

AN EPIGENETIC MODEL OF AUTISM AND A WARNING REGARDING RISPERDAL

William J. Walsh, Ph.D.
Walsh Research Institute
Naperville, IL

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
- 6,500 Autism-Spectrum Disorder
- 6,500 Mental Illness

Massive Autism Database



- **More than 1.5 million chemical assays of blood, urine and tissues.**
- **Striking biochemical differences between ASD children and non-affected children.**

Autism Database Highlights

- **Autism imbalances more severe than in violent behavior and mental illness,**
- **Discovery of undermethylation in more than 95% of ASD patients (1999),**
- **Clear evidence of oxidative stress and metallothionein depletion (2000).**

Pervasive Biochemical Abnormalities in Autism

- Depressed Glutathione & Cysteine
- Elevated toxic metals
- Hypomethylation
- Copper/Ceruloplasmin dysregulation
- 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**.*

Some Consequences of Excess Oxidative Stress

- 1. Hypersensitivity to Hg & other toxic metals,**
- 2. Hypersensitivity to casein, and gluten,**
- 3. Poor immune function,**
- 4. Inflammation of the brain & G.I. tract,**
- 5. Depletion of glutathione & metallothionein.**

Most Popular Autism Therapies Have Antioxidant Properties

- **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**

CONCLUSION



**OXIDATIVE STRESS OVERLOAD IS A
DISTINCTIVE FEATURE OF AUTISM**

Oxidative Stress Can Impair Brain Development

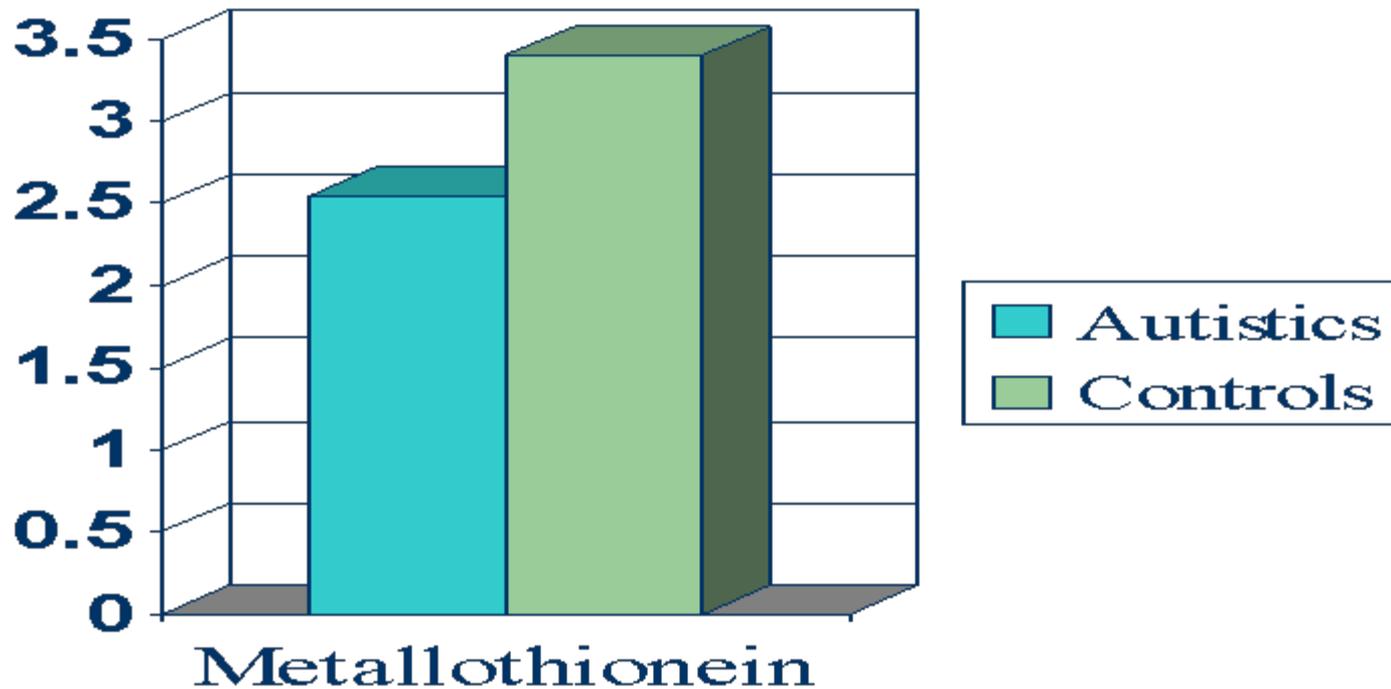
- **High oxidative stress depletes glutathione and metallothionein levels,**
- **Ample glutathione and metallothionein essential for proper brain development,**
- **Oxidative insults can alter epigenetics of gene expression.**

Autism Brains Are Different

- Narrowed minicolumns in brain cortex,
- Incomplete maturation in cerebellum, amygdala, pineal gland and hippocampus,
- Poverty of brain dendrites and synapses,
- Brain inflammation and increased head size,
- Damaged fats in autism brains,
- Abnormal levels of calcium and iron,
- Reduced structural connectivity between brain regions.

Low Metallothionein Levels in Autism

$p < 0.0092$



Why is Metallothionein Important?

- 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.

The McGinnis Hypothesis

- The brain-stem area receives little or no protection from the blood-brain barrier,
- Provides an avenue for oxidative damage to developing autism brains, caused by toxic metals, viruses, etc.
- This may explain immaturity in the limbic system & cerebellum not observed in other brain regions.

Consequences of Oxidative Overload in the G.I. Tract

- ❑ **Destroys digestive enzymes needed to break down casein & gluten,**
- ❑ **Increases candida/yeast levels,**
- ❑ **Diminishes Zn levels and production of stomach acid,**
- ❑ **Produces inflammation,**
- ❑ **Results in a “leaky” intestinal barrier, allowing toxics to enter the bloodstream.**

The Three Musketeers of Antioxidant Protection

Glutathione: First line of defense,

Metallothionein: Nature's back-up system,

Selenium: Speeds up the process.

Increasing Autism Rates

A Continuing Medical Mystery

- 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

How can there be an epidemic of a genetic condition?

The Role of Environment

- Concordance of only 60-80% in identical twins indicates that environment plays a significant role.
- Since DNA mutations can take centuries to develop, the autism epidemic has been attributed to changes in environment.

The Recipe for Autism



1. Inborn Predisposition

2. Environmental Insult

Environmental Insults: A Multitude of Possibilities

- Attention has focused on direct insults to the child from conception to age three.
- More than 30 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

- **Undermethylation can alter gene programming during pregnancy,**
- **Cumulative oxidative stress can produce deviant epigenetics “bookmarks” after birth,**
- **Epigenetic errors can be transferred to future generations and contribute to the autism epidemic.**

The Bermuda Triangle of Autism

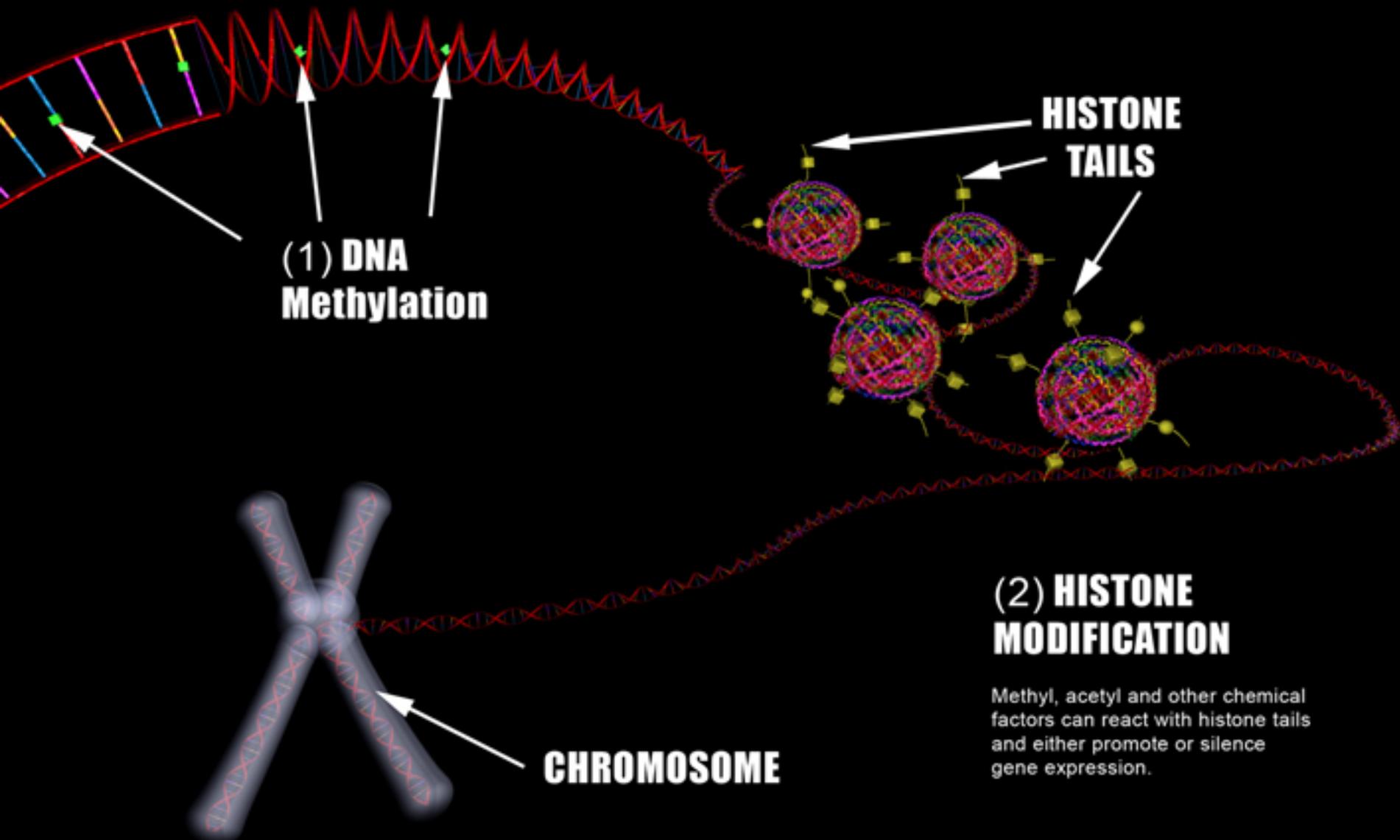
- **Undermethylation**
- **Oxidative Stress**
- **Epigenetic errors, triggered by environmental insults,**

Epigenetics

- Until recently, all heritable illnesses were presumed to have a genetic component,

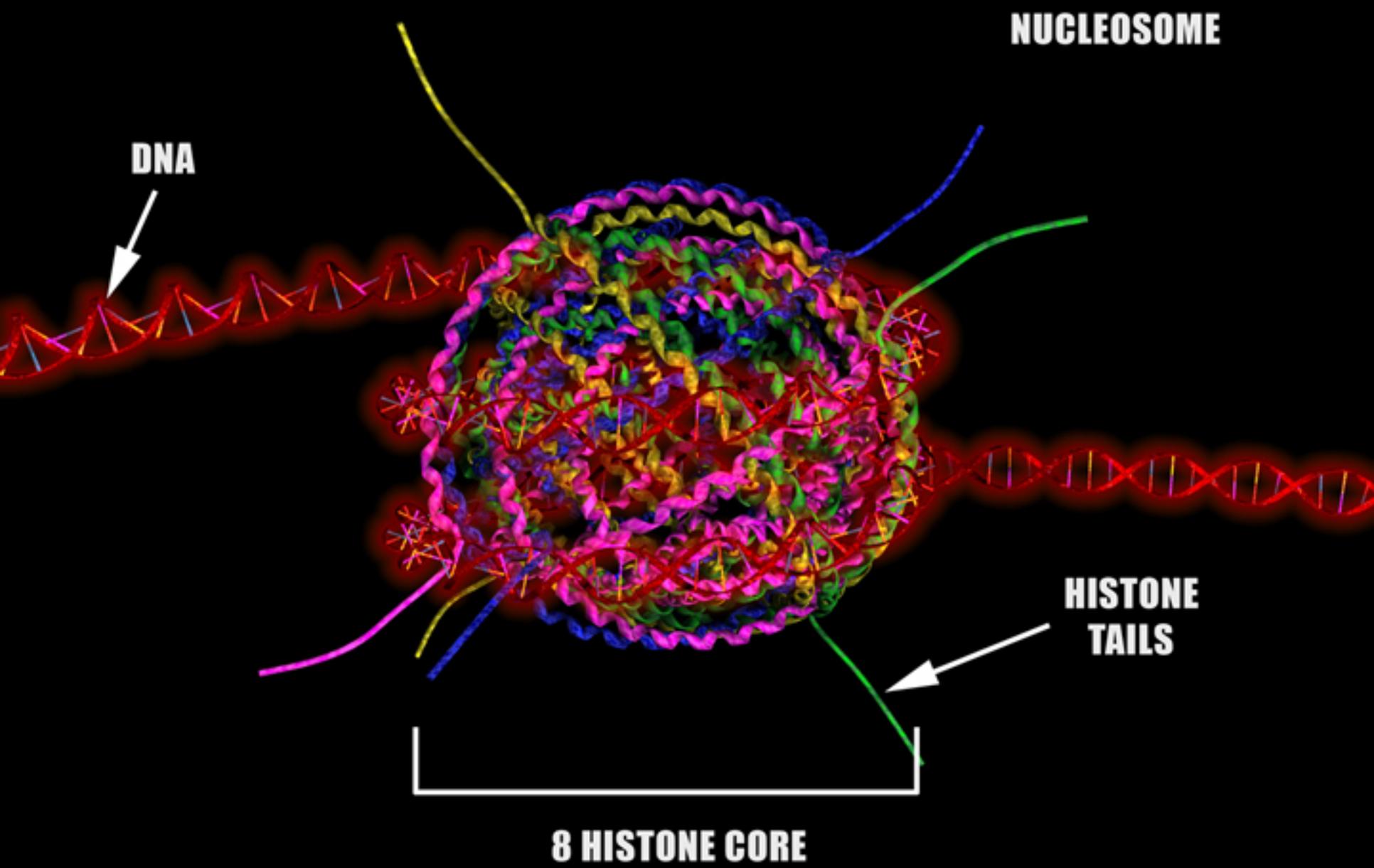
- Many disorders now appear to be epigenetic, rather than genetic:
 - Schizoaffective Disorder
 - Oppositional Defiant Disorder
 - Obsessive-Compulsive Disorder
 - Autism

The Two Main Components of the Epigenetic Code



Histones

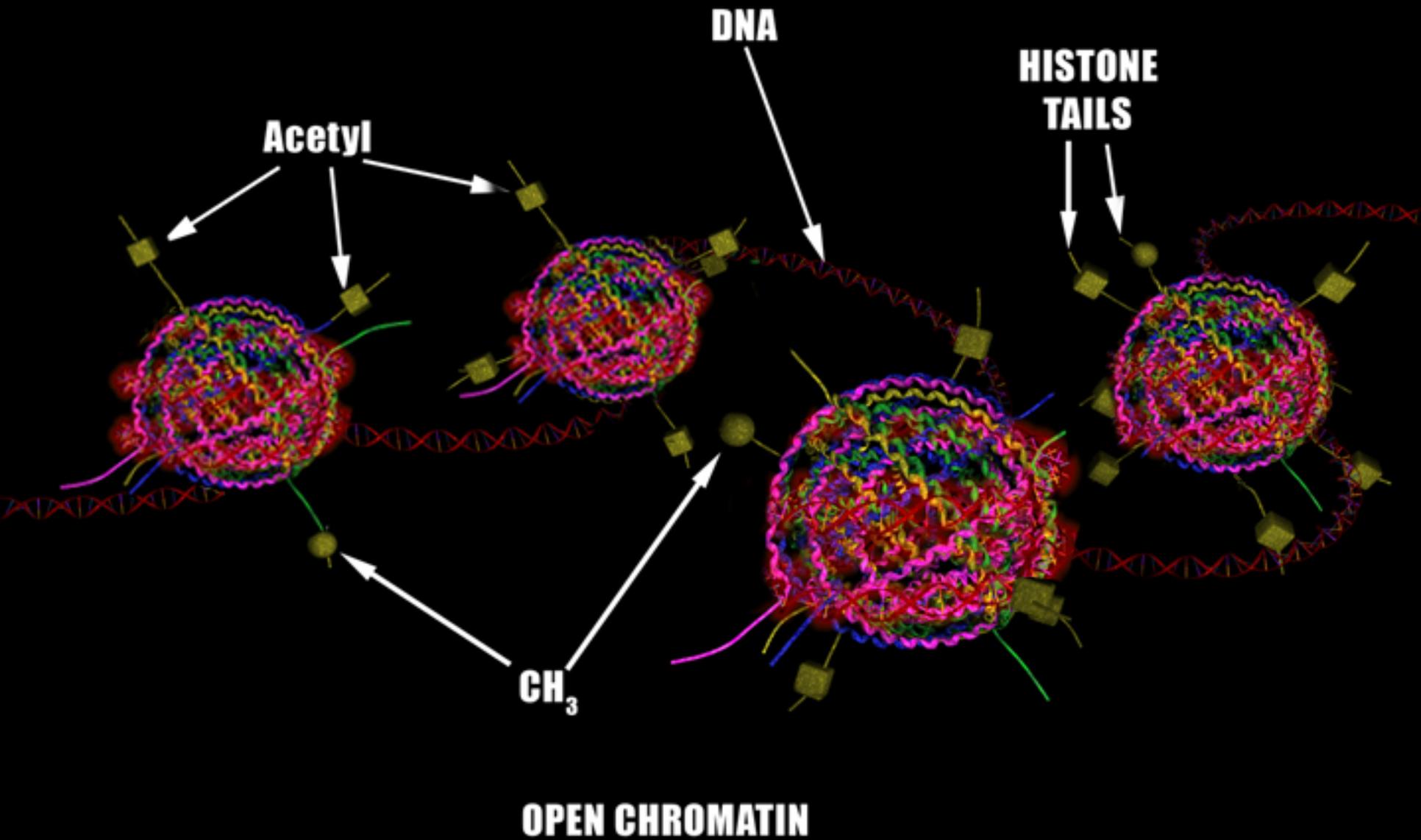
- Composed of 8 linear proteins twisted together like a ball of yarn,
- Originally believed to serve only as structural support for DNA packaging,
- Later found to inhibit/promote gene expression depending on chemical reactions at histone tails.



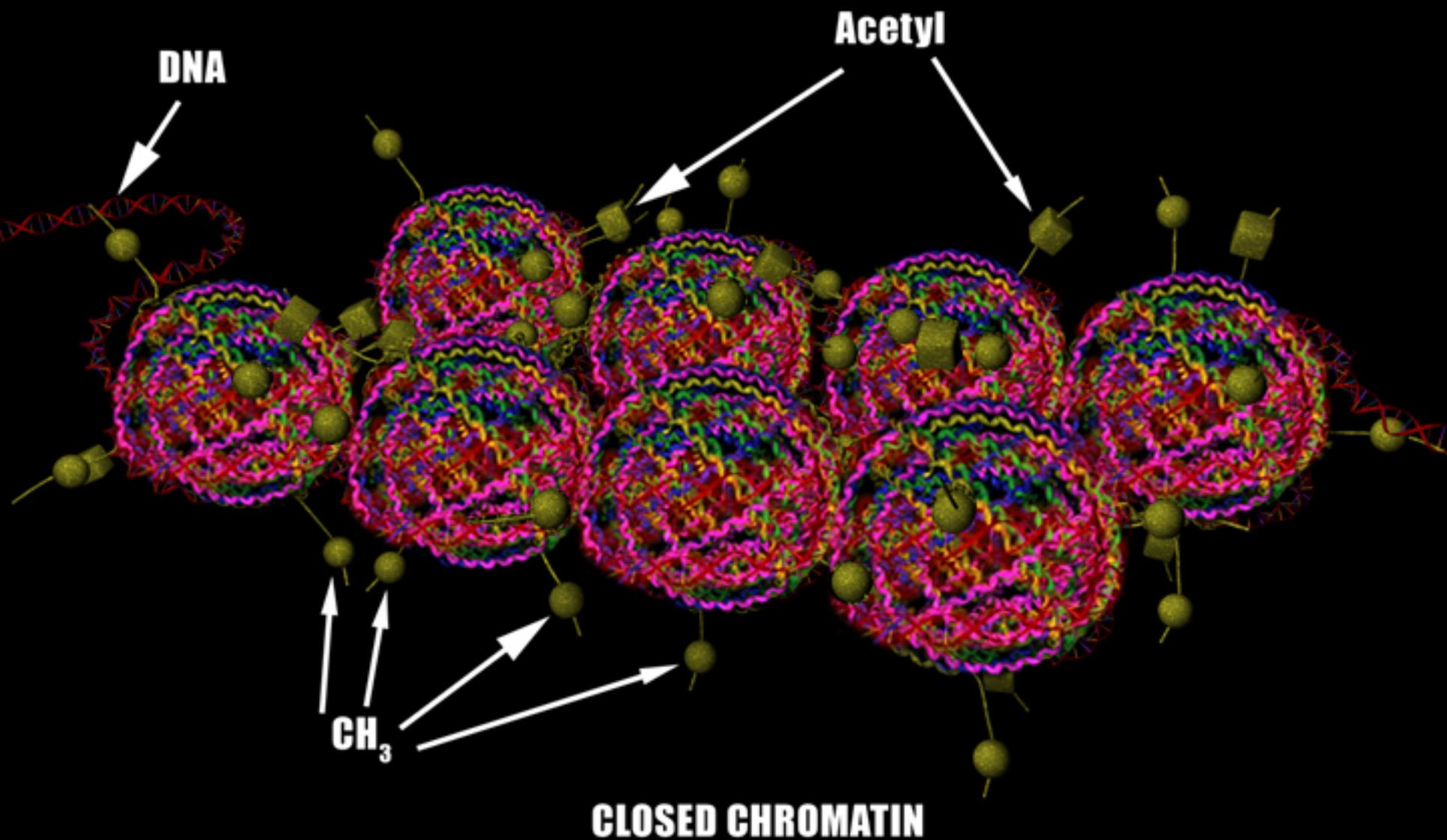
Methyl-Acetyl Competition

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

LOW METHYLATION PROMOTES GENE EXPRESSION



HIGH METHYLATION INHIBITS GENE EXPRESSION



Epigenetic versus Genetic

1. Epigenetic processes are far more vulnerable to toxic metals, viruses, oxidative insults, than genetic processes,
2. Epigenetic errors are enhanced by abnormal methylation,
3. Nearly all ASD individuals are undermethylated,
4. Autism violates classic laws of genetics.

Epigenetic Errors in Autism

1. Nguyen et al; Identical twin study (FASEB Journal, April 2010): Finding: Abnormal methylation at DNA CpG sites.
2. Beaudet (2007), Nat. Med. 13, 534-536.
3. Schanen (2006), Hum. Mol. Genet. 15(2), R138-R150.
4. Nakayama, et al (2006), NSSYZ Journal.

Characteristics of an Epigenetic Disorder

- **Abnormal methylation,**
- **Cases of sudden onset after normalcy,**
- **Persistence of condition after onset,**
- **A multitude of characteristic symptoms,**
- **Heritable condition that violates laws of genetics.**

Important Questions

- Why do most autism regressions occur during months 16-22?
- 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!!

Epigenetic Model of Autism

- **Undermethylated in-utero environment results in life-long vulnerability to oxidative stresses,**
- **Sometime after conception, cumulative oxidative insults reach a threshold that produces deviant epigenetic marks and the autism condition,**
- **Since deviant marks survive cell divisions, the autism condition can persist a lifetime,**
- **Epigenetic etiology explains violation of genetics laws, in a condition that “runs in families”.**

The Promise of Epigenetic Therapies for Autism

- **Deviant epigenetic marks appear to be reversible.**
- **Future epigenetic therapies may represent the best therapies for children and adults diagnosed with autism.**
- **Early epigenetic testing and treatment may enable autism prevention.**

Potential Epigenetic Therapies

1. Promotion of methylase enzymes and suppression of demethylases,
2. Promotion of deacetylases and suppression of acetylases,
3. Normalization of S_AMe and acetyl CoA levels,
4. Ultimate solution; Normalization of deviant gene expression bookmarks.

A Warning Regarding Risperdal

- Risperdal is a schizophrenia drug that can produce improved behavior in ASD children, and is frequently prescribed by mainstream doctors.
- Recent studies indicate that Risperdal (and Abilify) gradually shrink the cortex area of the brain.
- Ho, et al. Arch Gen Psych, 68:2

Experimental Finding

Cortical volume shrinkage is proportional to Risperdal dosage, and duration of treatment.

Conclusion: Risperdal therapy is difficult to justify, especially during early brain development.

Over his impressive career, Dr. Walsh has worked with 30,000 patients with conditions ranging from autism to schizophrenia to Alzheimer's. His book is an essential tool for anyone who would prefer to heal the brain with nutrients rather than drugs.

Teri Arranga, editor-in-chief, *Autism Science Digest*

NUTRIENT POWER

HEAL YOUR BIOCHEMISTRY
AND HEAL YOUR BRAIN



WILLIAM J. WALSH, PhD

Thank You!



Bill Walsh, PhD
Walsh Research Institute
Naperville, Illinois

www.walshinstitute.org