GENETICS
after Mendel

/A/ GENE as a material substance
in chromosome

/B/ „SWITCH OFF/ON“ of gene
and basic idea of EPIGENETIC

/C/ Non-mendelian variability

/D/ GENETIC ILLNESS PROBABILITY for
X-linkded and Y-linked genes

Problematic or 100% correct Mendelian genetics?

Menel theory of organism heredity was very precise and based on postulating of 2 alleles (one from father = paternal; one from mother = maternal) and very precise mathematical rule of combination of these alleles (in crating of gamets, or in crating of zygota from haploid gamets). Mendel was genial man, becaouse this postulate was derived from statistic of phenotype, he was not able to se microscopical structure of gene in chromosome or proteins which modifiy gene expresion**. These postulate and 3 Mendel Laws are true and valid for computing of heredity (transfer probality from parents for many anatomy marker, pigment of hair ,shape of nose, enzyme aktivity, anemic blood cell, and many other….)**

However another medicial experts during 20th century have found in patients and experimental animal set the exceptions to the Mendel rule. Mendel's laws are correct, however in real life none of the three laws is completely correct for all genes and all genetic transfr of illnesses. We know now that some hereditary factors are codominant, not completely dominant, to others; one can cross red with white petunias and get pink offspring, not red or white offspring as Mendel would have predicted. We also know that the law of segregation is not always true in its literal sense. In humans, the X and the Y chromosome are not passed along entirely at random from a father—slightly more boys than girls are conceived. And we also know that not all hereditary factors assort independently. Those that are located close together on the same chromosome tend to be inherited as a unit, not as independent entities. This aspcet will be presented in next chaptr /A/ and /B/ and /C/, and remeber that all these principes can be combined in ral organism and real patient.

/A/ GENE as a material substance in chromosome

- MENDEL:

Endowment / Natural Ability

- 20th CENTURY:

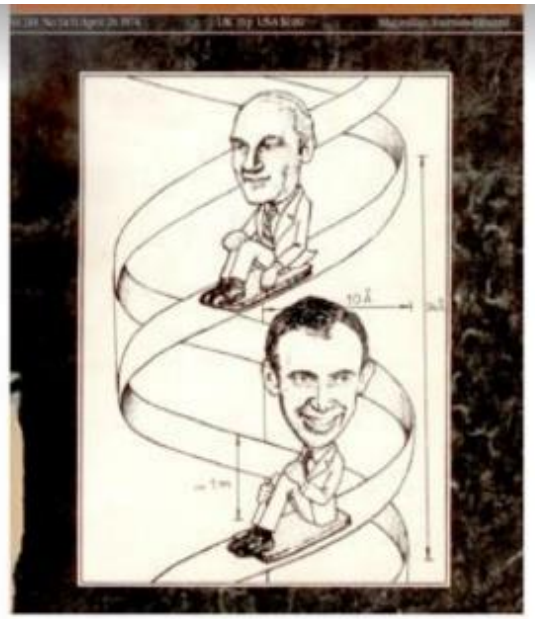
Gene / Genetic information

Short history of material substance exploring : 1871

Miescher 1871: discovered „nuclein“, a substance occuring in cell

Fig. 5. Glass vial containing nuclein isolated from salmon sperm by Friedrich Miescher while working at the University of Basel. The faded label reads Nuclein aus Lachssperma, F. Miescher (Nuclein from salmon sperm, F. Miescher). Possession of the Interfakult-res Institut fqr Biochemie (Interfacultary Institute for Biochemistry), University of Tubingen, Germany; photography by Alfons Renz, University of Tubingen.

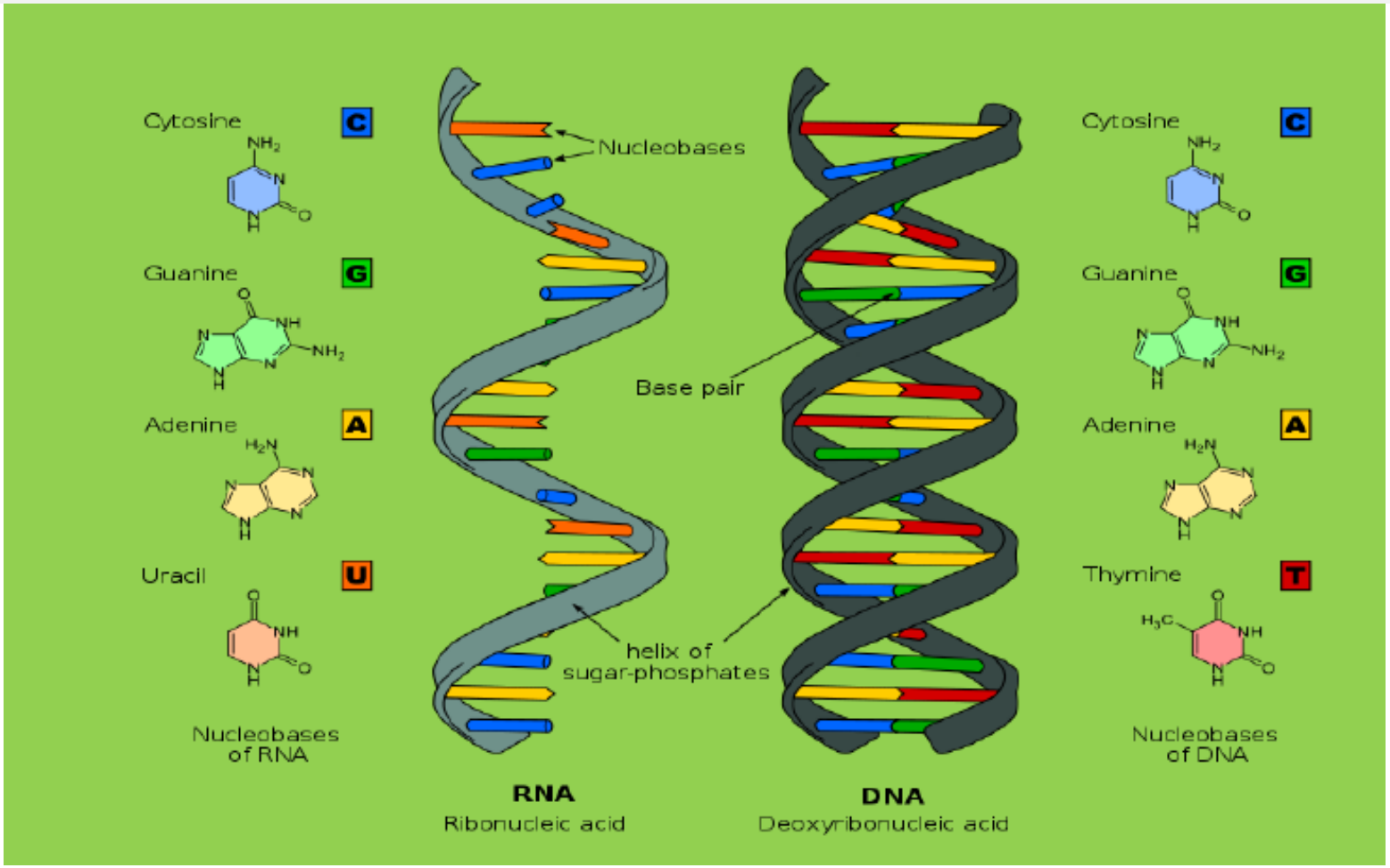
1953



1953: James Watson, Francis Crick, Rosalind Franklin, Maurice Wilkins: the DNA double helix

Structure of DNA and components

(learn the names of acids and possible combination of acid paris in RNA and DNA)

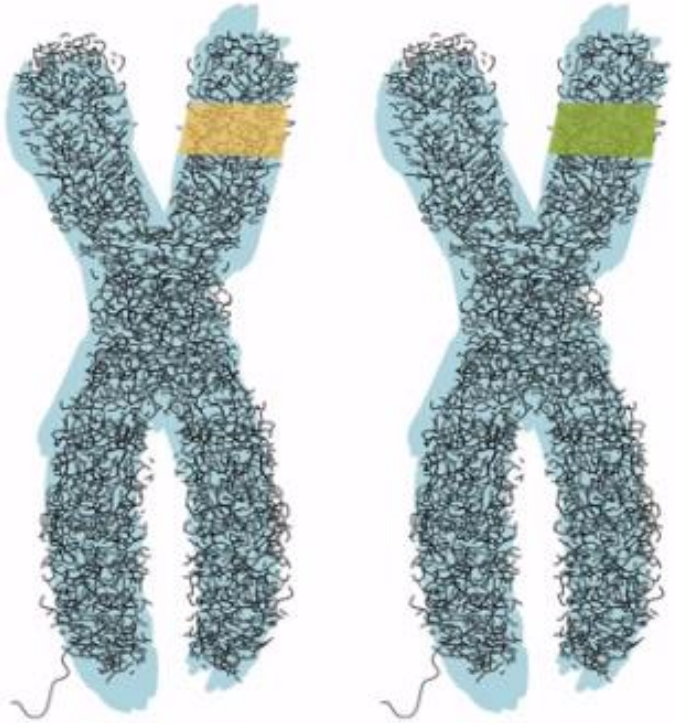


Example of Genetic code (C = cytosine, G = guanine, A = adenine, T = thymine…) of 1% of 3rd human chromosome

Example of one gene

AGCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATGAGGTTGTGAGGCGCTGC
CCCCACCATGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAA
GGAAATGAGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCT
CCTCAGCATCTTATCCGAGTGGAAGGAAATGAGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTGC
TCAGATAGCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATGAGGTTGTGAGG
CGCTGCCCCCACCA**TGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGCATC**TTATCCGA
GTGGAAGGAAATGAGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGGTCTG
GCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATAGGTTGTGAGGCGCTGCCCCCACCATGAGC
GCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATGAGGTTG
TGAGGCGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGCATCTTA
TCCGAGTGGAAGGAAATGAGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATG
GTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATGAGGTTGTGAGGCGCTGCCCCCACC
ATGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATG
AGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGC
ATCTTATCCGAGTGGAAGGAAATGAGGTTGTGAGGCGCTGCCCCCACCATGAGCGCTGCTCAGATA
GCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAGGAAATGAGGTTGTGAGGCGCTGCC
CCCACCATGAGCGCTGCTCAGATAGCGATGGTCTGGCCCCTCCTCAGCATCTTATCCGAGTGGAAG
GAAAT

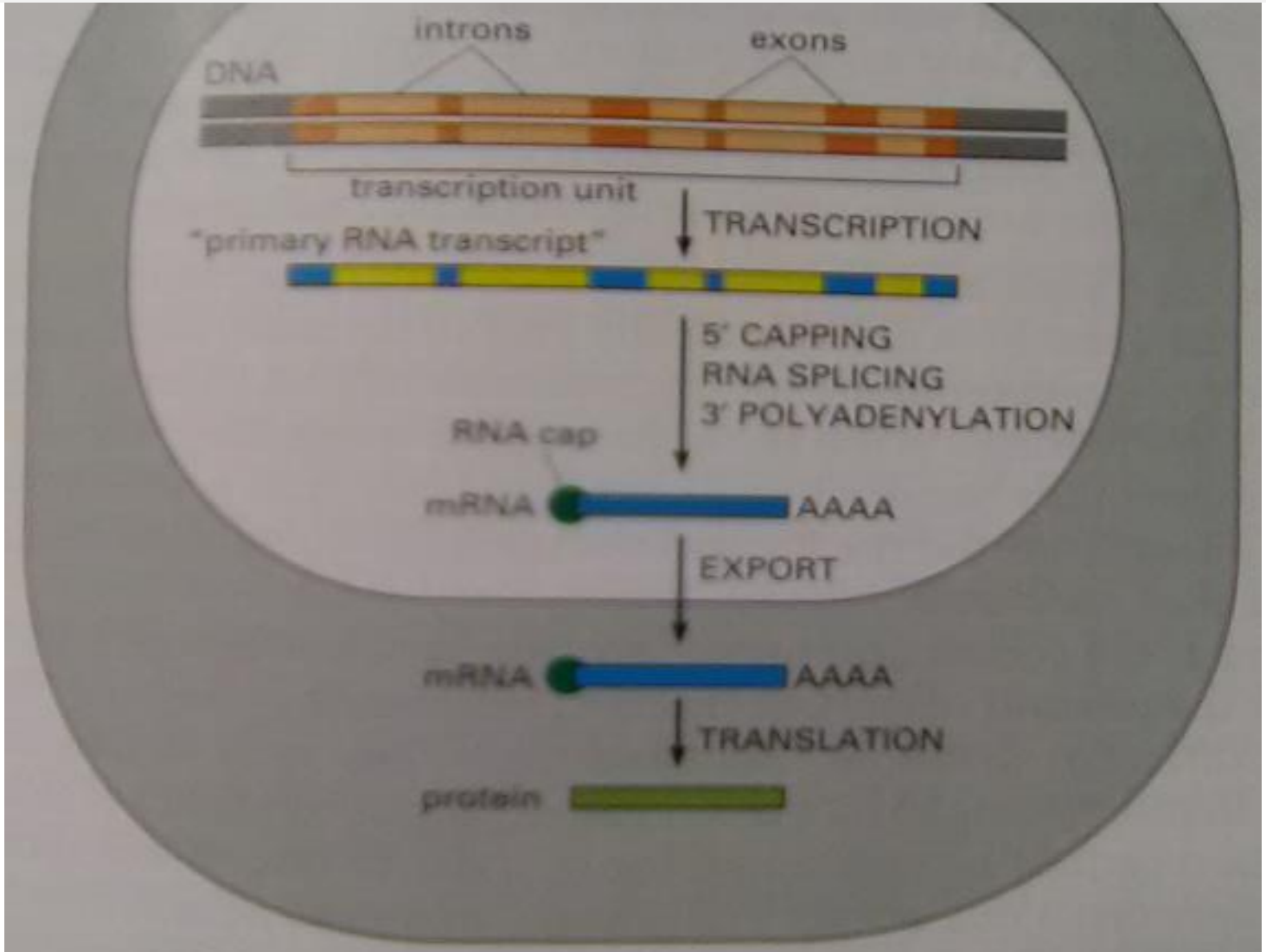
Every human organism have “2 genetic message“ of one gene



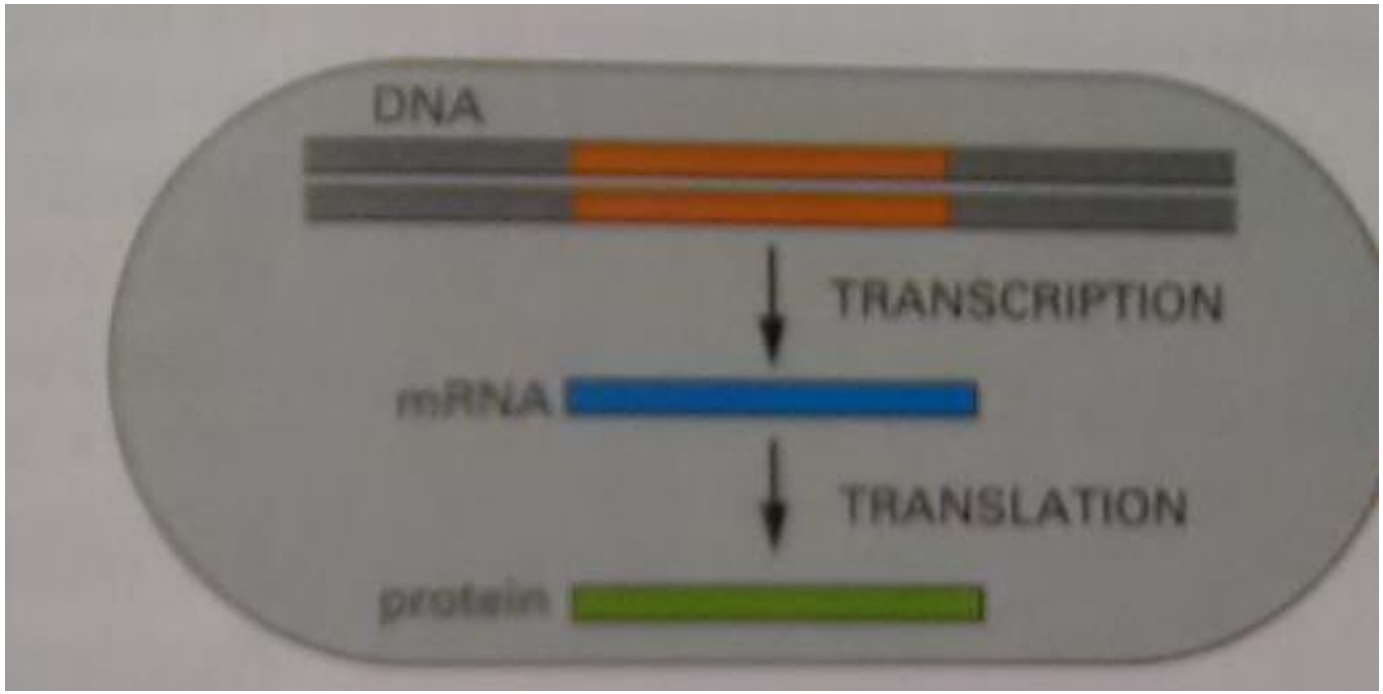
gene – a section of DNA that controls a trait (ex. seed color, eye color,blood type)

allele – a variation of a gene (yellow vs green)

(EUKARYOTA) Human cells: „Display“ of gene into real protein molecule



Different „delivery of information“ PROKARYOTA



/B/ „SWITCH OFF/ON“ of gene and basic idea of EPIGENETIC

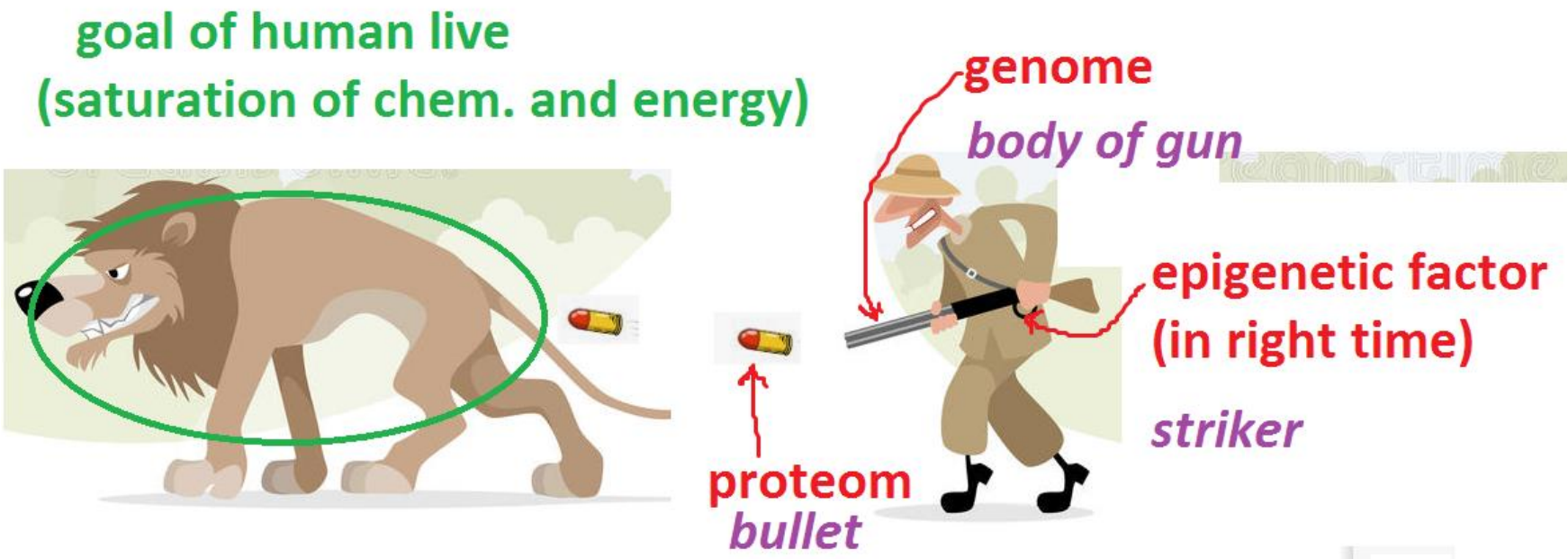
Two important facts:

1/ Human bodies have such different parts, like skin, eyes, and heart, **even if almost all our cells have the same DNA??????** It is because different parts of our DNA are switched “on” and “off” in different cells!

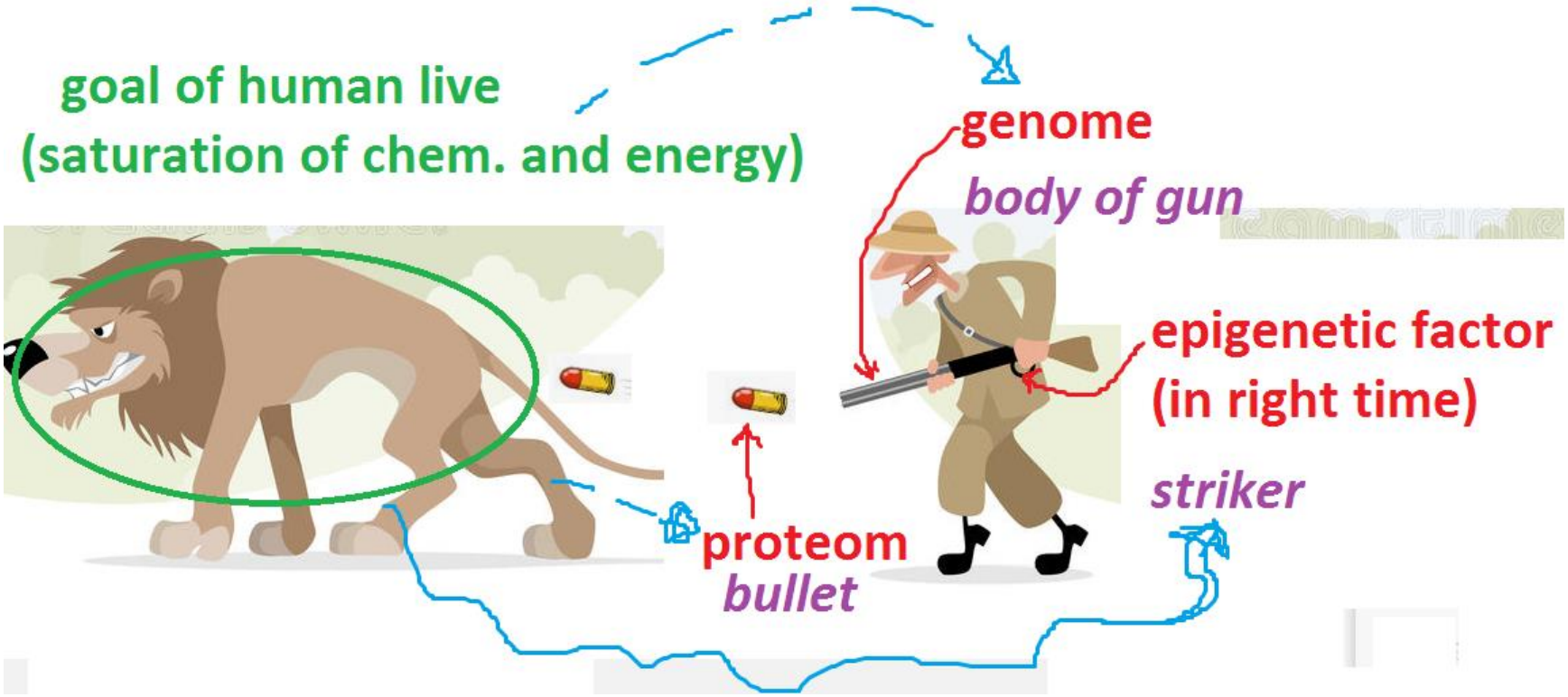
2/ Two rabbits (2 same genetic twins) have the same set of DNA code in muscle. However one rabbit can be famous sprinter and second not, becouse is in the farm where is a lot of smoke.

Then, let us take a close look at how the DNA is organized within the cells and translated:

Nice analogy



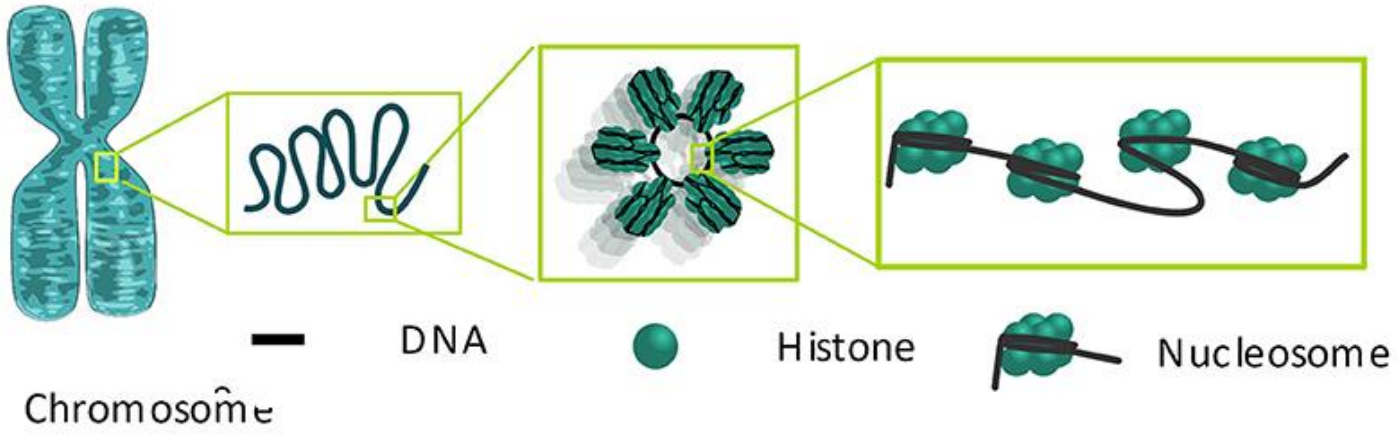
Nice analogy
(with described possible feedback)



A person's **genotype** is their unique sequence of DNA. More specifically, this term is used to refer to the two alleles a person has inherited for a particular gene.
Phenotype is the detectable expression of this genotype

What is the microcopical mechanism of this OFF/ON switching ??

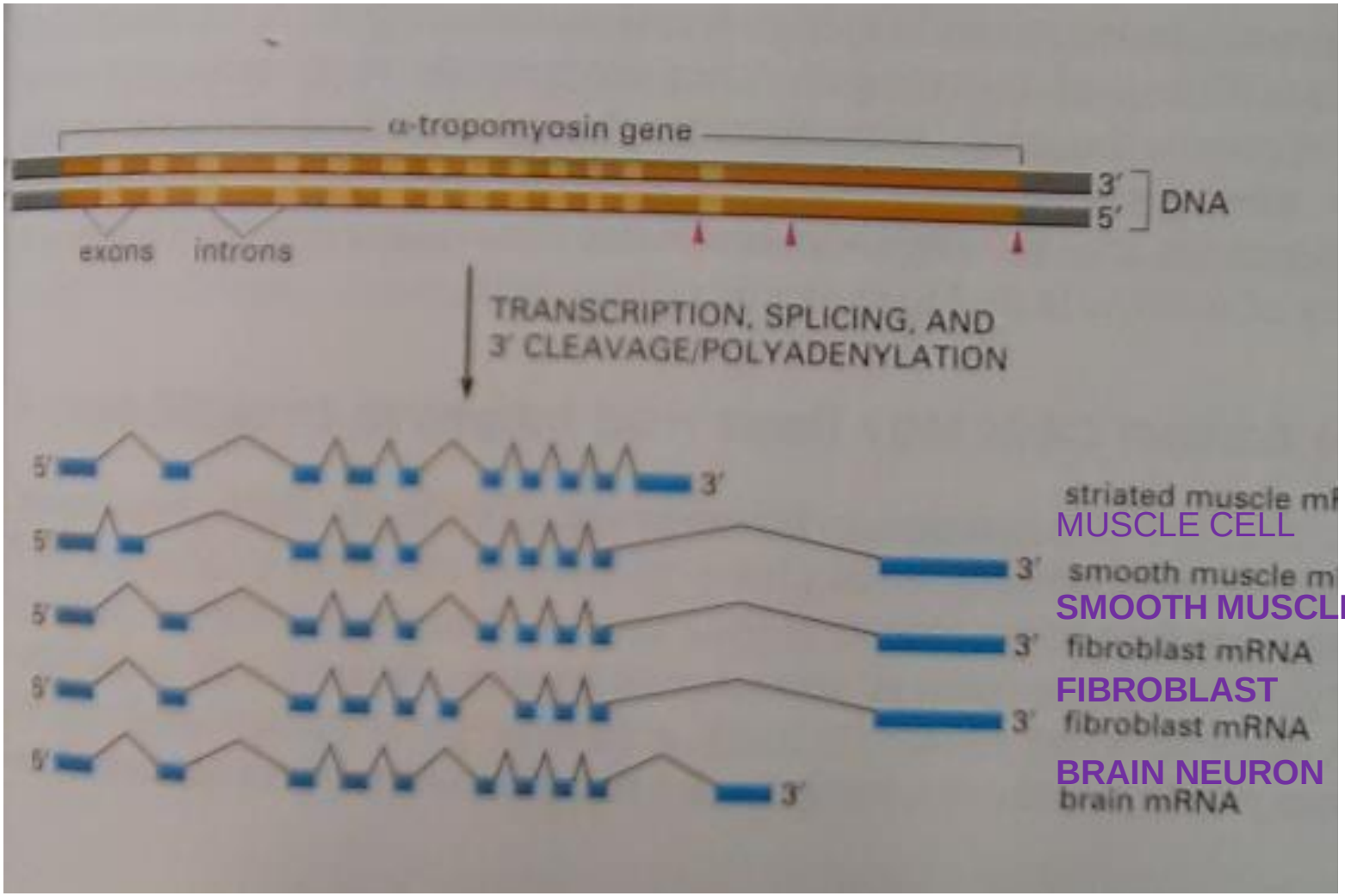
Well-packed DNA, wrapped tightly around histones, is not accessible to the cellular machinery that reads the information on the DNA and turns it into proteins.



(Analogy: *Imagine a book with some pages held together by a paper clip. You cannot read what is on those pages! They must be accessible to you before you can read them. The packaging of the DNA has the same effect*.

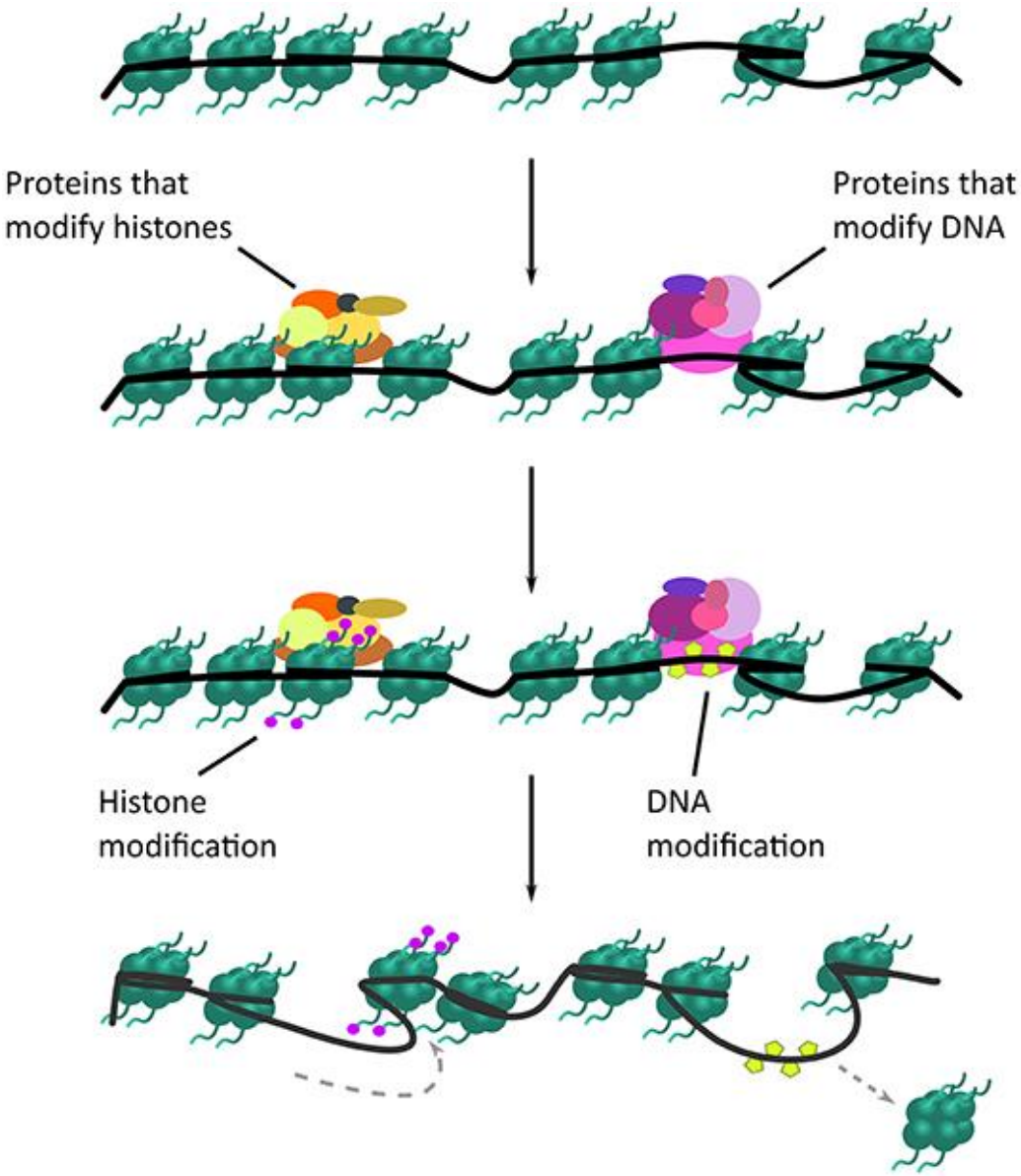
The human genome has more than 20,400 genes which contain information for the formation of proteins. This sounds like a lot, but proteins are extremely important for the proper functioning and development of our bodies, so we need all these proteins. But we do not need all of them at the same time, and it would be difficult for a cell to deal with producing and managing so many types of protein simultaneously. Thus, only a few proteins are produced at the same time in a cell. This means that only a few genes are active (switched "on") at a time in any cell. The genes that are "on" will determine what that cell can do—the function of the cell. Some genes need to be active in more than one body part or cell type, while other genes are active only in specific cells. Some genes are active only in specific time (new born time, beast-feeding, etc)

Structure of DNA code
(INTRONs and EXONs)
„delivery of information“



- **Epigenetic changes alter gene activity <u>without</u> modifying the DNA sequence** and are essential to normal development.

Epigenetic regulation is based on molecular mechanism of :



- A gene is switched “on” when the portion of chromatin where it is located “opens.” This process involves proteins that add little chemical modifications to histones or to the DNA. The modifications cause the histone to slide on the DNA or cause the DNA to unwrap from the histone, allowing the chromatin to open and the information on the gene to be read.

- Epigenetic modifications caused by these factors can be “memorized” for long periods of time. When a cell divides, its epigenetic modifications are passed on to the next generation of cells. It is interesting that this situation is different in reproductive cells. Most epigenetic modifications are erased during reproduction. In animals, the modifications that persist only last for about one or two generations.
- The epigenome of an organism is fluid, which means that it is constantly changing. It is shaped in response to stress, in ways that last from hours to months, years, or an entire life. For example, the epigenome of mice exposed to very stressful situations can change.

Example:

Epigenetic events that alter chromatin structure to regulate programs of gene expression have been associated with depression-related behavior, antidepressant action, and resistance to depression or ‘resilience’ rat.

You can see to very nice review article:

Neuropsychopharmacology REVIEWS (2013) 38, 124–137

www.neuropsychopharmacology.org

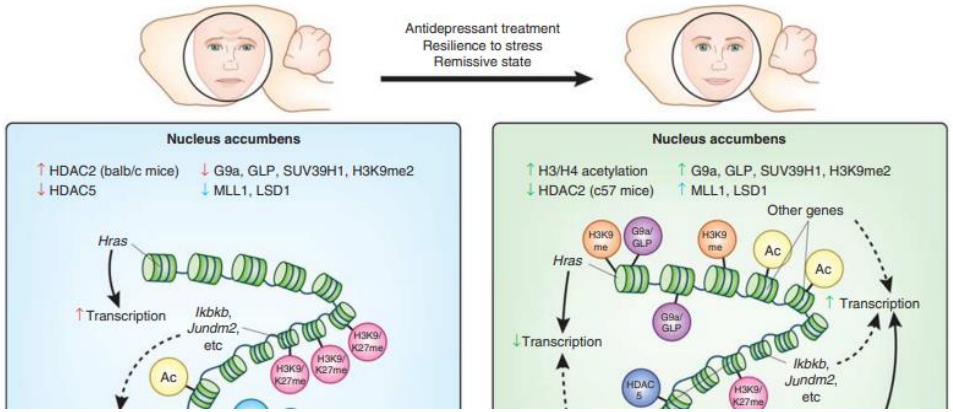
REVIEW

Epigenetics of the Depressed Brain: Role of Histone Acetylation and Methylation

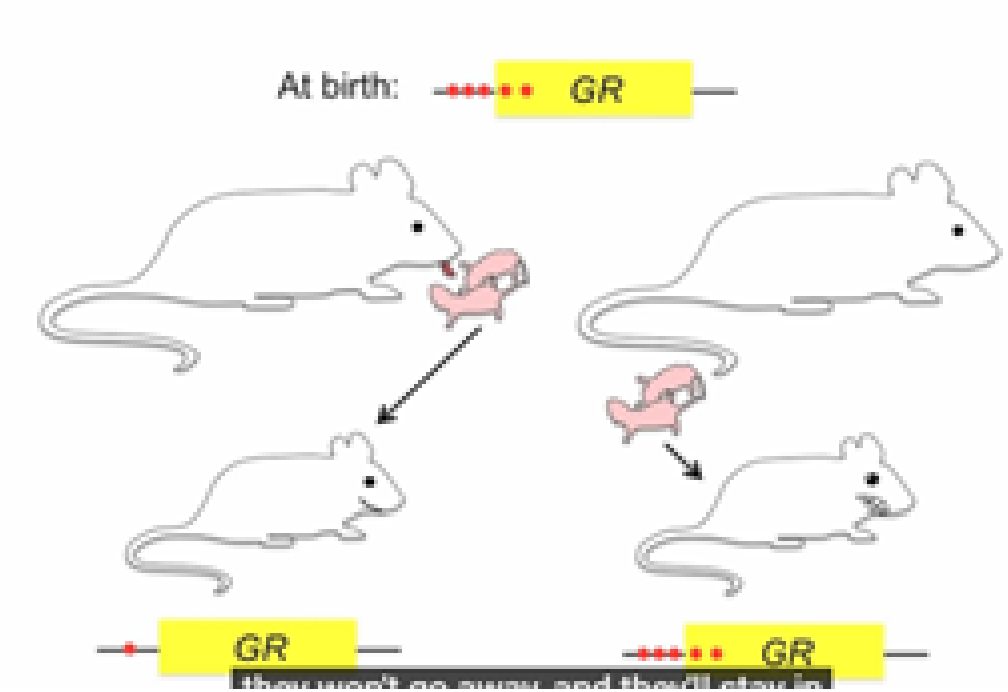
HaoSheng Sun[1], Pamela J Kennedy[1] and Eric J Nestler*,[1]
[1]Fishberg Department of Neuroscience and Friedman Brain Institute, School of Medicine, New York, NY, USA

Major depressive disorder is a chronic, remitting syndrome involving widely distributed circuits in the brain. Stable alterations in gene expression that contribute to structural and functional changes in multiple brain regions are implicated in the

Epigenetic for many illnesses is importnat and investigator bring new view to many mechanism their development, epigenetic iaspect are computed to modern pharamcology studies



Positive example of epigenetic



References

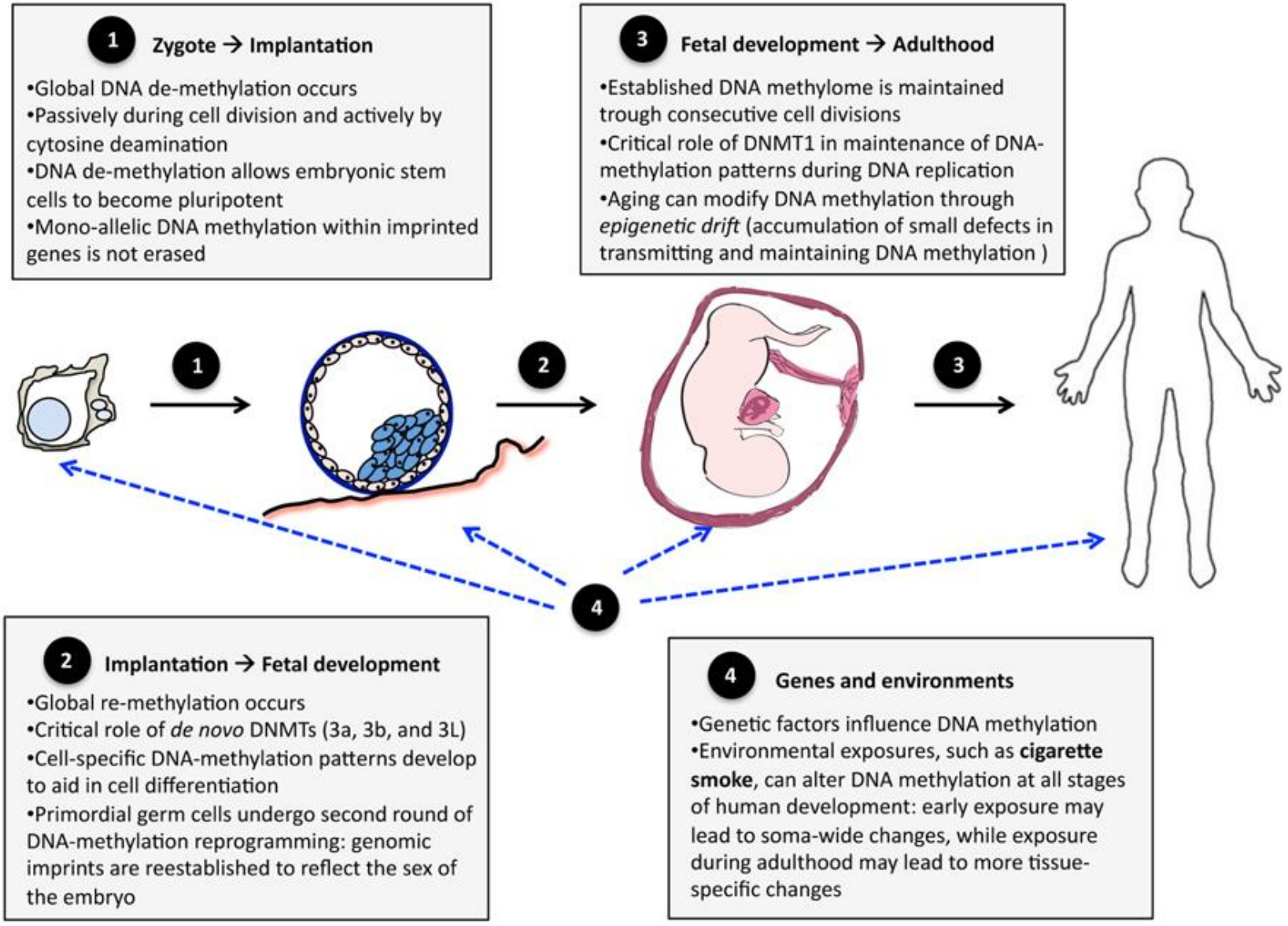
Danese, A., Moffitt, T.E., et al. (2009) “Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers.” Arch Pediatr Adolesc Med. 163 12: 1135–43.

Lucassen, P.J., Oomen, C.A., et al. (2015) “Regulation of adult neurogenesis and plasticity by (early) stress, glucocorticoids, and inflammation.” Cold Spring Harb Perspect Biol. 7 9: a021303.

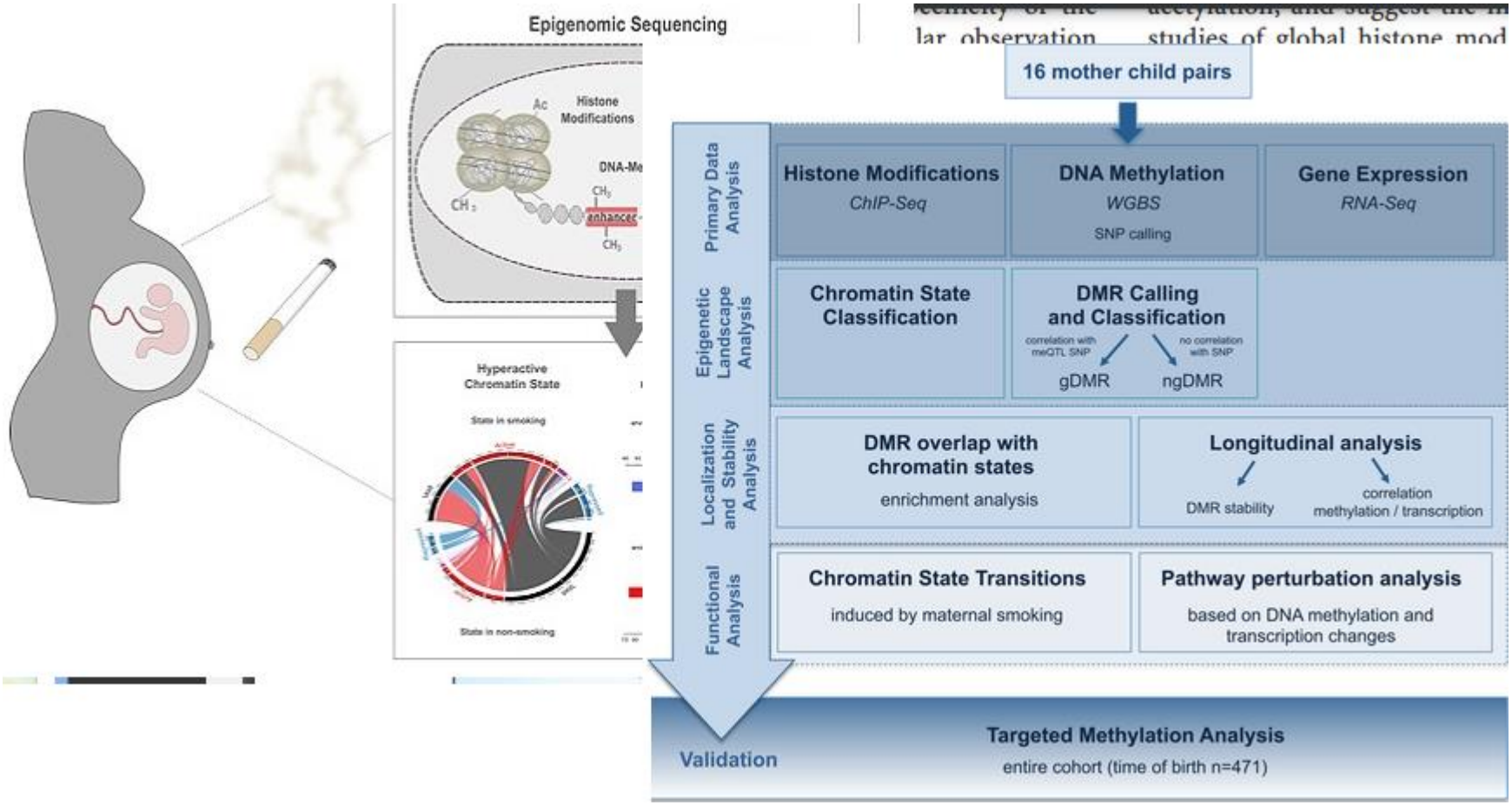
Lucassen, P.J., Naninck, E.F., et al. (2013) “Perinatal programming of adult hippocampal structure and function; emerging roles of stress, nutrition and epigenetics.” Trends Neurosci. 36 11: 621–31

Rat-Mom’s licking appears to provoke epigenetic changes in genes that can help pups manage stress. The most important stress hormone for mammals is called cortisol, and the level of cortisol in our bodies is regulated by glucocorticoid receptors. The gene for the glucocorticoid receptor is highly influenced by maternal care. Highly licked rat pups have lots of glucocorticoid receptors, so they can manage their body’s stress response rapidly and get back to normal quickly.

Negative exampel of epigenetic

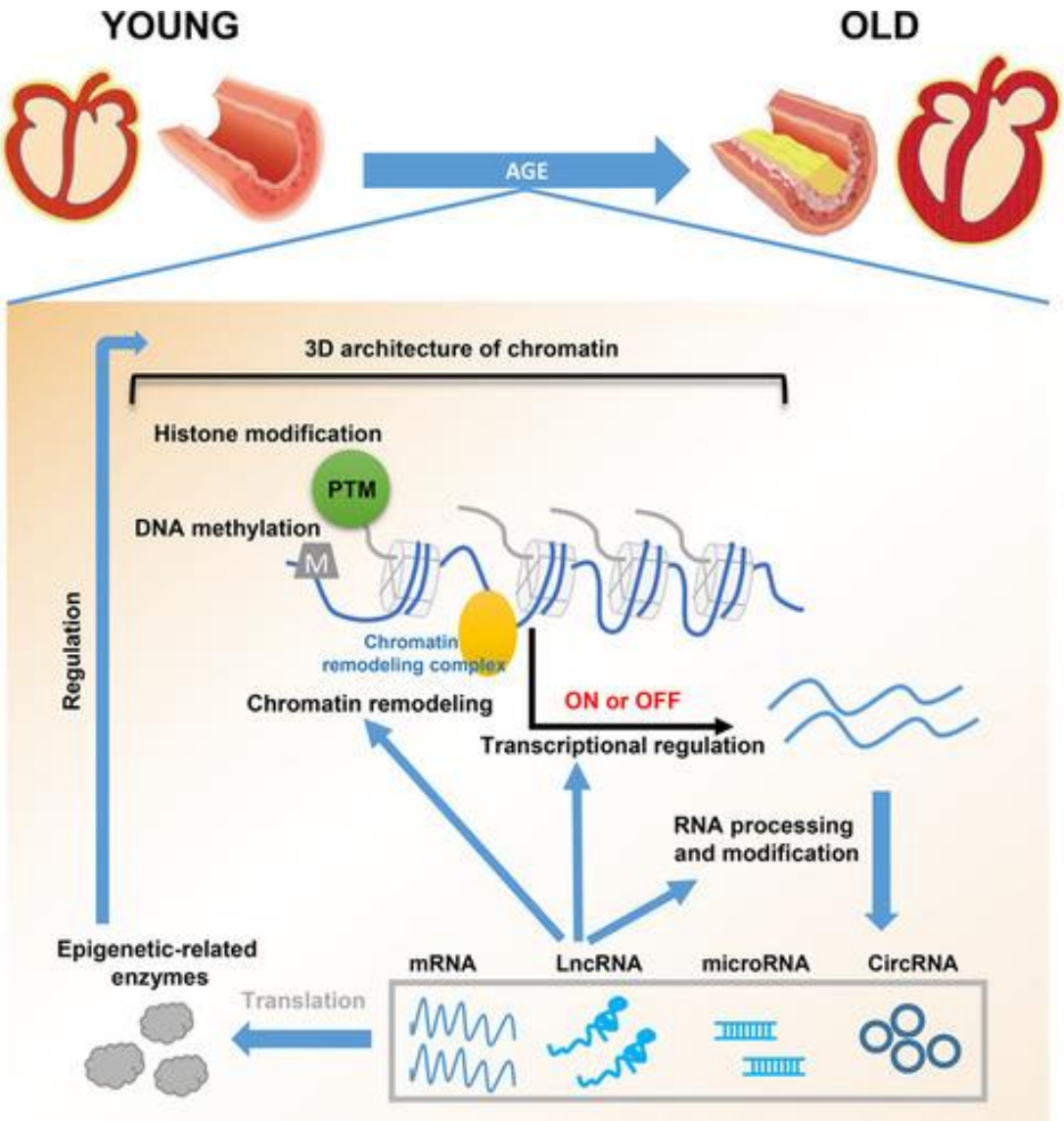


Example of epigenetic changes monitoring



https://www.embopress.org/doi/full/10.15252/msb.20156520

- https://www.ahajournals.org/doi/full/10.1161/CIRCRESAHA.118.312497



- Epigenetic stimul can hit the organism in prenatal and also in postnatal time

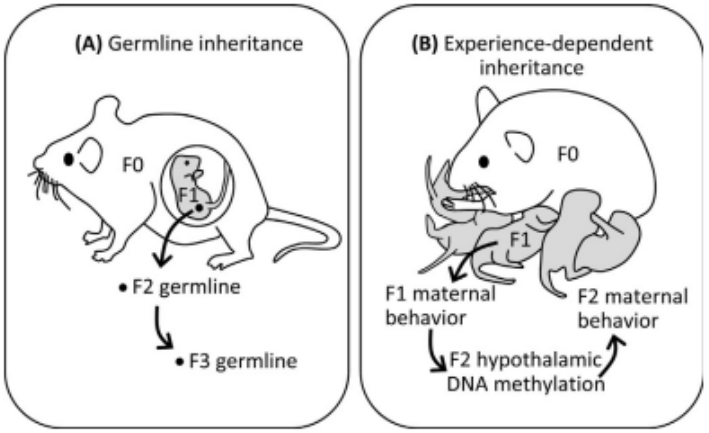


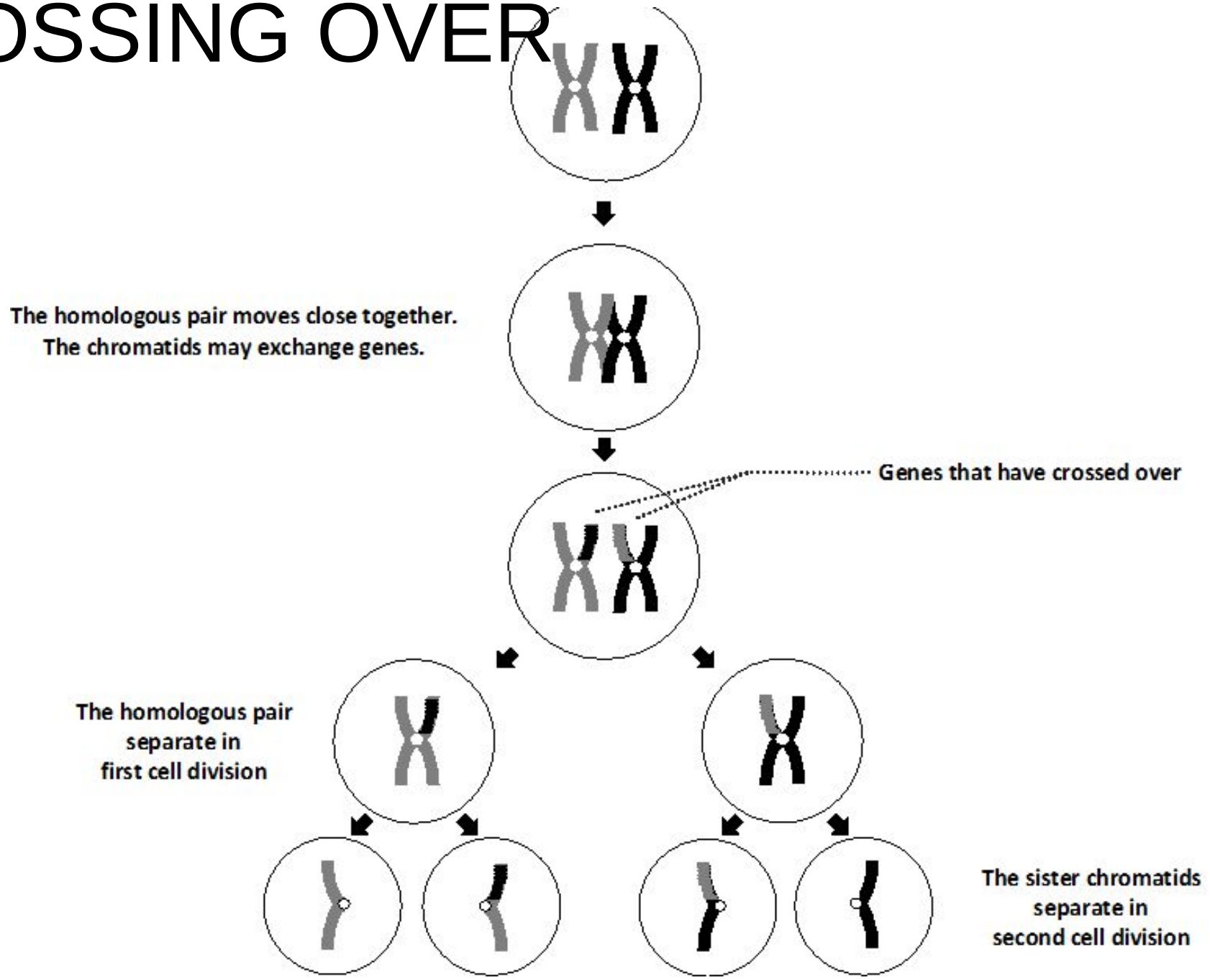
FIGURE 24.1 Illustration of the distinction between a paternal germline epigenetic inheritance (A) and an experience-dependent inheritance of an epigenetic effect (B). In an example of a paternal germ-

- Some epigentic result can be detected in F1 and also in F2 generation or later

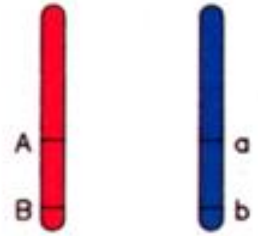
Nice review for advanced reading:
https://labs.la.utexas.edu/champagne/files/2018/01/Chpt24TransEpi.pdf

/C/ Non-mendelian variability

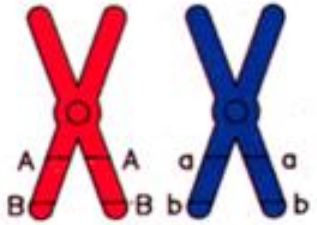
CROSSING OVER



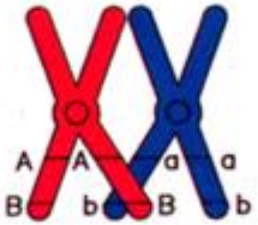
Linked genes on a pair of homologous chromosomes:



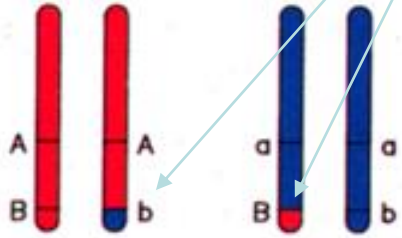
Replication takes place at the beginning of meiosis:



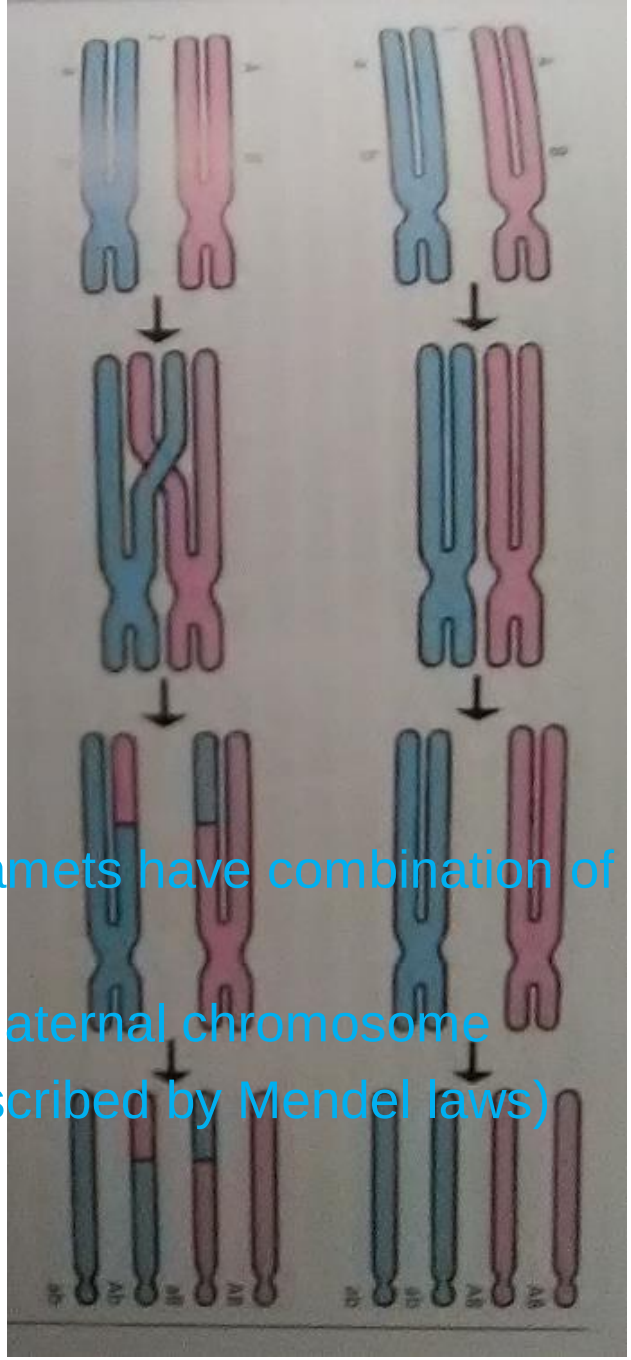
The homologous chromosomes undergo synapsis and crossover occurs between adjacent chromatids:



The chromatids separate:



Now four different kinds of gametes form



Certain final gamets have combination of gene from
paternal and maternal chromosome
(this is not described by Mendel laws)

BASIC SUMMARY of „post“-mendelian genetic is defined by MORGAN RULEs:

1) Genes are always stored in a linear sequence on the chromosome.

2) The genes of one chromosome form a linkage group. The number of linkage groups of an organism (for example human) is the same as the number of pairs of homologous chromosomes of the respective organism.

3) Gene exchange can take place between the genes of a homologous pair of chromosomes through crossing-over. The frequency of crossing-over is proportional to the distance of the genes.

/C/ GENETIC ILLNESS PROBABILITY

for X-linkded and Y-linked genes

Homework:

draw chromosome and compute%