



An Elegant

DEFENSE

THE EXTRAORDINARY NEW SCIENCE OF
THE IMMUNE SYSTEM

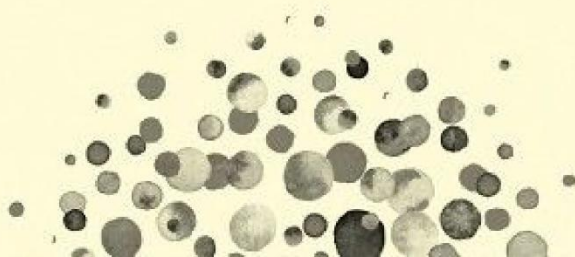
A Tale in Four Lives



PULITZER PRIZE-WINNER

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Author's Note

To distinguish between medical doctors and PhDs, I refer to medical doctors with the honorific Dr., whereas I refer to PhDs solely by last name. This is a painful trade-off given that PhDs not only have attained hard-earned doctorates but have made the most important discoveries in this field. I made the decision, following an informal *New York Times* style, in order to help guide the reader through a story with multiple characters, some with research expertise, tending to be PhDs, and others with clinical expertise, tending to be physicians. I beg the indulgence of the scientists, who are chief among this Odyssey's Argonauts.

Finally, I've used first names for Jason Greenstein, his family and friends, and for others whose intimacies I've shared, including Bob Hoff, Linda Segre, and Merredith Branscombe. The personal nature of their medical tales calls for more casual language.

Part I

Lives in the Balance

1

The Ties That Bind

A gray sky overhead, Jason Greenstein sat silently in the passenger seat of a Ford Windstar. It was Friday, March 13, 2015. Jason was heading to a miracle and traveling in the style to which he had become accustomed—filth.

His silver minivan, fast approaching Denver from its suburbs, looked like scrap metal on wheels. The heater coughed and spat and seemed to work only when it was hot outside. The back door didn't open. Various warning lights dotted the dashboard, alerting Jason to system failures he ignored. His maps and atlases overflowed compartments and littered the floor.

Then there was the smell. It permeated the cabin from the five-gallon gasoline jerry can he kept in back for emergencies, and from the accumulated greasy residue from endless fast-food stops. Jason could never resist 7-Eleven rotisserie hot dogs, despite referring to them as “witches’ fingers” and “disgusting.”

When Jason went on cross-country sales trips, which was often, he would sometimes sleep in the back of the van. He'd curl up on a stained orange Oriental rug, his head next to the gas can. Or he'd slumber on top of the boxes of shiny, bejeweled trinkets that he sold to far-flung casinos for use as

promotional items.

Jason was forty-seven, with an undergraduate diploma from an elite college, graduate degrees in business and law, and no reliance on or particular reverence for those trappings. He lived from one entrepreneurial idea to another, one adventure to the next. Never was he happier than when he was driving, a dip of Skoal Fine Cut packed in his lip, rocking out to Springsteen or to a local station on the dial with some new town on the horizon. Jason was determined to discover, explore, and live his way. He was a genuine American dreamer and the van his covered wagon.

“Ma, if anything ever happens to me, I want the van taken care of. Are you listening, Ma?” he told his mother. Jason and his mother, Catherine, alternately cherished each other and fought with vicious visceral passive-aggressive dialogue that would make Arthur Miller melt.

Now Jason sat in the passenger seat, his girlfriend, Beth, driving. He was heading to pull off as unconventional a trick as even he could ever have conceived. He was determined to become a medical marvel, a poster boy, as he termed it, for a miraculous new cancer treatment. Jason was going to defy death, while standing on its precipice, one foot already over the edge.

Jason suffered from late, late-stage cancer. By any reasonable definition, it was terminal.

Fifteen pounds of Hodgkin’s lymphoma was lodged in his lungs and back on the left side of his body, and it was doubling in size every few weeks. Four years of chemotherapy and radiation had ultimately failed, managing to beat back for only brief periods what is typically one of the most curable of

cancers. Doctors had tried nearly everything, some drugs twice or in combinations, with brutal side effects. The malignancy always returned. Now the tumor so protruded from his back that Beth affectionately referred to Jason as Quasimodo. The mass impinged on his ulnar nerve, which left him in agonizing pain and unable to move his left hand; it was bloated and looked like a fleshy blob.

The assault on his left hand was particularly cruel. When Jason was a kid—when we were kids together—Jason was a phenomenal athlete, cunning, tenacious, a slippery-quick southpaw. He wasn't tall, but he sure could jump, an antelope with frog legs, all-state in Colorado in basketball and baseball. He had the looks to match, dark hair and dark eyes, a generous smile, his half-Italian, half-Jewish ancestry yielding an all-American mutt the girls couldn't resist. But to me, his defining characteristic was his laugh. It exploded at a high pitch bordering on soprano, often at one of his own jokes. It was sheer delight.

As Beth drove the route to Denver from Boulder, sun skirted the clouds, as if March still couldn't decide whether it was winter or spring. Jason slumped with discomfort. He wore gray sweat pants, canvas loafers, a flannel shirt—all loose-fitting because that's all he could manage to slip over the painful lumps in his body. Even his feet swelled. Jason had taken everything cancer could throw at him. His oncologist had given Jason the nickname Steel Bull because he tenaciously endured every treatment they imposed on him, often managing a joke or smile along the way.

Then, the prior Monday, at an appointment with his oncologist, Jason had received his death sentence. The doctor

had examined the progression of Jason's tumor and explained tearfully that there was nothing left to do. They'd tried every treatment, all the toxic combinations. The cancer just kept roaring back. It was time to let go.

After the visit, the doctor wrote in a patient note that "the most reasonable approach, as emotionally taxing as it is, is to consider Mr. Greenstein for hospice care." He arranged a meeting with Jason's family to prepare him for palliative relief.

Further treatment, the doctor wrote, "is proving more toxic than beneficial" and would be unwarranted "unless he has a dramatic response."

Beth steered the minivan through the middle-class neighborhood around Presbyterian St. Luke's Medical Center. Jason usually loved to talk. He was a rapid-fire chatterbox. Now she could hardly get a word out of him.

After they parked, Beth held Jason by the arm as they took the elevator to the third floor. Jason had spent hours of his life in this oncology ward, sitting in a bulky tan recliner in one of the boxy rooms, enduring the noxious chemotherapy regimens. Not on this day.

Jason slowly edged himself into a chair. A nurse attached the intravenous line to the central port in his chest. First she dripped saline through to make sure the line was clean, then Benadryl to make Jason sleepy. Then the nurse swapped out those bags for another, also with clear liquid. This was something new.

Cancer is one of the world's leading killers. This is not a cancer story. Nor is it a story of heart disease or respiratory

disease, accidents, stroke, Alzheimer's, diabetes, flu and pneumonia, kidney disease, stroke, HIV, or diabetes. These are the things that ail and kill us. This is not the story of any particular disease or injury. It is the story of *all* of them and the extraordinary link that binds them, the glue that defines the whole of human health and wellness. This is the story of the immune system.

It is an account of the remarkable discovery of the immune system, particularly over the last seventy years, and of the role this system plays in every facet of our health. When a scratch or cut pierces the shield of our skin, itself a first line of defense, the immune system scrambles into action. Immune cells pour in to cleanse wounds, rebuild tissue, or repair internal damage from a bump or bruise, to tend to burns and bites. The complex defense network of cells attacks each cold virus—two to three a year—surveys the countless malignancies that threaten to become cancer, holds in check viruses like herpes that colonize huge swaths of the population, and confronts hundreds of millions of cases each year of food poisoning. Only recently have we begun to understand the pervasive role of our immune system in the brain, where damaged or outdated synapses get pruned by the organ's own immune cells, allowing ongoing neurological health.

This vigilance is constant and largely invisible to us, with the immune system a literal bodyguard that defines health in the broadest possible terms. For instance, the very mechanisms that defend our individual health appear to play a role in such essential functions as how we pick mates—helping us to avoid incestuous pairings that might damage

our collective security and survival.

The immune system is often described with the language of war, one that pits our internal forces against evil disease by using powerful cells capable of surveillance and spying, surgical strikes and nuclear attacks. To expand on the war metaphor, our defense network relies too on covert agents equipped with suicide pills, and it is connected by one of the world's most complex and instantaneous telecommunications networks. This defense apparatus also enjoys a status virtually unrivaled by any other facet of human biology. It roams the body freely, moving through and across organ systems. Like police in a time of martial law, the immune system seeks out threats and keeps them from doing mortal harm, ably discerning up to a billion different alien hazards, even ones not yet discovered by science.

This is an extraordinarily complex calling, given that life is a raucous festival, your body like a sprawling party, a chaotic and exuberant affair populated with a variety of cells. There are billions of them, tissue cells and blood cells, proteins and molecules and invading microbes.

The immune system's policing job gets complicated by the porous nature of our bodies' borders. Just about every organism that wants to get inside us can do so. Our body is a take-all-comers bash, a festival with open seating, coursing with every life-form that happens by—petty thieves and gangs; terrorists armed with nuclear suitcases; dumb drunk cousins and relatives; enemy agents cloaked as friends; and foes so unpredictable and alien that they seem as if beamed from another universe.

And yet, for all these threats, the war metaphor is

misleading, incomplete—even arguably dead wrong. Your immune system isn't a war machine. It's a peacekeeping force that more than anything else seeks to create harmony. The job of the immune system is to circulate through this wild party, keeping an eye out for troublemakers and then—this is key—tossing out bad guys while doing as little damage to other cells as possible. This is not just because we don't want to hurt our own tissue. It is also because we need many of the alien organisms that live on and in us, including the billions of bacteria that live in our guts. A convincing argument is now being made that some of these microbes, far from threatening us, are welcome as essential allies. Our health depends on our harmonious interaction with a multitude of bacteria. In fact, when we use antibiotics or antibacterial soaps or encounter toxins that harm our gut flora, we risk impairing bacteria that contribute to the effectiveness of our immune system's function.

And when our immune system gets overheated, look out.

Like an out-of-control police state, an unchecked immune system can grow so zealous that it turns as dangerous as any foreign disease. This is called autoimmunity. It is on the rise. Fully 20 percent of the American population, or 50 million Americans, develops an autoimmune disorder. By some estimates, 75 percent are women, with conditions like rheumatoid arthritis, lupus, Crohn's disease, and irritable bowel syndrome (IBS)—each terrible, frustrating, debilitating, hard to diagnose. Together, autoimmunity is the third most common disease category in the United States (after cardiovascular disorders and cancer). Diabetes, the leading killer in the country, is caused by the immune system's going

to war against the pancreas.

The last few decades of immunology, the science of the immune system, have taught us about another core facet of the immune system: It can be duped. Sometimes a disease takes root and starts to grow and spread and then tricks the immune system into thinking it isn't so bad after all. It deceives the entire defense system into helping it grow. This is what happened to Jason.

Cancer played a nasty trick on his elegant defense. It overtook the immune system's communication channels and instructed his body's soldiers to stand down. Then it used his immune system to protect the cancer as if it were a precious, healthy new tissue, and it would have sent him spiraling to his grave.

The clear liquid that dripped into Jason's chest that auspicious Friday the thirteenth was aimed at reversing cancer's trick. It was instructing his immune system to fight. Jason, one of the first fifty patients to try one of the greatest developments in the history of medicine, was now as much a hyperkinetic frontiersman as he ever dared dream. He stood at the very edge of human achievement as modern science challenged one of the most enduring and effective killing techniques in the pantheon of disease.

When it became clear that Jason just might exemplify a remarkable shift in medicine, I picked up my pen.

*The author with Jason Greenstein. “I’m back,” said
Greenie. (Nick Cote/New York Times)*

As a *New York Times* journalist but also as Jason’s friend, I began a journey to understand the immune system, how we’d gotten to this place where we might tinker with it, and what that means. What I found was a story of scientific discovery and heroics, a global detective yarn that spins through Europe, Russia, Japan, and the United States, with researchers stacking one hard-earned revelation on the next. The sum of my learning is a series of pivotal vignettes and lessons, personal histories and scientific aha moments, making this book less textbook than tale. It’s the story of the immune system’s mechanics and its reach into the practical side of health—into sleep, fitness, mood, nutrition, aging, and dementia.

It’s also the story of Jason and three other medical wonders you’ll meet: Bob Hoff, a man with one of the most unusual immune systems in the world, and Linda Segre and Merredith Branscombe, two stalwart souls fighting an

invisible killer—their own overactive immune systems.

Like Jason, they are part of a monumental scientific inflection point, an explosion of knowledge, with experts placing our new understanding of the immune system on par with the greatest human achievements.

These new discoveries are “as significant as the discovery of antibiotics,” said Dr. John Timmerman at UCLA, who has done pioneering research into the immune system. In terms of fighting a host of diseases impacting both quality of life and longevity, “we’re like Apollo 11 right now. We have touched down. The *Eagle* has landed.”

At St. Luke’s that Friday the thirteenth, the drug dripped into Jason’s system for an hour, after which Beth drove them forty-five minutes back to Boulder, where he planned to watch his nephew Jack’s high school basketball game at the Coors Events Center on the campus of the University of Colorado. When they arrived at the game, Jason lacked the strength to climb the arena’s stairs, so a family member talked the event staff into letting him in through a special entrance and directly onto the court.

This was how Jason used to go into games in his heyday, right onto the court, the center of it all. In fact, at this very arena, decades earlier, I’d sat in these stands and watched Jason drill one of the most improbable, thrilling shots I’m ever likely to witness again in my life. His winning shot from the top of the key came at the buzzer of a double-overtime game against a rival, allowing his team to advance in the state play-offs.

Many years later, Jason sat in the stands as friends wandered over and looked at a dwindled shell who they felt

certain was attending his last game.

“He looked so bad,” observed one of Jason’s old friends and teammates, a skinny sharpshooter named Danny Gallagher. “I wondered if he’d make it through the night.”

2

Jason

The immune system story is one of life and death, of course, a story of survival under the deadliest conditions. As much as that, it is about the struggle for peace and harmony, for successful integration, immigration of organisms across body and border, manifest destiny, and evolution. It is a story of friendship.

My earliest memories of Jason were in the infield and dugout. We were ten. Our Little League team was sponsored by McDonald's. White uniforms with yellow trim. Jason had a puff of big hair and a smile nearly as wide. In team pictures, he stood in the back row. I knelt in the front, happy in many ways and confident in school, but hiding the growing insecurity of a short kid craving attention.

Jason seemed to me to embody the ideal, an all-American boy, not just a great jock, but blessed as well with a natural curiosity, kindness, and mountains of charisma. In seventh grade, he was voted most outstanding student. When he was present, others yielded to him. He was nicknamed Golden. He was more appealing a person because he was the opposite of a bully. "Go get it, Rick!" he'd shout when I'd be at bat, likely to strike out, lucky to walk. "Next time," he'd tell me when I got

back to the bench.

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*Jason, second from left on top; author, bottom right, below
Jason's dad. (Courtesy of the author)*

We had some things in common, notably fathers we looked up to, who loomed large in our lives and in the community. My dad was a judge in our relatively small town. Jason's dad, Joel Greenstein, was a beloved divorce attorney, our Little League coach, *the* Little League coach in town, our own version of Walter Matthau, without the cursing or drinking. He chomped a stogie, had a wry smile and dry wit, was visible a ball field away in his navy blue Yankees windbreaker. He'd stand in the dugout with his knee up on a step, fist smacking into his cracked-leather catcher's mitt.

Joel doted on and gently but strategically steered Jason, like a judicious trainer who had lucked into a Thoroughbred.

"Jason adored my father," Jason's sister Yvette told me. "He was so close to my dad, and my dad just adored him. My dad was a more reserved kind of person, and here was Jason,

who always had it all out there, no filter, really, emotionally; he gave you whatever he had at the time.”

Guy, Jason’s older brother, said of Jason: “My dad was his guru.”

From a health perspective, there was a powerful material difference between our fathers—Murray (my dad) and Joel. Murray discovered jogging at the inception of the 1970s running craze and became as fanatical as anyone, eventually completing thirteen marathons. Joel was fit too, but he smoked cigars. Jason’s mother, Cathy, smoked a pack of cigarettes a day. Tobacco smells permeated the Greenstein house. Smoking tests the immune system like few human habits; the tiny nicks and cuts to the soft lung tissue don’t just create persistent injury but force cells to divide to replace the hurt tissue. Cell division heightens the possibility for malignancy, cancer. This is just simple math, and it can be deadly.

In eighth grade, Tom Meier, one of Jason’s closest friends, was standing in the school gym. The door flung open and Golden rushed in. “He was sobbing,” Tom recalled.

Before Tom could fully get Jason’s attention, Jason made his way to the locker room, and Tom followed. Jason sat on the locker room bench.

“What’s up, J?”

“My father is dying.”

Jason had learned his father had colon cancer.

Forty years later, Tom tears up as he tells the story. “Here was the strongest person I knew in the whole world,” Tom told me, “and he was absolutely shattered.”

Jason seemed outwardly impervious to the malignancy eating his father alive, the victim of his own growing emotional disconnect. In ninth grade, Jason ran for president of the student council. His speech exuded confidence and grace. He told the school he would never give up.

“If elected, I will try to be consistently committed and not lose my spice or vigor.” He had but one promise. “I will do my best and try my very hardest for you if elected president.”

If. Of course he won.

Then while we were in tenth grade at Boulder High School, Jason came up with the life philosophy that would define us all for a few naive and wonderful years. He gave a name to a group of friends: the Concerned Fellows League. The CFL.

It was a world view adopted as an organizing principle by Jason and six others of us who were a tight-knit group in high school—Josh, Noel, Tom, Adam, Bob, Jason, and me. The CFL philosophy essentially was the opposite of what it seemed to express. Jason’s point was that we were not particularly concerned. Worrying was for people who had lost perspective.

Like all of life’s enduring philosophies and religions, this macho idea folds in on itself and becomes a complete contradiction. Don’t look too closely. We were, to a person, worried about all kinds of things, scared as hell and insecure, despite our privilege. This kind of disconnect, as you’ll see, can lead to anxiety, and illness, all of it connected to the way the immune system deals with stress. But outwardly, at the time, we were a combination of the fortunate good students and athletes, the “cool crowd.” Jason carried the torch. In

eleventh grade, he did something remarkable.

As an undersized underclassman, he helped the Boulder High School Panthers on a magical run through the 1984 basketball state play-offs. He was five-nine in high-tops, not the lone star on the team—there were several top-notch seniors—but Jason arguably was the glue, point guard, and mascot, unmatched in intensity.

His high school coach of that championship-game team, a Bobby Knight-like figure named John Raynor, thought of Jason as the kid who couldn't be broken. "He played at times with reckless abandon," Coach Raynor recollected. He'd dive to the floor "and come up lame, and I'd think, Gosh, is this guy going to survive?"

In the stands at the championship game—for bragging rights of the whole darn state—the members of the CFL sat and cheered, our faces painted with the little purple paws of our Boulder Panthers.

Sitting not far away from us, a shrunken shadow holding on for dear life, Joel watched his beloved son.

The game went badly from the start.

Jason, already outmatched in size and strength, labored with a wobbly ankle he'd hurt in the previous game. He scored only four points. The Panthers' two great shooters were shaky. Final score: 52-42.

Just a few months later, on July 13, 1984, Joel Greenstein died. He was fifty.

Jason got the news and came home from work to find his father laid out on a stretcher in the living room, being attended by hospice. He sobbed. Jason somehow didn't

believe this could happen.

Jason would later tell me, “There are two things I hate in this world, hospitals and cancer.”

Some in his family wondered whether the death of his father, his ballast, left Jason so unmoored that he went on the run—physically, spiritually, emotionally. After Joel’s death, Jason ran harder and faster, a racehorse without his trainer. It was a full-tilt lifestyle, world travel—teaching in Japan, traipsing through Latin America—and multiple graduate degrees. Sort of. His fees unpaid, he could never get the law school diploma he’d earned. He became a serial entrepreneur and one-man sales band, selling mobile phone service, Crocs at the mall, juicers to restaurants. He built and ran a ski van company. Each of his ideas was devised with the enthusiasm of a guy drawing up the winning shot.

It would seem, looking back, that he was putting his health at risk, but it was I who had the first brush with illness. After college, I broke down, succumbing to the pressure of inflated, misguided ambitions without any real clue as to my true passions. Insomnia and anxiety came too. I had to find myself to survive. Out of the process I emerged as a person largely content in my own skin and suddenly able to follow my own muse without fear.

By the late nineties, I, healed and happy, and Jason, adventurous and coming up with one business idea crazier than the next, formed a deep, authentic friendship. Enthusiasm bonded us, and old times, along with an ability to simultaneously not take ourselves too seriously while becoming consumed by the righteousness of our respective muses. Then fate arrived for Jason.

He landed into a Phoenix airport under a gorgeous evening sky on May 9, 2010. It was a Sunday night and Jason had spent the weekend at a gambling industry trade show in Biloxi, Mississippi. His latest business entailed selling Chinese-made trinkets—small decorative enamel boxes—to casinos to give as prizes to loyal customers or to instant winners. The company name was Green Man Group.

It was as Jason as Jason could get. He lived in Vegas, the frontier of the gambling man, selling shiny things to fellow dreamers, and traveling the country to visit the growing numbers of casinos to ingratiate himself and explain why his trinkets would send their customer loyalty soaring. He drove a 1982 Chrysler Concorde, which he described to me as “98 percent of Jews’ last cars. Every one of those Jews died or couldn’t drive or sold the car to a Mexican family. And every one of those was owned by a Mexican family except the one that I’m driving.”

Then he squealed his high-pitched laugh, either with self-awareness at the slightly off-color comment or maybe the opposite—he just thought he was funny. And it was nearly impossible not to laugh along with him. This was Jason in his element, the windows down, the air warm, an adventure ahead. “I loved driving in the desert and being in the open road.”

He’d stopped in Phoenix on his way home to Vegas because he had some business in Arizona. When he landed, late on the ninth, the airline had misplaced his luggage, which included his sample kits of trinkets. He had to stand there, waiting. He felt a tickle in his throat. He thought, *Sometimes I get allergies in the desert, or I’ve got strep throat or a*

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