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Histories and Meanings of Epigenetics

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We are living through a revolution in our understandings of heredity, or so we are told by the media, buzzing with suggestions that our health and our personalities are determined not just by the genes passed across generations but also by the experiences of our parents and grandparents: the wars and famines they suffered, the psychological traumas they experienced, the foods they ate (Anonymous 2012; Blech 2010; Costandi 2011; Shulevitz 2012; Knapton 2014). These experiences are inscribed and, arguably, inherited through a network of mechanisms that act as 'the molecular memory of past stimuli', modifying gene expression to supplement the slower-changing information encoded in the DNA sequence (Bonasio et al. 2010). The best studied mechanisms are DNA methylation (binding of a small chemical group, CH_3, onto the cytosine base of DNA) and the modifications of histones, proteins that package DNA into nucleosomes and in turn change the spatial conformation of chromatin. But other, less studied mechanisms, in the first place the activity of RNAs of different types, may play equal or even more important roles (Heard and Martienssen 2014).

Epigenetic control of gene expression may have profound implications for biology, medicine and wider society. It may, for example, open up new avenues to explain, predict and treat disease. Furthermore, because phenomena such as pollution, nutrition, stress, deprivation and even parenting are understood to leave marks on our genomes, social scientists have taken great interest in epigenetics (Landecker 2011; Landecker and Panofsky 2013; Meloni

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M. Meloni et al. (eds.), *The Palgrave Handbook of Biology and Society*,
https://doi.org/10.1057/978-1-137-52879-7_8

2016), arguing that epigenetics is 'the missing link between the social and the life sciences' (Meloni 2015) that has 'reignited the nature/nurture discussion' (Lock 2013). More than a hundred years ago, a particular set of historical circumstances separated the 'social' and 'biological' disciplinary epistemological domains, and they remained disconnected—though never entirely (Renwick 2016). Now new ways of thinking in science, in novel social circumstances, may be bringing them together (Meloni et al. 2016).

Yet these high expectations should be treated with caution. The science underpinning this comprehensive epistemological shift is changing daily. Even the supposedly best researched and fundamental epigenetic mechanisms—such as methylation of CpG islands in promoter regions silencing the expression of the relevant gene—appear uncertain (Ngo and Sheppard 2015). And even if epigenetics does turn out to be the unifier bringing together two separate domains of knowledge, it is by no means obvious how the new epistemological space should look, which methods of inquiry should be used or what shape research hypotheses should take (Niewoehner 2015; Newton 2016). A *Nature* editorial extended an invitation to social scientists to join the shared project of bringing the two knowledge domains together, but on biologists' terms and under their leadership (Nature 2012). Epigeneticists, by and large, do not read social science research. Indeed, in their attempts to make sense of their forever shifting research object—the response of the genome to continuous and diverse influences—they draw on cybernetics and physics, rather than social sciences, as sources of models.

The most controversial aspect of this new field is the one that makes epigenetics exciting beyond the laboratory: the possibility that environmental influences, captured in epigenetic marks, may be transferred not just mitotically (cell-to-cell 'epigenetic inheritance') but also, by way of the gametes, to the offspring ('transgenerational epigenetic inheritance'). This proposal challenges many of the fundamental concepts upon which modern biology rests. Firstly, the fertilized egg (zygote) begins its life as a 'blank slate', a union of parental genomes wiped clean of the records of their past lives in the form of epigenetic marks, so that the new organism is in a pluripotent state ready to acquire cellular specialization through development (Reik and Kelsey 2014). Secondly and perhaps more importantly, the proposal of transgenerational epigenetic inheritance contravenes the idea central since the nineteenth century: that there is such a thing as 'heredity' that is by and large stable and is transmitted across generations with a high level of fidelity, regardless of the experiences each generation has or conditions in which it lives (Müller-Wille and Rheinberger 2012). Instead, a heritable epigenome reflects the constantly fluctuating environment: the new organism is seen not as a random combination

of genes making or breaking it in the potentially hostile world, but, rather, a carefully curated collection, an ensemble well prepared for what might await outside.

With all these controversies and open questions, it is no wonder that different actors in the field view the role, significance and history of epigenetics differently. For those who are critical of the existing model of heredity and indeed of the entire framework established by the Modern Synthesis in the 1940s—let us call them 'dissenters'—epigenetics offers an important solution to the question: what can replace the existing 'genetic' model (Jablonka and Lamb 2005; Laland et al. 2014)? For others, epigenetic phenomena are part and parcel of genomics and genetics, important and potentially useful but by no means paradigm-changing. We could call this group 'conformists'. They may accept the transgenerational transmission of epigenetic marks, but even if they do, they will generally argue that it is of limited significance and that the current model of heredity is still valid.[1] 'Dissenters' are more likely to have backgrounds in animal behaviour, evolutionary and developmental biology, ecology and philosophy of biology compared to 'conformists', who by and large come from genetics (Dawkins 2004; Haig 2004; Bird 2013).

While there has been no attempt to write a detailed history of epigenetics, there is no shortage of narratives in circulation. Different views on the significance and role of epigenetics, and in particular of transgenerational epigenetic inheritance, are reflected in the kinds of stories different actors tell. 'Dissenters' tend to view epigenetics as the latest chapter in an alternative and highly provocative history of heredity that may stretch back as far as Jean-Baptiste Lamarck—or even earlier (Gissis and Jablonka 2011; Ho 2014). This narrative reasserts the importance of the 'Neolamarckists' of the early twentieth century, with some proponents going so far as to explain in epigenetic terms those historical experiments that claimed to prove the inheritance of acquired characteristics (Vargas 2009; Vargas et al. 2016). By contrast, 'conformists'—and those who stand in the middle ground—do not go far back. They may look back to the mid-twentieth century and the work of geneticists whose research was considered controversial, for instance, Barbara McClintock and Alexander Brink (see below), to show how genetics withstood and then incorporated knowledge that challenged contemporary dogma (Riggs et al. 1996). But by and large their histories are short: the story of epigenetics is, in their view, contained within the history of genetics.[2] The only points where these two groups meet is the history of the term 'epigenetics' (introduced by the British biologist and polymath Conrad Waddington around 1940, yet, as I will discuss later, in a meaning that does not correspond with today's). Also, both groups tend to agree that epigenetics as understood today begins with

two essays published independently in 1975 that suggested that DNA methylation is involved in the regulation of gene activity (Holliday 1996; Jablonka and Lamb 2005, 128).

So, how should one write the history of epigenetics? In this, preliminary, account of the history of epigenetics, I want to look at both long and short accounts of heredity. I suggest that a long history is useful because it forces us to rethink the standard narrative of heredity, one that privileges the gene. It can also help illuminate certain historical episodes (Graham 2016) or answer larger questions about the relationship between the biological and the political (Meloni 2016). At the same time, such a broad perspective cannot provide a finely grained analysis of the particular conditions—in science but also in society—in which modern epigenetics emerged and, especially, became famous. So this chapter combines both. After an overview of the long history of heredity, I will provide a preliminary overview of modern epigenetics: its early, 'genetic' era, from 1975 to the late 1990s, and its second, 'developmental' or 'human' period, from ca. 2000 onwards. Together, I hope to sketch how epigenetics came to high public prominence, and what kind of larger developments in science and society this prominence reveals.

An Alternative History of Heredity?

Genealogy has always been at the heart of human social relations, yet before the 1800s the making of life was generally understood in terms of generation, a creative process malleable by influences ranging from divine wrath and earthly politics to the diet and emotions of the mother (Shildrick 2000; Buklijas and Hopwood 2008). These influences could change the shape of the child at any point between conception and birth. Similarity between parents and offspring was explained not by shared hereditary traits, but by similar influences acting upon each generation (Hopwood 2009). Although it is today associated with the name of Jean-Baptiste Lamarck, the idea that properties of organisms change under direct environmental influence was common knowledge (Burkhardt 1995). It was only in the mid-nineteenth century that the idea of heredity as a material property similar to the concept of inheritance in law began to gain currency (López-Beltrán 2007). Heredity came to be seen as separated from the circumstances of conception and development, transmitted unchanged across generations and distributed in a predictable manner. But heredity only became a general biological problem when organisms acquired (evolutionary) history and 'the forms of life ceased to be fixed by assumed species boundaries' (Müller-Wille and Rheinberger 2012, 75).

Charles Darwin offered no convincing theory of heredity, although he knew he needed one (Olby 2013). Although Darwin's own tentative concept of 'pangenesis' had Lamarckian undertones—he suggested that a change to one's body simultaneously changed heritable particles, 'gemmules'—a 'hard' concept of heredity insulated from environmental influence increased in popularity during Darwin's lifetime. 'Hard' heredity was central to his cousin Francis Galton's *Hereditary Genius* (1869) argument that humans inherited their characteristics from their ancestors and that their mentality could be improved through 'good breeding' (Kevles 1985). It underpinned pessimistic views of degenerating humankind, first in the 'degeneration theory' popularized by asylum psychiatrists, and then in eugenics, a widely ranging programme for social improvement through the control of reproduction (Pick 1989; Levine and Bashford 2010). Experimental scientists provided biological explanations for these social theories by linking heredity with cell theory. From the 1880s the German zoologist August Weismann persuaded many that the hereditary material contained in the germ cells is insulated from changes taking place in somatic cells (Churchill 2015). In the early 1900s, cell research was brought together with the recently rediscovered laws of inheritance, established by the Bohemian plant breeder Gregor Mendel, in a discipline called genetics. Transmission and distribution of hereditary properties became the core concern of this discipline in its early decades.

Yet this genetic view—one that privileged nucleus and genes, emphasized the constancy of transmitted properties and sidelined development—was not universally accepted. The reasons why 'hard' heredity and genetics were pioneered in the United Kingdom and United States and not in Continental Europe are diverse, to do with institutional organization but also with intellectual traditions and socio-economic structures. The rapid social and demographic changes caused by the industrial revolution, initially in the United Kingdom, inspired not only Friedrich Engels and Karl Marx but also Darwin and Galton, as well as the turn-of-the-century geneticists. In France, 'Mendelism' held little appeal because it went against the ideals of biological research set by physiology, microbiology and embryology (Burian et al. 1988). There, genetics only gained a firm foothold when, around 1940, geneticists internationally were no longer content to study transmission of visible differences between organisms capable of being cross-bred, but rather began to inquire how genes exercise control over the physiological and biochemical properties of the organism (Sapp 1987). In German-speaking countries, institutional, disciplinary and social traditions that favoured a holistic view of biology account for the continuing inclusion of development within genetics as well as interest in the study of cytoplasmic hereditary particles alongside

nuclear genes; there, 'Neo-Lamarckism' persisted at least into the 1920s (Sapp 1987; Harwood 1993). In the newly formed Soviet Union, the debate about heredity played out alongside discussions about the history and future of the working class. While initially the orthodox genetic view won, by the 1930s the balance had swung towards 'soft' inheritance (Graham 2016). This consensus came with the repudiation of any kind of eugenics: humans could only be explained in Marxist terms, not biological ones.

Early twentieth-century Vienna provides perhaps the richest story about the science and politics of 'soft' heredity. In the early 1900s, in Austria-Hungary, many tried to marry Darwin's evolution by natural selection with the inheritance of acquired characteristics (Logan 2013, 52). At the Institute of Experimental Biology ('Vivarium'), Paul Kammerer studied not fruit flies in a highly controlled laboratory but slowly reproducing amphibians in environments of varying temperature and humidity. Kammerer claimed to have permanently changed hereditary properties through environmental modification, but his results were difficult to reproduce and his leftist politics, Jewish origin, complicated personal and social life, as well as lack of institutional backing made him vulnerable. Accusations of scientific fraud were published in *Nature* in August 1926, and Kammerer died, allegedly by his own hand, in September. His death was long understood as an admission of guilt, but recent research indicates that—as suggested by the Soviet media in the late 1920s and then by Arthur Koestler (1971) though without concrete evidence—he might have fallen victim to a right-wing, anti-Semitic conspiracy (Taschwer 2016).

In Vienna, the inheritance of acquired characteristics had an impact that extended beyond the walls of the 'Vivarium' and underpinned the connection between biology and society. Rudolf Goldscheid, the founder of the Sociological Society (1907), agreed with Darwin's theory of evolution by natural selection but disagreed with the Malthusian argument that all organisms have a tendency to reproduce until limited by resources. Instead he proposed that reproductive ability varied in response to environment. A well-adapted variety did not necessarily produce many individuals, but they were of 'high quality'; 'high quality' here referred to parental investment and developmental condition rather than 'good stock' (Exner 2013, 52–6). In 1913, the Society established a Section for Social Biology and Eugenics with Kammerer as the secretary and Julius Tandler, anatomist and Social Democrat, as the chair. In 1919 Tandler became the municipal councillor in charge of health and welfare for the newly elected Social Democratic government of Vienna. The widespread reforms of 'Red' Vienna to improve education, housing, nutrition and health, of all inhabitants but especially children and mothers, were based

in Goldscheid's theories and ultimately in 'Neo-Lamarckism' (Baader 2007; Weindling 2009; Logan 2013). Many famous scholars who lived and worked in early twentieth-century Vienna, such as Sigmund Freud and Karl Popper, remained sympathetic towards a 'Lamarckian' view of inheritance long after it had fallen out of fashion (Slavet 2008; Aronova 2007).

But by the early 1930s, the position of 'soft' inheritance had grown weak nearly everywhere. Countries from Germany to the United States and Sweden used 'hard' heredity as the scientific legitimation for their eugenic programmes (Lombardo 2010; Levine and Bashford 2010; Broberg and Roll-Hansen 2005). Transmission genetics reached its peak in the late 1920s. The 1930s and 1940s are generally regarded as the era when genetics, building on its new interest in natural populations and use of mathematical models, brought in evolutionary theory—changed little since the days of Darwin—as its theoretical foundation. The union between the two fields in the form of the Modern Synthesis refreshed both and gave them unprecedented power. The only exception was in the Soviet Union where political and economic circumstances propelled Trofim Lysenko, a provincial agronomist advocating an outdated concept of heredity, to the position of most powerful scientist in the country (Graham 2016). Although Lysenko's version of 'soft' heredity had very little to do with contemporary science, the association of the inheritance of acquired characteristics with Stalinism and politically directed science influenced the reception of the inheritance of acquired characteristics in the West for decades (Sapp 1987).

And yet, many established scientists at US universities and other publicly funded institutions pursued research programmes that involved changing hereditary properties through environmental modulation. Between the late 1930s and early 1970s, Tracy Sonneborn, a highly respected American geneticist who studied under 'Lamarckist' Herbert Spencer Jennings, investigated the unicellular protozoan *Paramecium*, which exhibits functionally relevant and heritable variations in cell surface configuration yet without genetic difference (Sapp 1987). It was a Sonneborn student, David Nanney, who first defined 'epigenetic control systems' as 'auxiliary mechanisms' (i.e. not in the sequence) 'involved in determining which specificities are to be expressed in any particular cell' (Nanney 1958, 712). He chose the term 'epigenetic' to underline their involvement in development (see below). At the US Army Biological Warfare Laboratories in Fort Detrick, the German émigré Otto Landman forced bacteria to stop building cellular walls by changing the growth medium. He wondered whether the 'environmental modulation of inheritance that we have observed is confined to this rather pathological system in microorganisms or whether other inheritance systems display similar

properties' (Landman and Halle 1963). Others showed that the genome was a reactive, dynamic organ rather than a fixed set of instructions. These, most famously, included plant geneticists working with maize: Barbara McClintock, who observed the effects of transposons, small pieces of DNA that could change their position in the genome, and Alexander Brink, who described paramutation where one allele heritably changed the expression of the other allele on the same locus (Brink 1968; Comfort 2003).

The name most closely associated with epigenetics is that of the British developmental geneticist and experimental embryologist Conrad Hal Waddington (1905–1977), a polymath who supported radical left-wing politics in the 1930s (Peterson 2016). He argued that the heritable capacity to respond to an external stimulus could, after multiple generations, result in individuals capable of response even without the stimulus (Waddington 1942; Gilbert 2000). Waddington introduced the term *epigenetics* to describe mechanisms and processes by which, during development (under its historical name, *epigenesis*), genes bring about phenotypic effects (Waddington 1940). Although he is today credited as the 'father of epigenetics', the current understanding of the term has departed from the original definition.

Waddington chaired the successful and large Edinburgh Department of Genetics and persuaded the Medical Research Council (MRC) to establish, in 1965, a laboratory for the causal study of development—or in his words, epigenetics (Robertson 1977). Yet very little research in the (otherwise productive) MRC Epigenetics Research Group was about development, arguably because the contemporary science was all about restriction enzymes, cloning and sequencing of DNA (Holliday 2012). More research needs to be done to elucidate the link between the work of Conrad Waddington—in theoretical and experimental biology but also his broader intellectual and political interests—and contemporary epigenetics. A cursory follow-up of institutional and personal connections reveals that Waddington's deputy, Max Birnstiel (1933–2014), mentored Adrian Bird, whose 1970s work would prove crucial to establishing methylation as the key mechanism for setting gene expression patterns. Also, Birnstiel later established the Institute of Molecular Pathology in Vienna, an institution that would play a central role in the nascent field of epigenetics through the 1990s (Jenuwein 2006; Anonymous 2015; Grunstein and Bird 2015).[3]

All of these stories show that a past in which belief in the gene—and the DNA sequence—as the sole and ultimate source of biological information never really existed. Of course, 'soft' inheritance, in the form that existed in the early twentieth century when it opposed genetics, was not part of scientific canon. Yet, with the consolidation of genetics around 1930, genetic

orthodoxy came to encompass much more than the information contained in the sequence: it was also about interactions between genes, regulation of gene expression, the role of carriers of heredity in the cytoplasm and the actions of the associated enzymes. For all the language of 'breaks' and 'revolutions', with regard to programmes of scientific research, there is much continuity between epigenetics today and twentieth-century genetics. The next section will explain this in detail.

1975 and the Origins of Epigenetics

The 1970s were the heyday of the Modern Synthesis and genetics. This was the decade of the 'selfish gene' and socio-biology, and also the decade of recombinant DNA, typified by the use of bacterial enzymes to cut and stitch together bits of the sequence and express them in experimental organisms to produce clinically and commercially useful protein in bulk. Nothing appears more emblematic of gene-centred biology than recombinant genetics; yet it was from recombinant DNA research that the first observations of phenomena were made that later came to be understood as epigenetic.

These first observations are contained in two papers that, as mentioned in the introduction, feature in most accounts of the history of epigenetics. Both were published in 1975, both by established geneticists, and both engaged with the central question of genetics of the era: how are patterns of gene expression established and maintained? Both reviews proposed, though using different models, that methylation changes gene expression. But both were highly speculative, and neither had much impact at the time of publication; so in both cases their significance was established retroactively.

The first paper was written by the prominent British geneticist Robin Holliday and his PhD student John Pugh (Holliday and Pugh 1975). Holliday, a former Cambridge student, was at that time the head of genetics at the National Institute for Medical Research at Mill Hill, London. Working on the fungus *Ustilago maydis*, Holliday had produced an influential model of genetic recombination ('Holliday junction') before embarking on DNA repair studies. In particular, in this period, Holliday became interested in DNA modification and restriction in bacteria: how enzymes can distinguish between short DNA sequences that are methylated and the same sequences that are unmethylated. It was Pugh who, while working on isolating mutants of *U. maydis* with increased recombination frequency, developed an interest in the possible function of the methylation of cytosine in DNA. This phenomenon, Holliday wrote years later, had been observed a few years earlier in bacteria (where

methylation occurs on both adenine and cytosine), but its function was not understood (Holliday 2011).

The puzzle that Holliday and Pugh attempted to explain was the existence of 'developmental clocks' or how, during development, certain genes are turned on (and then perhaps off too) at specific moments. Their proposal was that (1) methylation had a role in the control of gene expression, (2) de novo methylation was sequence and tissue specific and required a specific DNA methylase enzyme and (3) maintaining a pattern of methylation depended on the existence of an enzyme that recognized hemimethylated sequence and methylated the other strand at the replication fork.

The very same year, another scientist proposed a key role for methylation in gene expression. In terms of disciplinary affiliation, Arthur Riggs described himself as a physical chemist. He began his career by studying *lac* repressor, a protein binding to DNA to repress genes involved in lactose metabolism: this model of how genes are turned on and off had earned François Jacob, Jacques Monod and André Lwoff a Nobel Prize in 1965. Riggs accepted a position at the City of Hope in Duarte, California, a former tuberculosis sanatorium turned biomedical research centre, which entailed establishing a laboratory, but as he later wrote, he had 'no useful ideas' how to proceed with his research. It was the meeting with another City of Hope scientist, Susumu Ohno, which proved a 'light bulb moment'.[4] Ohno, a Japanese-born pioneer of what would become evolutionary cytogenetics, worked on the evolution of sex chromosomes: in 1956 he had proposed that the dense area of chromatin found only in females, called the 'Barr body', was an inactivated X-chromosome (Beutler 2002). But none of the several theories on how inactivation could occur met all the criteria for X inactivation: randomness in some animals and preferential maternal/paternal inactivation in others, reversibility in the next generation and permanence across mitosis (Riggs 1975). Riggs took inspiration from his own earlier work on enzymes and the way that *lac* repressor binds on the outside of DNA and then reads the bases. He combined this research with reports on methylation in bacteria to argue that known properties of bacterial DNA methylation enzymes are ideally suited to explain how inactivation of X occurs (Riggs 1975).

The immediate reception of both Holliday and Pugh's and Riggs' articles was modest. While their arguments were plausible, the texts were highly speculative. Riggs's paper had been rejected by several journals before it found home in a not very prestigious journal. Soon afterwards Riggs struck gold when his collaboration with Keiichi Itakura on the chemical synthesis of short

DNA sequences attracted the attention of Herbert Boyer, pioneer of recombinant genetic technology (Smith Hughes 2011). Their work famously resulted in the commercial production of synthetic insulin and the world's first biotech company, Genentech; this success also took Riggs temporarily away from further work on methylation. By contrast, Holliday, an established scientist, managed to place the paper in *Science*, but his attempts to interest leading developmental biologists in his hypothesis failed (Holliday 2011).

Yet by the early 1980s, experimental support for Riggs' and Holliday's hypotheses accumulated, most prominently through the work of Adrian Bird—whose interest in methylation began during a postdoc with Max Birnstiel—and Edwin Southern in Edinburgh (Bird and Southern 1978; Gitschier 2009). Various phenomena in which the activity of genes was altered came to be explained using methylation: from the expression of retroviruses inserted into DNA genomes to the phenomenon of 'imprinting', where alleles that come from one parent are expressed, and from the other silenced (Jaehner et al. 1982; Reik et al. 1987). By the end of the decade, gene expression control through methylation was no longer a tentative hypothesis, but, rather, an established fact. And it was not just about methylation: the 1980s saw a rise in interest in 'chromatin biology' and recognition that gene expression can be regulated in multiple ways, of which methylation could either be the most important or just the most easily recognizable readout of more comprehensive changes in chromatin shape and density (Lappé and Landecker 2015).

In 1985, Holliday, in a short conference summary, introduced the term 'epimutation' to describe 'heritable changes in gene expression' (Holliday 1985). Holliday was an innovative thinker who viewed the contemporary molecular biology as conceptually impoverished. He echoed Conrad Waddington when he wrote about the need to focus on the 'strategy of genes' in the control of gene expression (Holliday 1989, 16). Yet when he wrote about inheritance and heritability, he referred to the cellular level: does the information inherited as cells divide entail more than DNA sequence? Do outside signals change the pattern of gene expression, is this a rejection of the 'central dogma' and could we speak of 'Lamarckism at the cellular level' (Holliday 1988, 259)? While he did consider the possibility of the inheritance of methylation patterns and/or chromatin conformation in the germ line, this was never his key concern (Holliday 1987). The first strong argument in favour of 'transgenerational epigenetic inheritance' was put forward around the same time by the Israeli geneticist-turned-historian and philosopher of science, Eva Jablonka, together with the British geneticist Marion Lamb. They

argued, for the first time, that 'the inherited epigenetic changes in the structure of chromatin can influence neo-Darwinian evolution as well as cause a type of 'Lamarckian' inheritance' (Jablonka and Lamb 1989). Lamb and, especially, Jablonka would go on to become the staunchest proponents of epigenetic inheritance, 'dissenters' against the extant paradigm of heredity and evolution (Jablonka and Lamb 2005).

Throughout this period, the term *epigenetic*(*s*) was still used—if at all—in Waddington's sense, to denote causal mechanisms at work in development. Holliday defined 'epigenetic' as 'changes in gene activity *during development*'. But Jablonka and Lamb expanded and updated this definition, saying that 'in addition to the instructions coded in the base sequence of DNA, genes can carry and transmit information embedded in the structure and conformation of chromatin. Such information is epigenetic information (…) it will reflect the developmental and functional history of the genes, and it will be involved in their present and future activity' (Jablonka and Lamb 1989). The new meaning of *epigenetic*, as a catch-all term to describe anything around and on, but not within, the sequence began to gain popularity soon afterwards.

Could, then, 1975, and these two articles, be regarded as the beginnings of epigenetics? They were the first papers to suggest methylation as a mechanism for regulation of gene expression in vertebrates. Methylation would then go on to become the best studied, and best known, epigenetic mechanism. The story of papers rejected by journals and ignored by peers until much later also fits into a narrative of innovation ahead of its time. With his suggestions of epigenetic inheritance, Holliday's work was of interest to 'dissenters'. In that sense, 1975 appeals across the board.

But if we read these papers closely, then a different picture emerges. The mid-1970s genetics was all about the possibilities opened up by new technologies that used enzymes to cut out and then stick together pieces of DNA. An enzyme, methylase, plays a central role in the two 'methylation' papers too: indeed, we could easily read them not as papers about a mechanism for gene regulation, but rather about the activity of an enzyme acting upon DNA. The abstract of Riggs' article says that 'a key feature of the model is the proposal of sequence-specific DNA methylases that methylate unmethylated sites with great difficulty but easily methylate half-methylated sites'. Pugh and Holliday's paper calls the modification of bases 'enzymic', not 'epigenetic'; the most prominent section of the paper is dedicated to 'modification enzymes'. And in that sense these papers, rather than breaking up with the genetic tradition, make epigenetics firmly part of it.

Of Famines and Ancestors: How Epigenetics Became Famous

By 1996, the field had grown enough to require a book-sized overview of epigenetic research across the range of mechanisms, problems and experimental models: plants, mammals and microbes (Riggs et al. 1996). Riggs and Holliday occupied prominent positions as co-editors (Riggs) and/or authors of several chapters (both). Reprints of their 1975 articles cemented their status as the founding fathers of the field. Though much larger than just ten years previously, epigenetics was still a field practised by geneticists, within departments of genetics, and solving questions that had troubled geneticists for decades. Genetic imprinting, for instance, may be considered the main epigenetic research problem through the late 1980s and 1990s, pursued by multiple research groups. It was also the question that had puzzled geneticists for decades: a non-random inheritance process defying the rules of classical Mendelian inheritance. But in the early 2000s, several groups studying problems directly relevant to human health, located in or closely connected to medical schools and using mammalian experimental models, entered the field. Their appearance changed the key questions in the field and its public perception. Through the work of these groups and the publicity that they received, epigenetics both became a household name and attracted much controversy.

Of these, three would become the best known: Michael Skinner's laboratory at Washington State University, Michael Meaney and Moshe Szyf's group at McGill in Montreal and the Southampton group (Skinner and Anway 2005; Weaver et al. 2002; Lillycrop et al. 2005). Michael Skinner came into epigenetics from reproductive toxicology, where he studied how exposure to certain chemicals, in particular those acting on the endocrine system, changes the reproductive function of affected animals and their offspring. Michael Meaney's long-term interest in how early life events—and in particular parental care—influence later-life response to stress was in the early 2000s turned into an epigenetic problem. A crucial component was the collaboration with Moshe Szyf, a geneticist with a long-term interest in the reversibility of epigenetic marks and its clinical applications: the development of 'epigenetic drugs' that would reverse pathological chromatin modifications (Szyf 2009). Meaney's research, with its focus on psychological stress, emotions and parent-child relationships, later extended to intergenerational trauma, attracted the most attention both by media and social scientists—and most controversy, for its focus on maternal care (Richardson et al. 2014). Finally, the Southampton group was originally a foetal physiology laboratory that in the early 1990s was central to the establishment of the field of 'developmental origins of health

and disease' (DOHaD). The field originated in observations of correlations between conditions of early-life and later-life health in historical cohorts in British public records and turned them into clinical and experimental physiological problems (Gluckman et al. 2015). DOHaD hugely expanded through the 1990s, yet it was also plagued by accusations that it found correlations rather than causations. Epigenetics provided a plausible mechanism to show how events present in early life exerted influences later on. In the process, parental and infant nutrition became recognized as part of the 'molecular environment' of the organism (Landecker 2011).

Disentangling the multiple influences that made epigenetics the buzzword that it is today is a demanding task. Epigenetics is often pitched against genetics—'soft' versus 'hard' heredity—and, certainly, relations between 'new' epigeneticists, in particular those bold enough to advocate transgenerational genetic inheritance, and 'orthodox' geneticists have not always been harmonious.[5] Yet, as this chapter has shown, epigenetics arose from genetics and, largely, remains part of it. The field emerged out of attempts to solve the pressing problem of post-war genetics: the control of gene expression. Although the research of the 'new' epigeneticists applies epigenetic tools to questions intractable to clinical and experimental physiological methods, the rise of epigenetics is perhaps better explained by the limitations of biological knowledge acquired by DNA sequence alone, as exemplified by the Human Genome Project (HGP). As predicted by Evelyn Fox-Keller more than 15 years ago, the completion of the HGP, instead of supporting, undermined the very concept of the gene (Fox-Keller 2000, 5–6). The realization that knowledge of the DNA sequence is just the start of understanding the phenotype fuelled the rise of genomics and epigenetics. The failure of expensive genome-wide association studies, projects focusing on correlating sequence variation with phenotypic (often disease-related) outcomes, has further increased interest in other approaches (Maher 2008).

These are the narrow reasons for the success of epigenetics: but how should we explain the broader change in our outlook? A biological perspective that acknowledges complexity but continues to look inward, into the cell, is easily imaginable. Instead, epigenetics has turned outward to study how our changing environment—food, relationships with people, chemicals—increases the risk of common illnesses and affects reproductive function. This outlook, of course, speaks to the main concern of our times: how we (and what better symbol for us than our genomes?) interact with our environment. Epigenetics is a facet of a larger transformation in biological science towards characterizing the organism as interconnected, plastic, permeable and responsive to changes in its surroundings: a symbiotic community of micro- and macroscopic life. Meloni, Williams et al. (2016) summarize this shift as:

> (1) An unprecedented temporalization, spatialization, permeability to material surroundings, and plasticity of genomic functioning, with profound implications for the notion of heredity; (2) a shift in evolutionary thinking from individualism utilitarianism to the current view of evolution as favouring prosocial behaviours; (3) the increasing understanding that the brain is a multiply connected device profoundly shaped by social influences (…) (4) an increasing emphasis on symbiotic processes (5) a new attention to microbial life and its conceptual implications in terms of networks of ecological interaction.

This is why epigenetics has become so popular among those evolutionary scientists, developmental biologists and philosophers of biology who view the evolutionary model built on the Modern Synthesis as an overly reductionist and unsatisfactory explanation for observed change in the organic world (e.g. Laland et al. 2014). I characterized this very diverse group as 'dissenters' in the introduction to this chapter. Their view of epigenetics does not necessarily correspond with the prevailing position in the field. And yet it holds much appeal. This, I propose, could be seen as an expression of a large shift in biological science, privileging 'connectivity', 'crosstalk' and 'exchange' over one of 'control' that characterized earlier decades.

Notes

1. For example, Richard Dawkins described the inheritance of epigenetic effects as 'a flash in the pan, both in its evolutionary significance and the "15 minutes of fame" which he declares it is enjoying undeservedly' (Webb 2016).
2. Robin Holliday, who can be regarded the founder of modern epigenetics, devotes a short paragraph to the era before Waddington, and that paragraph is mostly about genetics, Morgan and Mendel—and then another short paragraph to Waddington (to say that 'not many scientists were influenced by him') and genetics in the 1960s. See Holliday(2012).
3. 'To Waddington, epigenetics was the study of the way the phenotype was determined by the genotype, and he felt that the only way to get at this was to understand how genes work at the molecular level.' So Birnstiel focused on separating out genes—later moving onto histone genes. See in Grunstein and Bird (2015).
4. An overview of Riggs' early research career at the City of Hope may be found here http://breakthroughs.cityofhope.org/art-riggs-epigenetics
5. So Michael Skinner has been cited to say that one of the forces working against him were 'genetic determinists clinging to an old paradigm' (Interlandi 2013).

Acknowledgements This chapter is an early output of the project titled 'A history of the "epigenetic revolution"', supported by the Royal Society of New Zealand Marsden Fund. I am grateful to the book editors for their valuable comments; to my Liggins Institute colleagues—in the first place Sir Peter Gluckman, Allan Sheppard, Sherry Ngo, Felicia Low and Alan Beedle, and many others—for numerous conversations about epigenetics over the years, and to Klaus Taschwer of *Der Standard*, Vienna, for an insight into media perceptions of epigenetics.

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