



THE  
EMPEROR  
OF ALL  
MALADIES



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A BIOGRAPHY OF CANCER

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SIDDHARTHA  
MUKHERJEE

"A compulsively readable, surprisingly uplifting, and vivid tale. Thrilling."

—O, THE OPRAH MAGAZINE

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“[An] **ESSENTIAL** piece of medical journalism.” —**TIME**

“A meticulously researched, panoramic history . . . What makes Mukherjee’s narrative so remarkable is that he imbues decades of painstaking laboratory investigation with the suspense of a mystery novel and urgency of a thriller.” —**THE BOSTON GLOBE**

“**RIVETING AND POWERFUL.**” —**SAN FRANCISCO CHRONICLE**

“**REMARKABLE . . .** The reader devours this fascinating book . . . Mukherjee is a clear and determined writer. . . . An unusually humble, insightful book.” —**LOS ANGELES TIMES**

“**EXTRAORDINARY . . .** So often physician writers attempt the delicacy of using their patients as a mirror to their own humanity. Mukherjee does the opposite. His book is not built to show us the good doctor struggling with tough decisions, but ourselves.”  
—**JOHN FREEMAN, NPR**

# The Emperor of All Maladies

A Biography of Cancer

Siddhartha Mukherjee

*The Emperor of All Maladies* is a magnificent, profoundly humane “biography” of cancer—from its first documented appearances thousands of years ago through the epic battles in the twentieth century to cure, control, and conquer it to a radical new understanding of its essence. Physician, researcher, and award-winning science writer, Siddhartha Mukherjee examines cancer with a cellular biologist’s precision, a historian’s perspective, and a biographer’s passion. The result is an astonishingly lucid and eloquent chronicle of a disease humans have lived with—and perished from—for more than five thousand years.

The story of cancer is a story of human ingenuity, resilience, and perseverance, but also of hubris, paternalism, and misperception. Mukherjee recounts centuries of discoveries, setbacks, victories, and deaths, told through the eyes of his predecessors and peers, training their wits against an infinitely resourceful adversary that, just three decades ago, was thought to be easily vanquished in an all-out “war against cancer.” The book reads like a literary thriller with cancer as the protagonist.

From the Persian Queen Atossa, whose Greek slave may have cut off her diseased breast, to the nineteenth-century recipients of primitive radiation and chemotherapy to Mukherjee’s own leukemia patient, Carla, *The Emperor of All Maladies* is about the people who have soldiered through fiercely demanding regimens in order to survive—and to increase our understanding of this iconic disease.

Riveting, urgent, and surprising, *The Emperor of All Maladies* provides a fascinating glimpse into the future of cancer treatments. It is an illuminating book that provides hope and clarity to those seeking to demystify cancer.

*Illness is the night-side of life, a more onerous citizenship. Everyone who is born holds dual citizenship, in the kingdom of the well and in the kingdom of the sick. Although we all prefer to use only the good passport, sooner or later each of us is obliged, at least for a spell, to identify ourselves as citizens of that other place.*

—Susan Sontag

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*In 2010, about six hundred thousand Americans, and more than 7 million humans around the world, will die of cancer. In the United States, one in three women and one in two men will develop cancer during their lifetime. A quarter of all American deaths, and about 15 percent of all deaths worldwide, will be attributed to cancer. In some nations, cancer will surpass heart disease to become the most common cause of death.*

## Author's Note

This book is a history of cancer. It is a chronicle of an ancient disease—once a clandestine, “whispered-about” illness—that has metamorphosed into a lethal shape-shifting entity imbued with such penetrating metaphorical, medical, scientific, and political potency that cancer is often described as the defining plague of our generation. This book is a “biography” in the truest sense of the word—an attempt to enter the *mind* of this immortal illness, to understand its personality, to demystify its behavior. But my ultimate aim is to raise a question beyond biography: Is cancer’s end conceivable in the future? Is it possible to eradicate this disease from our bodies and societies forever?

Cancer is not one disease but many diseases. We call them all “cancer” because they share a fundamental feature: the abnormal growth of cells. And beyond the biological commonality, there are deep cultural and political themes that run through the various incarnations of cancer to justify a unifying narrative. It is not possible to consider the stories of every variant of cancer, but I have attempted to highlight the large themes that run through this 4,000-year history.

The project, evidently vast, began as a more modest enterprise. In the summer of 2003, having completed a residency in medicine and graduate work in cancer immunology, I began advanced training in cancer medicine (medical oncology) at the Dana-Farber Cancer Institute and Massachusetts General Hospital in Boston. I had initially envisioned writing a journal of that year—a view-from-the-trenches of cancer treatment. But that quest soon grew into a larger exploratory journey that carried me into the depths not only of science and medicine, but of culture, history, literature, and politics, into cancer’s past and into its future.

Two characters stand at the epicenter of this story—both contemporaries, both idealists, both children of the boom in postwar science and technology in America, and both caught in the swirl of a hypnotic, obsessive quest to launch a national “War on Cancer.” The first is Sidney Farber,



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the father of modern chemotherapy, who accidentally discovers a powerful anti-cancer chemical in a vitamin analogue and begins to dream of a universal cure for cancer. The second is Mary Lasker, the Manhattan socialite of legendary social and political energy, who joins Farber in his decades-long journey. But Lasker and Farber only exemplify the grit, imagination, inventiveness, and optimism of generations of men and women who have waged a battle against cancer for four thousand years. In a sense, this is a military history—one in which the adversary is formless, timeless, and pervasive. Here, too, there are victories and losses, campaigns upon campaigns, heroes and hubris, survival and resilience—and inevitably, the wounded, the condemned, the forgotten, the dead. In the end, cancer truly emerges, as a nineteenth-century surgeon once wrote in a book's frontispiece, as “the emperor of all maladies, the king of terrors.”

A disclaimer: in science and medicine, where the primacy of a discovery carries supreme weight, the mantle of inventor or discoverer is assigned by a community of scientists and researchers. Although there are many stories of discovery and invention in this book, none of these establishes any legal claims of primacy.

This work rests heavily on the shoulders of other books, studies, journal articles, memoirs, and interviews. It rests also on the vast contributions of individuals, libraries, collections, archives, and papers acknowledged at the end of the book.

One acknowledgment, though, cannot be left to the end. This book is not just a journey into the past of cancer, but also a personal journey of my coming-of-age as an oncologist. That second journey would be impossible without patients, who, above and beyond all contributors, continued to teach and inspire me as I wrote. It is in their debt that I stand forever.

This debt comes with dues. The stories in this book present an important challenge in maintaining the privacy and dignity of these patients. In cases where the knowledge of the illness was already public (as with prior interviews or articles) I have used real names. In cases where there was no prior public knowledge, or when interviewees requested privacy, I have used a false name, and deliberately confounded dates and identities to make it difficult to track them. However, these are real patients and real encounters. I urge all my readers to respect their identities and boundaries.



# Prologue

*Diseases desperate grown  
By desperate appliance are relieved,  
Or not at all.*

—William Shakespeare,  
*Hamlet*

*Cancer begins and ends with people. In the midst of  
scientific abstraction, it is sometimes possible to forget  
this one basic fact. . . . Doctors treat diseases, but they also  
treat people, and this precondition of their professional  
existence sometimes pulls them in two directions at once.*

—June Goodfield

On the morning of May 19, 2004, Carla Reed, a thirty-year-old kindergarten teacher from Ipswich, Massachusetts, a mother of three young children, woke up in bed with a headache. “Not just any headache,” she would recall later, “but a sort of numbness in my head. The kind of numbness that instantly tells you that something is terribly wrong.”

Something had been terribly wrong for nearly a month. Late in April, Carla had discovered a few bruises on her back. They had suddenly appeared one morning, like strange stigmata, then grown and vanished over the next month, leaving large map-shaped marks on her back. Almost indiscernibly, her gums had begun to turn white. By early May, Carla, a vivacious, energetic woman accustomed to spending hours in the classroom chasing down five- and six-year-olds, could barely walk up a flight of stairs. Some mornings, exhausted and unable to stand up, she crawled down the hallways of her house on all fours to get from one room to another. She slept fitfully for twelve or fourteen hours a day, then woke up

feeling so overwhelmingly tired that she needed to haul herself back to the couch again to sleep.

Carla and her husband saw a general physician and a nurse twice during those four weeks, but she returned each time with no tests and without a diagnosis. Ghostly pains appeared and disappeared in her bones. The doctor fumbled about for some explanation. Perhaps it was a migraine, she suggested, and asked Carla to try some aspirin. The aspirin simply worsened the bleeding in Carla's white gums.

Outgoing, gregarious, and ebullient, Carla was more puzzled than worried about her waxing and waning illness. She had never been seriously ill in her life. The hospital was an abstract place for her; she had never met or consulted a medical specialist, let alone an oncologist. She imagined and concocted various causes to explain her symptoms—overwork, depression, dyspepsia, neuroses, insomnia. But in the end, something visceral arose inside her—a seventh sense—that told Carla something acute and catastrophic was brewing within her body.

On the afternoon of May 19, Carla dropped her three children with a neighbor and drove herself back to the clinic, demanding to have some blood tests. Her doctor ordered a routine test to check her blood counts. As the technician drew a tube of blood from her vein, he looked closely at the blood's color, obviously intrigued. Watery, pale, and dilute, the liquid that welled out of Carla's veins hardly resembled blood.

Carla waited the rest of the day without any news. At a fish market the next morning, she received a call.

"We need to draw some blood again," the nurse from the clinic said.

"When should I come?" Carla asked, planning her hectic day. She remembers looking up at the clock on the wall. A half-pound steak of salmon was warming in her shopping basket, threatening to spoil if she left it out too long.

In the end, commonplace particulars make up Carla's memories of illness: the clock, the car pool, the children, a tube of pale blood, a missed shower, the fish in the sun, the tightening tone of a voice on the phone. Carla cannot recall much of what the nurse said, only a general sense of urgency. "Come now," she thinks the nurse said. "Come now."



I heard about Carla's case at seven o'clock on the morning of May 21, on a train speeding between Kendall Square and Charles Street in Boston. The

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sentence that flickered on my beeper had the staccato and deadpan force of a true medical emergency: *Carla Reed/New patient with leukemia/14<sup>th</sup> Floor/Please see as soon as you arrive*. As the train shot out of a long, dark tunnel, the glass towers of the Massachusetts General Hospital suddenly loomed into view, and I could see the windows of the fourteenth floor rooms.

Carla, I guessed, was sitting in one of those rooms by herself, terrifyingly alone. Outside the room, a buzz of frantic activity had probably begun. Tubes of blood were shuttling between the ward and the laboratories on the second floor. Nurses were moving about with specimens, interns collecting data for morning reports, alarms beeping, pages being sent out. Somewhere in the depths of the hospital, a microscope was flickering on, with the cells in Carla's blood coming into focus under its lens.

I can feel relatively certain about all of this because the arrival of a patient with acute leukemia still sends a shiver down the hospital's spine—all the way from the cancer wards on its upper floors to the clinical laboratories buried deep in the basement. Leukemia is cancer of the white blood cells—cancer in one of its most explosive, violent incarnations. As one nurse on the wards often liked to remind her patients, with this disease “even a paper cut is an emergency.”

For an oncologist in training, too, leukemia represents a special incarnation of cancer. Its pace, its acuity, its breathtaking, inexorable arc of growth forces rapid, often drastic decisions; it is terrifying to experience, terrifying to observe, and terrifying to treat. The body invaded by leukemia is pushed to its brittle physiological limit—every system, heart, lung, blood, working at the knife-edge of its performance. The nurses filled me in on the gaps in the story. Blood tests performed by Carla's doctor had revealed that her red cell count was critically low, less than a third of normal. Instead of normal white cells, her blood was packed with millions of large, malignant white cells—*blasts*, in the vocabulary of cancer. Her doctor, having finally stumbled upon the real diagnosis, had sent her to the Massachusetts General Hospital.



In the long, bare hall outside Carla's room, in the antiseptic gleam of the floor just mopped with diluted bleach, I ran through the list of tests that would be needed on her blood and mentally rehearsed the conversation I would have with her. There was, I noted ruefully, something rehearsed and

robotic even about my sympathy. This was the tenth month of my “fellowship” in oncology—a two-year immersive medical program to train cancer specialists—and I felt as if I had gravitated to my lowest point. In those ten indescribably poignant and difficult months, dozens of patients in my care had died. I felt I was slowly becoming inured to the deaths and the desolation—vaccinated against the constant emotional brunt.

There were seven such cancer fellows at this hospital. On paper, we seemed like a formidable force: graduates of five medical schools and four teaching hospitals, sixty-six years of medical and scientific training, and twelve postgraduate degrees among us. But none of those years or degrees could possibly have prepared us for this training program. Medical school, internship, and residency had been physically and emotionally grueling, but the first months of the fellowship flicked away those memories as if all of that had been child’s play, the kindergarten of medical training.

Cancer was an all-consuming presence in our lives. It invaded our imaginations; it occupied our memories; it infiltrated every conversation, every thought. And if we, as physicians, found ourselves immersed in cancer, then our patients found their lives virtually obliterated by the disease. In Aleksandr Solzhenitsyn’s novel *Cancer Ward*, Pavel Nikolayevich Rusanov, a youthful Russian in his midforties, discovers that he has a tumor in his neck and is immediately whisked away into a cancer ward in some nameless hospital in the frigid north. The diagnosis of cancer—not the disease, but the mere stigma of its presence—becomes a death sentence for Rusanov. The illness strips him of his identity. It dresses him in a patient’s smock (a tragically cruel costume, no less blighting than a prisoner’s jumpsuit) and assumes absolute control of his actions. To be diagnosed with cancer, Rusanov discovers, is to enter a borderless medical gulag, a state even more invasive and paralyzing than the one that he has left behind. (Solzhenitsyn may have intended his absurdly totalitarian cancer hospital to parallel the absurdly totalitarian state outside it, yet when I once asked a woman with invasive cervical cancer about the parallel, she said sardonically, “Unfortunately, I did not need any metaphors to read the book. The cancer ward *was* my confining state, my prison.”)

As a doctor learning to tend cancer patients, I had only a partial glimpse of this confinement. But even skirting its periphery, I could still feel its power—the dense, insistent gravitational tug that pulls everything and everyone into the orbit of cancer. A colleague, freshly out of his fellowship, pulled me aside on my first week to offer some advice. “It’s called an

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immersive training program,” he said, lowering his voice. “But by immersive, they really mean drowning. Don’t let it work its way into everything you do. Have a life outside the hospital. You’ll need it, or you’ll get swallowed.”

But it was impossible not to be swallowed. In the parking lot of the hospital, a chilly, concrete box lit by neon floodlights, I spent the end of every evening after rounds in stunned incoherence, the car radio crackling vacantly in the background, as I compulsively tried to reconstruct the events of the day. The stories of my patients consumed me, and the decisions that I made haunted me. *Was it worthwhile continuing yet another round of chemotherapy on a sixty-six-year-old pharmacist with lung cancer who had failed all other drugs? Was is better to try a tested and potent combination of drugs on a twenty-six-year-old woman with Hodgkin’s disease and risk losing her fertility, or to choose a more experimental combination that might spare it? Should a Spanish-speaking mother of three with colon cancer be enrolled in a new clinical trial when she can barely read the formal and inscrutable language of the consent forms?*

Immersed in the day-to-day management of cancer, I could only see the lives and fates of my patients played out in color-saturated detail, like a television with the contrast turned too high. I could not pan back from the screen. I knew instinctively that these experiences were part of a much larger battle against cancer, but its contours lay far outside my reach. I had a novice’s hunger for history, but also a novice’s inability to envision it.



But as I emerged from the strange desolation of those two fellowship years, the questions about the larger story of cancer emerged with urgency: How old is cancer? What are the roots of our battle against this disease? Or, as patients often asked me: Where are we in the “war” on cancer? How did we get here? Is there an end? Can this war even be won?

This book grew out of the attempt to answer these questions. I delved into the history of cancer to give shape to the shape-shifting illness that I was confronting. I used the past to explain the present. The isolation and rage of a thirty-six-year-old woman with stage III breast cancer had ancient echoes in Atossa, the Persian queen who swaddled her diseased breast in cloth to hide it and then, in a fit of nihilistic and prescient fury, possibly had a slave cut it off with a knife. A patient’s desire to amputate her stomach, ridden with cancer—“sparing nothing,” as she put it to me—

carried the memory of the perfection-obsessed nineteenth-century surgeon William Halsted, who had chiseled away at cancer with larger and more disfiguring surgeries, all in the hopes that cutting more would mean curing more.

Roiling underneath these medical, cultural, and metaphorical interceptions of cancer over the centuries was the biological understanding of the illness—an understanding that had morphed, often radically, from decade to decade. Cancer, we now know, is a disease caused by the uncontrolled growth of a single cell. This growth is unleashed by mutations—changes in DNA that specifically affect genes that incite unlimited cell growth. In a normal cell, powerful genetic circuits regulate cell division and cell death. In a cancer cell, these circuits have been broken, unleashing a cell that cannot stop growing.

That this seemingly simple mechanism—cell growth without barriers—can lie at the heart of this grotesque and multifaceted illness is a testament to the unfathomable power of cell growth. Cell division allows us as organisms to grow, to adapt, to recover, to repair—to live. And distorted and unleashed, it allows cancer cells to grow, to flourish, to adapt, to recover, and to repair—to live at the cost of our living. Cancer cells can grow faster, adapt better. They are more perfect versions of ourselves.

The secret to battling cancer, then, is to find means to prevent these mutations from occurring in susceptible cells, or to find means to eliminate the mutated cells without compromising normal growth. The conciseness of that statement belies the enormity of the task. Malignant growth and normal growth are so genetically intertwined that unbraiding the two might be one of the most significant scientific challenges faced by our species. Cancer is built into our genomes: the genes that unmoor normal cell division are not foreign to our bodies, but rather mutated, distorted versions of the very genes that perform vital cellular functions. And cancer is imprinted in our society: as we extend our life span as a species, we inevitably unleash malignant growth (mutations in cancer genes accumulate with aging; cancer is thus intrinsically related to age). If we seek immortality, then so, too, in a rather perverse sense, does the cancer cell.

How, precisely, a future generation might learn to separate the entwined strands of normal growth from malignant growth remains a mystery. (“The universe,” the twentieth-century biologist J. B. S. Haldane liked to say, “is not only queerer than we suppose, but queerer than we *can* suppose”—and so is the trajectory of science.) But this much is certain: the

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story, however it plays out, will contain indelible kernels of the past. It will be a story of inventiveness, resilience, and perseverance against what one writer called the most “relentless and insidious enemy” among human diseases. But it will also be a story of hubris, arrogance, paternalism, misperception, false hope, and hype, all leveraged against an illness that was just three decades ago widely touted as being “curable” within a few years.



In the bare hospital room ventilated by sterilized air, Carla was fighting her own war on cancer. When I arrived, she was sitting with peculiar calm on her bed, a schoolteacher jotting notes. (“But what notes?” she would later recall. “I just wrote and rewrote the same thoughts.”) Her mother, red-eyed and tearful, just off an overnight flight, burst into the room and then sat silently in a chair by the window, rocking forcefully. The din of activity around Carla had become almost a blur: nurses shuttling fluids in and out, interns donning masks and gowns, antibiotics being hung on IV poles to be dripped into her veins.

I explained the situation as best I could. Her day ahead would be full of tests, a hurtle from one lab to another. I would draw a bone marrow sample. More tests would be run by pathologists. But the preliminary tests suggested that Carla had acute lymphoblastic leukemia. It is one of the most common forms of cancer in children, but rare in adults. And it is—I paused here for emphasis, lifting my eyes up—often curable.

*Curable.* Carla nodded at that word, her eyes sharpening. Inevitable questions hung in the room: How curable? What were the chances that she would survive? How long would the treatment take? I laid out the odds. Once the diagnosis had been confirmed, chemotherapy would begin immediately and last more than one year. Her chances of being cured were about 30 percent, a little less than one in three.

We spoke for an hour, perhaps longer. It was now nine thirty in the morning. The city below us had stirred fully awake. The door shut behind me as I left, and a whoosh of air blew me outward and sealed Carla in.



PART ONE

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“OF BLACKE CHOLOR,  
WITHOUT BOYLING”

*In solving a problem of this sort, the grand thing is to be able to reason backwards. That is a very useful accomplishment, and a very easy one, but people do not practice it much.*

—Sherlock Holmes, in Sir Arthur Conan Doyle’s  
*A Study in Scarlet*

## “A suppuration of blood”

*Physicians of the Utmost Fame  
Were called at once; but when they came  
They answered, as they took their Fees,  
“There is no Cure for this Disease.”*

—Hilaire Belloc

*Its palliation is a daily task, its cure a fervent hope.*

—William Castle,  
describing leukemia in 1950

In a damp fourteen-by-twenty-foot laboratory in Boston on a December morning in 1947, a man named Sidney Farber waited impatiently for the arrival of a parcel from New York. The “laboratory” was little more than a chemist’s closet, a poorly ventilated room buried in a half-basement of the Children’s Hospital, almost thrust into its back alley. A few hundred feet away, the hospital’s medical wards were slowly thrumming to work. Children in white smocks moved restlessly on small wrought-iron cots. Doctors and nurses shuttled busily between the rooms, checking charts, writing orders, and dispensing medicines. But Farber’s lab was listless and empty, a bare warren of chemicals and glass jars connected to the main hospital through a series of icy corridors. The sharp stench of embalming formalin wafted through the air. There were no patients in the rooms here, just the bodies and tissues of patients brought down through the tunnels for autopsies and examinations. Farber was a pathologist. His job involved dissecting specimens, performing autopsies, identifying cells, and diagnosing diseases, but never treating patients.

Farber’s specialty was pediatric pathology, the study of children’s diseases. He had spent nearly twenty years in these subterranean rooms star-

ing obsessively down his microscope and climbing through the academic ranks to become chief of pathology at Children's. But for Farber, pathology was becoming a disjunctive form of medicine, a discipline more preoccupied with the dead than with the living. Farber now felt impatient watching illness from its sidelines, never touching or treating a live patient. He was tired of tissues and cells. He felt trapped, embalmed in his own glassy cabinet.

And so, Farber had decided to make a drastic professional switch. Instead of squinting at inert specimens under his lens, he would try to leap into the life of the clinics upstairs—from the microscopic world that he knew so well into the magnified real world of patients and illnesses. He would try to use the knowledge he had gathered from his pathological specimens to devise new therapeutic interventions. The parcel from New York contained a few vials of a yellow crystalline chemical named aminopterin. It had been shipped to his laboratory in Boston on the slim hope that it might halt the growth of leukemia in children.



Had Farber asked any of the pediatricians circulating in the wards above him about the likelihood of developing an antileukemic drug, they would have advised him not to bother trying. Childhood leukemia had fascinated, confused, and frustrated doctors for more than a century. The disease had been analyzed, classified, subclassified, and subdivided meticulously; in the musty, leatherbound books on the library shelves at Children's—Anderson's *Pathology* or Boyd's *Pathology of Internal Diseases*—page upon page was plastered with images of leukemia cells and appended with elaborate taxonomies to describe the cells. Yet all this knowledge only amplified the sense of medical helplessness. The disease had turned into an object of empty fascination—a wax-museum doll—studied and photographed in exquisite detail but without any therapeutic or practical advances. “It gave physicians plenty to wrangle over at medical meetings,” an oncologist recalled, “but it did not help their patients at all.” A patient with acute leukemia was brought to the hospital in a flurry of excitement, discussed on medical rounds with professorial grandiosity, and then, as a medical magazine drily noted, “diagnosed, transfused—and sent home to die.”

The study of leukemia had been mired in confusion and despair ever since its discovery. On March 19, 1845, a Scottish physician, John Bennett,

had described an unusual case, a twenty-eight-year-old slate-layer with a mysterious swelling in his spleen. "He is of dark complexion," Bennett wrote of his patient, "usually healthy and temperate; [he] states that twenty months ago, he was affected with great listlessness on exertion, which has continued to this time. In June last he noticed a tumor in the left side of his abdomen which has gradually increased in size till four months since, when it became stationary."

The slate-layer's tumor might have reached its final, stationary point, but his constitutional troubles only accelerated. Over the next few weeks, Bennett's patient spiraled from symptom to symptom—fevers, flashes of bleeding, sudden fits of abdominal pain—gradually at first, then on a tighter, faster arc, careening from one bout to another. Soon the slate-layer was on the verge of death with more swollen tumors sprouting in his armpits, his groin, and his neck. He was treated with the customary leeches and purging, but to no avail. At the autopsy a few weeks later, Bennett was convinced that he had found the reason behind the symptoms. His patient's blood was chock-full of white blood cells. (White blood cells, the principal constituent of pus, typically signal the response to an infection, and Bennett reasoned that the slate-layer had succumbed to one.) "The following case seems to me particularly valuable," he wrote self-assuredly, "as it will serve to demonstrate the existence of true pus, formed universally within the vascular system."\*

It would have been a perfectly satisfactory explanation except that Bennett could not find a source for the pus. During the necropsy, he pored carefully through the body, combing the tissues and organs for signs of an abscess or wound. But no other stigmata of infection were to be found. The blood had apparently spoiled—suppurated—of its own will, combusted spontaneously into true pus. "A suppuration of blood," Bennett called his case. And he left it at that.

Bennett was wrong, of course, about his spontaneous "suppuration" of blood. A little over four months after Bennett had described the slater's illness, a twenty-four-year-old German researcher, Rudolf Virchow, independently published a case report with striking similarities to Bennett's case. Virchow's patient was a cook in her midfifties. White cells had explo-

\*Although the link between microorganisms and infection was yet to be established, the connection between pus—purulence—and sepsis, fever, and death, often arising from an abscess or wound, was well known to Bennett.

sively overgrown her blood, forming dense and pulpy pools in her spleen. At her autopsy, pathologists had likely not even needed a microscope to distinguish the thick, milky layer of white cells floating above the red.

Virchow, who knew of Bennett's case, couldn't bring himself to believe Bennett's theory. Blood, Virchow argued, had no reason to transform impetuously into anything. Moreover, the unusual symptoms bothered him: What of the massively enlarged spleen? Or the absence of any wound or source of pus in the body? Virchow began to wonder if the blood itself was abnormal. Unable to find a unifying explanation for it, and seeking a name for this condition, Virchow ultimately settled for *weisses Blut*—white blood—no more than a literal description of the millions of white cells he had seen under his microscope. In 1847, he changed the name to the more academic-sounding “leukemia”—from *leukos*, the Greek word for “white.”



Renaming the disease—from the florid “suppuration of blood” to the flat *weisses Blut*—hardly seems like an act of scientific genius, but it had a profound impact on the understanding of leukemia. An illness, at the moment of its discovery, is a fragile idea, a hothouse flower—deeply, disproportionately influenced by names and classifications. (More than a century later, in the early 1980s, another change in name—from *gay related immune disease* (GRID) to *acquired immuno deficiency syndrome* (AIDS)—would signal an epic shift in the understanding of that disease.\*) Like Bennett, Virchow didn't understand leukemia. But unlike Bennett, he didn't pretend to understand it. His insight lay entirely in the negative. By wiping the slate clean of all preconceptions, he cleared the field for thought.

The humility of the name (and the underlying humility about his understanding of cause) epitomized Virchow's approach to medicine. As a young professor at the University of Würzburg, Virchow's work soon extended far beyond naming leukemia. A pathologist by training, he launched a project that would occupy him for his life: describing human diseases in simple cellular terms.

\* The identification of HIV as the pathogen, and the rapid spread of the virus across the globe, soon laid to rest the initially observed—and culturally loaded—“predeliction” for gay men.

It was a project born of frustration. Virchow entered medicine in the early 1840s, when nearly every disease was attributed to the workings of some invisible force: miasmas, neuroses, bad humors, and hysterias. Perplexed by what he couldn't see, Virchow turned with revolutionary zeal to what he could see: cells under the microscope. In 1838, Matthias Schleiden, a botanist, and Theodor Schwann, a physiologist, both working in Germany, had claimed that all living organisms were built out of fundamental building blocks called cells. Borrowing and extending this idea, Virchow set out to create a "cellular theory" of human biology, basing it on two fundamental tenets. First, that human bodies (like the bodies of all animals and plants) were made up of cells. Second, that cells only arose from other cells—*omnis cellula e cellula*, as he put it.

The two tenets might have seemed simplistic, but they allowed Virchow to propose a crucially important hypothesis about the nature of human growth. If cells only arose from other cells, then growth could occur in only two ways: either by increasing cell numbers or by increasing cell size. Virchow called these two modes hyperplasia and hypertrophy. In hypertrophy, the *number* of cells did not change; instead, each individual cell merely grew in size—like a balloon being blown up. *Hyperplasia*, in contrast, was growth by virtue of cells increasing in *number*. Every growing human tissue could be described in terms of hypertrophy and hyperplasia. In adult animals, fat and muscle usually grow by hypertrophy. In contrast, the liver, blood, the gut, and the skin all grow through hyperplasia—cells becoming cells becoming more cells, *omnis cellula e cellula e cellula*.

That explanation was persuasive, and it provoked a new understanding not just of normal growth, but of pathological growth as well. Like normal growth, pathological growth could also be achieved through hypertrophy and hyperplasia. When the heart muscle is forced to push against a blocked aortic outlet, it often adapts by making every muscle cell bigger to generate more force, eventually resulting in a heart so overgrown that it may be unable to function normally—pathological hypertrophy.

Conversely, and importantly for this story, Virchow soon stumbled upon the quintessential disease of pathological hyperplasia—cancer. Looking at cancerous growths through his microscope, Virchow discovered an uncontrolled growth of cells—hyperplasia in its extreme form. As Virchow examined the architecture of cancers, the growth often seemed to have acquired a life of its own, as if the cells had become possessed by a new and mysterious drive to grow. This was not just ordinary growth,

but growth redefined, growth in a new form. Presciently (although oblivious of the mechanism) Virchow called it *neoplasia*—novel, inexplicable, distorted growth, a word that would ring through the history of cancer.\*

By the time Virchow died in 1902, a new theory of cancer had slowly coalesced out of all these observations. Cancer was a disease of pathological hyperplasia in which cells acquired an autonomous will to divide. This aberrant, uncontrolled cell division created masses of tissue (tumors) that invaded organs and destroyed normal tissues. These tumors could also spread from one site to another, causing outcroppings of the disease—called metastases—in distant sites, such as the bones, the brain, or the lungs. Cancer came in diverse forms—breast, stomach, skin, and cervical cancer, leukemias and lymphomas. But all these diseases were deeply connected at the cellular level. In every case, cells had all acquired the same characteristic: uncontrollable pathological cell division.

With this understanding, pathologists who studied leukemia in the late 1880s now circled back to Virchow's work. Leukemia, then, was not a supuration of blood, but *neoplasia* of blood. Bennett's earlier fantasy had germinated an entire field of fantasies among scientists, who had gone searching (and dutifully found) all sorts of invisible parasites and bacteria bursting out of leukemia cells. But once pathologists stopped looking for infectious causes and refocused their lenses on the disease, they discovered the obvious analogies between leukemia cells and cells of other forms of cancer. Leukemia was a malignant proliferation of white cells in the blood. It was cancer in a molten, liquid form.

With that seminal observation, the study of leukemias suddenly found clarity and spurted forward. By the early 1900s, it was clear that the disease came in several forms. It could be chronic and indolent, slowly choking the bone marrow and spleen, as in Virchow's original case (later termed chronic leukemia). Or it could be acute and violent, almost a different illness in its personality, with flashes of fever, paroxysmal fits of bleeding, and a dazzlingly rapid overgrowth of cells—as in Bennett's patient.

This second version of the disease, called acute leukemia, came in two further subtypes, based on the type of cancer cell involved. Normal white cells in the blood can be broadly divided into two types of cells—myeloid cells or lymphoid cells. Acute myeloid leukemia (AML) was a cancer of the

\*Virchow did not coin the word, although he offered a comprehensive description of *neoplasia*.



*myeloid* cells. Acute lymphoblastic leukemia (ALL) was cancer of immature *lymphoid* cells. (Cancers of more mature lymphoid cells are called lymphomas.)

In children, leukemia was most commonly ALL—lymphoblastic leukemia—and was almost always swiftly lethal. In 1860, a student of Virchow's, Michael Anton Biermer, described the first known case of this form of childhood leukemia. Maria Speyer, an energetic, vivacious, and playful five-year-old daughter of a Würzburg carpenter, was initially seen at the clinic because she had become lethargic in school and developed bloody bruises on her skin. The next morning, she developed a stiff neck and a fever, precipitating a call to Biermer for a home visit. That night, Biermer drew a drop of blood from Maria's veins, looked at the smear using a candlelit bedside microscope, and found millions of leukemia cells in the blood. Maria slept fitfully late into the evening. Late the next afternoon, as Biermer was excitedly showing his colleagues the specimens of “*exquisit Fall von Leukämie*” (an exquisite case of leukemia), Maria vomited bright red blood and lapsed into a coma. By the time Biermer returned to her house that evening, the child had been dead for several hours. From its first symptom to diagnosis to death, her galloping, relentless illness had lasted no more than three days.



Although nowhere as aggressive as Maria Speyer's leukemia, Carla's illness was astonishing in its own right. Adults, on average, have about five thousand white blood cells circulating per microliter of blood. Carla's blood contained ninety thousand cells per microliter—nearly twentyfold the normal level. Ninety-five percent of these cells were blasts—malignant lymphoid cells produced at a frenetic pace but unable to mature into fully developed lymphocytes. In acute lymphoblastic leukemia, as in some other cancers, the overproduction of cancer cells is combined with a mysterious arrest in the normal maturation of cells. Lymphoid cells are thus produced in vast excess, but, unable to mature, they cannot fulfill their normal function in fighting microbes. Carla had immunological poverty in the face of plenty.

White blood cells are produced in the bone marrow. Carla's bone marrow biopsy, which I saw under the microscope the morning after I first met her, was deeply abnormal. Although superficially amorphous, bone marrow is a highly organized tissue—an organ, in truth—that generates blood in adults. Typically, bone marrow biopsies contain spicules of bone

and, within these spicules, islands of growing blood cells—nurseries for the genesis of new blood. In Carla's marrow, this organization had been fully destroyed. Sheet upon sheet of malignant blasts packed the marrow space, obliterating all anatomy and architecture, leaving no space for any production of blood.

Carla was at the edge of a physiological abyss. Her red cell count had dipped so low that her blood was unable to carry its full supply of oxygen (her headaches, in retrospect, were the first sign of oxygen deprivation). Her platelets, the cells responsible for clotting blood, had collapsed to nearly zero, causing her bruises.

Her treatment would require extraordinary finesse. She would need chemotherapy to kill her leukemia, but the chemotherapy would collaterally decimate any remnant normal blood cells. We would push her deeper into the abyss to try to rescue her. For Carla, the only way out would be the way through.



Sidney Farber was born in Buffalo, New York, in 1903, one year after Virchow's death in Berlin. His father, Simon Farber, a former bargeman in Poland, had immigrated to America in the late nineteenth century and worked in an insurance agency. The family lived in modest circumstances at the eastern edge of town, in a tight-knit, insular, and often economically precarious Jewish community of shop owners, factory workers, bookkeepers, and peddlers. Pushed relentlessly to succeed, the Farber children were held to high academic standards. Yiddish was spoken upstairs, but only German and English were allowed downstairs. The elder Farber often brought home textbooks and scattered them across the dinner table, expecting each child to select and master one book, then provide a detailed report for him.

Sidney, the third of fourteen children, thrived in this environment of high aspirations. He studied both biology and philosophy in college and graduated from the University of Buffalo in 1923, playing the violin at music halls to support his college education. Fluent in German, he trained in medicine at Heidelberg and Freiburg, then, having excelled in Germany, found a spot as a second-year medical student at Harvard Medical School in Boston. (The circular journey from New York to Boston via Heidelberg was not unusual. In the mid-1920s, Jewish students often found it impossible to secure medical-school spots in America—often

succeeding in European, even German, medical schools before returning to study medicine in their native country.) Farber thus arrived at Harvard as an outsider. His colleagues found him arrogant and insufferable, but, he too, relearning lessons that he had already learned, seemed to be suffering through it all. He was formal, precise, and meticulous, starched in his appearance and his mannerisms and commanding in presence. He was promptly nicknamed Four-Button Sid for his propensity for wearing formal suits to his classes.

Farber completed his advanced training in pathology in the late 1920s and became the first full-time pathologist at the Children's Hospital in Boston. He wrote a marvelous study on the classification of children's tumors and a textbook, *The Postmortem Examination*, widely considered a classic in the field. By the mid-1930s, he was firmly ensconced in the back alleys of the hospital as a preeminent pathologist—a "doctor of the dead."

Yet the hunger to treat patients still drove Farber. And sitting in his basement laboratory in the summer of 1947, Farber had a single inspired idea: he chose, among all cancers, to focus his attention on one of its oddest and most hopeless variants—childhood leukemia. To understand cancer as a whole, he reasoned, you needed to start at the bottom of its complexity, in *its* basement. And despite its many idiosyncrasies, leukemia possessed a singularly attractive feature: it could be measured.

Science begins with counting. To understand a phenomenon, a scientist must first describe it; to describe it objectively, he must first measure it. If cancer medicine was to be transformed into a rigorous science, then cancer would need to be counted somehow—measured in some reliable, reproducible way.

In this, leukemia was different from nearly every other type of cancer. In a world before CT scans and MRIs, quantifying the change in size of an internal solid tumor in the lung or the breast was virtually impossible without surgery: you could not measure what you could not see. But leukemia, floating freely in the blood, could be measured as easily as blood cells—by drawing a sample of blood or bone marrow and looking at it under a microscope.

If leukemia could be counted, Farber reasoned, then any intervention—a chemical sent circulating through the blood, say—could be evaluated for its potency in living patients. He could watch cells grow or die in the blood and use that to measure the success or failure of a drug. He could perform an "experiment" on cancer.

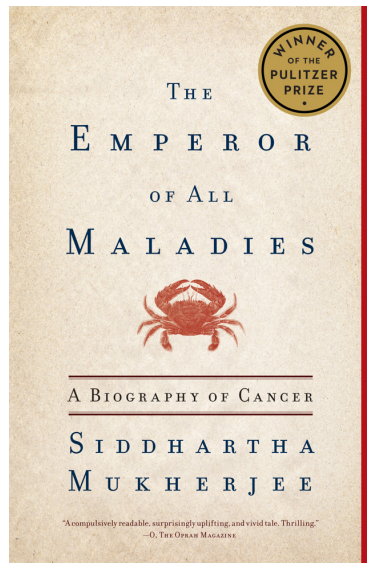
The idea mesmerized Farber. In the 1940s and '50s, young biologists were galvanized by the idea of using simple models to understand complex phenomena. Complexity was best understood by building from the ground up. Single-celled organisms such as bacteria would reveal the workings of massive, multicellular animals such as humans. What is true for *E. coli* [a microscopic bacterium], the French biochemist Jacques Monod would grandly declare in 1954, must also be true for elephants.

For Farber, leukemia epitomized this biological paradigm. From this simple, atypical beast he would extrapolate into the vastly more complex world of other cancers; the bacterium would teach him to think about the elephant. He was, by nature, a quick and often impulsive thinker. And here, too, he made a quick, instinctual leap. The package from New York was waiting in his laboratory that December morning. As he tore it open, pulling out the glass vials of chemicals, he scarcely realized that he was throwing open an entirely new way of thinking about cancer.

# The Emperor of All Maladies

A Biography of Cancer

Siddhartha Mukherjee



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