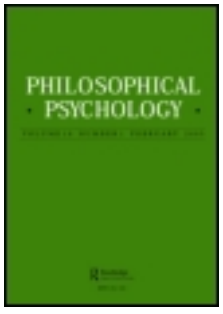

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The Nurture of Nature: Hereditary Plasticity in Evolution

Ehud Lamm and Eva Jablonka

The dichotomy between Nature and Nurture, which has been dismantled within the framework of development, remains embodied in the notions of plasticity and evolvability. We argue that plasticity and evolvability, like development and heredity, are neither dichotomous nor distinct: the very same mechanisms may be involved in both, and the research perspective chosen depends to a large extent on the type of problem being explored and the kinds of questions being asked. Epigenetic inheritance leads to transgenerationally extended plasticity, and developmentally-induced heritable epigenetic variations provide additional foci for selection that can lead to evolutionary change. Moreover, hereditary innovations may result from developmentally induced large-scale genomic repatterning events, which are akin to Goldschmidtian "systemic mutations". The epigenetic mechanisms involved in repatterning can be activated by both environmental and genomic stress, and lead to phylogenetic as well as ontogenetic changes. Hence, the effects and the mechanisms of plasticity directly contribute to evolvability.

Keywords: Epigenetic Inheritance; Genome Organisation; Macroevolution; Natural Genetic Engineering; Richard Goldschmidt

'Hereditary plasticity' sounds like a contradiction in terms, a category mistake. Taking the view of heredity that dominated the last century, what is plastic, is, by definition, not hereditary, because plasticity refers to individual ontogeny, to the ability of a single genotype to develop several different phenotypes depending on environmental/developmental conditions. During the long and stormy history of the nature/nurture debate, the relationship between hereditary/genetic inputs and

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environmental/developmental inputs has been under scrutiny, and the supposed dichotomy between them, as well as their distinctness, was questioned. Many biologists, psychologists and sociologists (e.g., Gottlieb, 1976, 1992; Oyama, 1985), argued convincingly that within an individual's ontogeny, genetic inputs and environmental inputs interact, and it is this developmental interaction that constructs the phenotype. The critics used the interactive developmental perspective to show the problematic nature of terms such as 'instinct' (Gottlieb, 1992; Lehrman, 1953), 'innateness' (Griffths, 2002; Mameli & Bateson, 2006), and 'genetic program' (Fox-Keller, 2000; Lewontin, 2000). They showed that individual development provides a unifying framework, in which a separation between nature and nurture makes no sense.

We want to approach this issue from the complementary perspective—that of heredity and evolution. We argue that the traditional distinctions between evolution–heredity on the one hand and development–plasticity on the other hand, are breaking down, at least for some sets of processes and problems. Heredity may be developmentally constructed, and this has far reaching effects on our concepts of heredity and evolution (Jablonka, 2007; Jablonka & Lamb, 2007a, b). In this article, we shall focus (i) on the developmental origins of heritable epigenetic variations, which introduce a temporal, trans-generational dimension to developmental plasticity; (ii) on the role of epigenetic control mechanisms in the generation of macroevolutionary innovations. Not only heredity, but evolvability as well, may have epigenetic, developmental aspects.

Before we develop our arguments, we would like to position our approach within the modern framework of developmental evolutionary biology.

1. The Evo-Devo synthesis

The relationship between development and evolution has recently become the focus of evolutionary studies. The emerging synthesis between development and evolution, known as 'Evolutionary Developmental Biology' or Evo-Devo, focuses on the processes of evolutionary innovation (Müller & Newman, 2005), on the constraints and generic properties of developmental systems (Hermisson & Wagner, 2004), on comparative studies of developmental genes with major effects (Carroll, 2005), on the architecture of genetic-developmental networks (Davidson, 2006), and on the evolution of the ability to develop and learn (Gilbert, 2003). From the Evo-Devo perspective, in order to explain the evolution of a morphological, physiological or behavioral trait, it is necessary to explain the developmental processes that contribute to its construction during ontogeny. Whatever the origin of a new variation, it must become integrated into a network of developmental interactions: its expression, its modifiability, and the scope of its effects depend not only on its own intrinsic nature but also—and often much more—on the regulatory structure of the network in which it is integrated. Processes leading to developmental flexibility and sensitivity to environmental variations on the one hand (plasticity), and to the buffering of

environmental and genetic 'noise' on the other hand (canalization), are therefore important subjects of research in Evo-Devo.

The focus on plasticity and canalization and the processes underlying them was central to the views of Waddington (e.g., Waddington, 1957) and Schmalhausen (1949), but was peripheral to the interests of most other evolutionary biologists until recently. This developmental perspective on evolution has now been developed and extended by West-Eberhard (2003), who suggested it as an integrated framework for evolutionary theory. The focus of enquiry and the starting point of this approach are the integrated phenotype, its development, and its responsiveness to the environment. An adaptive novelty begins as a new developmental response to a new input—a new mutation, or, more commonly, a novel, recurrent environmental-inductive change. The phenotypic response to the novel input leads to the restructuring of developmental units: the deletion, amplification, temporal, and spatial re-organization of body parts, stages in the life-cycle, etc. Following this phenotypic adjustment (or *phenotypic accommodation*) to the new input, genetic changes that simulate, facilitate, complement, or ameliorate the effects of the phenotypic accommodation may be selected, a process that West-Eberhard calls *genetic accommodation*. The genetic variation selected for (or against) can affect the focal trait itself or its side-effects.

The processes that underlie plasticity and evolvability seem to lead to conflicting consequences, and involve selection at different levels. Plasticity is defined in terms of the potential of a single genotype to generate several *different* phenotypes. According to West-Eberhard (2003), plasticity is:

> The ability of an organism to react to internal or external input with a change in form, state, movement, or rate of activity. It may or may not be adaptive (a consequence of previous selection). Plasticity is sometimes defined as the ability of a phenotype associated with a single genotype to produce more than one continuously variable alternative form of morphology, physiology and/or behaviour in different environmental circumstances (Stearns 1989). It refers to all sorts of environmentally induced phenotypic variation (Stearns 1989). Plasticity includes responses that are reversible and irreversible, adaptive and nonadaptive, active and passive, and continuously and discontinuously variable. (p. 33)

Plasticity is therefore, defined within the framework of the life cycle of a single individual organism. It can be said to be a property exhibited by an individual's development.

Evolvability, in contrast, is a property of lineages or clades, not of individuals, because it is defined in terms of the potential for evolutionary change. Evolvability was defined by Kirschner and Gerhart (1998) as "an organism's capacity to generate heritable phenotypic variation" (p. 8420). Wagner distinguishes between two related but nonidentical meanings of evolvability: (i) a system is evolvable if its properties show heritable genetic variation and if natural selection can thus change these properties; (ii) a system is evolvable if it can acquire novel and adaptive functions through genetic change (Wagner, 2005). The difference between the two notions of evolvability is that the second focuses not just on any heritable and

selectable variation, but on heritable and selectable variations that also affect the developmental system in a way that leads to real innovation.

The structure of the developmental system as well as that of the hereditary system is of central importance within this framework. The basic organization of biological systems is hierarchical and modular, that is, they are made up of more or less autonomous developmental units, which are delimited by developmental switches. There are degrees of modularity and of integration between modules, but in general, it seems that a high degree of developmental modularity is associated with increased evolvability, since the combinatorial possibilities are greater than those of a system with limited modularity (Wagner, 2005; West-Eberhard, 2003). Statistical analysis of the modular architecture of genetic networks suggests that modules are mostly conserved during evolution, with intermodule connections serving as a source of evolutionary innovation (reviewed in Koonin & Wolf, 2006). It should be noted, however, that the evolutionary origin of modularity remains an open question and does not seem to be the result of direct selection for evolvability (Wagner, Mezey, & Calabretta, 2005).

Plasticity and evolvability clearly differ with respect to the level at which natural selection operates. Moreover, it may be argued that plasticity reduces evolvability: by allowing an organism to survive in an environment for which it is not adapted plasticity may reduce the selection pressure leading to evolutionary change. Furthermore, plasticity seems to conceal the differences between genotypes from the direct scrutiny of selection, thus preventing the selection of better-adapted genotypes. However, as we show below, the same molecular mechanisms may underlie both plasticity and evolvability; the two processes are, we argue, complementary and continuous.

The role of epigenetic inheritance and epigenetic control mechanisms in evolution is rarely discussed within the framework of Evo-Devo. However, epigenetic developmental control mechanisms are directly related to the generation of heritable variations in two important ways: (i) epigenetic variations generate some of the variations that are the raw material for natural selection and introduce new foci of selection, and (ii) systemic epigenomic (genetic and epigenetic) variations lead to some types of genome repatterning and macroevolutionary changes. We argue that the incorporation of these mechanisms within an evolutionary framework extends the notions of plasticity and evolvability, and affords new interpretation of evolutionary phenomena.

2. Epigenetic Inheritance: Transgenerationally Extended Plasticity

The types of plastic responses on which we focus in this article are persistent phenotypic responses—responses, which once induced, can last for a long time: for a significant portion of the life-time of an individual or throughout life, or for generations. Examples of persistent ontogenetic variations are the kind of plastic responses associated with the processes of cellular differentiation in multicellular

organisms, where different cell types are generated (e.g., skin cells, kidney cell, liver cells) from the same genotype, and once generated, are very stable and unlikely to change. Another well-known example is that of the inactivation of the X chromosome in female mammals: in different somatic cells of (eutherian) mammalian females, one of the X chromosomes, either the paternally derived or the maternally derived, becomes stably inactivated (Lyon, 1961). There are many other types of stable, life-long changes in the attributes of the phenotype, including stable changes in behavior that arise as a result of various inputs into development. For example, susceptibility to diseases and obesity is affected by early maternal inputs to the embryo's development and by postnatal inputs, in both humans and rats (Gluckman & Hanson, 2005; Gluckman, Hanson, & Beedle, 2007). In plants, vernalization is a good example for a long-term change that is induced by a developmental input: exposure to the prolonged cold of winter results in the acquisition of the competence to flower in the spring (Henderson & Dean, 2004). In all cases of plasticity, an organism with the same genotype can develop along different trajectories, depending on the inputs it receives.

Environmentally-induced maternal effects are examples of plasticity, which is extended beyond one generation. The term refers to environmentally-induced changes in the mother that influence gene expression in the offspring. For example, in many insects, the photoperiod, temperature, or host availability experienced by an ovipositing female will determine the probability of diapause in her offspring (Mousseau & Fox, 1998). Environmentally-induced maternal effects are also known in plants, were they can affect seed, seedling, and adult characteristics of offspring (Roach & Wulff, 1987). Maternal behavior has obvious effects on progeny characteristics, for example, the level of resistance to stress (Avital & Jablonka, 2000). There are also paternal effects, both physiological and behavioral, for example, when the father contributes to the offspring postnatal development as in song birds. Parental effects—both maternal and paternal—can be seen as responses to inputs into both parent and offspring development, with the effect on offspring mediated by the effect on the parent. Parental effects are manifestation of developmental plasticity, and are often, through not invariably, adaptive (Mousseau & Fox, 1998).

What are the developmental mechanisms that can underlie such persistence of plastic alternative responses? Can plasticity be extended beyond the offspring generation, for two, three, or even more generations? The concept of *epigenetic inheritance* refers to plastic responses that persist over several, possibly many generations. Environmentally-induced parental effects are therefore a special and limited case of epigenetic inheritance. Epigenetic inheritance occurs when environmentally-induced and developmentally-regulated variations, or variations that are the result of developmental noise, are transmitted to subsequent generations of cells or organisms (Jablonka & Lamb, 2005, 2007a). The term epigenetic inheritance is used in a broad sense and in a narrow sense. The broad usage includes cellular epigenetic inheritance through mitotic or meiotic cells, as well as information-transfer that by-passes the germline, for example, through early developmental (prenatal and early postnatal) inputs that depend on physiological feedback loops that regenerate previous

developmental conditions (e.g., hormonal and neural conditions). An example is the persistence of a male-biased sex-ratio in some Mongolian gerbil lineages, which is the result of interactions between testosterone concentrations in utero, maternal behavior, and offspring development, which re-creates in pregnant female offspring the hormonal conditions that they themselves experienced in the uterus (Clark & Galef, 1995). Another example is induction of a stress-sensitive phenotype in rats by altered maternal care (reduced licking and grooming) during a sensitive period. This phenotype is perpetuated in the lineage because when the daughters become mothers, they reproduce the early maternal care style of their mothers (Meaney, 2001; Weaver et al., 2004, 2005). Gluckman and his colleagues (Gluckman et al., 2007) have argued that the new obesity epidemic in human populations, which is driven by a change in diet, is affected by events that happened in the parental generation (and possibly in earlier generations as well). In all these cases, alternative phenotypes can persist for several, possibly many, generations. Inputs from the external environment that depend on the activities of the organism and are to a large extent the result of such activities (transgenerational ecological niche-construction, see Odling-Smee, Laland, & Feldman, 2003) often contribute to such trans-generational transmission of alternative phenotypes. Socially learnt activities are important inputs for the reconstruction of niches in social animals; socially learnt behaviors can persist in a group of animals for many generations and form traditions (Avital & Jablonka, 2000), and in our species, symbolically encoded communication and learning construct the persistent aspects of our society and culture (Boyd & Richerson, 2005; Jablonka & Lamb, 2005). However, as the earlier examples illustrate, recreating the developmental inputs causing the plastic change, or other plasticity-inducing developmental inputs, is not the only mechanism leading to persistent plastic responses.

A more restricted usage for epigenetic inheritance refers to the *cell-to-cell* transmission of variations that are not the result of differences in DNA sequence. This occurs during cell division in prokaryotes and mitotic cell division in eukaryotes, and during the meiotic divisions in the germline that give rise to sperm or eggs. Somatic cell heredity is manifest in the stability of different phenotypes of determined and differentiated cells within the same multicellular body. However, cellular inheritance also includes transmission through the germline, following meiotic divisions.

Jablonka and Lamb (2005) characterized several types of cellular mechanisms that underlie cellular epigenetic inheritance, mechanisms referred to as *epigenetic control mechanisms*. They include: (i) *Self-sustaining metabolic loops*, which are dynamic regulatory circuits that maintain cellular patterns of activity of genes and their products. The transmission of the components of the circuit (proteins, RNAs and metabolites) to daughter cells leads to the same patterns of gene activity being reconstructed in them (Ferrell, 2002; Malagnac & Silar, 2003). (ii) *Structural inheritance*, in which pre-existing cellular structures act as templates for the production of similar structures, which become components of daughter cells, for example, prion-based inheritance in fungi (Shorter & Lindquist, 2005), the inheritance of cortical structures in ciliates (Grimes and Aufderheide, 1991), and

the reconstruction of what Cavalier-Smith (2004) calls 'genetic membranes'. (iii) *Chromatin marking*, in which chromatin configurations (that consist of histone and nonhistone proteins that are noncovalently bound to DNA, and small chemical groups, such as methyls, that are covalently bound directly to DNA) are reconstructed in daughter cells (Henikoff, Furuyama, & Ahmad, 2004). (iv) *Heritable RNA-mediated variation in gene expression*, in which transcriptionally silent states are maintained through repressive interactions between small RNA molecules and the mRNAs or DNA to which they are partially complementary (Meister & Tuschl, 2004). The state of gene expression is maintained in daughter cells that inherit the small RNA molecules. Current studies suggest that the chromatin marking and the RNA-mediated epigenetic inheritance systems play a particularly large role in intergenerational inheritance in sexual multicellular organisms. As we argue in the next section, the epigenetic control mechanisms underlying chromatin and RNA-mediated epigenetic cellular inheritance also play a central role in the generation of systemic mutations that may lead to macroevolution.

Is epigenetic inheritance an aspect of developmental plasticity or an aspect of heredity? It is clear that one needs to treat it as both, and the perspective one chooses is dictated by the biological question one asks. Epigenetic inheritance can be a direct agent of evolutionary change, for the frequency of heritable epigenetic variation can change in a population and such variations may accumulate. Moreover, epigenetic inheritance may accelerate the process of genetic accommodation, and often an adaptation or an accidental divergence process may start with an epigenetic heritable variation, which later becomes accommodated genetically. When the direct effects of epigenetic inheritance on evolutionary change are the focus of attention, the heredity aspect of the phenomena is most important. On the other hand, if we are interested in the evolution of epigenetic inheritance as an adaptive strategy, the preferred focus is on how it leads to extended plasticity (Jablonka & Lamb, 2005). A single perspective is both too limiting and potentially misleading.

The hereditary aspect of plasticity means that when heredity is developmentally constructed, as it is in the case of epigenetic inheritance, 'nurture' (inputs from the environment that affect ontogeny) participates in the construction of 'nature' (heredity). This is a Lamarckian mode of inheritance, which for a long time was considered a biological impossibility, and was explicitly excluded from the modern synthesis. We suspect that the historical stigma associated with it is the main reason for its reluctant incorporation within the developing Evo-Devo Synthesis.

3. Epigenetic Control Mechanisms in Evolution: A Source of Systemic Mutations

The relationship between plasticity and evolvability is illuminated from an additional angle if we consider developmentally-controlled DNA rearrangements. The differentiation of some cell-types, for example immune system cells that undergo targeted rearrangements during development, the polytenization

(repeated replication of chromosomes without separation of daughter chromatids resulting in multi-stranded giant chromosomes) of the trophectoderm in female mammals, the many cases of polyploidization (replication of chromosomes not followed by cell division resulting in multiple number of chromosomes in a cell) of somatic tissues in plants and insects, and developmentally-regulated gene amplification and deletions, are all well-known examples in which the developmental processes of determination and differentiation occur via genomic rearrangements (Jablonka & Lamb, 1995). A survey of different taxa suggests that developmentally-regulated genome rearrangements are an ancient feature of eukaryotes, and are brought about by epigenetic control mechanisms (Zufall, Robinson, & Katz, 2005). For example, chromatin marking systems, involving histone modifications and RNA silencing, guide the DNA rearrangements in the immune system of mammals (Busslinger & Tarakhovsky, 2007). In the normal life cycle of ciliates, the (somatic) macronucleus is extensively rearranged (noncoding segments are deleted, coding segments are amplified, etc.), a process directed by RNA-mediated chromatin marking mechanisms (Mochizuki & Gorovsky, 2004). It is interesting to note that sequence-specific information is transferred to the new zygotic macronucleus from the parent macronucleus via RNA-mediated epigenetic processes, an adaptive process which is part of the normal life cycle of cilates, and which provides an extreme form of transgenerational adaptive plasticity (Mochizuki & Gorovsky, 2004).

As Shapiro (1999) has noted, the existence of a cellular genetic engineering kit in all existing prokaryotic and eukaryotic cells that enables cutting, sewing, and reorganizing the genome during development, suggests that these same developmental mechanisms may also lead to extensive and rapid evolutionary alterations under some conditions. The plasticity mechanisms of ontogeny may therefore operate in phylogeny, and can be considered as evolvability mechanisms. We suggest that these repatterning mechanisms, that were discovered in the context of development and are mechanisms of epigenetic control, underlie the systemic mutations suggested by Richard Goldschmidt, and that they lead to these systemic epigenomic (epigenetic and genetic) alterations in conditions of stress.

Goldschmidt (1940) applied the Evo-Devo-like notion of *norm of reactivity*, according to which "the genotype is . . . the inherited norm of reactivity to the ensemble of conditions which may influence phenotypic expressions" (p. 250), to the discussion of macroevolutionary change. Goldschmidt observed that the range of modifiability of one species under conditions of developmental stress is on a similar scale as the range of phenotypic differences between related species under natural conditions (p. 253); differences which he argued are the result of *systemic mutations*—a term by which he meant chromosomal repatterning. He observed that new species are usually chromosomally different from their parental species, and suggested that evolution above the species level usually involves such repatterning. McClintock suggested that genomic repatterning occurs under conditions of stress and that transposable elements play a major role in this process (McClintock, 1984).

In order to re-evaluate Goldschmidt's and McClintock's ideas about systemic mutations, we need to establish that processes of chromosomal and genomic repatterning are indeed common during evolution, uncover the conditions under which such repatterning takes place, and identify the cellular mechanisms that bring it about. Contemporary experimental results show that stress can lead to large-scale genomic restructuring events (Jablonka & Lamb, in press). For example, nutritional stress causes epigenetic and genetic changes in r-RNA genes and repetitive sequences in flax (Cullis, 2005), heat shock causes similar epigenomic stress in *Brassica* (Waters & Schaal, 1996), and hydrostatic pressure causes genome wide changes in methylation patterns in rice (Long et al., 2006). Radiation seems to induce both genetic and epigenetic genome-wide instabilities that last for several generations in both animals and plants (Dubrova, 2003; Moliner, Ries, Zipfel, & Hohn, 2006). Transposable elements—usually relatively silent—are activated as a result of various stresses, such as wounds and pathogen attacks, just as McClintock suggested, and the activity is in many cases restricted to germ cells, and hence transgenerational (reviewed in Kidwell & Lisch, 2001). Following McClintock, Kidwell and Lisch argue that while the evolution of this behavior of transposable elements may be attributed to the benefits it provides to the transposable elements themselves (which increase their chance of survival into the next generation of offspring of the stressed individual), the increased genomic variation may be evolutionarily advantageous to the stressed host plant. In microorganisms, stress leads to specific responses, such as the SOS response (a postreplication DNA repair system that allows bypassing of lesions or errors in the DNA) that increases variations, and Radman (1999) argued that this system evolved not only to patch up a damaged genome but also because it increases evolvability in an adaptive manner—mutations happen just when an evolutionary response to catastrophe is required (Caporale, 2003).

Genomic stresses due to hybridization and polyploidization are frequent in plant evolution. In most flowering plants (70–90%) speciation through hybridization has occured, and in some clades this is a recurrent process. Studies of the effects of genomic stress caused by auto- and allo-polyploidization indicate that the genomic reorganizations exhibit repeatable, wide-ranging, yet specific, genomic, and chromosomal changes that involve massive epigenetic changes involving DNA methylation and histones modifications, transcriptional and posttranscriptional gene silencing through the RNAi system, as well as targeted genetic changes (see, e.g., Comai et al., 2000; Levy & Feldman, 2004; Mittelsten Scheid, Afsar, & Paszkowski, 2003; Pikaard, 2000, 2001; Rapp & Wendel, 2005). Polyploidy and hybridization are not restricted to flowering plants and were also important in the phylogeny of bryophytes (Natcheva & Cronberg, 2004), parthenogenetic fish, and some groups of rodents and frogs (Arnold, 2006). These events and the wide-ranging epigeneomic changes that accompany them, therefore underlie speciation in many taxa. They cannot be considered as having a minor importance in evolutionary history, and are relevant to the recent discussions about the universal applicability of the Tree of Life metaphor for describing the relationship between species and the significance of

hybridization and horizontal gene transfer in speciation events (Doolittle & Bapteste, 2007; Goldenfeld & Woese, 2007).

In animals, behavioral stress can lead to rapid heritable morphological changes. This was observed by Belyaev and co-workers in their work on the domestication of silver foxes, and later the domestication of other mammalian species (Belyaev & Borodin, 1982; Belyaev, Ruvinsky, & Trut, 1981a; Belyaev, Ruvinsky, & Borodin, 1981b; Jablonka & Lamb, in press; Popova, 2006; Ruvinsky, Lobkov, & Belyaev, 1983a, 1983b, 1986; Trut, Plyusnina, & Oskina, 2004). The neuro-endocrine system is destabilized under domestication, and this seems to lead to heritable changes in gene expression, as well as an increase in the frequency of microchromosomes (Belyaev, Volobuev, Radjabli, & Tryt, 1974). A heritable effect of hormonal stress on extensive epigenetic heritable variations was also observed in rats. Anway, Cupp, Uzumcu, and Skinner (2005), Anway, Memon, Uzumcu, and Skinner (2006a), Anway, Leathers, and Skinner (2006b), and Crews et al. (2007) injected pregnant females with vinclozolin, and showed that the abnormalities induced in male offspring were inherited through the male line for at least four generations. They found several different DNA sequences that had altered methylation patterns in the F1 males, and these were transmitted from the F1 to the F3 generation.

Our understanding of the mechanisms involved in hereditary changes, especially under stress, is challenging the accepted dichotomy between plasticity and evolvability and many of the related terms and assumptions that this dichotomy suggested. For example, the assumption that evolution is driven solely or mainly by 'random' mutations is misleading, and the term itself is used in different ways that should be distinguished and questioned (Jablonka & Lamb, 2007a). The assumptions about random mutations are that: (i) '*Random*' *mutations are not highly targeted*, i.e., identical (or very similar) changes in DNA do not occur in many different individuals within a population. However, as we have seen, programmed response to genomic stress, as seen in some cases of polyploidization (Levy & Feldman, 2004), are recurrent and directed to the same genomic and chromosomal regions. The recurrence in this case seems dictated by the nature of these sequences (e.g., their repetitive sequences and transposable elements), which are targets of the epigenetic control mechanisms, and targeting is therefore dependent on the genetic architecture of the parent species, the level of divergence between them, and the direction of the cross. (ii) *Random mutations are not developmentally or environmentally induced*, i.e., identical changes in conditions do not result in identical mutations. However, as the cases we discussed suggest (e.g., the induced mutational changes in flax) this is often not the case under stress. (iii) *Random mutations are not adaptive*, i.e., they do not increase the chances that the individuals carrying them will survive and reproduce. However, there is evidence that the mutational mechanisms that generate certain classes of mutations may be adaptive (Caporale, 2003). Of course, the nature of the mechanisms involved, and the unpredictability of the environmental triggers, cannot guarantee that the variation produced is adaptive, but the processes that give rise to these mutations increase the probability of survival and reproduction as compared to chance mutations alone.

It is possible to see these genomic reorganization processes as part of the processes of phenotypic accommodation, which is in this case, also a process of genetic accommodation. (iv) '*Random*' *mutations are local*: *they do not involve coordinated changes to the genotype*. However, as we saw, large scale genome reorganization, of the type emphasized by Goldschmidt and seen in hybridization, seems to be triggered in stressful conditions. Thus, all the four notions associated with the assumption that all evolutionarily important mutations are 'random' are challenged by recent molecular studies. There is a developmental aspect to evolutionary change, which the assumption about the 'randomness' of mutations fails to acknowledge.

'Randomness' is just one concept that needs to be reconsidered and qualified in the light of an extended perspective on heredity. The ubiquity of epigenetic inheritance and the new information about the origin and nature of genetic variations, problematize all the traditional concepts of evolutionary biology.

4. Conclusions

The nature/nurture dichotomy, which has been shown to be problematic and incoherent in the context of an individual's ontogeny, remains embodied in the notions of plasticity and evolvability, as commonly understood. We argued that plasticity and evolvability, like development and heredity, are mechanistically and conceptually continuous. The very same mechanisms may be involved in both, and the choice of perspective depends to a large extent on the type of problem being explored, and the kinds of questions being asked.

Attention to the mechanisms that underlie both epigenetic changes and genome repatterning highlights the complex relationships between plasticity and evolvability: a continuum from counter-acting processes to complementary ones, based on the very same molecular phenomena. Instead of an unchanging relationship, the epigenetic mechanisms may serve both ontogenetic and evolutionary purposes to varying degrees, and the relationship between the two aspects may change over time. It is possible that the molecular responses that lead to epigenomic repatterning—either to changes in DNA methylation and histone modifications or to DNA rearrangements during stress—were selected to deal with various hazards, including DNA damage, genomic parasites, infections, and physiological (nutritional, chemical, climatic) extremes. However, as in the example of the transposable elements and bacterial SOS systems, the mechanisms may have persisted also because of their variational, evolutionary effect, because of their contribution to evolvability. Hence not only their hereditary and evolutionary effects, but also the evolution of the mechanisms that lead to plasticity-based evolvability may have been intertwined.

The epigenetic mechanisms we discussed lead to evolvability in the two senses discussed by Wagner (2005). The first, simple, meaning—that of adding additional foci for selection is clearly exhibited by epigenetic heritable variation that can be developmentally induced. The second, more radical notion

of evolvability—the ability to produce hereditary *innovations*—was discussed here in the context of developmentally-induced large-scale genomic repatterning, or systemic mutations, which lead to macroevolutionary changes, including speciation. The epigenetic mechanisms involved in repatterning can be activated by both environmental and genomic stress, and lead to hereditary as well as ontogenetic changes.

The focus in this article on the similarity (indeed, the identity) of the molecular mechanisms underlying plasticity and evolvability is compatible with the developmental perspective that highlights the importance of the interactions between different types of inputs to development. The developmental perspective, however, runs deeper, as the examples discussed above show. The inescapable conclusion is that even heredity itself can be, and often is, developmentally constructed.

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