Annotating the Book of Life

If genes write your story, external factors help mold how it's told

by

REGINA NUZZO

SO HERE'S A CRAZY THOUGHT: WHAT if your DNA is not your destiny? Sure, after scientists mapped the human genome in 2001, they giddily referred to it as "the essence of mankind" and "our own instruction book." A decade-plus down the road, though, those proclamations ring a little less true. Our destiny, scientists now believe, is contained as well in the complicated scribblings jotted in the margins of that manual by our environment. These penciled-in notes—about toxins, nutrients and stresses we've been exposed to—don't rewrite the story of DNA itself, but they are changing how we read the book.

And not just our own book. Some of that marginalia may be getting passed on to our children, and to their children too. That's right, choices you made as a teenager could reach forward in time to affect the health of still-unborn descendants, and your own biological makeup likely reflects the experiences and environment your parents and grandparents encountered long before you were a twinkling in any of their eyes. As scientists like to quip, "You are what your grandmother ate."

These ideas are the cornerstone of a burgeoning field of biology called epigenetics, the study of what happens "on top of the genes" rather than in DNA itself. "Epigenetics is the vital bridge between genes and environment, between nature and nurture," says Nessa Carey, author of *The Epigenetics Revolution: How Modern Biology Is Rewriting Our Understanding of Genetics, Disease and Inheritance*. "We finally have a way of understanding how the world around us talks to the DNA embedded in our cells." Though in its infancy, epigenetics promises to help explain some of life's mysteries that DNA alone can't solve: Why do early experiences shape us so strongly? Is it possible to overcome the lingering effects of a "tough" life? Which environmental chemicals wreck our health and which lifestyles save it? How do diseases develop, and how can we block them? "DNA is the starting point for life," Carey explains, "but epigenetics explains the great diversity of life."

THIS LEADING EDGE of genetics is so complex that for a long time it made no sense at all. Consider this head-scratcher, which stumped scientists until the middle of the 20th century: If each one of our cells contains the exact same DNA, how do they all end up doing something different? "Why doesn't your kidney become an eyeball?" asks Gerald Weissmann, a professor emeritus of medicine at the New York University School of Medicine and the author of *Epigenetics in the Age of Twitter: Pop Culture and Modern Science*. "The answer is epigenetics." A cell attaches chemical annotations to the DNA chromosomes coiled in its center, Weissmann explains, like a diligent student underlining important textbook passages while crossing out paragraphs that won't be on the exam. These annotations tell the cellular machinery how to read its DNA code, which genes should be highlighted and which silenced.

So eyeball cells follow only eyeball-specific genetic instructions, and kidney cells listen only to kidney genes. It took a while for scientists to grasp this, and a while longer to make the next leap: that those prime-mover notations continue to be written and erased throughout our lives in continual response to what we eat, drink, smoke, inhale and feel.

Sip a glass of wine, for example, and in minutes cells in your liver and elsewhere spring into epigenetic action. Chemical notes appear at particular places along your chromosomes to prod your body to deal with the cabernet that's now circulating through your veins. Genes are triggered that metabolize alcohol; others are put to work combating the inevitable drowsiness. Most of these annotations are erased within a day or so. Spend a couple of weeks in Italy on a wine tour, though, and the chemical changes will stick around to build up a tolerance to all the imbibing.

Every organism's genome, its A-to-Z owner's manual, has been honed through natural selection over millennia to provide instructions that offer the best chance to survive its environment. That's how ocean-dwelling fish got gills and land-loving mammals got lungs. An organism's epigenome, on the other hand, probably provides important margin notes about what kind of environment lies ahead. Food has been scarce lately, so switch on the genes that control calorie hoarding. Or it's an unfriendly social scene, so switch on the genes that boost wariness.

In this context, what pregnant women have long known—that what they ingest can have health consequences for their baby—sounds about right. Consider this: children conceived during the Dutch Hunger Winter of 1944 (in which, because of Nazi blockades, people resorted to eating tulip bulbs and grass to survive, getting by on as few as 500 calories a day) had higher risks of obesity, heart disease and diabetes 60 years later, even though they experienced no deprivation after they were born.

Explaining exactly how and why experiences in the womb are so influential is something epigenetics can do. It's already begun to sort sound medical advice from old wives' tales. For starters, diet really is a big deal. When pregnant mice were exposed to high levels of the plastics chemical bisphenol A (BPA), they gave birth to pups with startling epigenetic changes and a tendency to develop a range of serious health problems, from infertility to cancer. But when BPA-exposed pregnant mice also ate a diet rich in epigenetic-friendly nutrients—vitamins like folic acid and B vitamins—the effects of the plastics were thwarted, and their pups stayed healthy.

Surprisingly, what happens before conception seems to demand attention as well. When female mice guzzled alcohol for a few months before mating, they gave birth to pups with epigenetic changes, even though the moms stayed "sober" while pregnant. Another study found that mice born to moms that ate an unhealthy diet low in an essential fatty acid before their pregnancy were born with epigenetic changes to the gene that controls fatty-acid metabolism. Think of it this way: you may be what your mother ate on her honeymoon.

Dads have their own epigenetic responsibilities. A study of nearly 10,000 British fathers found that those who had started smoking before puberty went on to have sons who were between 10 and 20 pounds overweight as teens. In mice, males who ate a fatty diet ended up siring daughters that showed changes in pancreatic genes and went on to have problems regulating insulin and glucose levels. And mouse fathers who showed only early signs of diabetes produced pups more prone to diabetes themselves. All of it is probably because the state of a father's health is written as epigenetic signatures on the sperm he produces, signatures that then get passed on to offspring. Put another way, sperm is a snapshot of a male's health and his environment.

TRAUMA, ESPECIALLY IN early childhood, can leave its own mark on the genome. One study found that men who had been abused as children and later in life committed suicide showed particular epigenetic markers attached to genes in their brain. These markers look similar to those that show up in rats subjected to neglectful mothering, particularly in genes that control the body's response to stress. But new research suggests that the lingering effects of a tough childhood can be undone. When one study put rats that had been neglected as pups into a nurturing environment, the lingering epigenetic marks of their traumatic puphood were largely erased.

Some preliminary research indicates that we can pass down changes to our children and grandchildren as well. Such inheritance might serve as a helpful time capsule, leaving coded warnings for ensuing generations about environmental conditions ahead. For example, dandelions that find themselves in nutrient-poor environments pass on stress markers to the next generation of buds, which grow longer roots in response, even though they were planted in perfect conditions. Similarly, mice taught to fear a particular odor pass on instructive epigenetic signatures to their pups, who are born afraid of the odor. What's more, the fear persists into the next generation. Exactly how these notes get passed down remains a mystery.

If all this hereditary overkill seems a bit fatalistic, the flipside makes it easier to swallow. Just as certain epigenetic notations are the product of a challenging past environment, a pleasant present environment may remove those scribbles, effectively turning a fresh page. Confirming studies are extraordinarily hard to conduct on humans, but a few have provided tantalizing results. When healthy but sedentary middle-aged Swedish men embarked on a six-month exercise regime, they showed dramatic changes in the epigenetic signatures of their fat cells, especially in genes involved in obesity and Type 2 diabetes. In another study, when men with prostate cancer turned to a low-fat diet, exercised more and reduced stress, their tumor cells changed gene expresssion after only three months. And when skilled meditators practiced mindfulness meditation during an eight-hour workshop, their inflammation-controlling genes changed in ways that most likely offered better hormonal responses to stress.

Researchers have recently found one more card to play: epigenetic tools for disease prevention and therapy. "I think we will make major changes in our approach to cancer over the next 10 years based on discoveries in epigenetics," says Andrew Feinberg, director of the Center for Epigenetics at Johns Hopkins School of Medicine. Much of cancer is not a matter of genetic mutations per se, but rather of epigenetics, he says. And the signatures show up early. That's good news, because it paves the way for chemoprevention, a radical treatment approach. "People forget that cancer takes decades to develop. We just don't notice it until it's pretty bad," he says. "With some clever discoveries, we might be able to intervene much earlier than we have." If epigenetic changes are, in fact, responsible for causing cancer, it may be possible to erase them, with targeted drugs. A handful of currently available blood-cancer drugs change epigenetic signatures, and trials involving other cancers are under way too.

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That's tomorrow's story. Today epigenetics might be most useful for teenagers in need of one more reason to heap guilt on their elders. "Blame it on my epigenetics," laments one T-shirt for sale. Loving parents would buy one and pass it along to their kids.