Colloids and epigenetic marks: A comparison of two fashions, 1900 and 2000

Ute Deichmann, Jacques Loeb Centre for the History and Philosophy of the Life Sciences, Ben-Gurion University, uted@post.bgu.ac.il

Abstract:

At the beginning of the 20th century a fast-rising new area of research, biocolloidy, began to dominate biological chemistry. Biocolloidists replaced the 19th-century idea of macromolecules with that of colloidal aggregates of small molecules, which were influenced by inorganic ions. At the end of the 20th century another fast-rising area of research, epigenetics, began to call into question the view that the genetic information in the genome is the major cause of heredity and development. In what may be called an extended version of epigenetics, chromatin marks, i.e. small molecules bonded to DNA or histones, form another type of inheritance and are suitable for bringing about a "Lamarckian" kind of evolution. Based on historical sketches of biocolloidy, epigenetics, and extended epigenetics, I will demonstrate similarities in reasoning and attitudes across differences of time, as well as analyze the scientific and philosophical motivation behind them.

Keywords: Epigenetics, chromatin, transcription factors, neo-Lamarckism, modern Lysenkoism, biocolloidy

Introduction:

Looking at the growing calls among evolutionary biologists for a major revision of neo-Darwinism (though for very different reasons) paleobiologist Douglas H. Erwin (2007) concluded that "there is nothing scientists enjoy more than the prospect of a good paradigm shift," referring to the concept of paradigm shifts by historian/philosopher of science Thomas Kuhn. Kuhn (1962), however, had come to the opposite conclusion, namely that "novelty emerges only with difficulty, manifested by resistance, against a background provided by expectation."

Kuhn's view is supported by many cases of scientific change, irrespective of whether or not we accept Kuhn's view of scientific revolution. The slow acceptance of the notion of macromolecules by synthetic organic chemists and biochemists and the

initial opposition to Avery's et al.'s demonstration of DNA as carrier of hereditary properties are examples from 20th century chemistry and biochemistry. However, Erwin's observation that scientists enjoy the prospect of a paradigm shift is prevalent too. As the following shows, claims of the existence of new paradigms seem to be accepted especially fast when these paradigms appear not only to be scientifically desirable, but also psychologically or philosophically.

This is exemplified by two fast-rising fields of bioscience, namely epigenetics and biocolloidy. The rise of epigenetics since the turn of the 21st century has been accompanied by claims that this concept is leading to a "paradigm shift" in almost all fields of biological and medical research, such as genetics, disease and inheritance (Carey, 2011), evolution (Ellington, 2011; Evolution News & Views, 2014: nutrition (Ho and Domann, 2014): and understanding Alzheimer's disease (Zawia and Lahiri, 2012). Epigenetics is used as a major explanatory concept in the fast rising neo-Lamarckism in modern biology (Gissis and Jablonka, 2011).

At the beginning of the 20th century, another fast-growing area of research in biological chemistry, based on the novel theoretical and experimental concepts of biocolloidy, set out to solve problems in the chemistry of life. At the time the terms paradigm or paradigm shift were not yet in vogue. Biocolloidists expected that these concepts would help them find solutions for phenomena that chemistry - at the time - was unable to explain convincingly. Denying the importance of organic chemistry and strong chemical bonds (covalent bonds or their predecessors valency and electron pair bond) for the explanation of basic biological phenomena, biocolloidists claimed that all major biologically relevant molecules, such as proteins and nucleic acids, were colloidal aggregates held together by weak forces, and attributed great biological importance to small molecules and ions.

By comparing the development of biocolloidy and epigenetics as two fashionable areas of research in the past and present, this essay aims at (i) depicting many similarities in scientists' motivations and reasoning despite the differences of time; (ii) understanding how non-scientific predilections influenced and influence researchers' scientific outlook; and (iii) addressing the question of their revolutionary nature. The essay begins with short reviews of developments in biocolloidy and chromatin research before the emergence of epigenetics.

1. A century ago: Chromatin, DNA and the dark age of biocolloidy[1]

Chromatin, nuclein, and DNA until 1900

In 1869 the physiological chemist Friedrich Miescher discovered DNA: He isolated "nuclein", a phosphorus-containing high molecular substance, from the nuclei of lymphocytes. Chemical analyses soon showed that nuclein consisted of an organic acid, which was called nucleic acid (today DNA), and alkaline proteins, which later were called histones. In 1879, cytologist Walther Flemming first described mitosis in detail and introduced the term “chromatin” for the stainable structures in the cell nucleus. Unable to predict the word’s longevity, Flemming suggested that “the word chromatin may stand until its chemical nature is known” (Portugal and Cohen, 1977, p. 40). He believed that chromatin might be identical with nuclein.

In 1888, cytologist and embryologist Theodor Boveri proposed the theory of the continuity of chromosomes over the cell cycle (despite their becoming invisible between cell divisions) and their individuality, i.e. qualitative differences. These theories were of crucial importance for the recognition of chromosomes as causal factors for heredity and development. By the end of the 19th century, cytologist Edmund B. Wilson attributed to nuclein or chromatin a central function in the processes of heredity (Wilson, 1896, as quoted in Sturtevant, 1965, p. 104).

A few scientists shared Wilson's idea of relating heredity to a chemical compound, namely DNA. Most remarkably, Emil Fischer, arguably the most renowned organic chemist at this time, envisioned genetic engineering with artificially synthesized DNA as early as 1914 – he had identified and synthesized the purine and pyrimidine bases which were building blocks of DNA nucleotides. However, within a few years, research into the macromolecular structure and function of chromatin, DNA and proteins declined drastically due to the rise of biocolloidy (Deichmann, 2004; 2007).

The rise of biocolloidy

The term “colloid” was coined by the British chemist Thomas Graham in 1861 to describe the “pseudosolutions” such as silver chloride or starch described by Francesco Selmi in 1854. Colloids were characterized by a low rate of diffusion through membranes that were permeable to salt solutions, a lack of crystallinity and

[1] For a detailed history of chromatin research, see Deichmann 2016.

sedimentation, and a size of at least 1 nm in diameter (in modern terms) and an upper size limit of approximately 1µm. Until around 1900, colloids remained an esoteric topic (Servos 1990, p. 300). Then, a new interest in this topic arose in various areas of research, in particular biology and biochemistry. The resulting biocolloidy rejected the late-19th-century notion of proteins and nuclein (DNA) as large molecules with physical or chemical individualities, claiming instead that they were colloidal aggregates of a changing composition. Physiological chemist Franz Hofmeister compared living systems to gelatine, a colloid. These systems would not follow the chemical laws of solution. According to biochemist Marcel Florkin (1972, pp. 279-280), "its supporters claimed that many biological phenomena such as parthenogenesis, muscle contraction, production of action currents in nerves, heart activity, ciliary movements etc. were influenced by inorganic ions according to a series of degrees of influence of the same series of ions on heat coagulation, on lecithin precipitation etc. The induction that biological phenomena were the results of changes introduced by ions in agglutination, lytic processes, dispersion, hydration or dehydration of colloid micelles believed to compose the protoplasmic 'gel' became widespread."

Biocolloidy strongly affected biochemical research for decades. Research at that time focused on adsorption, aggregation, and the so-called Hofmeister series, all of which are unspecific operations, in biological processes. The structures of enzymes, other proteins, and DNA and their relationship to function were not explored. The following examples illustrate some of the biochemical and genetic research:

- Though one of the few researchers at the time who dealt with polymeric, non-degraded DNA, cytochemist Einar Hammarsten (1972, pp. 279-280) did not examine its properties but explained the biological action of DNA through its ability to act on small environmental changes as a colloid, that is, to increase or reduce its state of aggregation, and thus influence the physico-chemical properties of the nucleoplasm. 15 years later, however, in 1938, he was one of the researchers who established the macromolecular nature of DNA (Deichmann, 2007).

- Biochemist Albert Matthews and Richard Goldschmidt regarded the nucleic acid component of chromosomes as "a colloidal, gelatinous substratum" like an organic skeleton to which the specific hereditary enzymes were adsorbed (Wilson, 1925 (1928), p. 652).

- Chemist and Nobel laureate Richard Willstätter in 1926 (the year in which James B.

Sumner obtained the first crystals of an enzyme, urease, as a pure protein) claimed that enzymatic action was related to a small molecule adsorbed to a large protein compound without catalytic properties. Willstätter assumed that small organic molecules, as chemically active groups bound to large unspecific colloidal material, were responsible for the catalytic process.

Scientific and non-scientific reasons account for the strong and long-lasting rise of biocolloidy. Most organic chemists, with the notable exception of Hermann Staudinger, focused their work on the structures of small molecules or subunits of macromolecules such as nucleotides, amino acids and small peptides. This left a vacuum for speculative research concerning biologically active "high molecular weight substances", which was filled by those physical chemists and biochemists, who were strongly influenced by colloid chemistry. Biocolloidy offered seemingly promising explanations for basic life phenomena which chemists either did not deal with at all or tackled with complicated methods and uncertain results, for example research concerning protein size and structure.

The vision of new, colloidal laws for the phenomena of life was especially appealing to those scientists who had a preference for descriptive research and rejected the idea that basic life phenomena could be explained mechanistically. In addition, the missionary zeal of zoologist-turned-colloidal-scientist Wolfgang Ostwald and his success as discipline builder contributed strongly to the growth of biocolloidy (Deichmann, 2001). Ostwald was a son of the physical chemist and Nobel laureate Wilhelm Ostwald. Wolfgang Ostwald was the main promoter of colloid chemistry in Germany but propagated his views also during an extended lecture tour in the Unites States. He tried to convince his audiences of the importance and fundamental new character of colloid chemistry, arguing that colloids constituted the most universal and the commonest of all things we know; they formed a world of neglected dimensions, a middle country between the chemical and microscopic levels, following special yet undiscovered colloid-chemical laws. Therefore colloid chemistry deserved the right "to existence as a separate and independent science".[2]

[2] Wolfgang Ostwald, *Die Welt der vernachlässigten Dimensionen, Eine Einführung in die moderne Kolloichemie mit besonderer Berücksichtigung ihrer Anwendungen*, Steinkopff, Dresden, 1915, preface and passim.

His best-known book *Die Welt der vernachlässigten Dimensionen* (The world of neglected dimensions) which appeared in German in 1914, was published until 1927 in ten German and three English editions.

One of biocolloidy's first severe critics was experimental biologist Jacques Loeb. Not only did he resent its far reaching speculations, but he also disliked it for political reasons. To him, Wolfgang Ostwald's missionary striving for biocolloidy formed "a particularly pernicious basis for 'metaphysical romance'" (Pauly, 1987, p. 46). Loeb's aversion to the vague, speculative and inherently vitalistic concepts of colloid chemists and his concern about their increasing acceptance by American scientists stimulated him to refute these claims by experiment. In a long series of publications on proteins and membrane equilibria, he showed that the physical properties of proteins, such as osmotic pressure and electrical potential, could be derived from existing theories of physical chemistry, such as the Donnan equilibrium and the theory of solution, if the influence of different pH values was taken into account: "It is possible to explain quantitatively the colloidal behavior of proteins on the basis of theoretical mathematical derivations. The so-called colloid chemistry that initially gave the impression of a new chemistry, appears to have been based only on the non-observance of a condition of equilibrium of classical chemistry, at least insofar as proteins are concerned." (Loeb, 1923) This sharp statement shows the gap between biocolloidists and some of their critics.

Further developments

Colloid biochemistry had brought about a renewed emphasis on surface phenomena and adsorption, and it led to the development of some laboratory techniques such as the ultracentrifuge, which later proved fertile for molecular biological research. But biocolloidists' basic concepts proved untenable.

In addition, despite the fact that the concept of colloidal aggregates heavily relied on the existence of intra or intermolecular weak forces, these forces were not explored further by biocolloidists. The first explanation of hydrogen bonds, based on quantum mechanics, was given in 1935 by Linus Pauling who in 1936 successfully used this concept to explain the three-dimensional structure, function, and specificity of proteins. His hypothesis was based on the notion of proteins being macromolecules characterized by the sequence of their building blocks, amino acids. In 1952 he proposed the α-helix as a structural element in globular proteins, stabilized by

hydrogen bonds; a year later James Watson and Francis Crick suggested the double helix structure of DNA, with the two chains linked by hydrogen bonds. Biocolloidy had no part in the emergence of molecular biology, and the current study of colloidal phenomena, for example at the level of nano-particles, is not a result of the earlier biocolloidy.

The overall evaluation of the era of biocolloidy by prominent scientists such as Loeb, Leonor Michaelis, and Fritz Lipmann, was negative. Biochemist-historian Marcel Florkin (1972) was most outspoken. According to him, the search for deeper information on the relations of structure and function was alleviated in "irrelevant theories" related to surface actions, electric charges and adsorption. He called the period in which biocolloidy strongly influenced biologists' and biochemists' work "the dark age of biocolloidy" (pp. 279-280).

Biocolloidy started to decline in the 1930s, following the demonstration of the existence of large molecules by organic chemist Hermann Staudinger and Theodor Svedberg. The latter demonstrated the macromolecular nature of proteins in sedimentation studies using an ultracentrifuge at the end-1920s. The disappearance of biocolloidy marked the beginning of the (macro-)molecular approach in biology.

2. From chromatin to epigenetic marks

The term "epigenetics" has drastically changed its meaning over time; particularly many changes occurred after 2000 (for details see Bird, 2007; Felsenfeld, 2014; Haig, 2011a; and Morange, 2013). The adjective "epigenetic", related, however to "epigenesis" (see below), existed many centuries before the noun "epigenetics". The history of epigenetics can be roughly divided into two sections: a) epigenetics as development and b) epigenetics as biochemistry.

a) Epigenetics as development

In 1942 embryologist Conrad Waddington introduced the term "epigenetics" into modern biology, emphasizing its relationship to the classical concept of "epigenesis". The latter term was coined by William Harvey around 1650 for the conception of development as a gradual process of increasing complexity from initially homogeneous material, an idea that was originally proposed by Aristotle. Epigenesis

contrasted with preformationism, according to which the embryo or parts of it are preformed from origination. The term *genesis* (gr.) can be translated as origin, and *epi* as on or after. It should be emphasized that until the 1990s, no claim was made that phenomena of *epigenesis* and *epigenetics* are inherited.[3]

Waddington defined "epigenetics" as the "whole complex of developmental processes" that lie between "genotype and phenotype". In his characterization of the "epigenotype" he speculated about a biological system in which "concatenations of processes [are] linked together in a network, so that a disturbance at an early stage may gradually cause more and more far-reaching abnormalities in many different organs and tissues" (Waddington, 1942, p. 10). His often cited model of an "epigenetic landscape", illustrating the various developmental pathways a cell might take during differentiation, includes genes which underlie the landscape, acting to structure it. That is to say, according to Waddington, the presence or absence of particular genes determines which path the cell will follow from a certain point of divergence (Waddington, 1957, pp. 19 and 26).

Another conception of "epigenetics" was suggested by microbiologist David Nanney (1958). He distinguished two cellular control systems: first, a "library of specificities" accomplished by template replicating mechanisms based on DNA sequences, the "genetic system", and, second, "auxiliatory mechanisms" which were involved in determining which specificities were to be expressed in a particular cell, i. e., the control of gene expressions. Referring to Waddington's 1942 paper, he called these auxiliatory mechanisms "epigenetic" to "emphasize the reliance of these systems on the genetic systems and to underscore their significance in developmental processes"

[3] An exception was Theodor Boveri, who around 1900, in the frame of the classical concept of epigenesis, contrasted epigenetic characteristics, which he thought were determined by the nucleus - we would call them today "genetic" - with preformed ones in the cytoplasm. Shortly after, he abandoned this distinction completely because he became convinced that the cytoplasmic "preformation", too, was based on nuclear "epigenetic" mechanisms (Deichmann, 2014).

(Nanney 1958, p. 712). Most of his examples were phenomena in micro-organisms, including biochemical processes such as environmentally induced enzyme synthesis.

Research labelled "epigenetics" remained marginal until the end of the millenium (see below). In modern terms, Waddington's understanding of epigenetics can be regarded as a mechanism for the regulation of gene expression. But research that could have been labelled so according to the definitions above, did take place: The operon model of gene regulation in bacteria by Francois Jacob and Jacques Monod (1961) provided the first comprehensive model of such a regulation. It would also fit Nanney's concept of epigenetics. However, from the outset, this research had been part of (molecular) genetic, not epigenetic, research. Moreover, Waddington (in line with all his colleagues) would not have conceived of prokaryotes as organisms which might be relevant for the study of either genetics or development.

Subsequent research on the regulation of gene expression in the development of higher organisms likewise was not labelled epigenetic. It began in the 1960s, carried out by molecular biologists whose focus was on development, most vigorously Eric Davidson (Davidson, 1968, 2014; Morange, 2002, 2013). Convinced that models based on specific repressors, which were developed in bacteria, were not applicable to higher organisms, he postulated non-specific inhibition of gene expression in eukaryotes by histones combined with selective activators (Davidson, 1968, pp. 315-323).

In a theoretical model proposed by Roy Britten and Eric Davidson, various types of genes at different hierarchical levels of regulation interact to control the fates of cells in development through differential gene expression (Britten and Davidson, 1969). This theory not only contained the first detailed model of gene regulation in higher organisms, but also predicted wide evolutionary implications: Fundamental changes in the regulatory regions, which lead to changes in the process of transcription, may result in stable systems of genes that could enable evolutionary novelties. The model, in which the concept of genetic information in the form of DNA sequences was

central, was further developed by experimental research on gene regulation in development and by the study of evolutionary mechanisms for the changes of body plans (Peter and Davidson, 2015; an assessment is in Morange, 2009; see also Wolter, 2013).

b) Epigenetics as biochemistry: DNA methylation and histone marks

Unlike Walther Flemming predicted at the end of the 19th century, the term 'chromatin' did not disappear once its molecular composition was resolved but continued to be used for the complex of DNA with basic proteins, mainly histones. Research into chemical chromatin modifications, in particular histone and DNA marks originated in the 1960s. Research on DNA methylation and histone modifications developed separately from one another for about two decades. Only from the 1990s, this research began to be labelled "epigenetics". For a detailed account of chromatin research, see Deichmann (2015).

Histone modifications

The pioneers of modern chromatin research were Vincent Allfrey and Alfred Mirsky who confirmed the inhibitory effect of histones on transcription and showed that their acetylation and methylation alleviated the inhibition. This work did not have much impact, in part, because it was not clear whether the modifications caused inhibition or just correlated with it (Morange, 2013).

The discovery of nucleosomes in 1973-4 formed the structural origin of modern chromatin research (see e.g. Morange, 2013; Olins and Olins, 2003). Nucleosomes are basic units of the eukaryotic chromatin structure; they consist of approx. 150 bp DNA wrapped around a protein core that is formed by eight histone proteins. However, these first structural studies did not reveal an obvious effect of histone modifications on the overall structure of the nucleosome (Morange, 2013).

New research on chromatin structure modification started in the 1990s. Histone modifications consist of small organic compounds, mostly methyl and acetyl groups. It was shown that the enzymes attaching these groups to the histone tails of nucleosomes are not DNA sequence-specific. In some cases the modifications were shown to be transmitted by cell division, and in rare cases also the germ line. The modifications are not stable and not faithfully copied, and they disappear after a few cell generations. Assumptions that these modifications affect gene activity led to their designation as epigenetic marks (Felsenfeld, 2014). But so far, there are only correlations. What has been shown is that histone acetylation is generated as a consequence of transcription (Felsenfeld, 2014). Whether they precede or follow transcription, histone modifications play an important role in transcription mechanisms, and interference with the modification process has multiple effects on the phenotype (Felsenfeld, 2014).

DNA methylation

DNA methylation studies were initiated in the 1970s by Howard Cedar and Aharon Razin (Deichmann, 2015). Starting in the late 1970s they conducted key experiments in which they showed conclusively that in *in vitro* experiments methylation can cause gene repression and that in animal cells "there is a pattern of methylation and that pattern is maintained from generation to generation" (Cedar, 2014, Naveh-Many and H. Cedar, 1981; Stein et al., 1982a, 1982b).

DNA methylation plays a crucial role in early mammalian development. At an early stage (before the blastocyst stage) massive DNA de-methylation erases almost every methyl group of the DNA (which had been copied from the methylation patterns of the egg and sperm) so that the cells become pluripotent. Only a few especially marked genes, such as imprinted genes, are not de-methylated (except for those cells that are destined to make gametes). Subsequently *de novo* methylation affects almost the

whole genome, except for sequences called CpG islands that are protected (Deaton and Bird, 2011).

According to Howard Cedar, all changes in methylation from the time of implantation are specific changes, directed by transcription factors or repressors. An example is the turning off of pluripotency genes, such as Oct-4, Nanog and Sox, as a pre-requisite for differentiation. Cedar emphasizes that DNA methylation occurs only after genes have been turned off by a sequence-specific repressor protein. The methylation itself does not turn off a gene, because it is not an active repressor, but it renders the repression permanent. Methylation patterns are not inherited from parents, because their methylation patterns are erased.

In the same way that DNA methylation does not turn off genes, the demethylation itself does not turn on a gene, but renders the decision to turn on a gene permanent. The process is initiated by a specific transcription factor. As soon as it touches down on the gene, the machinery to open the chromatin and do demethylation is brought about to this place. “Most people misunderstand the role of methylation.” (Cedar, 2014)

DNA methylation and histone modifications as epigenetic marks

In the 1990s epigenetics became closely associated with DNA methylation, following the discovery of imprinted genes in mice and men (Haig, 2011a). Robin Holliday, who in the 1980s and 90s proposed several extended definitions of epigenetics and was in part responsible for the plurality of meanings of the term (Morange, 2013), proposed that changes in gene expression through (de-)methylation of DNA be called epigenetic. In addition, he strongly promoted the idea that epigenetic defects in germ line cells could be inherited by offspring (Haig, 2011a). Contrary to what Waddington believed, intergenerational heritability was increasingly considered to be a basic property of phenomena of epigenetics.

A decade later modifications of histone proteins were considered to be another mechanism of “epigenetic inheritance” (Haig, 2011a). Epigenetics was now concerned with the transmission of phenotype through mitosis or the germ line by mechanisms that did not involve changes in the DNA sequence (Felsenfeld, 2014). A new definition of epigenetics as "the study of mitotically and meiotically heritable changes in gene function that cannot be explained by changes in DNA sequences" was proposed (Riggs et al. 1996), followed by many others (Felsenfeld, 2014). According to Gary Felsenfeld (2014), most of these definitions do not distinguish between situations in which the modifications may be propagated through cell division, thus helping to maintain a pattern of gene expression, and other cases in which the modifications are simply part of the transcriptional apparatus. Most of these new concepts of epigenetics focus on biochemistry, not on genetic information in the form of DNA sequences.

It should be added that epigenetics, meanwhile, means very different things to different researchers. Large parts of epigenetic research consist of studies on correlations: causation is not analyzed. Other studies examine the involvement of epigenetic factors in gene regulation processes, with the genome as first cause. Ellen Rothenberg holds that “the major players driving changes in the epigenetic landscape (histone marks, chromatin compaction and looping, etc.)” are sequence-specific transcription factors, “as part of the mechanism of their roles in controlling gene expression.” She thinks that “the transcription factors are critical for setting initial positions for histone marks, and then as development proceeds, determining where the patterns of histone marks must change.” In the post-embryonic cells she studies, “these positionings of histone marks as a result of prior differentiation events sit at the crossroads between regulatory past and regulatory future. By affecting DNA accessibility, they create an inertia resistance to change. But when transcription factor ensembles cross the threshold to cause further differentiation, they change the histone

mark distribution, reshaping the epigenetic landscape" (personal communication to the author, 19 August 2015).

Extended epigenetics or the "Epigenetics Hype"

The term "hype about epigenetics" was introduced by Florian Maderspacher (2010) to describe the widespread claims of victory over genes by epigenetics in scientific and popular literature. Similarly, "Epigenetics Hype" here is used for an extended version of epigenetics, i.e. the far-reaching, revolutionary claims of having discovered entirely new mechanisms of heredity and evolution through epigenetics.

Claims that "DNA Is Not Destiny ...The new science of epigenetics rewrites the rules of disease, heredity, and identity" (http://discovermagazine.com/2006/nov/cover) belong to the category of Epigenetics Hype, as do the proclamations of comprehensive paradigm changes in biology through epigenetics, stated in the introduction. The opinion that the idea of soft inheritance - often equated with "Lamarckian inheritance" - will be, or has already been, justified through epigenetics, is a widespread claim of Epigenetics Hype. It is dealt with here in greater detail.

<u>Epigenetics and modern Lamarckism</u>

Statements that epigenetics rehabilitates so-called Lamarckian inheritance have been made in scientific publications - those of the history and philosophy of science, and the popular press. To mention just a few:

In her opening speech at the 111th General Meeting of the American Society for Microbiology, Susan Lindquist (2011), referring to epigenetics, purported the view that "Lamarck was excoriated during his lifetime and ridiculed ever since, but I think he was right."

The Journal of Experimental Zoology in 2009 published an article that belatedly justified Paul Kammerer's early-20th-century highly questionable research on

amphibians, where Kammerer claimed to have found evidence for the inheritance of acquired characteristics, by relating it to epigenetics (Vargas, 2009). He does not mention that Kammerer's experiments, which he conducted in Vienna in the 1920s to support his Lamarckian conviction, could never be reproduced, neither by those who believed that he committed scientific fraud nor by those who did not.

Kammerer's case was also revived by Klaus Taschwer (2013), a journalist in residence at the Max-Planck Institute for the History of Science in Berlin. According to him, Kammerer's suicide in 1926, interpreted by many as an acknowledgement of having committed fraud, marked the end of neo-Lamarckian approaches in Western biology until the advent of epigenetics, and "recent discoveries seem to confirm that epigenetic mechanisms for Lamarckian inheritance (of acquired characteristics) might be plausible." Claims like this one are completely speculative and not supported by any new scientific evidence.

Support for the notion of "Lamarckian inheritance" also comes from industry: Under the headline "Epigenetic inheritance - Lamarck's (partial) rehabilitation", the large German state-funded biotechnology company Biopro claimed that gene expression patterns "are not regulated on the DNA sequence level but rather on the chromatin level" (Biopro, 2014). The article concludes with the statement that "epidemiological studies suggest that environmentally induced properties such as underweight and the low birth weight of humans are inherited epigenetically. This suggests that acquired traits and properties can be inherited. This also reconstitutes (at least partially) Lamarck."

However, even if there was clear evidence of cases of soft inheritance, the term "Lamarckian inheritance" would be inappropriate for most of them, as a brief view of Lamarck's ideas concerning inheritance and evolution shows. Unlike Susan Lindquist stated, Jean-Baptiste Lamarck (1744-1829) was a renowned French naturalist. His work in botany and zoology, his introduction of the term "biology", and his evolutionary theory were widely accepted. Lamarck's evolutionary theory, which he

put forward around 1800, was the first comprehensive theory of organic evolution. It included the notion of progress, i.e. evolution towards higher perfection and complexity, not driven by chance, and consequently the spontaneous generation of lower organisms from non-living material. In this theory he proposed mechanisms for the transformation of species through the inheritance of characteristics that were actively acquired during an organism's lifetime and led to better adaptation: The use or disuse of an organ would lead to its amplification or atrophy, and both would be inherited.

It should be emphasized that the idea of the inheritance of acquired characteristics was not invented by Lamarck. It was already proposed in Greek antiquity, and supported, for example, by Aristotle. It was adopted by most naturalists before and after Lamarck until the early 20th century, including by Charles Darwin, who amended, not replaced it, with the concept of natural selection. However, Darwin did not share Lamarck's conviction of evolution being directed towards greater perfection. The idea of the inheritance of acquired characteristics as a means for adaptation was first rejected by August Weismann in 1883. This gave rise to Weismannian neo-Darwinism in late 19th century, in which Darwinism was stripped of “Lamarckism”. The idea of the inheritance of actively acquired characteristics as a means for adaptation was abandoned by most biologists in the West in the 1920s and 30s with the advent of population genetics, a synthesis of Mendelian genetics and evolutionary theory generated by Ronald Fisher, JBS Haldane, and Sewall Wright.

According to Lamarck, the environmentally induced inherited variations are actively acquired, adaptive changes with a long-lasting impact on evolution. Phenomena of inherited variation related to epigenetic marks do not belong to this category, because: a) They are not actively acquired; b) they are not adaptive (except by chance) and in many cases even detrimental for the organisms; c) epigenetic marks are not stable over many generations and thus do not have a long-lasting impact on evolution.

There are more obstacles to the belief that epigenetics "reconstitutes Lamarck". According to Adrian Bird (2013), there is no hard evidence for the influence of the environment on inherited epigenetic marks: “Because this is something that’s talked about an awful lot, there is the view that the environment influences our epigenome. And I have a skeptical stance on that. Not because I will never believe it no matter what anybody says, but just because I feel there is a great tendency to want it to be true. And I much prefer to see some hard data on that.” Similarly, Howard Cedar (2014) points out: “First of all, we don't know if the environment affects DNA methylation or how it affects it. But there are lots of problems with this idea. The biggest problem is the one of inheritance. The fact that methylation patterns are erased in the early embryo makes it very difficult to explain how an environmental effect could then be inherited to later generations.” In addition to this erasure, the early divergence of germ line and soma cells, as first suggested by Weismann in late 19th century, would prevent the transmission of epigenetic changes in somatic cells through the germ line.

According to EJ Richards (2006), the transmission of environmentally induced or influenced epigenetic changes which are generated in the germ line is possible in principle. But, he continues, "there is no reason to propose that these epialleles will have any adaptive significance, without resorting to the contortion of invoking a parallel induction of epigenetic changes in reproductive and somatic lineages."

In plants the situation is different. Future germ cells arise from somatic cells and epigenetic silencing mechanisms play a big role in development (Henderson and Jacobson, 2007). These phenomena are not examined in the present paper.

Epigenetics and modern Lysenkoism

The most distorted version of Epigenetics Hype is currently developing in Russia, where epigenetics is used to rehabilitate Trofim Lysenko, a Soviet agronomist, who gained political power under Stalin and came to rule Soviet biology for decades.

Rejecting as bourgeois ideas cell theory, Weismann's germ-soma cell separation, and the chromosome theory, Lysenko in the 1930s developed a holistic, pre-scientific concept of heredity. His concept resembled Darwin's pangenesis hypothesis, in which the inheritance of acquired characteristics combined with mass selection played a major role (Deichmann, 2014). His methods were completely unscientific, for example rejecting statistics as a valuable tool of enquiry (Joravsky, 1970). Lysenkoism did not have its roots in Lamarckism but in the ideas of the popular agricultural practitioner Michurin.

Lysenko, supported by Stalin, succeeded in making his "genetics" the only accepted view in the Soviet Union. Not only did he oppress other scientific opinions, but he also denounced disagreeing Soviet biologists and agronomists to the secret police. As a consequence, many of them were imprisoned and murdered. The wave of suppression and murder of dissident scientists that followed Lysenko's rise to power, especially from the late 1940s, has not yet been fully revealed, although it has been analyzed by Zhores A. Medvedev (1969), David Joravsky (1970), and Loren Graham (1993).

Most disturbingly, recent years have seen a rebirth of Lysenkoism in Russia. Conducting research in Russia for his forthcoming book on Lysenko, historian Loren Graham has been following dozens of publications praising Lysenko highly and claiming that his 1930s views were confirmed by modern-day epigenetics, as expressed in titles such as "The truth of Trofim Denisovich Lysenko is confirmed by modern biology" or "A Sensation: Academician Lysenko Turned Out to Be Right!" (Graham, 2014) That is, epigenetics in Russia is now used to rehabilitate work, the methodology of which was already considered unscientific by the standards of the time. According to Loren Graham (1914), some of these Russian scientists praise Lysenko (who rejected any kind of molecular explanations) as "an outstanding natural scientist" who anticipated epigenetics. Moreover, they invoke politics suggesting that Stalin should be lauded for his policies toward science. It should be remembered that

these policies destroyed the flourishing fields of genetics and population genetics in the Soviet Union.

Pointing to Lysenko's incompetence and ignorance of statistical methods, other Russian geneticists strongly oppose these tendencies. However, the trend to rehabilitate Lysenko is supported by "Putin's revival of Soviet attitudes" (Graham, 2014). A new biology textbook with Lysenko's views has been produced by nationalists who are pushing for its adoption in local schools. According to Graham (2014), "the conflict between political views and scientific standpoints is not unique to Russia, as debates over evolution and global warming in the United States illustrate, but Russia throughout its history has been particularly vulnerable to the undermining of science by politics."

3. Comparison of epigenetics with biocolloidy

This comparison relates, in most parts, to the extended version of epigenetics, the Epigenetics Hype.

a) Strong increase within a short period of time

As was the case with biocolloidy, which was marginal before 1900, but grew rapidly thereafter, research labelled "epigenetics" was marginal until 2000 and increased rapidly thereafter. For epigenetics this can be demonstrated quantitatively, using a citation analysis: I compared the number of citations of articles with epigenetics in the title[4] in 1990 and 2013 in the Science Citation Index Expanded of the Web of Science, and found an increase by a factor of 66.5 (table 1). This Citation Index covers over 8,500 major journals across 150 disciplines. To find out whether this increase is specific to epigenetics, I compared it with that of the number of papers with genetics in the title in this period of time and thereby showed that the increase of epigenetics

[4] In this analysis and the following ones I used epigenetic*, not epigenetics, whereby the star stands for all possible endings. I proceeded accordingly with genetic*.

compared to genetics is higher by a factor of 15.8 (table 1). Interestingly, in the same period of time, there is also a significantly stronger increase in papers with epigenetics in the title compared to genetics in the Social Science Citation Index (table 1), which covers over 3,000 journals across 55 social science disciplines. A newly created field, behavioural epigenetics, may account, at least in part, for this increase.

Number of articles with 'genetics' or 'epigenetics' in title	**Web of Science Sci Exp Citation Index**		**Web of Science Soc Sci Citation Index**	
Year	**1990**	**2013**	**1990**	**2013**
Genetics	3388	14159	364	956
Increase by factor	**4.2**		**2.6**	
Epigenetics	21	1929	5	60
Increase by factor	**66.5**		**12**	
Difference	**15.8**		**4.6**	

Table 1. Comparison of the number of articles with genetics and epigenetics in the title in 1990 and 2013 in the Science Citation Index Expanded and the Social Sciences Citation Index of the Web of Science

The increase is not linear: While there is hardly any increase between 1990 and 2000, the number of papers in the sciences and (to a lesser extent) social sciences with "epigenetics" in the title (measured by the ratio of epigenetics/genetics) rises drastically only starting in 2000 (fig. 1 and 2).

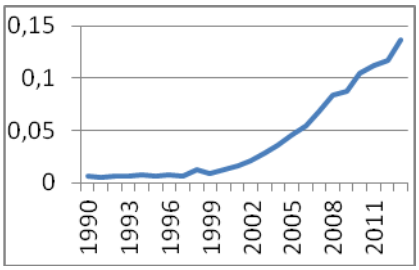

Figure 1: Ratio of "epigenetics" to "genetics" in titles of papers in the Science Citation Index Expanded (of the Web of Science) between 1990 and 2013.

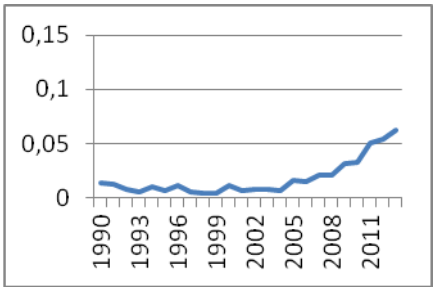

Figure 2: Ratio of "epigenetic" to "genetic" in titles of papers in the Social Sciences Citation Index of the Web of Science between 1990 and 2013.

This late increase seems surprising, given the fact that the term "epigenetics" was already proposed in 1942, and research into DNA methylation and histone modification had been conducted since the 1960s. The fact that during the same period of time, i.e. 1990 to 2013, the number of articles with "chromatin" in the title did not increase more than that with genetics in it (table 2) supports the view that the strong increase of "epigenetics" is not, or not only related to the increase of research on chromatin modifications or DNA methylation.

	Web of Science Sci Citation Index		Web of Science Soc Sci Citation Index	
Year	**1990**	**2013**	**1990**	**2013**
Genetics	3388	14354	363	973
Increase by factor	4.23		2.68	
Chromatin	227	953	0	1
Increase by factor	**4.19**		**-**	
Difference	0.99		-	

Table 2: Ratio of "chromatin" to "genetics" in titles of papers in the Science Citation Index Expanded and the Social Sciences Citation Index of the Web of Science between 1990 and 2013.

Figure 3 shows a boom in chromatin research in the early 1970s, which most probably is explained by the discovery of the nucleosome and expectations at the time that it was not only a structural but also a functional unit.

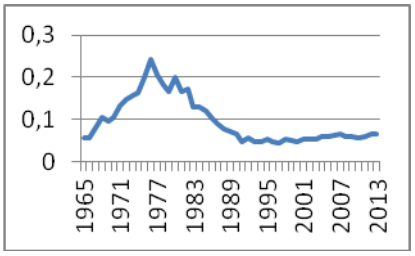

Figure 3: Ratio of "chromatin" to "genetics" in the titles in the Science Citation Index of the Web of Science between 1965 and 2013

b) Offering solutions for unresolved problems

The strong increase in the number of papers with "epigenetics" in their title is, at least in part, due to the fact that epigenetics offers explanations for phenomena which genetics and genomics cannot (yet?) explain, as biocolloidy had done in regard to chemistry. According to Howard Cedar, the strong rise of epigenetics in the last decade is related to the fact that many people were disappointed with the genome project. In many cases, the correlation of inheritable traits or diseases with genes was low. Epigenetics all of a sudden appeared as a solution: "If you don't know the cause, you say it's epigenetic" (2014). Similarly, Adrian Bird (2010) holds: "Epigenetics is a useful word if you don't know what's going on—if you do, you use something else." This view is supported by many unwarranted claims such as in a Nature editorial (2010), in which the explanation for the diversity of life is expected from epigenetics because, allegedly, "genome sequences, within and across species, were too similar to be able to explain [it]." In "The epidemiology of epigenetics", David Haig (2011a) calls the strong increase of the use of "epigenetics" after 2000 a "meteoric rise". According to him, "the indefinite definition of epigenetics (together with the connotation of being 'above' or 'beyond' genetics) has meant that scientists from

divergent disciplines, studying only loosely related phenomena, could all feel they were engaged in epigenetic research near the cutting edge of modern biology."

It can be assumed - and is the opinion of many scientists in the field - that the designation of research as epigenetic clearly helps receive funding. Concerning biocolloidy, it is known that industry supported colloidal science (in addition to chemistry) and that conducting research with the label colloid science helped young scientists receive positions (Deichmann, 2007).

c) Questioning generally accepted principles; revolutionary attitudes

As indicated above, the recent rise of epigenetics has been accompanied by some of its proponents' far-reaching claims and revolutionary attitudes towards well established knowledge, similarly as in biocolloidy. Eva Jablonka's statement (2001) that "Epigenetics is going to have an impact on everything ... because it is a fundamental part of what it means to be a biological creature" is reminiscent of protein biochemist Wolfgang Pauli's claim (1905) that "there is not a chemical, but a colloid-chemical explanation for every single phenomenon in biology and medicine." While biocolloidists claimed to have found new laws of biology, denying the relevance of structural organic chemistry and covalent bonds for biological phenomena, representatives of extended epigenetics claim to have found new principles of hereditary transmission, development, and evolution.

Other scientists raised the concern that statements such as those in the Nature editorial cited above disregard "principles of gene regulation and of evolutionary and developmental biology that have been established during the past 50 years" (Ptashne, Hobert, and Davidson, 2010). They point out that "chromatin 'marks' and local chemical modifications of DNA are the consequences of DNA-sequence-specific interactions of proteins (and RNA) that recruit modifying enzymes to specific targets." Investigators of "epigenomics" expressed their concern about scientists' attributing to the "epigenome" the same value as the genome. They, too, criticize the

non-consideration of established knowledge concerning the importance of sequence-specific DNA recognition events and transcriptional networks in controlling epigenetic changes (Madhani et al., 2008).

d) Focus on short-term mechanisms based on small chemical compounds; fluidity instead of sharp specificity

Colloids, by their very nature, are of varying compositions. Biological specificity such as genetic or enzymatic specificity was usually attributed to small molecules adsorbed to the colloids by weak forces, forming unstable aggregates. The fluidity of processes replaced that of sharp specificities.

Epigenetic marks consist of small molecules, in particular methyl or acetyl groups. The enzymes which bring about DNA methylation or histone modification are not DNA sequence-specific and need DNA sequence-specific proteins to find their locations; in addition, the binding of histone modifications is not stable and the replication of DNA methylation less reliable than DNA replication. Here, too, fluidity superimposed specificity.

The view that epigenetic marks drive gene regulation was rejected by scientists who, like Mark Ptashne (2013) think that this "obviously cannot be true because the enzymes that impose such modifications lack the essential specificity." Gary Felsenfeld (2014) makes it clear that "there is no question that the initial signals to determine the activity state of a gene during development have to come from DNA sequence-specific transcription factors that recognize the regulatory elements associated with the gene."

e) Antipathies towards mechanistic explanations of basic biological phenomena

Most biocolloidists shared an antipathy to a mechanistic interpretation of life, i.e. the idea that basic biological phenomena have their cause in chemical and physical mechanisms. Descriptive research was prevalent; causal mechanistic analyses were marginalized (Deichmann, 2007). Extended epigeneticists share an antipathy towards mechanistic interpretations of development and heredity. The assumption of a multiplicity of causes replaces the idea first brought forward by Boveri and Wilson around 1900, and later supported by developmental genetics that the information in the genome is the major cause for heredity and development. According to Jean Gayon, a new theory of heredity, "extended inheritance", has been promoted, in which DNA (genes) is not the only vector of inheritance, but is complemented by inheritance through epigenetic marks, and ecological and cultural inheritance (Gayon, 2015). Developmental Systems Theory, which was founded before the rise of modern epigenetics, uses epigenetics to relativize the importance of genes and genomes in development. A developmental system, it is claimed, emerges not from the interactions between genes, as is the assumption in developmental genetics, but rather from interactions between "the whole matrix of resources that are required for development" (Griffith and Gray, 2005; Sterelny and Griffith, 1999, p.95). This trend to disregard the predominant role of the genome also marginalizes causal analysis altogether.

It should be emphasized again that epigenetic research is most fruitful in the framework of the genomic control of gene regulation. As was pointed out most clearly by Gary Felsenfeld (2013), the term epigenetics in its modern definition is highly problematic because many of these marks are not transmitted through cell division or the germ line: "Whatever you call them, they are mechanisms for the regulation of gene expression, and that's what you have to study." Similarly, Adrian Bird (2013) believes that the layers of genetics and epigenetics will be dissolved: "So the way in which genetics and epigenetics interact, I think, is dissolving the distinctiveness of epigenetics. And I think that's a good thing."

4. Personal predilections and scientific revolutions

Trying to understand the current wave of neo-Lamarckism, David Haig (2011b) came to the conclusion that "arguments ... often are based on differences of preference and thinking style rather than matters of substance." According to him, modern neo-Lamarckists distinguished themselves, among other things, by preferences for physiological over genetic adaptation and time-scales of a few generations rather than much longer periods. Many of these neo-Lamarckists believe in extended epigenetics to bring about direct, environmentally-mediated adaptation. The idea of a purposeful generation of organisms' harmony with the environment seems to be easier to accept for many than that of heredity and early development being hard-wired in gene-regulatory networks, i.e. mechanisms that do not bring about fast adaptation.

The comparison of biocolloidy and epigenetics shows that speculative personal predilections have strongly impacted on biological research in areas where causal-mechanistic explanations are not yet available. It reminds us of the fact that once-influential concepts such as biocolloidy can be discarded, while other concepts continue to be confirmed over long periods of time, though sometimes with modifications. Examples are the DNA double helix model and its implications for genetic information, replication and mutation, and the principles of differential gene activation and gene regulation in development. It can be detrimental to research to reject novelties without careful examination, but also, to discard well-established principles without sufficient evidence of their failure.

The tendency to, implicitly or explicitly, perceive one's work as revolutionary is another predilection, prevalent among biocolloidists and extended epigeneticists. This leads to the question raised in the beginning: Did biocolloidy and epigenetics bring about a revolution or paradigm shift in the meaning of Thomas Kuhn (1962)? In the beginning of biocolloidy there was a paradigm shift. Its basic concepts were incommensurable with existing notions of the chemistry of life; in addition, its

methods were different. Biocolloidy, at least as far as its basic concepts were concerned, disappeared with the advent of (macro-) molecular biology. The situation is different in regard to epigenetics. There is no revolution in the meaning of Kuhn, because there is no paradigm shift, neither concerning methods nor basic concepts, despite some claims to the contrary. Research into chromatin modification, DNA methylation, etc. did not replace genetic and genomic research, but opened up new areas of research related to gene regulation in eukaryotes. Attempts to replace the basic concept of genomic information as major cause of heredity and development have not been accepted by the majority of researchers.

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