

THE ROLE OF EPIGENETICS IN MENTAL HEALTH

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Walsh Research Institute

- **Nonprofit public charity**
- **Experimental research**
- **Expertise in biochemical therapy**
- **International physician training**

Clinical Experience

William J. Walsh, Ph.D.

- 10,000 Behavior & ADHD
- 3,500 Schizophrenia & Bipolar
- 3,200 Depression
- 6,500 Autism

Massive Chemistry Database

- About 90 to 150 assays of chemical factors in blood, urine, or tissues for each of 25,000 patients,
- More than 3 million chemical test results for patients diagnosed with ADHD, depression, autism, schizophrenia, etc,
- An additional 2 million blood/urine/tissue chemistries from research experiments.

Comparison with the General Population

**Major chemistry differences
between
mental illness populations
and the rest of society.**

Symptom/Trait Correlations

- About 50-150 symptoms, traits, and physical characteristics recorded for each patient and research subject,
- Correlations between these factors & specific chemical imbalances,
- Biochemical classifications developed for depression, behavior, and schizophrenia.

High-Incidence Chemical Imbalances in Mental Disorders

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- Zinc Deficiency
- Copper Overload
- Methylation Disorder
- Folate Imbalances
- Pyrrole Disorder
- Toxic metal Overload
- Severe Oxidative Stress

Certain imbalances observed in completely different disorders:

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Example 1: Copper overload present in most cases of hyperactivity, post-partum depression, paranoid schizophrenia, and autism.

Example 2: Undermethylation observed in most cases of OCD, anorexia, seasonal depression, schizoaffective disorder, and antisocial personality disorder.

The Repeat Offenders

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Question: Why are these biochemical abnormalities seen in diverse mental disorders?

Answer: Each is directly involved in either the synthesis or regulation of major neurotransmitters.

Frequent Questions From Medical Professionals

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1. How could vitamins, minerals, and amino acids possibly help a person with a serious mental illness?
2. Don't you really need a powerful drug medication to get the job done?

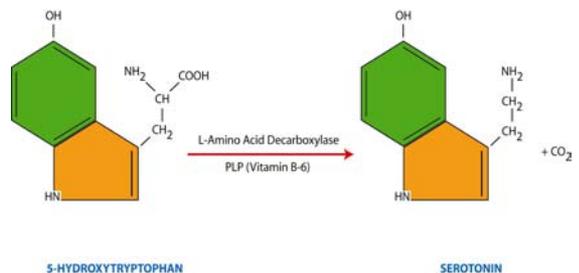
The Brain Is a Chemical Factory

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- Serotonin, dopamine, and other NT's are synthesized in the brain from amino acids vitamins, and minerals.
- A genetic or epigenetic imbalance in a nutrient needed for NT synthesis or regulation can result in serious mental problems.

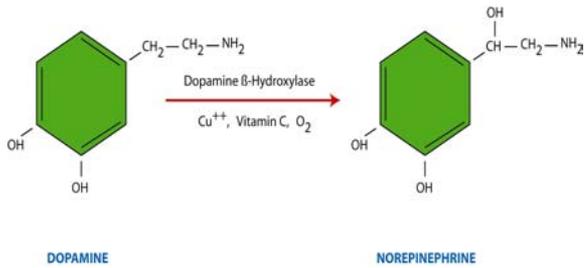
Serotonin Synthesis

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Norepinephrine Synthesis

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Animal Studies – Impact of Cu Level on Dopamine and Norepinephrine

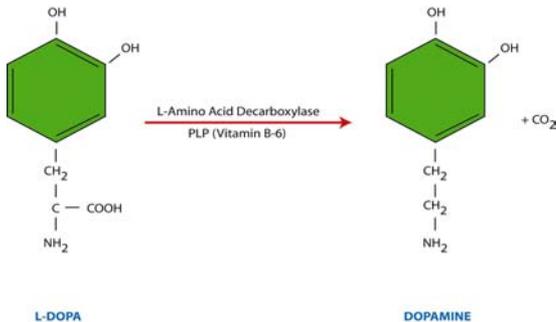
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- Cu-deficient diet reduced blood levels to 25% of normal,
- Brain tissue assayed for dopamine and norepinephrine.

**RESULT: Norepinephrine/Dopamine Ratio
Reduced by a Factor of Four.**

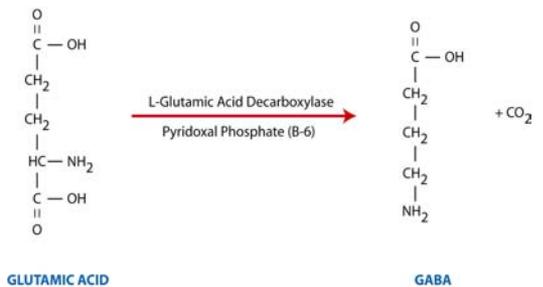
Dopamine Synthesis

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GABA Synthesis

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Zn Deficiency and Brain Function

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- Zn is needed for regulation of GABA in brain,
- GABA is a “calming” NT that combats overloads of norepinephrine,
- Zn deficiency is associated with irritability, anxiety, and violent behavior.

Biochemical Individuality

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- Humans are genetically & epigenetically diverse.
- Because of genetics and epigenetics, most people are deficient in several nutrients and overloaded in others.

Biochemical Balancing

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- Nutrient deficiency may require many times the RDA to achieve normalization, since we may be fighting genetics,
- Nutrient overloads can cause great mental problems & focused biochemical therapy can eliminate the nutrient excess.
- Multiple vitamins are rarely effective.

Individualized Nutrient Therapy

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- Medical History and Review of Symptoms
- Extensive Chemical Testing
- Diagnosis of Chemical Imbalances
- Prescribed Nutrient Program Aimed at Normalizing Body & Brain Levels.

Populations With Positive Outcomes Following Biochemical Therapy

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- Behavior Disorders
- ADHD
- Autism
- Depression
- Bipolar Disorder
- Schizophrenia
- Alzheimer's Disorder

Populations With Negative Outcomes Following Biochemical Therapy

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- Down's Syndrome
- Tourette's Syndrome
- Severe OCD

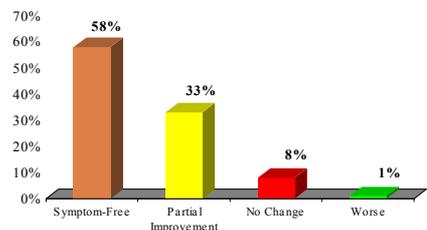
Major Behavior Phenotypes

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- Antisocial-Personality Disorder (low Zn & Cu, low methyl, pyrroles, hypoglycemia, toxic metal overload)
- Intermittent Explosive Disorder (high Cu/Zn ratio)
- Conduct Disorder (severely-elevated pyrroles)
- Oppositional/Defiant Disorder (high histamine, low methyl, low-normal Cu, low Ca & Mg)

Treatment Outcomes Compliant Assaultive Subjects

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Five Depression Phenotypes

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1. Undermethylation (high blood histamine)
2. Low Folate (low blood histamine)
3. Pyrrole Disorder
4. Copper Overload
5. Toxic Metal Overload

Undermethylated Depression

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- OCD tendencies
- Low serotonin activity
- Seasonal affective disorder
- High libido
- Competitive & perfectionistic
- Seasonal allergies
- SSRI medications usually effective
- Treatment using Methionine, Ca, Mg, Zn, TMG, Inositol, SAMe, Vitamins B-6, C, E.

Low Folate Depression

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- Tendency for high anxiety, panic, underachievement
- Food/chemical sensitivities
- Elevated dopamine and norepinephrine
- Adverse reaction to SSRI medications
- Low libido
- High musical or artistic ability
- Treatment involves Folic Acid, B-12, GABA, Zn, DMAE, and Vitamins A, B-3, B-6, B-12, C, E.

Pyrrole Depression

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- Severe mood swings
- Fearfulness
- Poor short-term memory, reading disorder
- Sensitivity to light, noise
- Poor immune function
- Very poor morning appetite
- Low serotonin, GABA
- Treatment focus on B-6 and Zn

Hypercupremic Depression

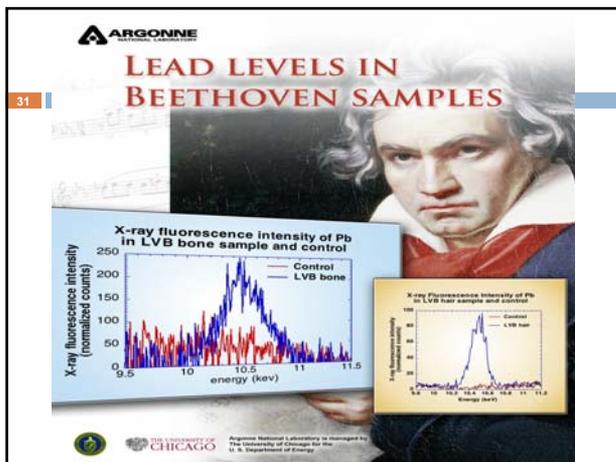
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- More than 95% are female,
- Inability to eliminate excess copper
- Present in most women with history of PPD
- Adverse reaction to estrogen treatments
- Onset during hormonal event (puberty, pregnancy, menopause)
- Decoppering treatment involves Zn, B-6, MT Promotion, GABA, Omega 3 oils, and Vitamins C and E.

Toxic Metal Depression

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- Absence of trauma or emotional triggers
- Abdominal distress
- Unrelenting depression
- Cognitive deficits (children only)
- Metallic taste in mouth
- Irritability, anger
- Food sensitivities
- Treatment involves Ca, Zn, GSH, B-6, C, E, and MT-Promotion.



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- ## Biochemical Subtypes of Schizophrenia
- 45% - Overmethylated Schizophrenia
 - 18% - Undermethylated Schizophrenia
 - 27% - Pyrrolic Schizophrenia
 - 4% - Wheat Gluten Intolerance
 - 6% - Other

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- ## Schizophrenia Outcome Studies (open-label)
- 85% report that "life is better" after nutrient therapy,
 - 75% report ability to reduce (or eliminate) medication,
 - Highest efficacy for overmethylation and pyrrole disorder,
 - Many cases of complete recovery

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- ## Prominent Schizophrenia Theories
1. Dopamine Theory
 2. Glutamate Theory (NMDA)
 3. Oxidative Stress Theory
- My data suggests the cause of schizophrenia may be different for each biochemical phenotype.

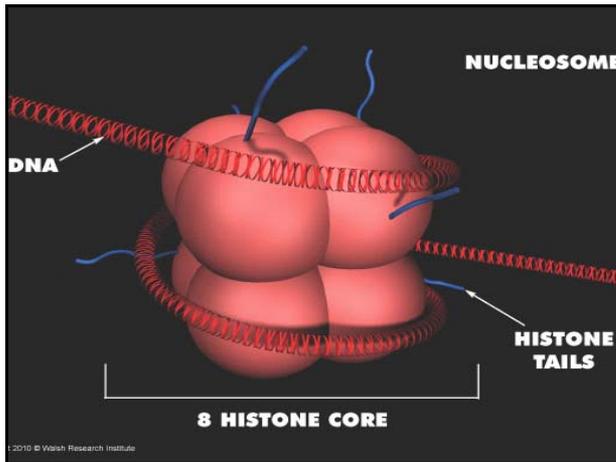
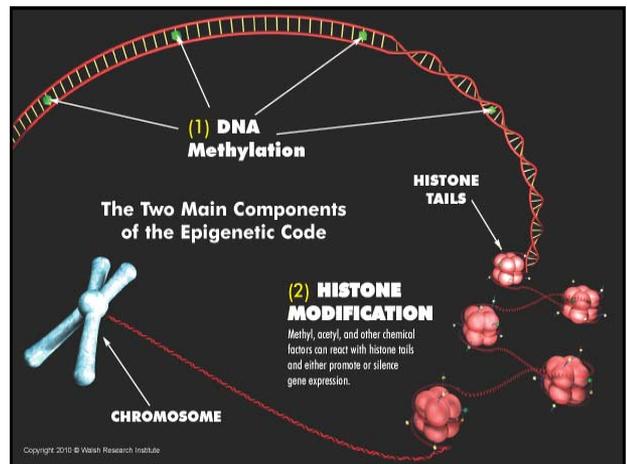
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- ## Promising Schizophrenia Therapies
1. Glutathione-Enhancement Therapies
 2. Sarcosine
 3. D-Serine
 4. D-Cycloserine

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- ## The Epigenetics Revolution
- Until recently, heritable illnesses were presumed to be genetic in nature,
 - Several heritable disorders now appear to be epigenetic, rather than genetic:
 - Schizoaffective disorder
 - OCD
 - Cancer
 - Oppositional Defiant Disorder
 - Autism

Epigenetics

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- Altered gene expression without changes in DNA sequence,
- Abnormal chemical environment during in-utero bookmarking of genes,
- Post-natal gene expression changes resulting from toxics or chemical imbalances,
- Two major epigenetic mechanisms:
 - Direct DNA Methylation
 - Histone Modification



Histones

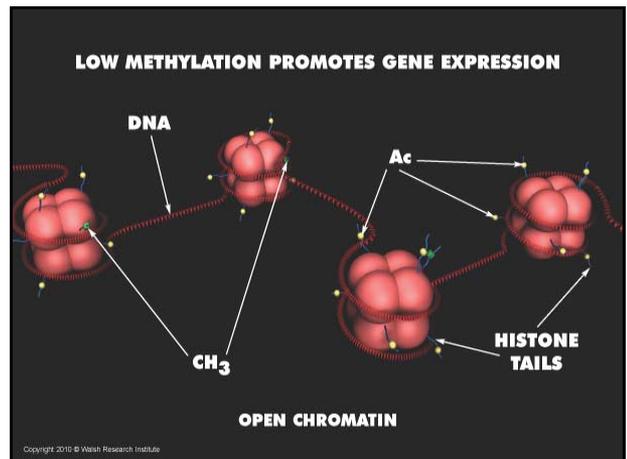
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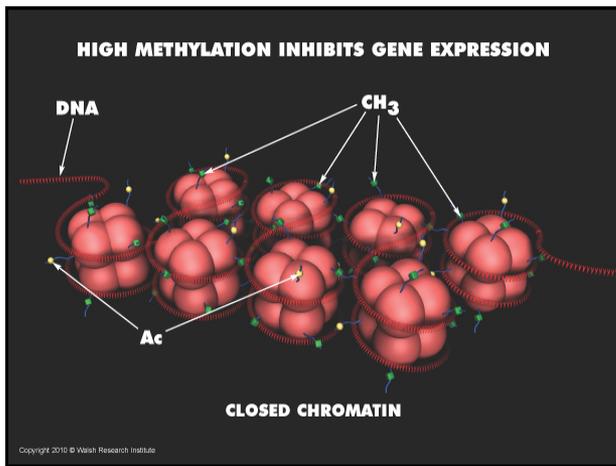
- Composed of 8 linear proteins twisted together like a ball of yarn,
- Originally believed to serve only as structural support for DNA packaging,
- Later found to inhibit/promote gene expression depending on chemical reactions at histone tails, that alter electrostatic attraction to DNA's double helix,
- Complex histone code under development.

Methyl-Acetyl Competition

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- Competition between acetyl and methyl groups at histone tails often determines whether genes are expressed or silenced,
- Acetylation tends to promote gene expression,
- Methylation generally inhibits expression.





Histone Modification Complexity

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- Sixty-one different core histone proteins,
- Multiple sites for chemical interaction,
- Numerous chemical factors involved:
 - Acetylation
 - Methylation
 - Phosphorylation
 - Ubiquitination
 - Biotination
 - Etc.

A 25 year mystery!

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1. Folic Acid is a very effective methylating agent.
2. Undermethylated mental patients are intolerant to folic acid, but most overmethylated mental patients improve after folic acid supplements.

WHY?

Mystery Solved by Epigenetic Science

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- Folic Acid generates acetylase enzymes that alter histones, promoting expression of SERT and DAT transporter proteins.
- SERT and DAT enhance reuptake at serotonin and dopamine synapses.... thus reducing NT activity.
- For undermethylators, the harmful impact of folic acid at NT synapses greatly exceeds the benefits of normalizing methylation.

Undermethylation Therapy

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- 1. Mental illness:** Methionine and SAMe supplements; folates must be avoided like poison;
- 2. Autism:** Folic & folinic acids are promising nutrients since autism is not dominated by NT imbalances.

Efficacy of Niacin An Epigenetic Explanation

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1. Niacin converts to niacinamide in the body,
2. Niacinamide inhibits sirtuin molecules,
3. Sirtuins are powerful deacetylases that inhibit production of transporter proteins.

Niacin supplements reduce dopamine activity benefiting many schizophrenia patients.

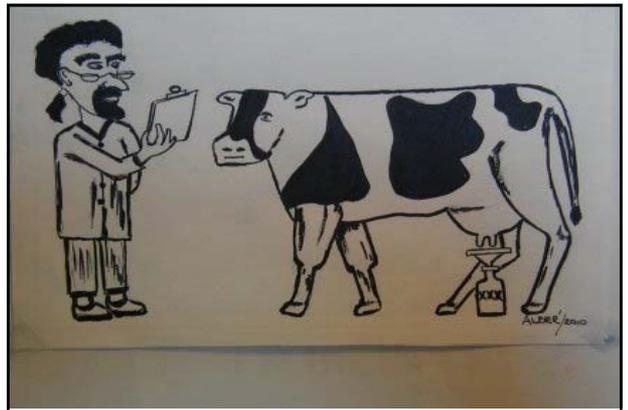
“Epigenetics”

A Limerick by George Marino

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Said a scientist once feeling frisky
I know altering genes can be risky

but I want to learn how
to develop a cow....



That will stop giving milk and give whiskey.

AUTISM

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- Developmental disorder,
- Onset: Prior to age 4,
- Deficits in cognition, speech, socialization – Many autistics institutionalized,
- Worldwide epidemic – More than 1 in every 110 USA births (2009 data),
- About 80% involve regression – Normalcy followed by major decline at 16-24 months.

Autism Spectrum Database

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- About 90 to 150 assays of chemical factors for each of 6,500 patients,
- More than 800,000 chemical test results.

-- *Compared with reference levels* --

Autism Database Analysis

53

- Major biochemical abnormalities observed in the autism population.
- Autism biochemical imbalances are more severe than those for violent behavior, depression, and schizophrenia.
- Discovery of hypomethylation in >95% of persons in the autism spectrum (1999),
- Evidence of metallothionein depletion (2000).

High Incidence Biochemical Abnormalities in Autism

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- Depressed Glutathione & Cysteine
- Elevated toxic metals
- Hypomethylation
- High Copper & low Ceruloplasmin
- Depleted Zinc & Metallothionein
- Elevated Pyrroles
- Low B-6, C, and Selenium
- Elevated Urine Isoprostanes

Note: Each of these imbalances is associated with elevated OXIDATIVE STRESS.

Oxidative Stress and Autism

55

1. Excessive oxidative stress is evident throughout the autism spectrum,
2. An oxidative stress model can explain most symptoms of autism,
3. Most autism therapies have antioxidant properties,
4. Oxidative stress has become a leading focus of autism research.

Most Popular Autism Therapies Enhance Antioxidant Protection

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- Methyl B-12
- Metallothionein Promotion
- Transdermal or Injected Glutathione
- Zn, Se, CoQ-10, Vitamins A,C,D,E
- Chelation with DMSA, DMPS, EDTA.
- Alpha Lipoic Acid
- Risperdal

Distinctive Features of Autism

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- Strong inborn predisposition
- Onset after environmental insult
- High oxidative stress
- Altered brain development

Autism Brains Are Different

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- Incomplete maturation – Excessive short, undeveloped brain cells in cerebellum, amygdala, pineal gland and hippocampus,
- Poverty of brain dendrites and synapses,
- Narrowed minicolumns in brain cortex,
- Brain inflammation and increased head size,
- Damaged fats in autism brains,
- Abnormal levels of calcium and iron.

Oxidative Stress Can Impair Brain Development

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- High oxidative stress depletes glutathione,
- Ample glutathione is required for proper functioning of metallothionein,
- Metallothionein is a key factor in early brain development.

Why is Metallothionein Important?

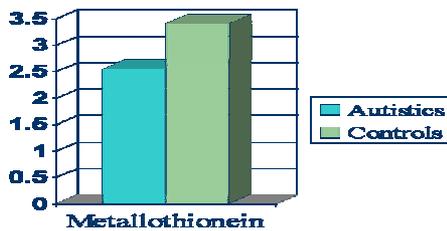
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- Required for pruning, growth and growth-inhibition of brain cells in early development,
- Prevents Hg, and other metal toxics from passing intestinal and blood/brain barriers,
- Required for homeostasis of Cu and Zn,
- Supports immune function.

Note: MT functioning can be disabled by severe oxidative stress.

Low Metallothionein Levels in Autism $p < 0.0092$

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Autism Rates

A Continuing Medical Mystery

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- Clear inborn predisposition: Greater than 60% concordance in identical twins; Less than 10% concordance in fraternal twins,
- Dramatic increase in autism cases over the past 50 years.
- Autism rates continue to escalate – October, 2009 data indicates one case per 110 births.

How can there be an epidemic of a genetic condition?

The Recipe for Autism

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1. Inborn Predisposition
2. Environmental Insult

Environmental Insults: A Multitude of Possibilities

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1. Attention has been focused on direct insults to the child from conception to age three.
2. More than 25 environmental insults have been proposed, including mercury exposures, vaccines, changes in diet, viruses, increased Cu in the water supply, etc, etc.

A New Explanation - Epigenetics

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- Environmental insults during the first month of gestation can produce abnormalities in gene expression that may persist throughout life
- In some cases, these abnormalities can be transferred to future generations.
- This could result in a geometric increase in the number of autism-prone families.

Epigenetic Processes During Early Fetal Development

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- Every cell has the potential for expressing any of the >20,000 genes in DNA,
- In utero chemical environment determines which genes will be expressed or silenced throughout life (bookmarking),
- Gene expression errors can be transmitted to future generations by a process called transgenerational epigenetic inheritance (TEI),
- Methylation is a dominant factor in TEI, and is abnormally low in autistic children.

Undermethylation Enclaves and Increasing Autism Rates

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- Undermethylation is associated with OCD, perfectionism & high career accomplishment,
- High frequency for doctors, lawyers, CEO's, scientists, great athletes; also in affluent neighborhoods and universities,
- Increased social mobility in the past 50 years has resulted in increasing numbers of low-methyl persons who marry each other,
- Undermethylated parents are more vulnerable to epigenetic insults that can cause autism.

A Clue From the Past -- Thalidomide Babies

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- Deformed thalidomide babies of the 1960's had a high incidence of autism,
- Autism occurred only if the anti-nausea pill was taken between days 20-24 of gestation,
- Most epigenetic decisions regarding gene expression or inhibition are established at this time,
- This suggests the greatest vulnerability to autism-causing environmental insults may be during in-utero epigenetic bookmarking.

Epigenetic versus Genetic

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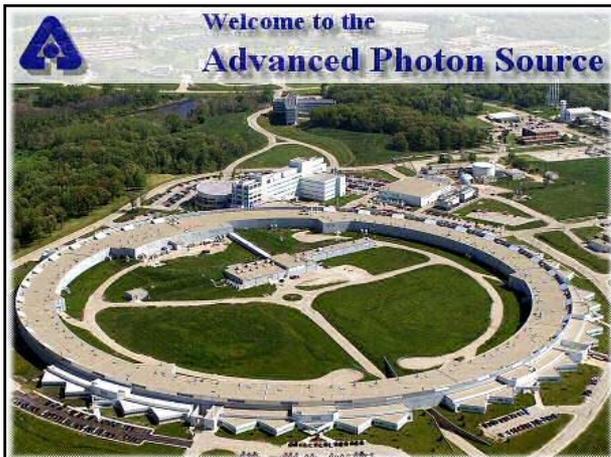
1. Epigenetic processes are far more vulnerable to toxic metals, viruses, etc., compared to genetic processes,
2. Epigenetic abnormalities are enhanced by undermethylation,
3. Nearly all autism spectrum persons are undermethylated,
4. Epigenetic errors may be passed on to future generations.

AUTISM APPEARS TO BE AN EPIGENETIC DISORDER!!

Recent Research

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- Dominant importance of oxidative stress,
- Evidence of neurodegeneration,
- Hypomethylation is a feature of autism,
- Poverty of brain dendrites & synapses
- Male/Female differences in brain chemistry,
- Evidence that Hg brain levels are at normal levels several years after significant exposure.



Photon Beam Nanoanalysis of Brain Tissues

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- Double blind, controlled study,
- 176 brain tissues from U. of Maryland's Autism Brain Bank,
- Elemental analysis for 16 elements, including Hg, Pb, Cu, Zn, and Se using high-brilliance photons,
- First elemental assays ever attempted for autism & control brain tissues.

Brain Regions Studied

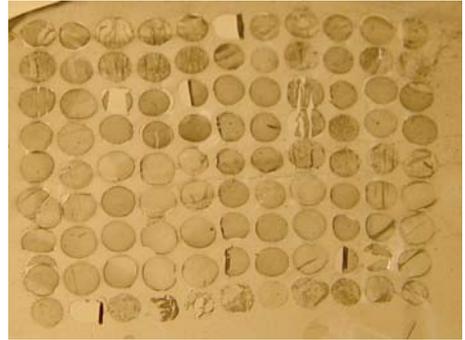
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- Cerebellum
- Superior Cortex
- Deep Cortex
- White Matter

Note: 20 autistic & 20 control tissue samples from each brain region.

Autism/Control Tissue Array

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Results of Brain Tissue Study

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1. World's first extensive chemical assays for elements in autism brain tissue – More than 500,000 individual assays achieved,
2. Male autistics: Very elevated iron,
3. Female autistics: Very elevated calcium,
4. Results suggest that male & female autism involve different mechanisms & etiologies,
5. Mercury overload NOT observed in brains of autistics aged 5-11 years who were exposed to mercury-containing vaccines.

Autism and Neurodegeneration

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- Recent evidence of neurodegeneration in autism.... attributed to severe oxidative stress,
- Gradual loss of brain cells and IQ may occur if antioxidant therapy is not provided,
- Young autistics appear very bright despite behavioral, speech, and socialization deficits,
- Most adult autistics exhibit mental retardation (exception: Aspergers patients).

Antioxidant therapy may be needed throughout life.

Important Questions

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- Why do most autism regressions occur during months 16-22? Environmental insults are present throughout development.
- Why do many autism regressions result in radical changes in speech, socialization, food sensitivities, etc., in just a few days?
- Why do autism symptoms persist after onset?

Conclusion: A dramatic EVENT has occurred!!

An Epigenetic Theory of Autism

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1. Fetal undermethylation promotes epigenetic errors,
2. In-utero environmental insults alter epigenetic bookmarking producing weakened defenses against oxidative stress,
3. Oxidative insults gradually deplete GSH, MT, SOD, catalase, and other protective factors,
4. A threshold is reached in which antioxidant protection collapses, causing (a) sudden brain & G.I. tract inflammation, (b) leaky intestinal & brain barriers, (c) interruption of normal brain development (the regression event).

Result = Autism

The Bermuda Triangle of Autism

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- Hypomethylation
- Epigenetic errors, triggered by environmental insults,
- Oxidative Stress

Alzheimer's Disease

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- Severe oxidative stress
- Amyloid plaque and neurofibrillary tangles
- Metal-metabolism disorder
- Elevated toxic metals
- Low levels of metallothionein in ALZ brains.

Low MT Levels Can Produce Amyloid

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- MT proteins protect the brain from metal free radicals,
- Metal free radicals (iron, copper, zinc) enhance formation of beta amyloid plaque in the brain,
- AD autopsy studies show MT levels less than 1/3 of normal concentrations.

Metallothionein-Promotion Therapy for Alzheimer's Disease

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- Formulation of 22 nutrients that promote synthesis and functioning of MT.
- Zinc loading followed by MT-Promotion.

Note: MT-Promotion is aimed at overcoming brain oxidative stress & inflammation, and repair of the blood/brain barrier.

Clinical Results: First 70 Patients

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- Most patients reported partial improvement of memory followed by stabilization of condition.
- Several patients lost the diagnosis of AD.
- Caretaker needed for effective compliance.
- We consider this therapy highly promising, but unproven.

Summary

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- Biochemical imbalances are exhibited by most persons with mental disorders.
- These imbalances can adversely impact neurotransmitter synthesis & regulation.
- Most families report improvement, following nutrient therapy to normalize chemistry.
- The emerging science of epigenetics will lead to vastly improved therapies.

Pfeiffer's Law

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“For every drug that benefits a patient, there is a natural substance that can produce the same effect”.

Carl C. Pfeiffer, MD, PhD

THANK YOU!

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