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The expanded evolutionary synthesis—a response to Godfrey-Smith, Haig, and West-Eberhard

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Abstract In responding to three reviews of *Evolution in Four Dimensions* (Jablonka and Lamb, 2005, MIT Press), we briefly consider the historical background to the present genecentred view of evolution, especially the way in which Weismann's theories have influenced it, and discuss the origins of the notion of epigenetic inheritance. We reaffirm our belief that all types of hereditary information—genetic, epigenetic, behavioural and cultural—have contributed to evolutionary change, and outline recent evidence, mainly from epigenetic studies, that suggests that non-DNA heritable variations are not rare and can be quite stable. We describe ways in which such variations may have influenced evolution. The approach we take leads to broader definitions of terms such as 'units of heredity', 'units of evolution', and 'units of selection', and we maintain that 'information' can be a useful concept if it is defined in terms of its effects on the receiver. Although we agree that evolutionary theory is not undergoing a Kuhnian revolution, the incorporation of new data and ideas about hereditary variation, and about the role of development in generating it, is leading to a version of Darwinism that is very different from the gene-centred one that dominated evolutionary thinking in the second half of the twentieth century.

Keywords Epigenetic inheritance · Cultural evolution · Inherited variation · Information · Modern synthesis · Neo-Darwinism · Waddington · Weismannism

We are grateful to the three reviewers of *Evolution in Four Dimensions* (henceforth *E4D*) for their interesting and useful comments, and for the opportunity these reviews give us to clarify some of our ideas and arguments. Our aim in *E4D* was to

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show how new facts about heredity, particularly those that indicate that in some cases heredity should be seen as an aspect of development, are transforming ideas in evolutionary biology. We argued that evolutionary theory is undergoing a revolutionary change: that after 60 years of domination by the Modern Synthesis, with all the expansions and modifications it has undergone, a radical reorganisation of the theoretical framework of evolutionary studies is taking place. We discussed this reorganisation from the specific perspective of heredity. The reviewers of *E4D* question the need for, nature and scope of what we see as a markedly different synthesis. Since their critiques differ in focus and tenor (although there are some common themes), we will discuss most of the points they raise separately.

Haig confines his comments to just one of our four dimensions of heredity, epigenetic inheritance, and largely to only one aspect of this, the transmission of chromatin marks. He claims that there is no problem in incorporating modern epigenetics into neo-Darwinian evolutionary theory. His arguments are based on (i) his historical interpretations of Weismann's ideas, neo-Darwinism, and the concept of epigenetics; (ii) the assumption that the evolutionary effects of epigenetic variations are limited because they are reversible, transient, very constrained, and depend on the genetic system. In what follows, we will show how Haig's interpretations of history differ from ours, why we think his attempt to reduce epigenetic inheritance to genetics is doomed to failure, and why we disagree with his assumption that the role of epigenetic inheritance in evolution is limited.

West-Eberhard's review is very different. There is a large area of overlap between our views and those expounded in her *Developmental Plasticity and Evolution* (2003), where she stressed the need to incorporate the environmental influences on development into evolutionary theory. However, West-Eberhard thinks that our focus on heredity rather than development is too restrictive. She questions the frequency of transgenerational epigenetic inheritance, maintains that behavioural variations that are transmitted through social learning are not common, and points out that cultural evolution based on transmission through symbolic systems is unique to our own and possibly a very few other species. While agreeing with her about symbolic systems, we maintain that epigenetic inheritance is ubiquitous, and that behavioural transmission is common in vertebrates, especially birds and mammals. Incorporating the role of persistent, non-DNA, environmentally induced, heritable variations transmitted through all four types of inheritance system complements and extends West-Eberhard's own views on evolution. West-Eberhard maintains that this expanded view of heredity is a reform of evolutionary theory rather than a revolutionary change, and suggests that our endorsement of Lamarckism is a strategic mistake. She also questions the usefulness of our definition of information, and argues that our position vis à vis the 'units of selection' question is unclear and inconsistent. We recognise that our explicit acceptance that there are Lamarckian processes in evolution is in some ways problematical, but we believe that it is not hindering acceptance of new approaches to evolutionary thinking. Our definition of information was intended to highlight the developmental aspects of its transmission (which a focus on DNA information obscures) and is, we shall argue, useful in focusing attention on developmental processes of accommodation. We did not discuss the 'units of selection' question in *E4D*, but we think that our approach and usage of terms is consistent, and welcome the opportunity to clarify our position.

Godfrey-Smith's review centres around three conceptual issues. His main argument is that the developments in molecular and developmental biology are not

leading to a revolutionary change (in the Kuhnian sense) in evolutionary theory. He believes, however, that there has been a shift in focus in biology away from the idea that the sequence properties of molecules such as nucleic acids and proteins have primacy, and sees our approach to heredity and evolution as part of that shift. In the light of this, he wonders whether our usage of information language is helpful, since informational concepts in biology grew from and fed on the emphasis on sequence. We agree with Godfrey-Smith that the change that is occurring in evolutionary theory is not a Kuhnian revolution, but will argue that there are good reasons for thinking that the new facts and ideas coming from cell biology, molecular biology and developmental biology, although not revolutionary within the framework of their own domains, do have radical, revolutionary, implications for evolutionary theory.

Weismannism not Weismann rules, and it's not OK

Haig leans on Weismann's theory of the continuity of the germ-plasm to explain why evolutionary biologists reject the idea that acquired characters can be inherited. Since this theory (and its distortions) had such far reaching influences on the history of biology, we want to stress some aspects of it that Haig did not discuss and probably has no sympathy with. The first is that Weismann's mature germ-plasm theory, which is a theory of ontogeny and variation, as well as heredity, posits that new heritable variations are environmentally induced. The second is that the theory incorporates an extreme, deterministic model of development: Weismann explicitly rejected epigenesis in favour of a model in which the properties of each cell are predetermined in particles of chromatin in the fertilised egg (Weismann 1893: xiii–xiv). The way the 'determinants' in these particles are organised directs how they are shared between daughter cells during ontogeny, and the eventual disintegration of each type of determinant dictates the specific structure and properties of the cell type it determines. The nuclear contents of somatic cell lineages get simpler and simpler as ontogeny proceeds. They cannot give rise to germ cells because they lack a complete set of determinants, and consequently environmental influences on somatic cells do not affect heredity. Only cells in the germ track, which retain a complete set of determinants (the germ plasm), contribute to the next generation.

Although Weismann insisted that somatic changes could have no effect on what is inherited, he nevertheless gave external conditions a major role in the generation of new variation. Winther (2001) has made a detailed analysis of Weismann's views on the cause of variation, and shown that whereas for most of the 20th century his ideas have been presented in a way that suggested he believed variations were not and could not be induced by the conditions of life, this is a total misrepresentation. In fact, Weismann believed that changes in external conditions were *essential* for the production of new variation. Thus, as Winther says, Weismann was not a Weismannian: he actually championed 'the inheritance of acquired germ-plasm variations'. Moreover, the mechanism he proposed could result in what he referred to as 'definitely directed variation' (Weismann 1902). In other words, Weismann believed both that the production of variation is controlled by external conditions, and that some of the variation produced is non-random.

Not only was Weismann not a Weismannian about acquired and directed variations, he was not a Weismannian about the continuity of the germ-line either. Haig claims that ''we now accept something close to Weismann's theory of the continuity

of the germ-plasm'', but as Griesemer and Wimsatt (1989) have argued, what is generally accepted as Weismannian today does not reflect Weismann's views. Through their analysis of the way it has been presented in figures, they have shown how over the decades Weismann's theory of germ-plasm continuity has been simplified and misinterpreted. One very influential account of it was that given in E.B. Wilson's *The Cell in Development and Inheritance*, first published in 1896. In the introduction, Wilson presents a pared down version of Weismann's view that that acquired somatic characters cannot be inherited because of the continuity of the germ-line, and illustrates it with a figure (reproduced in Fig. 1). This figure, which is clearly the ancestor of many later ones (including Fig. 1.3 of *E4D*), ignores phenotypic differentiation, exaggerates the continuity of the germ-plasm by ignoring sexual recombination, erroneously shows the continuity of germ cells rather than germ-plasm or chromatin, and in no way reflects Weismann's recognition that germ cells are products of development, like any other differentiated cell. Griesemer and Wimsatt show how this grossly over-simplified representation of Weismann's ideas has itself been simplified in ways that emphasise the non-inheritance of acquired characters and the continuity of the genetic material from generation to generation (see also Griesemer 2002). In their opinion, which we endorsed in *E4D*, this distortion of Weismann's views, in which the development of the phenotype is ignored, has contributed to the narrow gene-centred approach to evolution. Whereas Weismann's mature germ-plasm theory was an integrated view of development, heredity, and variation, Weismannism, which ruled most of 20th-century evolutionary biology, was not.

Heredity as an aspect of development

The ideas about the continuity of the germ-line that Weismann and others developed in the mid-1880s made it easier for biologists to treat heredity as something separate from development. The separation can be seen clearly in Johannsen's (1911) concept of heredity. This was explicitly 'ahistorical' and non-developmental, emphasising that it is genotypes, not phenotypes, that are inherited:

> The genotype-conception [of heredity] is thus an ''ahistoric'' view of the reactions of living beings—of course only as far as true heredity [biological as opposed to cultural] is concerned.... I suggest that it is useful to emphasise this ''radical'' ahistoric genotype-conception of heredity in its strict antagonism to the transmission- or phenotype-view. (Johannsen 1911: 139)

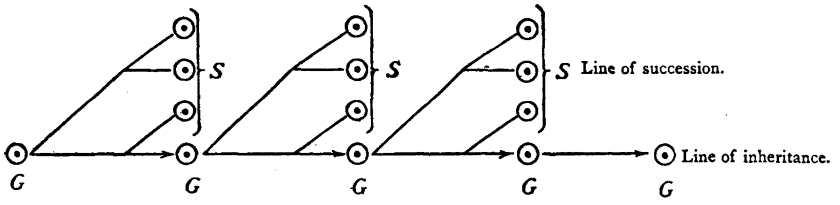

Fig. 5. — Diagram illustrating Weismann's theory of inheritance.

G. The germ-cell, which by division gives rise to the body or soma (*S*) and to new germ-cells (*G*) which separate from the soma and repeat the process in each successive generation.

Fig. 1 Wilson's depiction of Weismann's germ-plasm theory (Wilson 1900: 13)

At the time, this approach, which denied ancestral influences on the hereditary material, was crucial, because it made it possible to focus on the transmission of the newly discovered Mendelian genes. Johannsen's genotype concept therefore became the basis of genetics, and consequently was part of the Modern Synthesis of evolution built in the 1930s. Nevertheless, although Johannsen's ideas about heredity have contributed so much to theoretical and empirical research in genetics and evolution, today, nearly100 years after he developed them, we are convinced that a broader notion of heredity is required.

In *E4D* we discussed the empirical data and the theoretical developments on which a modern concept about heredity should be built, highlighting the evolutionary implications of changing views about inheritance. We limited our discussion of evolution by giving way to our own biases (we are both geneticists by training), and following the narrow, heredity-based approach used by most 20th-century evolutionists. It was through the lens of heredity that we focussed on the developmental aspects of evolution. We did not adopt the much wider developmental perspective that West-Eberhard (2003) takes in *Developmental Plasticity and Evolution*, and therefore did not address many of the evolutionary problems that she discussed. We agree with West-Eberhard's important general point that phenotypic traits induced by mutation as well those induced by the environment are reconstructed and filtered during development: all non-lethal newly induced changes are subject to processes of phenotypic accommodation, and in this sense mutationally induced changes are also developmental. We also fully agree that ''Since development (including learning and other epigenetic phenomena) is the source of all selectable phenotypic variation, environmentally influenced development, and (when it occurs) the inheritance of developmental variants, affect evolution''. Our approach stresses the importance of environmentally induced variations, but is focussed on the last part of her sentence—on the *inheritance* of environmentally influenced variants. In *E4D* we emphasised the aspects of developmental plasticity that are transmitted between generations through evolved epigenetic inheritance systems, social learning and symbolical transmission, because we believe that these are pervasive and of crucial importance for understanding heredity and evolution. One of the main differences between our position and West-Eberhard's is our different evaluations of the importance of environmentally influenced inheritance, especially cell-mediated epigenetic inheritance. We will come back to this point in the last section of this response.

Neo-Darwinism and Neo-Lamarckism

Haig points out that the way biologists define terms, and the 'spin' they put on evidence, can have consequences for how they understand biological systems. We agree, and therefore wonder why, having explained the origin of the term 'neo-Darwinian', he says he is happy to accept the label for himself. As Haig acknowledges, neo-Darwinism now means different things to different people, so his acceptance of the label is not informative. Is Haig's brand of neo-Darwinism Darwinism minus the inheritance of acquired characters, which is how he interprets Romanes (1888) views? Or is it Darwinism purged of everything except natural selection (i.e., without the Lamarckian elements, without sexual selection, and with all change being entirely gradualistic), which is how Romanes (1893) defined it? Or is it what many biologists assume it to be, the 'Modern Synthesis' developed in the

1930s, which combined elements of Darwinism with Mendelian genetics? The ambiguity in the term was already obvious in the 1940s, when George Gaylord Simpson, a major contributor to the Modern Synthesis, wrote:

> The theory has often been called neo-Darwinian, even by those who have helped to develop it, because its first glimmerings arose from confrontation of the Darwinian idea of natural selection with the facts of genetics. The term is, however, a misnomer and doubly confusing in this application. The full-blown theory is quite different from Darwin's and has drawn its materials from a variety of sources largely non-Darwinian and partly anti-Darwinian. Even natural selection in this theory has a sense distinctly different, although largely developed from, the Darwinian concept of natural selection. Second, the name ''neo-Darwinian'' has long been applied to the school of Weismann and his followers, whose theory was radically different from the modern synthetic theory and certainly should not be confused with it under one name. (Simpson 1949: 277)

The term neo-Lamarckism is equally confusing. It was applied to a heterogeneous collection of late 19th- and early 20th-century evolutionary theories which gave factors such as habitat, isolation, climate, geological conditions, nutrition, as well as the animals' habits and mode of life, a role in producing heritable modifications. In general, neo-Lamarckian theories had little to do with Lamarck's ideas about adaptive evolution, save that they gave biotic and/or abiotic factors a causal, directional role in the production of variation. According to Simpson (1960: 970), ''Neo-Lamarckism is more Darwinian than Lamarckian and is, indeed, about as Darwinian as Neo-Darwinism''.

Because of the ambiguity surrounding the terms neo-Darwinism and neo-Lamarckism, we have generally avoided using them to describe our view of evolution. The term neo-Lamarckism seems to have fallen into disuse already, and we would be happy to see neo-Darwinism go the same way, since the 'neo-' no longer has any descriptive value. Haig says ''Jablonka and Lamb proudly identify themselves as modern Lamarckians'', but this statement caricatures our position. As we made clear in *E4D* (e.g., page 4) and earlier writings about the role of epigenetic inheritance in evolution (e.g. Jablonka and Lamb 1995: 1), our views are basically Darwinian. Like Darwin, we believe that some of the heritable variations on which natural selection acts are the result of the reactions of the organism to its environment. It is in this sense that we associate ourselves with Lamarckian ideas.

No information without interpretation

Both Godfrey-Smith and West-Eberhard question the value of our use of informational concepts. However, since 'information' is used so frequently in contemporary studies of genetics, development and evolution, where it is strongly associated with the DNA inheritance system (Maynard Smith 2000), we thought that it was necessary to offer an explicit discussion and definition of our own concept of information, which is broader than the DNA-based one, and is organism and development oriented.

We suggested in *E4D* that biological information should be seen in terms of the *interpretation* (or processing) of inputs, rather than as an inherent property of these inputs. Information should be defined, we argued, through its effects on the receiver:

a source becomes an informational input when an interpreting receiver can react to the form of the source (and variations in this form) in a functional manner. (For an extended discussion, see Jablonka 2002.) West-Eberhard objects to our use of the word 'interpretation' in this context. However, we used it not to suggest a hidden mentalistic teleology, but because it directs attention to the processing mechanisms in the receiver. In fact, according to our definition, the concept of information can be used *only* with reference to living (or designed-by-living) entities that have developmental reactions. Since our notion of information is focused on the organism (the receiver) rather than the input, it is explicitly developmental. Using West-Eberhard's terms, we could say that only to the extent that inputs are phenotypically accommodated can they be called 'informational'. Events and processes in the world that have different effects, such as throwing water into sand and throwing a brick into sand, can be called informational only when the difference is responded to in a functional manner by an 'interpreting' system—a living (or designed by living) system. For example, to an animal (the receiver), water thrown into the sand might be a cue indicating a flood, so it may look for shelter, whereas a brick thrown into sand might be a cue for the arrival of hostile humans, so it may run away. Sand, water, and bricks are informational only because of the effects they have on the animal. Although the usefulness of information-talk in biology has rightly been challenged (Oyama 1985), we think that this is because 'information' has been defined too narrowly. As we see it, the concept of information, like that of function, is a fundamentally biological term, and is useful because it highlights and refers to exclusively biological processes.

Since our focus in *E4D* is on heredity—on the transmission of information *between generations* through reproduction or through communication—it is mainly in this context that we use the term 'information'. Information transmitted between generation requires that a receiver *developmentally reconstructs* (interprets or processes) an informational input from a sender who was previously a receiver. When this reconstruction process leads to the same or a slightly modified organisation-state as that in the sender, and when variations in the sender's state lead to similar variations in the receiver, we define this process as the hereditary transmission of information. The generality of our definition calls for and enables comparison between the processing and transmission systems associated with different types of informational inputs and different types of reconstruction processes. Although we use the term 'information' without commitment to any specific source of input, the input may be, but does not have to be, a DNA sequence.

On units of heredity, units of evolution and targets of selection

In *E4D* we deliberately avoided discussing units of selection. We thought that so much had been written about the whole issue, and it had led to so much misunderstanding, that it was safer to avoid it altogether and simply be careful with our own use of terms. For example, in Table 1.1 we carefully distinguished between units of hereditary variation, units of evolution, and targets of selection. In the first two pages of *E4D*, we presented our own view of evolution and contrasted it with the view that sees genes as the sole focus of natural selection, and the sole source of heritable variation. This should not be taken to imply that we think that the gene is a legitimate unit of selection, and that all that evolutionary theory needs is the

addition of a few other units. On page 41 we criticised Dawkins, who regards the gene as both the unit of selection and as the unit of heritable variation. We pointed to the misleading dichotomy in Dawkins' presentation of the issue, and argued that it is the heritably varying trait that is the unit of evolution, referring readers to more extensive discussion in Jablonka (2004). However, we agree that West-Eberhard's alternative wording regarding the relation between epigenetic and genetic changes is better and less open to ambiguity than that which we used (*E4D*:264). Since we were not clear about units, we are happy to try to remedy this by accepting West-Eberhard's challenge to present a well-defined scheme of cause-and-effect to fit each of our four dimensions of evolution:

Selection means differential survival and reproduction. Selection does not necessitate evolution. Evolution through natural or artificial selection will occur only when the variations that lead to differential survival and reproduction are inherited across generations.

Units of heritable variation are (i) genes (alleles); (ii) some cellular epigenetic variations (epialleles); (iii) variant developmental legacies transmitted during embryogenesis by the mother; (iv) variant behavioural legacies; (v) variant symbolic information; (vi) variations in ecological legacies constructed by ancestral generations. The different types of variations all depend on evolved developmental processes: genes depend on evolved systems of DNA replication; the transmission of epigenetic variants depends on evolved cellular systems—the types of cellular epigenetic inheritance systems (EISs) described in chapter 4 of *E4D*; behavioural variations depend on evolved mechanisms that allow social learning; and symbolic communication depends on various evolved cognitive mechanisms, with language being especially important in humans. Once a particular transmission mechanism is in place, many variations of the specific type can be transmitted.

Units of evolution are the types whose frequency changes over evolutionary time, mainly heritably varying traits. The developmental resources that contribute to the heritably varying traits are genetic (DNA), epigenetic in the wide sense (including ecological legacies constructed by ancestral generations), and persistent environmental conditions which are independent of the organisms' activities.

Units of selection (we much prefer, and use, '*targets of selection*') are reproducers—entities displaying differential reproduction, which are mainly classical individuals, but also groups and species.

These definitions are appropriate for each of the four dimensions of heredity and evolution we discussed in *E4D*, and for their combinations. Evolutionary change in all organisms can involve genetic and epigenetic variations; in some groups (mainly social vertebrates), behavioural variations based on socially mediated learning are also present; and in our own species there is, in addition, a very important role for symbolic variations.

Epigenetics and epigenetic inheritance

Haig's two sections, Epigenetics I and Epigenetics II, relate to what he previously described as the dual origins of epigenetics (Haig 2004). In Epigenetics I he refers to Waddington's coining of the term epigenetics in the 1940s, and summarises Waddington's ideas about genetic assimilation. About these Haig writes ''The proposed mechanism is interesting, and may be important, but does not challenge any

fundamental tenets of neo-Darwinism. ... When he is not lambasting neo-Darwinists, Waddington concedes as much''.

To anyone unfamiliar with Waddington's work and ideas, Haig's choice of words could easily leave the impression that Waddington thought that neo-Darwinian ideas should be abandoned. He did not. Waddington was emphatic that genetic assimilation is ''founded on the selection of pre-existing mutations rather than on mutations induced by the conditions which are adapted to'' (Waddington 1957: 187), and we largely share this view. Waddington, an embryologist, thought that the Modern Synthesis version of neo-Darwinism was an incomplete theory because it made the unjustifiable simplifying assumption that selection acts directly on genotypes, and gave no role to the capacity of individuals to adapt developmentally. Neo-Darwinism, for Waddington, meant ''the view that Weismann's doctrine—that there is no influence of the phenotype on the genotype—can be transferred from the individual level to the population level, and that an adequate theory of evolution can be formulated in which 'fitnesses' are attributed to genotypes'' (Waddington 1969, reprinted in Waddington 1975: 251).

In Epigenetics II, Haig suggests that the use of the term epigenetics in studies of cellular inheritance stems from Nanney's (1958) use of 'epigenetic' to describe the many cellular control systems that produce persistent changes in cell characteristics. Nanney recognised that differences between cells do not always depend on the primary genetic material (DNA) and, according to Haig, ''From this beginning, epigenetic has come to refer to causes of heritable differences that are not dependent on changes in DNA sequence. The paradigmatic example of an epigenetic inheritance system is DNA methylation''.

We agree with Haig that 'epigenetics' is now used in two somewhat different senses, and this is confusing (Jablonka and Lamb 2002). On the one hand the term is used for the study of the developmental processes that relate genotypes to phenotypes, and on the other it is used to describe non-DNA heredity—something we always refer to as 'epigenetic inheritance'. We are not convinced, however, that Haig's version of the history of these two different usages is correct. In particular, we see no evidence that using 'epigenetic' for the paradigmatic DNA methylation system of cellular inheritance stems from Nanney rather than Waddington. Nanney's (1958) essay recognised and described in a very clear way how the presence of inducible systems within and outside the nucleus can bring about heritable differences between cells, and it was certainly referred to and discussed by those studying unicellular organisms and cells in culture. But there were other threads that contributed to the recognition at about this time that cells must have additional inheritance systems. For example, the work on nuclear transplantation in amphibians, on transdetermination in *Drosophila*, and on X-chromosome inactivation were all significant (see Holliday 1987, 2006). The background against which many of the ideas about epigenetic inheritance were developed was that of the problems of determination and differentiation in multicellular organisms. Robin Holliday, one of the founding fathers of methylation studies and modern epigenetics, began his seminal 1987 paper *The inheritance of epigenetic defects* by attributing the term 'epigenetics' to Waddington. The concluding paragraph begins ''Epigenetics is concerned with the strategy of genes in unfolding the genetic program for development. This strategy is not understood and the lack of a theoretical framework severely hinders experimental advances''. This is surely a conscious reference to Waddington's book *The Strategy of the Genes* (1957), and Holliday here seems to

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

Perhaps because Holliday's pioneering ideas were centred on DNA methylation, many people see epigenetic inheritance almost entirely in terms of transmitted states of potential gene activity brought about by DNA methylation and DNA-associated proteins. These are referred to as 'epigenetic marks' or 'chromatin marks'. Nanney's approach to epigenetic control systems was much broader, and included transmissible non-nuclear structures and functions. Our view of cellular epigenetic inheritance is also a broad one, which includes structural templating, self-sustaining feedback loops, and the RNA interference system, as well as chromatin marks. At the cellular level, the mechanisms through which some cells, such as those in the mammalian immune system, make sequence changes in the DNA they transmit is also an epigenetic system, so epigenetics can even involve DNA changes. Nevertheless, epigenetic *inheritance* is distinct and distinguishable from DNA inheritance.

One of the consequences of restricting epigenetic inheritance to the transmission of chromatin marks, which are replicated in association with DNA, is that when they have evolutionary consequences, it is easy to shift the focus from the epigenetic to the genetic system. For example, Haig says that the ability to change epigenetic state is in part ''a property of the DNA sequence itself, and, therefore, subject to natural selection on conventional mutations''. If one thinks in terms of gene selection, this is true. It is also true that DNA-encoded enzymes can reconstitute some epigenetic marks if they are destroyed. But these truths do not alter the fact that alternative marks associated with the same DNA sequence can be transmitted between generations of cells and organisms, have different phenotypic effects, and consequently provide material for evolution through natural selection. Epigenetic variations have properties that gene-based evolutionary theories do not incorporate and consequences that they do not predict. For example, Haig sees no evolutionary difference between hereditary epimutations in mice that are induced by dietary folate, and genetic mutations caused by exposure to radiation or a chemical. But there is an important difference: folate-feeding can induce the *same* epimutation in many individuals, whereas each radiation or chemically induced mutation is effectively unique. This difference can have profound effects on the dynamics of evolution through natural selection: contrary to the assumptions of 'foundational models of neo-Darwinism' (Haig's term), the production of a particular heritable change is not a rare event, and its occurrence is not independent of the environment in which it is selected.

In *E4D* we discussed the peloric variant of *Linaria vulgaris*, which we said was originally described by Linnaeus as a new species, was then assumed to be a mutation, and recently has been found to be 'a fairly stable epimutation'. Haig pointed out that there is no reason for thinking that the recent studies were made on direct descendents of Linnaeus's specimen, and we agree that this is extremely unlikely. However, we think that Haig's suggestion that Linnaeus's peloric plant might have carried a mutation rather than an epimutation is implausible, first because we know of no molecular evidence of peloric mutations in this species, and secondly because peloric variants arise so frequently. This is why de Vries (1906) chose *Linaria vulgaris* for his studies of the origin of mutation. In controlled experimental conditions, he found 16 wholly peloric specimens among 1,750 plants. This 1% frequency of new 'mutations' is so high that it strongly suggests that most peloric variants in *Linaria* are the result of epimutations.

Haig says that ''the peloric epimutation resulted in a *loss* of adaptation and a reversion to an ancestral symmetry, rather than the production of an evolutionarily novel structure''. This suggests that he thinks that epimutations like this cannot have adaptive significance. However, there is good phylogenetic evidence that species with peloric-type (radially symmetrical) flowers have been derived from species with specialised, asymmetrical flowers (Rudall and Bateman 2003), so the peloric phenotype presumably can have adaptive advantages. We are not suggesting that epigenetic changes produced the derived species, although as we argued in chapter 7 of *E4D*, we do believe that epimutations can initiate changes that are later stabilised by DNA sequence substitutions.

Revolution or reform?

The main subject of Godfrey-Smith's review is the nature of the changes that are now taking place in evolutionary theory. In *E4D* we claimed that biological thinking about heredity and evolution is undergoing a revolutionary change. Godfrey-Smith questions whether what is happening is indeed a revolution. What exactly is a revolution in biology? he asks. What changes in evolutionary theory would amount to one? As he indicates, the answers to these questions are not straightforward.

Evolutionary theory has undoubtedly undergone many modifications since the Modern Synthesis of the late 1930s. For example, it has been acknowledged that some variations in single genes are selectively neutral, that some evolutionary change is saltational, and that sometimes group selection is important. Now it is being claimed that some of the heritable DNA variation that is the raw material for natural selection is non-random—it can be both induced by environmental conditions and targeted to specific types of sequences. Moreover, induced changes sometimes involve not just a single site, but many different genomic sequences and chromosomes. Natural selection of classical allelic variations with small effects, which was seen by the architects of the synthesis as the basis of adaptive evolution, is now often regarded as secondary, refining the primary phenotypic change, which may be the outcome of mutation, but is usually environmentally induced. As West-Eberhard puts it, genes are usually followers not leaders in evolution. So what now, in the first decade of the 21st century, is the state of the evolutionary theory forged 60 years ago? Is it still essentially neo-Darwinian in the Modern Synthesis sense? Is it just a better, updated version of that Synthesis?

The answers to these questions depend on how one evaluates the data on heredity and evolution that have accumulated during the last 25 years, and on how one sees the theoretical implications of the new discoveries. There are some differences between our evaluation and interpretation and those of our reviewers, so we will end this response by focusing on these issues. We will briefly address four questions. First, how common are heritable variations that do not depend on DNA sequence differences? Since our reviewers focused mainly of the epigenetic inheritance system, this will also be our main focus. Second, how diverse and stable are non-DNA variations? Third, what is their evolutionary significance? Fourth, if one accepts that these hereditary variations do play an important role in evolution, how should we reformulate the basic concepts of evolution, and what kind of evolutionary theory do we then have?

How common are trans-generationally inherited non-DNA variations?

In *E4D* we did not attempt to review the rapidly growing literature on cellular epigenetic inheritance and the various types of soma to soma transmission. Clearly we cannot attempt to do so here either. However, we can point to articles that give an idea of the range of phenomena involved and the amount of data available. This literature shows that epigenetic inheritance and related processes are not merely marginal and interesting curiosities: it is now clear that a substantial amount of heritable variation does not have the properties that were assumed for it in the Modern Synthesis.

Information about the transgenerational transmission of cellular epigenetic variations through each of the EISs we described in *E4D*, particularly through the chromatin marking and RNA-mediated systems, is becoming overwhelming. Most comes from studies of plants, and extensive reviews about its occurrence and significance for understanding ecological and evolutionary processes have been provided by, for example, Grant-Downton and Dickinson (2005, 2006), Rapp and Wendel (2005), Takeda and Paszkowski (2006), and Zilberman and Henikoff (2005). One topic that is getting a lot of attention from botanists is the importance of massive epigenetic (and genetic) changes in speciation via hybridisation and polyploidization (e.g., see Adams et al. 2003 and articles in *Biological Journal of the Linnean Society* 82(4), 2004). In addition to the many examples of cellular epigenetic inheritance given in these reviews, the recent research by Lolle and colleagues (2005), to which Godfrey-Smith refers, has uncovered what looks like a totally new type of RNA-mediated inheritance in plants. In microorganisms such as yeast and *Podospora* there is now clear evidence that prion variants can be transmitted through meiosis (Wickner et al. 2004), although as yet prion transmission through eggs and sperm has not been observed.

Examples of transgenerational epigenetic inheritance in mammals are fewer than for plants, but more and more are being found (see Chong and Whitelaw 2004; Richards 2006, and notes to chapter 4 of *E4D*). Recently, the process of paramutation, a type of heritable epigenetic modification found many years ago in plants (Stam and Mittelsten-Scheid 2005), has been found in mice, and the mechanisms behind it are being worked out (Rassoulzadegan et al. 2006). As awareness of their implications for human health increases, meiotically transmitted epigenetic variations that are induced in the germ-line in utero are being recognised and studied (Anway et al. 2005).

The soma to soma route of transmission is very common in mammals, including humans (Gluckman and Hansen 2005). Substances in the mother can affect the embryo's development, and sometimes produce effects that are heritable, although the phenotype in subsequent generations is not always the same as that induced in the first one. After birth, animals can be affected by substances in their mother's milk, faeces and saliva, and by various forms of parental behaviour; some of these effects can be passed on to later generations. The literature about this is huge and scattered. Avital and Jablonka (2000) discussed the transmission of information through social learning, and additional examples are given in Fragaszy and Perry (2003). A recent study of the transmission of maternal styles of parenting in rats, which combined behavioural, physiological and molecular studies, has uncovered the biochemical processes underlying this type of behavioural inheritance (Meaney 2001; Weaver et al. 2004), and more such studies can be expected.

It is unnecessary to discuss cultural transmission through language and other symbolic systems here, since it is not controversial. It is also unnecessary to examine the profound effect such transmission has on all aspects of human life, including heredity and evolution. Richerson and Boyd (2005) have recently explored the ways in which cultural transmission has shaped the short-term and long-term evolution of hominids.

Taken together, the available data leave no doubt that there is a lot of variation whose origin and transmission does not depend directly on DNA changes and DNA replication. If, as it seems, such inheritance is common, and the origin of the transmitted variations is often by induction, then it follows that environmentally induced heritable variations that do not depend on DNA differences must affect evolution.

How significant is non-DNA inheritance?

Haig argues that because the number of epigenetic states that can be associated with a particular DNA sequence is always far fewer than the number of nucleotide changes that are possible, DNA will always have evolutionary primacy. In *E4D* we acknowledged that the amount and range of variations allowed by cellular epigenetic inheritance and behavioural (non-symbolic) transmission is not as vast as that which is possible with digital information systems like DNA and symbolic language, but insisted that non-DNA variation can still be significant. Godfrey-Smith gives such an excellent account our argument that there is no need to repeat it here. As he said, even if combinations of epigenetic variants provide fewer possibilities than the genetic system, there can still be enough to have evolutionary importance.

Godfrey-Smith wonders if evolution through the epigenetic systems is not just fine tuning of what evolution based on the genetic system has produced. Certainly, in present-day organisms, DNA replication and information processing through transcription, splicing, translation, and post-translational modification are fundamental to epigenetic inheritance. Given this, however, how far can evolution go if we follow our thought experiment with the Jaynus creatures (*E4D*:114–118), whose DNA is unchanging? The answer is, we think, quite far. The fly larva and the adult fly have the same DNA, but the morphological, physiological and behavioural differences between them are huge: not for nothing did it take such a long time for scientists to realise that the same individual can assume such different forms. Similarly, when sex-determination is environmental, differences between males and females are sometimes enormous, as are the differences between different castes of social insects. West-Eberhard (2003) has given many examples of how organisms sometimes show dramatic changes in morphological, physiological and behavioural features after accommodation to changed environmental inputs.

Both West-Eberhard and Haig comment on the evolutionary limitations of the ephemeral nature of many non-DNA variations. Haig maintains that the low fidelity of replication of epigenetic variants compared with that of genetic variants means that significant adaptations are unlikely to be encoded epigenetically. However, as he admits, numerical data on the stability of epigenetic variants are scarce. Those he gives are based on the failure to maintain epigenetic states at two loci in the somatic cells of ageing mice (Bennett-Baker et al. 2003), but these are unlikely to be representative of epimutation rates, even for somatic cells. First, in old animals, because the efficiency of the cell maintenance machinery declines, epimutation rates are

probably increased, just as mutation rates are (Drake et al. 1998). Second, the loci involved are an imprinted locus and an X-chromosome locus, both of which change state during normal development and have probably been selected for 'switchability'. In other words, their capacity to change is important for the adaptations of which they are part.

We think that even relatively ephemeral variations are very important in evolution, and West-Eberhard also recognises that short-term behaviourally inherited variations may have evolutionary consequences. However, we are not sure that all or even most non-DNA variations are so ephemeral. We have given several non-mutually exclusive reasons why socially learnt behavioural patterns can be stably inherited (*E4D*:176–180, 182–184), and with cellular epigenetic variations there seems to be a wide range of stabilities. The stability of epigenetic marks associated with protein-coding DNA varies (see Richards 2006), but those on repetitive DNA sequences are often very stable (Levy and Feldman 2004). In general, the epigenetic marks involved in transposon silencing rarely change. What evidence there is suggests that the rate of epigenetic change, like the rate of genetic change (Drake et al. 1998), is probably an evolved property that depends on the locus, the species, the age, and the sex of the organism under consideration.

What are the effects of transmitted non-genetic variations on evolution?

We have explored the evolutionary implications of cellular epigenetic inheritance and behaviourally transmitted information in earlier books (Jablonka and Lamb 1995; Avital and Jablonka 2000), and in *E4D* included some of the more recent data that support the view that transmitted epigenetic, cultural, and symbolic variations influence the direction and nature of evolutionary change. In particular, we argued that when new variants arise in response to genomic or environmental stress, and therefore their occurrence is not independent of the environment in which they are selected, they can have consequences that are not fully recognised in most current evolutionary theory. In brief, some of the effects of the non-genetic dimensions of heredity are:

Non-genetic variants can contribute to medium-term and long-term adaptation

Non-genetic inheritance systems provide a different source of selectable variation, which may be crucial if populations are small and lack genetic variability. For example, in the absence of genetic variation, adaptation can occur through the selection of heritable epigenetic variation resulting from differences in methylation patterns or other aspects of chromatin structure. Epigenetic variants often arise when environmental conditions change, which is exactly the time when new phenotypes are likely to have a selective advantage. Moreover, because many individuals in the population may acquire similar modifications at the same time, adaptation can be very rapid. The stability with which a phenotype is transmitted across generations can vary, and may itself evolve epigenetically (Lachmann and Jablonka 1996).

Cellular epigenetic variations can bias the rate and direction of genetic evolution

As we discussed in chapter 7 of *E4D*, epigenetic changes can unmask hidden genetic variation, and therefore affect gene frequencies. If the epigenetic changes are

themselves inherited, this effect will be even more significant. Even when epialleles are not as stable as genetic alleles, adaptations based on epiallelic variation may be able to do a 'holding job' that allows a population to survive until a process of genetic accommodation occurs. The same is true for behavioural variants.

Epigenetic variations can affect the production of genetic changes

Heritable variations in chromatin structure can affect genetic variation: rates of mutation, transposition, and recombination are lower in condensed than in open chromatin (Jablonka and Lamb 1995, chapter 7). The movement of transposable elements is widely recognised to be a major cause of genomic change (Kidwell and Lisch 1997), and is markedly influenced by various types of internal (genetic) and external (environmental) stress. Often even a small DNA insertion can lead to a gross phenotypic change—a 'macromutation', a 'hopeful monster'. The notion that these 'hopeful monsters' have a role in evolution used to be derided, but it is becoming clear that there are circumstances in which they can be honed by selection into adapted organisms (Bateman and DiMichele 2002). Sequence studies have shown how during plant and animal phylogeny developmental genes have been duplicated and re-used (Cronk 2001; Garcia-Fernàndez 2005), and Rodin et al. (2005) have suggested how epigenetic silencing may play a role in this. Rapp and Wendel (2005) have described how genomic stresses such as hybridisation and polyploidisation induce massive epigenetic reorganisation in plants, and suggested that the ecological stresses that lead to population bottlenecks may not only affect genetic variation, but also induce epigenetic changes that may lead to novel phenotypes.

Non-genetic variation can initiate speciation

Reproductive isolation may begin when non-genetic behavioural differences prevent mating taking place (Avital and Jablonka 2000), or when differences in chromatin structure result in hybrid offspring that either fail to develop normally, or are sterile because the two sets of parental chromosomes carry incompatible chromatin marks (Jablonka and Lamb 1995, chapter 9). For example, incompatibility between parental marks is thought to be the reason why hybrids between two species in the rodent genus *Peromyscus* develop abnormally (Vrana et al. 2000). Epigenetic inheritance also has a significant role in speciation through polyploidisation and hybridisation, which are of central importance in plant evolution (Rapp and Wendel 2005). Recent studies have shown that in many naturally occurring and experimentally induced polyploids and hybrids, DNA methylation patterns are dramatically altered, and genes in some of the duplicated chromosomes are heritably silenced. Following polyploidisation or hybridisation, there is therefore a very rapid enhancement of selectable variation, with all the opportunities for adaptation that this provides.

Cellular epigenetic inheritance is a powerful constraint on the evolution of development

Reasonably reliable cellular EISs were a pre-condition for the evolution of complex multicellular organisms with specialised cell lineages, because cells in such lineages

have to maintain and transmit their determined state, even when the conditions that initiated it are long past. However, as we argued in chapter 7 of *E4D*, the cells that give rise to the next generation of organisms need to have an uncommitted state, and efficient EISs could jeopardise this. EISs have therefore been a strong constraint on the evolution of ontogeny, and there are several features of development that may be outcomes of selection to prevent cells with inappropriate epigenetic legacies from founding the next generation. First, it may be one of the evolutionary reasons why many epigenetic states are so difficult to reverse, because irreversibility prevents a rogue somatic cell from becoming a germ cell and carrying its inappropriate epigenetic marks to the next generation. Second, the early segregation and quiescent state of the germ-line, which is seen in many different animal groups, may be the result of selection against acquiring the epigenetic 'memories' associated with somatic cell determination and chance epimutations. Third, the massive changes in chromatin structure that occur during meiosis and gamete production may in part be the outcome of selection against the transmission of epigenetic variations that would prevent a zygote from starting its development with a clean epigenetic slate.

Non-genetic inheritance plays a central role in the major evolutionary transitions

In *E4D* (chapter 9) and in greater detail in a recent article (Jablonka and Lamb 2006) we have argued that non-genetic inheritance systems played a crucial role in all the major evolutionary transitions identified by Maynard Smith and Szathmáry (1995). As we see it, epigenetic inheritance, which maintains patterns of gene activity following replication, was crucial for the evolution of long nuclear chromosomes, as well as for the transitions to eukaryotic cells and to multicellularity. Similarly, in the transition to social groups, non-genetic behavioural transmission was instrumental in forming cohesive units, and cultural transmission though symbols was central to the social and cognitive evolution of humans.

From the sketch just given, it should be clear that we think that there are many effects of all forms of non-genetic inheritance, and, although their relative importance varies between taxa, all are significant in evolution. Unfortunately very few evolutionary biologists study these effects. In particular, EISs have not been incorporated into the body of evolutionary theory and practice. The empirical data we cite are largely by-products of studies of non-evolutionary problems, and there are still very few theoretical studies or discussions directed at the evolutionary effects of epigenetic inheritance. The only exceptions to this are studies of the evolution of genomic imprinting and X-chromosome inactivation. Even the evolution of the epigenetic systems themselves has been neglected: there have been discussions of DNA methylation and RNA interference systems as genomic defence systems, but little attention has been given to the broader question of how the various EISs evolved and the ecological and developmental contexts in which this took place.

Theoretical implications: new definitions and new terminology

How should the changes that are now taking place in evolutionary theory be seen? Is a revolution in evolutionary thinking under way? Like Godfrey-Smith, we see no reason for describing what is happening as a Kuhnian revolution. However, we do believe that there is a limit to the patching-up and extending one can do to a theory,

and that in view of the massive amount of new data and wealth of new ideas that have to be incorporated, the Modern Synthesis no longer provides an adequate general framework for 21st-century evolutionary thinking. This does not mean that we believe that the processes that were regarded as basic and all-important in the Modern Synthesis can be dismissed: there is no doubt that the cumulative selection of small random genetic variations plays a role in evolution. It also does not mean that we think that all evolution is Lamarckian, although we are convinced that Lamarckian processes are important, and in our work we have focused on this neglected aspect of evolution. As we see it, evolution involves saltational, neo-Darwinian, and Lamarckian processes.

Our four-dimensional view of heredity is not just about there being more types of selectable variation for natural selection to work with. What is far more significant is that the origin, effects and extent of the extra types of variation are very different from those assumed in the Modern Synthesis. Even genetic variation may not stem from the rarely changing, discrete, particulate units that were assumed in that theory. Heritable variation (both genetic and epigenetic) can be extensive and lead to saltational changes; sometimes it is also targeted and induced. To some extent the Modern Synthesis defined itself negatively, through what it excluded—mainly Lamarckian and saltational processes. If both now have to be included, surely something rather drastic has happened to the theory? We think that Godfrey-Smith is right in predicting that in 20 years time biologists looking back at the late 1990s and first decade of the 21st century will see it as a period of dramatic and revolutionary change.

Godfrey-Smith believes that the sequence-centred view of biology that dominated the last quarter of the 20th century is now in decline, and we agree with him. Sequence information was the focal point of Crick's central dogma, and is still basic to the views of people like Dawkins, who think that if non-cultural heritable changes do not involve changes in nucleotide sequence, their significance is diminished. From our point of view, although the different effects and implications of the various types of heritable variations are interesting, whether a heritable difference involves a sequence change, or a conformational change, or a change in a pattern of activity at a higher level of biological organisation is not very important. This is nicely illustrated by the case of a yeast prion involving vacuolar protease B, which can exist in two cell-heritable stable states, active and inactive (Roberts and Wickner 2003). Although it shows all the properties of a prion, with this protein the difference in form is not solely conformational. The active form of the protein is necessary to remove amino acid sequences from molecules of its own precursor, thereby converting them from the inactive to active form. It is a self-propagating process: once a protein has been modified, it catalyses the same amino acid change in other precursor molecules. Formally, therefore, this seems to be a case in which sequence information is transferred from one protein molecule to another, which the central dogma says is something that should never occur. However, like Godfrey-Smith we think that the focus on sequence is misguided, and the fact that in this case the prion's switch in form involves a sequence change is unimportant. In evolution, it is not sequence but modularity and the combinatorial possibilities that it enables that matter. This point is central to our view of inherited variation, as well as to the broader syntheses being developed by West-Eberhard (2003) and others.

Evolutionary thinking is, we believe, lagging behind events in developmental biology and molecular biology. There is no revolution in these disciplines—they

simply expand and grow as they race ahead. However, 20th-century evolutionary biology was based on certain theoretical premises, which were fundamental to it. These can be stretched and modified, but there comes a point when all the extensions, modifications and additions amount to a qualitative change. We believe that we have reached a point where we need to alter our basic definitions of evolution and heredity. Since not only variations in genes but also other types of heritable variation have to considered, Dobzhansky's classical definition, according to which evolution involves a change in the genetic composition of population, is inadequate. It is too narrow. A better description might be that evolution *involves a set of processes that lead to changes in the nature and frequency of heritable types in a population*. Heredity, too, needs to be redefined to incorporate processes beyond DNA replication. We suggest that heredity should be defined as *the developmental reconstruction processes that link ancestors and descendants and lead to similarity between them*.

If, as we believe, we need new definitions of fundamental terms, and processes that were emphatically excluded from the Synthesis need to be added, then whatever words we use to describe the changes that have happened, the theory it is no longer the same. Elaborating on Godfrey-Smith's metaphor, we think that so many of the original supporting beams of the Modern Synthesis structure of Darwinism have been dispensed with, yet so many of the additions to it have assumed these beams are still in place, that not only is the original edifice now almost unrecognisable, it is also structurally unsound. It is time that it was rebuilt, this time using Darwinian, rather than neo-Darwinian, materials.

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