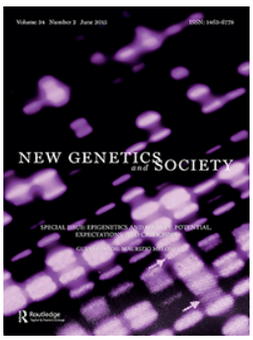

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How the genome got a life span

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In the space of little more than a decade, ideas of the human genome have shifted significantly, with the emergence of the notion that the genome of an individual changes with development, age, disease, environmental inputs, and time. This paper examines the emergence of the genome with a life span, one that experiences drift, instability, and mutability, and a host of other temporal changes. We argue that developments in chromatin biology have provided the basis for this genomic embodiment of experience and exposure. We analyze how time has come to matter for the genome through chromatin, providing analysis of examples in which the human life course is being explored as a set of material changes to chromatin. A genome with a life span aligns the molecular and the experiential in new ways, shifting ideas of life stages, their interrelation, and the temporality of health and disease.

Keywords: environmental epigenetics; embodiment; health; development; aging

The following pages take up the question of how the human genome has come to be seen within the parameters of the human life span: how it got an early life and an old age, and to a more limited degree, an adolescence, middle age, and other stages. The biomedical research developments we analyze connect aspects of life experience over time with molecular states of the epigenome and genome. The key descriptors of these research foci are redolent of change and perpetuation, from parent-of-origin imprinting to epigenetic drift, from metabolic memory to genome instability. We analyze how time and context have come (in)to the genome, opening up fault lines in past understandings of DNA and presenting new questions about its futures both practically and conceptually.

The genomes, human and otherwise, that came into being through the massive sequencing efforts of the 1990s and 2000s, were strikingly implacable. Genomes

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were understood as shaped by evolution and marked by mutation, but in any given individual, the genome was the same in every cell of the body for all of that body's life. The popular and scientific imagery of the double helix ascribed timelessness to DNA; it was simultaneously ancient and present, antique and highly technical. As biologist Robert Pollack told readers in 1995,

> Each of us has always had in each of our cells a DNA text that guided our development from fertilized egg cell to embryo, fetus, and person; it is a precise copy of our sole and complete inheritance, one that is far more ancient than any human artifact. (1995, 17)

Note the temporal structure here: the DNA text stays the same, and from it unfolds the human "embryo, fetus and person." These stages are fleeting manifestations of the ancient artifact that is inherited rather than developed.

Times have changed. We argue in this paper that the life span has come, not just to the epigenome, but to the genome proper. This is because temporal experience is being investigated in the body of chromatin, which by definition is the complex of proteins *and* DNA constituting chromosomes. The study of chromatin allows quantitative measurement of the physical registration of environmental experience originating outside the body as shifts in conformation deep inside cells: changes to the three-dimensional shape of the chromatin fiber. We begin the tale of how the genome got a life span by examining the renaissance in chromatin biology entwined with the rise of developmental epigenetics. We then analyze how the exposure-embodiment pathway opened up by the body of chromatin is experimentally formalized in the study of distinct periods in the human life course, from the periconceptual to old age. Maurizio Meloni and Giuseppe Testa note that a unifying characteristic of epigenetics is the promise to capture the "analogical vastness of … 'environmental signals' … through the digital representation" of their molecular responses as methylation marks or histone modifications – we take this acute observation one step further and ask how the digital readout is being narratively ordered in terms of the human life span (2014, 5).[1]

The history and characterization of the genome with a life span is important to track empirically as it is a significant shift in biological theory of biomedical consequence. At the same time, it is an important analytic for social scientists engaging with contemporary life sciences. This is for two reasons. First, the relationship between the molecular topography of the genome and life experience taken up below opens up new questions about our understandings of health and disease as temporal phenomena. The embodiment of experience and memory in the three-dimensional body of chromatin rather than the mutation of the linear memory of the DNA changes the grounds for understanding health within the life course. In particular, the concept of health with age and its converse, chronic disease and cancer with age and experience, are recast. This logic is consequential at the level of study design and diagnosis, as well as clinical and social interventions, whether pharmaceutical or environmental. Social scientists have long engaged

disease, health, normalcy, and disability as social and historical categories, and with this paper, we bring attention to how these categories are shifting clinically and conceptually. How these findings are mobilized and what responses they elicit will be important questions to track going forward.

Second, distinctions between genome and epigenome (and allied partitioning of genes and environments) are challenged by thinking through a genome with a life span. These distinctions rely in part on an increasingly implausible platonic view of genes and genomes, in which the genome is unchanging and the epigenome is plastic. The analysis and critique of these boundaries is important to the social study of the biosciences. As more scholars seek to understand the implications of epigenetics, the relationships between these "post-genomic" sciences and those that have preceded them become increasingly important to trace. Rather than bracketing off "epigenetics" as its own subject, the relationships between epigenetics and genetics, or epigenomics and genomics, require explicit examination. This distinction between epigenetics and genetics is something to understand and analyze, not to accept as a given framework for our inquiry. We argue here that a close attention to how time has come to matter is central to understanding developments on both sides of the "epi-" divide. The article thus closes with an explicit meditation on the social and categorical work performed by the definition of epigenetics as that which does not impinge on DNA sequence.

To begin: epigenetics in development

It is natural to turn to epigenetics in thinking about how lifetimes matter to genomes. *Epigenetics* is a term already native to early life, derived from the ancient term *epigenesis*, to refer to gradual unfolding of development (Maienschein 2003). In Waddington's adaptation of the term to *epigenetics* in the mid-twentieth century, the sense of an alternative to the idea of preformation was retained; it pointed to something that unfolded over time rather than always having been there. At the same time, the term was modernized to encompass the interaction of genes with one another and with the environment (Haig 2004). Importantly, Waddington's "epigenotype" was an answer to the question of how phenotypic difference arose between cells of the same organism, despite shared genotype (Waddington 1942). Only many decades later was the word epigenetics affixed to a triumvirate of molecular processes – methylation of DNA, histone protein modification, and non-coding RNAs mediating gene expression.

The first of these was the methylation of DNA, the binding of a small chemical group (CH_3) to the cytosine base in the DNA sequence. A number of authors in the 1970s simultaneously theorized methylation as a means of controlling gene expression, by which the specific control settings could be perpetuated through cell division (Holliday and Pugh 1975; Riggs 1975). Early work on methylation concerned patterns of gene expression or repression established in all cells and then maintained going forward. For example, in every female cell, one of two X

chromosomes is highly methylated and becomes heterochromatic. There is transcription from only one of them. This does not have to be reestablished with every cell generation – it begins, and then it persists. Similarly, while there are two alleles of each gene inherited from parents, in the cases of *imprinted genes*, one of those alleles is expressed and the other is silenced. As with X-inactivation, this is not a temporary state, but continues in all the descendants of the cells in which it is established. Which allele is left open and which methylated and heterochromatic is specific to whether the allele came from the male or the female parent, suggesting a "memory" of its parent of origin (Barlow 1995).

Although methylation changes during development were understood as systemic (X-inactivation and imprinting were in every cell in the body), paradoxically there was a percepton of these phenomena as highly specific, even idiosyncratic. The stability of difference was at first seen as a feature of sex – perhaps women were more "mosaic" than men because of X-inactivation (Richardson 2013, 122). Parental imprinting was initially regarded as a minor oddity, concerning a small number of genes and generating rare disorders when it went awry. However, imprinting would come to suggest an alternative model of experience and heredity, and the concept of the "imprint" entered a new stage of use with the development of epigenetic theory, which we turn to now.

How time came to matter in the body of chromatin

Developmental time came to the genome as a material pattern of DNA methylation and chromatin conformation in the last decades of the twentieth century. Developmental time, as historians of embryology have demonstrated, is a temporal system with distinctive conventions of representation of rhythmicity, seriality, and progression (Hopwood 2000; Hopwood, Schaffer, and Secord 2010; Wellmann 2010). It is worth pausing to highlight the material way in which this developmental time previously visualized at the cellular, tissue, or morphological level was now brought to DNA. While a great deal has been written about methylation as a biomarker or a modulator of DNA transcription, little attention has been paid to studies of methylation as temporal schema in which the key words are *persistence* and *perpetuation*.

Developmental time at the DNA level was visualized using bacterial enzymes that cut DNA sequences – nucleases. After the discovery of nucleases in the late 1960s, much happy snipping ensued, along with the search for more enzymes to make "cutting and pasting" more sequence specific. The use of nucleases also led to the close attention to what they were *not* able to cut up in the nucleus. If the chromatin complex of DNA and histone proteins is too tightly wound in a "closed" conformation state, the enzyme is physically blocked from cutting the strand at that point. Mapping the regions of the genome sensitive or resistant to cutting contributed to the ability to represent chromatin as having different states of "open," "relaxed," or "closed." Importantly, it allowed scientists to visualize

these chromatin states changing with time and differentiation. Coupled with chemical methods that could detect methylated cytosines in the DNA sequence, nucleases allowed scientists to trace allele-specific and sequence-specific patterns of methylation and heterochromatic/euchromatic states as they appeared in cells and tissues at particular points in development and persisted from those times onward.

The physicality and experimental tangibility of methylation and chromatin conformation was central in bringing environmentally mediated developmental time to the genome. These physical properties of conformation underwrote a shift from inheritance theories based on mutations in sequence information, to persistence theories based on shape changes in chromatin. Even as DNA sequences were being increasingly technically disembodied by being purified and informaticized (Doyle 1997; Stevens 2013), an important countervailing trend was also being set into motion to re-embody DNA in chromatin, and to re-animate chromatin as the dynamic physical body of the genome. And chromatin needed reanimating, because it had been relegated to a role as inert scaffold for DNA: "the nucleosome and higher order chromatin structures were viewed as essentially static entities of high intrinsic stability within which DNA was sequestered" (Wolffe and Guschin 2000, 102). The change from a static structure to a dynamic body occurred in the literature in more than one way, but a close reading of one important example helps illustrate this theoretical shift, what we are calling a moment when time came to matter.

Eva Jablonka and Marion Lamb's seminal theorization of epigenetic inheritance of acquired characteristics in the late 1980s, a paper called "The Inheritance of Acquired Information," begins with the observation that while "genetic information resides in the sequence of DNA bases," what is actually transmitted from one cell generation to the next is chromatin (1989, 69). DNA base sequence does not change in cells even as they become differentiated through the changed capacity for their genes to be transcribed: "what seems to change is chromatin structure and conformation; it is the *gene's phenotype* which determines its functional state" (1989, emphasis in original, 71). This rather strange locution of the gene's phenotype draws attention to chromatin as the gene's body and behavior. Jablonka and Lamb drew on evidence that sites sensitive to nucleases, once established in a differentiated cell, are clonally inherited by that cell's descendants. Likewise, cytosine methylation is heritable across cell division. And, importantly, these chromatin states can be shifted by environmental inputs – changes in temperature, exposure of an embryo to ether, hormones – and then persist in this changed shape through subsequent cell generations after the stimulus ended.

This depiction of chromatin as an impressionable material was meant to counter the assumption, prevalent with the central dogma, that there was no direct route by which the environment could imprint on DNA. Jablonka and Lamb mobilized the specific case of parent-of-origin imprinting (discussed earlier) as a single instance of a generalized property of chromatin: the ability to pass on information through time via shape. There is much more to say about this hypothesis that the *structure of*

information – not information itself – is transmitted (Landecker 2015). What we wish to highlight here is the contrast drawn between DNA that is mutated versus chromatin that is reshaped after environmental input. The mutation bears no functional relationship to the environmental exposure, whereas the change in shape is called forth in some functionally specific way: it is a logic of imprint, not one of error. These are two different models of memory. Where the linear sequence information can remember only itself (with changes being copied faithfully onward once they occur), the imprint carries experience forward via three-dimensional impressions linked to gene transcriptional responses to experience.

The language of the gene's phenotype did not persist, but key features of the distinction between logics of mutation and those of imprinting remain recognizable today. The genome acquired a dynamic and plastic body with the capacity for epigenetic memory, and that body was chromatin. Of course, a reader acquainted with the field might protest immediately that the dominant register in this research in the twenty-first century has been DNA methylation, not chromatin. We include methylation as a characteristic of chromatin for a number of reasons. First, chromatin is by definition DNA plus the proteins it is wound around. Second, while methylation is often discussed as if it were alone in the cell, this is simply a black-boxing of a technically accessible binary readout at the level of nucleotides (methylated/non-methylated) that presumes a set of connections – even if they are not actually fully fleshed out – in which DNA methylation is linked to histone modification and to the recruitment of other proteins to the DNA surface (including the methylase enzymes that maintain methylation). In short, DNA methylation is part of the *biophysical* alteration of the chromatin fiber through which time and experience come to matter (Black and Whetstine 2014). Biophysical properties in turn are seen to be constitutive of the three-dimensional space that the genome has come to occupy, depicted through a geographical language of landscapes, islands and shores, mesas and canyons, or through the visualization techniques of chromatin conformation capture, live cell imaging, or nanoparticle tracking.

Chromatin biology is now key to explanatory models that see environmental input at one time causing change to the transcriptional potential of the genome later in life. It is being hailed as: "the physiological form of our genome" (Maze, Noh, and Allis 2012, 1), as "the common structural framework for transcriptional control in eukaryotes" (Wolffe and Guschin 2000, 102), and as a platform that integrates, stores, and relays cellular signals onward (Badeaux and Shi 2013). Chromatin has a topography in the nucleus, demonstrating both highly organized spatial organization, and the capacity to move dynamically within chromosome "territories." Calorie restriction, vigorous exercise, or other mild stressors that trigger transcriptional responses are described as positive ways to exercise chromatin (Vaquero and Reinberg 2009).[2] The practical correlate of this focus on chromatin as an architectural, topographical site of impressed memory is the search for pharmaceuticals: "manipulating chromatin structure continues to gain support as a viable avenue for therapeutic intervention to restore cognitive and emotional health" (Roth *et al.* 2009, 767).

In the examples of experimental work on the relationship between environmental exposures and epigenetic persistence given below, having a body is a prerequisite to embodiment (Lock, forthcoming). The rise of chromatin biology as the register of much epigenetic research has opened the door for experience over time, particularly over a lifetime, to impinge on the formerly implacable and sequestered genome. Here we work through examples of research into the intersection of experience and the genome at particular points during the life span, with the caveat that it is somewhat artificial to separate the different phases of life. The research itself may question assumptions of the delimitation of any particular stage. Looping appears between one period and another as the events of one are consequential for another: these are the conditions under which Alzheimer's researchers began to study early life (Lahiri and Maloney 2010; Faulk and Dolinoy 2011) and chronic disease epidemiologists came to focus on fetal development (Barker 1992).

Both the periodization given here and the assumptions about purity with youth and decrepitude with aging are particularly Western and particularly framed by pathology – it is not a universal life span that the genome is attaining but one deeply influenced by the context of the science. It is clear that some life stages matter far more than others to scientists and their funders. Yet it remains useful to see how and why the genome is being experimentally elaborated as temporal within human life – and how a temporal genome is itself shifting comprehension of life stages and life spans. Thus, we move stepwise through periods from the prenatal to the senescent. In so doing, we focus on how experience is being understood to make a physical and lasting impression well beyond its time of occurrence, and how this impressionability is itself theorized as specific to a life stage.

Fetal development

The theory of the developmental origins of adult health and disease underlies research that seeks causal roots for adult chronic disease in the prenatal stage. Following on epidemiological work linking low birth weight with risk of cardiovascular disease later in life, this research provides an important link between the world of human medical phenomena and the world of genes and proteins. At the same time, molecular-level analysis of development as an epigenetic process, in which the histones and DNA in dividing cells are progressively and stably differentially marked, raises the question of the role of the uterine and external milieu in this process. Indeed, we have noted that a common feature in presentation of this research is what we have come to think of as "the toggle," in which the researcher will say "let me turn to *the biology* for a moment." From an outside observer's perspective, this seems funny – were we not talking about the biology all along? But it marks the tethering maneuver in which spatial and temporal scales are being aligned: the time of bodies at a macro scale of physiology or behavior, and the time of molecules at the micro DNA-near scale of genomes

embodied in chromatin are joined by a pivoting presentation that helps fix the physiological or epidemiological manifestation as a gaze directed at a molecular topography (Foucault 1973).

Embryonic and fetal development are intensively studied periods in attempts to toggle between environmental exposure, time, genomic states of becoming, and persistent epigenetic states. This research has generated high volumes of individual analyses of epigenetic processes before and during fetal development within and beyond the womb.[3] However, this vast welter of the literature on epigenetics of embryonic and fetal development may be parsed by asking in each instance the question that animates this paper: how does experience in development become a spatial, material form that can persist into later life stages? The answers to this question point to either (1) metabolic logics and/or (2) hormonal or signaling logics.

Metabolic logics center on the fact that epigenetic modifications, whether they be methylation, acetylation, or the many other possibilities, are only possible because they are provided in the right time, place, and amount by cellular metabolism. One-carbon metabolism, for example, is the source of the methyl groups (CH_3) added to cytosine nucleotides in DNA or to lysine tails of histone proteins in chromatin. Acetylation of histones is likewise possible because intermediary metabolites and the energy are generated in a metabolic process that adds an acetyl group to a protein. At a more distal scale, these substrates come from food.

Therefore, there is a certain focus during this stage on *supply*. The developing organism goes through rapid cell division and differentiation. Cells have to make many new molecules with each replication, and the supply of substrates and energy can have a profound effect on what gets made. There is still much that is not understood about the relationship between supply of epigenetic substrates and their distribution as methylation (Waterland 2014). Nonetheless, this life stage with its large amount of building and modification, is seen as particularly sensitive to diet (Anderson, Sant, and Dolinoy 2012).

Supply logics are complemented by the study of *demand*. One-carbon metabolism is not exclusive to DNA and histone methylation – it contributes to DNA synthesis itself, and is linked into various detoxification processes in the cell. Therefore, the exposure of a developing organism to substances requiring detoxification, such as flame retardants, can create a greater demand for methylation substrates (LaSalle 2014). At the same time, genomes can vary in size because of copy number variation – literally different numbers of bases in one genome versus another. More DNA requires more chromatin and more methylation. Geneticist and autism researcher Janine LaSalle has proposed a "methylome sink" model that sees various factors drawing down the pool of methylation substrates provided by diet. Findings indicate modulation of autism phenotype in children by the use of prenatal folic acid supplements (Surén *et al.* 2013). Work in animal models also points to an interaction between supply of methyl donors and exposure to pollutants such as bisphenol-A and lead (Dolinoy, Huang, and Jirtle 2007).

Thus, metabolism is a very material logic, focused on the stuff out of which genomes and epigenomes are built and maintained. Yet dividing and growing is not the same thing as differentiating. Hormonal or cell signaling logics complement metabolic ones by focusing on the *experience of use* rather than the history of supply and demand. Because the embryo is moving from a state of less differentiation to more differentiation, the developmental signals that driving the transcriptional history of cells as they shift into epigenetically stabilized differentiated forms become important formative moments. One researcher described this as a time in which cells get "personalities" – a vast number of genomic possibilities are mostly foreclosed, while others are potentiated or opened in the chromatin landscape as certain sites are "occupied" by transcription factors and regulatory protein complexes and others are left vacant.[4] *Occupancy* is tracked with increasingly sophisticated techniques to detail exactly which proteins are associated with chromatin and DNA at what times and with what consequences for transcription.

Hormones such as the glucocorticoids involved in stress and immune responses in the maternal body are thought to be important in the immediate moment but also over the long term. Signals elicit responses. The response itself is not what persists, what persists is the "epigenetic memory" of use or disuse of genome areas during development. Even the spatial position of an actively transcribed region of DNA, near the center of the nucleus rather than at the periphery, can be "remembered" in stem daughter cells, meaning that transcriptional activation at one point can under some conditions become the history that drives the future transcriptional activation potential of that locus (Therizols *et al.* 2014). This underlies the meaning of (and the concern about) studies that correlate maternal stress, infection, or obesity with changed methylation or histone acetylation in fetal and infant genomes (for which cells in cord blood is often a proxy).

The phenomenon of "epigenetic memory" is studied for the most part in model organism systems such as yeast and fruit flies, but this is nonetheless seen as a set of basic and conserved mechanisms with homologous molecules and pathways in humans. A recent review of epigenetic memory in fruit fly development argues: "In any biological system with memory, the state of the system depends on its history" (Steffen and Ringrose 2014, 340). Thus, the life history of the organism – its metabolic or signaling history and ensuing transcriptional responses – becomes relevant to understanding the "state of the system" at any later point. And what defines a sensitive or plastic life stage becomes its openness to closure: to the physical imprint of supply, demand, and signals.

Life begins before conception: where to begin with history

The notion of a preconceptual stage extends the abundant attention paid to fetal development into earlier periods of "life." The emergence of the "periconceptual" as a life stage provides an example of the circular relationship between assessing life stages for their effect on genomic becoming, and those material conditions

of genomic becoming as new parameters for life stages. Rather than "prenatal" and "postnatal" as a periodization, some investigators now prefer to study a temporal slice that precedes conception and extends through embryogenesis, spanning conception. This reformulation begs the question: "the life span of what?" The metabolic logic described above is at play in the periodization. Sensitivity to the environment is engendered by the centrality of one-carbon metabolism to the cells that will constitute an offspring's history:

> We define "periconception" as a 5–6 month period in women embracing oocyte growth, fertilization, conceptus formation and development to Week 10 of gestation (coinciding with the closure of the secondary palate in the embryo). During this period significant epigenetic modifications to chromatin occur that correspond with normal development. Subtle variations in 1-C metabolism genes and deficiencies in 1-C substrates/cofactors together with poor lifestyle, such as smoking and alcohol consumption, disturb 1-C metabolism and contribute to subfertility and early miscarriage and compromise offspring health. (Steegers-Thenissen *et al.* 2013, 640)

Gamete life, as much as embryonic life, is part of this historical narrative. Development is not just the development of the embryo after fertilization, but includes oocyte maturation, or gametogenesis. Because the most active phase of ovarian follicular development commences around 14 weeks preconception, the biology of oocyte epigenetic modification is taken as the proper way to define the beginning point for thinking about lifestyle exposures in terms of the health of the oocyte that will become embryo that will become adult with chronic disease.

Indeed, an active research agenda to understand the impact of preconception maternal dietary supplementation with micronutrients on DNA methylation in offspring has complicated the picture of the role of folic acid supplementation considerably (Burdge and Lillycrop 2012). In addition, it has heightened uncertainty about the epigenetic effects of *in vitro* fertilization, both in terms of the effects of ovarian hyperstimulation, and the hours the ova and embryos spend in cell culture medium outside the body (Fleming *et al.* 2004). Of course, epigenetics might be seen as simply late to the table of "parenting from before conception" with all this molecular detail (Lane, Robker, and Robertson 2014). According to sociologist Miranda Waggoner, "expanding the concept of prenatal care to encompass the time before conception" has been in process since the 1980s (2013, 345). This insight pushes us to think about how the available social and medical narratives for what times matter feed into epigenetics, and are in turn transformed from the molecular viewpoint. The preconception health paradigm "promoted an ethic of anticipatory motherhood and conflated women's health with maternal health," which we may now extend to anticipatory *parenthood*, since male gametogenesis is equally likely to be seen as epigenetically significant now that life – or at least relevant life/chromatin history – begins before conception (Waggoner 2013, 345).

Early life

The question of where to draw the line between different stages of life continues to be troubled by studies of postnatal development. Studies in cows, monkeys, and humans indicate that the sex of the fetus *in utero* can influence the composition and quantity of breast milk subsequently produced at birth (Hinde 2007; Powe, Knott, and Conklin-Brittain 2010; Petherick 2010). This implies that fetal life literally sets the stage for its own conditions after birth by an interaction with maternal plasticity. While it has been long understood that breast milk can influence infant development in terms of providing nutrients and antibodies (or "passive immunity"), attention is shifting to breast milk as a different kind of input with the realization that it also contains cell signaling molecules and microRNAs with gene regulatory functions. The molecular profile of milk's signaling molecules shifts over prenatal life in humans and other animals, that is, milk (and therefore, the physiology of its generation) has a developmental temporality too. The kind and amount of cytokines – cell signaling molecules involved in immune responses – have been shown in mice to affect not just immunity in the infant, but to change brain development and "have effects on memory that last into adulthood" (Parylak, Deng, and Gage 2013, 8). Thus, the experience of the signal does not just evoke a response useful to the infant in infancy itself, but persists as a structure of gene transcription, cellular architecture, and brain function.

Indeed, the question of how *early life* experiences and exposures are materialized and persist as physical impressions has been dominated by this kind of attention to postnatal brain development. As with prenatal development, the theoretical basis for understanding early postnatal and childhood periods as "critical" or "optimal" in the establishment of persistent epigenetic change is that these are already periods of profound epigenetic change as it is. It is a developmentally time-specific period in which environmental input is used as a resource for cellular differentiation and functional specialization. For example, research on "critical periods" for visual perception and language development explains the opening and closing of windows of opportunity for learning in terms of a set of molecular triggers that set off reconfiguration of neural circuits and "brakes" that then shut down plasticity, such as epigenetic modifiers that "silence gene programs necessary for synaptic rewiring" through histone deacetylation (Werker and Hensch 2015, 178). In this way, "epigenetic memory" and cognitive memory begin to overlap in the body of chromatin.

With the field being motivated by the search for the causes and origins of adult diseases such as schizophrenia, depression, or neurodegenerative disorders, one can easily forget that environmentally modulated epigenetic changes are not necessarily pathological or risk-enhancing, and in fact environments provide constitutive input from an epigenetic point of view. From model organism studies, it is clear that particular environmental inputs are necessary for differentiation to occur at all. For example, in animals raised in white noise without any pattern,

differentiation and structural change are not triggered in the relevant brain areas for processing sound (Werker and Hensch 2015). Fruit flies raised in food devoid of odor fail to maintain the stem cell progenitors necessary to forming a functional blood system (Shim *et al.* 2013). Patterned sound, odor, light – these inputs trigger epigenetically mediated establishment of differentiated genomes. Along the same lines, juvenile rodents housed in enriched environments (which can mean toys, more complex spaces, and access to exercise wheels) show structural changes to brain cells: increased histone acetylation (thought to be related to more "open" or activated chromatin) in certain brain tissues, more neurogenesis and dendritic branching, which in turn correlates with better performance on cognitive tests, and lowered hormonal response and less extreme behavioral response to stress (Champagne 2010).

This focus on the brain has led to extensive study of molecular correlations with early life stress, deprivation, poverty, and abuse and adult psychiatric disorders in humans. This version of social neuroscience has been discussed extensively elsewhere (Singh 2012; Meloni 2014). With its connection to social disparities in health and issues about "enrichment" of early environments, it is a socially and culturally sensitive issue raising a great deal of interest in all sectors. What our analysis adds to this discussion is to point to the chromatin landscape as both the material ground of investigation and the site of intensive speculation and investment in therapies that can remodel the material of embodied memory. The proof of the pudding in many animal model experiments is the ability to disrupt the epigenetic effects established in early life with the application of histone deacetylase inhibitors or chemicals that disrupt methylation, for example, to make animals forget what they learned in fear conditioning (Champagne 2010). The key characteristics of epigenetic infancy and childhood lie in the phrases that capture the oxymoronic state of the fixation of malleability: it is a time of the "stable change," the "heritable modification," where what is fixed in the midst of plasticity is the site of latent causation.

Adolescence

Distinct but overlapping logics are present in research on epigenetics and adolescence. Mirroring the characterization of adolescence as a unique period of transition in Western culture, epigenetics researchers position this life stage variously as (1) a unique time when the effects of earlier exposures and experiences may become phenotypically expressed, (2) when particular activities or exposures can influence later health, and/or (3) an ideal period for epigenetic research due in part to its transitional nature. In these characterizations, adolescence is a life stage deeply connected to bodies' histories and futures. Researchers report DNA methylation patterns that reflect potential biomarkers (Lévesque *et al.* 2014; Su *et al.* 2014), risks (Biro and Deardorff 2013; van der Knaap *et al*. 2014), and protective factors (Abel and Rissman 2013) for multiple health outcomes ranging from cancer to mental health to obesity to substance use.

As in earlier stages, the state of cellular transformation grounds the periodization and the characterization of the period as sensitive to environmental experience:

> adolescence is a unique period characterized by both physical and emotional development and exposure to novel environmental stressors. It is a period of active brain maturation, characterized by processes such as synaptic pruning, and is the developmental stage when the signs of many psychiatric disorders first manifest. (Dempster *et al.* 2014, 977)

Because human brains are hard to get at, the field is beset by questions about measuring methylation in proxy tissues, and the meaning of methylation as a marker of these complex processes in different cell types in neural tissue. If methylation is more variable in individuals with depression, does this mean "the methylome of the group with depression is generally more reactive to external stimuli or stochastic processes"? (Dempster *et al.* 2014, 981). Adolescents constitute a population exhibiting early symptoms of depression, while not yet influenced by the potential epigenetic effects that medication can confer (Su *et al.* 2014, 7).

The depiction of adolescence as simultaneously pre-disease and post-exposure is also evident in research on substance abuse, where epigenetics is used to identify intermediate processes in the "chains of failure" leading to "problem behavior" (Wills, Sandy, and Yaeger 2000, 1129), and in obesity where links between maternal diet during pregnancy and adolescent adiposity as outcome connect seemingly distinct life stages (Sasaki *et al.* 2014). Obesity researchers also note that "by focusing on youth and young adults at a pre-disease stage, we were optimizing chances to detect disease-specific epigenetic alterations, as presumably they are not yet masked by the background of age-related and medication-arising epigenetic drift" (Su *et al.* 2014, 7). This point positions adolescents as a population not yet affected by epigenetic effects of aging and later exposures, including medication (Su *et al.* 2014). Thus, life stages are imbued with different degrees of "purity" and mobilized as unique opportunities to translate epigenetic findings into health benefits.

Pregnancy

Extensive attention has been paid to the epigenetics of fetal life, but by contrast, "There has been much less attention paid to the effects of pregnancy on the mother, even though epigenetic modifications to chromatin are clearly an important aspect of long-term responses to hormonal signaling" (Best and Carey 2013, 3). Observers of epigenetic research have criticized the focus on the maternal body, concerned that it is producing new forms of surveillance as women become individually responsible for the integrity of the fetus's epigenome *in utero* (Mansfield 2012; Richardson 2015). Yet the epigenetics of the life stage of pregnancy itself is virtually nonexistent. In this sense, the maternal body is not *enough* of a focus – at least not in ways that privilege the epigenetic effects of pregnancy on women's bodies and lives in their own right. Research attention is unequally

allocated in terms of the long-term health of all the bodies involved in pregnancy – and parenting more generally.

Therefore, we cannot point to any examples in which pregnancy is seen to make an epigenetic impression, but must rather point out that the logic we have analyzed in other sections *should* also be active here. The pregnant body undergoes substantial change, with tissue remodeling, an expansion in blood volume by as much as 100%, immunological and metabolic alterations, and large shifts in hormone levels. Health conditions that can arise during pregnancy, such as gestational diabetes and pre-eclampsia have long-term effects for the mother beyond their immediate risks. Women with gestational diabetes have substantially raised risk of going on to develop type-2 diabetes, years or decades later. They are at higher risk of developing pre-eclampsia during pregnancy, a life-threatening condition in which the pregnant woman suffers from extremely high blood pressure. Pre-eclampsia is also a condition that appears with pregnancy and whose symptoms subside after birth, yet it increases the risk of developing hypertension, kidney disease, or stroke in later life (Bellamy *et al.* 2007).

Long-term consequences arising years or decades later might well be manifestations of epigenetic changes. As we have shown, persistent effects of transient stimuli experienced during periods of growth and plasticity, is a hallmark of epigenetic models of explanation for later life effects of earlier life events. What limited evidence there is indicates that children can affect the longevity of their parents, not just the other way around (Relton 2014). Thus, could pregnancy not be understood as a "critical period" relevant to the later life of the woman, not just the fetus? It is not only some times in life that are studied more than others, some epigenomes and genomes are also studied far less than others.

Middle age

Cells' ability to "remember" earlier exposures such as the hyperglycemia of gestational diabetes brings us to research on adulthood or middle age. Here we explore a single example to understand how "epigenetic memory" is being pulled away from its origins as a concept specific to embryonic development and is proliferating into derivative forms in later life stages, in this case "glycaemic memory" or "metabolic memory" in diabetes. Over 30 years ago, a clinical trial called the Diabetes Control and Complications Trial (DCCT) was launched with type I diabetics, to see if intensive blood glucose control would prevent complications of eye, kidney, and nerve tissue damage. Between 1983 and 1993, patients (aged 13–39) practicing intensive monitoring and control were compared to patients practicing "conventional" blood glucose control. Conventional meant that blood glucose was tested less frequently, and less effort was made to adjust blood glucose with insulin in response to food intake and exercise. The results were clear even in 1993 that intensive control led to less development of, and slower progression of the complications of diabetes (Miao *et al.* 2014). The participants were then followed in a second study, the

Epidemiology of Diabetes Interventions and Complications (EDIC), and all began practicing intensive control of blood glucose. This long-standing study has allowed the study of consequences of the different regimes in the 1983–1993 period even after subsequent decades in which all subjects came to equivalent blood glucose levels (Miao *et al.* 2014).

The comparison has yielded a surprise that researchers term "metabolic memory": "Surprisingly, despite nearly equivalent glycemic control during EDIC, subjects in the original DCCT conventional therapy group continued to develop complications at significantly greater rates than participants in the original intensive therapy group" (Miao *et al.* 2014, 1749). This is paradoxical – if high blood glucose is the cause of these pathologies, then normalizing it with insulin should be protective. What happened in the 1983–1993 period that is "remembered" even in a body in which blood glucose is subsequently tightly controlled? Researchers find that the genomes of blood monocytes taken today from patients who were conventionally treated so many years ago show higher levels of histone acetylation in chromatin associated with the promoters of genes involved in inflammatory signaling pathways. This histone acetylation is an "active" mark, promoting transcription. In this explanatory schema, glycemic history is recorded as the potentiality for a chromatin region to be permissive to gene expression later. It is not clear how a blood monocyte in 2014 in a body that experienced hyperglycemia in the 1980s has "remembered" through multiple cell generations that those particular chromatin regions should stay poised for action. Indeed, the authors hypothesize that it is not the modified histone protein itself, but the enzymes that acetylate histones that remain associated with chromatin through cell division, and thus pass on the potentiality (Miao *et al.* 2014).

While this study was specific to diabetes patients, it is an example of a more general sense that experience over time in the form of treatment regimes (pharmaceutical, dietary, or exercise-based) can make a difference to the course of health and disease many years later, long after treatment has ceased or changed. In addition, these are interventions that occur not in fetal life or childhood, but in adolescence and early adulthood, that nevertheless manifest much later. Other studies correlating occupation and genome-wide methylation status or telomere length similarly indicate that long-term stable early adult or adult exposures can become imprinted on the genome in ways that are consequential for post traumatic stress disorder, even if adulthood is understood to be much more fixed than fetal development, childhood, or adolescence (Rusiecki *et al.* 2012).

Old age: epigenetic drift and the epigenetic clock

"Epigenetic drift" is a term that came into the literature in the mid-2000s to refer to progressive and gradual change in the number of methylated cytosines in DNA in genomes across lifetimes. Although cross-sectional studies comparing individuals of different ages far outnumber longitudinal studies looking at methylation in the

same individuals over time, the results are still taken to indicate change with age (Fraga *et. al*. 2005; Bollati *et al.* 2009). Drift can be toward more methylation (hypermethylation) and toward less (hypomethylation), with the two occurring at comparable rates, but the changes are not random; they are gene specific and tissue specific. For example, methylation of imprinted genes seems to "drift" less than other areas of the genome, tissues that proliferate at higher rates show more drift, and gene promoters tend toward hypermethylation. Given the link between methylation and transcription, this means that loss or gain of methylation presumably affects what parts of a genome can be transcribed.

The high correlation between methylation changes and chronological age has been described as an "epigenetic clock" (Horvath 2013). Methylation drift has proved predictable enough to be proposed as a "signature" that could be used as a marker for biological age (Bocklandt *et al.* 2011). A mismatch between the so-called DNAm age and chronological age is presumably larger in those tissues or those individuals who have some cause for accelerated or delayed biological aging. Researchers have observed that the deviations between epigenetic age and chronological age increase after four decades of life. However, it is far from clear what either the cause or the phenotypic and clinical outcome of epigenetic drift is – or what determines the baseline norm from which any one individual will drift more or less slowly. As one author put it quite bluntly: "this biomarker of aging has a major limitation: it is not yet understood what it measures" (Horvath *et al.* 2014, 15542).

The clinical relevance of epigenetic drift is being pursued with great intensity in cancer research, where it is often repeated that the greatest risk factor for cancer is age. Scientists note the similarities between chromatin changes seen in senescent cells (no longer dividing) and those seen in cancer cells. DNA methylation age measures applied to cancer cells show that "tumors appear to have aged 40% more than matched normal tissue from the same individual" (Wagner, Weidner, and Lin 2015, 22). Suppression or inappropriate activation of gene expression can explain changes in cell physiology that are not caused by a sequence mutation. Some of the first work that brought age-specific epigenetic changes to scientific notice showed that cytosine-rich areas of the promoter region of estrogen receptor α, not methylated in young individuals, gain methylation at a rate of 1% every 3 years in human colon tissue, important to understanding the increasing risk with age of colon cancer (Issa *et al.* 1994). Hypermethylation at gene promoters of tumor-suppressor genes has since been found in many cancers; paradoxically, the stability of this aberrant epigenetic silencing through mitotic cell division contributes to cancer development (Jones and Baylin 2007). If it goes awry, it stays awry.

"Drift" implies a passive process. However, many investigators are asking what the effect is of environmental factors on epigenetic drift (Huidobro, Fernandez, and Fraga 2013). Occupational, dietary, or residential exposure to various environmental toxins such as polybrominated flame retardants, arsenic, cadmium, benzene, and air pollution have been correlated with reductions of methylation

of transposable element and repeat sequences (Hou *et al.* 2014). To circle back to early life for a moment, environmental lead exposure in early life has been suggested as a contributing factor to rates of epigenetic drift in later life, and to risk of Alzheimer's disease caused by ensuing destabilization of cellular regulation (Bakulski *et al.* 2012). This work is correlational: it takes a measure of exposure in the past or in the present through whatever proxy is available, and it measures some aspect of methylation in the genome, and it looks for a relation between the two.

Whether accelerated by the environment, or a function of time, "drift" would suggest that shifts in methylation of the genome are progressive losses of the kind often seen as inevitable, sort of like thinning hair or hearing loss. The "epigenetic clock" by comparison points toward a clock mechanism – and a more active view of machine failure. The geneticist Steven Horvath has suggested that loss of methylation over time can be seen as the power of the mechanism for maintaining the methylome. When this mechanism works at lower power, the maintenance of the methylome slows down – which appears as "drift." Thus, it is not so much that methylation is progressively lost, as the rate or power of its maintenance slows. An intriguing source of evidence for this argument is that different cell types in the body that possess different life spans (neurons versus blood cells, for example) nonetheless show the same "epigenetic age" from the same individual. Thus, it is not the age of the cell that determines methylation states, but the power of the mechanisms that have to continually and actively maintain the methylome in every cell, no matter how recently it was generated. At the same time, as we noted above, some biological conditions seem to splinter the unity in epigenetic age across tissues: high body mass index in humans has been correlated with accelerated DNA methylation age specifically in liver cells (Horvath *et al.* 2014). Since obesity is a risk factor for liver cancer, the link between chronological age, epigenetic age, tissue age, and disease is strengthened by these associations.

All these might lead a reader to conclude that the genome has gotten an epigenome. And the epigenome has gotten a life span. However, it is in aging research that the distinctions between epigenome and genome are beginning to be particularly troubled. We sensed this through the repeated appearance of concerns about stability, or more precisely, instability, in the context of discussions of epigenetic age or drift (Lappé and Landecker, forthcoming). We saw repeated juxtaposition of statements about the genome as invariant with discussions of genomic instability, loss of integrity, and disrepair mediated by epigenetic modification of chromatin. For example, one of the functions of methylation in early life is to shut down the transcription of mobile genetic elements (or "jumping genes") and de-repression of these elements with increasing demethylation in aging can lead to their insertions elsewhere, causing new mutations (Maxwell, Burhans, and Curcio 2011). Genomic instability, which is defined as the tendency of the genome to acquire mutations when processes of genetic maintenance and replication are dysfunctional, can arise from jumping genes or from misrepair of DNA strand breaks or damage from UV light or free radicals.[5] Since chromatin has to open for DNA to be

repaired, and epigenetic mechanisms modulate the pairing and drawing apart of chromatids during cell division, the intimate connections between the state of chromatin and the state of the DNA sequence itself belie the oft-repeated definition of epigenetics as being changes to gene function in the absence of DNA sequence change. There are many examples in which change to the epigenome over time is also change to the genome over time. The genome too has a life span. As one scientific speaker we observed put it, "The is no DNA in cells." He let the room sit in silence for a few seconds, and then continued, "There is only chromatin."[6]

Conclusion: epigenetics as "a space to play around in"

Philosopher Jim Griesemer has commented with some puzzlement that the designation of certain molecular phenomena as *epi*genetic was based on the assumption that these modifications did not affect DNA sequence (2002). Methylation, however, is a process that changes cytosine to methylated cytosine, changing the character of the nucleotide base. Indeed, methylated cytosine is sometimes referred to as "the fifth base" in this context. We may equally observe that chromatin, being defined as proteins plus DNA, cannot exist separately from the genome, cannot be a different thing except as an artifact of chemical separation.

Rather than calling out the apparent irrationality of definitional work in epigenetics, however, this constant separation of the manifestly not-separate points toward an important social function for these distinctions. Indeed, as ethnographers, we are constantly being admonished either to not believe the hype of epigenetics or to ignore the blustering "bulwark" of genomics. These admonitions are telling, as the political and social work they do is often to re-emphasize the difference between epigenetics and genetics, exogenous and endogenous, environmental and genetic risks, just at a time when these distinctions are increasingly troubled. As writers, even if we do not want to define epigenetics as "changes in gene expression without change to the underlying DNA sequence," journal editors insist on it, and the mantra of separateness becomes entrenched as a *pro forma* obligatory distinction between changes to the epigenome and changes in the DNA sequences constituting the genome.

Paradoxically, after reading this definition a mind-numbing number of times, and perhaps after reading too many technical explanations of chromatin immunoprecipitation (in which antibodies are used to bring down specific proteins out of solution so they can be analyzed), the *pro forma* suddenly shifted for us and became foundational to explaining how the genome – not just the epigenome – came to have a life span. Paying attention to uses of the distinction between the epigenetic and the genetic worked to "chelate" or highlight certain passages in the mix of our potentially disparate interviews and field notes. We noted that the distinction actually was working as a kind of cushion, allowing a separate space of experimentation and explanation from that of genetics and genomics, allowing the genome to remain invariant while the epigenome varied above it and around it. In a sense, the

separation allowed investigators to hold the genome still (which was not hard, because it had been conceptualized as such) while opening shop just next door.

In a field such as autism research, in which large-scale genomics projects are perceived to have provided some but not enough in the way of answers, environmental epigenetics provides an attractive way to study the "non-genetic," while still remaining within a framework of molecular causal explanation. In genetic epidemiology, "everything that's not coded by your DNA sequence is often lumped into environment," meaning that both chemical exposure and behavioral risk factors are thought of as potential "environments" affecting development in ways that are increasingly cast as epigenetic.[7] Here and elsewhere, a discontent with mainstream genetics in the early 2000s made epigenetics appear an appealing new alternative.

After long and frustrating searches for the genetic explanation of behavioral phenotypes or complex diseases, finding a different source of difference was experienced by many as a new frontier. While an individual's genetics remain "initial conditions," those conditions are seen as invariant. Methylation is another "layer" that is easily collectible, and importantly, is demonstrably variant over time with diet, stress, and disease. As one scientist explained, it is as much a data frontier as a conceptual one: "With genetics you collect one data set. Epigenetics is boundless (laughs). You can take a sample every five minutes."[8]

One academic clinical geneticist whom we interviewed admitted readily that "as a medical geneticist, I think of the genome as a very fixed thing," because "it would make life much more difficult" if it was not. He explained,

> you have a phenotype, which is often severe, and if you find something, is it going to change through time? If you do not find something, should you do test again later, because maybe you were not looking in the right tissue at the right time?

This did not mean, he continued, "that we are right." Between offering diagnoses to patients based on sequence findings, and the conceptual dissatisfaction with genetic explanations of the conditions he studies, the epigenome seemed to offer a third way, "a space to play around in" through research, without disrupting clinical practice.[9]

The definition of epigenetics – changes to gene function without changes in DNA sequence – made the study of methylation of DNA and histone protein modifications appealing to geneticists as the realm of potential change against the backdrop of the unaltered sequence. The result has been a flourishing of studies that formalize environmental exposures over time as a kind of weathering force that wears down the maintenance potential of the epigenome. What we have come to understand is that this area of research simultaneously reinforces the mantra of the separation of the genetic and the epigenetic while increasingly producing data that contradict this very distinction. In the work we have analyzed above, we see the simultaneous insistence on variant epigenomes and invariant genomes, and the steady production of data about epigenomic changes specific

to human life stages linked to genomic instability. Paradoxically, then, it is exactly the separating of the epigenome from the genome conceptually and experimentally that has opened the door through which time and experience have come to the genome itself.

Of course, the genome with a life span matters not only for genomes and epigenomes, but for lives as well. The relationships we are tracing here are both reciprocal and in constant motion as research "toggles" from scale to scale. In the research we have discussed, environments, exposures, and experiences have both temporally specific and potentially lasting effects. How these are narratively ordered and experimentally formalized is increasingly coming to matter beyond the laboratory, as medical and policy decisions build upon these findings (Gorelick 2004; Halfon *et al.* 2014). Together, the cultural conditions and scientific practices of this research may imbue particular phases of life with great importance and obscure others, while at the same time shifting the sense of phase boundaries and their interactions, potentially recasting the meaning of one generation's experiences in relation to another. Close attention to the temporal and spatial contours of these endeavors – when and where they focus, and how they are taken up – constitutes an important critical viewpoint on the long-term shifts traced here, from life as information to lifetime as conformation.

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Notes

1. This paper draws on two research projects, one on causal understandings of autism 2007–2013 (Lappé 2014) and the other studying developments in chromatin biology 2010–2014 (Landecker 2013). In this paper, we draw on our interviews, historical and textual analysis, and ethnographic observations of scientific settings (classes, lectures, conferences, and research practices), as well as review of contemporary scientific literature.

2. We have observed speakers in this field exhorting scientific audiences to "exercise your chromatin," by positive challenges of exercise and eating a wide variety of foods. Landecker, field notes 11.6.14.
3. Another life span has emerged from epigenetic studies of prenatal life, and that is the life span of the placenta. In humans, birth weight is positively correlated with placental weight, and the emphasis on birth weight as a proxy for *in utero* conditions has therefore trained attention on this attendant and mediating organ that comes into being with the fetus, and ages along with it, coming to the end of its life at about 40 weeks of age. It has both its own epigenetic development, with DNA methylation and chromatin modifications changing according to developmental age, and a mediating role in the epigenetics of the fetus. It is both a metabolic and a hormonal organ, and thus the epigenetic modulation of its metabolic processes and signal production in turn plays a role in forming the fetal epigenome. This duality of recipient of environmental imprint and purveyor of environmental information can be seen in the research enthusiasm for the placental epigenome coming as a potential "time capsule of environmental exposures in utero" (Schroeder and LaSalle 2013, 651), that can be harvested at birth and screened for "biomarkers of exposure" to either maternal anxiety, which via glucocorticoids can change gene expression in the placenta, or to maternal diet, which can change the DNA methylation of imprinted genes regulating fetal growth (Hogg *et al.* 2012, 724).
4. Landecker, field notes 1.12.15.
5. This definition comes from the PubMed Mesh term *Genomic Instability*, which was established in 2004.
6. Gordon Hager, during "Dynamics of Transcription Factor Action – The Fourth Dimension," a talk at the UCLA Molecular Biology Institute 2.27.14. Quoted with permission. Hager emphasizes that his work is about the regulation of gene transcription, and does not focus on the epigenetic persistence of chromatin changes. What interests us is the shift in perspective prompted by getting the audience of molecular biologists to see chromatin in their minds instead of just DNA.
7. Lappé, field notes 4.4.09. Interview with a genetic epidemiologist who works in autism research.
8. Landecker, field notes 10.15.14.
9. Landecker and Lappé, field notes 4.21.14. Interview with a clinical geneticist who also conducts research on methylation in human subjects as part of his research.

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