CLASS 4 - 16 March: GENE

1. History of the concept
2. Gene as information
3. Genes and development
4. Genes and evolution

Bibliography: sent or cited

FOR MATERIAL, SEND EMAIL TO:
dvecchi@fc.ul.pt

Enrolment: Gabinete de Estudos Pos-graduados

1.1 Prehistory

Only in the nineteenth century heredity became a major problem to be dealt with in biology: why?

What was known from breeding experiments is that there were two kinds of variations: fluctuating/quantitative changes (deviation from normal trait) and discontinuous/qualitative ones (appearance of qualitatively new traits). All the rest was a matter of debate (cytology or cell biology was developing).

Two main sets of problems

1. Nature of the units of heredity: localisation in the body; material constitution (what kind of stuff and what kind of structure);
2. Mechanism of transmission from one generation to the other.

1.2 Pre-history: transmission view

<u>Nature of the units of heredity: localisation in the body; material constitution (what kind of stuff and what kind of structure);</u>

“BIOLOGY has evidently borrowed the terms ‘heredity’ and ‘inheritance’ from everyday language, in which the meaning of these words is the ‘transmission’ of money or things, rights or duties—or even ideas and knowledge … Hippocrates …. suggested that the different parts of the body may produce substances which join in the sexual organs, where reproductive matter is formed. Darwin’s hypothesis of ‘pangenesis’ is in this point very consistent with the Hippocratic view … Also the Lamarckian view as to the heredity of ‘acquired characters’ is in accordance with those old conceptions.”

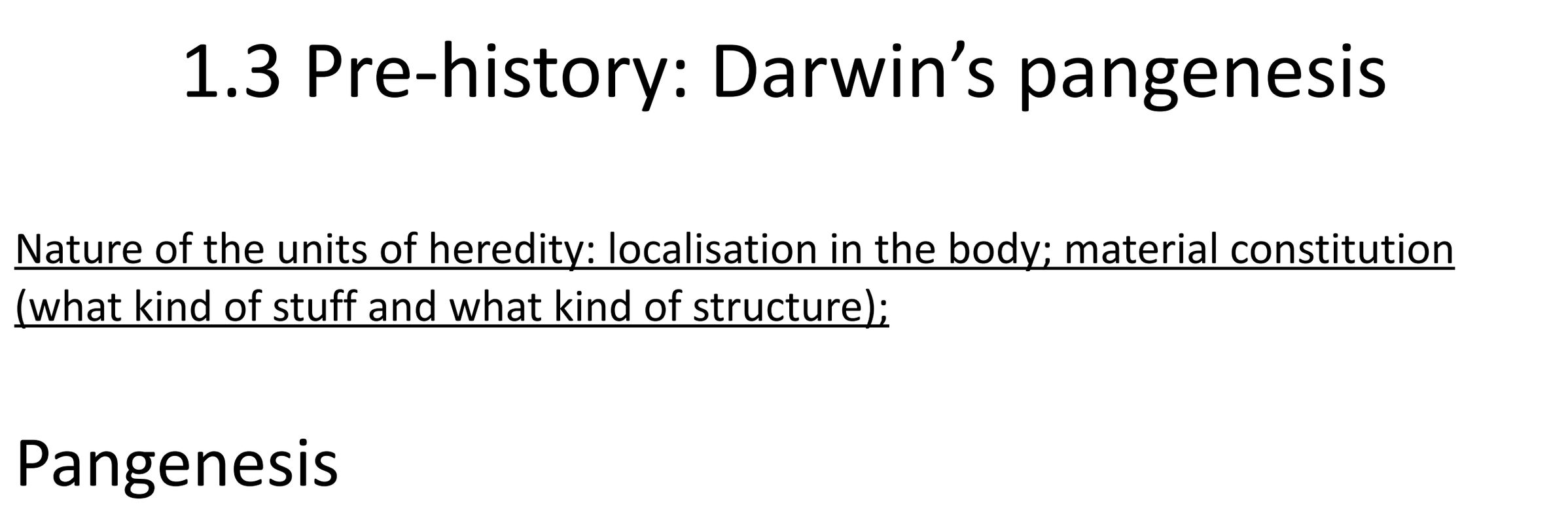
Johannsen W. The Genotype Conception of Heredity. The American Naturalist 1911;45:129-159. p. 989

What is Johannsen suggesting as an alternative view?

1.3 Pre-history: Darwin’s pangenesis

<u>Nature of the units of heredity: localisation in the body; material constitution (what kind of stuff and what kind of structure);</u>

Pangenesis

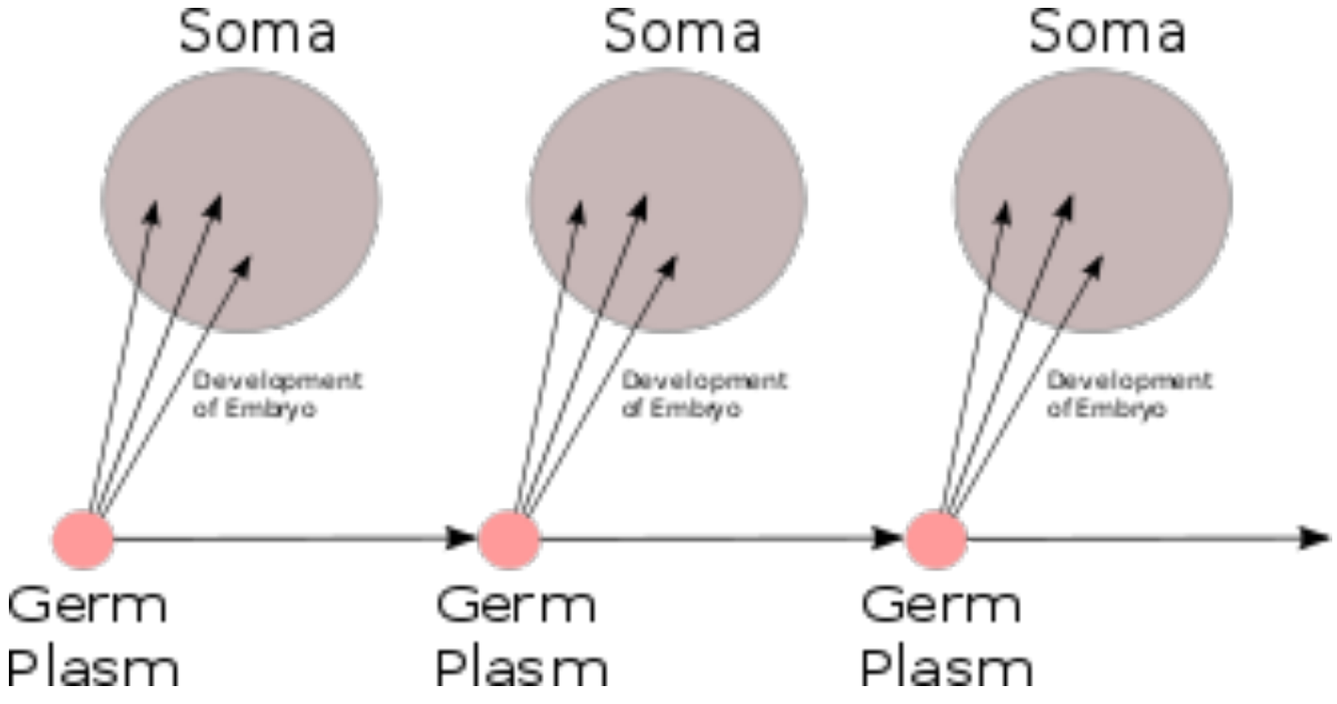


1.4 Pre-history: Darwin's pangenesis

<u>Nature of the units of heredity: localisation in the body; material constitution (what kind of stuff and what kind of structure);</u>

Reaction to Darwin's pangenesis hypothesis:

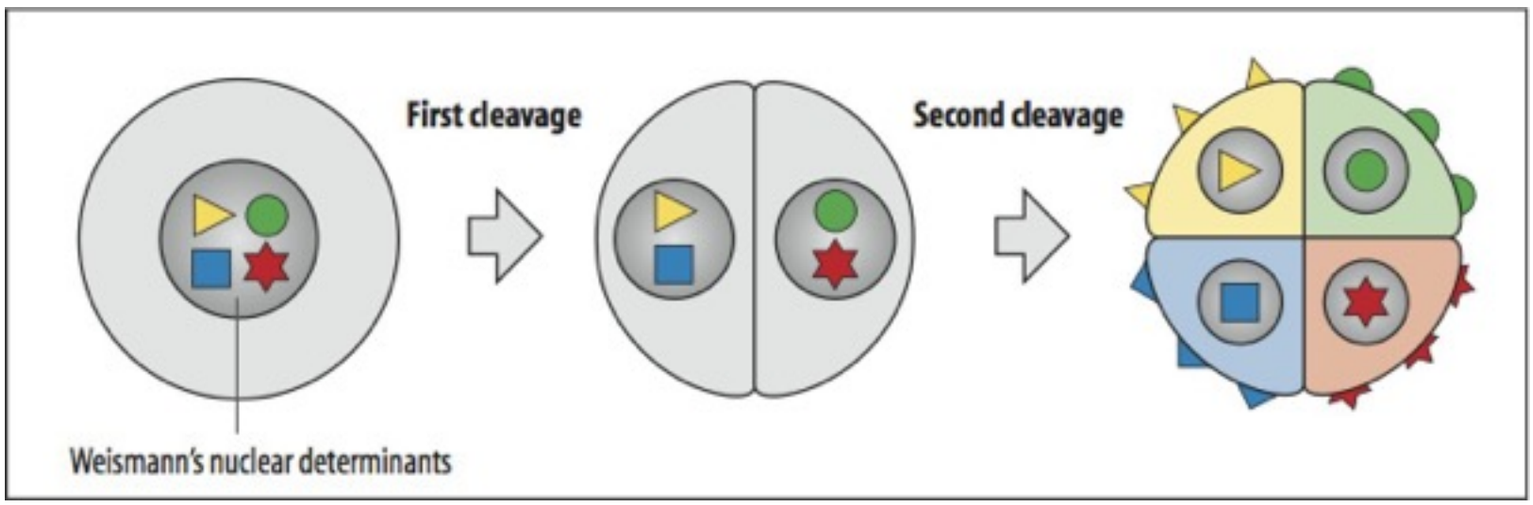
- Francis Galton: gemmules are not circulating through blood stream (experiments with 88 rabbits with "no alteration of breed" as a result);
- De Vries: units of heredity stay in the cells;
- August Weismann: transmission from somatic tissue to germinal tissue does not happen;



1.5 Prehistory: what kind of stuff

<u>Nature of the units of heredity: localisation in the body; material constitution (what kind of stuff and what kind of structure);</u>

- Herbert Spencer: units of heredity are entities with a dimension between molecules and cells;
- August Weismann: localisation in the nucleus of the cell, specifically in the chromosomes; chromatin particles are bearers of special organising functions in development:



- Rediscovery of Gregor Mendel's work

1.6 Prehistory: Mendelism

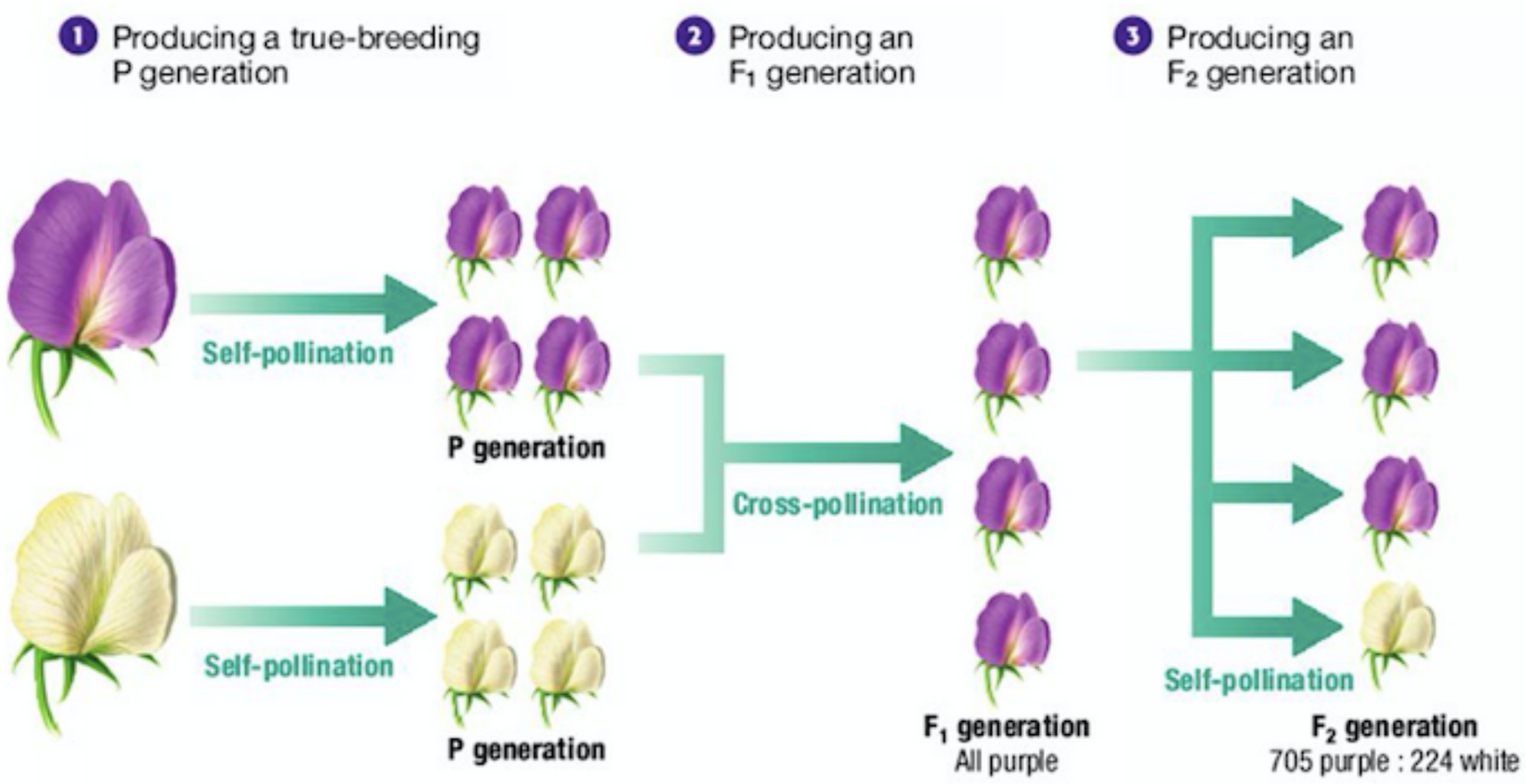
<u>Mendel:</u>

Favourite theory of inheritance at the time of Mendel: blending inheritance (vs particulate; i.e., the idea that characters from parents are inherited in a mixed form by offspring; the problem of this view was how to explain the appearance of qualitatively new variants not present in previous generations) + inheritance of acquired traits (e.g., transmission model of inheritance: personal qualities of individual organism cause the qualities of its offspring).

Pea plants have many dichotomous traits (not compatible with blending inheritance).

Start with true breeding lines (which are genetically pure or monistic, with just one type of allele per trait); create mono-hybrid cross by cross-fertilising two garden pea plants with dichotomous traits and see what happens.

1.7 Prehistory: Mendelism



Parental Generation: Purple & White flowers

Filial Generation 1: PPPP (disappearance of trait…. explained by dominance)

Filial Generation 2: PPPW (reappearance in the same proportion…explained by reappearance of recessive trait)

1.8 Prehistory: Mendelism

<u>Mendel:</u>

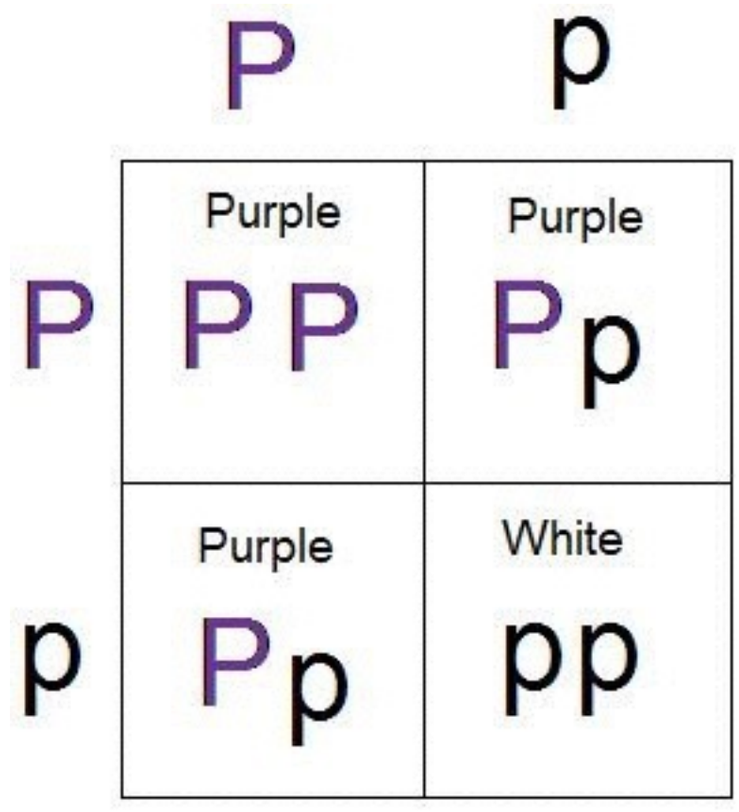
Homozygous (2 alleles of the same type) vs heterozygous organisms;

PP – purple G/P map
Pp – purple G/P map
pp – white G/P map

1 TO 2 TO 1 RATIO

LAW OF SEGREGATION: allele pairs separate during gamete formation, and randomly unite at fertilisation.

LAW OF INDEPENDENT ASSORTMENT: individual hereditary factors assort independently during gamete production, giving different traits an equal opportunity of occurring in next generation.



1.9 Prehistory: Mendelism

<u>Rediscovery of Mendel's work in 1900 by Hugo de Vries, Carl Correns, and Erich Tschermak. New paradigm of inheritance:</u>

1. Heritable factor (different versions of the gene, e.g., allele) responsible for appearance of trait;
2. In diploid organisms (i.e., having two homologous chromosomes in each cell) there are 2 alleles/particles/heritable factors for each trait;
3. One allele could be dominant and the other recessive;
4. When gametes are formed by parents in preparation for sexual reproduction, the gametes get only one of the two forms; hence 50 % chance;
5. Alleles are the heritable factors, not the personal qualities (i.e., the morphological, physiological and behavioural manifestations of the heritable factors, that is, the phenotypes) of organisms;
6. Alleles are particulate, discrete objects (vs blending inheritance).

1.10 Pre-history: genotype conception

"The *personal qualities* of any individual organism do not at all cause the qualities of its offspring; but the qualities of both ancestor and descendant are in quite the same manner determined by the nature of the 'sexual substances' — i.e., the gametes—from which they have developed. Personal qualities are then the *reactions of the gametes* joining to form a zygote; but the nature of the gametes is not determined by the personal qualities of the parents or ancestors in question. This is the modern view of heredity."

Genotype conception of heredity: " … I have proposed the terms "gene" and "genotype" and some further terms, as "phenotype" … to be used in the science of genetics. The "gene" is nothing but a very applicable little word, easily combined with others, and hence it may be useful as an expression for the "unit-factors," "elements" or "allelomorphs" in the gametes, demonstrated by modern Mendelian researches. A "genotype" is the sum total of all the "genes" in a gamete or in a zygote ……. phenotypes are *real things* …"

Johannsen W. The Genotype Conception of Heredity. The American Naturalist 1911;45:129-159. pp. 990 + 991

1.11 Genotype conception: issues

Two main sets of problems:

Nature of the units of heredity: localisation in the body; material constitution (what kind of stuff and what kind of structure);

Mechanism of transmission from one generation to the other.

3 basic distinctions concerning nature of genes:

1. germ vs soma (Weismann);
2. discrete vs continuous genetic factors (Mendel);
3. genes vs phenotypes (Johannsen).

Pending issues:

- Localization in the cell;
- Mechanism of inheritance;
- Deployment in development.

“As to the nature of the ‘genes’ it is as yet of no value to propose any hypothesis; but that the notion “gene” covers a reality is evident from Mendelism ….”

Johannsen W. The Genotype Conception of Heredity. The American Naturalist 1911;45:129-159. pp. 990 + 991

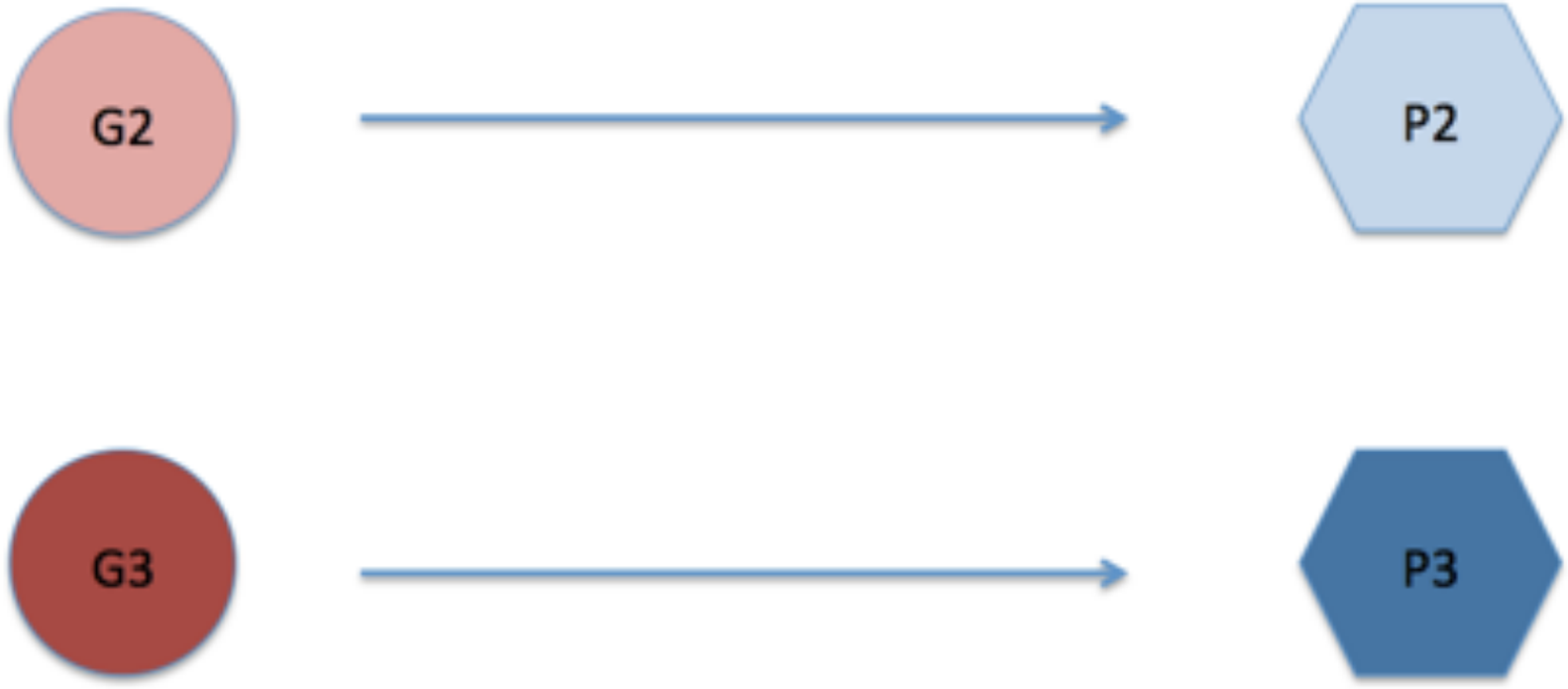
2.1 From theoretical entities to material ones

Thomas Hunt Morgan and the fruit fly *Drosophila melanogaster* group.

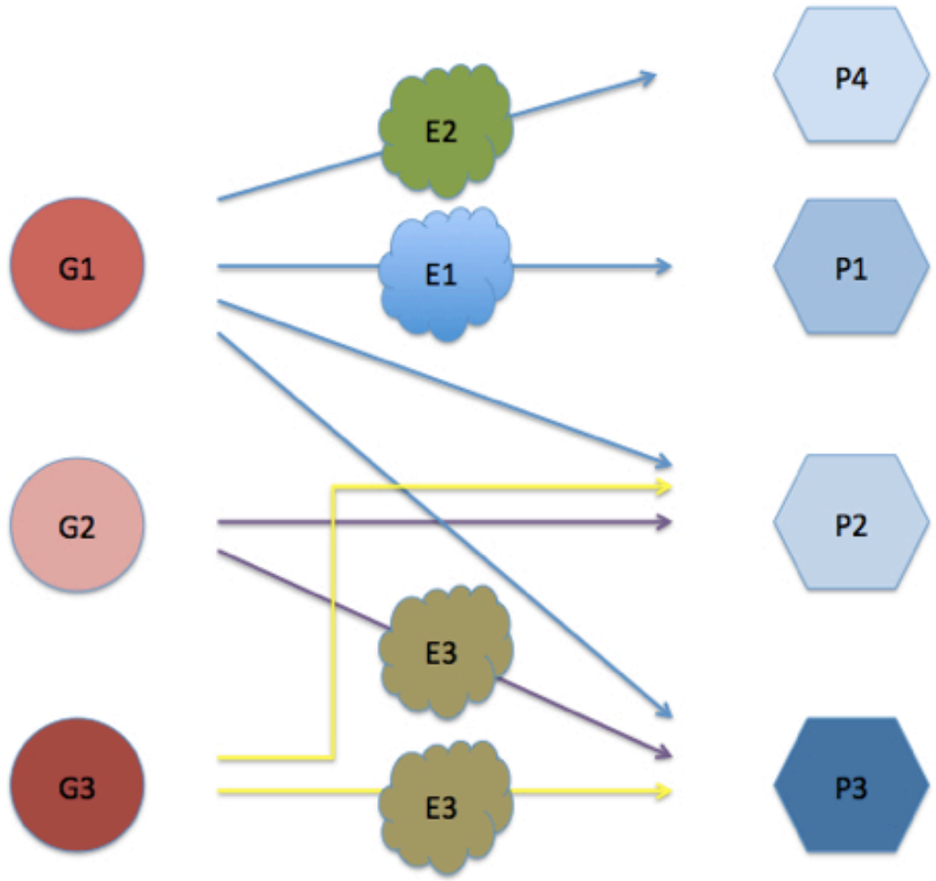
Genes located in a linear order along the different chromosomes (like "beads on a string”, Morgan, T.H., 1926. The theory of the gene, New Haven: Yale University Press. p. 24)

Morgan’s programme was formal, thus agnostic concerning material nature of genes and complexity of G-P map (i.e., the “genotype-phenotype map”; see Rheinberger, Müller-Wille and Meunier section 2).

Interlude: the genotype-phenotype map as a bijective function —> every gene causes one phenotype in development



Interlude: the genotype-phenotype map as a complex function



1. same genotype associated with several phenotypes (i.e., pleiotropy, for instance represented by G1 influencing development of P1, P2, and P3);
2. several genotypes associated with the same phenotype (i.e., polygenic control of development, represented by P2 being influenced by G1, G2 and G3);
3. same genotype associated with different phenotypes in different environments (a form of environmental control of gene expression, represented by G1 influencing development of P1 in environment E1 and P4 in environment E2);
4. different genotypes in the same environment producing same phenotype (a form of "environmental determination" of phenotype, represented by G2 and G3 influencing development of P3 in environment E3)

2.2 From theoretical entities to material ones

Aim of classical genetics: finding a formal correlation between individual genes (characterised as specific loci on the chromosomes) with certain characters.

Very important for development of mathematical population genetics: "… Ronald A. Fisher, J. B. S. Haldane, and Sewall Wright could make use of the classical gene with equal rigor and precision to elaborate testable mathematical models describing the effects of evolutionary factors like selection and mutation on the genetic composition of populations (Provine 1971). As a consequence, evolution became re-defined as a *change of gene frequencies in the gene pool of a population* … " (see Rheinberger, Müller-Wille and Meunier section 2).

2.3 Genes in population genetics

"Scott Gilbert (2000) has singled out six aspects of the notion of the gene as it had been used in population genetics up to the modern evolutionary synthesis. **First, it was an abstraction**, an entity that had to fulfill formal requirements, but that did not need to be and indeed was not materially specified. **Second, the evolutionary gene had to result in or had to be correlated with some phenotypic difference that could be "seen" or targeted by selection**. Third, and by the same token, the gene of the evolutionary synthesis was the entity that was ultimately responsible for selection to occur and last across generations. Fourth, the gene of the evolutionary synthesis was largely equated with what molecular biologists came to call "structural genes." Fifth, it was a gene expressed in an organism competing for reproductive advantage. And finally, it was seen as a largely independent unit."

(see Rheinberger, Müller-Wille and Meunier section 4)

2.4 Genes as autocatalytic and heterocatalytic

Herman J. Muller: genes as material particles:

“Muller saw genes as fundamentally endowed with two properties: that of autocatalysis and that of heterocatalysis. Their autocatalytic function allowed them to reproduce as units of transmission and thus to connect the genotype of one generation to that of the next. Their concomitant capability of reproducing mutations faithfully once they had occurred gave rise, on this account, to the possibility of evolution. Their heterocatalytic capabilities connected them to the phenotype, as units of function involved in the expression of a particular character. With his own experimental work, Muller added a significant argument for the materiality of the gene, pertaining to the third aspect of the gene as a unit of mutation. In 1927, he reported on the induction of Mendelian mutations in *Drosophila* by using X-rays.” (Rheinberger, Müller-Wille and Meunier section 2).

2.5 Gene as autocatalytic entities

Muller: genes as autocatalytic entities able of self-replication thus explaining the mechanism of inheritance.

Genes are DNA molecules, not proteins: Oswald Avery, Colin MacLeod, and Maclyn McCarty 1944

DNA structure as a double helix: Francis Crick and James D. Watson 1953

2.6 Gene as autocatalytic entities

Frederick Griffith's experiment (1928):

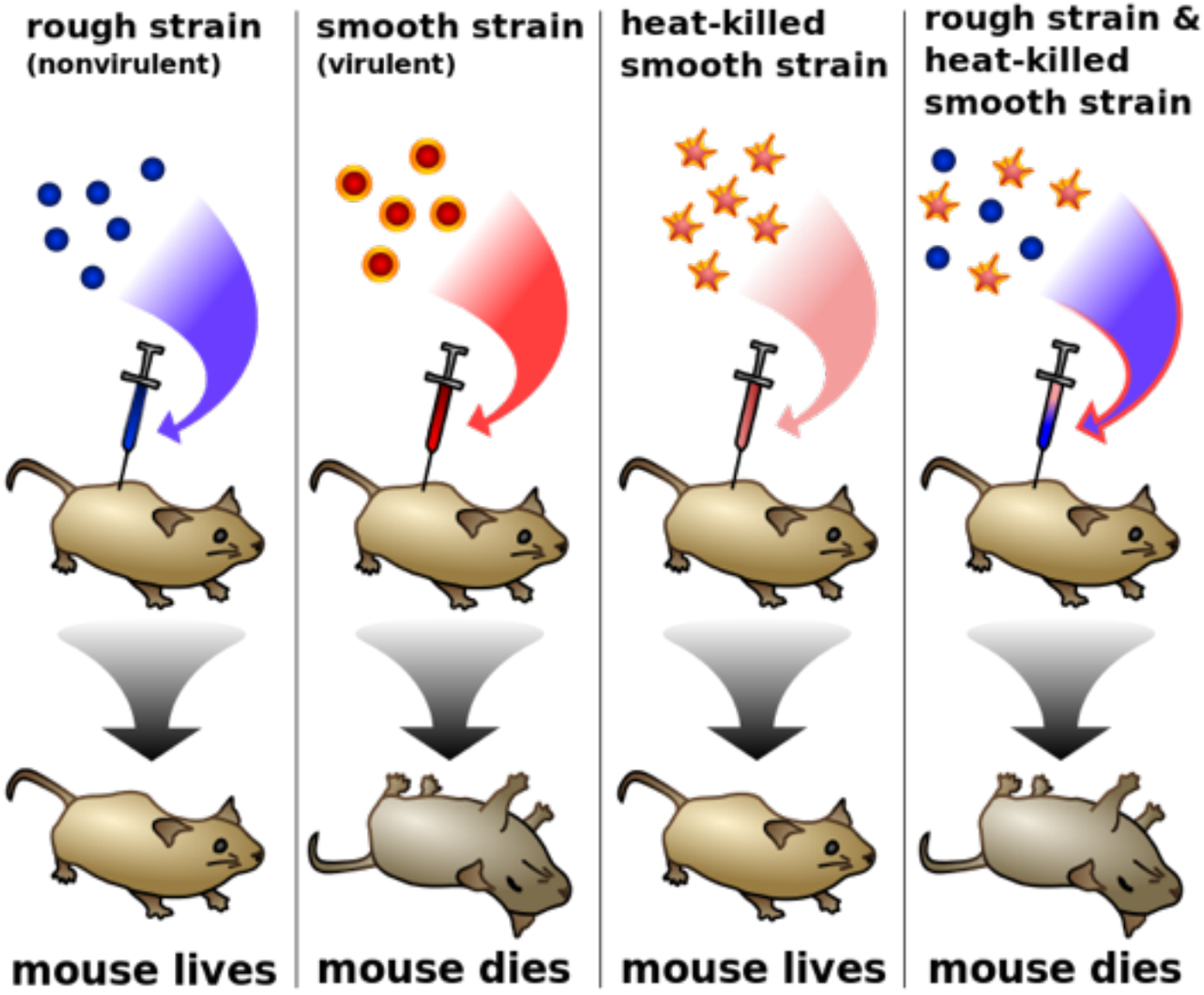
Type II-R (non virulent) strains of bacteria —> no dead mice

Type III-S (virulent) strain —> dead mice

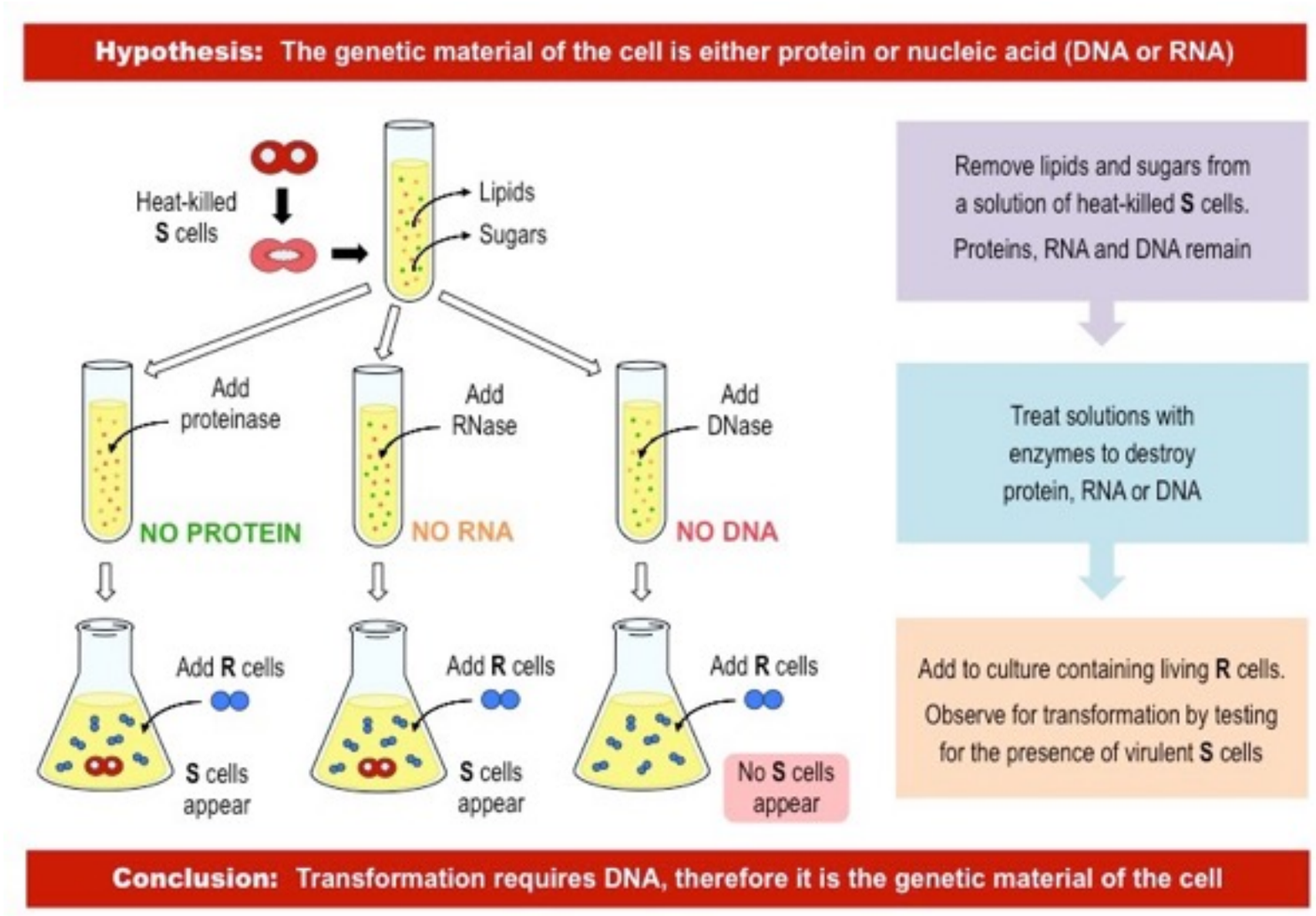
Kill by heat bacteria of type III-S strain —> no dead mice

Mix heat-killed type III-S strain with type II-R strain —> dead mice

What molecular agent is responsible for TRANSFORMATION of type II-R (non virulent) strain bacteria into type III-S (virulent) ones? Proteins or some other molecular agent?



2.7 Gene as autocatalytic entities

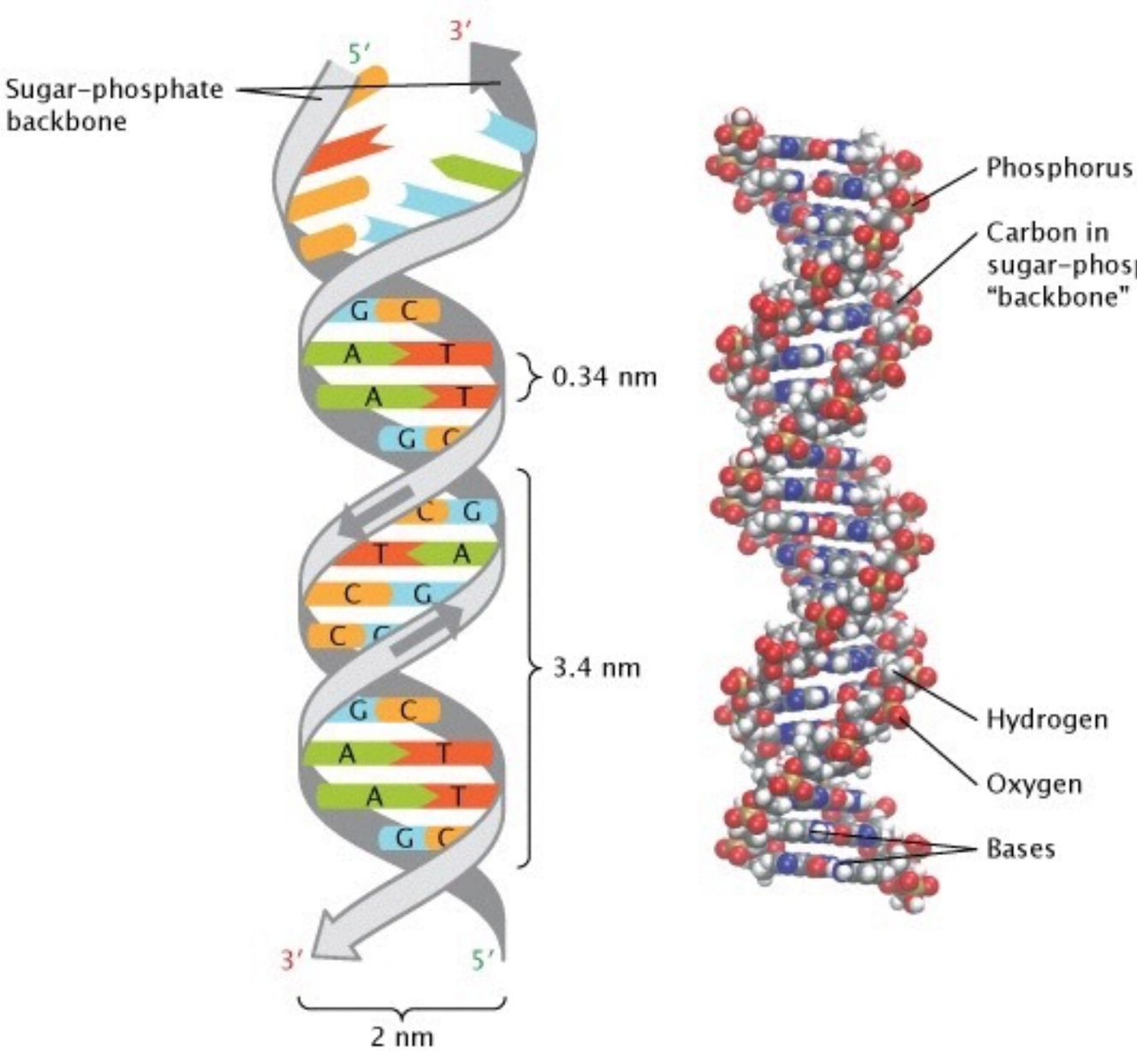


Avery et al. experiment 1944

Only in the culture treated with DNase did the S strain bacteria fail to grow;
no DNA = no transformation —> genes = DNA stuff

cf. https://ib.bioninja.com.au/higher-level/topic-7-nucleic-acids/71-dna-structure-and-replic/dna-experiments.html

2.8 Gene as autocatalytic entities



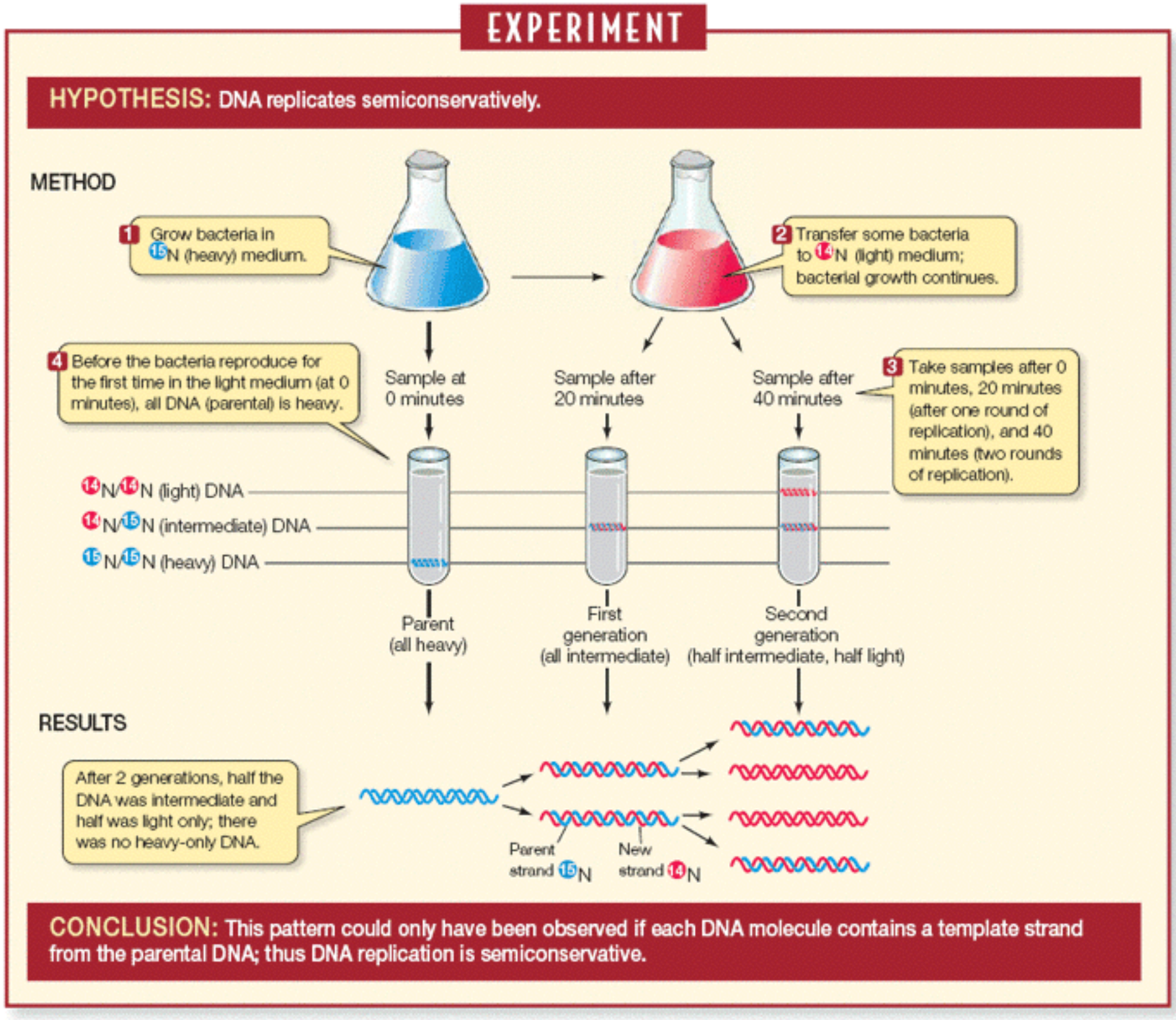
2.9 Gene as autocatalytic entities

DNA as genetic material: but what about its structure?

DNA as double helix: Francis Crick and James D. Watson 1953 (slide 2.8).

And how can it have autocatalytic properties?

Matthew Meselson and Franklin Stahl in 1958: DNA replicates semi-conservatively (cf. https://www.nature.com/scitable/content/the-meselson-stahl-experiment-18551/).



2.10 Gene as autocatalytic entities

Muller: genes as autocatalytic entities able of self-replication thus explaining the mechanism of inheritance.

Genes are DNA molecules, not proteins: Oswald Avery, Colin MacLeod, and Maclyn McCarty 1944

DNA as double helix: Francis Crick and James D. Watson 1953

DNA replicating semi-conservatively: Meselson and Stahl 1958

"… the structure of the DNA double helix had all the characteristics that were to be expected from a molecule serving as an autocatalytic hereditary entity …" (Rheinberger, Müller-Wille and Meunier section 3).

But are genes truly self-replicating?

3.1 The molecular gene and development

Genes as heterocatalytic entities (slide 2.4) causally associated with particular phenotypes:
- one to one mapping (Morgan's school);
- one gene x for one enzyme (George Beadle and Edward Tatum);
- genes are **informational units** that **determine** developmental outcomes.

Watson and Crick popularised information talk in genetics. They hypothesised that genes might be encoded in the DNA molecule, more precisely in the nucleotides:

"… in a long molecule, many different permutations are possible, and it therefore seems likely that the precise sequence of the bases is the code which carries the genetical information." (Watson, J.D. & Crick, F.H. (1953). Molecular Structure of Nucleic Acids: a structure for deoxyribose nucleic acid. Nature, 171(4356): 737–738., p. 964)

Sequence hypothesis: "… the sequence of bases determines the sequence of amino acids of the protein being synthesized". (Crick, F. (1958) On Protein Synthesis. The Symposia of the Society for Experimental Biology, 12,138-163., p. 158)

3.2 The molecular gene as information

The ontological foundation of the informational interpretation is a double reification:

1. **of genetic information as a non-physical entity;**
2. of informational specificity as a non-physical form of specificity.

Williams (1966) proposed a cybernetic conception of the gene that makes it independent of its molecular substrate:

“A gene is not a DNA molecule; it is the transcribable information coded by a molecule....the gene is a packet of information, not an object.” (Williams, G.C. (1992). Natural Selection: Domains, Levels, and Challenges. Oxford University Press, p. 11)

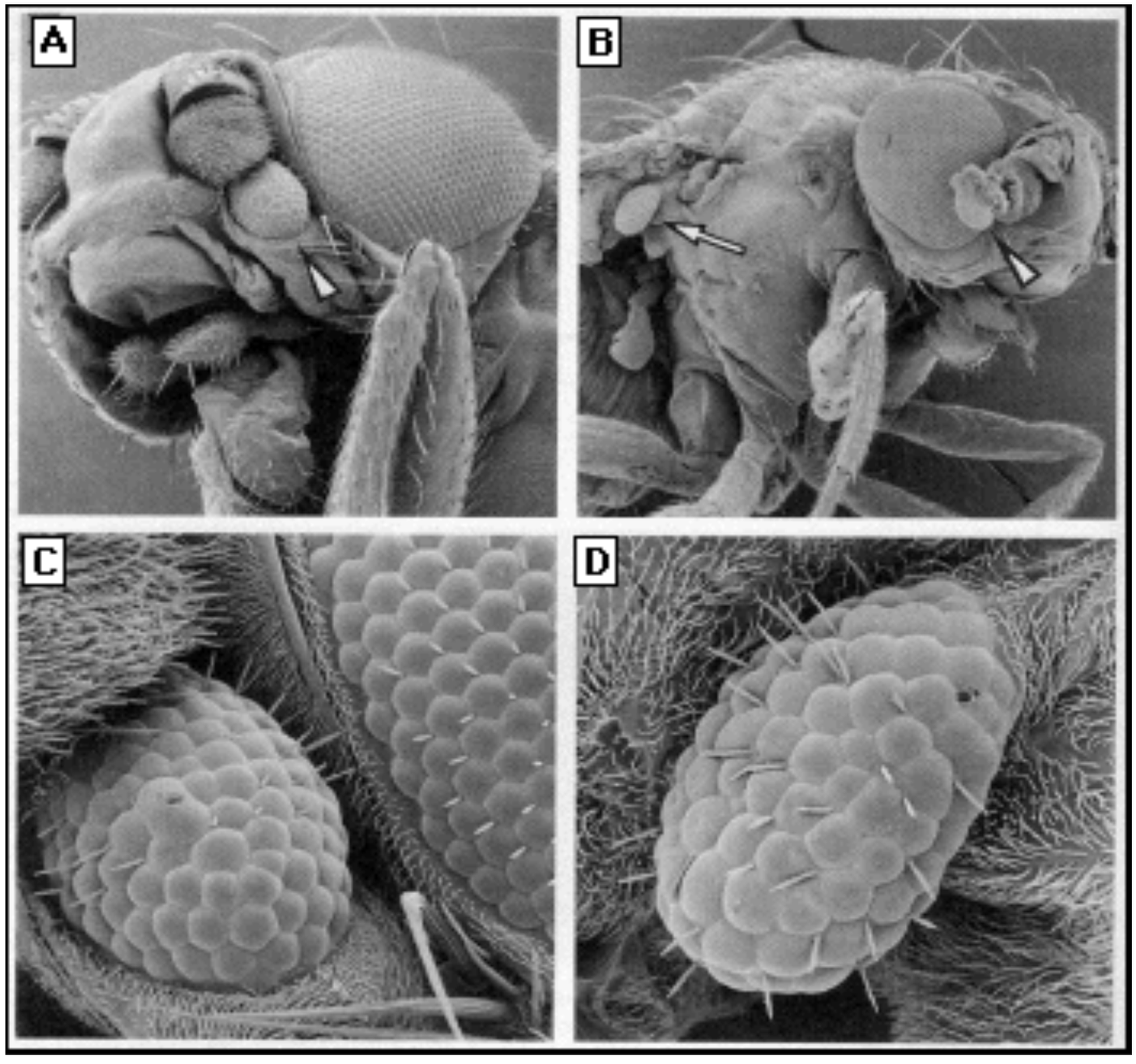
“... heredity is concerned with the transmission of information, not just of matter or energy.” (J. Maynard-Smith 2001. The concept of information in biology. Philosophy of Science, 67:177-194 p. 182)

3.3 The molecular gene as information

"If [*eyeless*] is activated in a developing leg, then an eye develops at the site .... This suggests that the gene is sending a signal, 'make an eye here'..."

J. Maynard-Smith 2001 p. 188

Induction of ectopic eye structures in *Drosophila*.



3.4 The molecular gene as information

The ontological foundation of the informational interpretation is a double reification:

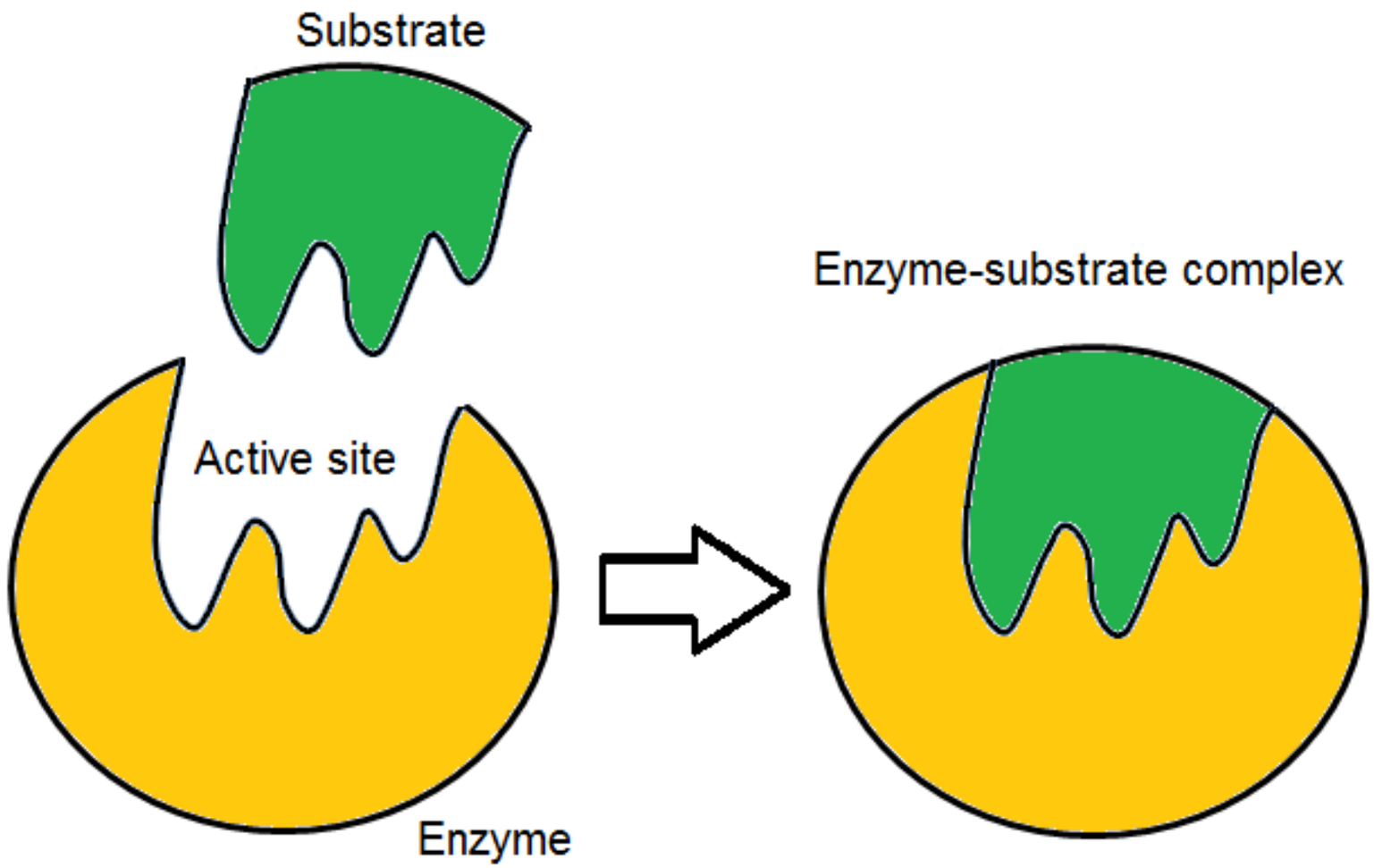
1. of genetic information as a non-physical entity (Williams 1966, 1992).

2. **of informational specificity as a non-physical form of specificity**;

Informational specificity is ontologically different from biochemical specificity. Crick's informational specificity was reified as a peculiar kind of relationship between DNA sequence and developmental outcome:

"The specificity of the gene-gene product (nucleic acid or protein) relationship was informational and thus different from specificity at every other level of biological organization, which remained physical (or stereospecific)." (Sarkar 2005, p. 367)

3.5 The molecular gene as information



Conformational complementarity of enzymes and substrate is a physical relationship, but that of DNA with its gene-products (RNA transcripts and proteins) is purely informational. What does this mean?

3.6 Molecular biology vs information talk

Main drawback is the creation of two suspicious asymmetries:

1. **between processes like transcription, translation and protein folding that can be represented in informational terms on the one hand, and all other developmental processes not amenable to a straightforward informational representation;**
2. between the putative causal role of DNA and extragenomic developmental resources in development.

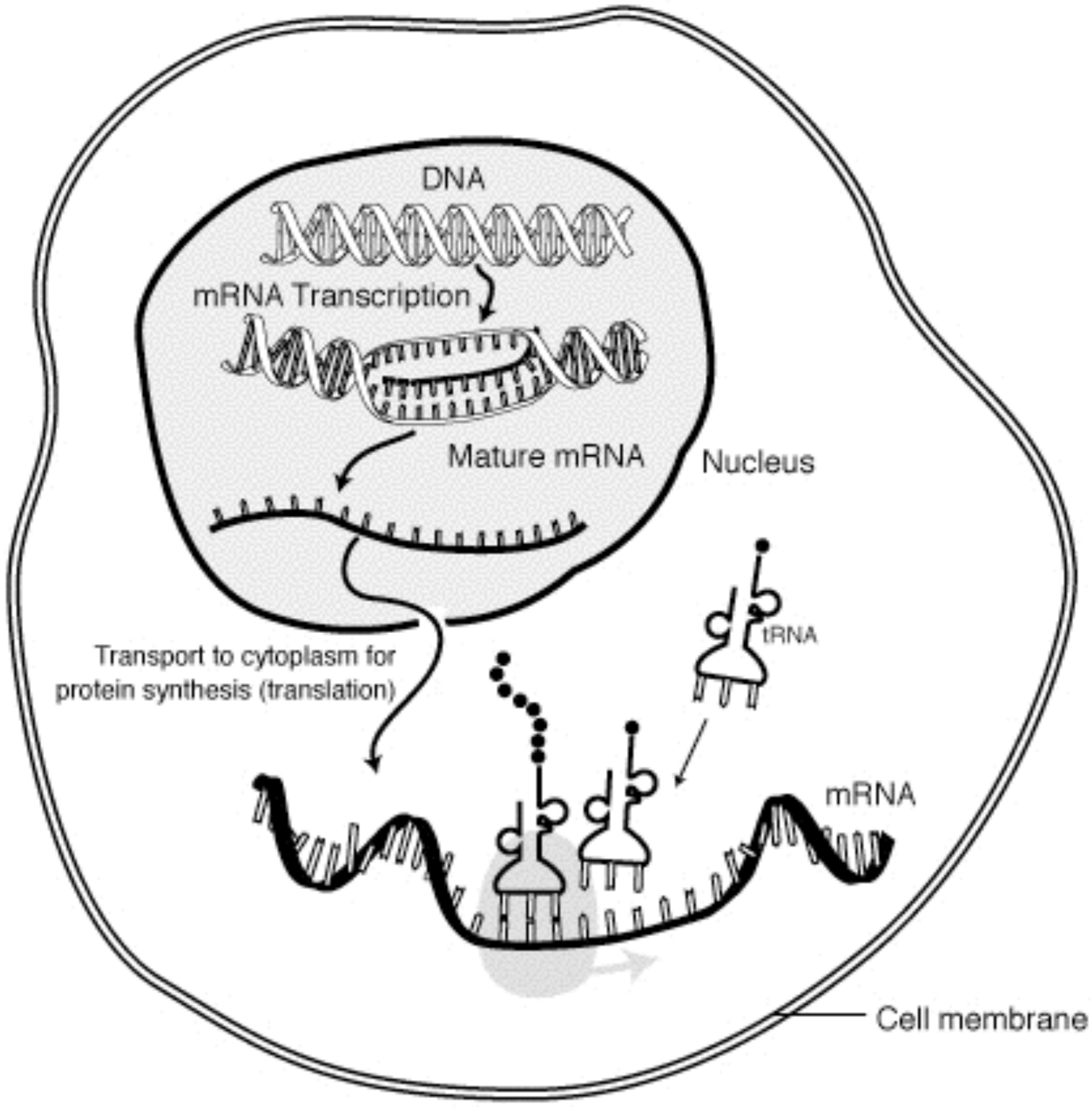
The first asymmetry is unjustified because processes like transcription, translation and protein folding turned out to be extremely complex biochemical processes, no different in kind from all other developmental ones.

Knowledge about eukaryotic translation revolutionised by the discovery of alternative splicing in 1977:

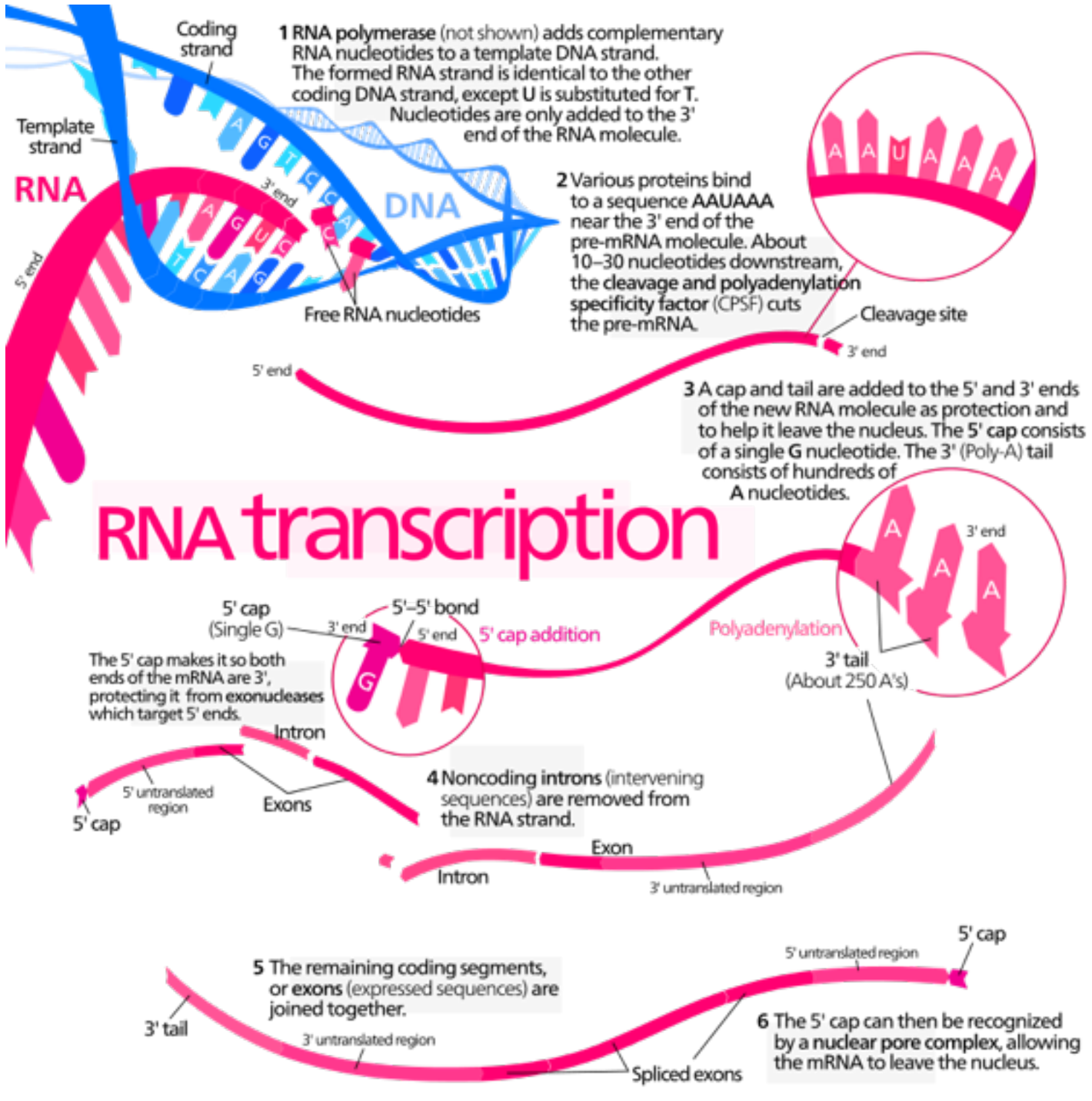
“In the case of the egg-laying hormone of *Aplysia*, to take just one example, one and the same stretch of DNA gives rise to eleven protein products involved in the reproductive behavior of this snail.” (Rheinberger, Müller-Wille and Meunier section 3)

Protein folding (based on Anfinsen’s “dogma”: the primary structure of the protein is determined by the protein's amino acid sequence): discovery of the role of chaperones and folding catalyists in the process.

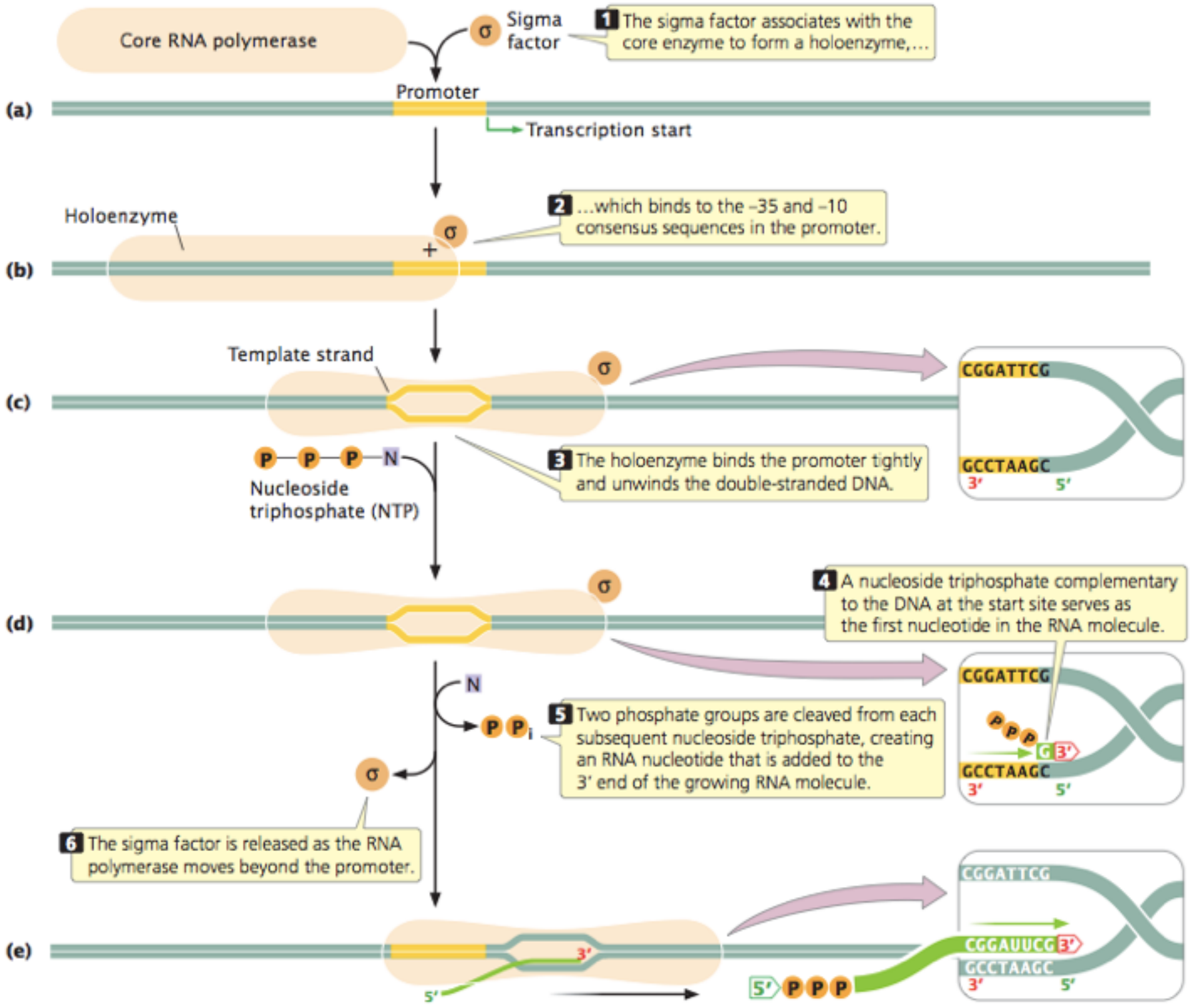
3.7 Protein biosynthesis



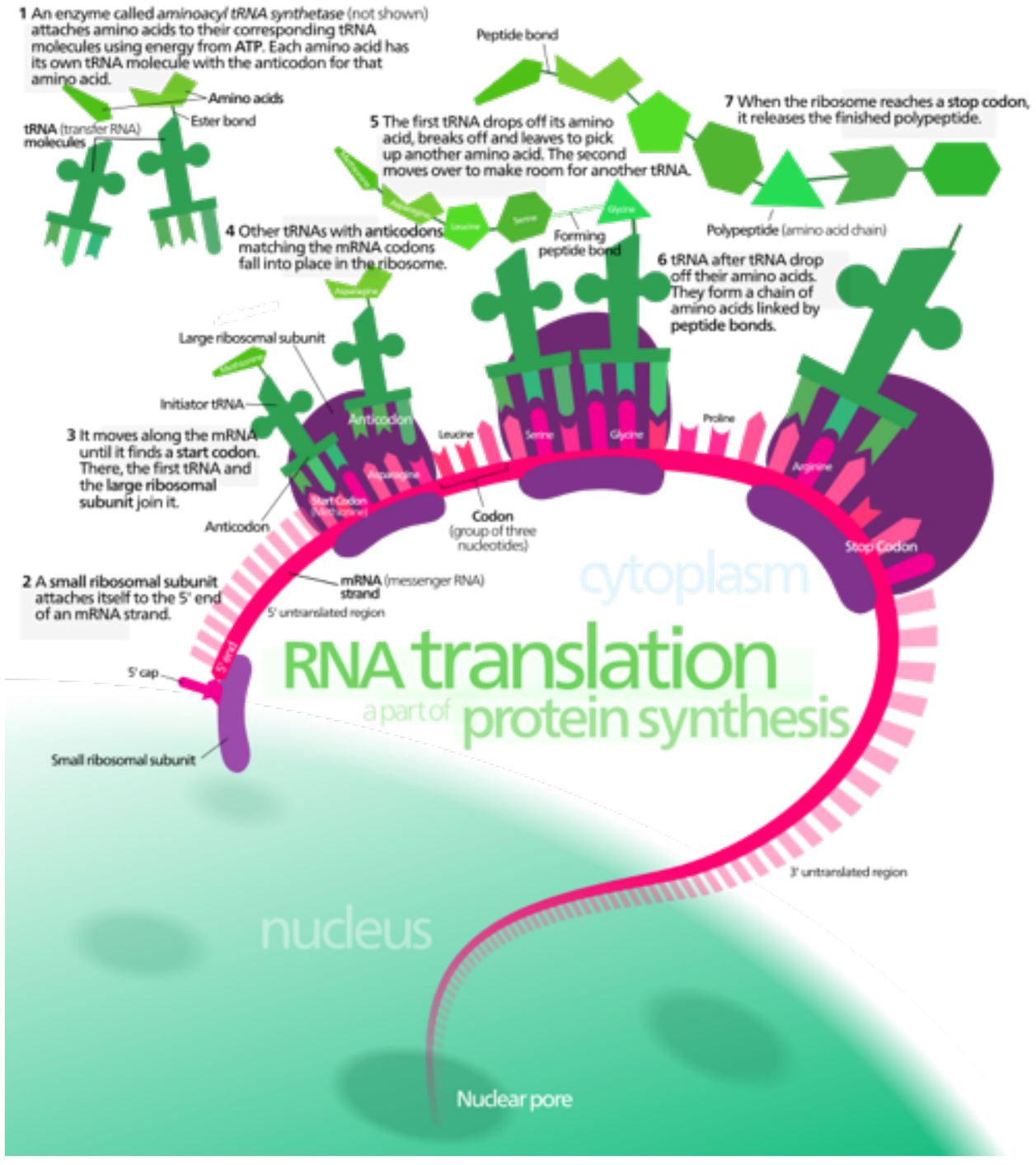
3.8 Protein biosynthesis



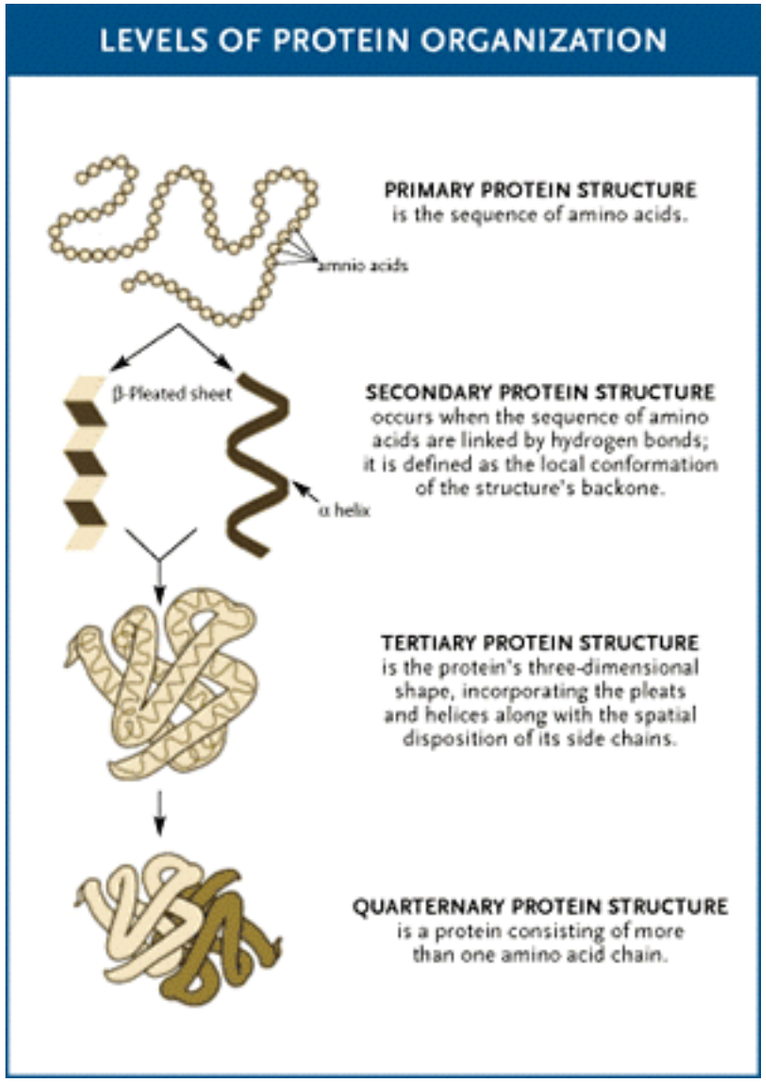
3.9 Contrivances of prokaryotic transcription

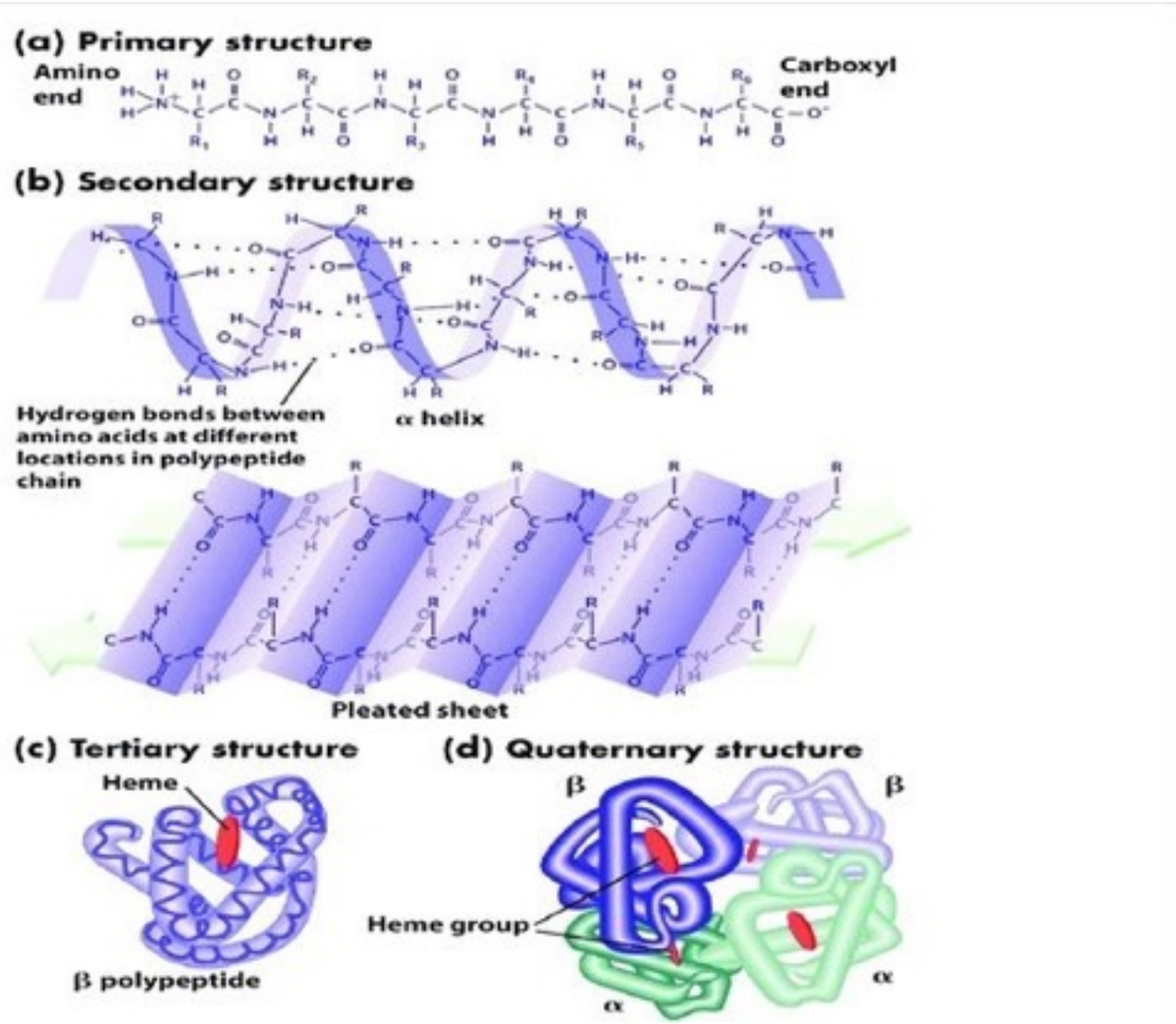


3.10 Protein biosynthesis



3.10 Protein biosynthesis





4.1 DNA's causal role in development

Main drawback is the creation of two suspicious asymmetries:

1. between processes like transcription, translation and protein folding that can be represented in informational terms on the one hand, and all other developmental processes not amenable to a straightforward informational representation;
2. **between the putative causal role of DNA and extragenomic developmental resources in development.**

Genes determine phenotypic outcomes (see also class 3 on development).

Genes possess a qualitatively different kind of specificity.

4.2 Do genes determine phenotypic outcomes?

Conrad Hal Waddington proposed an interpretation of gene action that was deterministic despite the well-known complexity of the genotype-environment relationship (remember Woltereck's experiments with daphnia in 1909, slide 3.10 class 2).

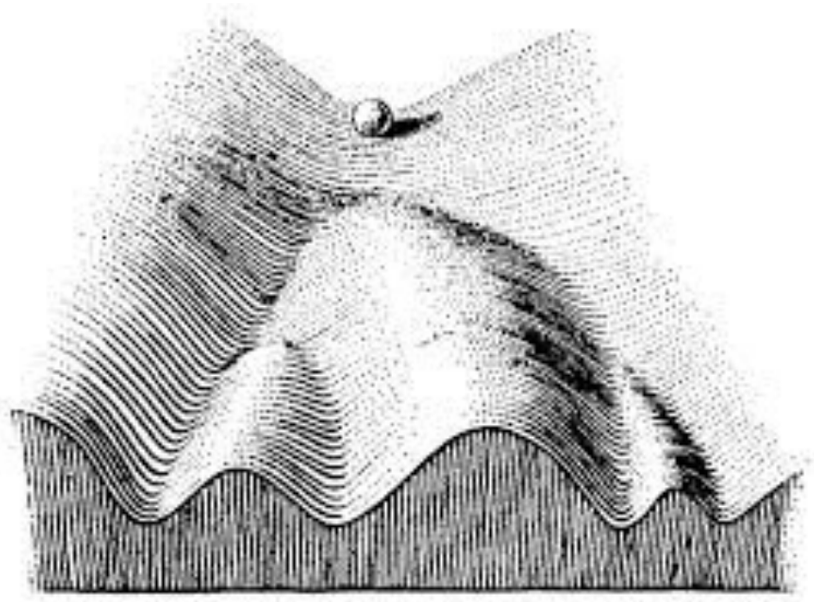
"…the factor which, in the development of vertebrates, decides which of the alternative modes of development shall be followed is the organiser, or, more specifically, the active chemical substance of the organiser which has been called the evocator." (Waddington 1939, p. S37)

The evocator (a molecular agent) plays the causal role in developmental processes by "deciding" which developmental path is taken.

4.3 Do genes determine phenotypic outcomes?

Remember Waddington's epigenetic landscape (slide 3.4 class 2):

1. development is a process that can be represented as consisting of many discrete steps or bifurcations with no intermediates between them;
2. evocators "decide" which path is taken by the developing organism at every bifurcation;
3. in this sense, evocators are determinants of development.



4.4 Do genes determine phenotypic outcomes?

Waddington's inference: genes identified with evocators:

"… genes . . . act in a way formally like . . . evocators, in that they control the choice of alternative." (Waddington 1939, p. S37)

Developmental biology becomes therefore the province of developmental genetics.

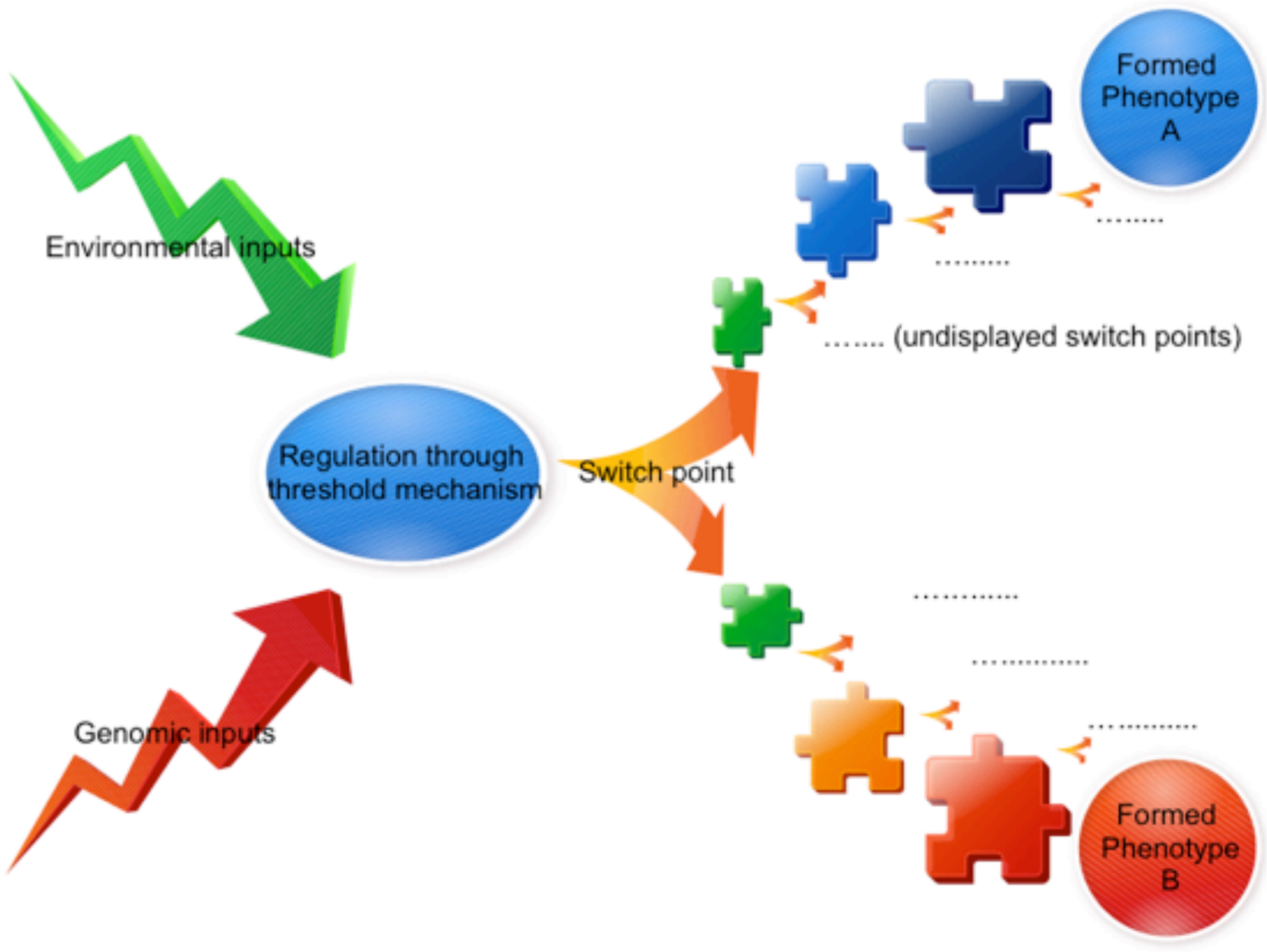
As Waddington claimed later:

"… we know that genes determine the specific nature of many chemical substances, cell types, and organ configurations; and we have every reason to believe that they ultimately control all of them." (Waddington 1962, p. 4)

The idea that DNA is a developmental determinant finally found its conceptual underpinning.

(Cf. Sarkar 2005 + Vecchi 2019).

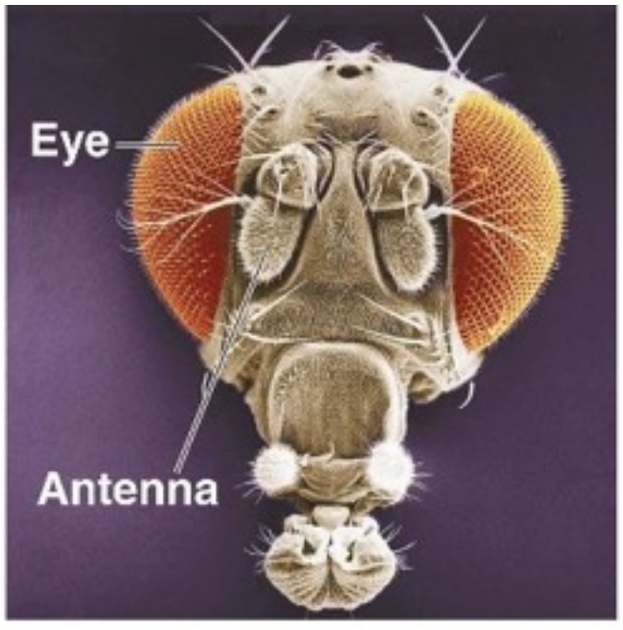
4.5 The switch-point model of development



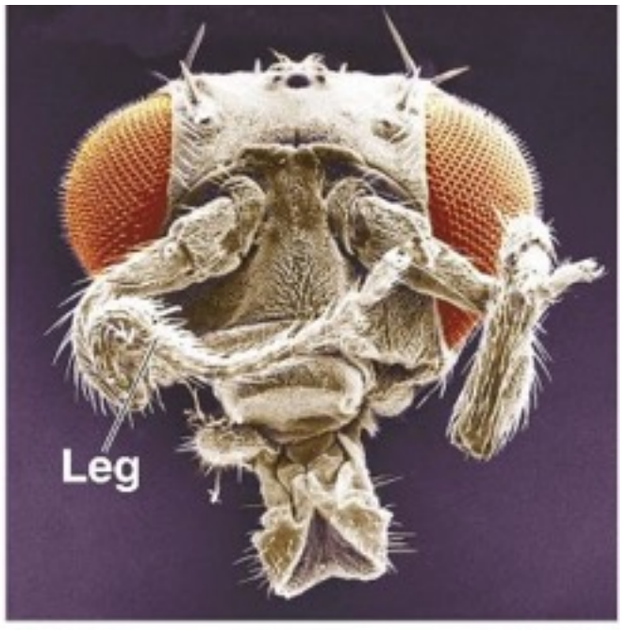
4.6 Genetic “determination”

Given that there cannot be entire developmental trajectories that are totally genetically or environmentally determined, the use of the language of determination is misleading (West-Eberhard, 2003, p. 99-100). This is sufficient to dispel the traditional idea of genetic determination (i.e., that an adult phenotype is fully determined by genomic inputs; cf. gene x for phenotype P idea).

But is the developmental outcome besides compatible with this model?



Wild type



Mutant

4.7 Developmental structuralism

Sometimes genes seem to determine developmental outcomes. However, this view is not incompatible with other developmental approaches that consider genes as secondary, and sometimes irrelevant in development.

Developmental structuralism is one such approach:

“By focusing on the elastic and viscous features of the cytoskeleton, and neglecting the extremely small accelerations, these authors succeeded in proving that the contraction of a single cell propagates to the adjacent cells and generates an invagination in the epithelium. Such models are philosophically interesting … because they help to dispense with preformationist myths: "[...] once triggered, the morphogenetic process of invagination proceeds on its own, directed solely by the global balance of mechanical forces generated locally by each cell, and with no requirement for individually preprogrammed sequences of patterns of cell shape change" (Odell et al. 1981, p. 450). Mahner and Bunge p. 298

4.8 Developmental constructivism

Developmental constructivism endorses the “causal parity” thesis:

“…. no causal or determinative priority in development can be assigned either to the genes, i.e., to internal factors, or to the environment, i.e., to external factors. It is emphasized that "phenotypes" are not transmitted from one generation to the next, e.g., in coded form in the genetic material, but that they are constructed anew in each generation through organism-environment interactions during development.” Mahner and Bunge p. 299

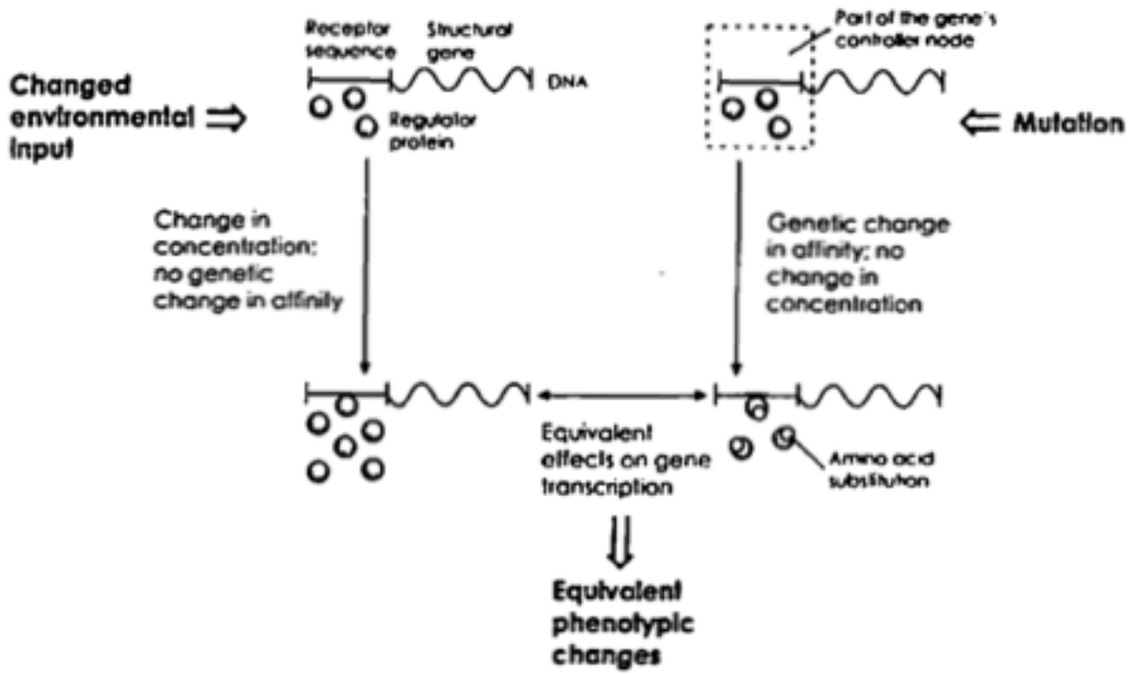
“The constructionist view of development also calls for an expanded notion of inheritance (Oyama 1985). If phenotypic traits are not in any way transmitted but constructed anew during development, then the question arises what, if anything, do organisms inherit. Of course, organisms inherit genes, but they also inherit cytoplasmic factors (actually the entire initial organization of the cell) and, after all, a certain environment (Gray 1992).” Mahner and Bunge p. 300

Epigenetic inheritance

4.9 Do genes possess a qualitatively different kind of specificity?

The argument is frequently made that DNA is a highly specific developmental cause.

But, a specific phenotypic change can be produced either through a mutation or through a change in the concentration of a gene product caused by environmental factors. These two kinds of changes are biochemically equivalent (Zuckerkandl and Villet 1988).



4.10 DNA as a peculiar resource

Contemporary genomics and molecular biology make clear that knowledge of DNA sequence is insufficient to predict accurately protein structure and – even more so - any higher level phenotypic outcome (even though exceptions exist, e.g., *eyeless* gene).

DNA is a developmental resource, not a determinant (Sarkar 2005).

Given all this, can we still defend the idea that DNA has a central role in development? Or should the so-called “parity thesis” be endorsed?

4.11 DNA as a peculiar resource

Back in 1926, Hermann Joseph Muller explained the centrality of genes in this manner:

"… in all probability all specific, generic, and phyletic differences, of every order, between the highest and lowest organisms, the most diverse metaphyta and metazoa, are ultimately referable to changes in . . . genes." (Muller 1962, p. 195)

The peculiarity of this claim lies in the fact that it was made in 1926. Back then, nobody knew what genes are made of and nobody had a clue about how contrived the relationship between genes and phenotype is. But Muller was hypothesizing that phenotypic complexity is dependent on genetic complexity. Was he right?

Summing up

The complex history of genetics is paved with many experimental and theoretical advances: from the emergence of the Mendelian paradigm of inheritance to the genotype-conception of heredity, from the molecularization of the gene to the advances of comparative genomics.

The claim that genes are information is metaphorical: the causal role of genes cannot be uncovered without a biochemical understanding of gene expression.

Genes are not developmental determinants but they are highly specific causes not on a par with other developmental ones.

The causal role of genes in evolution has yet to be understood: if phenome (i.e., the set of phenolypes an organism can manifest) complexity depends on genome (i.e., the set of genomic resources an organism possesses) complexity, then genes are central in evolution.

To claim that gene-based models of development and evolution might eventually disappear because the gene might not turn out to be a primitive ontological category of biology (end of Rheinberger, Müller-Wille and Meunier essay) is in my personal opinion a very questionable conclusion.

CLASS 5 - 23 March: EVOLUTION

1. Vecchi, D. (2018). Biodiversiade: O que é e porque é importante. Chapter 2. (I will send also the English version)

2. Sober: chapter 1