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The Potential of Epigenetics Research to Transform Conceptions of Phenotype Development

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Abstract

Epigenetics remains an exciting subdiscipline of biology, generating discoveries and insights about development. Because epigenetic phenomena can draw attention to the dynamic, interactional, and probabilistic nature of phenotype development, epigenetics research could hasten the demise of both nature-nurture debates and reductionist, genetically determinist perspectives on phenotype development. However, new data alone will not inevitably transform conceptualizations of phenotype origins, because it remains possible to assimilate epigenetic phenomena into traditional conceptual frameworks; epigenetic discoveries could even strengthen biologically determinist conclusions if traditional conceptualizations are retained. Although epigenetics will not *force* conceptual transformation, epigenetics research encourages the dismissal of the nature-nurture dichotomy by emphasizing *mechanisms* underlying phenotype development, thereby fostering clearer conceptions of how phenotypes emerge from interactions between biological and nonbiological components of developing systems. The developmental systems perspective, which acknowledges the vital roles of contexts in development, offers benefits not provided by reductionist perspectives, making it an appropriate conceptual framework for developmental science.

Epigenetics remains big news. One measure of its ascendance is the number of times the word has appeared in books over the last several decades. Within 10 years of being introduced in the late 1940s by developmental biologist Conrad Waddington [Jablonka & Lamb, 2002; Richards, 2006], the word started showing up in books, and in the 4–5 decades preceding the year 2000, its use had doubled. Then, in just the first

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8 years of the new millennium, the frequency with which the word appeared had *sextupled*. Google Books Ngram Viewer, the source of these data, does not consider books published after 2008, but if the trajectory of the growth curve has continued into the next 9 years of this century, it is no wonder that many writers now consider "epigenetics" to be a buzzword [e.g., Park, 2015; Rutherford, 2015].

But what *is* epigenetics? For a word coined relatively recently, it is surprisingly difficult to offer a consensus definition. In part, this is because Waddington self-consciously chose his word to hearken back to classical antiquity: Aristotle had used the word "epigenesis" to refer to the process by which a mature organism comes into being [Van Speybroeck, 2002; Waddington, 1956]. Specifically, Aristotle concluded that development is an "epigenetic" process (using the adjectival form of the word "epigenesis"), meaning that features of living things develop over time, emerging from prior states in which those features are not present. Given this historical meaning, "epigenetic" can properly be used to describe *any* process in which a new characteristic of an organism arises in development, whether it is a new behavior, a new physiological process, or a new organ. "Epigenetic" continues to be used in this broad way by so-called developmental systems theorists who argue that organisms' phenotypes arise during development as a result of mechanical interactions that occur between components of developing organism-environment systems, components such as genes, proteins, cells, organisms, and their physical and social contexts [Ford & Lerner, 1992; Gottlieb, 1991, 1997, 2007; Johnston, 1987; Lewkowicz, 2011; Lickliter & Honeycutt, 2015; Michel & Moore, 1995; Overton, 2010; Overton & Lerner, 2012; Oyama, 1985/2000].

Waddington chose the word "epigenetics" purposefully to evoke Aristotle's ideas about development, recognizing that phenotype development is influenced by ecological and other factors "above" the genes (the prefix "epi," from Greek, literally means "above," "over," or "on"). However, as Jablonka and Lamb noted, "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" [2002, p. 83]. Perhaps because of this focus on genetic activity, many theorists by the 1990s had begun using "epigenetics" much more narrowly, to refer only to how genes are regulated during embryonic development [Russo, Martienssen, & Riggs, 1996]. By the end of that decade, some definitions had even reserved the word to refer only to *heritable* changes in cell nuclei that do not involve changes to the DNA sequence [Jablonka & Lamb, 2002]. More recently, a 2010 article in *The Journal of Experimental Biology* identified more than a half-dozen different definitions of "epigenetics," making it clear that this word does not refer to just one thing [Ho & Burggren, 2010].

Despite the many definitions of "epigenetics," Waddington's decision to root his neologism in Aristotle's conception has ensured that all discussions of epigenetics are ultimately about development. And this persistent focus on development is one reason epigenetics has become the big news that it has; it is a focus that is decidedly at odds with what was the prevailing view in biology through most of the 20th century. By the 1950s, biologists considered adaptive phenotypes to be determined by the sequence of nucleotide bases making up an organism's DNA. This genetic determinism, which remains a central feature of the modern synthesis of Darwin's theory of evolution-by-natural-selection and the gene theory that emerged early in the 20th century, treated development as a relatively unimportant process in biology [Lickliter, 2017; Mayr & Provine, 1980; Moore, 2001, 2008b]. After all, if development simply unfolds as it does because there are "instructions" in DNA that specify how it will unfold, then the process of development is significantly less interesting than are the genetic instructions themselves. Faith in the genetic determinist viewpoint helps explain why the US federal government budgeted approximately USD 3 billion between 1990 and 2003 for scientific activities related to genomics [United States Department of Energy, 2013]. Nonetheless, it has become increasingly clear that genes do not determine phenotypes, and that instead, phenotypes emerge as a result of developmental processes that are inherently probabilistic [Gottlieb, 1991, 1992, 1998, 2007; Karmiloff-Smith, 2013; Lickliter, 2013; Noble, 2006]. Given the benefits that are likely to accrue by focusing on development rather than on DNA sequences alone [Moore, 2001], it stands to reason that a branch of biology that is fundamentally about development – epigenetics – would now be drawing increasing attention.

Epigenetics might also be expected to cause a stir because of how Waddington effectively situated it at the interface between DNA and its environment [Meaney & Szyf, 2005a; Moore, 2015b; Peedicayil, 2012]; seen in this way, epigenetics could hold the key to understanding how nature and nurture work together to produce phenotypes. In fact, several writers have pointed out that our emerging understanding of epigenetics should render the traditional nature-nurture debate moot [González-Pardo & Álvarez, 2013; Meaney, 2010; Weaver, 2007]. There have now been numerous empirical demonstrations of environmental factors having epigenetic effects wherein a particular experience causes changes in genetic activity via alterations of so-called epigenetic marks, chemical groups that become attached to DNA itself or to proteins closely associated with DNA [Provençal et al., 2012; Tung et al., 2012; Waterland & Jirtle, 2003; Weaver et al., 2004]. Given the discovery that factors typically associated with nurture – such as an animal's diet, social status, and the behavior of its mother early in life – can have dramatic effects on the operation of factors typically associated with nature (i.e., genes), the idea that nature or nurture can affect development *independently of the other* becomes increasingly untenable. The possibility that research on epigenetic phenomena might finally resolve a debate that is hundreds of years old is reason enough for this work to be causing excitement among life scientists.

Nature/Nurture: A Persistent Problem

The idea that nature and nurture can be construed as independent contributors to development has proven remarkably durable [Moore, 2008a, 2013b]. There are at least two reasons why the persistence of such a dichotomous conceptualization should be surprising. First, theorists such as Lehrman [1953], Schneirla [1957], Kuo [1967], Gottlieb [1976], Oyama [1985/2000], and Lerner [1986] have been offering cogent critiques of this perspective for more than 60 years [Moore, 2013a, 2016b]. Second, empirical work in several disparate sciences has overwhelmingly supported the claim that the development of all phenotypes is always influenced by factors generally associated with nature (e.g., DNA segments) *and* by factors generally associated with nurture (e.g., experiences of the physical and social environments) [Stotz, 2006]. For example, neuroscientists now recognize that basic, species typical brain structures and functions in mammals are influenced by an organism's experiences during development [Edelman, 1992; Greenough, Black, & Wallace, 1987; Pantev et al., 1998].

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Likewise, developmental biologists have established that environmental factors – no less than genetic factors – regulate the emergence of phenotypes [Gilbert & Epel, 2015]. Similarly, molecular biologists now know that the products of genetic activity are dramatically affected by the contexts in which DNA segments are located [Amara, Jonas, Rosenfeld, Ong, & Evans, 1982; Noble, 2006, 2012; Pan, Shai, Lee, Frey, & Blencowe, 2008; Wang et al., 2008]. The discovery that an organism's experiences can directly affect genetic activity via epigenetic processes [Harper, 2005; Meaney, 2007; Meaney & Szyf, 2005b; Weaver et al., 2004] is only the latest datum available to reinforce the belief that nature and nurture always work *inter*dependently to influence phenotypes [Moore, 2008a, 2013a]. For all of these reasons, theorists in many quarters no longer think about phenotype development in terms of a nature/nurture dichotomy. Nevertheless, dichotomous thinking about nature and nurture has proven surprisingly resilient.

For example, in a best-selling book on human nature that was a finalist for the Pulitzer Prize, Steven Pinker encouraged dichotomous thinking about nurture and nature when he argued that "in some cases, an extreme environmentalist explanation is correct … [whereas in] other cases … an extreme hereditarian explanation is correct" [Pinker, 2002, p. viii]. Even in more recent writing that consistently refers to the importance of nature-nurture interactions, there remains an assumption that some of our phenotypes are "biological" and "innate," as if the development of those phenotypes cannot be influenced by factors that would ordinarily be considered "nurture" [e.g., Lewis, 2014]. Likewise, twin studies conducted by behavioral geneticists continue to generate data that contribute to the impression that some phenotypes are more influenced by genetic than environmental factors, or vice versa [see Polderman et al., 2015, for numerous examples].

The question before us is whether research on epigenetics will *more effectively* undermine the conceptual foundations that have long supported the nature-nurture debate, compared to previous challenges to those foundations. A look at the recent literature focusing specifically on *behavioral* epigenetics – the branch of epigenetics concerned with psychological phenomena such as stress reactivity, psychopathology, learning, and memory [Lester et al., 2011] – suggests that many theorists are optimistic that these new discoveries will produce a sea change in our conceptions. To provide just a few examples out of many that are available, Loi, Del Savio, & Stupka [2013] stated that "epigenetics provides a chain of connections between what used to be qualified as *social* and *natural* inequality, leading to a reformulation of these contested boundaries" (p. 143), and Meloni [2015] concurred that "epigenetics makes the inappropriateness of the natural/social divide … even more flagrant" (p. 133). Highlighting the potentially revolutionary implications of some epigenetic phenomena, Keller [2014] argued that work in this domain "challenges the very distinction between 'genetic' and 'non-genetic.' As such, it is part of a … revolution in our thinking both about the relation between genes, genomes, and organisms, and about the relation between all three of these entities and their environments" (p. 2423). Clearly, numerous theorists agree that behavioral epigenetics is poised to finally end the nature-nurture debate once and for all [Moore, 2015b].

However, such optimism might not be warranted. To some observers, it seems as if epigenetics might merely move the boundary between nature and nurture closer to the gene. From this perspective, new data on epigenetics affirm a broader role for nurture in phenotype development, but do not fundamentally change the conceptual relationship between nature and nurture; accordingly, these two contributors to development continue to be seen as distinct, independently operating factors. Likewise, the very sorts of conceptual obstacles that have prevented a half-century of theoretical and empirical work from vanquishing the nature-nurture debate remain real threats to fundamental conceptual change. Before concluding that epigenetics will necessarily bring a new *weltanschauung* to western society, it might be worth examining how epigenetics could fail to undermine traditional dichotomous thinking about nature and nurture.

The Potential Failure of Epigenetics as a Dichotomy Breaker

Literature searches for publications on epigenetic phenomena reveal an enormous number of papers that are deeply rooted in traditional molecular biology. This is not surprising, as epigenetics in the modern sense is about how genes are regulated, and not specifically about how phenotypes emerge during development from interactions between system components. As such, publications in this tradition are preoccupied with structures and processes in cell nuclei, and remain focused only on a molecular level of analysis. This focus on gene expression can have the consequence of reinforcing traditional *non*developmental views of phenotype causation. Specifically, rather than challenging the idea that there are biological molecules that single-handedly cause phenotypic outcomes, this focus could *reinforce* that very idea; in this case, research on epigenetics could simply shift attention from one kind of molecule, such as DNA and the "code" it carries, to other kinds of molecules, such as histone proteins and the putative codes they carry [Strahl & Allis, 2000]. This change of focus would not be expected to encourage transformation of our conceptions, because it would allow traditional genetic determinism to be merely replaced with a conceptually similar *epi*genetic determinism [Moore, 2015b].

To get a feel for how traditional conceptualizations could persist even in the face of new understandings about epigenetics, one only needs to consider a couple of examples from the burgeoning epigenetics literature. A 2012 paper in the journal *Blood* reported that a human gene variant introduced into experimental mice can induce epigenetic changes at a particular location in the mouse genome, which accelerates the abnormal growth of blood cells in bone marrow [Khandanpour et al., 2012]. Similarly, a recent paper in *Scientific Reports* announced the finding that genetic variants involved in the epigenetic regulation of sperm production are associated with a form of infertility in men [Li et al., 2015]. In both cases, one could expect readers to take away the message that individuals with the identified epigenetic changes will manifest the associated sperm or blood abnormalities in a biologically determined fashion, that is, independently of any other factors. As with genetic determinism, such "epigenetic determinism" would imply that these pathologies are *inherent* and not subject to influence by environmental (or any other nonmolecular) factors during development. An ongoing and exclusive focus on molecular processes could strip epigenetic phenomena of their potential to draw attention to a fundamental feature of phenotype development, namely its quality of being *open* to influences arising at other levels of developing systems, such as the environment.

Thus, the epigenetics literature in some biological subdisciplines might perpetuate reductionist, biologically determinist ways of thinking about the causes of phenotypes. In contrast, the epigenetics literature in the behavioral and social sciences is more likely to contain papers acknowledging the crucial importance of contextual factors in phenotype development. However, even some of this literature depicts epigenetics in a way that allows for the persistence of more traditional conceptualizations of phenotype development. A key characteristic of this less revolutionary depiction is its reliance on a statistical conception of interaction. This conception is quite different from a causal-mechanical conception of interaction, and could interfere with the conceptual transformations that discoveries about epigenetics might otherwise provoke.

A comprehensive explication of the distinction between statistical and causal-mechanical interactions is beyond the scope of this paper, but the distinction has been analyzed in other publications [Griffiths & Tabery, 2008; Moore, 2015a; Tabery, 2014]. Here, a brief illustration will suffice. Various branches of the biological sciences have established beyond any doubt that phenotypes emerge because of *physical* interactions that occur, during development, between genetic and nongenetic constituents of developing systems [Blumberg, 2009; Edelman, 1992; Gilbert & Epel, 2015; Gottlieb, Wahlsten, & Lickliter, 1998; Johnston, 2010; Lewkowicz, 2011; Michel & Moore, 1995; Noble, 2006]. Griffiths and Tabery [2008] identified these as "causal-mechanical" interactions; such interactions are recognized by developmental systems theorists as playing an essential role in phenotype development [Lickliter, 2017]. In contrast, the traditional methods of behavioral genetics, such as those used in many studies of twins, are capable of revealing only *statistical* interactions between genetic and nongenetic factors, interactions that sometimes account for observed variation in phenotypes across a population [Plomin, DeFries, McClearn, & McGuffin, 2008]. The distinction between statistical and causal-mechanical interactions becomes apparent when one considers that behavioral genetics studies sometimes report that variation in a particular phenotype is *not* accounted for by gene × environment (statistical) interactions, even though *all* phenotypes are, in fact, caused by physical interactions between genes and their environments.

By relying on notions of statistical interaction, behavioral geneticists have contributed to the impression that some phenotypes are *un*influenced by environmental factors; such conclusions support traditional genetic-determinist thinking and are inconsistent with the known facts of biology. The conceptualizations underlying behavioral genetics have their roots in the biologically naïve 19th century writings of Francis Galton, and it is these conceptual underpinnings that stand to be undermined by new discoveries about epigenetics; because epigenetic phenomena are *physical* interactions, research findings about epigenetics *should* challenge the genetic determinism that is permitted by traditional behavioral genetics conceptualizations [Keller, 2014; Lester, Conradt, & Marsit, 2016; Meloni, 2015]. However, if epigenetic phenomena are merely incorporated into 19th century theoretical structures, their discovery could fail to spur conceptual change. Consider the following example.

Although papers in the behavioral and social sciences often acknowledge the roles of the environment in phenotype development, some papers in this literature nonetheless retain traditional behavioral genetics conceptualizations, despite their intention to report on the transformative potential of epigenetics research. Such papers can exemplify how epigenetics research can be depicted in ways that might leave traditional, biological-determinist conceptions of phenotype development undisturbed. For instance, van IJzendoorn, Bakermans-Kranenburg, and Ebstein wrote in

2011 that “it seems worthwhile to add methylation [an epigenetic phenomenon] to the G × E equation to fully appreciate the effects of the environment on child and adult functioning … the findings of our study on methylation and unresolved trauma might be cast in terms of G × M × E where M stands for methylation status” (p. 308). By simply adding another term to the traditional behavioral genetics equation – an equation developed to account for phenotypic variation in a population rather than to explain what *causes* phenotypes in individuals [Moore, 2013a, b; Moore & Shenk, 2016] – these authors allow for the retention of traditional conceptualizations of phenotype development, even as they acknowledge the importance of epigenetic phenomena. Specifically, if a behavioral genetic study of a particular phenotype were to reveal no *statistical* interaction involving epigenetic phenomena (e.g., if all of the phenotypic variation in the studied population could be accounted for statistically by referencing genetic variation in that population), then it might seem reasonable to conclude that the development of the phenotype does not involve epigenetic phenomena. However, this would be a mistake, because the development of all phenotypes involves mechanical, epigenetic phenomena at some level.

As long as confusion persists about the distinction between statistical and causal-mechanical interaction, researchers remain at risk of considering statistical accounts-of-variation to be reasonable proxies for mechanistic explanations of phenotype development. In such cases, traditional, dichotomous nature-nurture explanations for phenotype development will not be rejected, even if the molecular evidence for epigenetic phenomena indicates quite clearly that such dichotomous explanations *should* be rejected. This is because it will always remain possible to launch correlational studies of mono- and dizygotic twins or of individuals reared in the “same” environments, and such studies have the potential to reveal *statistical* main effects of genes on particular phenotypes, even if those phenotypes *must* emerge from physical interactions between genetic *and* nongenetic factors.

Of course, it is likely that variation in epigenetic marks often contributes to variation in phenotypes in a population. But if we think of epigenetic phenomena in this way only – as merely a contributor to variation rather than as a causal factor – such findings will not fundamentally change our conceptions of phenotype development. In contrast, studying how nongenetic factors *physically* influence genetic activity in ways that affect phenotypes has the potential to genuinely transform ideas about phenotype origins in ways that could eliminate the dichotomous conception of nature and nurture that has obfuscated thinking in this domain for well over a century. Only in this way will the promise of epigenetics be fulfilled.

Conclusion: Fostering the Promise of Epigenetics as a Dichotomy Breaker

The study of epigenetics can best help theorists transcend the nature-nurture debate by helping them recognize the importance of focusing on the causal mechanics underlying phenotype development. By conducting experiments that measure phenotypic outcomes after actual manipulations of components of developing systems – whether those components are in an organism’s environment, cell nuclei (e.g., DNA), or somewhere in between (e.g., RNA molecules in cytoplasm, hormones in the bloodstream, or synapses in neural structures some distance away) – researchers who focus on the causal mechanics underlying phenotype development will attend to what

DNA segments (and other components of developing systems) actually *do* during development. Focusing on genetic activity, rather than on *correlations* between genetic polymorphisms and phenotypic outcomes, reveals that DNA segments do what they do only in particular contexts [Lickliter, 2017; Moore, 2015b, 2016a]. Epigenetic phenomena can alert us to the fundamentally collaborative nature of phenotype development, but only if we remain focused on the causal-mechanical ways in which such phenomena serve as physical links between genetic and nongenetic factors.

Ultimately, epigenetics research will probably be a source of data that will help undermine traditional, dichotomous thinking about how nature and nurture contribute to phenotype development. This is likely, because it now appears that a particular DNA segment's epigenetic state is *responsive* to environmental and other nongenetic factors, including factors such as nutrition [Anderson, Sant, & Dolinoy, 2012; Lillycrop, Phillips, Jackson, Hanson, & Burdge, 2005; McGowan, Meaney, & Szyf, 2008; Sinclair et al., 2007], hormones [Kamakura, 2011; Weaver et al., 2007], neural activity [Orozco-Solis & Sassone-Corsi, 2014; Roth, 2012; Zhang & Meaney, 2010], and the segment's local genetic context [Noble, 2006, 2012; Pan et al., 2008; Wang et al., 2008]. Thus, this line of research has extraordinary potential to highlight the dynamic, interactive, probabilistic nature of phenotype development in biological systems. In so doing, this line of research could truly help theorists finally transcend the nature-nurture debate.

Epigenetics research has the potential to promote a bona fide conceptual transformation that renders traditional, dichotomous ways of thinking about nature and nurture obsolete. Specifically, by revealing the physical ways in which environmental factors influence the activity of DNA – and (perhaps more obviously) by revealing how our own genetic activity influences our environments – this research could validate the conclusion that phenotypes never reflect one of these kinds of factors more than the other. In fact, when considered from a developmental systems perspective, epigenetics research encourages a shift of attention away from the components of the developing system themselves and toward the effects that those components have on one another as development proceeds. As Witherington and Lickliter suggested in their introduction to this special issue, the source of developmental organization resides not in the components that make up the developing organism or in its environment, but in the relational activity among these components. If epigenetics research ultimately promotes understanding of the critical importance of this relational activity, it will have fulfilled its promise to advance developmental science by leaving the nature-nurture debate in history's dustbin.

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