METHYLATION, EPIGENETICS, AND MENTAL HEALTH

William J. Walsh, PhD Walsh Research Institute

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Walsh Research Institute Naperville, Illinois

- 501c3 Public Charity
- Expertise in behavior disorders, ADHD, autism, depression, schizophrenia, bipolar disorder, and Alzheimers
- International Physician-Training Program
- Research

Clinical Experience

William J. Walsh, Ph.D.

- 10,000 Behavior
- 5,600 ADHD
- 3,500 Schizophrenia & Bipolar
- 3,200 Depression
- 6,500 Autism

Massive Chemistry Database

- Laboratory testing of 30,000 mental health patients and controls.
- More than 3 million chemical test results for patients diagnosed with schizophrenia, depression, ADHD, depression, autism, etc.

More than 2 million medical history factors for these populations.

Database Findings

Striking blood/urine chemistry differences between mental illness populations and the rest of society.

Walsh WJ (2012). *Nutrient Power.* Skyhorse Publishing, New York, NY. Crayton JW, Walsh WJ (2007). J Trace Elements Med Biol.21:17-21.

High-Incidence Imbalances in Mental Disorders

Methylation Disorder

Zinc Deficiency

Copper Overload

Folate Deficiency or Overload

Pyrrole Disorder

Toxic-Metal Overload

EPA, DHA, and/or AA Deficiency

These factors have a powerful impact on synthesis of neurotransmitters and regulation of receptor activity.

Individualized Nutrient Therapy

Medical history and review of symptoms,

Special blood/urine lab tests,

- Diagnosis of chemical imbalances,
- Prescribed nutrient program aimed at normalizing brain chemistry.

Reports of Significant Improvement

ADHD: 74%

Behavior: 82%

Anxiety: 75%

Depression: 85%

Bipolar Disorder: 65%

Schizophrenia: 70%

Based on open-label outcome studies

Recent Advances in Understanding of Brain Disorders

Epigenetics

Methylation Processes

New Capability in Nutrient Therapy

Regulation of enzyme gene expression,

Control of serotonin & dopamine reuptake,

Improved antioxidant protection in the brain,

Promising treatments for addiction disorders.

"I did then what I knew how to do. Now that I know better, I do better."

Maya Angelou

Methylation and Brain Disorders

 Methylation status has been determined for 30,000 patients over a 30 year period,

 Most persons diagnosed with mental disorders exhibit a serious methylation imbalance,

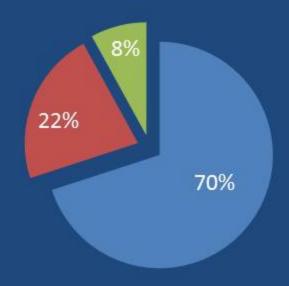
 Accurate diagnosis of methylation status is essential to effective treatment.

Methylation and Mental Health

- Methylation is a dominant factor in epigenetic processes that regulate NT activity at serotonin and dopamine receptors,
- The methyl/folate ratio has a powerful impact on gene expression of reuptake transport proteins,
- More than 60% of anxiety, depression and psychosis patients exhibit a serious methylation imbalance.

Incidence of Methylation Disorders in the General Population





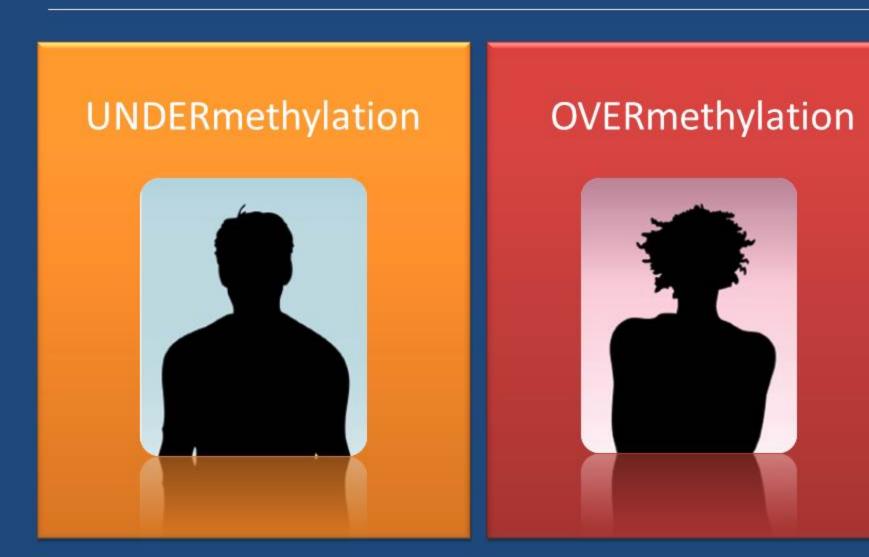
Normal Methylation = 70%

Under Methylation = 22%

Over Methylation = 8%



Methylation Disorders – Two Types



Incidence of UNDERmethylation

Autism-Spectrum	98%
Antisocial Personality Disorder	95%
Schizoaffective Disorder	90%
Oppositional-Defiance	85%
Anorexia	82%
Depression	38%

Incidence of OVERmethylation

Panic/Anxiety Attacks	64%
Paranoid Schizophrenia	52 %
ADHD	28%

Behavior Disorders 23%

Depression 18%

Primary Causes of UNDERmethylation

1. Enzyme Mutations (SNPs) in Methylation Cycle MTHFR, MS, BHMT, MAT, SAHH, etc...

2. Histamine Overload

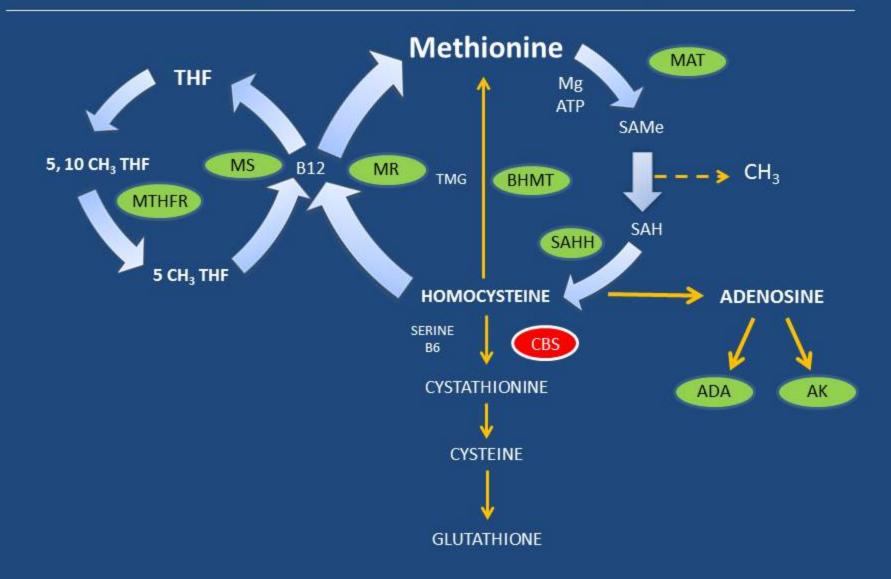
3. Protein Deficiency or Malabsorption

Methyl Donation

SAMe



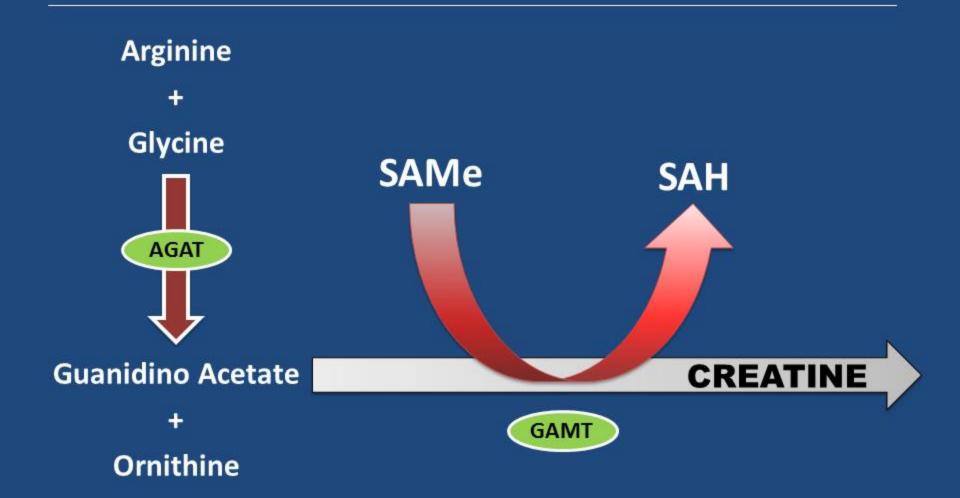
Methylation Cycle Enzymes



SAMe Utilization



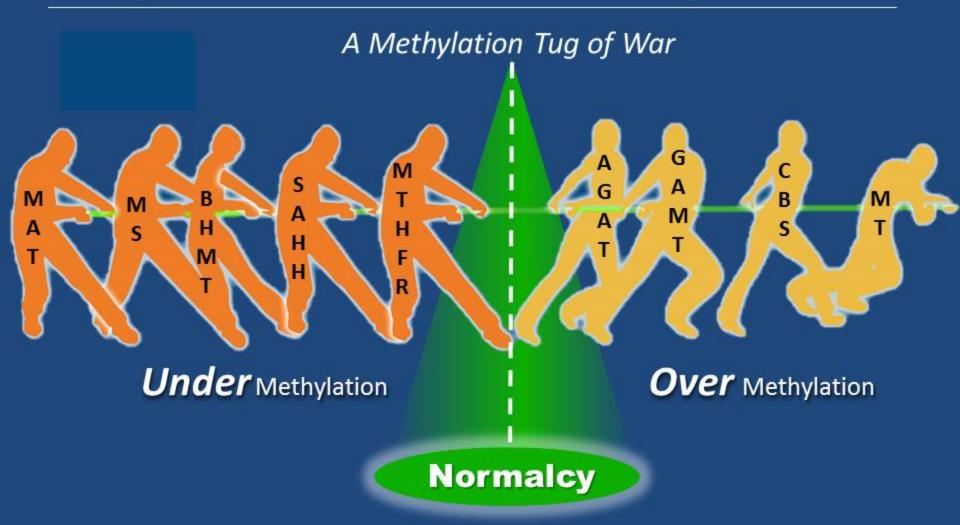
Creatine Synthesis



Primary Causes of OVERmethylation

- 1. Impaired Creatine Synthesis
 - AGAT or GAMT SNP's
 - Arginine or Glycine Deficiency
- Impaired Cystathionine Synthesis (CBS SNP)
- 3. Methyltransferase SNPs

Enzyme Mutations and Methylation



Lab Tests for Methylation Status

- 1. SAMe/SAH Ratio (limited availability)
- 2. Whole-blood histamine (methylation marker)

Note: Present genetic tests (MTHFR, etc.) cannot determine *net effect* of SNPs that enhance/depress methylation

Under Methylation: Symptoms & Traits

Partial List

- Very strong willed; oppositional to authority
- Seasonal inhalant allergies
- Competitive in sports or games
- Calm demeanor but high inner tension
- High fluidity (tears, saliva, etc.)
- OCD tendencies; controlling behavior
- Good response to SSRI's
- High libido

Over Methylation: Symptoms & Traits

Partial List

- High anxiety; panic tendency
- Hyperactivity; nervous legs; pacing
- Sleep disorder
- Low libido
- Absence of seasonal allergies
- Food, chemical sensitivities
- Dry eyes and mouth
- Excellent socialization, empathy
- Non-competitiveness in sports, academics
- Adverse reaction to SSRIs, anti-histamines

ENZYME SNPs

- More likely in very-large enzymes,
- Most SNPs have little or no effect on enzyme function,

 Some strategically-placed SNPs significantly weaken enzyme function (MTHFR 677T etc).

Impact of a SNP varies from person to person.

Single Nucleotide Polymorphisms

We share 99.9% of our DNA with everyone of the same gender -- It's the 0.1% that makes us different.

- SNPs are gene mutations that developed over thousands of years.
- More than 10 million SNPs have been identified in the human genome. Most humans have more than 1,000 SNPs.

Epigenetics

- >20,000 genes in every cell's DNA, each capable of producing a specific protein,
- Liver, skin, brain, and other tissues require a unique combination of proteins,
- During pregnancy, chemical "bookmarks" attach to DNA to enhance or inhibit gene expression in each tissue,
- Environmental insults at any age can alter gene bookmarks and produce mental disorders and other disease conditions.

Two Epigenetic Processes

1. DNA Methylation (established in the womb)

2. Histone Modification

DNA Methylation

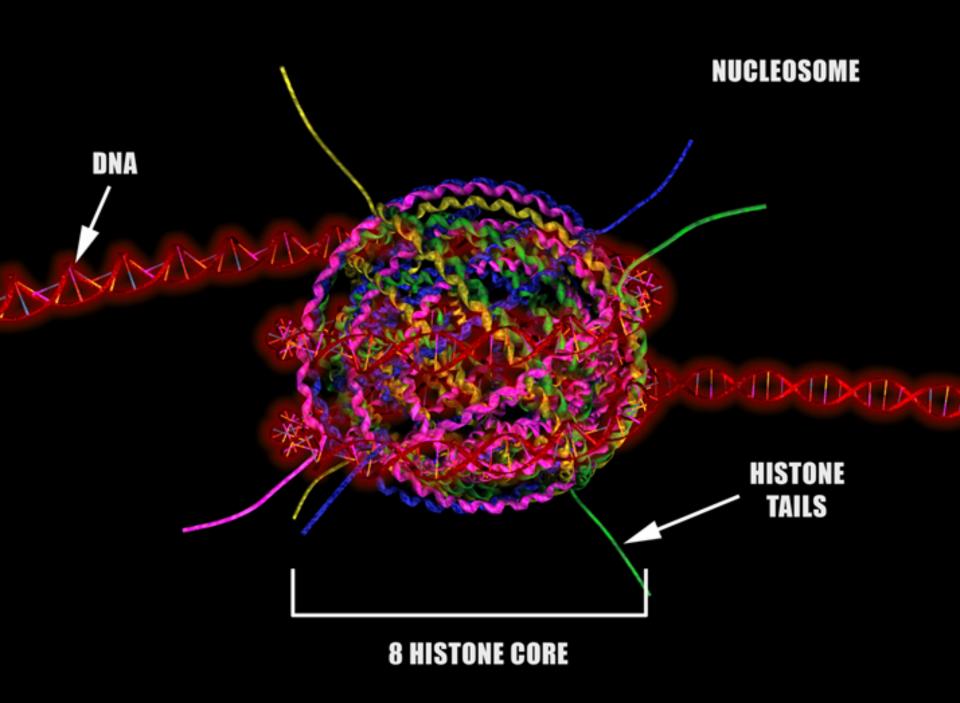
- Established in the womb,
- Methylation of cytosine at promoter CpG island clusters can reduce expression (protein production) for the corresponding gene. These methyl "bookmarks" usually remain in place throughout a lifetime,
- In-utero environmental insults can produce deviant bookmarks & serious disorders or birth defects,
- Throughout life, a severe environmental insult may alter one or more gene-regulation marks and produce an epigenetic disorder such as cancer or a mental illness.



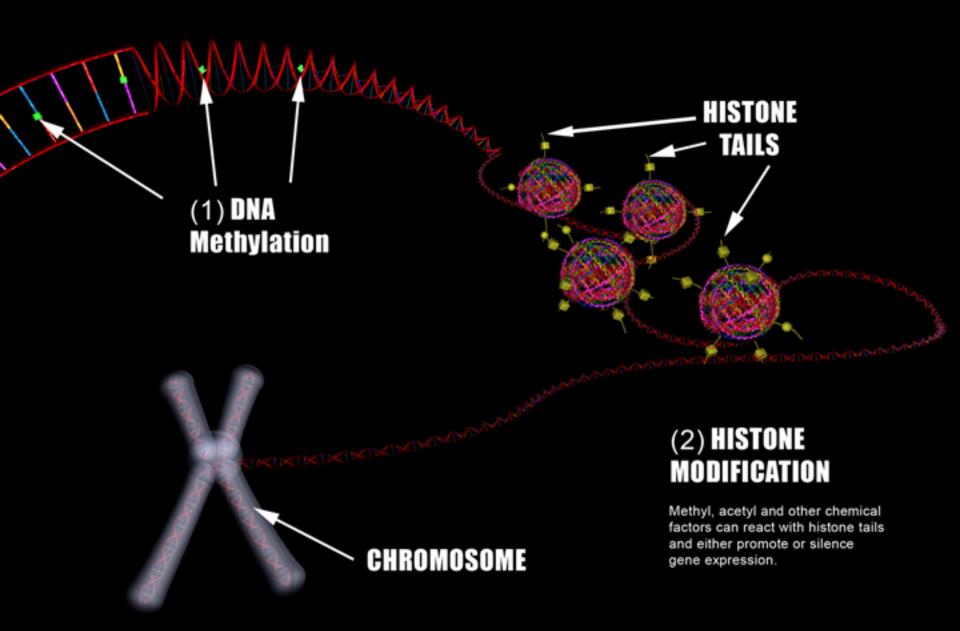
DNA Methylation

Histones – Support Structures for the Fragile DNA

- 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 or promote gene expression depending on chemical reactions at histone tails.
- Nutrient therapies can modify histones that control reuptake of serotonin, dopamine, and other NTs.



The Two Main Components of the Epigenetic Code



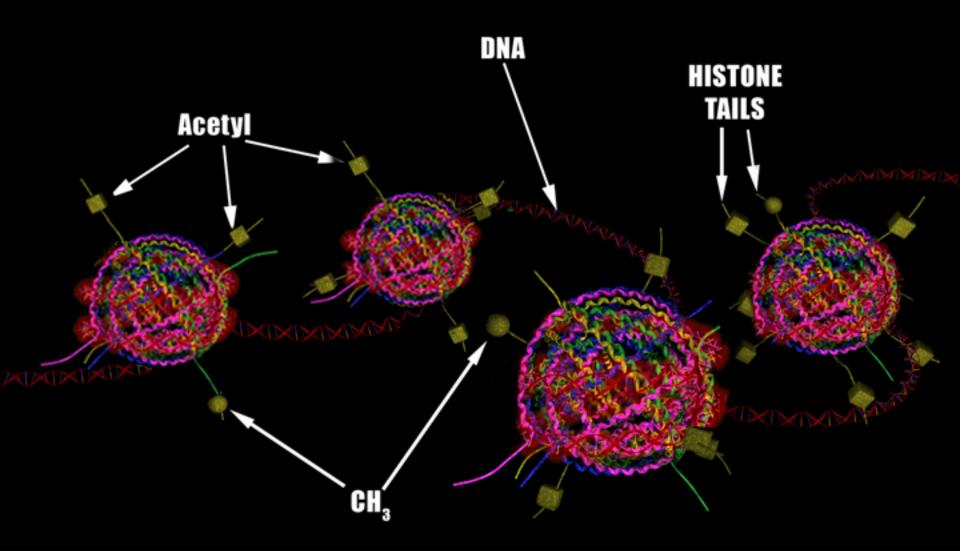
Methyl-Acetyl Competition

- Competition between acetyl and methyl groups often determines whether genes are expressed or silenced,
- Histone acetylation promotes gene expression,
- Histone methylation inhibits expression,
- Nutrient therapy can change methyl/acetyl ratios and adjust production of proteins & enzymes that control serotonin and dopamine neurotransmission rates.

Gene Expression Requires Uncoiling of DNA

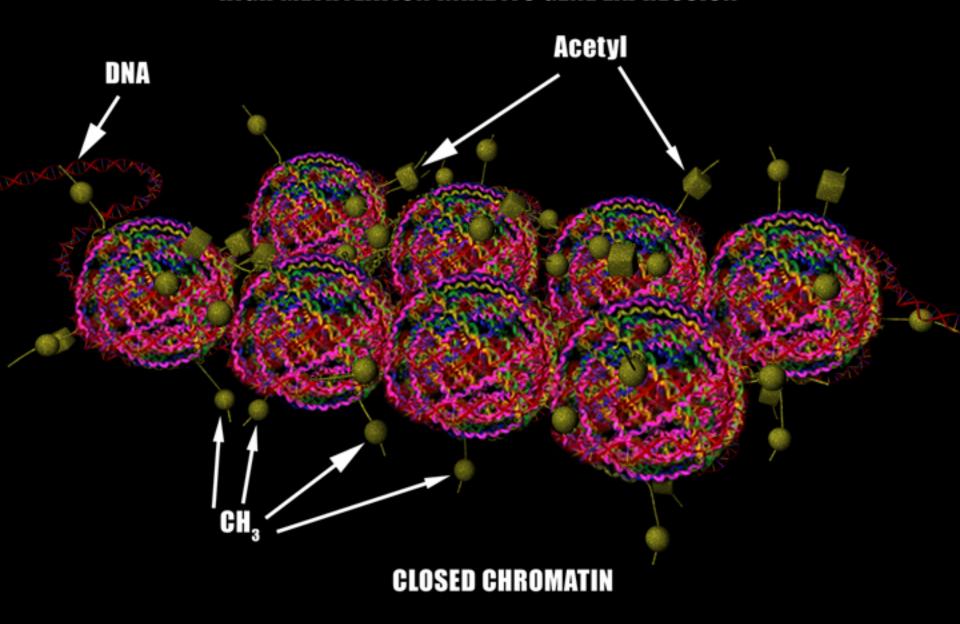
- Gene expression involves direct interaction of RNA polymerase and transcription factors with DNA. These large molecules cannot gain access to DNA/histone regions that are densely compacted,
- The gentle attachment of DNA to histones involves electrostatic attraction – DNA is a weak acid and histones are strong bases (pH above 7),
- Acetylation decreases histone pH, causing uncoiling of DNA; methylation increases histone pH, increasing DNA/histone compaction.

LOW METHYLATION PROMOTES GENE EXPRESSION



OPEN CHROMATIN

HIGH METHYLATION INHIBITS GENE EXPRESSION



Reuptake Transport Proteins

- Primary determinant of neurotransmitter activity at serotonin & dopamine receptors – brain concentrations of serotonin and dopamine are less important,
- Transmembrane proteins that remove neurotransmitters from the synapse (reuptake) like a vacuum cleaner inhaling dust particles,
- Formed by gene expression: amount present depends on methyl/acetyl competition at specific DNA regions.

Enzymes Dominate the Methyl-Acetyl Competition

- Acetyl-Coenzyme A and SAMe are the donors of acetyl and methyl, respectively – but their concentrations in brain cells are relatively unimportant.
- Acetylases, deacetylases, methylases and demethylases dominate attachment or removal of acetyl or methyl groups.
- Epigenetic nutrient therapy for adjustment of serotonin or dopamine activity concentrates on the enzymes.
- Example: B-3 inactivates a major deacetylase inhibitor, increasing expression of DAT transporters thus reducing dopamine neurotransmission.

Epigenetic Complications

Approximately 76 different histone proteins,

About 2,600 transcription factors,

■ More than 1,000 miRNA molecules.

FOLATES REDUCE NT ACTIVITY

- Folic Acid, folinic acid, and L-methylfolate are effective methylating agents.
- However, folates also increase gene expression of SERT transport proteins, resulting in reduced serotonin neurotransmission.

Most undermethylated depressives with lowserotonin activity are intolerant to folates.

Epigenetic Insights Into Nutrient Therapy

- Niacin & niacinamide act as dopamine reuptake promoters,
- Methionine and SAMe are serotonin reuptake inhibitors,
- Folates reduce synaptic activity at serotonin, dopamine, and norepinephrine receptors,
- Zinc and glutathione increase NMDA activity,
- Many nutrients influence neurotransmitter activity and brain function.

Undermethylated Depression Nutrient Therapy Example

- Enhance methylation and suppress acetylation of histones,
- SAMe and methionine act as serotonin reuptake inhibitors – reduced gene expression of SERT,
- Avoidance of folate supplements,
- Augmenting nutrients zinc, serine, inositol, TMG,
 Cal/Mag, Vitamins A, B-6, C, D, E.

Overmethylated Schizophrenia Nutrient Therapy Example

- Support acetylation of histones with folic acid and niacinamide (powerful deacetylase inhibitors).
- Augmenting nutrients DMAE, zinc, selenium, chromium,
 Vitamins B-6, B-12, C, D, E.
- Especially promising for paranoid schizophrenics with excessive dopamine activity.



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.

A Clue From Cancer Research

Severe oxidative stress can alter established DNA bookmark patterns, initiating a cancer condition,

The mechanism usually involves introduction of unwanted methylation at CpG island sites that silences a cancer-protective gene,

Oxidative stress may be a central factor in epigenetic mental disorders.

Oxidative Stress What Can Go Wrong?

 Some persons are born with low levels of natural antioxidants glutathione, MT, etc.

 Illnesses, injuries, and emotional trauma can increase oxidative stress.

 Exposure to toxic metals, pesticides, and industrial pollutants increases oxidative stress.

The Three Musketeers of Antioxidant Protection in the Brain

Glutathione: First line of defense,

Metallothionein: Nature's back-up system,

Selenium: Speeds up the process.

Apparent Epigenetic Gene-Regulation Disorders

- Cancer
- Heart Disease
- Schizophrenia
- Autism
- PTSD
- Wilson's Disease
- Bipolar Disorder
- Alzheimer's Disease

Characteristics of an Epigenetic Disorder

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

The Good News of Epigenetic Disorders

 Genetic Disorders: After decades of research, very little progress in development of genetic therapies.

 Epigenetic Disorders: Altering deviant DNA bookmark patterns has been achieved in early cancer research.

A Look at the Future

- Identification of misbehaving genes in cancer, autism, schizophrenia, and other epigenetic disorders will be achieved in the near future. Therapies to normalize deviant gene expression will eventually be developed.
- Epigenetic therapies of the future may enable a cure for persons who develop these disorders.
- Future newborn babies may be screened for epigenetic errors and receive treatment to prevent these disorders.

Summary

- Methylation imbalances play a critical role in most mental disorders,
- Autism, schizophrenia, PST, and several other mental illnesses appear to be epigenetic in nature,
- Epigenetic science is providing a roadmap for advanced nutrient therapies that can benefit patients challenged by these disorders,

THANK YOU!

William J. Walsh, PhD

Walsh Research Institute www.walshinstitute.org

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