CLASS 3 - 10 March: DEVELOPMENT

1. What is development and what biological systems develop
2. History of developmental biology: epigenesis vs preformation
3. The molecular basis of genetic preformationism
4. How to conceptualise development
5. Developmental causation: the causal roles of genome and environment in development

Bibliography: in final slides.

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1.1 What is development

One of the common (I would say necessary) properties of life is the capacity to self-maintain and to preserve integrity through developmental changes or ontogeny. In brief, life develops.

Development as the central problem in biology before evolution.

Some central questions:

a. How many kinds of developmental processes can be identified?

b. What kinds of biological systems develop?

(With evolution entering the picture: what is the relationship between ontogeny (e.g., the life history of an organism) and phylogeny (e.g., the evolution of the lineage)? This will be an issue in the next class).

1.2 What is development

In order to give an answer to the previous questions, let us characterise developmental processes generally:

“…. a period (or stage) in the life history of an organism is a process of development only if it is accompanied by the emergence or submergence of at least one generic property (or quality), whether compositional or structural…. This qualitative change, however, does not transform the biosystem in question into a member of a new species….the qualitative change in question must be an internal event or process, that is, one involving some organismic activity or function.” Mahner and Bunge 1997 pp. 271-2

1.3 What is development

"…. a period (or stage) in the life history of an organism is a process of development only if it is accompanied by the **emergence or submergence of at least one generic property (or quality), whether compositional or structural**…. This **qualitative change**, however, **does not transform the biosystem in question into a member of a new species**….the qualitative change in question must be an **internal event or process**, that is, one involving some organismic activity or function." Mahner and Bunge 1997 pp. 271-2

Emergence vs submergence: appearance or disappearance of new compositional or structural properties;

Generic property: compositional vs structural properties (constitution vs organisation of biosystems);

Qualitative change through preservation of type: novelty with respect to biosystem itself, not the evolutionary lineage;

Organismic activity vs change merely induced by environment.

1.4 What is development

Three basic developmental processes: morphogenesis, differentiation and growth.

1. <u>Morphogenesis</u>:

"A developmental process of a biosystem *b* is a process of *morphogenesis* if, and only if, *b* acquires a *new* (external) shape or a *new* (internal) structure through the formation of at least one *new* subsystem, that is, one that did not exist before the onset of the process - or through the loss of an existing one." Mahner and Bunge 1997 p. 274

1.5 What is development

Three basic developmental processes: morphogenesis, differentiation and growth.

2. <u>Differentiation</u>:

"… 'differentiation' is a relational concept: it presupposes the existence of a population of systems (or subsystems of a system) whose members (may) become different from each other…. A developmental process in a biosystem *b* is a process of *differentiation* (or *diversification*) if, and only if, the number of kinds of subsystems in *b* and, thereby, the number of specific functions in *b* increases." (Mahner and Bunge 1997 p. 275)

1.6 What is development

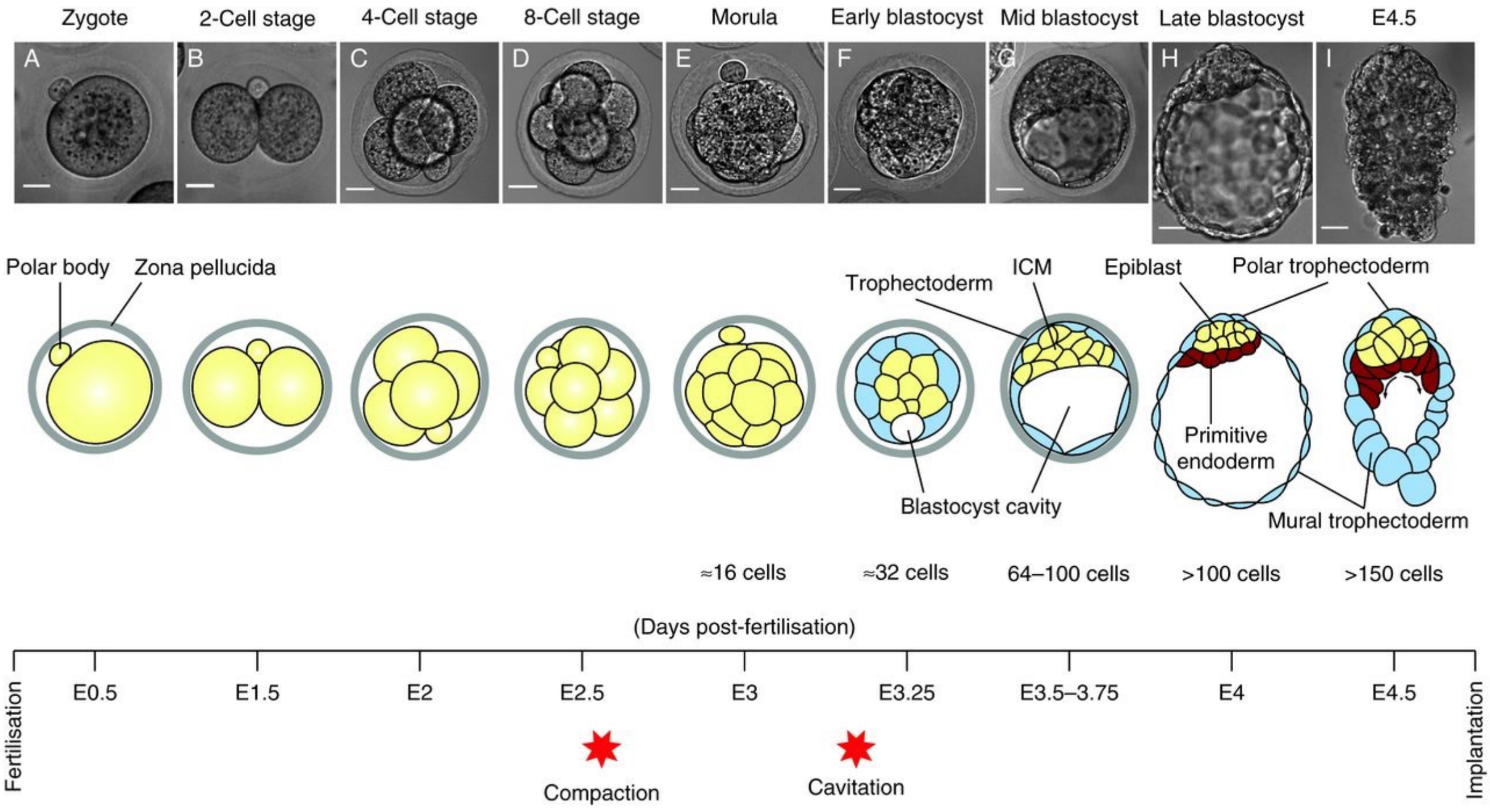
Three basic developmental processes: morphogenesis, differentiation and growth.

3. <u>Growth</u>:

Quantitative vs qualitative growth (otherwise inconsistency with definition of developmental process): thus, *qualitative growth* is either the change in the chemical composition of the biosystem (through incorporation of external environmental materials or synthesis of new kinds of molecules) or growth is combined with morphogenesis (Mahner and Bunge 1997 p. 276)

Totipotency vs. Pluripotency: the first refers to capacity to develop into an entire organism; the second to capacity to differentiate into all kinds of body cell types. I'm unsure at what stage of human development the cells are totipotent. Here it says at the 8 cell stage, i.e., E2.5 (Maienschein, J. 2016. Embryos, microscopes, and society. Studies in History and Philosophy of Biological and Biomedical Sciences 57:129-136. However, I think it's the 16 cells stage, E3.
It's a complex issue: https://academic.oup.com/molehr/article/20/7/599/2459859

1.7 What is development



1.8 What is development

What kinds of biological systems develop?

West-Eberhard (2003, pp. 89-90) characterises development similarly to Mahner & Bunge (1997, pp. 271-6): **the series of qualitative changes a responsive biological system undergoes during ontogeny due to genomic and extra-genomic causal influence**.

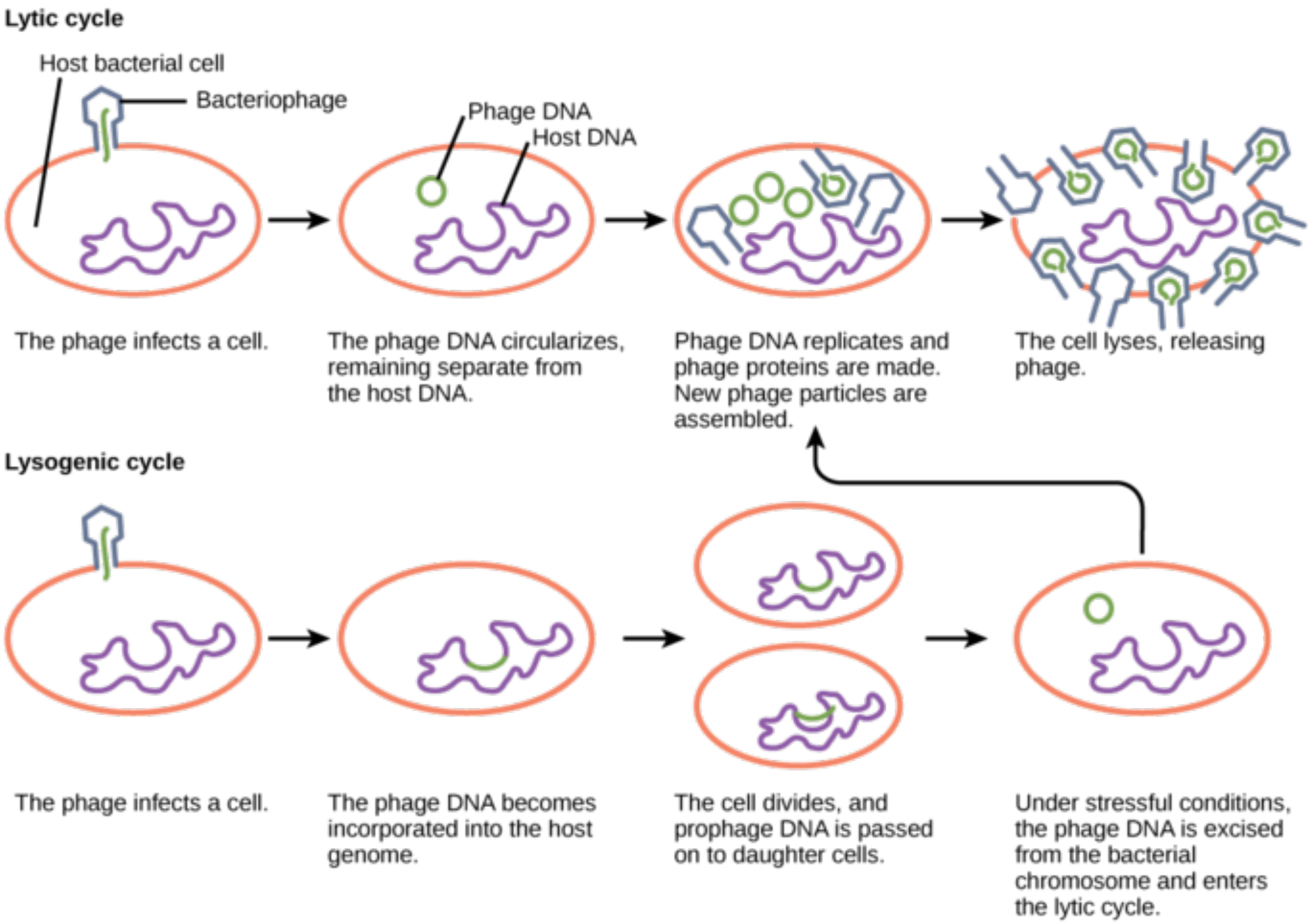
Qualitative changes = changes in the composition, organisation or function of the developing organism.

Thus, any molecular process, such as DNA replication, transcription and translation, might be considered a developmental process.

If development is characterised in these general terms, every organism, by undergoing qualitative changes during its life history, develops.

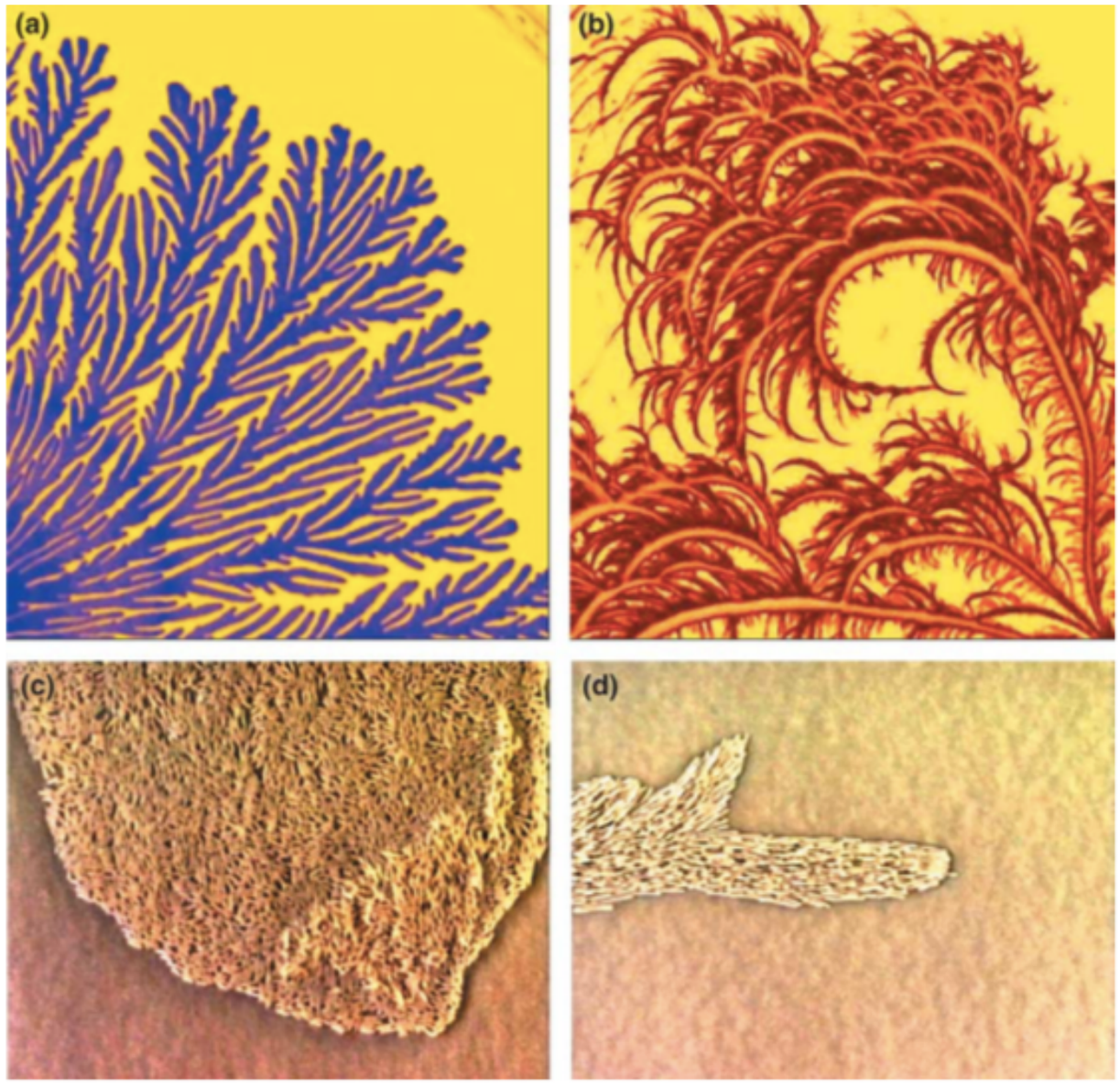
1.9 What is development

What kind of biosystems develop? Viruses.



1.10 What is development

What kind of biosystems develop? Unicellular organisms.

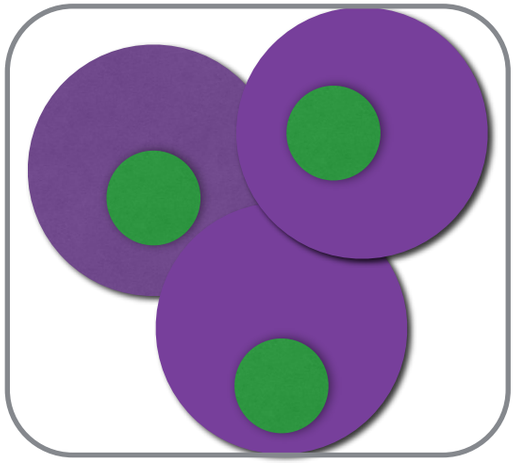


B (branching) and C (chiral) morphotypes of *Paenibacillus dendritiformis* bacteria

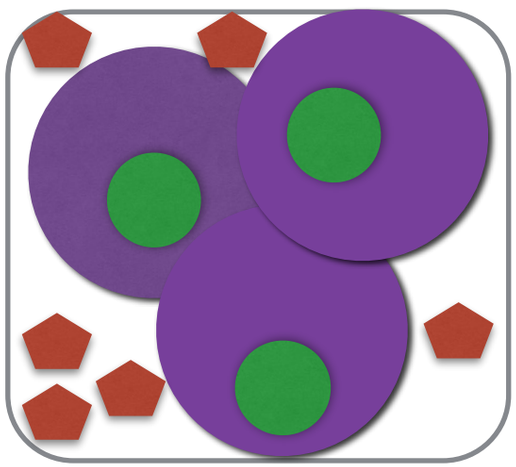
Round (soft substrates and surfaces) and elongated (hard substrates) cellular types

1.11 What is development

What kind of biosystems develop? Most obviously, the composite, multi-cellular, bounded organismal biosystems seen in slide 4.6 in class 2.



6. **Multi-cellular and bi-lineage composite organism with boundary and two types of incorporation** = multicellular organism as set of eukaryotic cells surrounded by a boundary (epidermis) without microbiota.



8. **Multi-cellular and multi-lineage composite organism with boundary and two types of incorporation** = multicellular organism as set of eukaryotic cells surrounded by a boundary (epidermis) with incorporated (i.e., within epidermis) resident microbiota.

1.12 What is development

These multicellular organisms are observable with the naked eye and they are clearly capable of growth, differentiation, morphogenesis and, also, regeneration.

Discovering the mechanisms governing these processes has been the central problem of developmental biology.

The history of developmental biology is a history of experimental advances in the context of the clash between two “ideologies”: preformationism and epigenesis.

2.1 Preformationism vs epigenesis

Preformationism: formation of new features during development is only apparent: it consists merely in the unfolding or unrolling of characters preformed in the “germ” (i.e., the sperm, the egg, or the zygote). Basically, development = growth.

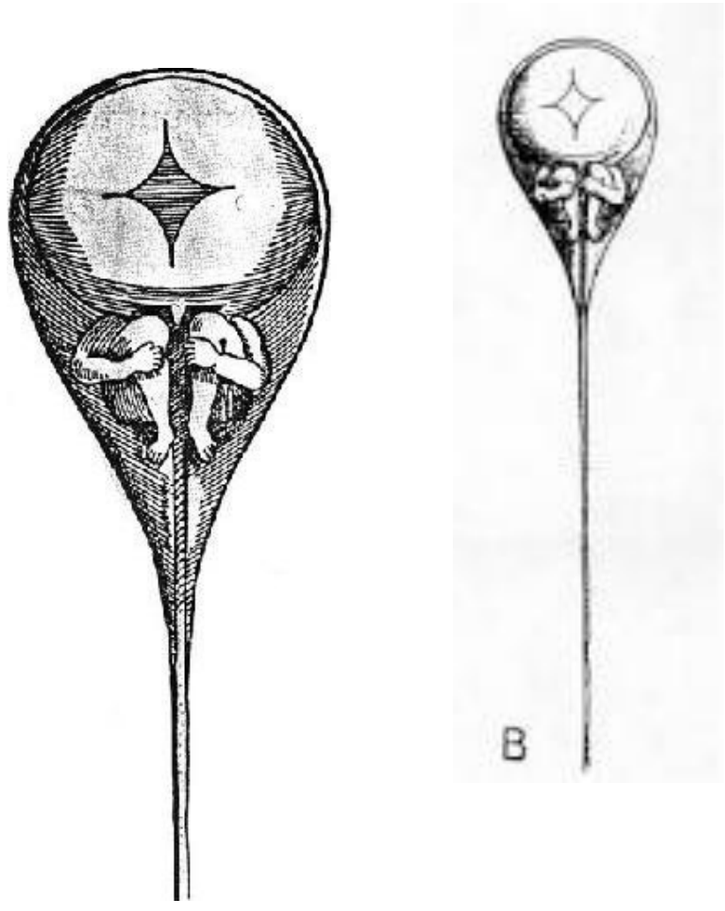
Epigenesis: no pre-existing form but emergence of genuinely new characters from an unstructured, formless, or homogeneous “germ” (i.e., the sperm, the egg, or the zygote).

Initially two radically opposing views whose distance has been reduced during the course of the history of biology. Localisation of the “developmental plan” in the developing organism (e.g., sperm, egg, zygote, cell nucleus, constituents of the nucleus etc - cf. Aristotle’s position on slides 4.2-4.3) as a main issue.

2.2 Preformationism vs epigenesis

<u>Experimental advance I: microscopy</u>: embryo is endowed with some form and therefore is not amorphous and homogeneous.

Naive preformationism: Nicholaas Hartsoeker's "homunculus" (1694).



The "germs" of all living beings preformed since Creation. Ovist encapsulation: "It follows that the ovary of an ancestress will contain not only her daughter but also her granddaughter, her greatgranddaughter and her greatgreatgrand-daughter, and if it is once proved that an ovary can contain many generations, there is no absurdity in saying that it contains them all." Albrecht Von Haller (cf. Needham 1959, p. 178).

2.3 Preformationism vs epigenesis

Major postulation in preformationism: the apparently unstructured embryo must contain unobservable features that have a developmental role (i.e., a developmental “plan”).

Compatible with the idea that God is the only creator and that matter cannot be attributed the ability to create qualitative novelty without any previously implanted form.

Compatible with the mechanistic world view of the 17th century: every cause is mechanical (i.e., by contact) and efficient and no other types of causes or modes of causation are necessary.

2.4 Preformationism vs epigenesis

Compatible with the mechanistic world view:

"…. if one knew in detail all the parts of the seed of a particular species of animal, for instance, Man, one could deduce from that alone for reasons entirely mathematical and certain, the whole figure and conformation of each of its parts."

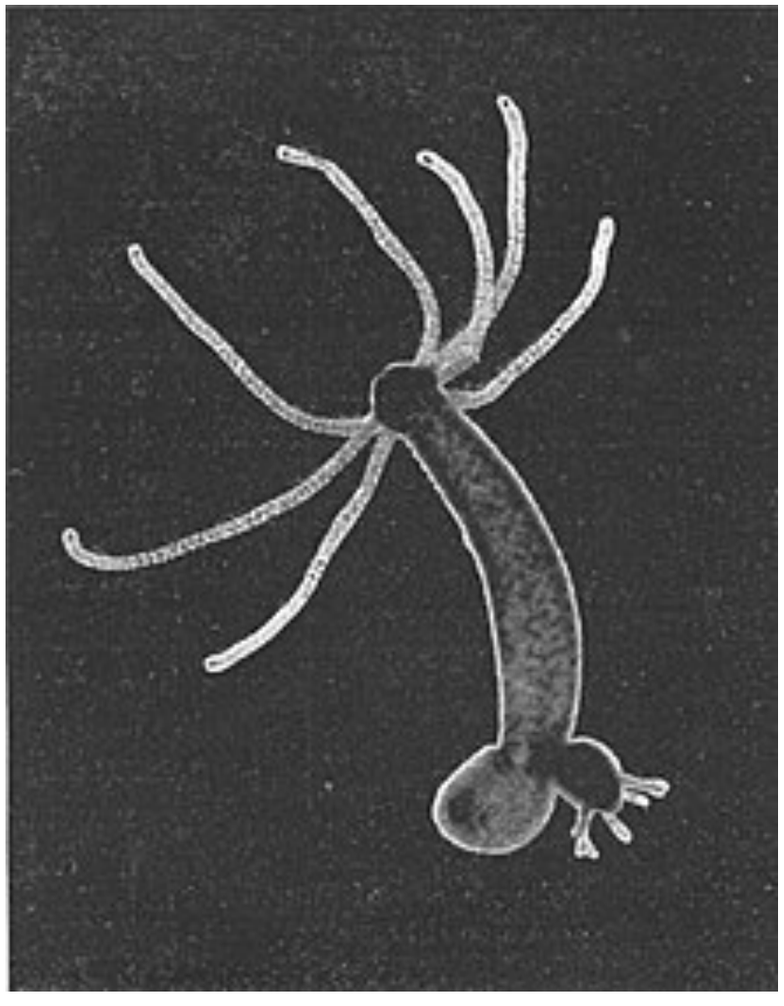
Descartes 1909 p. 277.

From a scientific point of view, preformationism was able to explain the constancy of species and it rejected spontaneaus generation (all life from life).

2.5 Preformationism vs epigenesis

Experimental advance II: in the 18th century not only observations but controlled experiments.

Abraham Trembley (1710 - 1784): experiments with Hydra: is it animal or plant? Cutting off a part and see if it regenerates: if it does, it's a plant. It did.



But how could the regeneration of a completely developed adult come from a part? Is the developmental plan just in the gametes or in other parts of the body?

https://embryo.asu.edu/pages/abraham-trembley-1710-1784

2.6 Preformationism vs epigenesis

Epigenesis was more in line with the experimental results of the 18th century - such as Trembley's - and the existence of hybrids, monsters and other malformations; thus, preformationism "faded away" (momentarily).

However, how could epigenetists account for the continuity of species and for the source of the morphological complexity of developing organisms?

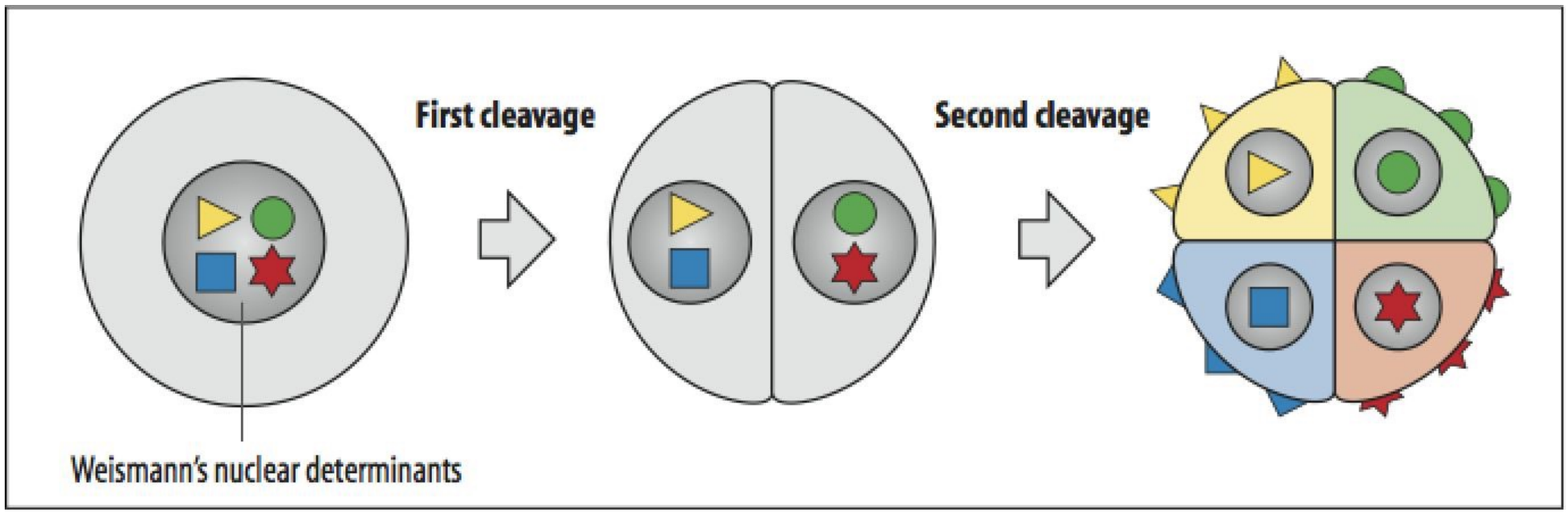
Postulation of an unobservable "force". Connection between epigenesis and vitalism (animistic or "materialistic"). The nature of "forces": mechanical, Newtonian (other types?).

2.7 Preformationism vs epigenesis

<u>Experimental advance III</u>: cell theory

August Weismann (1893): ontogeny depends on a series of gradual qualitative changes in the nuclear substance of the egg-cell; cellular differentiation is determined by forces situated within them, not by external influences.

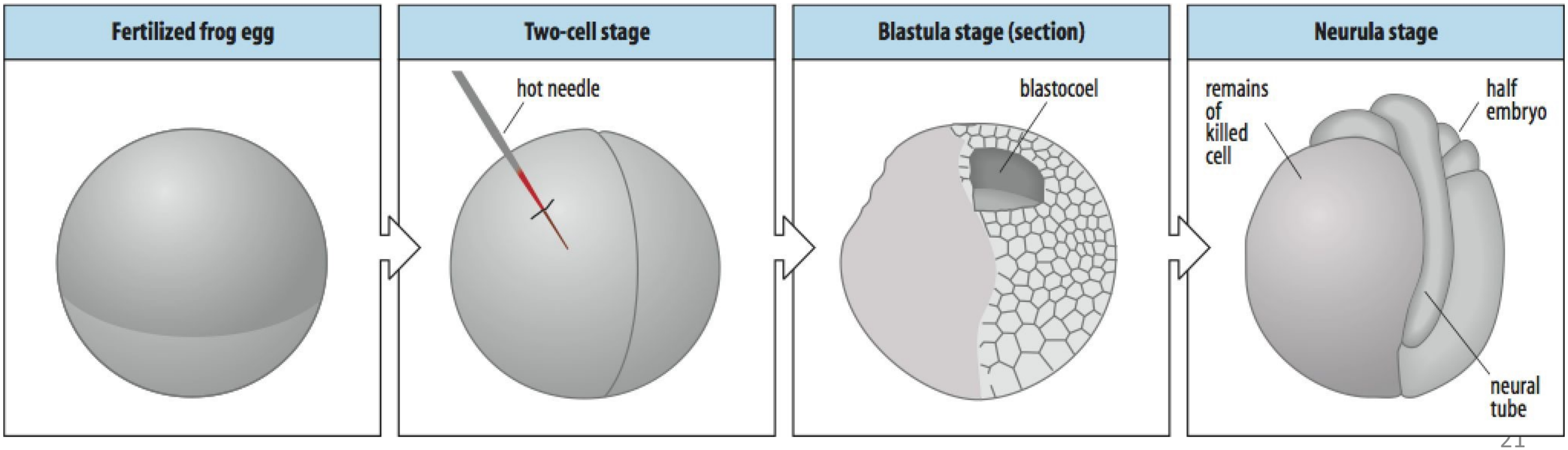
Development: totipotency + gradual loss of causal capacities of the embryo.



2.8 Preformationism vs epigenesis

Wilhelm Roux (1888): result of ablating one cell of the two cell embryo was a half embryo. This was consistent with Weismann's prediction of localised determinants.

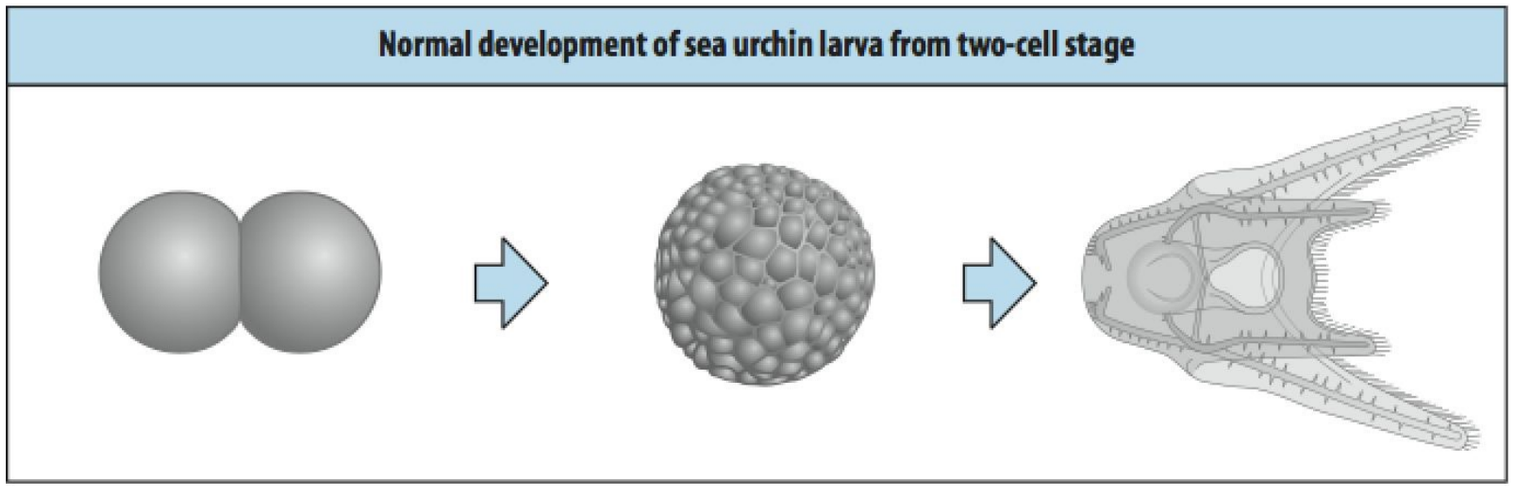
But what would happen if you separate the two blastomeres?

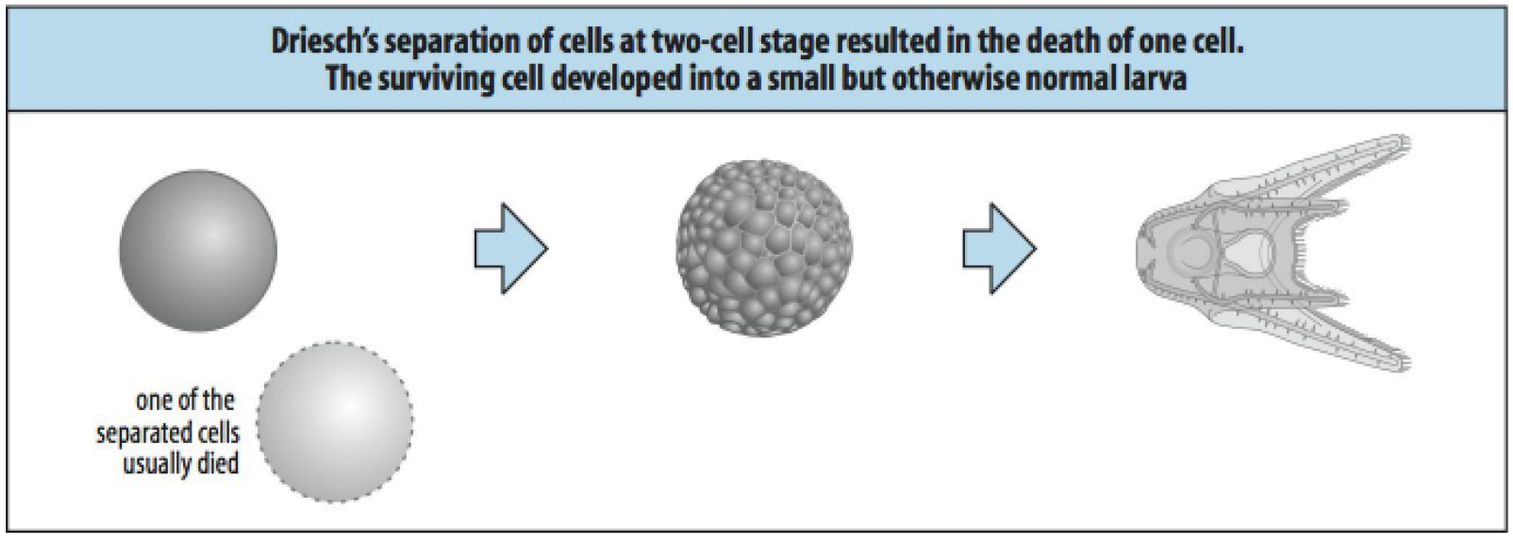


2.9 Preformationism vs epigenesis

Hans Driesch (1885): separation of blastomeres by agitation.

Inconsistent with Weismann's preformationist model. Regulative development.

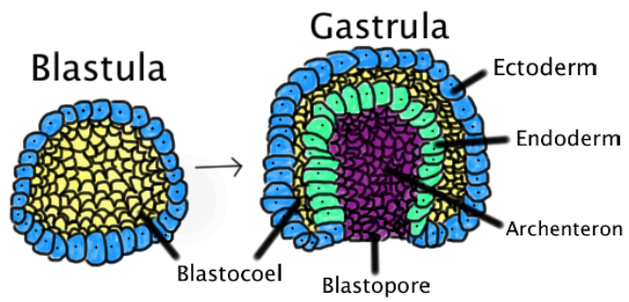


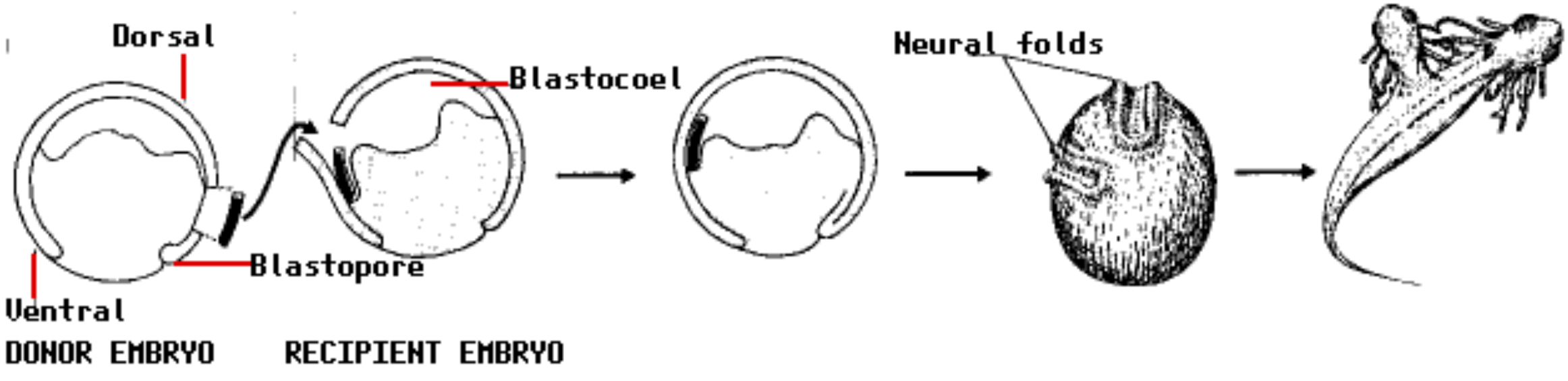


2.10 Preformationism vs epigenesis

<u>Experimental advance IV</u>: transplantation experiments. Cell-cell interactions are paramount.

Hilde Mangold and Hans Spemann (1921): postulation of "morphogenetic field": cross-species transplant between different species with different tissue colour; excision of blastopore tissue from donor organism of species 1 and transplantation under the ectoderm of recipient organism of species 2; blastopore tissue differentiated into notochord, while the ectoderm differentiated into a completely separate central nervous system.





2.11 Preformationism vs epigenesis

Experimental advance V: discovery and analysis of the structure and composition of DNA. Localisation of developmental plan. Strong neopreformationism or informational preformationism:

“A theory of development would effectively enable one to compute the adult organism from the genetic information in the egg. The problem may be approached by viewing the egg as containing a program for development, and considering the logical nature of the program by treating cells as automata and ignoring the details of molecular mechanisms.” Wolpert and Lewis 1975 p. 14.

(cf. Maienschein 2005 + Vecchi & Hernandez 2015.).

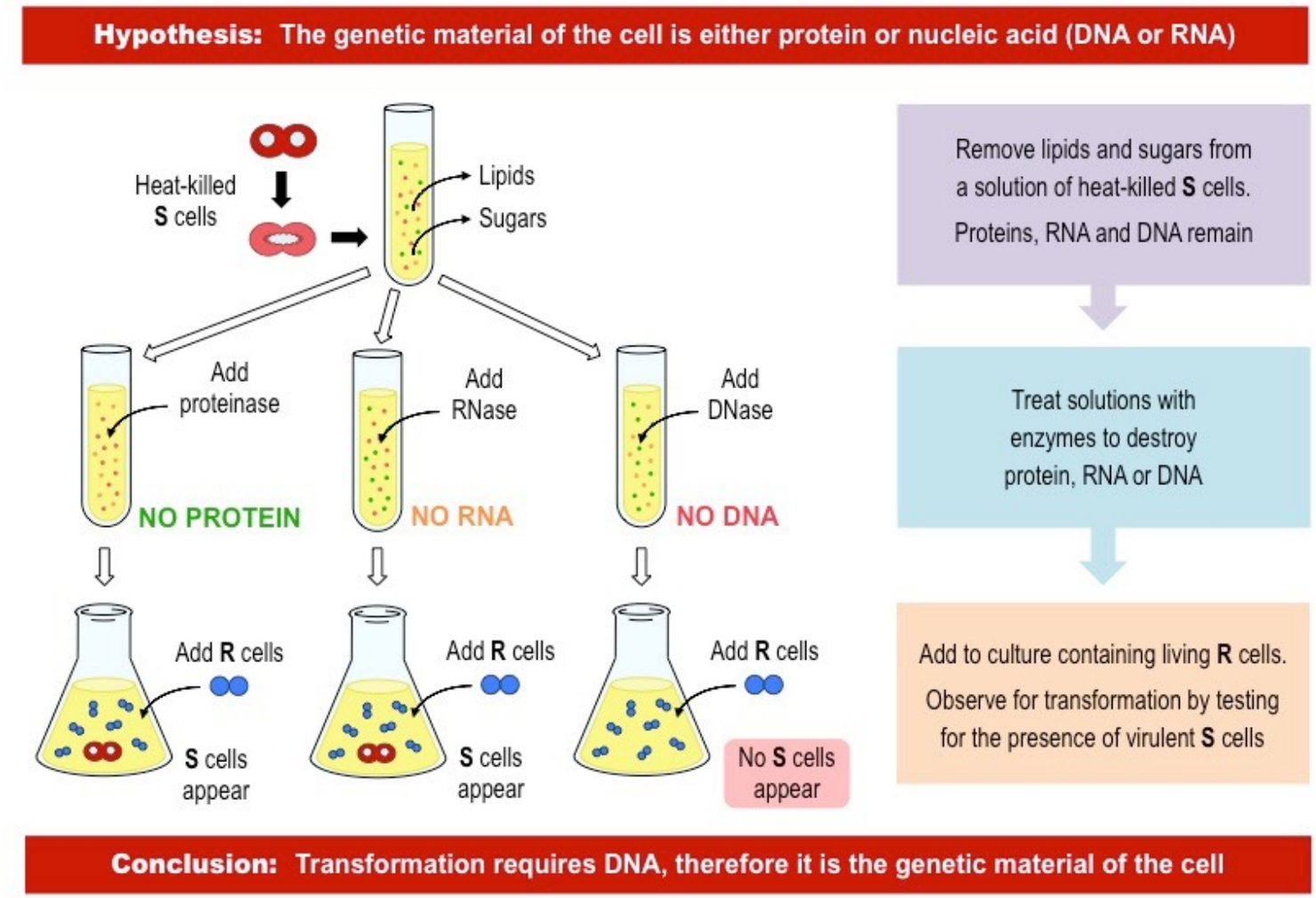
3.1 The molecular basis of genetic preformationism

Lewis Wolpert captured the informational Zeitgeist in developmental biology paraphrasing William Harvey's dictum "*ex ovo omnia*" (cf. slides section 3 class 1) to "*ex DNA omnia*": all phenotypes come out of the DNA of the genome.

Let's take a look at some milestones in DNA history:

- Genes are DNA molecules, not proteins: Avery, MacLeod and McCarty 1944;
- Double helix structure of DNA: Crick, Franklin, Watson and Wilkins 1953;
- Central dogma of molecular biology: Crick 1958;
- Triplet codons of nucleotides are matched to amino acids: Gamow and many others during 50s & 60s;
- The thermodynamic hypothesis: Anfinsen 1973;
- Human genome sequenced: 2001.

3.2 The molecular basis of genetic preformationism



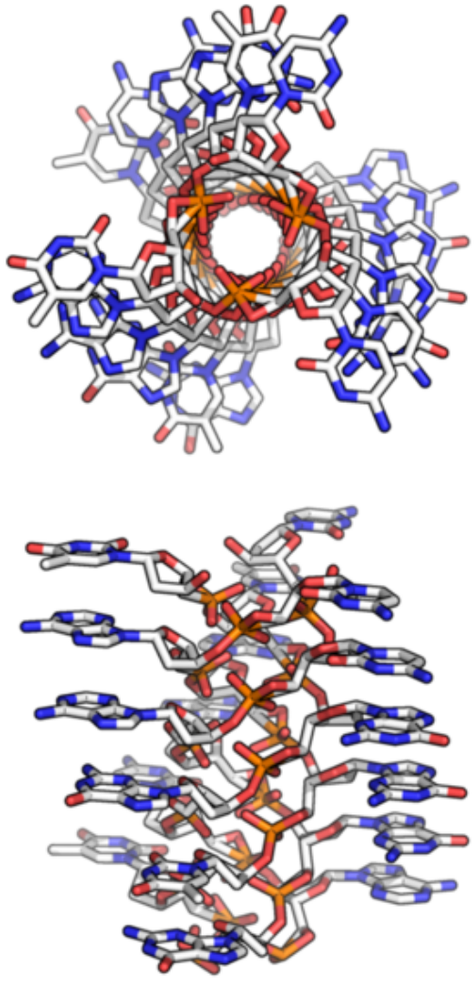
Two types of cells:

1. With virulent strain of pneumococcus (S);
2. With non-virulent strain of pneumococcus (R)

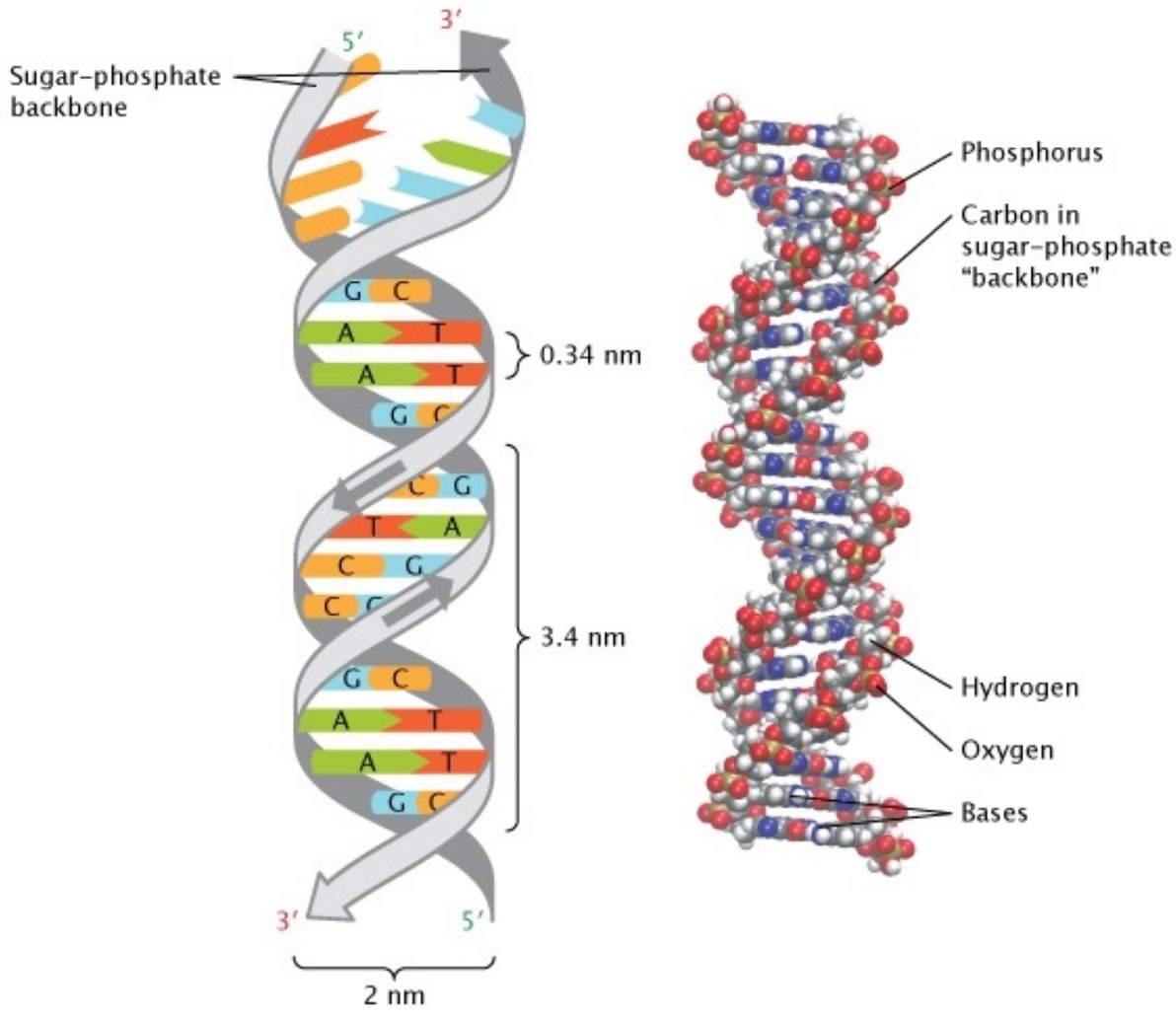
Avery et al.'s experiment 1944: only in the culture treated with DNase (a protein degrading DNA molecules) did the S strain of virulent bacteria fail to grow; hence, no DNA = no transformation —> genes = DNA stuff

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

3.3 The molecular basis of genetic preformationism

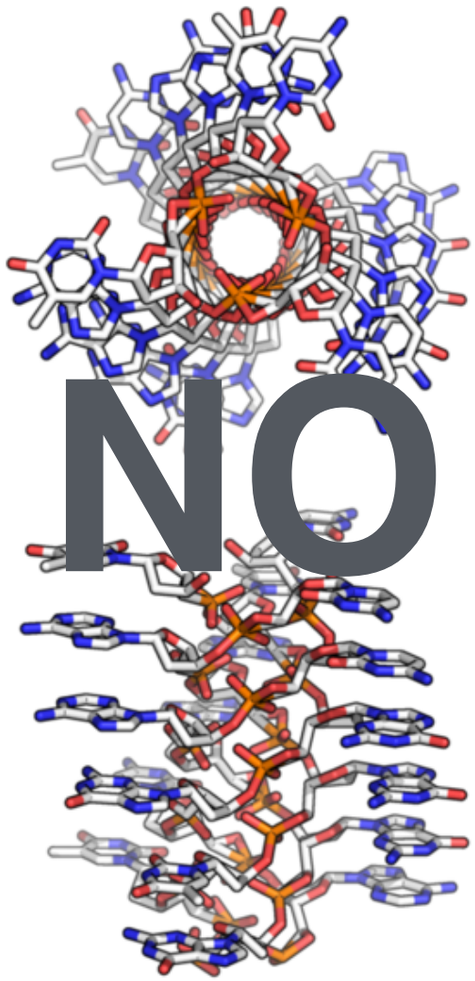


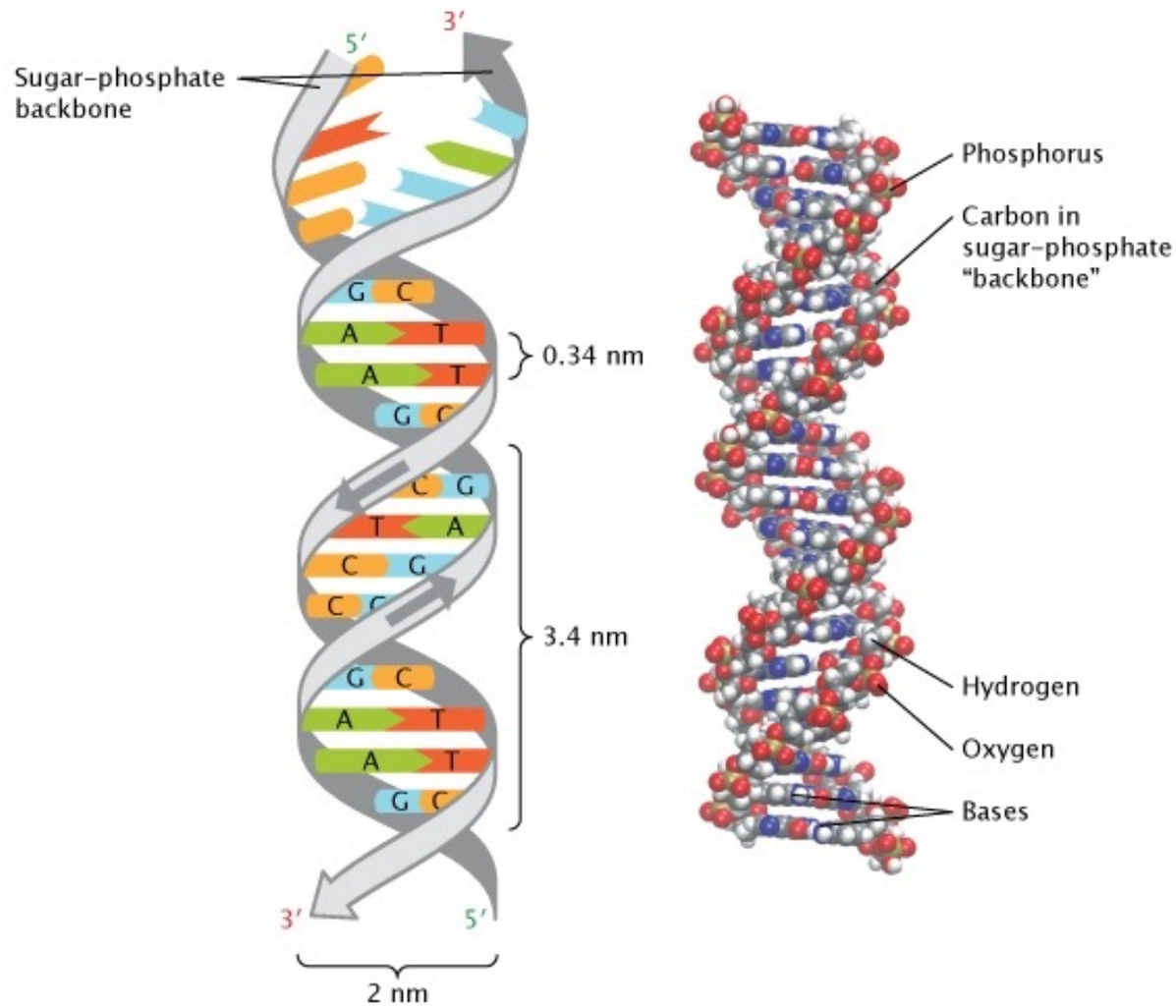
Pauling and Corey: triple helix model



Watson and Crick: double helix model

3.3 The molecular basis of genetic preformationism





Watson and Crick hypothesised that genes might be encoded by the nucleotides: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material." (Watson & Crick 1953 p. 737)

3.4 The molecular basis of genetic preformationism

Central dogma of molecular biology: "… once 'information' has passed into protein it cannot get out again. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible." Crick 1958 p. 153 (below Crick 1970)

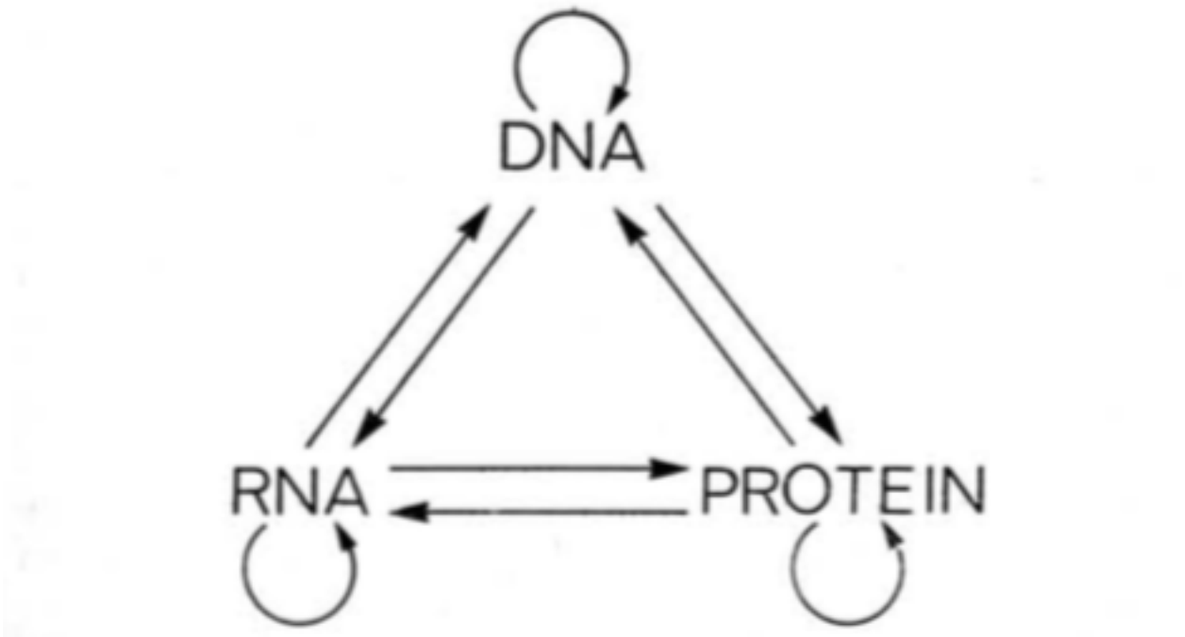


Fig. 1. The arrows show all the possible simple transfers between the three families of polymers. They represent the directional flow of detailed sequence information.

3.4 The molecular basis of genetic preformationism

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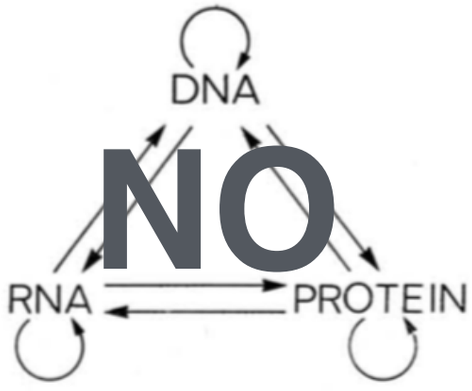

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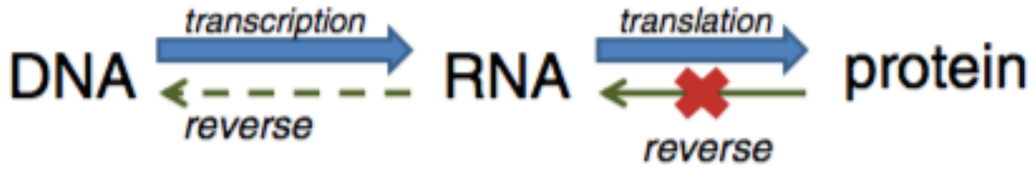


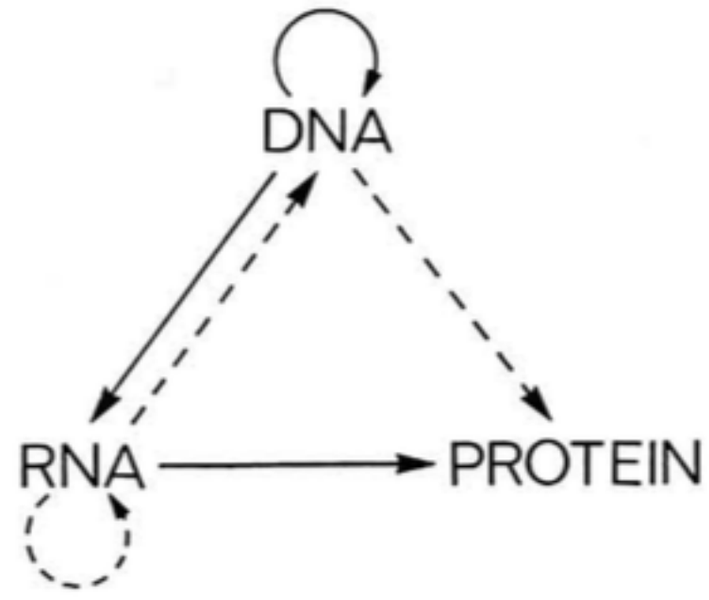
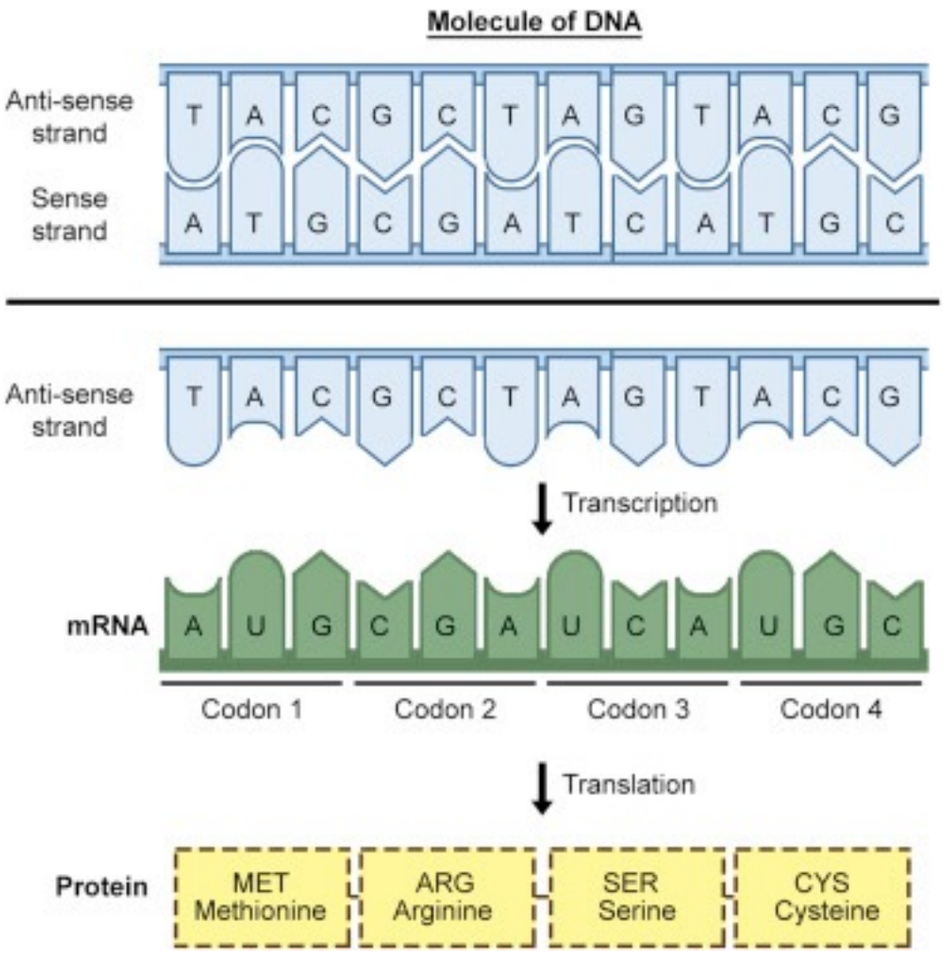
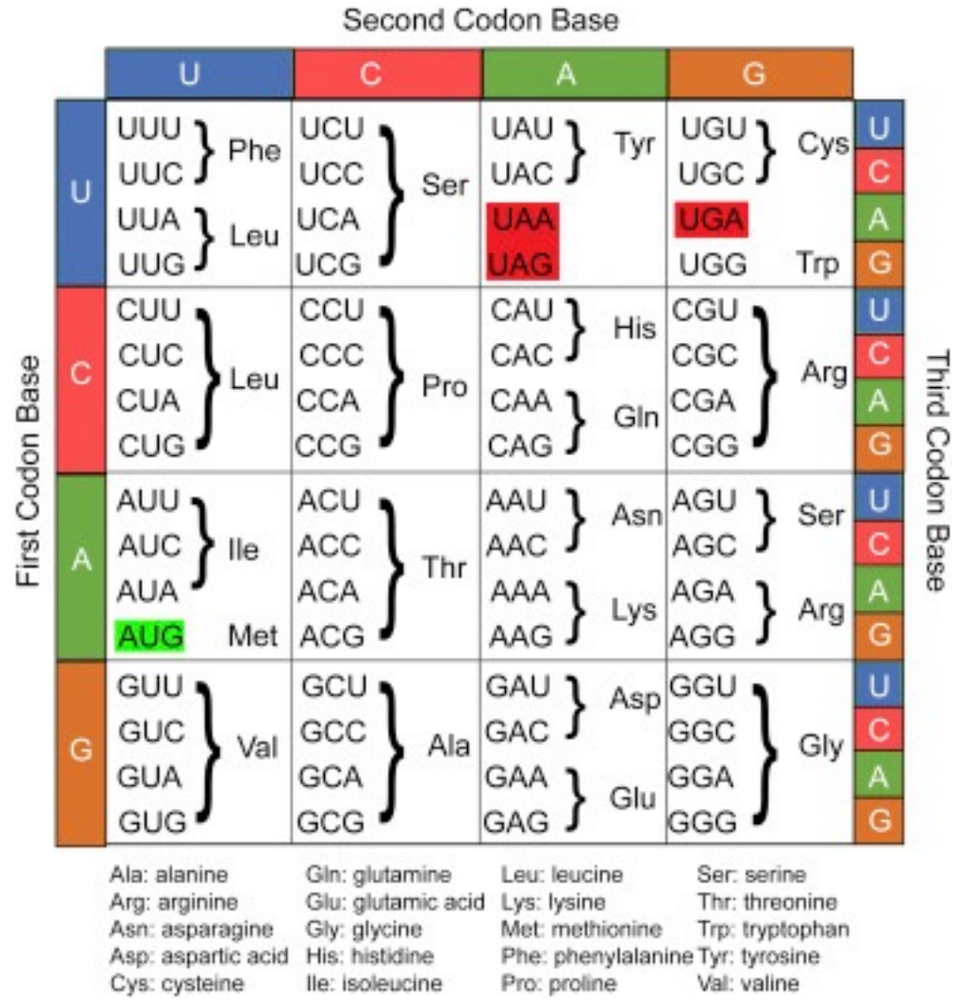


Fig. 3. A tentative classification for the present day. Solid arrows show general transfers; dotted arrows show special transfers. Again, the absent arrows are the undetected transfers specified by the central dogma.

3.5 The molecular basis of genetic preformationism

How is the DNA molecule processed in protein synthesis? Triplet RNA codons are matched to the amino acid constituents of proteins. The genetic code is understood within roughy 20 years starting from 1953.





3.6 The molecular basis of genetic preformationism

The thermodynamic hypothesis ("Anfinsen's dogma"): "... the three-dimensional structure of a native protein in its normal physiological milieu .... is determined by …. the amino acid sequence, in a given environment" (Anfinsen 1973, p. 223).

Given that the amino acid sequence is determined by the "coding" DNA sequence or gene, it follows that the structure of proteins is determined by DNA.

A simplified picture of the causal developmental chain (compare with 5.15).

DNA molecule	→	RNA transcript	→	Amino acid sequence	→	Folded functional protein	→	**Organismal phenotype**
…. AATGGC …		… UUACCG ….		… leucine + proline ….		Titin		**Human muscle**

3.7 The molecular basis of genetic preformationism

If Crick's and Anfinsen's "dogmas" were exceptionalness generalisations and organismal phenotypic complexity (i.e., compositional, structural and functional) were determined by proteins, then the developmental potential of any organism would be determined by its genome.

This is the meaning of Wolpert's "ex DNA omnia" maxim.

The history of molecular biology shows how the support in favour of genetic preformationism has strengthened, leading to widely shared conceptions such as genetic determinism and reductionism.

Molecular biology in 30-40 years unravelled the molecular basis of inheritance (i.e., DNA-based or genetic inheritance is biologically primary, cf. next class when we talk about evolution) and development (specifically protein synthesis).

3.8 The molecular basis of genetic preformationism

But genetic preformationism, determinism and reductionism are simplifications.

What does it mean to claim that the genome "determines" the developmental potential of organisms?

Is organismal complexity "determined" by the proteins "coded" by genomes?

If organismal complexity were genetically determined, then we would expect that genes (e.g., protein-coding sequences) are correlated to phenotypes approximately bijectively, as in the one gene for one enzyme hypothesis (Beadle and Tatum 1941).

3.9 The molecular basis of genetic preformationism

And we would expect that phenotypically complex organisms (e.g., humans) possess many more genes than phenotypically simpler organisms (e.g., bacteria).

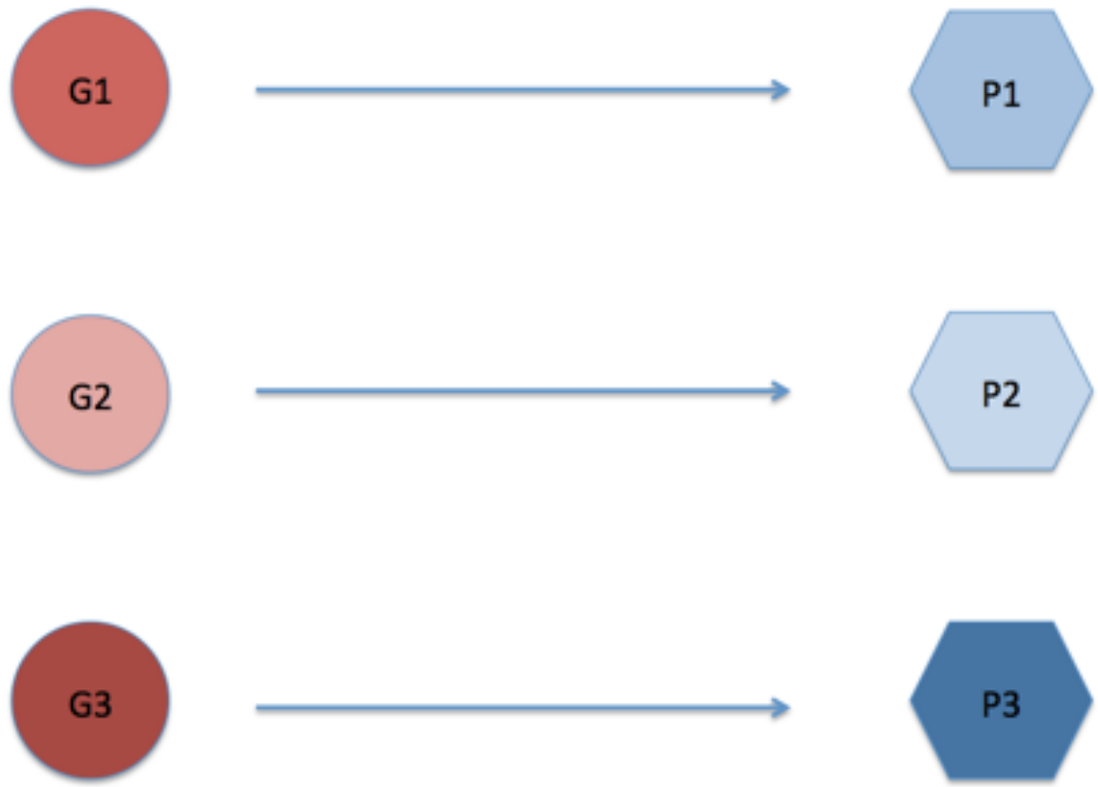
This is why estimates concerning human genes ranged from 60.000 at the minimum to 300.000 before the human genome was sequenced.

Interestingly, the current estimate of the genes in the human genome (first sequenced in 2001) is around 22.000, roughly the same as the mouse *Mus musculus* and *C. elegans,* while *D. melanogaster* has 16,000 and the rice plant (*Oryza sativa*) around 60.000.

What does this mean?

C. Elegans
1 mm length

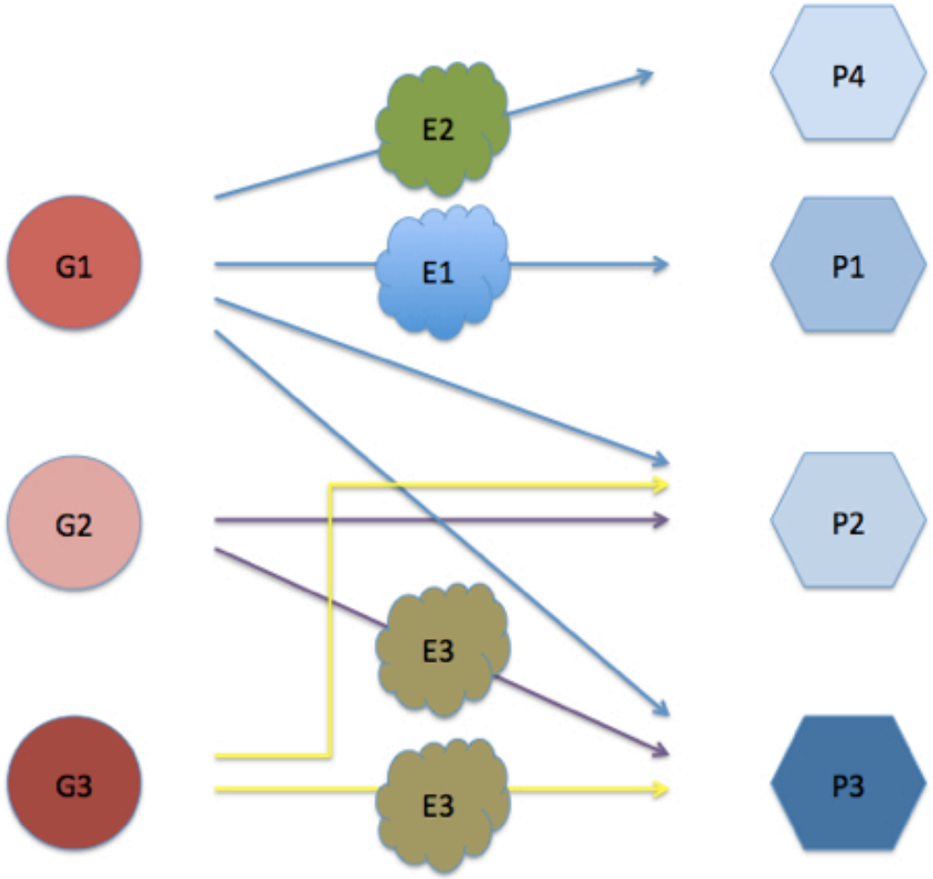
3.10 The molecular basis of genetic preformationism



The genotype-phenotype map as a bijective function: every gene causes one phenotype in development.

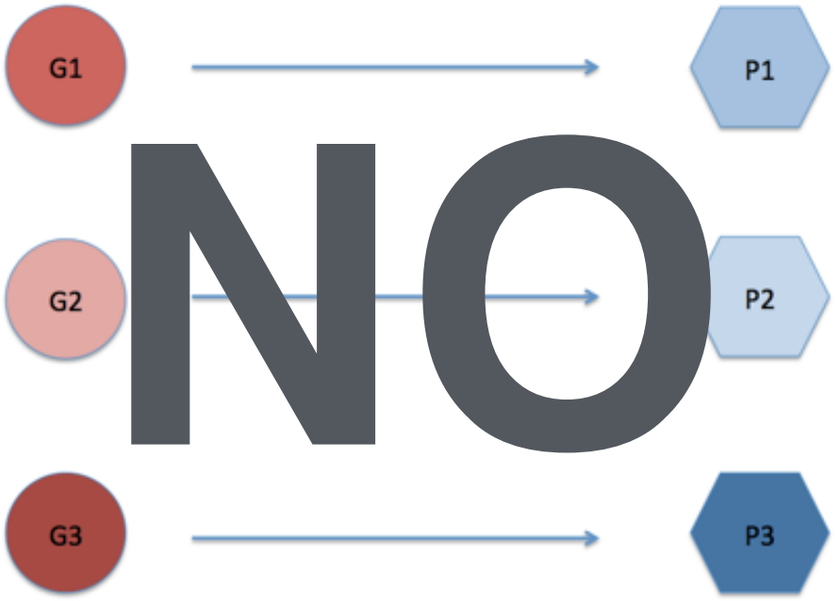
The genome determines the phenome (i.e., the set of possible phenotypes of the developing organism).

3.10b The molecular basis of genetic preformationism



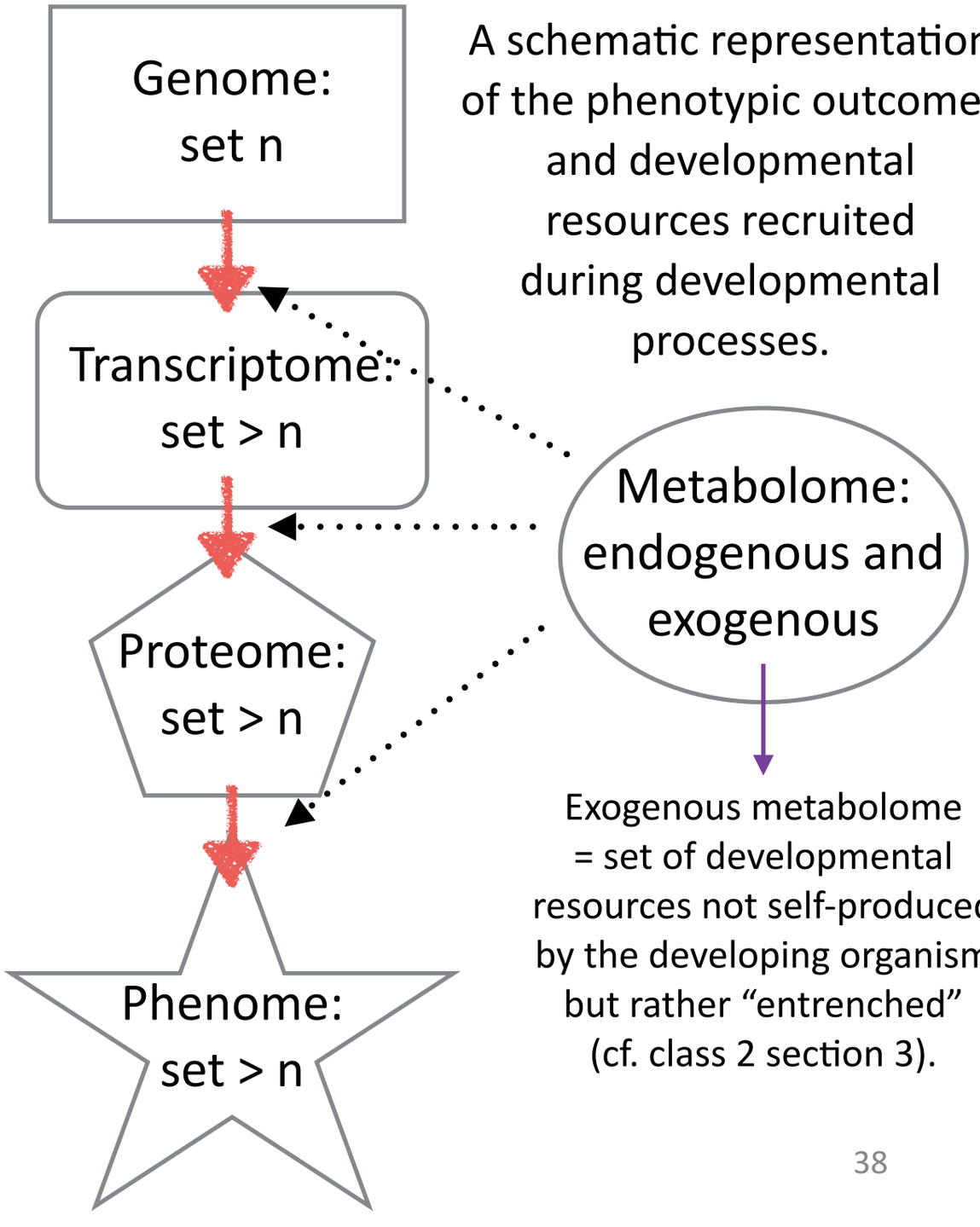
1. same genotype associated with several phenotypes (i.e., **pleiotropy**, for instance represented by G1 influencing development of P1, P2, and P3);
2. several genotypes associated with the same phenotype (i.e., polygenic control of development or **epistasis**, represented by P2 being influenced by G1, G2 and G3);
3. same genotype associated with different phenotypes in different environments (i.e., **plasticity** or 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)

3.11 The molecular basis of genetic preformationism



NO

NO



A schematic representation of the phenotypic outcomes and developmental resources recruited during developmental processes.

Exogenous metabolome = set of developmental resources not self-produced by the developing organism but rather “entrenched” (cf. class 2 section 3).

3.12 The molecular basis of genetic preformationism

Genetic preformationism, determinism and reductionism are also simplifications in the sense that the causal models they propose lead astray, specifically to unrealistic conceptualisations of developmental processes.

What causal role is played by extra-genomic causes in development?

These are all complex philosophical, theoretical and experimental questions (cf. Santos et al. 2020 and Vecchi 2020 for analysis).

4.1 How to conceptualise development

Before passing to the issue of the role of DNA and extra-genomic (i.e., environmental) causes in development in section 5, let us first:

1. compare two models of development;
2. understand the concept of developmental normality;
3. understand which entities are involved in developmental processes.

On this basis, we shall finally approach the issue concerning the causal role of DNA and environment in development.

4.2 How to conceptualise development

Aristotle: in the book IV of his treatise “On the Generation of Animals” argued that if the development of the animal embryo reproducing sexually proceeds perfectly successfully, the offspring would be male and closely resemble the father.

This was no “sexist” view of development, but the result of observationally informed theorising. Aristotle reasoned that, given that most animals did not reproduce by parthenogenesis, the male semen must be the source of the *developmental plan* (if, on the contrary, animals reproduced by parthenogenesis, then the developmental plan would be localised in the female egg). Thus, in sexually reproducing animals, male semen and female egg are different kinds of developmental causes.

4.3 How to conceptualise development

Aristotle used an analogy to make his case; the organism produced by the fertilised egg is like a bed manufactured by the carpenter:

“The male emits semen in some animals and where he does, it does not become part of the embryo; just as no part of the carpenter enters into the wood in which he works …. but the form is imparted by him to the material by means of the changes which he effects .... (GA I,22;230b, 10_19).” (from Delbrück 1971, p. 54)

Thus, the male semen is, like a carpenter, an imposer of form on the embryo, while the female egg in turn is like the material, the wood, out of which the bed is constructed.

4.4 How to conceptualise development

To postulate that the default outcome of a developmental process is the production of a certain phenotypic outcome (i.e., perfectly resembling one's father) is to postulate the existence of a natural developmental state or natural phenotype.

Aristotle used the "natural state model" in physics and biology alike (Sober 1980).

Why is there "deviant or abnormal" development then? Interfering forces must be identified to account for this deviation from the natural phenotypic state.

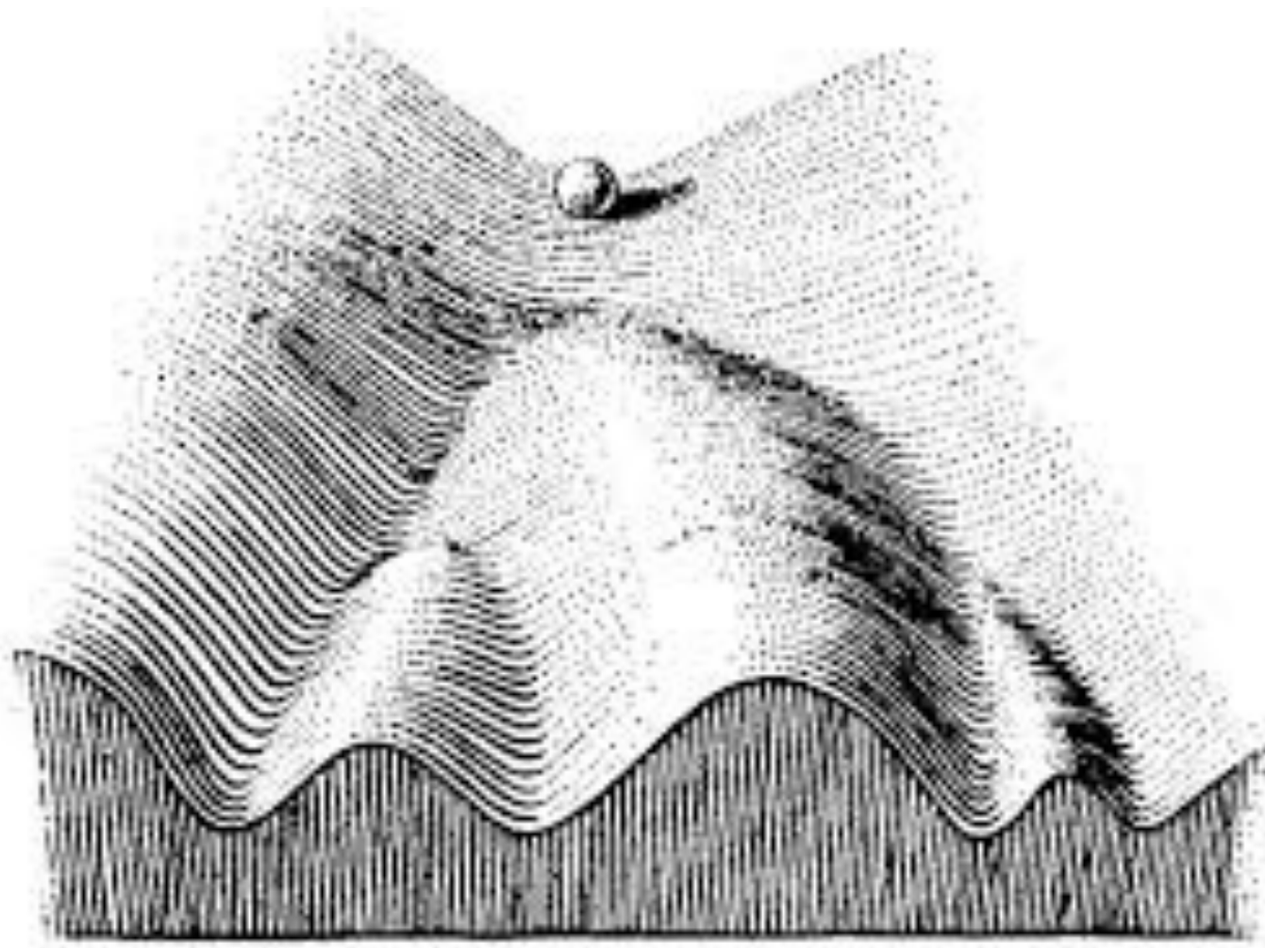
A corollary of this view is that the developmental plan, acting undisturbed, would produce the natural phenotype.

If developmental plan = genome, the idea is that environmental influence in development is disruptive.

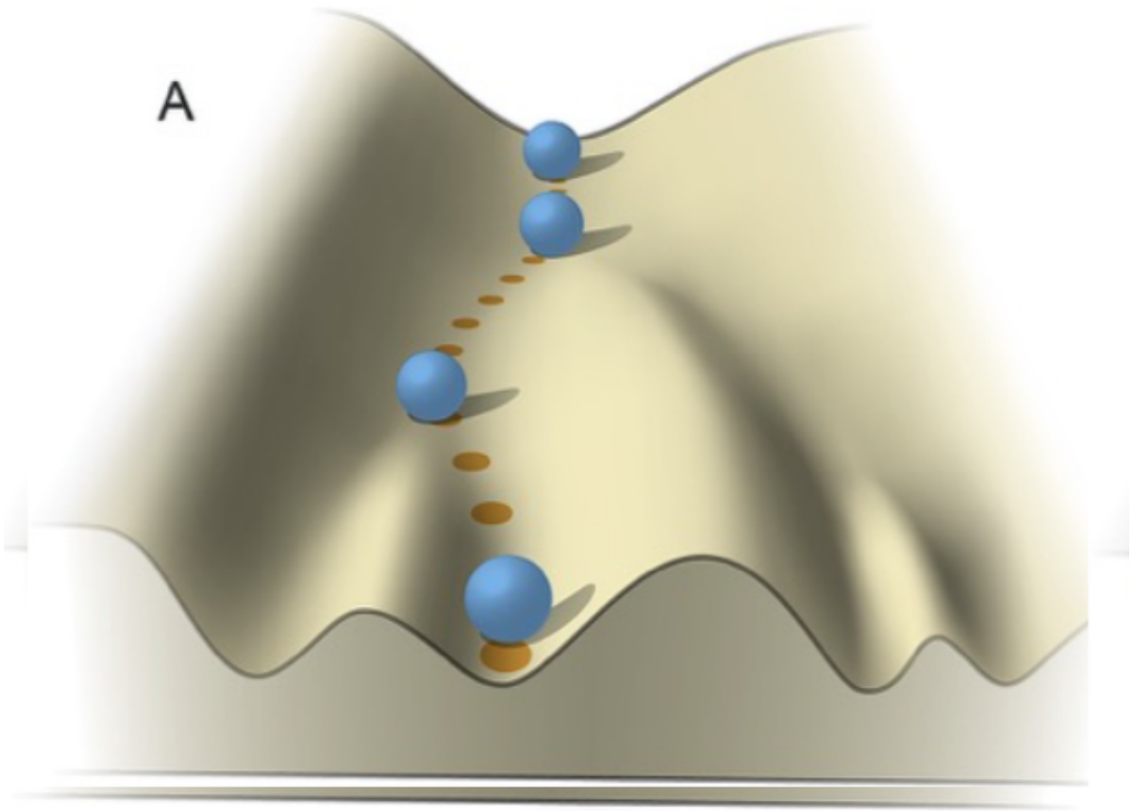
4.5 How to conceptualise development

In order to make sense of Aristotle's view, let us consider Waddington's (1957) epigenetic landscape :

1. imagine that the ball at the top is the developing organism;
2. development is a process that can be represented as the ball rolling downhill;
3. development consists of many bifurcation points;
4. what are the causes of the ball taking a particular path?



4.6 How to conceptualise development



The “natural phenotype” is an “attractor” in the developmental process.

Aristotle’s “natural state model”: development is a process canalised towards normal functionality; development produces an “abnormal” phenotype because of environmental interference (of interference not caused by the developmental plan localised in the male semen in sexually-reproducing organisms).

4.7 How to conceptualise development

Does it make sense to postulate a normal developmental outcome given the existence of extensive variation concerning basically all phenotypes?

Can we associate some phenotypic variants to “developmental normality” and “good” biological function?

Today we use the concept of reaction norm to understand the relationship between gene and environment.

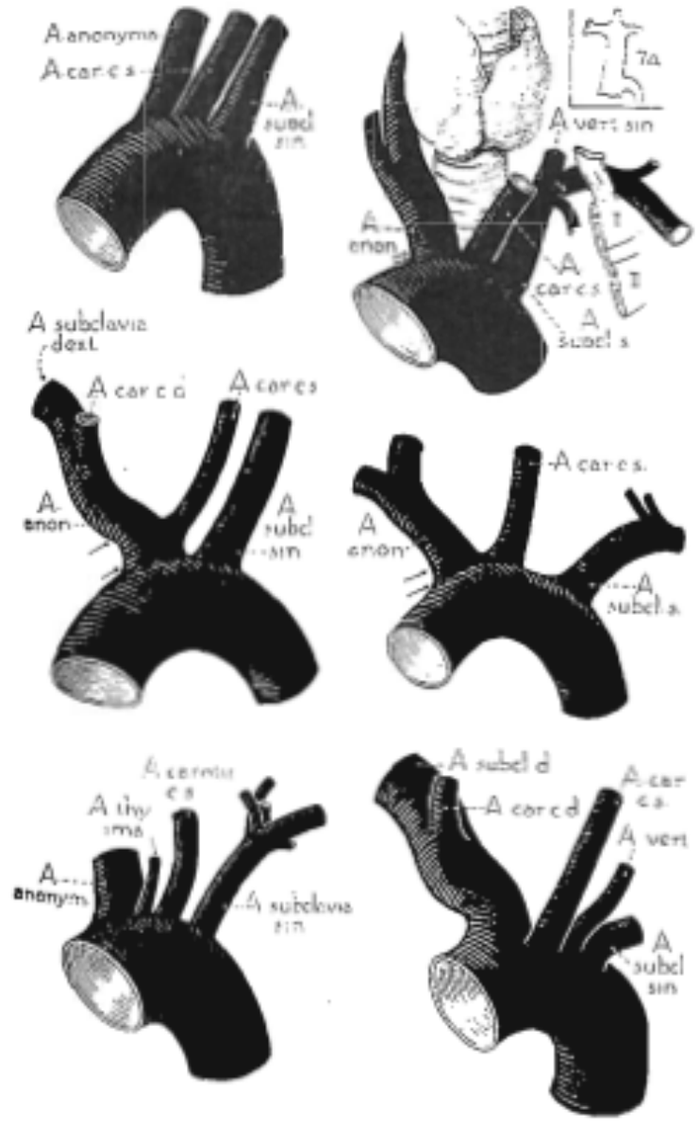
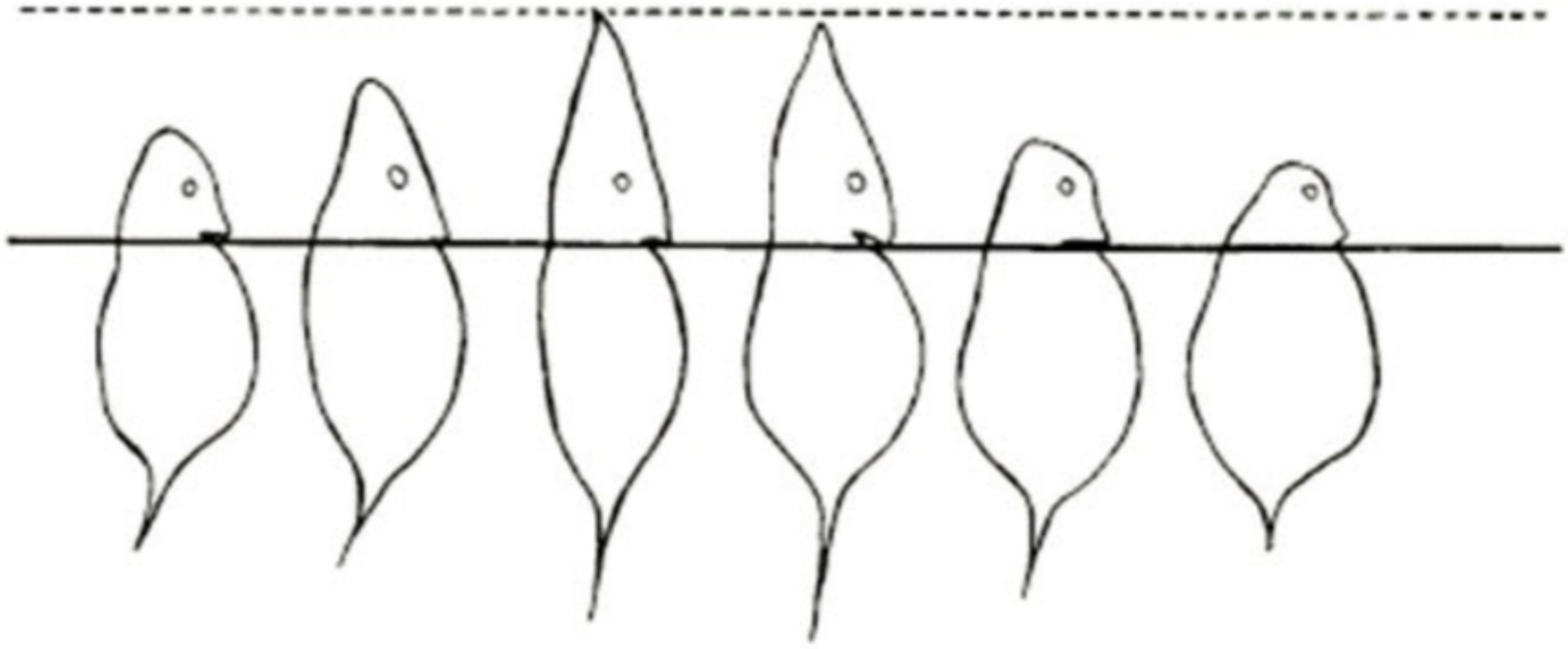


Fig. 3.10. Variation in arterial branches of the human aortic arch. Six common types of branching are shown. From McDonald and Anson (1940), *American Journal of Physical Anthropology*, © John Wiley and Sons, Inc. 1940. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

West-Eberhard 2003, p. 50

4.8 How to conceptualise development



Woltereck, R. (1909). Weitere experimenteUe Untersuchungen tiber Artveranderun~ speziell tiber das Wesen quantitativer Artunter- schiede bei Daphniden [Further experimental investigations of species alteration, particularly of the quantitative nature of species differences in Daphnia]. In E. Korschelt (Ed.), Verhandlungen der Deutschen Zoologischen Gesellschafi auf der neunzehnten Jahres- versammlung (pp. 110-173). Leipzig, Germany: Verlag von Wil- helm Engelmann.

Reaction norm: *Daphnia* clones develop a different phenotype (i.e., protective helmet) in response to season and predator presence. Same genotype + different environment = different phenotypes representable as a statistical distribution.

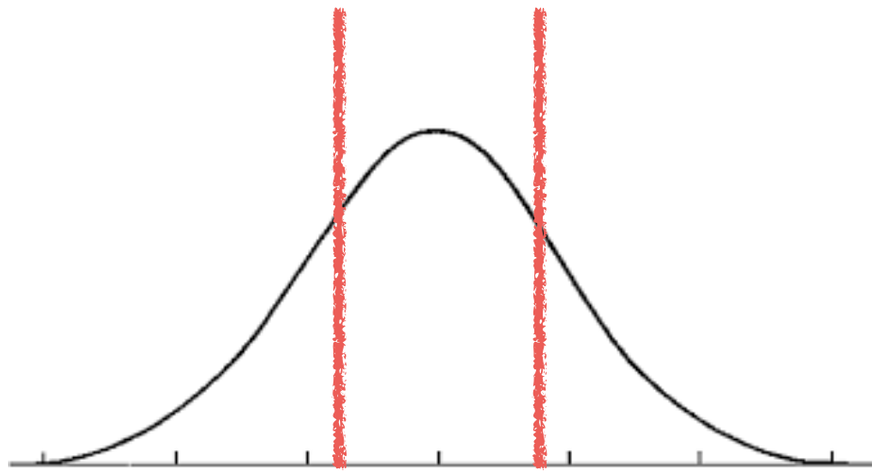
4.9 How to conceptualise development

The concept of normal phenotype is a statistical abstraction (variously called “standard design” or “conventional phenotype” in the biomedical literature etc.)

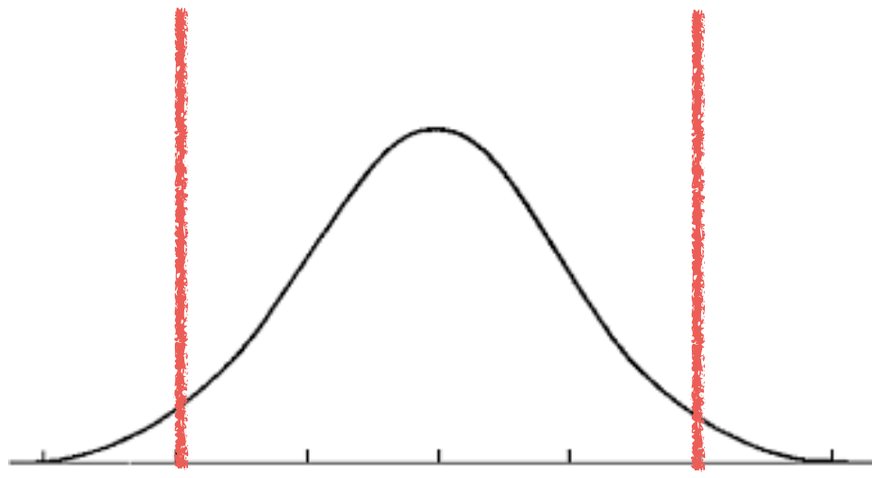
The statistically frequent becomes the species-typical, hence the normal and hence the healthy —> often dubious argument.

“….. our ‘modern’ conceptions of health and disease and our notion of normality as something other than a statistical average enshrine Aristotle’s model.

“ Sober 1980 p. 363 (cf. part 4)



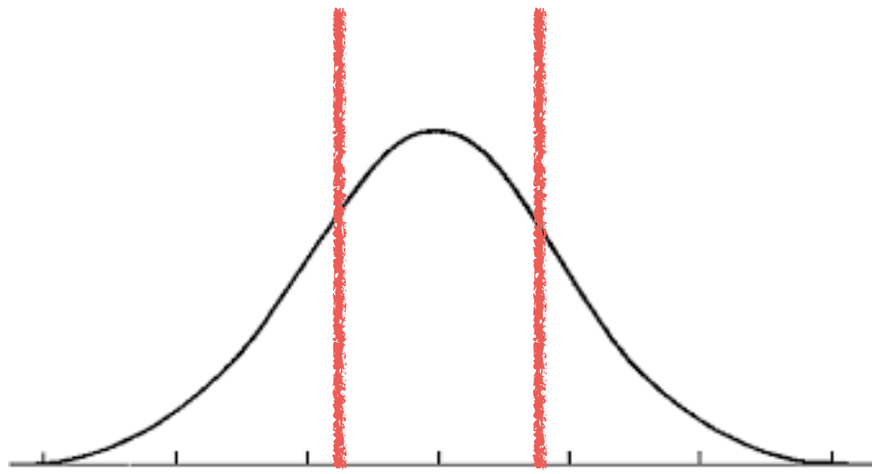
Reaction norm with narrow normal function range



Reaction norm with wide normal function range

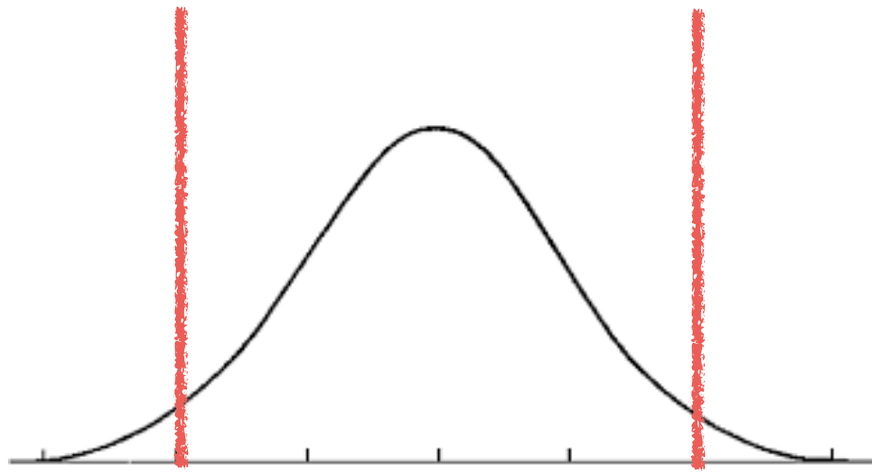
4.9.1 How to conceptualise development

The Aristotelian model is committed to conceptualise variation in terms of deviation from type/natural phenotypic outcome/single developmental tendency. The underlying idea here is the natural type, i.e., the natural state towards which a process like development tends:



Reaction norm with narrow normal function range

"Nature, and not just living nature, was understood by the pre-Darwinians only in terms of the ideal; and the failure of individual cases to match the ideal was a measure of the imperfection of nature" (Lewontin, The Genetic Basis of Evolutionary Change, 1974, p. 5)

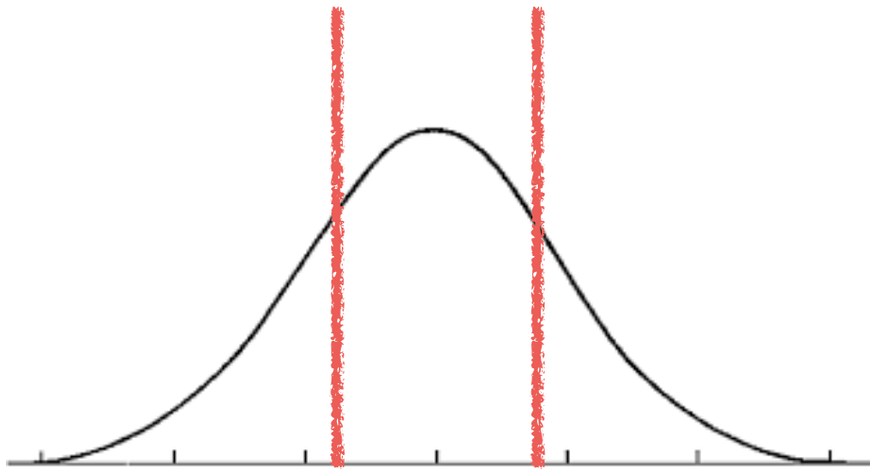


Reaction norm with wide normal function range

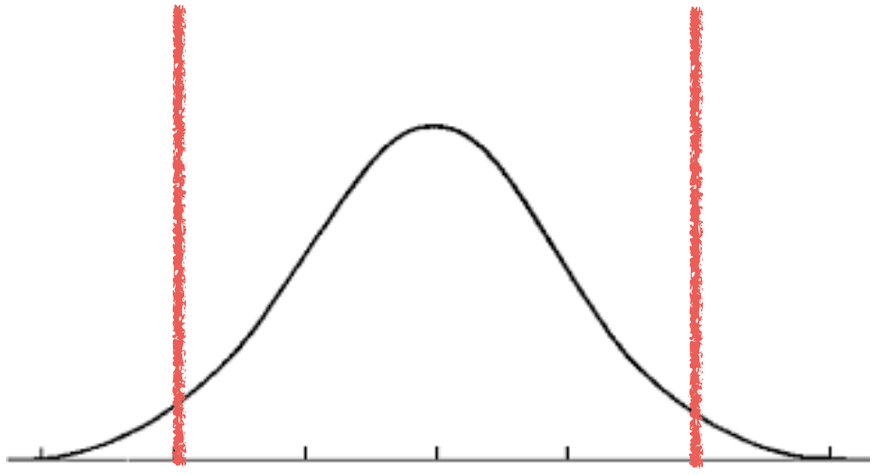
4.9.2 How to conceptualise development

Behind this postulation there's a tendency to think that the endogenous and intrinsic properties of the organism (e.g., the genome) has a prominent causal role and that the environment explains its deviation from natural outcome:

"It may be misleading to say that the carriers of a certain genotype must reach certain 'intrinsic' height, or weight, or skin color, or intelligence level. Any height or weight or intelligence a person may have is 'intrinsic', in the sense that the phenotype observed is the necessary outcome of the development brought about by a certain genotype in a certain succession of environments." (Dobzhansky, T. 1955. Evolution, genetics and Man. John Wiley and Sons, New York. p. 77)



Reaction norm with narrow normal function range

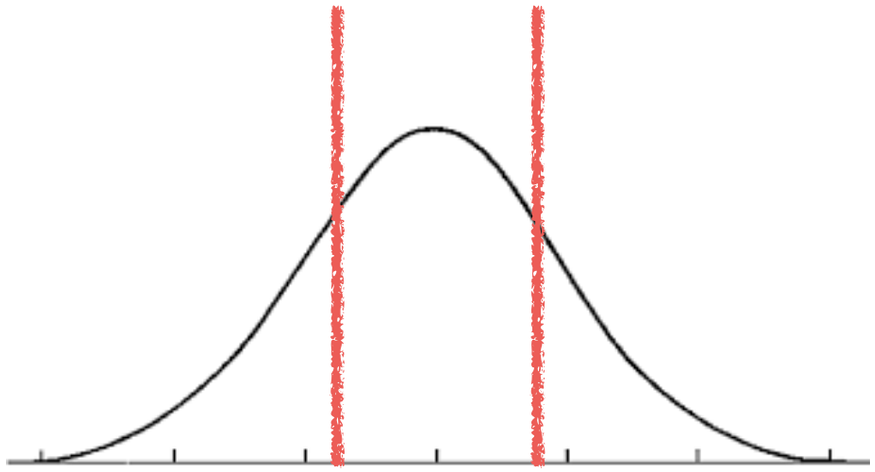


Reaction norm with wide normal function range

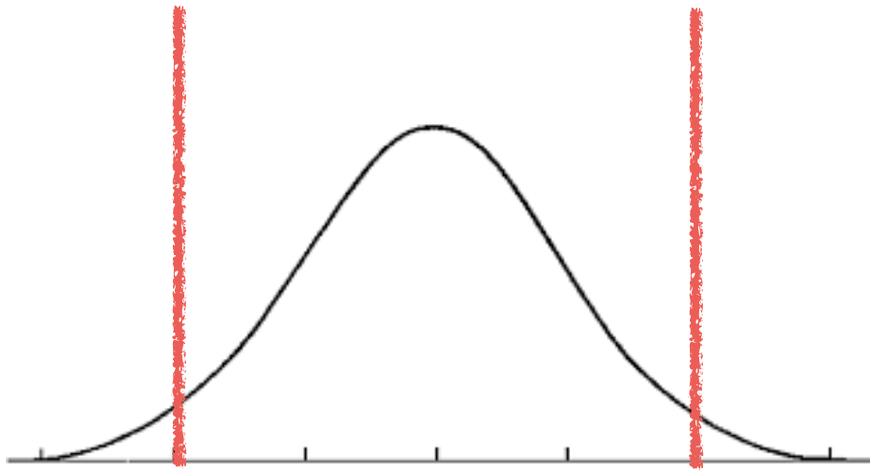
4.9.3 How to conceptualise development

The view that development produces a monistic design and that it is a process insulated from environmental influence is based on a:

"…widely shared intuition that the true nature of something is best revealed by removing exogenous influences and allowing it to develop under the influence of endogenous factors alone." (Griffiths, P. (2011). Our Plastic Nature. In Gissis, S.B. and Jablonka, E. (Eds.) Transformations of Lamarckism: from subtle fluids to molecular biology. (pp. 319-330). Cambridge: MIT Press, p. 324)



Reaction norm with narrow normal function range



Reaction norm with wide normal function range

4.9.4 How to conceptualise development

The implication of this in medicine is to think about one phenotypic variant as normal and the other variants as functionally abnormal:

"Development yields adults that function, but not adults that function identically." (Amundson, R. (2000). Against normal function. Studies in the history and philosophy of the biological and biomedical sciences, 31, 33:53).

"Like the concept of race, the concept of normality is a biological error…..Diversity of function is a fact of biology."
Amundson (p. 34)

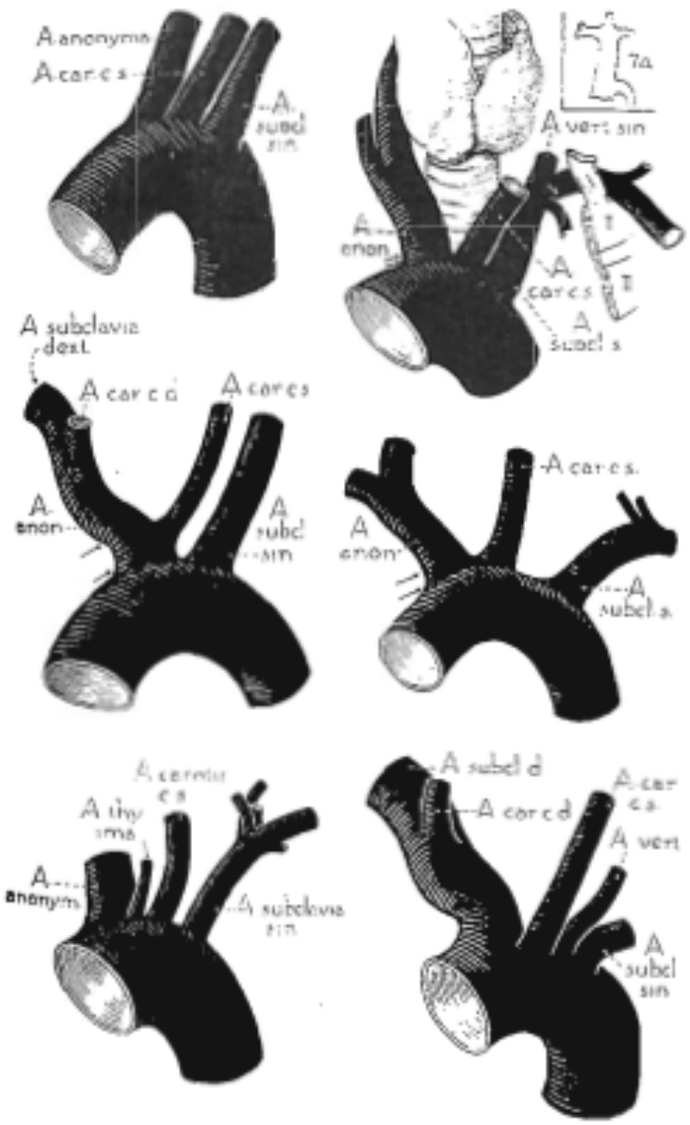


Fig. 3.10. Variation in arterial branches of the human aortic arch. Six common types of branching are shown. From McDonald and Anson (1940), *American Journal of Physical Anthropology*, © John Wiley and Sons, Inc. 1940. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

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4.9.5 How to conceptualise development

At this juncture another issue crops up: what is a biological function?

1. Aetiological notion: the function of a biological trait is the historical reason why the trait has evolved (mostly by selection);

2. Causal role notion: the function of a biological trait is its causal role within a larger system (e.g., the organism).

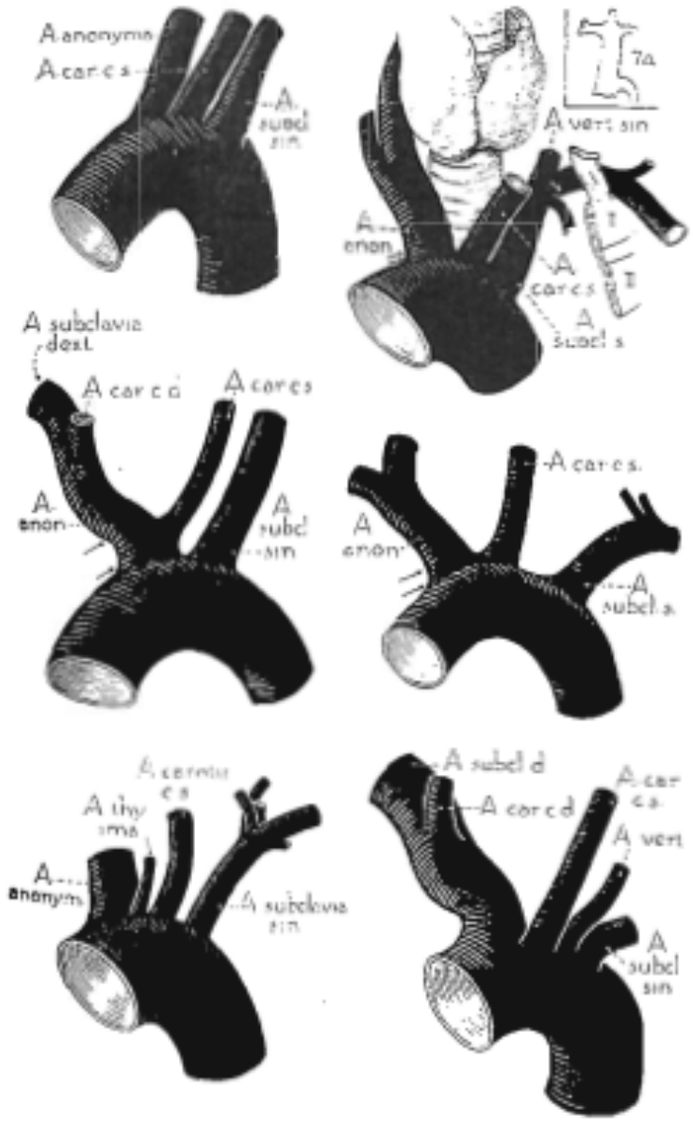

Fig. 3.10. Variation in arterial branches of the human aortic arch. Six common types of branching are shown. From McDonald and Anson (1940), *American Journal of Physical Anthropology*, © John Wiley and Sons, Inc. 1940. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley and Sons, Inc.

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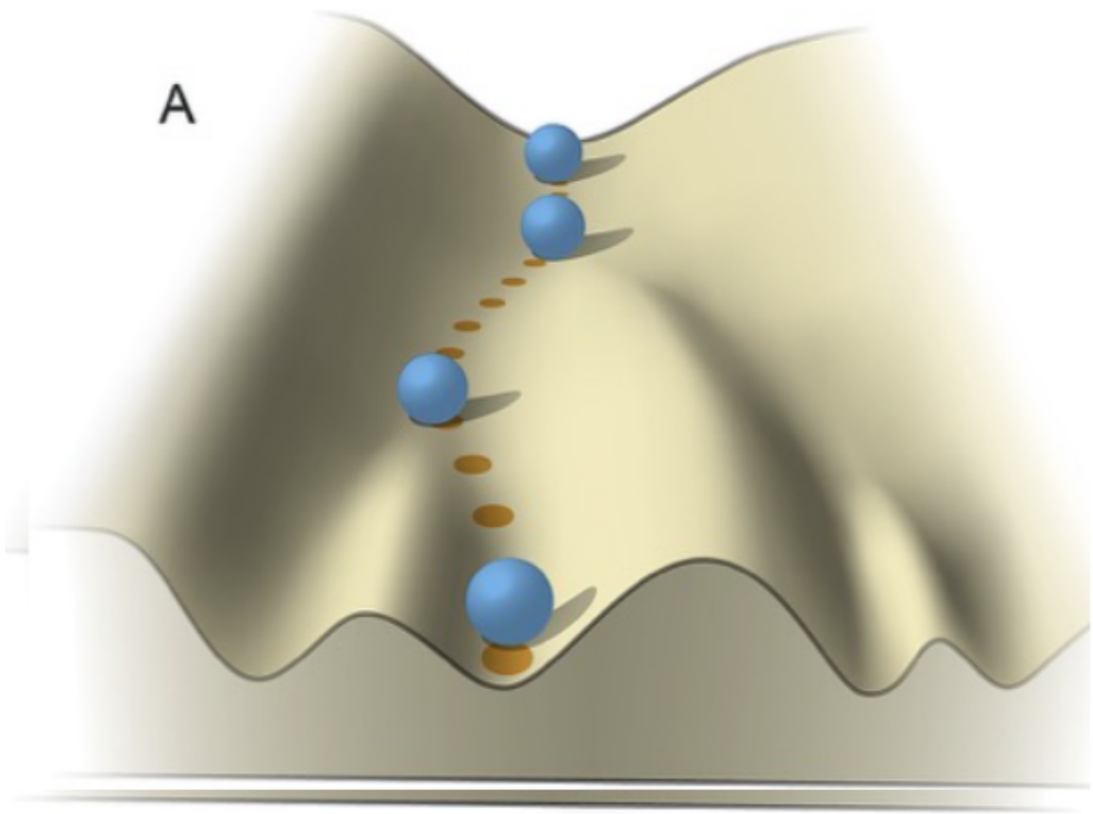
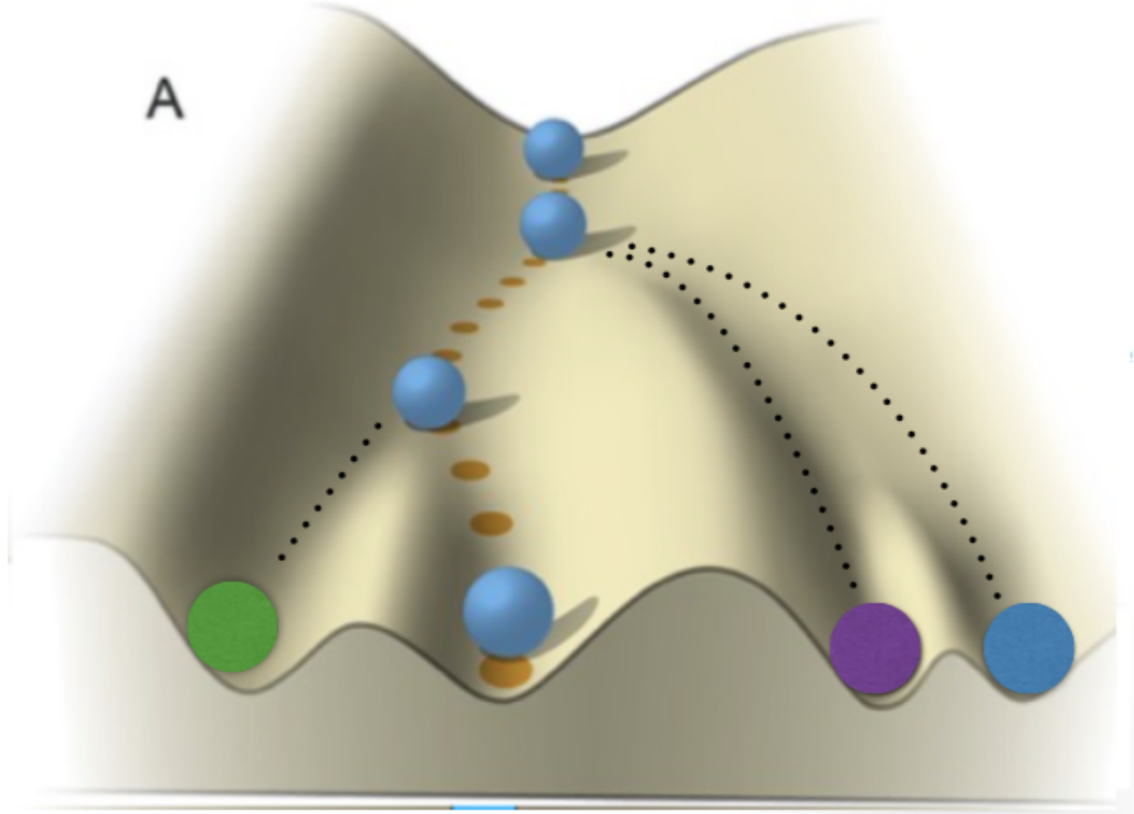
4.10 How to conceptualise development



The “natural phenotype” is an “attractor” in the developmental process.



Each phenotype might be equally viable.

Aristotle’s “natural state model” interpreted from the vantage point of the epigenetic landscape representation: development produces a variety of more or less viable phenotypes. Environmental influence in development is not necessarily disruptive.

4.11 How to conceptualise development

In order to characterise developmental processes, it is conceptually useful to discriminate between three entities:

1. **the genome**: a system that remains somehow organisationally stable through development and that is largely structurally identical in all cells of the developing organism;
2. **the developing organism:** a system that continuously changes compositionally, organisationally and functionally during ontogeny (i.e., developmental stages). The developing organism grows, undergoes morphogenetic changes and its parts differentiate.
3. **the environment**: the set of developmental resources available to a system of reference: if the system of reference is the genome, the relevant environment is extra-genomic, including all the set of molecular resources to process DNA molecules in replication and transcription: if the system of reference is the developing organism, the relevant environment is the external environment to the organism itself.

4.12 How to conceptualise development

Three important caveats:

a. Some of the qualitative changes undergone by developing organisms are caused by the assimilation, functional integration and eventual deployment of environmental resources (see section 3 class 2 + slide 3.11);

b. Given that the developing organism is a continuously changing biological system, the external environment can only be characterized vis-à-vis a particular <u>developmental stage</u> rather than generally. For instance, the external environment of a developing fetus might be a uterus, while after delivery it is extra-uterine.

c. The environment provides a <u>constantly changing</u> set of developmental resources to the developing organism, as it constantly undergoes modifications caused abiotically and biotically.

5.1 Developmental causation

Waddington proposed an interpretation of gene action that was deterministic already in 1939:

“…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)

When, with the molecular revolution (slides in part 3), it was understood that “evocator" = DNA, genetic determinism followed:

“… 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)

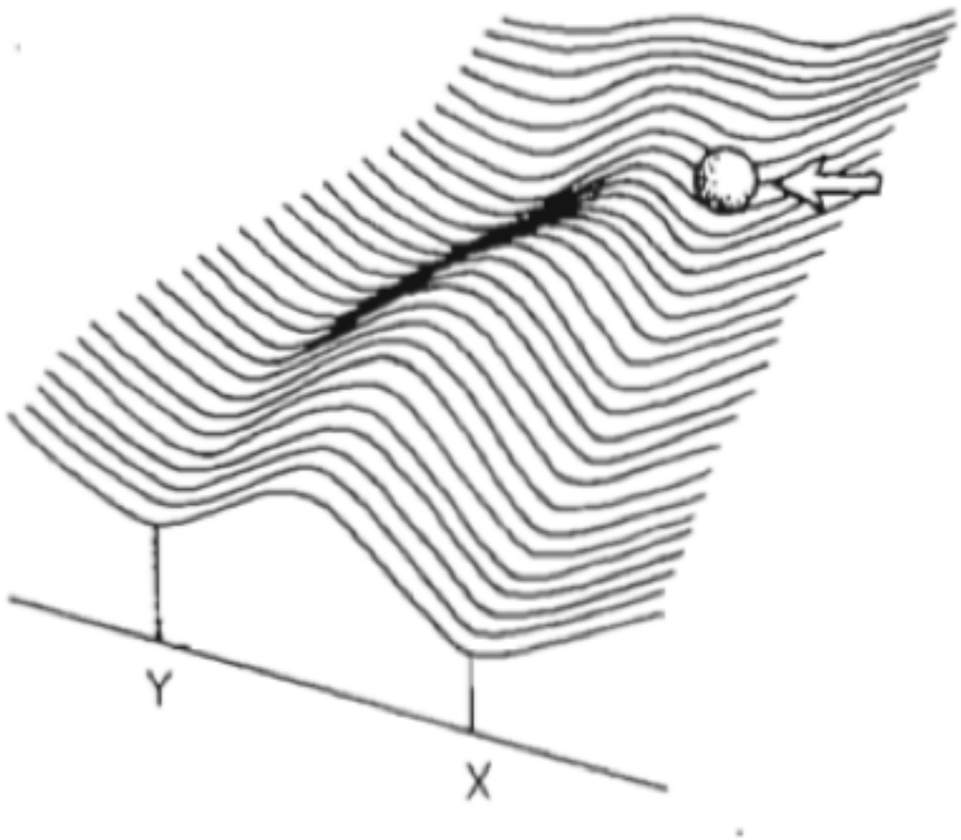
5.2 Developmental causation

But what is the role of the environment in development?

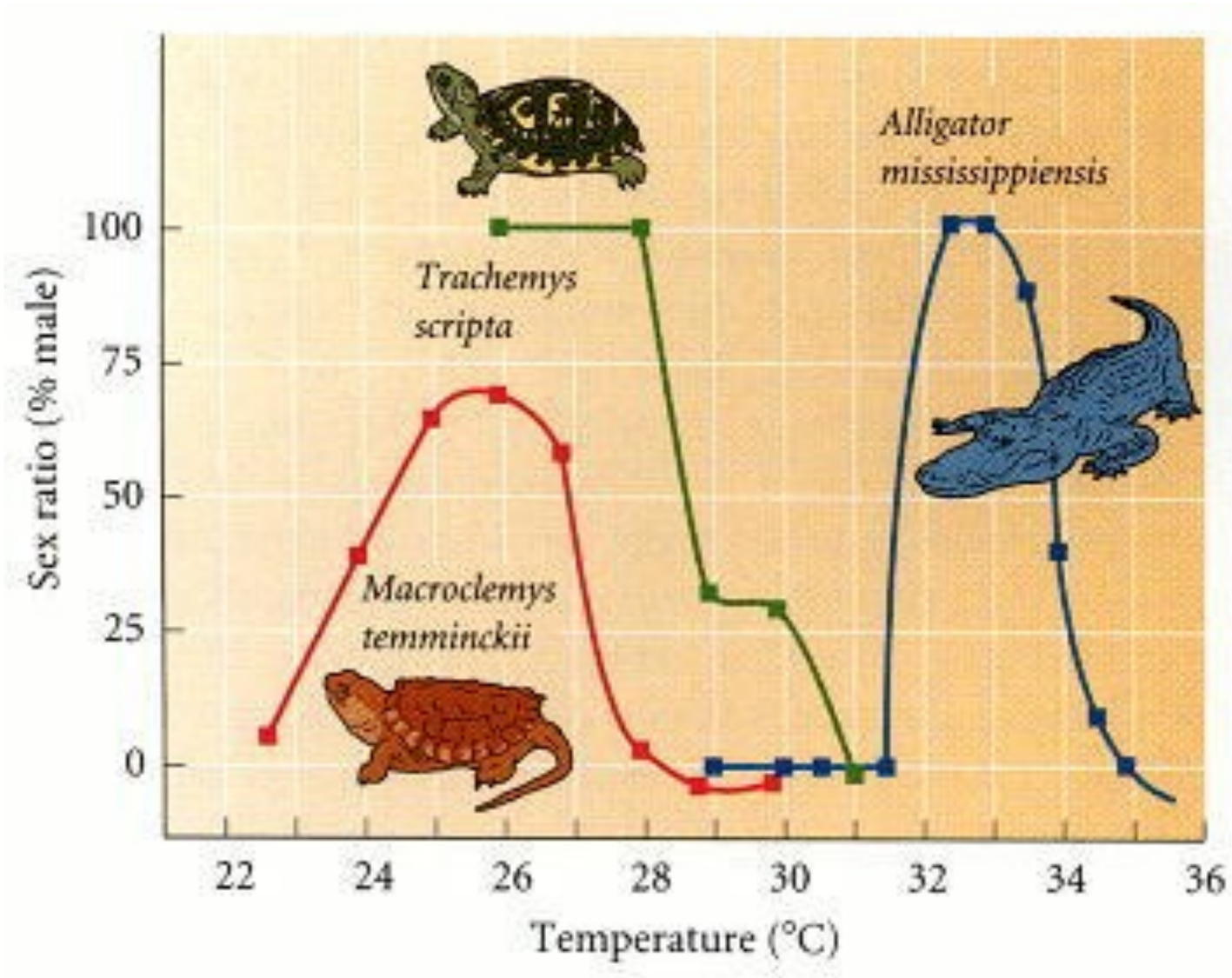
"All that the environment can do, in Waddington's scheme, is deflect development into a new genetically specified path." West-Eberhard 2003, pp. 13-16

Y and X are **genomically determined developmental paths**.

One causal role of the environment is to co-determine whether the organism (the ball), will swerve right or left (as in sex morphogenesis in reptiles, slide 5.3).



5.3 Developmental causation

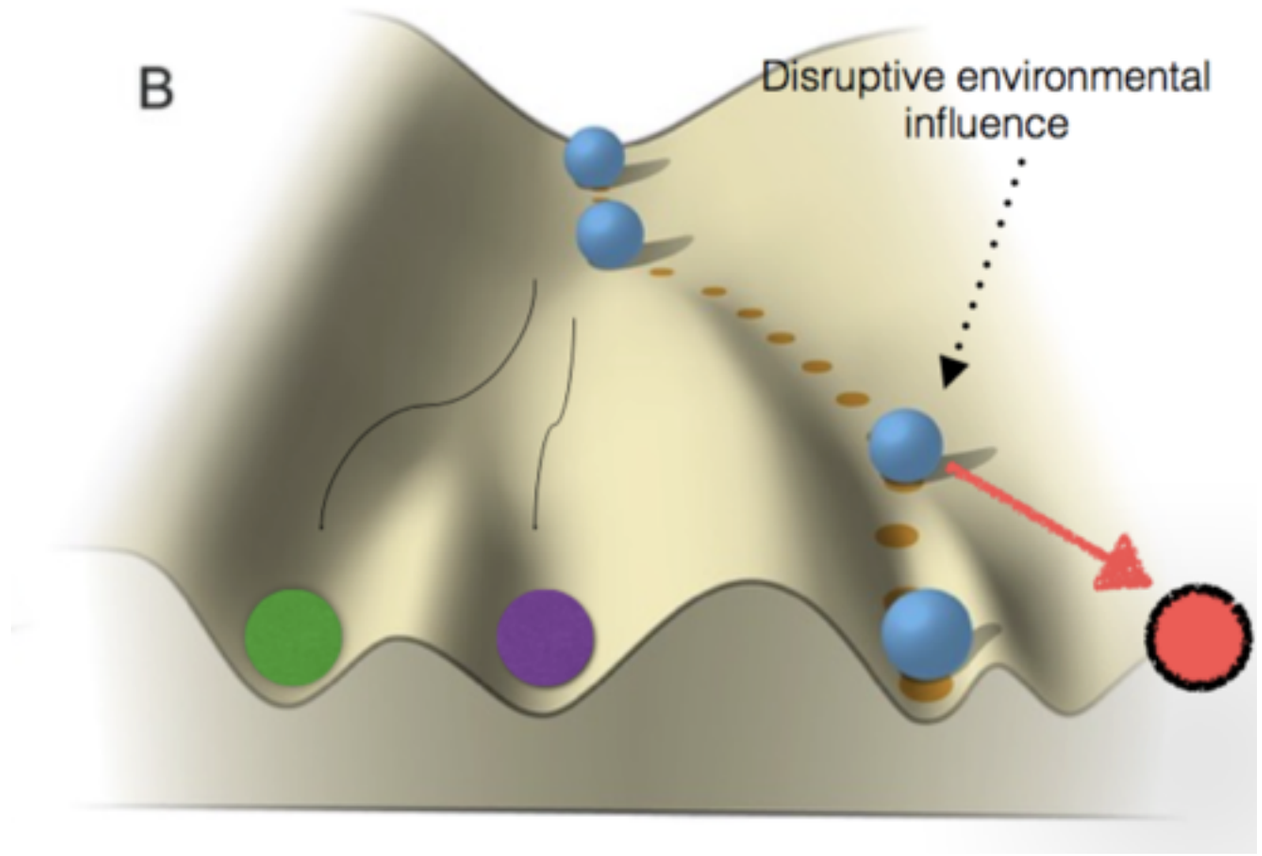


5.4 Developmental causation

Another possible causal role of the environment is disruptive, i.e., to generate an unviable phenotype.

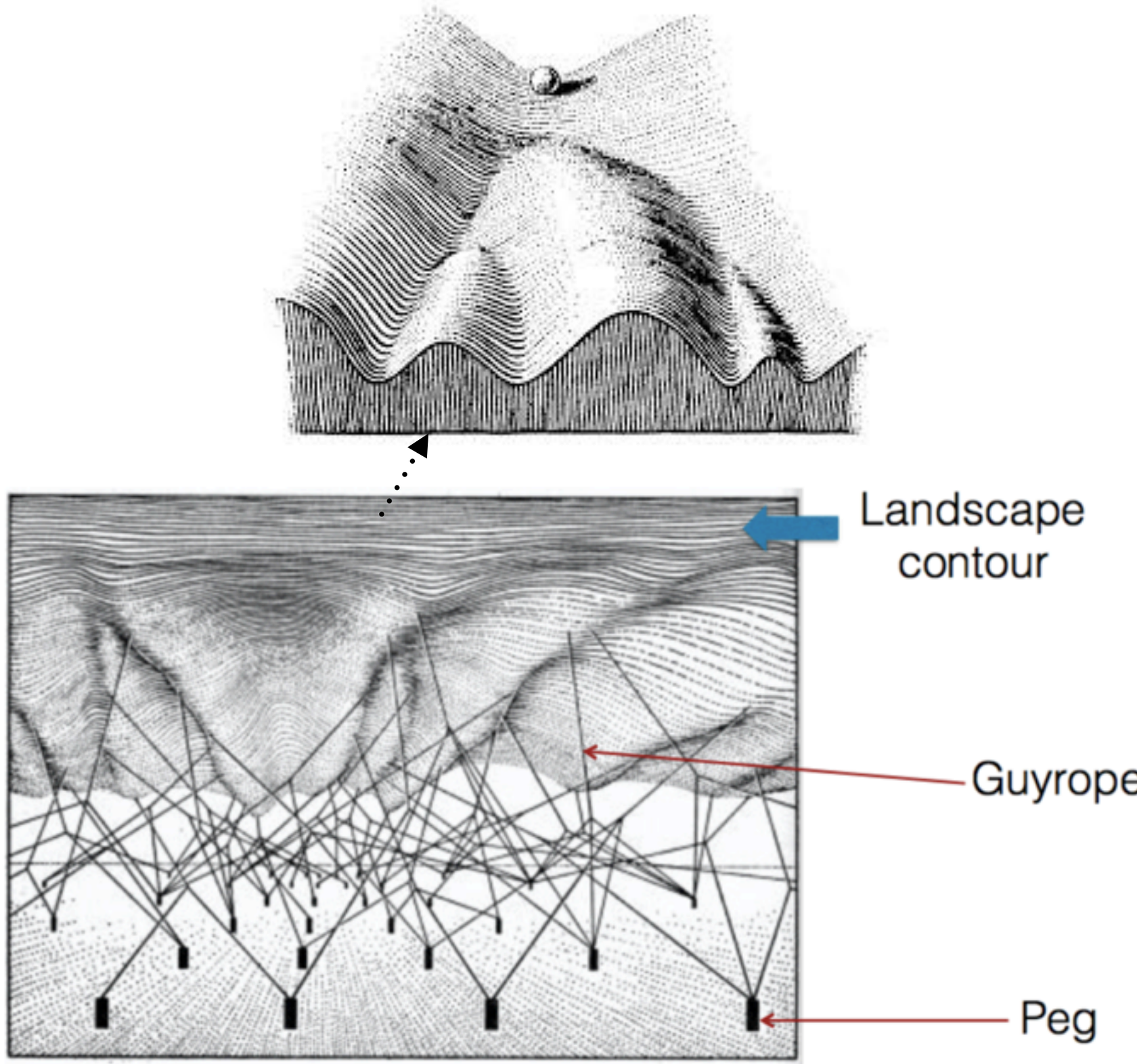
For instance, a low temperature might not be conducive for embryogenesis, leading to the death of the developing organism.

Or the environment (e.g., X-ray radiation) might induce deleterious genomic changes leading to the death of the developing organism.



5.5 Developmental causation

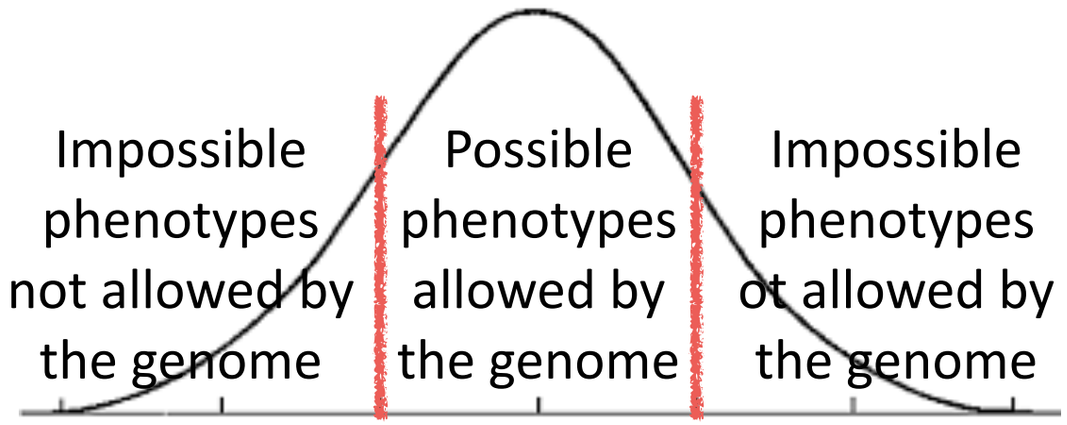
One thing the environment cannot do is to change the contour of the epigenetic landscape, which is genomically determined. Genes (i.e., the pegs) are determinants of the shape of the landscape because they control from below (i.e., through guy-ropes) the contours of the landscape.



5.6 Developmental causation

A corollary of this view is that the genome poses a limit to the developmental capacities of the organism: developmental potential = genomic potential.

The peg-structure is fixed, where this fixity explicates the idea of “reaction range”: the genome sets the phenotypic and developmental limits, while the environment determines where within those limits the phenotype will fall but cannot accrue the developmental potential of the organism.



5.7 Developmental causation

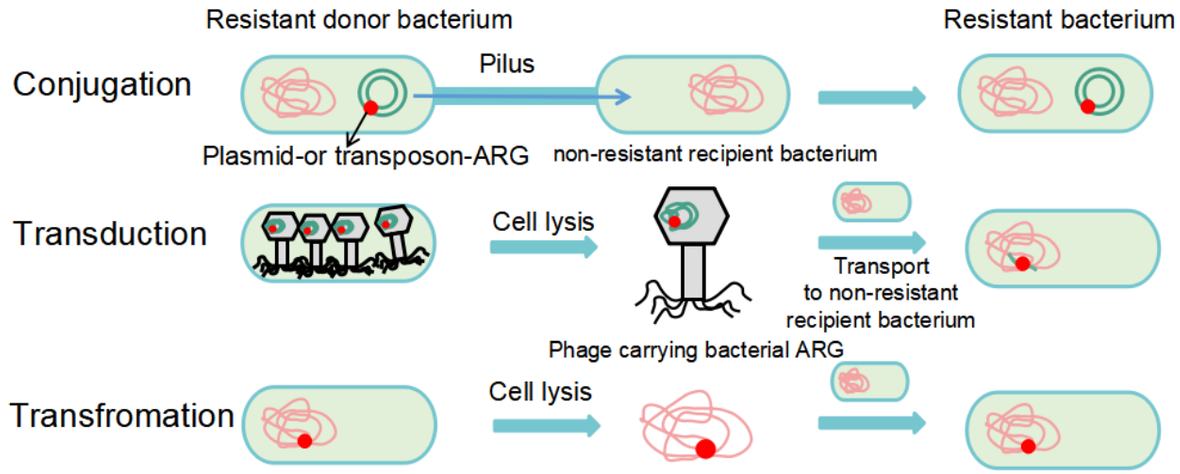
“We can think of a person's genes as imposing a top and a bottom limit on intelligence, or establishing a range of intellectual ability. Environmental influences..., will determine where the person's IQ will fall within that range. In other words, genes do not specify behavior; rather, they establish a range of probable responses to the environment, which is called the reaction range.” Atkinson, R. L., Atkinson, R. C., Smith, E. E., & Hilgard, E. R. (1987). Introduction to psychology (9th ed.). New York: Harcourt Brace Jovanovich. p. 409 (quoted in Anderson Platt et al. 1988, p. 256)

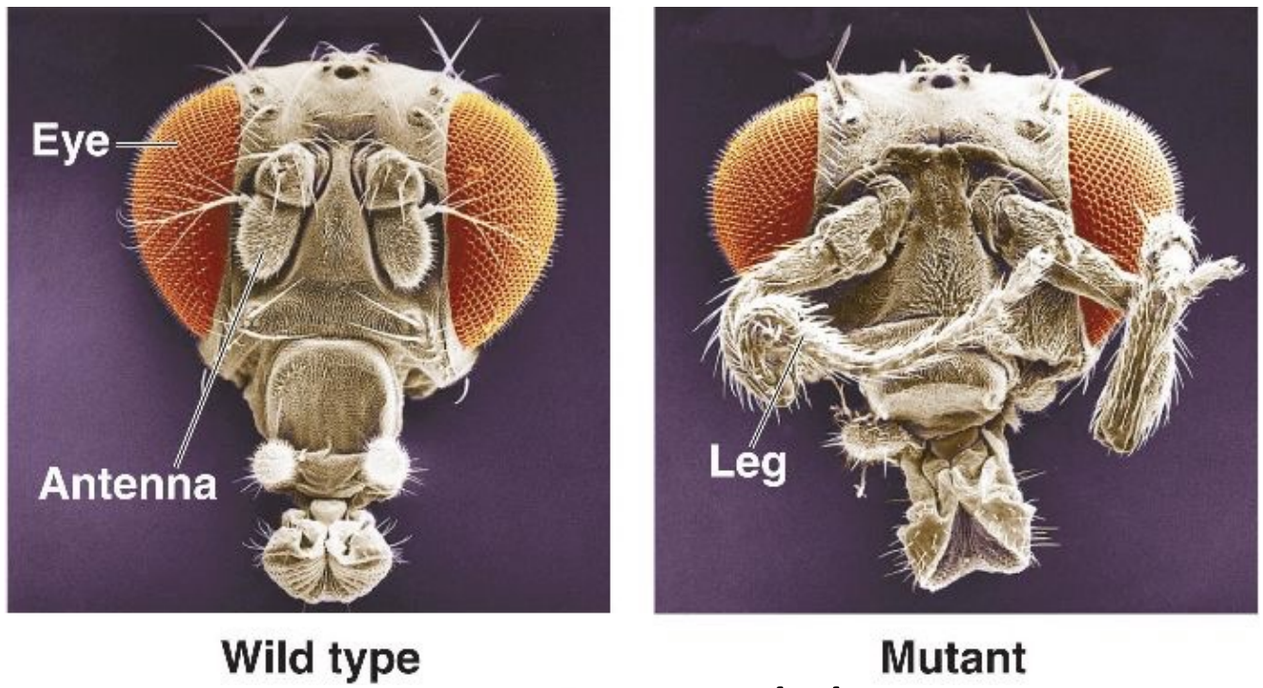
5.8 Developmental causation

Is this view acceptable in the light of evidence?

Let me first note that there are cases - experimentally verifiable - whereby the causal influence of the genome is particularly strong.

Experiments with gene knockout or gene transfer (e.g., when a gene is expressed in a location of the developing organism where it is not naturally expressed or when a gene from an organism is transplanted in a gene of another, as in genetic modification or lateral gene transfer) raise the bar high for critics of genetic determinism and related views.





Poor *Drosophila*

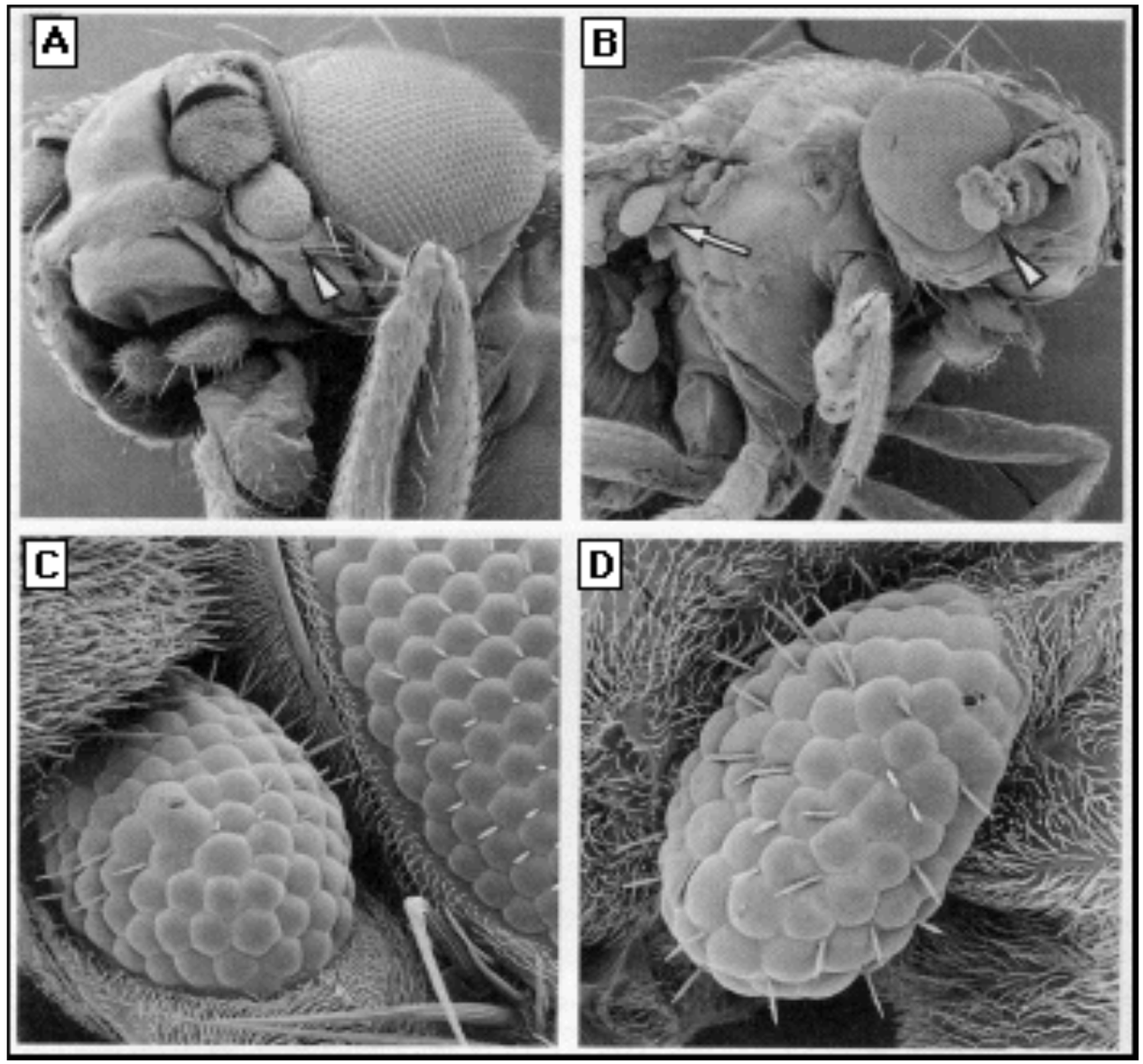
5.9 Developmental causation

Genetic experiments with *Drosophila* in which the expression of gene *Ey* is argued to be “necessary and sufficient to induce ectopic eyes” (Halder et al. 1995, p. 1791) even in wings and antennae.

Does *Ey* “determine” eye morphogenesis?

This gene is not the only one regulating this morphogenetic process because “...we estimate that more than 2500 genes are involved in eye morphogenesis” (Halder et al. 1995, p. 1791).

Nonetheless, is the entire developmental trajectory regulated solely by genomic resources?



Poor *Drosophila*

5.10 Developmental causation

I would argue that genetic determinism is more an ideological position that is tailored to neglect the causal contribution of the environment.

Some reasons:

1. genes are akin to formal causes, not to efficient or material causes (5.11-5.12);

2. the reaction range is not static and genomically fixed (5.13-5.14);

3. the longer the causal chain, the stronger environmental causal influence (5.15-5.16).

5.11 Developmental causation

Let’s go back to Aristotle, according to whom (slide 4.3) the male semen imposes “form” on the embryo:

“ … if that committee in Stockholm, which has the unenviable task each year of pointing out the most creative scientists, had the liberty of giving awards posthumously, I think they should consider Aristotle for the discovery of the principle implied in DNA …. "unmoved mover" perfectly describes DNA: **it acts, creates form and development, and is not changed in the process**.” Delbrück 1971 pp. 54-55

Let us use Aristotle’s account of causation to understand development by distinguishing three types of causes (without using the concept of final cause).

5.12 Developmental causation

1. **<u>Formal causes</u> - DNA "coding" for a series of structures** (e.g., the RNA transcript, templated on the DNA molecule, cf. 3.5; all the molecular machines involved in protein synthesis, like RNA polymerases, ribosomes etc.);

2. **<u>Material causes</u> - "coding" without recruitment of materials does not go anywhere** (e.g., to produce an RNA transcript, the organism needs building blocks like nucleoside triphosphates, synthesised by the developing organism; however, some of the materials involved in developmental processes are not produced by the developing organism, but they are "entrenched" - slides section 3 class 2 + slide 3.11 on exogenous metabolome -, such as some amino acid constituents of proteins in humans and other animals);

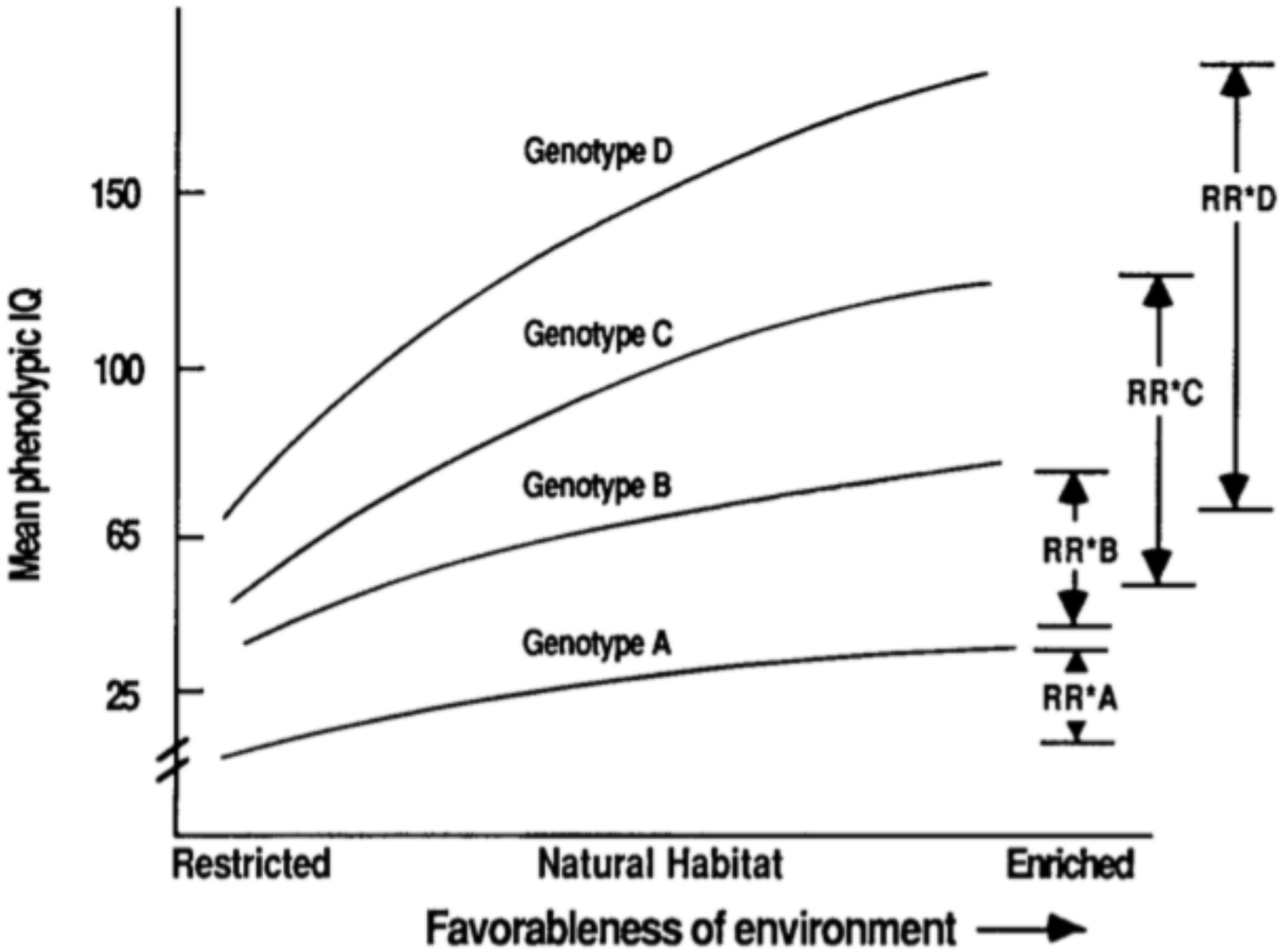
3. **<u>Efficient causes</u> - "coding" and material recruitment without specific molecular agents actually doing the "building" does not go anywhere** (e.g., RNA synthesis without an RNA polymerase is impossible, polypeptide synthesis without tRNA and ribosome too etc. etc).

Why privileging 1 to 2 and 3?

5.13 Developmental causation

The idea that there is a limit to developmental potential (e.g., that a frog cannot become a human) seems sensible.

But it should not be over-interpreted as to mean that the environment cannot extend the reaction range (remember the environment constantly changes, slide 4.12).



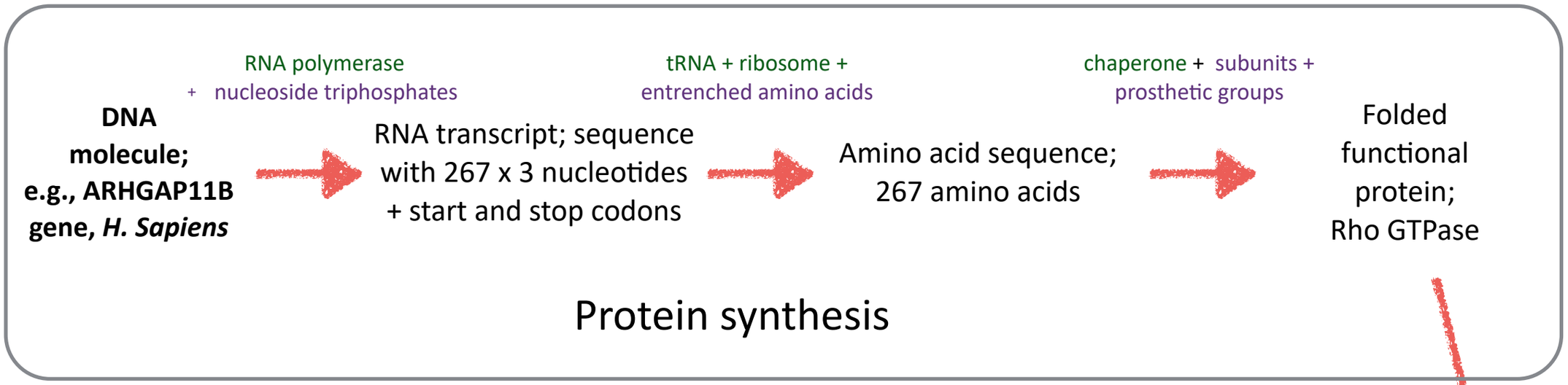
Reaction range of 4 genomes (Anderson-Platt p. 255): can richer environments extend the reaction range?

5.14 Developmental causation

"The norm of reaction of a genotype is at best only incompletely known. Complete knowledge of a norm of reaction would require placing the carriers of a given genotype in all possible environments, and observing the phenotypes that develop. This is a practical impossibility. The existing variety of environments is immense, and new environments are constantly produced. Invention of a new drug, a new diet, a new type of housing, a new educational system, a new political regime introduces new environments." (Dobzhansky 1955 pp. 74-75)

Consider now the length of the causal developmental chain in slide 5.15 with the more simplified representation in slide 3.6.

5.15 Developmental causation



Every red arrow represents a series of causal interactions in the long chain from DNA as formal cause to phenotype; these causal interactions depend on a variety of material and efficient causes (slide 5.12); this representation does not even attempt to specify the causal complexity of steps 4+5+6+7. **It is conceptually confusing to think that there can be long (or even short) developmental trajectories that are totally genetically determined.**

Cellular interactions through Rho signalling pathway activation: triggering specific patterns of cell division

Tissue formation: neocortex formation by triggering specific patterns of cell adhesion and differentiation

Organo-genesis: neocortex folding by triggering a specific pattern of brain development

Organismal phenotype: ARHGAP11B causes neocortex expansion, a precondition for peculiar human "intelligence"

5.16 Developmental causation

There cannot be entire developmental trajectories or causal chains that are totally genetically (or even environmentally) determined (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).

Can we decompose genomic and environmental causal contribution to development? More nature or more nurture?

“In the analysis of genotype-environment interactions, to assign proportions of responsibility is akin to asking of the equation for the area of a rectangle, how important is the length?” Anderson Platt et al. p. 260

From development to evolution

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 were made of and nobody had a clue about how contrived the relationship between genes and phenotype is.

But Muller was hypothesising that biodiversity can be understood in terms of genetic evolution. Was he right? We'll see in next class.

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