
Shinya Yamanaka

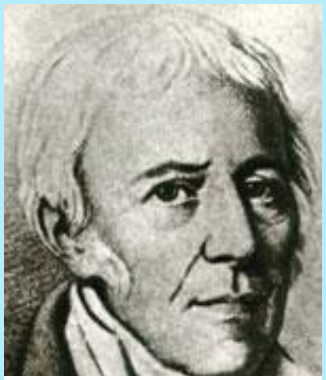

John Gurdon


Adrian Bird

Epigenetics
An introduction for Psychiatrists


Andrew Fire

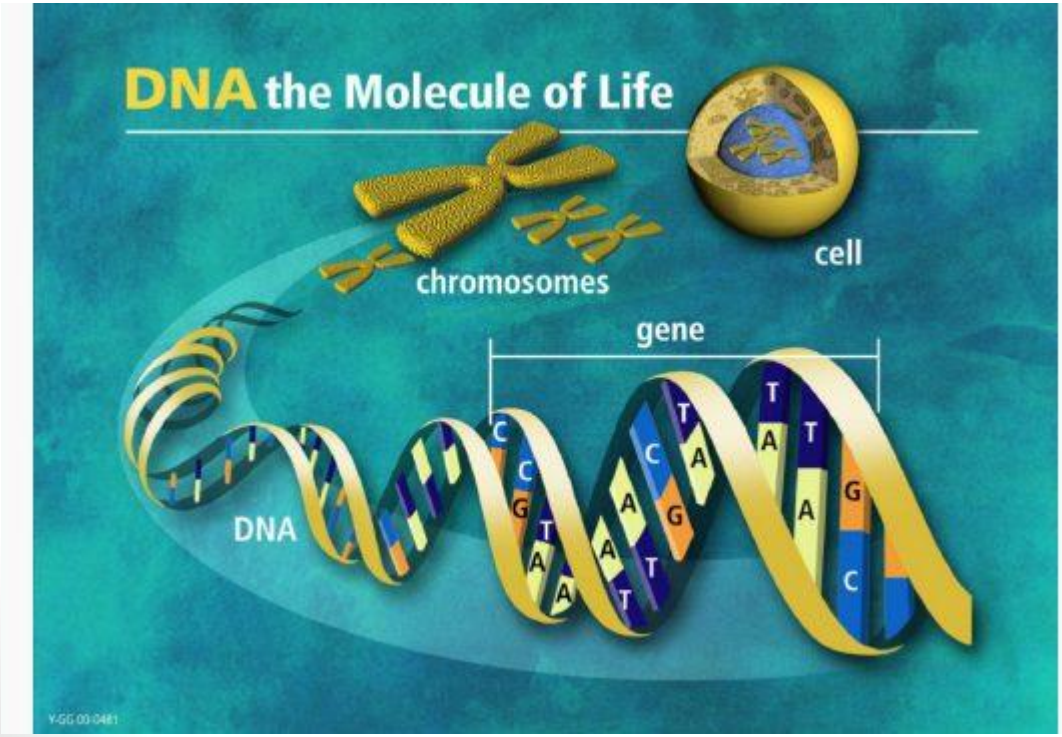

Craig C. Mello, PhD.

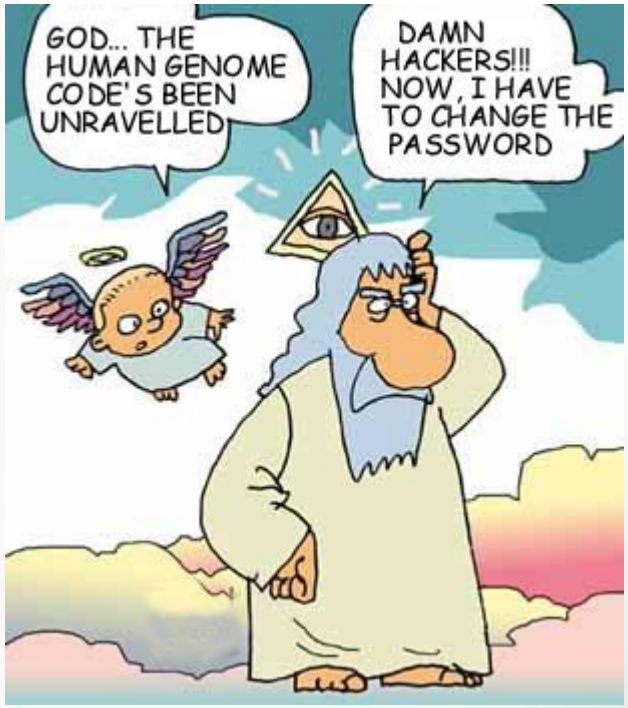

Jean Baptiste Lamarck


CH Waddington

Biological Dictum?

- DNA makes RNA makes protein.
- Know thy genome and thou knowest thyself.



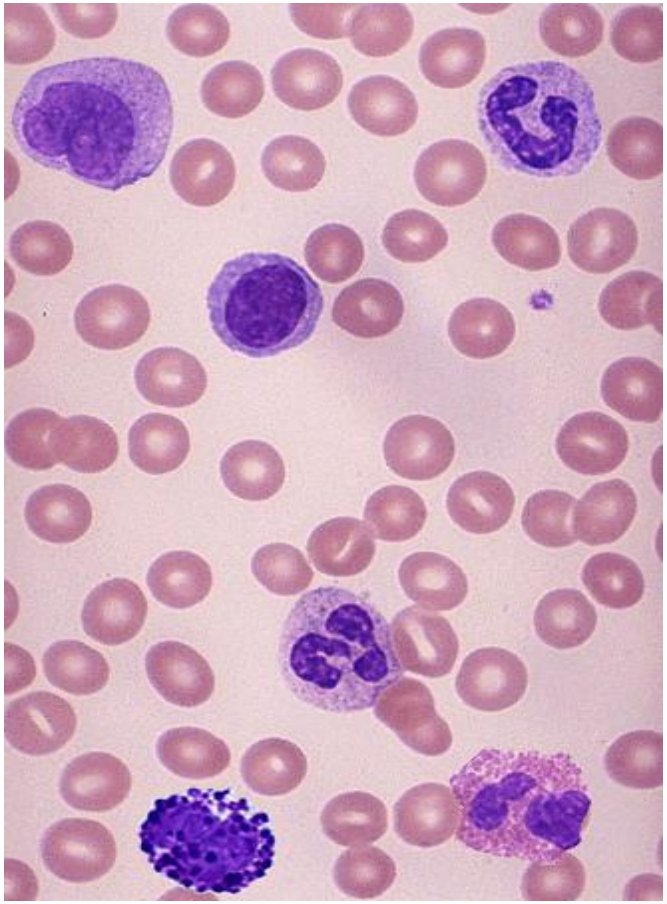


Have you ever wondered….?

- Whether the genome of a caterpillar and the butterfly into which it turns are the same?
- They are.

Have you ever wondered….?

- How clonal, multicellular organisms such as ourselves generate organs and tissues of such diversity?
- Differentiation through control of genetic expression



Have you ever wondered….?

- Why the patchwork colours of a calico cat occur only in females?
- Random X inactivation

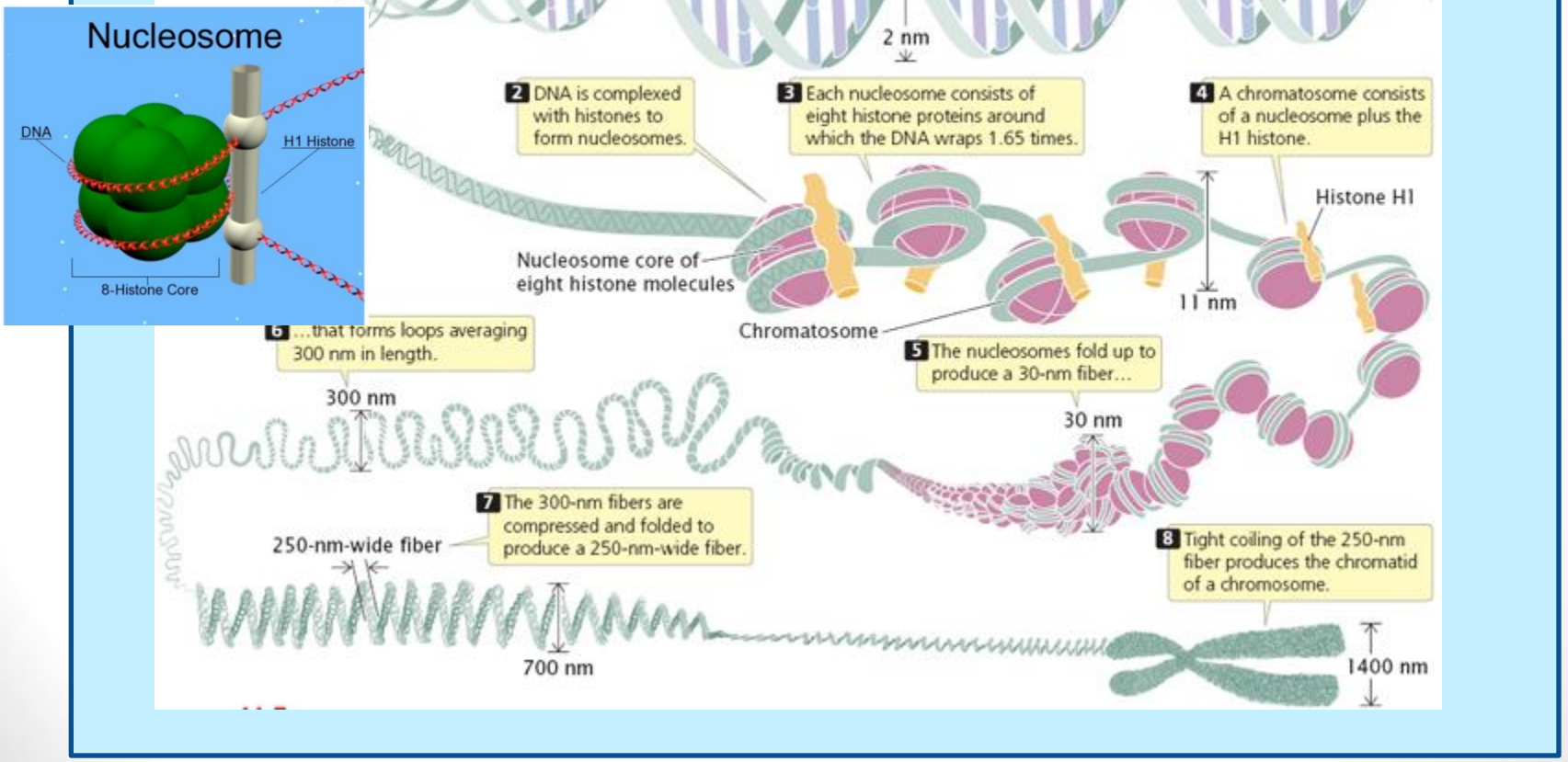
Have you ever wondered….?

- Whether identical twins are truly identical
- They are not

The common thread is Epigenetics

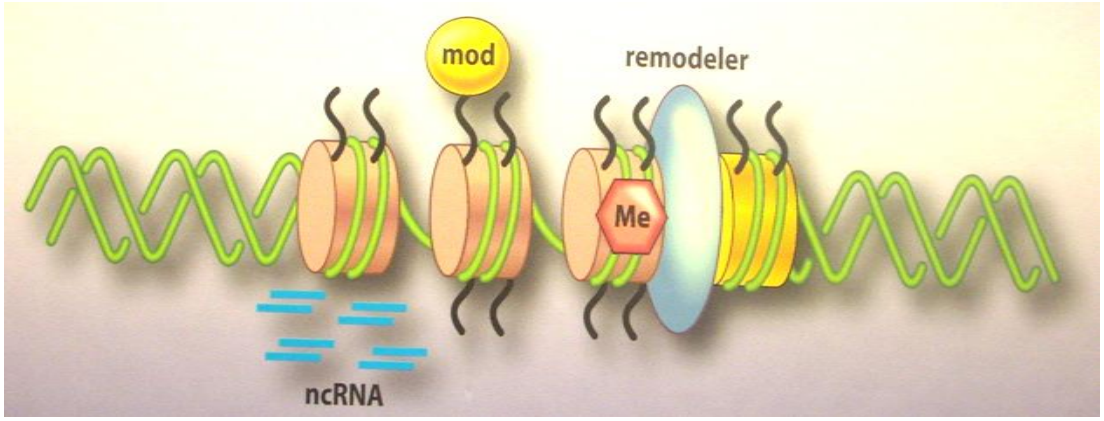
- A change in the state of expression of a gene that does not involve a mutation
- All differentiation processes are triggered and maintained through epigenetic mechanisms.
- Many external factors can act on gene expression through epigenetics.

Organization of chromatin



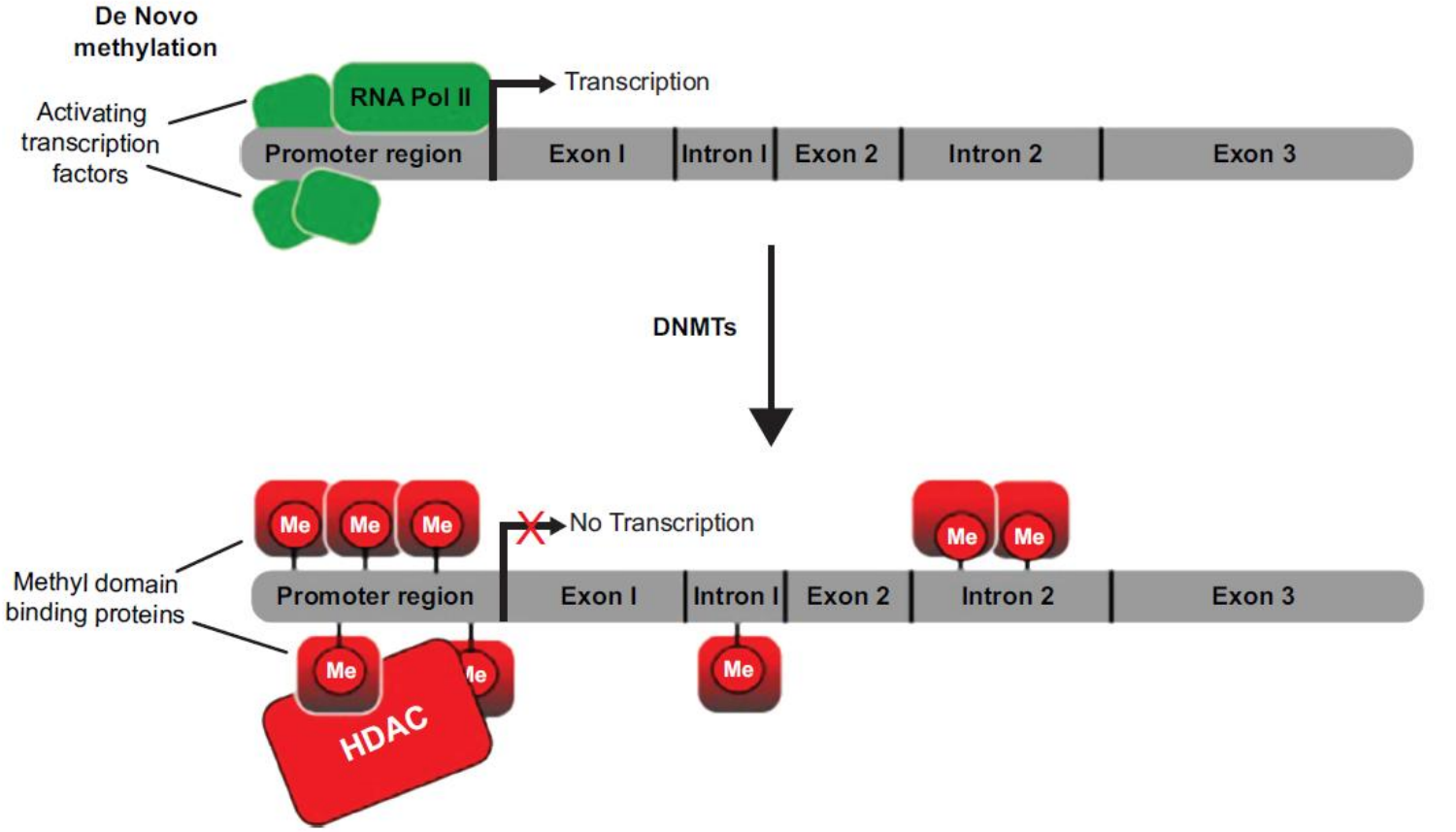
How does epigenetics work?

- DNA methylation
- Changes in Chromatin Structure- Histone modification and nucleosome remodelling
- Small regulatory RNAs
- Polycomb & Trithorax genes



DNA methylation

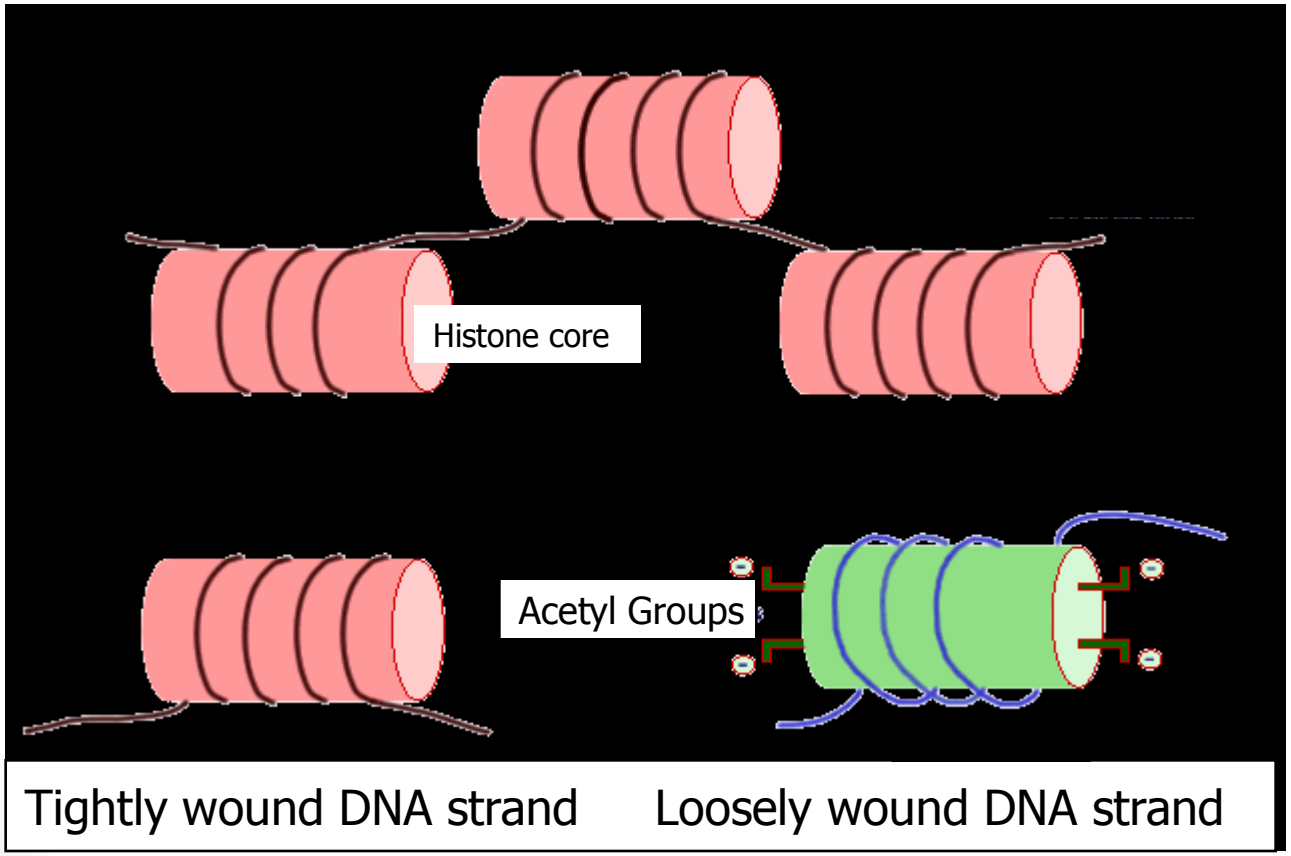
p = phosphodiester bond

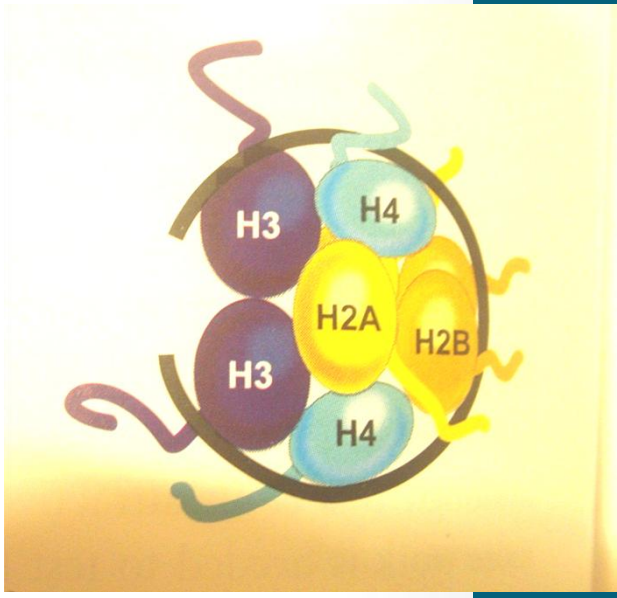


Cytosine methylation in mammals

- Gene expression
- Chromosomal stability
- Cell differentiation
- Imprinting
- X- inactivation
- Carcinogenesis
- Aging

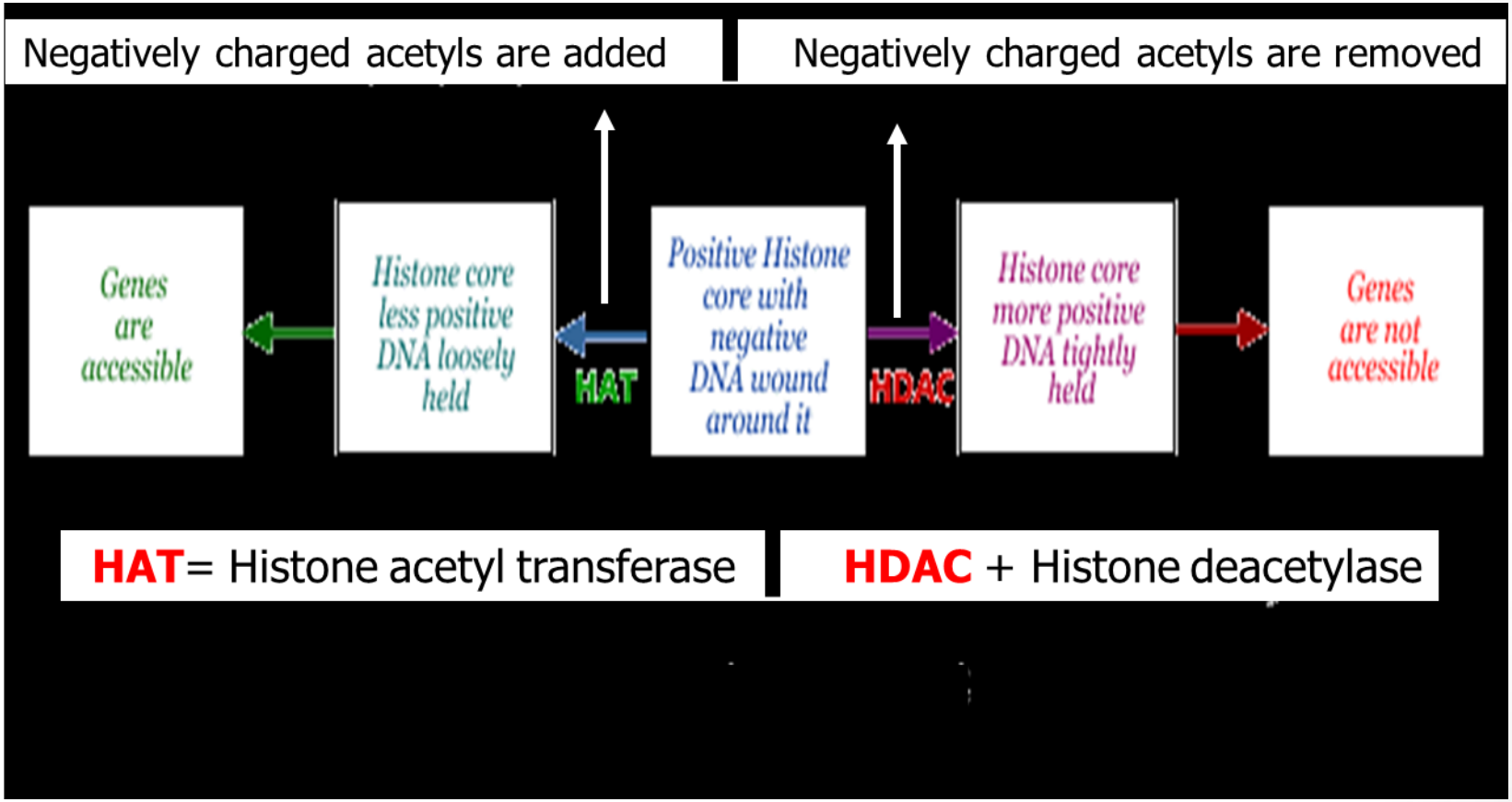
Chromatin Structure



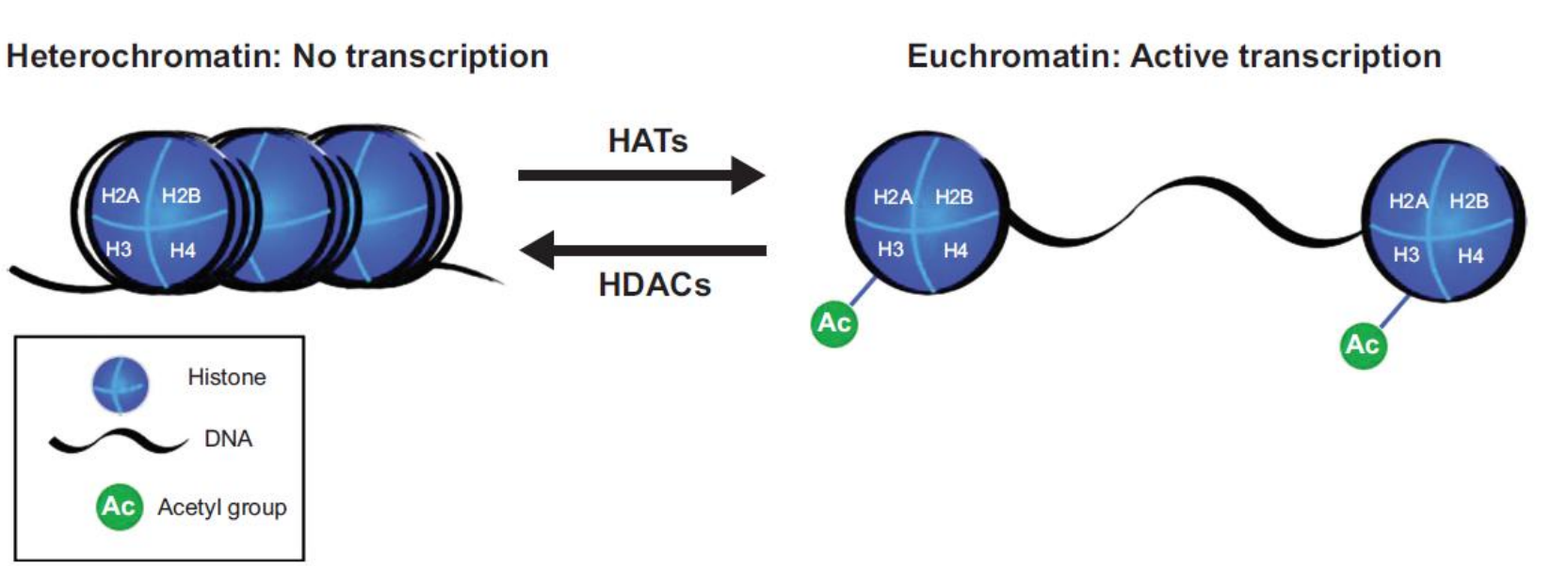


Nucleosome

Histone modification



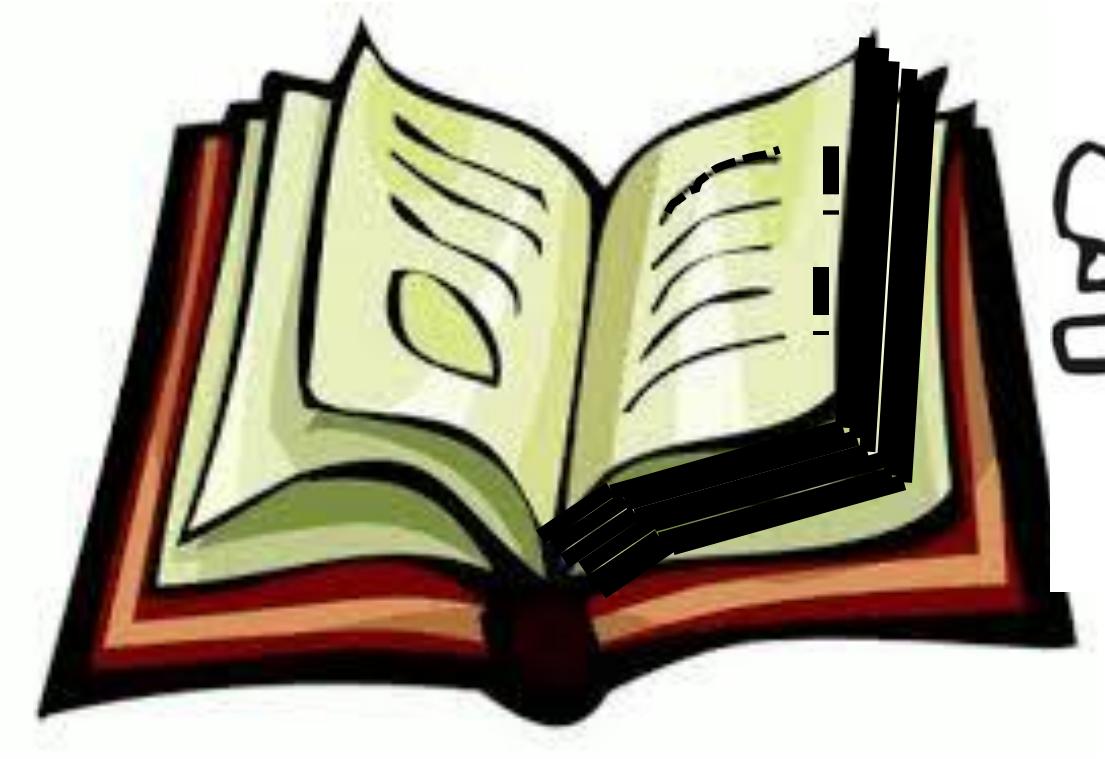
Chromatin states



Constitutive eg. centromeric chromatin
Facultative eg. X inactivation (Barr body)

Epigenetic Modifications

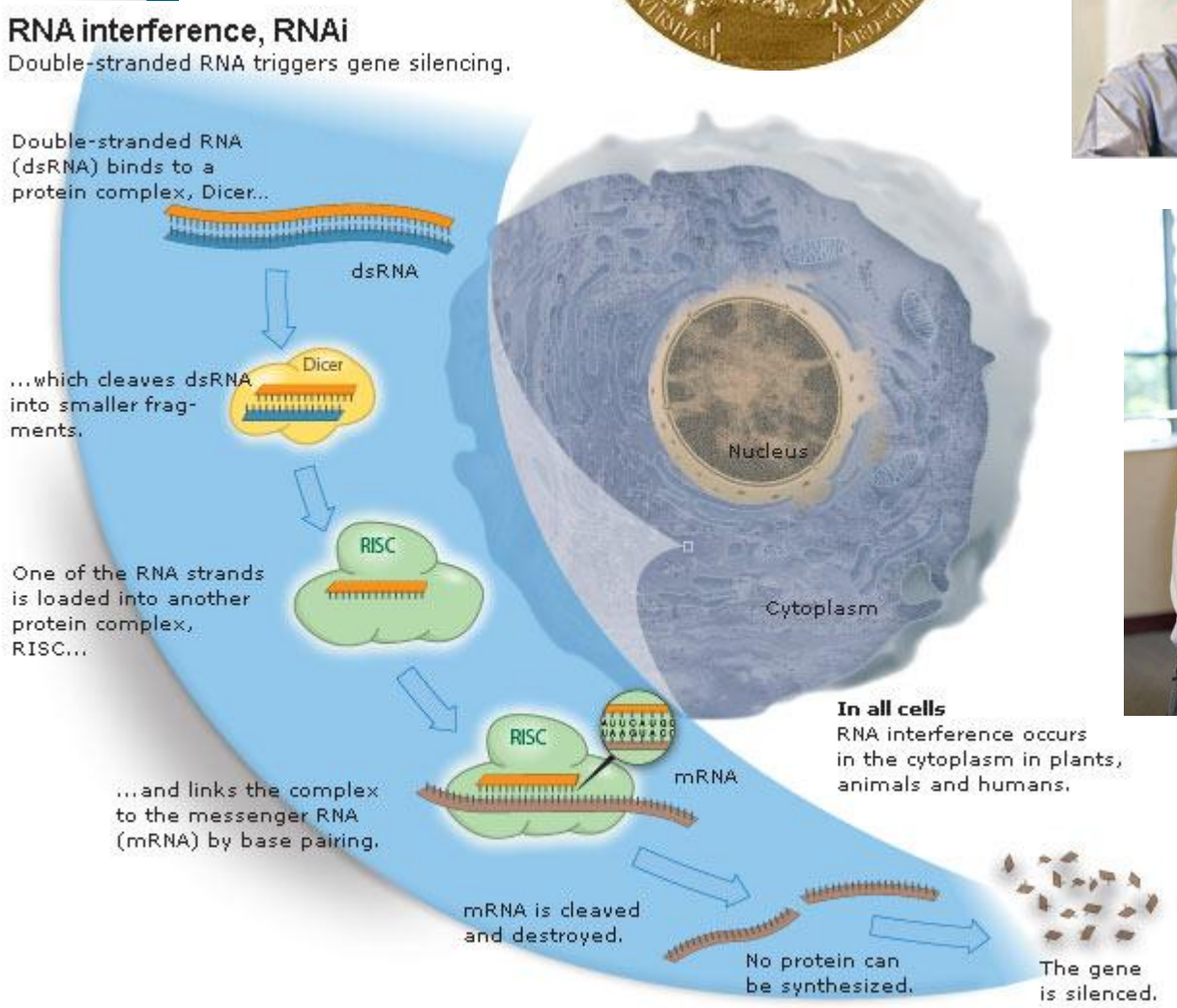
DNA Methylation

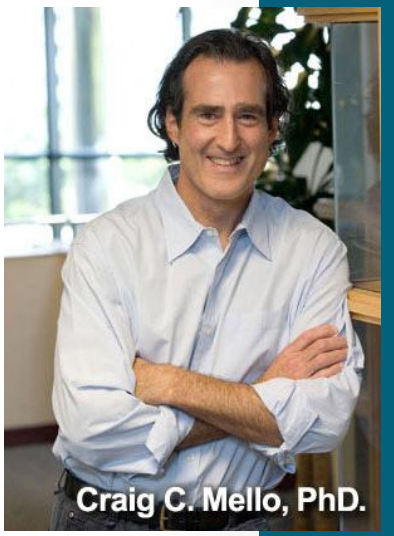


Small Regulatory RNAs

- Non coding RNAs
  - MicroRNAs (miRNAs)
  - Short interfering RNAs (siRNAs)
- Regulate gene expression
  - Chromatin architecture
  - RNA editing & stability
  - Translation, ?Transcription & Splicing
- Hemopoiesis, adipocyte differentiation etc

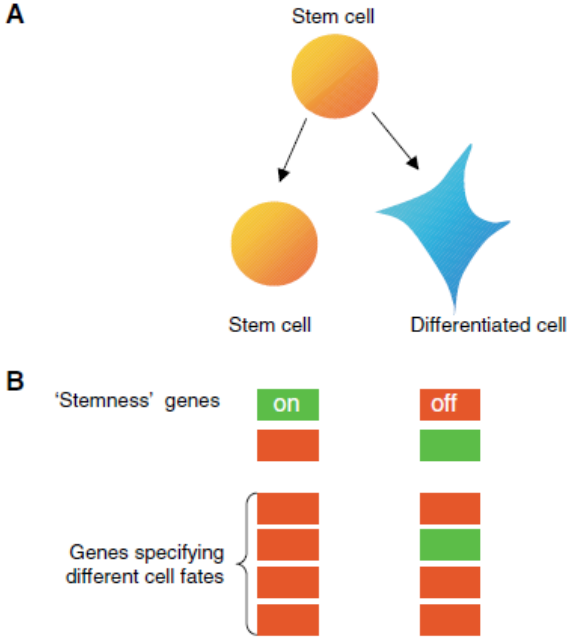
2006

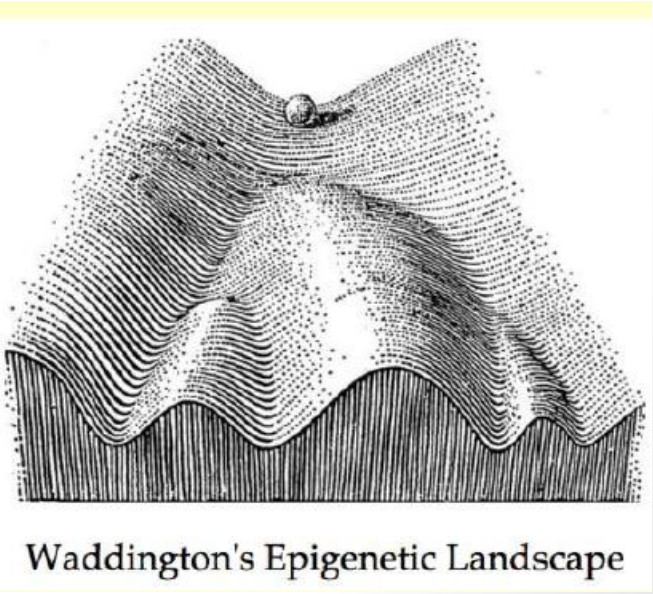


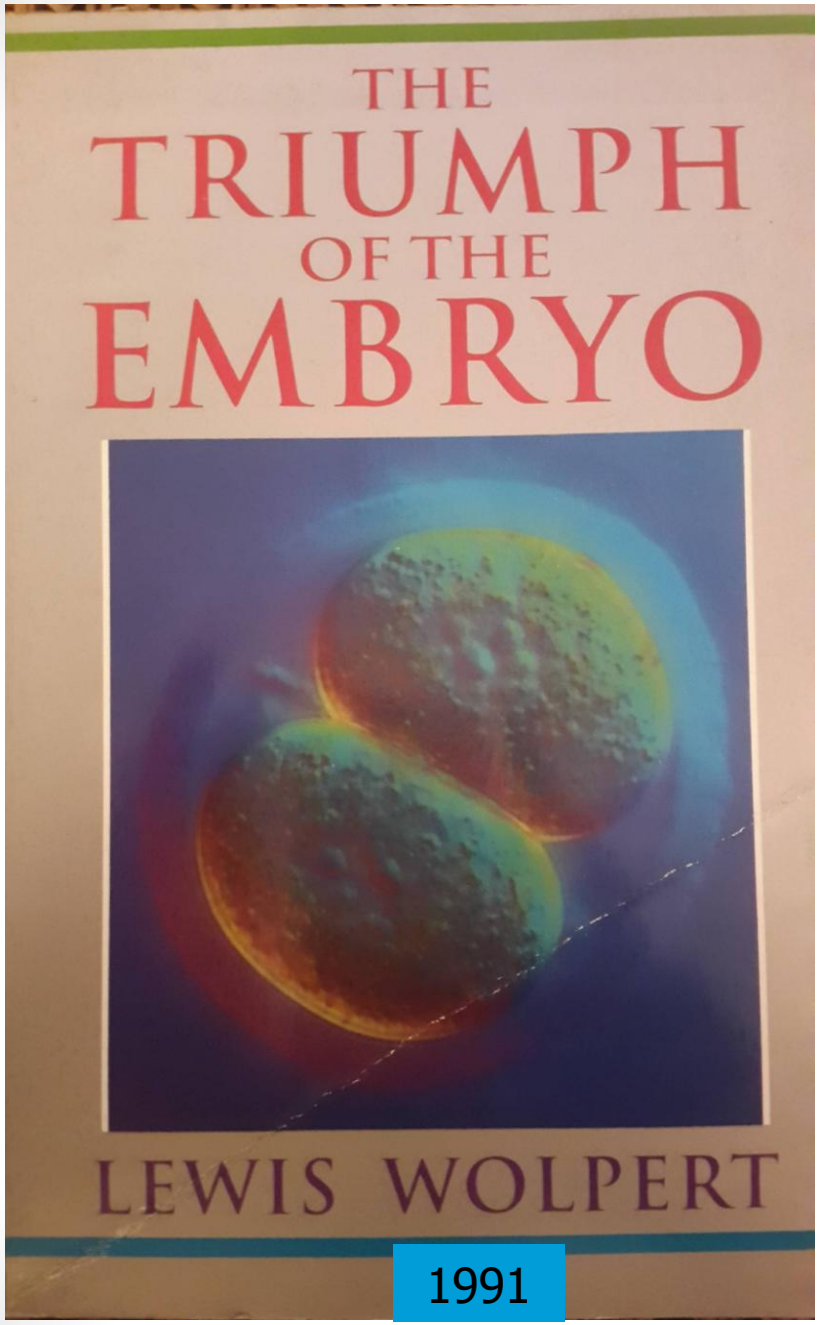


Maintenance of transcriptional memory

- The transcriptional history of each gene is maintained throughout development and into adulthood, by the ubiquitously expressed Polycomb group (PcG) and Trithorax (TrxG) group proteins.
- TrxG maintains activated and PcG maintains silenced gene states through response elements (RE), PRE/TRE.



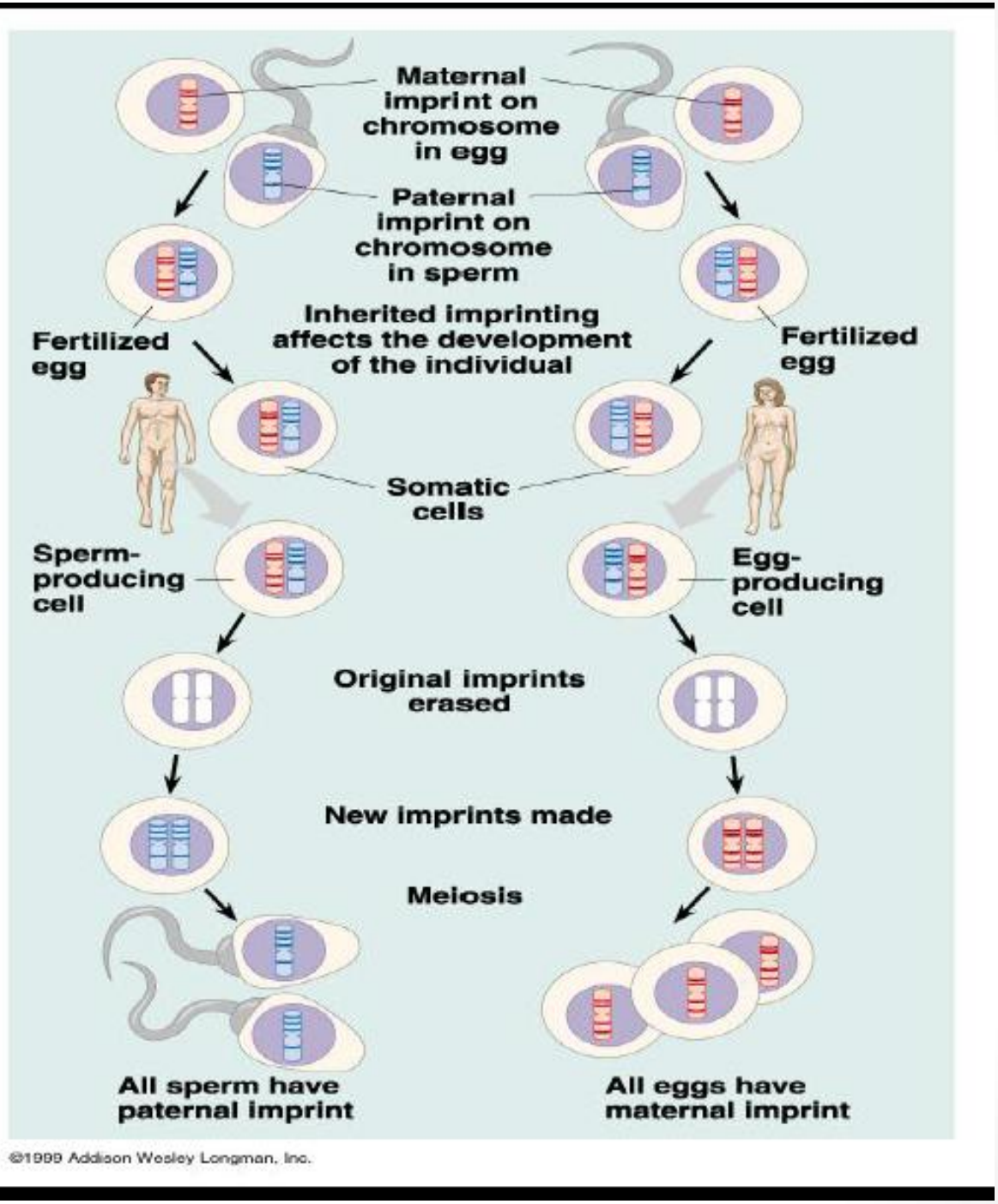




- How a single fertilized cell gives rise to a complex organism.
- How differentiation occurs and is maintained.
- Regeneration, growth and aging.
- How maternal & paternal imprints are created.
- What happens if things go wrong.

Genomic imprinting

- Form of epigenetic regulation in which gene expression depends on whether it is inherited from the maternal or paternal chromosome.
- Process of marking some alleles during gametogenesis leading to differential expression of the gene in all somatic cells in the offspring.

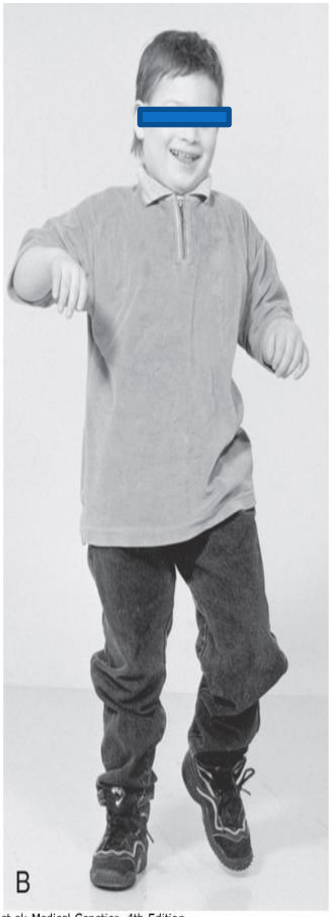

Maternal imprint on chromosome in egg
Paternal imprint on chromosome in sperm
Inherited imprinting affects the development of the individual
Fertilized egg
Fertilized egg
Somatic cells
Sperm-producing cell
Egg-producing cell
Original imprints erased
New imprints made
Meiosis
All sperm have paternal imprint
All eggs have maternal imprint
©1999 Addison Wesley Longman, Inc.

Disorders of genetic imprinting

- Prader-Wili Syndrome (15q 11-13)
- Angelman Syndrome (15q 11-13)
- Beckwith Weideman Syndrome (H19 & IGF2)
- Silver-Russel syndrome (H19 & IGF2)
- Pseudo-hyperparathyroidism

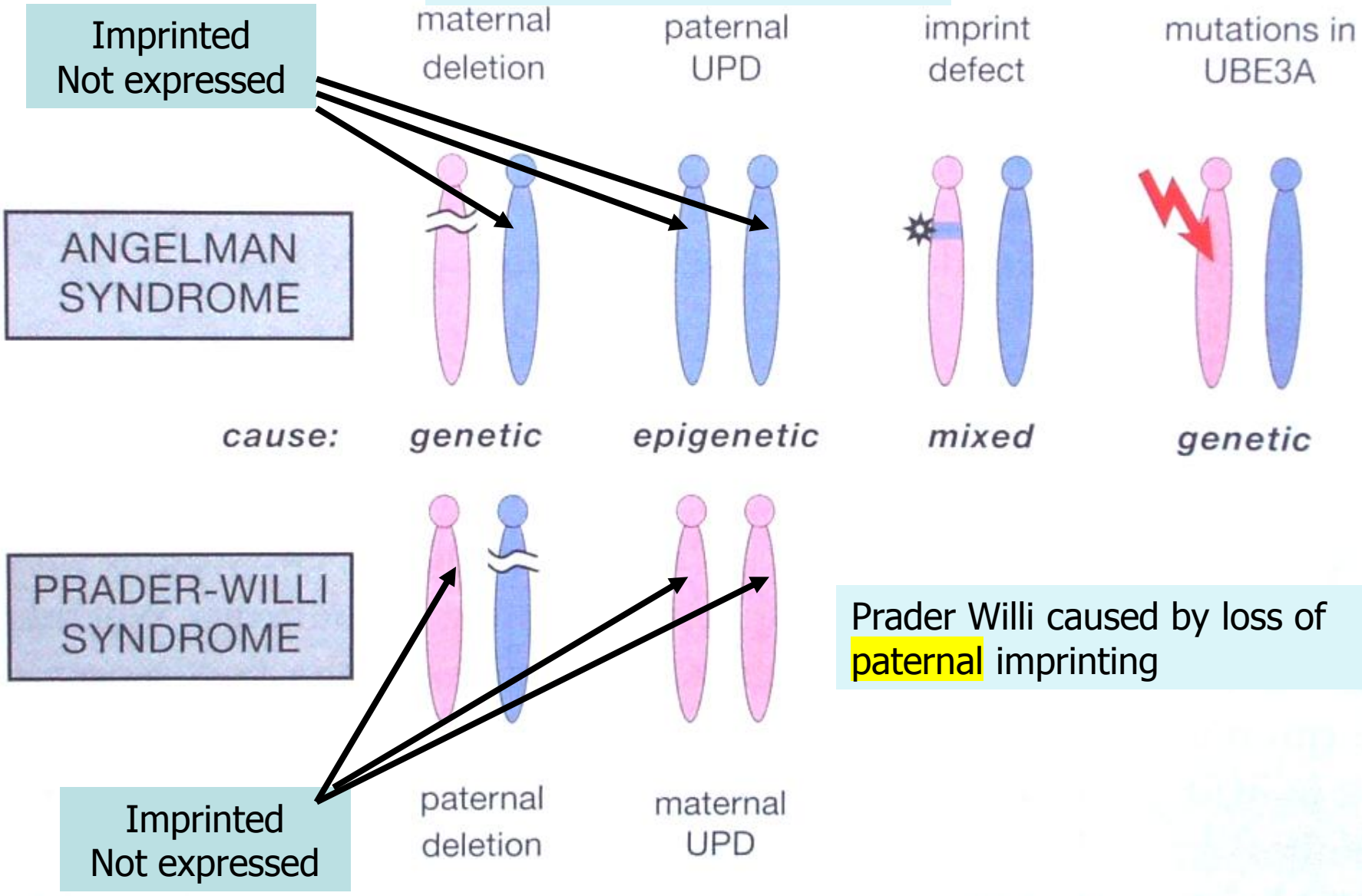
Sister epigenetic syndromes

Prader-Willi



Angelman

Angelman caused by loss of maternal imprinting



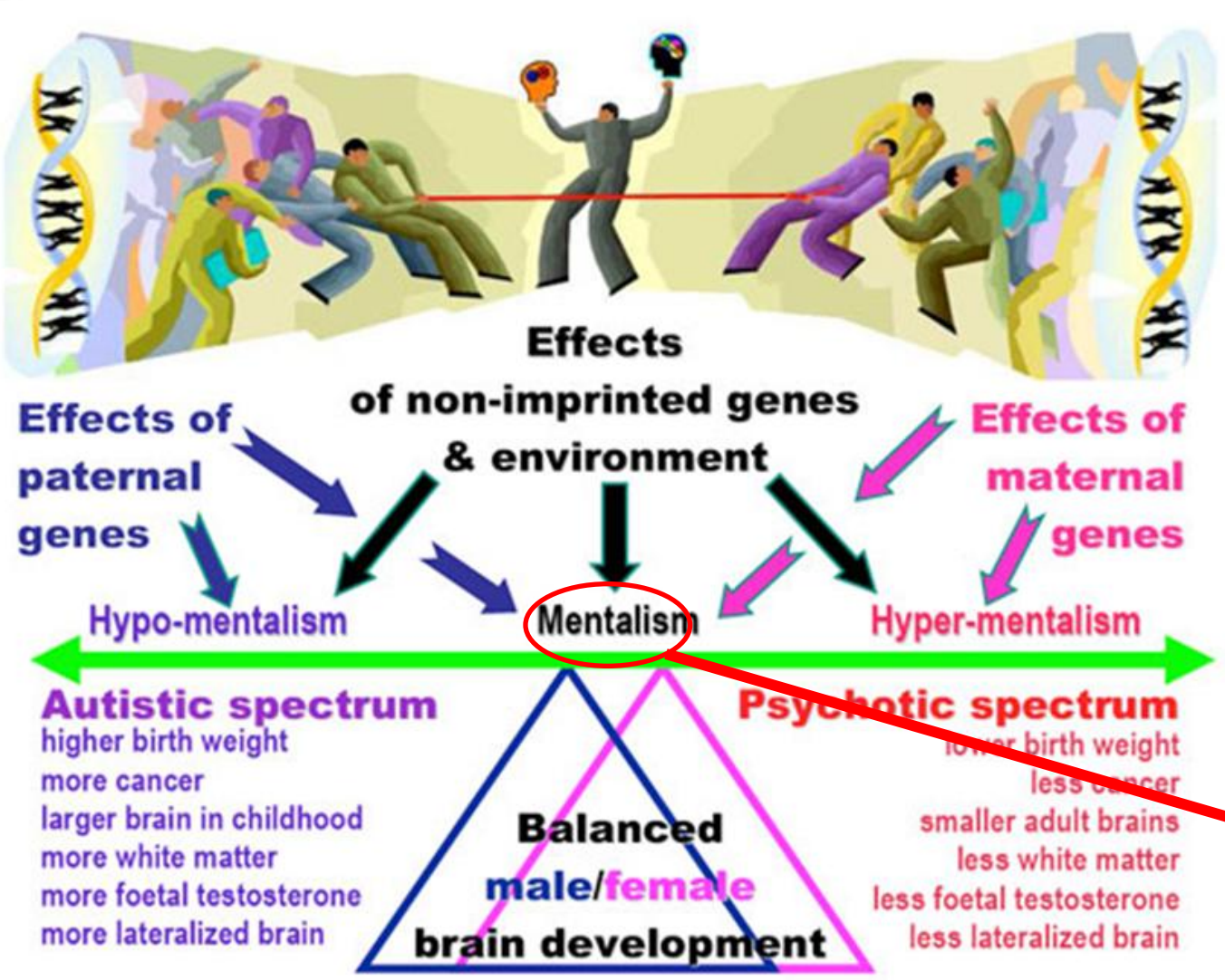
Prader Willi caused by loss of paternal imprinting

15q11.2-q13.1 expression

CONVERSATION : MIND

THE IMPRINTED BRAIN THEORY

Christopher Badcock [11.19.08]



The Diametric Mind

2016

Insights into AI, IQ, the Self and Society:
a sequel to *The Imprinted Brain.*

Christopher Badcock

People skills

Epigenetics & reproduction

AOGS
Acta Obstetricia et Gynecologica Scandinavica

Acta Obstet Gynecol Scand 2016; 95:10–15.

AOGS COMMENTARY

Epigenetics and assisted reproductive technologies

Abstract

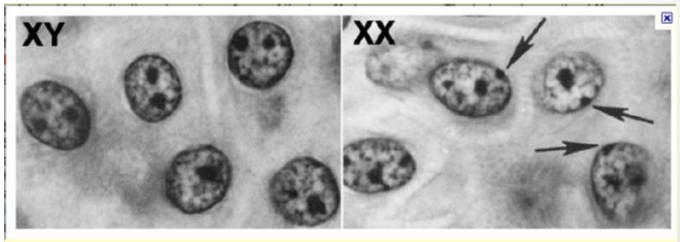
Epigenetic modification controls gene activity without changes in the DNA sequence. The genome undergoes several phases of epigenetic programming during gametogenesis and early embryo development, coinciding with assisted reproductive technologies (ART) treatments. Imprinting disorders have been associated with ART techniques, but disentangling the influence of the ART procedures per se from the effect of the reproductive disease of the parents is a challenge. Epidemiological human studies have shown altered birthweight profiles in ART compared with spontaneously conceived singletons. Conception with cryopreserved/thawed embryos results in a higher risk of large-for-gestational-age babies, which may be due to epigenetic modification. Further animal studies have shown altered gene expression profiles in offspring conceived by ART related to altered glucose metabolism. It is controversial whether human adolescents conceived by ART have altered lipid and glucose profiles and thereby a higher long-term risk of cardiovascular disease and diabetes. This commentary describes the basic concepts of epigenetics and gives a short overview of the existing literature on the association between imprinting disorders, epigenetic modification and ART.

Have you ever wondered….?

- Why the patchwork colours of a calico cat occur only in females?
- Random X inactivation

X Inactivation- Dosage Compensation

- 1949 Barr & Bertram- Sex Chromatin body
- 1961 Mary Lyon hypothesis of X inactivation in females
- N minus 1 rule
- Developmentally regulated
- Both Xes are active in the zygote and inactivation proceeds with cellular differentiation
- Inactivation is random
- Chromatin based- facultative heterochromatin



Barr, M. L., Bertram, E. G., (1949), A Morphological Distinction between Neurones of the Male and Female, and the Behaviour of the Nucleolar Satellite. *Nature*. ***163*** *(4148): 676-7.*

Rett Syndrome

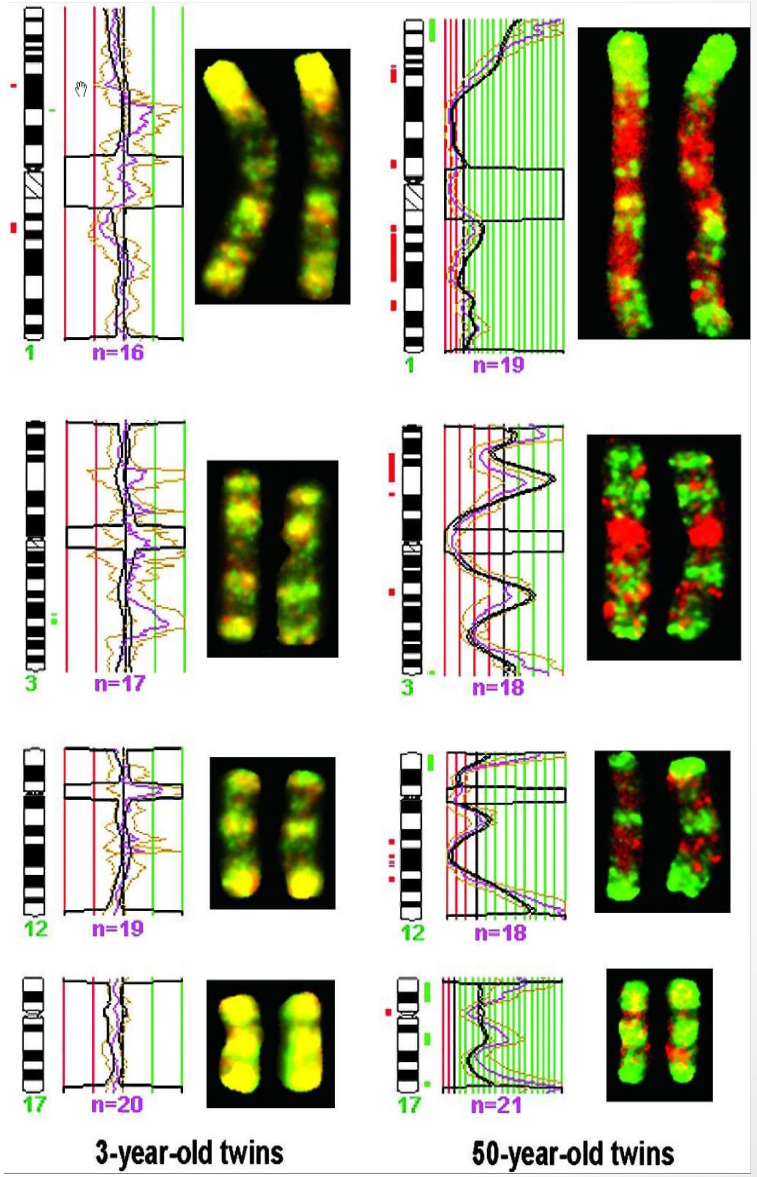
- Severe mental retardation in girls.
- Mutations in the methyl-CpG binding repressor protein MECP2.
- MECP2 belongs to a family of proteins that bind to mDNA. Silences transcription by attracting proteins that switch the gene off or prevent transcription factors from binding to promoter.
- X-linked gene. Males do not survive.
- Random inactivation of X = half of the cells are normal and half do not express MECP2.

Have you ever wondered….?

- Whether identical twins are truly identical
- They are not

Chromosomal Level

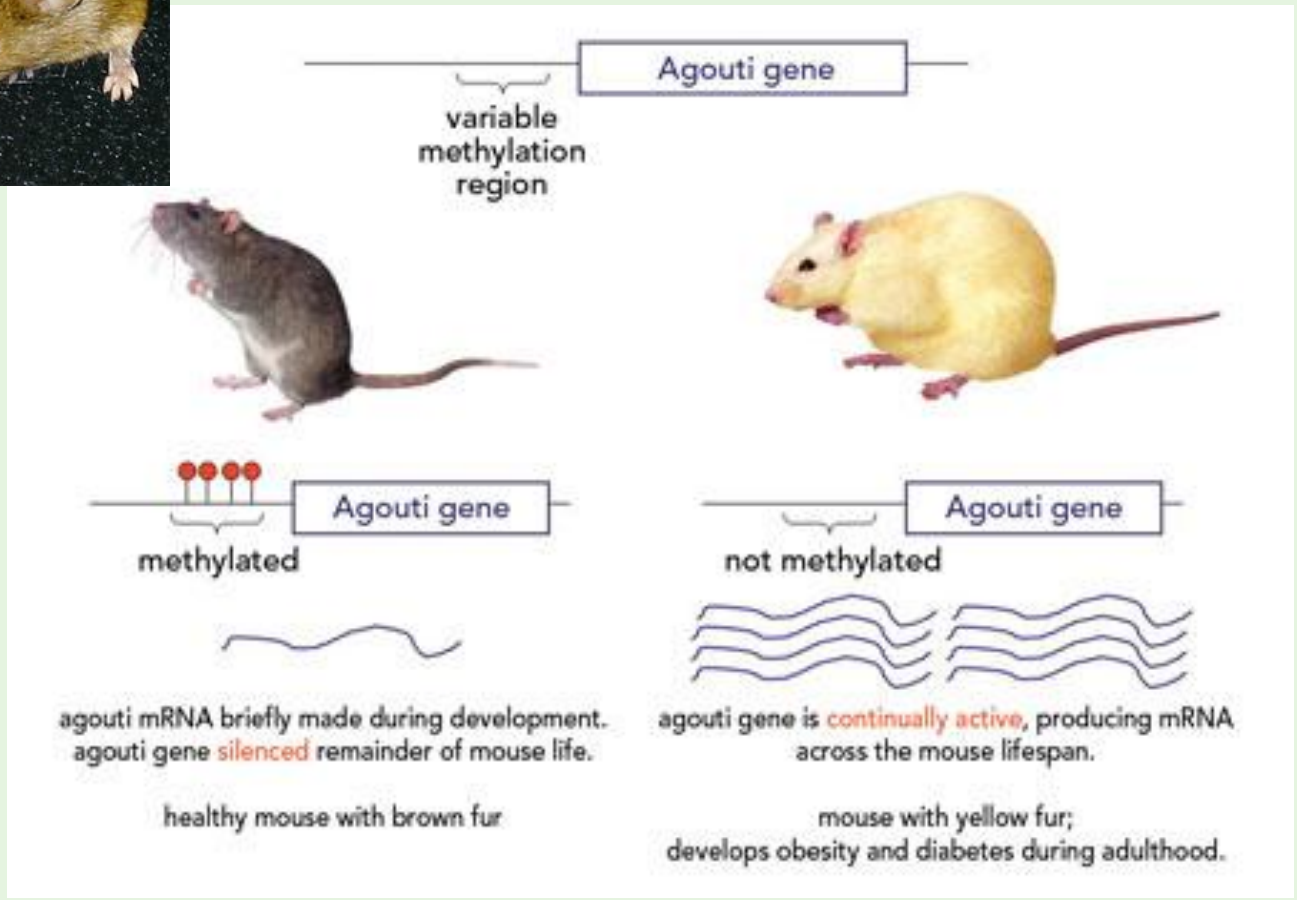
- Comparative genomic hybridization for methylated DNA
  - Yellow = similar chromosome methylation pattern between twins.
  - Red = regions of hypomethylation in one twin compared to the other.
  - Green = regions of hypermethylation in one twin compared to the other.



Nurture versus nature
Effect of diet on isogenic mice

Mother fed on normal diet

Mother fed on diet supplemented with methyl donors



Nature or Nurture or both?

- DNA methylation patterns fluctuate in response to
  - Changes in diet,
  - Inherited genetic polymorphisms
  - Exposures to environmental chemicals
- Methyl groups are acquired through the diet and are donated to DNA through the folate and methionine pathways.
- Low dietary levels of folate, methionine or selenium can have profound clinical consequences viz. neural tube defects, cancer and atherosclerosis.
- The common polymorphism MTHFR 677CT in the methylene-tetrahydrofolate gene has been shown to increase the risk of breast cancer up to 3-fold in premenopausal women. Other studies suggest that the 677TT genotype confers a 40% decreased risk of breast cancer, particularly in women using HRT.

Epigenetics affects the “mind”?

- What is “mind” ?
- Thoughts, behaviour, cognition, consciousness?
- Modulated by molecules eg.
  - Dopamine
  - Serotonin
  - Endorphins
  - Receptors
- These are all proteins coded for by DNA, the expression of which is modulated by epigenetic mechanisms.
- These epigenetic controls may be permanent or reversible.

Epigenetics & mental health

Epigenetic influences of diet, and other environmental factors may modulate stress

NATURE | NEWS

Poverty linked to epigenetic changes and mental illness

Impoverished adolescents acquire DNA marks, brain changes and depression over time.

•Sara Reardon

24 May 2016

Epigenetics & mental health

Figure 1. Stress and, in Particular, Early Life Adversities Activate the Stress Hormone System and May Epigenetically Program the System toward a Lifelong Alteration of the Hormonal Response to Even Minor Stressors

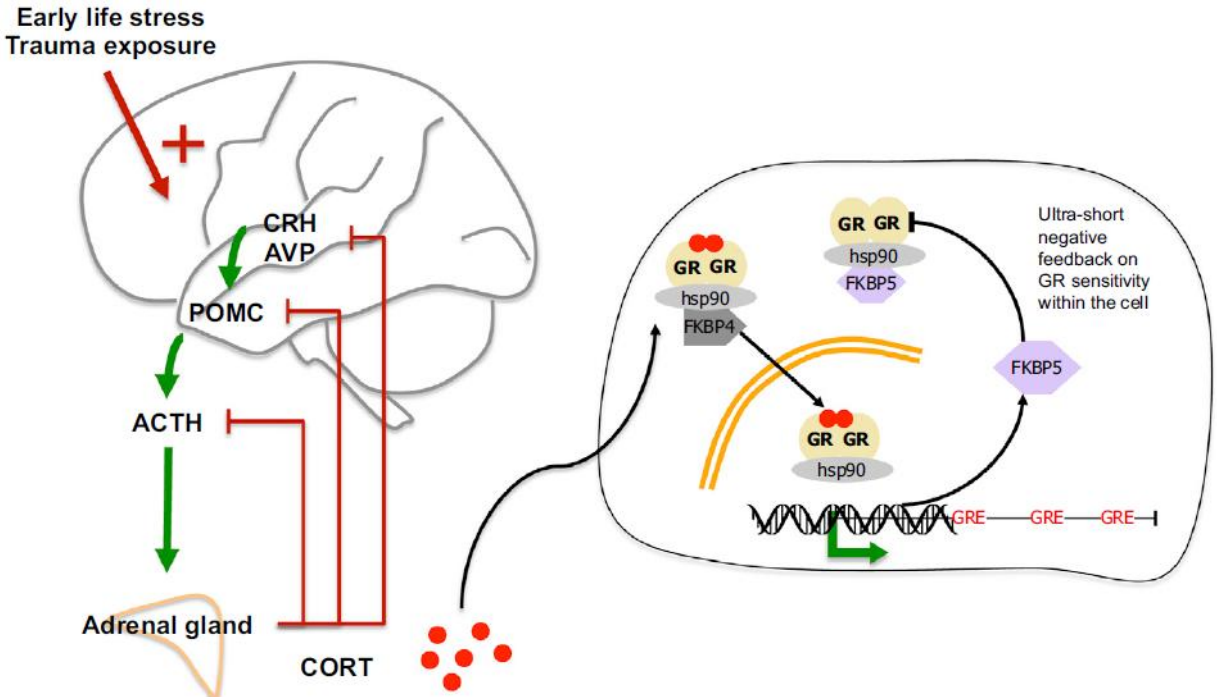


Figure 1. Stress and, in Particular, Early Life Adversities Activate the Stress Hormone System and May Epigenetically Program the System toward a Lifelong Alteration of the Hormonal Response to Even Minor Stressors

The neuropeptides corticotrophin-releasing hormone (CRH) and vasopressin (AVP), released from the hypothalamus in response to stress, activate the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, finally leading to an increased systemic cortisol secretion from the adrenal gland. Cortisol binds to steroid receptors, the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR), that act as transcriptional activators or repressors in the nucleus through binding to glucocorticoid response elements. This influences the expression of numerous genes involved in the stress response, immune function, and metabolism. Binding of the GR and transcriptional activation of, for example, FKBP5 provide an ultrashort feedback to the GR, terminating the stress response and secretion of cortisol.

Epigenetics of Stress-Related Psychiatric Disorders and Gene × Environment Interactions

Torsten Klengel[1,2] and Elisabeth B. Binder[1,2,*]
[1]Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich 80804, Germany
[2]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA

Neuron
Review
2015

Neurotherapeutics (2013) 10:734–741
DOI 10.1007/s13311-013-0213-6

REVIEW

Epigenetics and Psychiatry

Melissa Mahgoub · Lisa M. Monteggia

Basic research

Epigenetic approaches to psychiatric disorders

Carolyn Ptak, BScH; Arturas Petronis, MD, PhD

Dialogues in Clinical Neuroscience - Vol 12 · No. 1 · 2010

Selected abbreviations and acronyms

AD	*Alzheimer's disease*
ASD	*autism spectrum disorders*
BD	*bipolar disorder*
DNMT	*DNA methyltransferase*
GABA	*γ-aminobutyric acid*
GAD	*glutamate decarboxylase*
HDAC	*histone deacetylase*
LOAD	*late-onset Alzheimer's disease*
RTT	*Rett syndrome*
SZ	*schizophrenia*

Epigenetics in mental illness: Hope or hype?

J Psychiatry Neurosci 2010;35(6)

Paul R. Albert, PhD

Department of Neuroscience, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, Ont.

Editorial

iMedPub Journals
http://www.imedpub.com/

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Psychiatric Epigenetics: A Personal Perspective

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Editorial

Based on reading two popular science books by the noted Kenyan anthropologist Richard Leakey[1,2], I hypothesized in 2001 and 2002 that psychiatric disorders like schizophrenia (SZ), bipolar disorder (BD) and major depressive disorder (MDD), are due to epigenetic, rather than genetic, defects

In retrospect, how has this theoretical research in psychiatric epigenetics fared in the light of experimental evidence?. At the turn of this century, when this theoretical work was initially published, there was very little experimental evidence to support it. However, over the past 15 years, the

Are epigenetic marks heritable through the germ line?

Överkalix Study

- Retrospective study conducted in Överkalix, Sweden.
- Divided population into three cohorts:

Born 1890	Born 1905	Born 1920

- **Assessed each cohort for access to food during slow growth period (SGP) of adolescence (8-10 girls, 9-12 boys).**

- Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. Kaati G, Bygren LO, Edvinsson S. *Eur J Hum Genet*. 2002, 10:682-8.

Överkalix Study Results

- When the father (P=0.05) was exposed to a famine during his SGP, his offspring exhibited protection against cardiovascular causes of death.
- Paternal grandmother exposure to famine also showed a trend (P=0.11) towards similar protection in grandchildren.
- If the paternal grandfather lived through a famine during his SGP it tended to protect grandchildren from diabetes (P=0.09).
- If the paternal grandfather had an abundance of food during their SGP, the grandchildren had a four-fold increased risk for death of diabetes mellitus.

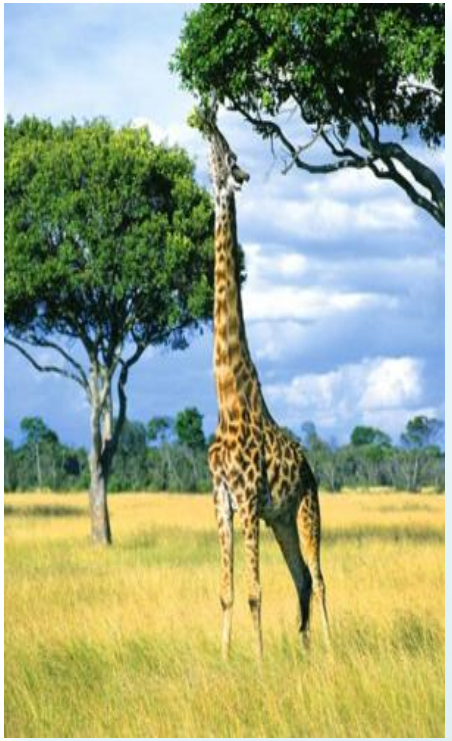
Överkalix Study Results

You are what your grandparents ate!

- One mechanism to explain these results is transmission of epigenetic markers that were influenced by the environment of the parent.
- Effect on grandchildren suggests the markers are maintained through multiple generations.

Lamarkism?

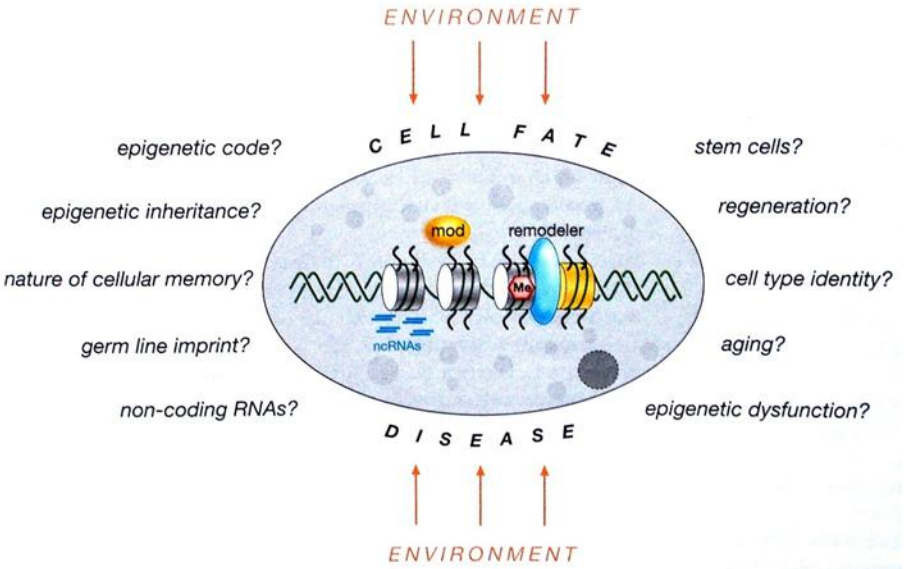
- Jean Batiste Lamark (1744-1829)
  - Inheritance of acquired characteristics.

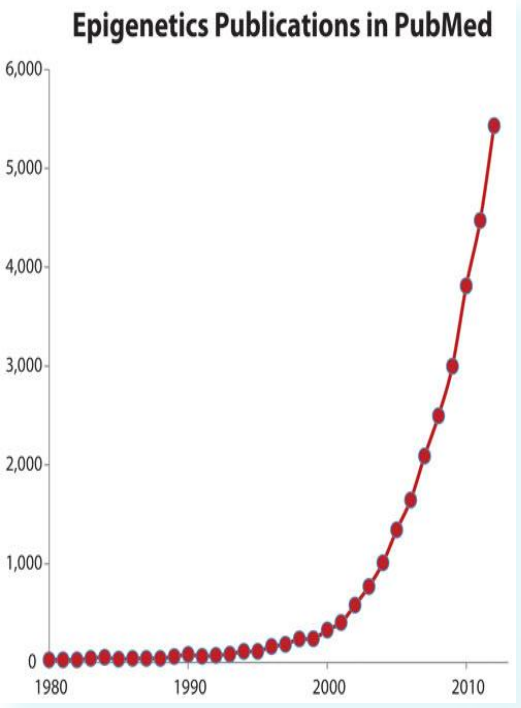


- **Largely discounted with Darwin's publication of Origin of Species and the rediscovery of work of Mendel.**
- **Recent work in epigenetics suggest Lamark may have been correct to some degree.**

Epigenetic Research

- Epigenetics stands at the center of modern medicine because epigenetic changes, unlike DNA sequence which is the same in every cell, can occur as a result of dietary and other environmental exposure. They may also be heritable.





- Genetic Engineering and Biotechnology News Feb 1, 2013 (Vol. 33, No. 3)

DNA is not Destiny

- The new science of epigenetics rewrites the rules of disease, heredity, and identity.


If they ask you anything you don't know, just say it's due to epigenetics.