

EPIGENETICS AND MENTAL HEALTH

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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

Gene Bookmarking

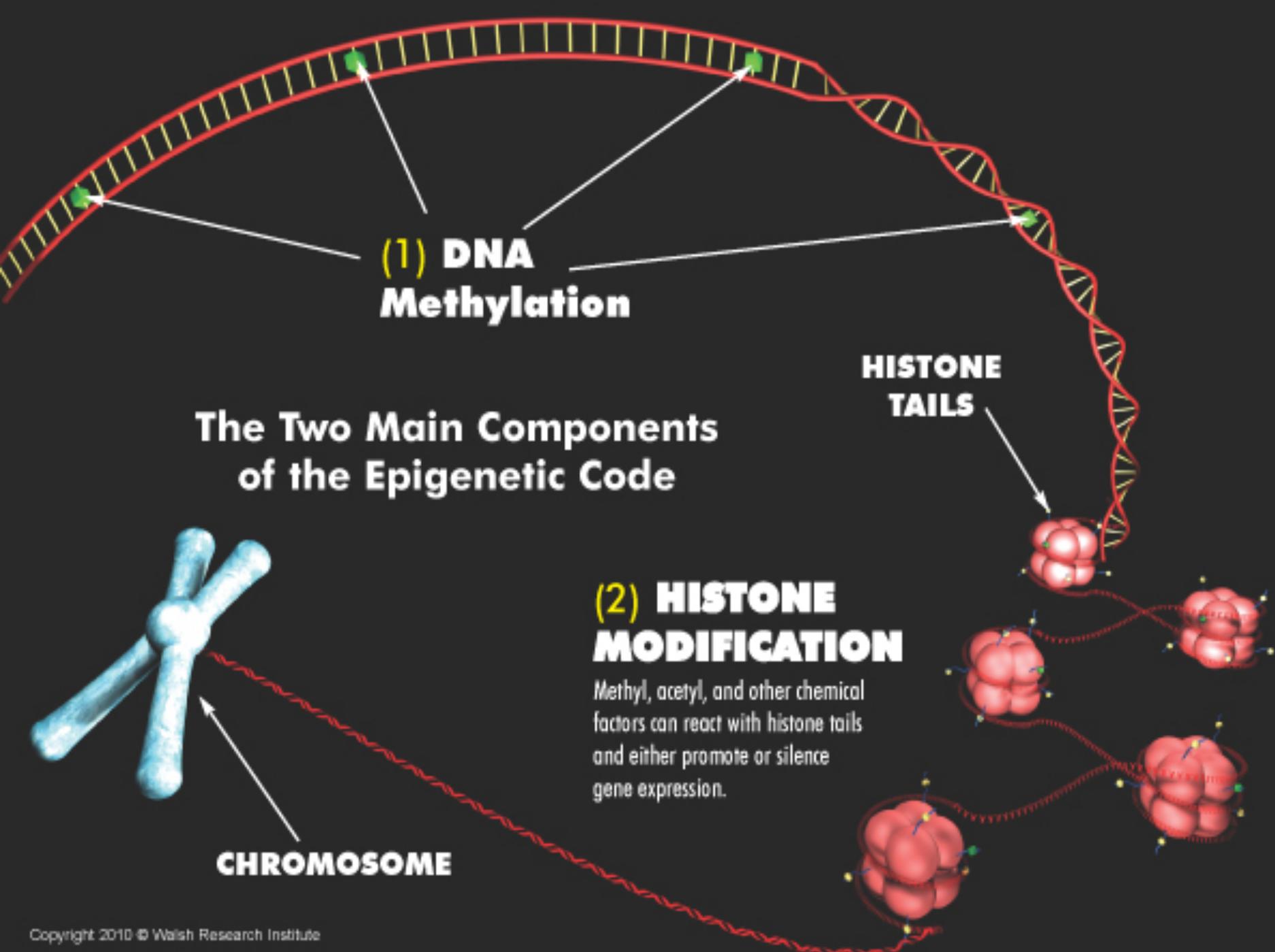
- >20,000 genes in every cell's DNA, each with potential for producing a specific protein,
- Liver, skin, brain, kidney, and other tissues require a unique combination of proteins,
- For each tissue, in-utero chemical environment determines which genes will be expressed or inhibited throughout life (bookmarking),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

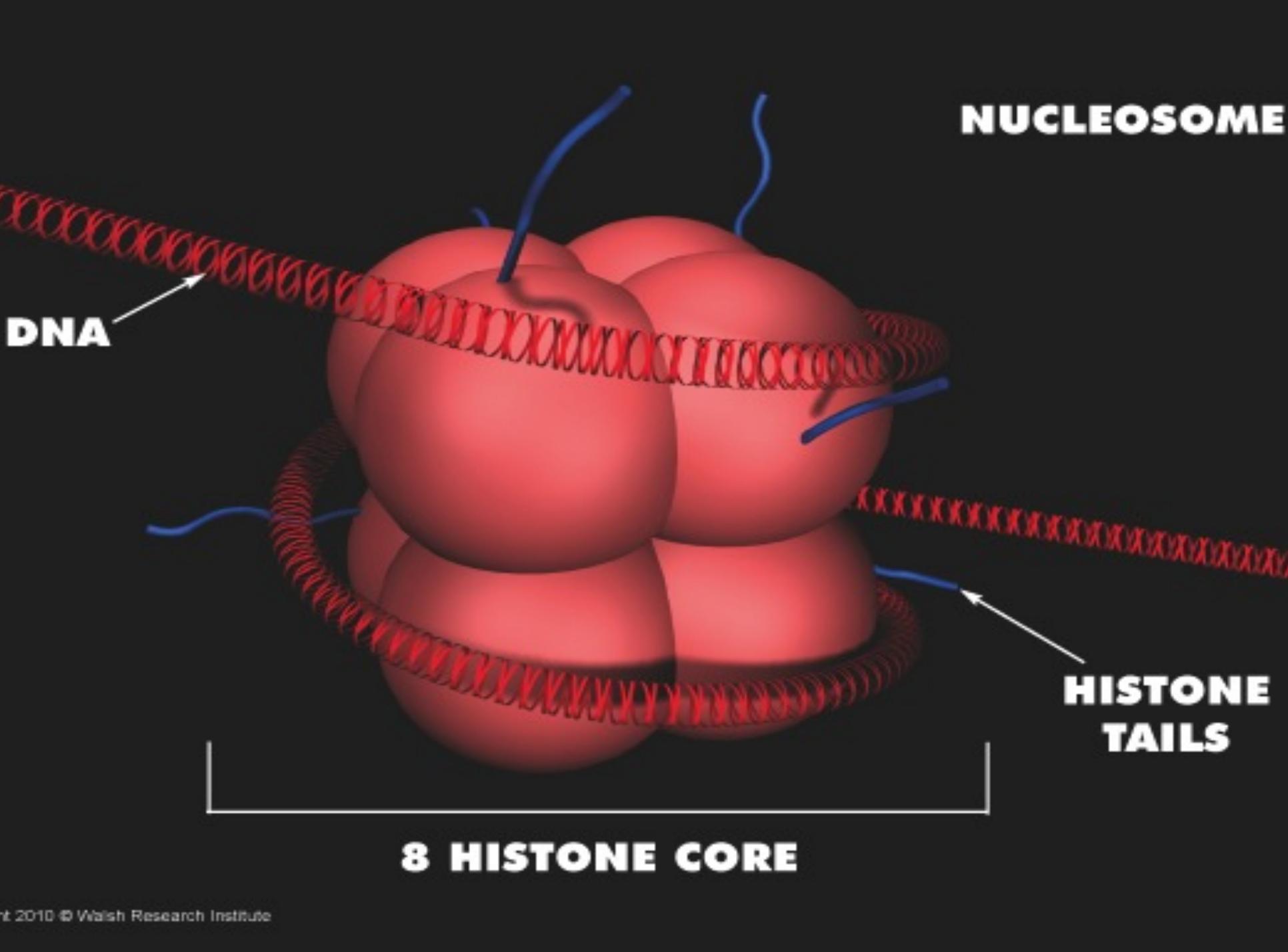
(2) HISTONE MODIFICATION

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.



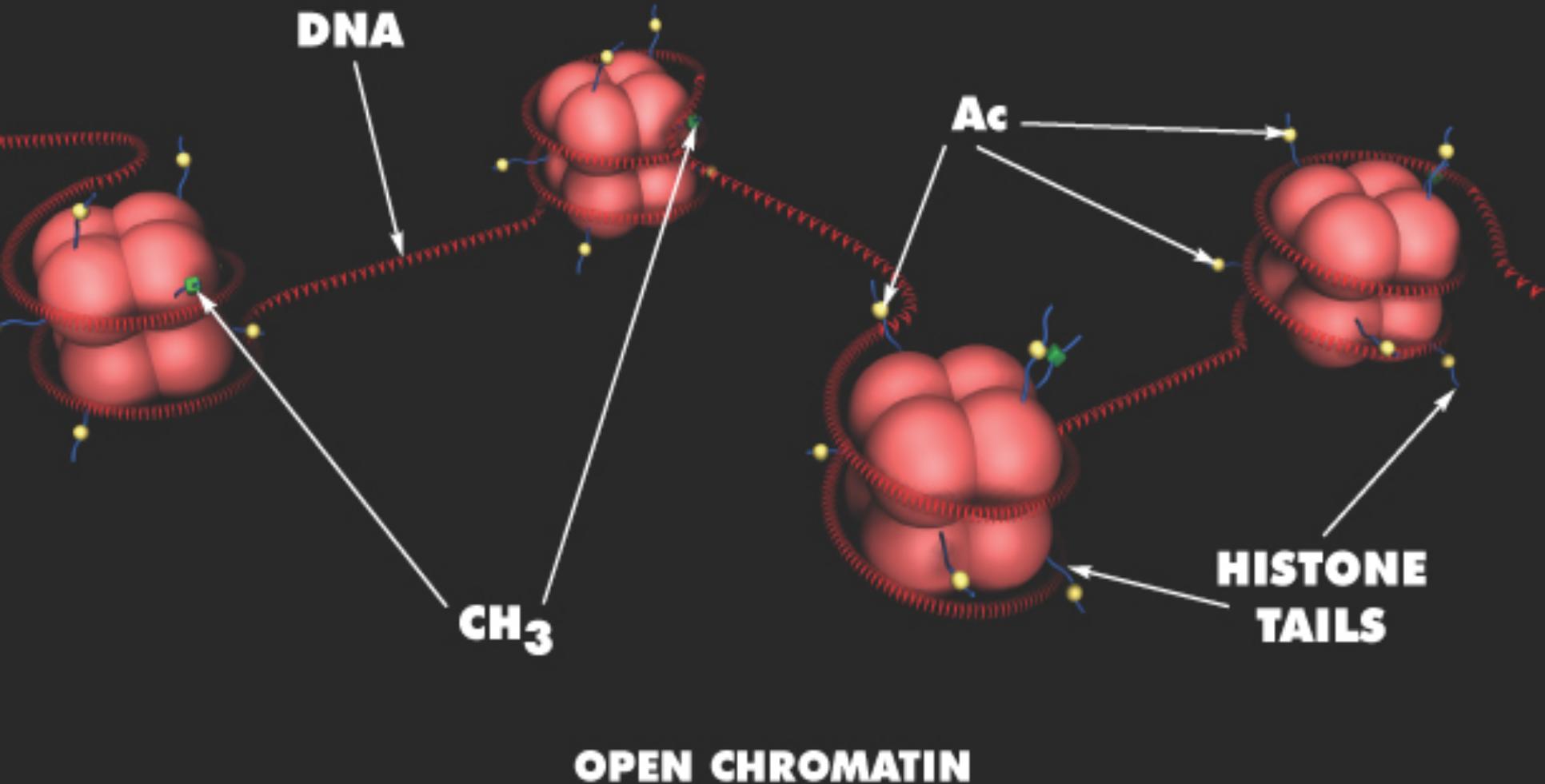
Histones

- 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.

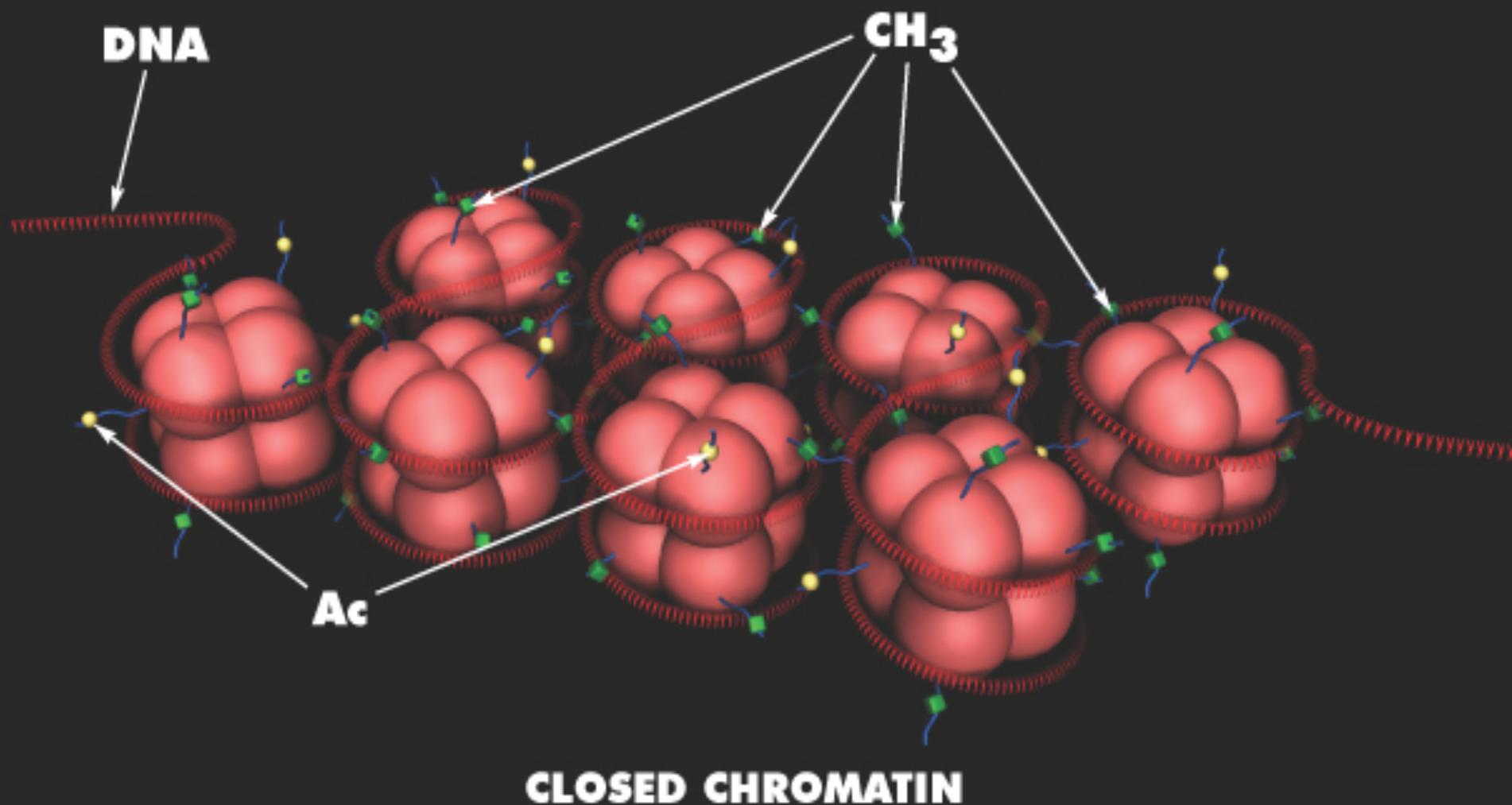
Methyl-Acetyl Competition

- 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

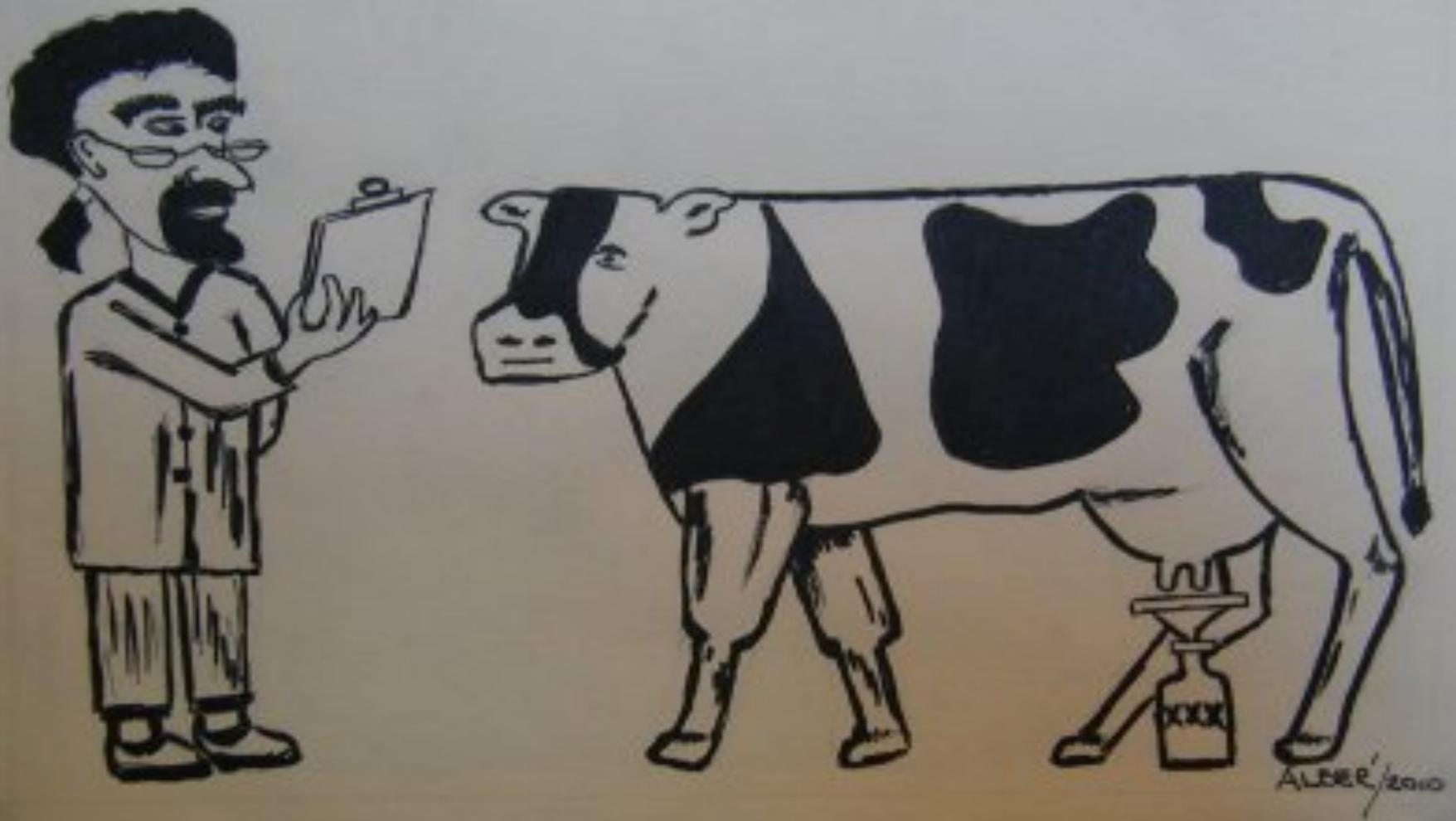
- A multitude of diseases and disorders appear to be epigenetic in nature,
- Researchers will eventually identify the specific gene expression errors for most of these conditions,
- Epigenetic therapy has potential for normalizing gene expression and curing many diseases.

“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.

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!



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