The Epigenetic Turn

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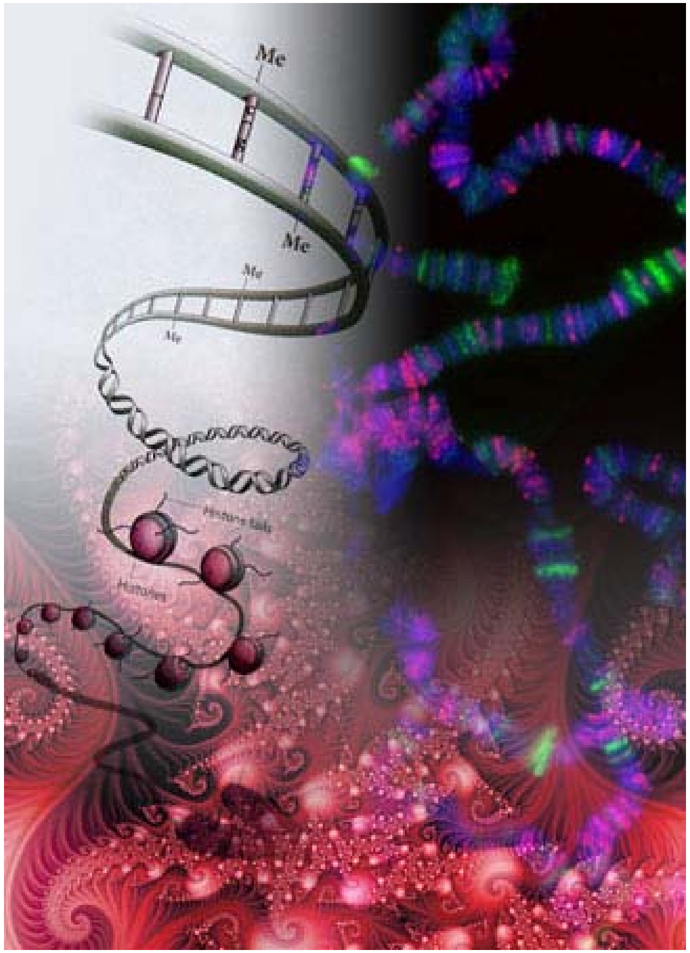
April 2016, Abbazia di Spineto, Sarteano



Epigenetic-oriented approaches all have the developing phenotype rather than the gene as their starting point, and focus on aspects of development that lead to flexibility and adjustment when the environment or the genome changes.

Although their roots are old and varied, these approaches became influential during the 1990s, and today are an important part of the extended view of evolution that is taking shape. Marion Lamb and I call this revival, extension, and elaboration of epigenetic approaches the “epigenetic turn”.

Epigenetics and Evolution: Three Main strands

1. Waddington in Great Britain (and Schmalhausen in the Soviet Union) took a view of evolution that was centered on the complementary aspects of developmental canalization and phenotypic plasticity. Studied the processes that decouple genetic and phenotypic variations, and suggested that the capacity to react should be the focus of evolutionary studies. Reasoned that through selection for the developmental capacity to respond to a new environmental stimulus in an adaptive way, a genetic constitution that facilitates adaptation can be built up.

2. Cell heredity: a focus on its role in development, heredity and evolution

3. Emphasis on the generative mechanisms that give rise to phenotypic plasticity. These include processes that arise from the fundamental physico-chemical properties of biological matter, which, when interacting with new environmental conditions, lead to new patterns of development that can be the basis of dramatic morphological innovations), and to evolved plasticity mechanisms that are based on exploration and selective stabilization processes.

C H Waddington

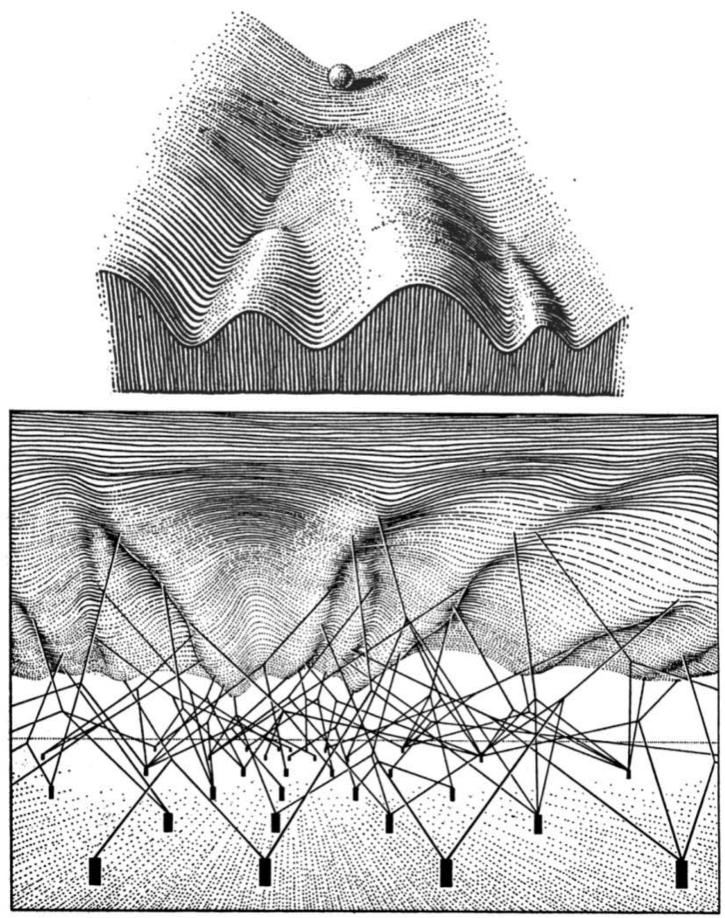
Epigenetics

Some years ago I introduced the word 'epigenetics', derived from the Aristotelian word 'epigenesis', which had more or less passed into disuse, as a suitable name for the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.

Waddington 1968

Waddington's Epigenetic Landscape

Canalization: the adjustment of developmental pathways so as to bring about a uniform developmental result in spite of genetic and environmental variations



Plasticity: the ability of a single genotype to generate variant forms of morphology, physiology and/or behavior, in response to different environmental circumstances

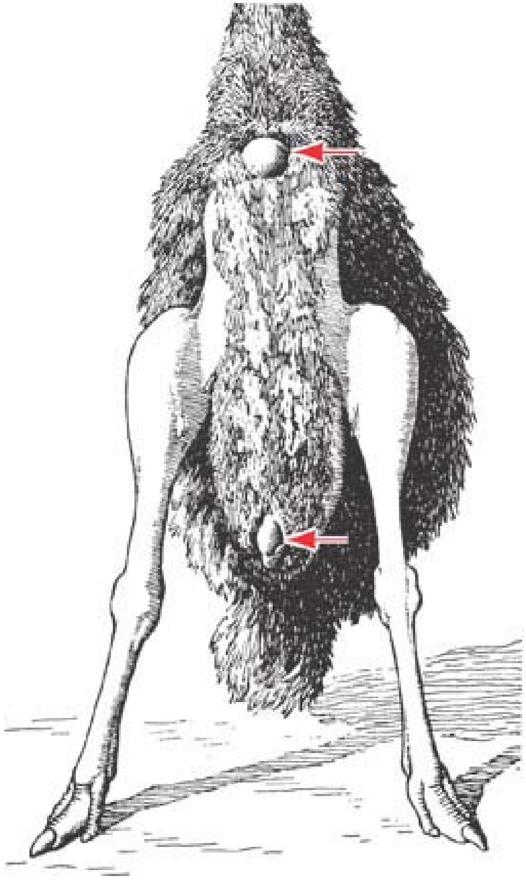
Network thinking

Waddington 1970 “Gene Regulation in Higher Cells” reacted to Britten's and Davidson model of gene regulation.

He was happy with the model, but wanted something that can explain not only activation but also determination (competence):

“We need a mechanism that accounts not only for gene activation or derepression in such instances as the puffing of particular salivary bands after treatment with ecdysone or a changed ionic medium;… We also have to show what has happened previously to "determine" which particular bands will Puff;” (p. 639).

Waddington and the ostrich



Canalization of Development and the Inheritance of Acquired Characters

Nature 1942

“If we are deprived of the hypothesis of the effects of the inheritance of use and disuse, we seem thrown back on an exclusive reliance on the natural selection of merely chance mutations. It is doubtful, however, whether even the most statistically minded geneticists are entirely satisfied that nothing more is involved than the natural selective filter.”

Although Waddington focused on the developmental system, and his assimilation model is a “phenotype-first” model, he did not think that soft inheritance is possible. His thoughts were influenced by the then dominant idea that there was no soft inheritance.

Soft inheritance: “Inheritance during which the [genetic] hereditary material is not constant from generation to generation but may be modified by the effects of the environment, by use or disuse, or other factors.” Mayr 1982

However, at the same time there were observations and experiments that suggested that the hegemonic view is incomplete

The genetical data on which the modern conception of the gene is based are intensely selected data.

(Lindegren 1949)

It is perhaps only natural that investigations of ‘messy’ characteristics are discontinued before publication and that investigators move on to traits more readily analysed.

(Nanney 1957)

Some problems for the dominant view of the MS gene (1950-65)

- Phage transduction in bacteria
- Pseudo-hybrids of *Amoeba* (Danielli)
- Cortical inheritance in *Paramecium* (Sonneborn)
- Jumping genes in maize (McClintock)
- Paramutation (Brink)
- Heritable temperature-induced changes in peas (Highkin)
- Heritable fertiliser-induced changes in flax (Durrant)
- Heritable fertiliser-induced changes in *Nicotiana* (Hill)

Determined and differentiated cell states can be transmitted

- Mammalian cells in culture
- *Drosophila* imaginal discs
- X-chromosome inactivation
- Microorganisms
- Studies on plant cells in culture

David Nanney (1958) published a paper called “Epigenetic control systems” where he argued that heritable differences between cells do not depend solely on the “primary genetic material”

Epigenetic Inheritance trough DNA methylation

DNA methylation

Holliday and Pugh (1975)

Riggs (1975)

Sager and Kitchin (1975)

Genomic imprinting (studied at the molecular level during the late 1980’s, mainly through studies of transgenes)

Holliday ended his 1987 paper “The inheritance of epigenetic defects” saying:

“Epigenetics is concerned with the strategy of genes in unfolding the genetic program for development. This strategy is not understood and the lack of a theoretical framework severely hinders experimental advances”.

Holliday here seems to position his work on epigenetics and epigenetic inheritance firmly within the framework created by Waddington. Holliday saw DNA methylation as part of the epigenetic system which relates genotype to phenotype.

The concept of epigenetics shifted more and more towards a view centered on cell heredity.

Robin Holliday (1932-2014)

"Epigenetics can be defined as the study of the mechanisms of temporal and spatial control of gene activity during development of complex organisms. ….Mechanisms of epigenetic control must include the inheritance of particular spectrum of gene activities in each specialized cell. In addition to the classical DNA code, it is necessary to envisage the superimposition of an additional layer of information which comprises the part of the hereditary material, and in many cases this is very " stable. The term epigenetic inheritance has been introduced to describe this situation." (Holliday 1990).

"The study of the changes in gene expression, which occur in organisms with differentiated cells, and the mitotic Inheritance of given patterns of gene expression. …Nuclear inheritance which is not based on differences in DNA." (Holliday 1994).

Developmental molecular genomics since the 1990s: the epigenetic explosion

The exponential growth of molecular biology and focus on gene expression; realization of the ubiquity of epigenetic mechanisms and epigenetic inheritance

Growth of medical epigenetics

Integration of developmental psychobiology with molecular epigenetics; neuroepigenetics;

Population ecological studies and theoretical modelling

Realization of the bridging role of epigenetic research for interdisciplinary research

Epigenetics today

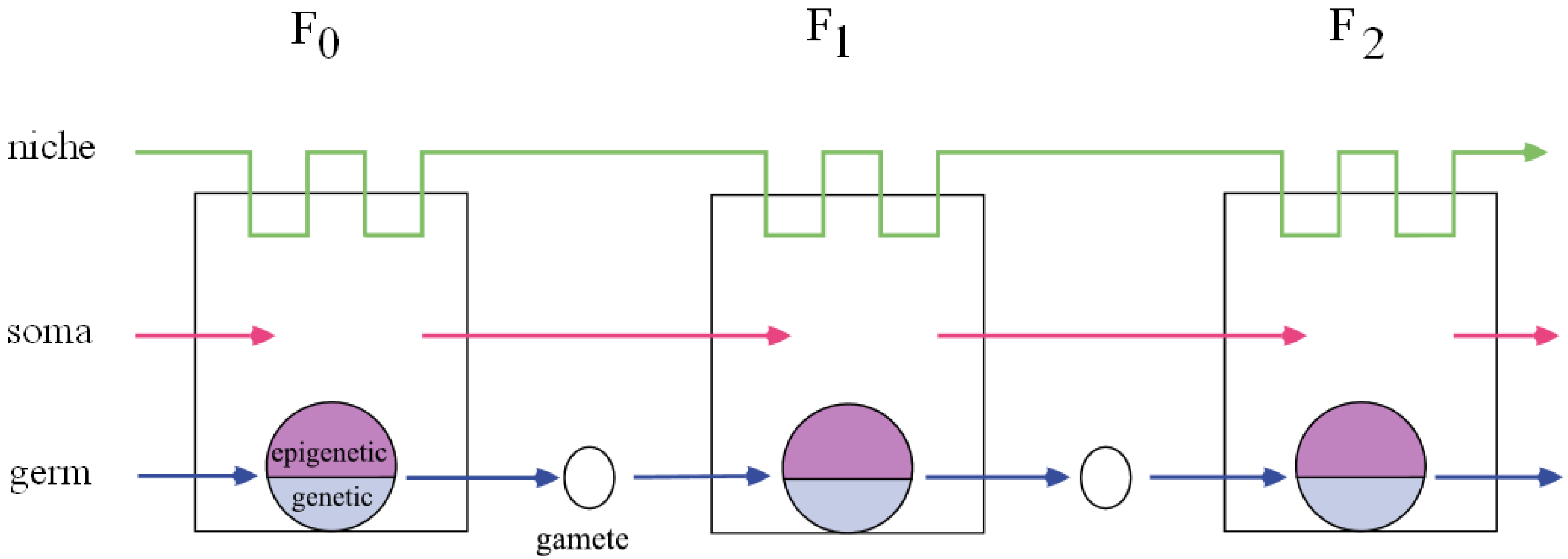
Epigenetics is the study, in both prokaryotes and eukaryotes, of the processes that can lead to long-term, persistent developmental effects. At the cellular level these are the processes involved in cell determination and differentiation. At higher levels of biological organization, epigenetic mechanisms underlie self-sustaining interactions between groups of cells that lead to physiological, behavioral morphological persistence.

Epigenetic inheritance

Epigenetic inheritance is a *component* of epigenetics. It occurs when phenotypic variations that do not stem from variations in DNA base sequence are transmitted to subsequent generations of cells or organisms.

It is used in a broad and a narrow (cellular) sense.

Epigenetic inheritance: broad and narrow conceptions



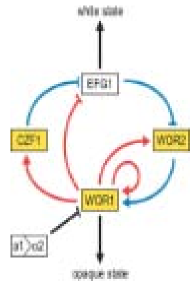
Cellular epigenetic inheritance

Cellular epigenetic inheritance is the transmission from mother cell to daughter cell of variations that are not the result of differences in DNA base sequence or the present environment. The cell is the unit of transmission.

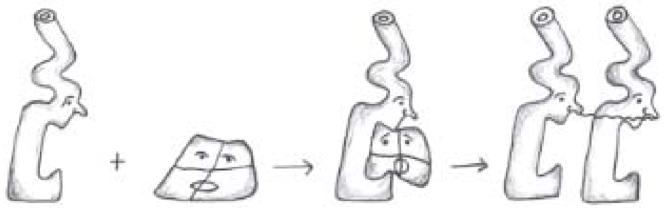
It occurs during cell division in prokaryotes, mitotic cell division in the soma of eukaryotes, and sometimes during the meiotic divisions in the germline.

Epigenetic mechanisms

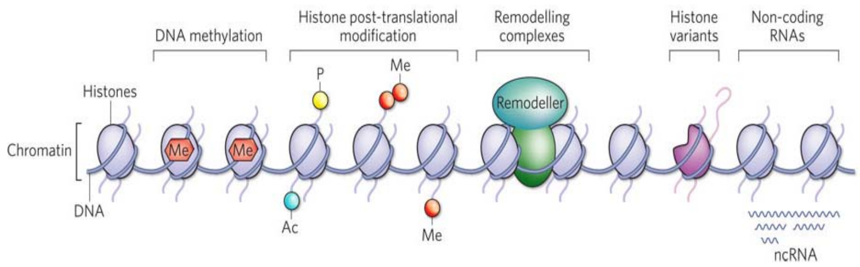
- self-sustaining metabolic loops



- self-reconstructing three-dimensional structures



- chromatin marks



- RNAs

Cases of trans-generational epigenetic inheritance

Jablonka and Raz (2009, Quarterly Review of Biology) surveyed the literature on transgenerational cellular epigenetic inheritance and found:

- 12 cases of epigenetic inheritance in bacteria
- 8 cases of epigenetic inheritance in protists, mostly in ciliates where a large number of loci and traits have been studied
- 19 cases in fungi, involving many phenotypes and loci
- 38 cases in plants, involving **many** loci and many traits; often they were induced by genomic stresses.
- 27 cases in animals, some involving many loci; stress sometimes induced multiple epigenetic changes.

Many loci and factors are involved. In plants, 50% of methylation patterns maybe inherited.

- Medical epigenetics (e.g. Epigenetic epidemiology, Psychiatric epigenetics, Epigenetic toxicology)
- Behavioral epigenetics (includes neurepigenetics)
- Quantitative epigenetics
- Population epigenetics
- Ecological epigenetics
- Evolutionary epigenetics

Evolutionary considerations:

1. What are the **evolutionary origins** of epigenetic inheritance systems? How did this type of temporally extended plasticity evolve?

2. **Under what conditions is epigenetic inheritance advantageous**? General theoretical considerations; taxon-specific considerations.

3. What are the **effects of epigenetic inheritance**? What can we infer about the significance of epigenetic inheritance in evolution from current effects and functions?

a. Contribution to genetic evolution

b. Effects on the dynamics of populations (rates, trends)

c. **Adaptive evolution and contribution to genetic assimilation**

d. Contribution to macroevolution and genome evolution

e. Contribution to the major evolutionary transitions

Usually, “Genes are followers, not leaders in adaptive evolution” (West-Eberhard 2003)

Many routes towards genetic assimilation accommodation (induced transposition; polygenetic basis and selection for genetic combination/s with many small effects genes; assimilation mediated by induced and then heritable changes in the microbiome; involvement of epigenetic inheritance)

A possible (gradual) route to genetic assimilation (suggested for example by Badyaev):

Evolution of environmentally-induced Parental effects → longer term epigenetic inheritance → genetic assimilation

Selection of epigenetic and genetic variations

Cultural, behavioral and epigenetic adaptive variations construct an ecological and developmental niche which selects heritable variations that fit this niche.

Developmental adjustments to novel challenges

- In yeast and *Drosophila* some adaptive adjustments are epigenetically inherited
- In *C. elegans* the RNAi system is recruited as a transgenerational cellular immune system
- Domestication processes may involve epigenetic changes that eventually become genetically assimilated
- Behavioral adaptation can be initiated by socially acquired and transmitted variations
- The evolution of the language capacity in humans is the product of the co-evolution of genetic, epigenetic and symbolic systems, with the symbolic system leading.

Although Waddington did not think that soft inheritance is possible, I think that he would have been very happy with what we have learned