

II

Diagnosis

The Drive-By and the Bear

IT WAS CHILLY, WHICH was typical for a December night in San Francisco, but as I walked down Mission Street with my friends, I remember hugging myself to try and warm up. Home for the holidays from public-health school in Boston, I'd optimistically left the house without a coat. I told myself to be grateful; after all, it wasn't snowing. I was so amped up from a night out with old friends that my poor clothing choice was just another thing to laugh about. The four of us all talked simultaneously, our voices drowning out the sounds of the city as we made our way back to the car. We lingered on the corner of Nineteenth Street and Mission, not wanting to part ways as the evening came to an end. None of us noticed the red car slowing down across the street from us until seconds later when we heard *Pop! Pop! Pop!* As the car peeled out toward Twentieth Street, my friend Michael initially laughed it off.

"It's just some stupid kids playing with firecrackers," he said, collecting himself after the startle. But a few moments later, he picked up on an uneasy vibe and ushered us toward the car. "We gotta get out of here. Something's going down."

We were almost to Michael's vehicle when we saw the man lying on the sidewalk. Three men I assumed were his friends were a few feet away, yelling and punching in the windows of the cars parked on that side of the street.

"Oh my God," cried my cousin Jackii, "he's been shot!"

As if by reflex, I headed toward the victim, not noticing that my friends were running in the opposite direction.

"Nadine!" Michael said. He grabbed at my arm, but he was too late. I dropped to my knees when I reached the man's side. All I could think about was saving his life. I had finished medical school the year before: my doctor instincts now took over. As I got a good look at his face, I could see that despite his size, he was still a boy. He couldn't have been more than seventeen. There was an entry wound above his right eyebrow, and because he was lying on his side I could see a fist-size exit wound at the back of his head. My inner narrator began calling out a status report like we had been trained to do in the trauma bay: "Gun-shot wound to the head! No other signs of penetrating trauma!"

In the movies, the guy would have been out cold, but in real life he was throwing up on himself. I'd seen a lot of scary stuff in hospitals, but this was different. Time seemed to slow down and I found myself going on autopilot. I kept checking things off the list that I had learned in medical school: *ABCD — airway, breathing, circulation, disability. Keep his airway clear. Make sure he's breathing. Check his pulse. Maintain the position of his cervical spine in case his neck is broken. At the same time, a voice in the back of my head kept telling me that I wasn't in the safety of the emergency department — there was no security guard at the door, and the red car could come back! My heart was pounding and my hands shook. Every cell in my body was telling me to get the hell out of there, but I stayed by his side until the paramedics arrived.*

Hours later, as we sat in the Mission district police station giving our best descriptions of what we had seen, we got the news that he didn't make it. It was a heartbreaking end to the evening, but I knew there wasn't anything else I could have done. After I got home that night, I couldn't sleep. In the following weeks and months, every time I saw a red car approaching quickly or heard a car backfire, I felt transported back to the fear I felt that night. Physically, I would have the same responses: my heart would pick up its pace, my eyes would dart around, and I'd feel tightness in my stomach. I see now that my biology was reacting to an unusually high level of stress by temporarily linking red cars with danger. My body was remembering what happened and sending a flood of stress hormones shooting through my system in case the red car *now* was as dangerous as the red car *before*.

My body was doing what it was designed to — keep me out of harm's way.

Day to day, your brain has to process *a lot* of information — trees creaking in the wind overhead, dogs barking next door, the wall of air hitting your face as the subway car hurtles by — and interpret the risk. In order for humans to survive, the brain and body had to come up with efficient ways of processing information, and the stress-response system is one of them. If a little kid touches a hot stove, his body remembers. Biochemically, it tags or bookmarks the stove (and all the stimuli associated with it) as being dangerous, so the next time the boy sees someone turning on the burners, his body sends him all kinds of warning signs: vivid memories, muscle tension, and rapid pulse. Usually, this is enough to dissuade him from doing the same thing again. In this way, our bodies are trying to protect us, which makes a lot of sense. The prehistoric creatures that didn't evolve that mechanism didn't live to reproduce.

But the stress response can do its job a little *too* well sometimes. This happens when the response to stimuli goes from adaptive and lifesaving to maladaptive and health-damaging. For example, almost everyone knows that soldiers sometimes come back from the front lines with posttraumatic stress disorder. This condition is an extreme example of the body remembering too much. With PTSD, the stress response repeatedly confuses current stimuli with the past in such a dramatic way that it becomes hard for these vets to live in the present. Whether it's a B-52 bomber in the sky or a commercial airliner overhead taking tourists to Hawaii, their bodies feel the same — *in mortal danger*. The problem with PTSD is that it becomes entrenched; the stress response is caught in the past, stuck on repeat.

For me, the specific trigger of a red car would eventually decouple from my body's most ancient defense mechanism and stop being interpreted by my brain as a threat. Now when I see one go by me on a city street I don't flinch. What I didn't know until years later was *why*. Why was my body able to recover from that intense instance of stress? What made the sensory connection between the red car and the biological reaction of my stress response fade? I wouldn't think to ask those questions until many years later, when Diego set me on my path.

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In the months after first discovering the ACE Study, I once again dived into the research. I found that some robust and incredibly exciting advances had been made in the biology of stress and its impact on child health and development. What I know now is that what happened in my body that night in the Mission district is the same thing that happens to my patients' bodies when they experience a whole host of adversities ranging from abuse to abandonment. The body senses danger, and it sets off a firestorm of chemical reactions aimed to protect itself. But most important, *the body remembers*. The stress-response system is a miraculous result of evolution that enabled our species to survive and thrive into the present. We all have a stress-response system, and it is carefully calibrated and highly individualized by both genetics and early experiences. What makes the stress response of a child with zero ACEs different from Diego's stress response is a complicated question that we will begin to unravel, but it all starts with the same system. When it's in good working order, it can help save your life, but when it's out of balance, it can shorten it.

Stress Response

Flipping through a magazine in the checkout line or circling the Internet vortex, you've probably come upon stories of superhuman strength: the father who lifts the car that was pinning his child (maybe an urban legend?) or the woman who fought off the mountain lion that was mauling her husband (that one really is true). Even more cinematic, there's the average Joe turned hero who crosses the battlefield to save his buddy despite having two bullets in him. If you've ever wondered what makes a person able to achieve such feats, I can tell you it's not the daily bowl of Wheaties—it's the elegantly designed, evolutionarily imperative stress-response system. Essentially, it works like this: Imagine you're walking in the forest and you see a bear. Immediately, your brain sends a bunch of signals to your adrenal glands (perched on your kidneys) saying, "Release stress hormones! Adrenaline! Cortisol!" So your

heart starts to pound, your pupils dilate, your airways open up, and you are ready to either fight the bear or run from the bear. That's the response commonly known as *fight or flight*. It has evolved over millennia to save your life. Another lesser-known way your body might respond is by freezing, in the hopes that the bear will think you're a rock. For that reason, some people use the term *fight, flight, or freeze*, but to keep it simple, I'm just going to use *fight or flight*.

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To understand and appreciate how the stress-response system can go wrong or, as we doctors say, "become dysregulated," there are a few basic things to know about what happens when it goes right. Be warned that this biological system is one of our species' oldest and most complicated. People take entire courses on this stuff and still walk away slightly confused. I'll try to keep it as simple and accurate as possible. Here are the main players involved.

- The amygdala: the brain's fear center
- Prefrontal cortex: the front part of the brain that regulates cognitive and executive function, including judgment and mood and emotions
- Hypothalamic-pituitary-adrenal (HPA) axis: initiates the production of cortisol (longer-acting stress hormone) by the adrenal glands
- Sympatho-adrenomedullary (SAM) axis: initiates the production of adrenaline and noradrenaline (short-acting stress hormones) by the adrenal glands and brain
- Hippocampus: processes emotional information, critical for consolidating memories
- Noradrenergic nucleus in the locus coeruleus: the within-the-brain stress-response system that regulates mood, irritability, locomotion, arousal, attention, and the startle response

Now let's go back to the forest.

When you see the bear, your amygdala immediately sounds the

alarm telling your brain to be afraid because bears are scary! Your brain then activates your SAM and HPA axes, triggering the fight-or-flight response. Signals from the SAM axis travel along nerves from the brain to the adrenal glands telling them to make adrenaline, which is responsible for many of the feelings that we associate with being terrified. Adrenaline causes the heart to beat stronger and faster, sending blood to all the places that need it. It causes your airways to open so that you can take in more oxygen. It raises your blood pressure and shunts blood toward your skeletal muscles (necessary for running and jumping) and away from that tiny muscle that holds your bladder closed, which is why scared people feel like they're going to pee in their pants and sometimes do. It also converts fat to sugar for energy.

The SAM axis also activates the noradrenergic nucleus of the locus coeruleus, which, as I like to say, is the scientific term for the part of the brain responsible for "I don't know karate but I do know c-razy!" This is the within-the-brain stress-response center, and it gets you amped up. (Picture Oakland Raiders fans after a winning game or, worse, a losing game.) Adrenaline and noradrenaline are powerful stimulants, designed to help you think more clearly so that you can figure out the quickest path to safety. They also create feelings of euphoria, that adrenaline rush that makes you think you can conquer the world. But, like everything body-chemistry-related, it's all about balance. A graph of the response of the prefrontal cortex (the part of the brain responsible for reason, cognition, and judgment) to adrenaline and noradrenaline looks like an inverted U—a little bit improves functioning, but too much will mess up your ability to focus.

Now your heart is pumping, your muscles are primed, and you are feeling ready to fight. If you were to stop and think about it, fighting a bear might seem like a bad idea. After all, grizzly bears can weigh up to seventeen hundred pounds. They have huge teeth and fearsome claws. Odds are that you aren't going to fare very well. That's why when you're really scared, your fear center temporarily shuts down the thinking part of your brain—because you need to defy those odds. Your life depends on it. So the amygdala activates neurons that link to the prefrontal cortex and temporarily turns it off, or at least turns it way, way

down. The SAM axis is a very short-acting (seconds or minutes) response that primes your body by making available what you need most: blood, oxygen, energy, and chutzpah.

At the same time, the HPA axis triggers hormones in the brain that let loose a cascade of chemical messengers that ultimately result in the release of some longer-term stress hormones, most notably cortisol. Imagine if you lived in a forest where there were lots of bears. After the first one or two encounters, your body would want to become more efficient at responding to the bear problem. Essentially, cortisol helps the body adapt to repeated or long-term stressors, like living in bear-infested woods or handling prolonged food shortages. Some of the effects of cortisol are similar to those of adrenaline—it raises blood pressure and blood sugar, inhibits cognition (clear thinking), and destabilizes mood. It also disrupts sleep, which makes a lot of sense if you are living in a forest full of bears—better to be a light sleeper. Unlike adrenaline, which can decrease appetite and stimulate fat burning, cortisol stimulates fat accumulation and also triggers the body to crave high-sugar, high-fat foods. Think about your last breakup. If you're wondering why you couldn't sleep and were tunneling your way to the bottom of a pint of Häagen-Daz, that's cortisol. High levels of cortisol can inhibit reproductive function because if you are living in the forest next to bears, isn't it better to wait to have kids until you move to a safer part of the woods?

One not-so-obvious but incredibly important function of the stress response is activating the immune system. After all, if you are fighting a bear, he might get in a couple of licks. If he does, you want your immune system primed to heal, meaning that it's ready to bring inflammation to the area in order to stabilize the wound and keep you fighting long enough to beat the bear or get away.

Once you do get away and are back in the safety of your cave, both the SAM and the HPA axes are designed to shut themselves down. The body uses a sort of stress thermostat called feedback inhibition that triggers the stress response to turn itself off once it has done its job. High levels of adrenaline and cortisol feed back to the parts of the brain that initiate the stress response and turn them off. What an in-

credibly evolved system! Especially if you live in a forest and there are bears. But what happens when you can't experience safety in your cave because the bear is living in the cave with you?

Living with the Bear (aka Dysregulated Stress Response)

Over and over again in my practice I saw kids who had experienced terrifying situations. For one patient, the bear was his dad who verbally demeaned and physically abused his mom. For another, it was his mom when she didn't take her psychiatric medications and left the kids uncared for, often in dangerous situations. I'll never forget the fourteen-year-old girl for whom the bear was the very neighborhood she lived in after she was hit by a stray bullet walking home from school.

For many of my patients, the stress response was activated dozens and sometimes hundreds of times a day. I knew that if I wanted to get to the source of the problem for Diego and other patients, I needed to understand exactly when and how the stress response begins working against the body. What happens to children's brains and bodies when they are exposed to such high doses of adversity? Fortunately, some smart scientists were asking the same question.

During one of my trips down the research rabbit hole, I found some great work by Jacqueline Bruce, Phil Fisher, and colleagues. In a 2009 study, they set out to determine if the adverse experiences of preschool-age foster children had an effect on the functioning of the stress-response system, specifically the HPA axis. To do this, they analyzed the cortisol levels of 117 foster kids and 60 low-income kids who were *not* maltreated. What they found reinforced what I suspected about my own patients: the foster kids showed dysregulated cortisol levels in comparison to the kids who had not experienced the same adverse experiences.

It turns out that cortisol has a predictable daily pattern: it's high in the morning to help wake you up and get you ready for the day and then gradually decreases, reaching its lowest point in the evening, just

when you need to go to sleep. As a result, it's possible to determine if someone's cortisol pattern is disrupted. Fisher and Bruce found that children who had experienced maltreatment had higher overall cortisol levels as well as a disruption of the normal daily pattern of cortisol secretion. The morning peak wasn't quite as high and the daily decline was not as steep, leading to higher levels in the evening and higher to-tal daily cortisol.

One interesting part of the foster kids study was that the control group did not consist of children who were demographically all that different from the experimental group in terms of parental education and income. The major differences were that the control-group kids were all living with at least one parent, had not had any previous contact with child services, and were not maltreated. Undoubtedly, the low-income kids in the control group *had* been exposed to at least some level of adversity in their lives, and yet their cortisol levels were not abnormal. This sheds some light on how some children can experience stress without that stress tipping over into dysregulation.

We all know that adversity, tragedy, and hardship are a part of life. As much as we'd like to shield our children from illness, divorce, and trauma, sometimes these things happen. What the research tells us is that those daily challenges can be overcome with the right support from a loving caregiver.

Fisher went on to work with the National Scientific Council on the Developing Child as part of an ambitious effort to pull together the science of how early adversity affects the developing brains and bodies of children. The council, too, found that a dysregulated stress-response system was at the core of the problem.

The main issue is that when the stress response is activated too frequently or if the stressor is too intense, the body can lose the ability to shut down the HPA and SAM axes. The term for this is *disruption of feedback inhibition*, which is a science-y way of saying that the body's stress thermostat is broken. Instead of shutting off the supply of "heat" when a certain point is reached, it just keeps on blasting cortisol through your system. This is exactly what Fisher and Bruce were seeing in the foster kids.

Ultimately, the council described three different kinds of stress responses:

- Positive stress response is a normal and essential part of healthy development, characterized by brief increases in heart rate and mild elevations in hormone levels. Some situations that might trigger a positive stress response are the first day with a new caregiver or receiving an injected immunization.

A good example of positive stress is one that many athletes can relate to: pregame jitters. The moment before a big race, a track star might feel a rush of nervousness. Physically, her heart rate is amped up and she's got butterflies in her stomach. But the increase in adrenaline is doing important work. The track star is taking in more oxygen, shunting more blood to her muscles, and heightening her focus. When the starter's gun goes off, she's ready for it.

- Tolerable stress response activates the body's alert systems to a greater degree as a result of more severe, longer-lasting difficulties, such as the loss of a loved one, a natural disaster, or a frightening injury. If the activation is time-limited and buffered by relationships with adults who help the child adapt, the brain and other organs recover from what might otherwise be damaging effects.

Lots of kids wet the bed when they are little but grow out of it. An example of a tolerable stress response would be a child who reverts back to bedwetting after his parents' divorce. The split isn't acrimonious, and while the dad moved out, both adults are committed to co-parenting and understand that their child needs stability and extra support. As a result of that buffering of the child's stress, he stops wetting the bed after a few months. Like my drive-by-induced stress, the effects are temporary if a solid support network is in place.

- Toxic stress response can occur when a child experiences strongly frequent, and/or prolonged adversity—such as physical or emotional abuse, neglect, caregiver substance abuse or mental illness,

exposure to violence, and/or the accumulated burdens of family economic hardship—without adequate adult support. This kind of prolonged activation of the stress-response systems can disrupt the development of brain architecture and other organ systems, and increase the risk for stress-related disease and cognitive impairment, well into the adult years.

There was no question in my mind that Diego was experiencing a toxic stress response. Beyond Diego's sexual abuse when he was four, he and his family had dealt with other hardships that also put his system under strain. Diego's dad clearly had a drinking problem, and his mother was suffering from depression. Neither was able to be an adequate stress buffer for him. Diego's constellation of symptoms were directly in line with what we know happens when there is a prolonged activation of the stress-response system without adequate support.

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Healthy development of the stress-response system requires that a child experience both positive and tolerable stress. This allows the SAM and HPA axes to be calibrated to react normally in the face of stressors. But for every ACE a child has, the risk of tolerable stress tipping over into toxic stress increases, as the system responds more frequently and intensely to multiple stressors.

Just like tadpoles, children are particularly sensitive to repeated stress activation. High doses of adversity affect not only the brain structure and function but also the developing immune system and hormonal systems, and even the way DNA is read and transcribed. Once the stress-response system gets wired into a dysregulated pattern, the biological effects ripple out, causing problems within individual organ systems. Because the body is like one big, intricate Swiss watch, what happens in your immune system is deeply connected to what happens in your cardiovascular system. Next we'll see the downstream effects of a stress-response system that has gone off the rails.