Epigenetics: A Challenge for Genetics, Evolution, and Development?

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A system of philosophical concepts is not…a ready-made set of pigeonholes.… [I]t is something much more important, namely a way of thought. One of the best known half truths about science is that asking the questions is more difficult than answering them. Whether this is an exaggeration or not, asking questions is at least one of the essential phases of scientific activity. It is in this connection with this function that philosophy is most important. A new question implies a new context, that is to say, the attempt to fit a phenomenon into a system which has not previously been applied to it.

(WADDINGTON, *ORGANISERS AND GENES, 147*)

ABSTRACT: In this paper, it is argued that differences in how one relates the genome to its surrounding contexts leads to diverse interpretations of the term *epigenetics*. Three different approaches are considered, ranging from gene-centrism, over gene-regulation, to dynamic systems approaches. Although epigenetics receives its widest interpretation in a systems approach, a paradigmatic shift has taken place in biology from the abandonment of a gene-centric position on to the present. The epistemological and ontological consequences of this shift are made explicit.

KEYWORDS: dynamic systems; epigenetics; gene-centrism; gene regulation

It is often the case that scientific disciplines take off with a number of well-delineated results, expand by extrapolating from these, increase the production of reliable and successful data, enhance their authority on that basis, and nevertheless find themselves eventually in a situation of crisis and uncertainty, foreshadowing the contours of a paradigmatic shift.

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Does epigenetics today lead to such a paradigmatic shift in biology? With its embryological roots and its rapidly increasing importance in molecular biology, does it challenge traditional insights in genetics, development, and evolution? Is it prefiguring, from within biology, the end of a common ground, that is, the gene as master molecule symbolized in molecular biology's Central Dogma? Does it question the basic idea that genes *code for* the essential characteristics of life? Does it challenge the idea of the genome as the "ultimate causal layer" in the development and change of living systems, or will a complex extension of that ultimate causal layer suffice to incorporate epigenetic data? In sum: do epigenetic phenomena fit in the picture of the genome as the onset of a series of linear causal changes, making thereby the genome a causal core of a comprehensive theory of the living? Or shall the genome become one of many causal factors, important but not sufficient in itself, in the highly circular and intricate "fabric of life," making thereby the issue of causality itself quite problematic? Depending on how one answers these questions, epigenetics comes to denote different things.

Within a *gene-centric viewpoint*, epigenetic phenomena are thought to be encapsulated by the genetic landscape, and their emergence is to be explained solely from within this landscape. First come the genes, then comes what lies beyond, the "epi," a more complex addendum to the theory that depicts life as regulated from the bottom by genes only. Putting the genome into context will then only introduce an *epigenetic spirit* into molecular genetics,[1] thereby making epigenetic phenomena merely epiphenomenal or causally superfluous. There is, however, a growing list of facts that no longer fit the linear, one-gene-only approach of the genome. This shows that it is no longer sufficient to restrict research to classical genetic analyses in terms of genetic mutations, distinct phenotype–genotype distinctions, and metaphors of genetic programs.[2] From this angle, multiple contexts, such as the nuclear and intracellular contexts that directly impinge on the genome, but also the intercellular, organismic, and environmental contexts in which a functional genome is embedded, can no longer be neglected.[3]

Hence the currently common definition of epigenetics as the study of phenomena that lead to changes in gene function that are mitotically and/or meiotically transmissible *without* entailing a change in DNA sequence.[4,5] Here, epigenetics comprises studies on chromatin dynamics, the establishment of methylation patterns on DNA, parental imprinting of genes, gene silencing, the role of RNA and proteins in these processes, paramutation, position effects on gene expression, and so on. These phenomena are found in organisms as diverse as fungi, higher plants, and vertebrates and appear to be involved in both developmental cell differentiation and stabilization, cell-memory mechanisms, organismal defense against infections with foreign DNA, controlled responses to environmental stress, and mitotically and meiotically heritable variation.

Although this definition of epigenetics still focuses primarily on the expression and regulation of *genes*, it enables the limits and the contextual embeddedness of any form of genetic determination to be highlighted. Therefore, epigenetics is no longer confined within the boundaries of a traditional gene-centrism.

This does not mean, however, that the alternative to gene-centrism has been made fully explicit. Likewise, it does not mean that the possible interpretations of the prefix “epi” are sufficiently explored and analyzed. Indeed, what can be “epi” about epigenetics?[6]

Up to this day, the positions are divergent and not always clearly defined. Still, a more liberal conception of epigenetics is in the making. Some authors consider that epigenetic phenomena are to be studied as not only dependent on, but also as *independent* of genetic variation: like language and culture, epigenetic phenomena have their own dynamic rules[7] and systems[5] of heredity and evolution. In line with this approach are those who propose a reversal of priorities: instead of focusing on the relatively static or immutable genetic system, epigenetics focuses on the multilayered contexts surrounding and interacting with the genome. Moreover, according to this view the origin of the genetic system can be seen as an emergent product of the evolutionary dynamics in which epigenetic mechanisms play a central role. Hence, genetic integration cannot be taken for granted, as implied by a neo-Darwinian account of evolution.[2] On the contrary, genetic integration requires an explanation within a broader epigenetic, developmental, and evolutionary context.[8]

This viewpoint suggests a dynamic and organizational perspective on living systems. Therefore, it can be successfully embedded in a general theory of complexly organized dynamic systems, in which the mechanisms, the means, and the modalities by which such systems generate, organize, reorganize, and sustain their relative stability and autonomy at various organizational layers and in various time-scales is set out (cf. Collier and Hooker,[9] Bickardt,[10] and Oyama *et al.*[11]). Within this perspective, room is made for a more encompassing interpretation of epigenetics, including the molecular definition as a special case. Here, epigenetics is concerned with the broader study of the determinants of individual development as conditional, inductive interactions among the organism’s constituent components and structures and between these and external forces. These determinants are both temporal and spatial, related to various time-scales and various organizational layers. As a consequence, epigenetics incorporates a developmental and an evolutionary approach as legitimately as a genetic approach. As a matter of fact, an epigenetic theory needs to account for the processes by which living systems are formed and determined, processes that are different at different phases in development and evolution.[a] Moreover, it has to explain the impact of various sources of variation as well as the mechanisms by which living systems and genetically organized systems are highly robust to certain fluctuations.[b] In other words, it has to explain the reliability of phenotypic outcomes, by analyzing the interplay between various control mechanisms, epigenetic as well as genetic. Only such a theory can explain the energetic and/or informational interdependency as well as the relative independency of epigenetic and genetic systems.

Epigenetics in this broad sense challenges the metaphysics and epistemology of a gene-centric viewpoint: (i) it depicts the genome as a complex dynamic system that has developed under evolutionary constraints; (ii) it involves an ontological reversal implying a priority of dynamic interactions over static states, because it purports to describe the types of interactions that are energetically and/or functionally plausible and crucial within various spatial and temporal contexts (developmental or evolutionary) and considers these as prior to the frozen end-products these contexts can give rise to; (iii) it opens up the question of the levels and types of interaction that are at play in scientific research and offers the opportunity to reflect upon the aims and purposes determinative of them. (Rick Von Sternberg, in this volume, deals extensively with the ontology and epistemology of the genome.)

These points need further explanation: With the growing attention for the dynamics of complex systems and self-organizational processes, the genome tends to be seen more and more as a complex dynamic system of which the characteristic *cohesion*, *flexibility*, *changeability*, and *evolvability* are the focus of study. Instead of being more or less immutable or only blindly accessible, instead of being an unstructured collection of genetic "atoms," instead of containing the core program or the basic instructions of the living, the genome is viewed as a regulatory system that actively responds to internal and external fluctuations of various kinds and that is embedded in a variety of contexts that can selectively determine its expression. This viewpoint is incompatible with a "centrism" of any kind.[c] From the moment the genome is viewed as surrounded by constraining and enabling contexts as part of a circular causal system[d] and not as the onset of a linear causal change, its *identifiability* and *individuation* become much more problematic. As Scott Gilbert states, "Our 'self' becomes a permeable self."[14]

This has an impact on the role of the genome in a *theory of heredity.* Whereas during early Mendelian times, a gene was an abstract unit of hered-

[a]In this way, Newman and Müller distinguish epigenetic processes in a "pre-Mendelian" world from epigenetic processes in a Mendelian world, considering that genetic integration takes on a more prominent role after a character is established. The most important epigenetic mechanisms of morphological innovation to them are: "(1) interactions of cell metabolism with the physico-chemical environment within and external to the organism, (2) interactions of tissue masses with the physical environment on the basis of physical laws inherent to condensed materials, and (3) interactions among tissues themselves, according to an evolving set of rules."[12]

[b]In this volume, Evelyn Fox Keller addresses this issue in analyzing the concept of robustness. One of the general principles suggested to explain the high robustness of biological organizations is that anything that can feed back to anything else will. For a more general account of this idea, see *Closure: Emergent Organizations and their Dynamics*, Chandler and Van de Vijver, Eds.[13]

ity with a focus on its function with regard to the phenotype, after the discovery of the double helix in the 1950s, a gene became defined as a physical structure. More specifically, a gene was not only identified as a linear sequence of DNA, but was also taken out of its larger context and individuated from other molecular or nonmolecular entities. Within the context of epigenetics, the question is whether a gene, defined as a DNA sequence, still is a unit of heredity, especially as more and more evidence shows that epigenetic phenomena can be inherited both soma-clonally and transgenerationally, demonstrating that more than just DNA can be inherited.

As a final point, the implications of the epigenetic approach for the powerful *image of science* can and should be analyzed. Will molecular genetics have at its disposal the same manipulative powers as it promised until only a few years ago? Will it be able to create the conditions to control, even in a laboratory setting, the highly complex, multilayered, and diverse temporal embeddedness of living systems?

Even if molecular biology has made the question of the organization of the living much more precise, even if it has uncovered many of its layers and traced many of its internal pathways, it hasn't made the question of its most adequate understanding and explanation a trivial one. To Kant, an adequate understanding of living systems required an account of their essentially integrated, organized, and self-organized nature, their essential "wholeness." To him, the only way of accounting for their specific organization, the only way to *understand* them, was to consider them as intrinsically purposive, to "add meaning" in the sense of supposing a purpose that could not be objectively certified. With the advances of molecular biology, questions of wholeness, integrity, organization, purposiveness, of adequate understanding, and so forth haven't become superfluous. On the contrary, in so far as living systems are considered as highly complex organized dynamic systems, these questions appear to be crucial at every organizational layer living systems embody. Therefore, molecular biology is not relieved from questioning its epistemo-

[c]Cfr. Penissi: "Some of the weirdest genetic phenomena have very little to do with the *genes* themselves. True, as the units of DNA that define the *proteins* needed for life, genes have played biology's center stage for decades. But whereas the genes always seem to get star billing, work over the past few years suggests that they are little more than *puppets*. An assortment of proteins and, sometimes, RNAs, pull the strings, telling the genes when and where to turn on or off.... Enzymes are now considered the *master-puppeteers* of gene expression."[15] [italics added] Pennisi's citation places the new insights of epigenetics at the other side of balance, suggesting a protein-centrism. Still, does one need to think in terms of DNA *or* protein as controlling factors? Doesn't epigenetics rather suggest a system dynamics in which the interactions among DNA, proteins, and other molecules and factors form an integrated process?

[d]The idea of circular causality refers to the basically re- or self-organizational nature of living systems. One of the recurrent arguments in the history of philosophy in favor of the idea that "the whole is more than the sum of the parts," is the one related to circularity or reflexivity. It states that living systems are intrinsically different from nonliving systems because of their specific dynamic circular organization, that is, their basically re- or self-organizational nature. This philosophical idea was most lucidly expressed in Kant's *Critique of Judgment* (1791).

logical and metaphysical interests and purposes that determine its ways of interacting with living systems, it is not freed from defining its "knowledge attitude" towards living beings. Eventually, "What do you want science for?"[16] is not a trivial question, it is a question at the core of molecular biology today, and of epigenetic studies in particular.

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In biology, epigenetics is the study of heritable phenotype changes that do not involve alterations in the DNA sequence. The Greek prefix epi- (á¼Ï€Î¹- "over, outside of, around") in epigenetics implies features that are "on top of" or "in addition to" the traditional genetic basis for inheritance. Epigenetics most often involves changes that affect gene activity and expression, but the term can also be used to describe any heritable phenotypic change. Such effects on cellular and physiological... The challenges of epigenetics concern not only medicine and public health (see Epigenetics, the Genome and its Environment) but also evolution (see Theory of evolution: misunderstandings and resistance).Â In addition, the role of epigenetics is suspected and extensively studied in the development and progression of complex and multifactorial diseases, such as neurodegenerative diseases (Alzheimerâ€™s, Parkinsonâ€™s, amyotrophic lateral sclerosis, Huntingtonâ€¦) or metabolic diseases (obesity, type 2 diabetesâ€¦).Â The ultimate inquiry is that of the importance of epigenetic processes in Evolution. Epigeneticsâ€”an epic challenge to evolution. This growing discipline challenges a number of â€˜holy cowsâ€™ of neo-Darwinism. by Marc Ambler. Published: 21 April 2015 (GMT+10). Isogenic agouti mice of the same age and sex.Â Epigenetics suggests that latent genetic information of sorts is sitting in the DNA waiting for a particular environment in order to be switched on or off. One can easily imagine how a severe lack of nutrition could affect the health of the victims.Â A new discipline was born, the study of epigenetics (over, or above genetics). One of those doing research on this intriguing mechanism, Dr Bas Heijmans, says, â€œEpigenetics could be a mechanism which allows an individual to adapt rapidly to changed circumstances â€¦ Epigenetics has been the cause of rifts and controversies in the genetics community for almost as long as it has been researched. Well, I hear you ask, if something is the cause of a lot of arguments how can it be becoming just another footnote?Â Saying that the theory of evolution might be being shaken does not mean that survival of the fittest is no longer true. Instead, where the challenge to the theory comes from is the apparent ability of acquired epigenetic marks to be inherited and thus alter the gene expression of an individualâ€™s offspring.Â An epigenetic mark may be passed on to an individualâ€™s children and even grandchildren, but very few of these epigenetic changes survive more than two generations. Although epigenetics receives its widest interpretation in a systems approach, a paradigmatic shift has taken place in biology from the abandonment of a gene-centric position on to the present. The epistemological and ontological consequences of this shift are made explicit. Publication types. Review. MeSH terms. Animals. Evolution, Molecular*. Gene Expression Regulation, Developmental*.