

Original Article

Food as exposure: Nutritional epigenetics and the new metabolism

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Abstract Nutritional epigenetics seeks to explain the effects of nutrition on gene expression. For social science, it is an area of life science whose analysis reveals a concentrated form of a wider shift in the understanding of food and metabolism. Rather than the chemical conversion of food to energy and body matter of classic metabolism, food is now also a conditioning environment that shapes the activity of the genome and the physiology of the body. It is thought that food in prenatal and early postnatal life impacts adult-onset diseases such as diabetes and heart disease; exposure to food is seen as a point of potential intervention in long-term health of individuals and populations. This article analyzes how food has become environment in nutritional epigenetics, with a focus on the experimental formalization of food. The experimental image of human life generated in rodent models, it is argued, generates concepts of food as a form of molecular exposure. This scientific discourse has profound implications for how food is perceived, manufactured and regulated, as well as for social theories and analyses of the social body that have a long history of imbrication with scientific models of metabolism.

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Food as Exposure: Nutritional Epigenetics and the New Metabolism

This article examines one aspect of contemporary metabolism, an area of scientific research called nutritional epigenetics. The focus here is on how food functions as an ‘epigenetic’ factor in the regulation of gene expression; the field is particularly concerned to elaborate how nutrients affect regulation of genes whose expression is linked to cancer, metabolic syndrome, obesity and diabetes. Although interesting in and of itself as a scientific development, in this analysis nutritional epigenetics serves as a site to specify and characterize new concepts of metabolism and food emergent today. Rather than a chemical factory for the conversion of substrates, metabolism is a regulatory interface shaped by the environment; in turn, food is more than fuel or substrate, in fact it becomes understood

as a form of environmental exposure. These scientific shifts in the understanding of metabolism simultaneously constitute a molecular politics of eating; at stake are notions of personal and social responsibility for the future health of bodies and populations and the individual or governmental stewardship of the food environment.

My focus is on the *experimental formalization of food* in nutritional epigenetics. If gene expression is hypothesized in epigenetics to be altered by environmental factors acting on genetic regulatory mechanisms then the structure of experiment must include particular practices and concepts that formalize ‘environment’ as part of that system. As nutrition is the key ‘environmental factor’ under examination in this research subfield, food stands in for the environment in the dyad of ‘gene-environment interactions’. As results are generated from these highly specific experimental configurations, they are received by scientific and public audiences as findings about environmental influences on genetic processes. How is food becoming environment in these experimental settings?

Characterizing the experimental narrative of food is a first step toward specifying the political and cultural nature of experimental findings and explanatory models that explicitly and materially link gene regulation to social regulation. These experiments furthermore arise in a larger historical context in which food is increasingly simultaneously alimentary and therapeutic – increasingly a tool for intervention in the health and character of present bodies and those of future generations. The use of socially and economically important food substances such as folic acid and soy in experimental design, the politics of gender and governance both built into these experiments and implied by them, and the historical specificity of the discourse of food and metabolism characteristic to nutritional epigenetics are the targets of this article’s analysis.

Analysis of this small corner of biomedical endeavor is understood here to offer purchase on much broader scientific and social transformations that might otherwise be rather hard to fathom or narrate. This approach might be understood as akin to using a pinhole camera, where nutritional epigenetics is the small aperture held to the world, in order to produce a sharp image of contemporary transformations in the concepts of metabolism and environment and their interrelation. Stanley Cavell once observed that a camera is ‘an opening in a box’ that holds much of the world away as it holds on an object. As such, ‘the camera has been praised for extending the senses; it may, as the world goes, deserve more praise for confining them, leaving room for thought’ (1979, p. 24).

By analogy, I have sought to hold on the objects of nutritional epigenetics in order to hold away much of the welter of the world of change in contemporary life science, just long enough to think a few things through. Epigenetics, epigenomics, systems biology, microbiome studies, gene-regulatory network approaches, gene ecology, ecological development biology – these are all distinct but overlapping areas of research sometimes addressed as ‘post-genomic’, ‘complex’ or ‘systems’ biology – but might be more neutrally termed an increasingly relational biology (Wynne, 2005; Powell and Dupré, 2009). Rather than pursuing the qualities and quantities intrinsic to living things – their genetic sequences, their functional structures – these relational approaches are more likely to focus on the biology of the in between (Van de Vijver, 2009). For example, stem cells come to be understood in relation to the micro-niches they occupy in the body, and one sees articulations of the cell plus its milieu as ‘the entity of action’, displacing searches for ‘stem-cell-autonomous’ qualities such as genes for ‘stemness’ (Scadden, 2006). Similarly,

some cancer researchers are looking away from gene mutation and toward mechanobiology in asserting that tumor formation is a continuous reciprocal interaction between tumor cells and their surrounding microenvironment of stromal cells and the extracellular matrix (Rønnov-Jessen and Bissell, 2009).

Technical infrastructural developments that allow the fathoming in great detail of gene expression and post-transcriptional protein–DNA or protein–protein interaction have put a focus on the molecular phenotype as much as the genotype (Nachomy *et al*, 2007). The interactions between elements of the molecular phenotype, sometime known as ‘proteomics’, or studies of the ‘interactome’ – networks of proteins interacting in complex interlinked ways in and between cells – form the material basis of a biology of relationality (Weiss, 2005). The cell is becoming a site of integration of transcription signals and other dynamic proteinaceous activities. Epigenetics is both exemplar and driver of such relational biology, as it provides mechanistic molecular pathway explanations for the ‘between’ part of the biology of the in between: exactly how, down to the last de-phosphorylation, ‘environmental factors’ translate into internal biological changes, whether the entity/environment distinction is the organism in a macroenvironment, a fetus *in utero*, a cell in a tissue or even DNA in its immediate nuclear milieu. The reconfiguration of food and metabolism in nutritional epigenetics is a window onto profound changes to the material and conceptual constitution of ‘environment’ and ideas of environmental determinism in contemporary epigenetics more broadly, and in other emergent relational molecular biologies.

Despite these claims to focus and room for thought, the following essay may come across as rather complex. Here, then, are the set of interlinked theses and areas of discussion set out stepwise that may be referred back to in case of getting lost among the history of thinking about mutton, considerations of methylation, the composition of standard mouse chow, nanotechnology of breast milk and the ontology of being. Part One lays out a historical claim that metabolism is changing. This necessitates an exploration of the ‘old’ metabolism, in order to identify the characteristics and significance of the ‘new’ metabolism now emerging. The concept of metabolism has always implied particular understandings of alimentation, digestion and nutrition; to a certain extent it is easier to pin down the scientific discourse of food and read for the metabolism implied by it than it is to pursue metabolism itself. Part Two offers a detailed explanation of the logic of food as a determinant of gene expression in nutritional epigenetics and epidemiology. Part Three poses the question of what kind of environment food is, with a close examination of the material objects that stand for ‘food’ in laboratory practice, and an examination of the ethical and political stakes of this experimental image of human life, with its attendant tensions between ideas of social or individual interventions in health via food. It would be a mistake, however, to see this discourse and its political tensions as generated only in epigenetics, and flowing outward from there. In Part Four, the article turns to the task of embedding the discourse of food as exposure in broader historical and cultural context, discussing the attribution of pathogenic and therapeutic power to food molecules in biotechnology, food engineering and marketing, nanotechnology, nutrigenomics, and the toxicology of pesticides, food packaging and preservatives.

The argument synthesized from these interlinked foci is that a historically and culturally specific discourse of *food as exposure* is emerging in nutritional epigenetics: food as a miasma of biologically active molecules in which genomes are immersed, determining and disturbing the physiology of metabolic regulation with each new person that comes into the

food world (Landecker, 2010). This molecular understanding of the environment answers a previous intense era of molecularization of the body, but is distinct from it because of the foregrounding of molecular interrelation and critical timing rather than the search for answers in the structural enumeration of the molecules themselves; in epigenetics one sees an understanding of the body's molecules as hung in the same network of interaction as environmental molecules, a network anchored and organized through the temporally sensitive interface of metabolism. Close analysis of the material and conceptual structure of explanation of how food affects gene regulation and long-term health is a first step to understanding the ethics and politics of a health-determining environment and its social management. Nutritional epigenetics in both its content and context serves as a usefully narrow aperture through which to focus an image of a much larger set of scientific, social, economic and cultural transformations to food, metabolism and environment occurring in the contemporary era.

One: Nineteenth century metabolism and the 'singular inward laboratory'

What is metabolism? According to the *Oxford English Dictionary*, in biology and biochemistry the word means:

The chemical processes that occur within a living organism in order to maintain life; the interconnected sequences of mostly enzyme-catalyzed chemical reactions by which a cell, tissue, organ, etc. sustains energy production, and synthesizes and breaks down complex molecules; anabolism and catabolism considered together; the overall rate at which these processes occur. Also: the chemical changes undergone in an organism by any particular substance.¹

The word came into scientific use in the nineteenth century at the same time as a theological use to describe the change undergone by the Eucharistic elements when they are consecrated. The relevant history of the term has to include the German term *Stoffwechsel*, whose broad use as a term in physiology coincides roughly with the coalescence of a science of nutrition around 1840, 'when a fair number of professional chemists and physiologists explicitly began to relate the chemistry of foods to animal physiology' (Kamminga and Cunningham, 1995, p. 3).²

Changes in concepts of metabolism have clear cultural and political consequences for how food is perceived and regulated in society. What we should eat, what our food should include or exclude and who should decide are directly impacted by scientific findings linking nutrition and health; this much has been clear from the very inception of nutritional science in the 1840s. Whether marketing meat extracts or writing treatises 'for the people' on the centrality of food to human thought, labor and revolution, the science of nutrition has served as a legitimation and vehicle for a wide range of ideas about improving

1 The entry also lists metabolism as a modernist movement in Japanese architecture, founded in 1960 under the leadership of Kenzo Tange that was interested in large-scale dynamic structures as opposed to fixed form and function.

2 The use of the term metabolism or metabolic in English was at first confined to reference to Schwann's cell theory and his use of 'metabolic force' to describe 'the power possessed by living cells for changing the character of the substances brought in contact with them'. By the late 1870s, the scope of the word was broadened in meaning and connotation by its inclusion in Michael Foster's *Textbook of Physiology* in 1878, where it is used in the same manner as the German term *Stoffwechsel* (Bing, 1971, p. 175).

people through food, as well as an important framework for theories of the social body (Kamminga, 1995).

In physiology and biochemistry, *Stoffwechsel* and its English and French translations *metabolism* and *métabolisme* came to encompass the changes of state undergone by food in the body, previously variously described as metamorphosis, animal economy, destruction, putrefaction, combustion, fermentation and respiration (Mendelsohn, 1964; Bing, 1971). Theories of the animal as an apparatus of combustion fed by plants, apparatuses of reduction, depicted a symmetrical relationship of synthesis and destruction between the animal and plant world (Coleman, 1977). The physiologist Jakob Moleschott called this the *Kreislauf des Lebens*, the circle or cycle of life:

What man excretes nourishes the plant. The plant changes the air into solids and nourishes the animal. Carnivorous animals live on herbivorous animals, to fall victim to death themselves and so spread abroad newly germinating life in the plant world. The name ‘metabolism’ has been given to this exchange of material. We are right not to mention this word without a feeling of reverence. For just as trade is the soul of commerce, the eternal circulation of material is the soul of the world. (1857, quoted in Schmidt, 1971, p. 87)

This lending of ‘ontological dignity’ to metabolism, and the broader landscape of debate about the philosophical, theological and political valences of such a material understanding of the world meant that the experimental findings of nutrition science in Moleschott’s work as well as Justus Liebig’s *Animal Chemistry* had broad readership and uptake in the political philosophy of the day. Nutrition became a social problem, whose scientific study was imbricated with labor politics and the living wage (Aronson, 1982). Karl Marx was extremely taken by scientific models of life as a constant transformation of matter; ‘the metabolism between man and nature – a special case of the general interaction of natural things – was placed by Marx in the category of exchange and, inversely, he had recourse to the concept of metabolism when characterizing the process of exchange’ (Schmidt, 1971, p. 92). The term *Stoffwechsel* is employed in *Capital* to conceptualize the transformation of the material world by human labor according to human needs, as well as the ‘social metabolism’ arising from it: the exchange of the products of that labor (Fischer-Kowalski, 1997).

The physiologist Claude Bernard disputed this nice complementary schema of combustion and reduction, showing that all organisms both make and destroy sugars and fats within one body – it was not that plants reduced and animals combusted, but that all organisms did both in one body. From Bernard’s lectures of 1878 on the phenomena of life common to animals and plants emerges a clear image of life as an engine of conversion of food from its own form to that of the body consuming it: ‘One does not live by his present food, but by that which he has eaten previously, modified’ (Bernard 1974, p. 90). And: ‘The food first disappears, as a definite chemical material, and it is only after extensive organic work, after a complex vital elaboration, that the food comes to constitute the reserves, always identical, that serve for the nutrition of the organism’ (ibid, p. 103). This point was proven by the fact that animals and plants could live for a long time without taking food, and a starved body ‘lives on its reserves, accumulated within its own substance; it consumes itself’ (ibid, p. 91).

Note that in this reasoning, food disappears. What is important is a ‘complex vital elaboration’ (Bernard does not use the term metabolism) that turns food from what it is into the organism’s own substance. Always concise, Bernard put the point this way: ‘The dog does not get fat on mutton fat, it makes dog fat’ (ibid, p. 105).

Mutton and its digestion was clearly a point of common concern in the nineteenth century. In 1868, speaking to a lay audience on the topic ‘On the Physical Basis of Life’, biologist Thomas Huxley recounted the Balzac story of the *Peau de Chagrin* – a wild ass’s skin that yields its possessor the means of gratifying all his wishes (Huxley, 1869). Unfortunately, the trade-off is that the skin represents the duration of the owner’s life. Every time a wish is granted, the skin shrinks, eventually disappearing with the gratification of the last wish. Huxley told his audience that giving talks worked by some of the same principles. The speaker, he said, ‘burns so that others may have light – so much eloquence, so much of his body resolved into carbonic acid, water and urea’. Happily he continued, unlike Balzac’s story, this protoplasmic shrinkage due to the expenditure of energy could in his case be replenished by the act of eating some mutton:

A singular inward laboratory, which I possess, will dissolve a certain portion of the modified protoplasm; the solution so formed will pass into my veins; and the subtle influences to which it will then be subjected will convert the dead protoplasm into living protoplasm, and transubstantiate sheep into man. (p. 137)

Food enters the body, and is consumed and transubstantiated, again and again providing the stuff to burn, stoking the fires of the muscular work of the laborer’s body or the intellectual work of the scholar’s body.

Anson Rabinbach suggests that in the late nineteenth century the interest in the conversion of stuff was displaced by an obsession with food in and energy out of the human motor: ‘Until Max Rubner demonstrated conclusively in 1894 that “the exclusive source of heat in warm-blooded animals is to be sought in the liberation of forces from the energy supply of the nutritive materials,” it was impossible to speak of a decisive shift from a general theory of *Stoffwechsel*, or metabolism, to the modern theory of *Kraftwechsel*, or energy conversion’ (1992, p. 67). Of course, the understanding of food as a source of energy did not entirely replace the understanding of food as a source of building materials for the body, and the notion of food as substrate emerged with renewed force with the twentieth century elaboration of vitamins or ‘accessory food factors’, those things that bodies would perish without even if their food intake was calorically sufficient (Kamminga, 1998; Smith, 2009).

It took much of the first half of the twentieth century to elaborate the workings of the singular inward laboratory, coinciding with the ascendance of biochemistry as a powerful science of life. This was the period of the working out of the details of ‘intermediary metabolism’, such as the citric acid cycle: the sequential enzyme-catalyzed chemical reactions that convert biomolecules from one form to another and generate energy (Holmes, 1992). The phrase ‘inborn errors of metabolism’ was coined to designate individuals born missing one enzyme from important metabolic cycles, such that substrates built up or vital conversions went undone, resulting in illness (Garrod, 1909). During the early twentieth century, legions of rats had their diets selectively reduced bit by bit until

the minimum diet necessary for the maintenance of life was reached. In the 1930s, the first synthetic animal diet was achieved – the food was put together from purified and chemically synthesized molecular components – amino acids, vitamins, minerals, lipids and carbohydrates, without any recourse to a ‘whole’ food (Waymouth, 1965). Such control of the diet was necessary to figure out how much of which component was necessary for life, either for its maintenance, or as the minimum nutrition supportive of reproduction. Bernard’s logic of vital elaboration is still clearly visible here; it did not matter where the amino acid or the vitamin or the carbohydrate came from, because the body broke food down into these components anyway. If the researcher broke food down into these components first, it was simply a way of controlling the input into the chemical conversions of metabolism, it did not make any difference to those chemical reactions themselves.

This schematic history is only cursory; the point is that it forms the basis for an enduring scientific – and political – understanding of metabolism as a laboratory whose working is basically the same for everyone, except those whose laboratory contains a broken instrument – an ‘inborn error’. Food is also the same for everyone, as fuel or substrate; politics lies in how much of what quality of food is available to whom to build laboring, thinking bodies. This model also implies a certain logic of substitution that we still live with: energy bars and drinks are equivalent to meals, and synthetic nutrient supplements may be substituted without effect for their naturally occurring equivalents. One does not need food – one needs energy, and metabolic substrates.

This history is an important foundation for the analysis that follows, because it is both a point of comparison to the new metabolism emerging today, and – thinking very materially – its source. The industrialization and conversions of matter of the nineteenth century have produced a completely altered landscape of fuel, substrate and the body over the last 150 years: large-scale agriculture, refined sugars and oils, calorie-rich and micronutrient-poor highly processed preserved foods, mechanization of manual labor and transport, and pesticides and consumer goods leaching potential ‘obesogenic’ endocrine disruptors (Grün and Blumberg, 2006; Prentice, 2006). Thus, we may see metabolism today as ‘post-industrial’ in the doubled sense that it comes after industrialization, and, because of what industrialization has done to the body, the biomedical study of metabolism is increasingly more concerned with regulation than manufacture. The worldwide incidence of metabolisms exhibiting insulin resistance, imbalance in sugars and lipids, a derangement of blood pressure and fat distribution – preceding or coincident with diabetes, obesity, cancer and heart disease – has focused nutrition and metabolic sciences, as well as much social and cultural attention, on metabolism as a zone of regulation rather than of conversion.

Today, diverse biomedical sciences of metabolism – from the study of intestinal bacteria mediating digestion to the reconceptualization of fat as an endocrine organ – are beginning to suggest that different individuals may process the same food very differently, and that different foods have potential to shape the metabolic interface in very different ways (Ahima and Flier, 2000; Turnbaugh *et al*, 2007). Two individuals eating precisely the same food may metabolize it quite differently; in this emerging scientific model, it is cultures of eating, from breastfeeding habits to dietary fat content that are seen to shape the capacities and reactions of metabolisms in individuals and generations. These shifts to

a temporally and environmentally differentiated metabolism, one that arises and functions in context, are particularly evident in nutritional epigenetics.

Nutritional epigenetics is interested in the way in which food affects patterns of gene regulation. It is a resolutely molecular science focused on how the molecules in food interact, via metabolic systems, with the molecules that attach to DNA and control levels of gene expression in the body. The basic argument is that particularly early in life, *in utero*, in early postnatal life and in adolescence, the body goes through periods of plasticity and openness to the environment. In these times, food is one set of signals about the state of the world the body will grow up to occupy. To extend the Huxley analogy of the inward laboratory, food is not just broken down and synthesized in the laboratory, but can actually influence the construction and function of the laboratory itself – this many machines, that much capacity. When the laboratory is built in a certain way, it has a certain range of potential to operate on what comes into it. Thus, food in critical periods of development can affect the systems that the body will in the future use to process food; it has the capacity at certain times to set the conditions of its future reception. The ways that food matters to metabolism, and the fact that it ceases to ‘disappear as a definite chemical material’, are explored below as part of the argument that a ‘new metabolism’ is emerging, one as historically and culturally specific to the twenty-first century as the inward laboratory of chemical and energetic conversion was to the nineteenth and early twentieth centuries.

Two: Transubstantiation reconfigured – An introduction to nutritional epigenetics

Nutritional epigenetics is only one corner of a much larger phenomenon in biology that is going under the label of *epigenetics*. Epigenetics is frequently defined as the study of heritable changes in gene expression that occur in the absence of change in the DNA sequence; the emphasis is on the ‘epi’ – factors ‘above’ the level of genetic sequence that affect which genes in any given cell are turned on or turned off (Allis *et al*, 2007). Alternatively, the definition of ‘structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states’ has been put forward to free epigenetics from the obligation to refer to inheritance as either mitotic or meiotic (Bird, 2007, p. 398). As with many other terms in biology, debate over what the term encompasses is part of what constitutes the field in the first place. My focus here is on scientists who are working comfortably within molecular epigenetics, concerned with mechanisms of gene regulation that can be pinned down to the action and movements of particular molecules in the cell. The aim is not to probe the exact definition of epigenetics, but to characterize the work being done under the flag of ‘nutritional epigenetics’: work that either focuses on the molecules controlling gene expression, or connects those molecular mechanisms to epidemiological correlations linking human nutritional states with adult-onset diseases.

A great deal of the experimental work in nutritional epigenetics is conducted with inbred mouse populations and the measurement of methylation levels of particular pieces of their idiosyncratic genomes. In the agouti mouse model, for example, there is a retrotransposon inserted into the promoter region of a gene coding for agouti signaling protein (Bultman *et al*, 1992). Retrotransposons are ‘foreign’ pieces of genetic material that become permanently and heritably inserted into a ‘host’ genome; the agouti mouse happens to have one inserted in the area of the gene – the ‘promoter’ – that controls whether

the gene itself is expressed. Retrotransposon DNA tends to be heavily methylated; this means that the cytosine residues (the C's in the ATCG sequence) have an extra carbon and three hydrogen molecules (CH₃) attached to them. These little methyl 'tags' make the DNA less accessible to all the cellular machinery that drives the making of RNA and protein from the gene's coding region; heavily methylated areas of the genome are thus 'shut down'.

Methylation makes some evolutionary sense in the case of retrotransposons; one way to deal with foreign DNA inserted in the genome is to silence it, so that it does not interfere with what was already there. In the case of the agouti mouse, because of the placement of the foreign DNA in the regulatory region of the gene, shutting down the retrotransposon DNA also means turning off the associated gene, and thus the loss of production of the agouti protein. Conversely, lack of methylation causes the gene to be abnormally expressed all over the mouse body, in quantities and in cells that it does not normally appear. The agouti signaling protein influences both coat color and how fat the mouse is, and therefore mice with high methylation levels and low agouti protein production are thin and brown, whereas mice with little methylation and high agouti protein production are fat and yellow. One reason that these mice are seen as a model organism for humans – even though human obesity is certainly not caused by dysregulation of one gene – is that they are not only abnormally heavy, they also develop type II diabetes and have a predisposition to tumors. The so-called 'obese yellow syndrome' is characterized by hyperphagia – eating a lot – and hypometabolism – even if food is restricted, these mice will become fatter on the same amount of food.

Litters of agouti mice are genetically very similar because of being inbred for generations. This means the siblings are nearly identical in terms of genetic sequence but they can be epigenetically very different, with varying levels of methylation. These genetically similar but epigenetically distinct mice differ dramatically in phenotype – how they look, how heavy they are. Thus, they bear obvious macroscopic signs of what is happening at the molecular level in very specific parts of the genome; these mouse models have been referred to as 'epigenetic biosensors' – their external appearance can be visually 'read' for their microscopic internal molecular state (Waterland, 2006a; Dolinoy 2008). Yellow/heavy 'equals' low methylation of the gene promoter. Brown/light 'equals' high methylation. These readings are confirmed by extracting the mouse DNA, and measuring the level of methylation at the agouti gene, with a form of gene sequencing modified to detect methylated cytosine residues.

With these 'epigenetic biosensors', different diets can be tested for their effects on methylation and gene expression in a highly controlled fashion. Food supplemented with or stripped of 'nutrients likely to enrich the pool of methyl donors and vitamin cofactors required for methylation' such as folic acid, betaine, choline, methionine, given to pregnant mice, lead to offspring that are thinner and browner (Waterland and Jirtle, 2003; Rosenfeld, 2010, p. 478). These offspring show higher methylation levels at the agouti promoter than the offspring of mice fed a normal or methyl-donor deficient diet. The same effect is seen in other genes as well, notably the Insulin Growth Factor II locus (IGF2), a genetic location much studied because of its association with diabetes. In this case, the methyl group-donor content of diets of mice just after birth was varied – in the first 60 days of life (Waterland *et al*, 2006). Diets deficient in methyl group donors induce lowered methylation, an effect that persisted for the life of the mice even after they were switched to a nutritionally

sufficient diet after 60 days. Thus, the patterns of methylation set *in utero* or in early infancy seem constant even if the diet is changed later in life. The ability to manipulate gene expression and thus phenotype with diet is the most notable feature of this mouse model system.

In sum, the basic logic of nutritional epigenetics is that the outside environment, in this case the kind and quantity of food eaten by a parent or an infant mouse, changes the inside constitution of the mouse at the molecular level. This is not a mutation – a change in genetic sequence – but a change in the *potential* of genes to be expressed in the body as protein products. The molecules in food affect the kind and number of molecules attached to DNA, and these molecules end up affecting the kind of body an organism has. Importantly, the body is one that is regulated differently, and thus one that *processes* food differently via the molecular settings on its metabolic systems, to use the programming language that is common in this field. It is a body that suffers not an ‘inborn error of metabolism’, some fault in the system that breaks it, but ‘metabolic syndrome’, a cluster of signs that systemic regulation has gone awry: raised triglycerides, lowered HDL cholesterol, raised blood pressure, adiposity at the center of the body, high levels of glucose in the blood after fasting.

We have always known that diet can affect physiology, but this is a way of thinking about ingestion and the body that differs from the usual logics of you are what you eat. It is not the accustomed calculus of eating a lot or a little, or avoiding foods that clog arteries or decay teeth. It is not about food that accumulates as fat or is burned away as energy. It is about food that affects the very systems that metabolize food; for example, the presence or absence of nutrients may cause the body to be built with different numbers of cells in its digestive organs, or to have more or less receptors for metabolic hormones. If food intake influences production of proteins such as growth factors that regulate how much cells divide during development, then it could help determine the size of an organ; if it influences expression of proteins such as transcription factors that affect which genes are expressed in cells as they differentiate during development, it could help determine relative numbers of cell types in an organ.

In terms of animal experimentation in nutrition science, there is a long history of what might be called ‘input–output’ manipulations: starvations or selective deprivations to see the end physiological effect either on a starved individual body or on the offspring born to a food-deprived mother animal. Epigenetics is reconfiguring this practice by putting the focus on the molecular events between input and output. In experimental systems other than the agouti mouse model, various methods have been used to vary ‘nutrient signaling from mother to fetus’; it is reasoned that the diet of the mother is a cue to the developing fetus about the world it is about to be born into, and that cue will be reflected in the gene expression patterns of the offspring (Burdge *et al*, 2007, p. 1041). The micronutrients and macronutrients comprising the diet change the activity of enzymes that add methyl groups to DNA; changes in the complex breakdown and synthesis of molecules in the metabolic pathway are a ‘candidate mechanism for the transmission of information regarding maternal ... metabolism status to the fetus’, and for induction of one phenotype rather than another (Burdge *et al*, 2007, p. 1041).

These results taken as a whole suggest that early nutritional environments, whether they are *in utero* or in early infancy, can act to ‘set’ the range of possibility for gene expression for

the life of the organism and perhaps that of its descendents. The phrase ‘range of possibility’ is an important part of this model, though the point is rather subtle: the exact level of gene expression is not necessarily set, but the highest or lowest parameters of its expression might differ from organism to organism due to epigenetic factors. This is a model in which food enters the body and in a sense *never leaves it*, because food transforms the organism’s being as much as the organism transforms it. It is a model for how social things (food, in particular) enter the body, are digested, and in shaping metabolism, become part of the body-in-time, not by building bones and tissues, but by leaving an imprint on a dynamic bodily process.

These findings imply that in humans large-scale social changes can translate into large-scale, population-wide, heritable physiological changes through the medium of food – and that these changes can be tracked and mapped. Headline-producing findings in epidemiology show that food availability correlates with raised disease incidence in the male descendents of individuals experiencing a famine or a time of abundance: *You are what your grandfather ate* (Kaati *et al*, 2002). Researchers using detailed harvest records from the late nineteenth and early twentieth century in northern Sweden correlated food availability for pre-adolescent boys with life span of their grandchildren, finding that scarcity during this so-called ‘slow growth period’ just before puberty in the grandparent was associated with longer longevity in grandchildren, whereas abundance was associated with shorter life span. These results were later further detailed by an association between abundant harvest conditions in one generation and increased mortality from diabetes in the grandsons (Pembrey, 2002). By contrast, an increase in mortality was associated in women with grandmothers who had a limited food supply at the age of 0–3 years (Pembrey *et al*, 2006).

The biological basis for the inheritance of bodily changes wrought by external conditions experienced by distant ancestors is hypothesized to be the epigenetic mechanisms detailed in the laboratory – changes to the molecules that attach to the DNA strand, order the physical configuration of the chromosomes that genes reside on, or act at the level of small RNA molecules that work to silence gene expression. The gene remains the same, but its potential for expression in the lifetime of the individual changes, and that pattern of potential expression is heritable. Because heightened food intake or lack thereof can alter molecular control of DNA, the hypothesis goes, the nutritional milieu of the mother, father, fetus and infant can affect which genes are expressed and which genes are silent in generating the phenotype of the child.

Another powerful source of epidemiological evidence are the data collected from individuals who were *in utero* during the Dutch hunger winter of 1944. It has long been known that famine had long-term impact on the health of people who were *in utero* during that time, with raised incidences of complex diseases such as schizophrenia and diabetes. Similarly, low birthweight and poor prenatal nutrition has long been epidemiologically linked to incidence of cardiovascular disease by David Barker and colleagues in British populations. The ‘Barker hypothesis’ linking early nutrition and adult chronic disease conditions has been in circulation since the 1980s, though an epidemiological interest in long-term health effects of poor childhood nutrition can be traced back to earlier decades in Britain – before smoking and lifestyle as risk factors for adult-onset diseases came to dominate the discipline of epidemiology (Davey-Smith and Kuh, 1997). The study of the

‘developmental origins of health and disease’ (DoHaD) has been growing in tandem with a move to understand adult health conditions as part of the ‘life course’; both developmental origins and life course analysis are not necessarily connected to epigenetic research or explanation, but epigenetics has been enthusiastically incorporated into these broader areas (Gluckman and Hanson, 2006).

Epigenetics provides a molecular mechanism for connections that have previously been hard to explain. There has been no way to connect the marker of low birthweight (itself a very crude measure) mechanistically to health in the same individual many decades later, only a metaphorical invocation of ‘programming’ of the body in its early years that affects its health in later years. Now, with the rise of molecular epigenetics, and in particular the rise of the methylation paradigm described above, there is a direct route by which the molecules that make up food alter or become the molecules that regulate gene expression, and the patterns of gene expression drive the enzymatic and hormonal systems of the body’s metabolism. The language is changing from fetal programming to ‘induction’; the respective connotations of these words point in opposite directions: *programming* to a (genetic) program internal to the body and *induction* to a phenotype drawn out by an external influence (Bateson, 2001). Epidemiological connections are being molecularized: the individuals who were *in utero* as their mothers starved in Holland in the winter of 1944–1945 have been shown to have lower levels of methylation of IGF2 than their same sex siblings born after the war (Heijmans *et al*, 2008). Although the exact details of this system and the significance of methylation are far from being worked out, there is a plausible mechanism articulable in the language of molecular biology and visible via its tools: sequencing that picks up methylated cytosines, gene expression arrays and so on.³

In sum, this research is directed at the question of how things outside of the body are transformed into the biology of the body, in animals and humans. It proposes a specific molecular route from outside to inside, and suggests a mechanism by which the wars and famines and abundant harvests of one generation can affect the metabolic systems of another. It is a model by which social information organized as race, class, gender or economic status becomes embedded, not only in the bodies of those who eat, but in their capacity for replicating their own conditions of production. It has been suggested that so-called ‘racial’ disparities in health start as socioeconomic differences or events and become embedded biologically through epigenetic mechanisms: stress and poor nutrition disproportionately affect some people’s gene regulatory mechanisms according to the historically and culturally shaped striations of society – adult women who were compromised *in utero* suffer disproportionately from diabetes, obesity and high blood pressure, which in turn restrict fetal nutrition and birth size of offspring, putting them at higher risk of these diseases, in a biological perpetuation of embodied social difference (Kuzawa and Sweet, 2009). What may look like genetic ‘racial’ differences between groups of people in something like diabetes incidence is recast as the physiological sign of a population that has recently undergone ‘severe cultural and economic disruptions and

3 Historian Michel Morange has commented that assuming plasticity at a molecular level corresponds to plasticity at scales of whole bodies is often not backed up by any particular evidence, and glosses over the precise way in which plasticity might scale up from the molecular to the physiological level (Morange, 2009).

nutritional stress' (forced relocation, indentured labor, poverty), followed by rapid transitions to Western diets and sedentary lifestyles, political violence that shapes present and future metabolisms (Benyshek, 2007, p. 14). This is a very specific form of naturalization of social change that recasts social suffering as molecularly heritable, the past borne forward into the future via a metabolic interface that modulates 'predictive signaling' to subsequent generations about the world they will be born into (Kuzawa, 2005).⁴

This may sound like biological fatalism in just another form, but the great hope of epigenetics is the essential plasticity of the body: if the body is open to environment, then it is open to environmental intervention. Might we then be able to treat the metabolic diseases of adulthood – diabetes, obesity – by engineering the diets of pregnant women, infants, children and adolescents? This is a perspective that sees critical windows of development as 'critical windows of intervention' (Lawlor and Chaturvedi, 2006). Food as a kind of molecular delivery system to be incorporated into social engineering is the image implicit in the explicit question of manipulating long-term health through diet that frames almost every paper in nutritional epigenetics. Although the hopeful narrative is the possibility of overcoming past deprivations and difference, any interventions pursued – whether through the logic of consumer marketing, personalized medicine, social policy or public health – are themselves potential reinscriptions of social, economic and cultural difference.

Three: The experimental formalization of food

That the body is understood, depicted and (it is hoped) cared for in molecular terms in nutritional epigenetics is part of the broader 'molecularization' of biology over the past 100 years (De Chadarevian and Kamminga, 1998; Rose, 2006). Molecularization, as described by Rose, involves the progressive perception, manipulation, conceptualization and capitalization of molecular spaces and processes of the body in life science. The experimental and epidemiological logic described above depends on a subcellular mechanism interacting with the molecules of the outside world. The outside world, then, must enter into the metabolic process somehow; it too must be understood, investigated and manipulated at the molecular level to trace how inside and outside connect. Nutritional epigenetics is thus part of a twenty-first century molecularization of the environment answering to this twentieth century molecularization of the body (Shostak, 2005).

Not all molecularization is the same. Of significance is not the fact of delineation of environments as molecular, but that these environments are seen as bioactive with very high specificity – these molecules are investigated in relation to one another, within long chains or nets of causality across space and time that reach in and through the body. Previously, important boundaries between organism and environment – skin, mucous membranes, placentas, immune 'defenses' – are not particularly significant to the organization of these causal networks, causing definite ontological upset about outside and inside, about 'the social' becoming 'the biological' through bodily 'regulating transaction zone[s] with the ability to transform passing objects' (Beck and Niewöhner, 2006, p. 224).

⁴ The analysis offered in this paragraph was shaped by the commentary of Brad Weiss on a panel called 'Eating NatureCulture' at the 2010 meetings of the Society of Cultural Anthropology.

This is not a collapse of inside and outside because everything is molecular, but a rearrangement of interrelation. This rearrangement links gene regulation by food directly to social regulation of food, because both are part of a network that connects the human food environment to subcellular circuits of methyl groups and action at the surface of DNA through the intermediation of metabolism. The metabolic interface is not located anywhere in particular – it is not a structure or an organ that stands here or there, defining the spaces on either side of it – rather, it is a dynamic net of molecules that both interacts with environmental molecules and is iteratively conditioned in the parameters of that interaction by exposure to the environment.

To understand how food becomes a molecularized environment, I turn now to the question of what, exactly, is food in the experimental system. What do animals eat, in the experiments detailed above? It turns out that scientific animal diets are as much determined by the history of the industrialization of agriculture and the rise of processed foods as human diets are. Experimental animal diets are purchased from commercial suppliers and are of several types. First, there are the so-called ‘natural’ ingredient diets, formulated with agricultural products such as whole grains (for example, ground wheat, ground corn, ground oats), mill by-products (for example, wheat bran, wheat middlings, corn gluten meal) and high-protein meals (for example, soybean meal, alfalfa meal, fish meal), and contain added minerals and vitamins (Heindel and vom Saal, 2008, p. 389). ‘Purified’ diets are made with refined ingredients such as casein, soy protein isolate, sugar, starch, vegetable oil and cellulose. Finally, there are ‘chemically defined’ diets, which are made with chemically pure compounds such as amino acids, sugars, triglycerides, fatty acids and inorganic salts.

Rodents being used to test the epigenetic effects of different diets are often fed chemically defined – or ‘synthetic’ – diets with the methyl-group-donating substances present or absent. A synthetic diet allows the researcher to know exactly what is going into the animal, because the nutrients are mixed together from single pure compounds. It is supposed that the diet contains the same components as a natural one, with the same key nutrients – the only difference is supposed to be in the level of control the researcher has over the ‘input’ in the experiment. By contrast, a ‘natural’ diet is uncontrolled to a certain extent: a whole grain is a complex and variable thing. In one of the experiments described above, newborn mice were weaned and then fed three contrasting diets: a natural diet, a synthetic diet that had been depleted of methyl donors and then resupplemented, and a synthetic diet completely deficient in methyl donors (Waterland *et al*, 2006). The natural diet and the supplemented synthetic diet were controls: one is supposed to be the synthetic copy of the natural diet, only built from food’s basic building blocks by the researcher so that its content is precisely specified. The experimental hypothesis was that the deficient diet would result in less methylation, whereas the two methyl-sufficient diets would not.

However, it turned out that the two synthetic diets both resulted in lowered methylation. This anti-intuitive result suddenly brought the synthetic diets into focus. The investigators were moved to ask for the first time what exactly was in the synthetic diet – to read the label, as it were. It turned out that the synthetic diets differ from the natural ones in fiber and sugar content: they have a high sugar content to make them palatable to the mice. The exact cause of the difference in effect on metabolism between the natural diet and the supposedly exact synthetic copy remains obscure, but points to the difficulties of singling out single nutrients

for discrete epigenetic effects. The diets are treated as vehicles for a set of molecules whose effects will be measured by looking at the methylation of gene promoters; the rest of the content of the food disappears until it disrupts experimental expectations.

It is not surprising that these researchers should have assumed that a natural 'chow' diet could be exactly mimicked by a synthesized diet; the first synthetic laboratory animal diets were developed many decades ago, and under the classic model of metabolism elaborated in the first section of this article, it did not matter if a methionine came embodied in a grain or was added as an element to a synthetic diet. Internal chemistry was not seen to distinguish one molecule from another. This logic of equivalence is now crumbling, for animals and humans. For the researchers, the unexpected effects of the synthetic diet threw into question the basic logic of nutrient substitution, well beyond the laboratory: 'just as the synthetic control diet used here was previously thought to be an adequate substitute for natural ingredient diets, infant formulas are essentially semi-synthetic substitutes for human milk. It is, therefore, possible that persistent differences observed between formula-fed and human milk-fed individuals are the result of epigenetic alterations induced by subtle nutritional differences between human milk and infant formula' (Waterland *et al*, 2006, p. 712). We intentionally create animal models of human ills, but are nonetheless sometimes surprised by what appears when we look in that mirror.

There has been much thought devoted to how experimental animals have been bred, but up until now, little attention to how they have been fed. Such experimental disruptions have turned the scientific gaze back onto rodent chow, which has hitherto been an entirely banal part of experimental practice, barely meriting any attention other than standardization. This particular black box has now reopened. In 2007, the National Institutes of Health in the United States held two workshops dedicated to the question of the estrogen content of experimental rodent diets, and the batch-to-batch variability of commercially available animal food (Heindel and vom Saal, 2008). Because the diets are made from plant sources, and plants naturally produce hormonally active compounds, the diets can vary in their effect on animals. For example, soy contains two molecules that become estrogenically active upon digestion, genistein and daidzein. Eliminating plant-derived estrogens (phytoestrogens) from animal diets altogether does not seem to be a viable option, as complete absence of phytoestrogens from the diet also seems to cause abnormalities. The panel recommended heightened awareness of the exact content of experimental animal diets by feed manufacturers and experimental scientists, and an attempt to reduce batch-to-batch variability in naturally occurring bioactive substances such as soy isoflavones.

Soy-derived genistein is one of the molecules that nutritional epigenetics has focused on. Findings published in 2006 indicate that agouti mice whose diets were supplemented with genistein had offspring whose coat colors shifted toward brown, indicating increased methylation of the agouti promoter (Dolinoy *et al*, 2006). Genistein is a socially significant molecule, in part because soy is an economically and socially important foodstuff (Whatmore, 2002). Soy is consumed in the form of soymilk and tofu and edamame, but perhaps more importantly it is an ingredient commonly used to increase protein content or lend texture and form to foods, and is a central component of the feed given to agricultural animals such as pigs. Pigs have metabolisms, too, and we eat them. It is not at all clear what the effect on metabolism is of eating bodies that themselves have had their metabolisms patterned by industrial agriculture. 'You are what you eat' may be now

extended: you are what you eat eats. Soy is also frequently used as a base for infant formula; if nutrition in early life has an impact on gene regulation that is then carried through the life of the individual, soy content in infant formula would be of more concern than the soy content of adult diets. Of course, the experiment does nothing more than signal that soy in the diet can affect gene methylation; it does not indicate whether this is a good, bad or neutral occurrence, what kinds of dosage might have health effects, nor whether these effects happen in humans in the same way as in mice. Nonetheless, the results seem highly applicable to human affairs exactly because of the ubiquity of soy.

A second socially significant molecule that feeds these experimental animals is folic acid. To recapitulate, in the experiments described above with the agouti mouse model, the mice are given diets that are either short of or long on substances that participate in the methylation process: methyl group donors such as betaine, choline and folic acid. Folic acid is perhaps the substance most familiar to a non-scientific audience, due to relentless encouragement of women to make sure they get enough of it before and during pregnancy. Because folic acid supplementation has been shown to decrease the incidence of neural tube defects and anencephaly when consumed in the first trimester of pregnancy, mandatory folic acid fortification of all wheat products in the United States was instituted as a public health measure in 1998. Currently, over 65 countries worldwide have mandatory fortification of wheat or maize flour or both; it is an issue under active debate in the United Kingdom, whereas other European countries do not mandate fortification (Lawrence *et al*, 2009).

Folic acid is a synthetic form of a molecule whose natural form is called folate. Folate is present in many foodstuffs, particularly leafy green vegetables; above and beyond wheat fortification, folic acid is added to many 'functional foods' such as nutrition bars marketed to women. Consumers have little control over the amount of folic acid they consume, and pregnant or periconceptual women are encouraged to take an additional folic acid supplement on top of their regular diet, which of course includes fortified foodstuffs. Studies after 1998 in the United States have indicated that unmetabolized folic acid is present in the blood of most individuals – including children – sometimes at 'supraphysiologic' levels (Smith *et al*, 2008).

At first, fortification seemed a public health triumph, as the rate of neural tube birth defects has dropped markedly in the United States since the introduction of this policy. The debate has begun to reopen however, as questions are raised about fortifying the diet of the entire population in order to target a select class of women of reproductive age. The question has been raised whether mandatory folic acid fortification could be responsible for causing or exacerbating colon cancer in older adults, even as it prevents birth defects (Mason *et al*, 2007). Evidence from studies of maternal nutrition and birthweight in Pune, India raise troubling questions about the balance between folic acid and other vitamins: in the study, the children born to mothers with the greatest imbalance between high folate and low vitamin B12 levels were the most insulin-resistant (Yajnik *et al*, 2008). It is Indian national policy to provide iron and folic acid to all pregnant mothers, but B12 is not provided, exacerbating the unevenness in the nutritional landscape and in any single body.

Folic acid, then, is for many populations a pervasive substance rather than a discrete thing that can be consumed or not; even when it is offered as a supplement ingested separately from food, it comes with the weight of national policy and common medical practice.

In countries with mandatory fortification, other than avoiding all wheat or maize products, one cannot choose to not eat a supplemented ‘semi-synthetic’ diet. Again, I should emphasize that it is not at all clear whether this population-wide supplementation is beneficial, harmful, neutral or a combination of all of these. The important point is that folic acid is something in the food environment that is outside of most individual’s control or perception.

The linking of food environments to other discourses of environmental exposure can also be seen in the content of experimental animal diets. The same animals being fed soy and folic acid are also being fed pesticides and plasticizers. The laboratory of Randy Jirtle at Duke University has been particularly central to promoting the phrase ‘environmental epigenetics’ and been active popularizers of epigenetics for the general public. They have attempted to counteract the under-methylation caused by exposure to bisphenol-A with folic acid supplementation in the agouti mouse model system, as if you could pit one substance against the other (Dolinoy *et al*, 2007). The endocrine-disrupting effects of bisphenol-A first came to scientific attention by accident, although it was originally researched in the 1930s as a synthetic estrogen (Vandenberg *et al*, 2009). In the late 1990s, mice being maintained as experimental animals in the investigation of the biology of ovulation suddenly started experiencing unexplained reproductive difficulties (Hunt *et al*, 2003). A thorough examination of the laboratory protocol uncovered the fact that the polycarbonate cages and water bottles used in housing the animals leached bisphenol-A, particularly after becoming worn or being washed at high temperatures. Animals subsequently intentionally exposed to bisphenol-A show changes to their reproductive systems and heavier body weights (Gross, 2007). Somewhat controversially, these changes are thought to work through epigenetic alterations to cellular genomes.

The linking of food-borne endocrine disruptors to methylation changes in a wide range of genomic regions in exposed rodent fetuses is another important aspect of food becoming environment in the laboratory. Pregnant rats exposed to the antifungal agricultural spray vinclozolin in the developmental window of sex determination in the offspring bore male rats with low sperm counts and poor fertility. Upon growing up, these rats were mated to non-exposed female rats, but impaired fertility persisted in their male offspring, and in their offspring in turn, for four generations. These effects were thus transmitted through the male line, and researchers argue that the mechanism of heritable damage to the male reproductive organs is epigenetic in origin (Anway *et al*, 2006). Neither vinclozolin nor bisphenol-A is in itself a foodstuff. However, as fungicide and contaminant, they are ingested along with food; with them, food is drawn into the ‘chemical regime of living’ more usually associated with synthetic chemicals (Murphy, 2008). Vinclozolin is commonly used on crops such as wine grapes, whereas bisphenol-A is widely used in can linings in canned food and drinks, as well as plastic food containers, dental sealants and medical tubing.

In sum, food is transformed in these experiments into a set of significant molecules that have certain measurable effects on gene expression. Even when the ‘whole’ food imposes itself on the research agenda, as with the puzzling difference between natural diets and their synthetic copies, the molecular culprits for difference are sought – phytoestrogens, for example, have been singled out as in need of control in the experimental system. In these experiments, the aim is to measure how genistein or folic acid changes the molecular

status of the agouti gene promoter, and thus gain some insight into the effects of prenatal and early postnatal diet on methylation in the developing organism. Thus, while the animals are fed ‘chow’, whether of a natural or a synthetic origin, this system is meant to measure molecular effects. Molecularization has the effect of rendering the food itself a fuzzy background vehicle for bioactive molecules, both of the harmful and the helpful variety.

We may now answer the question of what kind of environment food is with some specificity. Both in its particular experimental configuration – focusing on molecules such as genistein, folic acid and bisphenol-A – and in hypothesis generation, food is depicted as an enveloping molecular medium. In the words of one researcher, nutrition is ‘the wind that blows over the developmental landscape’; the landscape is contoured by genetic possibility, but nutrition blows over it at critical periods in development (Waterland, 2006b, p. S138) (Figure 1). The image of the fetus immersed in its *in utero* environment accentuates this sense of the body forming in its medium; in turn the pregnant body as environment is a point of concentration of the pervasive. It is here that the various forms of regulation articulate, with maternal metabolism as the intersection of food, food regulation, nutrition as medicine, self-regulation, ideas of intervention, hormonal regulation and the heritability of patterns of gene regulation.

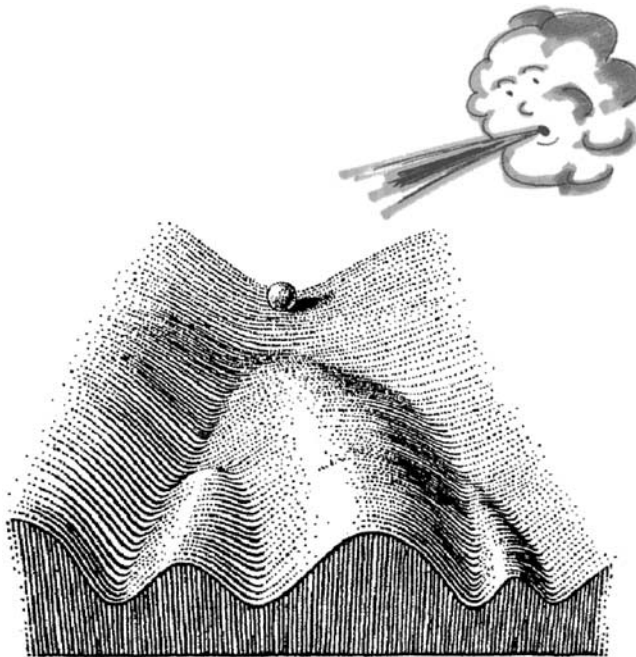


Figure 1: In this diagram by embryologist C.H. Waddington, the landscape is contoured by genes (represented by the straight lines) that pull on the landscape like guy-wires. The portion of the embryo poised at the top is not determined to go one way or another, but the landscape will make certain routes down the hill more likely, which Waddington referred to as ‘canalization’. Nutritional epigeneticist Robert Waterland likes to represent nutrition as the wind that additionally influences cells during development, adding a contemporary variation to the classic diagram (Courtesy of R. Waterland).

Four: The molecularization of food

The specific example of nutritional epigenetics, with its focus on methyl-donating micronutrients and genistein, is produced by – and is a force in producing – a more general molecularization of food in both science and consumer culture. Food's biological activity and its connection to human health, its pathogenicity or therapeutic power, becomes understood in terms of how outer molecules articulate with inner molecules in a life of eating. Although nutritional epigenetics does not necessarily have anything to do with the genetically modified organisms (GMOs), nutrigenomics, functional foods or food nanotechnology discussed below, it is important to think through their common context. For all these foods and food sciences, the distinction between food and drug is becoming blurred, and with it the distinction between eating and medicating. To borrow from epigenetic language itself, we may see developments in enhancement and preventive cultures – the 'better than well' culture of contemporary Western medicine – as an important environmental determinant for the shape of nutritional epigenetics (Elliott, 2003). Consumers eat 'for my wellness, not just my illness', in the reach for enhancement and imagined protection of the body from toxins or stress, and they try to consume the biological power perceived to reside in some molecules and not others (Nichter and Thompson, 2006).

Genetically modified foods are perhaps the most controversial example of how food is manipulated, discussed and, in this case, protested at the molecular level. Although genetically modified foods and nutritional epigenetics are not necessarily linked in any way – there is no indication, for example, that the genetic engineering of food changes its epigenetic effects – it is useful to think of them as separate instances of what we might call a vivid *molecular imagination*. This molecular imagination has been established in part by the public controversies around GMOs, exactly because the molecular structure of food is highlighted. Its genetic constitution is emphasized because it is partly manmade, and the controversial, potentially dangerous ingestion is the taking in of this man-made genetic construct. What modified genetic material does in the body that eats it, and how much it matters is of course a topic of much debate. Of interest here is not danger or safety, but the imaginative act of thinking, visualizing and controlling food as molecules that interact with our internal molecules, with a particular boundary-dissolving effect: one's corporeality is much more vividly rendered as continuous with the landscape and the social nature of agriculture through the necessary act of eating.

Genetic modification causes consumers to 'see' genes in foods, where before they did not, and wonder about the effect of those genes once digested. Surveys in Austria, for example, done in 1996 after widespread media coverage of the introduction of genetically modified crops into Europe, posed the question of whether only genetically modified tomatoes have genes and naturally grown ones do not, or if both have genes; this was answered correctly by 33.5 per cent of respondents, which is apparently slightly less than the European average in response to this question, at 35.1 per cent (Wagner *et al*, 1998, p. 19). Commenting on this result, Wagner *et al* point out that it is thus not surprising to see headlines appearing in 1997 such as 'Keep Austria Gene Free'. Whether or not one knows that there are genes in the food regardless of its engineered status, 'GM Free' labeling practices paradoxically highlight genes as things to think about when thinking about food.

Nutrigenetics and nutrigenomics, which seek to identify genetic variation relevant to food's absorption, processing and effect in the body, is also absorbed with the molecular relation between food and DNA. This research focuses on genetic sequence differences between individuals, and how different versions of particular genes might affect a body's reaction to food. For example, people process caffeine at different rates if they possess different alleles of a gene coding for an enzyme expressed in the liver involved in caffeine metabolism (Cornelis *et al*, 2006). The marketing of nutrigenomic tests to consumers that will putatively tell them how to eat 'for their genes' personalizes a sense of foods having a medical function in the body (Saukko *et al*, 2010). Nutrigenomics is interested in immediate and reversible nutrient–gene interactions, such as when polyunsaturated fatty acids bind to nuclear receptors and immediately affect gene expression in those cells. Other genes can be directly activated by amino acids; in this way the organism can respond metabolically to its changing diet, and these changes are both immediate and reversible. Epigenetic changes, by contrast, are thought to work by 'reprogramming' or 'resetting'; the nutrient changes the long-term set-up of gene expression, it acts early in life, and it 'sets' the pattern for the life of the organism and perhaps into further generations. Despite their differences, the fields share the understanding of food as being active in its component molecules, entering and interacting with the 'molecular makeup of each individual' (Mead, 2007, p. A584).

The rise of 'functional foods' places the emphasis on particular biologically active substances rather than on genes (or lack thereof), but the molecular optic here is also intensely cultivated. Food scientists, companies and consumers increasingly push toward foods that are supposed to carry a health benefit above and beyond the nutritive value provided by the caloric content, vitamins or minerals in that food (Lawrence and Germov, 2009). The antioxidant is a good example of the functional food; regardless of the nutritive value of the foodstuff, the antioxidant is supposed to reduce damage to cells and DNA from oxygen free radicals in the body, and thereby protect the consumer from cancer or other diseases. It is almost beside the point whether any given consumer understands what an antioxidant is; many consumers can rattle off a list of substances from omega-3 fatty acids to polyphenols that are supposed to benefit their health, learned through exposure to everyday supermarket labeling. It has been suggested that this category of foodstuffs should be renamed 'functionally marketed foods', for it is their mode of emphasizing component nutrients and claimed health benefits over other aspects of a foodstuff that distinguishes them from other kinds of food (Scrinis, 2008). The market share for functional foods has been steadily growing in developed nations worldwide, led by successes such as probiotic yoghurt, oat products advertised to have beneficial effects on cholesterol levels, and products containing omega-3 fatty acids (Heasman and Mellentin, 2001). Probiotics, of course, concern not molecules but bacterial cultures, but the sense of food being medically active because of its microscopic configuration is the same.

The rise of functional foods is related to food engineering, as the goal of intervention is to enhance or add the health benefit to a foodstuff. Food nanotechnology is now entering the field, with its distinctive 'bottom-up' approach to manufacturing, beginning with entities at the molecular-level scale and using their tendencies to self-assemble to build new things. Research in food nanotechnology is directed both at food packaging and food itself, sometimes focusing on the boundary between them with the development of edible packaging. The hope is that molecules with antimicrobial properties can contribute to food

safety through ‘self-cleaning’ packaging, that foods can be milled down to or self-assembled up to an optimum size for absorption in the gut (a kind of high-tech predigestion), that different tastes for the same food might arise from delivering its molecules at different sizes, and that nanostructures could be used to create the controlled release of nutrients in the body.

Nanotechnology is part of the drive toward making food functional – a thickener should not just thicken, it should provide protein and enhance mood. For example, an enzyme from a certain bacterium (*Bacillus licheniformis*) when applied to the milk protein alpha-lactalbumin generates ‘building blocks which self-assemble into nanometer sized tubular structures’ (Graveland-Bikker and de Kruif, 2006). These milk-derived nanotubes could serve as thickeners, because they are stiff, or as an encapsulating delivery mechanism for nutrients or perhaps pharmaceuticals, because they are hollow. As an added benefit, alpha-lactalbumin is the principal protein in human milk; as might be expected, it is highly digestible, and has a relatively high tryptophan content, an amino acid that (in the sanitized language of nutrition science) ‘has been linked to positive effects on satiety and mood’. As any baby can tell you. Thus, the thinking goes, this most benign of starting materials can be used as an agent in the construction of palatable, nutritious foods with additional ‘functional’ properties.

Of course, food engineering applies not just to what humans want food to be like, but also to ‘errors by design’: ‘the traces of scientific and economic rationalisations of plant and animal bodies which, in their multifarious incarnations as human foods, become incorporated into our own’. Whether an ‘accidental’ presence such as dioxin, or an intentional one, such as an engineered milk protein, the bioactive molecule as ‘vector of incorporeality’ with its promise or danger is foregrounded (Stassart and Whatmore, 2003, p. 449). The physical act of eating becomes an incorporation point of bioactive molecules that are simultaneously material and social. We cannot help but ingest and in the act of ingestion and digestion are drawn into the social, technical and political networks of food production, regulation and consumption. We are what we eat – but also what our parents and grandparents ate, and what we eat ate, and other expansions of networks of significant ingestions.

We are living in a time of the reconfiguration of food as medicine, as curative or preventive therapy; foods are central to the work consumers undertake to affect their present and future health or to work toward the ‘perfect, imperishable’ body (Chrysanthou, 2002). Aimed at what Stefan Beck has called the ‘preventive self’, even health foods and ‘whole’ foods are promoted for their abundance of beneficial molecules or their freedom from harmful ones; spinach becomes a ‘good source of phytonutrients’ in nutritionist framing (Pollan, 2007). Conversely, food can also figure as the carrier of molecular substances that act as toxins or misplaced signals that perturb the body’s regulation. That in this time food appears in nutritional epigenetics as a kind of mass molecular milieu for the epigenetic topography of populations is then one particular manifestation and intensification of this shift.

Conclusion: Food as exposure

In the nineteenth century, the connection between the chemistry of food and bodily chemistry that marks the emergence of nutrition science was from the outset seen to have

philosophical and political urgency for the social management of human biology. The physiologist Jacob Moleschott asserted *Ohne phosphur, kein Gedanke* – there is no thought without phosphorus, a claim that followed on chemical analyses showing the brain to be rich in phosphorus-containing fat. He recommended meat, bread, fish, eggs and peas in particular as furnishing the materials necessary to producing healthy brain tissue and thus robust products of brain tissue – thoughts. Inequality in the world reflected this material basis of human thought and work, and he decried the starch-based, low-protein diets of the world's oppressed in a passage that was, not surprisingly, not included in the English translation of *The Chemistry of Food and Diet: For the People*:

Sluggish potato blood, is it supposed to give muscles the power required for labour, or to give the brain the stimulating impulse of hope? Poor Ireland, whose poverty breeds poverty. You cannot win in the struggle against your proud neighbour ... You cannot win! For your diet calls forth powerless despair, not enthusiasm, and only enthusiasm is capable of resisting the giant through whose veins courses blood rich with power. (Moleschott, 1850, quoted in Kamminga, 1995, p. 26)

Today, both scientists and 'the people' might be more interested in diabetes than revolution, but the molecular materialism of the twenty-first century is no less consequential for social interventions in biological being through food; metabolism is no less of a source for understandings of the crucial interconversions of matter that tie society and biology together in specific circuits of exchange. The analysis provided above describes a set of scientific and social shifts that have profound consequences for food policies and individual food practices in their particular connections of gene regulation to social regulation. Methylation, thus far the key explanatory mechanism for tying the outside and the inside of the body to changed physiology with particular outcomes, is both a chemical change at the surface of DNA and an imprint of nutritional status and national policy regimes such as mandatory folic acid fortification of the food supply.

This is not to say that the politics of determining molecular environments are settled. Rather, this analysis points to the re-emergence of metabolism as a zone of contestation over who should eat what and where responsibility lies for stewardship of the food environment. Even as the pregnant body is brought into focus as a powerful potential forum for intervention in the metabolic systems of future generations, with clear ethical consequences for the management of diet during pregnancy as well as the regulation of food fortification for everyone, at the very same time responsibility is being distributed laterally and vertically away from pregnancy in experiments on the effects of pesticides on male rats, and epidemiological attention to grandparental and male nutrition (Anway *et al*, 2006; Pembrey *et al*, 2006). The idea of male/female or generational responsibility for the future health of generations is simultaneously in tension with the very idea that individuals could meaningfully control their environments in such a way as to intentionally direct future phenotype. There are clear implications for food as a discrete object that can be refused versus food as a miasma in which people are immersed, whatever the gender of the eater.

Although I have placed emphasis on the emergence of food as a pervasive environment in these studies, it should be noted that the very cultural forces that drive the search for health-giving molecules in food simultaneously pull epigenetics into relation with strong

individualizing features of contemporary consumer society. Food as exposure does not necessarily entail only one way of controlling that exposure in the name of human health. Food exposure controlled by individual choice implies that personalized nutrition will be part of personalized medicine, drives the production of consumables for health and increases the imperative to monitor food intake at the molecular level, thus increasing the susceptibility of publics to molecularized marketing. Already there are some indications that the logics of personalized privatized genomics are being directly converted into personalized epigenomics: a recent study argues that regions of the genome that show a lot of variation in their methylation levels between humans but stay stable within one individual over many years could be used ‘to uniquely identify individuals in an epigenetic signature akin to genetic fingerprinting’, a finding that forms the basis for a provisional patent filing by Johns Hopkins School of Medicine (Feinberg *et al*, 2010). Some genomes, the authors write, may be more susceptible to epigenetic lability than others, suggesting a combination of genomic identification and personalized epigenomic stewardship as a management technique for either innate or environmentally determined susceptibility to disease.⁵

Thus, even in the midst of the emergence of a powerful health-determining environment, politics to a certain extent depends on where you put your difference – or where you look for it. Some research varies diets on similar genetic backgrounds, other research queries methylation as a manifestation of innate genetic difference that determines how environments will matter. Although talk of ‘implications’ suggests that the impact of epigenetics will lie in the future and what we will do or might do with this knowledge, to a certain extent the outline of the ethics and politics of food as medicine is already visible in existing experimental design and explanatory models of metabolic disorder. Although there is heterogeneity around the individual–social axis, the two narratives of exposure and its control do not have equivalent force in the field. With choices of food-borne environmental toxins, micronutrients pervasive in the food supply by government mandate and substances infrastructural to food processing, these experiments depict food as a pervasive environment.

In addition, in terms of intervention, explicit doubts have been raised about individual energy or protein supplementation of pregnant women as a reasonable strategy for raising birthweights and improving infant health. Meta-analyses of studies of protein and energy supplements for pregnant women show very little movement in birthweight as a result of such intervention, and in the case of high-protein supplements, adverse effects (Kramer and Kakuma, 2003). As discussed above, epigenetic work throws previous modes of targeting individual nutrient consumption into doubt, increasing wariness about substitutability of synthetic or purified substances for whole foods, attention to potentially damaging effects of prior technical ‘improvements’ to food, and worry about the balance between nutrients in a complex metabolic environment. All of these factors act as additional brakes on any easy leap to translating the experimental and epidemiological work described above into particular changes to eating practices prescribed to individuals.

5 As Margaret Lock has observed, the rise of new biological thinking around RNA and chromatin does not necessarily translate into clinical practice, or practices of screening for disease predispositions at the genetic level (Lock, 2005). The politics of epigenetics emerges in relation to, rather than displacing the politics of genetics.

The broader molecularization of food discussed above intensifies a sense of food as an immersive environment. The epidemiological work correlated with molecular epigenetics also contributes to this framing, as researchers are unable to access information about what any one individual ate during a particular year in Northern Scandinavia, or just how food-deprived any particular mother was during the Dutch hunger winter and how that correlates to that individual's offspring. What *is* accessible is information about the size of harvest, the collective experience of populations – individuals are treated as immersed in their historical conditions, and as a group can be related to their descendants' health outcomes, also as a group – this is the statistical nature of epidemiology. Thus, folic acid and genistein are environmental exposures in the sense that consumers cannot necessarily know how much they are consuming – these bioactive substances are in so many foods, and one cannot tell from how they look or taste or how they are labeled exactly how much of these substances are being imbibed. Protein deprivation or over-nutrition are studied as conditions that surround a whole group of people like a cloud.

In sum, food can be biologically active in its 'natural' state, in its manufactured or engineered state and in its unintentionally polluted form. It is in this way that food becomes one environmental exposure among others. Food has always been understood to be part of the environments in which animals and humans live; however, our moment is a historically specific one in which food is being understood, studied, depicted, engineered and ingested as a set of molecules, which exist in a cloud around us, and over which we often have limited individual control. Epigenetics is neither the cause of nor the sole place where this discourse is under construction, but is a particularly intense site of the experimental exploration of food as a conditioning medium rather than an energy source or building block of the body.

These concepts depart from the energy flows and material transubstantiation wrought by the internal chemical factories of classic metabolism. Instead, food shapes the conditions of its own future reception; in the framework proposed by nutritional epigenetics, nutrients in themselves or as determinants of maternal metabolism are information about the world that a body will be born into or grow up to inhabit. Molecules that enter the body, particularly during its 'critical periods' of development, act to shape the very metabolic systems that the body will process food with in the future. Thus, nature of the systems that run and react to the incorporation of food are reset by molecular exposure.

This new metabolism is no longer the interface between Man and Nature, as it was for the nineteenth and twentieth centuries, but a metabolism for the human condition in technical society, where the food is manufactured and designed at the molecular level, the air and the water are full of the by-products of human endeavor and manufactured environments beget different physiologies. This is the character of the study of metabolism in post-industrial nature – the layers of human intervention go all the way down, and the role of biomedicine is to understand and heal the body in the world that humans have made for themselves. Insofar as scientific knowledge and technical innovation can be hoped to rescue human health from the effects of previous manufactures and innovations, metabolism becomes a primary site for the social reshaping of the body and the hope for therapeutic intervention.

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