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The evolutionary implications of epigenetic inheritance

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The Modern Evolutionary Synthesis (MS) forged in the mid-twentieth century was built on a notion of heredity that excluded soft inheritance, the inheritance of the effects of developmental modifications. However, the discovery of molecular mechanisms that generate random and developmentally induced epigenetic variations is leading to a broadening of the notion of biological heredity that has consequences for ideas about evolution. After presenting some old challenges to the MS that were raised, among others, by Karl Popper, I discuss recent research on epigenetic inheritance, which provides experimental and theoretical support for these challenges. There is now good evidence that epigenetic inheritance is ubiquitous and is involved in adaptive evolution and macroevolution. I argue that the many evolutionary consequences of epigenetic inheritance open up new research areas and require the extension of the evolutionary synthesis beyond the current neo-Darwinian model.

1. Introduction

Thirty years ago, in 1986, Karl Popper delivered the Medawar Lecture to the Royal Society. It was titled 'A new interpretation of Darwinism', and it was a contentious lecture [1]. This was not only because Popper suggested that the then-current version of Darwin's theory required serious revision, but also because he was deliberately provocative, adhering to his conviction that only sharp critique can awaken colleagues from their intellectual slumbers and stimulate discussions that lead to scientific progress. There is an interesting link between Popper's 1986 lecture and the topic of this issue of *Interface Focus*: Popper raised some of the very same points that the advocates of an extended evolutionary synthesis are putting forward today, and suggested that the then-current version of Darwinism—what was and is still called the Modern Synthesis (MS)—needed to be revised.

Although Popper's call for a change was not very effective, his lecture shows that discontent with the MS version of evolution is not new. The MS was forged by the middle of the twentieth century: one of the historical landmarks was the post-war Princeton Conference on Genetics, Palaeontology and Evolution held in 1947, which celebrated the successful unification of Darwinian ideas about natural selection with Mendelian genetics and palaeontology [2,3]. Of course, the MS has been updated and changed since then, but there are several aspects that right from the early days have been systematically downplayed or explicitly excluded [3]. One issue that was recognized but downplayed was the role of plasticity in evolution: Waddington's ideas did have some early impact, especially in Great Britain, but people lost interest very quickly [4]; similarly, there was little interest in the active role of the organism in the construction of its own selection regime and the evolutionary feedbacks that such niche construction generates, and little attention was given to the constraints and affordances imposed on phenotypic variations by the processes of development, or to the role of group selection (reviewed in [5]). What was explicitly excluded was soft inheritance, which Ernst Mayr, one of the architects of the Synthesis, defined as: 'gradual change of the genetic [hereditary] material itself, either by use or disuse, or by some internal progressive tendencies, or

through the direct effect of the environment' [6, p. 15]. Mayr regarded 'genetic' and 'hereditary' material as synonymous. He firmly believed that developmental changes occurring at the individual level cannot be passed on to the next generation and lead to cumulative evolutionary change. For Mayr, as for most of the MS architects and their followers, this exclusion was one of the defining features of the synthesis. In his discussion of the importance of the synthesis between genetics and Darwinian theory, Mayr wrote: 'It was perhaps the greatest contribution of the young science of genetics to show that soft inheritance does not exist' [6, p. 17]. Before I discuss this excluded possibility, I want to briefly consider Popper's challenges of 30 years ago.

His first challenge was the argument that evolutionary analysis should start by considering phenotypic variability and phenotypic adjustment, not random mutation. Popper was challenging the mantra that evolution amounts to 'natural selection of random mutations', a mantra which, although not strictly wrong, was, in his view, misleading. He argued that living organisms are active *agents*; they have goals (the ultimate evolutionary goal being reproduction) which they strive to fulfil through their activities. When the conditions of life change, organisms do not wait passively for a liberating mutation—they do what they can to cope, including changing where and how they live. This coping, this phenotypic adjustment, which can be the response to a new mutation as well as to a new change in external conditions, is far from random. It is such goal-directed developmental responses, Popper suggested, *not* random mutations that should be the point of departure of an evolutionary explanation.

Following Waddington, who had obviously influenced him [1], Popper argued that active phenotypic adjustments to challenges (or 'phenotypic accommodations', as we would call them today) were the outcome of changes in the activity of genes which were then selected in the new challenging regime. Popper would have been happy with West-Eberhard's suggestion that 'genes are followers not leaders in evolution' [7, p. 20], or, more generally, with 'phenotype first' views of evolution [8,9]. In 1994, focusing on the evolution of behaviour, he wrote: 'The main thing in my form of the theory is that mutations can succeed only if they fall in with an already established behavioural pattern. That is to say, what comes before the mutation is a behavioural change, and the mutation comes afterwards' [10, p. 59]. The idea that changed behaviour may initiate evolutionary change was not original, of course. It goes back to Baldwin, Morgan and Osborn at the very end of the nineteenth century [11], and Popper was aware that Waddington had developed these ideas within the framework of Mendelian genetics [12]. However, the evolutionary significance of the Baldwin effect and of genetic assimilation was downplayed, for example, by Simpson [13], and this position has been uncritically parroted by biologists ever since (for a notable exception, see [14]).

The second of Popper's suggestions was that the non-random, goal-directed processes that lead to the organism's phenotypic adjustments involve *developmental selection*. Internal processes generate variation, which is followed by processes of selection or stabilization at the ontogenetic level.

Popper's third suggestion was that developmental selection may lead to between-generation inheritance not only through genetic assimilation, but also through feedbacks between the soma and the germ line. How this happened was not entirely clear to him, but he was very excited by Ted Steele's hypothesis that selected somatic mutations in the immune system can affect the germ line through the reverse transcription of RNAs that were abundantly expressed during the immune response [15]. It is necessary to qualify the meaning of 'randomness' in immune system variations, because the mutations generated during the induction of the immune response are (evolutionarily) targeted to certain (hypervariable) regions, which, when translated, bind the antigen. Nevertheless, a strong element of stochasticity remains, and this allows the system to respond to the unexpected. For Popper, what was important in Steele's hypothesis was the combination of developmental, intra-organismal selection of stochastic variations and the intergenerational transmission of some selected variants, which resulted in a feedback between the effects of developmental selection in individuals and natural selection in populations.

Popper believed that incorporating developmental selection within evolutionary explanations reinforced Darwin's perception of the centrality of selective processes in evolution. Selection is not just natural selection in the classical sense, but any differential stabilization and amplification process occurring between and within organisms, with the different selection processes interacting. Hence, as he stressed, his ideas did not assume naive, directed 'Lamarckian' processes, although the outcome of the processes he envisaged does simulate Lamarckian evolution.

There were many problems with the evolutionary ideas Popper advanced in his 1986 lecture, and I shall not dwell on them here (for detailed discussion, see [1,12,16]). However, his insistence on the agency of organisms and his phenotype-first view of evolution, his focus on developmental selection and the possibility of interactions between within-individual developmental selection and between-individual selection resonate with the ideas developed by evolutionary biologists today [16]. Interestingly, Popper's view was almost identical to that expressed by Jean Piaget in the 1960s and 1970s, although the two men seem to have been unaware of their agreement and did not join forces to sophisticate and promote their point of view [17].

In the light of recent (post-Popper and Piaget) discoveries about epigenetic mechanisms and epigenetic inheritance, we can now take a fresh look at the challenges they and others posed to the MS in the twentieth century. My focus here is on the effect of epigenetic, often partially biased, developmentally generated variations on evolutionary change, which, I argue, requires an extension of the MS.

2. Epigenetics, epigenetic inheritance and epigenetic mechanisms

There are several factors, in addition to similarities in DNA sequence, that contribute to the hereditary similarity between parents and offspring. One is the inheritance of epigenetic variations originating in ancestors. I start with definitions of some epigenetic-related terms (discussed in more detail in [18]), because 'epigenetics' and 'epigenetic inheritance' are used in multiple, not always consistent, ways.

Epigenetics has a wide sense, defined by Waddington, and a narrow sense which pertains mainly to cell memory and cell heredity. In the wide sense, it denotes '…the branch of

biology which studies the causal interactions between genes and their products which bring the phenotype into being' [19, p. 218]. In the narrower, modern sense, it is the study, in both prokaryotes and eukaryotes, of the developmental processes that lead to changes in an organism's state that persist in the absence of the original inducing input (based on [18, p. 393]).

The *epigenetic mechanisms* that can lead to persistent developmental effects in both non-dividing (e.g. brain) and dividing (e.g. stem) cells include self-sustaining cellular metabolic loops; three-dimensional structural templating; chromatin marking through DNA methylation and modifications of histones; and RNA regulatory systems. These epigenetic control and cell memory mechanisms are commonly interconnected, sometimes forming persistent, self-maintaining, cellular networks, although they can, of course, lead to very transient changes. They are also important in the recruitment and regulation of the natural cellular engineering processes that are involved in DNA repair and the control of transposition and recombination [20]. At a higher level of biological organization, these epigenetic mechanisms underlie self-sustaining interactions between groups of cells or between an organism and its environment, which are mediated by physiological (e.g. hormonal) and behavioural means.

Epigenetic inheritance is a component of epigenetics, not a synonym. It refers to the transmission to subsequent generations of cells or organisms of phenotypic variations that do not stem from variations in the DNA base sequence. Transmission can occur during mitotic cell division, and also sometimes during the sexual processes of meiosis and gametogenesis. This latter type of transmission has been called 'gametic epigenetic inheritance' [21]. Mitotic and gametic epigenetic inheritance are mediated by essentially the same epigenetic mechanisms, although different factors and types of regulatory interactions are involved in different cell types.

Between-generation epigenetic inheritance need not, however, involve transmission through gametes. Marion Lamb and I refer to non-gametic, transgenerational, epigenetic inheritance as 'soma-to-soma transmission', which is an umbrella term covering the many ways in which information is transmitted through physiological reconstruction of developmental conditions, or through behaviour, niche construction, language, etc. [18].

For both gametic and soma-to-soma epigenetic inheritance, it is important to appreciate that the way information is 'copied' between generations need not be through a replication process that is blind to the function of the transmitted information ([22,23]; for a recent discussion of this, see [24]). We are all conditioned by DNA replication as *the* mode of information transmission, so we tend to think that all transmission must involve replicative processes. This preconception is wrong: in some types of both gametic and soma-to-soma transmission, inheritance takes place by a reconstruction rather than replication of parental states. For example, a particular chromatin configuration, such as a particular methylation pattern, might initiate a self-sustaining loop that generates a protein or an RNA product that can take part in the establishment and perpetuation of that configuration. Even when the configuration of chromatin is changed or 'erased' during development (e.g. methylation erasure in gametes), the continued presence of the gene product in gametes will lead to the reconstitution of the original configuration in new developmental conditions (e.g. in the embryo). This kind of mechanism may be involved in the transmission through the sperm of small RNAs that lead to hereditary similarity [25]. Alternatively, although most chromatin marks are erased, a fraction of them (e.g. 20%) may be retained as partial marks, which may seed the reconstruction of the full mark during the subsequent developmental conditions. Epigenetic inheritance seems to involve both replicative and reconstructive processes.

Epigenetic inheritance is ubiquitous. Today, no one doubts that this mode of inheritance occurs everywhere—it has been found wherever it was looked for, in all taxonomic groups (for reviews, see [26,27]), and it includes various routes of transmission, including transmission of small regulatory RNAs from soma to germ line, a mode of transmission that seems to vindicate Darwin's pangenesis theory [28]. The fidelity with which epigenetic states are transmitted is condition- and taxon-dependent and is clearly variable. There have been in-depth analyses of particular types of epigenetic inheritance in some model organisms, such as the inheritance of methylation marks in *Arabidopsis thaliana* [29–31], which have shown that there are tens of thousands of differentially methylated CG sites in the genome, and thousands of differentially methylated regions (DMRs). The lower bound of the epimutation rate is 4.46×10^{-4} per CG per generation. However, for most taxa, our knowledge about the rate and causes of epimutation is still rather poor, although the existing evidence suggests that heritable variations in epialleles cannot be ignored if we want to understand phenotypic variability in populations. For this reason, epigenetic inheritance is being taken very seriously in epidemiological studies and in medicine more generally.

But what does epigenetic inheritance mean for our conception of evolution? What new evolutionary questions does it raise? Do we need to change our models? If so, how? What is the conceptual significance of such changes?

3. Evolutionary questions and evolutionary implications

Answers to some of the evolutionary questions raised by epigenetic inheritance can be readily accommodated by the MS version of evolutionary theory, whereas others may require its extension and modification. While the evolutionary origins and the genetic evolution of epigenetic inheritance strategies are non-problematic supplements to the MS, some of the effects of heritable epigenetic variations on evolutionary change challenge the view that non-guided DNA variations are the ultimate source of hereditary variations, and require the amendment of the MS.

3.1. What are the evolutionary origins of the mechanisms behind epigenetic inheritance?

It is not difficult to find the precursors of the various epigenetic mechanisms in multicellular eukaryotes, in unicellular eukaryotes, and in bacteria, where their roles are varied. RNA-mediated inheritance may have its origins in the ancient RNA world, when RNA molecules were central in metabolism, heredity and regulation. In addition, RNA

molecules may have had a role in defence against genomic parasites. Chromatin marking probably originated within the context of chromosome evolution, through selection to ensure the stability of chromosomes and the continuity of expression patterns following cell division; it also seems to have had an ancient defence function—silencing genomic parasites. The self-reconstruction of three-dimensional structures ensures phenotypic stability and continuity of large protein complexes and complex membranes. Similarly, self-sustaining loops ensure phenotypic stability and continuity of gene expression following cell division, so these processes would have been selected (for an overview, see [18, pp. 318–327]). The origins of epigenetic mechanisms are therefore very ancient and related to basic biological maintenance and self-preservation functions. Considering these requires no change in conventional (MS) ways of thinking about evolutionary dynamics.

3.2. Under what conditions is epigenetic inheritance advantageous? How did this type of temporally extended plasticity evolve?

The genetic evolution of epigenetic strategies is related to the evolutionary origins question. Epigenetic inheritance can be seen as a strategy selected because it enables transgenerational plasticity through the selection of the reaction norm, with the family, groups or lineages being the unit of selection. Several models exploring the conditions in which epigenetic inheritance is beneficial have been constructed, and it has been shown that it is advantageous in randomly and regularly fluctuating conditions, when the cycle of changes is longer than the generation time of the individual [32,33]. The most general model accommodating this type of plasticity is that constructed by Rivoire & Leibler [34], which shows that epigenetic inheritance of acquired variations is adaptive under many different environmental conditions. Once epigenetic inheritance is in place, then provided its fidelity is not too low, evolution operating on this axis can be cumulative.

A situation that has been given less attention than the evolutionary advantages of epigenetic inheritance when environmental conditions fluctuate is the possible benefit of epigenetic priming. If gene expression depends on the presence of an inducer, but expressivity is heritably altered by past inductions, epigenetic inheritance of primed states may often be beneficial because it does not lead to inappropriate responses. Environmental induction is still necessary, but the threshold of response is lowered. In this case, the advantages of epigenetic priming are similar to those of neural learning, especially learning through sensitization [18, pp. 419–421].

3.3. What are the evolutionary consequences of epigenetic inheritance?

Both within-individual and between-individual epigenetic inheritance can have profound effects on adaptive evolution and on speciation. I start with the least controversial adaptive evolutionary effects of within-organism inheritance, and move to the more theoretically challenging consequences of between-generation epigenetic inheritance.

3.3.1. Somatic and germ-line heritable epigenetic variations affect the selection and generations of genetic variants

The most obvious role of epigenetic inheritance is in the evolution of multicellular organization: cell memory is a prerequisite for the evolution of complex multicellular organisms with lineages of different cell types [18,22]. There are, however, less obvious effects of somatic and germ-line epigenetic inheritance which can lead to evolutionary changes and, although these processes do not challenge the MS, it is curious that with a few exceptions (e.g. genomic imprinting) these effects of epigenetic mechanisms are rarely discussed. The potentially important evolutionary effects include:

— Stochastic epiallelic silencing that increases somatic variability, and hence the chances of somatic selection during development. This can be advantageous when conditions are rapidly and unpredictably fluctuating during ontogeny [35].
— Epigenetic silencing that can mask dominant deleterious mutations [36].
— Stochastic allele silencing that can increase the chances of fixing beneficial random recessive mutations by rendering their phenotypic effects dominant.
— Stochastic allele silencing that decreases the probability of pseudogenization (formation of pseudogenes) following gene duplication. Provided there is sensitivity to gene dosage, stochastic silencing of extra copies can drive the evolution of new genetic functions by exposing duplicated alleles to selection [37,38].
— Genomic imprinting (allele silencing according to parental sex of origin), which can lead to otherwise unlikely parent–offspring and male–female parent coevolutionary dynamics [39].
— Selection against the between-generation transmission of deleterious epimutations [22] and selection for the transmission of beneficial ones [40] may drive soma–germline segregation and germ-line-specific reprogramming.
— Epigenetic marks that alter DNA mutability and recombination. For example, the transition rate of methylated CpG to TpG is 10–50 times higher than other transitional changes [38], and DNA methylation leads to a lower probability of recombination and recombination-based repair [41].

3.3.2. Heritable epigenetic variations alter the dynamics of phenotypic evolution in populations

The existence of developmentally induced heritable and selectable epigenetic variations challenges the MS because it suggests that evolution can occur on an epigenetic axis, and that the rate at which variations are generated is sensitive to the environmental context. For there to be an epigenetic axis to evolutionary change, epigenetic variants must be independent of *cis*- or *trans*-acting DNA sequence changes, must be transmitted over generations and must be associated with heritable phenotypic variation. Provided the fidelity of transmission of epigenetic variants is high enough, cumulative evolution on the epigenetic axis can occur. In *A. thaliana*, the rate at which methylation is spontaneously gained (forward epimutation) or lost (backward epimutation) at individual cytosines suggests that the epimutation rates are high enough to rapidly uncouple genetic from epigenetic variation, but low enough for new epialleles to sustain

long-term selection responses [31]. Moreover, Cortijo *et al*. [42] have found that isogenic *Arabidopsis* lines segregate DNA methylation marks at hundreds of regions of the genome, and these marks have phenotypic effects affecting fitness. They write: 'Several of these DMRs act as bona fide epigenetic quantitative trait loci (QTLepi), accounting for 60–90% of the heritability for two complex traits, flowering time and primary root length. These QTLepi are reproducible and can be subjected to artificial selection. Many of the experimentally induced DMRs are also variable in natural populations of this species and may thus provide an epigenetic basis for Darwinian evolution independently of DNA sequence changes' [42, p. 1145].

Biologists are beginning to measure epigenetic variations in natural and experimental populations. The best organisms to study would be clonal organisms, parthenogenetic ones or inbred lines, all of which would minimize genetic variation, but data are at present scarce. We are in a similar situation to that of population genetics in the early 1930s: there are good models that consider the effects of both genetic and epigenetic inheritance on population dynamics [43,44], but not enough data from natural and experimental populations. For example, although more than 20 years ago it was argued that geographical or temperature clines in characters could at least in part be the result of the accumulation of environmentally induced epigenetic changes along the cline [22], this possibility has never been explored.

Epigenetic and genetic changes obviously interact, and epimutations can speed up genetic assimilation or accommodation. Population models show that because an adaptive phenotype appears before an adaptive genotype, and epigenetic variations can be induced in many individuals simultaneously (see, for example, [45,46]), rates of evolution can be much faster with epigenetic inheritance, and the distributions of heritable phenotypes and levels of polymorphism are drastically changed.

3.3.3. Epigenetically inherited variations can be the basis of adaptive responses

The discovery that developmentally induced, heritable epigenetic variations can contribute to adaptation is a challenge for the MS, because it means that soft inheritance is not only possible but that it can contribute to evolutionary change. I will highlight two ways in which epigenetic inheritance is directly involved in adaptation. In the first, adaptations are based on the inheritance between generations of epigenetic rather than genetic variations; examples are cellular immunity through the RNAi system in *Caenorhabditis elegans* [47], and heritable silencing of foreign elements through DNA methylation, as seen, for example, in *Neurospora* [48]. In *C. elegans*, the persistence of the epigenetically acquired cellular immunity seems to depend on conditions, but it can last for many generations, so epigenetically based immune responses may not only spread in a population, but may also accumulate.

The second way in which epigenetic inheritance can be directly involved in adaptation is through what Soen has termed 'adaptive improvisation'—epigenetic exploration or 'improvisation' followed by developmental selection and inheritance of the selected epigenetic variant [49]. Phenotypic accommodation following a novel stress is typically accompanied by chromatin re-patterning at many loci, and some of the changes in chromatin marks may be heritable. Like somatic mutations, heritable, stochastic epimutations that reduce the effects of stress can be ontogenetically selected, resulting in a highly biased population of variant cells. Although stress-induced, the epimutations can be inherited between generations in both unicellular and multicellular organisms. An example of such a process has been described by Braun and his colleagues in the yeast *Saccharomyces cerevisiae* (reviewed in [50]). They used a genetically engineered haploid strain in which the essential gene *HIS3*, which codes for an enzyme from the histidine biosynthesis pathway, was deleted from its normal chromosomal location and reintroduced into the cell on a plasmid under the promoter of *GAL1*, a gene from the galactose utilization system. The *GAL* system, and with it the essential *HIS3*, are strongly repressed in glucose medium, and hence in this new, severely challenging and never-before-encountered environment the engineered cells cannot produce histidine; a novel adaptation is required for their survival. Braun and his colleagues found that, after a lag period of 6–20 days, 50% of the cells maintained on glucose without histidine started to multiply. In these cells, the regulation of the *GAL1* promoter was altered, and this change in regulation was inherited for hundreds of generations. The basis of the altered regulation seems to have involved complex rewiring of metabolic circuits (promoter scrambling), with different cells finding different adaptive solutions. Some of these solutions were associated with genetic mutations (e.g. in the repressor or in the promoter of the *GAL* system), but most seem to have involved epimutations. A similar case of adaptive improvisation has been demonstrated in a multicellular organism, *Drosophila melanogaster*, using a similar experimental paradigm. In this case, it was found that both epigenetic and microbiome-based adaptive improvisation was involved [51,52].

Processes of stress reduction through epigenetic exploration and developmental selection may have been involved in processes of domestication. Over a more than 60-year period, selection for domestication in silver foxes led not only to rapid evolution of docility, but also to changes in pigmentation, modifications in skeletal morphology and hormonal profiles, altered vocalization, more frequent presence of B chromosomes and some non-Mendelian patterns of inheritance (reviewed in [53]). Although for these animals the molecular epigenetic basis of the changes has not yet been investigated, studies of chickens show that their domestication involved massive, genome-wide, heritable changes in methylation [54].

There are at least two more areas of adaptive evolution in which epigenetic inheritance is important. The first is the coevolution of parasites and hosts, which induce heritable epigenetic variations in each other [55]. While the holobiont, the community of interacting species (e.g. the mammalian host and its microbiome), can constitute the target of developmental and natural selection, when the interactions fail, for example because of acute stress to the microbiome, the host adapts by making changes in its epigenome, which can be inherited by subsequent generations [55]. The second area is sexual selection. As a recent model [56], supported by extensive data on epigenetic variations transmitted through male sperm [57], shows, favourable environmental conditions having advantageous effects expressed in the soma of males and transmitted in their sperm can guide female choice for male quality. As such

environmentally induced epigenetic effects are an ever-renewable source of selectable variation, epigenetic differences transmitted by the sperm can solve the lek paradox. Additional models and ideas exploring the effects of epigenetic inheritance on sexual selection are reviewed in [58].

3.3.4. Epigenetic inheritance affects macroevolution

During periods of ecological or geographical isolation, organisms are likely to accumulate random and induced epigenetic variations, which may be sufficient to establish some degree of reproductive isolation. Whereas their effects on prezygotic isolation may be similar to those of DNA sequence variations (although leading to more rapid isolation), the effect on postzygotic isolation though chromatin incompatibility is likely to be of special significance. One of the situations where the role of epigenetic mechanisms on evolutionary change has been acknowledged is when mis-imprinting or loss of imprinting leads to reproductive isolation because the patterns of imprinting of paternally and maternally imprinted genes are incompatible and prevent hybrid survival [59]. Such imprinting incompatibilities could be the initial basis for the numerous reported cases of reproductive isolation between parental genomes [22]. But chromatin incompatibilities are not confined to imprinted genes, and can lead, for example, to extensive transgressive expression of growth-related genes in hamster hybrids [60].

Convincing evidence for the importance of epigenetic compatibility for descendants' fertility and for the generation of novel *heritable* variation comes from a study by Rigal *et al*. [61] in *Arabidopsis*. They formed a 'hybrid' between two genetically identical lines, one lacking DNA methylation and one normally methylated (wild type). The outcome was a burst of novel epigenetic variation (in DNA methylation and histone methylation) and genetic variation (through transposable element activity). Their results suggest that epigenetic incompatibility between the chromatin of parental genomes, even when the parents have the same DNA sequence, alters the interactions between histone modifications and DNA methylation, and leads to the generation of novel altered epigenetic and genetic states in gametes and offspring.

That chromatin differences between differently methylated genomes can initiate reproductive isolation is also suggested by some work by Durand *et al*. [62], who found that incompatibility among *A. thaliana* strains is related to the epigenetic silencing of a pair of duplicate genes. In this case, a transposition event caused DNA methylation and transcriptional silencing, and the silenced state was stable over numerous generations even after the removal of the duplicated, rearranged gene copy.

There is growing evidence that speciation through hybridization is far more common than once thought in the evolution of animals as well as that of plants [63]. The epigenetic facets of animal hybridization are as yet under-researched. In plants, hybridization and polyploidization are associated with widespread alterations in DNA methylation patterns, in small interfering RNAs and microRNAs, and in gene expression. For example, in synthetic allopolyploid hybrids of wheat, 13% of the methylome is altered relative to the parental species. Following hybridization and genome duplication, there is a period of rapid change for five generations, followed by a stable and slower rate of evolution. In another well-researched case, that of the salt marsh plant *Spartina*, a classic example of speciation via hybridization, the change in DNA methylation in hybrids spans 30% of methylation sites. We do not know which and how many of the epigenetic variants are independent of genetic variations, but, in view of what we know about plant epigenetic inheritance, it is likely that some are [18, pp. 414–419]. The changes in the methylome and other components of epigenetic inheritance systems can be thought of as heritable epigenetic accommodation, which may, in due course, be accompanied by genetic accommodation.

It has been suggested that two other macroevolutionary changes, those leading to sex chromosome heteromorphism and to the inactivation of sex chromosomes, may have had epigenetic rather than genetic origins [64,65]. The epigenetic silencing of a sex-determining region in one of a pair of morphologically identical chromosomes carrying a major sex-determining locus could lead to a lack of conformational homology between the chromosome (proto-X) that retained the original pattern of gene expression, and the epigenetically silenced proto-Y. Such conformational differences between homologous regions of chromosomes can lead to meiotic pairing failure and a consequent reduction in fertility, but the pairing problem is avoided if, as commonly happens, the incompatible active regions are inactivated during meiosis. The processes involved, which have occurred in parallel in many lineages, are usually interpreted in terms of mutational change. As there are cases where the process is evolutionarily young, the role of epigenetic inheritance could be tested.

It is important to stress that, although the focus here is on the evolutionary effects of epigenetic inheritance, it is inevitable that in natural conditions, over long periods, epigenetic and genetic inheritance interact, so there is neither 'pure genetic' nor 'pure epigenetic' evolutionary change. However, because epigenetic variations are context-sensitive and more frequent than genetic variations, they may often initiate, bias, and facilitate evolutionary change.

3.3.5. Epigenetic inheritance contributes to the major evolutionary transitions

Jablonka & Lamb have argued [66] that information transmitted by non-genetic means has played a key role in all of the major evolutionary transitions that Maynard Smith & Szathmáry [67] analysed, from the origins of life to the origin of language. In addition, epigenetic inheritance was important for another major transition, one that was not listed by Maynard Smith & Szathmáry, the transition to neural organisms [66]. Epigenetic mechanisms are now known to play a critical role in neural learning and, by implication, in the transmission of learned behaviours between generations [68].

3.3.6. Epigenetic variations can be used to trace social history

Comparative epigenomics is a developing field that is already being used to decipher relations between species and between populations: a recent study of the methylomes of Neanderthals, Denisovans and present-day *Homo sapiens* identified around 2000 DMRs in archaic and present-day humans, some of which are related to genes associated with anatomical differences and diseases. These findings suggest that epigenetic variations may have been one of the factors

driving hominid evolution [69]. Such research can be extended to explore human history: studies of methylomes of past human populations as they migrate to new areas or recover after population bottlenecks and stresses (e.g. devastating epidemics like the Black Death, genocides, starvation) could tell us how humans coped with such changes over historical times. As the epigenome typically changes more rapidly than the genome, epigenomic changes may throw light on short-term adaptations through epigenetic accommodation. We have here a new tool for the anthropologists' and historians' toolbox.

4. Conclusion

Popper's challenge to the MS 30 years ago had three prongs: he demanded a phenotype-first approach, he was convinced that developmental selection was important, and he insisted there was some feedback (or relation) between the soma and the germ line. In the light of advances in molecular biology, especially epigenetics, and in studies of niche construction, his challenges are being met by the extended evolutionary synthesis that is being worked out today.

There are many open questions about epigenetic inheritance, and many things we do not understand and about which we need more information. But what is central to the various studies and ideas that I have discussed is that they alter the way we think about selection, about the generation of heritable variation and about the relation between them. The role of selection in evolution changes because, first, there are more targets for selection: not only genetic but epigenetic, not only between generations but also within a generation. As developmental selection interacts with natural selection, the role of selection in adaptive evolution increases. Second, induced or acquired epigenetic changes can be selected, and this adds a 'Lamarckian' aspect to evolution. Third, not every cumulative change needs to be explained by selection. Developmental induction coupled with epigenetic inheritance can drive cumulative evolution of neutral or even slightly deleterious variations and contribute to evolutionary trends. In this way, epigenetic inheritance may have a similar effect to that of genetic drift, which, in small populations, can lead to the fixation of otherwise unlikely genotypes.

Does this mean that we need to revise evolutionary theory? I do not think that what we have learned challenges *Darwinian* evolutionary theory, though clearly it extends it. Cumulative adaptive evolution would not occur without DNA or RNA, nor would it occur without epigenetic systems, which are required for all types of phenotypic continuity. If we want to understand not only the general patterns of phylogenetic relations among taxa, but also the dynamics of an evolutionary change in populations, or how speciation is initiated, we must incorporate into our analyses our growing understanding of epigenetic inheritance. I therefore believe that cumulative adaptive evolution cannot occur without processes of selection, and that both adaptive and non-adaptive long-term evolution is unlikely without genetic (DNA) changes. But if developmental selection is important and affects between-organism heredity (directly or indirectly), surely this has to be accommodated within the theory.

This perspective clearly challenges the MS, which excluded environmentally induced hereditary and developmental variations, and which is based on the assumption that selection is the only direction-giving process in evolution (i.e. that cumulative evolutionary change requires selection [70]). It is not merely a cosmetic modification of the MS. It is a different way of thinking about evolution, which can be fully appreciated when the implications of epigenetic inheritance and plasticity, evo-devo and niche construction are combined. The framework is a developmental-system framework, and the starting point of evolutionary analysis is the heritably varying traits (rather than genes). This view provides new predictions and helps our understanding of several thorny issues in evolutionary biology [71]. It also requires a different kind of representation: developmental systems computational models, in which population genetic and population epigenetic factors are specific, interacting inputs. If, as some evolutionary biologists claim, the effects of epigenetic inheritance do not require a revision of the MS, what, I wonder, would require such a change?

The realization that a change is needed is not new. In 1953, in the heyday of the recently constructed MS, there was already a feeling that it was in need of revision. In summing up a conference on evolution where biologists presented papers on unconventional heredity in amoeba (Danielli) and bacteria (Hinshelwood), on developmental constraints and parallel evolution (Willmer and Manton), and on the interaction between niche choice and evolution (Waddington), JBS Haldane wrote:

> a number of workers are groping from their own different standpoints towards a new synthesis, while producing facts which do not fit too well into the currently accepted synthesis. The current instar of the evolution theory may be defined by such books as those of Huxley, Simpson, Dobzhansky, Mayr and Stebbins. We are certainly not ready for a new moult, but signs of new organs are perhaps visible. [72, pp. xviii–xix].

The arrival of the new moult has taken a long time, but I think it has now arrived, and a new synthesis is emerging.

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