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A Brief Conceptual History of Epigenetics, and More Besides

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1.1. Introduction

Epigenetics concerns the expression of genetic information – or, more generally, non-genetic (biological) information altogether.

A polymorphous concept with multiple origins, sometimes used very liberally or absent where it is expected, epigenetics is deeply rooted in understanding “generation”, in other words, the way in which living beings are formed.

There are two main groups of answers to the question of generation: either the form is already there, pre-existing its manifestation in the organized being; or it is created as it grows.

The history of epigenetics is the history of a dialectic between these two groups, always in tension, always on the verge of resolution, always in transformation.

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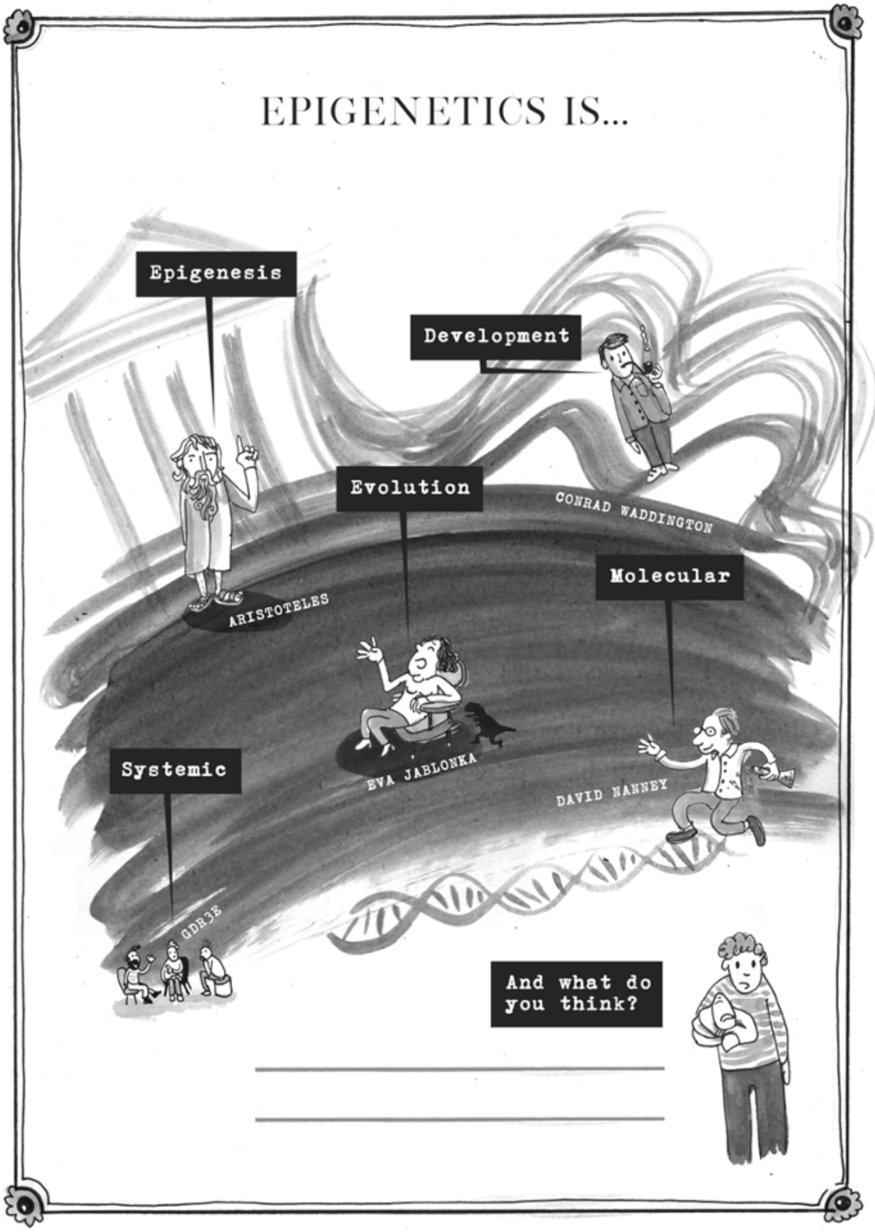

Figure 1.1. *Epigenetics has many faces. Its definition depends on the context in which we find ourselves, and it may yet evolve. Follow us in Chapter 1 to find out why. Illustration by Annette Köhn*

1.2. The birth of the term: from epigenesis to pangenesis

The term “epigenetics“ appeared in the 17th century as a noun, “epigenesis”, in a treatise by the English physician and anatomist William Harvey (1651, *Exercitatio* 45). In it, Harvey outlined his work on the causes of animal generation, responding in particular to Aristotle (330–322 BCE) (Aristotle 1887) and his own master, Fabricius (1621). Harvey distinguishes two possible modes of generation: either the material of the future animal is already present and receives its form like wax imprinted by a seal, all parts being formed simultaneously, which he calls metamorphosis; or the material is added as the form is born, like a potter’s pot, the parts of the animal coming into being from one another, which he calls epigenesis. For Harvey, the generation of the chick from the egg is clearly the result of epigenesis, not metamorphosis. It is an idea that is tempting to see already discussed, albeit ambiguously, by Aristotle; however, it is important to bear in mind the differences in frameworks and debates between eras (Lennox 2006; Goy 2018; Bolduc 2021).

In the 18th century, another vision of generation gained ground: mechanistic preformationism (Bowler 2001, pp. 26–28). Preformationism assumes that form pre-exists generation. From an empirical point of view, the idea is justified by the observation (thanks to the use of the microscope) of microscopic organs and organisms, which suggest the possible existence in the living world of structures of infinitesimal size and therefore undetectable to our senses (Malpighi 1666; Malebranche 1674, pp. 41–42; see Gasking 1967, pp. 45–46, quoted by Roe 1981, pp. 83–87). From a philosophical point of view, preformation allows the formation of a living being to be reduced to simple growth, a mechanism set in motion at conception, at a time when the mechanistic vision is gaining traction (Bowler 2001, pp. 26–28; Wolfe 2016, 2017). The most extreme form of this vision (known as pre-existing germs) assumes that all living beings pre-exist their generation, nested like nesting dolls within each other since Creation, such as aphids whose parthenogenesis and nested generations are demonstrated by a proponent of preformation (Bonnet 1745, 1762, Chapter 1, 1770, pp. 190–191). This vision resonates with a Christian point of view, which in turn justifies the comprehensibility of the world (God lays down natural laws) (Roe 1981, p. 111; Bowler 2001, pp. 29–31). Conversely, preformationists see epigenesis as synonymous with chance, chaos and indeterminacy (and hence incomprehensibility). Advocates of atheism favor epigenetic theories, as well as those of spontaneous generation, which dispense with the idea of Creation (Buffon 1749; see Roe 1981, pp. 16–18; Spallanzani 1765; d’Holbach 1770; Bowler 2001, pp. 29–36).

Mechanistic preformationism fell into disfavor at the turn of the 18th and 19th centuries (Roe 1981, p. 150; Bowler 2001, p. 32; Wolfe 2016, 2017). We would prefer an epigenesis whose mechanistic vision is supplemented by the idea of forces specific to living organisms, which organize them (e.g. Maupertuis 1745, Chapter XI–XII, 1756a, Chapter LXV–LXVII; see Ibrahim 2019; Wolff 1759, 1768; Blumenbach 1780; see Bowler 2001, pp. 40–42; Dupont 2007; Wolfe 2019; Schmitt 2021). This vision gives rise to mystical trends (Naturphilosophie: Schelling 1797; Oken 1809; Bowler 2001, pp. 41–42), as well as to so-called teleomechanist trends, which aim to naturalize the notion of finality in living organisms, embryogenesis appearing to be such a process oriented towards a finality, the formed organism (Kant 1790; Lenoir 1982; Bowler 2001, p. 42; Huneman 2006; Moreno and Mossio 2015). The vision that emerges is that of a homology between the individual and the lineage, with parents shaping their children in the same way a craftsman produces an artifact, in a process akin to copying the parent, part by part – there is therefore, said in today's terms, inheritance of acquired traits (Bowler 2001, p. 23, 38).

This is a vision carried forward by Jean-Baptiste de Lamarck (1809a, Chapter II) in particular, who produced a veritable physicalist theory of the transformation of living beings (and of their spontaneous generation). For him, living beings become organized and complex throughout life and across generations by virtue of movements of fluids, caused by the use of certain parts of the organism whose needs, according to circumstances, are felt (Lamarck 1809b, Chapter VI). The use of a part strengthens it, and the acquired form is transmitted to descendants: this is a law that Lamarck considers empirically evident – the same one that posterity has associated with the neck of the giraffe (Lamarck 1809a, Chapter VII, p. 235). This posterity, sometimes simplifying and very unfaithful, remained influential until the middle of the 20th century, particularly in France, where it resonated with nationalist impulses that were sporadically reactivated by the international context (Boesiger 1980; Limoges 1980; Sapp 1987, pp. 124–128). However, we must be wary of reducing Lamarck to transformism through the inheritance of acquired traits (Bowler 2001, p. 37; Corsi 2001): his intuitions on the self-organization of what we would today call open systems are more reminiscent of the physics of out-of-equilibrium systems (Nicolis and Prigogine 1977; Bejan and Lorente 2004), and, in biology, organizational approaches to viability (Moreno and Mossio 2015).

In the Germanic world, teleomechanism underwent influential developments, culminating in the formulation of the law of parallelism – in the course of its development, the embryo passed through the hierarchy of animal forms, from fish to reptile to mammal, with man at the top (Meckel 1821, 1828 *contra* Von Baer 1828; Russell 1916; Temkin 1950; Oppenheimer 1967; Bowler 2001, pp. 42–44);

a law which, when interpreted as the product of evolutionary history, forms the basis of recapitulation theory – the developing embryo recapitulates its evolutionary history (Haeckel 1866). Recapitulation theory, such as Lamarck's transformism, invites us to understand the transmission of traits between generations as analogous to memory (Haeckel 1876; Gould 1977; Robinson 1979; Bowler 2001, p. 52). However, teleomechanist embryologists are not so much interested in trait transmission as in how the "potentialities" of a fertilized egg develop (Lenoir 1982, Chapter 3; Bowler 2001, p. 44).

Meanwhile, heredity was emerging as a subject of study in its own right, particularly in the medical field, with the study of hereditary diseases (Lopez-Beltran 2007)[1]. In the 18th century, the notion of heredity could be prefigured by the study of noble diseases (such as gout), supposedly acquired through lifestyle (delicious food) and transmissible diseases, which resonated with the pressure put on the aristocratic family (Pomata 2003, p. 150; Müller-Wille and Rheinberger 2007, p. 11, 19). Mendelian-looking studies, such as that by Pierre Louis Moreau de Maupertuis (1756b, letter xiv, pp. 275–278) on the prevalence of polydactyly in a Berlin family, were in fact interpreted within a framework of epigenesis with the transmission of acquired traits (Bowler 2001, pp. 33–35; Terrall 2007, pp. 265–268). In the 19th century, the social tropism for the study of hereditary diseases changed (Müller-Wille and Rheinberger 2007, p. 19). Among other things, the aim was to improve hygiene: the poorer classes and their share of diseases, supposedly caused by the environment and being more or less hereditary, were perceived as the new threat to social order (Pomata 2003; Cartron 2007; Müller-Wille and Rheinberger 2007, p. 19). Other fields of study also fed into these reflections, such as animal and plant hybridization experiments (aimed at testing fixism and the possibility of establishing new species, along Linnaeus' lines), natural history and taxonomy (concerned with the constancy of traits), the maintenance and improvement of plants and animals for breeding and collection (their transport over great distances making it possible to better distinguish the intrinsic characteristics of

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[1] The resemblance between parents and children has been documented since Antiquity. Although it is not the cornerstone of any concept of life, it figures in discussions of generation as a fact to be explained. For some primary sources, see Hippocrates (ca. 440–360 BCE) (Hippocrates 1842), Herodotus (ca. 425 BCE) (Herodotus 1850, par. 180), Aristotle (ca. 330–332 BCE) (Aristotle 1850, par. 180). C.) (Aristotle 1887, Book i, Chapter xi, § 1–6, p. 23), Plato (ca. 375 BCE) (Plato 1933, book v), Pliny the Elder (ca. 77 CE) (Pliny the Elder 1848, Book vii, Chapter x), Plutarch (ca. 72–126 CE) (Plutarch 1844, § 21), Galen (ca. 165–175 CE) (Galen 1822, p. 603–604, 1992, p. 235), and, closer to us (Fernel and Plancy 1656; Paré 1971, XIII, p. 45; Montaigne 2001, XXXVII, p. 1188). For some secondary sources, see Lesky (1950), cited by Preus (1977); (Boylan 1984, 1986; Bonnard 2015; Giorgianni and Provenza 2015; Loviconi 2019).

varieties from the effects of the environment), and anthropology, which studies human diversity, in particular skin color (Müller-Wille and Rheinberger 2007, pp. 19–23). In the 1830s, French physiologists came up with a noun corresponding to the adjective "hereditary", which had been used to describe certain diseases since Antiquity – a noun that until then had only been used in the legal sphere, and which has now taken root in the study of living organisms: heredity (Lopez-Beltran 2007). With the study of heredity, the point of interest is no longer the material mechanism of reproduction (it would be a matter of understanding how a fellow human being is conceived), but the "transmission" of properties between parents and descendants (e.g. knowing the laws of transmission of hereditary diseases would suffice) (Sapp 1987, Chapter 2; Bowler 2001, p. 129; Müller-Wille and Rheinberger 2007).

At the same time as Darwin was proposing his theory of pangenesis, Gregor Mendel was conducting his now-famous hybridization experiments on peas (Mendel 1866, 1901). Mendel's work was part of a long line of hybridization experiments aimed at obtaining new horticultural varieties or, with a more theoretical ambition, testing the possibility of creating new species, within a framework inherited from Linné where genera were fixed (Linné 1760; Koelreuter 1761; Gärtner 1849; Olby 1979; Bowler 2001, p. 97). It is within this framework that Mendel distinguishes between constant hybrids (in which traits do not segregate, and which can give rise to new species), and variable hybrids (in which traits segregate, according to precise ratios, with some traits being dominant and others recessive) (Callender 1988). Such phenomena had been observed before, but no one had undertaken a systematic study of trait genealogy across generations (Bowler 2001, p. 99). Mendel never mentions particulate inheritance; his categories, far from being materialistic, instead evoke the philosophy of Aristotle in which he was trained: the notion of trait is reminiscent of essence; the dominant/recessive notions are reminiscent of actual/potential (Kalmus 1983; quoted by Bowler 2001, p. 104). The fact that Mendel was not interested – contrary to what early geneticists claimed – in establishing universal laws of heredity may explain the obscure trajectory of his work (Olby 1979, 1985; Sandler and Sandler 1985; Callender 1988). Indeed, his name seems to have been used by researchers as much as a rhetorical argument (to provide a historical anchor in a priority dispute) as a scientific one (Bowler 2001, pp. 113–116).

Box 1.1. *Mendel, a historical digression*

The term *heredity* was borrowed by Charles Darwin and his followers to name the transmission of individual variations in his theory of evolution by natural selection (Darwin 1837, 1838; Spencer 1864, Chapter viii; Keller 2010, p. 21). This theory is based on the notion of hereditary variation, which can either be blind (not directed towards adaptation) or acquired (as in Lamarck). Darwin backs up his theory of evolution with a theory of reproduction, but the latter remains dependent on its century – not to say the previous century: it involves "gemmules“, germs of infinitesimal size that come from all parts of the parent organism and reconstitute these parts in the child organism (Darwin 1865, 1868, Chapter XXVII, p. 375, n. 29; Olby 1963; Bowler 2001, pp. 54–64). Darwin called this the "theory of pangenesis": from pan, "all", in Greek. However, it was not the near obsolescence of the pangenesis hypothesis that stood in the way of Darwin's contemporaries accepting the principle of natural selection, but rather their attachment – even by his most enthusiastic supporters – to a "neo-Lamarckian" vision of evolution, in which selection by blind variation is insufficient to explain living things (Bowler 1983, pp. 27–28; Bowler 2001, pp. 54–64).

1.3. From pangene to classical gene

A fervent reader of Darwin, and nonetheless a good critic, was his cousin Francis Galton (Galton 1871a, 1871b; Bowler 2001, p. 64). From the outset, Galton was wary of pangenesis; he developed a theory of heredity (known as ancestral heredity), which defines the transmission of a particulate material that remains stable through generations: the ancestors of all previous generations participate in the material inherited by an individual, following a geometric progression that ensures that the most recent ancestors contribute the most (Galton 1886, pp. 260–261, 1889, p. 148, 1897 *contra* Johannsen 1911, p. 138; see Sapp 1987, p. 39; Gayon 1992, p. 138; Bulmer 1998; Bowler 2001, p. 67). This stability of hereditary material represents "hard inheritance", as opposed to "soft inheritance", which allows the transmission of acquired traits (Mayr and Provine 1998, p. xi; Bowler 2001, p. 68). Hard heredity introduces a decoupling between the transmission of traits and the generation of individuals. From a methodological point of view, this decoupling enables Galton to forego physiology and approach the question of heredity at a population level through statistics (Bowler 2001, p. 69). Galton's notion of hard heredity resonated with his social concerns: Galton founded eugenics, a utopian movement which, concerned about the effects of civilization on human beings, aimed to improve them, particularly (but not only) through the selection of their reproducers (Galton 1883, p. 4, 24–25, n. 1; Gayon 1992, pp. 168–180; Bowler 2001, pp. 66, 70–72, Chapter 8; Gayon 2004). This being said, some advocates of soft heredity defended similar programs, while others, supporters of hard heredity, opposed them (Sapp 1987, Chapter 6; Bowler 2001, Chapter 8).

The development of a notion of hard heredity was also nurtured by developments in cytology. Cell theory, which posits the cell as the basic unit of life, developed in the 1830s, nurtured by a teleomechanist view (Lenoir 1982, Chapter 3, Chapter 5), with many biologists accepting it by the 1850s in a crystallized version according to which the cell cannot be formed from non-cellular material – notably in contrast to the pangenesis hypothesis (Bowler 2001, p. 74, 85). Moreover, it seems clear since the discovery of the mammalian ovum (Von Baer 1827) that the embryo grows from a single cell, raising the question of cellular differentiation (Bowler 2001, pp. 78–79). Improved microscopy and new dyeing techniques began to bring attention to the cell nucleus around the 1870s, with work on phenomena such as the fusion of gamete nuclei during fertilization (Hertwig 1875), chromosome migration during mitosis (Flemming 1879; Paweletz 2001) and the reduction in number of chromosomes during meiosis (Van Beneden 1883), which are suggestive of copying processes at work in reproduction (Bowler 2001, pp. 85–86). Embryologists' attention gradually turned away from speculative edifices such as recapitulation theory, and instead towards experimentation and the search for physiological mechanisms (Bowler 2001, p. 77).

It was in this context that August Weismann (1891, p. 190) became a key supporter of hard heredity, in a research program aimed at synthesizing Darwinian theory and the cytology of his day. After initially accepting the inheritance of acquired characteristics (Weismann 1882), Weismann rejected it on the basis of both theoretical and philosophical arguments (the theory of natural selection is sufficient to explain adaptation), as well as cytological arguments (no mechanism for the transmission of acquired traits is known; moreover, it seems impossible to translate a trait into a hereditary determinant) (Weismann 1893b, Chapter XIII, 1893a, pp. 107–108, 1904, p. 63). Weismann assumes that in multicellular organisms, only the germ line is immortal and involved in the transmission of traits, and that the somatic line cannot alter it in a directed way (Bowler 2001, p. 88). Traits are assumed to be predetermined by chromosomes, and differentiation occurs through an asymmetrical distribution of chromosomes between daughter cells (ibid., p. 75). This position was notoriously characterized as nuclear preformationism, reactivating a cleavage with the proponents of epigenesis (Hertwig 1894; Wilson 1896, pp. 327–331) – it should be remembered, however, that in preformation, the form pre-exists and only grows; in Weismann, it is the potential of a form that pre-exists (Bowler 2001, pp. 75–76, 81). Defending his position with a vigor that tended towards dogmatism, Weismann exacerbated tensions with advocates of soft heredity, who called him a "neo-Darwinian", so as to distinguish his position from that of Darwin himself (Romanes 1888; Bowler 2001, p. 89). The late Weismann was greatly influenced by his contemporary Hugo De Vries (Bowler 2001, p. 90). From Darwin's pangenesis, De Vries retains the idea of particles (which he calls "pangenes") responsible for traits; but for him, these remain in the cell (they are supposed to group around chromosomes and leave the nucleus for trait expression). All cells possess them in their entirety, even in latent form, and their number is perhaps limited, as traits develop through their interactions: heredity can thus take place without mixing, and new traits, even new species, appear through mutation (Vries 1889, sec. iv; Bowler 2001, pp. 90–91).

The year 1900 saw the rediscovery of Mendel's laws – or rather, the reinterpretation of Mendel's work in light of the gradually emerging framework of Mendelian genetics (Correns 1900; Tschermak 1900; Vries 1900; see Bowler 2001, pp. 113–116). Embryologists such as Thomas Morgan, frustrated by the failure of their experimental techniques to explain trait formation, turned to hybridization experiments that only studied transmission (Bowler 2001, p. 78, 82). These early Mendelians produced a vision of transmissible variation that was discrete, underpinning a saltatory, non-selective vision of evolution in direct opposition to that of the neo-Darwinians (notably the so-called biometricians), for whom evolution is gradual and based on the natural selection of continuous variation, fiercely opposing Mendelism (Gayon 1992, Chapter VII–VIII). This was also the time when, in tandem with developments in cytology, the chromosomal theory of heredity developed, with Mendelian overtones: chromosomes would be the medium for determining traits (Sutton 1903; Boveri 1904). Many people resisted this theory, including leading geneticists such as Morgan (who was converted to it, in a particularly fruitful Drosophila genetic mapping program), as well as William Bateson and Wilhelm Johannsen, for whom the hereditary determinants of traits needed to be conceived holistically, in terms of energy levels or waves in the cell (Bateson and Mendel 1902, pp. 2–3; Morgan 1910, 1913; Morgan et al. 1915; Johannsen 1923; see Coleman 1970; Allen 1974; Darden 1977; Roll-Hansen 1978; Allen 1978, cited by Morange 2020, Chapter 26; Bowler 2001, pp. 120–121, 129–131; Roll-Hansen 2014). It was, however, Bateson who founded the first Mendelian school of genetics in Great Britain, and Johannsen, who is credited with establishing the concepts of gene (a contraction of the pangene, the determinant of hereditary traits), genotype (the set of genes) and phenotype (a measurable trait) (Johannsen 1909, p. 113, 1911, pp. 132–134). These conceptual distinctions were part of a conquering movement to base the study of heredity and evolution on experimentation, and to exclude approaches that were deemed to be more descriptive or speculative, such as morphological or biometric studies (Sapp 1987, pp. 21–22, 36–41). In so doing, Johannsen was careful not to forge hypotheses concerning the physical support of hereditary material: for him, genetics did not study genotypes, but genotypic differences (Johannsen 1911, p. 133; see Wanscher 1975; Roll-Hansen 2014). Even though the chromosomal and Mendelian theory of heredity was fairly generally accepted in the community around 1915, particularly across the Atlantic (Morgan et al. 1915; Sapp 1987, pp. xiii, 46–48, 221), where it founded what would later be called classical genetics (Bowler 2001,

p. 128), the Mendelian gene remained a mainly abstract entity – not a speculation, but a computational tool used to describe the results of hybridization experiments (East 1912, p. 634; Morgan 1935, p. 315; see Stent 1970, p. 910; Bowler 2001, p. 125; Rheinberger et al. 2015). Thus, crystallized, classical genetics put aside the question of trait formation to focus solely on their transmission (Sapp 1987, Chapter 2; Bowler 2001, p. 129).

The American school of genetics founded by Morgan rapidly gained in power: it was an opportunity to secure posts and funding, with the promise of applications in both agriculture and public health, with the eugenics program (Sapp 1987, pp. 46–47; Bowler 2001, pp. 132–137). In evolutionary biology, the development of population genetics reconciled Mendelism with neo-Darwinism: continuous transmissible variation – which was dear to biometricians – could be supported by the interaction of multiple Mendelian genes, each causing small differences (Fisher 1918; Fisher 1930; Wright 1931; Haldane 1932; see also Yule 1902). However, classical genetics did not totally reign supreme. The chromosomal theory hardly shuts down the paradox, in multicellular organisms, of cellular differentiation taking place under the control of genes that are assumed to be identical, and active, in all cells (Sapp 1987, p. 17). Cases of non-Mendelian heredity have been reported, particularly in plants (Baur 1908; Correns 1909a, 1909b; Sapp 1987, p. 26, 73–74). Ultimately, as they themselves admit, geneticists have failed in their attempts to produce new species in the laboratory (Sapp 1987, p. 17, 21–22).

The Germans and the French, in particular, resisted the objects of study of classical genetics: for them, the topic of interest related to trait formation; Mendelians studied the transmission of trivial traits, with no biological relevance (Sapp 1987, Chapter 3, Chapter 5; Bowler 2001, pp. 143–152). Embryologists notably saw the cytoplasm of the egg cell as the essential element determining the properties of the organism, and encouraged research into cytoplasmic heredity in open opposition to the nuclear, then chromosomal, theory of heredity (*contra* Morgan et al. 1915; Morgan 1926; see Sapp 1987, p. xiii, 3, 27, 56). Research on cellular organelles experienced renewed interest (Sapp 1987, p. 25); the cell appears, beyond the resolution of the microscope, as an ordered system of particles (whose size can be supramolecular, and called "colloids") where chemical reactions of incalculable diversity take place (Wilson 1923; Sapp 1987, p. 18, 213–214), and which can form a "field" of metabolic gradients (Sapp 1987, p. 144); the cytoplasm is supposed to harbor "plasmagenes" (*plasmatischen Gene*), self-replicating microscopic elements that are differentially distributed between daughter cells (Winkler 1924), or to constitute a reactive, integrated, transmissible system that conditions trait expression, known as the "plasmon" (Wettstein 1926), which is the plasma complement of the “genome“ (Winkler 1920, p. 165), in other words, the set of chromosomes (Sapp 1987, pp. 72–86, 2003, pp. 174–175).

In Europe, many geneticists are actively involved in cytoplasmic heredity research (Sapp 1987, p. 14, 54–55, 69, 73, Chapter 4, Chapter 5). Across the Atlantic, the differences between schools are more powerful: when a biologist of Jewish descent such as Victor Jollos, known for his discovery of *Dauermodifikationen* (environmentally induced variations transmissible over hundreds of vegetative generations in paramecia (Jollos 1920, 1921; Hämmerling 1929)) fled Germany for the US in 1934, he found it impossible to valorize his work and find a job again (Sapp 1987, pp. 62–65; Bowler 2001, pp. 148–149).

1.4. Classical epigenetics

It is in this context of resistance to classical genetics (as well as to the neo-Darwinism of this period, which reduces evolution, in its most extreme form, to dynamics of gene frequencies (e.g. Dobzhansky 1937, p. 11)) that Conrad Waddington coined a word to designate this study that was put aside by early geneticists: recalling the notion of epigenesis – perhaps, it must be said, rather vaguely (see Koltzoff 1935; Waddington 1956a; Wightman 1956) – he called the study of developmental processes that link genotype and phenotype “epigenetics” (Waddington 1942); see also Waddington 1939, pp. 154–156; Waddington 1957, p. ix, 151; cited by Haig 2004; Nicoglou and Merlin 2017). He calls this complex of developmental processes *epigenotype*. The reference to process is not random: Waddington is a reader of Alfred North Whitehead, the English mathematician and philosopher who built a philosophy of process (Whitehead 1925, 1929; Boisseau 2023). Waddington also suggests visualizing the development of an organism through a metaphor: that of a ball rolling down a landscape of hills and valleys. The genotype determines the landscape, which Waddington would later call the epigenetic landscape, in other words, the developmental potentials that are or are not actualized in the phenotype during development by the organism’s interaction with its environment (Waddington 1939, 1940, 1957). Here again, these categories of potential and actual are the tacit and classic Western heritage of Aristotelian categories (ca. 350 BCE), see (Aristotle 1879, 1986; Cohen and Reeve 2021). Waddington created these concepts at a time when the notion of a gene remained abstract: it was a difference causing differences, the material support for this causality not being clearly identified at the time. As a result, Waddington’s concepts bear the mark of this abstraction, making them highly flexible in terms of their material interpretation.

While the notion of the epigenetic landscape met with some success, particularly in the field of morphogenesis (Berry and Searle 1963; Herring 1993; cited by Haig 2004), Waddington's concepts of epigenetics and epigenotype did not catch on: apart from Waddington himself, hardly anyone referred to them, and these words were later independently reinvented to name different concepts. Waddington's real success was posthumous: from the 1990s and especially 2010, a new generation of evolutionary thinkers sought to extend evolutionary theory to reduce the explanatory share allocated to gene dynamics alone (Jablonka and Lamb 2002; Slack 2002; West-Eberhard 2003; Jablonka and Lamb 2005, pp. 63–64; Pigliucci and Müller 2010; see Morange 2009; Gilbert 2012; Haig 2012; Jablonka and Lamm 2012; Morange 2020, pp. 328–329). This new generation is re-appropriating Waddington's concepts (in what may look like a quest for historical legitimacy), and references to his work are multiplying.

1.5. Molecular epigenetics

Around the 1940s, biology became molecular, with the development of new techniques (crystallography, electrophoresis, etc.) and new models (fungi, bacteria, viruses, algae, protozoa) (Sapp 1987, pp. 88–89; Bowler 2001, p. 175; Rheinberger et al. 2015). Geneticists began to focus on the gene control of physiology and turned to microorganisms, which freed them from the complexities of cellular differentiation (Sapp 1987, p. 88). It was at this point that work on the *Neurospora* fungus suggested that each step of a metabolic pathway is under the control of a single gene (Beadle and Tatum 1941; Sapp 1987, p. 133), a result often summarized (somewhat anachronistically) as the "one gene – one enzyme" hypothesis (Morange 2020, Chapter 2). Work on bacterial transformation and bacteriophages suggests that the material support for genes is DNA (Avery et al. 1944; Hershey and Chase 1952; see Bowler 2001, p. 175; Morange 2020, Chapter 4). This vision is not self-evident: for many, DNA is not complex enough to carry genes; proteins are better candidates; on the other hand, the generality of results obtained on viruses and bacteria is questionable (Bowler 2001, pp. 174–175; Morange 2020, pp. 19–20, 35–39). However, when James Watson and Francis Crick proposed that the structure of DNA is a double helix, on the basis of X-ray diffraction patterns obtained by Rosalind Franklin and Raymond Wilkins, their model made it possible to explain both how genetic information can be encoded in DNA (via base sequence) and how this information can be replicated (via base complementarity) (Franklin and Gosling 1953; Watson and Crick 1953; Wilkins et al. 1953; see Bowler 2001, p. 176; Morange 2020, Chapter 11). The notion of a genetic code matching DNA and protein sequences quickly took root, and biologists tried to approach it from both the information-theoretic side (as a code to be broken) and the biochemical side – the latter ultimately being successful (Sarkar 1996)[2].

The domestication of microorganisms and the development of hybridization methods were accompanied by a broadening notion of heredity: the heredity of microorganisms became a model of the cellular heredity expressed during differentiation in multicellular organisms (viruses were also seen as vectors of heredity) (Sapp 1987, p. 89). However, this domestication of microorganisms ushered the discovery of many apparently non-Mendelian phenomena: for proponents of cytoplasmic heredity, genetics was on the eve of a major revolution that could mark the end of Mendelian supremacy and place the cytoplasm at the center of cellular functioning (Ephrussi 1953; see Waddington 1953; Sapp 1987, pp. 89, 166), thereby renewing the question of the evolutionary importance of the cytoplasm (Waddington 1940, p. 53; quoted by Sapp 1987, p. 101). A series of works are interpreted as marking the independence (if not pre-eminence) of non-nuclear cellular phenomena from the nucleus, involving, for example, the cell cortex or basal bodies (Just 1932, 1939; Lwoff 1990). In addition to this scientific turmoil, there was a political aspect: in the context of the Cold War, supporters of Lysenkoism (a scientific ideology that was then dominant in the USSR, defending a holistic vision of soft heredity) seized on work on cytoplasmic heredity to discredit Morgan’s work on chromosomal Mendelism, generating a controversy discussed daily in Western newspapers and directly interfering with the development of research programs (Sapp 1987, Chapter 6, p. 172, 183). Various models of cytoplasmic heredity were proposed, involving plasmagenes (Lwoff 1949; Sonneborn and Beale 1949; Lwoff 1950; Morange 2020, p. 145) or metabolic feedback loops generating environmentally inducible and stable states (Wright 1945; Delbrück 1949; see Novick and Weiner 1957; Jablonka and Lamb 1995, pp. 82–83; Morange 2020, p. 327). Subsequent research was established around the transmission of supramolecular cellular structures, such as cortical structures in paramecia (Beisson and Sonneborn 1965; Nanney 1968), and cytoplasmic genes, now understood as nucleic acids (Sager 1972).

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[2] Subsequently, half a century of molecular biology would shatter the dream of a simple correspondence between Mendelian genes and determined genomic regions: phenomena such as non-coding DNA, overlapping reading frames, alternative splicing of transcripts, protein splicing, to name but a few, would lead us to instead consider the gene as a materially fragmented object, “a union of genomic sequences encoding a coherent set of potentially overlapping functional products” (Gerstein et al. 2007, p. 677; see Rheinberger et al. 2015).

At the height of research into cytoplasmic heredity, the cytoplasm was presented, in opposition to the nucleus, as a highly responsive interface that could explain cellular differentiation. However, this “geographical” opposition was soon to be dissolved by the conceptual changes introduced by molecular biology (Sapp 1987, pp. 192–200). By the end of the 1950s, it had become clear that genes could be regulated: nuclear phenomena could therefore explain differentiation (ibid., p. 193). This molecularization of genetics gave rise to the a concept of epigenetics, proposed by Nanney (1958a).

Initially, a supporter of cytoplasmic heredity, Nanney took on the vision of cytoplasmic heredity as the only possible explanation of cellular differentiation (Sapp 1987, p. 199). For Nanney, the whole question of heredity, posed in “geographical” terms (nucleus/cytoplasm, soma/germen), is badly put forward, both conceptually and empirically (Nanney 1957, p. 143; quoted by Sapp 1987, p. 200). A “totalitarian” vision of genetic mechanisms, in which genes are the only relevant determinants of traits, must be instead contrasted with a more interactive (“democratic”) vision, in which biological organization is perpetuated as a stationary state by the interaction of its constituents (Nanney 1957; quoted by Haig 2004). At a conference on extrachromosomal heredity organized by Boris Ephrussi at the Centre de Génétique Moléculaire that he founded in Gif-sur-Yvette (Sapp 1987, Chapter 5), Nanney proposed that, in addition to a “library of specificities” produced by “genetic control systems”, there are “auxiliary mechanisms”, determining which “specificities” will be expressed in each cell, which he calls “epigenetic systems” (Nanney 1958a, p. 712). Although he refers to Waddington (1956b) after the fact, it seems that Nanney coined the term *epigenetics* independently, having first thought of calling these mechanisms “paragenetic” (Ephrussi 1958, p. 46; Haig 2004). Inflecting his concept, Nanney then proposed to see epigenetic systems as signal interpretation systems (that is, interpreting genetic signals), whose causal ability is constrained by the information contained in the genetic library, and which, he admitted, probably do not lead to irreversible changes (Nanney 1958b; quoted by Haig 2004). The terminology was defended by Ephrussi (1958, p. 47), who, from the perspective of a taxonomy of cytoplasmic heredity, took Nanney’s criticism of a “geographical” taxonomy to heart. Ephrussi thus distinguishes genetic mechanisms (based on the “transmission of particles carrying their own structural information”) from epigenetic mechanisms (“involving functional states of the nucleus”). In a commentary, Joshua Lederberg (1958, p. 384) embraces the concept, but not the term, which, he notes, is already used in a very different sense by Waddington (1952). Lederberg (1958, p. 385) prefers to distinguish between nucleic information (dependent on the sequence of nucleotides in a nucleic acid), epinucleic information (dependent on other aspects of the nucleic acid such as the presence of polyamines or polypeptides) and extranucleic information (dependent on molecules and reaction cycles that are not directly connected to the nucleic acid). Ironically, our current concepts are closer to Lederberg, and our terminology is from Nanney (Haig 2004).

The dichotomy between genetics and epigenetics has taken root: by the mid-1960s, it seemed sufficiently well known that it no longer required a definition in the literature (Cahn and Cahn 1966; Markert 1968; cited by Haig 2004). It has applications in a variety of fields, such as the biology of cancer (proposed as the result of an epigenetic mutation) or research into isozymes, enzymes with different sequences that catalyze the same reactions (Haig 2004). The term *epigenotype* was reinvented, this time to designate the set of self-replicating regulatory mechanisms that characterize the various cell lineages – under Waddington's approving view, who noted that he had already coined the term, with a different meaning (Abercrombie 1967; cited by Haig 2012). However, the early successes of epigenetic terminology were modest and, with the exception of isozymes, the association of what we would now call epigenetic research with the term itself remains anecdotal (see Morange 2002).

1.6. Epigenetics without knowing it, or Mr. Jourdain's epigenetics

Biology is first and foremost involved in epigenetics without knowing it, "à la Monsieur Jourdain"[3], in a disciplinary permeability context that is reminiscent of the intricacy of the mechanisms studied.

Barbara McClintock can be considered one of the first molecular epigeneticists before the word. Known today for her discovery of transposons, she conceived of them as elements controlling gene expression, in a highly organicist vision of biological functioning (McClintock 1948, 1951). However, two decades elapsed between her first publications and the genetic community's acceptance of her results – her results, but not so much her vision, organicism being cast aside (Keller 1983, Chapter 8, p. 193). Another heavyweight of genomic organicism, Richard Goldschmidt (1916, 1954), was similarly marginalized (Allen 1974; Keller 1983, p. 70, 98). While transposition can be seen today as a genetic phenomenon, this has not always been the case: Michel Morange (2002) notes that the dedicatee of the book *Epigenetic mechanisms of gene regulation* is McClintock herself (Russo et al. 1996). In a reverse move, Gary Felsenfeld (2014) counts the work of geneticist Hans

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[3] M. Jourdain, in Molière's *Le Bourgeois gentilhomme*, is delighted to discover, during a philosophy lesson, that he has been writing prose for 40 years without knowing it (1670, Act II, Scene IV).

Muller (1930) on chromosomal rearrangements caused by X-ray irradiation as precursors of epigenetics (see Carlson 1971).

In France – where, as we have said, a certain tradition exists that focuses on trait formation rather than transmission – Elie Wollman and François Jacob proposed a model similar to McClintock's, based on their work on bacterial conjugation, in which cellular differentiation (and, in a later version, regulation alone) would be under the control of genome modifications caused by mobile elements, "episomes" (Jacob and Wollman 1959, 1961; see Morange 2002). Work by Jacques Monod and other colleagues suggests other models of non-genetic differentiation, this time through the induction of enzyme formation by substrate molecules (such as the induction of lactose permease by intracellular lactose in *Escherichia coli*), with different stable states that can be achieved in the same environment (Monod 1956; Cohen and Monod 1957; see Thieffry 1996; cited by Morange 2002). Such models culminate in Jacob and Monod's operon model, in which a repressor (an allosteric protein encoded by a regulatory gene) binds to an inducer, with the conformational change of the allosteric repressor (and thus its binding capacity) depending on the presence of regulatory ligands (Jacob et al. 1960; Jacob and Monod 1961; see Morange 2002, 2020, p. 154). The allosteric model also provided the basis for the first model to explain the possible infectivity of a protein, the prion (Griffith 1967; Morange 2002).

The operon model is a geneticist's answer to the question of how traits are formed (and no longer simply transmitted); it provides the opportunity to forge a powerful metaphor, that of the genetic program: gene regulation would be comparable to the execution of a series of instructions (Jacob and Monod 1961, p. 354; Morange 2002, p. 55). This metaphor became fashionable in the late 1960s, and Jacob (1970) developed it further in *La Logique du vivant*: unlike a computer program, the genetic program requires its own outputs to be executed. For Jacob, the genetic program resolves the old unease between epigenesis and preformation: the egg does not contain the description of the future organism, but the instructions enabling it to develop in time and space (Jacob 1978, p. 249; quoted by Morange 2002, p. 55). The genetic program metaphor would go on to be severely criticized on philosophical and theoretical grounds, with its apparent determinism hardly relating to the improvisational capacity of biological systems (Morange 2002; Longo and Tendéro 2008; Pocheville 2018), but it only really fell out of favor from the 2000s onwards, in the post-genomic era – a time when the epigenetic reprogramming metaphor was gaining ground (Holliday 1990; Reik et al. 1993, 2001; Morgan et al. 2005; Suvà et al. 2013; see Brandt 2010).

The operon model is based on three assumptions: genetic material is stable during cell functioning (an assumption dating back to De Vries and Morgan); gene expression is controlled at the transcriptional level; and, lastly, this control is achieved by the binding of specific regulatory proteins to DNA (Morange 1997). While this vision of regulation has been successful to the point of turning to "mania" (ibid., p. 384), it has also led to reactions: for a whole section of the community, the operon cannot constitute a general explanation of regulation and differentiation, particularly in eukaryotes, where there is a lack of proof of its existence (Morange 1997, 2002, 2013). A series of alternatives have been proposed, such as the control of gene expression at the translation level (thanks to the stability of certain RNAs), at the DNA sequence level through gene amplification or reverse transcription, or at the enzymatic activity level (Morange 1997). Among these alternatives, those concerned with the regulation of transcription via structural and chemical modifications of DNA, histones and cytosine methylations, will be of particular interest to us.

The history of research into histones and DNA methylations is "long and tortuous", with the two fields developing in a remarkable lack of communication (Morange 2013, p. 453). The hypothesis that histones can inhibit gene activity was first speculatively proposed in the early 1950s (Stedman and Stedman 1950; Morange 2013, p. 451, 2020, p. 329). Histone modifications (acetylation and methylation) were described 10 years later, with the first in vitro results confirming histone inhibitory activity (Huang and Bonner 1962; Allfrey et al. 1963), as well as the role of acetylation in lifting this inhibition: the histone can function as a specific switch of gene activity (Allfrey and Mirsky 1964; Allfrey et al. 1964; Georgiev 1969; see Paik et al. 2007, p. 148; Morange 2013, p. 451, 2020, p. 329; Felsenfeld 2014, p. 5). However, these initial results were received with skepticism (Morange 2013, p. 451). Eric Davidson, for example, considered that in eukaryotes, inhibition of gene activity could not be achieved by specific repressors, the encoding of which would require too many genes; he preferred a model of gene regulation in which histones play a structural and global inhibitory role (the default state of the genome being inactivity), with activation by specific activators that he proposed to identify with RNAs (Davidson 1968, pp. 313–325; Morange 2013, p. 452). This model, subsequently developed with Roy Britten, has the advantage of predicting switches between global patterns of gene expression, which seem more plausible than cascades of local regulation to explain differentiation (Britten and Davidson 1969, p. 351; Morange 2002, p. 55, 2020, p. 268; García and Suárez 2010). Histones then appear to have a non-specific inhibitory activity; moreover, Morange (2013, p. 452) notes that the discovery of the nucleosome (Kornberg 1974; Olins and Olins 1974) and its subsequent characterization (Richmond et al. 1984) focused attention on the role of histones in chromatin structure (Kornberg 1977; McGhee and Felsenfeld 1980), with the suggested effect of their modifications on transcription remaining unknown (Holt 1985; Grunstein 1990) – at least until the 1990s, when proteins that recognize these modifications and act on transcription began to be discovered (Turner 1991; Wolffe 1994; Pazin and Kadonaga 1997; Kuo and Allis 1998; Kouzarides 1999; see also Felsenfeld 2014, p. 5; Morange 2020, p. 330).

As for cytosine methylations (5mC: 5-methylcytosine) of nucleic acids, results indicating their existence marked the first half of the 20th century (Wheeler 1904; Johnson and Coghill 1925; Hotchkiss 1948; see Mattei et al. 2022). The 1950s saw confirmation of their presence in variable quantities in plant and animal DNA (Wyatt 1950, 1951; Mattei et al. 2022), and as early as the 1960s, their potential role in eukaryotes was discussed: 5mCs could protect DNA (Srinivasan and Borek 1964) or, on the contrary, induce specific mutations that would participate in the differentiation process (Scarano et al. 1967) – this was a hypothesis, however, that was incompatible with recent results from cloning experiments (Gurdon 1962; see Morange 2013, p. 452). However, it is in prokaryotes that the first results flourished, thanks in particular to the in-depth description of the restriction-modification system (R-M system) in bacteria, a system in which so-called "restriction" enzymes cut DNA at specific sites via recognition of particular sequences (generally four to eight nucleotides long) (Luria and Human 1952; Luria 1953; Lederberg 1957; Gold et al. 1963; Arber 1965; Arber and Linn 1969; Morange 2013, p. 452, 2020, p. 331; Mattei et al. 2022). A bacterium possessing this system can digest the DNA of an infecting virus, the bacterial DNA being protected at the restriction sites by species-specific methylations (Arber 1965; Mattei et al. 2022). In addition to the role this system played in early genetic engineering experiments in the early 1970s (Jackson et al. 1972) and in the study of methylations themselves (Bird 1978; Bird and Southern 1978), it offers a possible analogy with the putative role of methylases in eukaryotic development (Morange 2013, p. 452, 2020, pp. 181, 331): the latter could recognize specific sites and control gene expression during differentiation, a mechanism that could explain the recently discovered inactivation of the X chromosome in mammals (a hypothesis that was later ruled out) (Lyon 1968; Lock et al. 1987; Morange 2013; Mattei et al. 2022, p. 12), as well as DNA loss during development in certain eukaryotes or senescence and apoptosis (Adams 1973; Holliday and Pugh 1975; Riggs 1975; Sager and Kitchin 1975; see Morange 2013, 2020, pp. 331–332; Mattei et al. 2022). That being said, this hypothetical ability of methylases to recognize specific sites has not been confirmed by subsequent studies (Morange 2013). While the precise role of methylations in the regulation of gene expression remains unknown (Felsenfeld and McGhee 1982; Doerfler 1983; cited by Morange 2013), converging studies based on improved locus-specific 5mC detection methods suggest that 5mCs are antagonistic to expression (Southern 1975; Waalwijk and Flavell 1978; Kuo et al. 1979; Mandel and Chambon 1979; McGhee and Ginder 1979; see Mattei et al. 2022). During the 1980s, technical advances (such as the possibility of inserting methylated or unmethylated DNA fragments into living cells) led to a more precise role for 5mC and, at least for mammals, a consensus emerged that 5’ promoter methylation inhibits transcription (Mattei et al. 2022). However, the absence of 5mC in model organisms such as the yeast *Saccharomyces cerevisiae*, the nematode *Caenorhabditis elegans* and the vinegar fly *Drosophila melanogaster*, leaves the community dubious as to the generality of the mechanism (Morange 2013, 2020, p. 333; Mattei et al. 2022). It was at this point that Robin Holliday (1987), in a well-received speculative article, revived the question of the heritability of cellular states via methylations, and their possible role in evolution, formulating it in an explicitly epigenetic framework (for which he credited Waddington) that would briefly catalyze the association in molecular biology between “epigenetics” and heritable methylations (Holliday 1994; Haig 2004; Morange 2020, p. 333). It was in the 1990s that the outlines of a paradigm were established: 5mCs were shown to be essential for mammalian development (Li et al. 1992, 1993; Lei et al. 1996; Okano et al. 1999); their roles in genomic imprinting, X chromosome inactivation (Lock et al. 1987) and the repression of transposable elements during embryonic development (Walsh et al. 1998) were better understood; this was also when thale cress (*Arabidopsis thaliana*) became a leading model organism for epigenetic studies (Mattei et al. 2022). The mid-1990s also saw “omics” approaches flourish (proteomics, transcriptomics, etc.) which, on the model of genomics, focus on the study of all the components of a certain type in a living material (cell, organelle, tissue, etc.). The study of methylations is part of this movement: bisulfite sequencing, published in 1992 (Frommer et al. 1992), rapidly became the method of choice in a growing number of sequencing studies – some of which claimed to be “epigenomic”.

1.7. Post-genomic epigenetics: epigenomics

In the early 2000s, several genome sequences began to be assembled, including those of Arabidopsis, mice and humans. The field was excited to enter the genomic era (Képès and Dardel 2002; Roses 2003), an era of abundant sequences that would pave the way for fine applications such as personalized medicine; but it was also, paradoxically, an era that would be referred to retrospectively as postgenomic – a “post” that initially only had temporal meaning (“after” the publication of the human genome) (Képès and Dardel 2002, p. 235), but which would soon be used in a roundabout way to signify a move beyond genomics, in a rhetorical pursuit for disruption aimed at singling out practices whose reality may show more continuity (Green 2016, p. 84). The era of genomics actually began two decades earlier, with the first sketches of the Human Genome Project in the mid-1980s (the project was officially launched in 1990) (Morange 2020, Chapter 27), and the assembly of several genomes (phage, murine and human mitochondria, *Marchantia* and tobacco chloroplasts, *Haemophilus influenzae* bacteria, *Saccharomyces cerevisiae* yeast), with published genomes accumulating at an exponential rate ever since (Fiers et al. 1976, 1978; Sanger et al. 1977; Anderson et al. 1981; Bibb et al. 1981; Ohyama et al. 1986; Shinozaki et al. 1986; Goffeau et al. 1996; Képès and Dardel 2002, p. 10; Smith 2016). The gradual completion of the Human Genome Project (with the publication of the very first draft sequence in 2000 (White House 2000)), however, is bittersweet: beyond its technical success, the project does not seem to be fulfilling all the – almost messianic – promises made by some of its leaders (Collins 1999; see Longo 2021). The field of molecular biology is always on the lookout for new territory: the situation is conducive to seeking explanations for cellular phenomena other than genetic sequences. The use of epigenetic terminology is exploding (Deichmann 2016), and epigenetics is becoming the focal point of the 21st-century biology (Figure 1.2).

From a mapping point of view, the publication of genomes (and, in the mid-2000s, the emergence of new sequencing and bioinformatics assembly techniques) paved the way for a broadening of methylation mapping, from the locus scale to that of the genome: these were the first methylomes, or genome-wide DNA methylation landscapes, the first maps being drawn up in the mid-2000s for *A. thaliana* and humans (Lippman et al. 2004; Tran et al. 2005; Weber et al. 2005; Rollins et al. 2006; Zhang et al. 2006; cited by Mattei et al. 2022). The mapping movement is moving towards both greater resolution (towards the base), and a more global description (towards the genome), an element which, alongside mechanistic results, will be essential to a better understanding of the dynamic character of methylations (Mattei et al. 2022). The field of epigenetics (like that of Morgan-style genetics before it) quickly thrives in topographical metaphors: the epigeneticist imagines herself as an explorer of a landscape made up of canyons, valleys and islands, which must be mapped, with each type of epigenetic modification representing a “layer” of this map (e.g. Mattei et al. 2022, p. 17). The inadequacy of one description (of the genome, for example) immediately calls for another (methylome, acetylome, etc.), until we obtain the most complete and precise description of the nucleic material. These metaphors can cause strange slippages, with some authors establishing a bridge between the methylation landscape, which concerns the methylation level profile along the sequence, and Waddington's epigenetic landscape, which concerns the potential curves that a developing organism can follow (Jenkinson et al. 2017).

From a mechanistic point of view, we are witnessing major advances in the biology of methylation readers, writers and erasers, which is an important step in the pursuit for explanations of methylation dynamics during differentiation and development (Mattei et al. 2022). It appears that most promoters are not regulated by 5mCs, which disrupts the previous promoter-centric paradigm and invites a more global study of genome function (Weber et al. 2007; Borgel et al. 2010; see Mattei et al. 2022, p. 21). Ultimately, these mechanistic advances will benefit from the development of epigenome-editing tools, with Cas9's ability to recognize sequences being used to produce targeted DNA methylations (Jinek et al. 2012; Hsu et al. 2014; Liu et al. 2016; cited by Mattei et al. 2022).

The early 2000s finally saw the convergence of research into cytosine methylation and histone modification, with results increasingly pointing to an interaction between these mechanisms (Tamaru and Selker 2001; Ooi et al. 2007; Weber et al. 2007; see Mattei et al. 2022). This point in time saw the hypothesis of a histone code (re)emerge, an epigenetic code of gene activity: histone modification, patterns (acetylation, methylation, phosphorylation, ubiquitination) would mark active or potentially active genes (Tsanev and Sendov 1971; Turner 2000; Jenuwein and Allis 2001; see Rando 2012; Morange 2020, p. 337). It has become clear that non-coding RNAs, particularly small RNAs, are involved in a whole range of epigenetic mechanisms, including cytosine methylations and histone modifications, and are of interest in phenomena such as transposon activity, X chromosome inactivation, parental imprinting or paramutation (Costa 2008), in other words, the heritable modification of one allele caused by the other allele at the same locus (Chandler 2007). Conversely, since the mid-2000s, there has been a renewed interest in epigenetic modifications of messenger RNAs and long non-coding RNAs, first discovered in the 1970s, with the latter emerging as an additional layer of epigenetic regulation of gene expression (Liu and Pan 2015). Epigenetic terminology, which until then only involved cytosine methylations, now encompasses all transcriptional effects, whether they are inherited or not, including histone modifications, followed by mechanisms involving RNAs (Haig 2012).

The meaning behind the term “epigenetics“ has changed significantly over its history (Jablonka and Lamb 2002; Van de Vijver et al. 2002; Nicoglou and Merlin 2017). Two main families of definitions can be identified.

Developmental epigenetics: epigenetics is the science of epigenesis, in other words, a developmental process in which form is not predetermined at conception (see, for example, Wilson 1896, pp. 327–330; Koltzoff 1935, pp. 8–9; Waddington 1939, pp. 154–155; Berry and Searle 1963). Epigenetics is the science of the development, in particular, within the framework of classical and then molecular genetics, of mechanisms linking genotype and phenotype (Waddington 1942, 1952, 1968; Løvtrup 1974; Medawar and Medawar 1983, pp. 113–114; Holliday 1990, p. 329; Hall 2013, pp. 89–91; see Jablonka and Lamb 2002).

Molecular epigenetics: epigenetics is the science of factors modifying gene expression, whose states can be inherited through mitosis (which can explain differentiation) (Nanney 1958a, 1958b; Davis 1964, see, for example Cahn and Cahn 1966, p. 107; Markert 1968, p. 1908; Rosen 1984, p. 320; Ptashne 2007, R233) or even meiosis (which can produce soft heredity) (Holliday 1987). These factors can be identified with nucleic acid methylations (model of Holliday and Pugh 1975; Riggs 1975; terminology of Holliday 1987) – a model that can explain the putative reversibility of an “epigenetic program” at meiosis (Holliday 1990, pp. 335–336) – or even other nuclear (Holliday 1994, definition 2, p. 454) or at least chromatin modifications (Bird 2007, p. 398). In a strong sense, heredity is required through mitosis (Holliday 1994, definition 1) and/or meiosis (Russo et al. 1996). Epigenetics is then the study of heritable variations through mitosis or meiosis that do not depend on variations in nucleic acid sequence (Russo et al. 1996; Berger et al. 2009, p. 781; see Jablonka and Lamb 2002, p. 88). In a weak sense, a simple (causal or consequential) biologically functional relationship of these factors with gene expression is sufficient (factors limited to chromatin modifications (Bird 2007, p. 398)).

Epigenetics, like genetics before it, is moving towards an increasingly material identification of its object of study, at the cost of an increasing relaxation (*contra* Ptashne 2007, R234) of various functional criteria (heritability, gene expression) whose relationship to material factors can be ambiguous (Bird 2007, p. 397). There is a seamless shift from epigenesis to the study of chromatin, firstly by identifying development – and in particular differentiation – with a cascade of modifications in gene expression, and then by shifting towards the material identification of the factors causing these modifications – factors whose study, however structural, is then of its own interest (see Jablonka and Lamb 2002, p. 89). “Epigenetics”, as a noun designating a discipline, only really came into use at the very beginning of the 21st century, once this material identification had been established (Figure 1.2).

Box 1.2. *Definitions of epigenetics*

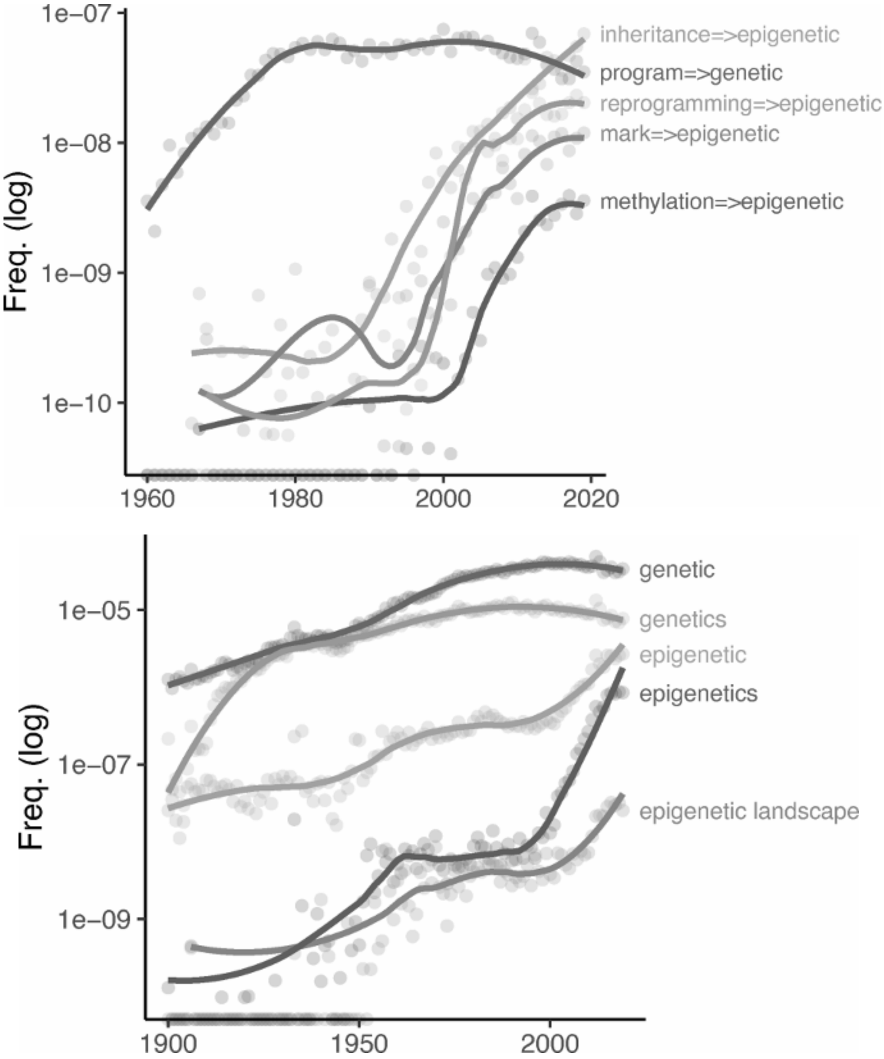

Figure 1.2(A). *Google Ngram representing the evolution of the frequency (in log) of some terms related to epigenetics, in Google's English-language corpus (texts prior to 2019). For a color version of this figure, see www.iste.co.uk/grunau/epigenetics.zip*

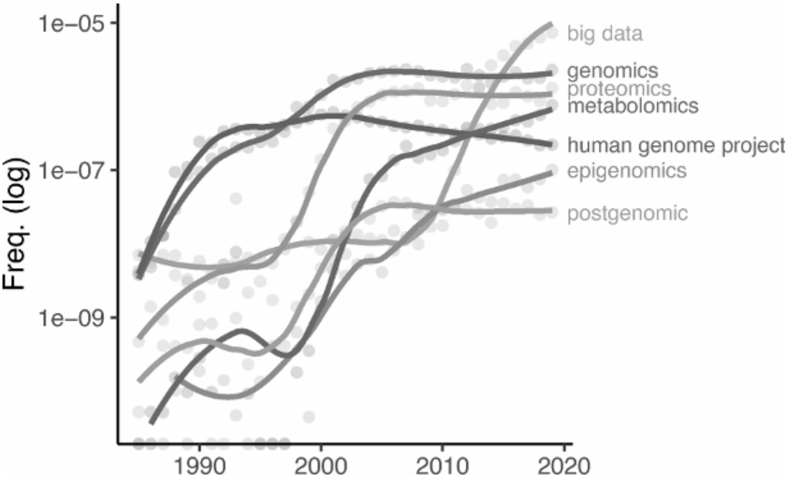

Figure 1.2(B). *Google Ngram representing the evolution of the frequency (in log) of some terms related to epigenetics, in Google's English-language corpus (texts prior to 2019) (continued). For a color version of this figure, see www.iste.co.uk/grunau/epigenetics.zip*

COMMENT ON FIGURE 1.2. – *The Ngram can be used to illustrate a major trend, but is no substitute for in-depth textual study; in particular, low frequencies are sensitive to false positives (e.g. document dating errors). The symbol ⇒ signifies a qualifying link (e.g. "epigenetic ⇒ mark" tracks the frequency of cases where "epigenetic" links together with "mark", as in the expression epigenetic methylation mark). "Epigenetic" as an adjective linking epigenesis has remained in use since Harvey, while the noun "epigenetics" designating a discipline only saw its use take off in the 2000s, when "omics" methods flourished and the use of genetic terminology decreased. From the 1990s onwards, the adjective "epigenetic" came into exponential use to describe mechanisms relating to chromatin.*

From a philosophical point of view, while approaches continue to move towards greater comprehensiveness (both in terms of the number of molecular species and the exhaustiveness of their sampling), the vision remains reductionist: we seek to explain the behavior of the whole by describing its parts.

1.8. Developmental, ecological and evolutionary epigenetics

While molecular biology and evolutionary biology have traditionally not interacted with one another very much – each assuming they can proceed with their research without a detailed knowledge of the other field – epigenetics is the site of encounters, resonances and even outright changes (Mayr 1961; see Morange 2012, 2020, Chapter 23). Morange (1997, p. 383, n. 63) notes that from the very beginnings of molecular epigenetics, similar criticisms were directed at models of gene regulation and the neo-Darwinian scheme of evolution, with the same "heretical" mechanisms (reverse transcription, transposition) and observations (abundance of repeated DNA, control of gene expression at a level other than transcription) being mobilized as putative explanations of evolutionary or developmental changes.

Two theoretical biologists were quick to take the measure of the changes that molecular biology encourages us to introduce into our vision of evolution: in a cutting-edge work, Eva Jablonka and Marion Lamb formulate a very precise proposal to go beyond the neo-Darwinian vision of a genome that would be a passive medium of information, evolving through the natural selection of blind variations (in other words, "random" mutations on an individual scale, which would be selected on a population scale) (Jablonka and Lamb 1995; see also Jablonka and Lamb 1989; Jablonka et al. 1992). For Jablonka and Lamb, the knowledge acquired over the last half-century in both genetics and epigenetics (of which they have a very inclusive, but still molecular, understanding that does not include cultural mechanisms (Jablonka and Lamb 1995, Chapter 4)) encourages us, on the contrary, to consider the genome as an active response system to environmental challenges, and to complement our vision of heredity by considering epigenetic heredity (Jablonka and Lamb 2005). Not only are epigenetic variations not necessarily blind to the challenges of the environment (the constant change of marks allows adaptation to fluctuating environments that genetic evolution alone would not allow, judged to be too slow) and mark patterns, if they are heritable, can be selected on a population scale (Lachmann and Jablonka 1996), but Jablonka and Lamb further argue that results obtained in bacteria suggest that epigenetic mechanisms can lead to directed (i.e. non-blind) genetic mutation on an individual scale: genes involved in responding to environmental challenges would be the target of epigenetic mechanisms that can be mutagenic, thus leading to increased variability at loci of physiological interest in response to the environment – a mechanism that Jablonka and Lamb call "mutational assimilation" (Jablonka and Lamb 1995, pp. 167–171; see Merlin 2010; Pocheville and Danchin 2017), in reference to genetic assimilation (Pigliucci et al. 2006). They thus advocate for a neo-Lamarckian vision of evolution, i.e. one that encompasses both neo-Darwinian mechanisms (selection of blind variation) and mechanisms of directed (non-blind) variation, mechanisms which they moreover assume may have been the result of earlier neo-Darwinian evolution (Jablonka and Lamb 1995, p. 25).

These theses were initially met with a rather hostile, if not totally hostile, response in the evolutionist community, who considered Lamarckism to be a long-dead and buried historical curiosity, with its occasional revivals to be the result of a misunderstanding of the explanatory power of neo-Darwinism (see Jablonka and Lamb 1995, p. vii; Griesemer 1998; Gouyon et al. 2007; Haig 2007; Dickins and Dickins 2008; Griesemer 2011; Bonduriansky 2012, box 1; Morange 2013, p. 453, 2020, p. 56). They would, by contrast, be regularly reinvented in molecular biology, as knowledge of evolutionary biology debates does not seem to have percolated deeply into this field (e.g. Costa 2008; Hilbricht et al. 2008; Martienssen 2008; Koonin and Wolf 2009; Schmidt and Kornfeld 2016; Veigl 2017; Wang et al. 2017; but see Koonin and Wolf 2016).

By the mid-2000s, the attitude of the evolutionary community began to change: a new generation of theorists saw epigenetics (and all developmental mechanisms in general) as an integral part of the evolutionary picture; no longer as a mere product of evolution, but as well as a producer of change, essential for understanding evolutionary trajectories (Odling-Smee et al. 2003; West-Eberhard 2003; Lehmann 2008; Helanterä and Uller 2010; Pigliucci and Müller 2010; Gissis and Jablonka 2011; Bonduriansky 2012; Sultan 2015; Bonduriansky and Day 2018; Pocheville 2019). In developmental biology, Waddington's epigenetics was exhumed and, from the 2010s onwards, became the spearhead of a whole series of theoretical (Bhattacharya et al. 2011; Wang et al. 2011; Huang 2012; Jaeger and Monk 2014; Matsushita and Kaneko 2020) and philosophical studies (Jamniczky et al. 2010; Baedke 2013; Allen 2015; Nicoglou and Merlin 2017; Baedke 2018; Fabris 2018; Nicoglou 2018); some experimental biologists are even getting into the game of explicitly measuring epigenetic landscapes (Banerji et al. 2013; Li and Wang 2013; Wang et al. 2014; Zwiessele and Lawrence 2017; Shi et al. 2020; Schiebinger 2021). The current perspective involves a re-coupling of developmental and evolutionary phenomena, which are no longer seen as separable, to be studied in isolation, but constituting one and the same phenomenon, in a vision that is ultimately very close to that of the 19th century before the establishment of neo-Darwinism (Pocheville 2019).

In ecology, the community seems to have taken more quickly to the epigenetic aspect, both conceptually and empirically (Bossdorf et al. 2008; Rey et al. 2020), although the deployment of epigenetic questions and methods still trails behind genetic approaches (but see Joly and Grunau 2018).

The central dogma of molecular biology is one of a pair of hypotheses formulated by Crick (1958), to specify the causal relationships existing between nucleic acids and proteins in present-day living beings (Crick considers that he is only making the dominant scheme of his day explicit). The first hypothesis, known as the Sequence Hypothesis, is that the sequence of a nucleic acid is a (simple) code for the sequence of an associated protein. The second is the "central dogma": information is only transferred from nucleic acids (to other nucleic acids or proteins), never from proteins (Figure 1.3). *Information* here means sequential information, in other words, precise determination of the sequence (of nucleic bases for DNA and RNA, of amino acids for proteins) (Crick 1958, 1970). The central dogma thus simply postulates the de facto non-existence (but not the impossibility in principle) of reverse translation, i.e. the reading of a protein sequence and its translation into a nucleic sequence[4], as well as protein replication (Figure 1.3). The reason for this hypothesis is that no trace of such machinery was known at the time, and it did not appear to be really necessary for life – the degeneracy of the genetic code, sometimes cited as an additional argument, was only hypothetical at the time (Sarkar 1996, pp. 192–199; Morange 2020, p. 122).

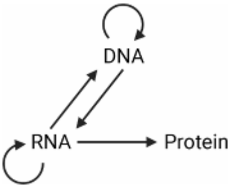

Figure 1.3. *The central dogma of molecular biology, in its contemporary version. From Crick (1970, Figure 2), with deletion of a hypothetical arrow between DNA and protein, and a confirmed arrow between RNA and DNA. Created with BioRender.com*

Many biologists consider that the discoveries of biology over the last half-century should bring about the refutation of the central dogma (e.g. Anon 1970; Temin 1976; Monk 1995; Koonin 2012). In particular, some epigenetic mechanisms seem to be interpretable as transfers, on an individual scale, of some information from the environment to DNA (Monk 1995; Koonin 2012). These arguments are based on a misunderstanding of the central dogma, and in particular of the notion of sequential information (Thieffry and Sarkar 1998; Rosenberg 2006; Ogryzko 2008; Saade and Ogryzko 2014; Steele 2016; Wang and Allard 2022). Clearly, transfers of sequence information from a protein are, by definition, not at work in mechanisms where the source of sequence information is RNA (*contra* Anon 1970; Temin 1976; Dhanasekaran et al. 2013), prion folding (a conformational transfer between proteins) (*contra* Bussard 2005; Koonin 2012), or the modulation, albeit functional, of epigenetic marks without modification of the nucleic sequence (*contra* Monk 1995) – unless 5-methylcytosine is interpreted as a fifth base (Griffith and Mahler 1969, p. 580; Millar et al. 2003) or histone

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[4] The possibility of reverse translation in vivo has occasionally been discussed (Cook 1977), particularly in the field of the origins of life (Nashimoto 2001; Vitas and Dobovišek 2017).

modifications as part of a code (Tsanev and Sendov 1971; Jenuwein and Allis 2001; but see Morange 2020, p. 337), in which case these modifications constitute edits to an extended alphabet sequence, both nucleic and epinucleic. Nor, strictly speaking, is there any transfer of information between sequences in mutagenic–epigenetic mechanisms (see, for example, Chahwan et al. 2010; Sassa et al. 2016), even in the case of mutational assimilation, mutation being assumed to amount to sequence noise (see Jablonka and Lamb 1995; Griesemer 2002; Merlin 2010; Pocheville and Danchin 2017). On the other hand – although not part of reverse translation or protein replication – the mechanisms of correction, editing, alternative splicing and protein splicing do represent cases of sequence information modification made possible by proteins (see Thieffry and Sarkar 1998; Stotz 2006; Morange 2008; Griffiths et al. 2015; Pocheville 2018).

This misunderstanding is encouraged by another misunderstanding: the association of the central dogma with neo-Darwinism (Figure 1.4). Under a reading of biology in which DNA represents the only relevant support of heredity (Mayr 1961), does the central dogma not signify the impossibility of directional modification of hereditary information on an individual scale (Maynard Smith 1993, pp. 79–81; see Lamb 2011, pp. 118–119)? In other words, does it not express the impossibility of heredity of acquired traits (Sarkar 1996, p. 196; Meloni 2015; Ashe et al. 2021)? Hence, do discoveries about the heredity of environmentally-induced epigenetic modifications not upset this sealed-off heredity postulated by the central dogma (Monk 1995; Watson and Goodman 2002; Koonin 2012; González-Recio et al. 2015; Chakravarty and Jarosz 2018)? There is additional confusion here regarding the level at which information transfers take place: the central dogma concerns cellular functioning, not heredity, in other words, information transfers between generations.

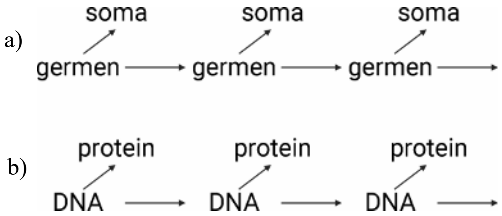

Figure 1.4. *The reinterpretation of Weismannism (a) in terms of the central dogma (b) according to Maynard Smith (1993, Figure 8, 1st edition, 1958). Maynard Smith notes that the validity of the central dogma alone would not establish the impossibility of heredity of acquired traits (ibid., p. 81), a point not all his commentators have taken on board. Created with BioRender.com*

These misunderstandings contribute to the perception of the central dogma as a great theoretical principle, whose refutation should lead to a revolution. In fact, it is a mechanistic hypothesis with a remarkably limited scope, aimed solely at organizing molecular biology research in its day (see also Morange 2008).

Box 1.3. *Epigenetics and the central dogma of molecular biology*

1.9. Epigenetics and ethics

By offering a new layer of biological causality, epigenetics encourages us to revisit ethical debates that were previously centered on genetics (Chiapperino 2018; Soulier 2019). A certain deterministic, fatalistic vision of the human biological condition (genes are fixed for the life of an individual) is succeeded by a richer vision, which takes up elements of previous determinism (which may be genetic or epigenetic, or even social), while mixing it with a certain voluntarism, due to the supposed responsiveness of epigenetic material to the biological and social environment, a responsiveness that puts the agency of each individual back at the center of ethical questioning: individuals are no longer condemned by their genes (according to a certain vision of genetics), but empowered towards themselves and future generations (see Meloni and Müller 2018). A whole series of philosophical and ethical questions can then be put forward in renewed terms: for example, will epigenetics offer an unexpected way out of the nature/nurture debates (Guthman and Mansfield 2013; Lock 2013; Moore 2017; see Dupras et al. 2019)? Under what conditions will the importation of epigenetic causality be liberating or stigmatizing, for example, if the empowerment of putative future mothers' behavior from childhood leads to increased control of women's bodies (Richardson et al. 2014; Richardson 2015; Kenney and Müller 2018; Dupras et al. 2019; Richardson 2021)? Could epigenetics lead to a new form of biological reification of certain ethnic or social groups, or even to a new epi-eugenics (Pickersgill et al. 2013; Juengst et al. 2014; Meloni 2016; Saulnier and Dupras 2017; see Dupras et al. 2019)? The weight of these questions and the penetration of epigenetics into the public sphere resonate with a long-term ethical impetus (ethics is a field that has been growing at an accelerated pace for three centuries) to produce a plethora of work, the pace of which has been increasing exponentially since the 2000s (Dupras et al. 2019; Figure 1).

1.10. Conclusion

The question of generation, in the sense of the formation of living beings, has led to the opposition, and sometimes articulation, of two families of schemes: in an epigenetic scheme, formation is contingent, taking place during growth, interacting with the environment; in a preformationist (or, today, genetic) scheme, formation is determined by constraints that pre-exist conception. The family resemblances are both profound and tenuous: Bonnet's preformation is as distantly related to our contemporary vision of developmental genes as Harvey's epigenesis is to a Waddington's conception of development; preformation and epigenesis, in their various historical meanings, would be "unthinkable today" (Bowler 2001, p. 32).

Each scheme, whether epigenetic or preformationist, responds to the alternative scheme of its time, in a conjugal relationship that is always tumultuous and renewed, and which, notwithstanding the proponents of extreme positions, is characterized by a remarkable fluidity that reflects the intricacy of the objects studied. In the 17th and 18th centuries, epigenesis was first conceived as a model for the formation of a living being by accretion, in opposition to a mechanistic preformationism that put aside the question of formation and reduced it to simple growth. In the 19th century, as cytology developed, the question was revisited in cellular and then nuclear terms. When the hypothesis of material structures in the cell nucleus determining traits crystallized, this vision was referred to as “nuclear preformationism”, and was opposed or articulated by explicitly epigenetic considerations that encouraged us to re-examine the role of the cytoplasm in development and heredity. In between the 19th and 20th centuries, by focusing on the transmission of traits, Mendelian and then classical genetics developed a theory of hard heredity that allowed it to be separated from embryology (dealing with the formation of traits), a separation against which the proponents of soft heredity, whose scheme is based on intergenerational epigenesis, continue to argue. In response to classical genetics, the adjective “epigenetic” was used to simply mean “pertaining to epigenesis” or “non-genetic” – a usage that persists today, notably in a certain understanding of epigenetic heredity (Morange 2020, p. 327). A particular case in point is Waddington, for whom “epigenetic” took on the meaning of “developmental”, and “epigenetics” the meaning of “developmental science” (or developmental genetics), in a quest to reconcile genetics and embryology – as well as overcome a certain neo-Darwinism of his day. In the mid-20th century, molecular biology reshuffled the deck. The production of a molecular gene concept and the specification of gene regulation models led Nanney to translate the relics of the dualism between cytoplasm and nucleus, into a dualism between structural information and modulation of the expression of this information. “Epigenetics” then took on the meaning of gene regulation, a regulation that could eventually be transmitted through mitosis or even meiosis. Epigenetics produces a profusion of terms modeled on genetics, in a lexical derivation whose slow pace – and perhaps capacity for attraction – suggests the long semantic drift of epigenetics from very different concepts and status to the quasi-“genetics bis” it is today (Figure 1.5). In fact, the use of epigenetic terminology boomed at the beginning of the 21st century, in the post-genomic era of “omic” abundance, when biology became eager for explanations of living phenomena other than genetic sequences. Epigenetics became the focal point of 21st-century biology. In molecular biology, epigenetics began to designate – to the dismay of biologists less liberal with this term (Ptashne 2007; see Pearson 2008) – the molecular field of close interactions with DNA, with molecular epigenetics crystallizing as a field revolving around 5mCs and histones as their relationships began to be better understood (before expanding by phagocytosis of other fields, such as small RNA research).

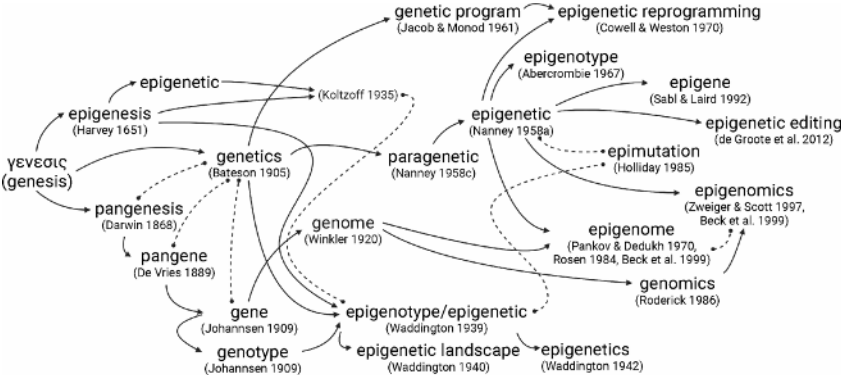

Figure 1.5. *Terminological linkages of epigenetics*

COMMENT ON FIGURE 1.5.– *The arrows represent inkages that are certain (ubiquitous term or direct quotation), the dotted links uncertain linkages. Many terms appear to have been invented several times, and some inventions or linkages may have escaped the author's notice. This tree does not represent conceptual linkage, which is partially decoupled from terminology. Nanney (1958c): see Ephrussi (1958) and Haig (2004). Koltzoff (1935): see Morange (2011). Holliday (1985): see Holliday (1987) citing Waddington (1956b), although a linkage via Nanney (1958a) also seems plausible. Cowell and Weston (1970): see also Lederberg (1966, 1967, cell reprogramming), Nirenberg (1967, cell programming), Gurdon and Woodland (1968, cytoplasmic chromosome reprogramming), Tsanev and Sendov (1971, epigenetic code and cell reprogramming) and Brandt (2010, review). Created with BioRender.com.*

Several components of meaning thus emerge that trace the contours of epigenetics more than they define it, none of which are entirely necessary or independent of the others: the non-genetic (or the non-nucleic, the non-sequential, etc., in an abundance of negative definitions), soft heredity, development, gene regulation (whether heritable or not through cell division), or even what we might call, after Lederberg, the epinucleic, or perhaps more aptly the "perinucleic" (the molecular domain of close interactions with nucleic acids). Some of these components of meaning are functional (epigenetic would be anything that produces traits, or, in a more restricted sense, heritable traits, and which does not rely on the DNA sequence); others are material (epigenetic would be anything that clings to DNA). The terminological drift that epigenetics has undergone is thus accompanied by a constant change in meaning, with some approaches being explicitly contradictory, concerning the requisite of heritability in particular (e.g. Bird 2007; *contra* Deans and Maggert 2015). Faced with this polysemy of usage, the scientist's reflex is to forge new definitions – with however low chances of changing usage – which the philosopher-lepidopterist is quick to pin down. Polysemy, ubiquitous in science, can just as easily lead to misunderstandings as to fruitful friction in our attempts to apprehend a vague reality. Putting concepts back into their historical context can give them meaning back – but not *their* meaning back, as history cannot provide access to its raw object in all its irreducible, rich ephemerality. In this respect, epigenetics, like genetics, has had many false ancestors – those venerable predecessors politely quoted without much reading – and the historical quest always seems to have to be the rewriting of a myth. However, the myth here is performative: these false ancestors, living large in their paper existence, end up attracting new readings and substantially influencing the field. The mischievous epigeneticist might see this as the equivalent of "libraries of specificities" transposed into a new reading frame and expressed anew[5].

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[5] Figures were produced with BioRender and R (version 4.2.2) using the ngramr package (Carmody 2023) and Google Books Ngram Viewer, corpus in 2019 (see: http://books.google.com/ngrams). The author thanks the participants of the Collioure workshop (October 15–18, 2021), in particular the editors of the present work for their proofreading and encouragement, as well as Francesca Merlin for nucleating the project. Michel Morange very kindly sent the author a reprint of his article "The relations between genetics and epigenetics". This chapter bears the mark of discussions with Emmanuelle Maciel on the naturalist epigeneticist and with Alexandra Soulier on the biosocial turn. Alexandra Soulier very kindly contributed to the bibliographical research on the creation of epigenetic terms (Figure 1.5) and passed on her best references on ethics. Alexis Boisseau and Jonathan Racine very kindly shared their unpublished work on Waddington. Charles Wolfe very kindly shared his best references on epigenesis and epigenetics. Clémentine Guillot very kindly improved Figure 1.4. Alexandra Soulier, Charles Wolfe and Clémentine Guillot very kindly reviewed an earlier version of this chapter. The author thanks Lou de Barrelles and Osean van Lilivil for their support.

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