The Social Life of Genes

A few years ago, Gene Robinson, of Urbana, Illinois, asked some associates in southern Mexico to help him kidnap some 1,000 newborns. For their victims they chose bees. Half were European honeybees, *Apis mellifera ligustica*, the sweet-tempered kind most beekeepers raise. The other half were *ligustica*'s genetically close cousins, *Apis mellifera scutellata*, the African strain better known as killer bees. Though the two subspecies are nearly indistinguishable, the latter defend territory far more aggressively. Kick a European honeybee hive and perhaps a hundred bees will attack you. Kick a killer bee hive and you may suffer a thousand stings or more. Two thousand will kill you.

Working carefully, Robinson's conspirators—researchers at Mexico's National Center for Research in Animal Physiology, in the high resort town of Ixtapan de la Sal—jiggled loose the lids from two African hives and two European hives, pulled free a few honeycomb racks, plucked off about 250 of the youngest bees from each hive, and painted marks on the bees' tiny backs. Then they switched each set of newborns into the hive of the other subspecies.

Robinson, back in his office at the University of Illinois at Urbana-Champaign's Department of Entomology, did not fret about the bees' safety. He knew that if you move bees to a new colony in their first day, the colony accepts them as its own. Nevertheless, Robinson did expect the bees would be changed by their adoptive homes: He expected the killer bees to take on the European bees' moderate ways and the European bees to assume the killer bees' more violent temperament. Robinson had discovered this in prior experiments. But he hadn't yet figured out how it happened.

He suspected the answer lay in the bees' genes. He didn't expect the bees' actual DNA to change: Random mutations aside, genes generally don't change during an organism's lifetime. Rather, he suspected the bees' genes would behave differently in their new homes—wildly differently.

This notion was both reasonable and radical. Scientists have known for decades that genes can vary their level of activity, as if controlled by dimmer switches. Most cells in your body contain every one of your 22,000 or so genes. But in any given cell at any given time, only a tiny percentage of those genes is active, sending out chemical messages that affect the activity of the cell. This variable gene activity, called gene expression, is how your body does most of its work.

The fish underwent massive surges in gene expression that immediately blinged up his pewter coloring with lurid red and blue streaks and, in a matter of hours, caused him to grow some 20 percent. It was as if Jason Schwartzman, coming to work one day to learn the big office stud had quit, morphed into Arnold Schwarzenegger by close of business.

Sometimes these turns of the dimmer switch correspond to basic biological events, as when you develop tissues in the womb, enter puberty, or stop growing. At other times gene activity cranks up or spins down in response to changes in your environment. Thus certain genes switch on to fight infection or heal your wounds—or, running amok, give you cancer or burn your brain with fever. Changes in gene expression can make you thin, fat, or strikingly different from your supposedly identical twin. When it comes down to it, really, genes don't make you who you are. Gene expression does. And gene expression varies depending on the life you live.

Every biologist accepts this. That was the safe, reasonable part of Robinson's notion. Where he went out on a limb was in questioning the conventional wisdom that environment usually causes fairly *limited* changes in gene expression. It might sharply alter the activity of some genes, as happens in cancer or digestion. But in all but a few special cases, the thinking went, environment generally brightens or dims the activity of only a few genes at a time.

Robinson, however, suspected that environment could spin the dials on "big sectors of genes, right across the genome"—and that an individual's social environment might exert a particularly powerful effect. Who you hung out with and how they behaved, in short, could dramatically affect which of your genes spoke up and which stayed quiet—and thus change who you were.

Robinson was already seeing this in his bees. The winter before, he had asked a new post-doc, Cédric Alaux, to look at the gene-expression patterns of honeybees that had been repeatedly exposed to a pheromone that signals alarm. (Any honeybee that detects a threat emits this pheromone. It happens to smell like bananas. Thus "it's not a good idea," says Alaux, "to eat a banana next to a bee hive.")

To a bee, the pheromone makes a social statement: *Friends, you are in danger*. Robinson had long known that bees react to this cry by undergoing behavioral and neural changes: Their brains fire up and they literally fly into action. He also knew that repeated alarms make African bees more and more hostile. When Alaux looked at the gene-expression profiles of the bees exposed again and again to alarm pheromone, he and Robinson saw why: With repeated alarms, hundreds of genes—genes that previous

studies had associated with aggression—grew progressively busier. The rise in gene expression neatly matched the rise in the aggressiveness of the bees' response to threats.

Robinson had not expected that. "The pheromone just lit up the gene expression, and it kept leaving it higher." The reason soon became apparent: Some of the genes affected were transcription factors—genes that regulate other genes. This created a cascading gene-expression response, with scores of genes responding.

This finding inspired Robinson's kidnapping-and-cross-fostering study. Would moving baby bees to wildly different social environments reshape the curves of their gene-expression responses? Down in Ixtapan, Robinson's collaborators suited up every five to 10 days, opened the hives, found about a dozen foster bees in each one, and sucked them up with a special vacuum. The vacuum shot them into a chamber chilled with liquid nitrogen. The intense cold instantly froze the bees' every cell, preserving the state of their gene activity at that moment. At the end of six weeks, when the researchers had collected about 250 bees representing every stage of bee life, the team packed up the frozen bees and shipped them to Illinois.

There, Robinson's staff removed the bees' sesame-seed-size brains, ground them up, and ran them through a DNA microarray machine. This identified which genes were busy in a bee's brain at the moment it met the bee-vac. When Robinson sorted his data by group—European bees raised in African hives, for instance, or African bees raised normally among their African kin—he could see how each group's genes reacted to their lives.

Robinson organized the data for each group onto a grid of red and green color-coded squares: Each square represented a different gene, and its color represented the group's average rate of gene expression. Red squares represented genes that were especially active in most of the bees in that group; the brighter the red, the more bees in which that gene had been busy. Green squares represented genes that were silent or underactive in most of the group. The printout of each group's results looked like a sort of cubist Christmas card.

When he got the cards, says Robinson, "the results were stunning." For the bees that had been kidnapped, life in a new home had indeed altered the activity of "whole sectors" of

genes. When their gene expression data was viewed on the cards alongside the data for groups of bees raised among their own kin, a mere glance showed the dramatic change. Hundreds of genes had flipped colors. The move between hives didn't just make the bees act differently. It made their genes work differently, and on a broad scale.

What's more, the cards for the adopted bees of both species came to ever more resemble, as they moved through life, the cards of the bees they moved in with. With every passing day their genes acted more like those of their new hive mates (and less like those of their genetic siblings back home). Many of the genes that switched on or off are known to affect behavior; several are associated with aggression. The bees also acted differently. Their dispositions changed to match that of their hive mates. It seemed the genome, without changing its code, could transform an animal into something very like a different subspecies.

These bees didn't just act like different bees. They'd pretty much become different bees. To Robinson, this spoke of a genome far more fluid—far more socially fluid—than previously conceived.

Gene Robinson, an entomologist at the University of Illinois, found that when European honeybees are raised among more aggressive African killer bees, they not only start to become as

belligerent as their new hive mates—they come to genetically resemble them. (PHOTO: COURTESY OF GENE ROBINSON)

ROBINSON SOON REALIZED HE was not alone in seeing this. At conferences and in the literature, he kept bumping into other researchers who saw gene networks responding fast and wide to social life. David Clayton, a neurobiologist also on the University of Illinois campus, found that if a male zebra finch heard another male zebra finch singing nearby, a particular gene in the bird's forebrain would "re up—and it would do so differently depending on whether the other finch was strange and threatening, or familiar and safe.

Others found this same gene, dubbed ZENK ramping up in other species. In each case, the change in ZENK's activity corresponded to some change in behavior: a bird might relax in response to a song, or become vigilant and tense. Duke researchers, for instance, found that when female zebra finches listened to male zebra finches' songs, the females' ZENK gene triggered massive gene-expression changes in their forebrains—a socially sensitive brain area in birds as well as humans. The changes differed depending on whether the song was a mating call or a territorial claim. And perhaps most remarkably, all
of these changes happened incredibly fast—within a half hour, sometimes within just five minutes.

ZENK, it appeared, was a so-called "immediate early gene," a type of regulatory gene that can cause whole networks of other genes to change activity. These sorts of regulatory gene-expression response had already been identified in physiological systems such as digestion and immunity. Now they also seemed to drive quick responses to social conditions.

One of the most startling early demonstrations of such a response occurred in 2005 in the lab of Stanford biologist Russell Fernald. For years, Fernald had studied the African cichlid *Astatotilapia burtoni*, a freshwater fish about two inches long and dull pewter in color. By 2005 he had shown that among *burtoni*, the top male in any small population

lives like some fishy pharaoh, getting far more food, territory, and sex than even the No. 2 male. This No. 1 male cichlid also sports a bigger and brighter body. And there is always only one No. 1.

I wonder, Fernald thought, what would happen if we just removed him?

So one day Fernald turned out the lights over one of his cichlid tanks, scooped out big flashy No. 1, and then, 12 hours later, flipped the lights back on. When the No. 2 cichlid saw that he was now No. 1, he responded quickly. He underwent massive surges in gene expression that immediately blinged up his pewter coloring with lurid red and blue streaks and, in a matter of hours, caused him to grow some 20 percent. It was as if Jason Schwartzman, coming to work one day to learn the big office stud had quit, morphed into Arnold Schwarzenegger by close of business.

These studies, says Greg Wray, an evolutionary biologist at Duke who has focused on gene expression for over a decade, caused quite a stir. “You suddenly realize birds are hearing a song and having massive, widespread changes in gene expression in just 15 minutes? Something big is going on.”

This big something, this startlingly quick gene-expression response to the social world, is a phenomenon we are just beginning to understand. The recent explosion of interest in “epigenetics”—a term literally meaning “around the gene,” and referring to anything that changes a gene’s effect without changing the actual DNA sequence—has tended to focus on the long game of gene-environment interactions: how famine among expectant mothers in the Netherlands during World War II, for instance, affected gene expression and behavior in their children; or how mother rats, by licking and grooming their pups more or less assiduously, can alter the wrappings around their offspring’s DNA in ways that influence how anxious the pups will be for the rest of their lives. The idea that experience can echo in our genes across generations is certainly a powerful one. But to focus only on these narrow, long-reaching effects is to miss much of the action where epigenetic influence and gene activity is concerned. This fresh work by Robinson, Fernald, Clayton, and others—encompassing studies of multiple organisms, from bees and birds to monkeys and humans—suggests something more exciting: that our social lives can change our gene expression with a rapidity, breadth, and depth previously

overlooked.

Why would we have evolved this way? The most probable answer is that an organism that responds quickly to fast-changing social environments will more likely survive them. That organism won't have to wait around, as it were, for better genes to evolve on the species level. Immunologists discovered something similar 25 years ago: Adapting to new pathogens the old-fashioned way—waiting for natural selection to favor genes that create resistance to specific pathogens—would happen too slowly to counter the rapidly changing pathogen environment. Instead, the immune system uses networks of genes that can respond quickly and flexibly to new threats.

We appear to respond in the same way to our social environment. Faced with an unpredictable, complex, ever-changing population to whom we must respond successfully, our genes behave accordingly—as if a fast, fluid response is a matter of life or death.

"If you actually measure stress, using our best available instruments, it can't hold a candle to social isolation. Social isolation is the best-established, most robust social or psychological risk factor for disease out there. Nothing can compete."

ABOUT THE TIME ROBINSON was seeing fast gene expression changes in bees, in the early 2000s, he and many of his colleagues were taking notice of an up-and-coming UCLA researcher named Steve Cole.

Cole, a Californian then in his early 40s, had trained in psychology at the University of California-Santa Barbara and Stanford; then in social psychology, epidemiology, virology, cancer, and genetics

at UCLA. Even as an undergrad, Cole had "this astute, fine-grained approach," says Susan Andersen, a professor of psychology now at NYU who was one of his teachers at UC Santa Barbara in the late 1980s. "He thinks about things in very precise detail."

In his post-doctoral work at UCLA, Cole focused on the genetics of immunology and cancer because those fields had pioneered hard-nosed gene-expression research. After that, he became one of the earliest researchers to bring the study of whole-genome gene-expression to social psychology. The gene's ongoing, real-time response to incoming information, he realized, is where life works many of its changes on us. The idea is both reductive and expansive. We are but cells. At each cell's center, a tight tangle of DNA writes and hands out the cell's marching orders. Between that center and the world stand only a series of membranes.

"Porous membranes," notes Cole.

"We think of our bodies as stable biological structures that live in the world but are fundamentally separate from it. That we are unitary organisms in the world but passing through it. But what we're learning from the molecular processes that actually keep our bodies running is that we're far more fluid than we realize, and the world passes through us."

Cole told me this over dinner. We had met on the UCLA campus and walked south a few blocks, through bright April sun, to an almost empty sushi restaurant. Now, waving his chopsticks over a platter of urchin, squid, and amberjack, he said, "Every day, as our cells die off, we have to replace one to two percent of our molecular being. We're constantly building and re-engineering new cells. And that regeneration is driven by the contingent nature of gene expression.

"This is what a cell is about. A cell," he said, clasping some amberjack, "is a machine for turning experience into biology."

When Cole started his social psychology research in the early 1990s, the microarray technology that spots changes in gene expression was still in its expensive infancy, and saw use primarily in immunology and cancer. So he began by using the tools of

epidemiology—essentially the study of how people live their lives. Some of his early papers looked at how social experience affected men with HIV. In a 1996 study of 80 gay men, all of whom had been HIV-positive but healthy nine years earlier, Cole and his colleagues found that closeted men succumbed to the virus much more readily.

He then found that HIV-positive men who were lonely also got sicker sooner, regardless of whether they were closeted. Then he showed that closeted men *without* HIV got cancer and various infectious diseases at higher rates than openly gay men did. At about the same time, psychologists at Carnegie Mellon finished a well-controlled study showing that people with richer social ties got fewer common colds.

Something about feeling stressed or alone was gumming up the immune system—sometimes fatally.

“You’re besieged by a virus that’s going to kill you,” says Cole, “but the fact that you’re socially stressed and isolated seems to shut down your viral defenses. What’s going on there?”

He was determined to find out. But the research methods on hand at the time could take him only so far: “Epidemiology won’t exactly lie to you. But it’s hard to get it to tell you the whole story.” For a while he tried to figure things out at the bench, with pipettes and slides and assays. “I’d take norepinephrine [a key stress hormone] and squirt it on some infected T-cells and watch the virus grow faster. The norepinephrine was knocking down the antiviral response. That’s great. Virologists love that. But it’s not satisfying as a complete answer, because it doesn’t fully explain what’s happening in the real world.

“You can make almost anything happen in a test tube. I needed something else. I had set up all this theory. I needed a place to test it.”

His next step was to turn to rhesus monkeys, a lab species that allows controlled study. In 2007, he joined John Capitanio, a primatologist at the University of California-Davis, in looking at how social stress affected rhesus monkeys with SIV, or simian immunodeficiency virus, the monkey version of HIV. Capitanio had found that monkeys with SIV fell ill and died faster if they were stressed out by constantly being moved into

new groups among strangers—a simian parallel to Cole's 1996 study on lonely gay men.

Capitanio had run a rough immune analysis that showed the stressed monkeys mounted weak antiviral responses. Cole offered to look deeper. First he tore apart the lymph nodes—"ground central for infection"—and found that in the socially stressed monkeys, the virus bloomed around the sympathetic nerve trunks, which carry stress signals into the lymph node.

"This was a hint," says Cole: The virus was running amok precisely where the immune response should have been strongest. The stress signals in the nerve trunks, it seemed, were getting either muted en route or ignored on arrival. As Cole looked closer, he found it was the latter: The monkeys' bodies were generating the appropriate stress signals, but the immune system didn't seem to be responding to them properly. Why not? He couldn't find out with the tools he had. He was still looking at cells. He needed to look inside them.

Finally Cole got his chance. At UCLA, where he had been made a professor in 2001, he had been working hard to master gene-expression analysis across an entire genome. Microarray machines—the kind Gene Robinson was using on his bees—were getting cheaper. Cole got access to one and put it to work.

Thus commenced what we might call the lonely people studies.

First, in collaboration with University of Chicago social psychologist John Cacioppo, Cole mined a questionnaire about social connections that Cacioppo had given to 153 healthy Chicagoans in their 50s and 60s. Cacioppo and Cole identified the eight most socially secure people and the six loneliest and drew blood samples from them. (The socially insecure half-dozen were lonely indeed; they reported having felt distant from others for the previous four years.) Then Cole extracted genetic material from the blood's leukocytes (a key immune-system player) and looked at what their DNA was up to.

He found a broad, weird, strongly patterned gene-expression response that would become mighty familiar over the next few years. Of roughly 22,000 genes in the human

genome, the lonely and not-lonely groups showed sharply different gene-expression responses in 209. That meant that about one percent of the genome—a considerable portion—was responding differently depending on whether a person felt alone or connected. Printouts of the subjects' gene-expression patterns looked much like Robinson's red-and-green readouts of the changes in his cross-fostered bees: Whole sectors of genes looked markedly different in the lonely and the socially secure. And many of these genes played roles in inflammatory immune responses.

Now Cole was getting somewhere.

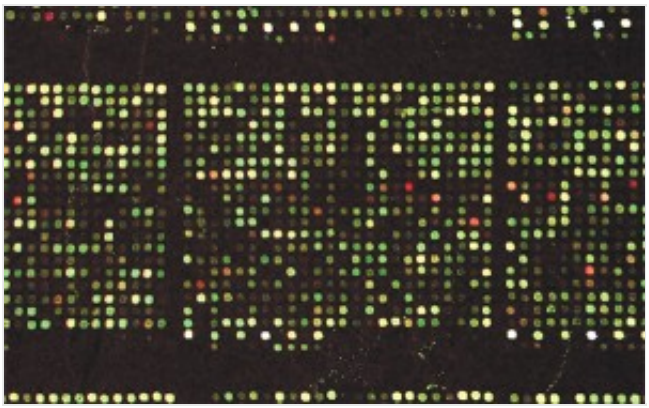
Normally, a healthy immune system works by deploying what amounts to a leashed attack dog. It detects a pathogen, then sends inflammatory and other responses to destroy the invader while also activating an anti-inflammatory response—the leash—to keep the inflammation in check. The lonely Chicagoans' immune systems, however, suggested an attack dog off leash—even though they weren't sick. Some 78 genes that normally work together to drive inflammation were busier than usual, as if these healthy people were fighting infection. Meanwhile, 131 genes that usually cooperate to control inflammation were underactive. The underactive genes also included key antiviral genes.

This opened a whole new avenue of insight. If social stress reliably created this gene-expression profile, it might explain a lot about why, for instance, the lonely HIV carriers in Cole's earlier studies fell so much faster to the disease.

But this was a study of just 14 people. Cole needed more.

Over the next several years, he got them. He found similarly unbalanced gene-expression or immune-response profiles in groups including poor children, depressed people with cancer, and people caring for spouses dying of cancer. He topped his efforts off with a study in which social stress levels in young women predicted changes in their gene activity six months later. Cole and his collaborators on that study, psychologists Gregory Miller and Nicolas Rohleder of the University of British Columbia, interviewed 103 healthy Vancouver-area women aged 15 to 19 about their social lives, drew blood, and ran gene-expression profiles, and after half a year drew blood and ran profiles again. Some of the women reported at the time of the initial interview that they were having

trouble with their love lives, their families, or their friends. Over the next six months, these socially troubled subjects took on the sort of imbalanced gene-expression profile Cole found in his other isolation studies: busy attack dogs and broken leashes. Except here, in a prospective study, he saw the attack dog breaking free of its restraints: Social stress changed these young women's gene-expression patterns before his eyes.



Gene-expression microarray printouts (this one comes from a study of autistic versus non-autistic people) depict snapshots of activity across a genome. Red squares represent genes that are more active, green squares represent genes that are less active. (PHOTO: PUBLIC DOMAIN)

IN EARLY 2009, COLE sat down to make sense of all this in a review paper that he would publish later that year in *Current Directions in Psychological Science*. Two years later we sat in his spare, rather small office at UCLA and discussed what he'd found. Cole, trimly built but close to six feet tall, speaks in a reedy voice that is slightly higher than his frame might lead you to expect. Sometimes, when he's grabbing for a new thought or trying to emphasize a point, it jumps a register. He is often asked to give talks about his work, and it's easy to see why: Relaxed but animated, he speaks in such an organized manner that you can almost see the paragraphs form in the air between you. He spends much of his time on the road. Thus the half-unpacked office, he said, gesturing around him. His lab, down the hall, "is essentially one really good lab manager"—Jesusa M. Arevalo, whom he frequently lists on his papers—"and a bunch of

robots," the machines that run the assays.

"We typically think of stress as being a risk factor for disease," said Cole. "And it is, somewhat. But if you actually measure stress, using our best available instruments, it can't hold a candle to social isolation. Social isolation is the best-established, most robust social or psychological risk factor for disease out there. Nothing can compete."

This helps explain, for instance, why many people who work in high-stress but rewarding jobs don't seem to suffer ill effects, while others, particularly those isolated and in poverty, wind up accruing lists of stress-related diagnoses—obesity, Type 2 diabetes, hypertension, atherosclerosis, heart failure, stroke.

Despite these well-known effects, Cole said he was amazed when he started finding that social connectivity wrought such powerful effects on gene expression.

"Or not that we found it," he corrected, "but that we're seeing it with such consistency. Science is noisy. I would've bet my eyeteeth that we'd get a lot of noisy results that are inconsistent from one realm to another. And at the level of individual genes that's kind of true—there is some noise there." But the kinds of genes that get dialed up or down in response to social experience, he said, and the gene networks and gene-expression cascades that they set off, "are surprisingly consistent—from monkeys to people, from five-year-old kids to adults, from Vancouver teenagers to 60-year-olds living in Chicago."

COLE'S WORK CARRIES ALL kinds of implications—some weighty and practical, some heady and philosophical. It may, for instance, help explain the health problems that so often haunt the poor. Poverty savages the body. Hundreds of studies over the past few decades have tied low income to higher rates of asthma, flu, heart attacks, cancer, and everything in between. Poverty itself starts to look like a disease. Yet an empty wallet can't make you sick. And we all know people who escape poverty's dangers. So what is it about a life of poverty that makes us ill?

Cole asked essentially this question in a 2008 study he conducted with Miller and Edith Chen, another social psychologist then at the University of British Columbia. The paper

appeared in an odd forum: *Thorax*, a journal about medical problems in the chest. The researchers gathered and ran gene-expression profiles on 31 kids, ranging from nine to 18 years old, who had asthma; 16 were poor, 15 well-off. As Cole expected, the group of well-off kids showed a healthy immune response, with elevated activity among genes that control pulmonary inflammation. The poorer kids showed busier inflammatory genes, sluggishness in the gene networks that control inflammation, and—in their health histories—more asthma attacks and other health problems. Poverty seemed to be mucking up their immune systems.

Cole, Chen, and Miller, however, suspected something else was at work—something that often came with poverty but was not the same thing. So along with drawing the kids' blood and gathering their socioeconomic information, they showed them films of ambiguous or awkward social situations, then asked them how threatening they found them.

The poorer kids perceived more threat; the well-off perceived less. This difference in what psychologists call "cognitive framing" surprised no one. Many prior studies had shown that poverty and poor neighborhoods, understandably, tend to make people more sensitive to threats in ambiguous social situations. Chen in particular had spent years studying this sort of effect.

But in this study, Chen, Cole, and Miller wanted to see if they could tease apart the effect of cognitive framing from the effects of income disparity. It turned out they could, because some of the kids in each income group broke type. A few of the poor kids saw very little menace in the ambiguous situations, and a few well-off kids saw a lot. When the researchers separated those perceptions from the socioeconomic scores and laid them over the gene-expression scores, they found that it was really the kids' framing, not their income levels, that accounted for most of the difference in gene expression. To put it another way: When the researchers controlled for variations in threat perception, poverty's influence almost vanished. The main thing driving screwy immune responses appeared to be not poverty, but whether the child saw the social world as scary.

But where did *that* come from? Did the kids see the world as frightening because they had been taught to, or because they felt alone in facing it? The study design couldn't

answer that. But Cole believes isolation plays a key role. This notion gets startling support from a 2004 study of 57 school-age children who were so badly abused that state social workers had removed them from their homes. The study, often just called "the Kaufman study," after its author, Yale psychiatrist Joan Kaufman, challenges a number of assumptions about what shapes responses to trauma or stress.

The Kaufman study at first looks like a classic investigation into the so-called depression risk gene—the serotonin transporter gene, or SERT—which comes in both long and short forms. Any single gene's impact on mood or behavior is limited, of course, and these single-gene, or "candidate gene," studies must be viewed with that in mind. Yet many studies have found that SERT's short form seems to render many people (and rhesus monkeys) more sensitive to environment; according to those studies, people who carry the short SERT are more likely to become depressed or anxious if faced with stress or trauma.

Kaufman looked first to see whether the kids' mental health tracked their SERT variants. It did: The kids with the short variant suffered twice as many mental-health problems as those with the long variant. The double whammy of abuse plus short SERT seemed to be too much.

Then Kaufman laid both the kids' depression scores and their SERT variants across the kids' levels of "social support." In this case, Kaufman narrowly defined social support as contact at least monthly with a trusted adult figure outside the home. Extraordinarily, for the kids who had it, this single, modest, closely defined social connection erased about 80 percent of the combined risk of the short SERT variant and the abuse. It came close to inoculating kids against both an established genetic vulnerability and horrid abuse.

Or, to phrase it as Cole might, the lack of a reliable connection harmed the kids almost as much as abuse did. Their isolation wielded enough power to raise the question of what's really most toxic in such situations. Most of the psychiatric literature essentially views bad experiences—extreme stress, abuse, violence—as toxins, and "risk genes" as quasi-immunological weaknesses that let the toxins poison us. And abuse is clearly toxic. Yet if social connection can almost completely protect us against the well-known effects

of severe abuse, isn't the isolation almost as toxic as the beatings and neglect?

The Kaufman study also challenges much conventional Western thinking about the state of the individual. To use the language of the study, we sometimes conceive of "social support" as a sort of add-on, something extra that might somehow fortify us. Yet this view assumes that humanity's default state is solitude. It's not. Our default state is connection. We are social creatures, and have been for eons. As Cole's colleague John Cacioppo puts it in his book *Loneliness*, Hobbes had it wrong when he wrote that human life without civilization was "solitary, poor, nasty, brutish, and short." It may be poor, nasty, brutish, and short. But seldom has it been solitary.

"A cell," Steve Cole said, clasping some amberjack, "is a machine for turning experience into biology."

TOWARD THE END OF the dinner I shared with Cole, after the waiter took away the empty platters and we sat talking over green tea, I asked him if there was anything I should have asked but had not. He'd been talking most of three hours. Some people run dry. Cole does not. He spoke about how we are permeable fluid beings instead of stable unitary isolates; about recursive reconstruction of the self; about an engagement with the world that constantly creates a new you, only you don't know it, because you're not the person you would have been otherwise—you're a one-person experiment that has lost its control.

He wanted to add one more thing: He didn't see any of this as deterministic.

We were obviously moving away from what he could prove at this point, perhaps from what is testable. We were in fact skirting the rabbit hole that is the free-will debate. Yet he wanted to make it clear he does not see us as slaves to either environment or genes.

"You can't change your genes. But if we're even half right about all this, you can change the way your genes behave—which is almost the same thing. By adjusting your environment you can adjust your gene activity. That's what we're doing as we move through life. We're constantly trying to hunt down that sweet spot between too much challenge and too little.

“That’s a really important part of this: To an extent that immunologists and psychologists rarely appreciate, we are architects of our own experience. Your subjective experience carries more power than your objective situation. If you feel like you’re alone even when you’re in a room filled with the people closest to you, you’re going to have problems. If you feel like you’re well supported even though there’s nobody else in sight; if you carry relationships in your head; if you come at the world with a sense that people care about you, that you’re valuable, that you’re okay; then your body is going to act as if you’re okay—even if you’re wrong about all that.”

Cole was channeling John Milton: “The mind is its own place, and in itself can make a heaven of hell, a hell of heaven.”

Of course I did not realize that at the moment. My reaction was more prosaic.

“So environment and experience aren’t the same,” I offered.

“Exactly. Two people may share the same environment but not the same experience. The experience is what you make of the environment. It appears you and I are both enjoying ourselves here, for instance, and I think we are. But if one of us didn’t like being one-on-one at a table for three hours, that person could get quite stressed out. We might have much different experiences. And you can shape all this by how you frame things. You can shape both your environment and yourself by how you act. It’s really an opportunity.”

Cole often puts it differently at the end of his talks about this line of work. “Your experiences today will influence the molecular composition of your body for the next two to three months,” he tells his audience, “or, perhaps, for the rest of your life. Plan your day accordingly.”