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Epigenetics: Embedded bodies and the molecularisation of biography and milieu

Jörg Niewöhner*

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Abstract: The molecular biological field of epigenetics has recently attracted attention not only in biology, but also in the broader scientific community and the popular press. Commentators paint a very heterogeneous picture with some arguing that epigenetics is nothing but another aspect of gene regulation, and others enthusiastically proclaiming a paradigmatic shift in developmental biology. This article analyses a particular approach to environmental epigenetics – a subfield of epigenetics that is central to the recent excitement. The focus lies on an ethnographic analysis of research practices that enable a particular lab group to study the impact of different levels of context, for example, changes in the social and material environment, on epigenetic modification and thus phenotypic variation. The article argues that changes in the practice of doing epigenetic biology contribute to a *molecularisation of biography and milieu*, suggest the configuration of *somatic sociality* and produce a different concept of the body: the *embedded body*. This article concludes with a brief discussion of *customary biology* as a potential new research agenda at the interface of material and social inquiry.

Keywords: epigenetics, molecularisation, ethnography, embedded body, biosociality

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*joerg.niewoehner@hu-berlin.de; ORCiD: 0000-0002-9034-9761

Epigenetics: Embedded bodies and the molecularisation of biography and milieu

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Introduction

Since the turn of the millennium, the concept of epigenetics has steadily risen from near obscurity to immense popularity in molecular biology, but also in the wider science community and the popular press. Epigenetics has become something of a hot topic. Research findings are being published in science's top journals and the number of prominent reviews that translate these findings into other disciplines has increased steadily. Epigenetics obviously strikes a chord – or better, it strikes several chords for the biological phenomena that are loosely gathered under the concept of epigenetics are interpreted in multiple ways and create excitement in different practices for different reasons. Many biologists today will agree that epigenetics refers to long-term functional change in gene expression through methylation or histone modification and not involving the DNA nucleotide sequence itself (see Appendix for details). Yet what exactly does this mean? To many molecular biologists, epigenetic modifications are little more than another layer of DNA related activity that needs to be taken into account when analysing gene expression. To others, epigenetics is a new, or at least a newly invigorated paradigm in biology that will not only change the way biology studies gene expression and thus disease aetiology, but that also challenges long-established theories of evolution, development and inheritance. And yet another community talks about the biotechnological, medical and economic potential of epigenetic biomarkers in cancer diagnosis, prognosis and therapy. Last, but not least, some quarters of the social science community have become excited about the prospect of a better understanding of the effects of social life on the human body, particularly effects that may be passed on across generations.

This diversity is perhaps not all that unusual. Historians of science have pointed out repeatedly that the concept of the gene has always been tied to particular experimental systems (for example, Rheinberger, 2000). Throughout the twentieth century, the gene has escaped attempts of an all-encompassing definition and proved productive as an epistemic object of exquisite versatility capturing structural, functional and agential aspects of heredity, evolution and self-organisation (Fox Keller, 2006). It is, therefore, not surprising that epigenetics, that is, the science of something that is 'above' or 'beyond'

the genes (Griesemer, 2002), would also benefit or suffer from a similar versatility. The many definitions emanating from the research field of epigenetics attest to this.[1] It is thus not readily transparent where this new field of research is headed and how its findings may affect post-genomics biology more generally or indeed broader patterns of social practice.

A closer look at what is actually going on in this emerging field of epigenetics is warranted. This article provides an analysis of an important subfield of epigenetics – environmental epigenetics – that has been very much at the centre of recent excitement. The research on which this article is based has been conducted in an anthropological mode of inquiry, that is, it is centred around a 3-month laboratory ethnography in Moshe Szyf's epigenetics laboratory at McGill University, Montreal, Canada. Yet, it also draws on a broader historical and discursive analysis of the different facets of epigenetics. The article opens with a brief sketch of recent developments in molecular biology that have begun to incorporate epigenetic phenomena into established post-genomic DNA sequencing approaches. This area of research currently attracts the majority of public and private funding, as well as clinical interest. Emphasising the open question of how best to understand and handle the dynamic nature of epigenetic modification, the article then moves to a detailed analysis of one approach to respond to this dynamic nature: the environmental epigenetics research spearheaded by Moshe Szyf, Michael Meaney and their colleagues primarily in the laboratory 'understanding the epigenome and its developments for anti-cancer therapy' at McGill University's Department of Pharmacology and Therapeutics. The discussion section argues that the research conducted in this lab produces a different kind of body; that the research produces a style of biological research that increasingly molecularises common notions of biography and milieu; and, finally and very briefly, that the social science community, particularly social and cultural anthropology, may benefit in their theoretical development if they let themselves be challenged by these developments to rethink the role of materiality for the patterning of social practice.

Current Research in Epigenetics

Research in epigenetics has a considerable history. The dominant genealogy starting in the 1940s with Cambridge embryologist C.H. Waddington's notion of 'canalisation' in 'epigenetic landscapes' (Waddington, 1957) is well-known and has been told many times by the field itself and its observers (for example, Griesemer, 2002). Genealogies, however, are hardly ever simple, linear tales of progress. This is also the case for the focus of this article: environmental epigenetics. Environmental epigenetics certainly builds on the dominant epigenetics genealogy. In its technologies, laboratory practices and

[1] Of course, such definitions are not mere reflections of research practice. They are strategic interventions. Observers of developments in science and technology are well aware that emergent research fields tend to follow fairly predictable paths of enthusiastically (over)stating their potential to perpetuate dynamism and momentum, as well as creating and meeting expectations in related communities of practice, funding agencies and the wider public (Brown and Michael, 2003).

knowledge about cellular and molecular processes, it also shares relevant genealogies with much of molecular biology more generally. Yet, the theoretical agenda and experimental designs are in many important ways informed by a much broader range of research from epidemiology to neuroscience. Central to environmental epigenetics is the basic idea that environmental contexts have an impact on human physiology. This is almost entirely conceptualised through the notion of *chronic stress*. The long and prolific history of this notion will be familiar to most readers and this is not the place to delve into its manifold contingencies (see, for example, Niewöhner et al, 2008; Niewöhner, 2011). However, as it is so central to the conceptual development of environmental epigenetics, as well as the selection of its molecular targets, let me just very briefly recall three milestones in this complicated genealogy, which have led to today's molecularised concept of chronic stress as 'allostatic load'. In the 1920s, Walter Cannon's work on blood pressure regulation and shell shock (Cannon, 1923) established the idea of *homeostasis*, that is, the body maintains a stable equilibrium vis-à-vis the environment. Hans Selye's concept of the *general adaptation syndrome* postulated distinct physiological stages in response to external stressors: 'fight or flight' (Selye, 1956). His work thus paved the way for the notion of *allostasis*, that is, the body's continuous adaptive responses to maintain homeostasis, which was of particular relevance for scenarios of chronic stress, that is, stress that required the body to respond but not with an all-out fight or flight response. In its most recent neuropsychoendocrinological re-writing, the response to the cumulative impact of all chronic stressors on a given organism has been termed 'allostatic load' and this stress response has been molecularised largely to the brain; more specifically to the glucocorticoid system and its signature hormone cortisol secreted in the body's stress axis of hypothalamus, pituitary and adrenal gland (for example, McEwen, 1998; McEwen, 2008). Therefore, when analysing research today, which tries to correlate within a given population changes in socio-economic status with the methylation of transcription start sites of genes that code for glucocorticoid receptors in the human brain, it is useful to keep Walter Cannon in mind to not lose track of the multiple contingencies folded into this emerging strand of research.

Epigenomics

Throughout the second half of the twentieth century, epigenetic mechanisms have played a role in molecular biological research. Yet, they have largely been sidelined by the dominant research efforts that have put the focus firmly on structural and functional understandings of genes and DNA sequences. While the concept of epigenetics has a considerable history, in its current molecular form it is a relatively young field of research. It really only began to take shape in the early to mid-1990s as a relevant area of genomic research and over the past few years has rapidly advanced to become an important element of investigations into disease aetiology, particularly cancer. Today, the bulk of research efforts on epigenetic modification occurs within the well-established settings of genomic sequencing research (for example, Müller-Wille and Rheinberger, 2009). Technologies and experimental designs developed to map the human genome have

been adapted to deal with methylation patterns. Trying to map the 'methylome', that is, the entirety of methylation marks or the *epigenome*, has thus become one important way of investigating methylation within sequencing research efforts. In its currently most advanced stage, data on the genome and the methylome (and in some cases also the transcriptome) are combined in comparative analyses of healthy and sick subjects, that is, case-control studies following the principle of the well-established genome-wide association studies (for example, Butcher and Beck, 2008). Researchers are hoping that the analysis of large numbers of subjects on the one hand, and, on the other hand, the inclusion of more factors relevant for gene expression, will increase the explanatory power of their studies, that is, enable them to say more about the genomic components of disease aetiologies than they are currently able to do on the basis of DNA sequence[2] alone. A European consortium driven largely by Cambridge-based research centers has begun to talk of 'candidate hepitypes' as the result of overlaying genomic and epigenetic data (Murrell et al, 2005). In the same way that a particular genotype may be seen as causal for a monogenetic disease, a candidate hepitype may play a role for more complex diseases. This research is still at an early stage, but, particularly in the field of cancer research, attracts significant public and private research funds.[3]

For a number of reasons to do, *inter alia*, with the dominant understanding of mutation as a phenomenon that is binary in its functional relevance, the sequencing approach is currently seen by many molecular biologists to hold clinical promise in cancer research. However, there are obvious open questions that cannot be easily answered within this sequencing approach. Epigenetic modifications have been shown to be dynamic phenomena that are responsive to changes not only in cellular but also in organismic and environmental contexts. They are also gene and tissue specific. Thus, attempting to map and sequence epigenetic profiles as if they were binary, static and stable phenomena is not self-evident. It seems fair to say that in much of epigenomics, mapping currently proceeds the way it does primarily because the sequencing consortia's intrinsic logic and dynamic dictates this direction. It is a direction where clinical application and viable markets appear most likely. Yet, it is not in any necessary sense the most plausible way of investigating all aspects of epigenetic phenomena – a scepticism that many of those engaged in sequencing work are very much aware and that many of them share.

This scepticism towards ever larger sequencing studies in the context of epigenetics has become most tangible and explicit in the considerable debate around the 2008 US epigenetics funding initiative, the NIH Roadmap Epigenomics Project, which concentrates almost entirely on mapping the epigenome. Critics have argued,

> 'that this initiative, at least in its current form, will not yield significant benefits. If the use of the term "epigenome" is intended to equate the value

[2]Predominantly single nucleotide polymorphisms (SNPs) and copy number variants (CNVs).

[3]The epigenetics drug market, which is almost entirely based on sequencing research and cancer diagnostics and prognostics, is currently estimated by the company Business Insights to be 'worth over US $560 million derived from the sale of three anticancer products, which target two epigenetic pathways – DNA methyltransferase (DNMT) and histone deacteylase (HDAC) – and around 30 epigenetic drugs (...) under development from more than a dozen biotechnology companies' (Business Insights, 2009; Aldridge, 2010).

> of this Roadmap initiative with the Human Genome Project, it fails [because] it does not consider our current understanding of the roles of sequence-specific DNA recognition events and transcriptional networks in controlling epigenetic changes (...). [M]erely cataloguing modification patterns offers comparatively little new or useful information. We already know that most genes are associated with one of a few patterns of chromatin modifications and that the patterns themselves do not tell us how that gene is regulated or how its expression state is inherited. Most histone modifications are highly dynamic and change rapidly in response to changes in signals that turn genes on or off' (Madhani et al, 2008).

This critique, though to be expected from a science policy perspective, raises important questions about the dynamics and patterning of epigenetic modifications. To what extent and how these questions will be answered at the level of DNA sequence, structure or regulation remains to be seen and marks one of the major challenges in current research on gene expression – genomic and epigenetic alike. Different ways to tackle these questions exist. One of these that has been published with high impact over the past 7 years, is the environmental epigenetics research conducted by Moshe Szyf, Michael Meaney and their colleagues in their laboratories at McGill University to which this article now turns.

Environmental Epigenetics

Environmental epigenetics[4] asks *how* epigenetic modifications are responsive to different contexts. If epigenetic modifications are dynamic and reversible, then what influences their patterning and how does it change over time? Although using basically the same technologies as sequencing projects, the emphasis in environmental epigenetics lies primarily in the integration of *different levels of context* into experimental designs (cf. van Speybroeck, 2000). Environmental epigenetics adds to the long-standing interest in *cellular* context a focus on *organismic* and *environmental* contexts. More specifically, environmental epigenetics asks how individual and social behaviour impact on (patho)physiology through epigenetic pathways. How do changes in the social and material environment have a physiological impact on individuals and on forms of sociality and how may these be passed on to subsequent generations? These are well-established research questions in other research fields, for example, epidemiology. They are now being tackled within a molecular biological framework. Three recent studies in this area have been widely cited within the scientific community and have attracted considerable attention beyond the sciences:

[4]This field of research *in formation* is too heterogeneous to have received a single name or label as yet. Environmental epigenetics is sometimes used by those in the field to describe their own work, yet other labels such as developmental epigenetics or behavioural epigenetics are used interchangeably. This article uses environmental epigenetics and understands environmental to include not only the material but also the socio- and cultural-historical environment as something within which people dwell (Ingold, 2000).

1. In 2003, Rob Waterland and Randy Jirtle at Duke University, Durham, NC, were able to show that feeding a diet rich in methyl-donor nutrients to agouti mouse dams for 2 weeks before mating is able to increase methylation at a particular DNA locus in the offspring influencing coat colour (Waterland and Jirtle, 2003, 2004).

2. The research groups headed by Michael Meaney and Moshe Szyf at McGill University, Montreal, showed that a specific, naturally occurring pattern in nursing behaviour in rats produces hypermethylation of stress-related DNA loci in the offspring and the following generation (Weaver et al, 2004).

3. The McGill groups moved their ideas into human studies demonstrating that differential methylation patterns at functionally relevant sites in the hippocampus also exist in brains from suicide victims relative to controls and in suicide victims, who were abused in their childhood, relative to controls (McGowan et al, 2008).

These studies have attracted attention for two main reasons: (1) they provide a molecular mode of action and a mechanism for the many scientific findings showing the effects of 'chronic stress' on the material body; (2) they suggest that contextually induced alterations of gene expression are semi-stable and may be transmitted across generations. Particularly, the latter point has sparked a substantial debate in evolutionary biology. If the continuity of the germline and one-way information flow from DNA to RNA to protein loses its dogmatic grip on evolutionary biology, the Neo-Darwinian synthesis may need to be rethought and Lamarckian ideas may have to be reconsidered. These aspects of epigenetics have been widely discussed in philosophical biology and biologically informed philosophy and will not be pursued any further in this article.[5] Although note that all transgenerational studies so far show that epigenetic modifications persist only to the generation that has been exposed directly to the stimulus – unless effecting germline cells in the foetus.[6] Attempts to show effects in the first generation not directly exposed have produced negative results (Waterland et al, 2007). The search for transgenerational transmission of epigenetic patterns in the germline continues (for example, Furuhashi et al, 2010).

In this article, I am less concerned with the philosophical implications of emerging epigenetic knowledge. My focus is instead on changes in *doing* biology within environmental epigenetics based on an ethnographic laboratory study. Moshe Szyf's lab is based at McGill University's Department of Pharmacology and Therapeutics and is primarily involved in cancer biology. Moshe Szyf has been working on the role of epigenetic mechanisms in the control of cell proliferation and differentiation in the context of tumour genesis since the 1980s. The lab now comprises not only biologists but also behavioural psychologists, and has recently started to integrate an informatics specialist into a core group of about 10 people. Szyf may count as a bit of a maverick among

[5] For details and extensive discussion, see Griesemer, 2002; Jablonka and Lamb, 2002; Wilkins, 2005; Whitelaw and Whitelaw, 2008.

[6] n studies, exposing pregnant animals to stressors, the F3 generation is the first unexposed. In pre-conception exposure, it is the F2 generation.

mainstream cancer biologists. His style of doing biology is certainly unusual. Hence, I do emphasise here that my claim is not that this group's work is in any way representative of epigenetics research at large. Neither am I arguing that this particular lab is necessarily setting a trend in biological research that others are bound to follow. My point is that their work is interesting to think with. It challenges established biological thinking and practice and also, as I am about to show, social inquiry. Yet saying that their way of doing biology is somewhat unusual is not saying that it is a radical position not shared by anyone else in biology. To the contrary: the lab's research is published in high profile mainstream journals such as *Nature Neuroscience* and *PLoS One*.

The importance of context

Research on the epigenetic regulation of gene expression raises the question of context (cf. van Speybroeck, 2000). Context is primarily a matter of different temporal horizons and spatial scales. In epigenetic research, interpretations of findings often combine evolutionary time, transgenerational or biographic time and the 'real' time of cellular activity in order to construct a plausible argument (see Niewöhner, 2008 for more detail). Spatial context includes 'genomic neighbourhoods', for example, whether a DNA section is matrix-bound or not; the organism, for example, incorporating an organism's metabolic system into an experimental design by feeding methyl-donor enriched diets to mice rather than injecting them directly with methyl groups; and socio-material environments, for example, using data on child-abuse in studies of receptor methylation or changing nesting and bedding material in animal studies to induce stress.

Particular philosophers of biology with an interest in developmental systems theory have pointed out that epigenetics forces biologists to think about genomes in context (van Speybroeck, 2000; Neumann-Held and Rehmann-Sutter, 2006). Context here is not understood within a reductionist mode of thinking that reduces other levels of analysis to feeding into the baseline of DNA sequence. Rather the approach is systemic focusing on the multiple interactions between different levels of analysis. Although at the level of concepts, the researchers in the McGill lab would probably go some way along with this interpretation of genomes in context, their everyday research practice certainly looks very different. Consider one ongoing project in the lab: the lab collaborates with British epidemiologists in charge of the 1958 cohort (for example, Jefferis et al, 2002), a large cohort of children born in 1958 in Britain. Socio-economic data exist from birth to age 40 and blood samples exist at age 40. The aim of the project is to decipher the impact of early-life socio-economic status on epigenetic modification. Initial and as yet unpublished findings indicate that methylation status at a number of sites changes more within subjects that have experienced a change in their socio-economic status from birth to their 40th birthday compared to subjects that retain the same status – even if that is a low status. Thus, epigenetic modification may be more sensitive to relative change than to a low socio-economic status in absolute terms. More important than the preliminary results themselves are the discussions about this project within the group. The project becomes paradigmatic for a research programme, which they describe as a 'molecular

biology of social position'.[7] What does this say about the importance of context? First, such a programmatic calls up temporal contexts, that is, evolutionary and developmental time scales. The foetus is adapted to a certain environment through paternal imprinting, that is, it carries a certain somatised expectation about what life is going to be like, which reflects its parents' life and can be easily extended into evolutionary narratives.[8] Second, the concept of social position makes not only the social and material environment itself relevant for human development. The interpretation of these environments by its inhabitants also plays an important role. Exposure to socially differentiated collectives, is assumed to leave its epigenetic mark on the body during critical windows of development but possibly also in adult life.

The informal discussions within the lab around this latter point have revealed to me two important points. First, and unsurprisingly, reading up on twentieth-century social theory is not seen as the most useful way of advancing epigenetic research. Although there is an interest in learning more about how one may conceptualise social change, this is seen as a matter of clever cooperation rather than reading. Second, most members of the lab concerned with this study are very aware that socio-economic indicators taken from epidemiology are very crude indicators. Given that the lab members understand epigenetic markers to be highly sensitive to all kinds of influences, it makes sense to them that the ideal study would work with a more fine-grained analysis of social change. The structuralist stance that emanates from their writing and their discussions is a very pragmatic stance that is based not on any particularly well-informed social theory, but on the need to work with some form of indicators in their study designs. Hence, the implicit structuralist approach has most to do with the 'pragmatic reductionism' so widespread in the laboratory sciences (Beck and Niewöhner, 2006). And it has to do with the personal interest that many of the lab members take in better understanding the effects of social inequality on health – an issue most commonly problematised in structuralist terms in popular scientific and public discourse.

From black and white to shades of grey: Building thick significance

'There was a time in biology when you did not have to think to get your *Nature* publication. Knock out a gene and see what effect it has. This is over. We are entering an age in biology now where we have to start thinking'. This is the summary that Szyf draws from a lengthy discussion in the lab's morning 'data and journal club' about down- and up-regulation of genes in epigenetics. This comment epitomises a crucial shift in the practice of epigenetic research. The dominant practice in researching the regulation of gene expression not only in this research group has been and continues to be based largely on cancer research. The entire experimental system – materials, methods, analysis, validation – is geared towards cancer with an important consequence: working with knock-out systems and

[7] They have tried to talk about social class but switched to social position after sustained criticism from social scientists that class implies more than is measured with a few epidemiological variables on socio-economic status – if it is a relevant concept in late modern societies at all.

[8] See, for example, the discussions around thrifty phenotypes and genotypes in the context of cardiovascular disease (Niewöhner, 2011).

clonal cell lines produces black and white answers. Typical read-outs from gels or array data show binary results, because all cells in the affected tissue either carry the altered gene or they do not. Thus, the marker under investigation is either expressed in all cells of the sample or not at all. The typical imagery in this experimental system literally shows black bars next to white or light grey bars. Significance is obvious. Shades of grey result either from artefacts and need to be eliminated until results are clear. Or the results are correct and falsify the initial hypothesis.

In the McGill lab, knock-out is only one model, and an extreme one at that. Most of the time, the team deals with knock-down scenarios or rather with instances of up/down-regulation or modulation of gene expression, that is, genes are not switched on or off but regulated up or down to effectively produce more or less of a specific protein. Although it is possible to conceptualise methylation similar to knock-out as a binary phenomenon, that is, a particular DNA sequence site is either methylated or it is not, the McGill lab members pursue a different route: methylation is not uniform across all cells of a cell population. Yet standard methods do not and often cannot work with single cells but rather deal with groups of cells.[9] The lab thus measures methylation as a percentage of all DNA fragments measured. Hence, they do not get black and white answers of 100 per cent or 0 per cent of the sampled cells displaying methylation in the same positions. They are getting percentages – sometimes as low as 5 per cent of cells show methylation. Their approach literally produces shades of grey rather than the familiar black and white bars. Such 'shady' results may make some cancer researchers feel rather uncomfortable because their training predisposes them to look for clear-cut statistical significance and discard everything else.

The key difference to the binary model lies in the assessment of significance of particular findings. In any experimental science, deciding whether some finding is because of chance or some kind of systematic occurrence is vital. Most experimental systems thus employ a system of validation that includes some variant of the standard statistical measure of significance, the 95 per cent confidence interval. In fact, it is one of the key characteristics of a stable experimental system that it controls conditions such that the outcome variable only varies along a dimension that can be accurately assessed using relatively straightforward measures of statistical significance. And it is often an important art in a lab group to configure the results such that statistically significant figures can be presented.

The notion of significance and its assessment works a little differently in the McGill group and this difference relates directly to the kind of research questions that are being asked. Of course, the standard scientific criteria are well-known, respected and applied wherever possible. Yet rather than discarding the 'shady' results from cell populations, which are heterogeneous with respect to methylation, and designing experiments from which to expect more straightforward results, the group insists that this lack of clarity 'makes biological sense' as Szyf comments. The group regularly discusses studies that

[9] Single cell capture does exist as a valid approach but it is a highly resource intensive and thus expensive procedure that is rarely used, particularly not in countries where graduate students and lab technicians wages form a significant portion of the overall research budget.

indicate changes in methylation in response to changes in the environment. The lab believes that it does not make sense to expect all cells in a given tissue sample to react in the same way to a chronic environmental stressor. Tissues are heterogeneous and stressors do not act with pinpoint accuracy. Hence, low percentages in methylation rates are to be expected biologically. They are difficult to publish but they make sense to the group. The assessment of the significance of findings is not simply statistical, although bioinformatics is playing an increasing role. It involves considering the wider biology of the case at hand; it involves considering the mechanisms of gene expression that other regions may be implicated in the particular pathway in great detail; it involves recollecting the experimental procedure; and, last but not least, it involves imports of popular social theory to make plausible why certain instances of social change or perceptions of socio-economic difference may lead to certain somatic changes. Significance, then, is not produced through a singular statistical measure but rather builds up in layers of analysis and interpretation. As an anthropologist, it is tempting to speak of *thick significance* (Geertz, 1973). Producing thick significance is not something that the group chooses to do. In many ways, it is an instance of 'reality kicking back' that forces them to open up the experimental system (Barad, 1998). Asking questions that call up organismic and environmental contexts confronts them with the fact that complex phenomena such as social behaviour are difficult to control. Even working with animal models and epidemiological variables still leaves the experiments with an 'openness to the world' (Moss, 2002), which leads to a larger variance of outcome measures than usually tolerated in the laboratory sciences. This variance needs to be contained post-hoc through building thick significance.

What is perhaps most striking about the group's way of doing biological research is the fact that these issues are raised and debated at the level of everyday research practice. They are not a matter of the head of the group pondering what it may all be about. They are right there in the everyday doing of molecular research. The group's daily work is not dominated by a stable experimental system, where everything about the experiment is solidified and the result only confirms or falsifies the hypothesis. Their current way of doing biology is much more fluid. This is neither to romanticise their work nor do I want to build up a naïve straw man of 'real' molecular biology. What I want to emphasise with the practice of building thick significance is the fact that considering the impact of environmental context on methylation raises issues of control over heterogeneous phenomena that change everyday lab practices and that require a certain tolerance of messiness that is not necessarily all that frequent in biological labs.

'Early-life adversity' as an emerging epistemic object

Environmental epigenetics has not yet developed a stable experimental system and agenda comparable to molecular biology's international sequencing and mapping platforms (Cambrosio et al, 2009). It faces the problem that epigenetic modification is a process that is highly sensitive to change over time and at different levels of context: cellular, organismic and environmental. Therefore, while methylation and histone modification present two clearly defined and measurable objects, the experimental designs are potentially open

to any kind of contextual change. And the experiments so far have operationalised contextual change rather eclectically: from nursing behaviour to child abuse, in animals and in humans. Yet, in the process of stabilisation of an experimental system, the notion of early-life adversity is beginning to emerge as an epistemic object (Rheinberger, 1997). Early-life adversity provides a coherent interpretive frame that is able to harness at least part of this heterogeneity. It is at the same time an established concept anchoring ongoing research in relevant pasts and setting out a research strategy for the future that goes significantly beyond the current epistemic horizon by bringing the social and material environment into molecular research.

The epistemic object early-life adversity anchors ongoing environmental epigenetics research by providing important links to behavioural psychology and the work with standardised animal behavioural models (for example, Tolman, 1948; Denenberg and Rosenberg, 1967) to the concept of *critical windows of increased plasticity*, that is, the idea that the body goes through phases of increased sensitivity towards internal and external change, which finds strong support in the conceptual work and research practice of cellular and developmental biology, epidemiology, psychology and lately neuroscience;[10] and, through the notion of adversity, to the extensive research from the late 1920s onwards on the effects of chronic stressors on allostatic load.

Yet early-life adversity also enables the group to look forward as the following brief sequence illustrates: the group discusses a recent animal (rat) study judged to confirm that early-life adversity has an impact on methylation patterns. Early-life adversity is introduced into the study by placing a rat dam into a cage other than its own, containing reduced bedding and nesting material, and adding to this mother a pup at a time for half an hour each day for the first few days of the pup's life. The discussion is initially focused on the particular outcome measures. The group then agrees that this is an elegant study, because it does not induce adversity directly, for example, through electroshocks or near-drowning experiences, but only alters 'natural' environmental conditions, which then lead to stressed dams. The experiment is thus perceived to have an increased ecological validity. The suggestion by members of the group working on the link between socio-economic status and methylation is made that the rat model is actually a very good model for '[human] migrants in deprived urban neighbourhoods'. Although a giggle runs through the group, because short-circuiting rats and humans in this fashion seems a little rash even for biologists, the comment is not sanctioned. Rather, the ensuing debate about the finer details of human stressors implicitly confirms that early-life adversity is not only a valid concept that builds on a long history that need not be questioned. It also confirms that it is a concept that can help to organise the messiness of environmental context and social change for the group. Early-life adversity is stabilised as an epistemic object in daily research practice through standardised animal behavioural models that act as 'reified theory', for example, that reduce the messiness of environmental context in a way

[10]The notion of critical windows of increased plasticity is not restricted to molecular biology. It has a long tradition particularly in neuroscience and developments of brain function during ontogenesis. To what extent this rests ultimately on a Freudian notion of early-life impacts on adult existence remains to be discussed. Relevant here is the link to Konrad Lorenz's work on imprinting (Tzschentke and Plagemann, 2006). See also the recent work on neurogenesis. (e. g. Rubin, 2009).

suitable for lab work (Latour and Woolgar, 1986) – although the McGill group is very close to the animals compared to other molecular biology set-ups, where ready-to-study mice are ordered from central sites as standardised packages (Fujimura, 1992).

Discussion

The embedded body

Environmental epigenetics produces an 'embedded body', that is, a body that is heavily impregnated by its own past and by the social and material environment within which it dwells. It is a body that is imprinted by evolutionary and transgenerational time, by 'early-life' and a body that is highly susceptible to changes in its social and material environment (Niewöhner, 2008, 2011). This notion of the body differs significantly from the individual body with its notion of skin-bound self and autonomy (Bentley, 1941), steered through life by the individual mind and brain and therefore engrained in Western cosmology (Sahlins, 1996). Since the enlightenment, much of philosophy and science have worked hard to instil in Western culture the understanding of biological man as rational man, that is, as the context-free, universal human being epitomised by *homo oeconomicus* acting as an autonomous individual following rational choice. Biology has studied material man before culture, whereas the social sciences have dealt with contextualised symbolic man as if he were not embodied. It is almost ironic that the deeper biologists delve into the human body and the more fine-grained and molecularised their analyses of the body become, the less they are able to ignore the many ties that link the individual body and its molecules to the spatio-temporal contexts within which it dwells. The emerging embedded body is a body far more 'open to the world' (Moss, 2002), and it responds to the world not only by letting matter and meaning pass through its 'inner laboratory' (cf. Huxley in Landecker, 2010). The embedded body is not a machine that runs on input from the world by metabolising it without being affected. Rather, the inner laboratory itself is changed through operating in an embedded body. 'Dwelling' in a particular environment in the ontological sense of anthropologist, Tim Ingold (2000) leaves not only residues in the body, it also allows the environment to change the dweller's inner laboratory. It suggests an altogether different degree of entanglement between body and 'context'.

Is the research in environmental epigenetics and the embedded body likely to affect radical change in the way Western societies think about and practice early childhood, for example, the way we organise childcare or family life or the way we feel responsible for future generations? Epigenetic modifications have been shown to be semi-stable, that is, they persist beyond the stimulus that led to the change in the first place and they further affect the way the body operates. Such somatic memory effects extend the embedded body in time and across generations in ways that molecular biology has not produced before. One may argue that this emerging knowledge *in principle* is neither new to science nor is it new *in principle* to most people. The knowledge or belief that family, upbringing and everyday life manifest themselves somatically, is part of most

vernacular notions of embodiment and development anyway. Even in enlightened Western cosmologies, science never eradicated the firm belief that 's/he is a chip off the old block'. Thus, it would be misplaced enthusiasm or worry to suggest that epigenetic knowledge is likely to affect radical change in the way people understand themselves and lead their lives. Yet, it would also be analytical negligence to ignore the embedded body as an emergent phenomenon made plausible by environmental epigenetics.

Molecularisation of biography and milieu

In her analysis of nutrigenomics, historian of science Hannah Landecker develops the thesis of an increasing 'molecularisation of the environment' (Landecker, 2010). She argues that the interest in 'active substances' in food that may interfere with the human metabolism has extended the biological gaze. Rather than focusing inward on cellular and increasingly molecular processes only, researchers now also focus outward and scan the environment for active substances. Hence, the environment is being molecularised, that is, comes to be known in its molecular effect on human metabolism. In the case of nutrigenomics, the concern lies with the material environment. Environmental epigenetics extends this kind of molecularisation in space and time to include socio-material environments and people's lifespans: a *molecularisation of biography and milieu*. Key to this development are changes in molecular biological research practice and experimental design. The emergence of methylation and histone modification as a plausible mode of action and a measurable molecular endpoint means that some molecular biologists begin to extend their gaze from the molecular level and the lab towards suitable objects of study out in the real world. They are trying to figure out instances of rapid change in the social environment that have occurred during an organism's early-life.

As I have discussed already, such instances are relatively easy to configure in animal models with the help of behavioural psychology. Instances of rapid social change in human populations are much more difficult to find and operationalise. Although social change is ongoing everywhere at all times and most likely causes epigenetic modification in the process, current study designs and analytical techniques cannot separate such subtle effects from confounders, irrespective of their functional relevance. Environmental epigenetics thus requires radical social change that is clearly defined – a quasi-natural experimental system, if you will. And it also requires biomaterial and data about the nature of the change from before and after the event. The suicide brain study (McGowan et al, 2009) was only possible because the Douglas Mental Health University Institute in Quebec operates a brain bank including many specimen from suicide victims for whom part of their early childhood could be satisfactorily reconstructed using a forensic psychiatric interviewing method. Finding such instances and cohorts and creating such opportunities has now become an important part in study design in environmental epigenetics. The 1958 cohort study is a prime example. Yet, others are discussed in the McGill lab and related scientific circles: Romanian orphans that were brought to the United States or the United Kingdom towards the end of the Ceauşescu era may be a suitable case, because the children suffered extreme deprivation in Romania before reaching relatively safe havens in the West. They present a clearly defined and easily

identifiable cohort; and biomaterial may also be available due to medical exams on entry into the United States or the United Kingdom. Germany after the Second World War may be another example; or many groups in Eastern European countries transitioning into post-socialism. Somewhat less dramatic, changing urban neighbourhoods not least because of the ongoing financial crisis have also been discussed.

What we are witnessing here is the attempt to operationalise instances of social change according to criteria taken from the practice of molecular biological research. This is the process that I refer to as the *molecularisation of biography and milieu*. It is the extraction of significant events from people's biographies, from particular and situated socio-cultural histories and from their embeddedness in particular milieu and everyday lives, and their conversion into standardised representations of particular forms of social change that can be correlated with the material body. The molecularisation of biography and milieu results in standard models of social change, which are able to travel between labs and into the wider public discourse. The molecularisation of biography and milieu extends in important respects the notions of geneticisation and biologisation, as well as the molecularisation of life itself that have been diagnosed over the past 20 years (cf. Lippman, 1991; Franklin, 2000; Rose, 2001). These concepts refer to changes in our understanding of illness, disease, our own bodies and life itself through an increase in knowledge of *somatic* levels of analysis, namely genetics. Molecularisation extended this analysis and emphasised the global economic and political dimensions of this shift, as well as the implications for notions of subjectivity and ethics (for example, Novas and Rose, 2000; Rose, 2007). Environmental epigenetics captures life itself not only in its presentist and individualist shape but also in different socio-historical contexts. Beyond this new reach of biopower, the molecurisation of biography and milieu may also provide the conceptual grounds for a different kind of sociality.

Somatic sociality

The molecularisation of biography and milieu provides experimental and increasingly mechanistic knowledge on the role of the (patho)physiological effects not only of somatic, but also of *organismic* and *social* levels of analysis. Standard models of social change are being construed from a molecular vantage point. This is a kind of molecularisation of social life itself that does not require the same reflexive somatic expertise that Rose and Novas postulate (Novas and Rose, 2000). People do not need to translate their somatic self-understanding into a way of life any longer. Ways of life themselves are already standardised and correlated directly with their epigenetic effects on the human body. I suggest the term *somatic sociality* to mark this phenomenon. Somatic sociality means sociality understanding and reproducing itself on the basis of biological knowledge about its epigenetic effects on the individual body. In other words, somatic sociality is a form of sociality where the collectivising momentum is provided by molecular understandings of social life itself. It is not individuals with the same polymorphism understanding themselves through that polymorphism or forming a collective on the basis of that polymorphism. It is individuals slotting into forms of social life that molecular biology produces as forms of social life that are good for your body and your health, for example,

you have friends but do not expose yourself to large socio-economic differences.

Somatic sociality is related to but distinct from somatic individuality and biosociality (Rabinow, 1992; Novas and Rose, 2000). Somatic sociality refers not to the collectivisation of individuals on the basis of biological knowledge of a shared phenotype. Instead, the notion of somatic sociality marks instances and forms of sociality and of social life that are directly modelled on nature. Particular forms of social life come to be known and practised increasingly through their somatic, that is, 'natural' consequences. But, of course, somatic sociality shares with biosociality that 'nature (is) modelled on culture understood as practice' – and it shares its polemic character (Rabinow, 1992, p. 241). Thus, 'Pimp Your Milieu!' *may* become the late-modern battle cry of those in favour of choosing a way of life to fit their embedded bodies. Though outside of the Bay Area in the Western United States, I would not hold my breath.

Concluding remarks: From local to customary biology

Environmental epigenetics contributes to a notion of an increasingly embedded body and it engages in the molecularisation of biography and milieu. It is important to re-emphasise that most of the research efforts and funds are directed towards the sequencing efforts and its cataloguing programmatic in the hope of developing clinically relevant biomarkers in the not too distant future. Environmental epigenetics is at a very early stage. It is easy to get caught up in the visionary rhetoric and begin to deal with potential implications outside the labs before the results are in. Thus far, the dynamism and specificity of epigenetic modifications pose serious conceptual problems to molecular biology and it is by no means clear whether the answer to these problems will emanate from some form of environmental epigenetics or whether other areas in the vast field of molecular biology will provide more suitable approaches. Beyond the rather philosophical question whether epigenetics has initiated a paradigm shift in biology, it remains an important task for the observers of developments in science and technology to closely analyse the infrastructures (Bowker and Star, 1999) that support and drive knowledge practices in epigenetics, particularly with a view to their translations into public health.

In concluding, I want to raise the question whether environmental epigenetics does not also challenge sociology and particularly anthropology to think more creatively about how to deal with the human body. Didier Fassin has rightly pointed out that most analyses of *life itself* have focused on subjectification and governmentality, that is, on processes, rather than on their outcomes, that is, particular lives lived from birth to death or *life as such* (Fassin, 2009). Fassin frames the relationship between the two agendas – life itself and life as such – as the important task of a moral anthropology. Moral anthropology means not losing sight of human suffering in analyses of biopolitics. Yet, it also means understanding the moral, symbolic and political dimensions of human suffering as entangled with manifold material aspects. Lately, a number of scholars at the intersection of science and technology studies, anthropology and sociology have pointed to this need to take materiality more seriously for different reasons (Lock, 2001; Mol, 2002; Melby et al, 2005; Timmermans and Haas, 2008). Anthropologist Margaret Lock

made this point some time ago with her concept of *local biology*. If nature and culture are entangled, it is only sensible to assume that complex phenomena such as menopause should occur differently in North America and Japan (Lock, 1993). The researchers in Szyf's lab have been the first group of molecular biologists that I have encountered who appreciated the point of the notion of local biology. Trying to incorporate 'social life' into molecular analyses makes immediately plausible that even something seemingly hard-wired such as gene expression may be connected in significant ways to local cultural practices. This does not mean that they, or anyone else for that matter, know how to study such phenomena – this is not a trivial problem.

Critics have argued that the term local biology is misleading, because it is only the enactment of a particular physiology that is local, whereas the biological mechanisms underlying these processes remain more or less universal. Hence, many molecular biologists practice biology as if it were physics. They are trying to extract the law-like rules according to which the human body works: programmes, blueprints and circuits. What is ultimately at stake here is the dividing line between the universal material body and the contextual, encultured subject, that is, between biology and anthropology in the disciplinary understandings manifest since at least Parsons and Kroeber (1958). I suggest that it is worth using environmental epigenetics as a precedent to make plausible a different understanding of biology: *customary biology*, that is, a biology that is based on custom understood as time-honored, habituated forms of living everyday life situated in a specific environment.[11] Customary biology is a biology based on patterns of practice and regularities rather than 'natural' laws; a biology (and a biomedicine) that is attuned to investigations of bodies, which are being used by people in culturally specific ways to which they have grown ac*custom*ed over time; and a biology that may be able to productively engage anthropology and social inquiry and *vice versa*. Lorraine Daston has analysed the striking parallels in the genealogies of Western conceptions of natural and moral orders (Daston, 2002). She points out that with the shift from local principalities to nation states in early-modern Europe, moral orders change from customary orders to law-based orders (cf. Stolleis, 1990). At the same time, the dominant understanding of natural orders changes from one that is based on custom, that is, the observation of regularities, to one that is based on universal, law-like rules. I want to argue in favour of an early-modern biology, a biology that is based on regularities rather than laws, a 'customary biology' if you will. A 'molecular biology of social position' would then not seem so reductionist anymore. Rather than using crude structuralist indicators of social order from epidemiological studies and trying to short-circuit these with methylation profiles, anthropology could provide ethnographic data on relevant *patterns of practice* (Roepstorff et al, 2010). Understanding how people dwell, that is, how they use and conduct their bodies in everyday life, is a genuinely anthropological question (Ingold,

[11] A reviewer helpfully pointed out an important and potentially confusing second meaning of custom in the sense of custom-made. Although this is not the meaning I intend here, this reading does point to another important area of research currently discussed under the heading of individualisation of medicine. In this sense of custom-made biology, the concept would suggest a form of individualisation that is not centred on ever smaller populations of skin-bound individuals defined by similar genomes but of individuals defined by shared patterns of practice.

1990, 2000, 2007). And if we assume that dwelling leaves its marks on the body, trying to understand these marks also with biological means seems only sensible. Such an agenda is easier to envisage with a customary biology and it requires that both, anthropologists and biologists, understand their knowledge practices as situated and contingent.

Environmental epigenetics thus raises the opportunity to develop an *empirical* research agenda at the interface of social and material inquiry. Many, of course, have argued for all the right reasons that the notion of material-semiotic practice and subsequent praxiographic work has long been pursuing such inquiries (Haraway, 1991; Mol, 2002). In fact, the very distinction between material and social has become obsolete. Yet, it appears to me that human suffering often has a material dimension that deserves a more nuanced study than social scientists alone are able to offer. A customary biology may be a more careful approach to this material dimension and one that is more suitable to engage with social inquiry.

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Appendix

Mechanisms of epigenetic modification

In its broadest definition, epigenetics refers to 'the study of any long-term changes in gene function without changes to the actual DNA sequence' (McGowan and Szyf, 2010). Epigenetic changes in DNA activity and gene function may occur through a number of mechanisms, two of which have received the most attention in biological research over the last decade: (1) DNA methylation and (2) chromatin modification.

1. DNA methylation is the most intensely studied epigenetic mechanism. 'DNA methylation is the post-replication addition of a methyl group to the carbon-5 position of the cytosine pyrimidine ring by DNA methyltransferase to form 5-methylcytosine (5-MeC)' (Butcher and Beck, 2008). In other words, a methyl molecule (CH_3) is added to the DNA base cytosine through the actions of a group of enzymes: cytosine is said to be methylated. Methylated DNA is not transcribed. Thus,

increases in DNA methylation tend to decrease gene expression and vice versa. In contrast to DNA sequence changes, the process of methylation is reversible. Cytosine nucleotides can be demethylated either through incomplete maintenance during DNA replication or *de novo* through enzymatic action. Methylation patterns are semi-stable, can be transmitted through cell division and, in contrast to DNA sequence, are gene- and tissue-specific. (De)Methylation regulates gene expression in a way that is dynamic and highly responsive to cellular, organismic and environmental contexts.

2. Chromatin conformation refers to a number of changes that alter chromatin structure. The DNA double helix is folded around histones to form the so-called nucleosome, which in turn is folded into chromatin. Chromatin structure, or, as biologists tend to call it, chromatin conformation, influences to what extent particular sections of DNA can be transcribed, that is, an important step in gene expression. Closed chromatin conformations (heterochromatin) decrease transcription rates, open chromatin conformations (euchromatin) increase transcription rates. Epigenetic research has investigated a number of mechanisms that modify histones altering the meta-structure of chromatin: acetylation, phosphorylation, ubiquitinylation and others. This area of research is not well explored as yet and offers interesting links to structural biology that are not discussed in this context.

Note that 'long-term changes in gene function' in the above definition commonly refers to changes to gene function that are passed on through cell division. For many biologists, the heritability of epigenetic modifications through mitosis is a defining feature of epigenetic processes. They thus define epigenetics more specifically as 'the inheritance of DNA activity that does not depend on the naked DNA sequence' (Esteller, 2008, p. S90). Inheritance in this definition refers to cellular inheritance and not gamete-based, transgenerational inheritance. Gamete-based, transgenerational inheritance of epigenetic marks has not been conclusively shown so far (Waterland et al, 2007; Whitelaw and Whitelaw, 2008).

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