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SAME BUT DIFFERENT

How epigenetics can blur the line between nature and nurture.

BY SIDDHARTHA MUKHERJEE

The author's mother (right) and her twin are a study in difference and identity.

On October 6, 1942, my mother was born twice in Delhi. Bulu, her identical twin, came first, placid and beautiful. My mother, Tulu, emerged several minutes later, squirming and squalling. The midwife must have known enough about infants to recognize that the beautiful are often the damned: the quiet twin, on the edge of listlessness, was severely undernourished and had to be swaddled in blankets and revived.

The first few days of my aunt's life were the most tenuous. She could not suckle at the breast, the story runs, and there were no infant bottles to be found in Delhi in the forties, so she was fed through a cotton wick dipped in milk, and then from a cowrie shell shaped like a spoon. When the breast milk began to run dry, at seven months, my mother was quickly weaned so that her sister could have the last remnants.

Tulu and Bulu grew up looking strikingly similar: they had the same freckled skin, almond-shaped face, and high cheekbones, unusual among Bengalis, and a slight downward tilt of the outer edge of the eye, something that Italian painters used to make Madonnas exude a mysterious empathy. They shared an inner language, as so often happens with twins; they had jokes that only the other twin understood. They even *smelled* the same: when I was four or five and Bulu came to visit us, my mother, in a bait-and-switch trick that amused her endlessly, would send her sister to put me to bed; eventually, searching in the half-light for identity and difference—for the precise map of freckles on her face—I would realize that I had been fooled.

But the differences were striking, too. My mother was boisterous. She had a mercurial temper that rose fast and died suddenly, like a gust of wind in a tunnel. Bulu was physically timid yet intellectually more adventurous. Her mind was more agile, her tongue sharper, her wit more lancing. Tulu was gregarious. She made friends easily. She was impervious to insults. Bulu was reserved, quieter, and more brittle. Tulu liked theatre and dancing. Bulu was a poet, a writer, a dreamer.

Over the years, the sisters drifted apart. Tulu married my father in 1965 (he had moved to Delhi three years earlier). It was an arranged marriage, but also a risky one. My father was a penniless immigrant in a new city, saddled with a domineering mother and a half-mad brother who lived at home. To my mother's genteel West Bengali relatives, my father's family was the embodiment of East Bengali hickdom: when his brothers sat down to lunch, they would pile their rice in a mound and punch a volcanic crater in it for gravy, as if marking the insatiable hunger of their village days. By comparison, Bulu's marriage, also arranged, seemed a vastly safer prospect. In 1967, she married a young lawyer, the eldest son of a well-established clan in Calcutta, and moved to his family's sprawling, if somewhat decrepit, mansion.

By the time I was born, in 1970, the sisters' fortunes had started to move in unexpected directions. Calcutta had begun its spiral into hell. Its economy was fraying, its infrastructure crumbling. Internecine political movements broke out frequently, closing streets and businesses for weeks. Between the city's cycles of violence and apathy, Bulu's husband kept up the pretense of a job, leaving home every morning with the requisite briefcase and tiffin box, but who needed a lawyer in a city without laws? Eventually, the family sold the mildewing house, with its grand veranda and inner courtyard, and moved into a three-room flat.

My father's fate mirrored that of his adoptive city. Delhi, the capital, was India's overnourished child, fattened by subsidies, grants, and the nation's aspirations to build a mega-metropolis. Our neighborhood, once girded by forests of thornbushes and overrun with wild dogs and goats, was soon transformed into one of the city's most affluent pockets

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of real estate. My family vacationed in Europe. We learned to eat with chopsticks, twisted our tongues around the word "croissant," and swam in hotel pools. When the monsoons hit Calcutta, the mounds of garbage on the streets clogged the drains and turned the city into a vast, infested swamp. A stagnant pond, festering with mosquitoes, collected each year outside Bulu's house. She called it her own "swimming pool."

Why are identical twins alike? In the late nineteen-seventies, a team of scientists in Minnesota set out to determine how much these similarities arose from genes, rather than environments—from "nature," rather than "nurture." Scouring thousands of adoption records and news clips, the researchers gleaned a rare cohort of fifty-six identical twins who had been separated at birth. Reared in different families and different cities, often in vastly dissimilar circumstances, these twins shared only their genomes. Yet on tests designed to measure personality, attitudes, temperaments, and anxieties, they converged astonishingly. Social and political attitudes were powerfully correlated: liberals clustered with liberals, and orthodoxy was twinned with orthodoxy. The same went for religiosity (or its absence), even for the ability to be transported by an aesthetic experience. Two brothers, separated by geographic and economic continents, might be brought to tears by the same Chopin nocturne, as if responding to some subtle, common chord struck by their genomes.

One pair of twins both suffered crippling migraines, owned dogs that they had named Toy, married women named Linda, and had sons named James Allan (although one spelled the middle name with a single "l"). Another pair—one brought up Jewish, in Trinidad, and the other Catholic, in Nazi Germany, where he joined the Hitler Youth—wore blue shirts with epaulets and four pockets, and shared peculiar obsessive behaviors, such as flushing the toilet before using it. Both had invented fake sneezes to diffuse tense moments. Two sisters—separated long before the development of language—had invented the same word to describe the way they scrunched up their noses: "squidging." Another pair confessed that they had been haunted by nightmares of being suffocated by various metallic objects—doorknobs, fishhooks, and the like.

The Minnesota twin study raised questions about the depth and pervasiveness of qualities specified by genes: Where in the genome, exactly, might one find the locus of recurrent nightmares or of fake sneezes? Yet it provoked an equally puzzling converse question: Why are identical twins *different*? Because, you might answer, fate impinges differently on their bodies. One twin falls down the crumbling stairs of her Calcutta house and breaks her ankle; the other scalds her thigh on a tipped cup of coffee in a European station. Each acquires the wounds, calluses, and memories of chance and fate. But how are these changes recorded, so that they persist over the years? We know that the genome can manufacture identity; the trickier question is how it gives rise to difference.

David Allis, who has been studying the genome's face for identity and difference for three decades, runs a laboratory at Rockefeller University, in New York. For a scientist who has won virtually all of science's most important prizes except the Nobel (and that has been predicted for years), Allis is ruthlessly self-effacing—the kind of person who offers to leave his name on a chit at the faculty lunchroom because he has forgotten his wallet in the office. ("We *know* who you are," the woman at the cash register says, laughing.)

As a child, Allis grew up in the leeward shadow of his sister, a fraternal twin, in Cincinnati, Ohio. She was the studious one, the straight-A student; he was the popular kid, the high-school fraternity president casual about his schoolwork. "We were similar but different," Allis said. At some point in college, though, Allis's studies became a calling rather than a chore. In 1978, having obtained a Ph.D. in biology at Indiana University, Allis began to tackle a problem that had long troubled geneticists and cell biologists: if all the cells in the body have the same genome, how does one become a nerve cell, say, and another a blood cell, which looks and functions very differently?

In the nineteen-forties, Conrad Waddington, an English embryologist, had proposed an ingenious answer: cells acquired their identities just as humans do—by letting nurture (environmental signals) modify nature (genes). For that to happen, Waddington concluded, an additional layer of information must exist within a cell—a layer that hovered, ghostlike, above the genome. This layer would carry the "memory" of the cell, recording its past and establishing its future, marking its identity and its destiny but permitting that identity to be changed, if needed. He termed the phenomenon "*epi*genetics"—"above genetics." Waddington, ardently anti-Nazi and fervently Marxist, may have had more than a biological stake in this theory. The Nazis had turned a belief in absolute genetic immutability ("a Jew is a Jew") into a state-mandated program of sterilization and mass murder. By affirming the plasticity of nature ("everyone can be anyone"), a Marxist could hope to eradicate such innate distinctions and achieve a radical collective good.

Waddington's hypothesis was perhaps a little too inspired. No one had visualized a gene in the nineteen-forties, and the notion of a layer of information levitating above the genome was an abstraction built atop an abstraction, impossible to test experimentally. "By the time I began graduate school, it had largely been forgotten," Allis said.

Had Allis started his experiments in the nineteen-eighties trying to pin down words like "identity" and "memory," he might have found himself lost in a maze of metaphysics. But part of his scientific genius lies in radical simplification: he has a knack for boiling problems down to their tar. What allows a cell to maintain its specialized identity? A neuron in the brain is a neuron (and not a lymphocyte) because a specific set of genes is turned "on" and another set of genes is turned "off." The genome is not a passive blueprint: the selective activation or repression of genes allows an individual cell to acquire its identity and to perform its function. When one twin breaks an ankle and acquires a gash in the skin, wound-healing and bone-repairing genes are turned on, thereby recording a scar in one body but not the other.

But what turns those genes on and off, and keeps them turned on or off? Why doesn't a liver cell wake up one morning and find itself transformed into a neuron? Allis unpacked the problem further:

suppose he could find an organism with two distinct sets of genes—an active set and an inactive set—between which it regularly toggled. If he could identify the molecular switches that maintain one state, or toggle between the two states, he might be able to identify the mechanism responsible for cellular memory. "What I really needed, then, was a cell with these properties," he recalled when we spoke at his office a few weeks ago. "Two sets of genes, turned 'on' or 'off' by some signal."

Allis soon found his ideal subject: a bizarre single-celled microbe called *Tetrahymena*. Blob-shaped cells surrounded by dozens of tiny, whiskery projections called cilia, *Tetrahymena* are improbable-looking—each a hairy Barbapapa, or a Mr. Potato Head who fell into a vat of Rogaine. "Perhaps the strangest thing about this strange organism is that it carries two very distinct collections of genes," he told me. "One is completely shut off during its normal life cycle and another is completely turned on. It's really black-and-white." Then, during reproduction, an entirely different nucleus wakes up and goes into action. "So we could now ask, What signal, or mechanism, allows *Tetrahymena* to regulate one set of genes versus the next?"

By the mid-nineteen-nineties, Allis had found an important clue. Genes are typically carried in long, continuous chains of DNA: one such chain can carry hundreds of thousands of genes. But a chain of DNA does not typically sit naked in animal cells; it is wrapped tightly around a core of proteins called histones. To demonstrate, Allis stood up from his desk, navigated his way through stacks of books and papers, and pointed at a model. A long plastic tube, cerulean blue, twisted sinuously around a series of white disks, like a python coiled around a skewer of marshmallows.

"Histones had been known as part of the inner scaffold for DNA for decades," Allis went on. "But most biologists thought of these proteins merely as packaging, or stuffing, for genes." When Allis gave scientific seminars in the early nineties, he recalled, skeptics asked him why he was so obsessed with the packing material, the stuff in between the DNA. His protozoan studies supplied an answer. "In *Tetrahymena*, the histones did not seem passive at all," he said. "The genes that were turned 'on' were invariably associated with one form of histone, while the genes that were turned 'off' were invariably associated with a different form of histone." A skein of silk tangled into a ball has very different properties from that same skein extended; might the coiling or uncoiling of DNA change the activity of genes?

In 1996, Allis and his research group deepened this theory with a seminal discovery. "We became interested in the process of histone modification," he said.

"What is the signal that changes the structure of the histone so that DNA can be packed into such radically different states? We finally found a protein that makes a specific chemical change in the histone, possibly forcing the DNA coil to open. And when we studied the properties of this protein it became quite clear that it was also changing the activity of genes." The coils of DNA seemed to open and close in response to histone modifications—inhaling, exhaling, inhaling, like life.

Allis walked me to his lab, a fluorescent-lit space overlooking the East River, divided by wide, polished-stone benches. A mechanical stirrer, whirring in a corner, clinked on the edge of a glass beaker. "Two features of histone modifications are notable," Allis said. "First, changing histones can change the activity of a gene without affecting the sequence of the DNA." It is, in short, formally *epi*-genetic, just as Waddington had imagined. "And, second, the histone modifications are passed from a parent cell to its daughter cells when cells divide. A cell can thus record 'memory,' and not just for itself but for all its daughter cells."

By 2000, Allis and his colleagues around the world had identified a gamut of proteins that could modify histones, and so modulate the activity of genes. Other systems, too, that could scratch different kinds of code on the genome were identified (some of these discoveries predating the identification of histone modifications). One involved the addition of a chemical side chain, called a methyl group, to DNA. The methyl groups hang off the DNA string like Christmas ornaments, and specific proteins add and remove the ornaments, in effect "decorating" the genome. The most heavily methylated parts of the genome tend to be dampened in their activity.

In the ensuing decade, Allis wrote enormous, magisterial papers in which a rich cast of histone-modifying proteins appear and reappear through various roles, mapping out a hatchwork of complexity. (His twin, Cathy Allis, is an ace crossword-puzzle constructor, having supplied *Times* readers with nearly a hundred puzzles—an activity that is similar but different.) These protein systems, overlaying information on the genome, interacted with one another, reinforcing or attenuating their signals. Together, they generated the bewildering intricacy necessary for a cell to build a constellation of other cells out of the same genes, and for the cells to add "memories" to their genomes and transmit these memories to their progeny. "There's an epigenetic code, just like there's a genetic code," Allis said. "There are codes to make parts of the genome more active, and codes to make them inactive."

And epigenetics could transform whole animals. "The idea that cells can acquire profoundly different properties by manipulating their epigenome was becoming known," Danny Reinberg told me. "But that you could create different forms of a *creature* out of the same genome using epigenetics? *That* was a real challenge."

Reinberg's lab is at New York University's School of Medicine. His office—by the East River around Thirty-first Street—is like Allis's: another nest of books and offprints, a wide river view, and another model of DNA twisted around histones, although this room is filled with Reinberg's private botanical obsession: huge, overgrown succulents from other climes that assert themselves with a defiant muscularity. Intense, articulate, with a cultivated stubble, Reinberg resembles an athlete—a gymnast, or a wrestler—whose skill depends on compaction and repetition. He grew up in Santiago, Chile, the child of parents who ran a jewelry business. He scored an A-minus in his first biochemistry

class in college, in Valparaiso, but felt that he hadn't really mastered the material, so he applied to take the class again. The professor looked at him as if he were mad before relenting.

Like Allis, Reinberg became interested in epigenetics in the nineteen-nineties. He explored how modified histones were copied when a cell divides, right down to the molecular level. Allis described Reinberg's early work as "some of the most elegant experiments in the field." But Reinberg sought a more advanced instance of epigenetic instruction—a whole animal, not just a cell, whose form and identity could be shifted by shifting the epigenetic code. "So imagine that you tighten some parts of the DNA and loosen other parts by changing the structures of the histones," Reinberg said. "Can you change the form or nature of an animal simply by coiling and uncoiling various parts of its genome?"

One blistering summer day in 2005, Reinberg found himself stuck in a van ferrying a group of scientists to an epigenetics meeting outside Mexico City. "The traffic was jammed for miles"—he shrugged, signalling South American resignation—"and I sat next to another scientist, Shelley Berger, whose work I had long admired, and we started talking." Berger, a molecular biologist who studies epigenetics at the University of Pennsylvania, had just returned from Costa Rica, where she had been looking at ant colonies.

Ants have a powerful caste system. A colony typically contains ants that carry out radically different roles and have markedly different body structures and behaviors. These roles, Reinberg learned, are often determined not by genes but by signals from the physical and social environment. "Sibling ants, in their larval stage, become segregated into the different types based on environmental signals," he said. "Their genomes are nearly identical, but the way the genes are *used*—turned on or off, and kept on or off—must determine what an ant 'becomes.' It seemed like a perfect system to study epigenetics. And so Shelley and I caught a flight to Arizona to see Jürgen Liebig, the ant biologist, in his lab."

The collaboration between Reinberg, Berger, and Liebig has been explosively successful—the sort of scientific story ("two epigeneticists walk into a bar and meet an entomologist") that works its way into a legend. Carpenter ants, one of the species studied by the team, have elaborate social structures, with queens (bullet-size, fertile, winged), majors (bean-size soldiers who guard the colony but rarely leave it), and minors (nimble, grain-size, perpetually moving foragers). In a recent, revelatory study, researchers in Berger's lab injected a single dose of a histone-altering chemical into the brains of major ants. Remarkably, their identities changed; caste was recast. The major ants wandered away from the colony and began to forage for food. The guards turned into scouts. Yet the caste switch could occur only if the chemical was injected during a vulnerable period in the ants' development.

Since 2012, Reinberg, continuing his partnership with Berger and Liebig, has been cultivating ant colonies in his own lab. One afternoon in April, I put on sky-blue sterile gloves and an apron, and accompanied a postdoctoral researcher in Reinberg's lab, Hua Yan, to the ant room. It is a neatly kept, gently lighted space with the slightly dank smell of sugar and dead maggots—ant food. In a nightmarish inversion of an American picnic idyll, the ants live inside Tupperware containers, and the people watch from outside.

The most mature colonies in Reinberg's collection belong to a species called the "jumping ant," a pugnacious social insect from southern India. Like most ant species, jumping ants segregate into castes. When the queen is removed from the colony, the workers, sensing opportunity, launch a vicious, fight-to-the-death campaign against one another—stinging, biting, sparring, lopping off limbs and heads, until a few workers win and become queenlike. The behavior of these "pseudo-queens," as Reinberg calls them, changes dramatically; their life spans increase. The pseudo-queen (the scientific term is "gamergate," not to be confused with the vicious, fight-to-the-death campaign against female video-game-makers) acquires reproductive fecundity, and dominates the colony.

I looked through a transparent Tupperware lid at a teeming colony of jumping ants, and thought, inevitably, of the city around us. The workers scurried around the edges of the container with inexhaustible energy, gathering food and garbage. The gamergates, in contrast, moved lazily above their brood in the center of the container. The workers worked. The gamergates *lounged*—waking late, moving little. When a worker approached a gamergate, the dominant ant Tasered it with her antennae, warning the worker to keep off her royal territory. The worker retreated, its antennae lowered.

"The remarkable thing about workers and gamergates," Yan told me, "is that

"Honey, it's never too early to apply for summer language programs."

they are almost genetically identical." The gene sequence before and after the transition is the same. Yet, as DNA methyl groups or histone modifications get shifted around those gene sequences, the worker transforms into a gamergate, and virtually everything about the insect's physiology and behavior changes. "We're going to solve how the change can have such a dramatic effect on longevity," Reinberg said. "It's like one twin that lives three times longer than the other"—all by virtue of a change in epigenetic information.

The impact of the histone-altering experiment sank in as I left Reinberg's lab and dodged into the subway. (How could I resist the urge, that spring afternoon, to categorize the passengers on the No. 6 train into the three basic New Yorker archetypes: worker, soldier, queen?) All of an ant's possible selves are inscribed in its genome. Epigenetic signals conceal some of these selves and reveal others, coiling some, uncoiling others. The ant chooses a life between its genes and its epigenes—inhabiting one self among its incipient selves.

Epigeneticists, once a subcaste of biologist nudged to the far peripheries of the discipline, now find themselves firmly at its epicenter. "Fifteen years ago, a meeting on cell biology would hold a session on histones or DNA methylation—and no one would be at that session," Allis told me. Now there are meetings on the epigenetics of human memory, of ants, of cancer, of mental illness. Part of the reason for the excitement is that epigenes may be vastly more tractable than genes. "Gene therapy was all the rage when I began my career, but manipulating genes has turned out to be much harder than envisioned," Allis said. Genes, after all, are the permanent repository of a cell's information system, and thus more tamperproof. (If genes are hardware, epigenes are firmware.) But by altering epigenes—the manner in which DNA is coiled or uncoiled, methylated or demethylated—one should be able to alter which genes are activated.

Medical epigeneticists are most excited about the implications for cancer. In some cancers, such as leukemias, malignant cells have markedly aberrant patterns of DNA methylation or histone modification. "Clearly, there's a signal that epigenetic information is important for a cancer cell," Allis said. "But can a drug safely change the epigenome of a cancer cell without touching a normal cell?" In my own leukemia- and lymphoma-focussed clinic, dozens of epigenetic drugs are on trial. Some alter methylation, while others perturb the histone-modification system. One woman with pre-leukemia had a spectacular remission on a drug called azacitidine, but, oddly, she began to have sudden spurts of anxiety. Were these symptoms related to the drug's effect on the epigenomes of brain cells?

Other researchers, following Reinberg and his colleagues, have looked at how epigenetics might change behaviors—not just cellular memory and identity but an *organism's* memory and identity. The neuroscientist and psychiatrist Eric Nestler, who studies addiction, gave mice repeated injections of cocaine, and found that the histones were altered in the reward-recognizing region of the brain. When the histone modification was chemically blocked, the mice were less likely to become addicted. In 2004, a team of researchers at McGill University noticed that rats raised by low-nurturing mothers were likely to be notably stressed as young adults. The memory of childhood neglect in rats appears to be related to epigenetic changes: a gene that acts as a set point for stress—an anxiety rheostat—is dampened in these poorly nurtured rats, resulting in higher levels of stress hormones. McGill researchers went on to study the brains of human beings who were abused as children and later committed suicide, and found similar epigenetic alterations.

The medical impact of epigenetics remains to be established, but its biological influence has been evident for nearly

"The Wi-Fi password is 'Don't call me sweetie.'"

a decade. Diffuse, mysterious observations, inexplicable by classical genetics, have epigenetic explanations at their core. When a female horse and a male donkey mate, they produce a longer-eared, thin-maned mule; a male horse and a female donkey typically generate a smaller, shorter-eared hinny. That a hybrid's features depend on the precise configuration of male versus female parentage is impossible to explain unless the genes can "remember" whether they came from the mother or the father—a phenomenon called "genomic imprinting." We now know that epigenetic notations etched in sperm and eggs underlie imprinted genes.

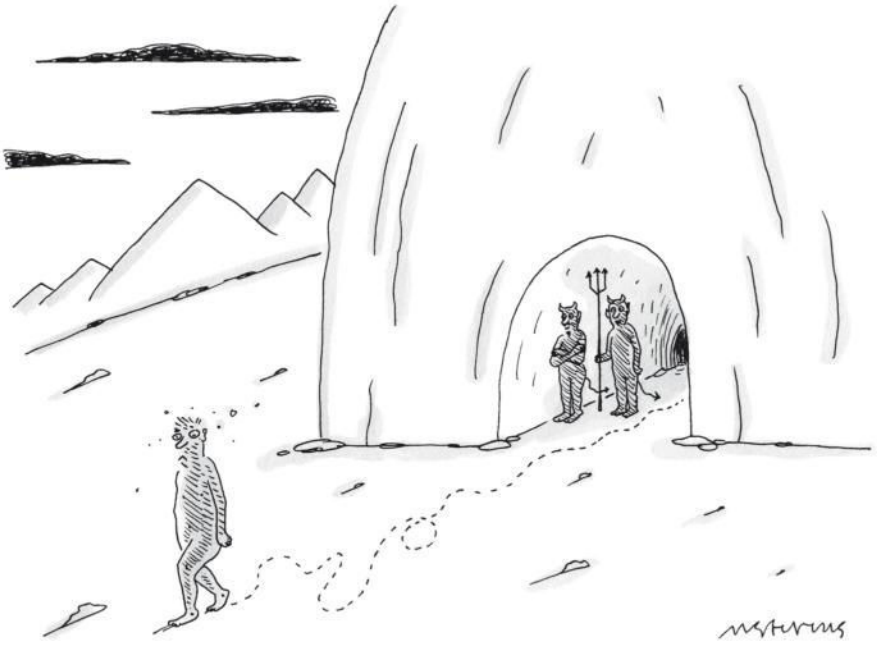
Perhaps the most startling demonstration of the power of epigenetics to set cellular memory and identity arises from an experiment performed by the Japanese stem-cell biologist Shinya Yamanaka in 2006. Yamanaka was taken by the idea that chemical marks attached to genes in a cell might function as a record of cellular identity. What if he could erase these marks? Would the adult cell revert to an original state and turn into an embryonic cell? He began his experiments with a normal skin cell from an adult mouse. After a decades-long hunt for identity-switching factors, he and his colleagues figured out a way to erase a cell's memory. The process, they found, involved a cascade of events. Circuits of genes were activated or repressed. The metabolism of the cell was reset. Most important, epigenetic marks were erased and rewritten, resetting the landscape of active and inactive genes. The cell changed shape and size. Its wrinkles unmarked, its stiffening joints made supple, its youth restored, the cell could now become any cell type in the body. Yamanaka had reversed not just cellular memory but the direction of biological time.

IT'S ONE THING to study epigenetic changes across the life of a single organism, or down a line of cells. The more tantalizing question is whether epigenetic messages can, like genes, cross from parents to their offspring.

The most suggestive evidence for such transgenerational transmission may come from a macabre human experiment. In September, 1944, amid the most vengeful phase of the Second World War, German troops occupying the Netherlands banned the export of food and coal to its northern parts. Acute famine followed, called the *Hongerwinter*—the hunger winter. Tens of thousands of men, women, and children died of malnourishment; millions suffered it and survived. Not surprisingly, the children who endured the *Hongerwinter* experienced chronic health issues. In the nineteen-eighties, however, a curious pattern emerged: when the children born to women who were pregnant during the famine grew up, they had higher rates of morbidity as well—including obesity, diabetes, and mental illness. (Malnourishment in utero can cause the body to sequester higher amounts of fat in order to protect itself from caloric loss.) Methylation alterations were also seen in regions of their DNA associated with growth and development. But the oddest result didn't emerge for another generation. A decade ago, when the *grandchildren* of men and women exposed to the famine were studied, they, too, were reported to have had higher rates of illness. (These findings have been challenged, and research into this cohort continues.) "Genes cannot change in an entire population in just two generations," Allis said. "But some memory of metabolic stress could have become heritable."

Both Allis and Reinberg understand the implications of transgenerational epigenetic transmission: it would overturn fundamental principles of biology, including our understanding of evolution. Conceptually, a key element of classical Darwinian evolution is that genes do not retain an organism's experiences in a permanently heritable manner. Jean-Baptiste Lamarck, in the early nineteenth century, had supposed that when an antelope strained its neck to reach a tree its efforts were somehow passed down and its progeny evolved into giraffes. Darwin discredited that model. Giraffes, he proposed, arose through heritable variation and natural selection—a tall-necked specimen appears in an ancestral tree-grazing animal, and, perhaps during a period of famine, this mutant survives and is naturally selected. But, if epigenetic information can be transmitted through sperm and eggs, an organism would seem to have a direct conduit to the heritable features of its progeny. Such a system would act as a wormhole for evolution—a shortcut through the glum cycles of mutation and natural selection.

My visit with Allis had ended on a cautionary note. "Much about the transmission of epigenetic information across generations is unknown, and we should be careful before making up theories about the kind of information or memory that is transmitted," he told me. By bypassing the traditional logic of genetics



"Every once in a while, it's fun to let one go, just to see what happens."

and evolution, epigenetics can arouse fantasies about warp-speeding heredity: you can make your children taller by straining your neck harder. Such myths abound and proliferate, often dangerously. A child's autism, the result of genetic mutation, gets attributed to the emotional trauma of his great-grandparents. Mothers are being asked to minimize anxiety during their pregnancy, lest they taint their descendants with anxiety-ridden genes. Lamarck is being rehabilitated into the new Darwin.

These fantasies should invite skepticism. Environmental information can certainly be etched on the genome. But such epigenetic scratch marks are rarely, if ever, carried forward across generations. A man who loses a leg in an accident bears the imprint of that accident in his cells, wounds, and scars, but he does not bear children with shortened legs. A hundred and forty generations of circumcision have not made the procedure any shorter. Nor has the serially uprooted life of my family burdened me, or my children, with any wrenching sense of estrangement.

In the fall of 2013, Bulu travelled to the United States. I had not seen her for nearly a decade, and I drove out to Robbinsville, New Jersey, with my family to visit her. It was October 6th, the birthday that she shared with my mother. She had cooked my favorite meal—shrimp curry, a signature Tulu dish, tangy with just a hint of bitterness from lime rind—and the house smelled of the heady mixture of boiled shellfish, lime, and the floral brand of hair oil that both sisters preferred, my private madeleine. Bulu's face was leaner and more angular than I remembered it, but when she smiled the angles rearranged themselves and softened into a distant evocation of my mother's.

We made our way to the park outside the house, while the kids played in the garden. The October light was oblique and sepulchral, a halo-endowing, New World light that does not exist in Delhi or Calcutta. There had been an uncomfortable irony in that Bulu, who loved adventure, had spent most of her life in the same stodgy city, while Tulu, an inveterate homebody, fussy about mattresses and food, had been dragged across the globe by my travel-obsessed father. I asked Bulu about her encounter with America, the adventure of it all.

"Oh, but I've been here so many times," she said, laughing. "Every time Tulu took a trip abroad, I bought a guidebook and travelled, too." There was something about the remark that reminded me of my mother. It was almost rueful, although without the aftertaste of bitterness. She shared my mother's lightness about fate—an equanimity that borders nobility but comes with no pride.

As we meandered through the park over fallen leaves, Bulu reminisced about how the vicissitudes of their lives had reshaped her and her sister in different ways, while I couldn't help noting how fiercely they had converged. In calculus, the first derivative of a curve at any point refers not to the position of the point but to its propensity to change its position; not where an object *is* but how it *moves*. This shared quality was the lasting link between my mother and her twin. Tulu and Bulu were no longer recognizably identical—but they shared the first derivative of identity.

It is easy to think of twins as comedies of nature. The rhyming names, the matching sailor suits, the tomfoolery of mistaken identities, the two-places-at-the-same-time movie plot—genetics for gags. But twins often experience parts of their lives as tragedies of nature. My mother and her sister grew up in a walled garden, imagining each other not as friends or siblings but as alternate selves. They were separated not at birth but at marriage, as sisters often are. *Jeta Tulur, sheta Bulur,* my grandfather would say: "What is Tulu's is also Bulu's." But that wistful phrase, a parent's fantasy of perfect parity for his children, was absurd; how could it possibly last? The grief that twins experience as they drift apart in life is unique, but it abuts a general grief: if eternal sameness will not guarantee eternal closeness, then what hope is there for siblings, or parents, or lovers?

Why are twins different? Well, because idiosyncratic events are recorded through idiosyncratic marks in their bodies. If you sequence the genomes of a pair of identical twins every decade for fifty years, you get the same sequence over and over. But if you sequence the *epigenomes* of a pair of twins you find substantial differences: the pattern of epigenetic marks on the genomes of their various cells, virtually identical at the start of the experiment, diverges over time.

Chance events—injuries, infections, infatuations; the haunting trill of that particular nocturne—impinge on one twin and not on the other. Genes are turned on and off in response to these events, as epigenetic marks are gradually layered above genes, etching the genome with its own scars, calluses, and freckles. Prospero, raging against the deformed Caliban in "The Tempest," describes him as "a devil, a born devil, on whose nature/Nurture can never stick." Caliban is destined to remain a genetic automaton, a windup ghoul—vastly more pathetic than anything human. He experiences the world, but he has no capacity to be changed by it; he has a genome that lacks an epigenome.

It is a testament to the unsettling beauty of the genome that it can make the real world stick. Hindu philosophers have long described the experience of "being" as a web—*jaal*. Genes form the threads of the web; the detritus that adheres to it transforms every web into a singular being. An organism's individuality, then, is suspended between genome and epigenome. We call the miracle of this suspension "fate." We call our responses to it "choice." We call one such unique variant of one such organism a "self."

A strange thing happened on the way out of Reinberg's ant room. One of the ants leaped out of the Tupperware box onto my shirt. There was a momentary commotion—"They bite," Yan said, matter-of-factly—and then we found the ant on my shoulder, making a desperate break for my ear. Yan pulled out a pair of forceps and, after a few attempts, she was returned to the colony.

The retrieval had been masterfully delicate, but the ant was injured: a leg had been bruised, and she waddled lopsidedly for a while. The wound would heal, I knew, but a scar would remain. She had done it: she had made difference out of similarity. The clone was somehow no longer quite a clone. I watched her make her way back to the colony—the One That Almost Got Away, to be memorialized in song and verse—until she vanished into the metropolis of soldiers, workers, and queens. ♦