UNIVERSITÀ
DEGLI STUDI
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15-17th April, 2016
Abbazia di Spineto

A celebration of the life and thinking of CONRAD WADDINGTON

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Wad, the evolutionist:
the relevance of Wad's breadth of interests 40 years later

TIMELINE

Conrad Hal Waddington: the last Renaissance biologist?

Jonathan M. W. Slack

works and development. He is not well known to younger biologists because his work lies to one side of the mainstream of molecular biology. However, one of the biggest challenges of today is how to relate a vast and rapidly growing mass of genomic information to a relatively much smaller number of key biological phenomena. Some form of theoretical biology will have to be devised to meet this challenge and, whether attributed or not, Waddington's ideas will doubtless re-surface in the process.

WAD'S THINKING AS A PATTERN THAT CONNECTS

1. Embriology and Genetics → 2. Genes to Genes → 3. Gene Regulation and Development → 4. Environments and Organisms → 5. Development and Evolution → 6. Organisms and Niches → 1. Embriology and Genetics

RT = Wad's relevance today

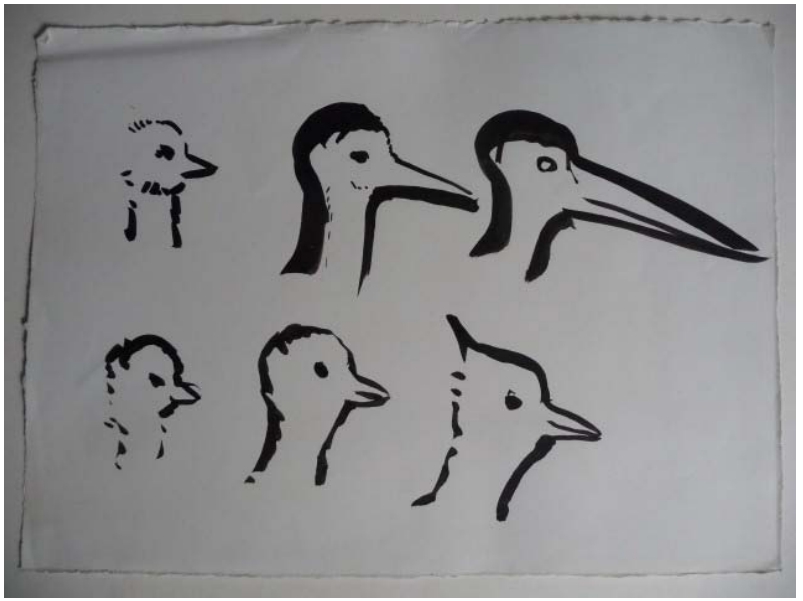
WAD'S THINKING AS A PATTERN THAT CONNECTS:
1. Embriology and Genetics

<u>First connection</u>

1935: **connect embryology and genetics**

The answers to embryology (i.e. early development in higher vertebrates) lay in genetics. How to explain:

1) Tissue differentiations (distinct pathways)
2) Discrete features of cell and tissue types (adaptive "canalizations" by natural selection)
3) Inducing factors active in early embryonic development.



Yolanda Sonnabend for WAD's *Tools for Thought*

Hypothesis: strong integration of developmental processes, under genetic control.

* **Philosophical background: Whitehead's metaphysics**
  a - from things to processes;
  b - developmental pathways as stable "knots" of relationships ("concrescences"), with mutations as breakdowns

WAD'S THINKING AS A PATTERN THAT CONNECTS:
2. Genes to Genes

Second connection

1938-1940: **connect genes to genes**

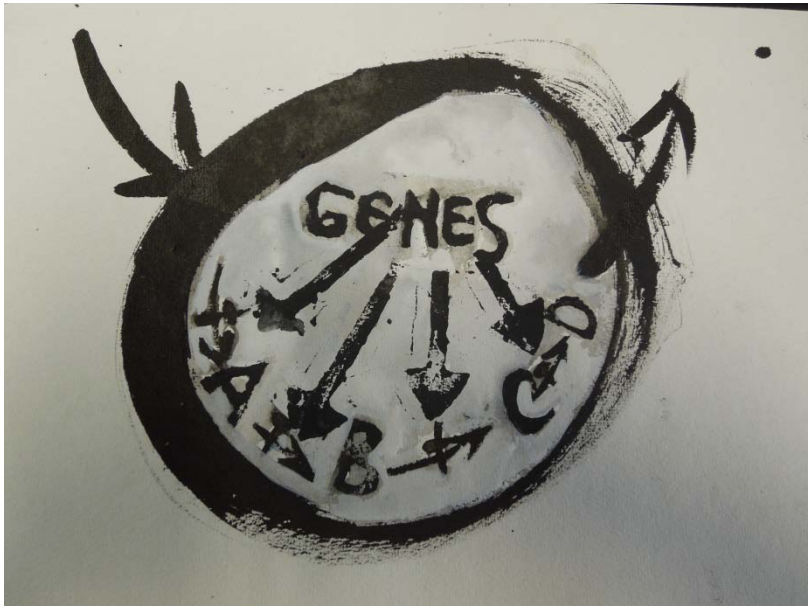
Large networks of genes interact in order to shape cell differentiation and developmental processes ("a great number of reciprocal interactive influences" – *Nature* 1941)

Against the "atomistic metaphysics" ("what a single gene does" is not the right scientific question; genes are involved in processes and relationships)

Genes with modular activation (development of body "regions" – today: Homeotic genes)

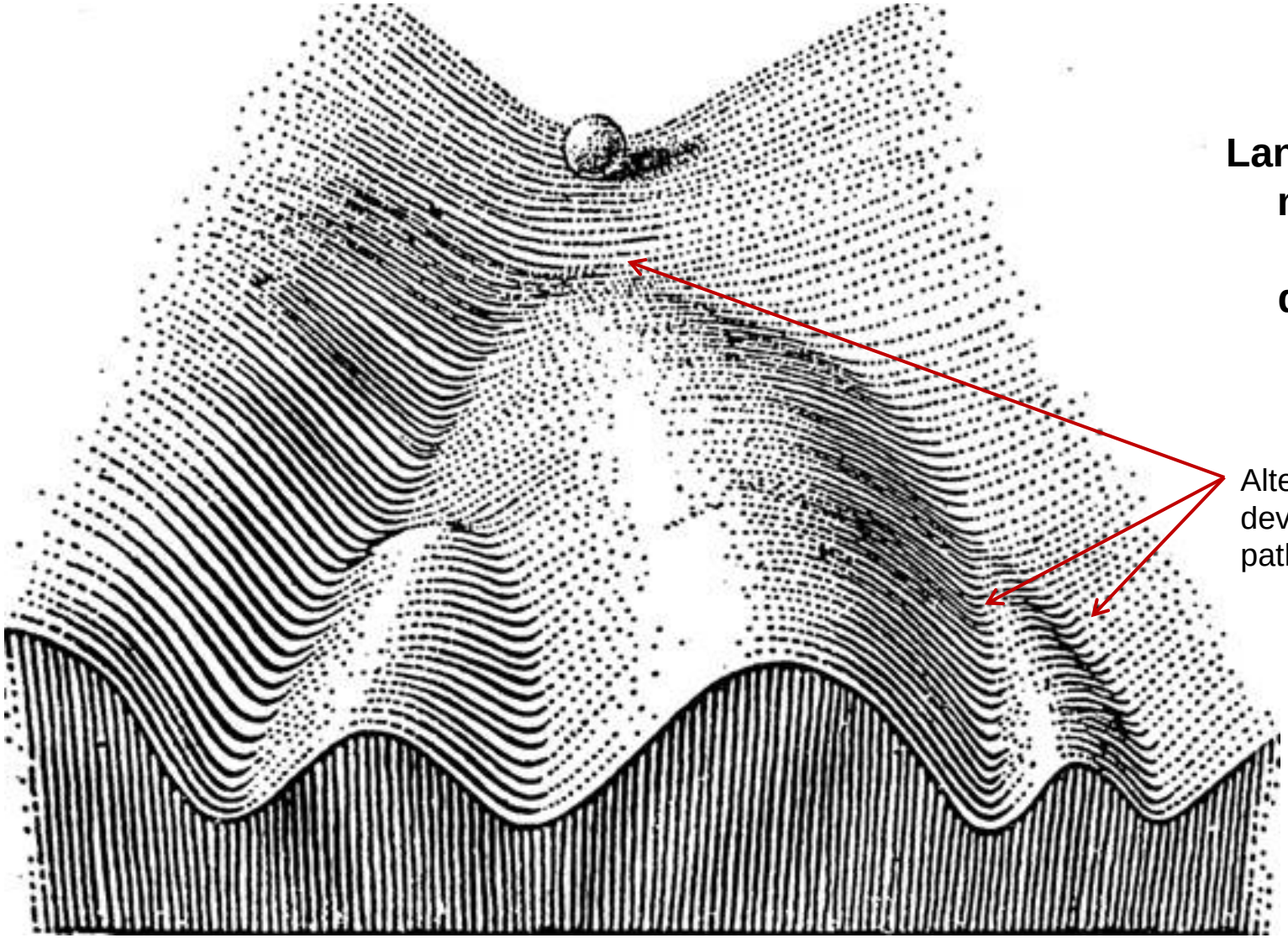
RT

A global "strategy of the genes" (systems effects and rates of change): **interactionism**



Yolanda Sonnabend for WAD's *Tools for Thought*

WAD'S THINKING AS A PATTERN THAT CONNECTS:
3. Gene Regulation and Development



Epigenetic Landscape as a metaphor for biological development

Third connection

1938-1940: **connect gene regulatory products and developmental phenotypes**

Models about how gene regulatory products could generate developmental phenomena: mechanisms underpinning Drosophila development

(today) studied through a systematic analysis of mutations that affected the embryogenesis of Drosophila wing.

Genetic control of embryonic development in *Drosophila m.*: Nobel Prize 1995 for Medicine to C. Nüsslein-Volhard, E.F. Wieschaus and E.B. Lewis

RT

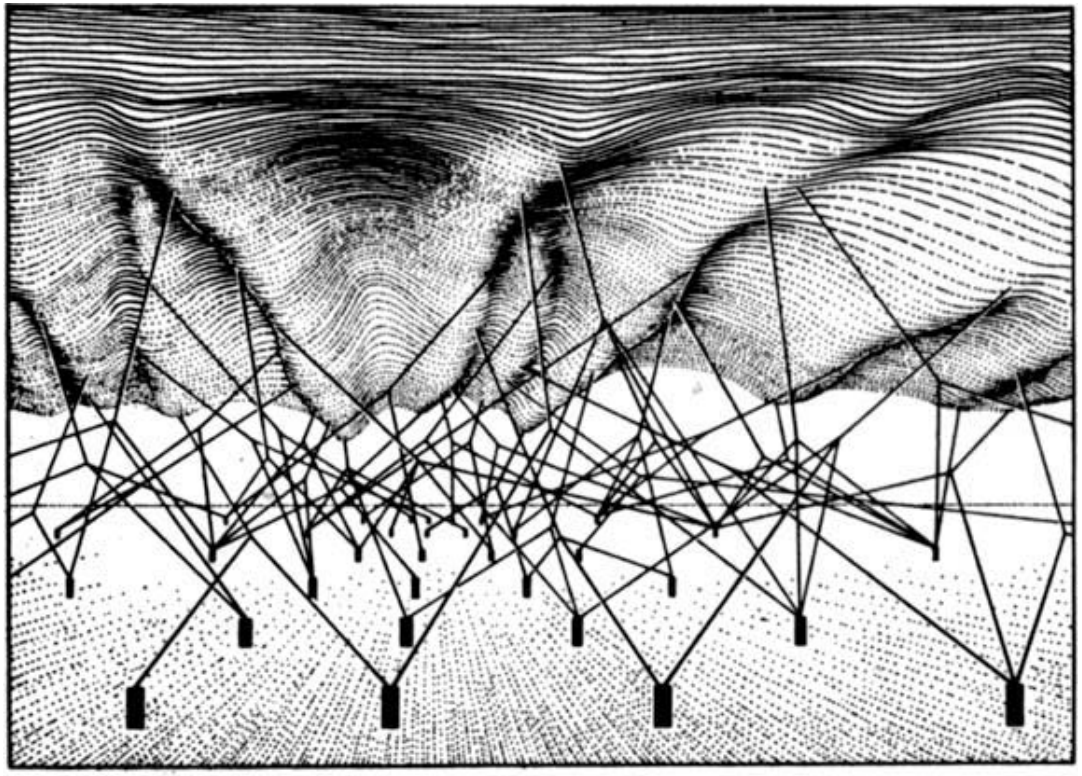
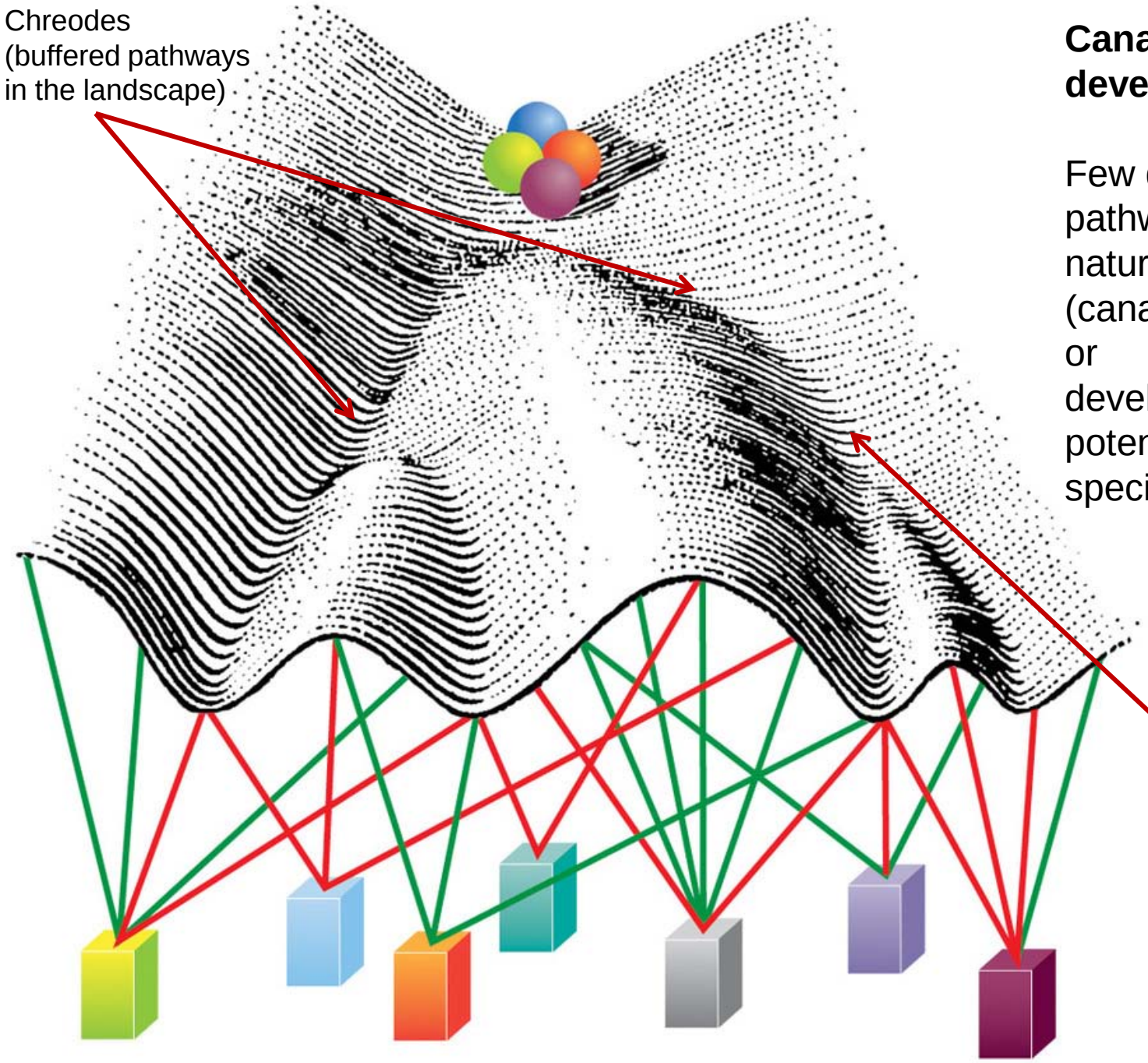


FIGURE 4.6. The epigenetic landscape. An illustration of the gene's modulation of the landscape's form. (After Waddington 1957, see n. 65.)



Canalizations of development

Few developmental pathways fixed by natural selection (canalizing selection) or developmental potentialities of a specific genotype

WAD 1947 - **Epigenetics**: (study of) the whole complex of developmental processes and causal mechanisms connecting genotype and phenotype (landscape; “epigenotype”) – **The causes of development** (histogenesis and morphogenesis)

Environment

Natural selection

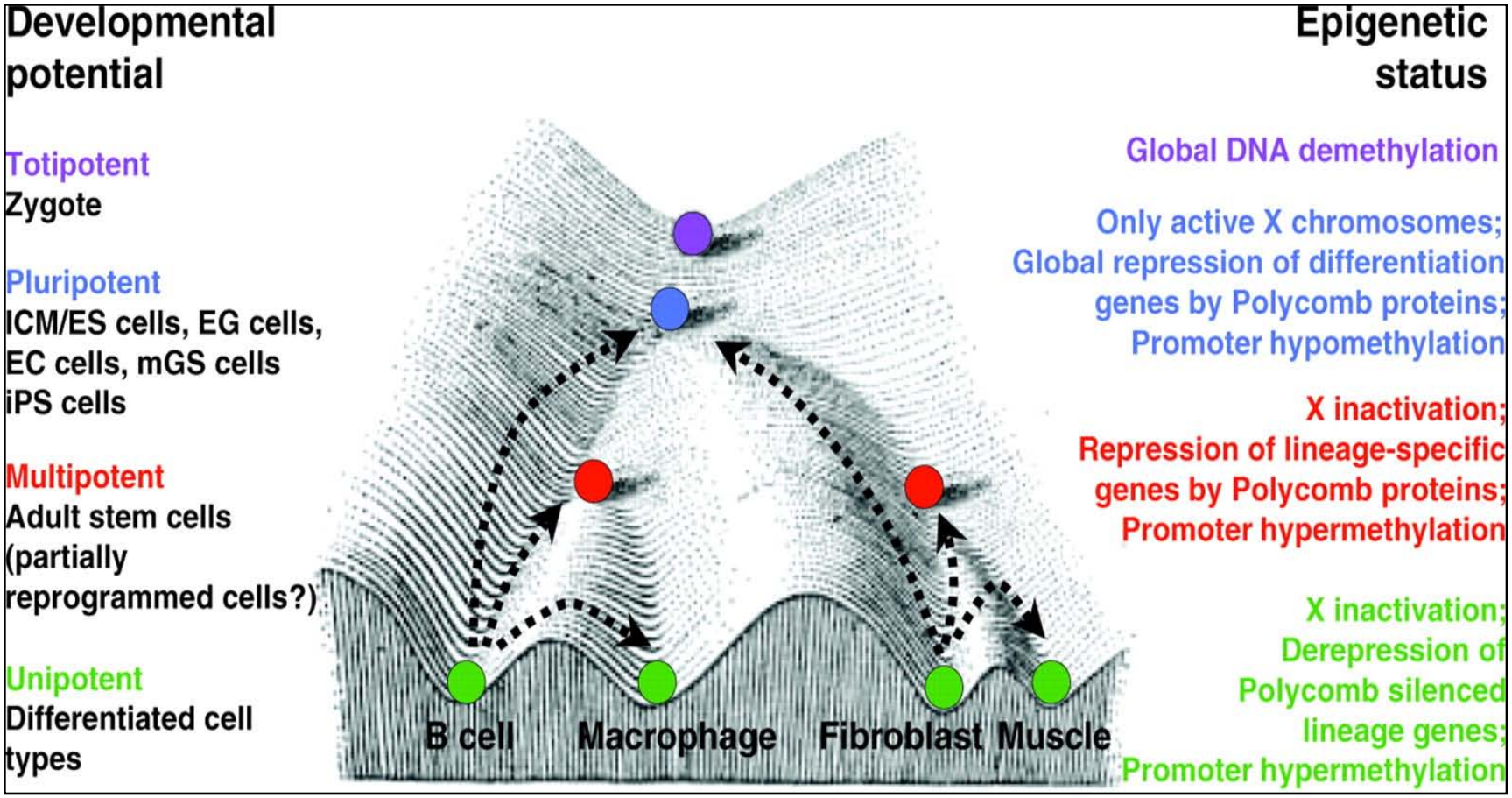
Genetic system

shift

(narrower sense) Epigenetics as anything <u>other than DNA sequence</u> that influences the development of an organism.

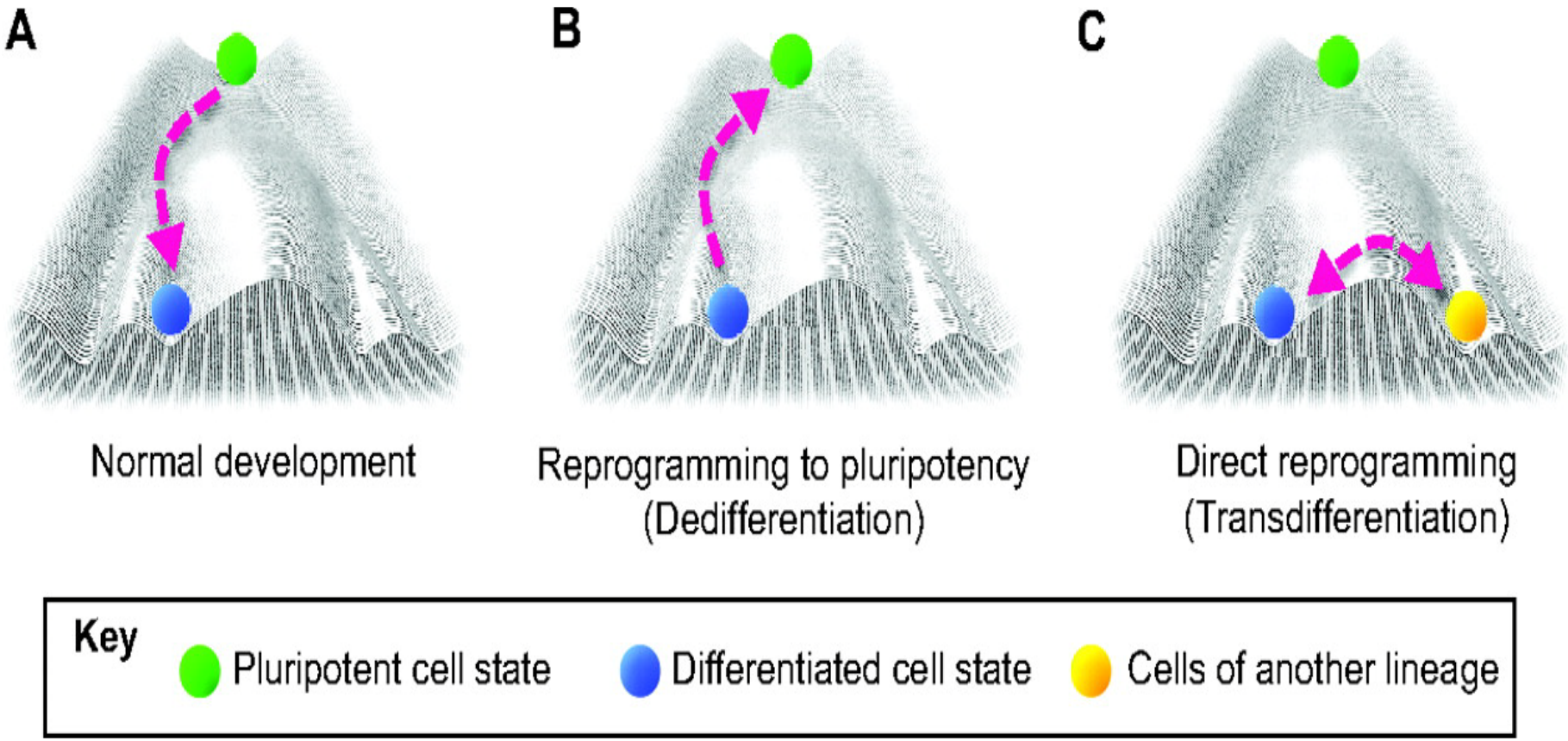
shift

2008, Cold Spring Harbor meeting: “stably <u>heritable</u> phenotype resulting from changes in a chromosome without alterations in the DNA sequence”.



Epigenetic reprogramming and induced pluripotency
Konrad Hochedlinger, Kathrin Plath
Development 2009 136: 509-523; doi: 10.1242/dev.020867

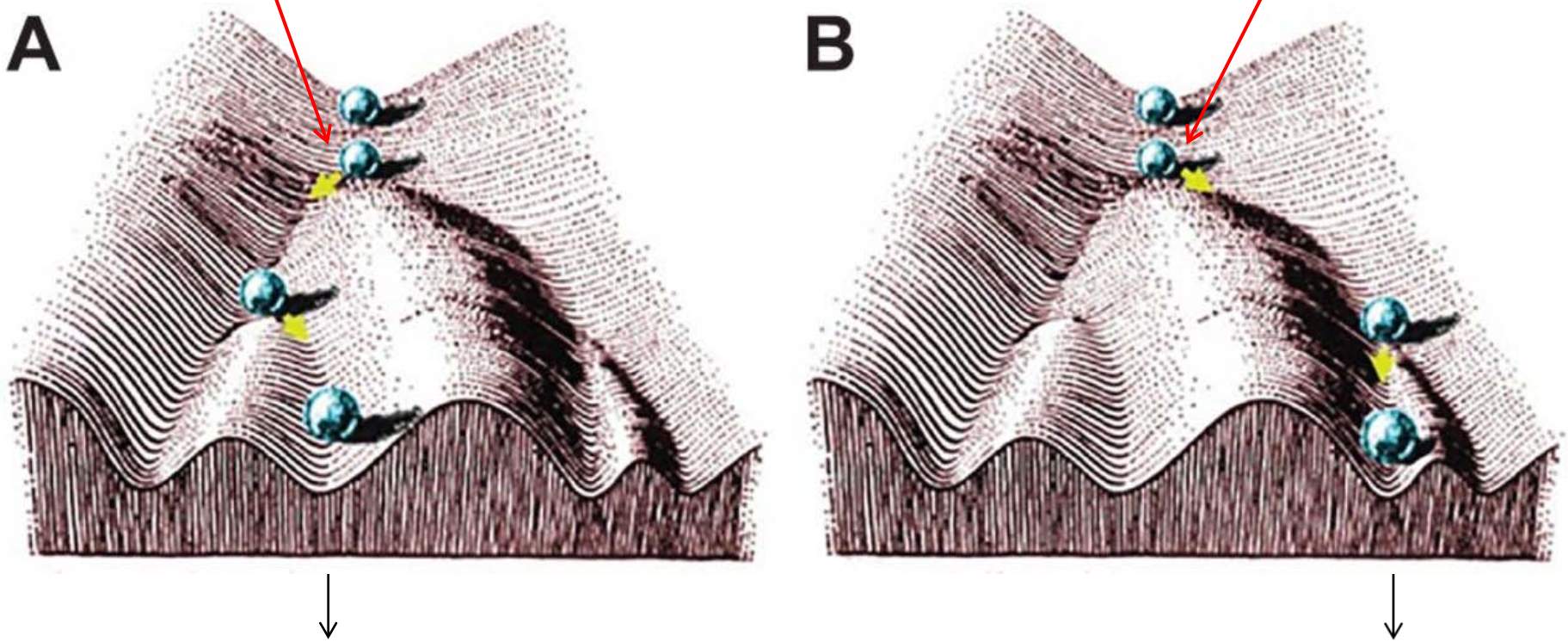
RT **Recent applications!**



Reversing the direction in the epigenetic landscape

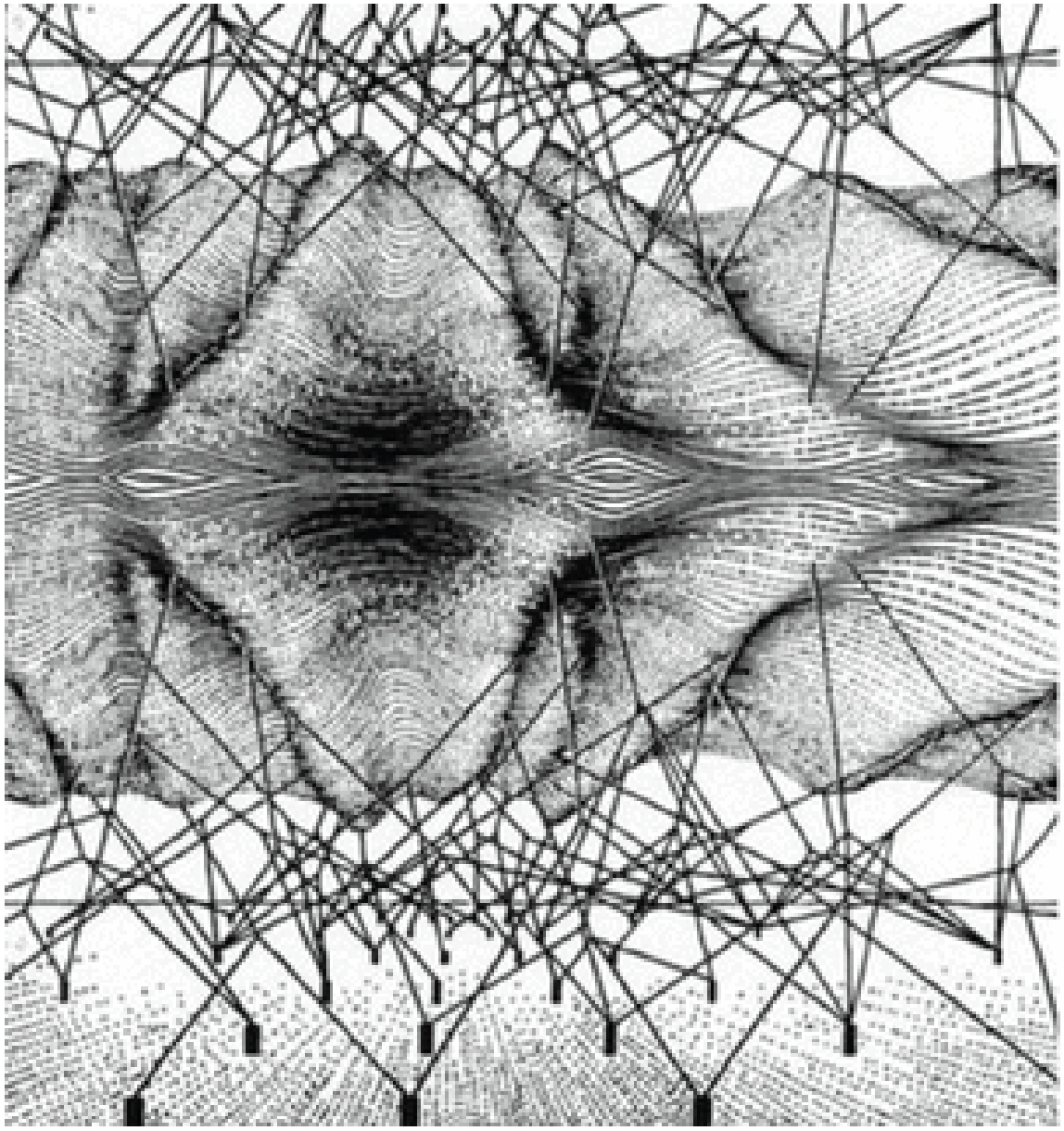
Point of «competence» (uncertainty state between different pathways) – Inherent Plasticity, reactivity to stimula

Environmental influences (i.e. heat shock in Drosophila) as diversions of dev. pathways (*Nature* 1950)



Different phenotypic outcomes

(WAD 1961 - paradox of dev. processes: to be modifiable and resistant to modifications)



Influence of environment

Developmental landscape

Functional networks

Genes

Denis Noble, “Conrad Waddington and the origin of epigenetics”
Journal of Experimental Biology , 2015, 218: 816-818

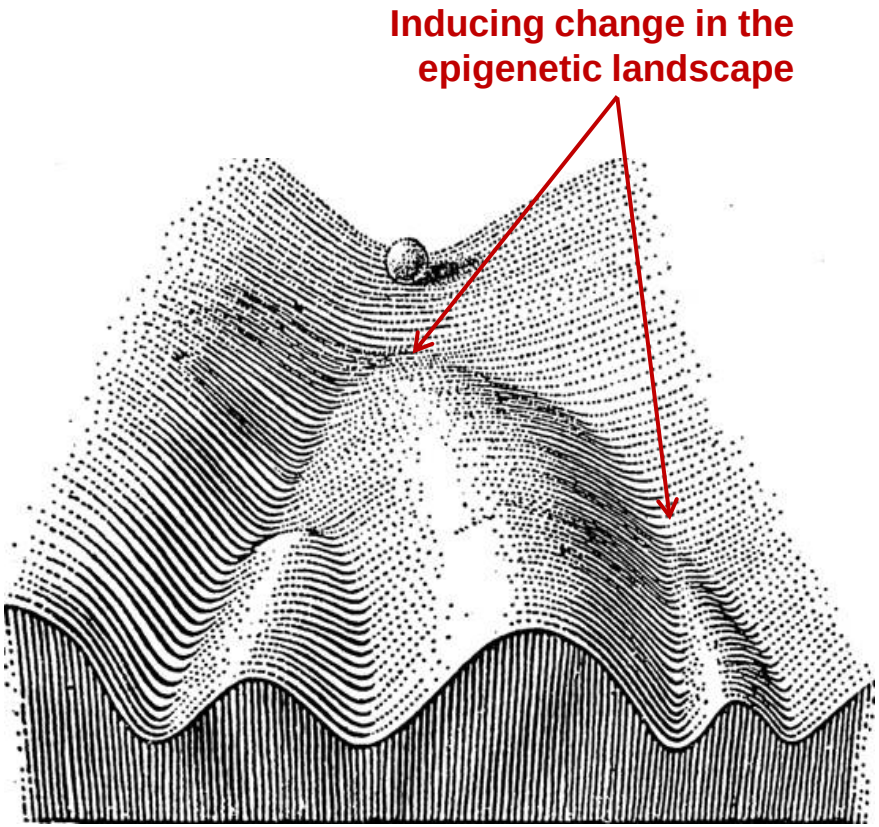
WAD'S THINKING AS A PATTERN THAT CONNECTS:
4. Environments and Organisms

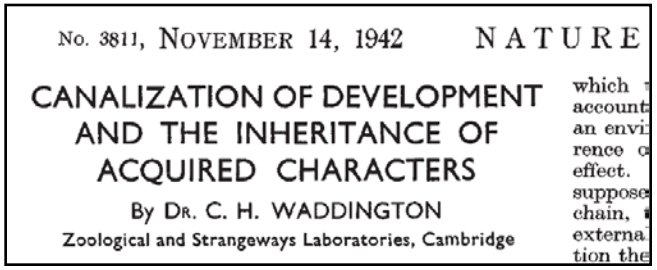
Fourth connection

Connect environments and organisms: **genetic assimilation**

- 1952 Experiment with heat-treated *Drosophila melanogaster*

- Multi-generational, selective conversion of acquired characters into heritable characters (80% of phenocopies without environmental stress): a Darwinian mechanism that allows certain acquired characteristic to become heritable and canalized.





No. 3811, NOVEMBER 14, 1942 NATURE

CANALIZATION OF DEVELOPMENT AND THE INHERITANCE OF ACQUIRED CHARACTERS

By DR. C. H. WADDINGTON

Zoological and Strangeways Laboratories, Cambridge

Causal mechanism according to WAD:

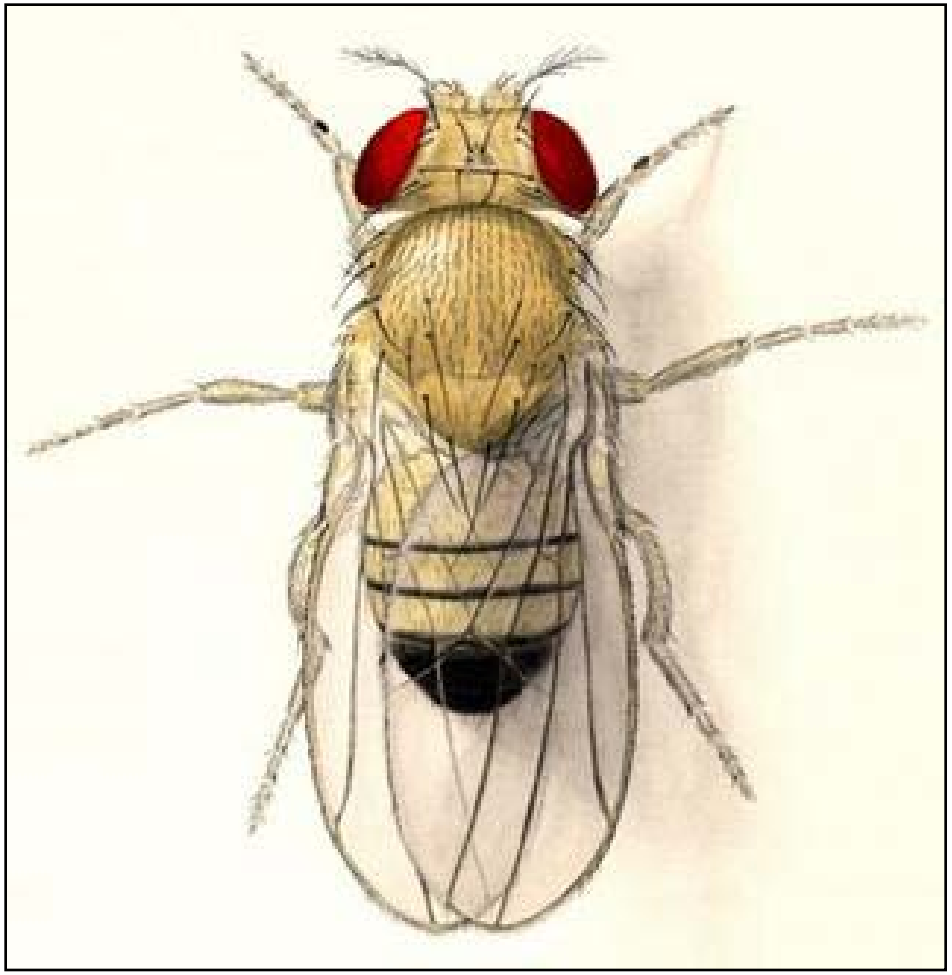
VS1 - No occurrence of a corresponding random mutation (standard Neo-Darwinism)

VS2 - No direct inheritance of acquired characters

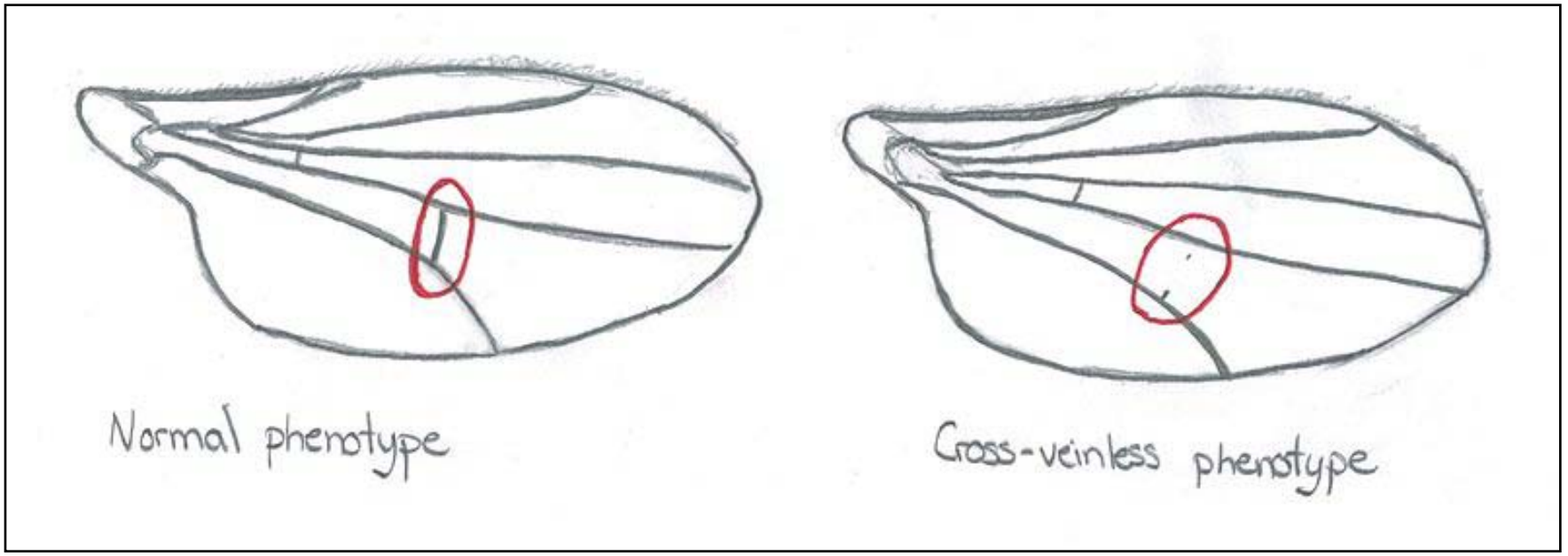
VS3 – No Baldwin Effect (organic selection: non-genetic plasticity + random mutation + selection)

Observation: great variety in the sensitivity to environmental influences, due to a huge genetic variability.

Hypothesis: assimilation of unmanifested genetic variation ("able to match any environmental influence" – 1942) – Selection of already existing genes (related to the capacity to react/adapt to environmental stresses) and stabilization of their effects.



Strong environmental stimulus: 40° degrees for 4 hours, in 17-23 hours after pupae



The initial adaptation to the new environment is already a genetic phenomenon (VS Baldwin Effect)

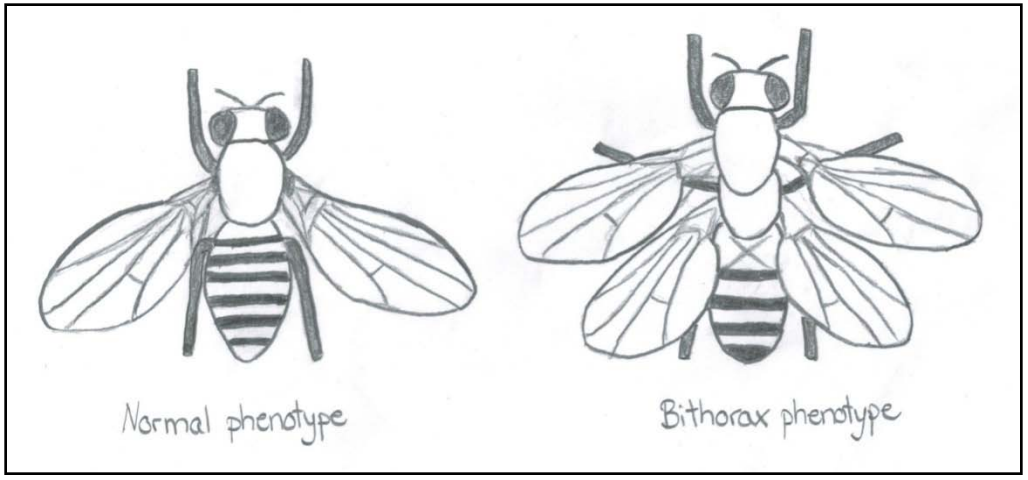
Natural selection can act directly on this genetic variation: no new rare and random mutations needed

The background is a genetically-based phenotypic plasticity, on which natural selection acts. The ontogenetic adaptation becomes irreversible and persists after the stress (canalization).

Canalization + Heritability of developmental reactions to environmental stimuli = Genetic Assimilation (1967)

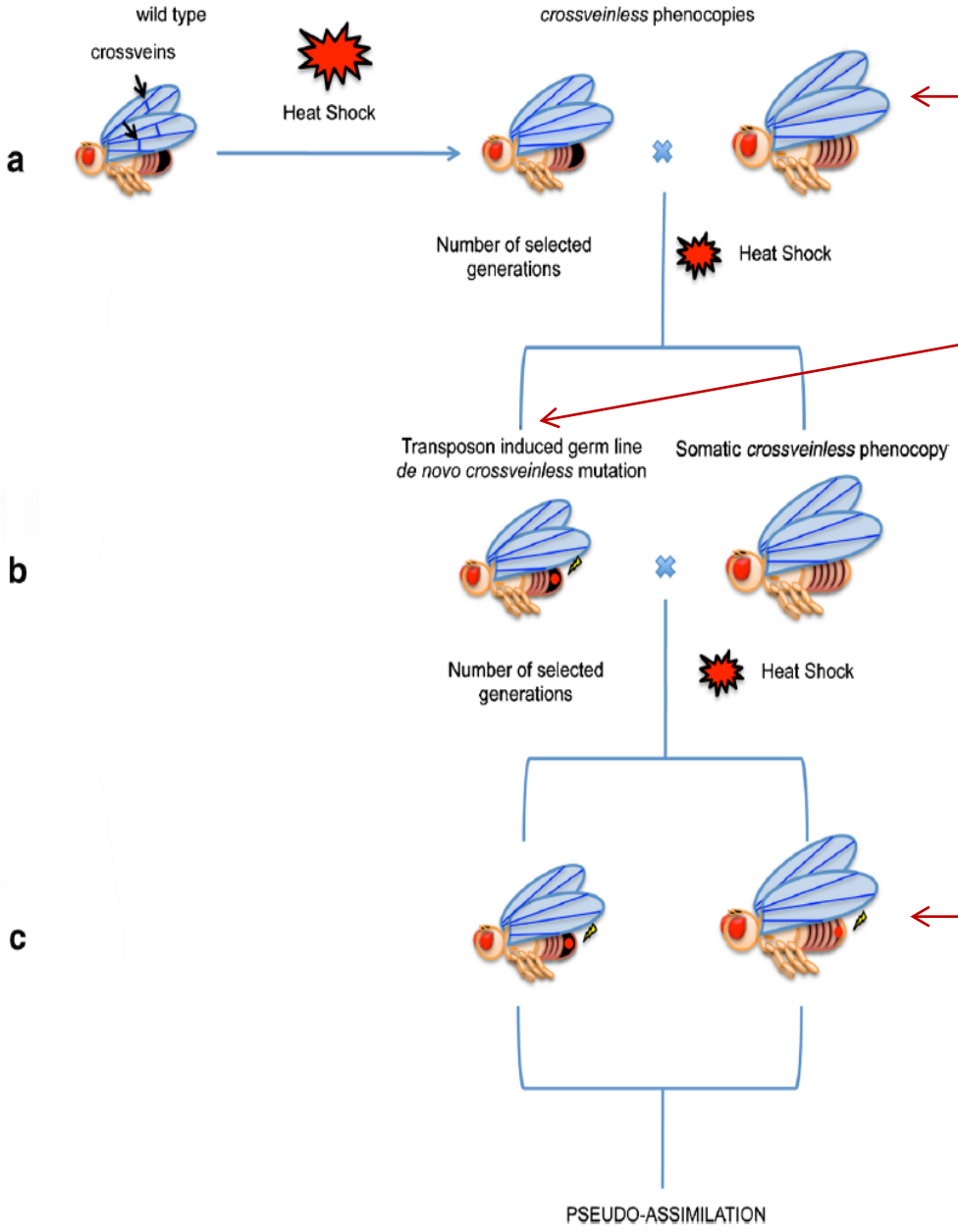
“There is no … reason which would prevent us from imagining that all the genes which eventually make up the assimilated genotype were already present in the population before the selection began, and only required bringing together” (p. 176).
TEST: “Attempts to carry out genetic assimilation starting from inbred lines have remained quite unsuccessful. This provides further evidence that the process depends on the utilisation of genetic variability in the foundation stock with which the experiment begins”. (p. 178)
(WAD, *The Strategy of the Genes*, 1957)

N.B. Wad’s genetic assimilation needs wildtype *Drosophila melanogaster* with natural and abundant genetic diversity (not inbred or cloned lines).



Genetic assimilation of bithorax phenotype (1956-1957)

Fig. 1 Assimilation of a stress-induced phenotypic trait. **a** Morphological change (phenocopy) induced by stress. **b** A mutation producing the same phenotype can be induced by the activity of transposons in the germ line of the same individual or other individual. **c** Co-selection of the somatically-induced morphological change with a corresponding germ line mutation eventually make the phenocopy apparently heritable (assimilation)



Morphological change induced by stress

Mutations (germ line), producing the same phenocopy, are induced by transposons (under stress)

Fitness of the phenocopy with the corresponding germ line mutation

RT

Other possible causal explanation in;
L. Piacentini *et al*. 2014, in "Cromosoma", 123: 345-354.

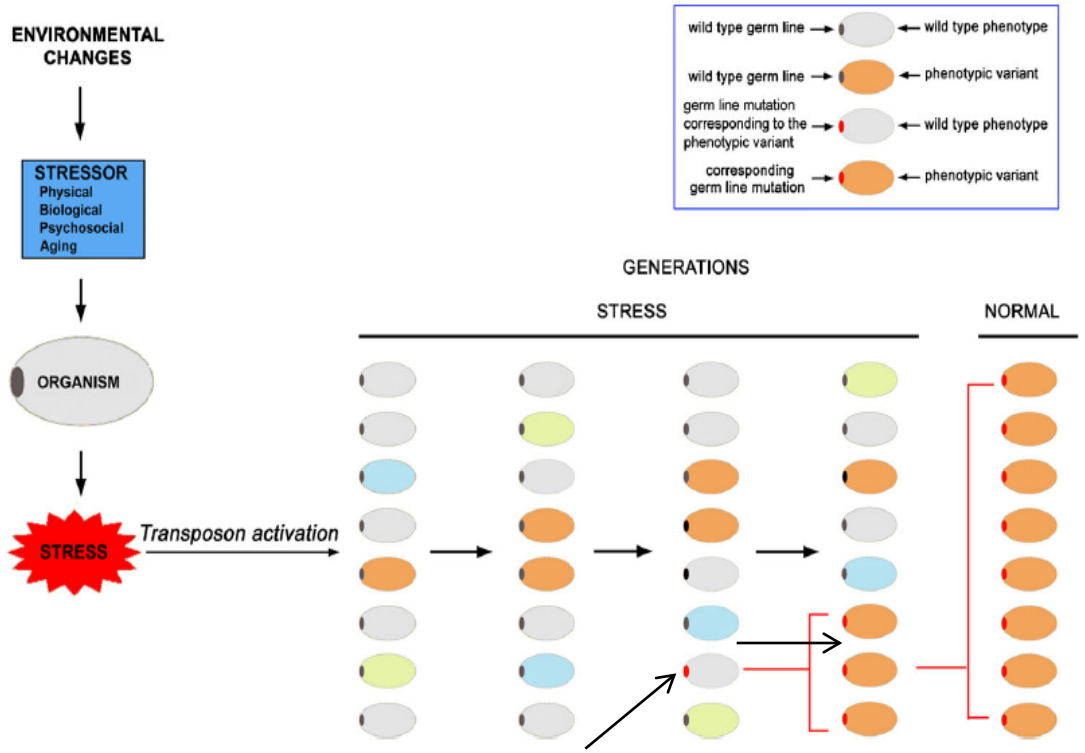
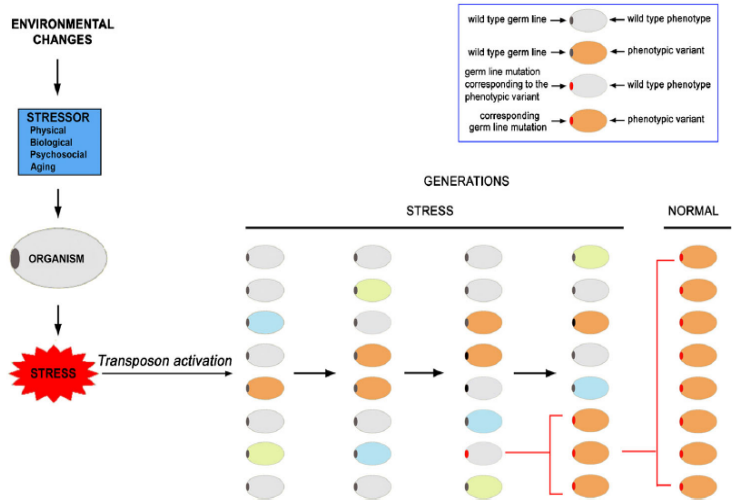


Fig. 2 In nature, environmental changes can induce morphological variants and the activation of transposons due to the susceptibility of organisms to different types of stress that can be maintained through the generations. The activity of transposons could cause the insorgence of a germinal mutation corresponding to one of the phenocopies that could be then fixed

- 1) Stress is cause of both phenocopies (phenotypic variants induced by environment) and transposon activation

- 2) Pseudo-assimilation is not due to already existing hidden variation, but to a germinal mutation corresponding to the phenocopy and induced by transposons (and eventually fixed; Baldwin Effect)
  RESULT OF THE MATCHING: HERITABLE PHENOCOPY



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BUT:

- F12 generations in Wad's experiment (1952): enough to have the matching between germinal mutation and phenocopy + fixation by natural selection?

- One mutation or few mutations enough?

- Noble's hypothesis (2015): all the alleles necessary for the inheritance of the characteristic were already present in the population (but not initially in any particular individuals in the correct combination): the shock simply brings them together (i.e. a modification of the pattern of the genome in response to the environmental change – no new mutations required)

- How can an environmental change induce a heritable modification in the genome pattern without genetic mutations?

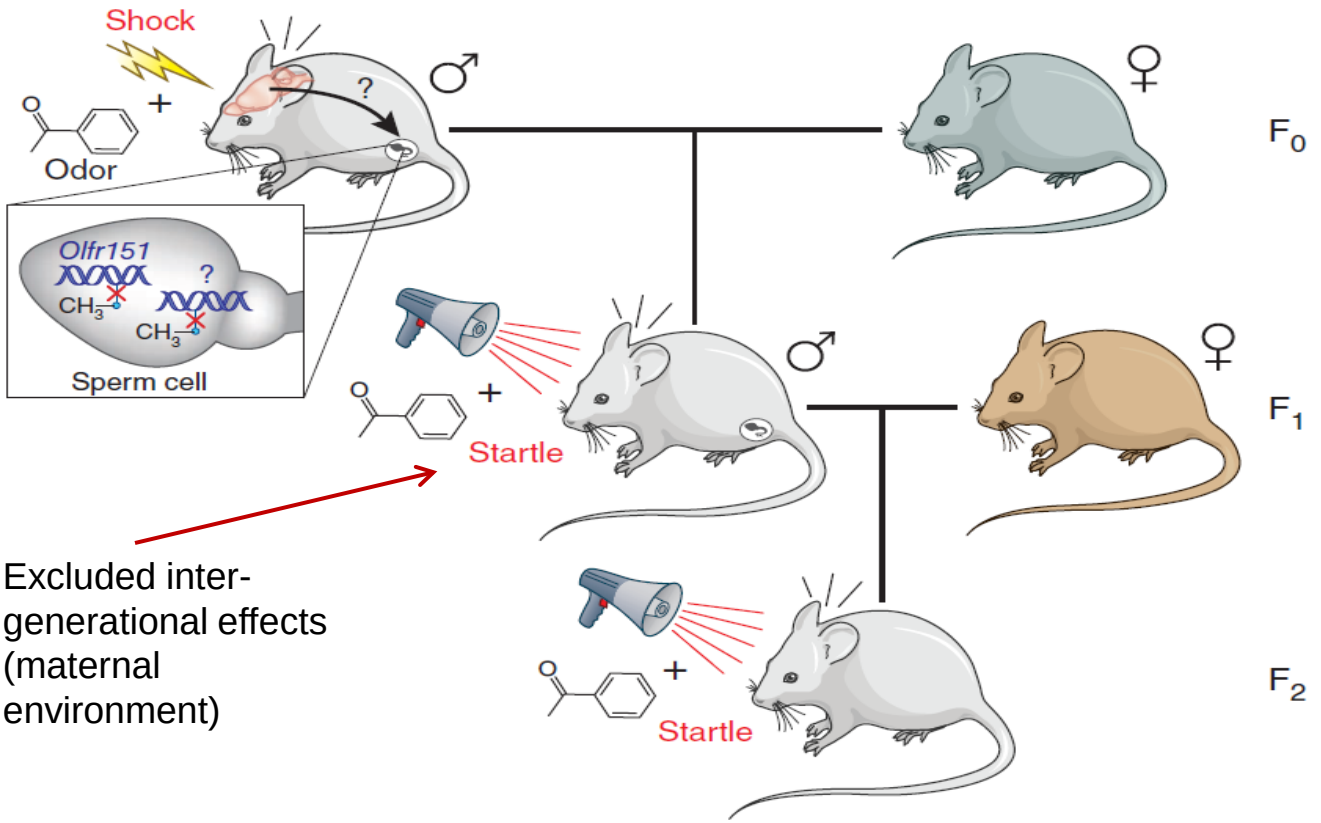


Figure 1 Model for epigenetic inheritance of odor fear conditioning. Association of acetophenone odor with an electrical shock conditions the mouse for an enhanced acetophenone startle response. Although the mechanism is unknown, this may trigger the release of circulating molecule(s), such as microRNAs or glucocorticoids, that act on spermatogonia to direct DNA methylation changes in both specific olfactory receptor genes, such as *Olfr151*, and other genes, as yet unknown, that are involved in the fear conditioning circuitry in the brain. When the demethylated sperm fertilizes a naive female, the methylation pattern is maintained in the fertilized eggs and may guide the differentiation of fear circuitry. The adult F_1 mouse exhibits enhanced startle in the presence of acetophenone. During primordial germ cell differentiation in the F_1 mouse, the methylation pattern triggered by the conditioned exposure to acetophenone is preserved. When the resulting marked sperm fertilizes a naive mouse, the offspring F_2 will develop the same conditioned fear response circuitry in the brain, using the epigenetic information in the F_1 sperm to guide differentiation. The adult F_2 mouse likewise shows a heightened startle response in the presence of acetophenone.

Dias B.G., Ressler K.J., Nat. Neurosc., 17, 89-96, Jan 2014.

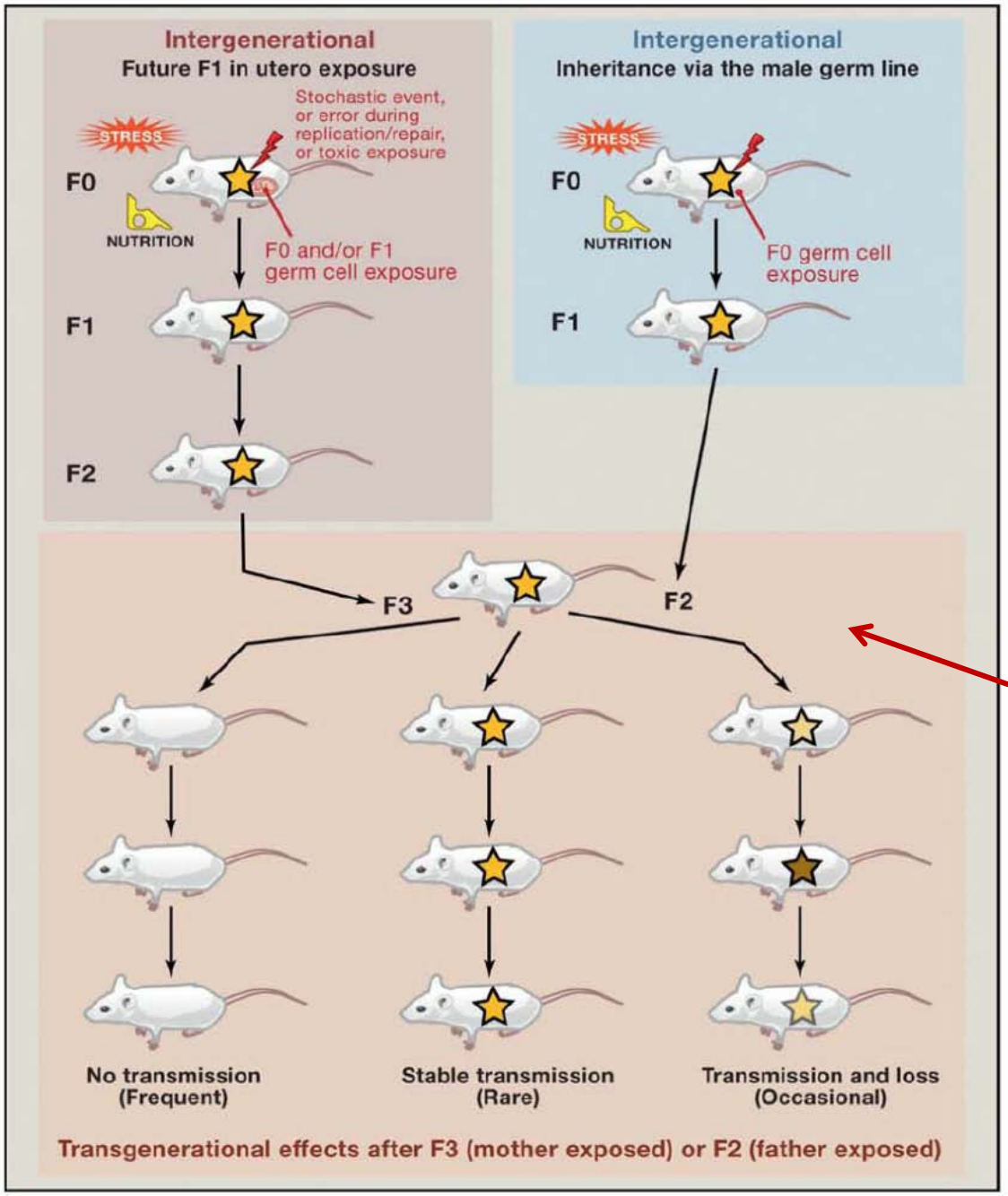


Figure 1. Transgenerational and Intergenerational Epigenetic Effects

Epigenetic changes in mammals can arise sporadically or can be induced by the environment (toxins, nutrition, and stress). In the case of an exposed female mouse, if she is pregnant, the fetus can be affected in utero (F1), as can the germline of the fetus (the future F2). These are considered to be parental effects, leading to intergenerational epigenetic inheritance. Only F3 individuals can be considered as true transgenerational inheritance (see Box 1) in the absence of exposure. In the case of males in which an epigenetic change is induced, the individual (F0) and his germline (future F1) are exposed; the F1 is thus considered as intergenerational. Only F2 and subsequent generations can be considered for evidence of transgenerational inheritance.

Epigenetic changes can survive to reprogramming in germ cells and early development (in mammals)

nature neuroscience April 13, 2014

First hypotheses about the «black box» (mechanism):

Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice

Katharina Gapp[1], Ali Jawaid[1], Peter Sarkies[2], Johannes Bohacek[1], Pawel Pelczar[3], Julien Prados[4,5], Laurent Farinelli[4], Eric Miska[2] & Isabelle M Mansuy[1]

Small non-coding RNAs (sncRNAs) are potential vectors at the interface between genes and environment. We found that traumatic stress in early life altered mouse microRNA (miRNA) expression, and behavioral and metabolic responses in the progeny. Injection of sperm RNAs from traumatized males into fertilized wild-type oocytes reproduced the behavioral and metabolic alterations in the resulting offspring.

Epigenetic alleles:
«epialleles contribute to the heritability of complex traits and therefore provide a substrate on which Darwinian evolution may act"
(Robert J. Schmitz, *Science*, 7 March 2014)

A - **Genetic Assimilation** (based on already existing genetic variation)
B - **Pseudo-assimilation** or Baldwin Effect (based on new mutations)
C - **Transgenerational Epigenetic Effects** (based on heritable epigenetic tags)
….

What is happening?
A diversification and extension of the sources of heritable variation

RT

WAD'S THINKING AS A PATTERN THAT CONNECTS:
5. Development and Evolution

Fifth connection

1941-1952: **Connect development and evolution**

Wad's early paleontological studies on ammonites: "organisms involved in evolutionary processes are themselves processes" (1969); evolution mainly occurred through mutations that affected developmental anatomy.

The evolution of organisms has to be seen as evolution of developmental systems (alterations of the topology of epigenetic landscapes)

"A theory of evolution must contain, as its fundamental part, a theory of development" (*Nature*, 1941) – evo-devo today.

RT

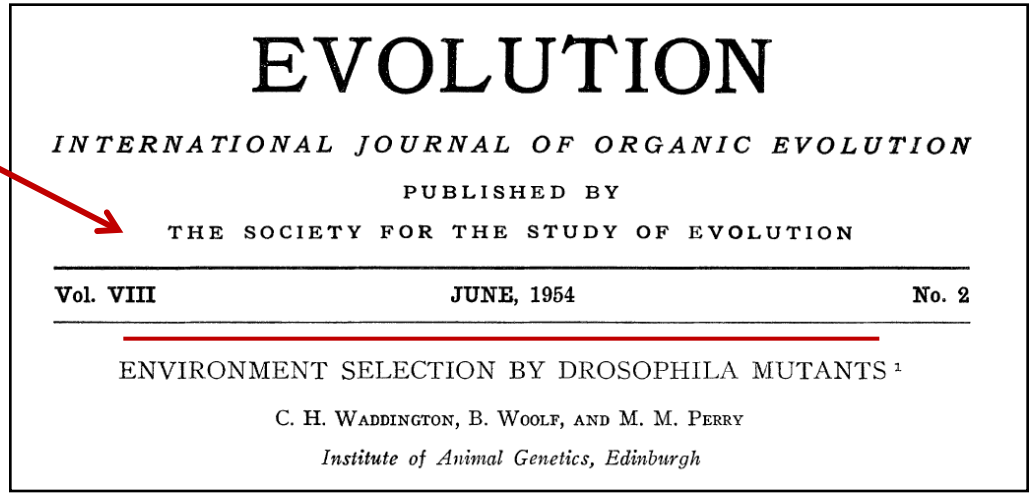
WAD'S THINKING AS A PATTERN THAT CONNECTS:
6. Organisms and Niches

Sixth connection

1959 – 1969: **connect organisms and niches** - "**exploitive systems**"

Environments are not uniform! (environment variations, that produced the high genetic variability in natural populations, and are causes of speciation)

Different genotypes choose different environmental varieties (habitat preferences; environment selection)



EVOLUTION

INTERNATIONAL JOURNAL OF ORGANIC EVOLUTION

PUBLISHED BY

THE SOCIETY FOR THE STUDY OF EVOLUTION

Vol. VIII JUNE, 1954 No. 2

ENVIRONMENT SELECTION BY DROSOPHILA MUTANTS [1]

C. H. Waddington, B. Woolf, and M. M. Perry

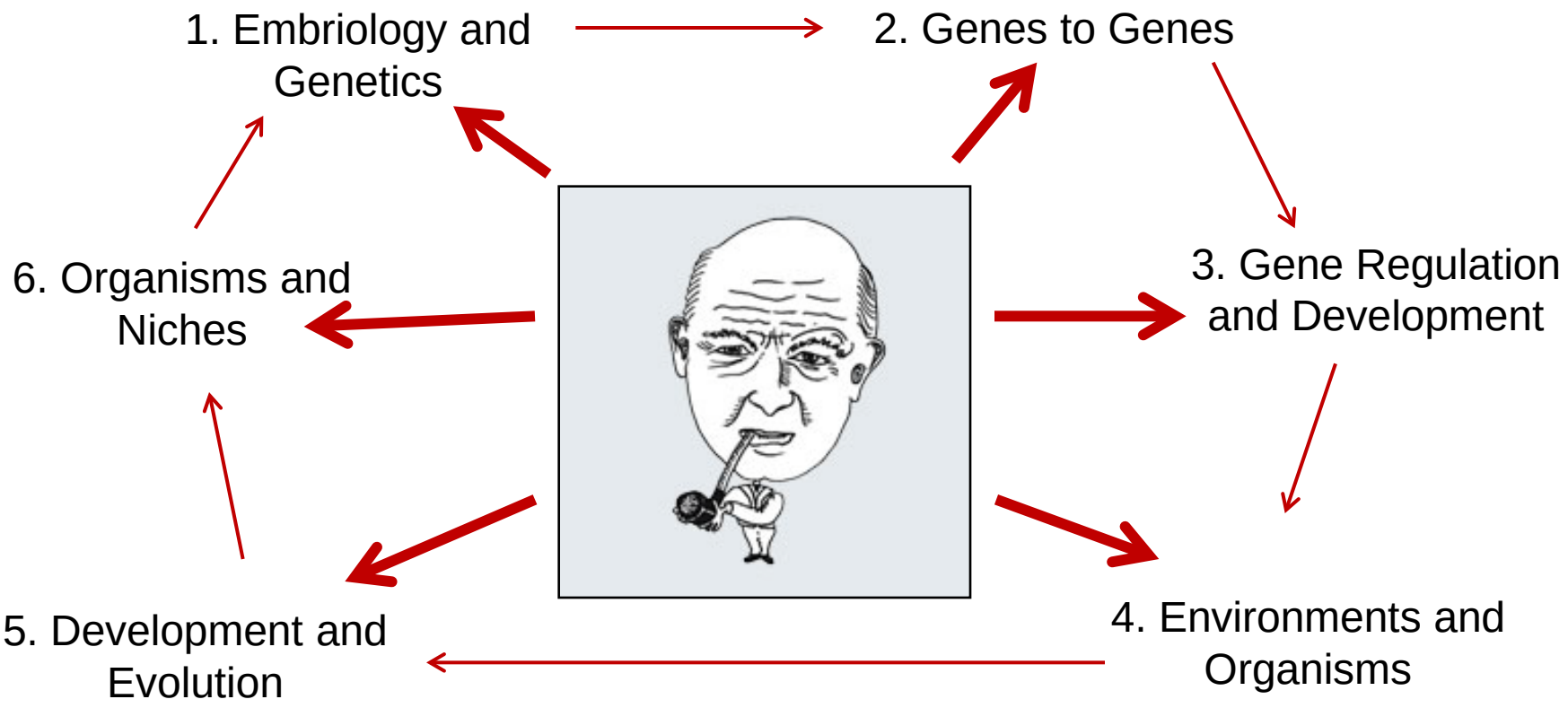
Institute of Animal Genetics, Edinburgh

Organisms choose their possible environments, so transforming their niches (WAD, 1954-1959)

"Feedback loop": Environmental stresses and selective pressures depend also on the activities of organisms in their habitats (WAD, 1965) – Niche Construction models

RT

WAD'S THINKING AS A PATTERN THAT CONNECTS



Evolutionary implications?

WAD THE EVOLUTIONIST: Post-Neo-Darwinism

Connect this multi-level interactionism to Neo-Darwinian evolutionary theory ("post-neo-Darwinian" perspective):

- 1) Against the gene-centered, "atomistic" models of gene selection and adaptation
- 2) Modern Synthesis (MS) neglected gene interactions and development
- 3) MS neglected "the role of behaviour in influencing the nature of selective forces" (WAD, 1961)
- 4) MS neglected that selective values do not apply to genes but to phenotypes as developmental systems.

WAD's theory is **still Neo-Darwinian** because:
a) the mechanisms causing genetic assimilation are still «population-genetic processes involving selection» (1959; "in line with the official theory");
b) Neo-Darwinism hardened the original Darwinian theory.
Towards **a revised, expanded neo-Darwinism** (today: Extended Ev. Synthesis).

RT

The incompleteness of Modern Synthesis (MS)

To Dobzhansky (1952): the theory of evolution needs a «more flexible theoretical core»

- 1) MS «core» is an over-simplification: **the role of the processes related to phenotypes** (we need «a general theory of phenotypes»).

- 2) Evolution is not only differential fitness of phenotypic random variations, but also (and mainly) **selection of genotypes that give to their bearers the capacity of adaptively reacting to «capricious» environments**.

- 3) **VS Adaptationism**: Ex. an ontogenetic adaptation assimilated and persisting after the stress is not optimal = **Canalization as constraint**, a dialectic between adaptability and developmental constraints (ex. limited number of body plans or “archetypes”)

From *chance and necessity* to *learning and innovation* (1974)

Figure 1 | **Conrad Hal Waddington.** Reproduced with permission from REF. 1 © (1977) The Royal Society.

The four «systems» of a post-neo-Darwinian theory of evolution

N.B. **Genealogical side of evolution** (random genetic variation; differential reproduction) + **Ecological-interactive side of evolution** (non-random phenotypic variation; ecological survival of phenotypes as dev. systems)

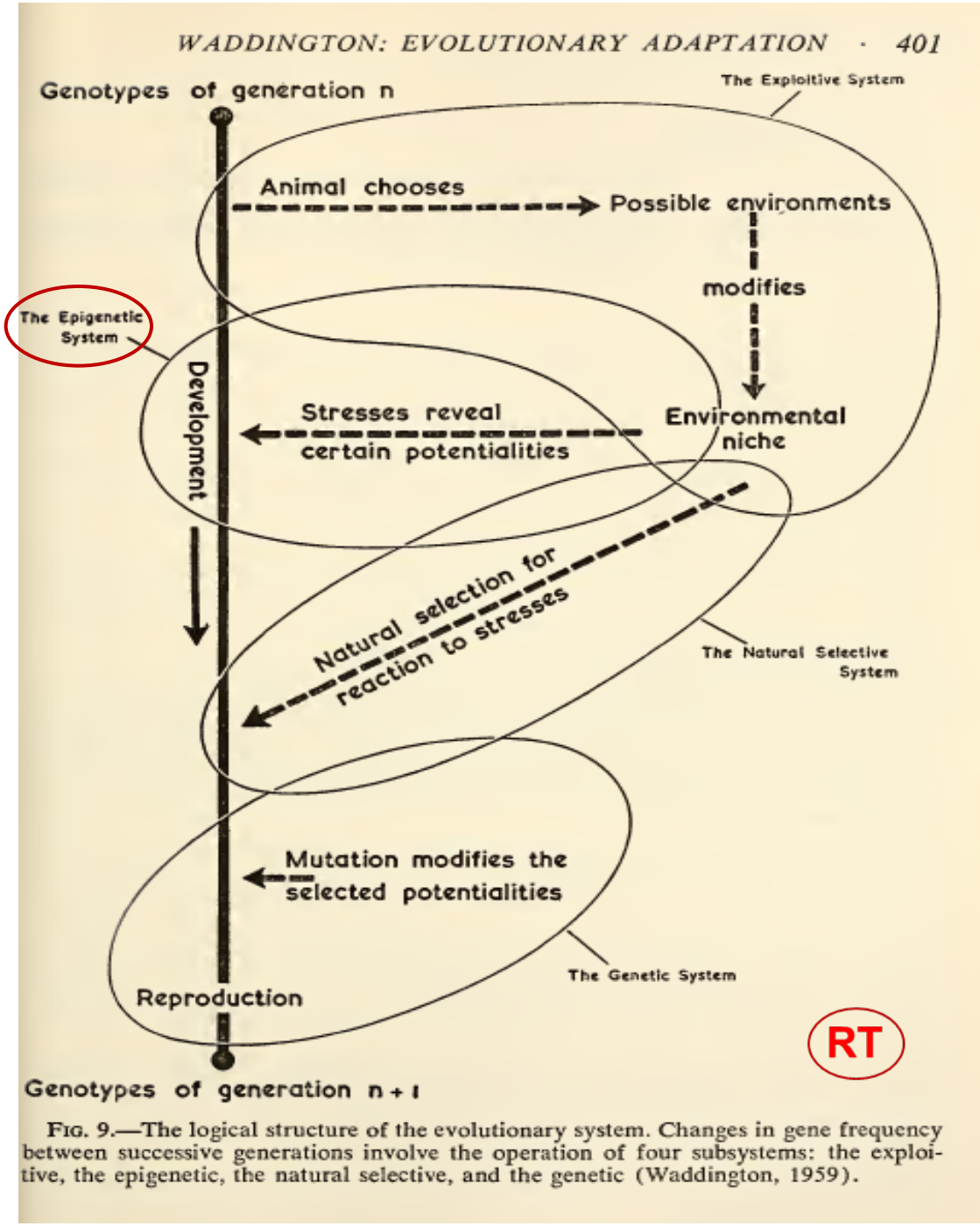
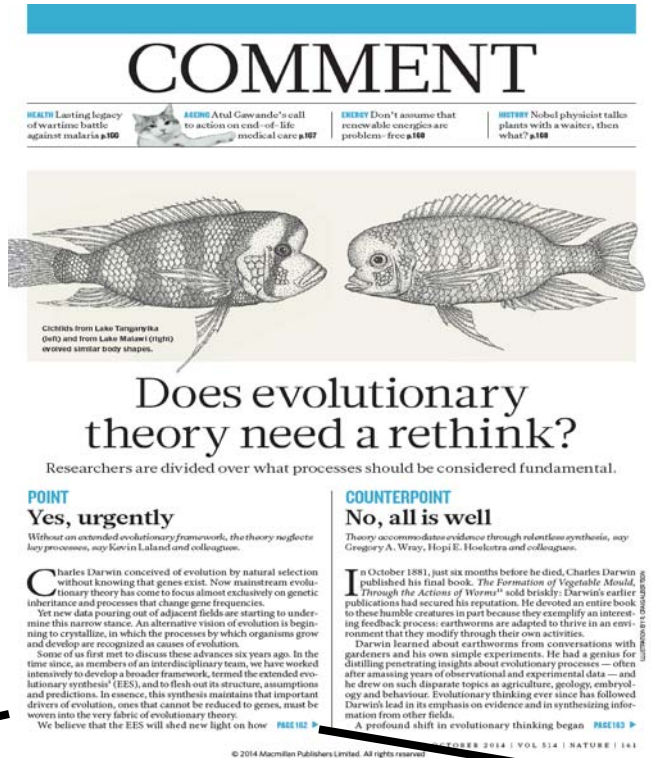


FIG. 9.—The logical structure of the evolutionary system. Changes in gene frequency between successive generations involve the operation of four subsystems: the exploitive, the epigenetic, the natural selective, and the genetic (Waddington, 1959).

WAD, «Evolutionary adaptation», in Aa. Vv., *Evolution after Darwin*, The University of Chicago Press, 1959, p. 401

RT

- VS Gene-centric focus
- Developmental bias (Evo-Devo)
- Plasticity
- Niche construction



COMMENT

HEALTH Lasting legacy of wartime battle against malaria p.100 | AGEING Atul Gawande's call to action on end-of-life medical care p.107 | ENERGY Don't assume that renewable energies are problem-free p.160 | HISTORY Nobel physicist talks plants with a waiter, then what? p.169

Cichlids from Lake Tanganyika (left) and from Lake Malawi (right) evolved similar body shapes.

Does evolutionary theory need a rethink?

Researchers are divided over what processes should be considered fundamental.

POINT

Yes, urgently

Without an extended evolutionary framework, the theory neglects key processes, say Kevin Laland *and colleagues.*

Charles Darwin conceived of evolution by natural selection without knowing that genes exist. Now mainstream evolutionary theory has come to focus almost exclusively on genetic inheritance and processes that change gene frequencies.

Yet new data pouring out of adjacent fields are starting to undermine this narrow stance. An alternative vision of evolution is beginning to crystallize, in which the processes by which organisms grow and develop are recognized as causes of evolution.

Some of us first met to discuss these advances six years ago. In the time since, as members of an interdisciplinary team, we have worked intensively to develop a broader framework, termed the extended evolutionary synthesis[1] (EES), and to flesh out its structure, assumptions and predictions. In essence, this synthesis maintains that important drivers of evolution, ones that cannot be reduced to genes, must be woven into the very fabric of evolutionary theory.

We believe that the EES will shed new light on how PAGE 102 ▶

COUNTERPOINT

No, all is well

Theory accommodates evidence through relentless synthesis, say Gregory A. Wray, Hopi E. Hoekstra *and colleagues.*

In October 1881, just six months before he died, Charles Darwin published his final book. *The Formation of Vegetable Mould, Through the Actions of Worms*[1] sold briskly: Darwin's earlier publications had secured his reputation. He devoted an entire book to these humble creatures in part because they exemplify an interesting feedback process: earthworms are adapted to thrive in an environment that they modify through their own activities.

Darwin learned about earthworms from conversations with gardeners and his own simple experiments. He had a genius for distilling penetrating insights about evolutionary processes — often after amassing years of observational and experimental data — and he drew on such disparate topics as agriculture, geology, embryology and behaviour. Evolutionary thinking ever since has followed Darwin's lead in its emphasis on evidence and in synthesizing information from other fields.

A profound shift in evolutionary thinking began PAGE 103 ▶

In our view, this 'gene-centric' focus fails to capture the full gamut of processes that direct evolution. Missing pieces include how physical development influences the generation of variation (developmental bias); how the environment directly shapes organisms' traits (plasticity); how organisms modify environments (niche construction); and how organisms transmit more than genes across generations (extra-genetic inheritance). For SET, these phenomena are just outcomes of evolution. For the EES, they are also causes.

SCIENTIFIC RESEARCH PROGRAMME

Protective belt in progress

Observative theories

Auxiliary assumptions

RP Core

Initial conditions

Open problems

- No longer debated explanations and concepts (corroborated; method. infalsific.)

- Positive and negative heuristics

Assumptions of marginality

Domains of relevance

Controversial issues

*Imre Lakatos, 1972-1978

MS - Modern Synthesis

Auxiliar assumptions

Gene-centric view

Philetic Gradualism

Extrapolationism
(Macroevolution from microevolution)

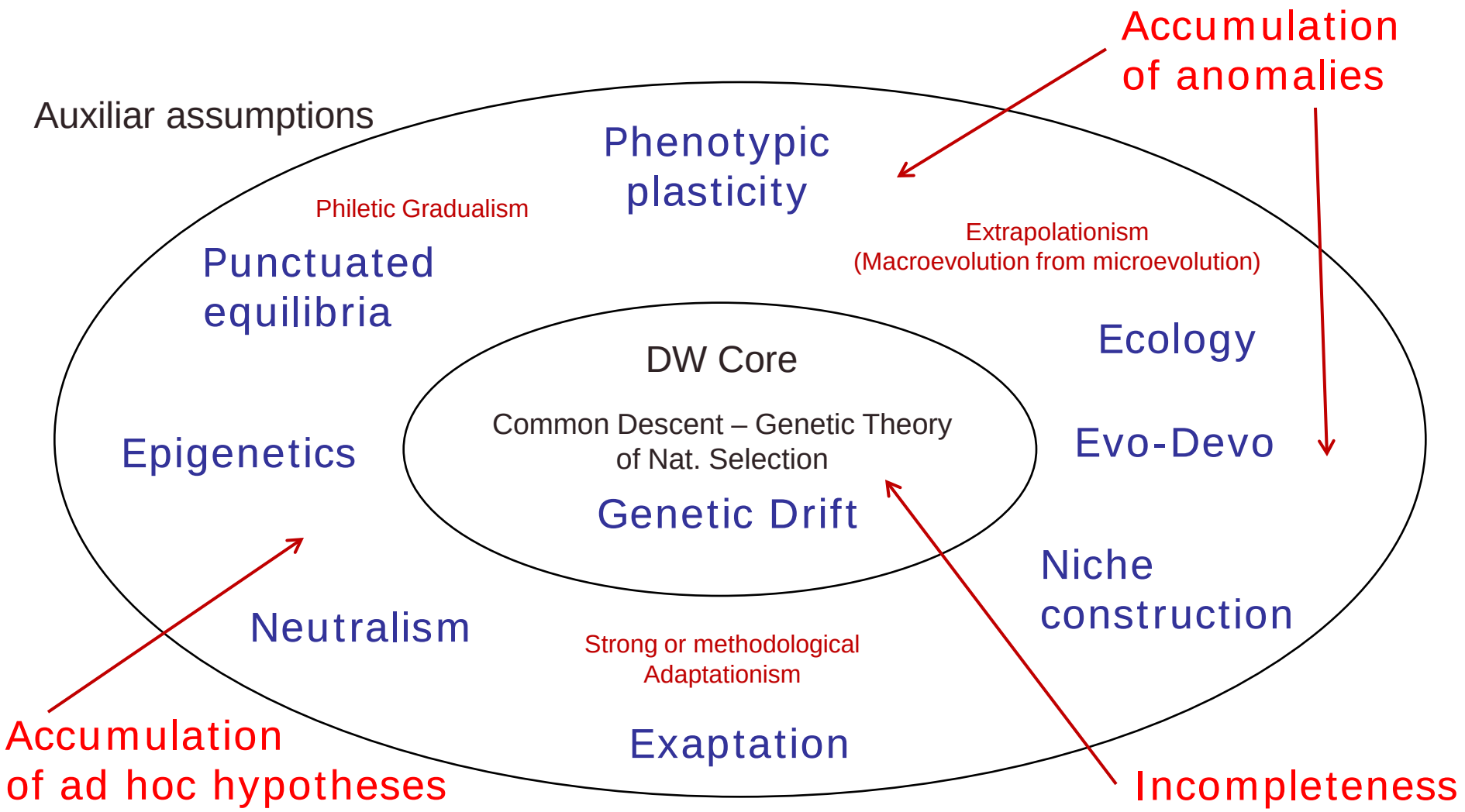
DW Core

Common Descent – Genetic Theory of Nat. Selection

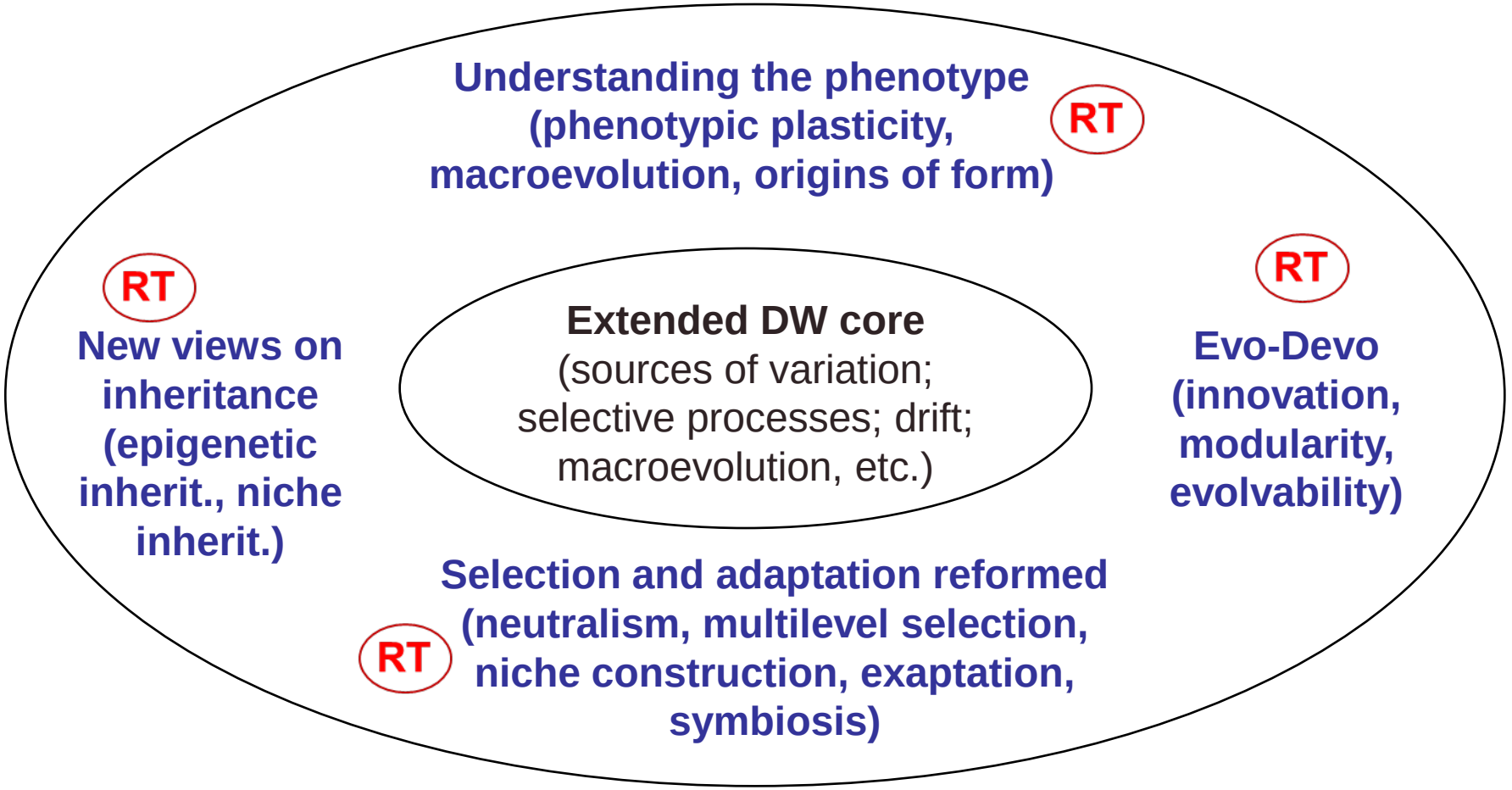
Strong or methodological Adaptationism

Ronald A. Fisher

Regressive phase of MS



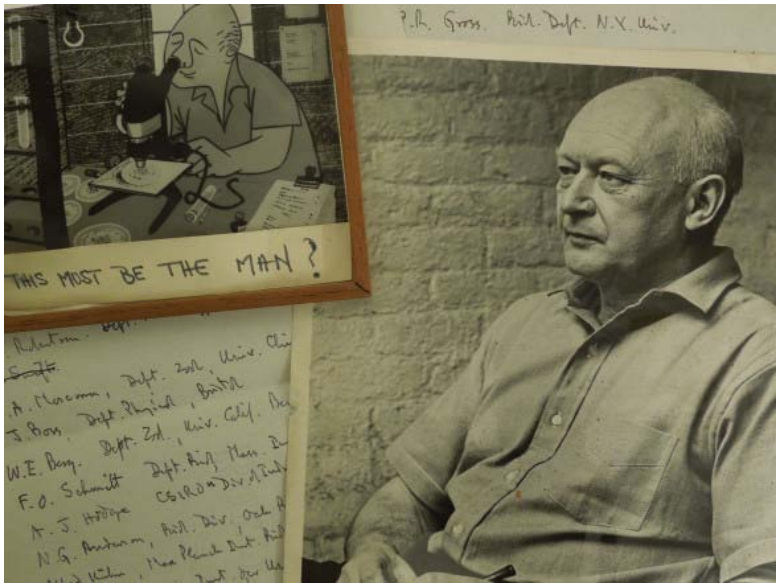
Shift to a new scientific research programme: Extended Evolutionary Synthesis



WAD, 1959: we need a «synthetic biology» (connecting the 4 systems of life)

Tail: WAD and human evolution, three tips

1 - The selection of genotypes that gave to their bearers the capacity to adaptively react to environment can explain also why our mind is able to understand surrounding natural phenomena (tuning between human cognitive apparatus and the nature of reality – «Evolution and Epistemology», *Nature* 1954)



2 - Cognitive and perceptual capacities, originally derived from environmental interactions, became subsequently innate (WAD 1968).

3 - The «global problem» (the powerful and wide-ranging effects of human societies) needs a global approach to complex systems (evolution of ethics; extra-genetic transmission).

a: *Homo sapiens* as a powerful «niche constructor» RT

b: Complex systems approach to climate change, global inequalities, loss of biodiversity. RT

TIMELINE

Conrad Hal Waddington: the last Renaissance biologist?

Jonathan M. W. Slack

works and development. He is not well known to younger biologists because his work lies to one side of the mainstream of molecular biology. However, one of the biggest challenges of today is how to relate a vast and rapidly growing mass of genomic information to a relatively much smaller number of key biological phenomena. Some form of theoretical biology will have to be devised to meet this challenge and, whether attributed or not, Waddington's ideas will doubtless re-surface in the process.

Yes!

Thanks