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—*Publishers Weekly* (starred review)

"Siddhartha Mukherjee's *The Emperor of All Maladies* left me shaken, fascinated, and not depressed, because he gives a face to our old enemy, cancer."

—Emma Donoghue, author of *Room*

"Sid Mukherjee's book is a pleasure to read, if that is the right word. . . . His book is the clearest account I have read on this subject. With *The Emperor of All Maladies,* he joins that small fraternity of practicing doctors who can not just talk about their profession but write about it."

—Tony Judt, author of *The Memory Chalet*

"Rarely have the science and poetry of illness been so elegantly braided together as they are in this erudite, engrossing, kind book."

—Andrew Solomon, National Book Award–winning author of *The Noonday Demon*

"At once learned and skeptical, unsentimental and humane, *The Emperor of All Maladies* is that rarest of things—a noble book."

—David Rieff, author of *Swimming in a Sea of Death*

"A magisterial, wise, and deeply human piece of writing."

—Adam Hochschild, author of *King Leopold's Ghost* and *Bury the Chains*

"*The Emperor of All Maladies* beautifully describes the nature of cancer from a patient's perspective and how basic research has opened the door to understanding this disease."

—Bert Vogelstein, director, Ludwig Center at Johns Hopkins University

"A labor of love . . . as comprehensive as possible."

—George Canellos, M.D., William Rosenberg Professor of Medicine, Harvard Medical School

"An elegant . . . tour de force. *The Emperor of All Maladies* reads like a novel . . . but it deals with real people and real successes, as well as with the many false notions and false leads. Not only will the book bring cancer research and cancer biology to the lay public, it will help attract young researchers to a field that is at once exciting and heart wrenching . . . and important."

—Donald Berry, Ph.D., MD Anderson Cancer Center, University of Texas

THE EMPEROR OF ALL MALADIES

A BIOGRAPHY OF CANCER

SIDDHARTHA MUKHERJEE

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To
Robert Sandler (1945–1948),
and to those who came before
and after him.

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

Contents

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,

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."

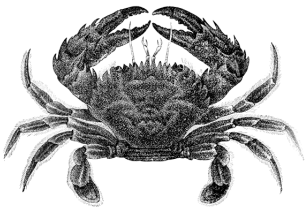
A disclaimer: in science and medicine, where the primacy of a discovery carries supreme weight, the mantle of inventor or discoverer is assigned by a community of scientists and researchers. Although there are many stories of discovery and invention in this book, none of these establishes any legal claims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

THE EMPEROR OF ALL MALADIES



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

sentence that flickered on my beeper had the staccato and deadpan force of a true medical emergency: *Carla Reed/New patient with leukemia/14th 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 tragicomically 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

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

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

"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.

"OF BLACKE CHOLOR, WITHOUT BOYLING"

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. Hyper*plasia,* 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 *neo*plasia—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 suppuration 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.

"A monster more insatiable than the guillotine"

The medical importance of leukemia has always been disproportionate to its actual incidence. . . . Indeed, the problems encountered in the systemic treatment of leukemia were indicative of the general directions in which cancer research as a whole was headed.

—Jonathan Tucker,
Ellie: A Child's Fight Against Leukemia

There were few successes in the treatment of disseminated cancer. . . . It was usually a matter of watching the tumor get bigger, and the patient, progressively smaller.

—John Laszlo, *The Cure of Childhood Leukemia: Into the Age of Miracles*

Sidney Farber's package of chemicals happened to arrive at a particularly pivotal moment in the history of medicine. In the late 1940s, a cornucopia of pharmaceutical discoveries was tumbling open in labs and clinics around the nation. The most iconic of these new drugs were the antibiotics. Penicillin, that precious chemical that had to be milked to its last droplet during World War II (in 1939, the drug was reextracted from the urine of patients who had been treated with it to conserve every last molecule), was by the early fifties being produced in thousand-gallon vats. In 1942, when Merck had shipped out its first batch of penicillin—a mere five and a half grams of the drug—that amount had represented half of the entire stock of the antibiotic in America. A decade later, penicillin was

being mass-produced so effectively that its price had sunk to four cents for a dose, one-eighth the cost of a half gallon of milk.

New antibiotics followed in the footsteps of penicillin: chloramphenicol in 1947, tetracycline in 1948. In the winter of 1949, when yet another miraculous antibiotic, streptomycin, was purified out of a clod of mold from a chicken farmer's barnyard, *Time* magazine splashed the phrase *"The remedies are in our own backyard,"* prominently across its cover. In a brick building on the far corner of Children's Hospital, in Farber's own backyard, a microbiologist named John Enders was culturing poliovirus in rolling plastic flasks, the first step that culminated in the development of the Sabin and Salk polio vaccines. New drugs appeared at an astonishing rate: by 1950, more than half the medicines in common medical use had been unknown merely a decade earlier.

Perhaps even more significant than these miracle drugs, shifts in public health and hygiene also drastically altered the national physiognomy of illness. Typhoid fever, a contagion whose deadly swirl could decimate entire districts in weeks, melted away as the putrid water supplies of several cities were cleansed by massive municipal efforts. Even tuberculosis, the infamous "white plague" of the nineteenth century, was vanishing, its incidence plummeting by more than half between 1910 and 1940, largely due to better sanitation and public hygiene efforts. The life expectancy of Americans rose from forty-seven to sixty-eight in half a century, a greater leap in longevity than had been achieved over several previous centuries.

The sweeping victories of postwar medicine illustrated the potent and transformative capacity of science and technology in American life. Hospitals proliferated—between 1945 and 1960, nearly one thousand new hospitals were launched nationwide; between 1935 and 1952, the number of patients admitted more than doubled from 7 million to 17 million per year. And with the rise in medical *care* came the concomitant expectation of medical *cure*. As one student observed, "When a doctor has to tell a patient that there is no specific remedy for his condition, [the patient] is apt to feel affronted, or to wonder whether the doctor is keeping abreast of the times."

In new and sanitized suburban towns, a young generation thus dreamed of cures—of a death-free, disease-free existence. Lulled by the idea of the durability of life, they threw themselves into consuming durables: boat-size Studebakers, rayon leisure suits, televisions, radios, vacation homes, golf clubs, barbecue grills, washing machines. In Levittown, a sprawling suburban settlement built in a potato field on Long Island—a symbolic

utopia—"illness" now ranked third in a list of "worries," falling behind "finances" and "child-rearing." In fact, rearing children was becoming a national preoccupation at an unprecedented level. Fertility rose steadily—by 1957, a baby was being born every seven seconds in America. The "affluent society," as the economist John Galbraith described it, also imagined itself as eternally young, with an accompanying guarantee of eternal health—the invincible society.

But of all diseases, cancer had refused to fall into step in this march of progress. If a tumor was strictly local (i.e., confined to a single organ or site so that it could be removed by a surgeon), the cancer stood a chance of being cured. Extirpations, as these procedures came to be called, were a legacy of the dramatic advances of nineteenth-century surgery. A solitary malignant lump in the breast, say, could be removed via a radical mastectomy pioneered by the great surgeon William Halsted at Johns Hopkins in the 1890s. With the discovery of X-rays in the early 1900s, radiation could also be used to kill tumor cells at local sites.

But scientifically, cancer still remained a black box, a mysterious entity that was best cut away en bloc rather than treated by some deeper medical insight. To cure cancer (if it could be cured at all), doctors had only two strategies: excising the tumor surgically or incinerating it with radiation—a choice between the hot ray and the cold knife.

In May 1937, almost exactly a decade before Farber began his experiments with chemicals, *Fortune* magazine published what it called a "panoramic survey" of cancer medicine. The report was far from comforting: "The startling fact is that no new *principle* of treatment, whether for cure or prevention, has been introduced. . . . The *methods* of treatment have become more efficient and more humane. Crude surgery without anesthesia or asepsis has been replaced by modern painless surgery with its exquisite technical refinement. Biting caustics that ate into the flesh of past generations of cancer patients have been obsolesced by radiation with X-ray and radium. . . . But the fact remains that the cancer 'cure' still includes only two principles—the removal and destruction of diseased tissue [the former by surgery; the latter by X-rays]. No other means have been proved."

The *Fortune* article was titled "Cancer: The Great Darkness," and the "darkness," the authors suggested, was as much political as medical. Cancer medicine was stuck in a rut not only because of the depth of med-

ical mysteries that surrounded it, but because of the systematic neglect of cancer research: "There are not over two dozen funds in the U.S. devoted to fundamental cancer research. They range in capital from about $500 up to about $2,000,000, but their aggregate capitalization is certainly not much more than $5,000,000. . . . The public willingly spends a third of that sum in an afternoon to watch a major football game."

This stagnation of research funds stood in stark contrast to the swift rise to prominence of the disease itself. Cancer had certainly been present and noticeable in nineteenth-century America, but it had largely lurked in the shadow of vastly more common illnesses. In 1899, when Roswell Park, a well-known Buffalo surgeon, had argued that cancer would someday overtake smallpox, typhoid fever, and tuberculosis to become the leading cause of death in the nation, his remarks had been perceived as a rather "startling prophecy," the hyperbolic speculations of a man who, after all, spent his days and nights operating on cancer. But by the end of the decade, Park's remarks were becoming less and less startling, and more and more prophetic by the day. Typhoid, aside from a few scattered outbreaks, was becoming increasingly rare. Smallpox was on the decline; by 1949, it would disappear from America altogether. Meanwhile cancer was already outgrowing other diseases, ratcheting its way up the ladder of killers. Between 1900 and 1916, cancer-related mortality grew by 29.8 percent, edging out tuberculosis as a cause of death. By 1926, cancer had become the nation's second most common killer, just behind heart disease.

"Cancer: The Great Darkness" wasn't alone in building a case for a coordinated national response to cancer. In May that year, *Life* carried its own dispatch on cancer research, which conveyed the same sense of urgency. The *New York Times* published two reports on rising cancer rates, in April and June. When cancer appeared in the pages of *Time* in July 1937, interest in what was called the "cancer problem" was like a fierce contagion in the media.

Proposals to mount a systematic national response against cancer had risen and ebbed rhythmically in America since the early 1900s. In 1907, a group of cancer surgeons had congregated at the New Willard Hotel in Washington to create an organization to lobby Congress for more funds for cancer research. By 1910, this organization, the American Association for Cancer Research, had convinced President Taft to propose to Congress

a national laboratory dedicated to cancer research. But despite initial interest in the plan, the efforts had stalled in Washington after a few fitful attempts, largely because of a lack of political support.

In the late 1920s, a decade after Taft's proposal had been tabled, cancer research found a new and unexpected champion—Matthew Neely, a dogged and ebullient former lawyer from Fairmont, West Virginia, serving his first term in the Senate. Although Neely had relatively little experience in the politics of science, he had noted the marked increase in cancer mortality in the previous decade—from 70,000 men and women in 1911 to 115,000 in 1927. Neely asked Congress to advertise a reward of $5 million for any "information leading to the arrest of human cancer."

It was a lowbrow strategy—the scientific equivalent of hanging a mug shot in a sheriff's office—and it generated a reflexively lowbrow response. Within a few weeks, Neely's office in Washington was flooded with thousands of letters from quacks and faith healers purporting every conceivable remedy for cancer: rubs, tonics, ointments, anointed handkerchiefs, salves, and blessed water. Congress, exasperated with the response, finally authorized $50,000 for Neely's Cancer Control Bill, almost comically cutting its budget back to just 1 percent of the requested amount.

In 1937, the indefatigable Neely, reelected to the Senate, launched yet another effort to launch a national attack on cancer, this time jointly with Senator Homer Bone and Representative Warren Magnuson. By now, cancer had considerably magnified in the public eye. The *Fortune* and *Time* articles had fanned anxiety and discontent, and politicians were eager to demonstrate a concrete response. In June, a joint Senate-House conference was held to craft legislation to address the issue. After initial hearings, the bill raced through Congress and was passed unanimously by a joint session on July 23, 1937. Two weeks later, on August 5, President Roosevelt signed the National Cancer Institute Act.

The act created a new scientific unit called the National Cancer Institute (NCI), designed to coordinate cancer research and education.* An advisory council of scientists for the institute was assembled from universities and hospitals. A state-of-the-art laboratory space, with gleaming halls and conference rooms, was built among leafy arcades and gardens in suburban

* In 1944, the NCI would become a subsidiary component of the National Institutes of Health (NIH). This foreshadowed the creation of other disease-focused institutes over the next decades.

Bethesda, a few miles from the nation's capital. "The nation is marshaling its forces to conquer cancer, the greatest scourge that has ever assailed the human race," Senator Bone announced reassuringly while breaking ground for the building on October 3, 1938. After nearly two decades of largely fruitless efforts, a coordinated national response to cancer seemed to be on its way at last.

All of this was a bold, brave step in the right direction—except for its timing. By the early winter of 1938, just months after the inauguration of the NCI campus in Bethesda, the battle against cancer was overshadowed by the tremors of a different kind of war. In November, Nazi troops embarked on a nationwide pogrom against Jews in Germany, forcing thousands into concentration camps. By late winter, military conflicts had broken out all over Asia and Europe, setting the stage for World War II. By 1939, those skirmishes had fully ignited, and in December 1941, America was drawn inextricably into the global conflagration.

The war necessitated a dramatic reordering of priorities. The U.S. Marine Hospital in Baltimore, which the NCI had once hoped to convert into a clinical cancer center, was now swiftly reconfigured into a war hospital. Scientific research funding stagnated and was shunted into projects directly relevant to the war. Scientists, lobbyists, physicians, and surgeons fell off the public radar screen—"mostly silent," as one researcher recalled, "their contributions usually summarized in obituaries."

An obituary might as well have been written for the National Cancer Institute. Congress's promised funds for a "programmatic response to cancer" never materialized, and the NCI languished in neglect. Outfitted with every modern facility imaginable in the 1940s, the institute's sparkling campus turned into a scientific ghost town. One scientist jokingly called it "a nice quiet place out here in the country. In those days," the author continued, "it was pleasant to drowse under the large, sunny windows."*

The social outcry about cancer also drifted into silence. After the brief flurry of attention in the press, cancer again became the great unmentionable, the whispered-about disease that no one spoke about publicly. In the early 1950s, Fanny Rosenow, a breast cancer survivor and cancer advocate, called the *New York Times* to post an advertisement for a support group for women with breast cancer. Rosenow was put through, puzzlingly, to

*In 1946–47, Neely and Senator Claude Pepper launched a third national cancer bill. This was defeated in Congress by a small margin in 1947.

the society editor of the newspaper. When she asked about placing her announcement, a long pause followed. "I'm sorry, Ms. Rosenow, but the *Times* cannot publish the word *breast* or the word *cancer* in its pages.

"Perhaps," the editor continued, "you could say there will be a meeting about diseases of the chest wall."

Rosenow hung up, disgusted.

❧

When Farber entered the world of cancer in 1947, the public outcry of the past decade had dissipated. Cancer had again become a politically silent illness. In the airy wards of the Children's Hospital, doctors and patients fought their private battles against cancer. In the tunnels downstairs, Farber fought an even more private battle with his chemicals and experiments.

This isolation was key to Farber's early success. Insulated from the spotlights of public scrutiny, he worked on a small, obscure piece of the puzzle. Leukemia was an orphan disease, abandoned by internists, who had no drugs to offer for it, and by surgeons, who could not possibly operate on blood. "Leukemia," as one physician put it, "in some senses, had not [even] been cancer before World War II." The illness lived on the borderlands of illnesses, a pariah lurking between disciplines and departments—not unlike Farber himself.

If leukemia "belonged" anywhere, it was within hematology, the study of normal blood. If a cure for it was to be found, Farber reasoned, it would be found by studying blood. If he could uncover how *normal* blood cells were generated, he might stumble backward into a way to block the growth of abnormal leukemic cells. His strategy, then, was to approach the disease from the normal to the abnormal—to confront cancer in reverse.

Much of what Farber knew about normal blood he had learned from George Minot. A thin, balding aristocrat with pale, intense eyes, Minot ran a laboratory in a colonnaded, brick-and-stone structure off Harrison Avenue in Boston, just a few miles down the road from the sprawling hospital complex on Longwood Avenue that included Children's Hospital. Like many hematologists at Harvard, Farber had trained briefly with Minot in the 1920s before joining the staff at Children's.

Every decade has a unique hematological riddle, and for Minot's era, that riddle was pernicious anemia. Anemia is the deficiency of red blood cells—and its most common form arises from a lack of iron, a crucial nutrient used to build red blood cells. But pernicious anemia, the rare variant

that Minot studied, was not caused by iron deficiency (indeed, its name derives from its intransigence to the standard treatment of anemia with iron). By feeding patients increasingly macabre concoctions—half a pound of chicken liver, half-cooked hamburgers, raw hog stomach, and even once the regurgitated gastric juices of one of his students (spiced up with butter, lemon, and parsley)—Minot and his team of researchers conclusively demonstrated in 1926 that pernicious anemia was caused by the lack of a critical micronutrient, a single molecule later identified as vitamin B_{12}. In 1934, Minot and two of his colleagues won the Nobel Prize for this pathbreaking work. Minot had shown that replacing a single molecule could restore the normalcy of blood in this complex hematological disease. Blood was an organ whose activity could be turned on and off by molecular switches.

There was another form of nutritional anemia that Minot's group had not tackled, an anemia just as "pernicious"—although in the moral sense of that word. Eight thousand miles away, in the cloth mills of Bombay (owned by English traders and managed by their cutthroat local middlemen), wages had been driven to such low levels that the mill workers lived in abject poverty, malnourished and without medical care. When English physicians tested these mill workers in the 1920s to study the effects of this chronic malnutrition, they discovered that many of them, particularly women after childbirth, were severely anemic. (This was yet another colonial fascination: to create the conditions of misery in a population, then subject it to social or medical experimentation.)

In 1928, a young English physician named Lucy Wills, freshly out of the London School of Medicine for Women, traveled on a grant to Bombay to study this anemia. Wills was an exotic among hematologists, an adventurous woman driven by a powerful curiosity about blood willing to travel to a faraway country to solve a mysterious anemia on a whim. She knew of Minot's work. But unlike Minot's anemia, she found that the anemia in Bombay couldn't be reversed by Minot's concoctions or by vitamin B_{12}. Astonishingly, she found she could cure it with Marmite, the dark, yeasty spread then popular among health fanatics in England and Australia. Wills could not determine the key chemical nutrient of Marmite. She called it the Wills factor.

Wills factor turned out to be folic acid, or folate, a vitamin-like substance found in fruits and vegetables (and amply in Marmite). When cells divide, they need to make copies of DNA—the chemical that carries all the genetic information in a cell. Folic acid is a crucial building block for

DNA and is thus vital for cell division. Since blood cells are produced by arguably the most fearsome rate of cell division in the human body—more than 300 billion cells a day—the genesis of blood is particularly dependent on folic acid. In its absence (in men and women starved of vegetables, as in Bombay) the production of new blood cells in the bone marrow halts. Millions of half-matured cells spew out, piling up like half-finished goods bottlenecked in an assembly line. The bone marrow becomes a dysfunctional mill, a malnourished biological factory oddly reminiscent of the cloth factories of Bombay.

These links—between vitamins, bone marrow, and normal blood—kept Farber preoccupied in the early summer of 1946. In fact, his first clinical experiment, inspired by this very connection, turned into a horrific mistake. Lucy Wills had observed that folic acid, if administered to nutrient-deprived patients, could restore the normal genesis of blood. Farber wondered whether administering folic acid to children with leukemia might also restore normalcy to their blood. Following that tenuous trail, he obtained some synthetic folic acid, recruited a cohort of leukemic children, and started injecting folic acid into them.

In the months that passed, Farber found that folic acid, far from stopping the progression of leukemia, actually accelerated it. In one patient, the white cell count nearly doubled. In another, the leukemia cells exploded into the bloodstream and sent fingerlings of malignant cells to infiltrate the skin. Farber stopped the experiment in a hurry. He called this phenomenon acceleration, evoking some dangerous object in free fall careering toward its end.

Pediatricians at Children's Hospital were furious about Farber's trial. The folate analogues had not just accelerated the leukemia; they had likely hastened the death of the children. But Farber was intrigued. If folic acid accelerated the leukemia cells in children, what if he could cut off its supply with some other drug—an *anti*folate? Could a chemical that blocked the growth of white blood cells stop leukemia?

The observations of Minot and Wills began to fit into a foggy picture. If the bone marrow was a busy cellular factory to begin with, then a marrow occupied with leukemia was that factory in overdrive, a deranged manufacturing unit for cancer cells. Minot and Wills had turned the production lines of the bone marrow *on* by adding nutrients to the body. But could the

malignant marrow be shut *off* by choking the supply of nutrients? Could the anemia of the mill workers in Bombay be re-created therapeutically in the medical units of Boston?

In his long walks from his laboratory under Children's Hospital to his house on Amory Street in Brookline, Farber wondered relentlessly about such a drug. Dinner, in the dark-wood-paneled rooms of the house, was usually a sparse, perfunctory affair. His wife, Norma, a musician and writer, talked about the opera and poetry; Sidney, of autopsies, trials, and patients. As he walked back to the hospital at night, Norma's piano tinkling practice scales in his wake, the prospect of an anticancer chemical haunted him. He imagined it palpably, visibly, with a fanatic's enthusiasm. But he didn't know what it was or what to call it. The word *chemotherapy,* in the sense we understand it today, had never been used for anticancer medicines.* The elaborate armamentarium of "antivitamins" that Farber had dreamed up so vividly in his fantasies did not exist.

Farber's supply of folic acid for his disastrous first trial had come from the laboratory of an old friend, a chemist, Yellapragada Subbarao (SubbaRow)—or Yella, as most of his colleagues called him. Yella was a pioneer in many ways, a physician turned cellular physiologist, a chemist who had accidentally wandered into biology. His scientific meanderings had been presaged by more desperate and adventuresome physical meanderings. He had arrived in Boston in 1923, penniless and unprepared, having finished his medical training in India and secured a scholarship for a diploma at the School of Tropical Health at Harvard. The weather in Boston, Yella discovered, was far from tropical. Unable to find a medical job in the frigid, stormy winter (he had no license to practice medicine in the United States), he started as a night porter at the Brigham and Women's Hospital, opening doors, changing sheets, and cleaning urinals.

The proximity to medicine paid off. Subbarao made friends and connections at the hospital and switched to a day job as a researcher in the Division of Biochemistry. His initial project involved purifying molecules out of living cells, dissecting them chemically to determine their compositions—in

* In New York in the 1910s, William B. Coley, James Ewing, and Ernest Codman had treated bone sarcomas with a mixture of bacterial toxins—the so-called Coley's toxin. Coley had observed occasional responses, but the unpredictable responses, likely caused by immune stimulation, never fully captured the attention of oncologists or surgeons.

essence, performing a biochemical "autopsy" on cells. The approach required more persistence than imagination, but it produced remarkable dividends. Subbarao purified a molecule called ATP, the source of energy in all living beings (ATP carries chemical "energy" in the cell), and another molecule called creatine, the energy carrier in muscle cells. Any one of these achievements should have been enough to guarantee him a professorship at Harvard. But Subbarao was a foreigner, a reclusive, nocturnal, heavily accented vegetarian who lived in a one-room apartment downtown, befriended only by other nocturnal recluses such as Farber. In 1940, denied tenure and recognition, Yella huffed off to join Lederle Labs, a pharmaceutical laboratory in upstate New York, owned by the American Cyanamid Corporation, where he had been asked to run a group on chemical synthesis.

At Lederle, Yella Subbarao quickly reformulated his old strategy and focused on making synthetic versions of the natural chemicals that he had found within cells, hoping to use them as nutritional supplements. In the 1920s, another drug company, Eli Lilly, had made a fortune selling a concentrated form of vitamin B_{12}, the missing nutrient in pernicious anemia. Subbarao decided to focus his attention on the other anemia, the neglected anemia of folate deficiency. But in 1946, after many failed attempts to extract the chemical from pigs' livers, he switched tactics and started to synthesize folic acid from scratch, with the help of a team of scientists.

The chemical reactions to make folic acid brought a serendipitous bonus. Since the reactions had several intermediate steps, Subbarao's team* could create variants of folic acid through slight alterations in the recipe. These variants of folic acid—closely related molecular mimics—possessed counterintuitive properties. Enzymes and receptors in cells typically work by recognizing molecules using their chemical structure. But a "decoy" molecular structure—one that nearly mimics the natural molecule—can bind to the receptor or enzyme and block its action, like a false key jamming a lock. Some of Yella's molecular mimics could thus behave like *antagonists* to folic acid.

These were precisely the antivitamins that Farber had been fantasizing about. Farber wrote to Subbarao asking him if he could use their folate antagonists on patients with leukemia. Subbarao consented. In the late summer of 1947, the first package of antifolate left Lederle's labs in New York and arrived in Farber's laboratory.

* D. R. Seeger and B. Hutchings were other key members of the team.

Farber's Gauntlet

Throughout the centuries the sufferer from this disease has been the subject of almost every conceivable form of experimentation. The fields and forests, the apothecary shop and the temple, have been ransacked for some successful means of relief from this intractable malady. Hardly any animal has escaped making its contribution, in hair or hide, tooth or toenail, thymus or thyroid, liver or spleen, in the vain search by man for a means of relief.

—William Bainbridge

The search for a way to eradicate this scourge . . . is left to incidental dabbling and uncoordinated research.

—*The Washington Post*, 1946

Seven miles south of the Longwood hospitals in Boston, the town of Dorchester is a typical sprawling New England suburb, a triangle wedged between the sooty industrial settlements to the west and the gray-green bays of the Atlantic to its east. In the late 1940s, waves of Jewish and Irish immigrants—shipbuilders, iron casters, railway engineers, fishermen, and factory workers—settled in Dorchester, occupying rows of brick-and-clapboard houses that snaked their way up Blue Hill Avenue. Dorchester reinvented itself as the quintessential suburban family town, with parks and playgrounds along the river, a golf course, a church, and a synagogue. On Sunday afternoons, families converged at Franklin Park to walk through its leafy pathways or to watch ostriches, polar bears, and tigers at its zoo.

On August 16, 1947, in a house across from the zoo, the child of a ship worker in the Boston yards fell mysteriously ill with a low-grade fever that

waxed and waned over two weeks without pattern, followed by increasing lethargy and pallor. Robert Sandler was two years old. His twin, Elliott, was an active, cherubic toddler in perfect health.

Ten days after his first fever, Robert's condition worsened significantly. His temperature climbed higher. His complexion turned from rosy to a spectral milky white. He was brought to Children's Hospital in Boston. His spleen, a fist-size organ that stores and makes blood (usually barely palpable underneath the rib cage), was visibly enlarged, heaving down like an overfilled bag. A drop of blood under Farber's microscope revealed the identity of his illness; thousands of immature lymphoid leukemic blasts were dividing in a frenzy, their chromosomes condensing and uncondensing, like tiny clenched and unclenched fists.

Sandler arrived at Children's Hospital just a few weeks after Farber had received his first package from Lederle. On September 6, 1947, Farber began to inject Sandler with pteroylaspartic acid or PAA, the first of Lederle's antifolates. (Consent to run a clinical trial for a drug—even a toxic drug—was not typically required. Parents were occasionally cursorily informed about the trial; children were almost never informed or consulted. The Nuremberg code for human experimentation, requiring explicit voluntary consent from patients, was drafted on August 9, 1947, less than a month before the PAA trial. It is doubtful that Farber in Boston had even heard of any such required consent code.)

PAA had little effect. Over the next month Sandler turned increasingly lethargic. He developed a limp, the result of leukemia pressing down on his spinal cord. Joint aches appeared, and violent, migrating pains. Then the leukemia burst through one of the bones in his thigh, causing a fracture and unleashing a blindingly intense, indescribable pain. By December, the case seemed hopeless. The tip of Sandler's spleen, more dense than ever with leukemia cells, dropped down to his pelvis. He was withdrawn, listless, swollen, and pale, on the verge of death.

On December 28, however, Farber received a new version of antifolate from Subbarao and Kiltie, aminopterin, a chemical with a small change from the structure of PAA. Farber snatched the drug as soon as it arrived and began to inject the boy with it, hoping, at best, for a minor reprieve in his cancer.

The response was marked. The white cell count, which had been climbing astronomically—ten thousand in September, twenty thousand in November, and nearly seventy thousand in December—suddenly stopped

rising and hovered at a plateau. Then, even more remarkably, the count actually started to drop, the leukemic blasts gradually flickering out in the blood and then all but disappearing. By New Year's Eve, the count had dropped to nearly one-sixth of its peak value, bottoming out at a nearly normal level. The cancer hadn't vanished—under the microscope, there were still malignant white cells—but it had temporarily abated, frozen into a hematologic stalemate in the frozen Boston winter.

On January 13, 1948, Sandler returned to the clinic, walking on his own for the first time in two months. His spleen and liver had shrunk so dramatically that his clothes, Farber noted, had become "loose around the abdomen." His bleeding had stopped. His appetite turned ravenous, as if he were trying to catch up on six months of lost meals. By February, Farber noted, the child's alertness, nutrition, and activity were equal to his twin's. For a brief month or so, Robert Sandler and Elliott Sandler seemed identical again.

Sandler's remission—unprecedented in the history of leukemia—set off a flurry of activity for Farber. By the early winter of 1948, more children were at his clinic: a three-year-old boy brought with a sore throat, a two-and-a-half-year-old girl with lumps in her head and neck, all eventually diagnosed with childhood ALL. Deluged with antifolates from Yella and with patients who desperately needed them, Farber recruited additional doctors to help him: a hematologist named Louis Diamond, and a group of assistants, James Wolff, Robert Mercer, and Robert Sylvester.

Farber had infuriated the authorities at Children's Hospital with his first clinical trial. With this, the second, he pushed them over the edge. The hospital staff voted to take all the pediatric interns off the leukemia chemotherapy unit (the atmosphere in the leukemia wards, it was felt, was far too desperate and experimental and thus not conducive to medical education)—in essence, leaving Farber and his assistants to perform all the patient care themselves. Children with cancer, as one surgeon noted, were typically "tucked in the farthest recesses of the hospital wards." They were on their deathbeds anyway, the pediatricians argued; wouldn't it be kinder and gentler, some insisted, to just "let them die in peace"? When one clinician suggested that Farber's novel "chemicals" be reserved only as a last resort for leukemic children, Farber, recalling his prior life as a pathologist, shot back, "By that time, the only chemical that you will need will be embalming fluid."

Farber outfitted a back room of a ward near the bathrooms into a makeshift clinic. His small staff was housed in various unused spaces in the Department of Pathology—in back rooms, stairwell shafts, and empty offices. Institutional support was minimal. Farber's assistants sharpened their own bone marrow needles, a practice as antiquated as a surgeon whetting his knives on a wheel. Farber's staff tracked the disease in patients with meticulous attention to detail: every blood count, every transfusion, every fever, was to be recorded. If leukemia was going to be beaten, Farber wanted every minute of that battle recorded for posterity—even if no one else was willing to watch it happen.

That winter of 1948, a severe and dismal chill descended on Boston. Snowstorms broke out, bringing Farber's clinic to a standstill. The narrow asphalt road out to Longwood Avenue was piled with heaps of muddy sleet, and the basement tunnels, poorly heated even in the fall, were now freezing. Daily injections of antifolates became impossible, and Farber's team backed down to three times a week. In February, when the storms abated, the daily injections started again.

Meanwhile, news of Farber's experience with childhood leukemia was beginning to spread, and a slow train of children began to arrive at his clinic. And case by case, an incredible pattern emerged: the antifolates could drive leukemia cell counts down, occasionally even resulting in their complete disappearance—at least for a while. There were other remissions as dramatic as Sandler's. Two boys treated with aminopterin returned to school. Another child, a two-and-a-half-year-old girl, started to "play and run about" after seven months of lying in bed. The normalcy of blood almost restored a flickering, momentary normalcy to the childhood.

But there was always the same catch. After a few months of remission, the cancer would inevitably relapse, ultimately flinging aside even the most potent of Yella's drugs. The cells would return in the bone marrow, then burst out into the blood, and even the most active antifolates would not keep their growth down. Robert Sandler died in 1948, having responded for a few months.

Yet the remissions, even if temporary, were still genuine remissions—and historic. By April 1948, there was just enough data to put together a preliminary paper for the *New England Journal of Medicine*. The team had treated sixteen patients. Of the sixteen, ten had responded. And five chil-

dren—about one-third of the initial group—remained alive four or even six months after their diagnosis. In leukemia, six months of survival was an eternity.

Farber's paper, published on June 3, 1948, was seven pages long, jam-packed with tables, figures, microscope photographs, laboratory values, and blood counts. Its language was starched, formal, detached, and scientific. Yet, like all great medical papers, it was a page-turner. And like all good novels, it was timeless: to read it today is to be pitched behind the scenes into the tumultuous life of the Boston clinic, its patients hanging on for life as Farber and his assistants scrambled to find new drugs for a dreadful disease that kept flickering away and returning. It was a plot with a beginning, a middle, and, unfortunately, an end.

The paper was received, as one scientist recalls, "with skepticism, disbelief, and outrage." But for Farber, the study carried a tantalizing message: cancer, even in its most aggressive form, had been treated with a medicine, a chemical. In six months between 1947 and 1948, Farber thus saw a door open—briefly, seductively—then close tightly shut again. And through that doorway, he glimpsed an incandescent possibility. The disappearance of an aggressive systemic cancer via a chemical drug was virtually unprecedented in the history of cancer. In the summer of 1948, when one of Farber's assistants performed a bone marrow biopsy on a leukemic child after treatment with aminopterin, the assistant could not believe the results. "The bone marrow looked so normal," he wrote, "that one could dream of a cure."

And so Farber did dream. He dreamed of malignant cells being killed by specific anticancer drugs, and of normal cells regenerating and reclaiming their physiological spaces; of a whole gamut of such systemic antagonists to decimate malignant cells; of curing leukemia with chemicals, then applying his experience with chemicals and leukemia to more common cancers. He was throwing down a gauntlet for cancer medicine. It was then up to an entire generation of doctors and scientists to pick it up.

A Private Plague

We reveal ourselves in the metaphors we choose for depicting the cosmos in miniature.

—Stephen Jay Gould

Thus, for 3,000 years and more, this disease has been known to the medical profession. And for 3,000 years and more, humanity has been knocking at the door of the medical profession for a "cure."

—*Fortune,* March 1937

Now it is cancer's turn to be the disease that doesn't knock before it enters.

—Susan Sontag, *Illness as Metaphor*

We tend to think of cancer as a "modern" illness because its metaphors are so modern. It is a disease of overproduction, of fulminant growth—growth unstoppable, growth tipped into the abyss of no control. Modern biology encourages us to imagine the cell as a molecular machine. Cancer is that machine unable to quench its initial command (to grow) and thus transformed into an indestructible, self-propelled automaton.

The notion of cancer as an affliction that belongs paradigmatically to the twentieth century is reminiscent, as Susan Sontag argued so powerfully in her book *Illness as Metaphor,* of another disease once considered emblematic of another era: tuberculosis in the nineteenth century. Both diseases, as Sontag pointedly noted, were similarly "obscene—in the original meaning of that word: ill-omened, abominable, repugnant to the

senses." Both drain vitality; both stretch out the encounter with death; in both cases, *dying,* even more than death, defines the illness.

But despite such parallels, tuberculosis belongs to another century. TB (or consumption) was Victorian romanticism brought to its pathological extreme—febrile, unrelenting, breathless, and obsessive. It was a disease of poets: John Keats involuting silently toward death in a small room overlooking the Spanish Steps in Rome, or Byron, an obsessive romantic, who fantasized about dying of the disease to impress his mistresses. "Death and disease are often beautiful, like . . . the hectic glow of consumption," Thoreau wrote in 1852. In Thomas Mann's *The Magic Mountain,* this "hectic glow" releases a feverish creative force in its victims—a clarifying, edifying, cathartic force that, too, appears to be charged with the essence of its era.

Cancer, in contrast, is riddled with more contemporary images. The cancer cell is a desperate individualist, "in every possible sense, a nonconformist," as the surgeon-writer Sherwin Nuland wrote. The word *metastasis,* used to describe the migration of cancer from one site to another, is a curious mix of *meta* and *stasis*—"beyond stillness" in Latin—an unmoored, partially unstable state that captures the peculiar instability of modernity. If consumption once killed its victims by pathological evisceration (the tuberculosis bacillus gradually hollows out the lung), then cancer asphyxiates us by filling bodies with too many cells; it is consumption in its alternate meaning—the pathology of excess. Cancer is an expansionist disease; it invades through tissues, sets up colonies in hostile landscapes, seeking "sanctuary" in one organ and then immigrating to another. It lives desperately, inventively, fiercely, territorially, cannily, and defensively—at times, as if teaching *us* how to survive. To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are.

This image—of cancer as our desperate, malevolent, contemporary doppelgänger—is so haunting because it is at least partly true. A cancer cell is an astonishing perversion of the normal cell. Cancer is a phenomenally successful invader and colonizer in part because it exploits the very features that make *us* successful as a species or as an organism.

Like the normal cell, the cancer cell relies on growth in the most basic, elemental sense: the division of one cell to form two. In normal tissues, this process is exquisitely regulated, such that growth is stimulated by specific signals and arrested by other signals. In cancer, unbridled growth gives

rise to generation upon generation of cells. Biologists use the term *clone* to describe cells that share a common genetic ancestor. Cancer, we now know, is a clonal disease. Nearly every known cancer originates from one ancestral cell that, having acquired the capacity of limitless cell division and survival, gives rise to limitless numbers of descendants—Virchow's *omnis cellula e cellula e cellula* repeated ad infinitum.

But cancer is not simply a clonal disease; it is a clonally *evolving* disease. If growth occurred without evolution, cancer cells would not be imbued with their potent capacity to invade, survive, and metastasize. Every generation of cancer cells creates a small number of cells that is genetically different from its parents. When a chemotherapeutic drug or the immune system attacks cancer, mutant clones that can resist the attack grow out. The fittest cancer cell survives. This mirthless, relentless cycle of mutation, selection, and overgrowth generates cells that are more and more adapted to survival and growth. In some cases, the mutations speed up the acquisition of other mutations. The genetic instability, like a perfect madness, only provides more impetus to generate mutant clones. Cancer thus exploits the fundamental logic of evolution unlike any other illness. If we, as a species, are the ultimate product of Darwinian selection, then so, too, is this incredible disease that lurks inside us.

Such metaphorical seductions can carry us away, but they are unavoidable with a subject like cancer. In writing this book, I started off by imagining my project as a "history" of cancer. But it felt, inescapably, as if I were writing not about some*thing* but about some*one*. My subject daily morphed into something that resembled an individual—an enigmatic, if somewhat deranged, image in a mirror. This was not so much a medical history of an illness, but something more personal, more visceral: its biography.

So to begin again, for every biographer must confront the birth of his subject: Where was cancer "born"? How old is cancer? Who was the first to record it as an illness?

In 1862, Edwin Smith—an unusual character: part scholar and part huckster, an antique forger and self-made Egyptologist—bought (or, some say, stole) a fifteen-foot-long papyrus from an antiques seller in Luxor in Egypt. The papyrus was in dreadful condition, with crumbling, yellow pages filled with cursive Egyptian script. It is now thought to have been written in the seventeenth century BC, a transcription of a manuscript

dating back to 2500 BC. The copier—a plagiarist in a terrible hurry—had made errors as he had scribbled, often noting corrections in red ink in the margins.

Translated in 1930, the papyrus is now thought to contain the collected teachings of Imhotep, a great Egyptian physician who lived around 2625 BC. Imhotep, among the few nonroyal Egyptians known to us from the Old Kingdom, was a Renaissance man at the center of a sweeping Egyptian renaissance. As a vizier in the court of King Djozer, he dabbled in neurosurgery, tried his hand at architecture, and made early forays into astrology and astronomy. Even the Greeks, encountering the fierce, hot blast of his intellect as they marched through Egypt centuries later, cast him as an ancient magician and fused him to their own medical god, Asclepius.

But the surprising feature of the Smith papyrus is not magic and religion but the absence of magic and religion. In a world immersed in spells, incantations, and charms, Imhotep wrote about broken bones and dislocated vertebrae with a detached, sterile scientific vocabulary, as if he were writing a modern surgical textbook. The forty-eight cases in the papyrus—fractures of the hand, gaping abscesses of the skin, or shattered skull bones—are treated as medical conditions rather than occult phenomena, each with its own anatomical glossary, diagnosis, summary, and prognosis.

And it is under these clarifying headlamps of an ancient surgeon that cancer first emerges as a distinct disease. Describing case forty-five, Imhotep advises, "If you examine [a case] having bulging masses on [the] breast and you find that they have spread over his breast; if you place your hand upon [the] breast [and] find them to be cool, there being no fever at all therein when your hand feels him; they have no granulations, contain no fluid, give rise to no liquid discharge, yet they feel protuberant to your touch, you should say concerning him: 'This is a case of bulging masses I have to contend with. . . . Bulging tumors of the breast mean the existence of swellings on the breast, large, spreading, and hard; touching them is like touching a ball of wrappings, or they may be compared to the unripe hemat fruit, which is hard and cool to the touch.' "

A "bulging mass in the breast"—cool, hard, dense as a hemat fruit, and spreading insidiously under the skin—could hardly be a more vivid description of breast cancer. Every case in the papyrus was followed by a concise discussion of treatments, even if only palliative: milk poured through the ears of neurosurgical patients, poultices for wounds, balms

for burns. But with case forty-five, Imhotep fell atypically silent. Under the section titled "Therapy," he offered only a single sentence: "There is none."

With that admission of impotence, cancer virtually disappeared from ancient medical history. Other diseases cycled violently through the globe, leaving behind their cryptic footprints in legends and documents. A furious plague—typhus, perhaps—blazed through the port city of Avaris in 1715 BC, decimating its population. Smallpox erupted volcanically in pockets, leaving its telltale pockmarks on the face of Ramses V in the twelfth century BC. Tuberculosis rose and ebbed through the Indus valley like its seasonal floods. But if cancer existed in the interstices of these massive epidemics, it existed in silence, leaving no easily identifiable trace in the medical literature—or in any other literature.

More than two millennia pass after Imhotep's description until we once more hear of cancer. And again, it is an illness cloaked in silence, a private shame. In his sprawling *Histories,* written around 440 BC, the Greek historian Herodotus records the story of Atossa, the queen of Persia, who was suddenly struck by an unusual illness. Atossa was the daughter of Cyrus, and the wife of Darius, successive Achaemenid emperors of legendary brutality who ruled over a vast stretch of land from Lydia on the Mediterranean Sea to Babylonia on the Persian Gulf. In the middle of her reign, Atossa noticed a bleeding lump in her breast that may have arisen from a particularly malevolent form of breast cancer labeled inflammatory (in inflammatory breast cancer, malignant cells invade the lymph glands of the breast, causing a red, swollen mass).

If Atossa had desired it, an entire retinue of physicians from Babylonia to Greece would have flocked to her bedside to treat her. Instead, she descended into a fierce and impenetrable loneliness. She wrapped herself in sheets, in a self-imposed quarantine. Darius' doctors may have tried to treat her, but to no avail. Ultimately, a Greek slave named Democedes persuaded her to allow him to excise the tumor.

Soon after that operation, Atossa mysteriously vanishes from Herodotus' text. For him, she is merely a minor plot twist. We don't know whether the tumor recurred, or how or when she died, but the procedure was at least a temporary success. Atossa lived, and she had Democedes to thank for it. And that reprieve from pain and illness whipped her into a frenzy of gratitude and territorial ambition. Darius had been planning a cam-

paign against Scythia, on the eastern border of his empire. Goaded by Democedes, who wanted to return to his native Greece, Atossa pleaded with her husband to turn his campaign westward—to invade Greece. That turn of the Persian empire from east to west, and the series of Greco-Persian wars that followed, would mark one of the definitive moments in the early history of the West. It was Atossa's tumor, then, that quietly launched a thousand ships. Cancer, even as a clandestine illness, left its fingerprints on the ancient world.

But Herodotus and Imhotep are storytellers, and like all stories, theirs have gaps and inconsistencies. The "cancers" described by them may have been true neoplasms, or perhaps they were hazily describing abscesses, ulcers, warts, or moles. The only incontrovertible cases of cancer in history are those in which the malignant tissue has somehow been preserved. And to encounter one such cancer face-to-face—to actually stare the ancient illness in its eye—one needs to journey to a thousand-year-old gravesite in a remote, sand-swept plain in the southern tip of Peru.

The plain lies at the northern edge of the Atacama Desert, a parched, desolate six-hundred-mile strip caught in the leeward shadow of the giant furl of the Andes that stretches from southern Peru into Chile. Brushed continuously by a warm, desiccating wind, the terrain hasn't seen rain in recorded history. It is hard to imagine that human life once flourished here, but it did. The plain is strewn with hundreds of graves—small, shallow pits dug out of the clay, then lined carefully with rock. Over the centuries, dogs, storms, and grave robbers have dug out these shallow graves, exhuming history.

The graves contain the mummified remains of members of the Chiribaya tribe. The Chiribaya made no effort to preserve their dead, but the climate is almost providentially perfect for mummification. The clay leaches water and fluids out of the body from below, and the wind dries the tissues from above. The bodies, often placed seated, are thus swiftly frozen in time and space.

In 1990, one such large desiccated gravesite containing about 140 bodies caught the attention of Arthur Aufderheide, a professor at the University of Minnesota in Duluth. Aufderheide is a pathologist by training but his specialty is *paleo*pathology, a study of ancient specimens. His autopsies, unlike Farber's, are not performed on recently living patients, but on the mummified remains found on archaeological sites. He stores