Under Pressure: The Search for a Stress Vaccine

Baboons are nasty, brutish, and short. They have a long muzzle and sharp fangs designed to inflict deadly injury. Their bodies are covered in thick, olive-colored fur, except on their buttocks, which are hairless. The species is defined by its social habits: The primates live in troops, or groupings of several dozen individuals. These troops have a strict hierarchy, and each animal is assigned a specific rank. While female rank is hereditary — a daughter inherits her mother's status — males compete for dominance. These fights can be bloody, but the stakes are immense: A higher rank means more sex. The losers, in contrast, face a bleak array of options — submission, exile, or death.

In 1978, **Robert Sapolsky** was a recent college graduate with a degree in biological anthropology and a job in Kenya. He had set off for a year of fieldwork by himself among baboons before he returned to the US for grad school and the drudgery of the lab. At the time, Sapolsky's wilderness experience consisted of short backpacking trips in the Catskill Mountains; he had lit a campfire exactly once. Most of what he knew about African wildlife he'd learned from stuffed specimens at the Museum of Natural History. And yet here he was in Nairobi, speaking the wrong kind of Swahili and getting ripped off by everyone he met. Eventually he made his way to the bush, a sprawling savanna filled with zebras and wildebeests and elephants. "I couldn't believe my eyes," Sapolsky remembers. "There was an animal behind every tree. I was inside the diorama."

Sapolsky slowly introduced himself to a troop of baboons, letting them adjust to his presence. After a few weeks, he began recognizing individual animals, giving them nicknames from the Old Testament. It was a way of rebelling against his childhood Hebrew-school teachers, who rejected the blasphemy of Darwinian evolution. "I couldn't wait for the day that I could record in my notebook that Nebuchanezzar and Naomi were off screwing in the bushes," Sapolsky wrote in *A Primate's Memoir*. "It felt like a pleasing revenge."

Before long, Sapolsky's romantic vision of fieldwork collided with the dismal reality of living in the African bush. His feet itched from a fungal infection, his skin was covered in bug bites, the Masai stole his stuff, he had terrible diarrhea, and he was desperately lonely. Sapolsky's subjects gave him no glimpse of good fellowship. They seemed to devote all of their leisure time — and **baboon life is mostly leisure time — to mischief and malevolence.** "One of the first things I discovered was that I didn't like baboons very

much," he says. "They're quite awful to one another, constantly scheming and backstabbing. They're like chimps but without the self-control."

While Sapolsky was **disturbed by the behavior of the baboons** — this was nature, red in tooth and claw — he realized that **their cruelty presented an opportunity to investigate the biological effects of social upheaval**. He noticed, for instance, that the males at the bottom of the hierarchy were thinner and more skittish. "They just didn't look very healthy," Sapolsky says. "That's when I began thinking about **how damn stressful it must be to have no status**. You never know when you're going to get beat up. You never get laid. You have to work a lot harder for food."

So Sapolsky set out to **test the hypothesis** that the **stress involved in being at the bottom of the baboon hierarchy led to health problems.** At the time, stress was mostly ignored as a medical subject. It was seen as an unpleasant mental state with few long-term consequences. "A couple of studies had linked stress to ulcers, but that was about it," he says. "**It struck most doctors as extremely unlikely that your feelings could affect your health.** Viruses, sure. Carcinogens, absolutely. But stress? No way." Sapolsky, however, was determined to get some data. He wasn't yet thinking lofty thoughts about human beings or public health. His transformation into one of the leading researchers on the science of stress would come later. Instead, he was busy learning how to shoot baboons with anesthetic darts and then, while they were plunged into sleep, quickly measure their immune system function and the levels of stress hormones and cholesterol in their blood.

In the **decades since**, Sapolsky's **speculation has become scientific fact**. **Chronic stress,** it turns out, is an **extremely dangerous condition**. And not just for baboons: People are as vulnerable to its effects as those low-ranking male apes. While stress doesn't cause any single disease — in fact, the causal link between stress and ulcers has been largely disproved — it **makes most diseases significantly worse.** The list of ailments connected to stress is staggeringly diverse and includes everything from the common cold and lower-back pain to Alzheimer's disease, major depressive disorder, and heart attack. Stress hollows out our bones and atrophies our muscles. It triggers adult-onset diabetes and is a leading cause of male impotence. In fact, numerous studies of human longevity in developed countries have found that **psychosocial factors such as stress are the single most important variable in determining the length of a life**. It's not that genes and risk factors like smoking don't matter. It's that our levels of stress matter more.

Furthermore, the effects of chronic **stress directly counteract improvements in medical care and public health**. Antibiotics, for instance, are far less effective when our immune system is suppressed by stress; that fancy heart surgery will work only if the patient can learn to shed stress. As Sapolsky notes, "You can give a guy a drug-coated stent, but if you don't fix the stress problem, it won't really matter. For so many conditions, stress is the major long-term risk factor. Everything else is a short-term fix."

Reduce Stress with Science

Make Friends

Social relationships are a powerful buffer against stress. In fact, several **studies in Europe and the US have found that people with fewer friends and family members they're close to have significantly shorter life expectancies.** (The magnitude of the effect is roughly equivalent to smoking cigarettes.) One likely explanation for this phenomenon is the stress of loneliness. **Studies of monkeys found that more socially isolated animals have higher levels of stress hormones, a reduced immune response, and a higher mortality rate.**

Get enough sleep

Sleep deprivation is not just about feeling tired. Recent studies have found that even a single night of insufficient sleep — whether it's spent working the night shift or playing *World of Warcraft* — triggers an automatic spike in stress hormones. And here's where **biology gets cruel:** This stress response then makes it harder to fall asleep when you actually want to, since your sympathetic nervous system is revving at a higher rate. The result is more stress and more insomnia, which helps explain why sleep problems are such an important risk factor for depression.

Don't fight

While observing baboons, Stanford biologist Robert Sapolsky found there was a set of personality traits linked reliably with lower levels of stress hormones. One of these was the ability to walk away from provocations that might send a normal baboon into a snarling hissy fit. Interestingly, this less aggressive personality turned out to be exceedingly effective: The nice baboons remained near the top of the troop hierarchy about three times longer than the baboons who were easily provoked into a fight. They also had a lot more sex, which is a great stress reliever.

Meditate

Numerous studies have demonstrated that even a short training session in meditation can dramatically reduce levels of stress and anxiety. In fact, a recent study led by Sian Beilock, a psychologist at the University of Chicago, demonstrated that a 10-minute lesson in mindfulness meditation seemed to reduce stress in those taking a high-stakes math exam, leading to a five-point increase on average. She argues that meditation allows people to do a better job of not fixating on negative and stressful thoughts, thus freeing up brain space to focus on the arithmetic.

Confront your fears

When paratroopers are **first learning to parachute, they experience a massive stress** response. In fact, one study of Norwegian airmen found that this response started before the jump and lasted for hours afterward. But **something interesting happened** when the soldiers kept jumping out of planes. Instead of being stressed for hours at a time, they showed elevated levels of stress hormone only while in midair, which is precisely when they needed it. The chronic stress response that causes long-term harm had all but disappeared.

Drink in moderation

Alcohol is an anxiolytic — it melts away anxieties by dampening the response of the sympathetic nervous system and reducing the release of stress hormones. That's why a beer tastes so good after a long day. But don't get carried away: While the moderate consumption of alcohol might reduce the stress response, blood alcohol levels above 0.1 percent — most states consider 0.08 the legal limit for driving — trigger a large release of stress hormones. Although you might feel drunkenly relaxed, your **body is convinced it's in a state of mortal danger.**

Don't force yourself to exercise

While exercise is **remarkably effective at blunting the stress response**, at least for a few hours, this effect exists **only if you want to exercise** in the first place. After all, a big reason **working out relieves stress** is that it **elevates your mood**; when mice are forced to run in the lab, their levels of stress hormones spike. So when you **force yourself to go to the gym** and then suffer through 30 minutes on the treadmill (lamenting the experience the entire time), you **don't reduce your stress levels**. In fact, you might be making things worse.

The **emergence of stress as a major risk factor** is largely a **testament to scientific progress**: The deadliest diseases of the 21st century are those in which damage accumulates steadily over time. (Sapolsky refers to this as the "luxury of slowly falling apart.") Unfortunately, this is precisely the sort of damage that's exacerbated by emotional stress. While modern medicine has made astonishing progress in treating the fleshy machine of the body, it is only beginning to grapple with those misfortunes of the mind that undo our treatments.

The power of this new view of stress — that our physical health is strongly linked to our emotional state — is that it **connects a wide range of scientific observations**, from the

sociological to the molecular. On one hand, stress can be **described as a cultural condition, a byproduct of a society that leaves some people in a permanent state of unease**. **But that feeling can also be measured in the blood and urine, quantified in terms of glucocorticoids and norepinephrine and adrenal hormones**. And now we can see, with scary precision, the devastating cascade unleashed by these chemicals. The end result is that stress is finally being recognized as a critical risk factor, predicting an ever larger percentage of health outcomes.

To Sapolsky, the next step was obvious: Attack the condition head-on. In **2003**, he **proposed a vaccinelike treatment that protects people against stress**. It's a hugely ambitious attempt to combat a societal scourge at the level of our DNA. Although years of work remain, Sapolsky now insists that, given the public health consequences, it's time to take the problem seriously, to move our treatments beyond talk therapy and Valium. "Sometimes it's not enough just to tell people, 'Jeez, you should really learn to relax,'" Sapolsky says. "If stress is half as bad for you as we currently think it is, then it's time to stop treating the side effects. It's time to go after stress itself."

After that first trip in 1978, Sapolsky began spending every summer in Kenya. In the early 1980s, he happened upon a rare event in the baboon troop: The highest-ranking female and a low-ranking female gave birth to daughters just a few days apart. Sapolsky realized that these newcomers would allow him to compare the effects of social status on development. The first thing he noticed was that the **high-ranking daughter hit every developmental landmark faster.** She walked first, ate solid food earlier, and had far more interactions with other baboons. The lesson, Sapolsky says, is that **"status comes with privileges,"** and these privileges are present from the start of life.

Sapolsky describes a poignant scene that took place a few weeks after the births, when the newborns encountered each other for the first time. "They can barely get around, but they're both so excited to see another baby," he says. "And so the low-ranking kid goes wobbling over to say hi. But then, just as she gets near, the low-ranking mom grabs her daughter and drags her back. The poor kid has no idea what's happened, but **she's just gotten her first lesson in the social hierarchy. The high-ranking kid is not somebody she can play with."**

For Sapolsky, the tragedy of such interactions is their **lasting legacy**. "I can come back 25 years later, when these kids are two old matriarchs, and they'll be acting out the exact same dynamic. When they **meet, the low-ranking baboon will just stare at the ground**. That's what her mom was trying to teach her. She was being taught how to live with low rank. She was learning how to cope."

That **coping comes with a steep cost.** Look, for instance, at a controlled lab experiment led by Jay Kaplan at Wake Forest University School of Medicine in North Carolina. The study involved macaques, small primates that, like baboons, live in a rigid social hierarchy. The scientists quickly discovered that **macaques of high rank were less likely to develop heart disease,** despite the fact that all of the animals were fed a diet high in saturated fat and cholesterol. But the scientists didn't stop there. They also conducted

experiments in which **monkeys were put into a new enclosure, a move that forced the animals to struggle to maintain their status**. This led to increased heart rate and blood pressure. (In fact, Kaplan saw a rise in arterial plaque even when the stressed monkeys were fed a low-fat diet.) The **effect was particularly pronounced for females**. Normally, male primates are **twice as likely to suffer from heart disease**. This difference between the sexes disappears, however, when females lose their rank.

A similarly destructive process is at **work in humans**. While doctors speculated for years that increasing rates of cardiovascular disease in women might be linked to the increasing number of females employed outside the home, that correlation turned out to be nonexistent. Working women didn't have more heart attacks. There were, however, two glaring statistical exceptions to the rule: **Women developed significantly more heart disease if they performed menial clerical work or when they had an unsupportive boss**. The work, in other words, wasn't the problem. It was the subordination.

Robert Sapolsky is working on a vaccinelike treatment for stress.
Photo: National Geographic Television

One of the **most tragic aspects of the stress response** is the way it **gets hardwired at a young age** — an early setback can permanently alter the way we deal with future stressors. The **biological logic of this system is impeccable**: If the world is a rough and scary place, then the brain assumes it should invest more in our stress machinery, which will make us extremely wary and alert. There's also a positive feedback loop at work, so that chronic stress actually makes us more sensitive to the effects of stress.

The physiology underlying this response has been elegantly revealed in the laboratory. When **lab rats are stressed repeatedly, the amygdala** — an almond-shaped nub in the center of the brain — **enlarges dramatically**. (This swelling comes at the expense of the hippocampus, which is crucial for learning and memory and shrinks under severe stress.) The **main job of the amygdala is to perceive danger and help generate the stress response**; it's the brain area turned on by dark alleys and Hitchcock movies.

Unfortunately, a **swollen amygdala means that we're more likely to notice potential threats in the first place**, which means we spend more time in a state of anxiety. (This helps explain why a more active amygdala is closely correlated with atherosclerosis.) The end result is that we **become more vulnerable to the very thing that's killing us.**

This acute sensitivity, in turn, also makes us more vulnerable to stress-related diseases. Consider a **natural experiment that took place during World War II**, when about 70,000 young Finnish children were evacuated to temporary foster homes in Sweden and Denmark. For the **kids who stayed behind in Finland**, life was certainly filled with moments of acute stress — there were regular air bombardments. **But** for those sent to Sweden, the **stress of being separated from their parents was unceasing**. This early shock had **lifelong consequences.** A 2009 study found that Finnish adults who had been sent away between 1939 and 1944 were nearly twice as likely to die from cardiovascular illness as those who had stayed at home. Although more than 60 years had passed since the war, they were also significantly **more likely to have high blood pressure, type 2 diabetes, and clinical depression.**

Of course, you don't have to be shipped off to Sweden to experience stress; it's a simple fact of life for everyone. But emerging evidence suggests that the effects of chronic stress are worse for some people — especially those at the bottom of any given pecking order.

Just ask Michael Marmot, a professor of epidemiology and public health at University College London. For the past 25 years, he's been running the Whitehall study, an exhaustive longitudinal survey launched in 1967 that has tracked some 28,000 British men and women working in central London. What makes the Whitehall study so compelling is its uniformity. Every subject is a British civil servant, a cog in the vast governmental bureaucracy. They all have access to the same health care system, don't have to worry about getting laid off, and spend most of their workdays shuffling papers.

The **British civil service** comes with one other feature that makes it ideal for studying the health effects of stress: **It's hierarchical,** with a precise classification scheme for ranking employees (in other words, it's the **human equivalent of a baboon troop)**. At the bottom are messengers, porters, and security guards. Just above them are the clerical officers, followed by staff scientists and other professionals. This last group implements the policies dictated by powerful administrators who run the governmental agencies. Marmot wanted to investigate how **differences in status** "in people who are neither very poor nor very rich" might lead to **measurable differences in health**.

The **differences are dramatic**. After tracking thousands of civil servants for decades, Marmot was able to demonstrate that between the ages of 40 and 64, **workers at the bottom of the hierarchy had a mortality rate *four times higher* than that of people at the top**. Even after accounting for genetic risks and behaviors like smoking and binge drinking, civil servants at the bottom of the pecking order still had nearly double the mortality rate of those at the top.

What, then, determines our health? Why were people in the lower ranks of Whitehall dying at a younger age? Marmot was forced to conclude that the significant majority of **health variation is caused by psychosocial factors, most notably stress.** People of lower status in the Whitehall study experienced more negative stress, and this stress was deadly. (To take but one data point: Fully two-thirds of an individual's risk of stroke was attributable to the person's socioeconomic status.) In fact, we're so sensitive to the effects of status that getting promoted from the lowest level in the British civil service reduced the probability of heart disease by up to 13 percentage points. Climbing the social ladder makes us live longer.

However, the Whitehall results aren't a straightforward analysis of stress, at least not as it's usually defined. After all, people in **leadership positions often** describe their jobs as **extremely stressful**. They work longer hours and have more responsibilities than those at the bottom of the bureaucratic hierarchy. **Consider the self-report of Nigel,** a high-status administrator: "There were 2,000 people, and I was responsible for all the personnel aspects, contracts, and all the common services … It had every **sort of challenge** that you could ever wish to meet. A very active job and a lot of stress, but a very enjoyable job, and you got a tremendous amount of satisfaction from doing a good job."

Notice the reference to stress; undoubtedly Nigel thought of himself as a person under lots of pressure. **In contrast**, here's the self-report of **Marjorie, a lowly typist:** "I went to the typing pool and sat there typing documents. Which was absolutely soul-destroying … The fact that we could eat sweets and smoke was absolute heaven, but we were not allowed to talk."

The recurring theme in the self-reports of people like Marjorie **isn't the sheer amount of stress — it's the total absence of control.** Researchers call it the "demand-control" model of stress, in which the damage caused by chronic stress depends not just on the demands of the job but on the extent to which we can control our response to those demands. "The man or woman with all the emails, the city lawyer who works through the night has high demands," Marmot writes. "But if he or she has a **high degree of control over work, it is less stressful and will have less impact on health**." (This helps explain why the women with mean bosses and menial work showed the highest incidence of heart disease.) The Whitehall data backs up this model of workplace stress: While a relentlessly intense job like a senior executive position leads to a slightly increased risk of heart disease and death, a job with no control is significantly more dangerous.

The same effect applies even to the rich and famous. A few years ago, Donald Redelmeier, an epidemiologist at the University of Toronto, led a study of Academy Award-winning actors. His hypothesis was that having an Oscar gave people more control over their stressful careers. Instead of being forced to accept bad roles or work on mediocre movies just for the money, these stars could pick and choose their parts. This creative control, in turn, would lead to improved health outcomes. Redelmeier compared the award winners to two groups: (1) actors who had appeared in the same film as a nominated actor and didn't get a nomination and (2) actors who had been nominated for an Academy Award but never won. The results were clear: People with Oscars lived, on

average, four years longer than their less-successful peers, which represented a 28 percent reduction in death rate. As Redelmeier notes, this longevity boost is roughly equal to the effect that would come from "curing all cancers in all people for all time."

The moral is that the most dangerous kinds of stress don't feel that stressful. It's not the late night at the office that's going to kill us; it's the feeling that nothing can be done. The person most at risk for heart disease isn't the high-powered executive anxious about their endless to-do list — it's the frustrated janitor stuck with existential despair.

Stress is a chemistry problem. When people feel stressed, a tiny circuit in the base of their brain triggers the release of glucocorticoids, a **family of stress hormones** that puts the body in a heightened state of alert. The **molecules** are named after their ability to **rapidly increase levels of glucose in the blood,** thus providing muscles with a burst of energy. They also shut down all nonessential bodily processes, such as digestion and the immune response. "This is just the body being efficient," Sapolsky says. "When you're being chased by a lion, you don't want to waste resources on the small intestine. You'll ovulate some other time. You need every ounce of energy just to get away."

But **glucocorticoids have a nasty side effect:** When they linger in the bloodstream, as they might due to chronic stress related to low rank, **damage accumulates.** It's the physiological version of a government devoting too many resources to its defense department, Sapolsky says. The body is so worried about war that it doesn't fix the roads or invest in schools. Interestingly, the effects of **stress appear particularly toxic to the brain**. Elizabeth Gould, a neuroscientist at Princeton, is best known for demonstrating that the birth of new neurons — a process known as neurogenesis — takes place in the adult brain. For the past several years, Gould has been studying the relationship between neurogenesis and stress in primates. She has found that when **stress becomes chronic, neurons stop investing in themselves. Neurogenesis slows. Dendrites shrink.** Neuronal arbors retreat. (In fact, the very act of keeping primates in standard lab enclosures — often just bare wire cages — is so stressful that for years scientists had a warped understanding of the primate brain. Gould has become an ardent advocate of "enriched enclosures," which provide the animals with things to play with and social interaction.) These cellular alterations help explain why, as researchers noted in a recent review article, a "large part of the changes in brain structure and function [induced by chronic stress] have similar characteristics to those observed in neurodegenerative diseases, most notably Alzheimer's." And the **higher the level of stress hormone, the greater the level of cognitive decline.**

One of the most disturbing aspects of these stress effects is the way they're **transmitted across generations, from parent to child**. Gould has demonstrated, for instance, that if a **pregnant rhesus monkey is forced to endure stressful conditions, like being startled by a blaring horn, her offspring are born with reduced neurogenesis, even if they never actually experience stress after birth**. This prenatal trauma, just like trauma endured in infancy, has lifelong implications. The offspring of monkeys **stressed during pregnancy have smaller hippocampi, suffer from elevated levels of stress hormone and anxiety.**

Or look at **humans**: A recent study found that **individuals abused by their parents during early childhood showed epigenetic changes to their DNA**, which altered how their genes were read. The **most prominent changes involved genes encoding glucocorticoid receptors**, which led to a **magnified stress response**. The abuse might be temporary, but the damage is permanent, a **wound that never heals**.

Not every bout of stress is so devastating. As the Whitehall data demonstrates, **executives** in the corner office report high levels of stress and yet seem to survive just fine. Other experiments show that intense exercise — like running for hours on a treadmill — can lead to the release of glucocorticoids. And yet physical exercise is reliably associated with all sorts of positive health effects.

These anomalies have led some scientists, including Gould, to search for the additional molecules in the brain that might serve as buffers for the stress response. Gould's short list of candidates **focuses on neuromodulators like dopamine and oxytocin** that are **released when we experience pleasure**. She argues that these **feelings of enjoyment** — the ability to find meaning in our work, even if it's stressful work — may counteract the toxic effects of glucocorticoids. These molecules might also explain why not every janitor dies of heart disease at a young age and why enjoyable forms of exercise are good for us. "There are important individual differences in how people respond to stress," Gould says. "Soldiers experience lots of stress in war, but most of them won't get posttraumatic stress disorder. What accounts for those differences? And how can we help the people who are most vulnerable?"

Robert Sapolsky looks out of place on the Stanford campus. He's surrounded by manicured lawns and preppy students, but his appearance is deliberately untamed. His long hair is tied back in a loose ponytail, and he's constantly tucking the stray tendrils behind his ears. Sapolsky's face is hidden by a bushy beard, which extends below his neck in the style of late Darwin. (It's as if Sapolsky stopped shaving after meeting the baboons and never started again.) All that remains visible are his pale blue eyes and the sun-worn wrinkles that tell you he's smiling.

In recent years, it has gotten harder for him to study primates in the wild. The main problem is the intrusion of humans. "The original beauty of studying stress in baboons was that they didn't act like people," Sapolsky says. "The animals don't smoke, they don't lie on questionnaires, and they all eat the same basic diet." Unfortunately, the increasing sprawl of human settlements means the baboons now supplement their natural menu of fruit, seeds, and small antelopes with human trash. As a result, it has become all but impossible to disentangle the negative effects of stress from the negative effects of bad diet.

The difficulty of conducting field research has led Sapolsky to focus increasingly on his lab work. The theme remains the same — **he is single-minded about stress — but the tools are different**. Instead of tranquilizing baboons, he **oversees a molecular-biology lab**, its shelves and counters cluttered with fridges, notebooks, and salt solutions. "It kills

me that I can't spend more time in Africa," he says. "But you take what you can get. And right now, the lab is what I've got."

This doesn't mean Sapolsky has stopped thinking big thoughts. In fact, his **main research project is absurdly ambitious: He wants to create a vaccinelike treatment for chronic stress, a genetic therapy that can prevent the struggles of life from wrecking brain and body**. He first started thinking about the possibility of such a treatment in 1992, during the early days of gene therapy, when the field was flush with optimism. At the time, his idea seemed simple: If the chronic drip of glucocorticoids is so toxic, why can't the chemicals be stopped before it's too late?

That straightforward goal concealed a **series of technical challenges**. The **first** was that Sapolsky couldn't just eliminate glucocorticoids from the bloodstream, because they are involved in all sorts of important functions, like helping you run for your life. **Second,** Sapolsky needed to get his treatment past the blood-brain barrier — the specialized capillaries that prevent blood contaminants from entering the brain. Sapolsky's vaccinelike cocktail needed to deliver a potent mixture of genes to the cortex — these genes would counteract the stress response — but the most common mechanisms of delivery, like free-floating strands of DNA called plasmids, were denied entry. There were a few years of false starts, but Sapolsky and his postdocs continued to play around with the herpes simplex virus, which has been used as a viral vector in gene therapy research for two decades. Herpes was a good candidate because it's able to slip easily into brain cells. Sapolsky then set about deleting all the dangerous genes in the herpes virus, replacing each of them with an assortment of "neuroprotective" ones, which increase the production of growth factors, various antioxidants, and substances that mimic estrogen. (Estrogen counters many of the deleterious effects of stress on the brain.) As a result, brain cells infected by Sapolsky's version of herpes would be protected in case they were subjected to stress.

The question was how to get the engineered herpes to turn on at key moments, then turn off so the cells could resume normal function. Fortunately, natural selection had already solved the biologist's technical problem. "Viruses aren't dumb," he says. "They don't want to become active until we're really vulnerable and our immune response is suppressed." How does the virus know we're stressed? To Sapolsky's pleasant surprise, the virus already had the necessary genetic machinery: It automatically monitors the flux of glucocorticoids in the bloodstream. It had evolved to start expressing its genes whenever its host felt overburdened by the world.

After several years of genetic engineering — it's not easy to substitute all the dangerous genes with their therapeutic replacements — Sapolsky began introducing the modified herpes virus into rodent brains. Then he induced a series of tragedies, such as a massive stroke or an extended seizure, which would trigger the release of glucocorticoids. (Chronic stress is like a slow-motion stroke.) Within minutes, the modified herpes virus began pumping out neuroprotective proteins, which limited the extent of cell death. As a result, the damage was contained. For instance, rats given the herpes treatment were able to stave off practically all cell loss, while control rats lost nearly 40 percent of neurons in

a given region. In the hippocampus, neuronal death was reduced substantially. “To be honest, I’m still amazed that it works,” he says. “It’s not going to help anybody soon” — the research is still years away from clinical trials — “but we’ve proved that it’s possible. We can reduce the neural damage caused by stress.”

Sapolsky has now begun applying the same therapies to rodents experiencing chronic stress. He has shown that by injecting the amygdala with a modified herpes virus, he can dramatically reduce the anxiety the animals suffer when they’re placed in an open space, where they instinctively fear predators. Furthermore, this gene therapy was able to prevent the expansion of neurons in the amygdala after repeated stressors. The positive feedback loop of stress had been stopped.

The power of Sapolsky’s stress vaccine is that it can rescue us from ourselves, at least in theory. Like those baboons in the bush, we live in a stratified society that comes with real costs. There is nothing hypothetical about these costs: They make us depressed and give us back pain. They shrink parts of the brain, clog the arteries, and weaken the immune system. They shorten our already short lives.

The science of stress can illuminate the damage. It can document the chemistry that unravels us from the inside. One day, it might even give us options for preventing the damage, silencing the stress response at its source. But these are mere band-aids, fancy fixes for what remains an inherently societal problem. **We tell our kids that life isn’t fair, but we fail to mention that the unfairness can be crippling, that many of us will die because of where we were born. This is the cruel trick of stress:** If it were only a feeling, if there were only the despair of having no control or the anxiety of doing without, then stress would be bad enough. But the feeling is just the trigger. We are the loaded gun.

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