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Defining Epigenetics in Deterministic Terms

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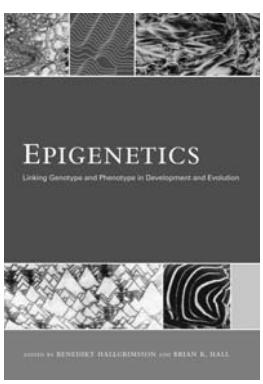
Epigenetics: Linking Genotype and Phenotype in Development and Evolution. Benedikt Hallgrimsson and Brian K. Hall, eds. University of California Press, 2011. 472 pp., illus. $85.00 (ISBN 9780520267091 cloth).

The Epigenetics Revolution: How Modern Biology Is Rewriting Our Understanding of Genetics, Disease, and Inheritance. Nessa Carey. Columbia University Press, 2012. 352 pp., illus. $26.95 (ISBN 9780231161169 cloth).

Epigenetics is a contentious topic. To some, it is the future of biology—already revolutionizing our understanding of life's complexity and diversity—whose tremendous medical implications and promise were recognized by recent Nobel Prizes (including the 2012 award), are researched by dedicated programs at the National Institutes of Health, and are financed by multibillion-dollar investments by the pharmaceutical industry. To others, particularly in the field of evolutionary biology, it is easily dismissed as hype, an asterisk in the great genetic alphabet of life, whose effects are too variable and short term to matter in evolutionary theory or processes. Those in the field of epigenetics, in turn, who are focused on uncovering life's patterns at neck-breaking speed, remain largely unconcerned about the lack of acceptance into the evolutionary club, which they deem unnecessary because virtually none of the field's recent empirical advances were predicted by or even required knowledge of the theory of evolution.

The two sides, however, need each other more than ever. The more fast and cheap our methods for obtaining genomic profiles of organisms, the more frequently we realize that this information does not, by itself, translate into an understanding of the development and function of those organisms' phenotypes. Instead, such data often unveil a complex epigenetic road across multiple levels of organization—from transcription regulation to cell interactions and tissue feedbacks—that is needed to take the genotype on a journey to the phenotype that is most appropriate in a particular developmental or ecological context. The crucial question is whether traveling on this road from genotype to phenotype is synonymous with moving from cause to effect. To this question, two recent books—one academic, *Epigenetics: Linking Genotype and Phenotype in Development and Evolution*, and one popular, *The Epigenetics Revolution: How Modern Biology Is Rewriting Our Understanding of Genetics, Disease, and Inheritance*—give different answers.

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In *Epigenetics*, editors Benedikt Hallgrimsson (professor at the University of Calgary) and Brian Keith Hall (professor at Dalhousie University) argue that the complexity of biological systems prevents the construction of an exhaustive deterministic and directional framework. Instead, different aspects of development—sequence variation, emergence, self-organization, induction, modularity—acquire different causal roles at different levels of organization, and their variable and evolving integration is the developmental basis of phenotypic variation. Over evolutionary time, some effects therefore become the causes, and some causes become the effects. In turn, the "revolution" in *The Epigenetics Revolution* is not so much a revolution as it is a new form of government regulation—DNA sequence variation is a blueprint and the cause for phenotypic variation, but it has now acquired an additional layer of interpreters and modifiers whose origins and evolutionary destinies are not clear.

There are some similarities between these two books: Both illustrate the extent to which epigenetic processes seem to rule every aspect of our lives. We learn that these processes create and regulate uniquely medically relevant tradeoffs between stem cell and cancer cell lineages; they regulate parthenogenesis through imprinting and methylation and thus shape mating and life-history systems; they underlie sex determination, reconfigure our skeleton for current mechanical needs, and shape our memories and create behavioral phenotypes; they assimilate past environmental events and create new ecological cycles. But how did these epigenetic effects become so powerful in evolutionary processes? What is their historical origin and evolutionary future? When do epigenetic processes get involved in evolution by natural selection? And are they, themselves, a product of natural selection?

Answering these questions would require a synthesis of epigenetic patterns into evolutionary processes or, at the very least, an examination of the relationship between epigenetic effects and associated DNA sequences. Neither of these books ventures particularly deep into these areas, however. Instead, both titles invoke the conceptual framework of Conrad Waddington (1953, 1957), who used the concept of *canalization* to understand developmental integration of genetic and environmental influences in the appearance of distinct tissue types in place of a continuous variation. The

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Waddington concept seems to be a more natural fit to the approach and focus of *Epigenetics*, although, aside from the original intent of the book's opening chapters, canalization is not significantly developed or updated here. In *The Epigenetics Revolution*, the Waddington framework is mentioned every few pages as an illustration of cellular heredity and stem cell differentiation, notwithstanding that the mechanisms of differentiation and stabilization envisioned by Waddington in the premolecular era were conceptually distinct from the nature of the actual molecular players now known to accomplish stem cell specialization. A coherent, evolutionary integration of newly discovered epigenetic phenomena would have provided a clearer focus and a unifying theme in both books.

Epigenetics is framed at both ends by chapters written by the coeditors Hallgrimsson and Hall—the first two chapters outline the purpose of the book, and the last categorizes epigenetic modifications by the levels at which they arise (i.e., genes, cells, tissues, organisms). The coeditors argue that only the epigenetic approach could succeed where molecular genetics, evolutionary developmental biology, and population genetics have failed before—in fully unraveling the complexity of the emergent relationship between DNA sequences and phenotypic variation. Through diverse approaches to the study of the phenotype–genotype map, the authors of the book's 26 chapters each emphasize the emergent and not easily defined features of a new discipline. The editors' roadmap, showing their common root, proves essential here.

What is unusual about this book is that, with a few notable exceptions, most of the contributors do not explicitly address the evolutionary implications of epigenetics. Rather, advances in fields ranging from traditional developmental biology to quantitative genetics are only implicitly integrated into the overall theme of *Epigenetics*. In some chapters, such integration takes the form of only a couple of sentences; in others, it is not attempted at all. The result is an emphasis on the undiluted depth and breadth of the authors' expertise and, ultimately, on the diversity of epigenetic approaches. At the same time, this emphasis leaves synthesizing and tracing the authors' conclusions regarding the overall theme of the book to the readers. In this way, a delineation of epigenetics, itself, emerges only after reading all the contributions.

There is much to synthesize in this book. In chapter 3, we revisit the distinction between limited (e.g., epigenetic) and unlimited (e.g., genetic) inheritance (see also Maynard Smith and Szathmáry 1995, Jablonka 2001), their relationship to the speed of adaptive evolution, and the evolutionary retention options that are open to epigenetic effects. In chapters 4 and 5, we learn of the surprising conservatism of the mechanisms behind genomic imprinting across metazoans; the conservatism of the epigenome here matches that of its genomic counterpart. Such conservation suggests that epigenetic effects have less to do with context-dependent regulation of development—as is commonly assumed—and more to do with the regulation of ancient genomic sequences. Epigenetic effects essentially coevolve with the genomic sequences that they regulate. These chapters are also an excellent primer for genomic methylation and histone modification—classic mechanisms of epigenetics.

One of the most surprising discoveries in biology is that the exceptional diversification of organismal forms is produced by rearrangements of remarkably conserved generative modules, all at levels below cell aggregation (Shubin et al. 2009, Newman 2010, Badyaev 2011). The developmental processes that could produce such patterns are discussed in chapter 7. The author specifically focuses on emergent and self-organizing aspects of development and makes explicit use of Waddington's concept to suggest that epigenetic context exerts selection on the most consistent "preformed" element of development—the genome—such that lower levels of organization produce emergent phenomena at higher levels. This chapter most closely echoes the coeditors' framework.

The subsequent three chapters deliver a comprehensive description of epigenetic processes involved in essentially all levels of the organization of major organ systems, from stem cell regulation to morphogenesis and tissue transitions. Such firsthand authoritative treatments of development are uncommon in evolutionary books and illustrate the diversity of epigenetic effects and their overwhelming importance in development. Chapter 10 extends the theme into self-organizing processes of biological pattern formation and traces the mechanisms behind the organizing mechanisms, from ontogenetic origins to phylogenetic distribution.

The reciprocal interaction of form and function is the cornerstone of epigenetics at the organismal level, and chapters 13–15 review the machinery behind such effects, with a specific focus on the postontogenetic remodeling of form by current function. Particularly informative are discussions of the proximate bases for the differential sensitivity of skeletal elements to muscle loading, of the surprising extent to which ongoing physical activity constantly reshapes skeletal and skull elements, and of interactions between genomic and epigenetic elements in the evolution of skeleton and skull. From experimental studies of knockout mutants that fail to develop any musculature (chapter 15; see also Müller 2003), we learn of the proximate mechanisms behind the well-known inductive effects of muscular activity on organ formation; there is no development of embryonic lungs in the absence of neural twitching imitating fetal breathing, no development of retina in the absence of ocular movements, and no development of the middle ear ossicles in the absence of surrounding musculature.

The theme of ontogenetic integration of form and function is extended into the explicitly evolutionary domain in chapters 17 and 20, in which the authors argue that epigenetic integration during development can be an adaptation to integration of functionally linked traits, which can ultimately be a subject of natural selection for evolvability. Fundamentally, these two chapters address the evolution of the phenotype–genotype map—the book's subtitle. The conceptual theme

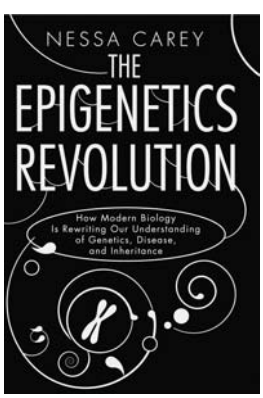
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is brought into the empirical realm through the study of epigenetic regulation in the ontogeny and evolution of the head (chapter 16)—the structure that combines tremendous complexity with equally astonishing evolvability.

The most controversial aspect of epigenetics is its evolutionary retention, and chapters 18 and 19 show how genetic accommodation and assimilation, originally envisioned by Baldwin (1902) and subsequently developed by Schmalhausen (1938) and Waddington (1953), can provide a mechanism for both the short-term effects of environmentally induced plasticity over the course of evolution and the long-term genetic assimilation of induced modifications. Chapter 19 further shows how the developmental plasticity of morphology and the developmental plasticity of behavior can amplify each other and accomplish a surprisingly rapid evolutionary stabilization of even the most elaborate morphological innovations (see also West-Eberhard 2003).

Hallgrimsson and Hall's book concludes with a *tour de force* review of epigenetic disorders in mammals. Because a discussion of such disorders requires, as a starting point, understanding of the nonpathological importance of epigenetic effects in development, chapter 22 succinctly, but comprehensively, synthesizes most of the information contained in the previous chapters. We learn why normal development requires differentially imprinted genes (which explains the evolutionary conservatism of imprinting mechanisms described in chapter 5), why there is sex specificity in the patterns of methylation and how these evolve, and what the epigenetic basis of cancer is. Following a review of established epidemiological associations of epigenetic effects that include everything from mental disorders to cancer, the authors predict that in the near future, epigenetic effects will be shown to also play a key role in cardiovascular disease, adult-onset diabetes, mood disorders, obesity, osteoporosis, and aging. They conclude with the intriguing possibility of using epigenetic biomarkers, which are detectable very early in life, as prognostic indicators for medical treatments. They make, in short, a convincing case for an "epigenetic revolution", at least in medicine.

The Epigenetics Revolution—the book by Nessa Carey—takes its reader on a 340-page journey through the world of modern discoveries in epigenetics. Although the main focus of the book is on methylation and imprinting, everything else is here, too: noncoding RNA, microRNA, small interfering RNA, induced pluripotent stems, somatic cell nuclear transfer, inner cell mass, and much else. There are fascinating stories of tortoiseshell cats, the Dutch Hunger Winter of 1944, microbiomes, calorie restriction, cancer versus stem cells, cellular heredity, bee and rat behaviors, and mental disorders—all compiled from primary scientific sources. The book is unusually comprehensive and up to date. It references media stories that must have played out literally days prior to the printing of this book. If such a remarkable collection and a wealth of knowledge had a better structure or a clearly spelled out overall goal, the book would be truly invaluable. But structure it does not have. Neither does it attempt a synthesis or any integration that would make sense of such new knowledge and technical information.



Instead, *The Epigenetics Revolution* is a kaleidoscope of diverse media stories—a huge collection of science news clippings, loosely arranged according to the epigenetic mechanism that they feature. Each story starts with an important question; however, it takes pages of frustrating anticipation to realize that we almost never return to these questions. The best strategy, then, is to forget about the destination and enjoy the truly fascinating ride, in which one story freely morphs into another while offering curious sound bites of knowledge along the way (e.g., "cardiomyocytes are terminally differentiated," "Dolly the sheep had prematurely arthritic legs," "only well-equipped labs can carry on epigenetic research"). Along the way, however, there is a surprising amount of technical information. And in some places, especially after the first 100 pages, the passing landscape periodically comes into focus; the mechanisms are explained, their significance is established, and opportunities arise to peer under the hood of some of the most interesting epigenetic phenomena (e.g., an excellent discussion of X-chromosome inactivation on pages 174–176 or a discussion of a non-protein-coding genome and "transcriptional noise" on pages 181–186). Unfortunately, the coverage is uneven, and the excursions often get off track and mired unexpectedly in technical detail. On some pages, without warning (or a glossary), every third word becomes an abbreviation of a gene, protein, or technique (e.g., p. 226).

After reading the whole book twice, I came to the realization that the text really consists of two books, glued together, each one written in a distinct style. The first conveys the tone of a science radio show for teens ("look through your microscope," "the frogs we all kept"); the second, starting roughly around page 180, has a clearer focus, asks (and answers) pertinent questions, and gives fewer analogies and shorter detours into side stories. In such places, the book is a fascinating read.

Although not many popular books could rival *The Epigenetics Revolution* in the diversity of contexts in which epigenetic effects play out, it is difficult to imagine a reader who would actually be able to learn these mechanisms from their presentation here. It is better to study these mechanisms elsewhere and to come to this book to admire their medical and evolutionary implications. No other popular books on epigenetics, such as the classic *Evolution in Four Dimensions* (Jablonka and Lamb 2005),

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are cited in this book, although further references of the same concepts and mechanisms would have been a helpful addition.

The distinctive feature of the book is that every now and then, the journey detours to visit a few selected people behind the discoveries. These characterizations, unfortunately, tend toward cardboard descriptions of oversized personal virtues. They come with detailed descriptions of facial features, hair, and clothing styles, as well as manners, but are not given a voice, either active or passive. They all, however, uniformly (and eventually tiresomely) "cut an instantly recognizable figure at conferences."

In some chapters, the quantity of diverse epigenetic phenomena and the contexts in which they play out does transform into quality, and the big picture emerges, but most often, we are left yearning for some roadmap to make sense of these new and bizarre mechanisms that make life so "wonderful, complex, and diverse" and prevent us from "all looking like big amorphous blobs" made of identical cells. Where did these mechanisms come from? What is their relationship to the DNA sequences that they modify? How long will they stay around? Here, the book sits uncomfortably on two conceptual chairs. On one, DNA is still "without a doubt, a blueprint of all life on earth," mutations are the source of evolutionary novelties (when *art* in the Shakespeare sonnet becomes *fart* [p. 46], it changes, we are told, the sonnet's meaning), and studying Lamarckian inheritance is like "investigating the hypothesis that at least some parts of the Moon are made of cheese" (p. 99). On the other, there are distinctly Lamarckian illustrations of multigenerational effects of a nutritional state during growth (e.g., the example of the Dutch Hunger Winter that opens the book) and the fact that most of the book's stories illustrate either persistent effects of environments long gone or the outright inheritance of environmentally modified features. The Darwinian theory of evolution, presented here as a conceptual antagonist of Lamarckian inheritance, in fact, required, in its original version, direct inheritance of modified traits. And it is exactly the absence of known mechanisms by which the inheritance of acquired traits can direct long-term evolution that makes the discoveries of modern epigenetics so fascinating and unusual from the perspective of current evolutionary theory.

A lack of conceptualization forces the author into making more complex analogies than is warranted by the actual events to which they refer. Here is, for example, a description of genomic imprinting:

> Imagine a nighttime summer party in a friend's garden, beautifully lit by candles scattered between the plants. Unfortunately, this lovely ambience is constantly ruined because the movement of the guests keep triggering a motion detector of a security system and turning on a floodlight. The floodlight is too high on the wall to be able to cover it, but finally, it dawns on the guests that they don't need to cover the light. They need to cover the sensor that is triggering the light activity. This is very much what happens in imprinting.
>
> p. 140

If one knows genomic imprinting well, prior to reading the book, it could be entertaining to guess who is who among the participants here. However, understanding the mechanism directly from such analogies requires step-by-step instructions.

This is a long book, and, eventually, such an unabashed diversity of facts and presentation styles become endearing. You cannot help but admire the author who is so fluent in such a great diversity of topics, manages to presents such a wealth of information from primary scientific sources, ventures into predictions of Nobel Prize winners (correctly for the 2012 award, at least), and sheds a different light on even the most overplayed media stories. If you are teaching an undergraduate class on epigenetics, this is a phenomenal collection of facts to generate class discussions. However, better editing of the subsequent editions would undoubtedly result in a more readable book.

The Epigenetics Revolution ends with predictions for the future that combine on the same page "a rather important understanding of the mechanisms for crocodilian sex determination," especially relevant "in relation to climate change," and predictions of Nobel Prizes in physiology and medicine until the year 2016. The future, in short, lacks conceptual clarity and structure just as much as the present. It might be, in a way, the most fitting summary of an exciting field in search of its conceptual framework.

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