

# BIOCHEMICAL IMBALANCES IN MENTAL HEALTH POPULATIONS

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

# Walsh Research Institute

- **Public Charity**
- **Expertise in Biochemistry & Nutrient Therapy**
- **Brain Research**
- **Clinical Development**
- **Book Project**
- **International Physician Training**

# Dublin Conference Topics



1. Biochemical Imbalances in Mental Health Populations
2. Epigenetics and Mental Health
3. Schizophrenia
4. Depression
5. Autism Spectrum Disorders
6. Behavioural Disorders and ADHD

# Nutrient Therapy Pioneers

---

**Roger Williams:** Concept of biochemical individuality.

**Abram Hoffer:** First clear demonstration of the power of nutrient therapy.

**Carl Pfeiffer:** Chemical classification of schizophrenia.

# Clinical Experience

William J. Walsh, Ph.D.

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

# Chemistry Database

- About 90 to 150 assays of chemical factors in blood, urine, or tissues for each of 25,000 patients,
- More than 2.5 million chemical test results,
- Comparison with known “normal” levels.

# Database Findings



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

# High-Incidence Chemical Imbalances in Mental Disorders

- Zinc Deficiency
- Copper Overload
- Methylation Disorder
- Folate Deficiency
- Pyrrole Disorder
- B-6 Deficiency
- Toxic metal Overload
- Oxidative Stress



# Some imbalances are present in diverse mental disorders:

**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



**Question:** Why are these biochemical abnormalities seen in so many mental disorders?

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

# Frequently Asked Questions From Medical Professionals

---

1. How could vitamins & minerals 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

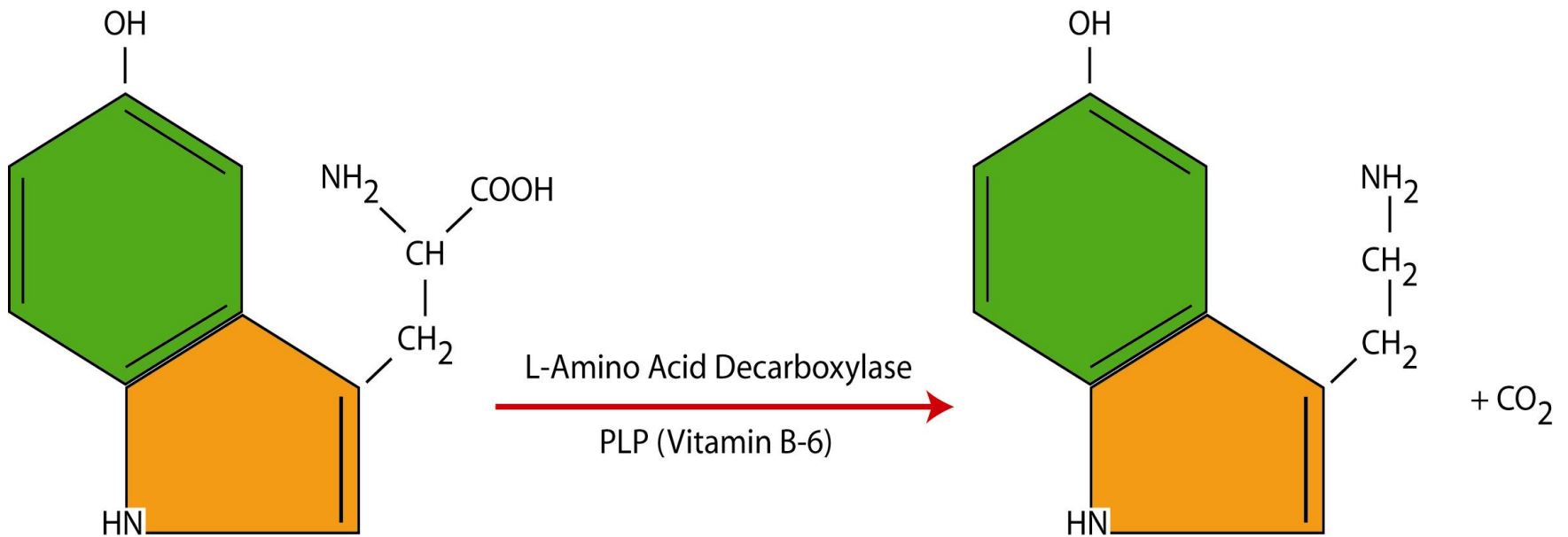
---

- Serotonin, dopamine, and other NT's are synthesized in the brain.
- The raw materials for NT synthesis are nutrients: vitamins, minerals, and amino acids.
- A genetic or epigenetic imbalance in a nutrient needed for NT synthesis can result in serious brain chemistry problems.

# Nutrient Imbalances Impact NT's

- Serotonin synthesis requires B-6,
- Norepinephrine is  $\text{Cu}^{++}$  dependent,
- GABA synthesis and regulation requires Zn and B-6,
- Dopamine, norepinephrine, serotonin activities are impacted by methyl and folate.

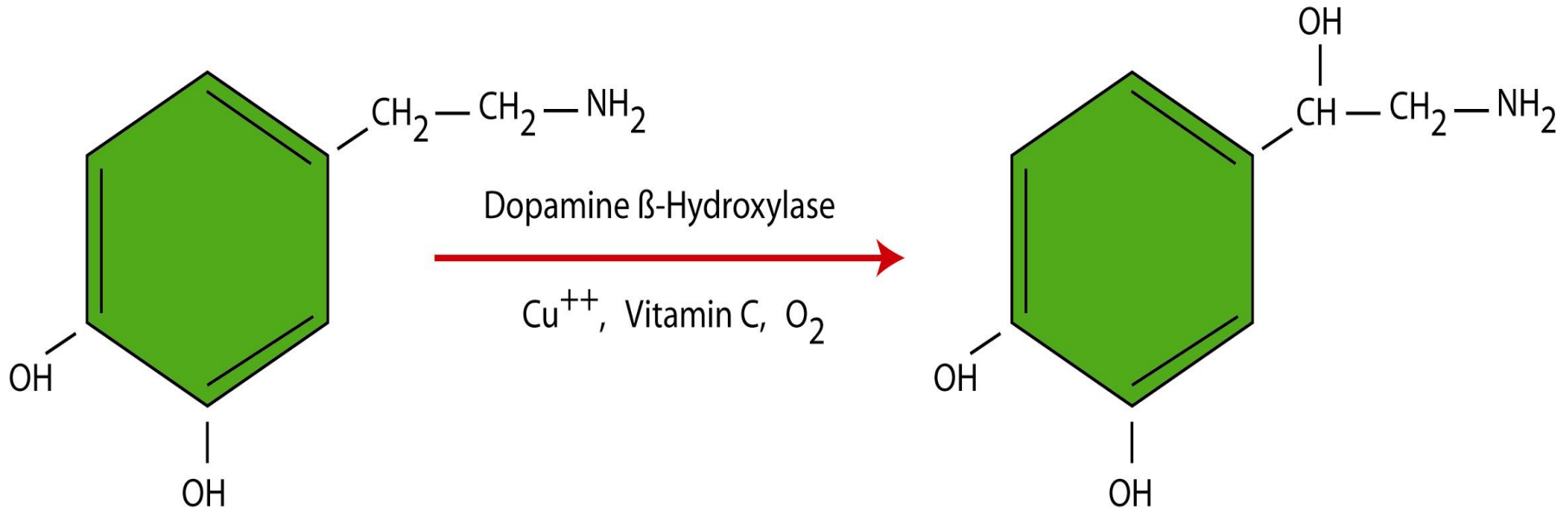
# Serotonin Synthesis



**5-HYDROXYTRYPTOPHAN**

**SEROTONIN**

# Norepinephrine Synthesis



**DOPAMINE**

**NOREPINEPHRINE**

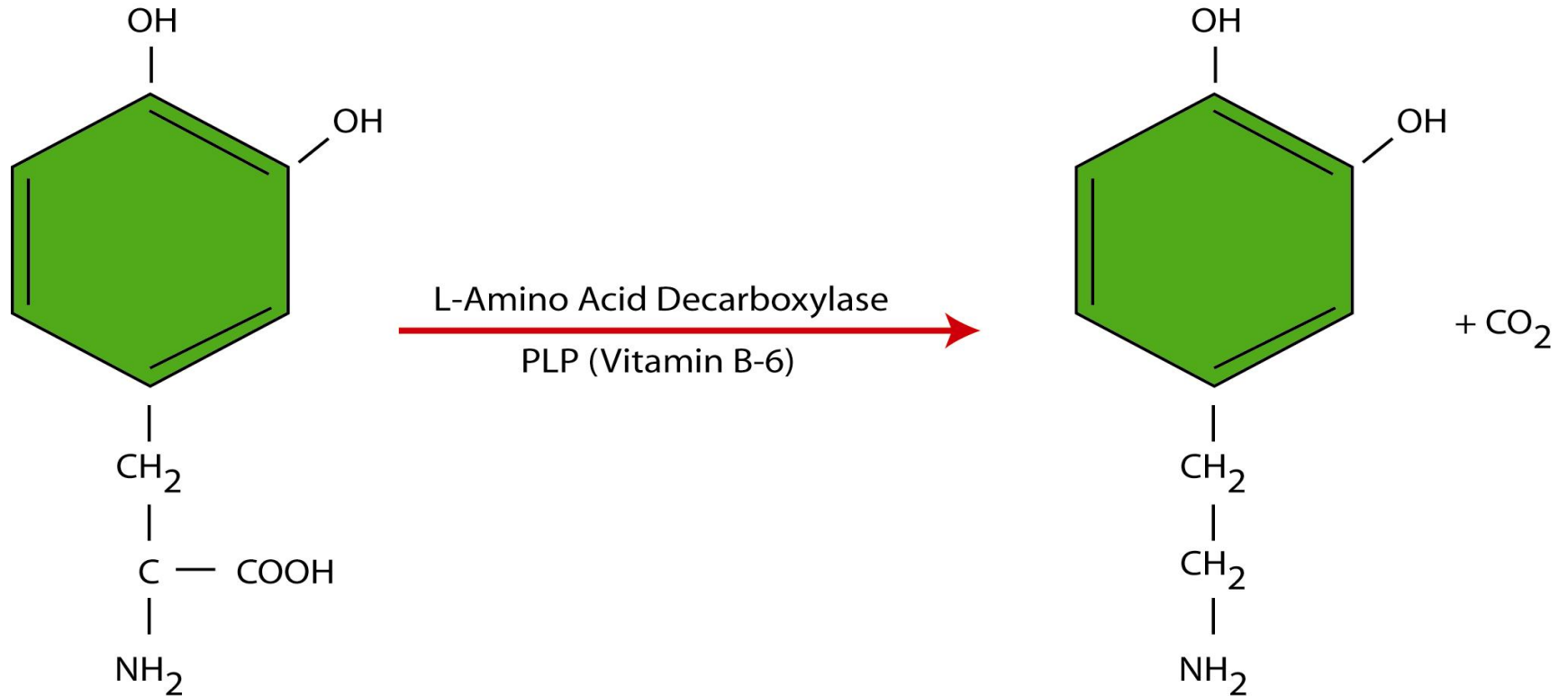
# Animal Studies – Impact of Cu Level on Dopamine and Norepinephrine

- 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.***



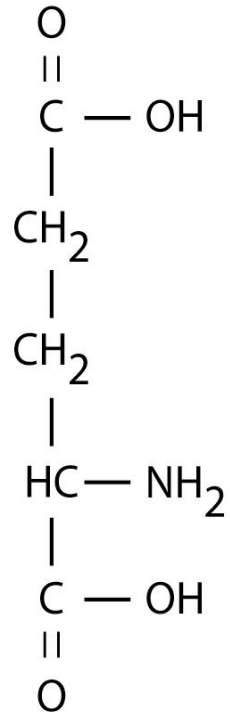
# Dopamine Synthesis



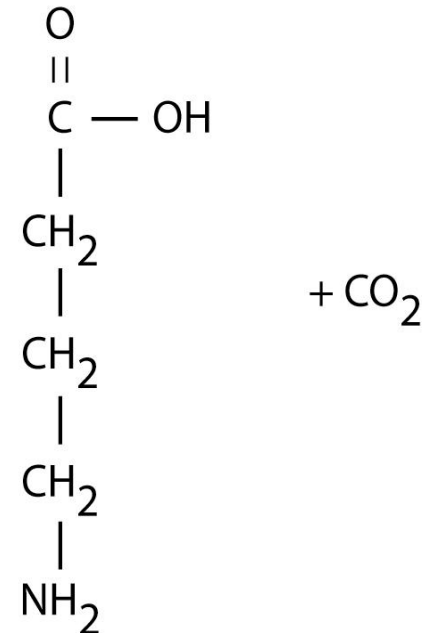
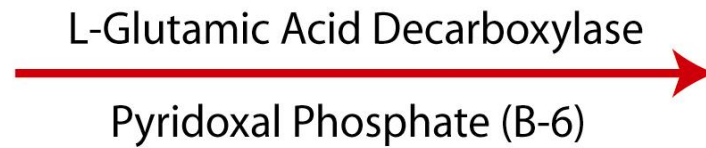
**L-DOPA**

**DOPAMINE**

# GABA Synthesis



**GLUTAMIC ACID**



**GABA**

# Zn Deficiency and Brain Function

- 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.

# Cu Overload and Zn Deficiency

## A Double Disaster!

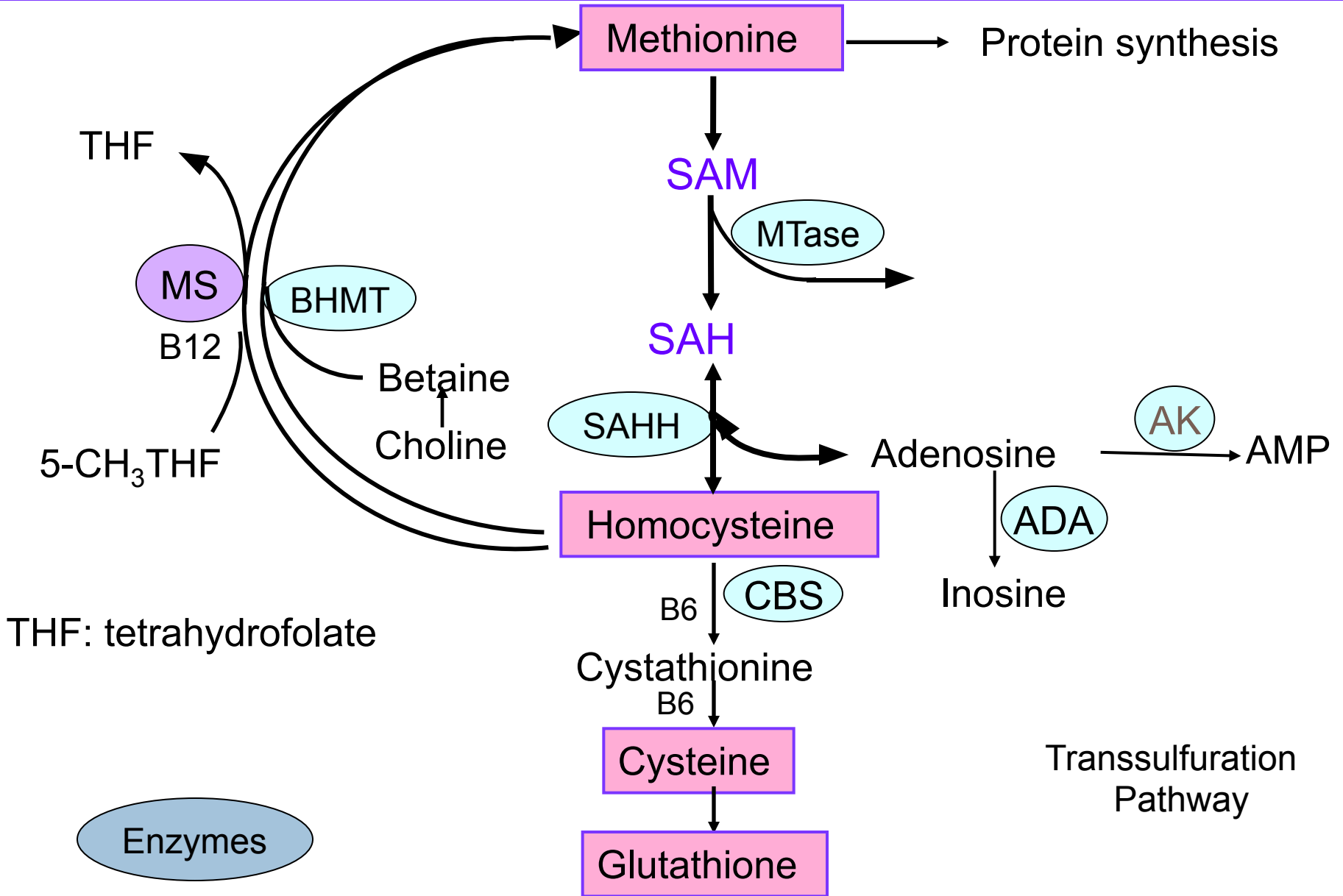
1. Elevated Cu increases norepinephrine levels,
2. Zn-dependent metallothionein proteins unable to eliminate Cu overload,
3. Reduced GABA in brain magnifies symptoms of norepinephrine overload.

**Elevated Cu/Zn ratios have been associated with violent behavior, anxiety attacks, autism, post-partum depression, and schizophrenia.**

# Methylation Disorders

- Methyl is a dominant factor in epigenetic processes,
- Methyl has a powerful impact on neurotransmitter activity at synapses,
- About 70% of mentally-ill persons exhibit a methylation disorder,
- > 95% of autistics are undermethylated.

# METHYLATION CYCLE



# Pyrrole Disorder

- Double deficiency of B-6 and Zinc
- Depletion of Serotonin, Dopamine, GABA
- Depletion of GSH, MT, Cys, SOD, Catalase
- Supplements of B-6 and Zinc can normalize pyrrole levels, often resulting in elimination of symptoms and the need for psychiatric medication.

# Biochemical Individuality



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



# Biochemical Balancing

- Genetic nutrient deficiency may require many times the RDA to achieve normalization.
- Genetic overloads may require biochemical therapy to eliminate the nutrient excess.
- Multiple vitamins are rarely effective.

# Common Nutrient Deficiencies that Impact Brain Function

- Zinc
- Methionine
- Folic Acid
- Vitamins B-6 and B-12
- Niacin/Niacinamide
- DHA, EPA, AA (essential fatty acids)
- Antioxidants: Se, GSH, Vitamins C & E, etc.
- Chromium

# Common Overloads that Impact Brain Function

- Copper
- Folic Acid
- Iron
- Methyl groups
- Toxics: Lead, Mercury, Cadmium, etc.

# Nutrient Imbalances and Impaired Brain Function

- Altered production of serotonin, dopamine, GABA, and other NT's,
- Impaired regulation of NT activity at the synapse (epigenetics),
- Improper rates of NT metabolism (MAO, etc),
- Insufficient antioxidant protection,
- Myelin sheath abnormalities,
- Impaired BBB function.

# Individualized Nutrient Therapy

- 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

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

# Populations With Negative Outcomes Following Biochemical Therapy

---

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

# Summary

---

- 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.





# EPIGENETICS AND MENTAL HEALTH

..

# 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

# Gene Bookmarking

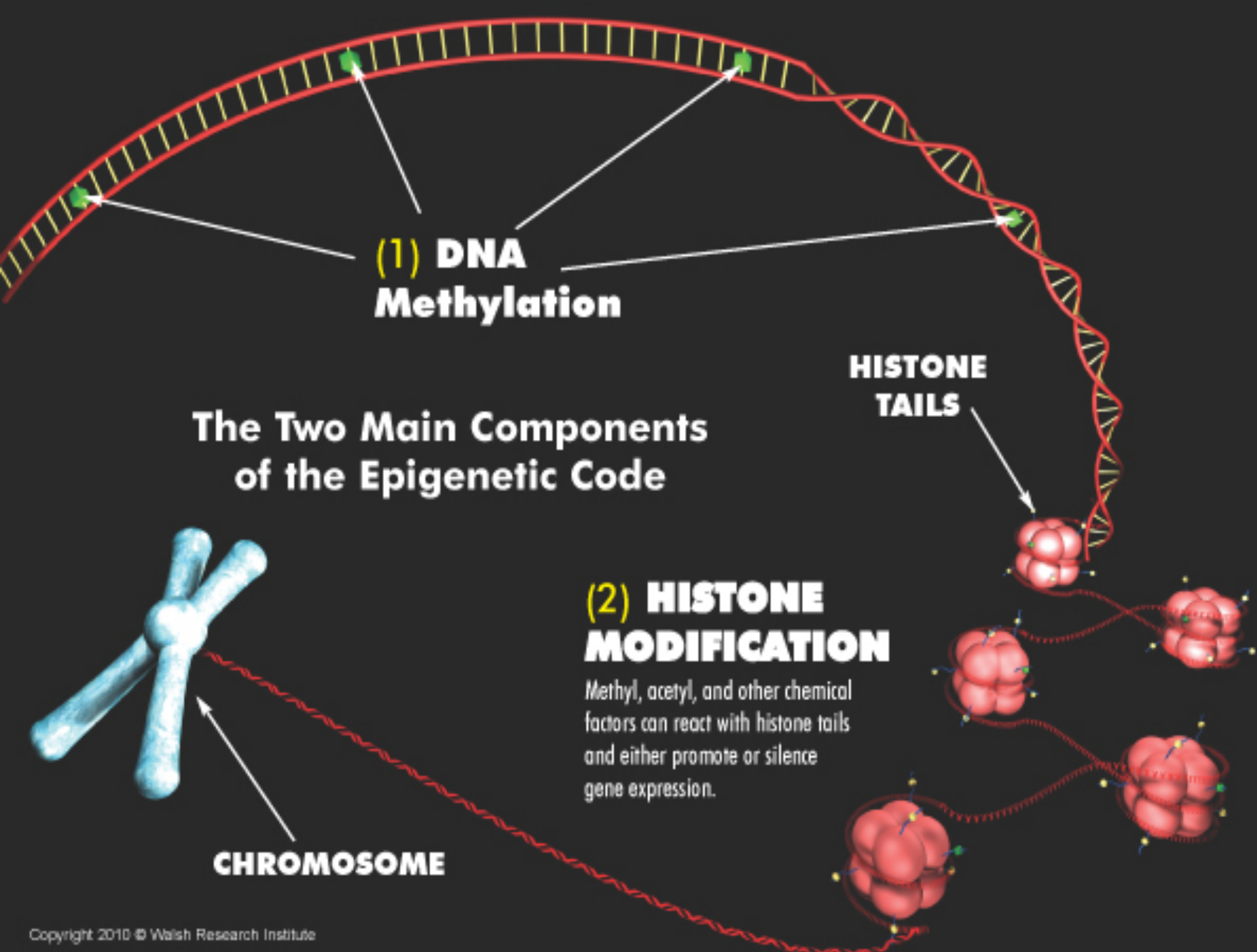
- >20,000 genes in every cell's DNA, each with potential for producing a specific protein,
- Liver, skin, brain, kidney, and other tissues require a unique combination of proteins,
- For each tissue, in-utero chemical environment determines which genes will be expressed or inhibited throughout life (bookmarking),
- Environmental insults or chemical imbalances can result in improper gene expression (epigenetics).

# Epigenetics

- 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

# DNA PACKAGING

- Each DNA double helix is nearly two meters long, and amazingly packaged into a tiny cell nucleus 10,000 times smaller in diameter.
- The fragile DNA is wrapped around a multitude of tiny proteins called “histones” to form chromatin.
- The chromatin is efficiently compressed into highly compacted chromosomes.



## The Two Main Components of the Epigenetic Code

**(1) DNA Methylation**

**HISTONE TAILS**

**(2) HISTONE MODIFICATION**

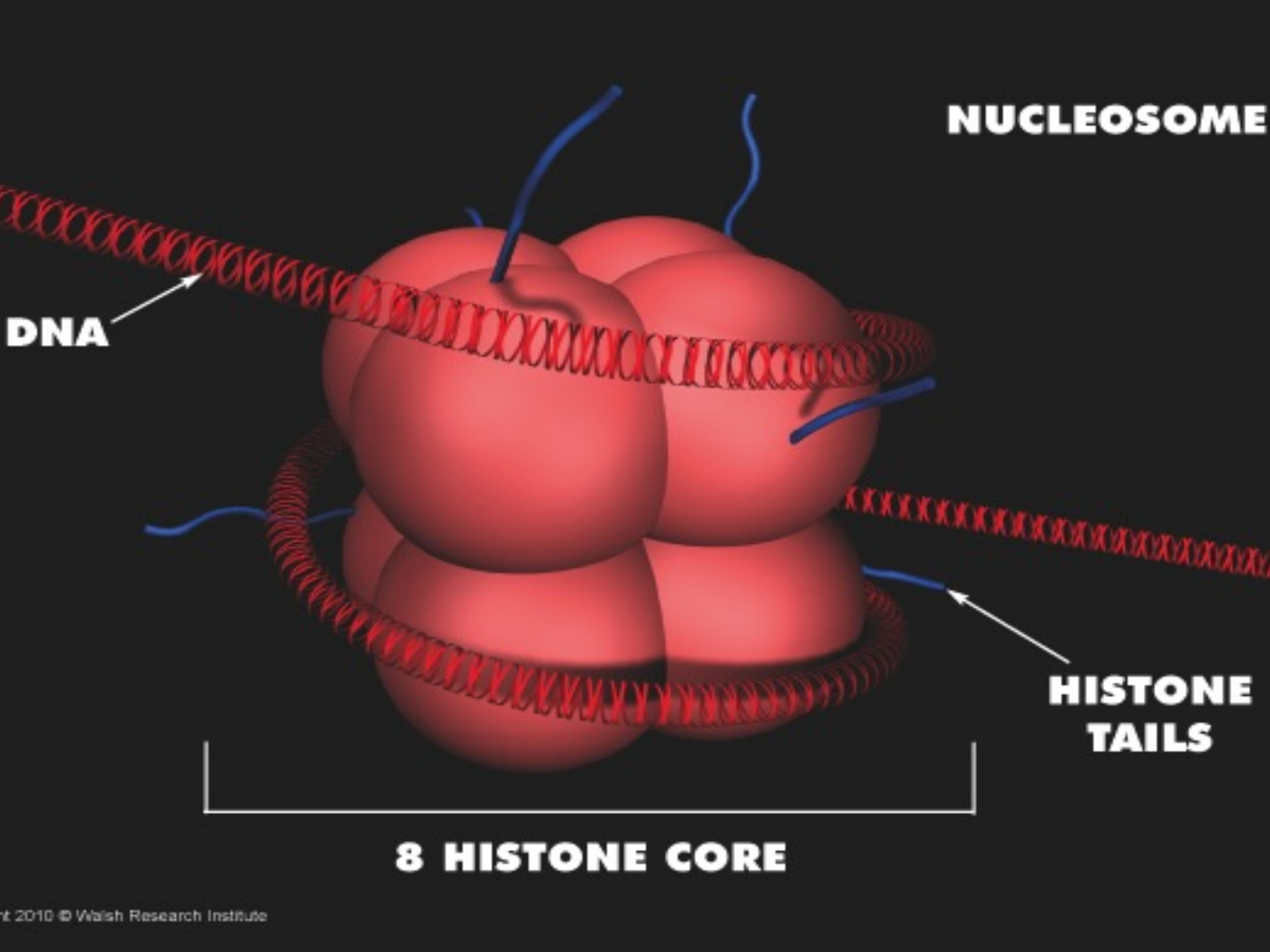
*Methyl, acetyl, and other chemical factors can react with histone tails and either promote or silence gene expression.*

**CHROMOSOME**

# DNA METHYLATION

- Essential process in human development,
- Selective methylation or non-methylation at a multitude of CpG islands along double helix,
- DNA methylation in the vicinity of a gene usually inhibits expression (protein production),
- DNA methylation code is under development and is leading to novel epigenetic therapies.





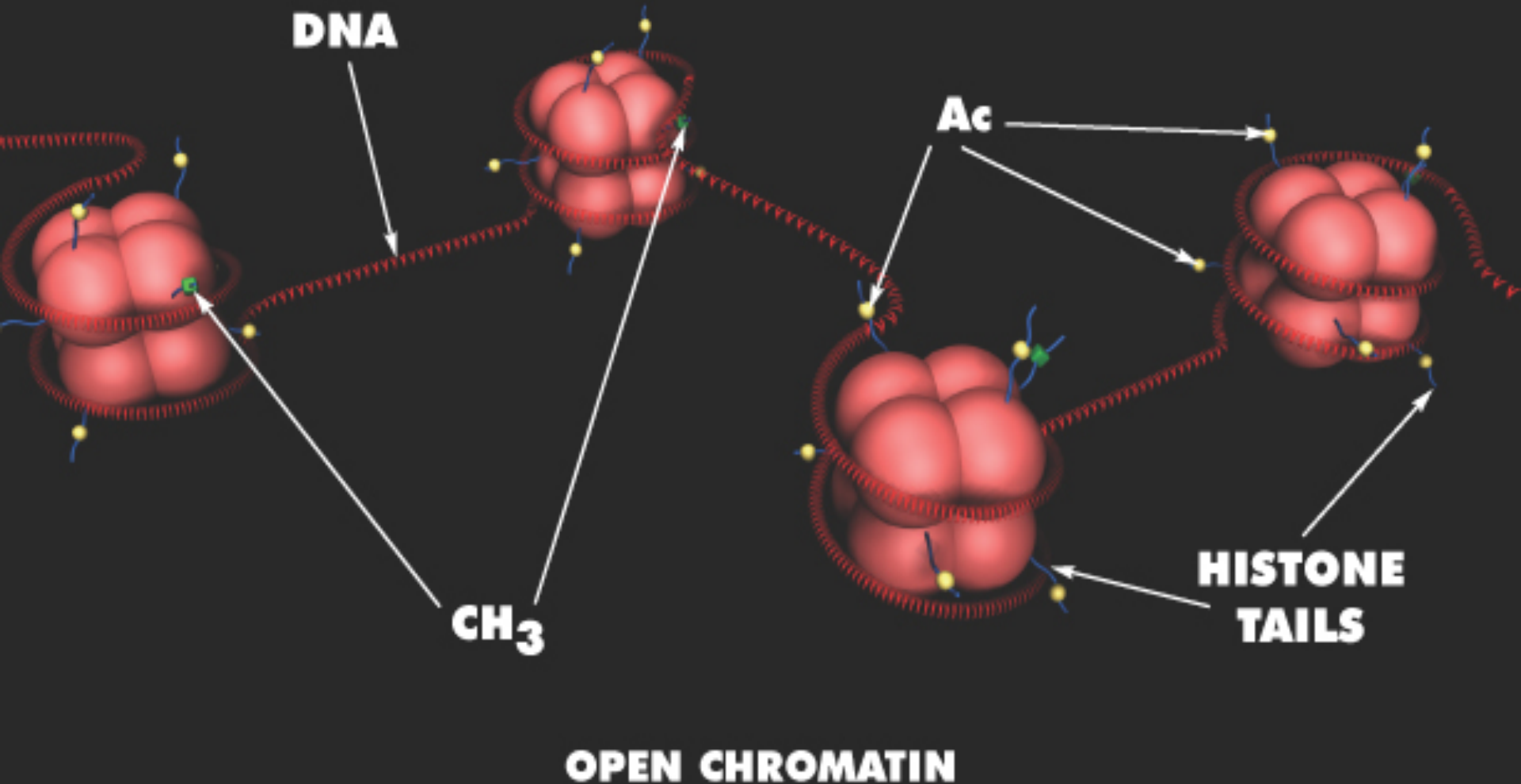
# Histones

- 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, that alter electrostatic attraction to DNA's double helix,
- Complex histone code under development.

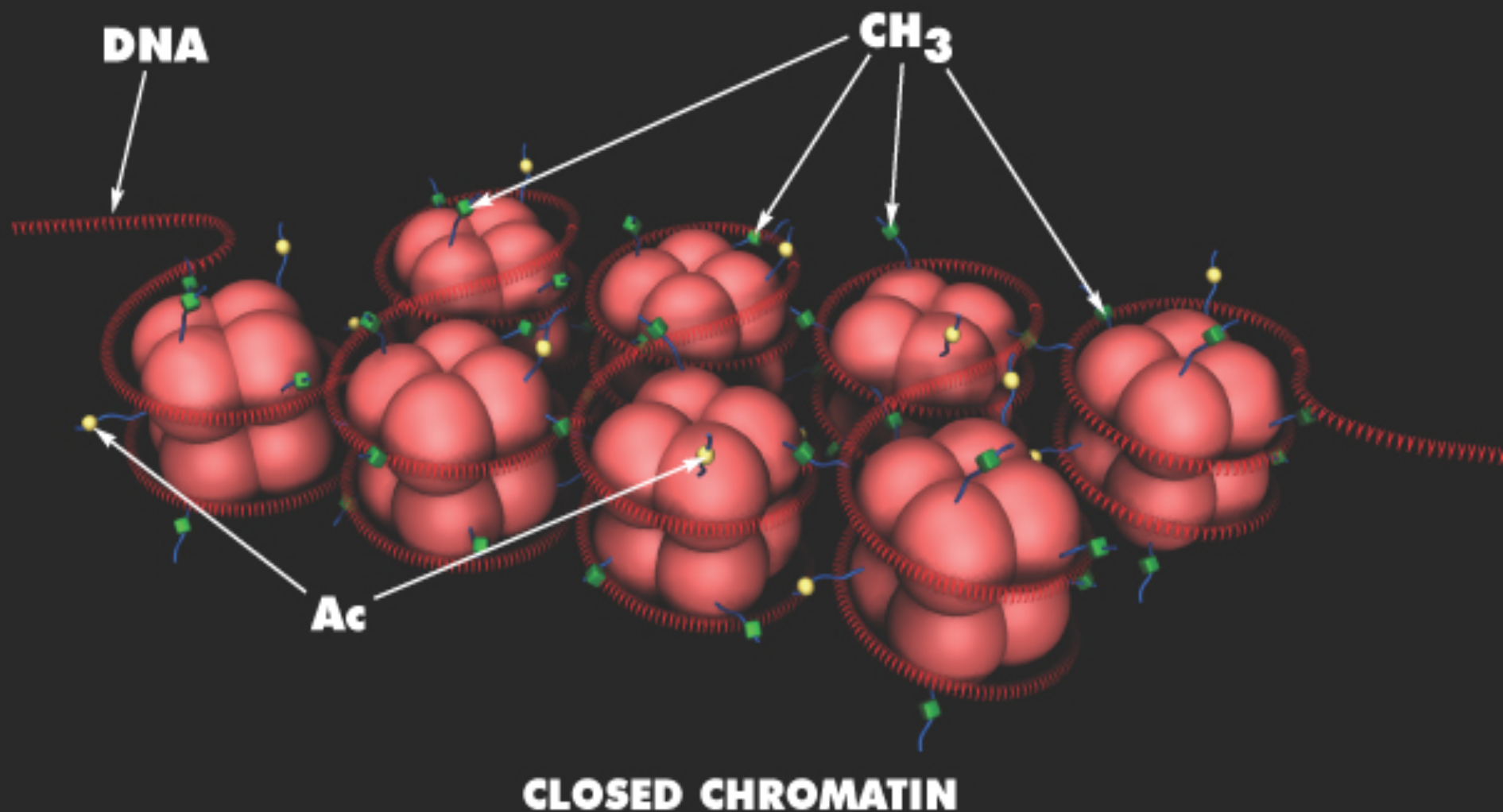
# Methyl-Acetyl Competition

- 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.

# LOW METHYLATION PROMOTES GENE EXPRESSION



# HIGH METHYLATION INHIBITS GENE EXPRESSION



# Histone Modification Complexity

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

# Epigenetic Therapies to Modify Gene Expression

- DNA methylation at specific CpG sites (example: silencing of a cancer gene).
- Acetylation at histone tails:
  - acetylases
  - deacetylases
- Methylation at histone tails:
  - methyltransferases
  - demethylases
- Other histone modifications.

# The Exciting Potential of Epigenetic Therapies

- A multitude of diseases and disorders appear to be epigenetic in nature,
- Researchers will eventually identify the specific gene expression errors for most of these conditions,
- Epigenetic therapy has potential for normalizing gene expression and curing many diseases.

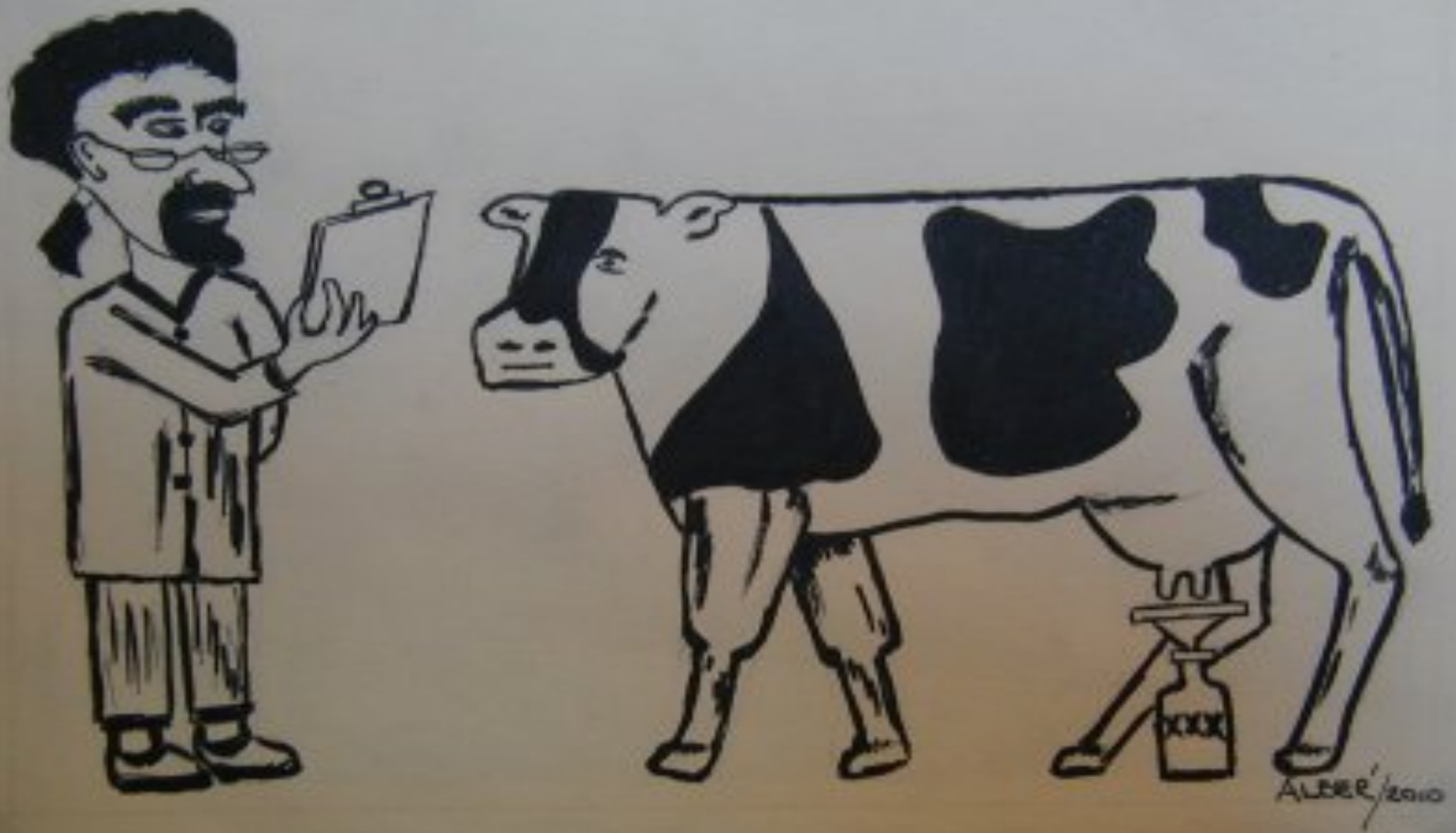


# “Epigenetics”

A Limerick by George Marino

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.**

# Major Epigenetic Impacts on Mental Functioning

- Disordered brain development caused by in-utero bookmarking errors,
- Altered expression of NT synthesis enzymes,
- Abnormal production of reuptake transporter proteins.

# Reuptake Transporter Proteins

- Transporters are transmembrane proteins that remove neurotransmitters from the synapse like a vacuum cleaner inhaling dust particles,
- Formed by gene expression: amount present depends on methyl/acetyl competition at histone tails,
- Dominant effect on neurotransmitter activity.

# Major Transporter Proteins

---

- SERT (Serotonin)
- DAT (Dopamine)
- NET (Norepinephrine)
- GAT (GABA)

# Epigenetics of NT Reuptake

1. SERT, DAT, NET, and GAT production is controlled by methyl/acetyl levels at histone tails,
2. SSRI antidepressants work by blocking the action of reuptake transporters,
3. Epigenetic therapies have potential for direct adjustment of reuptake, without the need for foreign molecules (drugs),
4. Epigenetic nutrient therapies have potential for overcoming depression without side effects.

# Example of Epigenetic Therapy: Low-Serotonin Depression

- Most modern antidepressants are selective serotonin reuptake inhibitors (SSRI's).
- Epigenetic errors can cause overproduction of SERT proteins and excessive reuptake.
- Reuptake can be normalized by methylation therapy and/or use of deacetylases to reduce the population of SERT proteins.

# Nutrients That Impact NT Reuptake



Methionine

SAMe

Folic Acid

Niacinamide

CoEnzyme A

Choline



# Epigenetic Insights Into Nutrient Therapy

- Niacin & niacinamide act as dopamine reuptake promoters,
- Methionine and S-adenosylmethionine (SAMe) are serotonin reuptake inhibitors,
- Foliates reduce synaptic activity at serotonin, dopamine, and norepinephrine receptors,
- Undermethylated mental illness patients are intolerant to folic acid,
- Acetyl groups, biotin, and coenzyme A influence gene expression/inhibition.

# Epigenetic Errors May be Passed On To Future Generations

- Gene expression errors can be transmitted to future generations by a process called transgenerational epigenetic inheritance (TEI).
- The harm from environmental poisons or other insults may be inherited by the next 2 to 3 generations.
- This may explain why several heritable disorders violate the classical laws of genetics.

# SUMMARY

---

- The emerging field of epigenetics will soon revolutionize treatment of mental illness and other medical conditions.
- Epigenetics is providing a roadmap for greatly-improved nutrient therapies.



# SCHIZOPHRENIA



# Schizophrenia

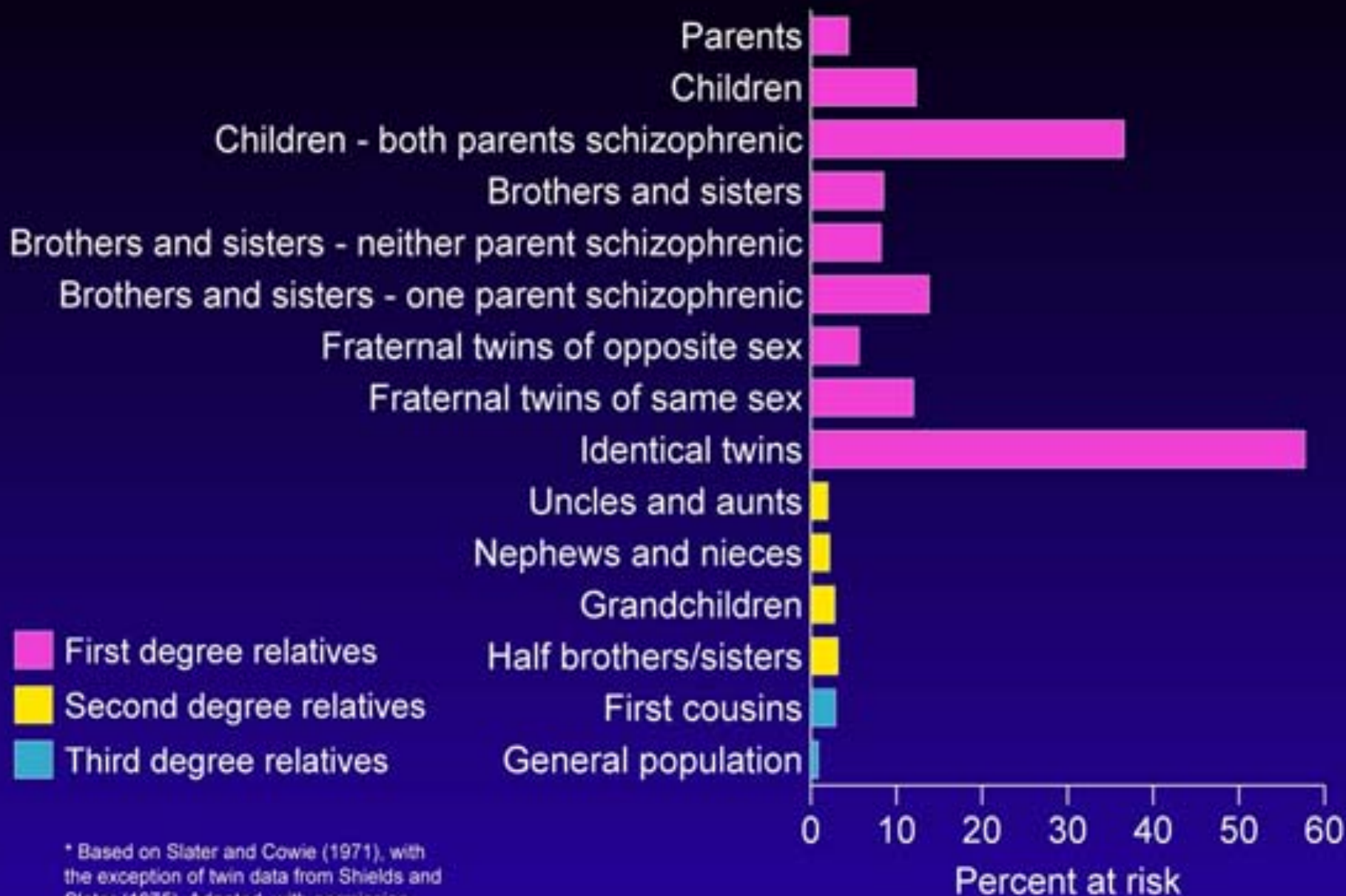
- Incidence: 1% of World Population
- Inherited Predisposition: > 50% Concordance in Identical Twins
- Typical Onset Between 15-26 yrs
- Higher incidence in northern Scandinavia and western Ireland

# Defining Characteristic = Psychosis

---

- Auditory hallucinations
- Visual/tactile hallucinations
- Delusional beliefs
- Severe Paranoia

## Rates of Schizophrenia Among Relatives of Schizophrenic Patients\*



\* Based on Slater and Cowie (1971), with the exception of twin data from Shields and Slater (1975). Adapted, with permission, from Tsuang and Vandermev (1980).



# History of Schizophrenia

- Ancient times to year 1800: Belief in possession by evil spirits..... treatments included exorcism and trepanation (drilling holes in skull).
- 1800: Recognition of SZ as mental disease.
- 1905: Belief SZ caused by negative life experiences; advent of psychotherapy.
- 1950: Use of antipsychotic medications.
- 1975: Advent of biological psychiatry..... focus on neurotransmitters, receptors, etc.

# Present Schizophrenia Theories



1. Dopamine Theory
2. Glutamate Theory (NMDA)
3. Oxidative Stress Theory
4. Epigenetic Theory
5. Virus Theory

# Common Flaw in SZ Theories

- ❑ Failure to recognize that schizophrenia is an “umbrella term” given to several different mental disorders.
- ❑ The schizophrenia phenotypes likely have different causes, and involve differences in brain chemistry.
- ❑ Optimal treatment requires a therapy tailored to each phenotype.

# Identification of Schizophrenia Phenotypes



- Chemical studies of 25,000 schizophrenics by Pfeiffer (Princeton, NJ) and Walsh (Naperville, IL).
- > 1 million chemical assays of blood & urine.
- Very high incidence of chemical abnormalities, compared to the general population.

# Symptom/Trait Database

- About 50-150 symptoms, traits, and physical characteristics were recorded for each patient and research subject,
- The symptoms & traits associated with specific chemical imbalances were identified,
- Biochemical classifications of schizophrenia were developed.

# Biochemical Classification of Schizophrenia

- 45% - Overmethylation
- 18% - Undermethylation
- 27% - Pyrrole disorder (severe oxidative stress)
- 4% - Wheat gluten intolerance
- 6% - Other

# Biochemistry of Overmethylated Schizophrenia

- Elevated S<sub>Ado</sub>Me/SAH ratio in blood
- Depressed whole-blood histamine
- Elevated serum copper
- High absolute basophils
- Overmethylation dominant imbalance
- High norepinephrine & dopamine

*Note: The most common psychiatric diagnosis is*

***Paranoid Schizophrenia***

# Symptoms of Overmethylated Schizophrenia

- Auditory Hallucinations
- Paranoia
- High Anxiety
- Non-Bizarre Delusions
- Religiosity & Grandiosity
- Depression
- High Physical Activity
- Intolerance to SSRI Antidepressants



# Effective Nutrients for Overmethylated Schizophrenia

- Folic Acid
- Vitamin B-12
- Niacin or Niacinamide
- Zinc and Manganese
- Vitamins B-6, C, and E
- DMAE
- GABA
- Metallothionein Promotion Therapy

# Generally-Effective Medications for Overmethylated Schizophrenia

1. Risperdal

2. Geodon

## Notes:

- SSRI Antidepressants must be avoided
- Antihistamines must be avoided
- Klonopin may assist in reducing anxiety.

# Undermethylated Schizophrenia

---

- Elevated Blood Histamine
- Elevated Absolute Basophils
- Undermethylation
- Low Ceruloplasmin

# Undermethylation Schizophrenia

## Symptoms & Traits

- ❑ Severe Delusions
- ❑ Obsessive/Compulsive Behaviors
- ❑ Social Isolation
- ❑ High Internal Anxiety
- ❑ Catatonic Tendencies
- ❑ Phobias

# Effective Nutrients for Undermethylated Schizophrenia

- L-Methionine
- S-AdoMet
- Calcium, Magnesium
- Vitamin B-6
- Serine
- Zinc
- Metallothionein Promotion

# Generally-Effective Medications for Undermethylated Schizophrenia

1. Zyprexa
2. Seroquel
3. Abilify
4. Clozaril

# Pyroluric Schizophrenia

- Elevated Urine Pyrroles
- Severe Deficiencies of B-6, Zinc
- Severe Oxidative Stress
- Low Arachidonic Acid Level
- Biotin Deficiency

# Pyroluric SZ Symptoms

- Onset During Severe Stress
- Mixed Psychotic Symptoms
- Extreme Anxiety & Fear,
- Social Isolation
- Intolerance to Stress
- Severe Mood Swings



# Nutrient Therapy for Pyroluric Schizophrenia

- Vitamin B-6
- Pyridoxal-5-Phosphate
- Zinc
- Manganese
- Primrose Oil
- Biotin, Vitamins C & E

# Generally-Effective Medications for Pyrrole Schizophrenia

- All atypical antipsychotics
- Benzodiazapines (especially Klonapin)

## Note:

Medication support may become unnecessary after pyrrole disorder is corrected.

# Gluten Intolerance

- 4% of Psychosis Cases
- Incomplete Breakdown of Gluten Proteins in the G.I. Tract
- Short Peptides with Opioid Properties

**Treatment:** Dietary Avoidance of Wheat, Oats, Barley, and Rye

# Interface With Psychiatric Medication

Initiation of Nutrient Therapy: Meds continued at full dosage for several months, unless sedation becomes excessive.

Months 4-12: After significant improvement, med dosages may be cautiously reduced to tolerance;

Long-Term Care: Low-dose medication support usually needed to avoid relapse.

# Vitamin B-3 Generally Beneficial for All Schizophrenia Phenotypes

- Overmethylation: Major Improvement
- Pyrrole Disorder: Moderate Improvement
- Undermethylation: Slight Improvement

# Oxidative Stress Theory for Adult Onset of Psychosis

- Oxidative stresses gradually increase until GSH and MT proteins are overwhelmed, resulting in sudden brain inflammation, alteration of NT levels, and disruption of the blood brain barrier.
- As in Wilson's Disease, sudden onset of a mental illness in young adulthood may result.

# Schizophrenia and Oxidative Stress

- All major phenotypes of schizophrenia involve severe oxidative stress,
- Oxidative overload depletes GSH and reduces glutamate activity at NMDA receptors,
- Clear evidence of brain cell loss in schizophrenia: *Archives of General Psychiatry, January 2006.*
- Most antipsychotic medications have antioxidant properties (Risperdal, etc).

# Schizophrenia: An Epigenetic Disorder?

---

- Abnormal methylation and severe oxidative stress are major causes of epigenetic errors.
- Greater than 95% of schizophrenics exhibit abnormal methylation or oxidative overload.
- This could explain failure of schizophrenia to obey classical laws of Mendelian genetics.



# Schizophrenia Outcome Studies (open-label)

- 85% report that “life is better” after nutrient therapy,
- 75% report ability to reduce medication,
- Highest efficacy for overmethylation and pyrrole disorder,
- Many cases of complete recovery.



# DEPRESSION



# Depression Database

- More than 3,000 patients diagnosed with clinical depression,
- > 250,000 assays of blood and urine,
- 50 to 150 symptoms or traits recorded for each patient.

# Database Studies



A wide range of abnormal chemistries and behaviors were observed in the depressive population.

5 chemical classifications (phenotypes) were identified, representing 95% of depressives.

Distinctive symptoms and traits were identified for each depression group.

# Chemical Classification of Depression



38% Undermethylation

20% Folate Deficiency

17% Copper Overload

15% Elevated Pyrroles

5% Toxic Metal Overload

# Implications of Database Findings



- Depression is a name given to a variety of different mood disorders.
- Each depression phenotype has unique chemical imbalances and symptoms.
- Different treatment approaches are needed for these disorders.

# A 25-Year Mystery!

- Folic Acid is a very-effective methylating agent.
- Undermethylated depressed patients are intolerant to folates.
- Overmethylated depressives thrive on folates.

**WHY?**



# Mystery Solved by Epigenetic Science

- Folic Acid generates acetylase enzymes that alter histones & promote expression of SERT.
- SERT increases serotonin reuptake, thus reducing serotonin activity.
- For low-serotonin depressives, the harmful impact of folic acid at the synapse exceeds the benefits of normalizing methylation.

# Epigenetics of Methyl and Folate

- SAMe modifies histones to block production of transporter proteins: This reuptake inhibition increases activity of serotonin & dopamine.
- Folates have the opposite effect on histones and lower serotonin and dopamine activity.

# Nutrients That Increase Serotonin Neurotransmission

- S-Adenosyl Methionine (SAME)
- Methionine
- Tryptophan
- 5-HTP

# Nutrients That Decrease Dopamine Neurotransmission

- Folic Acid
- Niacin or Niacinamide
- DMAE or Choline
- Manganese

# Nutrients That Decrease Norepinephrine Neurotransmission

- GABA
- Folic Acid
- Niacin or Niacinamide
- Pantothenic Acid
- Zinc

# Five Depression Phenotypes



1. Undermethylation
2. Low Folate
3. Copper Overload
4. Pyrrole Disorder
5. Toxic Metal Overload

# Phenotype #1

## Undermethylated Depression

- Elevated Blood Histamine
- Low S<sub>AMe</sub>/S<sub>AH</sub> Ratio
- Low Basophils
- Low Serotonin Activity

# Symptoms & Traits

## Undermethylated Depression

- ❑ OCD tendencies
- ❑ Seasonal affective disorder
- ❑ Competitive & perfectionistic
- ❑ SSRI medications usually effective
- ❑ Calm exterior, but inner tension
- ❑ Strong willed
- ❑ High libido
- ❑ Seasonal allergies



# Useful Nutrients

## Undermethylated Depression

- SAMe
- Methionine
- Calcium
- Magnesium
- Zinc,
- Trimethylglycine (TMG)
- Vitamins B-6, C, E
- Inositol

# Phenotype #2

## Low-Folate Depression

- Low Serum Folates
- Low Blood Histamine
- Elevated S<sub>AMe</sub>/S<sub>AH</sub> Ratio
- Elevated Dopamine & Norepinephrine

# Symptoms and Traits of Low-Folate Depression

- Tendency for high anxiety, panic
- Non-competitive in sports or games
- Absence of inhalent allergies
- Food/chemical sensitivities
- Adverse reaction to SSRI medications
- High musical or artistic ability
- Underachievement
- Sleep disorder
- Low libido

# Useful Nutrients For Low-Folate Depression

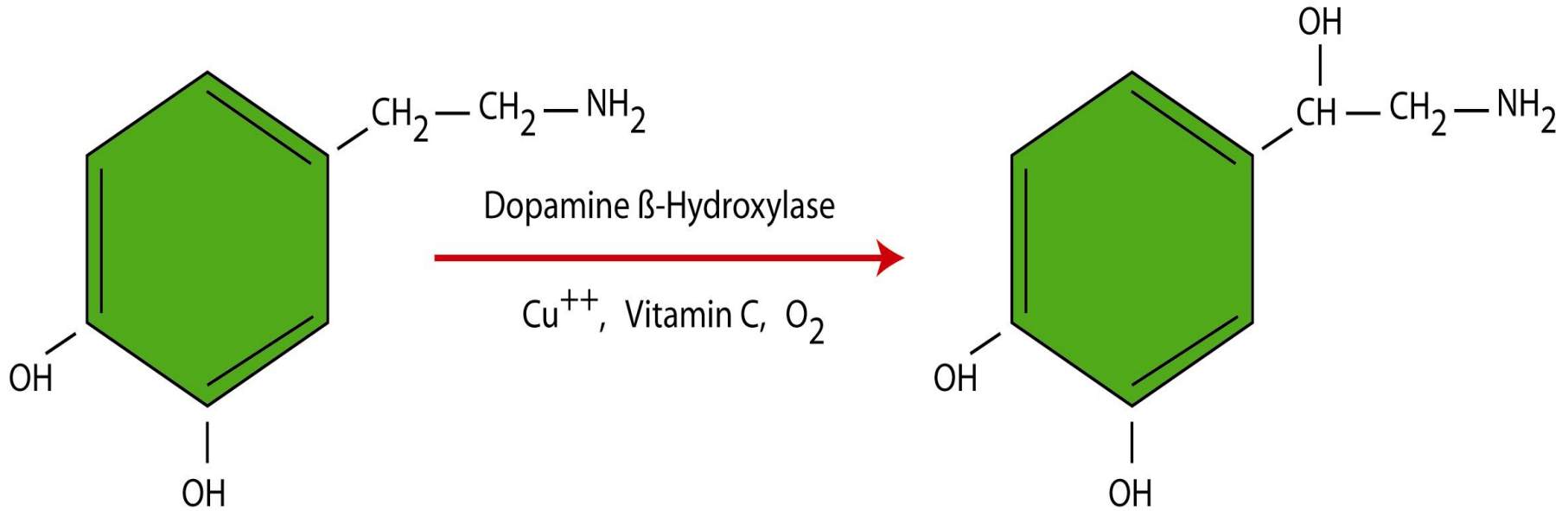
- Folic Acid
- B-12
- GABA
- DMAE
- Manganese
- Niacin or Niacinamide
- Vitamins A, B-6, C, E
- Zinc

# Phenotype #3

## High-Copper Depression

- Elevated Serum Copper
- Insufficient Serum Ceruloplasmin
- Zinc Depletion
- Low Metallothionein Activity
- Elevated Norepinephrine & Adrenaline

# Norepinephrine Synthesis



**DOPAMINE**

**NOREPINEPHRINE**

# Symptoms and Traits of High-Copper Depression

- More than 95% are female
- Inability to eliminate excess copper
- High anxiety
- Tendency for post-partum depression
- Onset during hormonal event (puberty, birth control, pregnancy, menopause)
- Estrogen intolerance
- Tinnitus (ringing in the ears)
- Sensitive skin, intolerance to cheap metals.

# Useful Nutrients for High-Copper Depression

- Zinc
- Vitamin B-6
- MT-Promotion Nutrients
- Manganese (avoid if undermethylated)
- Selenium
- Vitamin C
- Vitamin E



# Decoppering Protocol Issues

- The excess copper departs via the blood stream.
- Gradual introduction of zinc is recommended to minimize copper elevations in blood & increased irritability and anxiety during early treatment.
- Zinc dosages should be increased to tolerance.

# Depression Phenotype #4

## Pyrrole Disorder

- Elevated urine pyrroles
- Zinc deficiency
- Vitamin B-6 deficiency
- Severe oxidative stress
- Low serotonin & GABA

# Pyrrole Depression

- ❑ Severe mood swings
- ❑ Poor stress control
- ❑ Extreme anxiety
- ❑ Poor short-term memory, reading disorder, absence of dream recall
- ❑ Sensitivity to light, noise
- ❑ Poor immune function
- ❑ Very poor morning appetite
- ❑ Abnormal fat distribution,
- ❑ Inability to tan.

# Treatment of Pyrrole Disorder

---

- Zinc Therapy
- Supplements of B-6, P-5-P
- Omega-6 (Primrose Oil, Borage Oil)
- Biotin

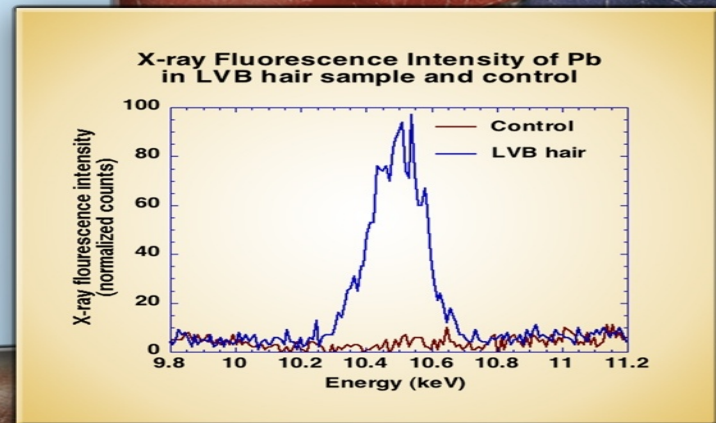
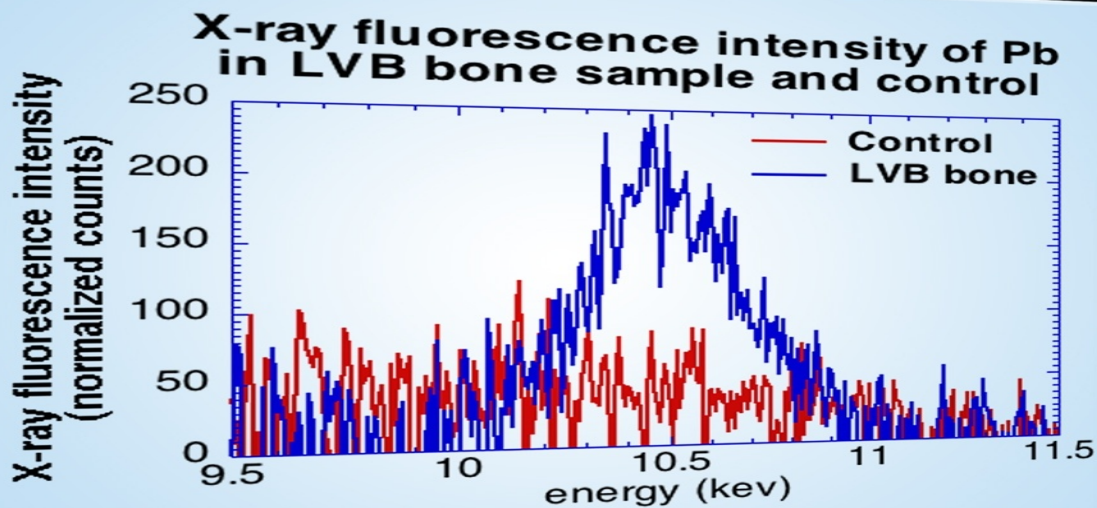
# Toxic Metal Depression

- ❑ Absence of trauma or emotional triggers
- ❑ Abdominal distress
- ❑ Unrelenting depression
- ❑ Cognitive deficits (children only)
- ❑ Metallic taste in mouth, bad breath
- ❑ Irritability, anger
- ❑ Food sensitivities
- ❑ High oxidative stress

# Useful Nutrients: Toxic Metal Depression

- Zinc
- Manganese
- Glutathione
- Selenium
- MT-Promotion Nutrients
- Calcium (lead poisoning)
- Vitamin C
- Vitamin E

# LEAD LEVELS IN BEETHOVEN SAMPLES



# Open-Label Outcome Studies

- 20% non-compliance rate
- 85% of compliant patients report improvement and reduced medication needs
- Many reports of zero depression without medication support.



# Treatment Time Frames

- Pyrrole Disorder: 1-4 weeks to achieve full effect.
- Copper Overload: No progress until week 3; 60-90 days to normalize blood Cu levels.
- Low Folates: Clear improvement by week 4; 3-6 months to achieve full effect.
- Undermethylation: No progress until month 2; 6-12 months to achieve full effect.



# AUTISM SPECTRUM DISORDERS



# AUTISM

- 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

- 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

- 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

- **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

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.



# Consequences of Oxidative Stress

## Mirror Classic Symptoms of Autism

- Hypersensitivity to Hg and other toxic metals
- Hypersensitivity to certain proteins (casein, gluten, etc)
- Poor immune function
- Disruption of the methylation cycle
- Inflammation of the brain & G.I. tract
- Depletion of glutathione & metallothionein
- Excessive amounts of “unbound” copper

# Most Popular Autism Therapies Enhance Antioxidant Protection

- 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

---

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

# Autism Brains Are Different

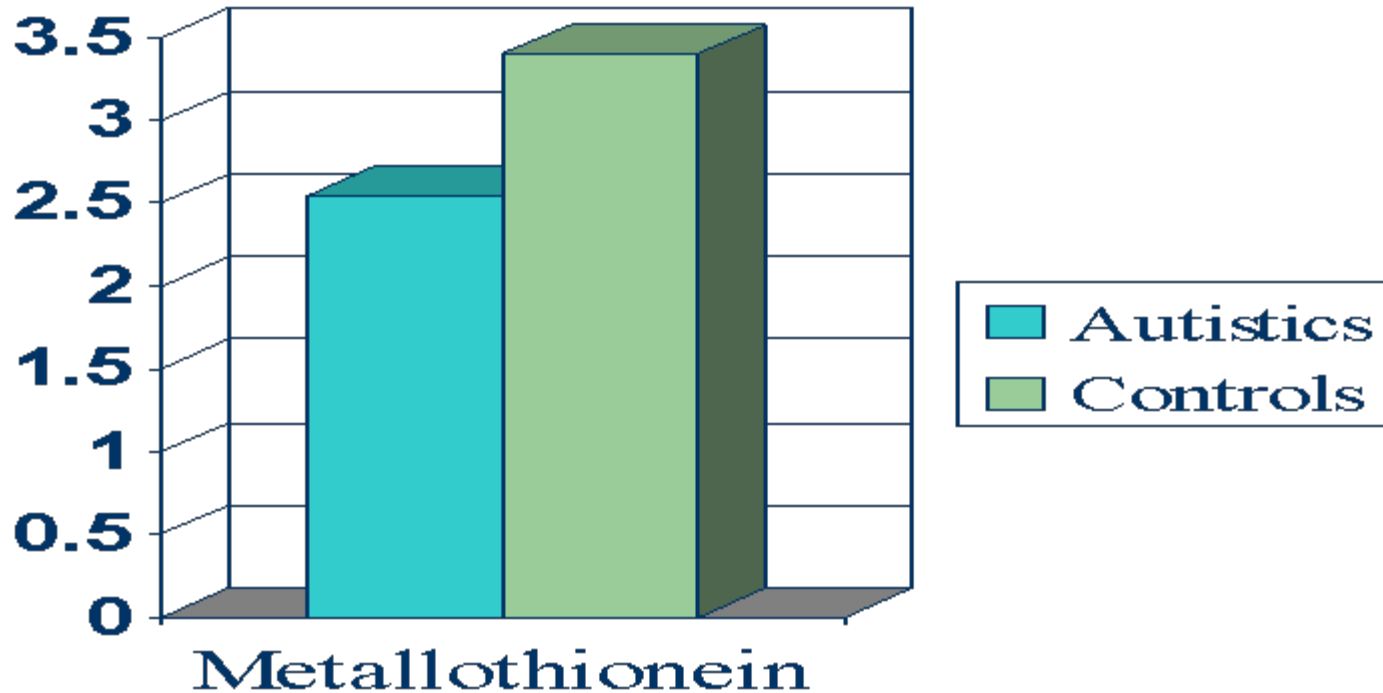
- Incomplete maturation – Excessive short, undeveloped brain cells in cerebellum, amygdala, pineal gland and hippocampus,
- Poverty of brain dendrites and synapses,
- Narrowed minicolumns in brain cortex,
- Brain inflammation and increased head size,
- Damaged fats in autism brains,
- Abnormal levels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

# Oxidative Stress Can Impair Brain Development

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

# 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,
- This provides an avenue for oxidative damage to developing autism brains, caused by toxic metals, viruses, etc.

Note: This may explain the immaturity in the limbic system & cerebellum that is not observed in cortex or other brain locations.



# Consequences of Oxidative Stress 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.

# 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 – October, 2009 data indicates one case per 110 births.

*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

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

- 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.

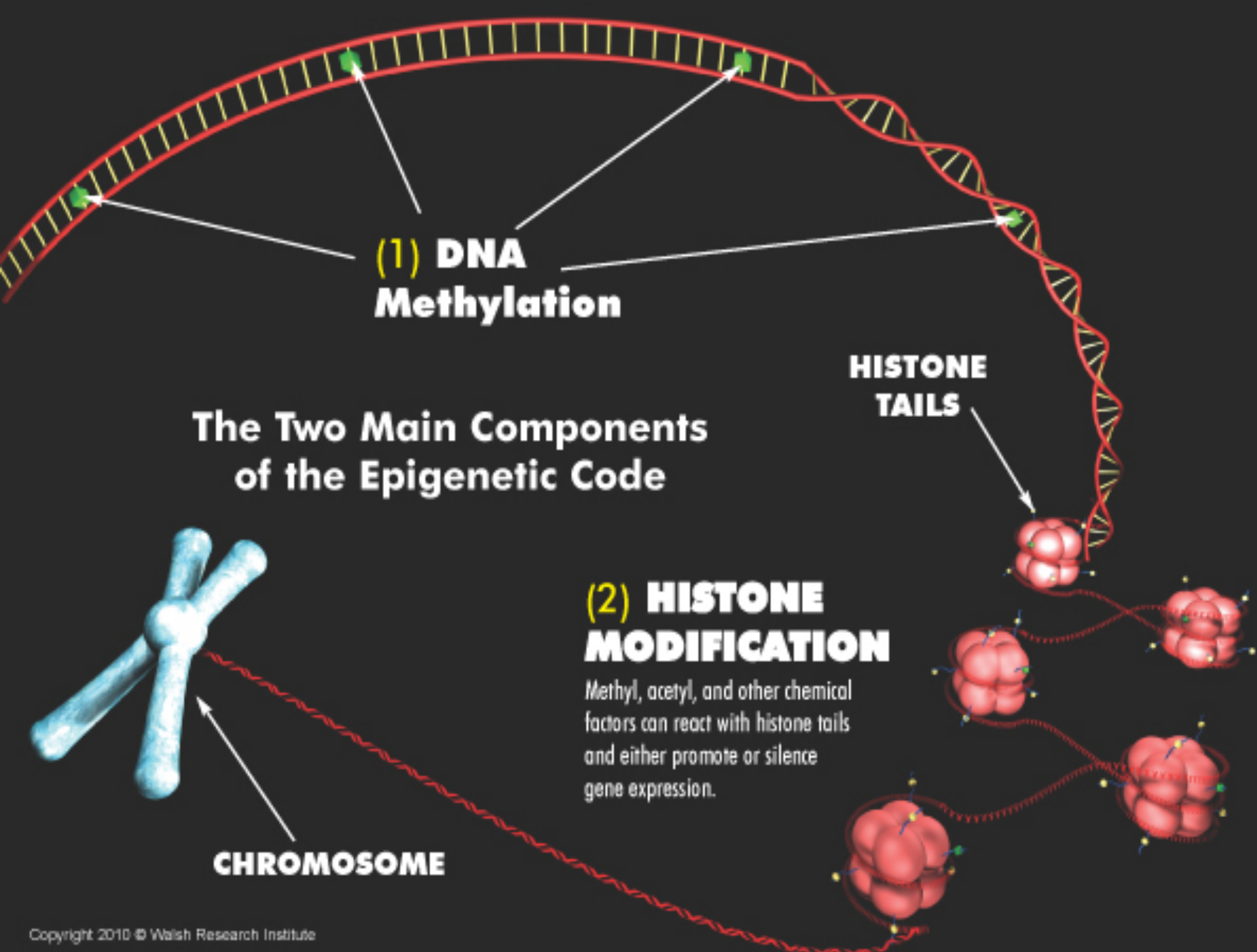
# Epigenetic Processes During Early Fetal Development

- 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 inhibited 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

- 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.





## The Two Main Components of the Epigenetic Code

**(1) DNA Methylation**

**HISTONE TAILS**

**(2) HISTONE MODIFICATION**

*Methyl, acetyl, and other chemical factors can react with histone tails and either promote or silence gene expression.*

**CHROMOSOME**

# A Clue From the Past -- Thalidomide Babies

- 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

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.

## CONCLUSION

**AUTISM MAY BE AN EPIGENETIC DISORDER**

# Recent Research

- 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.

# Autism and Neurodegeneration

- 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.

# The Final Battlefield – The Brain

- Autism involves a brain that has not completed the maturation process,
- Brain cells and organelles may have been damaged in early development,
- In either case, development of immature brain cells, and production of new dendrites and synapses is a high priority in autism therapy.

# Behavioral Therapies and Brain Plasticity

- ABA stimulates organization of synaptic connections & cortex minicolumns.
- ABA promotes brain maturation, but is greatly slowed by oxidative overload and inflammation.
- ABA is especially promising when coupled with antioxidant therapy.

## Hebb's Rule:

Brain cells that fire together, wire together.

# Unique Advantages of Metallothionein-Promotion Therapy

- Directly aimed at development of brain cells,
- Potential for permanently correcting the intestinal and blood/brain barriers,
- Restores a key antioxidant system.

Limitation: Does not directly enhance development of dendrites and synapses.



# Important Questions

- 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

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),
5. Result: Autism

# The Bermuda Triangle of Autism

---

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

# A Strategy for Enhanced Cognition, Speech, and Socialization

- Powerful antioxidant therapy,
- Methylation protocols,
- Biochemical therapies aimed at reversing epigenetic errors,
- Therapies that enhance brain maturation.

# Potential Epigenetic Therapies

- Methylation normalization (S<sub>A</sub>Me, demethylases, etc),
- Deacetylase promotion,
- Acetyl- CoA adjustments,
- Therapies to stimulate or suppress DNA promoter regions,

**Autism is Treatable**

**Recovery is Possible**



# BEHAVIOR DISORDERS

William J. Walsh, Ph.D.



# Origins of Behavior Research

- Volunteer at maximum-security prison in Illinois (1972-1990),
- Coordinated 125 volunteers,
- Prisoner visitation,
- Aid to abused prisoners,
- Chess league,
- Prison Art Shows,
- Ex-Offender program.

# Ex-Offender Program

1. Pre-release job counseling
2. Housing assistance
3. Financial support
4. Food & clothing
5. Transportation
6. Medical care

**Primary Objective: Crime Prevention**

# Nature or Nurture?

- Most ex-convict clients were from high-poverty, high-crime neighborhoods,
- However, many others were raised in stable homes in affluent suburbs or rural areas along with well-behaved law-abiding siblings,
- Many parents reported their future criminal was alarmingly “different” from birth.

# 1975 Question: What is the Cause of a Severe Behavior Disorder?

- Tabula rasa (blank slate) theory: dominance of life experiences,
- Adoption & twin studies indicate inborn predisposition for schizophrenia, bipolar disorder, clinical depression, autism,
- New focus on neurotransmitters, receptors, chemical imbalances,
- Early testing of body chemistry for convicted felons (Walsh ,Argonne National Laboratory).

# Metal-Metabolism Abnormalities

- Study of death row residents & other convicted murderers revealed unusual levels of Cu, Zn, Mn, Na, K, Li, Co.
- Similar chemical imbalances found in violent children.
- Formal experiments initiated at Argonne National Laboratory.

# Sibling Experiment

## **Test Group**

24 violent males

Age range: 8-18 years

Multiple violent incidents

## **Control Group**

24 brothers, living in same domicile

Age range: 8-18 years

No violence or delinquency

# Results of Sibling Experiment

- Most controls exhibited expected levels of metals; Most violent subjects had abnormal levels of Cu, Zn, Mn, Pb, Cd, Na, K, Ca.
  
- Two distinctive patterns of trace metals observed in violent subjects:
  - Type A: Elevated Cu, Cd, Pb  
Depressed Zn, Na, K, Li, Co
  - Type B: Elevated Na, K, Cd, Pb, Mn  
Depressed Cu, Zn, Li, Co

# Family Survey of Violent Siblings

---

**Type A Subjects:** Episodic violence, genuine remorse, high incidence of ADHD, LD, and academic underachievement.

**Type B Subjects:** Oppositional, defiant, cruel, assaultive, high pain threshold, fascination with fire, weapons.



# Double-Blind Field Test (n=192)

---

Test Group: 96 extremely violent prison residents, ex-convicts, and assaultive children.

Controls: 96 non-violent males, matched for age and socioeconomic level in childhood.

# Field Test Results

- Results of sibling experiment confirmed
- Type A & B patterns predominate in violent cohort; Most controls exhibit expected trace metal levels.
- $P < 0.001$

## **Conclusion:**

*Most violent persons exhibit abnormal metal metabolism.*

# Metabolic Studies by Carl Pfeiffer

## **Type A (Episodic Rage disorder)**

Elevated Cu/Zn ratio in blood, high toxic metals, histamine disorder, hypoglycemia, 30% exhibit pyrrole disorder.

## **Type B (Antisocial Personality Disorder)**

High blood histamine, low blood spermine, pyrrole disorder, hypoglycemia, elevated toxic metals.

# Forensics Cases

- James Oliver Huberty
- Charles Manson
- Richard Speck
- Patrick Ryan
- Patrick Sherrill
- Ludvig van Beethoven
- Twenty other notable cases

# Examples of Forensics Findings

- Charles Manson: Severe Type B chemistry
- James Huberty: Cd poisoning; mild Type B
- Richard Speck: Severe Type A chemistry
- Patrick Ryan: No abnormalities detected
- Patrick Sherrill: Pb poisoning, Type A
- Beethoven: Severe Pb poisoning.

# Pfeiffer Treatment Center

- Founded in June, 1989 in Illinois
- Non-profit outpatient clinic
- Collaboration between medical doctors and scientists
- Specialty = body/brain chemistry

***\*Named in honor of Dr. Carl Pfeiffer who died in 1988.***

# Individualized Nutrient Therapy



1. Medical History and Review of Symptoms
2. Extensive Chemical Testing
3. Diagnosis of Chemical Imbalances
4. Prescribed Nutrient Program

*Note: Best results for younger patients*

# Behavior Database

- World's largest chemistry database for behavior disordered and delinquent populations.
- More than 1.5 million chemical analyses of blood, urine, and hair for 10,000 behavior-disordered persons.
- About 50-150 symptoms, traits, and physical characteristics recorded for each subject.



# Behavior Database Findings



Major biochemical differences between behavior disordered persons and the rest of society.

Several observed chemical imbalances directly impact brain neurotransmitters.

# Major Behavior Phenotypes

- 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)

# High Incidence Chemical Imbalances Observed in ADHD

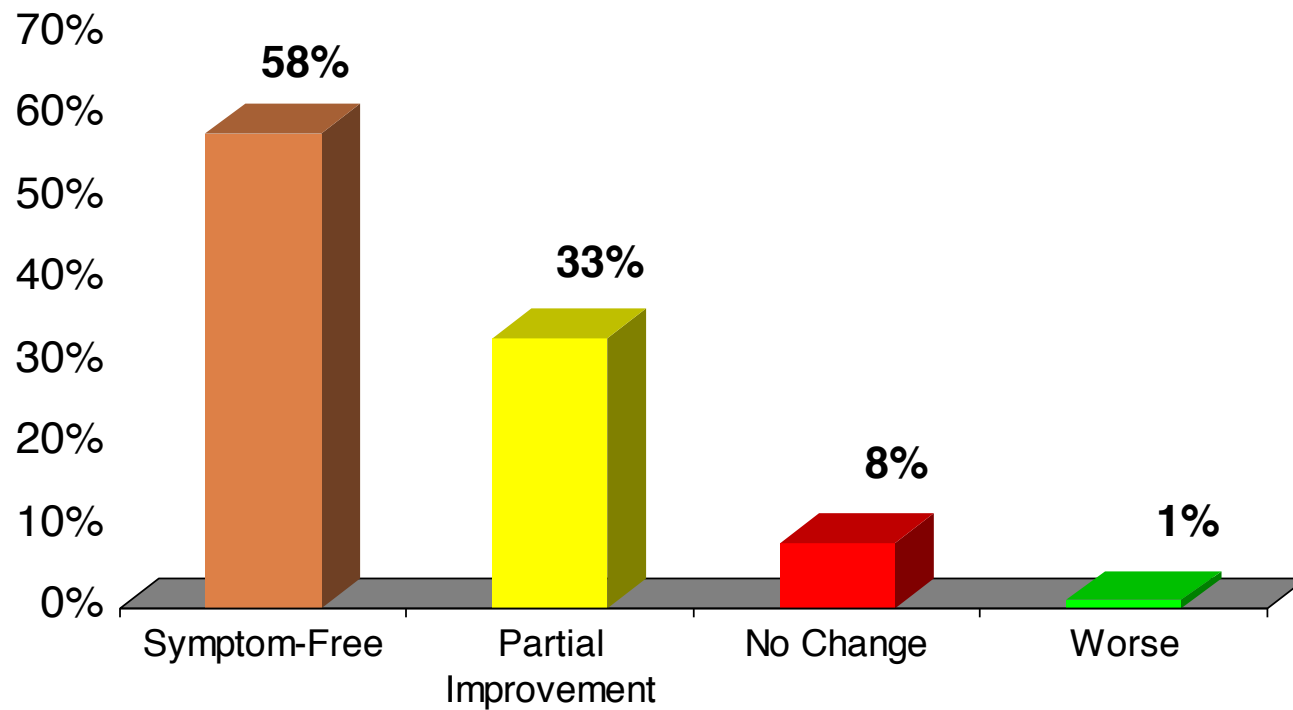
- Elevated Cu (68%)
- Insufficient ceruloplasmin (92%)
- Zinc depletion (96%)
- Methylation disorder (55%)
- Pyrrole Disorder (30%)
- Malabsorption (11%)

# Outcome Study – PTC Protocol for Behavior-Disordered Children & Adults

- 207 behavior-disordered subjects
- Identification of biochemical imbalances
- Individualized nutrient therapy to correct imbalances
- Measurement of frequency of physical assaults and property destruction before & after treatment

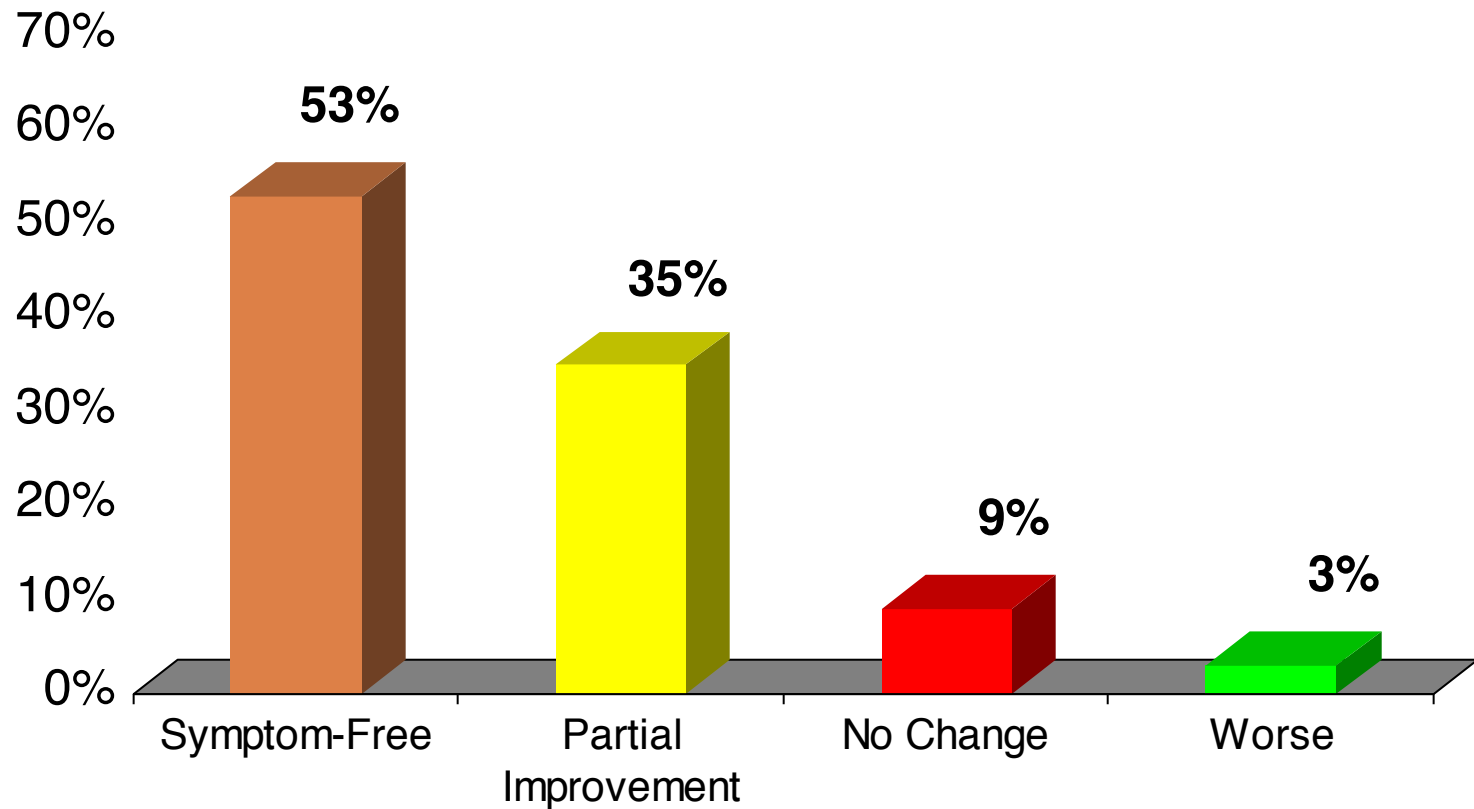
# Treatment Outcomes

## Compliant Assaultive Subjects



# Treatment Outcomes

## Compliant Destructive Subjects



# Case History: Mike

- Father in prison; mother a recovering alcoholic.
- At age 12: oppositional, defiant, cruel to animals, truant, and assaultive.
- Dx: ODD, Antisocial Personality disorder.
- Head of youth gang -- major thefts.
- After 3 months therapy, he became well-behaved and a straight-A student.
- Family moved to Kansas to give Mike a fresh start.

# Case History: Brian

- Adopted son of scientist & social worker,
- At age 16: violent, destructive, truant, failing academically,
- Dx: Episodic rage disorder,
- Within 2 months of nutrient therapy, he became calm, ceased truancy & became honor student & joined football team.
- Brian enrolled at University of Colorado.



# ADHD Case History: Danny

- Son of prominent scientist (physicist),
- At age 8, diagnosed with LD/ADD: Special Education and Ritalin recommended,
- Disability disappeared within 2 months of nutrient therapy,
- Danny became superior student and entered graduate school at University of Chicago at age 18.

# Summary

- Distinctive chemical imbalances are exhibited by most behavior-disordered or ADHD children & adults.
- Most families report major benefits following individualized nutrient therapy.
- Individualized nutrient therapy represents a promising approach for reducing crime & violence.

# Pfeiffer's Law

---

***“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!



William J. Walsh, PhD  
Walsh Research Institute  
[www.walshinstitute.org](http://www.walshinstitute.org)