



CHAPTER 1

Introduction

► **SEMANTIC**

Adjective /sɪ'mæn.tɪk/

Of, relating to, or arising from the meanings of words, the study of meaning

Semantic has become a term of dismissal. *That's just semantics..., I'm not going to enter into a semantic argument with you..., if you want to get semantic about it...*—you use the word today to suggest that the discussion is not worth your while. It's as if semantic is taking on the meaning of pedantic, the excessive, inappropriate, and annoying attention to minor details, in Finland described (impolitely) as *pilkunnussija* or (politely) one who has intimate intercourse with commas.

In telling the story of epigenetics, you must embrace semantics while keeping your inner pedant firmly under control. Today, this rich and fascinating avenue of scientific enquiry has not only captured imaginations, it has also captured multiple meanings. Two people discussing epigenetics may think they are talking about the same concept but have completely different and even opposing views of what it means. Someone seeking to construct a hypothesis based on epigenetics can find scraps of evidence from the multiple definitional buckets, building a structure that to the uncritical eye may look solid but lacks the compatible mortises and tenons for stability.

We can illustrate this house of epigenetic cards with a made-up example of a terrible study¹ idea justifiable by assembling the sprawling definitions of epigenetics.

¹The fact that I had to search to make sure nobody is actually doing this study at present is worrisome by itself.

► **HYPOTHESIS: SUNLIGHT CAUSES OBESITY IN GRANDCHILDREN THROUGH “EPIGENETICS”**

- Somebody’s epidemiology study showed that today’s grandparents were more sun-exposed as children, and today’s grandchildren are more obese, so sunlight is a candidate for nongenetic (epigenetic) effects on the health of these kids.
- We know that sunlight helps to create the active form of vitamin D in human skin, and vitamin D binds to transcription factors to regulate gene expression (epigenetic).
- Part of a gene regulation response is mediated through changes in methyl groups added to DNA (epigenetic).
- The vitamin D response to sunlight is therefore changing DNA methylation (epigenetic).
- DNA methylation can be passed from parent to daughter cells and from generation to generation (epigenetic).
- The sunlight response can therefore be passed on to the next couple of generations in a non-DNA-mediated way (epigenetic).
- By eating copious amounts of kale or another currently fashionable superfood, you can reverse the DNA methylation changes and change your health, overcoming the epigenetic curse of your ancestors (epigenetic).

This logic, deliberately exaggerated, is uncomfortably close to that underpinning real studies being funded and published today. Each step of the logic contains a basis in fact but also a weakness. In the final chapter we will break down this series of statements based on the deep dives of the intervening chapters, so that the reader can come away equipped to look more critically at today’s less well-supported research while retaining the excitement that should be prompted by our insights into epigenetics today.

This is why semantics must be an early and prominent part of a systematic exploration of the world of epigenetics. There are good reasons that there are multiple uses of this word—rooted in distant and recent history—involving some very human instincts and decisions. This book starts with an archaeological dig that reveals how we got to today’s definitional ambiguity and then carries all the definitions through the chapters as we explore their implications for human diseases.

So What Exactly Is Epigenetics?

At present, the common understanding of what is meant by the word epigenetics is that it describes how the DNA sequence of the genome is used, a higher level of regulation that can be influenced by the environment of the organism. Having said that, some people extend the use of the word to mean long-term memory, including from parent to daughter cells after a cell divides. Extending this further, some include the inheritance of a memory of a past event from one generation to another in multicellular organisms. Those who study regulators of gene expression, chromatin states, nuclear architecture, and other biochemical processes influencing the genome often describe their work as the study of epigenetic regulators. Researchers seeking a mechanism for how the environment leads to changes in health see these biochemical genomic processes as strong candidates for mediating these effects. The use of studies to test for changes in these biochemical genomic processes in people with certain diseases or exposures has become a major area of research, the epigenome-wide association study.

The common theme is one of a molecular mechanism for disease that resembles that due to genetic influences but is not mediated by DNA sequence changes. This concept is such an intriguing possibility that it has resurrected the idea that a characteristic acquired by someone during their lifetime can be passed on to their offspring, the idea of Lamarckism. All of these definitions and ideas have entered into the broader discussion of epigenetics, which has led to confusion when multiple definitions collide but has also been a major reason for enthusiasm about the possibilities in this field of biology.

WHY THE EXCITEMENT ABOUT EPIGENETICS?

The idea that there is a layer of information beyond the DNA sequence itself is very attractive, especially for those trying to understand puzzling questions about why certain individuals develop phenotypes and others do not. For example, there are conditions that are highly heritable, indicating that they involve substantial contributions of DNA sequence-mediated susceptibility. However, even for these conditions, identical (monozygotic [MZ]) twins, who share (almost) exactly the same DNA sequences (apart from a small number of de novo and somatic variants), are not always both affected, but have higher rates of concordance than for nonidentical twins or siblings,

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who only share half their DNA. This higher rate of concordance has been used as evidence revealing the genetic influence on these phenotypes, but the fact that the MZ twins are not 100% concordant for the conditions has been taken to indicate that nongenetic factors are also involved—what has been called “missing heritability” (Kaprio 2012).

Nongenetic factors in disease susceptibility could include numerous potential influences, but mostly end up grouped into the very broad category described as the influences of the environment. For example, it is quite reasonably assumed that someone having excess weight involves not only a genetic predisposition but also the influence of the individual’s diet (Walter et al. 2016). Apart from diet, the environmental exposures tested in these “Gene X Environment” interaction studies often include medications, toxins, psychological stress, metabolic factors, infections, and a range of other influences that are frequently studied using epidemiological approaches.

At the same time, there is interest in how genetic nondeterminism can be turned to one’s advantage. If genetic susceptibility increases risk but does not uniformly lead to disease, is the opposite possible? Can some sort of intervention tilt someone’s balance to make them relatively less likely to develop a condition? If there is an environmental influence that tilts risk toward disease, the logic is that there should exist a counterinfluence that decreases this risk.

A convergence of these interests has occurred in the study of epigenetics. If environmental exposures and stresses exert their effects on cells, there must exist a molecular mediator of these responses. There are multiple biochemical processes involved in expressing a specific set of genes in a defined cell type—if this property indicates a malleability of programming of the same DNA sequence in normal development, could it not also be malleable as a response to the environment and change the properties of a cell in a way that promotes or reduces risk of disease?

Epigenetics as a concept has stimulated interest for other reasons also. The property of malleability has also prompted the idea that therapeutic approaches involving new types of pharmacological agents or other interventions could reverse detrimental changes. The idea has been that, unlike gene therapy to reverse DNA sequence mutations, which is resisted by cellular processes that guard against DNA damage of any kind, the inherent reversibility of epigenetic regulatory mechanisms should make them easier to treat.

Furthermore, there is a definition of epigenetic properties that involves how a cell remembers past perturbations and exposures, retaining

an “imprint” of these stresses at the molecular level in the absence of the original stimulus. The potential that epigenetic mechanisms could confer a memory of past events on a cell is possibly their most intriguing property, prompting studies that link molecular processes to events that occurred earlier in the life of an organism, during the period of its development, and even to events that occurred in prior generations that appear to have left residual phenotypic characteristics.

In short, the excitement about epigenetics is prompted by several quite distinct avenues of research, which in turn reflects the breadth of the processes currently encompassed by the word “epigenetics.” This broad field of research includes many disciplines now worth our attention.

THE FOUNDATIONS OF MODERN EPIGENETICS

Although this book emphasizes the links between epigenetic processes and phenotypes—in particular, mammalian organisms and disease phenotypes—the roots of the field include many nonmammalian model organisms. In fact, probably the first striking example of what later came to be called an epigenetic process was from studies of the fungus gnat *Sciara coprophila*, which was found to have a mechanism for sex determination involving selective elimination of paternal X chromosomes from the cell nucleus (Crouse 1960). The fact that the embryo could distinguish between maternal and paternal chromosomes was assumed to involve an “imprint,” or a molecular memory of the origin of a chromosome, based on the germline in which it had been most recently. Implied was that this could not be determined by DNA sequence differences between the chromosomes, as it was always the paternal chromosome that was lost whatever its genetic characteristics.

This observation combines two elements to which this book will return in more detail—epigenetics as a cellular memory and epigenetics as a molecular process. In the early days, epigenetics was more synonymous with cellular memory, but, perhaps inevitably with the explosion of biochemical and genomics assays and analytical methods, the research began to be focused on the molecular processes involved.

Technology has been a major driver of insights into the human and other genomes and has also driven insights into the molecular regulators of the expression of the genes embedded in these genomes. One early tool that proved extremely useful was the use of enzymes that selectively failed to cut DNA when the sequence at which it acted was modified. Normally we think

of the DNA making up the genome as being composed of adenine, cytosine, guanine, and thymine (A, C, G, and T). What became apparent was that cytosines could be selectively modified, adding a small molecule consisting of a carbon and three hydrogens, a methyl group, creating what can be thought of as a fifth nucleotide, methylcytosine. When researchers studied DNA from living organisms, they were intrigued that methylcytosine looked like it varied in content between cell types, in response to environmental exposures, and with gene activity. A pivotal biochemical discovery was that the pattern of DNA methylation on a DNA molecule acted as a template to recreate the same pattern in daughter cells after their division. This finding linked the ideas of epigenetic memory and the biochemical mediators at the molecular level.

The ability to test the methylation of DNA was exciting but was soon accompanied by the realization that not all organisms methylate their genomes, raising the question whether DNA methylation is of major importance in the regulation of memory and gene expression. A more universal property of eukaryotes (from the Greek *εὖ* true, *κάρυον*, nut, referring to the readily visualized nucleus of everything from yeast to mammals) is the packaging of DNA by histones to form chromatin. By chopping up the chromatin into small pieces and then isolating proteins or modifications of proteins using antibodies, we were able to enrich regions of DNA where these (modified) proteins were located. This chromatin immunoprecipitation (ChIP) technique added layers of insights into the regulation of genes and was applied to understand the memory involved in phenomena like imprinting.

Although initially it was only possible to explore one locus at a time in the genome for DNA methylation or chromatin properties, or sequences that were highly repetitive in the genome, the advent of DNA microarrays representing large numbers of loci and the later development of massively parallel sequencing technologies transformed the insights we could obtain. The ability to look broadly throughout the genome began to be referred to as the study of the “epigenome” and the technologies as “epigenomic.” Examples of these technologies will be profiled more comprehensively in Chapter 6.

In addition to the biochemists, epidemiologists became deeply involved in the field of epigenetics. An influential early figure in the field was David Barker (1938–2013) from the University of Southampton in England. His insight was that adult disease risk may not be mediated solely by events

during adulthood but may also be influenced by events occurring as early as during our prenatal development in the womb. This was the inspiration behind the field that came to be known as the developmental origins of health and disease (DOHaD). When considering a mechanism for how a temporally remote perturbation could manifest its effects later in life, attention focused on the same epigenetic mechanisms that mediate memories in normally developing cells instead mediating disturbed and disease-predisposing signals following a stress earlier in life.

Other epidemiological observations were also prompting consideration of epigenetic mechanisms. Two separate studies were being performed concurrently that were asking similar questions. One was a study of individuals in Överkalix in Sweden whose grandparents had experienced a limited food supply; the other examined the offspring of Dutch mothers who suffered famine during the winter of 1944–1945. In each case there were associated phenotypes—increased disease risk and mortality in the Swedish cohort and obesity in the Dutch cohort. Once again, in considering a likely mechanism for this presumably nongenetic heritability of these disease risks, epigenetic mechanisms became the focus of attention.

Events occurring that mediate human diseases tend to get the headlines in the popular press, but during this period the mammalian models were much less fruitful than the studies in other organisms. In plants, it was being shown conclusively that information could indeed be transmitted from parent to offspring through mechanisms not involving DNA sequence changes. The phenomenon of paramutation was especially exciting, in which the presence of a silenced allele somehow transmitted that information to an active homolog, which became silenced and maintained that state, even in the next generation of plants in which the silenced allele that started the process was no longer present. The field of epigenetics was therefore drawing together researchers from an unusually broad range of disciplines in the hope that there could be an exchange of insights in this emerging area of biology.

MAJOR PARADIGMS IN EPIGENETICS

If we were to ask ourselves to choose a few examples of replicable or especially intriguing findings that link epigenetic changes with mammalian phenotypes, there are a few that stand out. As will be discussed later in Chapter 7, there is a general problem with interpretability of the large number of epigenetic association studies that have been published to date. This significantly limits

the number of studies that can confidently be believed to have the ability to stand the test of time. The four studies listed below have been influential in shaping our opinions about what epigenetics can offer practically when trying to understand processes involved in human disease. Although each will be discussed in more detail later, it is worth including them in overview here to help describe how epigenetics became such an intriguing field.

The Viable Yellow Mouse

The names of mouse strains are now standardized but in the past were descriptive of the trait being manifested by that strain. Of the mice with spontaneous mutations causing yellow fur color, there was a separate strain that did not survive embryogenesis when the mutant allele was present on both parental chromosomes and was described as the lethal yellow mouse strain. In contrast, the viable yellow mice survive even when homozygous for the mutation, prompting their descriptive name.

In the 1990s, the work of two researchers converged to create a compelling story that contributed to the foundation of the field of epigenetics. In Arkansas, George Wolff, at the National Center for Toxicological Research, had been working for decades on the viable yellow strain of mice. His work and these mice will be described later in Chapter 7, but they are worth introducing here. These mice were fascinating—littermates with exactly the same genetic state had a range of coat color phenotypes, from “pseudoagouti,” the same brown color as animals lacking the mutation, to being covered entirely with yellow fur. This dissociated genotype from phenotype, a nice example for those seeking to understand nondeterminism of the genetic makeup of the organism. In 1965, Wolff also noted that the more yellow the mouse, the greater their tendency to gain weight (Wolff 1965). In Australia three decades later Emma Whitelaw (University of Sydney) cloned the mutation causing the viable yellow phenotype and found it to be due to an unexpected mechanism. Mammalian and other genomes contain virus-like sequences that are capable of replicating themselves and inserting a copy elsewhere in the genome, collectively called transposable elements. This is what had happened to cause the viable yellow mutation—an endogenous retrovirus type of transposable element called the intracisternal A-particle (IAP) had copied itself and landed upstream from the *nonagouti* (*a*) gene (Morgan et al. 1999). The function of the *nonagouti* gene includes the addition of dark pigment to hair. The reason that littermates in Wolff’s colony could have

dark or yellow hair was because the IAP element was variably influencing the expression of the *nonagouti* gene. In exploring the mechanism of the IAP effects, DNA methylation at the IAP element was found to be present when the element was silenced and had no effect on *nonagouti* and absent when the IAP element was active and causing abnormal regulation of this pigment gene, leading to the addition of yellow pigment to the hair.

Although this on its own was a striking model of DNA methylation being causally associated with an obvious phenotypic outcome, overriding the DNA sequence information present, George Wolff took it a step further in the 1990s and asked whether altering the diet of the mother of such a litter during pregnancy could influence whether the IAP element was silenced by DNA methylation. He fed pregnant mothers bearing the viable yellow mutation a diet designed to increase DNA methylation. The mothers fed these diets had an increased proportion of pups born with the brown hair phenotype, indicating silencing of the IAP element.

There is one more twist to add—the phenotype of these yellow mice was not limited to their fur color. They also gained weight to a much greater extent than their genetically identical, brown littermates and had a metabolic phenotype resembling type 2 diabetes mellitus in humans. When Wolff fed the pregnant mothers the diet designed to promote DNA methylation, he was influencing not just the cosmetic outcome of fur color but also a disease resembling an increasingly prevalent human disorder.

These findings resonated across multiple domains of research. The idea that a simple dietary change during pregnancy could modify a phenotype that included the risk of adult obesity provided striking support for the DOHaD model proposed by Barker almost a decade earlier. It also suggested that an unbiased test of DNA methylation across the genomes of the animals discordant for the phenotype would have picked out the causative locus as differentially methylated, not only finding the mechanism for a memory of a past (dietary) exposure but also the gene (*nonagouti*) mediating the phenotype. The finding also supported the idea that interventions could not only be harmful but could also be helpful, by mitigating genetic risk. All of these lessons continue to resonate today, reflecting the substantial influence of this mouse model.

Cigarette Smoking

As we developed the epigenomic technologies to survey DNA methylation and other presumed regulators of gene expression, an obvious place to start

in human cohort studies was the large number of samples stored away in freezers from genetic studies. Almost universally these samples were collected from peripheral blood cells and were stored as DNA. DNA methylation is a very stable biochemical modification, so it was easy to defrost these samples and start asking questions about the patterns of DNA methylation in these cells and how they correlated with the characteristics of the donors.

A very reproducible finding that has emerged from these studies is the distinctive pattern of DNA methylation in people who smoke cigarettes, looking at individual genes (Breitling et al. 2011; Monick et al. 2012) or throughout the genome (Shenker et al. 2013). It was also shown that your DNA methylation profile in blood cells reflects whether your mother smoked during pregnancy (Richmond et al. 2015).

This excellent example of a robust epigenetic biomarker represents another reason why people became interested in epigenetics. If past exposures, even to your mother during pregnancy, can be reflected by DNA methylation patterns in your peripheral blood, you have the potential to develop numerous biomarkers that could be helpful in both research and in medical care.

Epigenetic Clock CpGs

The second major epigenetic biomarker to be developed associated DNA methylation with age in humans. Steve Horvath from the University of California in Los Angeles took the conceptually relatively straightforward approach of mining data in public databases representing the DNA methylation in individuals of different ages. By studying almost 8000 samples from 51 different cell types or tissues, he could test which loci changed their DNA methylation most consistently with chronological age. As methylation of cytosines typically occurs when the cytosine is followed by a guanine in the DNA sequence, a so-called CpG dinucleotide, he used that term to describe the 353 loci that change DNA methylation with age as “epigenetic clock CpGs.” This biomarker has been tested repeatedly since its first description and has proven to be very reproducible.

What this association between DNA methylation and aging highlights is an assumption that is pervasive in epigenetics research. When a molecular marker like DNA methylation is found to be associated with something (e.g., a phenotype or an exposure), it is very tempting to assume that the relationship is causal. We know that DNA methylation can be associated with a

gene being silenced, so when we see a change in DNA methylation associated with age, we assume the DNA methylation changes actually mediate the cell's aging. In fact, as will be discussed in Chapter 7, this is a very difficult conclusion to make, given what we now know about why DNA methylation can differ between individuals or over time.

The second assumption that follows is that by intervening and thus changing DNA methylation, we can alter the rate of biological aging. An association does not have to involve causation; our updated perspective on DNA methylation is that it may, in fact, reflect a footprint of where transcriptional regulatory proteins bind in the genome, as discussed later in this book. Altering DNA methylation may therefore be less valuable as an intervention than altering the control of the transcriptional regulatory proteins binding at the distinctively methylated loci.

Epigenetic Mechanisms in Gliomas

In Chapter 8 we will dive deeply into the fascinating field of cancer epigenetics, which has provided us with many reasons to be excited about epigenetics, especially because the potential for therapeutic intervention is much more tangible. One example of a story linking epigenetic events with the mechanism of malignancy was developed by Brad Bernstein at the Massachusetts General Hospital. His group was studying gliomas, tumors derived from the glial cells of the brain. His group linked together a number of steps in a cascade of events leading to the activation of an oncogene. First, they found that a mutation in a gene involved in metabolism started to generate an unusual metabolite, which interfered with the function of a gene regulating DNA methylation. The net effect was to increase the amount of DNA methylation in these glioma cells, which in turn led to the addition of methylation to sequences where a protein called CTCF usually bound. The binding of CTCF to DNA can be influenced by methylation of the target site, causing CTCF to have difficulty in its role to partition the regulatory regions of the genome away from each other at the *PDGFRA* gene. The outcome was to increase the expression of *PDGFRA*, a known glioma oncogene, driving the malignant transformation of these cells. This glioma example demonstrates nicely how the study of epigenetics now encompasses everything from metabolism to the three-dimensional organization of chromatin in the cell nucleus and the recognition of interventions that may be helpful in human diseases.

FROM RESEARCH TO CLINICAL INTERVENTION

From the earliest days of epigenetics research, there has been the hope that if we can define an abnormal pattern of epigenetic regulation in a disease, the inherent malleability of epigenetic regulatory processes should allow these to be targeted for reversal. This remains a high priority, with cancer the focus for much of the drug development to date.

Drugs in oncology have been developed to target DNA methylation and modifications of the proteins in chromatin as major priorities. Clinical trials have shown that inhibitors of enzymes adding DNA methylation to the genome improve outcomes in a blood cancer called myelodysplastic syndrome (Cabezón et al. 2021). Other tumors have high expression of bromodomain and extraterminal motif (BET) proteins, which bind to chromatin where acetyl groups have been added to the histones in chromatin. The use of BET protein inhibitors is being evaluated as a potential aide to conventional therapies (Sun et al. 2020; Trojer 2022).

In the current era of immunotherapy of cancers, another avenue has opened up for epigenetic drugs. The relatively nonselective actions of drugs that target genome-wide regulators like DNA methylation or histone modifications have the effect of reactivating the transposable elements, mentioned earlier in the story of the viable yellow mice. These reactivated elements make the cancer cell more likely to produce molecules that can be recognized by the immune system. An area of scrutiny for epigenetic drugs is therefore focused on the possibility that pretreating the patient with these drugs before activating the immune system to seek out the cancer cells may be a useful addition to immunotherapy (Jones et al. 2019).

Cancer is a serious condition, which has allowed exploration of epigenetic therapies that may have toxic effects because the risk–benefit ratio remains favorable even when the use of the drug influencing the epigenome has significant side effects (Sun et al. 2020). Applying similar therapies in other, less dangerous conditions believed to involve epigenetic changes is not justifiable, which is the reason why epigenetic interventions remain focused on cancer. As drugs influencing the epigenome become less toxic, the range of conditions that could be explored for positive effects in clinical trials will broaden accordingly.

PROBLEMS THAT HAVE EMERGED IN EPIGENETICS

Hopefully the case is being made as to why there is currently so much excitement about epigenetics and the possibility that this area of research will allow us insights into the mechanisms of disease and into possible novel therapies.

A challenge for this book is to maintain that spirit of excitement while digging deeply into some reasons why we need to temper this excitement with caution. Possibly the biggest reason for dampening our enthusiasm is the overinterpretation of differences between samples in patterns of epigenetic regulators like DNA methylation. Although this will be addressed in detail in Chapter 7, in essence the problem boils down to the fact that DNA methylation is influenced by a number of factors. If you are pursuing the idea that DNA methylation changed in the cells studied, and you have not excluded the effects of confounding influences upon the DNA methylation patterns, then you cannot interpret positive findings as supportive of your starting hypothesis. There is no study to date that has accounted for all known confounding influences, so therefore it follows that no study to date can be said to be fully interpretable. This issue is not confined to DNA methylation but involves any functional genomic output, including gene expression and chromatin studies.

There are other issues that are causing scepticism in epigenetics research. The idea that epigenetic mechanisms can propagate memories from parent to daughter cells has led logically to the concept that memories of adverse events can be propagated through generations. This is where the strength of the science is most mismatched with the power of how the story captures the imagination. We have seen a major interest in the popular press and from the lay public in how the diet, habits, or stresses of prior generations pass on their effects to children or grandchildren. Sometimes this is prompted by epidemiological observations and sometimes by model organism work, but the same interpretability issues described above remain when attempting to link molecular changes with the phenotype. In plants, as mentioned earlier, there are indeed molecular mechanisms for epigenetic changes to be induced in one generation and propagated in subsequent generations, but their molecular regulators of transcription are quite distinct from those in animals, and it remains to be demonstrated in animals that our molecular mediators can perform the same way.

Annoyingly but perhaps inevitably for a loosely defined and exciting field like epigenetics is the rise of misuse of the term in commercial products and services. As mentioned earlier, the idea that interventions can either increase or decrease one's risk of developing a phenotype to which one is genetically predisposed has fostered ideas of genetic nondeterminism and has allowed a favored intervention to be touted as the way of protecting against disease. The upshot is a circus of epigenetic diets, epigenetic face creams and other cosmetics, epigenetic yoga and meditation, and even epigenetic

antidandruff shampoo, all to be found with a search of the internet. The foundation in evidence for any of these interventions is, at best, extremely weak. The resulting collective eye roll from the broader scientific community demands a response from epigenetics researchers, who individually may be performing rigorous research but who collectively suffer from what would be described in the world of marketing as “brand damage.”

Finally, there has been the tendency to treat epigenetic properties of an individual in odd ways. One occurs when a researcher succumbs to the temptation to treat epigenetic information the same way as genetic information, as if it is a fixed property of an individual. DNA methylation of peripheral blood leukocytes is a phenotype, and it varies as any phenotype can, undermining some of the assumptions that are foundational in the field of epigenetic epidemiology, for example. A second weird tendency was our enthusiastic embrace of every biochemical process occurring in the nuclear genome as epigenetic, but initially excluding transcription factors for some reason. Furthermore, our relentless focus on molecular processes ends up creating a blind spot—a failure to think in terms of how these molecular events reflect cellular properties. The bases for these tendencies become understandable when we delve into the history of our field, as will be the focus of the next couple of chapters and a theme throughout the book.

THIS BOOK

Why write a book in this day and age? An internet search allows most questions to find sources of information that can potentially provide answers, whereas review papers in journals offer deep dives into scientific topics. For epigenetics, the problem is that even a comprehensive review is only informative about one segment of what has become a sprawling field. This book is designed to be like a set of connected reviews—delving deeply into as many components as possible of today’s field of epigenetics while cross-referencing between these areas to create a coherent overall picture.

It is worth acknowledging that a book written by a single author is inherently biased. The research for this book involved reading monographs by Conrad Waddington and others, so apparently this kind of behavior used to be at least tolerated, if not encouraged. The challenge is to overcome your biases as you write so that the reader is not left with something resembling an opinionated rant. There are plenty of podcasts out there if that’s your thing. The hope is that this book will challenge the reader to explore

their preconceptions about epigenetics, reflecting the bias of a single author but expressed politely, and hopefully based on solid evidence. When Waddington and others wrote their books, the value of their work was in part because they injected some interpretation and opinion into the discussion. In this book, the goal has been to do likewise, a strange writing style to learn for one trained in the current era.

The breadth of the field of epigenetics today is daunting and requires some degree of focus even in a book trying to maintain a broad perspective. The choice of emphasizing mostly mammalian organisms and disease phenotypes in this book was based on several factors, including how these reflect the author's major interests, but also the degree to which mammalian and disease studies appear to dominate public narratives and publications in this field. However, what represented the most compelling rationale for this focus was the need to link what we call epigenetics today with the original definition of the term, which was based on cellular differentiation and lineage commitment and how this is influenced by the action of genes.

There will therefore be an overt goal in the chapters to come to refocus our attention on cellular properties as a primary way of thinking about epigenetics. The molecular mediators that have been studied enthusiastically and given the description epigenetic do not go to waste—they remain the means by which the epigenetic properties of cells are mediated but do not all need to be lumped into a single vague category of being “epigenetic” in their actions. Having used the words epigenetic and epigenomic promiscuously in this first chapter, the remainder of the book will attempt to avoid using the terms when a more accurate alternative way of saying the same thing—such as “transcriptional regulation” or “cellular memory”—can be substituted.

This clarity of terminology and the refocusing on cellular properties should make it easier for the newcomer to the field to create a framework to learn about epigenetics, which is otherwise an intimidating field. The goal is to allow better insights by specialist and nonspecialist alike, more productive and interpretable research, and a foundation for therapeutic interventions for human patients.