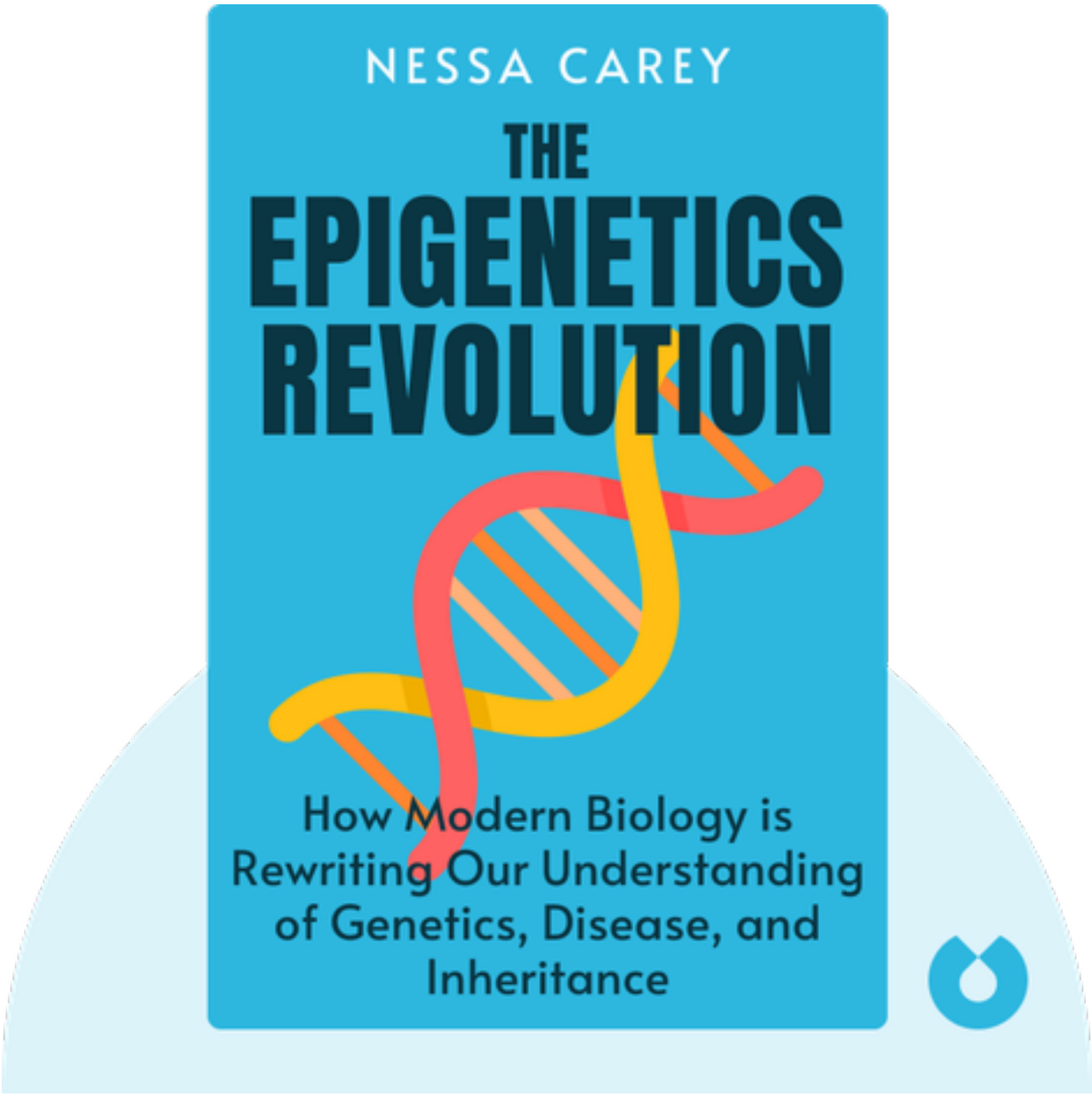

The Epigenetics Revolution

by Nessa Carey

9-minute read

Synopsis

The Epigenetics Revolution (2011) is an overview of the cutting-edge field of epigenetics – looking at the various factors that interact with your genes and modify the way they behave in order to make you, you. From mental health to obesity, it examines the fascinating and often unexpected ways that epigenetics can influence our lives and health.

Who is it for?

- Science enthusiasts interested in biology's new frontiers
- Dinner-party sages looking to wow friends with fascinating scientific wisdom
- Amateur psychologists open to an epigenetic interpretation of trauma

About the author

Nessa Carey has a PhD in virology from the University of Edinburgh and was formerly a senior lecturer in molecular biology at Imperial College, London. She now runs Carey International Impact Training and is the author of two other books, *Junk DNA* and *Hacking the Code of Life*.

What's in it for me? Delve deep into the human genome and discover what traditional genetics overlooks.

June 26, 2000, may well go down as one of the most monumental days in human history. It was a day of huge scientific achievement, as the international team behind the Human Genome Project announced they'd successfully mapped the human genome, for the very first time. We finally had the code to unlock the secrets of human life.

But, of course, things didn't end there. Science never stands still, and in these blinks, we follow the story of what's been happening since June 2000. We'll go beyond the human genome, zooming right in to focus on the new frontier of genomic research: the study of *epigenetics*.

We'll learn how the genetic code inside your cells gets turned on and off, what causes the changes, and how they happen despite your DNA remaining unchanged.

Epigenetics isn't important just because it's at the forefront of biological research. It's also significant because of the outsize role it plays in our lives more generally: from obesity to trauma and cardiovascular health to metabolism, epigenetics underlies some of the most important processes in our bodies.

Along the way, we'll see what a discredited evolutionary theory actually got right, discover what famine teaches us about human development, and examine the biological basis of psychological harm.

If you want to move past the simple 2D picture of human health that standard genetics provides, then you're in for a treat.

In these blinks, you'll learn

- why your DNA only tells half the story;
- how your granddad's diet might be affecting your health today; and
- what a few overstressed mice can teach us about childhood neglect.

Epigenetics explains what standard genetics can't.

Mapping the human genome was a gargantuan task. Identifying and analyzing all of the genes that make up a human being is no small feat, even for a team of dedicated experts – so it's no surprise that the project's completion led to wild fanfare and public enthusiasm.

Bill Clinton, who was president when the genome was first fully sequenced, went on record to say, "Today we are learning the language in which God created life." The UK Science Minister, Lord Sainsbury, declared, "We now have the possibility of achieving all we ever hoped for from medicine." Big statements, from powerful men – but in hindsight, were they all that accurate? Well, perhaps not entirely.

Part of the problem was that we overestimated the importance of DNA. We thought of it as a huge set of strict biological instructions, like a mold for making identical parts in a factory. But as it turns out, the reality is really quite different.

You see, we might be better off thinking of human DNA as a script rather than a mold. Let's consider an actual theater script for a minute. Take Shakespeare's *Romeo and Juliet*, for example – although every production takes Shakespeare's words and stage directions as their starting point, each performance ends up different, because the script can be interpreted in so many different ways.

During rehearsals, the director and actors will scribble their own notes and instructions in the margins of their starting scripts – and in doing so, they turn the initial work into something new and idiosyncratic.

So, what does that have to do with biology? Well, if we think of living things as theatrical productions, then DNA is the first script we're given to work with – our original masterpiece. Add in those all-important jottings in the margins that make each script unique? Well, that's epigenetics.

Epigenetics controls the expression of our genes – directing the extent to which any one gene carries out its function. Epigenetic modifications are like the actor's little notes saying, "Speak these words quietly," or "Shout this bit," or even "Skip this line entirely."

In other words, they're the unique instructions that tell the individual cells that make up your body how to behave in different circumstances. Epigenetic information is what stops a skin cell from turning into a neuron, or a liver cell from turning into skeletal muscle.

Just as Shakespeare's play can give rise to both traditional performances in Renaissance style, and modern interpretations like Baz Luhrmann's 1996 film, so too can a single "script" of DNA give rise to very different characteristics.

To understand this a bit more, let's forget about *Romeo and Juliet* for a minute, and focus on a less appealing topic: mice – inbred lab mice, to be exact.

Now, these mice aren't inbred through any fault of their own. Their human handlers have bred them selectively with their siblings generation after generation, to the point that they have become genetically identical. And yet, despite each mouse seeming identical to its siblings at birth, as the mice babies grow, they begin to show their differences – in things like their body weight and temperament, for example. And this is despite being kept in exactly the same environment.

This difference between genetic makeup, known as *genotype*, and real-life traits like weight gain, known

as *phenotype*, is often explained by epigenetics. So let's slow things down a minute and take a look at what that actually means for our mice.

In terms of mechanics, the expression of their genes is modified in two main ways.

The first is through what's called *DNA methylation*. That's when a chemical tag called a *methyl group* is added to DNA. Most of the time, this specific process results in genes being switched off.

The second type of epigenetic modification involves changes to *histones*, a type of protein that structures DNA in the nucleus. Changes to histone proteins can be more varied: instead of just turning a gene off, they can act like a dimmer switch, strengthening or weakening the expression of a gene in the same way you'd turn your house lights up or down.

For our young mice, where we see differences in weight, it's thought this is caused by both DNA methylation and histone modifications. And it's likely that these epigenetic differences are established very early on – maybe even in the womb.

If we return to our Shakespearean analogy, we can look at DNA methylation and histone modifications as a kind of shorthand that actors use to alter their scripts. DNA methylation says, "Omit this," while histone modifications tell an actor how loudly and intensely they should deliver certain lines.

Now that we know what epigenetics is, and how it works, let's look at some of its ramifications for humans. After all, it's not just inbred mice that are affected!

A tragic, mid-twentieth-century famine can help us understand how epigenetics works.

Sometimes it can be hard to study epigenetic modifications in humans. When we're dealing with lab mice, we can create genetically identical litters, carefully control the environment, and, in general, do with them pretty much as we please. With humans, not so much.

But that doesn't mean we're completely at a loss – sometimes the world creates its own experiments. Which is exactly what happened during the last winter of the Second World War, when a German blockade caused a period of intense and bitter food shortages in the Netherlands.

During the famine that followed, an estimated 22,000 people died, and the desperate survivors ate anything they could get their hands on – tulip bulbs, animal blood, you name it. In human terms, it was an unmitigated tragedy. But for science, the impact of the famine proved interesting. That's because this unplanned experiment, across such a large number of people, shed some much-needed light on a phenomenon known as *developmental programming*.

If you reckon that sounds like something a software engineer might do, think again. Developmental programming actually refers to the lasting influence on adults of events that took place during their prenatal development. In other words, it's an account of how events during gestation can affect the health of a child down the line, even as an adult decades later.

As we'll see, epigenetics plays a key role in some of these developments. But for now, let's turn our attention back to what became known as the Dutch Hunger Winter. From a scientific point of view, the terrible hardships that the survivors of this famine went through made them a fascinating population to study. Together they formed a clearly defined but numerous group – a group that had endured a single period of life-threatening malnutrition, all at the same time.

One of the first things that scientists turned their attention to was birth weight, and how the famine affected babies born to women who were pregnant at the time of the tragedy. They noticed two things.

First, they found that which stage of pregnancy a fetus was in when the famine struck mattered a lot. If the shortages hit during the last few months of pregnancy, the baby was likely to be born small. But, if the famine struck early in gestation, then the baby was likely to be a normal weight.

I'm going to say that again, as it's important for what comes next. When the famine hit late in gestation, the babies were generally small. And when it hit early, they were about average.

So far, so straightforward. But it's what the scientists went on to discover that really deserves our attention. You see, what they found was that these small babies tended to remain small, even into adulthood – experiencing obesity at a lower rate than the general population.

For the babies who were born a normal weight, though, things were different. They didn't just stay a normal, healthy size – they actually had an increased risk of obesity. This is consistent with what we know about developmental programming – that environmental factors, even in utero, can change how children grow and develop throughout their lives. And bit by bit, we're puzzling out what epigenetics has to do with this phenomenon.

Remember DNA methylation? It was one of the two forms that epigenetic modifications can take. Well, studies looking at DNA methylation in survivors of the Dutch Hunger Winter found alterations to some of the key genes involved in metabolism. And although this doesn't prove cause and effect, it certainly suggests that fetal malnutrition might influence adult weight and that it's down to epigenetic changes made during gestation.

Think of it this way: if a growing baby receives limited nourishment from its mother in the early stages of

pregnancy, that baby is likely to end up programmed to make the most of a restricted food supply. Once the baby is born and the famine has passed, some of these epigenetic modifications remain in place – and the very same things that helped the unborn child reach a healthy size, now actually predispose him to obesity in adulthood.

Some epigenetic changes can be passed from generation to generation.

But let's leave the 1940s now and head a little further back in time to the early nineteenth century, and a French biologist named Jean-Baptiste Lamarck. Lamarck was the author of a work called *Philosophie Zoologique*, in which he laid out a peculiar theory of evolution.

According to his theory, if an animal could acquire advantageous traits during its own lifetime it could pass them on to its offspring, and in doing so, drive evolution over the course of a single generation.

So, for example, a giraffe that lengthened its neck by constantly stretching for leaves could pass on a longer neck to its children. Or a blacksmith whose labor-intensive work strengthened his muscles could pass on that same strength to his sons and daughters.

Of course, in the wake of Charles Darwin, we understand that this isn't how evolution works at all – not by a long shot. What we know from Darwin is that, from time to time, random mutations occur in organisms, and if these mutations are helpful, they proliferate.

But acquired characteristics, the traits we develop over our lifetime, can't be passed on. Right? After all, acquired characteristics aren't anything to do with, and don't alter, our genes.

But that's the thing. In some situations, humans don't just pass on genetic information: they sometimes pass on epigenetic information too. In certain circumstances, then, acquired characteristics might indeed be transmitted from one generation to the next, just like Lamarck hypothesized two centuries ago.

Now think back to the Dutch Hunger Winter again because it comes into play here in our understanding of epigenetic inheritance. You'll recall from the last blink, that malnutrition during gestation could affect a baby's chances of becoming obese later in life. But, what's even more shocking is the fact that if that baby is a girl and goes on to become a mother herself, her own firstborn child is likely to be heavier than average at birth!

That's worth dwelling on: the grandchild of the famine survivor is likely to be heavier than normal, all because his or her grandmother endured a famine while pregnant two generations before.

But, as illuminating as this information is, it's still a somewhat imperfect example of epigenetic inheritance. And the main reason for that is that we can't say with absolute certainty that the underlying process is epigenetic. After all, a skeptic could argue that the gestating baby's malnutrition at the time of the famine, laid the foundations for her own abnormal pregnancy years later in a way that had nothing to do with epigenetics.

Luckily, we have other, more robust examples of epigenetic inheritance – and this time, it's the fathers' turn. You see, the thing about fathers is that they don't carry the fetus, and they also don't contribute much *cytoplasm* to the *zygote*. If you remember your high school biology, you'll recall that cytoplasm is the fluid inside a human cell and that zygote is the name for the fertilized egg cell that goes on to form the fetus. So, while the dad doesn't add a lot to the cytoplasm of the zygote, the mother does contribute quite a bit – which means you could argue that having an unusual cytoplasm is what explains the apparent inheritance – it's straightforward genetics. But that doesn't apply with fathers: the bottom line is that, if we see transgenerational inheritance from father to child, and we know that it isn't genetic, then epigenetic inheritance is a pretty likely explanation.

Once again, history created an "experiment," that showed this process in action. It did it in the same tragic way it had in the Netherlands: in the brutal form of food shortages – this time in northern Sweden around the turn of the twentieth century. The difference was that this time the shortages were intermittent, and they alternated with periods of great abundance.

The results? If a boy experienced protracted hunger during the few years before he hit puberty, his own son would be less likely than the average man to die of cardiovascular disease. But if a boy had access to lots of food at the same period of development, the news wasn't so good: his grandsons would be more likely than average to die due to diabetic illnesses.

Studies in mice seem to bear this observation out: a father's diet can trigger epigenetic changes that can be passed to his offspring. Maybe the familiar adage understates things. Instead of saying "You are what you eat," maybe we should really add, "and you are what your parents ate, and what your grandparents ate before that!"

If our dietary decisions weren't already fraught enough, we now face the added worry that every time we pig out, we're doing so at the expense of our descendants. With that in mind, maybe it would have been better if our nineteenth-century biology friend, Lamarck, had been completely wrong!

Childhood trauma seems to have epigenetic effects.

Here's a question for you: Have you ever come across a "misery memoir"? It's a kind of autobiography that presents a harrowing account of the author's troubled life, especially as a helpless child. In this kind of writing, tales of childhood neglect, trauma, and abuse abound – but somewhat surprisingly, the best-selling books tend to tell stories which are, on the whole, fairly optimistic.

You see, in the most popular narratives, the child grows up and eventually overcomes whatever adversity she faced early on. Instead of being held back by childhood trauma forever, the author succeeds despite the odds, and ultimately finds as an adult the happiness she longed for as a child.

It's a satisfying narrative arc – but one of the reasons we find it so fascinating is that we recognize how rare it is in the real world. The fact is that childhood abuse and neglect are pretty hard to overcome and often set children up for lifelong emotional difficulties.

To take just one shocking figure, people who were abused or neglected as children are three times more likely to kill themselves than average. But why? Well, the standard answer is that childhood trauma can lead to lasting psychological damage. That's true, of course – but it's more of a description than an explanation. From a scientific point of view, what is it that childhood trauma actually does that can so adversely affect adult mental health?

As you might have guessed, one theory is that childhood trauma is encoded epigenetically, exerting an effect on adults decades after the upsetting events have ended. So far, scientists have looked at a couple of mechanisms that they think might underlie this phenomenon, but we'll focus on just one, and that's *cortisol* production.

You've probably heard about cortisol: it's a hormone that we produce in response to stress. Put simply, the more stress we experience, the more cortisol we produce.

It won't surprise you to learn that adults who went through trauma as children show raised levels of cortisol when they grow up – they're chronically overstressed. And it shouldn't surprise you that this is also true of other species. Neglected baby rats, for example, also turn into overstressed adult rats.

So what does neglect look like in the rat world? Well, it's pretty simple – good rat parenting amounts to lots of licking and grooming during the first week or so of life. When rats are given lots of attention as babies, they grow up equipped to deal with stress in a healthy way. The mild stresses of life tend not to bother them.

But when rats aren't licked and groomed enough as babies – when they're neglected, in other words – they grow up with higher levels of stress and overreact to situations that are only mildly alarming.

In the animals that were shown lots of maternal affection, the cortisol receptor in a part of the brain known as the hippocampus was highly expressed. To return to our theatrical analogy from the first blink, the "dramatic script" of the rats' DNA had the added instruction to, "Make sure you say this line loud and clear!" And by expressing the cortisol receptor more strongly, cortisol levels are lowered.

Put simply: higher expression of the cortisol receptor means less cortisol in the rats' system, which in turn makes for pretty calm rats.

In the neglected rats, on the other hand, the relevant DNA is methylated to a greater extent. Remember – this is when a methyl group is added to DNA, and it often represses gene expression. So for these neglected rats, their script is telling them, "Don't emphasize this line. *Sotto voce* will do nicely, thank you very much." And so their cortisol goes up. It's that little epigenetic note that sets the neglected rat babies up for a very stressful future. Now scientists are wondering if what they're seeing in rats also applies to humans.

As we wind up, it's worth pointing out that this kind of research, sometimes referred to as neuro-epigenetics, is some of the most controversial work being done in the ever-evolving field of epigenetics.

Skeptics argue that the epigenetic modifications in question are too small to result in such pronounced behavioral differences. But, whatever the case, research into the epigenetic aspects of childhood trauma shows no signs of slowing. We can only hope that the coming years will unfold some of the field's lingering mysteries.

Final summary

The big learning to take away from these blinks:

Genetics is rightly seen as a groundbreaking field with much to tell us about human health, evolution, and heritability. But it doesn't tell the whole story – not by a long shot. The fact is that our DNA is like a script, one that can lend itself to many revisions and interpretations. Far from being wholly determined by our genes, our path through life is also affected by how those genes are expressed: affected, in other words, by *epigenetics*. And the implication of these epigenetic changes can be staggering – influencing everything from our mental health as adults to the likelihood we'll die of cardiovascular disease. As a new frontier in human health, epigenetics is a field you'll want to keep an eye on.