## Chapter 7

# Epigenetics: A Brief Introduction

You and I harbor trillions of “sub-creatures” in our bodies. I am not referring to the microorganisms in our guts, but rather the cells we consider our own — the constituents of our muscles and brains, our livers and bones, our lenses and retinas. Each of these cells, embedded in its supportive environment, sustains a dauntingly complex and unique way of life. If (which is impossible) we had first discovered such cells floating singly in a pool of water and had observed them through a microscope, we would have judged them to be distantly related organisms. Phenotypically (that is, in visible form and function) one cell type in the human body can differ from another as much as an amoeba differs from a paramecium.

And yet, all the cells in the human body have descended from a single cell (zygote) with a single genome.[1] And just as hundreds of different cell types have arisen from that one zygote, so, too, have the multicellular, intricately organized entities we know as lung, heart, eye, kidney, and pancreas, along with all our other organs. Supremely interdependent as these are, each is nevertheless a functioning organic world of altogether distinctive character.

For the past century these facts of development have been thought to present a (largely ignored) problem for the gene-centered view of life. The developmental biologist Frank Lillie, who had directed the prestigious Marine Biological Laboratory at Woods Hole, Massachusetts, and would go on to become president of the National Academy of Sciences, remarked in 1927 on the contrast between “genes which remain the same throughout the life history” of an organism, and a developmental process that “never stands still from germ to old age”. In his view, “those who desire to make genetics the basis of physiology of development will have to explain how an unchanging complex can direct the course of an ordered developmental stream” (Lillie 1927, pp. 367-68).

This ordered developmental stream, of course, includes generation of the hundreds of different cell types in our bodies. It is hard to understand how a single genomic “blueprint” — or any other way of construing a fixed genetic sequence — could by itself provide the definitive causal basis for these hundreds of radically distinct ways of living. If the blueprint is compatible with all of them, do we have compelling grounds for thinking that it fundamentally *determines* any one type of cell, or organ, let alone all of them together? One might reasonably expect that other factors direct the developmental process toward particular outcomes of such different sorts.

A more balanced understanding arises when we watch how every cell displays its character through its life as a whole. That character, in all its qualitative richness, somehow seems decisive. In the case of each cell type, DNA is *caught up in* a seamless and integral way of being. When we grasp this integral nature, we quickly realize that the idea of DNA as the crucial causal determinant of the whole is an impossible one. As a specific kind of liver cell passes through its developmental lineage, it must sustain its entire organization in a coherent and well-directed manner from one cell generation to the next — including, for example, the cytoskeletal and cell membrane organization described in Chapter 4 (”The Sensitive, Dynamic

Cell"). It must also bring about and orchestrate the elaborate performances of its chromosomes we saw in Chapter 3 ("What Brings Our Genome Alive?") — performances that are unique to each type of cell and that chromosomes themselves have no way to set in motion.

Every individual part, including DNA, is shaped by, and gives expression to, the character of a larger whole. Only when we recognize that genes participate in a living whole can we find an answer to Lillie's challenge "to explain how an unchanging complex can direct the course of an ordered developmental stream". The answer — so we will find — is that there is no unchanging complex. Genes, like all parts of a cell or organism, gain their identities and meanings only within the context of innumerable, interpenetrating, living narratives expressing diverse physiological characters.

## *An old problem newly recognized*

Passing from Lillie's day to our own, we find a peculiarly late-arriving acknowledgment of old problems. Here is where we encounter that rather mysterious and too often abused keyword of contemporary molecular biology: *epigenetics* (along with its companion, *epigenome*). The discipline of epigenetics drives today's effort to come to terms with the relationship between genes and the organisms that put those genes to such diverse uses.

But today the question has gained additional dimensions. The Human Genome Project and its successors surprised many by revealing an unexpectedly low number of human genes relative to many other organisms — roughly the same number, for example, as in the simple, one-millimeter-long, transparent roundworm, *Caenorhabditis elegans*. Many began to ask: If genes really do account for the organism in all its complexity, how can it be that a primitive worm boasts as many genes as we do? "As far as protein-coding genes are concerned", wrote Ulrich Technau, a developmental biologist from the University of Vienna, "the repertoire of a sea anemone … is almost as complex as that of a human" (Technau 2008, p. 1184).

A further revelation only compounded the difficulty: our own genome was found to have a great deal in common with that of many animals. It was reported, for example, that we share about 98.5% of our genome with chimpanzees. A good deal of verbal hand-wringing and chest-beating ensued. How could we hold our heads up with high-browed, post-simian dignity when, as the *New Scientist* reported in 2003, "chimps are human"? If the DNA of the two species is more or less the same, and if, as nearly everyone seemed to believe, DNA is destiny, what remained to make us special? Such was the fretting on the human side, anyway. To be truthful, the chimps didn't seem much interested.

All this news conspired to bring epigenetics to the fore. In 2010 the editors of the journal *Nature* wrote:

> By 2004, large-scale genome projects were already indicating that genome sequences, within and across species, were too similar to be able to explain the diversity of life. It was instead clear that epigenetics … could explain much about how these similar genetic codes

> are expressed uniquely in different cells, in different environmental conditions and at different times (Nature editors 2010).

And in 2015 a contributor to the same journal described a huge, epigenome-centered project, sponsored by the US National Institutes of Health, which was "likely to provide a leap forward in pinning down one of the central mysteries of biology: how do cells with the same genetic instructions take on wildly different identities?" (Ledford 2015). Lillie's old question had finally come center stage. But had the meaning of the question really been recognized? And what, after all, *is* this mysterious thing called *epigenetics*?

## *Epigenetics — a useful term?*

Etymologically, the word *epigenetics* suggests something like "on top of genetics" or "added to genetics". In common technical use, the word refers today to "heritable changes in gene function that are not due to changes in DNA sequence" — where the *DNA sequence* is a succession of nucleotide bases constituting the "letters" of the so-called genetic code, and *heritable* applies not only to what can pass from parent organisms to their progeny, but also what passes from any given cell to its daughter cells. In other words, *epigenetic* refers to that which is not rock-bottom genetics — not genetics proper (which conventionally centers on the DNA sequence alone) — while yet somehow bearing on *functional* genetics, both within organisms and between generations.

The common usage, however, remains deceptively gene-centered. This is shown by the prevailing notion that epigenetics has to do only with secondary "annotations" of the primary "genetic program". For example, researchers, having discovered certain chemical transformations of both DNA and the overall substance of chromosomes, typically refer to these transformations as innocent-sounding and transient "marks" on an otherwise fundamental and essentially unchanging entity.

It is hard to avoid the suspicion that biologists refer to the chemical transformations as mere marks only because they have concluded up front that whatever cells do with their genome cannot be considered genuinely transformative and creative — cannot redefine what a gene is. They prefer to keep the genome a kind of static, "eternal" essence (Chapter 22, "A Curiously Absolute Demand for Stable Variation") that, unlike every other part of an organism, need not continually *become* what it is or else cease to live.

Rather than think of epigenetics as the application of incidental marks, we could conceive it more realistically as encompassing all the ways DNA is caught up in the activity of its larger context and brought into service of the whole. I say "more realistically" because there is, in fact — as two molecular biologists have phrased it in the journal *Nature* — "an avalanche of biochemical evidence revealing a complex and versatile array of molecular mechanisms that regulate gene expression without changing DNA sequences" (Cervantes and Sassone-Corsi 2019).

In other words, what genes mean to the organism is not merely a matter of the DNA sequence or a “genetic code”. It is more a question of the many different ways an organism can employ its genes.

So the word *epigenetics* may usefully remind us that what is “on top of” DNA is nothing less than the functioning organism as a whole. But a word that threatens to encompass just about everything begins to lose its value as a special term. And this in turn suggests that we could just as well retire the word “epigenetics” and get on with describing how organisms carry out their organically integrated lives — express their own character — in part by “reconceiving” their genes in terms of that character.

## *Unexpected Discoveries*

In the mammalian genome, chromosomes normally come in pairs, one inherited from the mother and the other from the father. Any given gene occurs twice, with separate versions (*alleles*) located on the two chromosomes. These two alleles may or may not be identical. For example, there are mice that, in their natural (“wildtype”) state are dark-colored — a color that is partly dependent on a gene known as *Kit*. The mice normally have two identical copies of this gene. When, however, one of the *Kit* alleles is mutated in the laboratory a certain way, the mouse shows white feet and a white tail tip.

That result was perfectly natural (if you call such artificial gene manipulations "natural"). But it is also where the story becomes interesting. Scientists at the University of Nice-Sophia Antipolis in France took some of the mutant, white-spotted mice and bred them together (Rassoulzadegan et al. 2006). In the normal course of things, some of the offspring were again wildtype animals — neither of their *Kit* alleles was mutant.

However, to the researchers' surprise, these "normal", wildtype offspring maintained, to a variable extent, the same white spots characteristic of the mutants. It was an apparent violation of Mendel’s laws of inheritance: while the genes themselves were passed between generations properly, their effects did not follow the “rules”. A trait was displayed despite the absence of the gene previously corresponding to it. Apparently something in addition to the genes themselves — something “epigenetic” — figured in the inheritance of the mice offspring, producing the distinctive coloration.

Another group of researchers, led by Michael Skinner at the University of Washington, looked at the effects of the fungicide vinclozolin on laboratory rats. (Anway et al. 2006; Crews et al. 2007). Banned in Scandinavia and Europe at the time, but allowed on some crops in the U.S., vinclozolin is known as an endocrine-disrupting chemical. If pregnant female rats are exposed to it while their embryos are undergoing sexual organ differentiation, the male offspring develop serious problems as adults — death of sperm-generating cells, lowered sperm count and motility and, later, immune abnormalities and various diseases including cancer. The remarkable thing is that the effects were found to be transmitted over four generations without

weakening. That is, acquired characteristics — deficiencies in embryos brought on by fungicide exposure — were inherited by offspring who were not subject to the same exposure.

Puzzling results such as these put the question, “Are genes equivalent to destiny?” in a new light. In 2007 a team of researchers at Duke University reported that exposure of pregnant mice to bisphenol A (a chemical that was then used in many common plastics such as baby bottles and dental composites) “is associated [in the offspring] with higher body weight, increased breast and prostate cancer, and altered reproductive function”. The exposure also shifted the coat color of the mice toward yellow — a change again found to be transmitted across generations despite its not being linked to a gene mutation. Moreover, the changes brought on by the chemical were negated when the researchers supplemented the maternal diet with folic acid, a B vitamin (Dolinoy et al. 2007).

And so an epigenome that responds to the environment can respond to healthy as well as unhealthy influences. As another early illustration of this: researchers at McGill University in Montreal looked at the consequences of two kinds of maternal behavior in rats. Some mother rats patiently lick and groom their newborns, while others generally neglect their pups. The difference turns out to be reflected in the lives of the offspring: those who are licked grow up (by the usual measures) to be relatively confident and content, whereas the neglected ones show depression-like symptoms and tend to be fearful when placed in new situations.

This difference is correlated with different levels of activity in particular genes in the hippocampus of the rats’ brains. Not that the gene sequences are themselves mutated in the usual sense. Rather, the researchers found that various epigenetic modifications in the hippocampus alter the way in which the genes are employed (Weaver et al. 2004). Other investigations have pointed toward similar changes in the brains of human suicide victims who were abused as children (Poulter et al. 2009).

What has perhaps excited the general public most is this application of epigenetic studies to human beings. Take, for example, the frequently cited Dutch Hunger Winter during the winter and spring of 1944-45. The much-studied effects of this famine were found to extend, not only to the children of women who were pregnant during the months of hunger, but also to their grandchildren.

Such findings seemed to suggest that our environments and our responses to those environments can play a major, heritable role in shaping our lives. This encouraged in many the hopeful thought, “Maybe we are not really just gene-driven machines” — a thought that is surely is true enough, but also rather strange. I will try to explain.

## *Grasping at epigenetic straws — is it really necessary?*

Those early discoveries in epigenetics — especially when treated more expansively and brought more up-to-date (Chapter 14, ”How Our Genes Come to Expression”) — are truly profound and far-reaching in their implications. But they are profound only in the way everything about the character of organic life we have been discussing in the preceding chapters is profound.

Genes as self-sufficient or definitive First Causes simply don’t exist. They never did have a reasonable place in our conceptualization of living beings — something that early twentieth-century critics of gene theory clearly saw (Russell 1930). Every organic process, including every genetic process, is an expression of the life of the whole cell and whole organism. In other words, the only genetics we have is epigenetics.

All this is to say that the crucial thing, if we want to transcend the notion of organisms (or ourselves) as gene-driven machines, is to rise above the entire, spirit-killing picture of mechanistic, gene-programmed life processes. We need to recognize this picture for the fantasy it really is.

Anyone who doubts the scale of the challenge in this need only look at what began happening quickly after the discovery of “epigenetic” effects. No sooner had certain gene-regulatory “marks” been found on key elements of the chromosome than some began to suggest that they constituted just another “code” — an *epigenetic code* (Strahl and Allis 2000). An epigenetic “program” was said to contain “instructions” for “control of gene expression”. And so an editorial entitled “Time for Epigenetics” in the *International Journal of Biochemistry & Cell Biology* told us that

> The genome and epigenome together *determine* the phenotype and hence, the function and characteristics of a cell at any given point in development and during differentiation. At the core of gene regulation are elaborate *molecular programs* that alter the packaging of DNA into chromatin, thereby regulating DNA accessibility to transcription complexes and providing cues to the activation or repression of *gene regulatory programs* (Altucci and Stunnenberg 2009; emphasis added).

In other words, the attempt is to assimilate epigenetics to the existing understanding of genetic “programs” and “instructions”. The programs and the instructions simply become a little larger and more complex, but the same basic understanding of ourselves as collections of molecular automatons remains.

Or, again, we hear that the epigenome involves a “re-wiring of transcription factor circuits” (Tsankov et al. 2015), as if there were some fixed and standard genetic wiring scheme waiting to be rewired. But — as if biology as a discipline were somehow “of two minds” about such things — the authors of this paper healthily refer to the rewiring as “context-dependent” and “dynamic”. So the terminology appears to be impossibly conflicted. If in fact the governing

context is always to some degree fluid, dynamic, and shifting, where do we ever see anything remotely analogous to wires constraining all the relevant molecules to go where they need to go, and to do so in the right time, in the right quantities, and with the right molecular partners?

The picture of a wired cell may sound conveniently causal, but it makes no sense. Biologists are sooner or later going to have to decide which half of their descriptive language they are going to side with. Meanwhile, those of us trying to decipher what “epigenetics” really means can usefully remind ourselves that the deeper issue has to do with the overall terms of the description ultimately decided upon, not with particular “epigenetic” insights that are too eagerly assimilated to traditional, machine-based understanding.

Nothing is *merely genetic*. Every so-called genetic activity is an expression of its entire context, and therefore is altogether epigenetic. Genetics cannot be abstracted from the rest of the organism. So we can safely say, “All genetics is epigenetics”.

WHERE ARE WE NOW?

## Bringing Back the Organism

As we move along, we have been seeing more and more how the “molecule’s eye view”, whatever it may tell us about the physics and chemistry of molecules, is hardly definitive of biological meaning, for which a wider perspective is required. In the end, the meaning of things depends on what the cell or organism is *doing* in its coordination of countless diverse but interwoven processes. An organism just *is* its unified doings, its consistent way of living in its world.

It is perhaps in the field of genetics that biologists have most stoutly resisted this recognition of integral wholeness and significant context. Genes, conceived as First Causes, must exist in exalted isolation. But because of the intensity of research focused on genetics, it is also in this field that the illusions of strictly physical and chemical explanation of the organism are being most strikingly dispelled — even if geneticists are proving slowest at accepting the fact.

The brief introduction to epigenetics in this chapter will be greatly expanded in Chapter 14, “How Our Genes Come to Expression”. There I try at least to suggest the endless web of pathways through which the cell brings about its almost infinitely complex patterns of gene expression.

Then we will deepen this picture by bringing the gene into connection with heredity and evolution in Chapter 20 (”Inheritance and the Whole Organism”) and Chapter 21 (”Inheritance, Genetics, and the Particulate View of Life”). We will learn how it is that genes rendered the organism invisible to the evolutionist’s sight — and how false that substitution of genes for organisms has proven.

Finally, we heard Frank Lillie saying above, “those who desire to make genetics the basis of physiology of development will have to explain how an unchanging complex can direct the course of an ordered developmental stream”. We will get an entirely different view upon this statement when we discuss some work by the philosopher, Ronald Brady, in Chapter 12 (”Is a Qualitative Biology Possible?”). There we will encounter the perhaps initially disorienting truth that the “ordered developmental stream” is not what actually needs explaining, whether by genes or anything else. Order, after all, is itself the kind of explanatory understanding the scientist is always looking for. To recognize the *order* of the developmental stream is to recognize an organism’s explanatory principles. So the ideal formative movement of development might be regarded as itself the real “first cause” of the organism’s features, including its genetic features. The main thing in the way of our accepting this truth is our habit of taking material things as the explanation of movement.

## Notes

1. While this has often been taken to mean that the genome in all our cells is the same, we now know that this is far from the truth. Many people, in fact, possess some cells derived from entirely different bodies. For example, an embryo or fetus may assimilate cells from its mother, and there can be an exchange of cells between fraternal twins in the womb, even if they are oppositely gendered. Also, many gene mutations occur in cells during development and afterward, so probably no two cells in our body have *exactly* the same genome.

More important is the fact that, as shown by the radically different cell types in any one person's body, the *functional* genome differs radically from cell to cell.

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