

Dynamic Disruption

IF YOU WANT TO understand how a child's stress response is working, try walking into the examination room with a tray full of needles and telling him it's time for shots. By now, it seemed like I could almost guess the ACE score of a patient by the amount of commotion that took place when my nurse went in to give the vaccinations. We'd seen it all: screaming, kicking, biting, kids literally trying to climb the walls to get away from the needles. One patient got so upset he vomited on my white coat. Another ran out of the exam room and made it all the way down the block before we caught her. These extreme displays of fear were not your ordinary needle-phobic reactions; they were full-blown bear-in-the-woods reactions. Coincidentally, this natural stress-response provocation challenge gave us an opportunity to test the second, equally important ingredient for toxic stress — the caregiver's ability to act as a buffer. The kids who had the worst responses were also the ones whose caregivers were the *least* likely to hug, kiss, sing to, or otherwise soothe their child. We heard a lot of "Hold him down!" and "I don't have time for this, I have to be back at work in a half hour."

Observing that phenomenon and suspecting a correlation was one thing, but I needed to find a way to rigorously evaluate not just *whether* ACEs had an impact on my patients, but *how*. Dr. Victor Carrion, a child psychiatrist and the director of the Early Life Stress and Pediatric Anxiety Program at Stanford University Medical Center, soon became an ally.

There is still a lot we don't know about how stress affects the brain,

but every day, promising studies show us more and more. We know as much as we do about toxic stress's impact on the brain because of important research like Dr. Carrion's at Stanford.

Carrion had been working for a long time with kids who were exposed to high doses of adversity. Previous research in adults showed that high levels of cortisol were toxic to the hippocampus, but Dr. Carrion decided to look specifically at kids. Thanks to MRI technology, he was able to peek inside their brains and see cortisol's impact on kids who had experienced trauma. What's so compelling to physicians about Dr. Carrion's work is that it told the story in a language that we doctors were accustomed to hearing. When you put a kid who had experienced adversity in an MRI machine, you could see *measurable changes* to the brain structures.

For the study, Carrion and his team recruited patients from various local health services. The criteria were that they had to have been exposed to trauma, were between ten and sixteen years old, and had PTSD symptoms. Most of the kids had experienced multiple traumatic events—witnessing violence or suffering physical abuse or emotional abuse. Many of them were living in poverty. The control group had no history of trauma but were comparable to the experimental group in terms of income, age, and race. In preliminary interviews, the researchers asked the kids or their caregivers about PTSD symptoms and hyperarousal symptoms like difficulty sleeping, irritability, and trouble concentrating, to name just a few. Then they did an MRI and checked each kid's salivary cortisol four times a day. Once the brain scans were in, they looked at the size of each child's hippocampus by measuring the volume in 3-D. They found that the more symptoms a kid had, the higher his cortisol levels were and the smaller the volume of his hippocampus. After the first measurement of the hippocampus, they measured the same kids again twelve to eighteen months later and found their hippocampi were even smaller. Despite the fact that these kids were no longer experiencing trauma, the parts of their brains responsible for learning and memory were still shrinking, showing us that the effects of earlier stress were still acting on the neurological system.

Dr. Carrion agreed with me that it was important to assess my entire population of patients for the effects of toxic stress, and he was at

interested as I was in the results. We decided our focus would be on the association between ACE scores and two of the most common issues I saw in my patients: obesity and learning/behavior problems. After a careful review of each patient's chart, my research assistant Julia Hellman assigned everyone an ACE score. We even had another reviewer from Stanford review and score a random sampling of our patient charts to make sure that our scoring was accurate.

At first, the ACE scores of our study population of 702 patients looked a lot like Felitti and Anda's: 67 percent of our kids had experienced at least one ACE, and 12 percent had experienced four or more. I have to admit that I was surprised that our numbers weren't higher. After all, Bayview was a pretty rough neighborhood. I knew the questions that Felitti and Anda asked didn't cover everything my patients had been through, like community violence or having a family member deported, both common occurrences in the lives of my kids. But still, I expected our patients in Bayview to have experienced more ACEs than the Kaiser population. But then I had a forehead-slapping realization. Felitti and Anda had done their study among *adults*. The mean age of their patients was fifty-five. The subjects were asked to recall the number of ACEs experienced by the time they were eighteen. In our study, the mean age was *eight*. Many of our kids would likely have more ACEs before they reached their eighteenth birthdays. We also had to consider that it was the caregivers, not the children themselves, who reported the adverse experiences we were charting, and these caregivers might not have reported adversity accurately because of shame or fear or because "we just don't talk about those things."

Apart from these revelations, the profound discovery was that our patients with four or more ACEs were *twice* as likely to be overweight or obese and *3.6 times* as likely to have been diagnosed with learning and behavioral problems. When our statistician from Stanford first called to tell me how these numbers shook out, I was overwhelmed by a mix of emotions—elation at making an important discovery and a profound aching in my heart for all the kids who were struggling in school but being told that they had ADHD or a "behavior problem" when these problems were directly correlated with toxic doses of adversity.

The reason this is so important is that an accurate diagnosis *should* tell physicians the underlying biological problem so they can provide the best treatment and the most likely prognosis. For example, if a patient is found to have cancer in his liver, it's critical for his doctors to know whether the cancer originated in the liver or metastasized from the prostate or somewhere else in the body; the treatments and prognoses for various cancers are different, even though the initial physical finding may be the same. Currently, ADHD is a diagnosis based entirely on symptoms. If you remember, the criteria include inattention, impulsiveness, and hyperactivity, but the *Diagnostic and Statistical Manual of Mental Disorders* doesn't say a word about the underlying biology. What it does say is that if these same symptoms are associated with a *different* mental disorder, like schizophrenia, then it's no longer ADHD. Similarly, if we see impulsivity and hyperactivity but discover that those symptoms are caused by a brain tumor, we can't diagnose ADHD.

From Felitti and Anda's research, I was beginning to understand that the prognosis of toxic stress, the long-term risks that my patients faced, looked very different from run-of-the-mill ADHD. We have a ways to go before we fully understand whether the behavioral symptoms of toxic stress represent a totally different diagnosis. Part of the problem has been that, unlike ADHD, the diagnosis of toxic stress doesn't yet exist in the medical literature.

This clinical pattern has an echo in recent medical history. In the 1980s, the medical world was confronted with a new epidemic. People would go to see their doctors, complaining of rashes and sores. They would make their way to emergency rooms with tuberculosis and hepatitis C. Even more baffling, they showed up in droves with Kaposi's sarcoma, a rare type of cancer that attacks the skin, mouth, and lymph nodes. For a while, no one suspected there was any connection among these health problems because they were known quantities. Doctors did what they were trained to do and treated the sores, the hepatitis, the cancer. But symptomatic patients kept coming in at higher rates than anyone had ever seen. So doctors felt they had to get better and better at treating things like sores, hepatitis, and Kaposi's sarcoma—a strategy that didn't touch the underlying problem. These patients kept

getting sicker and sicker. Now we know that sores, tuberculosis, and Kaposi's sarcoma were all indicators of a more significant underlying problem, an infection compromising the entire immune system. These were AIDS-defining diseases; they were conditions that needed intervention and symptoms pointing to an underlying biological problem with a very different prognosis and treatment: HIV/AIDS.

So when I looked at my patients with high ACE scores, I couldn't help but think that if I treated *just* the asthma or the obesity or the behavior problem, I was a really poor student of history. We know from the research that the life expectancy of individuals with ACE scores of six or more is twenty years shorter than it is for people with no ACEs. For a patient with a high ACE score, it may not be the obesity that shortens his or her life but the underlying toxic stress that the obesity is signaling. To treat the root of the problem I had to look at both stories my patients' symptoms were telling me: the story on the surface and the story underneath. So when a patient named Trinity walked through the door with a chief complaint of ADHD, I was ready for her.

I was starting to get a reputation in the area for being the type of doctor who wouldn't just slap a prescription for Ritalin on the table. People brought their kids to me when they wanted someone to take a closer look. But before I knew just how close to look in Trinity's case, I had to know her ACE score. After the chart review of our initial 702 patients, I began asking about exposure to adversity for *all* of my patients to better understand their health risks. Just like height, weight, and blood pressure, the ACE score became another vital sign for my regular medical exams. With Trinity's complaint of learning and behavior problems, if her ACE score had been zero, a standard ADHD workup would have been warranted. But now I knew that if a patient had four or more ACEs, she was thirty-two times as likely to have learning or behavior problems, which suggested that the underlying issue was probably not ordinary ADHD. In those cases, I was convinced that the problem was chronic dysregulation of the stress-response system, which inhibited the prefrontal cortex, overstimulated the amygdala, and short-circuited the stress thermostat—in other words, toxic stress. When I flipped through Trinity's chart, I saw that she had an ACE score of six.

When I first walked into the exam room and met Trinity, I had an immediate childhood flashback. Before my family moved to the United States from Jamaica, I started first grade at Hope Valley Elementary School in Kingston. It was there that I found the thing that my household of four brothers lacked — other girls to play with. There was a gaggle of older girls who adopted me and taught me critical lessons like how to jump rope and climb the jungle gym with a skirt on. I would beg my mom to braid my hair into neat plaits just like theirs. They were long-limbed and lean, with cocoa-brown skin and bright white teeth. Trinity would have fit right in, down to the school uniform she wore — a crisp white cotton short-sleeved shirt and a navy-blue knee-length wool skirt. I noticed she was tall for her eleven years and slimmer than average, though I doubted she walked three miles to school every day like the girls from my childhood. Trinity was sitting quietly with her aunt, eyes scanning the room. She was polite and obedient and super-sweet. Before I even had to ask, Trinity's aunt launched into the story behind her niece's ACE score.

Trinity's mom was a heroin addict who made only unpredictable, cameo appearances in her daughter's life. She'd roll into town out of nowhere and pick Trinity up to go shopping. But what "shopping" really meant was hitting up department stores and using her daughter as a decoy while she boosted clothing and shoes. Trinity's aunt had stopped allowing the mom to visit when she found out Trinity herself had begun lifting lip gloss and other small items when she was out with her mom. Since then Trinity had been having major problems in school, and her teachers were at the end of their rope. Beyond the learning issues, she was having difficulty with emotional regulation. She'd act out and get into trouble with the kid next to her, and she couldn't sit still for more than five minutes. Sometimes she even ran out of the classroom.

As with most of my kids, I would never have suspected the trouble from the calm way Trinity behaved herself in my exam room. But I began my physical exam with my toxic stress lens on, giving Trinity an even more careful once-over than I would have for a kid with zero ACEs, kind of like how, if a patient lives with two parents who are heavy smokers, I sure as hell give an extra-close listen to that kid's

lungs. Knowing Trinity was at higher risk for a whole host of things, I listened hard to her lungs (no wheezing). I looked at her skin (it was warm and soft with no dryness or flaking). I looked at her hair (there was breakage at the edges, but that was a common finding among African American girls, depending on their hairstyle). Nothing seemed terribly out of the ordinary — until I got to her heart.

Most people know that a regular heartbeat (no skipping or murmurs) is something that doctors look for, but what we're also looking for is how hard it beats. When I laid my stethoscope on Trinity's chest, I had to pause to readjust my earpieces. It was as though the volume on her heartbeat was turned up just a little higher than normal. It was subtle, but instead of the soft *lub-dub* I expected to hear, it was more like a *LUB-DUB*. I took off my stethoscope and looked at her for a moment. Then I gently laid my hand on her chest. No, I wasn't imagining it. Not only did her heartbeat sound louder than normal, it felt stronger than normal as well. The heartbeat question combined with her slimness was enough of a red flag for me to send her for an EKG.

The next day, the EKG confirmed the abnormality with her heart. According to the results, it was beating faster and the muscle was working harder than normal. The cardiologist who interpreted the EKG included a note that reinforced my suspicions: *possible Graves' disease*. Slim builds and strong heartbeats (as well as hair breakage) can be signs of Graves', which is an autoimmune disease that results in the thyroid gland being overstimulated. Unlike the example I gave earlier of hypothyroidism (when the thyroid gland doesn't make enough thyroid hormone), Graves' disease is a case of *hyper*thyroidism, where the thyroid gland makes too much thyroid hormone. If you remember, adults with hypothyroidism gain weight easily and can be somewhat lethargic. By contrast, people with Graves' disease are often hyperactive and can't seem to keep weight on.

In Europe, hyperthyroidism is often called Basedow's disease, after Karl Adolph van Basedow, the German physician who described the condition contemporaneously with Dr. Robert Graves. In my research on toxic stress, I had come across some data describing the high number of cases of hyperthyroidism among refugees from Nazi prison

camps. In fact, the term *kriegs-Baseadow* (*kriegs* means “war,” so *kriegs-Baseadow* is “hyperthyroidism of war”) was coined following the observation of an increased incidence of hyperthyroidism during major wars. Trinity visited the endocrinologist, who confirmed that she did in fact have Graves’ disease. Undoubtedly, her hyperthyroidism was contributing to her issues in school. Once Trinity was on medication, her behavior and learning problems improved. They weren’t gone, but she was doing a heck of a lot better than she had been before.

It turns out that since 1825, researchers have known that Graves’ disease is often correlated with stressful life events, which Trinity had in spades. It was clear that her problems with emotional regulation were overlaid on the hyperthyroidism, making her time in the classroom that much more difficult. The crazy thing is that many busy physicians do their entire assessment of ADHD based on behavioral symptoms alone, without a stethoscope even touching the patient’s chest.

Once again, I saw how critical it was to take a whole-system approach to examining kids who were at high risk. Even if I didn’t always know exactly what I was looking for, using the ACE score as a measure of risk for toxic stress was making me a better doctor, helping me put the right lens on the problem so I could detect things I might otherwise overlook. After prescribing medication to treat Trinity’s Graves’ disease, which was the first story her symptoms were telling me, I prescribed family therapy to treat the second story her symptoms were pointing to—underlying toxic stress. The purpose of family therapy was to teach Trinity and her aunt how to create an environment that would limit the reactivation of her SAM and HPA axes. The goal was to give them the tools to prevent scary or stressful situations and to manage them better when they came up, essentially reducing Trinity’s dose of adrenaline and cortisol.

I didn’t start Trinity on any medications for her behavior. I favor a stepwise approach to treating toxic stress so I can see what’s working and what isn’t. There are certainly some patients for whom medications are an important part of treatment, but our clinical team is careful to use medications in a way that addresses the underlying biology. In the previous chapter, I mentioned that a graph of the response of

the prefrontal cortex to adrenaline and noradrenaline looks like an inverted U. Well, for kids with impaired impulse control and inattentiveness due to toxic stress, PFC function is likely to be on the downslope of the inverted U (kind of like if you drink way too much coffee, you can’t focus to save your life). In those cases, our clinical team tends not to use stimulants like methylphenidate (Ritalin) or drugs derived from amphetamines. Instead, we often use guanfacine, a nonstimulant that was originally developed to treat high blood pressure but has also been used to treat ADHD. Guanfacine targets specific circuits in the prefrontal cortex where adrenaline and noradrenaline exert their action, improving impulsiveness and concentration, even in situations of high stress.

While I felt good about taking a more systemic approach, like the doctors who first began to suspect that a compromised immune system was behind HIV/AIDS, I was working on a medical frontier. There wasn’t (and still isn’t) a clear set of diagnostic criteria or a blood test for toxic stress, and there is no drug cocktail to prescribe. My biggest guide for what symptoms might be toxic stress-related was the ACE Study itself, but I knew that the number of diseases and conditions it accounted for might just be the tip of the iceberg. After all, if a dysregulated stress-response system was the source of the problem, it could have far-reaching effects. A disrupted stress response doesn’t affect only the neurological system; it affects the immune system, the hormonal system, and the cardiovascular system as well. Because everyone’s biological and genetic makeup is different, how that dysregulation manifests itself will be similarly diverse.

Right about here is where my staff started to get overwhelmed with what we were learning, feeling as though *everything* could be toxic stress-related. When we talked through it, I reminded them that it was all about where you started with the problem. If you broke it down, the core issue was a dysregulated stress response. From there you simply followed the thread, looking at how that dysregulation affected each of the body’s systems. We made a choice to start our investigations with the underlying systems. If we wanted to identify and treat what was wrong, we had to know what was happening on a molecular level. We

turned back to the literature and tried to break it down system by system, figuring out as best we could exactly *how* toxic stress was disrupting the normal functions of the body.

Toxic Stress and the Brain

Based on the results of our chart review, it seemed that learning was the proverbial canary in the coal mine. The fact that our patients with four or more ACEs were 32.6 times as likely to have been diagnosed with learning and behavioral problems signaled to us that ACEs had an outsized effect on children's rapidly developing brains. I had learned a lot about brain development in medical school and residency. I understood that a child's brain forms more than one million neural connections every second during the first years of life. I'd also seen firsthand during my medical residency that if that process got disrupted, by a toxin, a disease, or even physical trauma, the consequences could be serious.

Now we needed to understand the many ways that toxic stress affected the brain. The science nerd in me liked to think me and my team were akin to the rebel army in the movie *Star Wars*, searching the plans of the Death Star, but in this case, the Death Star was toxic stress. If we knew how the Death Star worked, studied its blueprints, looked for its weaknesses, we might find a way to prevent the harm it could cause.

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In the previous chapter we talked about the cast of characters in the stress response: the amygdala, the prefrontal cortex, the hippocampus, and the noradrenergic nucleus of the locus coeruleus (which we'll refer to as the locus coeruleus from now on). Because these parts of the brain are on front lines of the stress response, it makes sense that a severe and prolonged disruption of the norm would hit them hardest, changing how they fundamentally do their jobs. Another very important region of the brain in understanding how ACEs create long-term

problems is the ventral tegmental area (VTA). This is the pleasure and reward center of the brain and it plays a huge role in behavior and addiction.

The Alarm (aka the Amygdala)

The amygdala is the brain's fear center. It's located deep inside the temporal lobe near the midline and is believed to be one of the first brain structures that evolved, which is why it's often referred to as the "lizard brain." The amygdala is a key player in a series of interconnected parts of the brain that together make up the limbic system, which governs emotions, memory, motivation, and behavior. The amygdala is one of the most important structures in the limbic system because it helps you identify and react to threats in your environment. Fear is an emotion that developed to help you save your skin from the bear and that erupts when you first hear a roar or catch a glimpse of the animal's hulking profile.

When the amygdala is repeatedly triggered by chronic stressors, it becomes overactive, and what we see is an exaggerated response to a stimulus like the bear or, as I was beginning to notice in clinic, a nurse with a needle. MRI studies of severely maltreated kids from Romanian orphanages shows dramatic enlargement of their amygdalae. The other thing that happens when the amygdala is chronically or repeatedly activated is that it starts messing up its predictions about what's scary and what's not. The amygdala begins sending false alarms to the other parts of your brain about things that shouldn't actually be scary, just like the little boy who cried wolf.

I Don't Know Karate but I Do Know C-Crazy (aka the Locus Coeruleus)

This part of the brain is the driving force behind aggressive behavior (sorry, Raiders fans, I'm still looking at you). It works closely with the prefrontal cortex, which is why we see overlap in how they both

regulate impulse control. The dysregulated locus coeruleus releases too much noradrenaline (the brain's version of adrenaline) and can result in increased anxiety, arousal, and aggression. It can also seriously mess with your sleep-wake cycles by overloading your system with hormones that tell it to remain vigilant because (hello!) a bear is in your cave.

The Conductor (aka the Prefrontal Cortex)

The prefrontal cortex (PFC) sits right behind your forehead at the front part of the brain. Unlike the amygdala, which is thought to be a very primitive structure, the PFC is believed to be one of the last to have evolved, and it confers faculties of reason, judgment, planning, and decision-making. It is often referred to as the seat of "executive functioning," which is the ability to differentiate among conflicting thoughts and inputs, consider future consequences of current activities, work toward a defined goal, and exhibit "social control" (that is, suppress urges that, if not suppressed, lead to socially unacceptable outcomes). In many ways, it's like the conductor of an orchestra, setting the tempo and volume for each of the different players, harmonizing all their inputs into something that is coherent and beautiful, not chaotic and loud. Think about your average day in a fifth-grade classroom. The teacher is talking, the kid beside you is throwing a wad of paper across the room, your archnemesis is kicking you ferociously under the table, and the girl you like just passed you a note telling you that she doesn't like you anymore. This is a lot for a *normally* functioning PFC to deal with.

For kids with toxic stress, the activity of the prefrontal cortex is inhibited in two ways. First, the overactive amygdala sends messages to the PFC telling it to decrease its functioning because something scary is happening; you don't want reason getting in the way of survival. The second is that the locus coeruleus is flooding the brain with noradrenaline, compromising the ability to override instincts and impulses. The PFC is the part of the kid's brain that puts the brakes on impulses and helps him or her make smarter decisions. Telling a kid to sit still, con-

centrate, and ignore stimuli that are flooding his brain with the *need* to act is a lot to ask. This down-regulation of the PFC can have different consequences for different people. For some, it results in an inability to concentrate and solve problems, but in others it manifests as impulsive behavior and aggression.

Memory Bank (aka the Hippocampus)

The hippocampi are two cute little seahorse-shaped parts of the brain responsible for creating and maintaining memory. When the amygdala gets activated during a major stress event, it sends signals to the hippocampus that disrupt its ability to knit together neurons, essentially making it more difficult for the brain to create both short-term and long-term memories. On brain scans of patients with Alzheimer's disease, the hippocampi are badly damaged. Knowing that, it's pretty obvious why this part of the brain is so critical to learning, and it's easy to see how kids with quick-trigger amygdalae are behind the eight ball when it comes to everything from memorizing multiplication tables to spatial memory.

Vegas, Baby! (aka the Ventral Tegmental Area, VTA)

If the locus coeruleus is a Raiders fan, then the VTA region of the brain is Las Vegas. Responsible for things like rewards, motivation, and addiction, this part of your brain is the one you really don't want running away with your credit card. Basically it all boils down to dopamine, which is the feel-good (or feel-*amazing*) neurotransmitter that peppers your brain with rewards when you have sex, shoot heroin, or say yes to that piece of triple chocolate cake at the end of the day.

When your body's stress-response system is overloaded again and again, it messes with the sensitivity of your dopamine receptors. You need more and more of the good stuff to feel the same amount of pleasure. The biological changes in the VTA that lead people to crave do-

panine stimulants like high-sugar, high-fat foods also lead to an increase in risky behavior. The ACE Study shows that there is a dose-response relationship between ACE exposure and engaging in many activities and substances that activate the VTA. A person with four or more ACEs is two and a half times as likely to smoke, five and a half times as likely to be dependent on alcohol, and ten times as likely to use intravenous drugs as a person with zero ACEs. So for anyone looking to prevent young folks from developing dependencies on bad-for-you dopamine stimulants like cigarettes and alcohol, understanding that exposure to early adversity affects the way dopamine functions in the brain is an absolute must.

Hormonal Harmony

Ladies, have you ever noticed that the *one* month you are sweating about whether you are going to get your period is the month that it seems to come late? Well, it's not just your imagination. Due to the impact it has on the hormonal systems, the stress response can affect everything from menstrual cycles to libidos to waistlines.

Hormones are the body's chemical messengers, responsible for kicking off a wide range of biological processes. Big ones include growth, metabolism (how your body gets and stores energy from food), sexual function, and reproduction. So, basically, everything. The hormonal system is very sensitive to the stress response. Which makes sense, because when you see the bear in the woods, it's hormones that get the party started ("*Adrenaline! Cortisol! Go!*").

Just about every one of the body's hormonal systems is affected by stress. Growth hormones, sex hormones (including estrogen and testosterone), thyroid hormone, and insulin (which regulates blood sugar) all tend to decrease during stress. Some of the major health impacts are dysfunction of the ovaries and testes (also known as gonads), psychosocial short stature, and obesity. In the case of gonadal dysfunction, for women this can lead to not ovulating, not having a period, or menstrual irregularity. In one study, researchers found that 33 percent of newly incarcerated women with stress (can you imagine a newly

incarcerated woman who *doesn't* have stress?) had irregular periods. Psychosocial short stature is what we saw with Diego—severe delay of growth in children and adolescents due to a pathological environment. In some cases, children have severely reduced levels of growth hormone, but other times, as we saw with Diego, growth hormone isn't measurably decreased. In these cases, we believe the disruption comes from the other factors that help growth hormone do its job. Obesity is a much more familiar foe, but in the hormonal system, we see the double whammy. As I mentioned above, because of its impact on the pleasure center (the VTA), chronic stress increases your cravings for high-sugar, high-fat foods, and elevated cortisol makes it harder for your body to metabolize sugars and easier for your body to store fat. But cortisol isn't the only bad guy here; the hormones leptin and ghrelin are also increased with activation of the stress response. Together they intensify appetite and work with cortisol to do their worst for your waistline.

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The chart review that we did at the clinic showed us that if a kid had an ACE score of four or more, he or she was twice as likely to be overweight or obese as a child with zero ACEs. This is where we see how biology and social determinants of health collide with significant consequences. We've talked about how kids living in vulnerable communities have a lot of intersecting risks driving ill health. Lack of access to good health care, few safe places to play, and food insecurity do contribute to striking health disparities in places like Bayview.

But our patients with zero ACEs lived in the same neighborhood and had the same access to health care, the same lack of safe places to play and nutritious food as our patients with high ACEs. When you realize what toxic stress does to the hormonal systems of kids who have experienced multiple ACEs, you understand that it's not *just* because they subsist primarily on a diet of fast food that they are overweight. It's not *just* that they are living in a food desert (a term that refers specifically to a neighborhood with a dearth of nutritious food) and are being brought up by parents who think Taco Bell is a healthy alterna-

tive to McDonald's. Those things compound the problem, to be sure, but they are not the whole story. Our data suggested how powerful the underlying mechanism of toxic stress can be — that the metabolic disruption was also an important driver. If you grow up in a food desert, of course it's going to be difficult for you to be healthy. But if you also have higher cortisol levels that are driving you to crave high-sugar, high-fat foods, it's going to be that much harder for you to choose broccoli over French fries.

Foreign Relations: Toxic Stress and the Immune System

Immunology was by far my most painful class in medical school, which is ironic considering that the immune system should be the doctor's best friend. The problem is the intricacy of it all. The immune system wields a lot of power; it is responsible for monitoring the relationships between what's inside and what's outside in the world and also for defending the body against foreign threats. Kind of like your own personal secretary of state and secretary of defense rolled into one. Because the body has so many different antagonists and so many different allies, sometimes it's hard to tell them apart. The immune system has to be an expert on *all* of it, knowing, for instance, that the protein on the outside of a bacteria or virus is *bad* and the microbe needs to be fought off, but also that the proteins in the lungs, nerves, and blood cells are *good* and should be left alone.

When the body's secretaries are pleased with foreign relations, they are very low-key. They quietly go about the business of maintaining order by constantly scanning the body for cells that are infected, injured, or becoming cancerous, and when they find them, they destroy them. But when a bad guy manages to evade the routine defenses and cause disease, the secretary of defense sounds the alarm, marshaling armies and launching strategic attacks. The immune system uses chemical signals called cytokines to activate your body's response to injury or illness. The word *cytokine* literally means "cell movers." They

prod your body to make more white blood cells, which fight off infection and activate different types of cells to do things like make antibodies and eat bacteria. The immune system also stimulates inflammation (like when a bug bite gets all red and swollen). Like everything else in the body, what's important in the immune system is balance.

Dysregulation of the stress response has a profound impact on immune and inflammatory responses because virtually all the components of the immune system are influenced by stress hormones. Chronic exposure to stress hormones can suppress the immune system in some ways and activate it in others, and unfortunately none of it's good. Stress can lead to deficiency in the part of the immune system that fights off the common cold, tuberculosis, and certain tumors. In Sweden, researcher Jerker Karlén and his colleagues found that kids with three or more exposures to early stress showed increases in cortisol levels and were more likely to be affected by common childhood health issues such as upper respiratory infections (colds), gastroenteritis (stomach flu), and other viral infections. We also know that dysregulation of the stress response can lead to increased inflammation, hypersensitivity (think allergies, eczema, and asthma), and even autoimmune disease (when the immune system attacks the body itself), as with Trinity's Graves' disease.

In the years since the ACE Study was first released, scientists have looked closely at the relationship between ACEs and autoimmune disease. Research findings show a strong correlation between childhood stress and autoimmune disease in both children and adults. In analyzing the data of over fifteen thousand ACE Study participants, looking at their ACE scores and how often they were hospitalized for autoimmune diseases such as rheumatoid arthritis, lupus, type 1 diabetes, celiac disease, and idiopathic pulmonary fibrosis. What Dube found was striking: a person with an ACE score of two or more had twice the odds of hospitalization for autoimmune disease as someone with zero ACEs.

Just as the brain or the nervous system is not fully developed when a child is born, the immune system is also still developing well after

birth. In fact, when babies are first born, they have very little functioning immunity; something that will develop with time and a little help from their moms. Breastfeeding is so important in part because the mom's antibodies protect the baby from infection and help grow his immune system. If you've ever wondered why people are hesitant to bring very young babies out into the world, that's why. (Well, that and the soul-crushing sleep deprivation.)

A baby's immune development occurs in response to his or her environment over the course of the first years of life. Think about it as the secretary of state in her first year in office, still meeting all the foreign heads of state, feeling out who is hostile and who is friendly. Unfortunately, getting a good read on the reality of the threat is difficult when there is an adrenaline and cortisol overload. This kind of disruption early on in development can lead to lifelong alterations in the function of the immune system and, in many cases, to disease. Think of it like this: If the secretary of defense is triggered to send in the troops to fight invaders in the body, sometimes the troops will attack the right enemies, but sometimes they'll find trouble where trouble doesn't exist. The more inflammation there is in the body, the greater the chance that some of that inflammation will attack the body's own tissues, leading to autoimmune diseases like rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis. Because early adversity increases inflammation, when you have higher numbers of troops roaming around the body, there is a greater likelihood that they'll make a mistake.

Researchers in Dunedin, New Zealand, demonstrated that the changes in levels of inflammation were actually measurable. They followed a group of a thousand people over the course of thirty years, observing and recording a number of important health data points over that time. In addition to reinforcing Felitti and Anda's findings, the Dunedin researchers discovered that even twenty years after their subjects had been maltreated as children, four different markers of inflammation were higher than they were in those who hadn't been maltreated. What makes this study a critical addition to the research on ACEs is that the patients' adverse childhood events had been reported

as they were happening, strengthening the case for causality by documenting that the adversity preceded the biological harms.

We know that a well-balanced immune system is critical to good health. When we realize that adversity in childhood harms the development and regulation of the immune system *throughout someone's life*, we begin to understand just how powerful the ACE science can be to combat some of the leading causes of disease and death.

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For me, the immune-system piece of the ACEs puzzle was important because I found that when people learned how toxic stress affects the immune system, they listened in a different way. It's counter to the story they may already have in their heads. People seem to know that if you eat too much, you mess with your hormones and gain weight, and if you make impulsive decisions or become addicted to alcohol, you'll affect your neurological system. But it's harder to connect those perceived human failings to something like Graves' disease or multiple sclerosis. Most people don't think about those conditions as being caused by anything other than genetic bad luck. What is so powerful about the follow-up ACE studies like the one Dube did is that they show a strong correlation between autoimmune diseases and exposure to something environmental and specific — childhood adversity.

Dr. Felitti's patient Patty is a perfect example of why it's important to pay attention to those correlations. Patty was extremely obese and also had some psychological and emotional problems (the sleep-eating is the tip-off there). Even for those who know that abuse often leads to emotional problems and sometimes to obesity, those issues might seem like the beginning and end of the impact of adversity on her life. But when we see that Patty actually died of idiopathic pulmonary fibrosis, an autoimmune disease (the odds of which increase with the number of ACEs a person has), the plot thickens. The consequences of toxic stress are not just neurologic and hormonal; they are also immunologic, and those symptoms are much more difficult to spot. Patty's childhood adversity threatened her immune system as much as it did

her mental well-being. The problem was that, for Patty, no one suspected that her immune system could be fatally compromised because of toxic stress. No one knew where to look.

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My understanding of how early adversity affected my patients had come farther in the past twelve months than it had in the previous decade, yet the picture wasn't quite complete. It made sense to me that an overactive stress response could do a lot of harm to someone's health. I felt I understood clearly how the changes to the neuroendocrine-immune systems could lead to problems for my kids. But the ACE Study also showed that adversity in childhood could lead to health problems decades later. By that time, many people would have escaped the challenging conditions of their childhood. So why was Dr. Felitti seeing the same or, arguably, worse problems in his patients? How was it that ACEs were the gift that kept on giving? I had the nagging sense that the blueprint of the toxic stress Death Star went one dimension deeper, drawn in even fainter lines. I knew these questions would take me even farther down the rabbit hole of toxic stress, but I had come this far and I had to find out how it worked on the deepest level of all: genetics.