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Chapter 1
More than Fifty Shades of Epigenetics for the Study of Early in Life Effects in Medicine, Ecology, and Evolution

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Abstract After being coined by Conrad Waddington in the context of development, today the term epigenetics focuses on the molecular machinery beyond genes. Epigenetics is central to early in life effects and their consequences in eco-evolutionary dynamics. I review the two historical understandings of epigenetics, i.e. its Developmental and Evolutionary understandings, both concerning the molecular mechanisms occurring within an organisms' lifetime. Although I unify them under a generic definition, these understandings are not suitable for studies at the intergenerational level. To fill this gap, I propose an inclusive understanding of epigenetics incorporating all the processes of parent–offspring resemblance that are not engraved into the DNA sequence. By integrating all mechanisms of phenotypic variation beyond the DNA sequence, this new understanding fully corresponds to the etymological meaning of the term "above, or beyond the gene." By integrating knowledge at all levels, this broader understanding of epigenetics should help transferring all the knowledge at the infra-individual level into the study of processes unfolding at the supra-individual level to build a continuum from molecules to ecology and evolution. Concepts of inheritance and early in life effects should play a major role in building such a continuum. Classifying more than 50 definitions of epigenetics in four groups using the actual terms of the definitions reveals interesting discrepancies between definitions and ultimate scientific goals. Finally, I present some examples of how a clear vision of the various understandings of epigenetics may influence biology and argue that epigenetics now needs to percolate in ecology and evolution.

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1.1 Introduction

The term early in life effects qualifies instances when environmental factors acting on organisms during their early development are the most efficient in deeply and lastingly affecting the resulting adult's phenotype. One goal of this chapter is to present and discuss the current knowledge on the molecular mechanisms responsible for these effects. Today, it is relatively well accepted that epigenetic change constitutes the major molecular process underlying all phenotypic plasticity and accommodation changes that mediate early in life effects. This is either implicit or explicit in most if not all the chapters of this book. However, different authors have different understandings of the term epigenetics (see below and Jablonka and Lamb 2002) and do not necessarily incorporate into this concept the same range of molecular mechanisms. Although this diversity of meanings and spans of the epigenetic concept constitutes its richness, a bit like this is the case for the biological concepts of fitness or information, it is nonetheless necessary to clarify the various understandings of this concept to avoid misunderstandings on its role in early in life effects. In this chapter, I adopt an historical perspective to identify the two major categories of understandings of the term epigenetics. I further propose two complementary understandings, one of which might be particularly useful for eco-evolutionary approaches, and one stressing the unifying deep molecular nature of all epigenetic processes.

The term epigenetics has a long history during which its general meaning changed. In biology, the term was popularized by Conrad Waddington in the context of genetic assimilation (see glossary and Waddington 1939, 1942). Note, however, that at that time the term genetic was not DNA sequence based and meant anything inherited (see Glossary). For Waddington, the term epigenetics highlighted the role of epigenesis (development) in phenotype formation. It encompassed all the causal processes of development occurring beyond the sole effect of genes (see also Jablonka and Lamb 2002; Van Speybroeck 2002; Haig 2004; Felsenfeld 2014; Nicoglou and Merlin 2017). For Waddington the term epigenetics had the potential to reconcile epigenesis, genetics, and evolution (Richards 2006; Nicoglou 2018). At that time, it did not necessarily focus on molecular mechanisms. Since that era, the meaning of the term epigenetics has gradually moved away from the original Waddingtonian motivation to become more and more molecular (Jablonka and Lamb 2002; Richards 2006; Bird 2007; Table 2 in Skinner et al. 2010) with a meaning now equivalent to "epi (above and by extension beyond)–genetics."

This trend accelerated with the development of high throughput sequencing at the turn of the millennium. These fantastic technological developments made it clear that the complexity of living organisms could not be fully explained by the sole information encoded into the DNA sequence of coding genes (Jablonka et al. 1998; Maher 2008; review in Danchin et al. 2019b). It appeared that even the most refined description of genetic variation could not fully explain the measured inheritance of the concerned trait in populational or epidemiological studies. This fostered a debate about the existence of missing heritability and its causes (Maher 2008; Danchin

2013; Bourrat et al. 2017; Bourrat and Lu 2017). As a consequence, today, many authors agree that the idea that inheritance mainly, if not exclusively, rests on the transmission of DNA sequence (i.e., the sequencic vision of inheritance, see Glossary), needs to be revisited and extended (e.g., Muller 2007; Pigliucci 2007; Pigliucci 2009; Helanterä and Uller 2010; Pigliucci and Müller 2010, reviews in Danchin et al. 2011; Bonduriansky 2012; Mesoudi et al. 2013; Laland et al. 2015; Huneman and Whalsh 2017; Lu and Bourrat 2017; Merlin and Riboli-Sasco 2017; Muller 2017; Uller and Helanterä 2017; Wang et al. 2017; Bonduriansky and Day 2018; Danchin et al. 2019b).

Today, a generic definition is that epigenetics encompasses the various molecular bearers of information that are independent from that engraved into the DNA sequence of nucleotides (Heard and Martienssen 2014). It usually includes three categories of mechanisms, namely (i) chemical change in the DNA (methylation, acetylation), (ii) histone modifications and substitutions, and (iii) the evermore prominent role of small non-coding RNAs (Brinkman and Stunnenberg 2008; Khalil and Wahlestedt 2008; Skinner et al. 2010; Mazzio and Soliman 2012; Chen et al. 2016b; Tollefsbol 2017; Wang et al. 2017; Danchin et al. 2019b).

Furthermore, the history of epigenetics interacts with that of non-genetic inheritance, which encompasses all inclusively heritable information that is not encoded into the DNA but that nonetheless participates to parent–offspring resemblance, i.e. to heredity. This field, that emerged as a central domain of evolutionary biology during the last decades, plays a major role in the study of early in life effects as many forms of biological memory—beyond DNA sequence—participate to these effects, and need to be incorporated into our analysis of heredity.

In this context, while the molecular basis of epigenetics is relatively well investigated, their ecological and evolutionary implications are less explored despite Waddington's and followers' claims about their evolutionary importance (e.g., Waddington 1953b, 1959). Usually epigenetic processes are viewed as having evolved with multicellularity for cell differentiation (Willbanks et al. 2016). However, epigenetic processes are probably much more ancient because they exist in bacteria and unicellular eukaryotes (Jablonka and Lamb 2005) where they play a role in adaptation to the environment (Brooks et al. 2011), and possibly in immunity against the most common parasite of those organisms, namely pieces of DNA (Jablonka and Lamb 2005).

Here, I review the various understandings of the term epigenetics with a historical and conceptual perspective. In doing so, I briefly describe how epigenetic states often constitute a transgenerational form of biological memory that can play a major role in adaptation to environmental change and more generally in biology, particularly when activated early in life (see also a suit of reviews among which Jablonka and Lamb 1989, 1995, 2005; Jablonka et al. 1998; Jablonka and Raz 2009; Wang et al. 2017; Bonduriansky and Day 2018; Danchin et al. 2019b). I then propose a generic definition of epigenetics centered on its most basic characteristics. Based on previous observations that the meaning of epigenetics often covers a broader spectrum of processes (Jablonka and Lamb 2002), I finally propose a third understanding (the inclusive understanding) of epigenetics that places early in life effects at the

heart of evolutionary processes and that should be particularly relevant to ecological and evolutionary studies. I argue that epigenetics needs to become an important theme of research in all domains of biology. Using an objective methodology, I then classify a sample of more than 50 published definitions of epigenetics into the developmental (itself with two sub-categories) and the evolutionary understanding of epigenetics. I also define a category encompassing all ambiguous definitions making it impossible to attribute them to one of the two classical categories. I finally discuss some of the applications of the new proposed understanding of epigenetics.

1.2 The Developmental Understanding of Epigenetics

Although almost all cells within a multicellular organism have the same sequencic information, they nonetheless exhibit contrasting phenotypes, such as neurons, bone, liver, skin, or lung cells. For instance, a human body contains about 200 different cell types. Furthermore, these characteristics are highly stable as differentiated cells almost exclusively produce daughter cells of the same type, thus generating lineages of same-type-cells. This raises the enigma of how such cell differentiation can occur. When, in the 1930s, Waddington used and defined the adjective epigenetic, his purpose was to answer that specific question.

In the 1950s, David Nanney (Nanney 1958) proposed a theoretical hypothesis. He suggested that the same genotype could be associated with different phenotypes because of the activity of mitotically stable "epigenetic control systems" regulating gene expression, a phenomenon today called "cellular memory," which is central to development and life. Nanney thought that most epigenetic control systems were situated in the cytoplasm, while today, we know that such variation in gene expression among cell lineages results from factors acting mainly, but not exclusively, within the nucleus.

The 1960s and 1970s saw a further connection between molecular epigenetics and cellular differentiation with the documentation of the link between chromatin state (heterochromatin and euchromatin) and gene expression, and the discovery of how the DNA is structured in nucleosomes. In 1975, two teams independently proposed that chemical modifications of the DNA (such as DNA methylation) may associate with gene expression (Riggs 1975; Pugh and Holliday 1978). For them, the DNA methylation patterns were "heritable" (i.e., copied in mitosis), potentially explaining cellular memory. The connection with epigenetics appeared a few years later in Holliday's paper on carcinogenesis (Holliday 1979). Pugh and Holliday had previously commented the debate on whether carcinogenesis has a mutational or epigenetic basis (Pugh and Holliday 1978). They suggested that "the methylated state of particular DNA sequences could stably control gene expression" as during development. Therefore, changes in gene expression following a mutation may not result from a mutation per se, but from the resulting epigenetic changes that in turn provoke a stable change in gene expression (Pugh and Holliday 1978).

The study of histone modifications and DNA methylation only converged in the 1990s (Deichmann 2016), and Holliday also specified his definition of epigenetics, including (i) changes in gene expression among differentiated cells and (ii) the transmission of these changes during mitosis (and possibly meiosis (Holliday 1994)). Finally, a general definition of epigenetics at the molecular and cellular level emerged as "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (p. 1 in Russo et al. 1996) [Note, however, that at that time, they used the term "meiotically heritable change", while it is now known that this is not always the case (Heard and Martienssen 2014), making the term "meiotic" rather inappropriate as epigenetic information may bypass meiosis]. That definition had three major features: (1) cellular memory enabled through mitotic and/or meiotic cell divisions; (2) the effect produced on gene expression; (3) changes do not involve DNA sequence mutations. Today, that definition still constitutes a generic template to most definitions of epigenetics.

However, the reference to cellular memory currently tends to loosen. For instance, with histone chemical modifications and the role of small non-coding RNAs, the term epigenetics has been used to refer to any modification other than change in DNA sequence affecting gene expression, *whether those modifications are stable or not during cellular divisions*. Thus, while cellular memory is central for development, it is sometimes considered as secondary for epigenetics, leading to incorporate into epigenetics any temporary variation that is not of sequencic origin.

In conclusion, the developmental understanding of epigenetics focuses on infra-individual processes (see Glossary) and traditionally mainly concerns complex multicellular organisms, although today the field also incorporates unicellular organisms. In this understanding, epigenetics refers to chromatin modification, DNA methylation, acetylation and other histone chemical modifications, small non-coding RNAs and the way they stably influence gene expression. Today, this understanding of epigenetics mostly looks at molecular marks and signals that affect cellular phenotypes within an organism, thus neglecting physiological aspects, such as metabolism and physico-chemical reactions at higher levels of organization (cell, tissue, and organism).

1.3 The Evolutionary Understanding of Epigenetics

The second major understanding of epigenetics is "the evolutionary understanding" that integrates epigenetics into the study of inheritance and evolution. Its premises are to be found in evolutionary developmental biology (Evo-Devo). However, although the initial goal of Evo-Devo was to integrate the role of development as a major component of adaptation and evolution, it never achieved that goal because it mainly reduced the Evo part to the accounting of the sequencic information into the study of development. In this sense, Evo-Devo is an important part of the Modern Synthesis of Evolution.

The evolutionary understanding of epigenetics really emerged following the discovery that some recently acquired plastic responses can persist intergenerationally, correlatively with epigenetic marks, implying that some epigenetic marks can somehow percolate across generations and participate to heredity. Historically, the concept of epigenetic inheritance states that some chromatin modifications affecting gene expression can be highly stable not only across mitosis, but also across the reproduction of multicellular organisms, potentially being maintained across many generations (Holliday 1994; Russo et al. 1996; Skinner 2011b). In effect, some epigenetic marks persist across generations of cells during development of multicellular organisms. This is why mother and daughter cells are of the same type (such mitotic stability is sometimes called "heritability," e.g., Skinner 2011b). The link with inheritance clearly emerged following the discovery that these stringent properties of persistence at the infra-individual level sometimes percolate across generations and thus participate to inheritance of multicellular organisms (reviews Mameli 2004, sometimes, surprisingly, over more than 80 generations Vastenhouw et al. 2006; Bonduriansky and Day 2009; Danchin and Wagner 2010; Pigliucci and Müller 2010; Danchin et al. 2011; Bonduriansky 2012; Danchin 2013; or 25 generations Devanapally et al. 2015; Chen et al. 2016a; Wang et al. 2017; Danchin et al. 2019b). Therefore, the focus of many biologists progressively shifted from the study of epigenetics in development to the role of epigenetics in evolution. This second understanding rests on the same mechanisms as the developmental understanding, but differs from it mainly in its ultimate target, namely inheritance and evolution rather than development.

Today, it is becoming more and more accepted that transgenerational epigenetic states can participate to parent–offspring resemblance (i.e., to heredity), in a form of epigenetic intergenerational inheritance, with all its evolutionary implications (Danchin et al. 2011; Grossniklaus et al. 2013; recent reviews in Jablonka 2013; Norouzitallab et al. 2014; Singh et al. 2014; Szyf 2014; Bohacek and Mansuy 2015; Wang et al. 2017; Danchin et al. 2019a, b). Evidence keeps on accruing at a fast pace (Devanapally et al. 2015; Sharma 2015; Szyf 2015; Tricker 2015; Chen et al. 2016a; Sharma et al. 2016), fostering the emergence of a new domain of epigenetics studying the role of epigenetics in heredity and evolution. Consequently, the mainstream vision of evolution (i.e., the Modern Synthesis of Evolution) that mainly, if not exclusively, considers DNA sequence variation as the sole source of heritable variation (i.e., parent–offspring resemblance), needs to be revised in order to incorporate the epigenetic source of heritable variation (Pennisi 2008; Pigliucci and Müller 2010; Laland et al. 2014, 2015).

In this context, more and more studies now focus on mechanisms of epigenetic inheritance and their potential evolutionary consequences (e.g., West-Eberhard 2003; Bonduriansky and Day 2009; Bonduriansky 2012; Geoghegan and Spencer 2012; Grossniklaus et al. 2013). An increasing number of authors, among which Eva Jablonka and collaborators, started to call for an evolutionary understanding of epigenetics (Jablonka and Lamb 1989, 1995, 2005; Jablonka and Raz 2009; Pigliucci and Müller 2010; Jablonka and Lamm 2011; Jablonka 2013; Huneman and Whalsh 2017). In this context, Jablonka and followers claim that epigenetic

transmission across generations of organisms challenges the traditional evolutionary theory, and calls for an Extended Evolutionary Synthesis (Pigliucci and Müller 2010; Laland et al. 2015).

To sum up, the evolutionary understanding of epigenetics, beautifully illustrated in Jablonka's work, although mainly relying on the infra-individual developmental approaches nonetheless goes beyond the lifecycle of individual organisms by tackling issues linked to epigenetic stability. In doing so, it sets the stage for the study of the consequences of epigenetics in evolution. However, this evolutionary understanding does not explicitly incorporate the wealth of populational concepts coming from disciplines, such as behavioral ecology, population dynamics, population and quantitative genetics into epigenetic studies (Danchin and Pocheville 2014). In other words, the evolutionary understanding of epigenetics has not really tackled the question of how epigenetic stability quantitatively translates into epigenetic inheritance, and its consequences at the supra-individual level (see Glossary). Furthermore, by focusing on the molecular basis of epigenetics (belonging to the infra-individual level approach), the evolutionary understanding of epigenetics may ignore non-molecular transmission modes, such as cultural and ecological inheritance. While the idea that epigenetic states can be passed on across generations emerged from the epigenetic literature, the extent to which this participates to inclusive heritability (see Glossary) and evolution has not been explicitly investigated yet. Such questions are particularly relevant to evaluate the evolutionary potential of epigenetic inheritance, and, more generally, how natural populations respond to selection. This suggests that we still need a more ambitious definition of epigenetics.

1.4 The Deep Nature of Epigenetics Under These Two Understandings

These two modern understandings of epigenetics rest on the same set of three major molecular mechanisms, namely (1) chemical change in the DNA (methylation, acetylation), (2) histone modifications, and (3) the role of small non-coding RNAs. While the two first processes directly produce changes in the DNA packaging within the cell nucleus, the third one constitutes more a media allowing part of an organism to affect gene expression within other parts of the body (soma and/or germline), thus mimicking hormones (Danchin et al. 2019a).

1.4.1 The Four Major Timescales of DNA Packaging Affecting Gene Expression

In effect, altogether, these processes modify the closing or opening of the chromatin (that is the packaging of the DNA molecule) of specific portions of the genome, which in turn affects the accessibility of the DNA sequence to the molecular machinery of gene expression. In other words, they change the 3D structure of the DNA. The resulting changes in gene expression are active at four very different time scales ranging from seconds up to hundreds and potentially thousands of generations or more, and that, as far as we know, are orthogonal to the three types of molecular mechanisms summarized in the previous paragraph. These contrasted timescales are:

- On the short-term, these processes fine-tune gene expression to accompany everyday cell metabolism in a transitory way.
- On the mid-term, they affect gene expression up to over the whole life of an organism in order to allow cell differentiation (development), as well as acclimation to current environmental conditions (plasticity). This is also the main timescale of early in life effects.
- On the long-term, they participate to inheritance in multicellular organisms, a process that emerges from some of the mid-term epigenetic processes including early in life effects.
- On the very long term of hundreds and thousands of generations, they may also facilitate the sequencic engraving of the corresponding adaptations (Danchin et al. 2019b).

Today, we still do not know the mechanisms responsible for such big differences in stability. The developmental and the evolutionary understandings of epigenetics only concern mid- and long-term processes, respectively, in that they both stress the importance of the stability of changes in DNA packaging. These two understandings thus mainly differ in their temporal scales. The developmental understanding focuses on intra-individual processes at the mid-term scale, while the evolutionary understanding concerns the larger timescale of transgenerational processes.

1.4.2 A Parallel with the Study of Proteins

Concerning the information carried out by the DNA molecule, there is an interesting parallel to be drawn with the study of proteins. After spending much energy in studying protein amino acid sequences, it appeared that their functional properties mostly result from their general shape. The latter is indeed influenced by the sequence of amino acids (called the primary structure), but also by the way the amino acid chain folds into a spiral (secondary structure), and at a larger scale by the way that spiral folds into its 3D shape (tertiary structure). Although the sequence of amino acids strongly influences protein shape, other factors determine the final 3D

structure of the resulting protein, and thus their biological function. In particular, environmental stresses can affect proteins' 3D shape, so that a given amino acid chain can lead to different shapes, some that are biologically functional and others that are not. Prion diseases are disorders that result from protein misfolding following environmental stress. These diseases result from the capacity of prions to serve as the ill-folding template for similar proteins leading to the propagation of their ill shape and their accumulation. Chaperon proteins—specific proteins that help maintaining other proteins in their functional shape—protect against such disorders, particularly after specific stresses such as heat shocks.

The same holds for DNA, in which the sequence provides some information, but the 3D structure ensures that information is used at the right place and at right time. Thus, ignoring the 3D structure of the DNA—which is the essence of the sequencic vision of DNA information—cannot allow us to understand life in all its complexity, and would be comparable to only studying protein amino acid sequences to understand their functions, which would lead us to misunderstand a good deal of their basic roles in life.

Nonetheless, as I do here and in my previous papers, I recommend to clearly separate the sequencic from the 3D components of the information carried out by the DNA molecule because they have drastically different properties and therefore play contrasting but complementary roles in evolution (Danchin et al. 2019a). The central point is that we should not forget the importance of these *two* components, genetics *and* epigenetics, in accommodation, inheritance, adaptation, and evolution.

1.4.3 Epigenetics: The Science of the 3D or Even 4D Structure of DNA

The above two main understandings of epigenetics are unified by the fact that they stress the importance of the 3D structure of the DNA molecule in metabolism, development, and evolution, beyond its sequencic information. A unifying definition of epigenetics can thus be that it is the science *of DNA 3D structure that is stable enough to persist across mitosis or generations.*

In fact, we can go beyond that 3D definition by incorporating the temporal dynamics of gene expression as a major fourth dimension of epigenetics. Indeed, the translation of mRNAs into proteins is strongly regulated by a range of factors, some of which are under environmental control.

A first factor involves synonymous codons. The genetic code is redundant in the sense that many amino acids can be coded by several "synonymous" codons. However, for a given organism, one of these codons is predominantly used to encode a given amino acid, the other codons being much rarer (this is the codon usage bias, Frumkin et al. 2018; Yang et al. 2019). Rare synonymous codons significantly affect the function of the concerned protein in slowing down, or even stopping prematurely, the translation of mRNA into protein in the ribosomes (Yang et al. 2019).

Rare codons can also influence the resulting folding of proteins, hence affecting their biological function. As a result, the protein is not produced at the right time to fulfill its function. For example, in *Escherichia coli*, disruption of the kinetics of synthesis of a highly expressed protein induced by a rare synonymous codon can decrease the efficiency of translation and reduce the bacterium's fitness (Frumkin et al. 2018). Thus, although synonymous codons code for the same protein sequence, the dynamics of protein synthesis may affect their biological function, thus introducing another source of phenotypic variation. This highlights the importance of the kinetics of protein synthesis and the fact that different kinetics generate variation due not to the 3D shape of the DNA, but to the fourth dimension of the dynamics of protein synthesis.

Furthermore, the regulation and efficiency of the translation of mRNAs into protein is also strongly influenced by numerous environmentally induced modifications of mRNAs or tRNAs that, by affecting the initiation of translation and the dynamics of codon–anticodon interactions, accelerate, stop, or slow down protein synthesis, thus affecting the phenotype [for modifications of tRNAs or mRNA, see Leppek et al. (2018); Ranjan and Leidel (2019), respectively]. The resulting variations in kinetics can affect the phenotype and, in particular, the health of organisms.

Many of such changes are influenced by environmental stresses (Leppek et al. 2018; Ranjan and Leidel 2019), and participate to phenotypic plasticity, producing variation in functional gene expression that is independent of sequencic variation. If these effects are transmitted during mitosis or between generations of multicellular organisms, they would belong to epigenetics. I do not know papers reporting the transmission of mRNA translation regulatory states during mitosis or between generations. However, this absence may only reveal the fact that these processes have been described too recently. The large international project on the dynamics of genome conformation in space and time (3D and 4D) might show that some of these processes are transmitted either in mitosis or across generations (Dekker et al. 2017).

Anticipating such discoveries, I propose a more complete definition focusing on the functional nature of epigenetics, which would be *the science of the 3D, or even 4D, structure of the DNA that is stable enough to persist across mitosis or generations of multicellular organisms beyond sequencic.* This definition of course includes all the 3D aspects related to the shape of nucleic acids within chromatin, but also all the components of the dynamics of gene expression itself, which, via its effects on the efficiency of gene translation, can influence phenotypic fitness.

This unified vision of epigenetics is in fact at the heart of several non-genetic inheritance systems. It is also at the heart of the study of early in life effects and of precision (or individualized) medicine. We can even envision the chromatin as a kind of gigantic prion as not only the DNA sequence is transmitted but also a significant part of its 4D structure.

This unified vision of epigenetics claims that the sequencic vision of life, by focusing only on sequence information, has made us blind to the information encoded into the 3D and 4D structure of the DNA. The sequencic vision of inheritance in effect led us to discard part of inheritance processes on the sole

basis of the fact that it is not engraved into the DNA sequence (Danchin et al. 2011; Danchin 2013).

1.5 The Inclusive Understanding of Epigenetics

The above-unified definition of epigenetics constitutes a step forward toward the integration of epigenetics within the Extended Evolutionary Synthesis (e.g., Pigliucci 2007; Pigliucci and Müller 2010; Huneman and Whalsh 2017; Muller 2017; Bonduriansky and Day 2018). However, I think that this constitutes only a first step in the necessary modernization of the Modern Synthesis of Evolution (see, for instance, Danchin et al. 2019a). I now discuss the necessity to go farther by transposing concepts of epigenetics into eco-evolutionary studies, and vice versa, which implies the use of a fourth understanding of epigenetics based on a generalized meaning of epigenetics, integrating all forms of non-genetic inheritance into the study of eco-evolutionary dynamics. Such a definition puts early in life effects at the center of the concept of epigenetics. In doing so, I follow and amplify the approach of previous authors such as Jablonka and Lamb who had already observed that "*the examination of recent books and articles with epigenetics in their titles show that the scope of the subject is far less narrow than some current definitions suggest*" (Jablonka and Lamb 2002). My aim here is to confirm this state of affairs by fully endorsing the implicit and more or less unacknowledged existence of this very general vision of epigenetics, which proves to be particularly well suited to medical, ecological, and evolutionary studies.

1.5.1 Injecting Eco-Evolutionary Concepts into Epigenetics

The scale change from infra- to supra-individual biology that I have been advocating implies injecting processes relevant at the scale of individuals, populations, and ecosystems into the definition of epigenetics. For that goal, a populational concept such as inclusive heritability (with its sequencic and non-sequencic components, the latter including early in life effects) is particularly relevant for several reasons (Danchin and Pocheville 2014; Pocheville and Danchin 2015).

First, when Darwin talked of heredity (see Glossary and Danchin and Wagner 2010; Danchin et al. 2011, 2019a) in saying that, "*Any variation which is not inherited is unimportant for us*" (p. 12 in Darwin 1859), he had an all-inclusive vision of inheritance, and claimed that what we now call inclusive heritability is central to evolution by natural selection. In modern language, the above quote can be rephrased in "for a trait to evolve by selection (whether natural, artificial or drift) it must be inclusively heritable, i.e. offspring must resemble their parents." This statement is independent from the mechanisms underlying resemblance. What matters is that a value of a trait be stable transgenerationally. Thus, the concept of

heritability is keystone in any evolutionary synthesis, and initially (i.e., at the time of Darwin) incorporated what we now call epigenetic inheritance alongside with many other processes that we are currently rediscovering, such as cultural and ecological inheritance.

Second, the fact that the concept of 'heritability' has been used (see Table 1.1) both in infra- and supra-individual approaches suggests that it has some relevance to both domains (Danchin and Pocheville 2014; Pocheville and Danchin 2015). Although historically developed at the population level (supra-individual), the concept of heritability thus appears to have some relevance to study the molecular basis of parent–offspring resemblance (infra-individual). In this sense, the concept of heritability (including its epigenetic component, as well as all other processes of parent–offspring resemblance) has the potential to bridge the infra- and supra-individual approaches, the latter concerning ecologists, as well as population and evolutionary biologists (Danchin and Pocheville 2014; Pocheville and Danchin 2015).

Third, confronting the sequencic and populational approaches of heritability revealed an inconvenient but interesting discrepancy between these two approaches. At the sequencic level, the most fine-grained descriptions of within-population genetic variation [sometimes involving millions of Single Nucleotide Polymorphisms (SNPs) in what is usually called Genome Wide Association Studies or GWAS] led to estimates of genetic heritability that were surprisingly low relative to the estimates calculated for the same trait at the populational level in ecology or epidemiology (i.e., the supra-individual level). This recurrent formidable discrepancy, which has been dubbed "missing heritability" (Maher 2008), raised considerable debates. To illustrate the intensity of the ongoing debates, while the expression "missing heritability" first appeared in 2008, searching for that term produced 1849 hits on the web of knowledge, and 19,100 hits in Google Scholar (Fig. 1.1). Missing heritability strongly suggests that the weight of non-genetic inheritance might be much higher than usually anticipated as the observed discrepancy may be partly because populational estimates of heritability in effect capture a good deal of non-genetic inheritance effects (Danchin 2013, Bourrat et al. 2017, Bourrat and Lu 2017).

Fourth, a striking characteristic of many identified mechanisms of non-genetic inheritance (reviews in Mameli 2004; Danchin et al. 2004, 2011, 2019b; Bonduriansky and Day 2009; Danchin and Wagner 2010; Pigliucci and Müller 2010; Bonduriansky 2012; Danchin 2013; Wang et al. 2017) is that they involve molecular processes classically viewed as developmental processes. For instance, epigenetics constitutes a major developmental hub in that resemblance involves transmitted epigenetic changes (which in turn can affect the stability of the DNA sequence, Danchin et al. 2019b). Similarly, social learning is a developmental process potentially leading to cultural transmission and parent–offspring resemblance under some specific conditions (Danchin et al. 2018). This underlines the existence of a continuum between infra- and supra-individual processes.

Fifth, many non-genetic processes of inheritance result from strong early in life effects, to the point that it might well be that the earlier in life an effect occurs, the

Table 1.1 From more than fifty to five shades of epigenetic gray to only five shades. A list of more than 50 definitions of epigenetics from the literature, including two new definitions. This constitutes a small subsample of existing definitions (others can be found in Jablonka and Lamb 2002). All texts in the definition column are quotes. The classification is based only on the terms found in the definition of epigenetics, independently form the context and goals of the concerned study. Definitions are grouped according to the method described in the text, and chronologically within groups. Terms like "heritable," "inheritance," "stable," or "perpetuate" often appear in definitions without specifying the timescale of the stability. Under the first understanding of along-asexual-cell-lineages, the definition should be classified as "Developmental definitions 2." Under the second understanding of along-generations-of-sexually-reproducing-organisms, it would be classified as "Evolutionary." All such ambiguous definitions are grouped under the Ambiguous group, and ambiguous term is underlined. Legend of shades of gray: **D1 in grayish white**: Group of Developmental definitions 1; **D2 in light gray**: Group of Developmental definitions 2; **A in light gray**: Group of Ambiguous definitions; **E in dark gray**: Group 2 of Evolutionary definitions; **I in black**: Group of Inclusive definitions

Definition	Reference	Shades of Epigenetic Grey
Developmental definitions 1		
Changes in genotypes only have ostensible effects in evolution if they bring with them alterations in the **epigenetic processes by which phenotypes come into being**; [bold text by chapter's author].	(Waddington 1953a)	**D1**
The science of developmental process in general (…). The analytical study of development "including the problem of" cellular differentiation.	(Huxley 1956)	**D1**
Epigenetic control systems are "auxiliary mechanisms with different principles of operation involved in determining which specificities are to be expressed in any particular cell".	(Nanney 1958)	**D1**
(…) a suitable name for the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being.	(Waddington 1968)	**D1**
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".	(Medawar and Medawar 1983)	**D1**
Epigenetics is concerned with the strategy of the genes in unfolding the genetic program for development.	(Holliday 1987)	**D1**
Generally speaking, epigenetic states or epigenetic regulation refer to situations in which several states of gene expression may coexist in similar environmental conditions, despite the absence of significant changes in the genomic sequence.	(Thieffry and Sanchez 2002)	**D1**
Epigenetic (…) has come to refer to the changes in chromatin and DNA structure which alter gene expression and hence phenotype that do not involve changes to the sequence of DNA.	(Champagne 2008)	**D1**
The study of emergent properties in the origin of the phenotype in development and in modification of phenotypes in evolution.	(Hallgrímsson and Hall 2011)	**D1**
Epigenetics or epigenetic control is the sum of the genetic and non-genetic factors acting upon cells to selectively control the gene expression that produces increasing phenotypic complexity during development.	(Hall 2012)	**D1**
What Waddington called developmental constraints and epigenetics can now be identified as the layers of molecular regulatory networks and cell-cell communication networks – a web of interactions through which genomic information must percolate to produce the macroscopic phenotype.	(Huang 2012)	**D1**
Epigenetics is a mechanism of gene transcription regulation that does not change the DNA sequence and is usually reversible.	(Willbanks et al. 2016)	**D1**
Developmental definitions 2		
(…) the study of mechanisms of temporal and spatial control of gene activity during the development of complex organisms. (…). 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.	(Holliday 1990)	**D2**

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
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.	(Holliday 1994)	**D2**
Imagine, therefore, my surprise in learning that "epigenetics" will ultimately be understood as the study of changes in gene function that are heritable and that do not entail a change in DNA sequence!	(Wu and Morris 2001)	**D2**
Epigenesis concerns the interactions through which the inherited potentials of the genome become actualized into an adult organism.	(Gilbert 2002)	**D2**
The term 'epigenetics', which literally means 'outside conventional genetics', is now used to describe the study of stable alterations in gene expression potential that arise during development and cell proliferation.	(Jaenisch and Bird 2003)	**D2**
That 'something else' is chemical modifications of genes that are heritable from one cell generation to the next and that affect gene expression but do not alter the DNA sequence.	(Bradbury 2003)	**D2**
Epigenetic alterations involve information heritable during cell division other than the DNA sequence itself.	(Bjornsson et al. 2004)	**D2**
Although several definitions for epigenetics have been proposed, the term epigenetics refers to changes in gene expression which can be maintained through cell divisions and are not coded in the DNA sequence itself.	(Khalil and Wahlestedt 2008)	**D2**
Epigenetics is the study of the processes that underlie developmental plasticity and canalization and that bring about persistent developmental effects in both prokaryotes and eukaryotes.	(Jablonka and Raz 2009)	**D2**
Epigenetics is the study of heritable changes in gene expression that occur without changes in DNA sequence. Epigenetic mechanisms are flexible genomic parameters that can change genome function under exogenous influence, and also provide a mechanism that allows for the stable propagation of gene activity states **from one generation of cells to the next.** [bold text by chapter's author]	(Bollati and Baccarelli 2010)	**D2**
Molecular factors and processes around DNA that are mitotically stable and regulate genome activity independent of DNA sequence.	(Skinner et al. 2010)	**D2**
(…) molecular factors or processes around DNA that regulate genome activity independent of DNA sequence and that are mitotically stable.	(Skinner 2011a)	**D2**
Epigenetics is defined today as the study of the mechanisms that lead to 'persistent' developmental changes in gene activities and effects, but do not involve altered DNA base sequences.	(Jablonka and Lamm 2011)	**D2**
Here we employ the term [epigenetics] in the more conservative sense that concerns the perpetuation of gene expression and function across cell divisions without changes in DNA sequence.	(Heard and Martienssen 2014)	**D2**
Epigenetics is defined as molecular factors and processes around the DNA that regulate genome activity independent of DNA sequence, and are mitotically stable.	(Guerrero-Bosagna and Skinner 2014)	**D2**
Epigenetics, the study of mitotically heritable and reversible molecular information outside of the DNA sequence (…).	(Ladd-Acosta and Fallin 2016)	**D2**
Epigenetics is the study of various intracellular factors that have an effect on the stability of developmental processes through their action on genome potentialities (i.e., the genome susceptibility to be differentially expressed).	(Nicoglou and Merlin 2017)	**D2**
Epigenetics focuses on mechanisms that govern accessibility to genetic information, independently of changes in DNA sequence. The establishment and maintenance of epigenetic profiles are essential for cell lineage determination and differentiation.	(Schang et al. 2018)	**D2**

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
Ambiguous definitions		
Epigenetic mechanisms, which involve DNA and histone modifications, result in the heritable silencing of genes without a change in their coding sequence.	(Egger et al. 2004)	A
The current use of the term epigenetics emphasizes heritable changes in gene expression that cannot be tied to genetic variation. (…) a positive definition has been proposed that equates epigenetic regulation with the active perpetuation of local chromatin states.	(Richards 2006)	A
Epigenetics refers to heritable changes in gene function that cannot be explained by changes in DNA sequence, with DNA methylation patterns being an important contribution to epigenetic memory.	(Pembrey et al. 2006)	A
The following could be a unifying definition of epigenetic events: the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states.	(Bird 2007)	A
Epigenetics, in a broad sense, is a bridge between genotype and phenotype—a phenomenon that changes the final outcome of a locus or chromosome without changing the underlying DNA sequence. (…) More specifically, epigenetics may be defined as the study of any potentially stable and, ideally, heritable change in gene expression or cellular phenotype that occurs without changes in Watson-Crick base-pairing of DNA.	(Goldberg et al. 2007)	A
Epigenetics refers to the heritable, but reversible, regulation of gene mediated principally through changes in DNA methylation and chromatin structure.	(Brinkman and Stunnenberg 2008)	A
We use the term epigenetics to classify those processes that ensure the inheritance of variation (-genetics) above and beyond (epi-) changes in the DNA sequence.	(Bonasio et al. 2010)	A
(…) the concept of epigenetics is relatively simple in that it describes a means by which genes are either turned on or off by a heritable epigenome.	(Mazzio and Soliman 2012)	A
Stable, heritable changes in gene expression can be caused by chromosomal modifications, exclusive of any alterations to the nucleotide sequence.	(Geoghegan and Spencer 2012)	A
Epigenetics is defined as the study of heritable changes in gene expression that are not linked to changes in the DNA sequence.	(Silveira et al. 2013)	A
Epigenetics refers to mechanisms of long-term or stable regulation of gene expression programs that do not involve a change in gene sequences.	(Szyf 2015)	A
Evolutionary definitions of epigenetics		
The study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence.	(Russo et al. 1996)	E
Refers to the mitotic or meiotic transmissibility of chromatin variation, independent of DNA sequence variation.	(Johannes et al. 2008)	E
Epigenetics is defined as molecular factors and processes around DNA that regulate genome activity, independent of DNA sequence, and that are mitotically or meiotically stable.	(Skinner 2011b)	E

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
Epigenetics (…) is mainly used to describe modifications that cause changes in gene expression that are stably transmitted during mitosis or meiosis, but that do not involve differences in the underlying DNA sequence.	(Weigel and Colot 2012)	E
Epigenetics refers to changes in gene expression that occur through changes in DNA methylation, histone modification, small or micro-RNAs, or most inclusively, other mechanisms that alter how DNA sequences are translated into functional gene products. With the discovery that epigenetic modifications to gene expression can be inherited across cell lineages or even across organismal generations. (…)	(Donohue 2014)	E
(…) "Epigenetics is typically defined as the study of heritable changes in gene expression that are not due to changes in DNA sequence." However, this definition depends on what one means by "heritable." If one is thinking in terms of cells, it means that the gene expression pattern of one cell is transmitted accurately to that cell's descendants. (…). But (…), we are coming to realize how agents causing epigenetic changes in germ cells can create stable patterns of gene expression that become transmitted from an organism to its progeny.	(Gilbert and Epel 2015)	E
There is also increasing evidence for more stable transgenerational epigenetic inheritance, or the transmission across generations of cellular states without modification of the DNA sequence, which demonstrates that adaptive evolution may proceed by selection on epigenetic variants as well as variation in DNA sequence.	(Laland et al. 2015)	E
As currently defined, epigenetics deals with heritable, metastable and usually reversible changes that do not involve alterations in DNA sequence, but alter the way that information encoded in DNA is utilized. The bulk of current research in epigenetics concerns itself with mitotically inherited epigenetic processes underlying development or responses to environmental cues (as well as the role of mis-regulation or dysregulation of such processes in disease and ageing), i.e., epigenetic changes occurring within individuals. However, a steadily growing body of evidence indicates that epigenetic changes may also sometimes be transmitted from parents to progeny, meiotically in sexually reproducing organisms or mitotically in asexually reproducing ones.	(Manjrekar 2017).	E
The DNA of all higher organisms is subject to different chemical modifications that influence gene activity and expression, and that are summed up under the term 'epigenetics' (…) Earlier evidence of natural variation in DNA methylation, as well as of the inheritance and phenotypic effects of this epigenetic variation (…), led to several conceptual papers that suggested its potential **relevance to ecology and evolution** (…), and empirical work has been catching up slowly. Ecologists and evolutionary biologists are particularly interested in the unique contributions that epigenetic mechanisms might make. First, environment-sensitive epigenetic mechanisms could transmit responses to environmental changes across generation boundaries. Second, heritable epigenetic variants that arise stochastically, i.e. epimutations, that affect phenotypes may be under natural selection and might contribute to adaptation, independently from DNA sequence variation. [bold text by chapter's author]	(Richards et al. 2017)	E
Inclusively heritable molecular variation in gene expression without change in DNA sequence resulting from DNA methylation or histone modifications, and often mediated by small non-coding RNAs (sncRNAs, i.e. RNA molecules that are not translated into proteins and that are less than 200 nt in size).	(Danchin et al. 2019b)	E
The science of the 3D, or even 4D, structure of the DNA that is stable enough to persist across mitosis or generations beyond sequencic.	This book chapter	E
Inclusive definitions of epigenetics		

(continued)

Table 1.1 (continued)

Definition	Reference	Shades of Epigenetic Grey
This term has now been somewhat redefined and although there are many variants of the definition of this term today, a consensus definition is that epigenetics is **the collective heritable changes in phenotype** due to processes that arise independent of primary DNA sequence. This heritability of epigenetic information was for many years thought to be limited to cellular divisions. However, it is now apparent that epigenetic processes can be transferred in organisms from one generation to another. [bold text by chapter's author]	(Tollefsbol 2017)	I
(…) epigenetics (i.e. non-DNA sequence-based rather than mutational) modifications. In this review, we summarize recent evidence on epigenetic inheritance from parental environment-induced developmental and physiological alterations (…). The epigenetic modifications demonstrated to be both susceptible to modulation by environmental cues and heritable, including DNA methylation, histone modification, and small non-coding RNAs, are also summarized. [bold text by chapter's author]	(Wang et al. 2017)	I
All the information bearers and processes of phenotypic variation (often involving environmentally driven variation in gene expression) that participate to parent–offspring resemblance, and that are not due to DNA nucleotidic sequence variation in the germline. This broad understanding incorporates the three classical molecular mechanisms of (i) chemical DNA modifications and (ii) histone modifications, and (iii) micro RNAs, as well as all other heritable processes of phenotypic variation, such as prions and chaperon molecules (…), cytoplasmic inheritance, parental effects, ecological inheritance, cultural inheritance, and the inheritance of the microbiota. It also incorporates DNA sequence variation that may arise in somatic cells, as in mammalian immunity. This all-inclusive understanding encompasses all the processes that can produce intergenerationally persistent phenotypic variation, thus participating to parent-offspring resemblance beyond the sole effect of genetics (sequencic). Hence, this understanding encompasses any process involved in heredity beyond genetics.	This book chapter	I

more likely it will be transmitted to subsequent generations and hence participate to inclusive heritability. This is, however, an entirely unexplored domain of the study of early in life effects.

All these characteristics make heritability (here understood in its inclusive meaning) particularly suitable for bridging properties at the infra-individual level with supra-individual processes (Danchin and Pocheville 2014; Pocheville and Danchin 2015). As epigenetics has emerged as a major mechanism of inheritance contributing to heritability, I now propose a definition of epigenetics that incorporates all the dimensions of inheritance beyond sequencic, which I call the inclusive understanding of epigenetics, with the goal of facilitating the merging with concepts used by ecologists and evolutionary biologists.

1.5.2 An Inclusive Definition of Epigenetics

In this context, an inclusive definition of epigenetics explicitly designed to help integrating the infra- with supra-individual levels could be *all the information bearers and processes of phenotypic variation (often generated by environmentally driven variation in gene expression) that participate to parent–offspring*

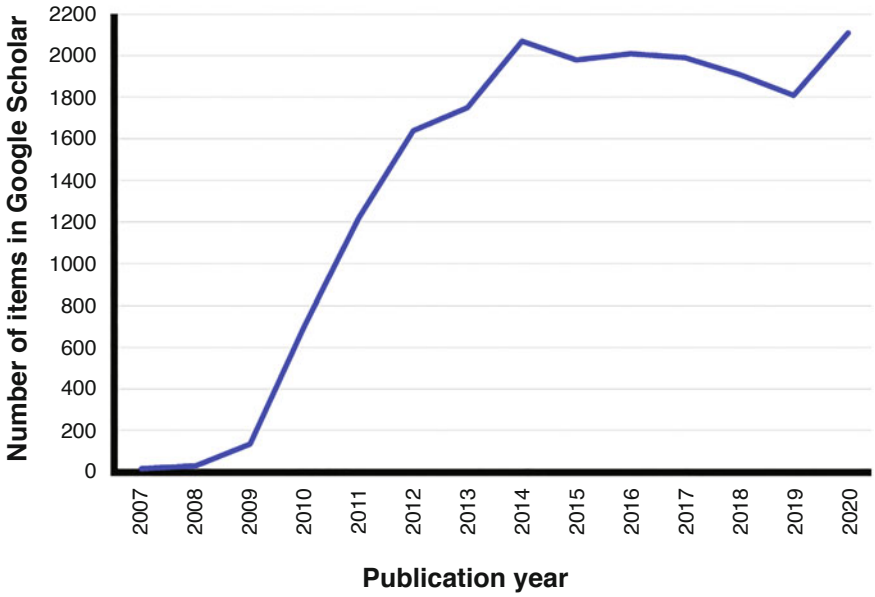

Fig. 1.1 Yearly number of hits for "Missing heritability" in Google Scholar. The first major paper was in 2008 (Maher 2008). Then the number of items dealing with missing heritability increased rapidly and stabilized around 2000 items per year in recent years. Data gathered on 19 April 2021

resemblance (i.e. that are inclusively heritable) and that are not due to DNA nucleotidic sequence variation in the germline.

This understanding is much broader than the two previous ones. It incorporates the three classical molecular mechanisms of (i) chemical DNA modifications, (ii) histone modifications, and (iii) the role of micro RNAs (Chen et al. 2016b; Tollefsbol 2017; Wang et al. 2017; Danchin et al. 2019a, b). It also incorporates all heritable processes of phenotypic variation usually ignored in this context, such as prions and chaperon molecules that constitute other forms of molecular memory (Halfmann and Lindquist 2010; Lindquist 2011; Halfmann et al. 2012; Saibil 2013; Manjrekar 2017; Newby et al. 2017), cytoplasmic inheritance (reviewed in Bonduriansky and Day 2018), parental effects (review in Danchin et al. 2011), ecological inheritance (Odling-Smee 1988, 2010; Odling-Smee et al. 2003; Odling-Smee and Laland 2011), cultural inheritance (van Schaik et al. 2003; Krutzen et al. 2005; Whiten et al. 2005; Whiten 2011, 2017; Whitehead 2017; Danchin et al. 2018), as well as the inheritance of the microbiota (Fellous et al. 2011).

This all-inclusive understanding encompasses all the processes that can produce intergenerationally persistent phenotypic variation, and thus parent–offspring resemblance. In this sense, it matches the classical view that epigenetics encompasses any process involved in heredity be it genetic or non-genetic. This understanding should stimulate the study of the role of epigenetic variation in medicine, ecology, and

evolution, as non-genetic inheritance and early in life effects are likely to affect strongly the fate of populations at all timescales. Bridging "infra-individual approaches" (molecular biology, development, physiology, neurobiology, to which the two previous understandings belong) with "supra-individual approaches" (behavior, demography, population genetics, ecology, and evolution) is in itself a big challenge. As a matter of fact, we need to acknowledge that there is an unnecessarily sharp border between these vast domains of biology (Danchin and Pocheville 2014; Pocheville and Danchin 2015), with the effect of forbidding any integration along the continuum from molecules to ecosystems. My goal is to make this border more permeable by unifying development and physiology with population dynamics in an ecological and evolutionary perspective to allow infra-individual studies to meet evolution (Danchin and Pocheville 2014; Pocheville and Danchin 2015). In this way, my hope is that it can help building bridges toward the Inclusive Evolutionary Synthesis, which I briefly describe in the next section.

1.5.3 We Need an Inclusive Rather than Only an Extended Evolutionary Synthesis

Adopting this fourth understanding of epigenetics can help going beyond the simple extension of the Modern Synthesis of Evolution (called the Extended Evolutionary Synthesis) that in effect only incorporates epigenetics in its developmental and evolutionary understandings (Pigliucci 2007, 2009; Pigliucci and Müller 2010; Danchin et al. 2011; Mesoudi et al. 2013; Laland et al. 2015; Muller 2017; Bonduriansky and Day 2018; Lu and Bourrat 2018), thus forbidding us from integrating all known mechanisms of inheritance into an "Inclusive Evolutionary Synthesis" (see Glossary; Danchin 2013; Cortez et al. 2017; Pocheville and Danchin 2017; Burunat 2019; Danchin et al. 2019a, b).

The inclusive understanding of epigenetics that I propose here, aims at connecting all fields of biology for a broader synthesis going beyond the sole sequencic component of inheritance to integrate all dimensions of heredity. All domains of biology are concerned as "Nothing in Biology Makes Sense Except in the Light of Evolution" (Dobzhansky 1973). Only such an integrative synthesis can allow us to understand and predict dynamical processes of interaction among individuals within populations, communities, and ecosystems at the ecological and evolutionary scales. I have qualified this ambitious new synthesis with the word Inclusive (Danchin and Wagner 2010; Danchin 2013; Danchin et al. 2011, 2019a, b) instead of Extended for the same reason as those that lead me to propose an inclusive definition of epigenetics. In effect, just adding one of the identified mechanisms of non-genetic inheritance (most likely epigenetics because of its molecular nature) would fully justify the word "extended," while the word "inclusive" would demand the inclusion of all known dimensions of inheritance. The expression Inclusive Evolutionary Synthesis thus flags that "all-inclusive" ambition in order to

incorporate all known processes of inheritance into the evolutionary theory of the twenty-first century. In other words, if we are to modernize the Modern Synthesis, we should do it thoroughly.

Finally, it is important to restate that, as Einstein did not invalidate Newton, the Inclusive Evolutionary Synthesis that we are currently building does not invalidate the current Modern Synthesis, but rather builds on it and broadens it in order to incorporate all processes of inheritance and hopefully all major characteristics of life into a unifying conception of biology.

1.6 A Practical Taxonomy of Epigenetics

I now propose a straightforward and easy to use classification of definitions that I suggest may help clarifying concepts of epigenetics for the various fields of biology in everyday research. With that goal, I purposely focus on the actual words of definitions, while ignoring the actual context in which the authors of these definitions worked. The resulting taxonomy is partly orthogonal and partly overlapping with the understandings developed above. This is a provocative approach revealing interesting discrepancies between the definition used and the actual goal of the approach of the corresponding research teams.

1.6.1 Principles of the Classification

Table 1.1 proposes a five-level classification only focusing on the current meaning of the terms of the definition itself and independently from the context in which each definition was produced and used. **Group D1** are developmental definitions that do not specify that the concerned phenotypic variation among cells is transmitted during mitosis. Such definitions thus incorporate transitory changes in gene expression that participate to everyday cell metabolism. **Group D2** are developmental definitions that incorporate the necessity that the epigenetic states are transmitted across cell generations (i.e., through mitosis). Groups D1 and D2 make a meta-group of developmental definitions, the latter being more complete. **Group A** encompasses definitions that are ambiguous because they do not specify whether the stability of epigenetic stages only concerns mitosis (in which case they would belong to the D2 category), or also implies a stability during the reproduction of multicellular organisms (in which case they would belong to group E). In Table 1.1, I underline the term (s) that is(are) ambiguous. **Group E** definitions add the criterion of stability of epigenetic marks across reproduction of multicellular organisms. This implies that epigenetic marks either can escape the waves of demethylation re-methylation occurring at meiosis and fertilization, or be reconstructed at every generation. I avoid the term "meiotic" because there are fascinating examples in which epigenetic information does not persist through meiosis but is added de novo later during

gamete maturation. For instance, the transmission of acquired diabetes (Type II diabetes) to offspring involves specific small non-coding RNAs injected into maturing sperm cells during their transfer through the epididymis (Chen et al. 2016a; Sharma et al. 2016). **Group I** correspond to the inclusive understanding of epigenetics proposed above. It is much broader than other definitions, and is particularly suited for ecologists to integrate all inclusively heritable causes of phenotypic variation be they genetic or not.

1.6.2 Applying this Taxonomy

Applying this logic to a sample of definitions highlights interesting discrepancies between the definition used and the ultimate goal of the corresponding studies (Table 1.1). All classifications have their pros and cons. To be efficient, however, a classification should be straightforward and minimize ambiguity. However, minimizing ambiguity often does not eliminate all ambiguities, as in the classification of Table 1.1, where ambiguities lie in the frequent use of the concept of heritability without specifying the time scale involved. The term heritability comes from evolutionary ecology and quantifies the statistical link between phenotypic similarity and the degree of kinship between pairs of individuals, usually measured as the coefficient of genetic relatedness. Nonetheless, the same term (as well as other terms such as inheritance, heredity, phenotypic stability, or perpetuation of variation) often qualifies cellular stability or memory, i.e. the fact that within a multicellular organism a cell of a given phenotype mitotically produces daughter cells of the same phenotype (Skinner 2011a). In itself, transposing the concept of heritability to cell lineages is not problematic when the term is qualified with a term such as "mitotically" or "meiotically" because this specifies the time scale of the concerned stability. However, using these terms without such qualifications makes them ambiguous (concerned definitions make a specific category in Table 1.1 where the ambiguous terms are underlined).

The discrepancies between the above historically driven parts and Table 1.1 stem from the fact when discussing the understandings above, I gave more weight to the scientific, conceptual, and historical context, while the classification reported in Table 1.1 is based only on the actual terms of the definition and nothing else. The resulting discrepancies suggest that scientists often adopt definitions that are not the most suitable for their specific approach, potentially generating some ambiguities. It is thus central for ecologists to adopt a definition of epigenetics that is adapted to their level of analysis, namely that of individuals within populations and ecosystems. I thus suggest that ecologists should use the inclusive definition of epigenetics proposed above.

1.6.3 Potential Applications

What can the above definitions of epigenetics bring to the different domains of biology? First, the fact that terms change significance according to the scientific domain is not problematic as long as the adopted definition is appropriate to the scientific questions. My goal here was to stress the plurality of concepts of epigenetics, in order to clarify their uses, hopefully leading scientists to use an appropriate definition in view of their specific approach.

Second, we all have engraved in our brains a sequencic vision of inheritance. We need to fight against this prejudice to integrate the multidimensionality of inclusively heritable sources of variation beyond and in interaction with sequencic. In other words, after observing that a trait is heritable, we should not limit ourselves to the sole exploration of DNA sequence variation and explore other inclusively heritable sources of parent–offspring resemblance.

Third, adopting an inclusive understanding of epigenetics would help avoiding that the new evolutionary synthesis gets trapped into a purely molecular vision of inheritance, hence ignoring important processes such as cultural inheritance that can affect many behavioral and non-behavioral traits, such as obesity and diabetes (Avital and Jablonka 2000; Danchin et al. 2019a, b). In effect, inheritance also implies mechanisms, such as cultural inheritance (a major form of early in life effects) that mainly involves learning, a process that emerges at the scale of the brain rather than at the sole molecular level. This statement is true, despite the fact that it is highly likely that a high proportion of non-genetic processes of inheritance have some kind of epigenetic basis (Danchin et al. 2019b), as this is the case, for instance, of learning (Miller and Sweatt 2007).

Fourth, accepting the inclusive understanding of epigenetics has many consequences for the study of early in life effects, as some of them become inclusively heritable after their acquisition before reproduction (among others see the many examples reviewed in Wang et al. 2017; Danchin et al. 2019b). When early in life effects produce parent–offspring resemblance, the risk is high that they are considered as genetic, because most of the time we do not witness the initial stress that initiated the effect and triggered inclusively heritable variation, which can only be of a non-sequencic nature, probably often implying some variation in epigenetic states. Qualifying them of genetic origin may trap generations of researchers into purely sequencic studies. For instance, we now know that the strong heritability of ill-parental behavior in mammals including humans is due to the fact that the mothers' behavior constitutes a component of their pups' environment that triggers the emergence of epigenetic marks leading their daughters to reconstruct the same ill-parental behavior when adults (Denenberg and Whimbey 1963; Francis et al. 1999; Champagne 2008, 2020; Curley et al. 2008). More generally, parents in any species providing parental care constitute a major early in life component of their offspring environment affecting their epigenetic marks and interacting with other types of information carried out by the germline in shaping the phenotype in a heritable way (Champagne 2020). This reasoning can be generalized to any species

as even parents of species without parental care can shape their offspring phenotype through non-sequencic information in their gamete. Such parental effects can be viewed as very early in life effects. This poses that plastic responses to environmental changes can be transmitted to offspring through pathways involving early in life effects for at least several generations, in a way that can perfectly mimic genetic transmission when tested over a single or even a few generations (Danchin 2013). The knowledge about the mechanisms underlying these effects opens fantastic research avenue to define therapies to cure such ill behavior in order to stop the vicious circle generated by this form of epigenetic inheritance in humans.

Fifth, similarly, the inclusive understanding of epigenetics has many consequences for the study of adaptation. For instance, transposons that strongly interact with epigenetics can participate to adaptation by translating phenotypic adaptation into genetic variability, in a form of genetic assimilation (Rey et al. 2016; see also Danchin et al. 2019b; Pimpinelli and Piacentini 2020). Furthermore, all in all the non-genetic part of inclusively heritable information vastly expands the range of the sources of heritable variation (e.g., genetic, epigenetic, cultural, ecological, microbiota, prions etc.) on which selection can act. It implies that many of the adaptations we observe in nature may be inherited at least partly through other bearers than the DNA sequence, one of which being epigenetics in its evolutionary understanding. Furthermore, the fact that the various inheritance systems are suspected to influence each other (Danchin et al. 2019b) makes an inclusive approach even more necessary, and adopting such an approach represents a considerable paradigm change for ecologists in particular because it fully changes the potential bearers of adaptation, which is at the heart of all eco-evolutionary approaches.

Sixth, such mechanisms can strongly affect the design of conservation actions in the context of global change with its series of directional environmental changes (e.g., steadily increasing temperature). For instance, epigenetic variation in itself should be considered as a component of biodiversity in a way that is similar to sequencic variation (Rey et al. 2020). The same holds for cultural variation. Several authors have recently argued that we should also account for cultural variation in conservation that is made inclusively heritable by social learning (Brakes et al. 2019). For instance, after reintroduction into a habitat that remained unoccupied for years, migratory ungulates took quite some time to rediscover migration routes and wintering grounds (Jesmer et al. 2018). This implies that the loss of ancient cultural knowledge adds further threats of extinction during the initial phase of reintroduction when organisms build a new knowledge about their environment. In other words, we should integrate all the dimensions of inclusive epigenetics into conservation in order to protect natural populations properly.

To sum up, the inclusive understanding of epigenetics teaches us that the variation underlying many heritable traits (which are called genetic traits for that sole reason) might be of a non-sequencic nature. This is particularly true for all inherited early in life effects. Furthermore, the existence of epigenetically mediated inheritance often involving early in life effects probably considerably increases the adaptive capacities of populations to global change. The fact that epigenetic states

constitute a hub in most if not all plastic responses (Danchin et al. 2019b), and that some of these epigenetic states can be transmitted across generations may reinforce adaptive virtuous circles or extinction vortexes.

1.7 Conclusions

The large variety of understandings of epigenetics stems from the fact that epigenetic processes are ubiquitous in all aspects of living organisms, a high proportion of them involving some kind of early in life effects. Therefore, it is necessary to adopt a definition of epigenetics that is relevant to the type of research question. To fit within this philosophy, here I propose and recommend the use of an inclusive understanding of epigenetics that is particularly relevant to medical, ecological, and evolutionary studies, in part because that understanding can naturally encapsulate all types of early in life effects. Furthermore, this broader vision of epigenetics is likely to help bridging concepts of epigenetics at the infra-individual biology with those of supra-individual biology including behavioral, populational, functional, and evolutionary ecology, as well as medicine. To me, the merging, or full integration, of all sub-disciplines of biology into an inclusive biology studying all processes within a continuum from molecules to ecosystems constitutes the current major ambition for biology. The implementation of such an Inclusive Evolutionary Synthesis that I advocate here will occur only if members of all disciplines of biology are able to listen to and respect the approaches of the other disciplines, which often proves to be difficult. Furthermore, the adoption of this broader vision of life is likely to greatly help understanding and predicting the consequences of climate change at the various scales of individual accommodation, population dynamics and adaptation, food webs, ecosystem and biodiversity dynamics. I am convinced that only such an inclusive theoretical framework incorporating all available knowledge at all scales of living systems, from molecular to ecological interactions can allow us to achieve such an ambitious and demanding goal for the future of humanity on planet Earth.

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Glossary

Extended Evolutionary Synthesis A trend in evolutionary science, that took momentum at the turn of the twenty-first century and that puts more emphasis

on the role of development, environmental factors, as well as some non-genetic forms of inheritance in the evolutionary processes (mainly if not exclusively epigenetics in its developmental and evolutionary understandings: Pennisi 2008; Pigliucci and Müller 2010; Laland et al. 2015; Lu and Bourrat 2017).

Genetic Here, I use this term in its most common modern sense of sequencic, i.e. information encoded in the DNA sequence of nucleotides. Note that this meaning is highly reductionist relative to the initial meaning that encompassed everything that participates to heredity.

Genetic assimilation A process by which a phenotype initially induced by a specific environmental factor, becomes genetically determined through selection. Note that, at the time of Waddington, the term genetic meant anything that is inherited. In particular, Waddington's experiments did not show that the initially plastic trait became encoded into the DNA sequence, but rather, that it lost its plasticity and became inclusively heritable (Danchin et al. 2019b).

Heredity Patterns of parent–offspring resemblance. It is widely accepted in biology that heredity results from parents transmitting information to their offspring, though the nature of this information is still at the heart of a hot debate (e.g., Sarkar 1996; Godfrey-Smith 2000; Maynard Smith 2000; Pocheville 2018; Danchin et al. 2019b).

Heritability Usually, this term quantifies the part of phenotypic variation that is inherited genetically, either additively (narrow sense heritability) or total (broad sense heritability). It is measured at the level of a population. It quantifies parent–offspring resemblance at play in quantitative genetics. Today heritability is usually associated to variation in DNA nucleotidic sequence alone (Danchin and Wagner 2010; Danchin et al. 2011). For more details, see (Bourrat 2015). In Table 1.1, I also point at the transposition of this term to depict the persistence of cell characteristics along cell lineages of multicellular organisms.

Inclusive Evolutionary Synthesis The evolutionary synthesis ambitioning to incorporate *all known dimensions of inheritance* into a single theoretical framework. It incorporates the inclusive understanding of epigenetics that I develop here.

Inclusive heritability Statistical term quantifying the degree of parent–offspring resemblance, *whatever the mechanisms responsible for it* (whether sequencic or not, Danchin and Wagner 2010; Danchin et al. 2011). It is the heredity of difference, whatever the underlying mechanism. Often in this book chapter, I use the term heritability in the meaning of inclusive heritability, because historically it was the initial meaning of this term. Inclusive heritability is the corner stone of evolution through natural selection and drift.

Infra-individual processes Biological processes occurring within an organism during its lifetime, including gene expression, cell functioning, physiology, neurobiology, as opposed to supra-individual processes. Corresponds to what Mayr (1961) called functional biology.

Inheritance The set of mechanisms producing parent–offspring resemblance.

Intergenerational epigenetic inheritance The set of epigenetic mechanisms that produce resemblance between two successive generations.

Modern Synthesis (of evolution) A trend in evolution, first coined by Julian Huxley in 1942, that brought together Darwinism, Mendelism, and population genetics in order to provide a powerful account of the mechanisms of evolution. Also called Neo-Darwinism although these two terms often cover different approaches. In this trend, the focus is mainly on genes (today understood as sequencic). A purpose of the extended or inclusive syntheses is to extend it beyond the gene.

Non-genetic inheritance Mechanisms of inclusively heritable variation that do not result from variation in the DNA sequence (Danchin and Wagner 2010; Danchin et al. 2011). Equivalent to non-sequencic inheritance.

Sequencic Term that was first casually used by Hervé Philippe in a discussion to depict the pervasive trend among biologists and the grand public to reduce inherited information to the sole information encoded into the DNA sequence of nucleotides. It can replace the term genocentrism that I used before that is ambiguous because of the many understandings of all the terms of the "gene" family (genetics, genomics...).

Supra-individual processes Interactions occurring among individuals within populations, communities, and ecosystems. These integrate transgenerational processes such as heredity. This is the domain of ecology and evolution. Corresponds to what Mayr (1961) called evolutionary biology.

Transgenerational epigenetic inheritance The set of epigenetic mechanisms that produces resemblance across multiple (≥ 2) generations of organisms.

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