INTRODUCTION

WHAT IS EPIGENETICS?

The potential is staggering. . . .
The age of epigenetics has arrived.
TIME, JANUARY 2010

THIS BOOK IS ABOUT how biologists in the booming field of epigenetics explain living systems. It directly responds to an idea seemingly omnipresent in the academic and non-academic world: the view that epigenetics imposes a major theoretical shift on modern biology by invoking previously neglected phenomena and new levels of biological complexity. More particularly, it addresses the question of whether epigeneticists *explain* differently—both from how other biologists explain their phenomena and from how philosophers of science usually conceptualize biological explanations.

Today, epigenetics is usually described as the investigation of regulatory non-DNA factors that are taken to be causally responsible for realizing genetic information. These factors are addressed not only to explain developmental phenomena, like phenotypic plasticity or, more specifically, cancer, schizophrenia, obesity, alcoholism, and aging, but also to aid in the search for successful associated medical applications, like stem cell therapy and cloning. In addition, epigenetic factors are highlighted in investigations of heredity phenomena, like disease etiology and sex-linked inheritance patterns, and in studies of the role of development in evolution. In short, epigenetics is currently one of the hottest topics in biology. The number of paper titles containing the word "epigenetic(s)" has increased more than tenfold since 2000, thus gradually chipping away at the predominance of genetics (fig. I.1). Moreover, both the highly ambitious Human Epigenome Project and the field's own journal *Epigenetics* have been launched since 2000.

However, despite its current topicality, the term "epigenetics" is anything but new. It was introduced by the prominent British embryologist Conrad Hal Waddington back in the 1940s. According to Waddington, epigenetics should, on the one hand, refer to the Aristotelian theory of epigenesis, which understands development as consisting of both gradual and qualitative changes. On the other hand, it should also highlight the need to investigate processes "above" the gene, as implied by the prefix *epi*, which means "over" or "upon." More specifically, Waddington (1952b, vi) understood epi-

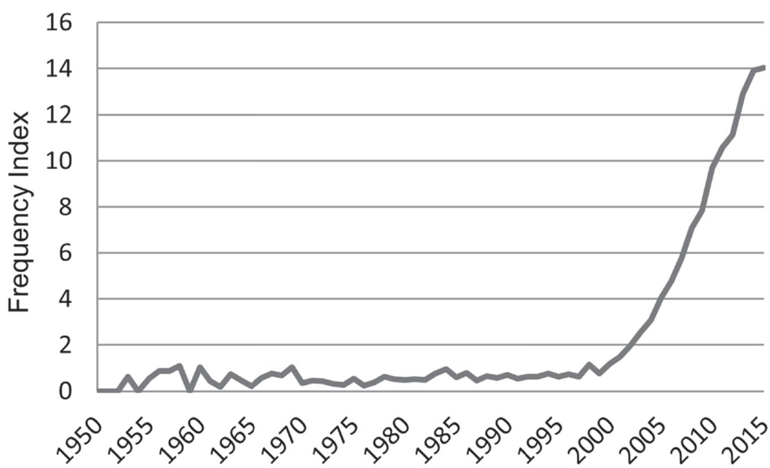

FIG. I.1. Relative frequency of articles with the word "epigenetic(s)" in their title (using ISI Web of Knowledge, 1950 to 2015). A frequency index of 1 means there is one title including the word "epigenetic(s)" for every one hundred titles including "genetic(s)." In total numbers, until the year 2000 there are fewer than one hundred articles for each year, and in 2015 there are more than twenty-four hundred.

genetics as the "science concerned with the causal analysis of development," especially the causal role of networks of interacting genes and how these networks bring phenotypes into being.

If we compare Waddington's classical epigenetics and contemporary epigenetics, we find a few general views that seem to have survived over the decades. First, both Waddington's epigenetics as well as substantial parts of its modern counterpart investigate development in a systemic, network-like manner. Waddington called this environmentally sensitive network of interactions the "epigenotype"—a web of processes that jointly gives rise to the phenotype. This network view currently reappears in epigenetic studies, such as the Human Epigenome Project, in which researchers seek not to "genotype" humans but to "epigenotype" them (i.e., to screen their whole epigenome).

Second, epigenetics remains closely linked to study of causal analysis. For example, in the mission statement of the journal *Epigenetics*, the editors define contemporary epigenetics as the field that "studies heritable changes in gene expression caused by mechanisms others [*sic*] than the modification of the DNA sequence" (*Epigenetics* 2017). In other words, while classical epigenetics was focused on the causal role of genes, many modern epigeneticists investigate how *nongenetic* changes are caused (e.g., through environmental influences) and how they lead to developmental and hereditary (transgenerational) effects. Thus, despite the fact that the causal factors of interest might have changed over the decades, from genes to everything but or, as one might now rightfully say, everything *above*—genes, the cornerstones of epigenetics' causality-based research program seem to have survived.

These general similarities should not convey the view that *classical* epigenetics was a success story. Figure I.1 clearly shows that it was not. In fact, until today almost no concepts and central ideas of the original field were picked up by mainstream biology. This is unsurprising, since Waddington's systemic view was not considered in line with the reductionist one-cause-one-effect thinking popular during the rise of molecular biology. Moreover, as Patrick Murray, a colleague of Waddington in the early 1930s, once noted, reading Waddington's books is like "wading through mud up to the armpits" (quoted in Hall 1992, 116). As a consequence, not only Waddington's view of the complex dynamics between gene interaction and development but also his attempt to unite genetics, embryology, and evolutionary theory were largely forgotten. That is, until recently.

Given this mostly unsuccessful and somewhat discontinuous history of the field, one might wonder not only what contemporary epigenetics exactly is but, more specifically, what some authors mean when they say that epigenetics currently introduces something new to modern biology—a novelty they describe as "epi-geneticization" (Van Speybroeck et al. 2007) or the "epigenetic turn" (Jablonka and Lamb 2010; Nicolosi and Ruivenkamp 2012). This recent epigenetic turn, which some may hold to be quantitatively expressed by Figure I.1, is usually considered as taking place in various biological fields, from molecular biology to evolutionary biology.

One could characterize this development as one in which the nongenetic factors that epigeneticists have identified in regulating and editing genetic information on the molecular level seem to be taking over genes' causal and explanatory supremacy. The supremacy of the gene was established in a step-by-step process over the course of the twentieth century: through recognition of the usefulness of the gene concept as an organizing instrument in early evolutionary studies on population changes in the 1930s; through awareness of the possibility of identifying genes, both with increasing precision and as material entities (namely as DNA sequences), since the late 1940s; and through the adoption of a gene-centered view of evolution that made it possible to unify natural selection and heredity under a sole causal unit, namely the gene, since the 1960s. The triumphant march of this genetic framework came to a (possibly interim) halt in the late 1990s, when biologists increasingly realized that humans have not only far fewer genes than expected but that on the level of the genome humans are nearly identical.[1]

If nothing else, these results led to a new theoretical framework becoming established, one that is commonly described as postgenomics (see, e.g., Griffiths and Stotz 2006; and Stotz 2008). This framework states that when and how genes are expressed is not determined intrinsically but rather by the genes' cellular and organismic environment. This new perspective gives epigenetic factors more causal and explanatory relevance in the biosciences. Importantly, these factors are thought to explain not only organisms' plastic and environmentally responsive development but also how changes in ontogenetic pathways can affect population dynamics and thus evolutionary trajectories. The latter refers to the idea that the nonrandom responsiveness of regulatory epigenetic factors to environmental cues, as well as their heritability, may drive and bias evolutionary change.

Eva Jablonka and Marion Lamb (1995, 2005, 2008, 2010) have famously argued in a number of books and papers that the evolutionary relevance of contemporary epigenetics has a somewhat unforeseen historical punchline—the return of Lamarckian ideas to modern biology. This argument has two components.

First, epigenetic variation is produced and inherited with a degree of autonomy from the DNA level. In other words, the emergence and transmission of genetic and epigenetic variation are causally decoupled to a certain degree. Accordingly, epigenetic variation might offer a distinct substrate for evolutionary change, which, so the argument goes, may guide genetic change. Thus, epigenetics challenges gene-centrism and, in stark contrast to the gene-centered view of evolution (Williams 1966; Dawkins 1976, 1982), invokes a broader notion of heredity that should be taken into consideration in accounts of evolution.

Second, because of the dual nature of epigenetic regulatory systems—being involved in development *and* inheritance—inducible *and* heritable epigenetic variation resembles Lamarckian "soft inheritance," or inheritance of acquired characteristics. This claim of the "Lamarckian dimension" of epigenetics has provoked a wide discussion, both in academia—among historians of science and biologists interested in the historical aspects of their field (see, e.g., E. Richards 2006; Gissis and Jablonka 2011; and Y. Wang et al. 2017)—as well as in the wider public (see, e.g., Young 2008; and Burkeman 2010), on whether the neo-Darwinian framework of evolutionary theory should be expanded to incorporate this "Lamarckian dimension."

This historical debate is in itself an important dimension of the discussion of epigenetics. In the 1990s not many biologists would have put their money on Lamarck's resurrection. Moreover, for some authors Lamarck still is a red flag of sorts. For example, Richard Dawkins (1982, 164) once noted that "a return to the theory of evolution that is traditionally attributed to Lamarck . . . is one of the few contingencies for which I might offer to eat my hat." Given this delicate promise, some authors might be even more inclined to consider giving Lamarckism a (last) chance. However, as this book attempts to show, assessing epigenetics' special theoretical structure, as well as the character of the current "epigenetic turn," should not be left completely to the participants in this Lamarckism debate. This is particularly important, because in recent years a less historically oriented, more general debate about possible expansions of evolutionary theory and their associated challenges has developed. It shows increasing focus on the theoretical structure, assumptions, and predictions of novel developmental approaches such as epigenetics.

Against this background, let us redirect our focus of attention away from the second claim (the Lamarckian turn) and toward the first claim (what may be described as the epigenetization of biological theory). This (at first glance) historically less radical argument for overcoming theoretical orthodoxy in biology carries with it a variety of still widely neglected philosophical issues concerning the explanatory characteristics of epigenetics, its methodological hurdles, and its conceptual challenges for theoretical integration.

These issues are foreshadowed, for example, by the debate currently being revisited on how to conceptually grasp evolutionary "ultimate" causes and developmental "proximate" causes with respect to novel, developmentally oriented evolutionary explanations. While many epigeneticists criticize this traditional dichotomy, those who adhere to traditional conceptual frameworks often do not attack epigenetics' Lamarckian dimension but rather epigenetics' explanatory framework more generally. For example, the population geneticist Michael Lynch claims, "There are more things to explain, but I think a lot of us are happy with the fundamental framework to do that explaining in" (quoted in Grant 2010). By taking such scattered discussions and comments as first stirrings of a growing philosophical debate on the conceptual foundations and explanatory standards of modern biology, this book argues that the so-called "epigenetic turn" is, above all, a shift in scientific explanation and in conceptualizing living systems.

This idea does not presuppose that one can sharply demarcate epigenetics from other fields, such as genetics, or that one can identify a unique kind of explanation or conceptualization in this field, distinct from all other biological explanations and concepts. As is usual in young research fields, epigenetics does not exhibit clear-cut and sharp boundaries. Nevertheless, it will be shown that it is possible to identify a bundle of crucial features of epigenetics. These features make three things possible:

1. They allow us to broadly characterize epigenetics and epigenetic explanation, respectively.
2. They allow us to better understand current trends in biology (especially in molecular and evolutionary biology).
3. They allow us to fill gaps in our current philosophical theories of scientific explanation.

Let me briefly describe these points. As for the first, we may understand the concept of epigenetics not as sharply circumscribed, or as showing necessary and sufficient conditions that demarcate this domain of study, but as a *cluster concept*, in the way described by Ludwig Wittgenstein (1958). This means that although epigenetics shows common features, certain particular features may be more relevant than others to single instantiations of the concept. In addition, some features may sometimes be entirely absent from single instantiations of the concept. Take, for instance, the concept of games. While a common feature of games is that there is usually a winner, some games do not necessarily possess this feature, soccer and solitaire being examples. In a similar manner, we may come across a particular epigenetic investigation that exhibits a number of features similar to other approaches we usually consider to be "epigenetic," but it also shows features distinct from (maybe all) other epigenetic investigations. Thus, in Wittgenstein's words, epigenetics only exhibits family resemblance. However, this result does not render meaningless any use of the concept of epigenetic(s). Nor does it suggest that one cannot get an idea about the set of features that is characteristic of epigenetics and how this set differs from those of other fields. What is more, it is wrong to suggest that "epigenetics" is only "a useful word if you don't know what's going on—if you do, you use something else," as Adrian Bird once commented (quoted in *Nature Biotechnology* 2010, 1031). "Epigenetics" can be characterized in further detail.

In order to trace the characteristics of epigenetics, a number of features widely shared in the field will be discussed. These features are, first and foremost, related to how epigeneticists *explain*. I will show that, as a consequence of their interest in grasping the complexity of developmental phenomena, many epigeneticists explain in a different manner than do other biologists, especially those in molecular and evolutionary biology. More specifically, they trace particular dependency relations and highlight as explanatorily relevant certain kinds of dependencies that are usually not central to explanations in other fields.[2]

Regarding the second point, investigating this set of features allows better understanding of the current so-called epigenetic turn. Here, it is important to mention that our Wittgensteinian perspective does not presuppose that the current trends in biology summarized by this term are driven only by epigenetics. In fact, certain elements characteristic of the epigenetic turn may be found in other fields as well, such as systems biology. Nonetheless, it will be argued that this shift is driven in a crucial and important manner by epigenetics. This makes epigenetics a privileged playground for philosophers of science interested in the dynamics of biology.

On the third point, there are many more virtues of philosophical investigations of epigenetics. It will be shown that a number of epigeneticists use particular concepts of causation and biological mechanism, as well as concepts of causal explanation and constitutive mechanistic explanation, that cannot be easily integrated with the way philosophers of science commonly conceptualize the explanatory relations traced in biology. Thus, we should also turn to epigenetics in order to improve our theories of scientific explanation.

Against this background, this book will consider various models and modeling strategies in epigenetics and investigate how they function in conceptualizing and explaining the properties and dynamics of complex epigenetic systems in development and heredity. In the chapters that follow, I use the notions of explanation and modeling interchangeably in those cases in which we are concerned with models identifying a causal or constitutive (usually mechanistic) dependency relation as an explanatory relation between *explananda* and *explanantia*. This does not include descriptive models or model organisms, which by themselves do not explain. The latter two may, however, play significant, yet more indirect heuristic roles in explanatory practices.[3]

For example, I consider models that serve as theoretical or material scientific representations (Hesse 1966; Giere 1988, 1999; Griesemer 1990; Baetu 2014), are used as instruments with which a biologist can intervene on the models' associated phenomena and theories (M. Morgan 2003; Leonelli 2007), and mediate the transfer of knowledge from a general class of objects (or a theory) to a more particular phenomenon (Morrison and Morgan 1999). More specifically, I investigate experimentation-based causal or mechanistic models, mathematical models, models inferring causality from statistical dependencies in observational data, and heuristic (visual) models, as well as their associated methodologies and modeling practices in a wide array of fields, ranging from molecular epigenetics and stem cell biology to ecological or evolutionary epigenetics.

This book contains five main chapters and a concluding chapter. The first two chapters (1 and 2) address mainly biological and historical topics, while the remaining ones (3–5 and the conclusion) deal with philosophical issues. Subsequent to the introductory notes presented here, chapter 1, "How Epigenetics Deals with Biological Complexity," reviews crucial challenges for biologists in general, and epigeneticists in particular, in modeling the complexity of living systems. These problems are accompanied by issues posed by philosophers of biology regarding how to conceptualize explanatory relations traced at higher levels of organization that physics alone cannot describe. Epigenetics intensifies these problems in a molecular context, since it investigates biological complexity in an expanded manner, both with respect to the number of components and their relations investigated in a particular system (i.e., structural complexity), as well as with respect to the nonlinearity of these relations and thus the seemingly unpredictable behavior of the system (i.e., dynamic complexity). This new layer of biological complexity is labeled "epigenetic complexity." In contrast to Waddington's foundation of classical epigenetics as a science concerned with genetic (or genomic) complexity, modern epigenetics is identified as the complexity science primarily concerned with nonsimple relations (i.e., not one-to-one relations between two factors but one-to-many or many-to-many relations) between *non*genetic factors and their role in plastic development and heredity. In addition, the Lamarckian dimension of the latter relations across cell divisions and especially between organisms is discussed by reviewing various cases of epigenetic inheritance.

In chapter 2, "Challenges of Epigenetics in Light of the Extended Evolutionary Synthesis," we step out from the shadow of Lamarck and the prevailing Lamarckism debate by discussing a number of inter- and intradisciplinary conflicts currently hindering theoretical integration. They arise due to both the explananda and explanantia chosen by epigeneticists and the modeling strategies applied to establish explanatory dependencies. Interdisciplinary conflicts mainly concern the theoretical integration of epigenetics into the neo-Darwinian framework of the modern synthesis and the theoretical expansion of the latter, respectively. This includes the issues of whether (and how) molecular epigenetic explanations can address evolutionary explananda although they are based on highly artificial experimental setups and focus on proximate causes rather than on ultimate causes. The latter problem in particular is central to the current so-called "extended evolutionary synthesis" debate. In addition, intradisciplinary conflicts are discussed. These concern issues on how to understand the field of epigenetics methodologically and conceptually, as well as on how epigeneticists should explain. This internal tension of epigenetics is revealed by comparing approaches of prominent advocates of stem cell epigenetics and molecular epigenetics. This analysis shows that Waddington's traditional methodological program—to develop mathematical models of developmental dynamic stability in his so-called "epigenetic landscape" framework—is still alive in epigenetics.

Chapters 3 and 4 discuss genuine philosophical issues related to the structure of epigenetic explanations, including both causal and mechanistic explanations. In particular, these chapters describe how epigenetics currently partakes in establishing a new explanatory agenda in molecular and cell biology. In chapter 3, entitled "Causal Explanation," I present an account of scientific explanation in line with philosophical orthodoxy, whereby generalizations are explanatory if they are invariant under intervention. Then this interventionist account is applied to elucidate how epigeneticists in molecular and cell biology conceptualize causation and causal explanation. Contrary to a mechanistic theory of causation, it is argued that an invariant generalization does not necessitate supplementary information taken from more fundamental (i.e., lower) levels of organization that explains why the relation under study holds. In other words, the appropriateness of higher-level generalizations in molecular epigenetics, which no longer consider genes the *primum movens* in development and heredity, will be justified. Lower-level genes neither possess a unique ontic or epistemic status, which would necessitate listing them in every *explanans* of causal explanations, nor do they share the explanatory realm in which epigenetic causes actually make a difference. In short, epigenetic complexity is assessed in a particular way by tracing *causes without mechanisms*. At the same time, this does not mean that epigeneticists seek to eliminate genetic dependencies from the "causality landscape" of complex living systems. Rather, genes and their causal roles are reassessed in epigenetic causal explanation in a specific and novel manner.

In chapter 4, "Mechanistic Explanation," I discuss the concept of mechanism in epigenetics. It is argued that this concept, which is central for so-called constitutive explanations of molecular and cell biologists, has been decisively "demachinized" by epigeneticists. In this new field, biological mechanisms are often conceptualized in a nonmachinelike manner, in contrast to how traditional molecular biologists and many of today's philosophers of science conceive of mechanisms. Independently, some epigenetic mechanisms cannot be described adequately in terms of the interventionist account of causation, in contrast to what several philosophers of science think about mechanisms in biological explanation more generally. Particularly in models representing dynamic stability of complex epigenetic systems, there are descriptions of mechanisms that entail explanatorily relevant relations and properties that cannot be considered as "causal" according to the standard accounts of biological mechanisms. These cases are labeled *mechanisms without causes*.

While the earlier chapters primarily deal with the *explanatoriness* of epigenetics (i.e., whether and how epigenetics explains), in chapter 5 we turn to the concept of *explanatory power*. In this chapter entitled "Assessing the Explanatory Power of Epigenetics," I seek to offer a solution to the problem of how to integrate novel and orthodox explanations into the pluralistic framework of an extended evolutionary synthesis. In particular, I present a contrastive framework, which is able to evaluate the explanatory value of distinct biological explanations. This account is able to give precise guidance to the advocates of an extended evolutionary synthesis by means of which criteria (why) and in which explanatory context (when) epigenetic explanations are legitimately chosen over orthodox molecular and evolutionary explanations.

By reviewing the results of the above investigation and discussing some loose ends, in the conclusion I argue for the necessity to establish a philosophy of epigenetics, hence the subtitle for the concluding chapter. This historically informed field should address philosophical issues on the interrelationship between methodology, modeling, biological concepts, and scientific explanation in epigenetics. Moreover, it should not only be understood as a philosophical appendage of the recent epigenetic turn but also establish itself as a field offering valuable insights both for epigeneticists, on the philosophical foundations of their still immature field, and for philosophers of science interested in biological concepts and scientific explanation in biology. It should do so by making use, first and foremost, of the philosopher's toolbox, not the empirical scientist's. This means, in short, a philosophy of epigenetics should be established as a genuine philosophical domain that goes beyond biology, so to speak.

As just initiated, however, this book is intended to be of interest not just for philosophers of biology or even philosophers of science more generally. It also seeks to address philosophically minded biologists in molecular, developmental, and evolutionary biology interested in clarifying the explanatory structure and power of epigenetic explanations and how they are shaping and possibly changing modern biology. Moreover, although the main purpose of this book is to approach the previously neglected philosophical dimensions of epigenetics, the historical dimension is not left out. A number of chapters (e.g., 1 and 2) explicitly focus on the methodological and conceptual history of epigenetics. In addition, throughout these pages the reader will find various historical case studies. For example, epigenetic explanations are discussed in the context of positions ranging from nineteenth-century experimental physiology (Claude Bernard), early twentieth-century genetics (Thomas Hunt Morgan), and developmental genetics (Conrad Hal Waddington) to the advent of molecular biology (Francis Crick and James Watson, François Jacob and Jacques Monod) and topological approaches of embryogenesis in the 1960s and 1970s (René Thom, Israel Gel'fand). However, especially in chapter 2 these historical cases are presented in a general manner in order to suit the systematic issues discussed. Nevertheless, these historical "hints" may motivate the historically interested reader to elaborate on still underrepresented topics in the history of epigenetics.[4]

From a biographical perspective, this book ties in with the interdisciplinary interest of epigenetics' founding father. Conrad Hal Waddington was not only a renowned embryologist and geneticist but also one of the most central figures in establishing the field of theoretical biology—a field that is understood to be genuinely concerned with interdisciplinary issues on the boundary between biology and philosophy. By taking his influential multivolume work *Towards a Theoretical Biology* (Waddington 1968, 1969b, 1970b, 1972) as a guiding light, this book was written under the slogan "Toward a Philosophy of Epigenetics."