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Epigenetics: ambiguities and implications

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Abstract Everyone has heard of 'epigenetics', but the term means different things to different researchers. Four important contemporary meanings are outlined in this paper. Epigenetics in its various senses has implications for development, heredity, and evolution, and also for medicine. Concerning development, it cements the vision of a reactive genome strongly coupled to its environment. Concerning heredity, both narrowly epigenetic and broader 'exogenetic' systems of inheritance play important roles in the construction of phenotypes. A thoroughly epigenetic model of development and evolution was Waddington's aim when he introduced the term 'epigenetics' in the 1940s, but it has taken the modern development of molecular epigenetics to realize this aim. In the final sections of the paper we briefly outline some further implications of epigenetics for medicine and for the nature/nurture debate.

Keywords Epigenetics · Epigenesis · Epigenetic inheritance · Exogenetic inheritance · Genetic assimilation · Genetic accommodation

This article is part of the topical collection "Sketches of a conceptual history of epigenesis".

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1 Introduction: the many meanings of epigenetics

The term 'epigenetics' was introduced by Conrad Hal Waddington through the fusion of 'epigenesis' and 'genetics', to mean the study of the causal processes by which the genotype gives rise to a phenotype (Waddington 1940; see also Griffiths and Tabery 2013). Waddington argued that the experimental embryology of his day supported a view of how genes are connected to phenotypes broadly in line with 'epigenesis'. Epigenesis is a tradition in developmental biology, dating back at least to William Harvey in the seventeenth century, according to which development produces genuinely new structure, rather than merely unpacking existing structures (the literal meaning of the Greek word is the successive creation of new parts). The term 'epigenetics' is thus not derived from 'genetics' and the prefix 'epi' meaning roughly 'on top of' as is often assumed (see Denis Noble below). Waddington intended epigenetics to bring genetics, a theory of heredity, together with experimental embryology (or epigenesis). Waddington also sought to go beyond the modern synthesis' focus on evolution as change in gene frequencies and integrate development into the theory of evolution. According to Denis Noble he conceived of 'epigenetics' "to describe the existence of mechanisms of inheritance in addition to (over and above) standard genetics" (Noble 2015).

The term epigenetics is still used in Waddington's broad, developmental sense today, but it has also acquired a related but much narrower sense in molecular biology as the "study of changes of gene expression, which occur in an organism with differentiated cells, and the mitotic [and/or meiotic] inheritance of given patterns of gene expression" (Holliday 1994, 453; see also Haig 2000). It is important to note that theses changes do not involve a change in the underlying nucleotide sequence. In addition to these two meanings of 'epigenetics' the term takes on additional meanings in the study of heredity. Here we again find narrow and broad conceptions of 'epigenetic inheritance' (see Box 1).

Waddington's broader sense of 'epigenetics' has remained popular amongst morphologists and developmental biologists, for some of whom "epigenetics refers to the entire series of interactions among cells and cell products which leads to morphogenesis and differentiation" (Herring 1993, p. 472, cited in Haig 2004; compare also Holliday 2006). The evolutionary developmental biologists Benedikt Hallgrimsson and Brian Hall's notion of epigenetics is even? much broader than Waddington's: it applies to many different levels of biological organization, from the molecular level to the population and species level. In the following quote, however, they are using the term "in the spirit of" Waddington's original sense when they claim that epigenetics links the genotype to the phenotype in both development and evolution:

> Epigenetics is the study of emergent properties in the origin of the phenotype in development and in modification of phenotypes in evolution. Features, characters, or developmental mechanisms/processes are epigenetic if they can only be understood in terms of interactions that arise above the level of the gene as a sequence of DNA. Methylation and imprinting of gene sequences are

Box 1 Definitions of epigenetic (from Griffiths and Stotz 2013)

Epigenesis: the idea that the outcomes of development are created in the process of development, not preformed in the inputs to development. 'Epigenetic' originally, and still sometimes today, refers to epigenesis; however, it can also be used in these senses:

Epigenetics (broad sense—Waddington 1940): the study of the causal mechanisms by which genotypes give rise to phenotypes; the integration of the effects of individual genes in development to produce the 'epigenotype'. Includes an epigenetic consideration of evolution

Epigenetics (narrow sense—Nanney 1958): the study of the mechanisms that determine which genome sequences will be expressed in the cell; the control of cell differentiation and of mitotically and sometimes meiotically heritable cell identity, that does not involve changes to the underlying genome sequence

Epigenetic inheritance (narrow sense): the inheritance of genome expression patterns across generations (through the germ line) in the absence of a continuing stimulus

Epigenetic inheritance (broad sense): the inheritance of phenotypic features via causal pathways other than the inheritance of nuclear DNA. This includes Transgenerational Epigenetic Effects, which are parental effects through behavioral or ecological inheritance mediated via epigenetic mechanisms that modify the gene expression in certain organ systems in the offspring. It is also sometimes used without any reference to molecular epigenetic mechanisms. We refer to all these nongenetic inheritance mechanisms as 'exogenetic inheritance' (West and King 1987)

> examples of epigenetics at the level of the structure and function of the gene (…). (Hallgrimsson and Hall 2011, p. 1).

The last sentence of this quotation connects Waddington's broader idea to the narrower, molecular sense of epigenetics. However the authors insist "much is lost to theoretical biology by throwing out this broader concept of epigenetics in favor of a narrower one focused only on chromatin modifications" (Hallgrimsson and Hall 2011, p. 2). Most molecular biologists today understand epigenetics in this narrow sense, as the study of changes in gene expression that are heritable either mitotically (via somatic cells) or meiotically (via germ cells), and that do not entail changes in underlying DNA sequence. According to David Haig, this sense originates from David Nanney's use of the term "epigenetic control systems" (Nanney 1958). Nanney was writing in the same year in which Francis Crick proposed that the nucleic acid sequence is a code that specifies the linear order of amino acids in a protein, thus stating the Sequence Hypothesis and the Central Dogma of Molecular Biology (see Sect. 2, below). Nanney tentatively accepted Crick's idea that specificity is transmitted via genetic templates, but argued that this necessitated additional regulatory mechanisms to determine which templates were used at a particular point in the life of the cell:

> This view of the nature of the genetic material, while certainly not established in detail, finds much support in experimental studies and gains great strength from its simplicity. It permits, moreover, a clearer conceptual distinction than has previously been possible between two types of cellular control systems. On the one hand, the maintenance of a "library of specificities," both expressed and unexpressed, is accomplished by a template replicating mechanism. On the other hand, auxiliary mechanisms with different principles of operation are involved in determining which specificities are to be

> expressed in any particular cell. …To simplify the discussion of these two types of systems, they will be referred to as "genetic systems" and "epigenetic systems." The term "epigenetic" is chosen to emphasize the reliance of these systems on the genetic systems and to underscore their significance in developmental processes. (Nanney 1958, p. 712).

What is remarkable about Nanney's discussion is the rapidity with which he realised that the new view of the gene proposed by Crick implies the necessity for something like the epigenetic mechanisms that have since been discovered. Interestingly Nanney later redescribed his 'epigenetic control systems' as "signal interpreting devices, yielding predictable results in response to specific stimuli from inside and outside the cell" (Nanney 1959). The next section will highlight the importance of environmental signals in epigenetics. Griffiths and Stotz (2013) have argued that epigenetic factors relay environmental signals to the genome, very much in line with Nanney's idea of them as interpreting devices.

The remainder of the paper will address in turn the relevance and implication of epigenetics, in all its four meanings, for development, heredity, and evolution. Haig suggests that Robin Holliday's paper 'The inheritance of epigenetic defects' (Holliday 1987) led to the much wider use of the term 'epigenetic' understood as the heritable control in gene expression (Haig 2004; see also Holliday 2006). The title of that paper highlights the importance of the medical applications of epigenetics for its wider acceptance in biology, a point that we will address in Sect. 5. A final section will discuss more briefly the relevance of epigenetics in medicine and for the broader nature-nurture debate.

2 Implications of epigenetics for development

In the 1950s Conrad Waddington drew an analogy between different views of the role of genes and the ancient rival theories of preformation and epigenesis:

> Some centuries ago, biologists held what are called "preformationist" theories of development. They believed that all the characters of the adult were present in the newly fertilized egg but packed into such a small space that they could not be properly distinguished with the instruments then available. If we merely consider each gene as a determinant for some definite character in the adult (as when we speak loosely of the 'gene for blue eyes, or for fair hair'), then the modern theory may appear to be merely a new-fangled version of the old idea. But in the meantime, the embryologists… have reached a quite different picture… This is the theory known as epigenesis, which claims that the characters of the adult do not exist already in the newly fertilized germ, but on the contrary arise gradually through a series of causal interactions between the comparatively simple elements of which the egg is initially composed. There can be no doubt nowadays that this epigenetic point of view is correct. (Waddington 1952, p. 156).

This statement was made before the rise of molecular genetics, which according to some vindicated at least some form of molecular preformationism. Although the structure of body parts is not preformed, the structure of the molecular parts of organisms, their proteins, is preformed in the DNA (Godfrey-Smith 2000). We have argued elsewhere that molecular preformationism, like its morphological predecessor, is mistaken. Like morphological structures, biomolecules are constructed by an epigenetic process. Multiple factors, none of which contain a full representation of the molecule, are brought together in processes regulated by the larger system of which they are part. The information ('Crick information', see below) manifested in a biomolecule is produced by an 'ontogeny of information' (Oyama 1985) or, as we have described it elsewhere, by 'molecular epigenesis' (Burian 2004; Stotz 2006a, b; Griffiths and Stotz 2013).

Historians of molecular biology credit Francis Crick with having supplemented the existing idea of stereochemical specificity, embodied in the three-dimensional structure of biomolecules and underlying the lock-and-key model of interaction between biomolecules, with the idea of informational specificity, embodied in the linear structure of nucleic acids (such as genes and other genetic elements) that determine the linear structure of a gene product (Sarkar 1996). This idea is present in Crick's statements of both the Sequence hypothesis, and the Central Dogma:

> *The Sequence Hypothesis* … In its simplest form it assumes that the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and that this sequence is a (simple) code for the amino acid sequence of a particular protein.
>
> *The Central Dogma* This states that once 'information' has passed into a protein it *cannot get out again*. In more detail, the transfer of information from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible. Information means here the *precise* determination of sequence, either of bases in the nucleic acid or of amino-acid residues in the protein. (Crick 1958, pp.152–153, italics in original).

Griffiths and Stotz (2013) have termed this encoding of specificity 'Crick information'. If a cause makes a specific difference to the order of elements in a biomolecule, it contains Crick information for that molecule. This definition embodies the essential idea of Crick's sequence hypothesis, without in principle limiting the location of biological information to nucleic acid sequences as Crick does. Crick's sequence hypothesis and Central Dogma were based on his initial, simple picture of how the specificity of biomolecules is encoded in living cells. We now know that, at least in eukaryotes, coding regions are surrounded by a large number of non-coding sequences that regulate gene expression. The discrepancy between the number of coding sequences and the sometimes vastly higher number of gene products lead to the insight that the informational specificity in coding regions of DNA must be amplified by other biomolecules in order to specify the whole range of products. The human proteome (the number of proteins found in human cells) outnumbers the number of protein-coding genes in the human genome by at least one order of magnitude, which suggests that gene products are

underdetermined by the coding sequences from which their precursor molecules are transcribed. In other words, transcriptional and post-transcriptional processes amplify the coding potential of the coding regions themselves (Davidson 2002, p. 291). To say that these factors 'amplify' the coding potential of the genome is to say that they partly determine which products the genome codes for. Recently we have attempted to defend this view by quantitatively measuring and comparing the specificity provided by the original sequence and that provided by splicing factors for one particular case (Griffiths et al. 2015).

Different mechanisms of gene regulation together co-specify the final product of the gene in question, first by *activating* the gene so it can get transcribed, second by *selecting* a chosen subset of the entire coding sequence (e.g. by alternative splicing), and thirdly by *creating* new sequence information through the insertion, deletion or exchange of single nucleotide letters of the RNA (e.g. by RNA editing). Thus sequence specificity, and hence Crick information, is distributed between a myriad of factors other than the original coding sequence: DNA sequences with regulatory functions, diverse gene products such as transcription, splicing and editing factors (usually proteins), and non-coding RNAs (Stotz 2006a, b).

We have chosen the term 'Crick information' because it embraces Crick's original understanding of genetic information as the 'precise determination of sequence', or 'the specification of the amino acid sequence of the protein', hence specificity. However, what is designated by this term is at the same time quite far removed from Crick's original definition as laid down in his sequence hypothesis, since we argue that the specificity for sequence information is distributed between a myriad of factors.

Specificity turns out to be not inherent in any single biomolecule in these networks but induced by regulated recruitment and combinatorial control (Ptashne and Gann 2002). And it is here that we will find that these networks cannot be reduced to DNA sequences and gene products, because many of the latter need to be recruited, activated or transported to render them functional. These processes, the recruitment, activation or transportation of transcription, splicing and editing factors, allow the environment to have *specific* effects on gene expression. As prefigured in Nanney's description of epigenetic systems as 'signal interpreting devices', some gene products serve to relay environmental (Crick) information to other locations in the genome. Much of the signaling is through post-translational modifications, particularly phosphorylation and methylation, and their intrinsic links with metabolic cellular states. These environmental, mechanical, signaling and metabolic cues are indeed beyond the information content of the genome; they are critical for embryology and morphogenesis.[1] While in embryology and morphogenesis it is often acknowledged that environmental signals play a role in the organisation of global activities, they are rarely seen to carry information for the determination of the nucleic acid or amino acid chains in gene products. But this is precisely what occurs. Not just morphogenesis at higher levels of organisation, but even the determination of the primary sequence of gene products is a process of

[1] We owe this point to one of the anonymous reviewers.

molecular epigenesis that cannot be reduced to information encoded in the genome alone (Stotz 2006b; Griffiths and Stotz 2013).

3 Implications of epigenetic for heredity

The idea of epigenetic inheritance was propelled to prominence by Eva Jablonka and Marion Lamb with their provocatively titled book *Epigenetic Inheritance and Evolution: The Lamarckian Dimension* (Jablonka and Lamb 1995; see also Badyaev and Uller 2009; Danchin et al. 2011; Bonduriansky 2012). 'Epigenetic inheritance' in this context is used primarily in its narrow meaning of the inheritance of chromatin modifications, although as we will see below it often spills over into the broader sense of exogenetic inheritance.[2]

3.1 Narrow-sense epigenetic inheritance

Some molecular biologists have argued that one should speak of epigenetic inheritance only in those cases when a methylation pattern is transmitted without change over several generations:

> If an epimutation is to have evolutionary importance, it must persist. … This matter is central to whether epimutations can be treated as equivalent to conventional mutations or whether, if they have some degree of stability, some new population genetic theory is needed. (Wilkins 2011, p. 391).

Some cases certainly meet this criterion. In a comprehensive review of transgenerational epigenetic inheritance Jablonka and Raz conclude that epigenetic inheritance is ubiquitous, and can show stability of transmission of up to three generations in humans and up to eight generations in other animal taxa (Jablonka and Raz 2009). Plants lack the comprehensive reprogramming of DNA in each generation and exhibit therefore much more stable epigenetic inheritance. It is certainly true, however, that many cases, particularly in mammals, would not meet the criterion of multi-generational stability. However, the criterion of multi-generational stability may not be one we should accept. It is simply not correct that epigenetic change will only affect evolution if the changes themselves persist for more than one generation. 'Parental effects' are correlations between parent and offspring phenotypes that are independent of correlations between parent and offspring genotypes, and are also not the result of a shared environment independently influencing both parent and offspring. Researcher who study parental effects have long known that one-generation parental effects substantially alter the dynamics of evolutionary models, and change which states a population will evolve towards as an equilibrium (Wade 1998; Lande and Price 1989). In conventional quantitative genetics, the importance of Mendelism is not that individual genes can

[2] Jablonka and Lamb's identification of epigenetic inheritance with the 'Lamarckian' inheritance of acquired characters is not unproblematic. Some scientists insist that the term Lamarckian inheritance should be restricted to the inheritance of phenotypic (somatic) characters that are acquired during development (Hall 2011, p. 11).

be tracked from one generation to the next—quantitative genetics does not do this—but that Mendelian assumptions let us work out what phenotypes (and hence fitnesses) will be likely to appear in the *next* generation as a function of the phenotypes in the present generation. Epigenetic inheritance changes that mapping from parent to offspring, and therefore, epigenetic inheritance will affect evolution even if it only lasts one generation.[3] For some there is no more central instance of the study of heredity than quantitative genetics, so the argument that epigenetic inheritance needs to be stable for several generations to count as a form of heredity appears to be a *non-sequitur.*

3.2 Wide-sense epigenetic inheritance (exogenetic inheritance)

Discussion of epigenetic inheritance often spills over from discussion of the specific phenomena of germline transmission of chromatin modifications to include exogenetic inheritance more widely. This makes sense because epigenetic mechanisms at the molecular level are often involved in the production of parental effects even when these effects do not involve epigenetic inheritance in the narrow sense just discussed. For example, in one well-studied example, epigenetic mechanisms have been shown to mediate the transgenerational inheritance of maternal care behavior and stress reactivity in rats without actual germline epigenetic inheritance. Maternal behavior in the form of licking and grooming establishes stable patterns of methylation in certain genes in the rat pup hippocampus. These affect gene expression and therefore brain development, with downstream effects on the behavior of the next generation of mother rats. The behavior of these second-generation mothers reestablishes the patterns of methylation in her pubs. But the actual patterns of methylation are not inherited through the germline (Meaney 2001a, b; Weaver et al. 2004a, b; Champagne and Curley 2009). The new mothers' behavior is to a certain extent malleable by environmental changes. So long as the environment remains constant, her phenotype will remain constant; if it changes, the mother rats may change their behavior. However, her epigenetic gene expression pattern predisposes her strongly to resemble the behavior of her mother. The authors call this environmental programming of certain types of behavior through DNA methylation "life at the interface between a dynamic environment and a fixed genome" (Meaney and Szyf 2005). An interesting factor to note here is that the parent-offspring correlations created through these transgenerational epigenetic effects are often much higher than those observed in narrow-sense epigenetic inheritance, as in the famous agouti mouse (Wolff et al. 1998). Mice with an un- or hypo-methyleted, 'viable yellow' agouti allele exhibit a yellow coat, obesity and high rate of diabetes. This epigenotype is not completely reset when inherited through the germline.

In a recent book, Jablonka and Lamb have attempted to organize the complex phenomenon of exogenetic inheritance around four 'dimensions' of heredity:

[3] Even non-heritable epigenetic variation can have an impact on evolution. Through its role in gene expression, this variation differentially changes the survival and reproduction of an individual organism and therefore enables other factors to be transmitted, which thanks to the epigenetic variant can therefore spread in the population (we owe this point to a comment by one of the reviewers).

Genetic, Epigenetic, Ecological and Behavioral, as well as Cultural and Symbolic (Jablonka and Lamb 2005). The Genetic Inheritance System comprises protein coding and non-coding RNA genes plus the regulatory motifs in the genome, as well as sequences with unknown functions. The Epigenetic Inheritance System includes modifications of DNA and chromatin. Beside these resources that are physically attached to the genome other developmental resources are transmitted through the cytoplasm of the egg, such as parental gene products. The cortical (cytoplasmic) inheritance system, a subset of the overall epigenetic system, consists of cellular structures such as organelles with their own membranes and genes (mitochondria and chloroplasts), membrane-free organelles (ribosomes and the Golgi apparatus), and the cellular membrane systems. All these structures cannot be reproduced from genetic information but act as templates for themselves. The Ecological and Behavioral Inheritance System forms a third dimension, in which information is transmitted through behavior-influencing substances, non-imitative and imitative social learning, as well as habitat construction, food provisioning, and other parental effects like that described in the last paragraph. The last dimension is formed by the Cultural and Symbolic Inheritance System. Offspring in some species inherit social structures and rules, cultural traditions and institutions, and technologies. This inheritance system importantly includes epistemic tools, such as language, competent adults, teaching techniques etc.

All four systems use different mechanisms of transmission and show changing degrees of fidelity. Some mechanisms may not be *intrinsically* stable. The nuclear genetic inheritance system achieves its exceptionally high fidelity by relying on several layers of proof reading and copy-error detection systems. A suitable mechanism of scaffolding can lend reliability to any transmission mechanism: proof reading supports genetic inheritance, epigenetics stabilizes gene expression. Learning is scaffolded by teaching or by the reliable affordances of stimuli "that define what is available to be learned…[and]… function to channel malleability into stable trajectories" (West et al. 2003, p. 618).

3.3 Differences between epigenetic and genetic inheritance

Epigenetic marks are sensitive to environmental factors in so far as they are first "established by transiently expressed or transiently activated factors that respond to environmental stimuli, developmental cues, or internal events" (Bonasio et al. 2010, p. 613). Hence epigenetic inheritance differs in important ways from nuclear genetic inheritance. Epigenetic variations are less stable than genetic ones, because these variations are in principle reversible. But this is not necessarily a disadvantage in a heredity system: many epigenetic mechanisms are sensitive to the environment, which arguably is their role during development, and consequently heritable epigenetic variations may not only be more plastic, but importantly also more directed and more predictable. These are all features that could render them more adaptive in the short term than genetic variation, particularly in variable environmental conditions (see for instance Jablonka and Lamb 1995; Holliday 2006; Lamm and Jablonka 2008). Many hypotheses about the evolutionary origins of epigenetic

inheritance stress its value in spatially and temporally heterogenous environments, where it allows rapid responses to change.

This kind of rapid, exogenetic response to the environment is known as adaptive transgenerational plasticity:

> … because the parental phenotype responds to some aspect of its environment that correlates with a feature that is of adaptive relevance to the offspring. This correlational information can be exploited by developmental processes because of the continuity between parental and offspring phenotypes (…). In genetic inheritance systems, on the other hand, correlational information requires a process of selection that builds up gene frequency differences between environments. (Uller 2012, p. 259).

The genetic heredity system may well have been optimized for the ability of organisms to transfer biological specificity reliably between generations (Bergstrom and Rosvall 2009). This ability, perhaps the key innovation in the history of life, was dependent on the invention of nucleic-acid based heredity. However, at least some exogenetic channels of inheritance may have been optimized for the ability to respond flexibly to environmental demands on different timescales, a flexibility that could be said to be at times quite stably inherited (plasticity as a trait). The optimal design for a 'multi-dimensional' heredity system is one that combines robustness and plasticity and enables each to be deployed where it is most adaptive. While we find the arguments in favour of this hypothesis compelling, it is still in need of better experimental support and is therefore not widely shared among more conservative evolutionary biologists.

4 Implications of epigenetics for evolution

We have already touched on the evolutionary significance of narrow-sense epigenetics and epigenetic inheritance. In this section we examine what implications epigenetics in the broad sense—exogenetic inheritance—has for the mechanisms of evolution.

4.1 Evolution and waddington's broad-sense epigenetics

At the outset of this article we described epigenetics as the link between genotype and phenotype, as explaining the origin of phenotypic variation, which is true for both Waddington's original understanding and the modern molecular use of the term. Epigenetics explains phenotypic plasticity, the ability of one genotype to produce more than one phenotype when exposed to different environments. There has been sporadic interest since the late nineteenth century in the influence of developmental plasticity on evolution (Weber and Depew 2003). There is abundant evidence that organisms can accommodate their phenotype to the environment, called phenotypic plasticity or accommodation, and that this process could set the stage for further adaptive evolution (West-Eberhard 2003; Gilbert and Epel 2009). In order to understand how a phenotypic response to environmental signals can

become heritable over time through the process of natural selection, processes such as 'genetic assimilation' (Waddington 1953a, b) and 'genetic accommodation' (West-Eberhard 2003) have been proposed. "For Waddington, genetic assimilation was one of the main ways in which epigenetic mechanisms were relevant to evolutionary change" (Hallgrimsson and Hall 2011, p. 4), and genetic accommodation is a closely related mechanism. These processes lead to evolutionary change through "cross-generational changes in frequency distribution of environmentally induced phenotypes" (Badyaev 2009, p. 1138). Organisms can also use plasticity to buffer themselves against genetic perturbation, a process that may allow for the accumulation of hidden genetic variation that can become visible—and even useful—when environmental conditions change. All of these processes of developmental plasticity could increase a lineage's 'evolvability', its capacity for evolutionary change.

From today's perspective Waddington and his contemporary Ivan Ivanovitch Schmalhausen (1949) are important for their focus on the developmental integration of genetic factors with each other and with the developmental environment. Both authors envisioned a similar process by which a phenotype that was originally induced by environmental factors could be genetically fixed through selection. This process, while not actually Lamarckian, is still quite different from a mere coincidence:

> By speaking of mutations as "random," which is true enough at the level of the gene as a protein-DNA complex, we obscure the fact that the effect of a mutation, as far as natural selection is concerned, is conditioned by the way it modifies the reaction with the environment of a genotype which has already been selected on the basis of its response to that environment. This is not neo-Lamarckism, but it is a point which has been unduly neglected by neo-Darwinism. (Waddington 1953b, p. 386).

The point Waddington is making here is that the developmental mechanisms that allow the organism to produce the phenotype in response to an environmental stimulus are the very same mechanisms that selection acts upon to produce the genetically assimilated version of the response. Waddington explained genetic assimilation with the exploitation of existing developmental plasticity in the population by natural or artificial selection. The fact that it is relatively easy to select for mutations or allele combinations which produce the phenotype *without* an environmental trigger is explained by the fact that the organism already has the developmental capacity to produce that phenotype, requiring only an environmental trigger to do so (Jablonka 2001; Griffiths 2003; Noble 2015).

In the past twenty years many researchers have followed Waddington and Schmalhausen's lead in investigating the evolutionary impact of organisms' ability to change their phenotype in reaction to changing environmental conditions (Gottlieb 1992, 1997; Schlichting and Pigliucci 1998; Bateson and Martin 1999; Pigliucci 2001; West-Eberhard 2003; Gluckman et al. 2009; Gilbert and Epel 2009; Sultan 2007; Bateson and Gluckman 2011). One of the best-known theorists working on this topic is Mary Jane West-Eberhard. In her view, the various examples of developmental plasticity "do not stand as isolated special cases but are

part of a larger and more coherent picture of flexible phenotype structure. Their converging views of developmental mechanisms as sources of flexibility that enhance evolvability are likely to have broad application within biology" (West-Eberhard 1998, p. 8418). West-Eberhard uses an argument that is similar to Waddington's to establish the evolutionary relevance of developmentally produced phenotypic novelties. Novel phenotypic variants, both physiological and behavioral, are produced by developmental plasticity and are then connected with the undirected genetic variation that is almost always present in natural populations to cause evolution. Changes in the frequency of a trait in the population could ultimately be explained by the "selection on genetic variation in the polygenic regulatory mechanisms influencing its threshold of expression. … Although mutation is the ultimate source of this variation, mutation need not be associated with the origin of a particular phenotypic novelty" (West-Eberhard 1998, p. 8418).

New approaches that call for the investigation of organisms embedded in a developmental environment, such as Ecological Developmental Biology ('eco-devo' or 'eco-evo-devo', Gilbert 2001; Gilbert and Epel 2009) or 'Developmental Ecology' (West et al. 2003), have inspired observations and experiments documenting the impact of the interaction between development and environment on evolution. Gilbert and Epel summarize the plasticity-driven evolutionary mechanisms invoked by Waddington, Schmalhausen and West-Eberhard as "change in governance" or "heterocyberny" (Gilbert and Epel 2009, p. 372). Control of a developmental process is reassigned from genes to environment or vice versa. The best known of these processes is the one that Waddington christened 'genetic assimilation', in which a phenotype which used to require a specific environmental trigger ceases to require that trigger. Genetic accommodation is the flipside of genetic assimilation, a process by which a phenotype can become *more* responsive to environmental conditions. Genetic assimilation is produced by selection for developmental robustness—the ability to buffer one preferred phenotype against variation in an environmental parameter. Genetic accommodation is produced by selection for developmental plasticity—the ability to react to a range of environmental parameters with different phenotypes. Waddington himself was able to demonstrate genetic assimilation experimentally (Waddington 1953a), and the viability of genetic accommodation has also, more recently, been supported by experimental evidence (Suzuki and Nijhout 2006; Braendle and Flatt 2006).

West Eberhard has defended the evolutionary significance of a third process, called "phenotypic accommodation" (West-Eberhard 2005a). This describes an adaptive developmental response to an environmental or developmental input that is not accompanied by any genetic change. It can be seen as the first step—a developmental plastic response to a perturbation before this developmental response becomes genetically stabilized—in the processes of genetic assimilation. This "capacity of organismal homeostasis to accommodate and direct a novel input enabling survival in a novel environment" (Badyaev 2009, p. 1137) is one of the necessary prerequisites for genetic accommodation and so, viewed in this light, phenotypic plasticity is a potential source of evolutionary innovation.

The impact of these processes on evolution is not yet clear, but some of their advocates think it is very substantial. West-Eberhard suggests that "genes are

probably more often followers than leaders in evolutionary change" (West-Eberhard 2005b, p. 6543).

4.2 Evolution and exogenetic inheritance

Exogenetic inheritance refers to all the causal pathways by which parents can influence offspring phenotypes other than via nuclear DNA. This is a very different conception of heredity from that associated with the modern synthesis. It has been argued that it is a return to a way of thinking about heredity that existed before Mendelian genetics. According to Ronald Amundson the early twentieth century saw a reconfiguration of the idea of heredity that radically separated it from development. The inheritance of a Mendelian allele explains the inheritance of a phenotypic trait, but it does so without explaining how that trait develops. The allele causes a certain character, say the color of flowers; in such a case:

> [We] may say that a particular factor (p) is the cause of pink, for we use cause here in the sense in which science always uses this expression, namely to mean that a particular system differs from another system only in one special factor. (Morgan et al. 1915, p. 209, cited in Amundson 2005, p. 149).

Morgan's idea of 'cause' thus did not require knowledge of the underlying mechanism by which the inheritance of the allele produces the phenotype. To say that an allele causes a phenotype is merely to say that it *makes a difference* to that phenotype. To earlier biologists, however, the reliable reappearance of a trait in the next generation called for an explanation in terms of its ontogenetic history. Accordingly, it seemed only natural to understand heredity in terms of development:

> Indeed, heredity is not a peculiar or unique principle for it is only similarity of growth and differentiation in successive generations. … The causes of heredity are thus reduced to the causes of successive differentiation of development, and the mechanism of heredity is merely the mechanism of differentiation. (Conklin 1908, p. 90, cited in Amundson 2005, p. 148).

Understanding heredity as the inheritance of difference-makers separates questions about heredity from questions about development—about how those difference makers produce their effects. However, to complete the modern synthesis picture of evolution as change in gene frequencies, it was necessary to exclude other difference-making factors from the theory of heredity. The relevant criterion was, and continues to be, the instability of what was termed 'soft inheritance'. Phenotypic changes due to the environment are either not inherited at all, or are too unstable and fluctuating to be the basis of cumulative change by natural selection. Since it is cumulative selection, rather than one-step selection, that produces complex adaptation this would seem to relegate exogenetic inheritance to a minor role at best. The key implication of this line of reasoning is that the influence of the environment on phenotypes can only affect the course of evolution if it can be somehow written into the genes (Bonduriansky 2012). This explains the recurrent interest in genetic assimilation as well as the short-lived excitement about the

discovery of reverse transcription from RNA to DNA in the 1970s, apparently contradicting Crick's 'Central Dogma'.

Advocates of extended heredity have two possible replies. First, they can argue that other forms of heredity are not as unstable as is normally supposed. Second, they can question whether the evolutionary significance of an inheritance system really turns on its stability across the generations. We described above how Eva Jablonka and her collaborators made a significant effort to mount the first kind of defense. They documented the surprising extent of behavioral and cultural inheritance across a wide range of animals (Jablonka and Avital 2001), and produced a review which reveals that epigenetic inheritance in the narrow sense—the transmission of gene expression patterns through meiosis—can last up to three generations in humans and up to eight in other animal taxa (Jablonka and Raz 2009).

But there is a second, and equally important kind of reply. This is to question whether stability is an appropriate requirement for evolutionary significance. To reiterate the point we made in Sect. 3.1, the role of a theory of heredity in evolutionary theory is to specify how the phenotypes of parents are related to the phenotypes of offspring. This is the role played by a Mendelian account of heredity in conventional population genetics and quantitative genetics. So in one very important sense of 'evolutionary significance' we already know that extragenetic inheritance is significant: if it is left out of an evolutionary model then the model will give inaccurate predictions about the evolutionary trajectory of the population. This point is already well appreciated in the population genetic literature on parental effects (Wade 1998).

Another reason not to accept that epigenetic inheritance systems must be stable across many generations to be of evolutionary significance is that their evolutionary significance may lie precisely in their relative instability. Because organisms have to cope with fluctuating environments as well as stable ones, inheritance systems may serve their collective purpose best if they are situated on a continuum between stability at the one end and induced malleability at the other (Badyaev 2009; Lamm and Jablonka 2008).

5 Epigenetics in biomedicine

An increasing body of evidence supports a role for epigenetics in disease susceptibility. Interaction with the environment may exert a major influence on health and disease in humans mediated by epigenetic mechanisms of gene expression. For example, the environment of the mother can affect the offspring's phenotype through the in utero transmission of epigenetic information. Such influences, often through epigenetic alterations of the genome, have been shown to influence both the susceptibility to the and pathogenesis of many human diseases (see for example Bell and Beck 2010; Jirtle and Skinner 2007; Petronis 2010). The medical importance of epigenetics has played a significant role in overcoming resistance to recognizing a phenomenon that adds unwelcome complexity to the consensus views of heredity and evolution established by the modern synthesis.

According to the Fetal Programming Hypothesis the human fetus reacts with vascular, metabolic and endocrine adaptations to circumstances in its environment. It is thought that nutritional or hormonal factors in the intrauterine environment induce epigenetic changes that affect the trajectory of prenatal development. Human infants who are exposed to under- or malnutrition in the womb and then encounter an abundance of food later in life develop obesity, cardiovascular disease and other metabolic disorders because the current environment was not predicted by the uterine environment (Bateson et al. 2004; Bateson and Gluckman 2011; Gluckman and Hanson 2005a, b; Gluckman et al. 2007, 2009). It has been proposed that the observed plasticity in developmental trajectories is achieved through the altered expression of key regulatory genes that regulate cell number and differentiation early in development, and which can permanently reset the levels of activity of many physiological homeostatic mechanisms. These epigenetic processes are induced by environmental cues mediated by the placenta. It has been shown that particular maternally imprinted genes are targeted in fetal programming through the omission of epigenetic marks in certain tissues. Other genes that are normally not imprinted, however, can also be the target of selective activation or silencing (Godfrey et al. 2011).

The interpretation of such effects as resulting from adaptive developmental plasticity has led to them being labeled 'Predictive Adaptive Responses' (PARs). PARs are evolved responses to environmental cues that shift developmental pathways to modify the phenotype in expectation of a particular later environment. These changes may only manifest their adaptive effect later in life. The advantage of such a plastic strategy crucially depends on the accuracy of the forecast of the postnatal environment (for a review of this work, see O'Malley and Stotz 2011). A thrifty phenotype with a high ratio of fat cells versus muscle cells, a highly efficient metabolism designed to make the most of a meal, and changed appetite and exercise regulation may have clear advantages in an environment with poor nutritional supply, but would likely lead to highly increased weight gain and an increased risk of associated diseases in an environment with an overabundance of high-fat food. Such a scenario has been dubbed the "Environmental Mismatch Hypothesis" (Gluckman et al. 2005).

This section highlights the important implication of epigenetics not just for theoretical considerations that are interesting to theoretical biologists, but also for much more pressing and practical matters. The same reason why epigenetics may matter in evolution may make it particularly interesting to health professionals: its inducibility through environmental signals renders it potentially more susceptible to medical intervention than disease due to genetic mutations. For instance, the potential for finding epigenetic causes of obesity and other metabolic diseases promises increased chances of medical and public-health intervention. "Knowledge of these pathways and their adaptive origins may open up possibilities for both the prevention of gene expression pathways in the fetus and the correction of already programmed, developmental responses to early cues" (O'Malley and Stotz 2011, p. 6).

6 Conclusion: goodbye to nature versus nurture?

Waddington introduced the term "epigenetic" in support of his vision of the future of biology, one in which the study of heredity would be reintegrated with the study of development, and in which this combined understanding would have implications for the theory of evolution. While the meanings of the term "epigenetic" have multiplied in the ensuing seventy years, all of them retain some connection with that original project and in many ways Waddington's vision has proved to be correct.

But the ideas and results reviewed in this paper have a still broader significance, one that explains why interest in, and enthusiasm for, epigenetics goes far beyond the disciplines directly concerned with the study of development and evolution. Epigenetics seems to transgress the boundary between nature and nurture, and thus to offer new possibilities to those who have always regarded that distinction with suspicion.

In an attempt to uncover the underlying "nature" of organisms, molecular biology has instead revealed the interdependence of organism and environment. Factors outside the gene not only activate, they differentially select and they create biological information. The basis of biological specificity is distributed between coding sequences, regulatory machinery, and the broader developmental niche. Many of the factors involved in genome regulation are highly context-sensitive, which allows them to relay environmental information to a reactive genome that has evolved to let environmental inputs play an instructive role in the determination of phenotypes. The overall picture is, as we have argued above, one of molecular epigenesis.

Epigenetics and related developments have proved equally disruptive to traditional conceptions of "nurture." Developmental plasticity—the ability of organisms to modify physiological, morphological or behavioral phenotypes in response to their environments—shows that evolutionary design is potentially as relevant to understanding labile, variable phenotypes as to understanding fixed and universal ones. The study of exogenetic heredity reveals that the developmental environment is as open to evolutionary explanation as the genes that interact with that environment. Much of the new science of nurture adopts a reductionistic research strategy, tracking both the process of nurture and its effects down to the molecular level, and an integrative explanatory strategy, where these effects are explained by and integrated into the wider organism in which they take place.

Some authors have argued for the retention of the nature-nurture divide as both an ontologically and epistemically useful distinction between systems of inheritance (Kronfeldner 2016a, b). We don't argue against the usefulness of fruitful distinctions; to the contrary. But we dismiss the idea that they will neatly fall into such a single dichotomy created by two classes of developmental resources. There are genetic, epigenetic and exogenetic resources, but none of them can be identified by a single role in development or a unique way of transgenerational transmission. None of them just exist (as the term "nature" suggests), but is like the others an outcome of a process. In this vein Oyama (2002) suggested to treat nurture

as this process of development, and nature as its product at each stage of development, or the life cycle as a whole.

In a world where the environment is an essential component of the evolved developmental system, and heredity is a mechanism for stability and resemblance as well as plasticity and difference, the distinction between nature and nurture seems to have finally past its used-by date.

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