TRANSGENERATIONAL EPIGENETIC INHERITANCE: PREVALENCE, MECHANISMS, AND IMPLICATIONS FOR THE STUDY OF HEREDITY AND EVOLUTION

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ABSTRACT

This review describes new developments in the study of transgenerational epigenetic inheritance, a component of epigenetics. We start by examining the basic concepts of the field and the mechanisms that underlie epigenetic inheritance. We present a comprehensive review of transgenerational cellular epigenetic inheritance among different taxa in the form of a table, and discuss the data contained therein. The analysis of these data shows that epigenetic inheritance is ubiquitous and suggests lines of research that go beyond present approaches to the subject. We conclude by exploring some of the consequences of epigenetic inheritance for the study of evolution, while also pointing to the importance of recognizing and understanding epigenetic inheritance for practical and theoretical issues in biology.

DEFINITIONS: EPIGENETICS AND EPIGENETIC INHERITANCE

EPIGENETICS has become one of the buzz words of biology in recent years. Following the success of genome projects in defining what genomes are, the emphasis has shifted to what they do, and there is renewed interest in understanding the epigenetic processes of development. The term "epigenetics," however, has undergone many transformations since its original definition by Waddington (see Waddington 1968 for a discussion), reflecting the changing foci of research in developmental molecular biology since the second half of the 20th century (Jablonka and Lamb 2002, 2007c; Haig 2004; Holliday 2006). "Epigenetics" is therefore often employed loosely and inconsistently, and is sometimes used as a synonym for "epige-

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netic inheritance." To avoid misunderstandings, we define both terms as they are used in this review:

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. At the cellular level, these are the processes involved in cell determination and differentiation. At higher levels of biological organization, epigenetic mechanisms generate the context-dependent, self-sustaining interactions between groups of cells that lead to physiological and morphological persistence. The regulatory mechanisms that establish and maintain variant cellular and organismal states are known as *epigenetic control mechanisms*, or *epigenetic control systems* (Nanney 1958).

Epigenetic inheritance is a component of epigenetics. It occurs when phenotypic variations that do not stem from variations in DNA base sequences are transmitted to subsequent generations of cells or organisms. Many of the discoveries about epigenetic inheritance between organisms are derived from studies in developmental biology that look at inheritance in cell lineages within an organism. Cell heredity in mitotically dividing cells underlies the persistence of determined states in multicellular organisms. That is, an individual's kidney stem cells and skin stem cells generally breed true, even though their DNA sequences are identical and the developmental stimuli that led to the different cell phenotypes are long gone. However, the same cell heredity mechanisms that have been found in cell lineages during development are also observed when epigenetic inheritance occurs between generations of individuals. In single-celled organisms, such as bacteria and asexually reproducing protists, epigenetic inheritance leads to the clonal persistence of induced and stochastically generated phenotypic variations. In sexually reproducing organisms, heritable epigenetic variations in germline cells can result in the transmission of developmentally induced and stochastically generated phenotypes from one generation of individuals to the next through the gametes. Like "epigenetics," "epigenetic inheritance" is not always consistently employed. It is used in both a broad and a narrow sense.

Epigenetic inheritance in the broad sense is the inheritance of developmental variations that do not stem from differences in the sequence of DNA or from persistent inducing signals in the present environment. As well as cell-to-cell transmission of epigenetic variations in unicellular and multicellular organisms (as will be explained below), the definition covers body-to-body (or soma-to-soma) information transference that can take place through developmental interactions between mother and offspring (e.g., Weaver et al. 2004), through social learning (Avital and Jablonka 2000), and through symbolic communication (Richerson and Boyd 2005).

Cellular epigenetic inheritance is a narrower aspect of epigenetic inheritance as discussed in the broad sense. It refers to epigenetic transmission in sexual or asexual cell lineages, and the unit of this transmission is the cell. Following Holliday (1994, 2002, 2006), some biologists restrict the term epigenetic inheritance solely to the transmission of chromatin marks and RNAs (e.g., Wu and Morris 2001). However, yeast geneticists use the term epigenetic inheritance to refer to the inheritance of protein conformations, such as prions (e.g., Uptain and Lindquist 2001), and the term is also used by biologists studying self-sustaining loops and chromatin inheritance in bacteria (e.g., Grandjean et al. 1998; Laurent et al. 2005). We therefore define cellular epigenetic inheritance as the transmission from mother cell to daughter cell of variations that are not the result of differences in DNA base sequence and/or the present environment. Transmission can be through chromatin marks, through RNAs, through self-reconstructing three-dimensional structures, and through self-sustaining metabolic loops (Jablonka et al. 1992; Jablonka and Lamb 1995, 2005, 2007a). It occurs following cell division in prokaryotes, mitotic cell division in the soma of eukaryotes, and sometimes following the meiotic divisions in the germline. The chromatin and RNA-mediated cellular inheritance systems seem to play an important role in inheritance through the germline in both females and males.

In Figure 1, we illustrate the difference between the broad and narrow sense of epigenetic inheritance by showing the main routes of between-generation transmission in a sexually reproducing multicellular organism. As our focus in this review is on *cellular transgenerational epigenetic inheritance*, we are concentrating on the route of between-generation transmission that involves a single-cell "bottleneck," i.e., transmission through a gamete or a spore in multicellular, sexually reproducing organisms, or through a single sexual or asexual cell in unicellular organisms. The environment may induce epigenetic variation by directly affecting the germline or by affecting germ cells through the mediation of the soma, but, in either case, subsequent transmission is through the germline. Although the direct soma-to-soma transmission route of epigenetic variations is of great importance for both development and evolution (Jablonka and Lamb 2005, 2007a,b), its discussion is beyond the scope of this review.

Mechanisms of Cellular Epigenetic Inheritance (EISs)

Jablonka and Lamb (1989, 1995; Jablonka et al. 1992) suggested that the different mechanisms of epigenetic inheritance should be understood and studied within a shared evolutionary framework that incorporates the developmental construction of heredity and that acknowledges the Lamarckian aspects of heredity and evolution. They called the processes and mechanisms that underlie cellular inheritance "epigenetic inheritance systems" (abbreviated to EISs by Maynard Smith [1990]). Cell heredity may occur when an induced gene-product is diluted very slowly by cell divisions, so that its concentration remains above the threshold required for its activity for several cell generations (Zacharioudakis et al. 2007), but such "memory" is short-term. For more persistent memory and cell heredity, autocatalysis is necessary, and all the EISs we describe depend on mechanisms that enable self-perpetuation. Four types of cellular EISs are recognized today: the EIS based on self-sustaining regulatory loops, the EIS based on three-dimensional

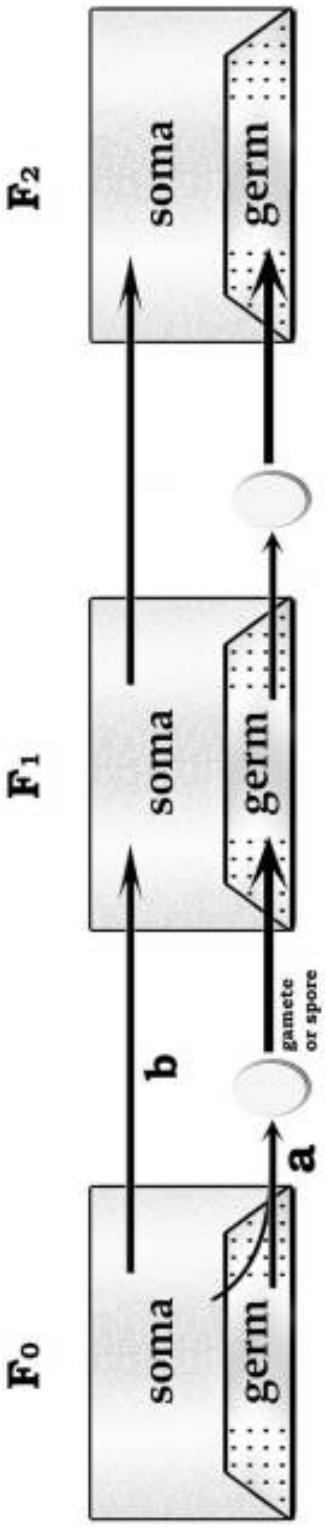

Figure 1. Routes of Transmission of Epigenetic Variations in a Multicellular, Sexually Reproducing Organism

Route **a** shows the germline-to-germline transmission of induced epigenetic variations (e.g., chromatin marks). A variation can be induced in the germline and can then be transmitted from one generation to the next, or it can first be induced in the soma, then affect the germline, and thereafter be inherited through the germline. Route **b** shows soma-to-soma transmission (for example, through the transmission of symbionts and parasites, or through the self-perpetuating effects of maternal behavior, social learning, and symbolic communication). A broad view of epigenetic inheritance encompasses both routes **a** and **b**, whereas the narrower, cellular view includes only route **a**—transmission through a single-cell "bottleneck," in this case, a gamete.

templating, the chromatin-marking EIS, and the RNA-mediated EIS. Although these EISs are usually seen as very different types of developmental mechanisms, all can contribute to between-generation epigenetic inheritance. Their dual nature as developmental mechanisms and as inheritance systems means that they can be studied from both perspectives. The developmental perspective is currently the dominant one, and the molecular basis of epigenetic control systems is one of the most intensely studied fields in biology today (e.g., see collections of articles in *Nature Reviews Genetics* 8(4) [Flintoft 2007], *Nature* 447(7143 Insight) [Campbell 2007], and *Cell* 128(4) [Marcus 2007], as well as Allis et al. 2007). In this review, we focus on the less discussed aspect of EISs and epigenetic inheritance—the transmission of cellular epigenetic states from one generation of organisms to the next. We therefore describe the four EISs from a heredity-focused point of view. All the examples to which we refer, as well as many others, are presented here in Table 1 and in our expanded table (available online, with accompanying table references, at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB).

INHERITANCE THROUGH SELF-SUSTAINING LOOPS

Self-sustaining feedback loops are metabolic circuits through which different patterns of activity can be maintained, resulting in alternative heritable cell phenotypes. The first experimental studies of such loops were those involving the bistability of the lac operon of *Escherichia coli* (Novick and Weiner 1957), and this system has since been thoroughly analyzed at both the molecular and theoretical levels (Laurent et al. 2005). These studies show that, when inducer concentrations are low, genetically identical cells can generate two alternative, true-breeding, stable phenotypes.

Many other self-sustaining feedback loops leading to alternative heritable phenotypes have been described in bacteria and other taxa (Dubnau and Losick 2006; Smits et al. 2006; Malagnac and Silar 2003, 2006). One well-characterized example of positive regulation leading to alternative cell phenotypes is found in the fungus *Candida albicans*, where an epigenetic switch underlies the transition between white and opaque cells—two states that are heritable for many generations (Zordan et al. 2006). Self-sustaining loops need not be based on transcriptional regulation; they can also occur at the post-translation stage, through protein self-processing. An example is the enzyme vacuolar protease B of *Saccharomyces cerevisiae*, whose active form is necessary for its own conversion from an inactive precursor to an active state. On glycerol media, where the precursor is synthesized in high amounts, the self-processing of the enzyme is indefinitely self-sustaining (Roberts and Wickner 2003). As noted by Wickner et al. (2004), it is likely that other protein-modifying proteins may also directly or indirectly affect their own modification and behave as self-sustaining, cell-transmissible loops.

STRUCTURAL INHERITANCE: SPATIAL TEMPLATING

Structural inheritance refers to the inheritance of alternative three-dimensional (3-D) structures through spatial templating: a variant 3-D structure in a mother cell guides the formation of a similar structure for a daughter cell, leading to the transmission of the architectural variant (Nanney 1968). The study of cellular structural inheritance was initiated by investigations of the inheritance of cortical variations in ciliates. Beisson and Sonneborn (1965) showed that an experimentally modified organization of the cilia on *Paramecium* can be inherited through many asexual and sexual generations. The inheritance of cortical variations induced by various physical and chemical manipulations has also been demonstrated for other ciliates (Nanney 1985; Frankel 1989; Grimes and Aufderheide 1991).

The propagation of prions is another form of structural inheritance. The fundamental characteristic of a prion—a transmissible protein—is that it has a conformation that can initiate and sustain the reproduction of a similar conformation in newly synthesized proteins. Prusiner (1998) suggested that infectious proteins are the

causative agents of mammalian neurodegenerative diseases such as kuru, scrapie, and mad cow disease and coined the term prion (*pro*teineceous *in*fectious particles) for such agents. He advanced and developed the concept of an infectious protein whose propagation is based on the spatial-templating of the variant prion conformation, which, in turn, converts a normally-shaped protein into its own shape. The concept was extended when Wickner (1994) characterized the [URE3] variant in yeast as a prion and explained its idiosyncratic biochemical and hereditary characteristics in terms of protein-based inheritance. Since then, more prions have been identified in yeast and other fungi (Baxa et al. 2006; Tuite and Cox 2006). Although some prions have deleterious effects, others seem to have important biological functions (Wickner et al. 2004; Shorter and Lindquist 2005; Benkemoun and Saupe 2006).

One of the most interesting findings about prions is that a single protein can misfold into several different conformations that have specific growth dynamics, stabilities, pathologies, and cross-species infectivity (Chien et al. 2004). Different prions may interact, leading to the formation of many different transmissible (cell-heritable and infectious) phenotypes. Therefore, unicellular organisms, which have the same genotype and live in the same environment, can exhibit heritably different morphologies and physiologies that are the consequence of differently folded identical proteins. The differences result from differences in the developmental histories of their ancestors.

Cavalier-Smith (2004) studied another aspect of spatial templating, an aspect associated with membrane reproduction. The reproduction of most membranes, including the plasma membrane, the endoplasmic reticulum, and the mitochondrial membrane, requires the presence and templating of pre-existing membrane structures. Cavalier-Smith identified 18 types of what he called "genetic membranes," the structures of which are cell-heritable through these guided processes, and he argued that the information embedded in this "membranome" is as essential for the construction of a cell as genomic information. He suggested that crucial events in the evolution of cells and major groups were associated with heritable changes in membranomes.

THE CHROMATIN-MARKING EIS

Chromatin, the stuff of chromosomes, includes DNA and all the factors physically associated with it: small chemical groups covalently attached to DNA (e.g., methyl groups), bound histone and nonhistone proteins, and associated RNA molecules. The organization of chromatin and chromosomes, their localization in the nucleus, and the dynamic interactions among the various components of chromatin determine when, where, and to what extent genes are transcribed, how DNA repair is orchestrated, how different chromosomal domains are organized, and how chromosomes, as units, behave during the various phases of the cell cycle. Patterns of chromatin are reconstructed following DNA transcription and replication, and, although the processes of reconstruction are not well understood, there is evidence that chromatin variations can be transmitted between generations of individuals. The study of the chromatin-marking EIS is therefore crucial for the understanding of both development and heredity.

DNA methylation, the best-understood system of chromatin inheritance, is an epigenetic modification found in Eubacteria, Archeabacteria, and Eukaryota. It is involved in many important functions (for general reviews see Casadesús and Low 2006; Vanyushin 2006a,b), including defence against genomic parasites (Kidwell and Lisch 1997), regulation and maintenance of gene activity patterns (Barlow and Bartolomei 2007; Li and Bird 2007), stabilization of chromosomal structure (Karpen and Hawley 2007), and DNA replication and repair (Mortusewicz et al. 2005; Schermelleh et al. 2007). In eukaryotes, methylation usually occurs on the cytosines in CpG doublets and also in CpNpG triplets in plants. Since CpG and CpNpG se-

quences are palindromic, the two strands of the duplex are mirror images of each other. Following replication, two hemimethylated duplexes are formed, and these hemimethylated regions are recognized by maintenance DNA methylases, which preferentially add methyls to nonmethylated C in the new strand (Allshire and Selker 2007; Henderson and Jacobsen 2007; Li and Bird 2007). The replication of methylation patterns is thus semi-conservative. The fidelity of transmission in cell lineages ranges from about 1% variation per cell generation up to the very high fidelity of 10^{-6} variations per cell generation (Genereux et al. 2005; Richards 2006).

Variations in a DNA methylation pattern can also be inherited between generations, and examples of this include paramutations in plants (interaction between alleles that leads to a directed epigenetic heritable change in one of the interacting alleles [Brink 1973; Chandler 2007]); silencing of foreign duplicated sequences in fungi (Allshire and Selker 2007); variations in telomeric, centromeric, and rRNA regions (Karpen and Hawley 2007); and variations in transgenes and endogenous genes. Specific examples of all these types of transgenerational inheritance are presented in Table 1.

How a DNA methylation pattern affects a cell's or an organism's phenotype depends on the way it interacts with the protein components of the chromosome, which are also heritable. In eukaryotes, important variations in chromatin are associated with histones, the proteins that make up the nucleosome core around which DNA is wrapped. The dynamic nature of histones, their variability, and their association with every conceivable cellular function (see Berger 2007; Groth et al. 2007; Blasco 2007; Morris and Moazed 2007) makes understanding the inheritance of their specific structure and organization both challenging and urgent. Several models of this process have been constructed, and according to all of them, the nucleosome variants and the post-transcriptional modifications (PTMs) of the parental nucleosomes are used as blueprints for the restoration of the same nucleosome configuration. These reconstructions may be assisted by other chromatin components such as DNA methylation patterns (Martin and Zhang 2007), RNAs (Grewal and Jia 2007; Ringrose and Paro 2007), and by the location of the chromosomal domains within the nucleus (Misteli 2007).

In addition to DNA methylation patterns, as well as histone variants and their PTMs, chromatin has various enzymes that associate dynamically with the histones and DNA bound to them and that participate in their regulatory and structural functions (Bantignies and Cavalli 2006). The patterns of association of these nonhistone proteins with other chromatin components can also be reconstructed between generations of cells and organisms (Ringrose and Paro 2004; Bantignies and Cavalli 2006; Schuettengruber et al. 2007). Recent data suggest that RNA produced at regions that bind nonhistone chromatin proteins may lead to the inheritance of the bound state through RNA-DNA pairing (Grewal and Jia 2007; Ringrose and Paro 2007).

THE RNA-MEDIATED EIS

During the last decade, it has become apparent that RNA is central to the regulation of cellular dynamics in eukaryotes and is also involved in cell and organism heredity. Gene silencing by small RNAs—RNA interference (RNAi)—has been found in all eukaryote phyla from yeast to man, although a few species (e.g., budding yeast) seem to have lost the capacity for this. In all of the RNAi pathways, double-stranded RNA molecules (dsRNA), which trigger the process, are chopped into shorter dsRNAs (usually between 21-30 nucleotides long) by the enzyme Dicer. After the original dsRNA is chopped, the resulting siRNA (small interfering RNA) is loaded onto a complex of proteins, one strand of the duplex is removed, and the other strand—the guide strand—directs silencing. Silencing may occur through any of the following mechanisms: (i) the siRNA is loaded onto an enzyme complex that interferes with the transcription or translation of mRNAs with a homologous se-

quence (Cullen 2004; Meister and Tuschl 2004); (ii) the siRNA is loaded onto an enzyme complex that targets chromatin regions with DNA that is homologous to the siRNA, and alters chromatin into a silent state (Matzke and Birchler 2005; Ekwall 2007; Huettel et al. 2007); or (iii) the siRNA is loaded onto an enzymatic complex that degrades and/or excises the DNA sequences complementary to the siRNAs. The latter processes of RNA-regulated DNA rearrangement are being intensely studied in ciliates (Meyer and Chalker 2007; Nowacki et al. 2008).

RNA can affect cell and organism heredity in at least three different, non-mutually exclusive ways. The first is the result of replication of siRNA through RNA-dependent RNA polymerase. This replication is a two-stage process, the details of which differ between taxa, and it leads to the amplification of siRNAs that act as repressors of gene expression (Baulcombe 2007; Pak and Fire 2007). These siRNAs are transmitted to daughter cells during cell division and can migrate to other cells as well (e.g., Palauqui et al. 1997; Himber et al. 2003). The second way in which RNAs can affect cell heredity is by guiding, targeting, and assisting in transmitting variations in chromatin structure that are reconstructed and reproduced in daughter cells through the chromatin-marking EIS (Matzke and Birchler 2005; Ekwall 2007; Huettel et al. 2007). The third way is by targeting DNA base sequences and guiding changes in them that are then replicated by DNA polymerases (Meyer and Chalker 2007; Nowacki et al. 2008). Heritable variations can be generated and perpetuated through all three routes of RNA-mediated heredity, and the formation of a particular dsRNA may be affected by local conditions and may be developmentally regulated. Once formed, such dsRNA may have long-term hereditary effects.

EISs and the germline

It is obvious from the foregoing descriptions that the different EISs are often mechanistically and functionally interrelated; therefore, the division of EISs into four categories is somewhat arbitrary and artificial. However, dividing EISs in this manner highlights the variety and complexity of the cellular mechanisms of inheritance. The details of how epigenetic variations are transmitted through mitosis in asexual clonal lineages remain a puzzle, but in sexually reproducing organisms, especially multicellular ones, the puzzle is even greater.

In sexually reproducing organisms, epigenetic variations have to survive the complex process of meiosis in order to be transmitted to the next generation, and, in multicellular organisms, they also have to survive gametogenesis and early embryogenesis—two developmental stages that involve significant restructuring of both cells and chromatin. Although there is as yet no evidence that prions and self-sustaining loops are transmitted between generations through sperm and egg, there is evidence that chromatin marks and RNAs can be transmitted in this manner, but it is not clear how this occurs. It seems likely that some footprints of chromatin marks remain and lead to the reconstruction of ancestral states, or that some remnants of ancestral states (including some RNAs) are retained. Even in male vertebrates, where a comprehensive replacement of histones by protamines takes place during gametogenesis, the erasure of histone marks is not complete. In the mouse, for example, about 1% of the DNA remains wrapped around histones, and two acetylated variants of H4 are maintained through spermiogenesis (Van der Heijden et al. 2006). Van der Heijden and his colleagues (2006) suggested that these histones, as well as methylated cytosines in centromeric DNA, are associated with the transgenerational maintenance of the structure of centromeric heterochromatin. Chong et al. (2007) reported that when male mice had mutations in genes involved in epigenetic programming—in a gene that encodes a chromatin remodeler protein, and in another that encodes DNA methyltransferase—there were phenotypic effects on their offspring, even when they did not inherit the defective gene. Extensive epigenetic

(methylation) variation has been found in human germ cells (Flanagan et al. 2006), but whether and to what extent this variation is passed between generations is not known.

In addition to some chromatin marks, certain RNAs may be transmitted through the germline. Cells in the germline contain small RNAs, known as Piwi-associated interfering RNAs (piRNAs), that are important for the proper maturation of germ cells (Kim 2006). One function of piRNAs may be the detection and silencing—or deletion—of regions of unpaired DNA during meiosis. Unpaired regions are targets of the RNAi machinery; RNA transcribed from them guides enzymatic complexes to the unpaired regions, which are then deleted or heterochromatinized (Shiu et al. 2001; Bean et al. 2004; Turner et al. 2005; Costa et al. 2006). Mammalian spermatocytes are filled with piRNAs, and similar RNAs have been discovered in oocytes too. The abundance of piRNAs suggests that they may be transmitted to the next generation and lead to transgenerational effects. The transmission of an epigenetic modification in male mice (induced in heterozygotes for a variant *Kit* gene) is known to be mediated through microRNAs with sequences partially complementary to that of Kit RNA (Rassoulzadegan et al. 2006; see supplementary material for details, available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB).

Transgenerational Epigenetic Inheritance: Prevalence, Distribution, and Induction

There is no recent review of cellular epigenetic inheritance between generations that encompasses all four types of EISs and their distributions across taxa. The only comprehensive survey was made by Jablonka and Lamb in 1995. Since then, many more cases have been described, and our understanding of the molecular mechanisms underlying epigenetic inheritance has deepened and expanded. The table we present here (Table 1) brings together over one hundred cases of inherited epigenetic variations in bacteria, protists, fungi, plants, and animals. We have included only cases where there is convincing evidence for epigenetic inheritance in the narrow cellular sense, either through a single asexual cell (as in bacteria, some protists, some fungi, and some plants) or through a sexually generated gamete or spore (most animals, plants, and fungi). In most (although not all) cases, molecular studies have revealed the involvement of one or more of the EISs, but a full molecular characterization through all the reproductive stages is not yet available for any organism. More details about the cases are given as supplementary material in an expanded table form (available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB).

How common is epigenetic inheritance? This question is often raised, and the answer, based upon the data we have accumulated, is that it may be ubiquitous. We believe that epigenetic variants in every locus in the eukaryotic genome can be inherited, but in what manner, for how long, and under what conditions has yet to be qualified. In other words, unlike the replication of DNA variations, which is largely context insensitive, whether and for how long a particular mark or cellular element is transmitted between generations depends on genomic, developmental, and external conditions. This does not mean that conditions that allow epigenetic inheritance are particularly rare. In fungi, for example, the widespread occurrence of epigenetic inheritance is generally acknowledged. As long ago as 1949, Lindegren, reviewing data on inheritance in *Neurospora,* said that two thirds of new variants do not show Mendelian segregation and are therefore discarded, and, in their recent review of protein inheritance in fungi, Benkemoun and Saupe (2006) commented: *"Many of us working with filamentous fungi know how often bizarre looking sectors or segregates that defy Mendelism appear on our plates. As a number of pioneering fungal geneticists have done in the past, maybe we should have a closer look before putting them in the autoclave"* (p. 793). They suggested that many of these "anomalies" may be caused

by some form of epigenetic inheritance. In all organisms, chromatin inheritance can theoretically occur at every locus in the genome, and the double-stranded nature of DNA provides a theoretical possibility (when transcription occurs from both strands) for every DNA segment to form small dsRNA molecules that can lead to heritable silencing. The potential of most proteins to form β sheets with spatial templating properties (Baxa et al. 2006) suggests that a prion-like transfer of conformation between cells may occur more frequently than previously thought.

CASES INCLUDED IN THE TABLE

In Table 1, we show only a small sample of representative cases of epigenetic inheritance in allopolyploid plant hybrids because, in all cases that have been investigated, allopolyploidy is accompanied by extensive epigenetic changes, some of which are inherited between generations. In most of the cases presented in the table, the molecular basis of the EIS has been unravelled, but we included a few cases for which the evidence for cellular epigenetic inheritance seemed overwhelming, despite the fact that molecular studies were lacking (e.g., inheritance of the star phenotype in silver foxes, and some cases of developmentally induced variability and inheritance in plants and fungi).

As our main goal in this review is to show that variations in epigenetic marks can be inherited for several generations, we did not include classical cases of genomic imprinting in the table. With genomic imprinting, the epigenetic marks that are imposed on parental chromosomes during oogenesis differ from those imposed during spermatogenesis; therefore, in the offspring, a gene's expression pattern depends on whether it was inherited from the father or from the mother (see Barlow and Bartolomei 2007 for genomic imprinting in mammals, Alleman and Doctor 2000 for flowering plants, and for general reviews of imprinting that include invertebrates, see Jablonka and Lamb 1995; Haig 2002). By definition, the genomic imprints characterizing one sex are reversed when chromosomes go through gametogenesis in the opposite sex in the next generation; thus, imprints are inherently reversible. However, molecular studies of imprinting have been important in the history of epigenetic inheritance because they have led to a general recognition of the role of epigenetic control mechanisms, such as changes in DNA methylation in critical regions, and have opened the way to unraveling cases that were similar to genomic imprinting but that were not parent-sex specific (e.g., the early studies by Hadchouel et al. 1987 and Allen et al. 1990, as discussed in Jablonka and Lamb 1995). The only imprinting-related case included in the table is that of an imprint in a human grandmother that was not erased in her son and that subsequently led to Prader-Willi syndrome in her grandchildren (Buiting et al. 2003). This is a clear case of an epigenetic imprinting mark being transmitted as a result of a fault in resetting. As yet, we are not aware of any studies showing that new variations in genomic imprints are transmitted over several consecutive generations.

In most of the cases that we included in the table, the epigenetic variations have been transmitted for more than two generations, and we can rule out repeated direct induction of the variation in each generation. However, when the induced parent carries an embryo, three generations may be necessary to confirm epigenetic inheritance. For example, when a female mammal is exposed to an inducing agent during pregnancy, direct induction of the embryo's germ cells has to be excluded; therefore, three generations of transmission (from F_0 to F_3) are required to establish that epigenetic inheritance, rather than direct induction of the embryo and its germline, has occurred (Jirtle and Skinner 2007). On the other hand, when a male mammal is exposed to an inducer, two generations of transmission (from F_0 to F_2) are sufficient to establish that there has been epigenetic transmission through the germline rather than through direct induction. When the epigenetic effects (e.g., patterns of methylation) in the F_1 and F_2 generations are identical, and when

TABLE 1
Transgenerational epigenetic inheritance in prokaryotes and eukaryotes

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
Bacteria and their viruses						
λ phage of *Escherichia coli*	Lysogenic/lytic cycle	*Cl* and *Cro*	Stable	Nutritional state of the host, phage density	Self-sustaining loops	Ptashne (2005)
Bacillus subtilis	Inactivation of chromosome	Whole chromosome	Stable	Polyethylenglycol (PEG)-induced fusion	Chromatin-marking	Grandjean et al. (1998)
	Lack of cell wall	Balance between peptidoglycan synthesis and destruction	Stable on agar	Experimental removal of cell wall	Structural inheritance	Landman (1991)
	Sporulation	Spo0A phosphorelay	Stable	Nutritional deprivation	Self-sustaining loops	Veening et al. (2005)
	Natural competence (K state)	*ComK* activity	10%–20% in lab strains, 1% in the wild	Stochastic, elevated by stress	Self-sustaining loops	Maamar and Dubnau (2005)
Escherichia coli	Utilization of lactose[a]	Lac operon activity	Stable under conditions of low inducer concentration	Stochastic, growth in low concentration of inducer	Self-sustaining loops	Cohn and Horibata (1959a,b), Laurent et al. (2005), Novick and Weiner (1957), Ozbudak et al. (2004)
	Fluffy	*Agn43*	Phase variation	Probably oxidative stress	GATC methylation	Casadesús and Low (2006)
	Pili	Pap operon	10^{-4} per generation, 10^{-3} reversion	Changed carbon source, temperature, and spontaneous	GATC methylation	Hernday et al. (2002)
	Growth rate (persister type II)[b]	Probably many genes	10^{-6} per generation, 10^{-1} per generation reversion	Spontaneous and antibiotic treatment	Self-sustaining loops	Balaban et al. (2004), Lewis (2007), N. Balaban (personal communication)
	Resistance to antibiotics (ampicillin, tetracycline, and nalidixic acid)	Altered regulation of β lactamase cryptic gene, glutamate gene, and decarboxylase gene; possible involvement of DNA methylase genes	3%–20% survival (depending on concentration of antibiotic) and 50% reversion rate	Low, and successively increased concentrations of antibiotics	Possibly self-sustaining loops and /or DNA methylation	Adam et al. (2008)
Pseudomonas aeruginosa	Toxin injection	TTSS system	Stable	Cell density	Self-sustaining loops	Filopon et al. (2006)

Synecococcus elongates (Cyanobacteria)	Circadian rhythm	Regulatory loop involving key KaiC protein	Several days	Light and dark pulses	Self-sustaining loops	Kondo and Ishiura (2000)
Protists						
Oxytricha trifallax (Ciliate)	Alteration of gene order: aberrant rearrangements	Genes that become unscrambled in the somatic macronucleus (i.e., most genes)	Stable through asexual reproduction; at least 3 generations following sexual reproduction	Experimental manipulation	RNA-mediated rearrangement	Nowacki et al. (2008)
Paramecium aurelia (Ciliate)	Serotypes expressed	Cilia proteins	Stable	Changes in pH, temperature, food supply, and salinity	Self-sustaining loops	Landman (1991)
	Induced tolerance to heat, salt, and arsenic	Not specified	Inherited for many generations before fading away gradually	Exposure to high temperature, high salt, and arsenic concentrations	Not known	Jollos (1921); reviewed in Jablonka et al. (1992)
Paramecium tetraurelia, Stylonchia lemnae, Tetrahymena thermophila (Ciliates)[c]	Various traits related to alternative genetic organization patterns in the macronucleus	In principal, any DNA sequence in the genome	Stable through macronucleus reproduction, both during asexual and following sexual reproduction	Sequence comparison of maternal (old) and zygotic (new) nucleus, based on non-expressed sequences, leads to the inheritance of maternal, nucleus-guided gene organization	Inherited DNA rearrangement/ editing/ programming of the macronucleus mediated by small RNAs and chromatin modifications	Garnier et al. (2004), Juranek et al. (2005), Liu et al. (2004), Meyer and Chalker (2007), Taverna et al. (2002), Yao et al. (2003)
	Cortical organization	Basal body and cortex proteins	Stable in mitosis and sometimes in meiosis	Experimental manipulation, stress	Structural inheritance (guided assembly)	Grimes and Aufderheide (1991)
Plasmodium falciparum (Malaria parasite)	Telomere inactivation	Telomere sequences	Switch every ~ 15 generations	Spontaneous	Chromatin-marking	Roberts et al. (1992)

continued

TABLE 1
Continued

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
Tetrahymena (Ciliate)	Increased insulin binding and production following exposure to diiodotyrosine (T_2)	Not specified	Very stable—hundreds of generations	Induction by insulin or diiodotyrosine	Probably methylation; treatment with 5-azacytidine can abolish response	Csaba (2008), Csaba et al. (1999), Csaba and Kovacs (1990, 1995), Csaba et al. (1982a,b)
Volvox carteri	Silencing of *in vitro* methylated transgene	*C-ars* transgene	More than 100 generations	DNA transformation	DNA methylation	Babinger et al. (2007)
Fungi						
Ascobolus immerses	Transgene inactivation	Any duplicated transgene	Stable	Pre-meiotically	DNA methylation	Martienssen and Colot (2001), Rhounim et al. (1992)
Candida albicans[d]	Cell morphology, ability to form colonies on various substrates, mating properties	Master regulator WOR1 protein	Switches every ~ 10,000 generations	Spontaneous, affected by temperature	Self-sustaining loop	Huang et al. (2006), Malagnac and Silar (2003), Zordan et al. (2006)
Coprinus cinereus	Methylation pattern	Centromere-linked locus	Stable when highly methylated	Unknown	Chromatin-marking, DNA methylation involved	Zolan and Pukkila (1986)
Podospora anserina (Filamentous fungus)	Crippled Growth (CG)	*C*—assumed to be a transmissible self-sustaining cascade factor involving a Map kinase module	Stable mitotic inheritance	Transformation of normal cells to CG cells induced by cytoduction, promoting stationary state and growth on medium supplemented with yeast extract	Self-sustaining loop	Kicka et al (2006), Malagnac and Silar (2006), Silar et al. (1999)
	[Het-s*] and [Het-s] variants affecting vegetative incompatibility	*het-s*	Stable; low frequency [Het-s] converted to inactive [Het-s*], but the reverse also occurs, albeit at low frequency	Spontaneous	Structural inheritance (prion)	Maddelein et al. (2002)

Saccharomyces cerevisiae	Enhanced resistance to starvation on dextrose- minimal plates and suppression of inability to sporulate in mutants	[β]-prion form of the PrB vacuolar protease	Indefinite propagation	Emerges in deletion-mutants; induction is increased as a result of PrB over-expression	Prion, through self-sustaining loop	Roberts and Wickner (2003)
	Growth phenotype	FLO genes near telomere	Switch every 10 to 15 generations	Spontaneous	Chromatin inheritance	Halme et al. (2004)
	Read through	[PS]	Stable	Various	Structural inheritance (prion)	Tuite and Cox (2006)
	Nitrogen catabolic gene expression	[URE3]	Stable	Spontaneous and over expression	Structural inheritance (prion)	Benkemoun and Saupe (2006)
	Ascus formation	$[PIN]^{+}$Rnq1p	Stable	Spontaneous and over expression of Sup35	Structural inheritance (prion)	Benkemoun and Saupe (2006)
	Expression of experimentally modified GAL network	GAL network	Stable	Low inducer concentrations	Self-sustaining loop	Acar et al. (2005)
	Induction of *GAL1* and *GAL7* by galactose	GAL genes	Up to 7 generations	Induction by galactose	Slow dilution of abundant regulatory *GAL1* protein	Zacharioudakis et al. (2007)
	Anti-suppressor	ISP^{+}?	Stable	Spontaneous	Probably based on structural inheritance	Benkemoun and Saupe (2006), Kunz and Ball (1977), Tallóczy et al. (2000), Volkov et al. (2002)
	Glucosamine resistance	GR?				
	Control of killer virus expression	KI-d? (suspected prions)				
	Slow growth and additional requirement for leucine	Structural alteration of the mitochondrion	More than 100 generations in the absence of leucine	Spontaneous inherited loss of mitochondrial DNA	Structural inheritance	Lockshon (2002)

continued

TABLE 1
Continued

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
Schizosaccharomyces pombe	Survival of mutant strain lacking the *hcd* region-encoding, highly conserved domain of the essential chaperone calnexin	[cif]	Calnexin independence inherited by 88.7% of spores	Mating cells lacking the gene coding for calnexin with calnexin-dependent cells	Structural inheritance, probably prion	Collin et al. (2004)
	Meiotic telomere clustering and chromatin structure	Interaction of telomeric and subtelomeric regions with Taz1	Stable	Normal; variation shown by deleting telomere sequences in chromosomes	Chromatin-marking, structural inheritance	Sadaie et al. (2003)
	Reporter transgene silencing and mating type switching	*KΔ::ura4* (transgene inserted at K-region)	At least 30 mitotic generations after meiosis	Transgenically induced	Chromatin-organizing factors probably involved	Grewal and Klar (1996)
Plants						
Antirrhinum majus (Snapdragon)	Flush/granulated phenotype (paramutation)	*nivea* locus	Variegated in F_1, more stable in F_2	Induced by crossing	Transposition suggested; chromatin-marking plausible	Krebbers et al. (1987)
Arabidopsis thaliana (Mouseear cress)	Reversion of dwarf morphology	*Cpr1–1* gene-epiallele interacting with *bal*	Effect seen in F_2 progeny but not in F_1	Induced by crossing	Unknown	Stokes and Richards (2002)
	Size, rosette, and petiole abnormalities; activity of GFP reporter gene	Transgenic loci *E82* and *L91* interacting with *COP1* endogene	At least 5 generations	Induced by crossing	Involvement of RNA-mediated DNA methylation suggested	Qin and von Arnim (2002)
	Delayed flowering	*fwa* (gene-epiallele)	Very stable	EMS, fast neutron treatment, or *ddm1* induced (Wild type DDM1 required to maintain DNA methylation)	DNA methylation, histone H3 methylation (siRNAs involved)	Kinoshita et al. (2007), Lippman et al. (2004), Soppe et al. (2000)

	Dwarfism, constitutive activation of defense response pathway	*Bal* locus	At least 5 generations	*ddm1* effect even when segregated out	Probably DNA methylation	Stokes et al. (2002)
	Number of reproductive organs	*SUP*	At least 2 generations	Various mutagens	DNA methylation	Jacobsen and Meyerowitz (1997)
	Expression levels of the retrotransposon *At2g10410*	*At2g10410* epiallele	At least 8 generations	Spontaneous, found in natural populations	DNA methylation	Rangwala et al. (2006)
	Increased levels of homologous recombination in soma	Not specified	At least 4 generations in case of UV-C radiation; at least 2 generations in case of introduced flagellin	Ultraviolet radiation or introduction of flagellin	Not specified	Molinier et al. (2006), J. Molinier (personal communication)
	Loss of hygromycin resistance (paramutation)	*hpt* transgene	No effect in F_1; F_2 affected	Transgene-induced	Involves DNA methylation	Scheid et al. (2003)
	Transcriptional activity of transposable elements	Various transposable elements	At least 6 generations	*ddm1* effect, even after segregated out	DNA methylation, chromatin modifications; RNAi probably involved	Lippman et al. (2003, 2004), V. Colot (personal communication)
	Blue fluorescence, tryptophan and IAA deficiency, morphological abnormalities	*PAI* (gene-epialleles)	At least 6 generations	T-DNA mutagenesis, crossing; variation found in natural populations	DNA methylation; DNA/DNA pairing is suggested	Bender and Fink (1995), Luff et al. (1999)
Arabidopsis Interspecfic hybrids[e]	Many traits	Many loci, both coding and noncoding	Stability varies according to locus, but many loci show stable inheritance	Induced by hybridization followed by polyploidization	Chromatin-marking, DNA methylation; RNAi system probably also involved	Comai et al. (2000), Scheid et al. (2003)

continued

TABLE 1
Continued

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
Beta vulgaris (Sugar beet)	Many traits in mitotic, agamospermic, and inbred lines including: single or multiple flower initiation, self-fertility, polymorphism of malic enzyme, and variation in number of chloroplasts	*Mm*, *li*, *Rf1*, and *Me1* loci	Variable, often 2 or more generations	Mode of reproduction, climatic conditions, direction of cross	DNA methylation is probably involved	Levites (2000), Levites and Maletskii (1999), Maletskii (1999)
Linaria vulgaris (Common toadflax)	Flower symmetry	*Lcyc* (gene-epiallele)	At least 2 generations	Natural variation in populations	DNA methylation	Cubas et al. (1999), J. Parker (personal communication)
Linum usitatissimum (Flax)	Plant weight, height, peroxidase isozyme pattern, seed capsule septa hair number	r-DNA genes and repetitive sequences	Stable	Fertilizer and heat regimes	Methylation and DNA-repatterning	Cullis (2005)
	Flowering age, main stem height at maturity, and number of leaves	Not specified, but epimutations in at least 3 independent, nonrandom loci are assumed to be involved	At least 9 generations	5-azaC treatment	DNA methylation, possibly associated chromatin remodeling as well	Fieldes and Amyot (1999), Fieldes et al. (2005)
Lycopersicon esculentum (Tomato)	Inhibition of ripening and development of a colorless pericarp	*KeSPL-CNR* (gene epiallele)	Very stable	Spontaneous epimutation	DNA methylation	Manning et al. (2006)
	Color variegation (Paramutation)	*Sulf* epialleles	Very stable	X-rays; regeneration	Chromatin inheritance suggested	Hagemann (1969, 1993), Hagemann and Berg (1977), Wisman et al. (1993), R. Hagemann (personal communication)

Melandrium album (White campion)	Bisexuality	Decrease in CG methylation in many loci	2 successive generations, inherited through the male parent	Treatment with 5-azacytidine	DNA methylation	Janoušek et al. (1996)
Nicotiana tabacum (Tobacco)	Loss of kanamycin resistance; paramutation-like effects	Nos_{pro} and *nos*	At least 2 generations	Transgenic silencing in doubly transformed plants	DNA methylation	Matzke and Matzke (1991), Matzke et al. (1989)
	Loss of hygromycin resistance	*Hpt* transgene	2 generations	Transgenic silencing	DNA methylation	Park et al. (1996)
	Requirement of leaf cell for cytokinin	Not specified	Arises at 10^{-2} per cell generation	Subculturing in media containing successively lower concentrations of cytokinin	Unknown; DNA methylation suggested	Meins (1986, 1989a,b), Meins and Thomas (2003)
Oryza sativa (Rice)	CpG methylation patterns show inherited cultivar specificity	Methylation state of cytosine in various CCGG sites across the genome	At least 6 generations	Crossing Nipponbare and Kasalath cultivars[5]	DNA methylation	Ashikawa (2001)
	Various traits	Methylation state in various CCGG sites across the genome	At least 2 generations	Introgression and selfing[5]	DNA methylation	Dong et al. (2006)
	Kernel shape and tiller number	*S2*, *S3*, and various unspecified methylation sites	3–6 generations of selfing	High-pressure treatment given to seeds	DNA methylation	Shen et al. (2006)
	Induced dwarfism; resistance to pathogen	General change in DNA methylation; Xa21G promoter	At least 9 generations	Induced by 5-azaC	DNA methylation involved	Akimoto et al. (2007), Sano et al. (1990)
Petunia hybrida (Petunia)	White-flowering	*An3* epiallele and the *dTph1* transposon	At least 3 generations of self-fertilization	Induced by heterozygosity	Unknown; epigenetic interaction between at least 3 *dTph1* copies	Van Houwelingen et al. (1999)
Triticum aestivum (Wheat)	Cytosine methylation	Glutenin gene	At least 2 generations	Inbreeding	Chromatin-marking, DNA methylation	Flavell and O'Dell (1990)
	Longer productive spikes, larger seeds, and other quantitative traits	*Hl1* and *pc* loci	57 generations	Nicotinic acid	Unknown	Bogdanova (2003)

continued

TABLE 1
Continued

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
Triticum interspecific synthetic hybrids[e]	Many traits	~13% of the genome	Stability depends on locus; many very stable	Hybridization and polyploidization	Chromatin and DNA methylation; RNAi system probably involved	Levy and Feldman (2004)
Triticale (Stable wheat-rye hybrid)	Increase in stature, number of tillers, changed time of ripening	Not specified	At least 2 generations	5-azaC treatment	Chromatin-marking; DNA methylation involved	Heslop-Harrison (1990)
Zea mays (Maize)	Reduced pigmentation (paramutation)	*B1* (gene-epiallele)	Very stable	Paramutagenic *B'* epiallele arises spontaneously from *B-I* allele at a frequency of ~1% to 10%	Chromatin inheritance; siRNA-directed chromatin modification is involved	Alleman et al. (2006), Chandler (2007), Chandler et al. (2000), Coe (1966), Stam et al. (2002)
	Reduced pigmentation (paramutation)	*r1* (complex loci)	Variable	Spontaneous, and exposure to varied light durations and temperature	DNA methylation	Chandler et al. (2000), Mikula (1995),Walker and Panavas (2001)
	Reduced, light-dependent pigmentation (paramutation)	*pl* (gene-epiallele)	Varies from metastable to very stable inheritance	Spontaneous	Chromatin-marking suggested	Chandler et al. (2000), Hollick and Chandler (1998), Hollick et al. (1995, 2000)
	Reduced pericarp color but dark pigmentation at the point of silk attachment (paramutation)	*p1* (gene-epiallele)	At least 5 generations	Spontaneous	DNA methylation	Cocciolone et al. (2001), Das and Messing (1994), Rajandeep et al. (2007), Sidorenko and Peterson (2001), Sekhon et al. (2007)
	Spotting of kernels	*MuDR* transposable element	Silencing effect of the *Muk* locus on *MuDR* was maintained over at least 4 generations, even when *Muk* had segregated away	Crossing leading to silencing of the regulatory transposon *MuDR*	DNA methylation; siRNAs are involved in maintaining heritable methylation states in *Mu1* and *MuDR* elements	Lisch et al. (2002), Slotkin et al. (2003), Slotkin et al. (2005)

Animals						
Caenorhabditis elegans (Nematode)	Small and dumpy appearance	RNAi of *ceh-13*	Over 40 generations	Feeding with bacteria expressing dsRNA targeting *ceh-13*	Chromatin remodeling; RNAi-mediated	Vastenhouw et al. (2006), N. Vastenhouw (personal communication)
	Silencing of green fluorescent protein (GFP)	RNAi of *gfp* transgene	At least 40 generations	Feeding with bacteria expressing dsRNA targeting *gfp*	Chromatin remodeling; RNAi-mediated	Vastenhouw et al. (2006), N. Vastenhouw (personal communication)
	Various effects, not reported	RNAi of 13 genes	At least 10 generations	Feeding with bacteria expressing dsRNA targeting the 13 genes	Chromatin remodeling; RNAi-mediated	Vastenhouw et al. (2006), N. Vastenhouw (personal communication)
Daphnia pulex (Water flea)	Expression of G6PD S and N variants	*G6PD* locus or its regulator	Spontaneous reversion rate between the 2 forms was 1 in 10 and 1 in 2.	Spontaneous and glucose induced; presence of S form related to stressful conditions	Not known	Ruvinsky et al. (1983 a,b, 1986)
Diaphanosoma celebensis (Cladoceran)	Timing of reproduction and number of offspring	Not specified	2 generations	Induced by the natural estrogen E2	Not known; parallel effect on induced parents and their offspring	Marcial and Hagiwara (2007)
Drosophila melanogaster (Fruit fly)	Modifying ability of Y chromosome	Imprintor gene interaction	11 generations	Transient effect of imprintor gene	Chromatin marks	Dorn et al. (1993)
	Ectopic outgrowth in eyes	*Kr* (*Kr*$^{If\text{-}1}$ allele), *vtd*^{3} (*TrxG* mutation)	At least 13 generations	Geldanamycin treatment given to Kr$^{If\text{-}1}$ strain, or transient presence of *TrxG* mutation *vtd3*	Chromatin-marking involved	Ruden et al. (2003), Sollars et al. (2003)
	Eye-color	Transgenic *Fab-7* flanking *lacZ* and mini-*white* reporter transgenes	At least 4 generations	Transient presence of GAL-4- protein	Probably chromatin inheritance	Cavalli and Paro (1998, 1999)

continued

TABLE 1
Continued

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
	Eye-color (due to de-repression of mini-*white* reporter gene cloned downstream to transgenic *Fab-7*)	Activation state of endogenous and transgenic *Fab-7* elements containing CMM	At least 4 generations (more than 4 years)	High temperature	Probably chromatin inheritance	Bantignies et al. (2003), F. Bantignies (personal communication)
	Suppression of wing deformations	De-repression of *sd*	Not specified (stability lower and harder to detect)	High temperature	Probably chromatin inheritance	
	Susceptibility to tumorigenesis	Probably several loci, including heritable epigenetic variation in the *ftz* promoter	Increased tumorigenicity (2 generations); modified *ftz* methylation (at least 1 generation)	Crossing with $hop^{Tum\text{-}l}$ and Kr^{1} mutants	DNA methylation, chromatin inheritance	Xing et al. (2007)
Ephestia kuehniella (Moth)	Reversion of shortened antennae and associated mating disadvantage	Suppressor of *sa* (sa^{WT})	Up to 5 generations; incompletely inherited from mother but almost fully inherited from father	Exposure of larva and pupa to lithium ions, alternate electrical field, or 25°C at late 5th instar larval and pupal phases	Probably chromatin inheritance	Pavelka and Kondelova (2001)
Homo sapiens (Human)	Cardiovascular mortality and diabetes susceptibility	Imprinted tandem repeat upstream of *INS-IGF2-H19* region	At least 2 generations	Food availability during childhood growth period	Possibly methylation; transmitted through male germ line	Kaati et al. (2002, 2007), Pembrey (2002)
	Angelman and Prader-Willi syndromes	15q11-q13	Inherited from paternal grandmother (no imprint erasure in the father)	Spontaneous	DNA methylation	Buiting et al. (2003), Zoghbi and Beaudet (2007)
Mus musculus (Mouse)	Probability of developing yellow coat color and obesity, as well as susceptibility to diabetes and cancer	A^{vy} (gene-epiallele) and probably other loci	Metastable (at least 2 generations of agouti epigenotype); cumulative, three-generation effect on obesity	Spontaneous; affected by diet	Chromatin-marking, including DNA methylation	Blewitt et al. (2006), Cropley et al. (2006), Morgan et al. (1999), Waterland et al. (2007), Wolff et al. (1998), Waterland et al. (2008)

Reduced body weight, reduced level of proteins involved in sexual recognition, and possibly higher mortality between birth and weaning	Not specified, but epimutation is connected to Major Urinary Protein (*MUP*) and Olfactory Marker Protein (*OMP*) genes	Preliminary results suggesting transmission of the traits to B_2 (the second generation)	Induced by transfer of mouse pronuclei at the one-cell stage to eggs of a different genotype; traits are transmitted to most of the offspring through male germ line	DNA methylation assumed to be involved	Roemer et al. (1997)
Probability of kinked tail shape	*Axin-fused* (gene-epiallele) and IAP transposable element	Spontaneous rate of inactivation 6%; rate of reactivation 1%	Spontaneous; influenced by diet. Injection of hydrocortisone during spermiogenesis reduces penetrance	Chromatin-marking including DNA methylation	Belyaev et al (1981a, 1983), Rakyan et al. (2003), Waterland et al. (2006), D. Martin (personal communication)
White-spotted tail and feet	*Kit* (paramutation)	2 generations of outbred crossing; 6 generations of inbred crossing between paramutants	Transient presence of Kit^{tm1Alf} mutation	RNA inheritance; RNAi involved	Rassoulzadegan et al. (2006), M. Rassoulzadegan (personal communication)
Repression of recombination of the *LoxP* element and concomitant methylation	Transgenic *LoxP* and surrounding chromosomal sequences	Methylated state maintained for at least 3 generations	Transient presence of *Sycp1-Cre*; exposure of wild type to recombinase activity	DNA methylation	Rassoulzadegan et al. (2002)
Genome stability	Many	At least 3 generations	Irradiation	Chromatin methylation	Barber et al. (2002), Dubrova (2003)
Glucose intolerance	Not specified	2 generations, some effect in the 3rd generation	Betel nut ingestion	Not known	Boucher et al. (1994)
Tendency to develop tumors	Elevated expression of gene coding for LF (an estrogen-responsive protein) and C-*fos*	Apparent in the F_1 and F_2 generations	Induced by diethylstilbestrol during F_0 pregnancy	DNA methylation probably involved	Newbold et al (2006)
Cardiac hypertrophy	The microRNA miR-1	At least 3 generations	Microinjection of miR-1 into fertilized eggs	RNA inheritance	Wagner et al. (2008)

continued

TABLE 1
Continued

Taxon	Trait	Locus/cellular system	Stability	Inducing conditions	EIS	Reference
Myzus persicae (Peach potato aphid)	Loss of insecticide resistance	Probably amplified resistance genes	Stable inheritance of lost resistance in clones that have amplified DNA	Induced by DNA amplification	DNA methylation involved	Field et al. (1989)
Rattus norvegicus (Rat)	Modified serotonin content in immune cells[g]	Not specified	2 generations	Intramuscular administration of β-endorphin during 19th day of pregnancy	Not specified	Csaba et al. (2005)
	Increased expression of genes coding for metabolic factors	Promoters of *PPARα* and *GR* in liver; increased expression of other RNAs	At least 2 generations	Protein-restricted diet during pregnancy	DNA methylation	Burdge et al. (2007), G. Burdge (personal communication)
	Decreased spermatogenic capacity; elevated incidence of tumor, prostate, and kidney diseases, serum cholesterol levels, and immune system abnormalities; premature aging and male mating disadvantage	Methylation state of 15 different DNA sequences. Reduced expression of *ankyrin 28*, *Ncstn*, *Rab12*, *Lrrn6a* and *NCAM1* found in vinclozolin group as well as increased expression of *Fadd*, *Pbm1b*, *snRP1c* and *Waspip*	At least 3 generations; transmission through the male germ line	Vinclozolin or methoxychlor treatment during gestation	DNA methylation	Anway et al. (2005, 2006[a], 2006[b]), Chang et al. (2006), Crews et al. (2007)
	Altered glucose homeostasis	Not reported	F_0–F_3 generations	Low-protein diet in F_0 from day 1 of pregnancy through lactation	Not specified, DNA methylation probably involved in F_1 animals	Benyshek et al. (2006), D. C. Benyshek (personal communication)
Vulpes vulpes (Fox)	Piebald spotting	Activation state of *Star* gene	*Star* (semidominant allele) activated in ~ 1% of domesticated animals; inherited for more than 2 generations	Spontaneous in tamed foxes raised in fur farms; hormonal stress suggested[f]	Possibly heritable chromatin modification	Belyaev et al. (1981b), Trut et al. (2004)

Note: The species in each category are ordered alphabetically. References to the table are available online at *The Quarterly Review of Biology* homepage, www.journals.uchicago.edu/QRB.

[a]Similar systems have been described for arabinose-utilization in *E. coli* (Khlebnikov et al. 2000) and the lactose operon in *Salmonella enterica typhimurium* (Tolker-Nielsen et al. 1998).

[b]Probably occurs in many pathogens (Lewis 2007).

[c]It seems that all ciliates show cortical inheritance and guided assembly of cortical structures (Frankel 1989). Ciliates have a silent micronucleus and an active macronucleus, from which noncoding sequences are excised and coding sequences are amplified. Following conjugation or autogamy, a new (zygotic) macronucleus is formed from the fused meiotic product of the micronucleus, and the old, maternal macronucleus degenerates. The complex processes, guided by the maternal nucleus, that lead to the inheritance of patterns of chromosomal rearrangements in the zygotic nucleus seem to be characteristic of all ciliate species (Meyer and Chalker 2007).

[d]Similar phenomena are found in *C. galborata*, *C. tropicalis*, *C. parpsilosis*, and in the basiomycetes fungus *Crystococcus neoformans*.

[e]Interspecific plant hybrids, and sometimes hybrids between cultivars, display epigenetic variations that are heritable across generations. When hybridization is followed by polyploidization, this seems to be a normal and invariant genomic response. In *The Biological Journal of the Linnean Society* 82(4) (Allen 2004), many examples of epigenomic effects of hybridization in plants, including maize, wheat, rice, cotton, and sunflower, are reviewed.

[f]There are similar, older studies of transgenerational effects following administration of hormones and drugs in a variety of mammals. These studies, which did not include molecular data, were reviewed by Campbell and Perkins (1988).

molecular data show that the gametes of the F_1 generation have acquired altered epigenetic marks, the transmission of epigenetic variations rather than the direct induction of such variations is a reasonable assumption. Based on this, we included some cases in our table in which only two generations of transmission following induction were reported. For instance, we included a case reported by Burdge et al. (2007) in which protein restriction during a rat grandmother's pregnancy led to identical somatic and epigenetic (methylation) variations in her F_1 and F_2 descendants, as well as a case reported by Newbold et al. (2006) that showed that F_0 female rats exposed to diethylstilbestrol had F_1 and F_2 offspring with an increased susceptibility to tumors associated with persistent changes in the DNA methylation and expression of an oncogene (see Ruden et al. 2005 for an epigenetic model explaining these data). The case of germline inherited epigenetic variants (and their corresponding phenotypes) that were acquired stochastically in the A^{vy} locus of the mouse was included since transgenerational epigenetic effects on coat color and obesity were reported. However, this is a complex case that seems to involve epigenetic modifications in the A^{vy} locus as well as in other loci in the genome (Blewitt et al. 2006; Cropley et al. 2006; Waterland et al. 2007, 2008). Another case we included was that reported by Csaba et al. (2005) in which the modified serotonin content induced in the immune cells of mice treated with endomorphin during pregnancy is subsequently transmitted to their grandchildren. We did not include the many cases of single generation inheritance, even though epigenetic inheritance seems quite plausible in some of them, as, for example, when a predisposition to cancer in humans is related to an epimutation (an epigenetic hereditary abnormality in gene expression) in a mismatch-repair gene, and this epimutation is transmitted from mother to son (Hitchins et al. 2007). We also excluded a similar case in mice which showed that tumor risk was increased following chromium III chloride exposure and that this risk was then transmitted from father to son (Shiao et al. 2005). Other cases of single-generation inheritance, such as protection against type I diabetes in humans (where a paramutation-like process has been reported) (Bennett et al. 1997), hydrostatic pressure-induced alterations in DNA methylation in Japonica rice (Long et al. 2006), and parallel alterations in gene expression profiles in White Leghorn chickens and their offspring following stress in the parental generation (Lindqvist et al. 2007), were also excluded, although epigenetic inheritance may well have occurred and may be revealed when subsequent generations are studied. However, within the limitations imposed by the research designs of the studies we reviewed and the qualifications we have mentioned, we believe that the table provides a fairly exhaustive overview of the recognized cases of cellular transgenerational epigenetic inheritance that have been described in English-language journals, although, inevitably, we likely missed some cases.

Taxonomic distribution and inducing conditions

The data in the table probably represent the tip of a very large iceberg. What is missing from the table is important, because the absences point to gaps that need to be filled. For instance, there is no information about epigenetic inheritance in the kingdom Archea, and most phyla are not represented. There are also few data directly addressing epigenetic inheritance in viruses, although it may plausibly be assumed that viruses exploit and use the epigenetic adaptations adopted by their hosts. Data on epigenetic inheritance in chloroplasts and mitochondria are also very scant. It is worth noting that the organisms that show the greatest evidence for epigenetic inheritance are the classical model organisms of genetics—*E. coli*, yeast, *Arabidopsis*, maize, rice, *Caenorhabditis*, *Drosophila*, the mouse, and the rat. However, a systematic investigation of epigenetic inheritance in different conditions is not yet available for any of these model organisms. It is also worth noting that all the model

animals studied belong to taxa in which the segregation between germline and soma occurs early, and, therefore, epigenetic inheritance may be more limited than in the non-represented animal taxa where segregation occurs late if it occurs at all (Buss 1987; Jablonka and Lamb 1995). Although the non-systematic way in which the data were collected precludes general conclusions, it seems as if epigenetic inheritance in multicellular organisms is most common in plants and fungi. This is probably in part due to the lack of segregation between soma and germline in these groups that enables developmentally induced epigenetic variations occurring in somatic cells to be transferred to the gametes when these somatic cells assume germline functions. However, there are two, additional considerations that may be relevant to the difference between animals, on the one hand, and plants and fungi, on the other. First, the lack of nervous system-directed mobility and activity in plants and fungi means that they cannot adapt to changing conditions behaviorally; if the conditions experienced by offspring are likely to be similar to those of their parents, then inheriting epigenetic adaptations from them is an alternative adaptive strategy to behavior and is likely to be positively selected in plants and fungi (Jablonka et al. 1995; Jablonka and Lamb 1995; Lachmann and Jablonka 1996). Second, mobility and CNS-dependent flexible learning in animals may often limit the predictability of the environment in descendent generations; therefore, wide-ranging stable epigenetic cellular inheritance through the germline may be selected against. In general, it seems that the difference between the life strategies of plants and animals may account for the observation that epigenetic inheritance in multicellular organisms is more common in plants and fungi than among animals.

The relative importance—and sometimes even the very presence—of particular EISs in different taxa varies. Budding yeast seems to lack the RNAi system, so epigenetic inheritance based upon it is impossible, although other types of RNA-mediated inheritance cannot be ruled out. In some groups of animals, DNA methylation appears to have been lost (Regev et al. 1998) and is not part of chromatin marking in these organisms. Transgenerational structural inheritance and inheritance through self-sustaining loops seem to be more common in unicellular organisms and in fungi where horizontal transfer of information through hyphal interaction is common. It may be that the development of a germline involves such drastic alterations in cellular functions and structures that self-sustaining loops and many cellular structures are destabilized and disrupted. The data presented in Table 1 lend support to this conjecture, although their paucity precludes decisive conclusions.

To understand why and when cellular epigenetic variants are inherited, we need to know the conditions that promote their induction and stability in cell lineages. Their developmental nature requires an approach that is sensitive to context. However, our knowledge of the chromatin-marking and RNA-mediated systems suggests that certain parts of the genome may exhibit chromatin- and RNA-mediated epigenetic inheritance more often than others. Repetitive DNA sequences (especially regions that code for RNAs that can form dsRNA or stem-loop structures), DNA regions where transcription is likely to start from both complementary strands, and repeated chromosomal segments that pair ectopically are all likely to exhibit RNA-mediated epigenetic inheritance under a wide range of conditions. These and other repeated sequences that cooperatively bind protein complexes and regions with CG doublets are all likely candidates for multigenerational chromatin- and methylation-based epigenetic inheritance.

The inducibility and transmissibility of epigenetic variants depend on developmental conditions. Conditions of stress seem to be particularly important as inducers of heritable epigenetic variation, and lead to changes in epigenetic and genetic organization that are targeted to specific genomic sequences. We mentioned earlier that the genomic stresses of allopolyploidization and, to a

lesser extent, autopolyploidization lead to epigenetic and genetic re-patterning (Grant-Downton and Dickinson 2005, 2006; Rapp and Wendel 2005). A well-known epigenetic phenomenon associated with hybridization is nucleolar dominance, or the expression in the hybrid of the rRNA gene complex (NOR) from only one parent. The preferential silencing of one NOR is a large-scale gene-silencing phenomenon associated with heritable DNA methylation and repressive histone modifications (Pikaard 2000, 2003). However, the epigenetic changes occurring in hybrids are not restricted to rRNA genes. An example we present in the table is that of the genome-wide changes that occur in synthetic wheat hybrids that were formed in order to simulate the evolution of domestic wheat. Levy and Feldman (2004) reviewed evidence showing that, in these hybrids, 13% of the genome undergoes significant methylation changes, while changes also occur in genome organization (e.g., rearrangements and elimination of some sequences). The methylation changes affect both low copy numbers and repetitive DNA sequences, and are associated with heritable transcriptional silencing. In addition, the activation of retroelements leads to heritable alterations in gene expression at other loci, thus resulting in major changes in the profile of gene expression. The changes in the epigenetic state of the genome are region and chromosome specific: they are targeted to particular genomic sequences and reoccur, with localized variations, upon repeated formation of the same type of allopolyploid. In species of the cordgrass *Spartina*, genome-wide epigenetic and genetic changes were observed in two recently formed, morphologically different, natural hybrids (and an allopolyploid), in which 30% of the parental methylation patterns were altered, in addition to similar structural changes in the DNA sequences of these two independently formed and genetically similar hybrids (Salmon et al. 2005). Many similar effects of allopolyploidization have been reviewed in the extensive and growing literature on plant polyploidy (e.g., see *The Biological Journal of the Linnean Society* 82(4) [Allen 2004]). The overall impression gained from these studies is that heritable epigenetic changes accompany the first stages of allopolyploidization, and that the types of repetitive sequences in the parental species, the amount of divergence between them (especially with regard to elements that may be involved in epigenetic control), and the direction of the cross all play important roles in specifying the extent and nature of epigenetic re-patterning.

Another form of genomic stress that may lead to heritable variation is that associated with a change in reproductive mode. For example, the transition from sexual to a-gametic reproduction in sugar beet leads to heritable activation of some genes (Levites 2000). DNA damage also leads to heritable epigenetic changes, and researchers are beginning to uncover some of the factors that affect this response. Following DNA repair, the epigenetic structure of the repaired region is not fully reconstructed and carries with it a repair-specific chromatin signature that can be transmitted to subsequent generations (Polo et al. 2006). Moreover, the loading of the histone variant γ-H2AX (which is associated with repaired DNA segments) with cohesin leads to sister-chromatid interactions that may contribute to the radiation-induced genome instability that arises and is inherited for several generations in the progeny of damaged cells (Little 2003). This may be the basis for the heritable genomic instability found in the offspring and grandoffspring of male mice that were exposed to irradiation (Dubrova 2003), as well as for the increased level of recombination seen for at least four generations after UV-C irradiation of *Arabidopsis* plants (Molinier et al. 2006).

Some of the cases included in Table 1 show that physiological stresses—for instance, nutritional stresses imposed during sensitive periods in the development of flax (Cullis 2005)—can lead to both genetic and epigenetic re-patterning, and both types of re-patterning seem to be correlated and share a common mechanistic basis. It seems likely that other cases in

which an environmental stressor has targeted effects on genome organization, such as the heat-induced changes in rRNA-encoding DNA repeats in *Brassica* (Waters and Schaal 1996), will also be found to be associated with heritable epigenetic changes in the genes or repeated elements involved. In animals, alterations in hormonal balance, especially those occurring over several generations, may also be followed by epigenetic changes. This may be the basis for the pattern of inheritance of white spotting seen in domesticated silver foxes (as we will discuss later) (Trut et al. 2004). However, stressful conditions may not only affect the chromatin-marking and the RNA-mediated EISs; if a new prion variant can be generated in stressful conditions, it might cross previously existing species barriers and have novel effects in its new "host" species.

EPIGENETICALLY-BASED SIMILARITIES AND DIFFERENCES BETWEEN GENERATIONS: INDUCING EPIGENETIC VARIATIONS IN THE GERMLINE

Many of the studies of multicellular, sexually reproducing organisms that we present in Table 1 show that, as a result of an inducing stimulus or of changed conditions in the F_0 (parent) generation, similar chromatin marks and similar phenotypes are reconstructed in subsequent generations. However, the F_0 generation itself may not show any phenotypic effects; changes in epigenetic marks and associated somatic phenotypes may first appear in the F_1 generation and may only then be inherited by subsequent generations. For example, in mice, the diethylstilbestrol-induced increase in the probability of developing tumors appeared only in the F_1 and F_2 generations (Newbold et al. 2006).

Understanding the inheritance of induced variation in sexually reproducing multicellular organisms is an important topic of research, not least because, in the past, much of the debate about the importance of acquired characters in evolution revolved around this issue (Delage and Goldsmith 1912). Traditionally, in multicellular organisms with a germline, three types of induced heritable effects have been distinguished: direct induction, parallel induction, and somatic induction. With direct induction, the germline is directly affected without any effect on the F_0 parent's soma, while with parallel induction, similar somatic phenotypic effects are apparent in both the induced ancestor and its descendants, but the induction events in the somatic and germ lineages are independent. Finally, with somatic induction, a change is induced in the soma, and this somatic effect causes a change in the germline that reconstructs the somatically-induced parental phenotype in the descendants (Fothergill 1952; Jablonka and Lamb 1995). There is, however, a fourth possibility: an induced effect on the soma of the F_0 generation may cause changes in the germline, but the resulting somatic changes in descendants are dissimilar from the effect on the soma in the F_0 generation. This is a case of parallel induction with nonparallel effects. The different types of induced heritable effects are represented schematically in Figure 2.

The literature shows that direct induction, parallel induction, and parallel induction with nonparallel or partially parallel effects are common. In Table 1, many of the cases of paramutation and of induced, heritable, transposable element activity can be classified as direct induction or parallel induction, because the inducing conditions directly affect events in the germline (and sometimes, in parallel, in the soma as well). Changes in hormone dynamics that specifically target the germline will either not affect somatic characters in the induced F_0 generation, or will affect them in a way that is unrelated to the effect seen in the F_1. For example, in one case, vinclozolin, an androgen suppressor, induced testis disease in at least three generations of males following its administration to a pregnant female ancestor (Anway et al. 2005, 2006a,b). This is an example of direct induction with differing effects in males and females. Parallel induction is seen in the case in which nutritional and temperature changes affected morphology

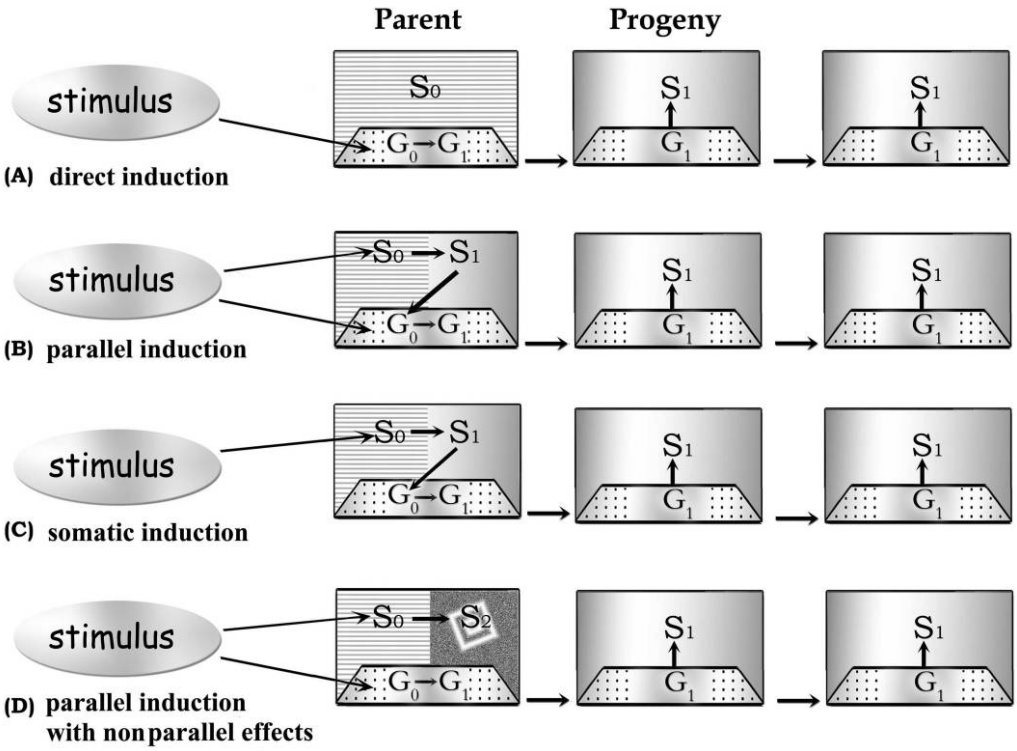

Figure 2. Inducing an Inherited Effect

(A) *Direct germline induction*: An external stimulus induces a germline change from G_0 to G_1 with no effect on the parental soma, which remains S_0. The G_1 state is inherited, and leads to the development of an S_1 soma. (B) *Parallel induction*: An external stimulus induces a change in the parent's soma from S_0 to S_1 and in its germline from G_0 to G_1. The G_1 state is inherited and causes the development of an S_1 soma in descendants. (C) *Somatic induction*: An external stimulus induces a change in the parent, altering its somatic phenotype from S_0 to S_1. The effect is transmitted from the S_1 soma to the germline, where G_0 is changed into G_1; G_1 is consequently inherited and results in the development of an S_1 soma. (D) *Parallel induction with nonparallel effects*: An external stimulus alters the soma from S_0 to S_2, and the germline from G_0 to G_1. The germline modification is inherited and leads to the development of S1 soma in subsequent generations. With all four types of induction, S_1 could have an effect on G_1 in all descendants of the original induced parents (not shown).

in the F_0 generation of flax, and similar phenotypic effects were found in subsequent generations (Cullis 2005). Another case of parallel induction is that seen in the moth *Ephestia kuehniella*, where subjecting the insect to modified temperature conditions, lithium ion treatment, or an alternative electric field during the first half of its pupal development resulted in the suppression of a mutant short antennae in the treated generation and five subsequent generations (Pavelka and Koudelová 2001). Also, glucose induction of the S form of the G6PD enzyme in *Daphnia pulex* may be illustrative of a further possible case of parallel induction (Ruvinsky et al. 1983a,b).

The distinction between direct and parallel induction is not always straightforward, as epigenetic changes may occur in only some of the somatic cells of the induced parent, thus resulting in a variegated somatic phenotype. This can be described as partial parallel induction. It can be seen in some cases of paramutation in plants where, when the induction rate is high, sectors that are the result of paramutation in somatic tissues can be seen in the F_0 generation (Chandler et al. 2000).

Several cases in the table can be interpreted as instances of somatic induction in which heritable variation is induced in the soma and is seen as a somatic character, and the resulting effect is then transferred from the soma to the germline. The ability of small RNAs to move from cell to cell may facilitate soma to germline information transmission and may form the basis of such inheritance. The most impressive example of somatic induction via small RNAs may be found in the case discussed by Vastenhouw et al. (2006), in which *C. elegans* were fed bacteria with DNA sequences coding for dsRNA, and the RNAs migrated from the somatic cells of the nematode to its germ cells, thus affecting subsequent generations. Steele et al. (1998) suggested another route of transmission that is initiated by RNA: the transfer of RNA transcripts from the immune cells of mammals to their germline, followed by reversed transcription and incorporation of the reverse transcribed DNA into the germline genome. Zhivotovsky (2002) has modeled the conditions that could lead to the evolution of such a system.

Another route of somatic induction is via inducing conditions that affect the secretion of hormones, which, in turn, affect the germline. The effect of a hormone on the somatic characters of the induced parent (F_0) and on its descendants may be similar, but it is unlikely to be identical. This is because even if the same genes are affected in the soma of the adult F_0 animals as well as in the F_1 and subsequent generations of offspring, it is unlikely that the pattern of activity of these genes will be the same. In descendants, the induced epigenetic change may be expressed during embryonic as well as adult stages, whereas, in the F_0 animals, the change is induced in adults. Only in rare cases in which the pattern of timing and spatial expression is identical in the F_0 and subsequent generations—and is limited to the stage at which it was induced in the F_0—will identical somatic characters occur in parent and offspring generations. An additional complication is the sex of the F_0 animals and their offspring, as sex-limited effects will obviously be transmitted in a sex-specific manner, and epigenetic variations in an induced F_0 parent may therefore be different for descendants of the opposite sex. These considerations are relevant to any kind of somatic induction, no matter the mechanism behind it, so, although partial similarity is likely, we expect that somatic induction leading to identical phenotypes in the F_0 and subsequent generations will be rare.

The foregoing discussion suggests that the traditional distinctions between direct, parallel, and somatic induction do not satisfactorily describe the possible interactions between the soma and germline. The similarity between the somatic characteristics of an induced ancestor and its descendants, which the traditional classification highlights, is, of course, of interest, but we think that the mode and mechanisms of the induction of germline variations rather than their effect (i.e., the similarity or lack of similarity between the F_0 and the F_1) should be the focus of study. An important aspect of the problem is whether external inducing conditions affect the germline directly or whether their effect is mediated through the soma. External environmental conditions that are independent of the organism's activity and its development can have important heritable epigenetic effects, but when there are somatic mediating signals (e.g., RNAs or hormones) these somatic signals may evolve to efficiently communicate information to the germline. We therefore expect that developmentally-mediated somatic effects may have adaptive consequences more often than signals that act on the germline directly, and that when there are such soma-mediated influences on the germline, the effects on the somatic cells of the F_0 will often differ from those that will be seen in the next generations (Figure 2D).

The possibility of a somatic effect on the germline that is mediated by hormones was raised shortly after hormones were discovered. The Austrian Lamarckian zoologist Paul Kammerer and the pioneer endocrinologist Eugen Steinach (1920) found that exposing male rats to high temperatures led to morphological and physiolog-

ical changes in their offspring and grandoffspring. They suggested that the presence of hormone-secreting interstitial cells adjacent to germ cells in the gonads facilitated hormonal interactions between them, and they claimed that heat produced a change in hormone production in interstitial cells, thus affecting germline cells and carrying hereditary consequences (see Logan 2007 for a discussion of Kammerer and Steinach's work). Although the validity of this claim and its possible interpretation in terms of epigenetic inheritance is at present unclear, the possibility that there are hormonal effects on epigenetic variation is no longer considered heresy.

The experimental work of Vanyushin et al. (2006a) has shown that methylation patterns in the rat genome are controlled by hydrocortisone dynamics, and that phytohormones of different classes cause a decline in global DNA methylation and the repression of de novo methylation in plants. Moreover, the evidence reviewed by Naz and Sellamuthu (2006) suggests that, despite doubts about some of the reported information, there are 8 hormone receptors and 16 cytokine/growth receptors in mature ejaculated sperm, thereby allowing for the possibility that hormones could exert their effects on male gametes. Hormone and neurotransmitter receptors have also been found in oocytes and in female germline cells. For example, the oestrogen receptor (Wu et al. 1992), serotonin receptor 5-HTID (Veselá et al. 2003), Notch1 and Notch2 receptors (Cormier et al. 2004), and the β2-andrenoceptor (Čikoš et al. 2005) have all been detected in oocytes, and the GH receptor has been detected in fertilized eggs (Pantaleon et al. 1997; Kölle et al. 2001). It is interesting to note that the changes in expression of some of the genes coding for these receptors coincide temporally with early waves of epigenetic re-programming during development. The presence of hormone receptors in gametes, and the modulation of receptors' synthesis during sensitive developmental periods when hormonal changes occur, suggest that induced variations in hormonal conditions may affect the epigenetic state of genes within germline cells, and these, in turn, can be transmitted to the next generation.

The involvement of hormones in the induction of heritable epigenetic variations is no longer a mere speculation: several of the mammalian examples presented in Table 1 suggest that changes in hormonal stimuli induce heritable epigenetic changes. For example, the penetrance of the fused phenotype is altered in the progeny of mouse parents treated with hydrocortisone (Belyaev et al. 1983). In silver foxes selected for tame behavior, hormonal effects in the serotonin system that controls aggression seem to be involved in the heritable activation of the star gene that leads to white spotting (Belyaev et al. 1981a,b; Trut et al. 2004; Popova 2006). The best investigated case of hormonally-mediated effects on epigenetic marks is that of the transgenerational effect of the estrogenic androgen disruptors vinclozolin and methoxychlor on testes development in male rats (Anway et al. 2005, 2006a,b; Chang et al. 2006; Crews et al. 2007). With vinclozolin, 15 different DNA sequences isolated from sperm were shown to have altered methylation patterns, and these patterns were transmitted to the F_1-F_3 generations of offspring of treated F_0 females. Crucially, vinclozolin was effective only when administered between 8 and 15 days post coitum, and had no effect when administered later, between 15 and 20 days. This sensitive developmental period coincides with the epigenetic remethylation phase in the male (Hajkova et al. 2002), thus suggesting that the hormonal effect of androgens is developmentally specific (limited to this period of epigenetic reprogramming) and is not a general toxic effect. If so, modifications in these methylation patterns in the soma of F_0 vinclozolin-treated females are not expected. In plants, where no epigenetic reprogramming phase similar to that in mammals is apparent, and the germline is continuously produced during development (Matzke and Scheid 2007), changes in hormonal stimulations during all phases of somatic development are

likely to affect epigenetic variations in the germline.

EPIGENETIC RECALL AND OTHER DIRECTIONAL CHANGES IN HERITABLE EPIGENETIC MARKS

We defined cellular epigenetic inheritance as the transmission from mother cell to daughter cell of variations that are not the result of differences in DNA sequence, or of persistent inducing signals in the cell's environment. The examples presented in Table 1 support our assertion that when epigenetic marks are inherited, the same pattern of marks is more or less faithfully reconstructed across generations. If a particular mark—for example, a pattern of 5 methylated cytosine sites—is induced at a particular locus in the germline, this pattern is then reconstructed (with a certain error rate) in the descendants and has similar phenotypic effects (Figure 3A). Stable epigenetic inheritance is at one extreme pole, and total reset to a single default state—that of the uninduced parents—is at the other pole of developmentally influenced inheritance. However, the developmental nature of epigenetic inheritance and our knowledge of the construction of chromatin marks suggest that we consider other possibilities; the examples in the table, therefore, represent only a very small fraction of the types of epigenetic hereditary phenomena that probably exist.

The first possibility is that of partial reconstruction—an intermediate between the two extreme poles of complete reset and faithful reconstruction. For example, of the 5 induced methylation sites, only 3 are reconstructed in the offspring, and, in the absence of the inducing stimulus, if the phenotype of the offspring is the same as that of an uninduced individual, this would not be seen as a case of epigenetic inheritance, even if the threshold for the developmental response was lowered or the speed of reaction was enhanced in descendants (see Figure 3B). The situation is similar to that found with neural memory, when the original stimulus that leads to the initial learnt response is required to trigger the response again, but because memory traces remain, there is recall—facilitated reconstruction of the learnt response upon re-induction. We suggest that the inheritance of some epigenetic memory traces may lead to *epigenetic recall*—a facilitated response in descendants that requires an inducer. The inherited, partial epigenetic patterns that facilitate a response are called *epigenetic engrams*. (Engram is a term that was invented by Richard Semon in 1904, to mean, roughly, "memory trace"; see Schacter 2001.) In order to recognize epigenetic recall, the kinetics of induced responses in the F_1 and subsequent generations need to be studied. None of the examples in Table 1 fulfils this requirement, and, to the best of our knowledge, this kind of investigation—searching for epigenetic engrams and for facilitated but still inducer-dependent responses—has not been part of the research program of epigenetics. Such responses, however, are likely to be common, as the mechanisms for them are all in place, and a system enabling the reconstruction of epigenetic engrams that allow recall would be selectively advantageous in many conditions, just as, in spite of the different timescale, the evolution of neural sensitization has been favored. Agrawal et al. (1999) studied induced defenses against predators in wild radish (*Raphanus raphanistrum)* and the water flea (*Daphnia cucullata)*, and showed that induction in the parental generation made offspring better adapted to predators than the offspring of uninduced parents. They suggested that the persistent parental effect in radish plants may be either a direct maternally-induced effect or the result of more rapid induction of plant defenses in the offspring of damaged mothers. If the latter proves correct, it will represent a case of epigenetic recall, underlain by as yet uncharacterized epigenetic engrams. (For an extended discussion of the possibility of learning in cells and non-neural organisms, see Ginsburg and Jablonka 2008.)

In addition to epigenetic recall based on partial reconstruction, we must also consider the possibility that although induced

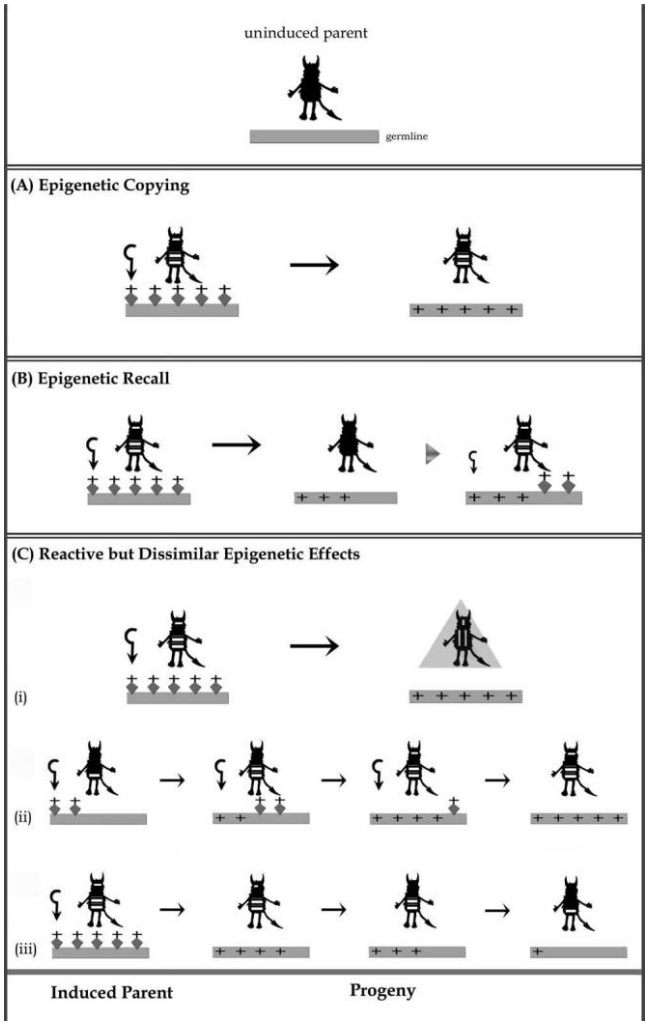

Figure 3. Types of Transgenerationally Inherited Epigenetic Effects

An inactive gene (gray rectangle) and its corresponding phenotype are depicted at the top of the figure. (A) *Epigenetic copying and corresponding phenotypic inheritance*: An epigenetic mark consisting of 5 + sites is induced in the parent and affects the marking of the gene and the phenotype of the induced individual. (The "+" signs indicate an altered methylation or histone modification site, and the inducer is indicated by a curved arrow.) The epigenetic mark is reliably transmitted through the germline, thus leading to a modified heritable morphology in the uninduced progeny (heritable site-states are indicated by "+" signs within the rectangle, and the straight black arrows indicate transitions between generations). (B) *Epigenetic recall*: Partial inheritance of the epigenetic pattern (represented by 3 internalized "+" signs) that was established in the induced parent does not lead to modified morphology in progeny. However, the amount of inducer needed to re-establish the full epigenetic pattern (5 + pattern) and the corresponding induced phenotype is much smaller than in the parent (the smaller curved arrow indicates low level stimulation). (C) *Reactive but dissimilar effects of inherited epigenetic patterns*: (i) *antagonistic* - The parental epigenetic mark (5 + signs) is inherited faithfully, but, in a mismatched postnatal environment (triangle around progeny), it leads to a different phenotype in the progeny. (ii) *accumulative* - Following recurrent induction in each generation, epigenetically modified and "internalized" sites accumulate, and result in correspondingly more extreme phenotypes. When the epigenetic pattern reaches a certain configuration (5 + internalized sites), it is inherited even in the absence of the inducer, and this is a form of epigenetic assimilation. (iii) *lingering-fading* - Following induction, the mark and its corresponding morphology are established, but fade away gradually in subsequent generations in a noninducing environment.

marks in one generation may be faithfully inherited, they might lead to a non-matching yet predictable phenotype in the subsequent generation if the environments of parent and progeny are drastically different (Figure 3Ci). The offspring's response could be interpreted as a misfired predictive response—the consequences of a strategy that evolved when the parents' and the offspring's conditions matched. The effects of such mismatches and their medical significance have been discussed by Gluckman and Hanson (2005; Gluckman et al. 2007).

Another possibility worth considering is that of directional changes in heritable epigenetic marks over the course of generations. For instance, if inducing conditions persist for several generations, epigenetic marks may accumulate (Jablonka and Lamb 2005). This could lead to a more extreme phenotype (Figure 3Cii) and, possibly, to a greater fidelity of transmission. Inducing conditions might endure due to the persistence of external environmental factors (e.g., there is multi-generational exposure to a chemical), continual transmission through one sex (i.e., for several generations a particular epiallele is transmitted only through females, or only through males), or continuous transmission through old parents, thus leading to the Lansing effect (see Lamb 1994). The opposite (Figure 3Ciii) may also occur; that is, when induction in the parental generation is followed by non-inducing conditions in the subsequent offspring generations, the induced epigenetic variations may linger and gradually fade away, with some marks being lost in each generation. This might be the basis of the "lingering" modifications described by Jollos (1921), who found that following exposure to high arsenic or salt concentrations, or to high heat, paramecia showed heritable phenotypes that slowly faded over many generations (Jablonka et al. 1992). We suggest that the study of epigenetic engrams, and the study of the kinetics of epigenetic memory changes in different conditions, will lead to an expansion of the research agenda of epigenetics (Ginsburg and Jablonka 2008).

Implications: Evolutionary, Practical, and Theoretical

Given that epigenetic variations are often less stable than genetic variations, what evolutionary significance do they hold? We argue that a view of heredity that incorporates the transmission of epigenetic information through cellular EISs presents challenges and opportunities to applied and theoretical research in evolutionary biology. Since, with few exceptions, the incorporation of epigenetic inheritance and epigenetic control mechanisms into evolutionary models and empirical studies is still rare, our discussion is, inevitably, somewhat speculative.

implications for the study of evolution

Heritable epigenetic variations and epigenetic control mechanisms are relevant for the empirical and theoretical study of evolution because they affect both the processes of adaptation and of divergence (Jablonka and Lamb 1995, 2005, 2006a, 2007b). Five types of effects are characterized: (i) evolutionary change occurring through selection of epigenetic variants, without involvement of genetic variation; (ii) evolutionary change in which an initial epigenetic modification guides the selection of correlated genetic variations; (iii) evolutionary change stemming from the direct effects of epigenetic variations and epigenetic control mechanisms on the generation of local and systemic epigenomic variations; (iv) evolutionary change resulting from the constraints and affordances that epigenetic inheritance imposes on development; and (v) evolutionary change that leads to new modes of epigenetic inheritance.

Evolution through Selection of Epigenetic Variants

Adaptation can occur through the selection of heritable epialleles, without any genetic change. This may be of particular importance when populations are small

and lack genetic variability (e.g., in situations of intense inbreeding following isolation or following changes in reproductive strategies). As the examples listed in Table 1 indicate, epigenetic variants are often induced when environmental conditions change, so several individuals in the population may acquire similar modifications at the same time. This means that adaptation through the inheritance of newly induced epigenetic variants may be very rapid (Jablonka and Lamb 1995, 2005; Kussell and Leibler 2005; Richards 2006; Bossdorf et al. 2008), thus leading to the accumulation of epigenetic variations. Several of the epigenetic variations presented in the table are beneficial for their carriers, such as increased epigenetically heritable antibiotic resistance in bacteria (Adam et al. 2008) and the switch between morphotypes in *Candida albicans* (Zordan et al. 2006). Other cases, such as increased mutability as a result of radiation in mice (Dubrova 2003), increased recombination rate in plants (Molinier et al. 2006), and alterations in flowering time, color, and flower morphology (see table for several specific examples and references) are likely to be adaptive under some conditions; therefore, positive selection of such variants is plausible.

In order to assess the role of epigenetic variation in microevolution, it is important to evaluate the extent and heritability of epigenetic variations in natural populations (Yi et al. 2004). In a programmatic paper that outlines the framework for ecological epigenetics, Bossdorf et al. (2008) present some of the fundamental research questions that need to be asked about epigenetic variations in natural populations, regarding the extent and structure of epigenetic variation, its correlation with phenotypic variation, its inducibility, and its effects on fitness.

The mechanisms of epigenetic control may play an interesting role in structuring epigenetic variation because they can coordinate patterns of gene expression. Zuckerkandl and Cavalli (2007) believe that repeated sequences in "junk DNA" might be carriers of epigenetic marks, and that marks on these sequences can be communicated to other regions in the genome. They suggested that an altered mark could therefore result in coordinated hereditary changes in the expression of several different genes simultaneously, hence accelerating adaptive evolution.

Coordinated hereditary epigenetic changes may have been involved in the process of domestication. For instance, forty-six generations of selection for tameness in silver foxes by Belyaev and his research group in Novosibirsk resulted in a complex of heritable changes. The foxes became dog-like in their behavior and displayed skeletal, hormonal, and spotting changes, as well as altered tail and ear posture, altered vocalizations, and an increased number of supernumerary chromosomes (Belyaev et al. 1981a,b; Trut et al. 2004). Analysis of the pattern of inheritance of white spotting revealed that spotting behaved like a dominant or semi-dominant trait, but the rate of appearance and disappearance of the character was far too high for new mutations to be a likely explanation. These reversible changes could not be explained as an effect of inbreeding either, because the coefficient of inbreeding was only 0.03 (Trut et al. 2004). A probable explanation is that the stress of domestication and selection for tameness targeted genes with large effects in the neuro-hormonal system (Trut et al. 2004; Popova 2006) and may have heritably reactivated some of them (Belyaev 1981a,b). This epigenetic interpretation, in terms of new epimutations rather than new mutations, explains the high rate of appearance and disappearance of some phenotypes, and support for this comes from the fact that at least two of the genes (*Agouti* and *C-kit*) that seem to be involved in the changes are known to have heritable epigenetic variants in mice (Trut et al. 2004). The induction and selection of epigenetic variations may also have been important in the domestication of plants: ecological and genomic stress conditions caused by moving plants to new conditions and crossing divergent strains induce many epigenetic variations, and selection of such variations probably played a part in domestic plant evolution.

Epigenetic Change Guiding the Selection of Genetic Variations

The guiding role of development in evolution has been a subject of discussion ever since the pioneering work of Waddington (1957, 1968, 1975) and Schmalhausen (1949). Their basic idea was that selection can lead to a change from a stimulus-dependent to a stimulus-independent (or less dependent) phenotypic response. The process leading to the change from a phenotype whose expression was dependent on an environmental inducer to a constitutive expression was called genetic assimilation (Waddington 1957; for recent discussion of the idea and its evaluation, see Pigliucci et al. 2006; for suggestions emphasizing its role in the evolution of behavior, see Avital and Jablonka 2000; Gottlieb 2002).

Ideas about the significance of developmental plasticity have recently been strengthened and extended to provide a general framework for evolutionary biology (Pigliucci 2001; Schlichting and Pigliucci 1998). West-Eberhard (2003) suggested that environmentally-induced changes during development guide the selection of genetic changes that simulate, stabilize, and ameliorate any detrimental effects of induced developmental changes. She called this developmental guiding process, which includes but is not limited to genetic assimilation, "genetic accommodation." Induced epiallelic variations that are epigenetically inherited may enhance the effectiveness of assimilation and accommodation processes—something that is likely to be particularly important during conditions of stress (Jablonka et al. 1992; Jablonka and Lamb 1995, 2005; Pál 1998; Sangster et al. 2004; Badyaev 2005; Siegal and Bergman 2006). An example showing the facilitating evolutionary effects of epigenetic inheritance was provided by True and Lindquist's (2000) study, in which they compared pairs of yeast strains differing only in whether or not they carried [PSI^+], the prion form of a protein that is involved in mRNA translation. By growing the pairs of strains in a variety of conditions, they uncovered strain-specific differences between them in colony morphology and growth characteristics. Since the presence of the [PSI^+] prion leads to the suppression of nonsense mutations, the production of a variety of new protein products in the [PSI^+] containing strains (that arose because translation goes beyond the normal endpoint of functional genes, or because stop-codons in the middle of nonfunctional genes are ignored) was increased and was beneficial in some conditions. The epigenetic, selectable variation that is generated in [PSI^+] strains might enable a lineage to adapt and "hold" the adaptation until genetic changes take over; thus, the heritable epigenetic variations in protein architecture pave the way for genetic adaptation (True et al. 2004; Sangster et al. 2004). As a theoretical model has shown, the adaptive effects of such a system may lead to its evolution even if the response is adaptive only once in a million years (Masel and Bergman 2003). Selection of the epigenetically-based variation generated by this type of system would be particularly important in asexual lineages, where the accumulation of mutational changes may be slow.

Epigenetic inheritance-driven accommodation has probably been important in chromosome evolution as well. It may, for example, have initiated the evolution of dimorphic X and Y chromosomes. Jablonka and Lamb (1995) suggested that the initial epigenetic silencing of a sex-determining locus could have produced an epigenetic heteromorphism between chromosomes, which led to pairing problems in meiosis and consequent heterochromatinization and silencing of the homologous region. This would have reduced recombination frequencies and driven degeneration of the Y chromosome; it could also have led to X-chromosome imprinting and dosage compensation in mammals (Jablonka 2004a).

Heritable epigenetic variations may also play an important role in the evolution of chromosomal structures such as centromeres. Henikoff et al. (2001) have proposed that the rapid evolution of centromeric sequences and some centromere-associated proteins may be driven by an epigenetically-guided arms race (Talbert et al. 2004; Henikoff and Smith 2007). They suggested that centromeres compete to enter the product of female meiosis that will form a gamete

(rather than a polar body, which is a dead end). Centromeres with DNA sequences that result in more efficient spindle fiber attachments out-compete others in the race to the prospective egg, thus leading to centromere-associated meiotic drive. However, meiotic drive often has deleterious effects on the organism's fitness, because deleterious genes that are linked to the chromosome with the driving locus—the "strong" centromere, in this case—reduce individual fitness. The ill effects of centromere-driven meiotic drive are neutralized by the selection of alleles of centromere protein genes with a lower binding affinity for the centromeric sequences; hence, centromere-binding proteins evolve rapidly and adaptively to counter the "selfish" centromere sequences. This evolution is driven by the centromere DNA sequences and their attached proteins. It is the functional epigenotype that must remain stable, whatever the specific identity of the DNA sequence and the proteins at the centromeric regions.

An important consequence of the generation and evolution of different epigenotypes across various populations is that, like genetic variations, they may initiate reproductive isolation. Differences in chromatin structure that arise by chance or during local adaptation may result in hybrid offspring that either fail to develop normally or are sterile because the two sets of parental chromosomes carry incompatible chromatin marks (Jablonka and Lamb 1995). For example, incompatibility between parental marks is thought to be the reason why hybrids between two species in the rodent genus *Peromyscus* develop abnormally (Vrana et al. 2000), and, in plants, crosses between parents of different ploidies fail because of the dysfunction of the hybrid endosperm, a tissue exhibiting genomic imprinting (Sokolov 2006).

The Effects of Epigenetic Variations and Epigenetic Control Mechanisms on the Generation of Local and Systemic Epigenomic Variation

Although in practice the biases imposed by epigenetic variations, such as methylation marks, on the generation of local changes in DNA are intertwined with epigenetic control mechanisms generating systemic genomic changes, we need to discuss them separately, for heuristic reasons. It has been known for some time that the rates of mutation, transposition, and recombination are lower in condensed than in open chromatin (Belyaev and Borodin 1982; Jablonka and Lamb 1995), and that the movement of transposable elements, which is recognized as a major cause of genomic change (Kidwell and Lisch 1997), is markedly influenced by various types of internal (genetic) and external (environmental) stresses. It is therefore clear that epigenetic variations bias genetic changes. However, the effect of epigenetic control mechanisms can go beyond the more or less localized mutational changes induced by local chromatin variations. Zufall et al. (2005) have suggested that developmentally regulated genome rearrangements brought about by epigenetic control mechanisms are an ancient feature of eukaryotes. If so, it is possible that, during periods of stress, the same epigenetic control mechanisms cause global epigenomic macro-variations that are inherited between generations and that lead to macroevolutionary changes (Jablonka and Lamb 2008; Lamm and Jablonka 2008). These epigenetic control mechanisms may underlie the systemic changes in the genome that Goldschmidt (1940) believed drove macroevolution. Goldschmidt proposed that macroevolutionary changes are the result of large changes in the genome that are based either on macromutations (mutations in single genes that have very large phenotypic effects) or on systemic mutations (changes in the organization of the genome, such as chromosomal rearrangements). Goldschmidt's ideas used to be derided, but recent data from many biological fronts are changing this attitude (Shapiro 1999; Bateman and DiMichele 2002; Fontdevila 2005). Sequence studies have shown that during plant and animal phylogeny, many developmental genes have been duplicated and re-used (Gu et al. 2004), and Rodin et al. (2005) have suggested how epigenetic silencing may

play a role in this. Epigenetic control mechanisms probably have a key role in speciation through polyploidization and hybridization, which are of central importance in plant evolution (Jorgensen 2004; Rapp and Wendel 2005). As we noted earlier, recent studies have shown that in many naturally occurring and experimentally constructed polyploids and hybrids, DNA methylation patterns are dramatically altered, and genes in some of the duplicated chromosomes are heritably silenced. Following auto- and allo-polyploidization, there is a burst of selectable variation, with all the opportunities for adaptation that this provides. This evidence is very much in line with the suggestions of McClintock (1984), who argued that stress leads to a reshaping of the genome.

Although we do not yet know how epigenetic control systems are involved in the generation of such systemic mutations, processes based on pairing, such as the mechanisms seen in ciliates (in which pairing with scanRNAs determines which sequences are degraded) and during meiotic mis-pairing (in which unpaired regions are deleted or heterochromatinized) may be recruited under conditions of genomic and ecological stress. Molinier et al. (2006, and personal communication) showed that exposing *Arabidopsis* to UV-C radiation in one generation caused a heritable increase in the recombination rate of the whole population of irradiated plants for at least four generations. This might be an example of an induced, pairing-based systemic, epigenetic change. Jablonka and Lamb (1995, 2008) suggested that there may have been selection for specific heritable epigenetic responses based on pairing, which are determined by the type of stress (e.g., direct radiation-induced damage to DNA, nutritional stress, heat stress), its severity, and its probability of reoccurrence.

Evolutionary Constraints and Affordances Imposed by Epigenetic Inheritance

Cellular EISs were a precondition for the evolution of complex multicellular organisms with specialized cell lineages, because cells in such lineages have to maintain and transmit their determined states, even when the conditions that initiated them are long past. Since the cells that give rise to the next generation of organisms need to have an uncommitted state, and efficient EISs could jeopardize this, EISs must have imposed a strong constraint on the evolution of ontogeny. There are several features of development that may be outcomes of selection to prevent cells with inappropriate epigenetic legacies from founding the next generation. For example, the difficulty of reversing some epigenetic states, the early segregation and quiescent state of the germline of many animal groups, and the massive changes in chromatin structure that occur during meiosis and gamete production, may all be the result of selection against transmitting the epigenetic "memories" associated with the developmental changes and chance epimutations that would prevent a zygote from starting its development in a totipotent epigenetic state (Jablonka and Lamb 1995, 2005). Recently, Pepper et al. (2007) have suggested that serial differentiation—the sequence of differentiation that starts with self-renewing somatic stem cells and proceeds through several non-self-renewing, transient, amplifying cell stages before ending with terminally differentiated cells—is also a strategy that evolved to avoid the somatic selection of selfish genetic and epigenetic variations.

Jablonka and Lamb (2006b) argued that the constraints and affordances of epigenetic control systems and epigenetic inheritance played a crucial role in all eight of the major evolutionary transitions identified by Maynard Smith and Szathmáry (1995). For example, the transition from independent genes to long chromosomes was probably dependent on epigenetic inheritance based upon chromatin marking, which maintains patterns of gene activity following DNA replication. Epigenetic control mechanisms may also have been important in the transition from prokaryotes to eukaryotes—a transition that was associated with processes of endosymbiogenesis. It is likely that massive and heritable inactivation of large parts of the symbiont-to-be genome, as well as the employment of

mechanisms of structural inheritance that enabled the integrity of the basic structure of the symbiont-to-be membranes to persist, were involved in this transition.

The Evolution of EISs: Their Origin and Selection

In light of the growing volume of work and the theoretical considerations that suggest that nongenetic mechanisms of information transfer play key roles in evolution, the evolutionary origin of nongenetic inheritance systems is of fundamental interest. There have been some theoretical and comparative studies that have addressed the evolution of EISs, but not all aspects have been explored. The evolutionary origins of DNA methylation have been considered, and several different hypotheses for the advantages it conferred have been suggested (Bestor 1990; Bird 1995; Regev et al. 1998; Colot and Rossignol 1999; Mandrioli 2004). There are also several comparative studies of histone evolution (Sandman et al. 1998; Felsenfeld and Groudine 2003), and the evolution of RNAi systems for defence against genomic parasites and as regulators in an ancient RNA world has been suggested (Cerutti and Casas-Mollano 2006).

Specific developmental processes that involve epigenetic inheritance, such as genomic imprinting and X-chromosome inactivation, have also been subjects of evolutionary study (e.g., Jablonka and Lamb 1995; Lyon 1998; Haig 2002; Jablonka 2004a; Wolf and Hager 2006). However, other developmental processes that depend on EISs (paramutation and stress-induced epigenomic alterations, for example) have not yet received much attention from evolutionary biologists, and the adaptive significance—if any—of epigenetic mechanisms leading to systemic changes during periods of genomic and ecological stresses is at present an open question.

The stability of epigenetic transmission is likely to be an evolved trait that depends on the relative cost of error and the cost of development (Rando and Verstrepen 2007). Epigenetic recall may be selectively superior to full epigenetic inheritance in environments that change every few generations because the cost of response-error that occurs when memory is perfect is reduced, as is the cost of development-from-scratch, which occurs when reset is complete and full induction is required. The transmission of epigenetic engrams that lead to an inducer-requiring yet facilitated response may therefore often be an optimal compromise between the danger of a tyrannically good memory, on the one hand, and the expensive response-delay that comes with "forgetting" too thoroughly, on the other. Direct evidence for epigenetic recall is needed, however, and theoretical exploration through modeling might point to biological systems with strategies that would qualify them as good targets for empirical research.

Epigenetic inheritance should be favored in fluctuating environmental conditions that last for more than one generation (but not for very long) and may be particularly important in the type of environments experienced by many microorganisms (Lachmann and Jablonka 1996; Balaban et al. 2004; Lewis 2007; Rando and Verstrepen 2007). In such fluctuating environments, efficient epigenetic inheritance is likely to evolve (i) if the parental environment carries reliable information about the offspring's environment (Jablonka et al. 1995), (ii) when the response to induction is lengthy and incurs a very high cost (Lachmann and Jablonka 1996), and (iii) when recall is not an option or incurs too high a cost.

THEORETICAL AND PRACTICAL IMPLICATIONS

Incorporating epigenetic inheritance into evolutionary theory extends the scope of evolutionary thinking and leads to notions of heredity and evolution that incorporate development. Dobzhansky's definition of evolution as "a change in the genetic composition of populations" (1937, p.11) appears to be too narrow because it does not incorporate all sources of heritable variations. Both evolution and heredity need to be redefined. Jablonka and Lamb (2007a,b,c) suggested that evolution should be redefined as the

set of processes that lead to changes in the nature and frequency of heritable types in a population, and heredity as *the developmental reconstruction processes that link ancestors and descendants and lead to similarity between them.* These deliberately broad redefinitions allow evolutionary possibilities denied by the "Modern Synthesis" version of evolutionary theory, which states that variations are blind, are genetic (nucleic acid-based), and that saltational events do not significantly contribute to evolutionary change (Mayr 1982). The epigenetic perspective challenges all these assumptions, and it seems that a new extended theory, informed by developmental studies and epigenetic inheritance, and incorporating Darwinian, Lamarckian, and saltational frameworks, is going to replace the Modern Synthesis version of evolution (Jablonka and Lamb 2005, 2007c). We believe, therefore, that the impact of epigenetics and epigenetic inheritance on evolutionary theory and the philosophy of biology will be profound.

As we noted earlier, it is now recognized that epigenetic inheritance is relevant for ecology, and new methods and approaches to the research questions to which it points should be developed (Bossdorf et al. 2008). The relevance of epigenetic variations to biodiversity in our rapidly changing world is also of obvious interest and clearly has to be explored.

A discussion of the implications of epigenetic studies for medicine is beyond the scope of this review, but since epigenetic defects can be transmitted between generations of cells and individuals, we direct the reader's attention to some recent reviews. Baylin and Jones (2007) review the epigenetics of cancer, and Zoghbi and Beaudet (2007) review diseases caused by defects in chromatin marking and imprinting. The epigenetic aspects of metabolic diseases and their transgenerational effects are also being intensely studied (see Bateson et al. 2004; Gluckman and Hanson 2005; Gluckman et al. 2007; Petronis 2004, 2006). The epidemiological aspects of epigenetic inheritance were reviewed by Jablonka (2004b), and the importance of epigenetics for aging research has been discussed by Vanyushin (1973), Holliday (1984), Lamb (1994), and Issa (2000). The recently reported ability of pathogenic microorganisms to evolve heritable epigenetic resistance to medication (e.g., antibiotics) may be of major medical importance (Adam et al 2008), and the relevance of epigenetic inheritance for therapeutic cloning and nuclear transplantation in animals, including humans, is self-evident (see Jaenisch and Gurdon 2007).

Heredity is a fundamental property of living organisms. It is therefore not surprising that, in the beginning of the last century, the rediscovery of Mendel's laws and the chromosomal mechanisms underlying them led to profound changes in all branches of biology. Today, at the dawn of the 21st century, another aspect of heredity—epigenetic inheritance and the epigenetic control mechanisms underlying it—is being unravelled. Like the early 20th-century discoveries, it, too, is driving a great expansion and transformation in our understanding of biology.

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