The Changing Concept of Epigenetics

EVA JABLONKA AND MARION J. LAMB

Cohn Institute for the History and Philosophy of Science and Ideas, Tel Aviv University, Tel Aviv 69978, Israel

ABSTRACT: We discuss the changing use of *epigenetics*, a term coined by Conrad Waddington in the 1940s, and how the epigenetic approach to development differs from the genetic approach. Originally, epigenetics referred to the study of the way genes and their products bring the phenotype into being. Today, it is primarily concerned with the mechanisms through which cells become committed to a particular form or function and through which that functional or structural state is then transmitted in cell lineages. We argue that modern epigenetics is important not only because it has practical significance for medicine, agriculture, and species conservation, but also because it has implications for the way in which we should view heredity and evolution. In particular, recognizing that there are epigenetic inheritance systems through which non-DNA variations can be transmitted in cell and organismal lineages broadens the concept of heredity and challenges the widely accepted gene-centered neo-Darwinian version of Darwinism.

KEYWORDS: canalization; epigenetic inheritance; epigenetic landscape; evolution; Waddington

Epigenetics is not a new discipline. It was born in the early 1940s, when Conrad Waddington first defined and began discussing it,[1] but only recently has it begun to be recognized as a distinct branch of biology. Now, in the wake of the Human Genome Project, it is at a critical crystallization stage. The way that it is defined, the boundaries that are drawn, and the language that is used will have long-lasting effects on future research and on the place of epigenetics in biological thinking. In what follows we will first look at how the definitions of epigenetics have changed during the past half century and at the position epigenetics occupies in relation to genetics and develop-

Address for correspondence: Eva Jablonka, Cohn Institute for the History and Philosophy of Science and Ideas, Tel Aviv University, Tel Aviv 69978, Israel. Voice: 972-3-640-9198; fax: 972-3-640-9457.
jablonka@post.tau.ac.il

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ment. We will then consider the practical importance of epigenetics in medicine, agriculture, and ecology and, finally, look at the implications that recent work in epigenetics has for the way we should think about heredity and evolution.

WADDINGTON'S EPIGENETICS

In the mid-1960s, Waddington wrote: "Some years ago [e.g. 1947] I introduced the word 'epigenetics,' derived from the Aristotelian word 'epigenesis,' which had more or less passed into disuse, as a suitable name for the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being."[2] He had coined a very clever little term. It related back to the Aristotelian theory of epigenesis, which stresses that developmental changes are gradual and qualitative, but also links to current and future studies of heredity. "Epi" means "upon" or "over," and the "genetics" part of epigenetics implies that genes are involved, so the term reflected the need to study events "over" or beyond the gene.

When Waddington invented his term, the gene's role in development was still completely mysterious. Waddington realized, however, that embryological development must involve networks of gene interactions. He was not alone in thinking this. For example, in 1939, in their *Introduction to Genetics*, Sturtevant and Beadle wrote, "…developmental reactions—reactions with which genes must be assumed to be concerned—form a complex integrated system. This can be visualized as a kind of three-dimensional reticulum…."[3]

Waddington's words and pictures leave little doubt that he saw development in terms of what today we would call differential gene expression and regulation. He illustrated his way of thinking with drawings in which the developmental system is depicted as a landscape in which bifurcating and deepening valleys run down from a plateau.[4,5] Examples of these "epigenetic landscapes" are shown in FIGURES 1 and 2. In FIGURE 1, the slightly undulating plateau is the fertilized egg, and the path that the ball would take represents the developmental route from the egg to a particular tissue or organ at the end of a valley. The course, slopes and cross-sections of the valleys are controlled by genes and their interactions. These Waddington depicted as a series of pegs (representing genes) and guy ropes (representing the "chemical tendencies" of the gene) underlying the landscape (FIG. 2). Through this image Waddington tried to show that there is no simple relationship between a gene and its phenotypic effects, because "if any gene mutates, altering the tension in a certain set of guy ropes, the result will not depend on that gene alone, but on its interactions with all the other guys."[5]

Waddington's epigenetics was not the same as what became known as developmental genetics. Both were concerned with the same processes, but

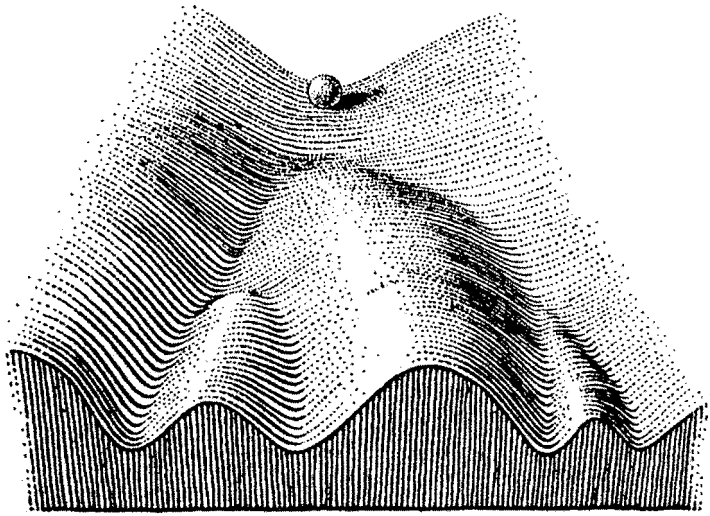

FIGURE 1. Waddington's epigenetic landscape. (Reproduced from Waddington,[5] p. 29, with permission from Taylor & Francis, London.)

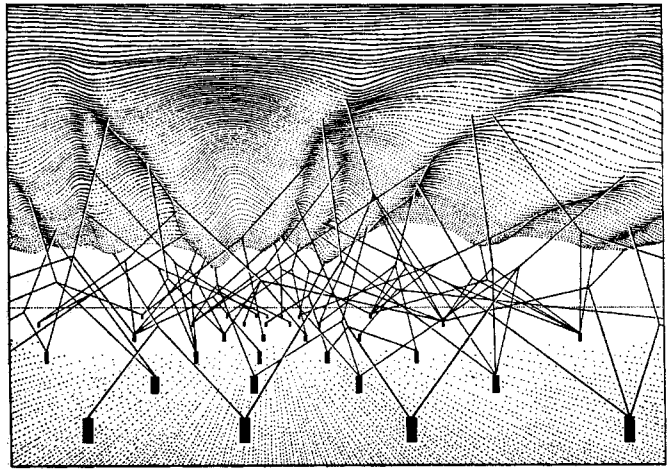

FIGURE 2. The interactions underlying the epigenetic landscape. (Reproduced from Waddington,[5] p. 36, with permission from Taylor & Francis, London.)

there were differences in perspective. Traditionally, the developmental geneticists' approach was to use genetic differences to throw light on embryological processes. For example, they would substitute a mutant gene for the normal one and study when and how this affected development, trying to trace the primary effect of the gene. What they were looking at was *the coupling between genetic and phenotypic variation*. The epigenetic approach taken by Waddington and others was somewhat different. Of course they recognized that studying the effect of genetic variation on phenotypic variation is important, but they saw this as only part of epigenetics. They also wanted to understand why very often *genetic and phenotypic variations are not coupled*. In other words, they were interested in situations in which genetic variation does not lead to phenotypic variation, and phenotypic differences are not associated with genetic differences.

Most natural genetic variations and many new experimentally induced mutations have little or no effect on the phenotype. The same is true for environmental variations: most make no difference to the final appearance of the animal. Development usually leads to the same well-defined end result in spite of variations in genes and in environmental circumstances. In Waddington's terminology, development is "canalized," and this canalization or buffering is the outcome of natural selection for genes whose actions and interactions make the valleys in his epigenetic landscape deep and steep sided.

Plasticity is the other side of the coin—genetically identical cells or organisms can differ markedly in structure and function. For example, kidney cells, liver cells, and skin cells differ phenotypically; and their daughter cells inherit their phenotype, but the variation is epigenetic, not genetic. Similarly, the differences between a worker bee and a queen bee are epigenetic, not genetic, because whether a larva becomes a worker or a queen depends on the way that it is fed, not on its genotype.

Although canalization and plasticity refer to diametrically opposite aspects of phenotypic changeability, what they have in common is that phenotypic variation is uncoupled from genetic variation. Recognizing this and accounting for it was central to the epigenetic approach. The distinction between epigenetics and developmental genetics was therefore a difference in focus, with epigenetics stressing complex developmental networks with a lot of redundancy and compensatory mechanisms, while developmental genetics was more concerned with the hierarchies of actions that led from a gene to its effects on the phenotype. Today, the situation is different, since all developmental biologists tend to talk and think in terms of complex gene networks and interactions; the epigenetics perspective has to a large extent replaced that of classical developmental genetics. Nevertheless, it would be wrong to think that epigenetics is the same as developmental biology. Developmental biology is a much broader discipline, embracing all aspects of embryology, regeneration, growth, and aging. Although genes are basic to all of these, it is possible to study many important aspects of development without worrying

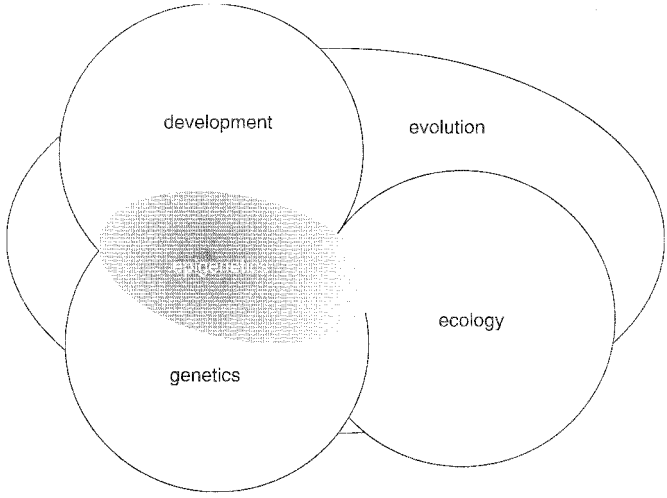

FIGURE 3. The place of epigenetics in biology. Waddingtonian epigenetics is located at the junction of genetics, developmental biology, and ecology, all of which are rooted in evolutionary biology.

about genes, particularly when focusing on higher levels of organization. Epigenetics in the sense Waddington used it is clearly *part* of developmental biology, a way of looking at it and studying it, but it is not a synonym.

Central to the thinking of Waddington, Schmalhausen,[6] and the other founders of epigenetics was evolution. They were interested in the evolution of developmental mechanisms—in the origins of the switches between alternative phenotypes and in the evolutionary routes to increased or decreased canalization and plasticity. Hence, epigenetics was a discipline that was to inform evolutionary theory, not just embryology. The experiments in which Waddington genetically assimilated various induced characters in *Drosophila* are a famous example of the productivity of applying the epigenetic approach to evolution.[7] A related research program, which is popular today, is the study of the evolution of reaction norms and reaction ranges—that is, of the plasticity of the phenotype in different environmental conditions. Epigenetics in Waddington's sense therefore relates to several different branches of biology; it stands at the intersection of developmental biology and genetics, but also impinges on ecology. Underlying everything is evolutionary biology (FIG. 3).

CHANGING DEFINITIONS

"Epigenetics" was little used during the first three decades of its existence. One exception is seen in the title of Løvtrup's book *Epigenetics: a Treatise*

on Theoretical Biology (1974),[8] but in spite of the title, Løvtrup tended to talk about "epigenetic events" rather than epigenetics and used epigenetics more or less as a synonym for developmental biology. Until the late 1980s, the few people who used the term epigenetics tended to use it in the same sense as Waddington. A 1982 dictionary of biology defined it as "Pertaining to the interaction of genetic factors and the developmental processes through which the genotype is expressed in the phenotype."[9] A year later, Medawar and Medawar wrote, "In the modern usage 'epigenesis' stands for all the processes that go into implementation of the genetic instructions contained within the fertilized egg. 'Genetics proposes: epigenetics disposes.'"[10]

In the early 1990s, epigenetics began to take on a new flavor. For example, in the first edition of his *Evolutionary Developmental Biology* (1992), Hall wrote, "Epigenetics or epigenetic control is the sum of the genetic and nongenetic factors acting upon cells to selectively control the gene expression that produces increasing phenotypic complexity during development."[11] Given the emphasis on canalization and plasticity in the early days of epigenetics, it was natural for the term to be applied to studies of the control of gene activity during embryonic development and differentiation. But the scope of epigenetics was narrowed even more as the decade progressed, so that a 1996 book entitled *Epigenetic Mechanisms of Gene Regulation* defined it as "The study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence."[12]

The change in the meaning given to epigenetics came about as the molecular mechanisms controlling gene activity and the inheritance of cell phenotypes began to be unraveled. Holliday's work on cell memory, mainly in relation to methylation, probably contributed more to the change than anything else, and the shift can be seen in his writings. In 1990, he wrote that epigenetics "can be defined as the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms."[13] This definition is very much in the spirit of Waddington's original definition and was repeated several times in more or less the same form around this time. Significantly, he added, "Mechanisms of epigenetic control must include the inheritance of a particular spectrum of gene activities in each specialized cell. In addition to the classical DNA code, it is necessary to envisage the superimposition of an additional layer of information which comprises part of the hereditary material, and in many cases this is very stable. The term epigenetic inheritance has been introduced to describe this situation." A few years later, Holliday was defining epigenetics as "The study of the changes in gene expression, which occur in organisms with differentiated cells, and the mitotic inheritance of given patterns of gene expression."[14] Holliday stated explicitly that this definition was intended to cover not only the DNA–protein interactions involved in the control of gene activity, but also the DNA rearrangements that go on in the immune system, and even mitochondrial inheritance. Because studies of genomic imprinting had shown that

non-DNA information can be transmitted from parents to offspring, however, he added as a supplementary definition: "Nuclear inheritance which is not based on differences in DNA sequence."

EPIGENETICS TODAY

By the end of the 20th century, epigenetics had grown to become a widely recognized subdiscipline of biology, but for many people epigenetics had become almost synonymous with "epigenetic inheritance." For example, the definition given in a 2001 issue of *Science* that focussed on epigenetics was "The study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence."[15] Even as a definition of epigenetic inheritance, rather than epigenetics, this wording presents problems, because it excludes the regularly occurring developmental changes that alter gene function through the reorganization of DNA (e.g., changes in mammalian immune system genes, amplification of chorion genes in *Drosophila*, and many other DNA changes[16]). The difficulty is that although one can usefully distinguish between DNA and non-DNA inheritance, there are no simple criteria for distinguishing between genetic and epigenetic phenomena. In general, genetics today deals with the transmission and processing of information in DNA, whereas epigenetics deals with its interpretation and integration with information from other sources. Epigenetics is therefore concerned with the systems of interactions that lead to predictable and usually functional phenotypic outcomes; it includes processes of spontaneous self-organization that depend on the physical and chemical properties of the internal and external environments, as well as on evolved gene-dependent mechanisms.

Because of the lack of consensus about what the term epigenetics means, Lederberg has suggested that it should be abandoned.[17] He maintains that epigenetics in Waddington's sense and epigenetics in the modern sense have little in common, so retaining the word simply leads to confusion. It would be better, he suggests, to talk about nucleic, epinucleic, and extranucleic information, rather than epigenetic information.

It is true that epigenetics today is very different from Waddington's epigenetics, but the same can be said for many other terms in biology, including Johanssen's "gene" and Bateson's "genetics." This has not been seen as a good reason for abandoning them. We feel that using Lederberg's "nucleic," "epinucleic," and "extranucleic" information would not be helpful, because information cannot be neatly parceled in this way. One valuable aspect of the term epigenetics is that it has always been associated with the interactions of genes, their products, and the internal and external environment, rather than with the individual facets of developmental regulation. Because of this, there

is a continuity between epigenetics in Waddington's sense and epigenetics today: both focus on alternative developmental pathways, on the developmental networks underlying stability and flexibility, and on the influence of environmental conditions on what happens in cells and organisms. It is only when epigenetics is equated solely with the inheritance of non-DNA variations that its original meaning is obscured.

Examination of recent books and articles with epigenetics in their titles shows that the scope of the subject is far less narrow than some current definitions suggest. It includes studies of the cellular regulatory networks that confer phenotypic stability, developmentally regulated changes in DNA such as those seen in the immune system, cell memory mechanisms involving heritable changes in chromatin and DNA methylation, and the self-propagating properties of some protein conformations and cellular structures. Cellular inheritance is an important aspect of some of these studies, and there is growing interest in the transgenerational inheritance of some epigenetic variations. One of the most productive areas of research in the past decade has been the study of the controlled responses of cells to genomic parasites and severe environmental insults, which involve DNA methylation, RNA mediated gene silencing, and enzyme-mediated DNA rearrangements and repair. Much of this work stems from McClintock's work and ideas on stress responses in plants,[18] but it is very clearly epigenetics in Waddington's sense, particularly when, as commonly happens, it is discussed within an evolutionary framework.

PRACTICAL IMPORTANCE

One of the reasons for the recent growth in epigenetics is that commercial companies, as well as the academic community, are taking an active interest in what goes on beyond the DNA level. They are well aware that epigenetics could revolutionize medicine and agriculture. It also has implications for other parts of biology, including ecology and conservation practices.

Cancer

An indication of the potential importance of epigenetics for medicine came in 1979 when Holliday suggested that heritable epigenetic changes in gene expression are responsible for cancer.[19] It took some time for a substantial research program to get under way, although there was early evidence that the DNA of some tumor cells is abnormally methylated, but today cancer epigenetics is a thriving field of research.[20] We now know that many tumor cells have aberrant, cell-heritable patterns of DNA methylation that are often associated with the silencing of tumor-suppressor genes.[21] Furthermore, the epigenetic changes seem to predispose cells to DNA sequence alterations that

enhance the process of tumorigenesis. The hope now is that looking for abnormal patterns of methylation and changes in the other components of chromatin will eventually enable better risk assessment, earlier diagnosis, and improved monitoring of the progression of cancers. Because epigenetic changes are potentially reversible, understanding how and why methylation patterns and the histone and nonhistone proteins associated with DNA are different in tumor cells may also lead to new methods of treatment.

Hereditary Disease

The medical importance of epigenetics is not limited to cancer. Some hereditary diseases are known to be caused by defects in imprinted genes—genes whose epigenetic state depends on whether they were inherited from the mother or the father.[22] In some cases the inherited disorder is caused by a mutation of the gene, but in others the defect may be epigenetic—an epimutation involving an altered methylation pattern. Epigenetic changes in methylation patterns are also involved in aging changes.[23] Such findings have exciting implications for medicine, since they open up the possibility of treating some diseases by altering the epigenetic states of genes.

Epigenetic Epidemiology

The fact that epigenetic effects can be transmitted to offspring also has important implications for medicine, because it may make it necessary to develop an epigenetic epidemiology. There is growing evidence (reviewed by Barker[24]) that maternal starvation and stress have persistent effects on children. This could be just the tip of a big iceberg. Relevant data about the effects of environmentally induced changes on the next generation are scarce, but that which is available for thalidomide suggests that it may have transgenerational effects, since the incidence of limb abnormalities in the offspring of thalidomide victims is far too high to be accounted for by mutations.[25] More data are available for mice and rats. For example, we know that the offspring of mice treated with carcinogens are predisposed to tumors and other abnormalities.[26] Moreover, some environmental effects go beyond the first generation: drug-induced abnormalities in endocrine function, as well as starvation-induced physiological and behavioral abnormalities, are heritable for at least three generations.[27] The nature of these heritable variations is unclear, but recently Hugh Morgan and colleagues have related inherited variations in coat color, diabetes, and other abnormalities in an inbred line of mice to variations in the methylation patterns of an inserted retrotransposon.[28] In this case the variations, which are transmitted through female meiosis, seem to have been the result of developmental noise, but in other cases they may be environmentally induced. Clearly, epidemiological research programs and

medical practice will have to accommodate information like this and develop ways of recognizing, avoiding, and curing disorders caused by epigenetic changes.

One epigenetic system that has already been in the epidemiological limelight is that associated with the human diseases CJD (Creutzfeldt-Jakob disease) and kuru, the cattle disease BSE (bovine spongiform encephalopathy), and scrapie in sheep. All seem to be caused by prions—transmissible infectious protein complexes, whose reproduction and reconstruction involve some type of three-dimensional structural templating.[29,30] It is possible that environmental pollutants such as asbestos and some of the natural effects of aging are associated with comparable self-propagating alterations in cellular and extracellular molecules and structures. Needless to say, understanding the mechanisms underlying the formation and propagation of such molecules and structures is essential if we are to combat such disorders.

Epigenetic Defense Mechanisms

There are other aspects of epigenetics that may be relevant to preventing or curing diseases. Cells have sophisticated epigenetic mechanisms for avoiding or destroying genomic parasites. They do this by methylating the foreign DNA or by RNA-directed degradation of certain types of RNA transcripts or by a combination of both.[31] One of the exciting possibilities is that it will be possible to control and use these natural, epigenetic defense mechanisms to silence the foreign or endogenous genes associated with various diseases.

Cloning

Cloning is another area of both medicine and agriculture in which epigenetics is important. It is quite clear that for normal development the somatic cell or nucleus that is used for cloning needs to be epigenetically reprogrammed.[32] The frequency of successful animal clones is still low, and many of the animals that manage to reach adulthood have abnormalities that can be attributed to aberrant reprogramming of the original somatic nucleus. Knowing which cells types to choose for cloning, how to treat them before their fusion with the enucleated egg, whether or not to do several serial transfers and so on is going to be crucial for the success of this important technique. Obviously, a good understanding of epigenetics is required.

Agriculture

In agriculture, the importance of epigenetic inheritance is already widely acknowledged, because it has caused many problems in genetic engineering aimed at crop improvement. Commonly, newly inserted foreign genes are

heritably silenced through extensive DNA methylation, so ways of circumventing this problem have had to be developed. On the positive side, since some epigenetic variations can be induced by environmental changes, it may be possible to develop agricultural practices that exploit these inducing effects and thus develop improved, "epigenetically engineered" crops.

Ecology

So far, epigenetics has had little impact on ecology, yet there is a great need for studies that look at the frequency of epigenetic variants in natural populations. Such studies could be important for conservation programs. Organisms interact with each other and with their abiotic environment, and through these interactions they acquire epigenetic information, some of which is inherited. By its nature, this epigenetic information is not something established once and for all—it is the result of gradual historical–developmental processes, constructed over many generations. This means that freezing seeds, embryos, or DNA in order to restore the plants and animals to nature in a better, more ecologically sane future may not work unless the conditions reflected in their epigenetic heritage are reconstructed too. In the same way as when we destroy a culture or a language we cannot console ourselves by saying that because frozen eggs and sperm still exist the culture can be reconstructed, we should not believe that creating seed or DNA banks will enable us to re-create viable populations of the plants and animals that were present in an ecological community. When we destroy ecosystems, we destroy a lot more variation and diversity than we imagine, epigenetic as well as genetic. The stability of communities often depends on this diversity, which stems from the interacting histories of the species in them.

THEORETICAL IMPLICATIONS

At first sight, incorporating modern epigenetics into today's neo-Darwinian theoretical framework does not require any radical modifications of the theory. Most biologists would say that, although we now need to think in a more sophisticated way about gene expression and plasticity, we do not need to change any fundamental assumptions. Even epigenetic inheritance can be accommodated within neo-Darwinism: it is possible to think about the inheritance of epigenetic variants as extended development, with the number of generations a phenotype persists being simply an aspect of the range of reaction of the genotype. The evolutionary questions that are of interest are about how variations in the regulatory regions of the genome affect this plasticity. For example, will the addition of some of the repetitive DNA sequences that bind certain proteins extend cell memory or transgenerational stability?

This type of question is, of course, legitimate and very interesting, but epigenetic inheritance raises other, equally important evolutionary questions. In fact it introduces new and, from the point of view of present day neo-Darwinism, subversive considerations into evolutionary theory. It is easy to see why if we think first about culture, rather than epigenetics. Human symbolic culture is undoubtedly undergoing evolutionary change, and important questions can be asked about the genetic changes that enabled humans to construct their symbolic culture and would enable them to extend it. However, equally important questions can be asked about the nature and dynamics of cultural evolution itself, because there is an axis of cultural change that is to some extent independent of genetic variations. Even in a world of genetically identical individuals, we can imagine evolutionary processes that would lead to many different cultures. Cultural variation is, to some extent at least, decoupled from DNA variation; and to understand cultural evolution, we need to study this autonomous aspect of variation. The same is true for epigenetic variation. Heritable epigenetic variation is decoupled from genetic variation *by definition*. Hence, there are selectable epigenetic variations that are independent of DNA variations, and evolutionary change on the epigenetic axis is inevitable. The only question is whether these variations are persistent and common enough to lead to interesting evolutionary effects.

Some people have argued that although epigenetic systems are crucial for the evolution of cell determination and differentiation in multicellular organisms, the transgenerational transmission of epigenetic variants is a rare and unimportant biological mistake. Usually, it is said, the variants are deleterious and are eliminated by selection, but even if beneficial variants do arise from time to time, they are too transient to have any interesting evolutionary effects.[33,34] There are problems with this argument, however.[16] First, there is no reason to think that epigenetic variations are rare: when actively sought, they have usually been found. Second, epigenetic variations can be transmitted very stably, certainly in cell lines. Furthermore, lack of fidelity in the transmission of epigenetic variants does not have the same implications as lack of fidelity in the genetic system, where changes usually reflect noise and lead to loss of functional adaptation. With epigenetic systems, lack of fidelity can reflect progressive functional changes that improve adaptation. Consider, for example, a gene that becomes inactive in response to an environmental change. Assume that this inactive state is adaptive, but is transmitted with low fidelity, so that the inherited epigenetic state (e.g., a pattern of methylation) is variable. If the environmental change persists and a stably inactive state continues to be beneficial, those cell lineages in which the inactive state is most stable and most stably inherited will be selected. Because in each generation the effect of the environment is to induce inactivation (impose an inactive pattern on the gene), epigenetic variation is likely to become biased toward ever more stably inactive states. And since the environment is not only the inducer but also the selector of the inactive state, there will be a progres-

sive shift toward stable inactivation and improved fidelity in transmission. Third, epigenetic inheritance is not limited to multicellular organisms: it is found in unicellular organisms too. If it is only important in differentiating tissues, what is its role in these organisms? Fourth, several different models have shown how, in certain conditions, transmitting some (not all) epigenetic variations from one generation to the next is a selective advantage, even if they are stable for only a few generations.[35,36] Fifth, epigenetic variations may influence the site and nature of genetic changes and affect evolution in this way.

If it is accepted that heritable epigenetic variations can underlie evolutionary change, then it has consequences for evolutionary theory. It means that evolution cannot be seen solely in terms of changing gene frequencies, since the frequency of epigenetic variants has to be considered too. More significantly, since epigenetic systems participate in the regulation of cellular activities and are at the same time heredity systems, the inheritance of acquired (regulated and induced) variation is possible. Consequently, there is a Lamarckian component in evolution, with the environment being an inducer as well as a selector of variation. Of course, in multicellular organisms the relevant epigenetic variation has to occur in the germ line and to persist through meiosis and embryogenesis in order to be passed to the next generation. But more and more cases show that this does occur, especially in plants,[37] where there is no segregation between soma and germ line. Many other multicellular organisms also have no or late germ-line–soma segregation, so have ample opportunity for transmitting somatically induced epigenetic variations.

This Lamarckian aspect of epigenetic inheritance has several interesting theoretical implications that relate to the interplay of evolution and development. The most obvious is that with some epigenetic inheritance systems there is no real equivalent of the phenotype–genotype distinction. When epigenetic inheritance involves self-perpetuating cellular structures or self-maintaining regulatory loops, there are no parallels with genotype/phenotype, because the reconstruction of the phenotype is an integral part of the transmission mechanism. Epigenetic inheritance also means that the distinction between developmental (proximate) causes and evolutionary (ultimate) causes is not as clearcut as we have been accustomed to believe, because developmentally acquired new information can be transmitted. Proximate causes are sometimes also direct evolutionary causes. The closely related assumption that instructive processes (processes that lead to the induction of the functional organization of a system) are the subject matter of development while selective processes (those that "choose" among variant systems) are sufficient to explain evolution also needs to be modified. If development impinges on heredity and evolution, then there are some instructive processes in evolution too. It follows from this that the distinction between replicator and vehicle, or even replicator and interactor, is in many cases inappropriate.

In summary, we can say that epigenetics requires a broadening of the concept of heredity and the recognition that natural selection acts on several different types of heritable variation. Although the current gene-centered version of Darwinism—*neo*-Darwinism—is incompatible with Lamarckism, Darwinism is not. In the past, Lamarckism and Darwinism were not always seen as alternatives: they were recognized as being perfectly compatible and complementary. In the light of epigenetics, they still are. Recognizing the role of epigenetic systems in evolution will allow a more comprehensive and powerful Darwinian theory to be constructed, one that integrates development and evolution more closely.

REFERENCES

1. WADDINGTON, C.H. 1942. The epigenotype. Endeavour **1:** 18–20.
2. WADDINGTON, C.H. 1968. The basic ideas of biology. In: *Towards a Theoretical Biology,* Vol. 1: Prolegomena. C.H. Waddington, Ed.: 1–32 (Edinburgh: Edinburgh University Press).
3. STURTEVANT, A.H. & G.W. BEADLE. 1939. *An Introduction to Genetics* (Philadelphia: W. B. Saunders & Co.)
4. WADDINGTON, C.H. 1940. *Organisers and Genes* (Cambridge: Cambridge University Press).
5. WADDINGTON, C.H. 1957. *The Strategy of the Genes* (London: Allen & Unwin).
6. SCHMALHAUSEN, I.I. 1949. *Factors of Evolution: The Theory of Stabilizing Selection*. Trans. I. Dordick (Philadelphia: Blackiston).
7. WADDINGTON, C.H. 1953. Epigenetics and evolution. Symp. Soc. Exp. Biol. **7:** 186–199.
8. LØVTRUP, S. 1974. *Epigenetics: A Treatise on Theoretical Biology* (London: John Wiley & Sons).
9. LINCOLN, R.J., G.A. BOXSHALL & P.F. CLARK. 1982. *Dictionary of Ecology, Evolution and Systematics* (Cambridge: Cambridge University Press).
10. MEDAWAR, P. & J. MEDAWAR. 1983. *Aristotle to Zoos* (Cambridge, MA: Harvard University Press).
11. HALL, B.K. 1992. *Evolutionary Developmental Biology* (London: Chapman & Hall).
12. RUSSO, V.E.A., R.A. MARTIENSSEN & A.D. RIGGS, Eds. 1996. *Epigenetic Mechanisms of Gene Regulation* (Plainview, NY: Cold Spring Harbor Laboratory Press).
13. HOLLIDAY, R. 1990. Mechanisms for the control of gene activity during development. Biol. Rev. **65:** 431–471.
14. HOLLIDAY, R. 1994. Epigenetics: an overview. Dev. Genet. **15:** 453–457.
15. WU, C.-T. & J.R. MORRIS. 2001. Genes, genetics, and epigenetics: a correspondence. Science **293:** 1103–1105.
16. JABLONKA, E. & M.J. LAMB. 1995. *Epigenetic Inheritance and Evolution: The Lamarckian Dimension* (Oxford: Oxford University Press).
17. LEDERBERG, J. 2001. The meaning of epigenetics. The Scientist Sept. 17: 6.

18. MCCLINTOCK, B. 1984. The significance of responses of the genome to challenge. Science **226:** 792–801.
19. HOLLIDAY, R. 1979. A new theory of carcinogenesis. Br. J. Cancer **40:** 513–522.
20. JONES, P.A. & P.W. LAIRD. 1999. Cancer epigenetics comes of age. Nature Genet. **21:** 163–167.
21. BAYLIN, S.B. & J.G. HERMAN. 2000. DNA hypermethylation in tumorigenesis. Trends Genet. **16:** 168–174.
22. MURPHY, S.K. & R.L. JIRTLE. 2000. Imprinted genes as potential genetic and epigenetic toxicological targets. Envir. Health Perspect. **108**(Suppl.1): 5–11.
23. LAMB, M.J. 1994. Epigenetic inheritance and aging. Rev. Clin. Gerontol. **4:** 97–105.
24. BARKER, D.J.P. 1994. *Mothers, Babies, and Disease in Later Life* (London: BMJ Publishing Group).
25. HOLLIDAY, R. 1998. The possibility of epigenetic transmission of defects induced by teratogens. Mutat. Res. **422:** 203–205.
26. NOMURA, T. 1982. Parental exposure to X rays and chemicals induces heritable tumours and anomalies in mice. Nature **296:** 575–577.
27. CAMPBELL, J.H. & P. PERKINS. 1988. Transgenerational effects of drug and hormonal treatments in mammals: a review of observations and ideas. Prog. Brain Res. **73:** 535–553.
28. MORGAN, H.D. *et al*. 1999. Epigenetic inheritance at the agouti locus in the mouse. Nature Genet. **23:** 314–318.
29. PRUSINER, S.B. 1998. Prions. Proc. Natl. Acad. Sci. USA **95:** 13363–13383.
30. CHERNOFF, Y.O. 2001. Mutation processes at the protein level: is Lamarck back? Mutat. Res. **488:** 39–64.
31. WOLFFE, A.P. & M.A. MATZKE. 1999. Epigenetics: regulation through repression. Science **286:** 481–486.
32. SOLTER, D. 2000. Mammalian cloning: advances and limitations. Nature Rev. Genet. **1:** 199–207.
33. MAYNARD SMITH, J. 1990. Models of a dual inheritance system. J. Theoret. Biol. **143:** 41–53.
34. JORGENSEN, R. 1993. The germinal inheritance of epigenetic information in plants. Phil. Trans. R. Soc. B **339:** 173–181.
35. JABLONKA, E., *et al*. 1995. The adaptive advantage of phenotypic memory in changing environments. Phil. Trans. R. Soc. B **350:** 133–141.
36. LACHMANN, M. & E. JABLONKA. 1996. The inheritance of phenotypes: an adaptation to fluctuating environments. J. Theoret. Biol. **181:** 1–9.
37. CUBAS, P., C. VINCENT & E. COEN. 1999. An epigenetic mutation responsible for natural variation in floral symmetry. Nature **401:** 157–161.