney, is involved in epithelial turnover and mucosal immune development, and is utilized by some gut pathogens in actin rearrangement. (Huett et al., *Exp Cell Res*, 2009)
Growing body of associations of environmental exposures with autism risk and prevalence

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

*What accounts for the incomplete concordance?*

- Conclusion of largest autism twin study to date:
  - Susceptibility to ASD has moderate genetic heritability and a substantial shared twin environmental component.
    - Hallmayer et al, July 2011, Arch Gen Psych
Intriguing question about concordance

• Swedish study of schizophrenic identical twins
  – Probable same placenta: 60% concordance
  – Different Placentas: 11% concordance
    – Davis, Phelps, & Bracha, 1995
Gene-Environment Interactions: Not Either-Or but Both-And,

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

**AUTISM AND ENVIRONMENTAL GENOMICS**
Neurotoxicology, 2006
also
Autism and Environmental Genomics
Chapter in AUTISM, Amaral/Dawson,Geschwind, 2011
Defective/deficient GABAAa Receptors in Autisms +
Pesticides that antagonize GABAAa Receptors =
Gene x Environment Interaction
Increased Excitation/Inhibition Ratio

Pesticides that are Non-Competitive GABA antagonists

Fipronil (4-alkyl-1-phenylpyrazole)
>800 tons applied in 2000

Regent®
Goliath®
Nexa®
Adonis®

Chipco Choice®
Frontline®

From Pessah
Factors that may increase autism risk

Environmental, Diet

• Air pollution (Volk, 2011; Windham, 2006)
• Pesticides (Roberts, EHP, 2007; Eskenazi, 2010)
• Low Vitamin D
• Flame retardants
• Antimicrobials in soaps
• Heavy metals

Medical

• Maternal obesity
• Maternal hypertension
• Maternal diabetes
• Maternal infection during pregnancy
• Familial autoimmune disease
• Antibiotics

Sources include Hertz-Picciotto; van de Water; Patterson; Smith; others
Environmental factors that may reduce risk

- Prenatal vitamins and One-Carbon Metabolism Gene Variants
  - Mothers of children with autism were less likely than those of typically developing children to report having taken prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy (OR = 0.62 [95% confidence interval = 0.42-0.93]).
  - Significant interaction effects were observed for maternal MTHFR 677 TT, CBS rs234715 GT + TT, and child COMT 472 AA genotypes, with greater risk for autism when mothers did not report taking prenatal vitamins periconceptionally (4.5 [1.4-14.6]; 2.6 [1.2-5.4]; and 7.2 [2.3-22.4], respectively)

Schmidt et al., *Epidemiology*, 2011
Metabolic Response to Genetic Polymorphisms in the Methionine Cycle

Metabolic endophenotypes and related genotypes are associated with oxidative stress in children with autism

Epigenetics

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

“Environment” is not a constant: Unprecedented production of new-to-nature substances

BodyBurden
The Pollution in Newborns
A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood

www.bodyburden.org
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 planet is not stable.

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
Genomic instability

• TOO MUCH
  – Toxic assaults on mitochondrial and cellular integrity

• TOO LITTLE
  – Nutrients in the diet that protect mitochondria, membranes and DNA repair mechanisms

• Inflammation, oxidative stress, hypomethylation
  – ?increase in baseline mutation rate?
The Autism Spectrum, the Tip of the Iceberg, and the Canary in the Coal Mine
Genomic Instability

Should autism be considered a canary bird telling that Homo sapiens may be on its way to extinction?

By Olav Albert Christophersen

*Microbial Ecology in Health and Disease*, 2012, free online.

http://www.microbecolhealthdis.net/index.php/mehd/article/view/19008

IN OPEN SOURCE **NEW ISSUE ON MICROBIOME**:

http://www.microbecolhealthdis.net/index.php/mehd/issue/current
GLUTATHIONE PROTECTS CELLS from environmental stress, but is often low in ASD (and many other chronic conditions)

- GLUTATHIONE is vital for detoxification
  - Mops up toxins and free radicals
- The body’s most potent anti-oxidant
- The most abundant antioxidant in the BRAIN
- Final common pathway:
  - Depleted by thousands of toxins, oxidative stress, infection, inflammation and nutrient-poor diet

Made in the liver from three amino acids: Glutamate + Cysteine + Glycine
LOW GLUTATHIONE

Glutathione - critical antioxidant and detox chemical - low levels in brains of depressed patients, lower in brains in Chronic Fatigue Syndrome – And low systemically in Autism


Shungu et al., 2012
Vulnerability with low GSH

Normal Homeostasis

OK GSH/GSSG

TOXIC THRESHOLD

Fragile Homeostasis (limited reserve)

↓ GSH/GSSG

S. Jill James
Environmental factors that may reduce risk

- **Prenatal vitamins and One-Carbon Metabolism Gene Variants**
  - Mothers of children with autism were less likely than those of typically developing children to report having taken prenatal vitamins during the 3 months before pregnancy or the first month of pregnancy (OR = 0.62 [95% confidence interval = 0.42-0.93]).
  - Significant interaction effects were observed for maternal MTHFR 677 TT, CBS rs234715 GT + TT, and child COMT 472 AA genotypes, with greater risk for autism when mothers did not report taking prenatal vitamins periconceptionally (4.5 [1.4-14.6]; 2.6 [1.2-5.4]; and 7.2 [2.3-22.4], respectively)

Schmidt et al., *Epidemiology*, 2011
Metabolic Response to Genetic Polymorphisms in the Methionine Cycle

These are the genetic variants that increased vulnerability in the prenatal vitamin study (Schmitz 2011)

Metabolic endophenotypes and related genotypes are associated with oxidative stress in children with autism

Genome-wide expression studies in Autism spectrum disorder, Rett syndrome, and Down syndrome
Lintas et al., *Neurobiol Dis*, 2010

...Our results surprisingly converge upon immune, and not neurodevelopmental genes, as the most consistently shared abnormality in genome-wide expression patterns. A dysregulated immune response, accompanied by enhanced oxidative stress and abnormal mitochondrial metabolism seemingly represents the common molecular underpinning of these neurodevelopmental disorders. This conclusion may be important for the definition of pharmacological therapies able to ameliorate clinical symptoms across these disorders.
The cause of autism remains largely unknown because it is likely multifactorial, arising from the interaction of biologic, genetic, and environmental factors. The specific role of metabolic abnormalities also is largely unknown, but current research may provide insight into the pathophysiologic underpinnings of autism, at least in some patients. We review a number of known neurometabolic disorders identified as having an autistic phenotype. We also discuss the possible involvement of mitochondrial disorders and dysfunction as well as a theory regarding an increased vulnerability to oxidative stress, by which various environmental toxins produce metabolic alterations that impair normal cellular function. Finally, we review various strategies for metabolic work-up and treatment. Accurate diagnosis of neurometabolic disorders and a broader understanding of underlying metabolic disturbance even in the absence of known disease have important implications both for individual patients and for research into the etiology of autism.
Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders
Martha R. Herbert

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.
Not necessarily just prenatal
TIMING OF POSTNATAL ATYPICAL BRAIN GROWTH: EARLY RAPID GROWTH

Tapering off after the first few years

Redcay and Courchesne 2004
Courchesne 2003
Dementieva 2005

Courchesne
Autism - Nosology
Autism - BU

2-3 yo 7-11 yo 7-13 yo 12-16 yo

Volume Ratio

Percent Difference

Redcay and Courchesne 2004
Ongoing postnatal cellular changes in the autistic brain

Neurons in autistic child:
- larger than control
- normal in appearance

Neurons in autistic adult male:
- small in size
- adequate numbers

Kemper & Bauman 1992
Bauman and Kemper 2005
Location of white matter enlargement points to postnatal brain changes

What do we need to learn about the brain and about autism to understand this?
Active Tissue pathophysiology in Brain
Inflammation and Oxidative Stress in Autism: chronic, ongoing postnatal medical problems, not confined to brain

- 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: increased concentration of isoprostanes
  Vargas et al, 2005, Annals of Neurology

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

Microgliosis

Herbert:  
Radiate White Matter Enlargement
Air Pollution and Brain Inflammation
Block and Calderon-Gardicuenas, TNS, 2009

Air pollution already linked to autism
(e.g. Palmer 2006; Windham 2006; Volk 2011)

Direct mechanisms
- Adsorbed compounds reach the brain
- Soluble compounds reach the brain
- Particulate matter reaches the brain

CNS pathology
- Neuroinflammation (iNOS, TNFα, IL-1β, COX2, & NFκB)
- Neuron damage/loss
- Microglia activation (HLA-DR & CD14) (ROS & cytokine production)
- Blood brain barrier damage/dysfunction (Changes in inflammatory, tight junction, & transport proteins)
- Aβ42 accumulation (Neuronal, vascular, & diffuse plaques)
- Aβ and α-Synuclein aggregation
- Lipid peroxidation
- DNA damage

Peripheral mechanisms
- Cardiovascular system
- Circulating monocytes
- Circulating cytokines
- Lung
- Liver

CNS Disease

TRENDS in Neurosciences
Brain cells in inflammation

- Excitatory chemicals created by activated glial cells
- Normal housekeeping functions of glial cells get neglected
- Chronic inflammation is irritating and promotes excitotoxicity
- Chronic inflammation can cause damage

Inflammation and Its Discontents: The Role of Cytokines in the Pathophysiology of Major Depression. Miller et al., BIOL PSYCHIATRY 2009;65:732–741
A FINAL COMMON PATHWAY?

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


Too Much Excitation = Reduced signal to noise ratio

Not Enough Inhibition

Loss of informational complexity and organization

More: irritability, hypersensitivity, overload

Reduced signal to noise ratio
Reduce *Total Load* of Stressors to get Better Health, that will give Brains more “Bandwidth”

**Poor Bandwidth:**
Limited Reception

**Lots of Bandwidth:**
Good Reception

Better Reception Allows Better Discernment of Differences and More Spontaneous Learning
Active tissue pathophysiology undermines the idea that brain structure changes cause abnormal function

- What if brain abnormal function led to abnormal structure?
- What if it is the PERSISTENCE OF THESE CELLULAR CHANGES that leads to the brain structure changes the brain scientists are measuring?
Common explanation of brain enlargement in ASD: Failure of “pruning”

- Testable through imaging: Failure of pruning implies
  - More fibers and fiber density
  - More cells

- Is this what we find?
Brain magnetic resonance spectroscopy summary of findings in literature to date:
Mostly lower density of metabolites

- 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

Shetty, Ratai, Ringer, Herbert, 2009
Dager review chapter 2008 and many papers
Metabolite level correlating with brain activation

- More NAA in controls than in autism
- Linear correlation of amount of functional activation to amount of NAA
  - NAA = N-acetylaspartate

Kleinhans et al, 2007
The “Fluid Theory” of Connectivity Alterations in ASD

- Water, not fiber changes in brain tissue
  Hendry 2005
- Less white matter integrity
- Less restriction of water flow
- More diffusivity
  Sundaram 2008

The idea that brain connectivity abnormalities arise from metabolic, immune and vascular disturbances that affect synaptic function.

• Lower perfusion in ASD brains (by many PET or SPECT studies) could impact brain function.
  How might this affect brain electrophysiology?
Lower FA in key regions
Linked to higher (worse) diagnostic scores

- White matter FA was significantly lower in key regions of prefrontal lobe and right ventral temporal lobe.
- Lower FA linked to higher (worse) diagnostic symptom scores
- Author interpretation:
  In light of spectroscopy showing lower NAA ➔ less neuronal integrity or number, lower structural integrity may be consistent with neuroinflammation

Cheung et al., 2009
Lower perfusion in ASD brains could impact brain function. It could be maintained by active pathophysiology.

- 17 of 19 PET and SPECT studies showed low perfusion
- Those that showed areas of high perfusion still showed lower perfusion more than higher
- Possible pathophysiology
  - Vasoconstriction
    - Oxidative stress acting on endovasculature
    - Astroglia swell when activated constricting capillary lumen
  - Blood viscosity
    - RBC lipid peroxidation (stiffer membranes → poor RBC deformability)
    - Platelet activation (increased thromboxane)
    - Increased nitric oxide (oxidative stress marker),
    - Depressed glutathione peroxidase
    - Depressed SOD
    - Depressed catalase
Functional problems in the brain

- Connectivity
- Sensory processing

- Are these caused by the large-scale structural problems?
- Or are they caused by cell metabolism problems?
- Most research has assumed the former, but not tested it as a hypothesis
Too much noise, not enough signal
BETTER BANDWIDTH SHOULD IMPROVE THIS

ASD has **more power** than controls... but **less coherence**

*More noise, less signal*
Structure $\rightarrow$ Function? 
Or Function $\rightarrow$ Structure

or

\[\text{STRUCTURE} \quad \text{FUNCTION}\]
Rabbit or duck?

Is autism a *BRAIN DISORDER*

or a

*DISORDER THAT AFFECTS THE BRAIN?*

Herbert, 2005
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
“The co-morbidity burden of children and young adults with autism spectrum disorders.”

• The comorbidities of ASD encompass disease states that are significantly overrepresented in ASD with respect to even the patient populations of tertiary health centers.

• Significantly more: epilepsy, schizophrenia, inflammatory bowel disease, other bowel disorders, CNS/cranial anomalies, diabetes type 1, muscular dystrophy, sleep disorders

HARVARD STUDY

Large Burden of Comorbidities in ASD Requires Broad Multidisciplinary Management

In a study of co-morbidities for 14,000 ASD patients in the Harvard system under the age of 35, the authors concluded:

“The comorbidities of ASD encompass disease states that are significantly overrepresented in ASD with respect to even the patient populations of tertiary health centers. This burden of comorbidities goes well beyond those routinely managed in developmental medicine centers and requires broad multidisciplinary management that payors and providers will have to plan for.” [emphasis added]

Source:
Kohane IS et al., (2012),
The Co-Morbidity Burden of Children and Young Adults with Autism Spectrum Disorders.
PLoS ONE 2012 (open access)
AAP Autism GI Consensus Reports January 2010

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report

Authors: Timothy Buie, MD,*,#; Daniel B. Campbell, PhD,###; George J. Fuchs, III, MD,*; Glenn T. Furuta, MD,###; Joseph Levy, MD,*; Judy Van de Water, PhD; Agnes H. Whitaker, MD; Dan Atkins, MD,###; Margaret L. Bauman, MD,###; Arthur L. Beaudet, MD,*; Edward G. Carr, PhD,*; Michael D.

Abstract
Autism spectrum disorders (ASDs) are common and clinically heterogeneous neurodevelopmental disorders. Gastrointestinal disorders

Recommendations for Evaluation and Treatment of Common Gastrointestinal Problems in Children With ASDs

Authors: Timothy Buie, MD,*,#; George J. Fuchs, III, MD,*; Glenn T. Furuta, MD,###; Koorosh Koors, MD,###; Joseph Levy, MD,*; Jeffery D. Lewis, MD; Barry K. Wershil, MD,* and Harland Winter, MD,*#.

Abstract
Children with autism spectrum disorders (ASDs) can benefit from adaption of general pediatric guidelines for the diagnostic evaluation of abdominal pain, chronic constipation, and gastroesophageal reflux disease. These guidelines help health care providers determine when gastrointestinal symptoms are self-limited and when evaluation be-
The Every Day of Some Autisms

What we need:
Clinical labs that will detect and report pertinent gut pathogens
Beyond the Human Genome to the **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
Glial Cells in the Gut: Immune, Signaling and Barrier Function
Ruhl, 2005

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.
THE OTHER BRAIN
by Douglas Fields, PhD, NIH scientist

ABOUT GLIAL CELLS

www.theotherbrainbook.com
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; cell membranes
  • Loss of bone density
- **Protection and defense** • Immune and Autoimmune problems
- **Elimination of waste** • Impaired intestinal function
  • Impaired detoxification
Symptoms and function

VISIBLE SYMPTOMS

UNDERLYING SYSTEMIC FUNCTIONAL DISTURBANCES

Ziggarut model: http://www.texasautism.com/
Autism is Complex: Levels that are all involved AT THE SAME TIME

Creativity
Social interaction
Learning
Behavior
Brain as information system
Brain as wet physical organ
Organs
Cells
Chemistry
Genes and environment
Chronic mechanisms can impact brain function

Functional Vulnerabilities

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

These are
- Cellular
- Widespread
- Impact timing, signal intensity, coordination
A Different Model of Autism: Autism as an emergent property of a system with altered parameters

- Autism could be a dynamic, active 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
- This could explain the dynamic features
- *Many cellular problems can be treated*

Herbert, 2009 in press, “Autism: The centrality of pathophysiology and the shift from static to dynamic encephalopathy” In Chauhan et al, Autism: Oxidative stress, inflammation and immune abnormalities
Reduce *Total Load* of Stressors to get Better Health, that will give Brains more “Bandwidth”

**Poor Bandwidth:**
Limited Reception

**Lots of Bandwidth:**
Good Reception

Better Reception Allows Better Discernment of Differences and More Spontaneous Learning
RECIPE for improvement

POOR BANDWIDTH, LOTS OF CHAOS
- Poor food: few nutrients, many allergens
- Lots of toxins and infectious issues
- Lots of stress, pressure, too much too fast

GOOD BANDWIDTH, RICH ORGANIZATION
- Excellent food: high nutrient density, minimal allergens
- Minimal toxic and infectious burden
- Love, learning, respect, sensitive sensory input, savor each moment
Toward a Physiological Model of Autistic Regression
A Theory of How Regression Happens: I: THINGS PILE UP

• Demands are placed on the whole body by some combination of poor food, toxics, bugs and stress, maybe with genetic vulnerabilities in the mix.

• This degrades the support system of the brain – not enough antioxidants, essential fatty acids and other nutrients.

• Meanwhile the body and brain start to get hypersensitive and overreact with more inflammation and oxidative stress as the problems continue.
A Theory of How Regression Happens: II: GLIAL CELLS GET SWAMPED

- The astrocytes start falling behind in supporting and protecting the neurons.
- The astrocytes and microglia get further distracted by having to be “activated” as these toxics, bugs and stressors make bigger demands on the brain.
- This astrocyte and microglia activation produces oxidative stress, which degrades things more.
A Theory of How Regression Happens: III: BLOOD AND ENERGY SUPPLY WEAKEN

- The blood supply to the brain starts getting crimped – sticky blood passes through vessels that are squished by swollen astrocytes.
- Neuronal excitation gets out of control, and produces more oxidative stress, which only makes things worse.
- Glutathione and other repair mechanisms are not replenished and things keep getting worse.
- Mitochondrial efficiency drops.
A Theory of How Regression Happens: IV: TIPPING POINT – SWITCH TO LOWER DEMAND STATE

• At some point the “Total Load” is too much, and a tipping point occurs:
  – Astrocyte networks start to fall apart – gap junctions close, communication degrades. Glutamate piles up, irritating neurons and networks.
  – Brain networks get weaker and less extensive as cells go into a disorganized, distracted “idling” mode to protect their challenged resources.
  – The brain stops being able to coordinate complicated information processing. It starts getting overwhelmed and producing autistic experience and behaviors.
A Theory of How Regression Happens: V: VICIOUS CIRCLES CREATE STUCKNESS

- So many vicious circles are making each other worse that it is difficult to reverse the cycle by changing just one part of the web. It therefore looks hopeless.
  - Brain cells are challenged,
  - Body cells are challenged,
  - Organ function is challenged,
  - Behavior is disorganized and disconnected which only adds stress,
  - And diet is the opposite of what would help the system repair itself.
Autism: **WHY** and **HOW**?

www.autismWHYandHOW.org

- A website reviewing multiple viewpoints and their intersections
- A literature repository
- A framework for reflective discourse
BRAIN CHANGES IN INFANTS DEVELOPING AUTISM

• From higher to lower “FA”
  • Decrease in fiber organization relative to controls
• This DEVELOPS over time
• It is probably DOWNSTREAM of the metabolic, cellular pileup of problems

Wolff et al., 2012
1. Regarding "How autism is caused", it is dysfunction in the health of these many cellular, chemical and electrical functions that is UPSTREAM of the problems with FA development in infants with autism, and that if we measure these upstream biological functions we might get more robust and clinically useful early brain indicators of autism and autism risk.
2. Regarding "what autism is", we might also understand autism better in terms of what I think are the ground zero mechanisms that intimately interrelate brain cell health problems with brain cell communication problems -- and that are disrupted by the extent to which the Total Load of exposures, insults, deficiencies and vulnerabilities overwhelms brain/body resilience
3. Regarding "how we can help," looking at brain cell health problems in a whole body strategy context gives us a lot we can do with what we know right now to improve the situation -- reducing “Total Load” and improving Resilience.

THIS IS

THE AUTISM REVOLUTION
Not broken, and not so hardwired
Not cognitive impairment
But largely normal or superior intelligence

- Wechsler Intelligence Scale vs. Raven’s Progressive Matrices.
  - Wechsler requires greater communication skills.
- Raven’s: ASD Children averaged 30 points higher (up to 70 points higher)
- Wechsler: 70 percent scored in the "retarded" range;
- Raven’s showed just 20 percent in this range

M. Dawson, I. Soulieres, M. A. Gernsbacher and L. Mottron
The level and nature of autistic intelligence. Psychol Sci 2007, 657-62
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

• Additional pertinent citations:
Rapid IMPROVEMENT 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)
Can Children with Autism Recover? If So, How?

Molly Helt · Elizabeth Kelley · Marcel Kinsbourne · Juhi Pandey · Hilary Boorstein · Martha Herbert · Deborah Fein

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Abstract Although Autism Spectrum Disorders (ASD) are generally assumed to be lifelong, we review evidence that between 3% and 25% of children reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills. Predictors of recovery include relatively high intelligence, receptive language, verbal and motor imitation, and motor development, but not overall symptom severity. Earlier age of diagnosis and treatment, and a diagnosis of Pervasive Developmental Disorder-Not Otherwise Specified are also favorable signs. The presence of seizures, mental retardation and genetic syndromes are unfavorable signs, whereas head growth does not predict outcome. Controlled studies that report the most recovery came about after the use of behavioral techniques. Residual vulnerabilities affect higher-order communication and attention. Tics, depression and phobias are frequent residual co-morbidities after recovery. Possible mechanisms of recovery include: normalizing input by forcing attention outward or enriching the environment; promoting the reinforcement value of social stimuli; preventing interfering behaviors; mass practice of weak skills; reducing stress and stabilizing arousal. Improving nutrition and sleep quality is non-specifically beneficial.

Keywords Autism spectrum disorders · Language development · Recovery · Stereotyped motor behavior

Introduction

Autism Spectrum Disorders (ASD) are a group of related developmental disorders that are characterized by immair-
Reversal in Mouse Models

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

Maasu L. Hayashi, B. S. Shankaranarayana Rao, Jin-Soo Seo, Han-Saem Cho, Bridget M. Dolan, Se-Young Cho, Sumantra Chattarji, and Susumu Tonegawa

*The Picower Institute for Learning and Memory, Howard Hughes Medical Institute, RIKEN–Massachusetts Institute of Technology Neuroscience Research Center, and Departments of Biology and Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; †Department of Neurophysiology, National Institute of Mental Health and Neurosciences, Bangalore 560029, India; ‡Department of Physiology, College of Dentistry, Seoul National University, Seoul 110-749 Korea, and †National Center for Biological Sciences, Tata Institute of Fundamental Research, Bangalore 560065, India

Contributed by Susumu Tonegawa, May 29, 2007 (sent for review May 21, 2007)

Fragile X syndrome (FXS), the most commonly inherited form of mental retardation and autism, is caused by transcriptional silencing of the fragile X mental retardation 1 (FMR1) gene and consequent at glutamatergic synapses, such as long-term potentiation (LTP) in the cortex and long-term depression in the hippocampus, is abnormal in FMR1 KO mice (11–13).

Reversal of Neurological Defects in a Mouse Model of Rett Syndrome

Jacky Guy, Jian Gan, Jim Selfridge, Stuart Cobb, Adrian Bird

Rett syndrome is an autism spectrum disorder caused by mosaic expression of mutant copies of the X-linked MECP2 gene in neurons. However, neurons do not die, which suggests that this is

Reversal of learning deficits in a Tsc2+/− mouse model of tuberous sclerosis

Dan Ehninger, Sangyeul Han, Carrie Shilyansky, Yu Zhou, Weidong Li, David J Kwiatkowski, Vijaya Ramesh & Alcino J Silva
“Wild-type microglia arrest pathology in a mouse model of Rett syndrome”

• Rett features had been attributed to neuronal dysfunction

• Astroglial cells now known to contribute

• Now microglia shown to contribute as well: bone marrow transplant of wild type microglia
  – Increased lifespan, normalized breathing, increased body weight, improved locomotor activity
  – *Improvement even without direct change to neurons*
  – Improvements lost when microglial phagocytic (garbage-collecting) activity inhibited
Excitotoxicity

Cell stress
Oxidative Stress

Excessive excitatory neurotransmitters
Excessive excitatory receptor responsiveness
Insufficient inhibitory neurotransmitters or receptor function

Cell Death, Cell loss

Excitotoxicity is a PROCESS before it becomes a STATE
Short-term immune triggers cause long-term brain inflammation

- *TNF-α* increases are triggered by bacterial and other exposures. (experiment used lipopolysaccharide (LPS) injection into gut cavity of rats)
  - In the bloodstream this *TNF-α* 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
Reversibility of reduced NAA after epilepsy surgery

- NAA (marker of neuronal density or function) reduced on the side opposite of a seizure focus
- After surgical resection of seizure focus, NAA on the other side returns to normal
- So – apparently those cells were not dead but “offline”

Pan, 2008
Neurometabolism in Human Epilepsy

NAA = n-acetylaspartate
Electron microscopy of therapeutically activated glia turning into “brain garbage collectors and transporters”

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

Model 1

<table>
<thead>
<tr>
<th>Cause:</th>
<th>Model 2</th>
<th>Mechanism:</th>
<th>Impact:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>Early Environment</td>
<td>Early Developmental Change</td>
<td>Fixed Functional Deficit</td>
</tr>
<tr>
<td></td>
<td>Epigenetics</td>
<td>Altered Gene Expression</td>
<td>Functional Deficit with Reversibility</td>
</tr>
</tbody>
</table>

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
Better Reception Allows More Spontaneous Learning

Worse SNR, Less Bandwidth

Less SIGNAL

More NOISE

Better SNR, Better Bandwidth

More SIGNAL

Less NOISE

SIGNAL to NOISE ratio (SNR) and BANDWIDTH
Linkage needed between **Pathophysiology** and **Cognitive Neuroscience**

Pathogenesis-Brain:
Targeting based on physical properties (receptors, growth factors, etc.)

Ground Zero:
Pathophysiology (including metabolism, immunology, metabolic imaging, neurology, neuropathology)

Brain-Behavior:
Behavior modulated by regional and neural systems alterations

Cognitive Neuroscience (including psychology, linguistics, functional neuroimaging, systems neuroscience)

Interaction of metabolic and electrophysiological disturbance

Herbert & Ziegler, Neurotoxicology, 2005
Integrative multimodal measurement platform
Optimization of measures that can detect change

- *Pathophysiology interacting with neurophysiology*

In development, in regression, in improvement

www.transcendresearch.org
transcend@partners.org
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

GENETIC EXPLANATIONS
Sense and Nonsense

Edited by SHELDON KRIMSKY and JEREMY GRUBER

Can genes determine which fifty-year-old will succumb to Alzheimer’s, which citizen will turn out on voting day, and which child will be marked for a life of crime? Yes, according to the Internet, a few scientific studies, and some in the biotechnology industry who should know better. Sheldon Krimsy and Jeremy Gruber gather a team of genetic experts to argue that treating genes as the Holy Grail of our physical being is a patently unscientific endeavor. Genetic Explanations urges us to replace our faith in genetic determinism with scientific knowledge about how DNA actually contributes to human development.

The concept of the gene has been steadily revised since Watson and Crick discovered the structure of the DNA molecule in 1953. No longer viewed by scientists as the cell’s fixed set of master molecules, genes and DNA are seen as a dynamic script that is ad-libbed at each stage of development. Rather than an autonomous predictor of disease, the DNA we inherit interacts continuously with the environment and functions differently as we age. What our parents hand down to us is just the beginning. Emphasizing relatively new understandings of genetic plasticity and epigenetic inheritance, the authors put into a broad developmental context the role genes are known to play in disease, behavior, evolution, and cognition.

Rather than dismissing genetic reductionism out of hand, Krimsy and Gruber ask why it persists despite opposing scientific evidence, how it influences attitudes about human behavior, and how it figures in the politics of research funding.

Sheldon Krimsy is Professor of Urban & Environmental Policy & Planning in the School of Arts and Sciences and Adjunct Professor of Public Health and Community Medicine in the School of Medicine at Tufts University. Jeremy Gruber is President and Executive Director of the Council for Responsible Genetics.

New Book with Critiques of Genetic Overexplanation

Ch.10 on Autism: From Static Genetic Brain Defect to Dynamic Gene-Environment-Modulated Pathophysiology

By Martha Herbert

One-page summary and section headers posted on www.marthaherbert.org under publications – click link for this article
Autism: WHY and HOW?

www.autismWHYandHOW.org

- A website reviewing multiple viewpoints and their intersections
- A literature repository
- A framework for reflective discourse
Autism Revolution: Ten Tips

1. Go for the extraordinary.
2. Know what you can’t control — and what you can.
3. Repair and support cells and cycles.
4. Get gut and immune systems on your side.
5. Build better brain health.
6. Calm brain chaos
7. Join your child’s world.
8. Love, rejoice, and make breakthroughs.
9. Lead the revolution!
10. Do it for yourself, your next baby, your family, and your world.
Systems biology of autism told through stories of people who get better:

The Autism Revolution: Whole Body Strategies for Making Life All It Can Be

www.autismWHYandHOW.org

www.transcendresearch.org

www.AutismRevolution.org

www.marthaherbert.com