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 amingoterin. 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 stigma 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 slate'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 mid-sixties. 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—"predilection" for gay men.
but growth redefined, growth in a new form. Presciently (although oblivious of the mechanism) Virchow called it neoplasia—novel, inexplicable, distorted growth, a word that would ring through the history of cancer.*

By the time Virchow died in 1902, a new theory of cancer had slowly coalesced out of all these observations. Cancer was a disease of pathological hyperplasia in which cells acquired an autonomous will to divide. This aberrant, uncontrolled 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 suppurative 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 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 milliliter of blood. Carla’s blood contained ninety thousand cells per milliliter—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

*Virchow did not coin the word, although he offered a comprehensive description of neoplasia.
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 collateral 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 Farbers 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,
*Elie: 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 care. 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 futile 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 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

*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.
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 criti-
cal micronutrient, a single molecule later identified as vitamin B₁₂. In 1934,
Minot and two of his colleagues won the Nobel Prize for this pathbreak-
ning 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 middle-
men), 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 colo-
nial 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 adventur-
ous 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 B₁₂.
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 sub-
stance 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 dysfunc-
tional 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 clini-
cal experiment, inspired by this very connection, turned into a hor-
rific 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 leu-
kemia might also restore normalcy to their blood. Following that ten-
uous 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 stop-
ing 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 phe-
nomenon acceleration, evoking some dangerous object in free fall career-
ning 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 sup-
ply with some other drug—an antifolate? 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 manu-
facturing 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 chemotheraphy, 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—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 adventurous 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 essence, performing a biochemical "autopsy" on cells. The approach required more persistence than imagination, but it produced remarkable dividends. Subbarao purifed 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 muscles. Any one of these achievements should have been enough to warrant him a professorship at Harvard. But Subbarao was a foreigner, a recluse, 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 B₁₂, 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 including Harriet Kiltie, a young chemist at Lederle.

The chemical reactions to make folic acid brought a serendipitous bonus. Since the reactions had several intermediate steps, Subbarao and Kiltie 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 Kiltie and Subbarao asking them 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.

* 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.
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 pteroylglutamic 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 starchy, 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 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 something but about someone. 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
THE EMPEROR OF ALL MALADIES

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 Djoser, he dallied 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 febrile plague—typhus, perhaps—blazed through the port city of Avaris in 1715 BC, decimating its population. Smallpox erupted volcanically in pockets, leaving its telltale poxmarks 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-
campaign 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 Auferheide, a professor at the University of Minnesota in Duluth. Auferheide is a pathologist by training but his specialty is paleopathology, 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 these human specimens in small, sterile milk containers in a vaultlike chamber in Minnesota. There are nearly five thousand pieces of tissue, scores of biopsies, and hundreds of broken skeletons in his closet.

At the Chiribaya site, Auferheide rigged up a makeshift dissecting table and performed 140 autopsies over several weeks. One body revealed an extraordinary finding. The mummy was of a young woman in her mid-thirties, found sitting, with her feet curled up, in a shallow clay grave. When Auferheide examined her, his fingers found a hard “bulbous mass” in her left upper arm. The papery folds of skin, remarkably preserved, gave way to that mass, which was intact and studded with spicules of bone. This, without question, was a malignant bone tumor, an osteosarcoma, a thousand-year-old cancer preserved inside of a mummy. Auferheide suspects that the tumor had broken through the skin while she was still alive. Even small osteosarcomas can be unimaginably painful. The woman’s pain, he suggests, must have been blindingly intense.

Auferheide isn’t the only paleopathologist to have found cancers in mummified specimens. (Bone tumors, because they form hardened and calcified tissue, are vastly more likely to survive over centuries and are best preserved.) “There are other cancers found in mummies where the malignant tissue has been preserved. The oldest of these is an abdominal cancer from Dakhleh in Egypt from about four hundred AD,” he said. In other cases, paleopathologists have not found the actual tumors, but rather signs left by the tumors in the body. Some skeletons were riddled with tiny holes created by cancer in the skull or the shoulder bones, all arising from metastatic skin or breast cancer. In 1914, a team of archaeologists found a two-thousand-year-old Egyptian mummy in the Alexandrian catacombs with a tumor invading the pelvic bone. Louis Leakey, the anthropologist who dug up some of the earliest known human skeletons, also discovered a jawbone dating from two million years ago from a nearby site that carried the signs of a peculiar form of lymphoma found endemically in southeastern Africa (although the origin of that tumor was never confirmed pathologically). If that finding does represent an ancient mark of malignancy, then cancer, far from being a “modern” disease, is one of the oldest diseases ever seen in a human specimen—quite possibly the oldest.

The most striking finding, though, is not that cancer existed in the distant past, but that it was fleetingly rare. When I asked Auferheide about this,
he laughed. "The early history of cancer," he said, "is that there is very little early history of cancer." The Mesopotamians knew their migraines; the Egyptians had a word for seizures. A leprosy-like illness, tsara'at, is mentioned in the book of Leviticus. The Hindu Vedas have a medical term for dropsy and a goddess specifically dedicated to smallpox. Tuberculosis was so omnipresent and familiar to the ancients that—as with ice and the Eskimos—distinct words exist for each incarnation of it. But even common cancers, such as breast, lung, and prostate, are conspicuously absent. With a few notable exceptions, in the vast stretch of medical history there is no book or god for cancer.

There are several reasons behind this absence. Cancer is an age-related disease—sometimes exponentially so. The risk of breast cancer, for instance, is about 1 in 400 for a thirty-year-old woman and increases to 1 in 9 for a seventy-year-old. In most ancient societies, people didn't live long enough to get cancer. Men and women were long consumed by tuberculosis, dropsy, cholera, smallpox, leprosy, plague, or pneumonia. If cancer existed, it remained submerged under the sea of other illnesses. Indeed, cancer's emergence in the world is the product of a double negative: it becomes common only when all other killers themselves have been killed. Nineteenth-century doctors often linked cancer to civilization: cancer, they imagined, was caused by the rush and whirl of modern life, which somehow incited pathological growth in the body. The link was correct, but the causality was not: civilization did not cause cancer, but by extending human life spans—civilization unveiled it.

Longevity, although certainly the most important contributor to the prevalence of cancer in the early twentieth century, is probably not the only contributor. Our capacity to detect cancer earlier and earlier, and to attribute deaths accurately to it, has also dramatically increased in the last century. The death of a child with leukemia in the 1850s would have been attributed to an abscess or infection (or, as Bennett would have it, to a "suppuration of blood"). And surgery, biopsy, and autopsy techniques have further sharpened our ability to diagnose cancer. The introduction of mammography to detect breast cancer early in its course sharply increased its incidence—a seemingly paradoxical result that makes perfect sense when we realize that the X-rays allow earlier tumors to be diagnosed.

Finally, changes in the structure of modern life have radically shifted the spectrum of cancers—increasing the incidence of some, decreasing the incidence of others. Stomach cancer, for instance, was highly prev-
Onkos

Black bile without boiling causes cancers.
—Galen, AD 130

We have learned nothing, therefore, about the real cause of cancer or its actual nature. We are where the Greeks were.
—Francis Carter Wood in 1914

It’s bad bile. It’s bad habits. It’s bad bosses. It’s bad genes.
—Mel Greaves, Cancer:
The Evolutionary Legacy, 2000

In some ways disease does not exist until we have agreed that it does—by perceiving, naming, and responding to it.
—C. E. Rosenberg

Even an ancient monster needs a name. To name an illness is to describe a certain condition of suffering—a literary act before it becomes a medical one. A patient, long before he becomes the subject of medical scrutiny, is, at first, simply a storyteller, a narrator of suffering—a traveler who has visited the kingdom of the ill. To relieve an illness, one must begin, then, by unburdening its story.

The names of ancient illnesses are condensed stories in their own right. Typhus, a stormy disease, with erratic, vaporous fevers, arose from the Greek tphon, the father of winds—a word that also gives rise to the modern typhoon. Influenza emerged from the Latin influenza because medi-
eval doctors imagined that the cyclical epidemics of flu were influenced by stars and planets revolving toward and away from the earth. Tuberculosis coagulated out of the Latin tuber, referring to the swollen lumps of glands that looked like small vegetables. Lymphatic tuberculosis, TB of the lymph glands, was called scrofula, from the Latin word for “piglet,” evoking the rather morbid image of a chain of swollen glands arranged in a line like a group of suckling pigs.

It was in the time of Hippocrates, around 400 BC, that a word for cancer first appeared in the medical literature: karkinos, from the Greek word for “crab.” The tumor, with its clutch of swollen blood vessels around it, reminded Hippocrates of a crab dug in the sand with its legs spread in a circle. The image was peculiar (few cancers truly resemble crabs), but also vivid. Later writers, both doctors and patients, added embellishments. For some, the hardened, matted surface of the tumor was reminiscent of the tough carapace of a crab’s body. Others felt a crab moving under the flesh as the disease spread stealthily throughout the body. For yet others, the sudden stab of pain produced by the disease was like being caught in the grip of a crab’s pincers.

Another Greek word would intersect with the history of cancer—onkos, a word used occasionally to describe tumors, from which the discipline of oncology would take its modern name. Onkos was the Greek term for a mass or a load, or more commonly a burden; cancer was imagined as a burden carried by the body. In Greek theater, the same word, onkos, would be used to denote a tragic mask that was often “burdened” with an unwieldy conical weight on its head to denote the psychic load carried by its wearer.

But while these vivid metaphors might resonate with our contemporary understanding of cancer, what Hippocrates called karkinos and the disease that we now know as cancer were, in fact, vastly different creatures. Hippocrates’ karkinos were mostly large, superficial tumors that were easily visible to the eye: cancers of the breast, skin, jaw, neck, and tongue. Even the distinction between malignant and nonmalignant tumors likely escaped Hippocrates: his karkinos included every conceivable form of swelling—nodes, carbuncles, polyps, protrusions, tubercles, pustules, and glands—lumps lumped indiscriminately into the same category of pathology.

The Greeks had no microscopes. They had never imagined an entity called a cell, let alone seen one, and the idea that karkinos was the uncon-
trolled growth of cells could not possibly have occurred to them. They were, however, preoccupied with fluid mechanics—with waterwheels, pistons, valves, chambers, and sluices—a revolution in hydraulic science originating with irrigation and canal-digging and culminating with Archimedes discovering his eponymous laws in his bathtub. This preoccupation with hydraulics also flowed into Greek medicine and pathology. To explain illness—all illness—Hippocrates fashioned an elaborate doctrine based on fluids and volumes, which he freely applied to pneumonia, boils, dysentery, and hemorrhoids. The human body, Hippocrates proposed, was composed of four cardinal fluids called humors: blood, black bile, yellow bile, and phlegm. Each of these fluids had a unique color (red, black, yellow, and white), viscosity, and essential character. In the normal body, these four fluids were held in perfect, if somewhat precarious, balance. In illness, this balance was upset by the excess of one fluid.

The physician Claudius Galen, a prolific writer and influential Greek doctor who practiced among the Romans around AD 160, brought Hippocrates’ humoral theory to its apotheosis. Like Hippocrates, Galen set about classifying all illnesses in terms of excesses of various fluids. Inflammation—a red, hot, painful distension—was attributed to an overabundance of blood. Tubercles, pustules, catarrh, and nodules of lymph—all cool, boggy, and white—were excesses of phlegm. Jaundice was the overflow of yellow bile. For cancer, Galen reserved the most malevolent and disquieting of the four humors: black bile. (Only one other disease, replete with metaphors, would be attributed to an excess of this oily, viscous humor: depression. Indeed, melancholia, the medieval name for “depression,” would draw its name from the Greek melas, “black,” and khole, “bile.” Depression and cancer, the psychic and physical diseases of black bile, were thus intrinsically intertwined.) Galen proposed that cancer was “trapped” black bile—static bile unable to escape from a site and thus congealed into a matted mass. “Of blacke cholor [bile], without boyling cometh cancer,” Thomas Gale, the English surgeon, wrote of Galen’s theory in the sixteenth century, “and if the humor be sharpe, it maketh ulceration, and for this cause, these tumors are more blacker in color.”

That short, vivid description would have a profound impact on the future of oncology—much broader than Galen (or Gale) may have intended. Cancer, Galenic theory suggested, was the result of a systemic malignant state, an internal overdose of black bile. Tumors were just local outcroppings of a deep-seated bodily dysfunction, an imbalance of physiology that had pervaded the entire corpus. Hippocrates had once abstrusely opined that cancer was “best left untreated, since patients live longer that way.” Five centuries later, Galen had explained his teacher’s gnomic musings in a fantastical swoop of physiological conjecture. The problem with treating cancer surgically, Galen suggested, was that black bile was everywhere, as inevitable and pervasive as any fluid. You could cut cancer out, but the bile would flow right back, like sap seeping through the limbs of a tree.

Galen died in Rome in 199 AD, but his influence on medicine stretched over the centuries. The black-bile theory of cancer was so metaphorically seductive that it clung on tenaciously in the minds of doctors. The surgical removal of tumors—a local solution to a systemic problem—was thus perceived as a fool’s operation. Generations of surgeons layered their own observations on Galen’s, solidifying the theory even further. “Do not be led away and offer to operate,” John of Arderne wrote in the mid-1300s. “It will only be a disgrace to you.” Leonard Bertigaglia, perhaps the most influential surgeon of the fifteenth century, added his own admonishment: “Those who pretend to cure cancer by incising, lifting, and extirpating it only transform a nonulcerous cancer into an ulcerous one…. In all my practice, I have never seen a cancer cured by incision, nor known anyone who has.”

Unwittingly, Galen may actually have done the future victims of cancer a favor—at least a temporary one. In the absence of anesthesia and antibiotics, most surgical operations performed in the dank chamber of a medieval clinic—or more typically in the back room of a barbershop with a rusty knife and leather straps for restraints—were disastrous, life-threatening affairs. The sixteenth-century surgeon Ambroise Paré described charring tumors with a soldering iron heated on coals, or chemically searing them with a paste of sulfuric acid. Even a small nick in the skin, treated thus, could quickly suppurate into a lethal infection. The tumors would often profusely bleed at the slightest provocation.

Lorenz Heister, an eighteenth-century German physician, once described a mastectomy in his clinic as if it were a sacrificial ritual: “Many females can stand the operation with the greatest courage and without hardly moaning at all. Others, however, make such a clamor that they may dishearten even the most undaunted surgeon and hinder the operation. To perform the operation, the surgeon should be steadfast and not allow himself to become discomfited by the cries of the patient.”

Unsurprisingly, rather than take their chances with such “undaunted”
surgeons, most patients chose to hang their fates with Galen and try systemic medicines to purge the black bile. The apothecary thus soon filled up with an enormous list of remedies for cancer: tincture of lead, extracts of arsenic, boar’s tooth, fox lungs, rased ivory, hull ed castor, ground white-coral, ipecac, senna, and a smattering of purgatives and laxatives. There was alcohol and the tincture of opium for intractable pain. In the seventeenth century, a paste of crab’s eyes, at five shillings a pound, was popular—using fire to treat fire. The ointments and salves grew increasingly bizarre by the century: goat’s dung, frogs, crow’s feet, dog fennel, tortoise liver, the laying of hands, blessed waters, or the compression of the tumor with lead plates.

Despite Galen’s advice, an occasional small tumor was still surgically excised. (Even Galen had reportedly performed such surgeries, possibly for cosmetic or palliative reasons.) But the idea of surgical removal of cancer as a curative treatment was entertained only in the most extreme circumstances. When medicines and operations failed, doctors resorted to the only established treatment for cancer, borrowed from Galen’s teachings: an intricate series of bleeding and purging rituals to squeeze the humors out of the body, as if it were an overfilled, heavy sponge.

Vanishing Humors

*Rack’t carcasses make ill Anatomies.*
—John Donne

In the winter of 1533, a nineteen-year-old student from Brussels, Andreas Vesalius, arrived at the University of Paris hoping to learn Galenic anatomy and pathology and to start a practice in surgery. To Vesalius’s shock and disappointment, the anatomy lessons at the university were in a preposterous state of disarray. The school lacked a specific space for performing dissections. The basement of the Hospital Dieu, where anatomy demonstrations were held, was a theatrically macabre space where instructors hacked their way through decaying cadavers while dogs gnawed on bones and drippings below. “Aside from the eight muscles of the abdomen, badly mangled and in the wrong order, no one had ever shown a muscle to me, nor any bone, much less the succession of nerves, veins, and arteries,” Vesalius wrote in a letter. Without a map of human organs to guide them, surgeons were left to hack their way through the body like sailors sent to sea without a map—the blind leading the ill.

Frustrated with these ad hoc dissections, Vesalius decided to create his own anatomical map. He needed his own specimens, and he began to scour the graveyards around Paris for bones and bodies. At Montfaucon, he stumbled upon the massive gibbet of the city of Paris, where the bodies of petty prisoners were often left dangling. A few miles away, at the Cemetery of the Innocents, the skeletons of victims of the Great Plague lay half-exposed in their graves, eroded down to the bone.

The gibbet and the graveyard—the convenience stores for the medieval anatomist—yielded specimen after specimen for Vesalius, and he compulsively raided them, often returning twice a day to cut pieces dangling from the chains and smuggle them off to his dissection chamber. Anatomy came alive for him in this grisly world of the dead. In 1538, collaborat-
ing with artists in Titian's studio, Vesalius began to publish his detailed drawings in plates and books—elaborate and delicate etchings charting the courses of arteries and veins, mapping nerves and lymph nodes. In some plates, he pulled away layers of tissue, exposing the delicate surgical planes underneath. In another drawing, he sliced through the brain in deft horizontal sections—a human CT scanner, centuries before its time—to demonstrate the relationship between the cisterns and the ventricles.

Vesalius's anatomical project had started as a purely intellectual exercise but was soon propelled toward a pragmatic need. Galen's humoral theory of disease—that all diseases were pathological accumulations of the four cardinal fluids—required that patients be bled and purged to squeeze the culprit humors out of the body. But for the bleedings to be successful, they had to be performed at specific sites in the body. If the patient was to be bled prophylactically (that is, to prevent disease), then the purging was to be performed far away from the possible disease site, so that the humors could be diverted from it. But if the patient was being bled therapeutically—to cure an established disease—then the bleeding had to be done from nearby vessels leading into the site.

To clarify this already foggy theory, Galen had borrowed an equally foggy Hippocratic expression, κατείς—it Greek for "straight into"—to describe isolating the vessels that led "straight into" tumors. But Galen's terminology had pitched physicians into further confusion. What on earth, they wondered, had Galen meant by "straight into"? Which vessels led "straight into" a tumor or an organ, and which led the way out? The instructions became a maze of misunderstanding. In the absence of a systematic anatomical map—without the establishment of normality—abnormal anatomy was impossible to fathom.

Vesalius decided to solve the problem by systematically sketching out every blood vessel and nerve in the body, producing an anatomical atlas for surgeons. "In the course of explaining the opinion of the divine Hippocrates and Galen," he wrote in a letter, "I happened to delineate the veins on a chart, thinking that thus I might be able easily to demonstrate what Hippocrates understood by the expression κατείς, for you know how much dissension and controversy on venesection was stirred up, even among the learned."

But having started this project, Vesalius found that he could not stop. "My drawing of the veins pleased the professors of medicine and all the students so much that they earnestly sought from me a diagram of the arteries and also one of the nerves. . . . I could not disappoint them." The body was endlessly interconnected: veins ran parallel to nerves, the nerves were connected to the spinal cord, the cord to the brain, and so forth. Anatomy could only be captured in its totality, and soon the project became so gargantuan and complex that it had to be outsourced to yet other illustrators to complete.

But no matter how diligently Vesalius pored through the body, he could not find Galen's black bile. The word autopsy comes from the Greek "to see for oneself"; as Vesalius learned to see for himself, he could no longer force Galen's mystical visions to fit his own. The lymphatic system carried a pale, watery fluid; the blood vessels were filled, as expected, with blood. Yellow bile was in the liver. But black bile—Galen's oozing carrier of cancer and depression—could not be found anywhere.

Vesalius now found himself in a strange position. He had emerged from a tradition steeped in Galenic scholarship; he had studied, edited, and republished Galen's books. But black bile—that glistening centerpiece of Galen's physiology—was nowhere to be found. Vesalius hedged about his discovery. Guiltily, he heaped even more praise on the long-dead Galen. But, an empiricist to the core, Vesalius left his drawings just as he saw things, leaving others to draw their own conclusions. There was no black bile. Vesalius had started his anatomical project to save Galen's theory, but, in the end, he quietly buried it.

In 1793, Matthew Baillie, an anatomist in London, published a textbook called The Morbid Anatomy of Some of the Most Important Parts of the Human Body. Baillie's book, written for surgeons and anatomists, was the obverse of Vesalius's project: if Vesalius had mapped out "normal" anatomy, Baillie mapped the body in its diseased, abnormal state. It was Vesalius's study read through an inverted lens. Galen's fantastical speculations about illnesses were even more at stake here. Black bile may not have existed discernably in normal tissue, but tumors should have been chock-full of it. But none was to be found. Baillie described cancers of the lung ("as large as an orange"), stomach ("a fungous appearance"), and the testicles ("a foul deep ulcer") and provided vivid engravings of these tumors. But he could not find the channels of bile anywhere—not even in his orange-size tumors, nor in the deepest cavities of his "foul deep ulcers." If Galen's web of invisible fluids existed, then it existed outside tumors,
outside the pathological world, outside the boundaries of normal anatomical inquiry—in short, outside medical science. Like Vesalius, Baillie drew anatomy and cancer the way he actually saw it. At long last, the vivid channels of black bile, the humors in the tumors, that had so gripped the minds of doctors and patients for centuries, vanished from the picture.

"Remote Sympathy"

In treating of cancer, we shall remark, that little or no confidence should be placed either in internal . . . remedies, and that there is nothing, except the total separation of the part affected.

—A Dictionary of Practical Surgery, 1836

Matthew Baillie's *Morbid Anatomy* laid the intellectual foundation for the surgical extractions of tumors. If black bile did not exist, as Baillie had discovered, then removing cancer surgically might indeed rid the body of the disease. But surgery, as a discipline, was not yet ready for such operations. In the 1760s, a Scottish surgeon, John Hunter, Baillie's maternal uncle, had started to remove tumors from his patients in a clinic in London in quiet defiance of Galen's teachings. But Hunter's elaborate studies—initially performed on animals and cadavers in a shadowy menagerie in his own house—were stuck at a critical bottleneck. He could nimbly reach down into the tumors and, if they were "movable" (as he called superficial, noninvasive cancers), pull them out without disturbing the tender architecture of tissues underneath. "If a tumor is not only movable but the part naturally so," Hunter wrote, "they may be safely removed also. But it requires great caution to know if any of these consequent tumors are within proper reach, for we are apt to be deceived."

That last sentence was crucial. Albeit crudely, Hunter had begun to classify tumors into "stages." Movable tumors were typically early-stage, local cancers. Immovable tumors were advanced, invasive, and even metastatic. Hunter concluded that only movable cancers were worth removing surgically. For more advanced forms of cancer, he advised an honest, if chilling, remedy reminiscent of Imhotep's: "remote sympathy."

* Hunter used this term both to describe metastatic—remotely disseminated—cancer and to argue that therapy was useless.
Hunter was an immaculate anatomist, but his surgical mind was far ahead of his hand. A reckless and restless man with nearly maniacal energy who slept only four hours a night, Hunter had practiced his surgical skills endlessly on cadavers from every nook of the animal kingdom—on monkeys, sharks, walruses, pheasants, bears, and ducks. But with live human patients, he found himself at a standstill. Even if he worked at breakneck speed, having drugged his patient with alcohol and opium to near oblivion, the leap from cool, bloodless corpses to live patients was fraught with danger. As if the pain during surgery were not bad enough, the threat of infections after surgery loomed. Those who survived the terrifying crucible of the operating table often died even more miserable deaths in their own beds soon afterward.

In the brief span between 1846 and 1867, two discoveries swept away these two quandaries that had haunted surgery, thus allowing cancer surgeons to revisit the bold procedures that Hunter had tried to perfect in London.

The first of these discoveries, anesthesia, was publicly demonstrated in 1846 in a packed surgical amphitheater at Massachusetts General Hospital, less than ten miles from where Sidney Farber’s basement laboratory would be located a century later. At about ten o’clock on the morning of October 16, a group of doctors gathered in a pitlike room at the center of the hospital. A Boston dentist, William Morton, unveiled a small glass vaporizer, containing about a quart of ether, fitted with an inhaler. He opened the nozzle and asked the patient, Edward Abbott, a printer, to take a few whiffs of the vapor. As Abbott lollled into a deep sleep, a surgeon stepped into the center of the amphitheater and, with a few brisk strokes, deftly made a small incision in Abbott’s neck and closed a swollen, malformed blood vessel (referred to as a “tumor,” conflating malignant and benign swellings) with a quick stitch. When Abbott awoke a few minutes later, he said, “I did not experience pain at any time, though I knew that the operation was proceeding.”

Anesthesia—the dissociation of pain from surgery—allowed surgeons to perform prolonged operations, often lasting several hours. But the hurdle of postsurgical infection remained. Until the mid-nineteenth century, such infections were common and universally lethal, but their cause remained a mystery. “It must be some subtle principle contained [in the wound],” one surgeon concluded in 1819, “which eludes the sight.”

In 1865, a Scottish surgeon named Joseph Lister made an unusual conjecture on how to neutralize that “subtle principle” lurking elusive in the wound. Lister began with an old clinical observation: wounds left open to the air would quickly turn gangrenous, while closed wounds would often remain clean and uninfected. In the postsurgical wards of the Glasgow infirmary, Lister had again and again seen an angry red margin begin to spread out from the wound and then the skin seemed to rot from inside out, often followed by fever, pus, and a swift death (a bona fide “suppuration”).

Lister thought of a distant, seemingly unrelated experiment. In Paris, Louis Pasteur, the great French chemist, had shown that meat broth left exposed to the air would soon turn turbid and begin to ferment, while meat broth sealed in a sterilized vacuum jar would remain clear. Based on these observations, Pasteur had made a bold claim: the turbidity was caused by the growth of invisible microorganisms—bacteria—that had fallen out of the air into the broth. Lister took Pasteur’s reasoning further. An open wound—a mixture of clotted blood and denuded flesh—was, after all, a human variant of Pasteur’s meat broth, a natural petri dish for bacterial growth. Could the bacteria that had dropped into Pasteur’s cultures in France also be dropping out of the air into Lister’s patients’ wounds in Scotland?

Lister then made another inspired leap of logic. If postsurgical infections were being caused by bacteria, then perhaps an antibacterial process or chemical could curb these infections. It “occurred to me,” he wrote in his clinical notes, “that the decomposition in the injured part might be avoided without excluding the air, by applying as a dressing some material capable of destroying the life of the floating particles.”

In the neighboring town of Carlisle, Lister had observed sewage disposers cleanse their waste with a cheap, sweet-smelling liquid containing carbolic acid. Lister began to apply carbolic acid paste to wounds after surgery. (That he was applying a sewage cleanser to his patients appears not to have struck him as even the slightest bit unusual.)

In August 1867, a thirteen-year-old boy who had severely cut his arm while operating a machine at a fair in Glasgow was admitted to Lister’s infirmary. The boy’s wound was open and smeared with grime—a setup for gangrene. But rather than amputating the arm, Lister tried a salve of carbolic acid, hoping to keep the arm alive and uninfected. The wound teetered on the edge of a terrifying infection, threatening to become an abscess. But Lister persisted, intensifying his application of carbolic acid paste. For a few weeks, the whole effort seemed hopeless. But then, like a fire running to the
end of a rope, the wound began to dry up. A month later, when the poultices were removed, the skin had completely healed underneath.

It was not long before Lister's invention was joined to the advancing front of cancer surgery. In 1869, Lister removed a breast tumor from his sister, Isabella Pim, using a dining table as his operating table, ether for anesthesia, and carbolic acid as his antiseptic. She survived without an infection (although she would eventually die of liver metastasis three years later). A few months later, Lister performed an extensive amputation on another patient with cancer, likely a sarcoma in a thigh. By the mid-1870s, Lister was routinely operating on breast cancer and had extended his surgery to the cancer-afflicted lymph nodes under the breast.

Antisepsis and anesthesia were twin technological breakthroughs that released surgery from its constraining medieval chrysalis. Armed with ether and carbolic soap, a new generation of surgeons lunged toward the forbiddingly complex anatomical procedures that Hunter and his colleagues had once concocted on cadavers. An incandescent century of cancer surgery emerged; between 1850 to 1950, surgeons brazenly attacked cancer by cutting open the body and removing tumors.

Emblematic of this era was the prolific Viennese surgeon Theodor Billroth. Born in 1821, Billroth studied music and surgery with almost equal verve. (The professions still often go hand in hand. Both push manual skill to its limit; both mature with practice and age; both depend on immediacy, precision, and opposable thumbs.) In 1867, as a professor in Berlin, Billroth launched a systematic study of methods to open the human abdomen to remove malignant masses. Until Billroth's time, the mortality following abdominal surgery had been forbidding. Billroth's approach to the problem was meticulous and formal: for nearly a decade, he spent surgery after surgery simply opening and closing abdomens of animals and human cadavers, defining clear and safe routes to the inside. By the early 1880s, he had established the routes: "The course so far is already sufficient proof that the operation is possible," he wrote. "Our next care, and the subject of our next studies, must be to determine the indications, and to develop the technique to suit all kinds of cases. I hope we have taken another good step forward towards securing unfortunate people hitherto regarded as incurable."

At the Allgemeines Krankenhaus, the teaching hospital in Vienna where he was appointed a professor, Billroth and his students now began to master and use a variety of techniques to remove tumors from the stomach, colon, ovaries, and esophagus, hoping to cure the body of cancer. The switch from exploration to cure produced an unanticipated challenge. A cancer surgeon's task was to remove malignant tissue while leaving normal tissues and organs intact. But this task, Billroth soon discovered, demanded a nearly godlike creative spirit.

Since the time of Vesalius, surgery had been immersed in the study of natural anatomy. But cancer so often disobeyed and distorted natural anatomical boundaries that unnatural boundaries had to be invented to constrain it. To remove the distal end of a stomach filled with cancer, for instance, Billroth had to hook up the pouch remaining after surgery to a nearby piece of the small intestine. To remove the entire bottom half of the stomach, he had to attach the remainder to a piece of distant jejunum. By the mid-1890s, Billroth had operated on forty-one patients with gastric carcinoma using these novel anatomical reconfigurations. Nineteen of these patients had survived the surgery.

These procedures represented pivotal advances in the treatment of cancer. By the early twentieth century, many locally restricted cancers (i.e., primary tumors without metastatic lesions) could be removed by surgery. These included uterine and ovarian cancer, breast and prostate cancer, colon cancer, and lung cancer. If these tumors were removed before they had invaded other organs, these operations produced cures in a significant fraction of patients.

But despite these remarkable advances, some cancers—even seemingly locally restricted ones—still relapsed after surgery, prompting second and often third attempts to resect tumors. Surgeons returned to the operating table and cut and cut again, as if caught in a cat-and-mouse game, as cancer was slowly excavated out of the human body piece by piece.

But what if the whole of cancer could be uprooted at its earliest stage using the most definitive surgery conceivable? What if cancer, incurable by means of conventional local surgery, could be cured by a radical, aggressive operation that would dig out its roots so completely, so exhaustively, that no possible trace was left behind? In an era captivated by the potency and creativity of surgeons, the idea of a surgeon's knife extracting cancer by its roots was imbued with promise and wonder. It would land on the already brittle and combustible world of oncology like a firecracker thrown into gunpowder.
A Radical Idea

The professor who blesses the occasion,
Which permits him to explain something profound
Nears me and is pleased to direct me—
“Amputate the breast.”
“Pardon me,” I said with sadness
“But I had forgotten the operation.”
—Rodolfo Figueroa,
in Poet Physicians

It is over: she is dressed, steps gently and decently down
from the table, looks for James; then, turning to the
surgeon and the students, she curtsies—and in a low,
clear voice, begs their pardon if she has behaved ill.
The students—all of us—wept like children; the surgeon
hopped her up.
—John Brown describing a
nineteenth-century mastectomy

William Stewart Halsted, whose name was to be inseparably attached to
the concept of “radical” surgery, did not ask for that distinction. Instead,
it was handed to him almost without any asking, like a scalpel delivered
wordlessly into the outstretched hand of a surgeon. Halsted didn’t invent
radical surgery. He inherited the idea from his predecessors and brought it
to its extreme and logical perfection—only to find it inextricably attached
to his name.

Halsted was born in 1852, the son of a well-to-do clothing merchant in
New York. He finished high school at the Phillips Academy in Andover
and attended Yale College, where his athletic prowess, rather than aca-
demic achievement, drew the attention of his teachers and mentors. He
wandered into the world of surgery almost by accident, attending med-
cal school not because he was driven to become a surgeon but because
he could not imagine himself apprenticed as a merchant in his father’s
business. In 1874, Halsted matriculated at the College of Physicians and
Surgeons at Columbia. He was immediately fascinated by anatomy. This
fascination, like many of Halsted’s other interests in his later years—
purebred dogs, horses, starched tablecloths, linen shirts, Parisian leather
shoes, and immaculate surgical sutures—soon grew into an obsessive
quest. He swallowed textbooks of anatomy whole and, when the books
were exhausted, moved on to real patients with an equally insatiable
hunger.

In the mid-1870s, Halsted passed an entrance examination to be a sur-
gical intern at Bellevue, a New York City hospital swarming with surgical
patients. He split his time between the medical school and the surgical
clinic, traveling several miles across New York between Bellevue and
Columbia. Understandably, by the time he had finished medical school,
he had already suffered a nervous breakdown. He recuperated for a few
weeks on Block Island, then, dusting himself off, resumed his studies with
just as much energy and verve. This pattern—heroic, Olympian exertion
to the brink of physical impossibility, often followed by a near collapse—
was to become a hallmark of Halsted’s approach to nearly every challenge.
It would leave an equally distinct mark on his approach to surgery, surgical
education—and cancer.

Halsted entered surgery at a transitional moment in its history.
Bloodletting, cupping, leaching, and purging were common procedures.
One woman with convulsions and fever from a postsurgical infection was
treated with even more barbaric attempts at surgery: “I opened a large or-
ifice in each arm,” her surgeon wrote with self-congratulatory enthusiasm
in the 1850s, “and cut both temporal arteries and had her blood flowing
freely from all at the same time, determined to bleed her until the con-
vulsions ceased.” Another doctor, prescribing a remedy for lung cancer,
noticed, “Small bleedings give temporary relief, although, of course, they
cannot often be repeated.” At Bellevue, the “internes” ran about in corri-
dors with “pus-pails,” the bodily drippings of patients spilling out of them.
Surgical sutures were made of catgut, sharpened with spit, and left to hang
from incisions into the open air. Surgeons walked around with their scal-
pels dangling from their pockets. If a tool fell on the blood-soiled floor, it
Halsted began to inject himself with the drug, testing it before using it to numb patients for his ambitious surgeries. He found that it produced much more than a transitory numbness: it amplified his instinct for tirelessness; it synergized with his already manic energy. His mind became, as one observer put it, “clearer and clearer, with no sense of fatigue and no desire or ability to sleep.” He had, it would seem, conquered all his mortal imperfections: the need to sleep, exhaustion, and nihilism. His resitve personality had met its perfect pharmacological match.

For the next five years, Halsted sustained an incredible career as a young surgeon in New York despite a fierce and growing addiction to cocaine. He wrested some control over his addiction by heroic self-denial and discipline. (At night, he reportedly left a sealed vial of cocaine by his bedside, thus testing himself by constantly having the drug within arm’s reach.) But he relapsed often and fiercely, unable to ever fully overcome his habit. He voluntarily entered the Butler sanatorium in Providence, where he was treated with morphine to treat his cocaine habit—in essence, exchanging one addiction for another. In 1889, still oscillating between the two highly addictive drugs (yet still astonishingly productive in his surgical clinic in New York), he was recruited to the newly built Johns Hopkins Hospital by the renowned physician William Welch—in part to start a new surgical department and in part to wrest him out of his New York world of isolation, overwork, and drug addiction.

Hopkins was meant to change Halsted, and it did. Gregarious and outgoing in his former life, he withdrew sharply into a coconned and private empire where things were controlled, clean, and perfect. He launched an awe-inspiring training program for young surgical residents that would build them into the man to his own image—a superhuman initiation into a superhuman profession that emphasized heroism, self-denial, diligence, and tirelessness. (“It will be objected that this apprenticeship is too long, that the young surgeon will be stale,” he wrote in 1904, but “these positions are not for those who so soon weary of the study of their profession.”) He married Caroline Hampton, formerly his chief nurse, and lived in a sprawling three-story mansion on the top of a hill (“cold as stone and most unlivable,” as one of his students described it), each residing on a separate floor. Childless, socially awkward, formal, and notoriously reclusive, the Halsteds raised thoroughbred horses and purebred dachshunds. Halsted was still deeply addicted to morphine, but he took the drug in such controlled doses and on such a strict schedule that not even his closest stu-
students suspected it. The couple diligently avoided Baltimore society. When visitors came unannounced to their mansion on the hill, the maid was told to inform them that the Halsteds were not home.

With the world around him erased and silenced by this routine and rhythm, Halsted now attacked breast cancer with relentless energy. At Volkmann’s clinic in Halle, Halsted had witnessed the German surgeon performing increasingly meticulous and aggressive surgeries to remove tumors from the breast. But Volkmann, Halsted knew, had run into a wall. Even though the surgeries had grown extensive and exhaustive, breast cancer had still relapsed, eventually recurring months or even years after the operation.

What caused this relapse? At St. Luke’s Hospital in London in the 1860s, the English surgeon Charles Moore had also noted these vexing local recurrences. Frustrated by repeated failures, Moore had begun to record the anatomy of each relapse, denoting the area of the original tumor, the precise margin of the surgery, and the site of cancer recurrence by drawing tiny black dots on a diagram of a breast—creating a sort of historical dartboard of cancer recurrence. And to Moore’s surprise, dot by dot, a pattern had emerged. The recurrences had accumulated precisely around the margins of the original surgery, as if minute remnants of cancer had been left behind by incomplete surgery and grown back. “Mammary cancer requires the careful extirpation of the entire organ,” Moore concluded. “Local recurrence of cancer after operations is due to the continuous growth of fragments of the principal tumor.”

Moore’s hypothesis had an obvious corollary. If breast cancer relapsed due to the inadequacy of the original surgical excitations, then even more breast tissue should be removed during the initial operation. Since the margins of extirpation were the problem, then why not extend the margins? Moore argued that surgeons, attempting to spare women the disfiguring (and often life-threatening) surgery were exercising “mistaken kindness”—letting cancer get the better of their knives. In Germany, Halsted had seen Volkmann remove not just the breast, but a thin, fan-like muscle spread out immediately under the breast called the pectoralis minor, in the hopes of cleaning out the minor fragments of leftover cancer.

Halsted took this line of reasoning to its next inevitable step. Volkmann may have run into a wall; Halsted would excavate his way past it. Instead of stripping away the thin pectoralis minor, which had little function, Halsted decided to dig even deeper into the breast cavity, cutting through the pectoralis major, the large, prominent muscle responsible for moving the shoulder and the hand. Halsted was not alone in this innovation: Willy Meyer, a surgeon operating in New York, independently arrived at the same operation in the 1890s. Halsted called this procedure the “radical mastectomy,” using the word radical in the original Latin sense to mean “root”; he was uprooting cancer from its very source.

But Halsted, evidently scornful of “mistaken kindness,” did not stop his surgery at the pectoralis major. When cancer still recurred despite his radical mastectomy, he began to cut even farther into the chest. By 1898, Halsted’s mastectomy had taken what he called “an even more radical” turn. Now he began to slice through the collarbone, reaching for a small cluster of lymph nodes that lay just underneath it. “We clean out or strip the supraclavicular fossa with very few exceptions,” he announced at a surgical conference, reinforcing the notion that conservative, nonradical surgery left the breast somehow “unclean.”

At Hopkins, Halsted’s diligent students now raced to outpace their master with their own scalps. Joseph Bloodgood, one of Halsted’s first surgical residents, had started to cut farther into the neck to evacuate a chain of glands that lay above the collarbone. Harvey Cushing, another star apprentice, even “cleaned out the anterior mediastinum,” the deep lymph nodes buried inside the chest. “It is likely,” Halsted noted, “that we shall, in the near future, remove the mediastinal contents at some of our primary operations.” A macabre marathon was in progress. Halsted and his disciples would rather evacuate the entire contents of the body than be faced with cancer recurrences. In Europe, one surgeon evacuated three ribs and other parts of the rib cage and amputated a shoulder and a collarbone from a woman with breast cancer.

Halsted acknowledged the “physical penalty” of his operation; the mammoth mastectomies permanently disfigured the bodies of his patients. With the pectoralis major cut off, the shoulders caved inward as if in a perpetual shrug, making it impossible to move the arm forward or sideways. Removing the lymph nodes under the armpit often disrupted the flow of lymph, causing the arm to swell up with accumulated fluid like an elephant’s leg, a condition he vividly called “surgical elephantiasis.” Recovery from surgery often took patients months, even years. Yet Halsted accepted all these consequences as if they were the inevitable war wounds in an all-out battle. “The patient was a young lady whom I was loath to disfigure,” he wrote with genuine concern, describing an opera-
tion extending all the way into the neck that he had performed in the 1890s. Something tender, almost paternal, appears in his surgical notes, with outcomes scribbled alongside personal reminiscences. “Good use of arm. Chops wood with it . . . no swelling,” he wrote at the end of one case. “Married, Four Children,” he scribbled in the margins of another.

But did the Halsted mastectomy save lives? Did radical surgery cure breast cancer? Did the young woman that he was so “loath to disfigure” benefit from the surgery that had disfigured her?

Before answering those questions, it’s worthwhile understanding the milieu in which the radical mastectomy flourished. In the 1870s, when Halsted had left for Europe to learn from the great masters of the art, surgery was a discipline emerging from its adolescence. By 1898, it had transformed into a profession booming with self-confidence, a discipline so swooningly self-impressed with its technical abilities that great surgeons unabashedly imagined themselves as showmen. The operating room was called an operating theater, and surgery was an elaborate performance often watched by a tense, hushed audience of observers from an oculus above the theater. To watch Halsted operate, one observer wrote in 1898, was to watch the “performance of an artist close akin to the patient and minute labor of a Venetian or Florentine intaglio cutter or a master worker in mosaic.” Halsted welcomed the technical challenges of his operation, often conflating the most difficult cases with the most curable: “I find myself inclined to welcome largeness [of a tumor],” he wrote—challenging cancer to duel with his knife.

But the immediate technical success of surgery was not a predictor of its long-term success, its ability to decrease the relapse of cancer. Halsted’s mastectomy may have been a Florentine mosaic worker’s operation, but if cancer was a chronic relapsing disease, then perhaps cutting it away, even with Halsted’s intaglio precision, was not enough. To determine whether Halsted had truly cured breast cancer, one needed to track not immediate survival, or even survival over five or ten months, but survival over five or ten years.

The procedure had to be put to a test by following patients longitudinally in time. So, in the mid-1890s, at the peak of his surgical career, Halsted began to collect long-term statistics to show that his operation was the superior choice. By then, the radical mastectomy was more than a decade old. Halsted had operated on enough women and extracted enough tumors to create what he called an entire “cancer storehouse” at Hopkins.

Halsted would almost certainly have been right in his theory of radical surgery: that attacking even small cancers with aggressive local surgery was the best way to achieve a cure. But there was a deep conceptual error. Imagine a population in which breast cancer occurs at a fixed incidence, say 1 percent per year. The tumors, however, demonstrate a spectrum of behavior right from their inception. In some women, by the time the disease has been diagnosed the tumor has already spread beyond the breast; there is metastatic cancer in the bones, lungs, and liver. In other women, the cancer is confined to the breast, or to the breast and a few nodes; it is truly a local disease.

Position Halsted now, with his scalpel and sutures, in the middle of this population, ready to perform his radical mastectomy on any woman with breast cancer. Halsted’s ability to cure patients with breast cancer obviously depends on the sort of cancer—the stage of breast cancer—that he confronts. The woman with the metastatic cancer is not going to be cured by a radical mastectomy, no matter how aggressively and meticulously Halsted extinguishes the tumor in her breast: her cancer is no longer a local problem. In contrast, the woman with the small, confined cancer does benefit from the operation—but for her, a far less aggressive procedure, a local mastectomy, would have done just as well. Halsted’s mastectomy is thus a peculiar misfit in both cases; it underestimates its target in the first case and overestimates it in the second. In both cases, women are forced to undergo indiscriminate, disfiguring, and morbid operations—too much, too early for the woman with local breast cancer, and too little, too late, for the woman with metastatic cancer.

On April 19, 1898, Halsted attended the annual conference of the American Surgical Association in New Orleans. On the second day, before a hushed and eager audience of surgeons, he rose to the podium armed with figures and tables showcasing his highly anticipated data. At first glance, his observations were astounding: his mastectomy had outperformed every other surgeon’s operation in terms of local recurrence. At Baltimore, Halsted had slashed the rate of local recurrence to a bare few percent, a drastic improvement on Volkman’s or Billroth’s numbers. Just
as Halsted had promised, he had seemingly exterminated cancer at its root.

But if one looked closely, the roots had persisted. The evidence for a true cure of breast cancer was much more disappointing. Of the seventy-six patients with breast cancer treated with the “radical method,” only forty had survived for more than three years. Thirty-six, or nearly half the original number, had died within three years of the surgery—consumed by a disease supposedly “uprooted” from the body.

But Halsted and his students remained unfazed. Rather than address the real question raised by the data—did radical mastectomy truly extend lives?—they clutched to their theories ever more adamantly. A surgeon should “operate on the neck in every case,” Halsted emphasized in New Orleans. Where others might have seen reason for caution, Halsted only saw opportunity: “I fail to see why the neck involvement in itself is more serious than the axillary [area]. The neck can be cleared out as thoroughly as the axilla.”

In the summer of 1907, Halsted presented more data to the American Surgical Association in Washington, D.C. He divided his patients into three groups based on whether the cancer had spread before surgery to lymph nodes in the axilla or the neck. When he put up his survival tables, a pattern became apparent. Of the sixty patients with no cancer-affected nodes in the axilla or the neck, the substantial number of forty-five had been cured of breast cancer at five years. Of the forty patients with such nodes, only three had survived.

The ultimate survival from breast cancer, in short, had little to do with how extensively a surgeon operated on the breast; it depended on how extensively the cancer had spread before surgery. As George Crile, one of the most fervent critics of radical surgery, later put it, “If the disease was so advanced that one had to get rid of the muscles in order to get rid of the tumor, then it had already spread through the system”—making the whole operation moot.

But if Halsted came to the brink of this realization in 1907, he just as emphatically shied away from it. He relapsed to stale aphorisms. “But even without the proof which we offer, it is, I think, incumbent upon the surgeon to perform in many cases the supraclavicular operation,” he advised in one paper. By now the perpetually changing landscape of breast cancer was beginning to tire him out. Trials, tables, and charts had never been his forte; he was a surgeon, not a bookkeeper. “It is especially true

of mammary cancer,” he wrote, “that the surgeon interested in furnishing the best statistics may in perfectly honorable ways provide them.” That statement—almost vulgar by Halsted’s standards—exemplified his growing skepticism about putting his own operation to a test. He instinctively knew that he had come to the far edge of his understanding of this amorphous illness that was constantly slipping out of his reach.

The 1907 paper was to be Halsted’s last and most comprehensive discussion on breast cancer. He wanted new and open anatomical vistas where he could practice his technically brilliant procedures in peace, not debates about the measurement and remeasurement of end points of surgery. Never having commanded a particularly good bedside manner, he retreated fully into his cloistered operating room and into the vast, cold library of his mansion. He had already moved on to other organs—the thorax, the thyroid, the great arteries—where he continued to make brilliant surgical innovations. But he never wrote another scholarly analysis of the majestic and flawed operation that bore his name.

Between 1891 and 1907—in the sixteen hectic years that stretched from the tenuous debut of the radical mastectomy in Baltimore to its center-stage appearances at vast surgical conferences around the nation—the quest for a cure for cancer took a great leap forward and an equally great step back. Halsted proved beyond any doubt that massive,meticulous surgeries were technically possible in breast cancer. These operations could drastically reduce the risk for the local recurrence of a deadly disease. But what Halsted could not prove, despite his most strenuous efforts, was far more revealing. After nearly two decades of data gathering, having been levitated, praised, analyzed, and reanalyzed in conference after conference, the superiority of radical surgery in “curing” cancer still stood on shaky ground. More surgery had just not translated into more effective therapy.

Yet all this uncertainty did little to stop other surgeons from operating just as aggressively. “Radicalism” became a psychological obsession, burrowing its way deeply into cancer surgery. Even the word radical was a seductive conceptual trap. Halsted had used it in the Latin sense of “root” because his operation was meant to dig out the buried, subterranean roots of cancer. But radical also meant “aggressive,” “innovative,” and “brazen,” and it was this meaning that left its mark on the imaginations of patients.
THE EMPEROR OF ALL MALADIES

What man or woman, confronting cancer, would willingly choose non-radical, or "conservative," surgery?

Indeed, radicalism became central not only to how surgeons saw cancer, but also in how they imagined themselves. "With no protest from any other quarter and nothing to stand in its way, the practice of radical surgery," one historian wrote, "soon fossilized into dogma." When heroic surgery failed to match its expectations, some surgeons began to shrug off the responsibility of a cure altogether. "Undoubtedly, if operated upon properly the condition may be cured locally, and that is the only point for which the surgeon must hold himself responsible," one of Halsted's disciples announced at a conference in Baltimore in 1931. The best a surgeon could do, in other words, was to deliver the most technically perfect operation. Curing cancer was someone else's problem.

This trajectory toward more and more brazenly aggressive operations—"the more radical the better"—mirrored the overall path of surgical thinking of the early 1930s. In Chicago, the surgeon Alexander Brunschwig devised an operation for cervical cancer, called a "complete pelvic excetration," so strenuous and exhaustive that even the most Halstedian surgeon needed to break midprocedure to rest and change positions. The New York surgeon George Pack was nicknamed Pack the Knife (after the popular song "Mack the Knife"), as if the surgeon and his favorite instrument had, like some sort of ghoulish centaur, somehow fused into the same creature.

Cure was a possibility now flung far into the future. "Even in its widest sense," an English surgeon wrote in 1929, "the measure of operability depends on the question: 'Is the lesion removable?' and not on the question: 'Is the removal of the lesion going to cure the patient?'" Surgeons often counted themselves lucky if their patients merely survived these operations. "There is an old Arabian proverb," a group of surgeons wrote at the end of a particularly chilling discussion of stomach cancer in 1933, "that he is no physician who has not slain many patients, and the surgeon who operates for carcinoma of the stomach must remember that often."

To arrive at that sort of logic—the Hippocratic oath turned upside down—demands either a terminal desperation or a terminal optimism. In the 1930s, the pendulum of cancer surgery swung desperately between those two points. Halsted, Brunschwig, and Pack persisted with their mammoth operations because they genuinely believed that they could relieve the dreaded symptoms of cancer. But they lacked formal proof, and as they went further up the isolated promontories of their own beliefs, proof became irrelevant and trials impossible to run. The more fervently surgeons believed in the inherent good of their operations, the more untenable it became to put these to a formal scientific trial. Radical surgery thus drew the blinds of circular logic around itself for nearly a century.

"OF BLACKE CHOLOR, WITHOUT BOYLING"

The allure and glamour of radical surgery overshadowed crucial developments in less radical surgical procedures for cancer that were evolving in its penumbra. Halsted's students fanned out to invent new procedures to extirpate cancers. Each was "assigned" an organ. Halsted's confidence in his heroic surgical training program was so supreme that he imagined his students capable of confronting and annihilating cancer in any organ system. In 1897, having intercepted a young surgical resident, Hugh Hampton Young, in a corridor at Hopkins, Halsted asked him to become the head of the new department of urological surgery. Young protested that he knew nothing about urological surgery. "I know you didn't know anything," Halsted replied curtly, "but we believe that you can learn"—and walked on.

Inspired by Halsted's confidence, Young delved into surgery for urological cancers—cancers of the prostate, kidney, and bladder. In 1904, with Halsted as his assistant, Young successfully devised an operation for prostate cancer by excising the entire gland. Although called the radical prostatectomy in the tradition of Halsted, Hampton's surgery was rather conservative by comparison. He did not remove muscles, lymph nodes, or bone. He retained the notion of the en bloc removal of the organ from radical surgery, but stopped short of evacuating the entire pelvis or extirpating the urethra or the bladder. (A modification of this procedure is still used to remove localized prostate cancer, and it cures a substantial portion of patients with such tumors.)

Harvey Cushing, Halsted's student and chief surgical resident, concentrated on the brain. By the early 1900s, Cushing had found ingenious ways to surgically extract brain tumors, including the notorious glioblastomas—tumors so heavily crisscrossed with blood vessels that they could hemorrhage any minute, and meningiomas wrapped like sheaths around delicate and vital structures in the brain. Like Young, Cushing inherited Halsted's intaglio surgical technique—"the slow separation of brain from tumor, working now here, now there, leaving small, flattened pads of hot, wrung-out cotton to control oozing"—but not Halsted's penchant for rad-
ical surgery. Indeed Cushing found radical operations on brain tumors not just difficult, but inconceivable: even if he desired it, a surgeon could not extirpate the entire organ.

In 1933, at the Barnes Hospital in St. Louis, yet another surgical innovator, Evarts Graham, pioneered an operation to remove a lung afflicted with cancer by piecing together prior operations that had been used to remove tubercular lungs. Graham, too, retained the essential spirit of Halstedian surgery: the meticulous excision of the organ en bloc and the cutting of wide margins around the tumor to prevent local recurrences. But he tried to sidestep its pitfalls. Resisting the temptation to excise more and more tissue—lymph nodes throughout the thorax, major blood vessels, or the adjacent fascia around the trachea and esophagus—he removed just the lung, keeping the specimen as intact as possible.

Even so, obsessed with Halstedian theory and unable to see beyond its realm, surgeons sharply berated such attempts at nonradical surgery. A surgical procedure that did not attempt to obliterate cancer from the body was pooh-poohed as a “makeshift operation.” To indulge in such make-shift operations was to succumb to the old flaw of “mishandled kindness” that a generation of surgeons had tried so diligently to banish.

The Hard Tube and the Weak Light

We have found in [X-rays] a cure for the malady.
—Los Angeles Times, April 6, 1902

By way of illustration [of the destructive power of X-rays]
let us recall that nearly all pioneers in the medical X-ray laboratories in the United States died of cancers induced
by the burns.

—The Washington Post, 1945

In late October 1895, a few months after Halsted had unveiled the radical mastectomy in Baltimore, Wilhelm Röntgen, a lecturer at the Würzburg Institute in Germany, was working with an electron tube—a vacuum tube that shot electrons from one electrode to another—when he noticed a strange leakage. The radiant energy was powerful and invisible, capable of penetrating layers of blackened cardboard and producing a white phosphorescent glow on a barium screen accidentally left on a bench in the room.

Röntgen whisked his wife, Anna, into the lab and placed her hand between the source of his rays and a photographic plate. The rays penetrated through her hand and left a silhouette of her finger bones and her metallic wedding ring on the photographic plate—the inner anatomy of a hand seen as if through a magical lens. “I have seen my death,” Anna said—but her husband saw something else: a form of energy so powerful that it could pass through most living tissues. Röntgen called his form of light X-rays.

At first, X-rays were thought to be an artificial quirk of energy produced by electron tubes. But in 1896, just a few months after Röntgen’s discovery, Henri Becquerel, the French chemist, who knew of Röntgen’s
work, discovered that certain natural materials—uranium among them—autonomously emitted their own invisible rays with properties similar to those of X-rays. In Paris, friends of Becquerel’s, a young physicist-chemist couple named Pierre and Marie Curie, began to scour the natural world for even more powerful chemical sources of X-rays. Pierre and Marie (then Maria Sklodowska, a penniless Polish immigrant living in a garret in Paris) had met at the Sorbonne and been drawn to each other because of a common interest in magnetism. In the mid-1880s, Pierre Curie had used minuscule quartz crystals to craft an instrument called an electrometer, capable of measuring exquisitely small doses of energy. Using this device, Marie had shown that even tiny amounts of radiation emitted by uranium ores could be quantified. With their new measuring instrument for radioactivity, Marie and Pierre began hunting for new sources of X-rays. Another monumental journey of scientific discovery was thus launched with measurement.

In a waste ore called pitchblende, a black sludge that came from the peaty forests of Joachimsthal in what is now the Czech Republic, the Curies found the first signal of a new element—an element many times more radioactive than uranium. The Curies set about distilling the boggy sludge to trap that potent radioactive source in its purest form. From several tons of pitchblende, four hundred tons of washing water, and hundreds of buckets of distilled sludge waste, they finally fished out one-tenth of a gram of the new element in 1902. The metal lay on the far edge of the periodic table, emitting X-rays with such feverish intensity that it glowed with a hypnotic blue light in the dark, consuming itself. Unstable, it was a strange chimera between matter and energy—matter decomposing into energy. Marie Curie called the new element radium, from the Greek word for “light.”

Radium, by virtue of its potency, revealed a new and unexpected property of X-rays: they could not only carry radiant energy through human tissues, but also deposit energy deep inside tissues. Röntgen had been able to photograph his wife’s hand because of the first property: his X-rays had traversed through flesh and bone and left a shadow of the tissue on the film. Marie Curie’s hands, in contrast, bore the painful legacy of the second effect: having distilled pitchblende into a millionth part for week after week in the hunt for purer and purer radioactivity, the skin in her palm had begun to chafe and peel off in blackened layers, as if the tissue had been burnt from the inside. A few milligrams of radium left in a vial in Pierre’s pocket scorched through the heavy tweed of his waistcoat and left a permanent scar on his chest. One man who gave “magical” demonstrations at a public fair with a leaky, unshielded radium machine developed swollen and blistered lips, and his cheeks and nails fell out. Radiation would eventually burn into Marie Curie’s bone marrow, leaving her permanently anemic.

It would take biologists decades to fully decipher the mechanism that lay behind these effects, but the spectrum of damaged tissues—skin, lips, blood, gums, and nails—already provided an important clue: radium was attacking DNA. DNA is an inert molecule, exquisitely resistant to most chemical reactions, for its job is to maintain the stability of genetic information. But X-rays can shatter strands of DNA or generate toxic chemicals that corrode DNA. Cells respond to this damage by dying or, more often, by ceasing to divide. X-rays thus preferentially kill the most rapidly proliferating cells in the body, cells in the skin, nails, gums, and blood.

This ability of X-rays to selectively kill rapidly dividing cells did not go unnoticed—especially by cancer researchers. In 1896, barely a year after Röntgen had discovered his X-rays, a twenty-one-year-old Chicago medical student, Emil Grubbe, had the inspired notion of using X-rays to treat cancer. Flamboyant, adventurous, and fiercely inventive, Grubbe had worked in a factory in Chicago that produced vacuum X-ray tubes, and he had built a crude version of a tube for his own experiments. Having encountered X-ray-exposed factory workers with peeling skin and nails—his own hands had also become chapped and swollen from repeated exposures—Grubbe quickly extended the logic of this cell death to tumors.

On March 29, 1896, in a tube factory on Halsted Street (the name bears no connection to Halsted the surgeon) in Chicago, Grubbe began to bombard Rose Lee, an elderly woman with breast cancer, with radiation using an improvised X-ray tube. Lee’s cancer had relapsed after a mastectomy, and the tumor had exploded into a painful mass in her breast. She had been referred to Grubbe as a last-ditch measure, more to satisfy his experimental curiosity than to provide any clinical benefit. Grubbe looked through the factory for something to cover the rest of the breast, and finding no sheet of metal, wrapped Lee’s chest in some tinfoil that he found in the bottom of a Chinese tea box. He irradiated her cancer every night for eighteen consecutive days. The treatment was painful—but somewhat successful. The tumor in Lee’s breast ulcerated, tightened, and shrank,
producing the first documented local response in the history of X-ray therapy. A few months after the initial treatment, though, Lee became dizzy and nauseated. The cancer had metastasized to her spine, brain, and liver, and she died shortly after. Grubbe had stumbled on another important observation: X-rays could only be used to treat cancer locally, with little effect on tumors that had already metastasized.*

Inspired by the response, even if it had been temporary, Grubbe began using X-ray therapy to treat scores of other patients with local tumors. A new branch of cancer medicine, radiation oncology, was born, with X-ray clinics mushrooming up in Europe and America. By the early 1900s, less than a decade after Röntgen’s discovery, doctors waxed ecstatic about the possibility of curing cancer with radiation. “I believe this treatment is an absolute cure for all forms of cancer,” a Chicago physician noted in 1901. “I do not know what its limitations are.”

With the Curies’ discovery of radium in 1902, surgeons could beam thousandfold more powerful bursts of energy on tumors. Conferences and societies on high-dose radiation therapy were organized in a flurry of excitement. Radium was infused into gold wires and stitched directly into tumors, to produce even higher local doses of X-rays. Surgeons implanted radon pellets into abdominal tumors. By the 1930s and ’40s, America had a national surplus of radium, so much so that it was being advertised for sale to laypeople in the back pages of journals. Vacuum-tube technology advanced in parallel; by the mid-1950s variants of these tubes could deliver blisteringly high doses of X-ray energy into cancerous tissues.

Radiation therapy catapulted cancer medicine into its atomic age—an age replete with both promise and peril. Certainly, the vocabulary, the images, and the metaphors bore the potent symbolism of atomic power unleashed on cancer. There were “cyclotrons” and “supervoltage rays” and “linear accelerators” and “neutron beams.” One man was asked to think of his X-ray therapy as “millions of tiny bullets of energy.” Another account of a radiation treatment is imbued with the thrill and horror of a space journey: “The patient is put on a stretcher that is placed in the oxygen chamber. As a team of six doctors, nurses, and technicians hover at chamber-side, the radiologist maneuvers a betatron into position. After slamming shut a hatch at the end of the chamber, technicians force oxygen in. After fifteen minutes under full pressure . . . the radiologist turns on the betatron and shoots radiation at the tumor. Following treatment, the patient is decompressed in deep-sea-diver fashion and taken to the recovery room.”

Stuffed into chambers, herded in and out of hatches, hovered upon, monitored through closed-circuit television, pressurized, oxygenated, decompressed, and sent back to a room to recover, patients weathered the onslaught of radiation therapy as if it were an invisible benediction.

And for certain forms of cancer, it was a benediction. Like surgery, radiation was remarkably effective at obliterating locally confined cancers. Breast tumors were pulverized with X-rays. Lymphoma lumps melted away. One woman with a brain tumor woke up from her yearlong coma to watch a basketball game in her hospital room.

But like surgery, radiation medicine also struggled against its inherent limits. Emil Grubbe had already encountered the first of these limits with his earliest experimental treatments: since X-rays could only be directed locally, radiation was of limited use for cancers that had metastasized.* One could double and quadruple the doses of radiant energy, but this did not translate into more cures. Instead, indiscriminate irradiation left patients scarred, blinded, and scalded by doses that had far exceeded tolerability.

The second limit was far more insidious: radiation produced cancers. The very effect of X-rays killing rapidly dividing cells—DNA damage—also created cancer-causing mutations in genes. In the 1910s, soon after the Curies had discovered radium, a New Jersey corporation called U.S. Radium began to mix radium with paint to create a product called Undark—radium-infused paint that emitted a greenish white light at night. Although aware of the many injurious effects of radium, U.S. Radium promoted Undark for clock dials, boasting of glow-in-the-dark watches. Watch painting was a precise and artisanal craft, and young women with nimble, steady hands were commonly employed. These women were encouraged to use the paint without precautions, and to frequently lick the brushes with their tongues to produce sharp lettering on watches.

Radium workers soon began to complain of jaw pain, fatigue, and skin and tooth problems. In the late 1920s, medical investigations revealed that

* Metastatic sites of cancer can occasionally be treated with X-rays, although with limited success.

* Radiation can be used to control or palliate metastatic tumors in selected cases, but is rarely curative in these circumstances.
the bones in their jaws had necrosed, their tongues had been scarred by irradiation, and many had become chronically anemic (a sign of severe bone marrow damage). Some women, tested with radioactivity counters, were found to be glowing with radioactivity. Over the next decades, dozens of radium-induced tumors sprouted in these radium-exposed workers—sarcomas and leukemias, and bone, tongue, neck, and jaw tumors. In 1927, a group of five severely afflicted women in New Jersey—collectively termed “Radium girls” by the media—sued U.S. Radium. None of them had yet developed cancers; they were suffering from the more acute effects of radium toxicity—jaw, skin, and tooth necrosis. A year later, the case was settled out of court with a compensation of $10,000 each to the girls, and $600 per year to cover living and medical expenses. The “compensation” was not widely collected. Many of the Radium girls, too weak even to raise their hands to take an oath in court, died of leukemia and other cancers soon after their case was settled.

Marie Curie died of leukemia in July 1934. Emil Grubbe, who had been exposed to somewhat weaker X-rays, also succumbed to the deadly late effects of chronic radiation. By the mid-1940s, Grubbe’s fingers had been amputated one by one to remove necrotic and gangrenous bones, and his face was cut up in repeated operations to remove radiation-induced tumors and premalignant warts. In 1960, at the age of eighty-five, he died in Chicago, with multiple forms of cancer that had spread throughout his body.

The complex intersection of radiation with cancer—cancer-curing at times, cancer-causing at others—dampened the initial enthusiasm of cancer scientists. Radiation was a powerful invisible knife—but still a knife. And a knife, no matter how deft or penetrating, could only reach so far in the battle against cancer. A more discriminating therapy was needed, especially for cancers that were nonlocalized.

In 1932, Willy Meyer, the New York surgeon who had invented the radical mastectomy contemporaneously with Halsted, was asked to address the annual meeting of the American Surgical Association. Gravely ill and bedridden, Meyer knew he would be unable to attend the meeting, but he forwarded a brief, six-paragraph speech to be presented. On May 31, six weeks after Meyer’s death, his letter was read aloud to the roomful of surgeons. There is, in that letter, an unfailing recognition that cancer medi-

cine had reached some terminus, that a new direction was needed. “If a biological systemic after-treatment were added in every instance,” Meyer wrote, “we believe the majority of such patients would remain cured after a properly conducted radical operation.”

Meyer had grasped a deep principle about cancer. Cancer, even when it begins locally, is inevitably waiting to explode out of its confinement. By the time many patients come to their doctor, the illness has often spread beyond surgical control and spilled into the body exactly like the black bile that Galen had envisioned so vividly nearly two thousand years ago.

In fact, Galen seemed to have been right after all—in the accidental, aphoristic way that Democritus had been right about the atom or Erasmus had made a conjecture about the Big Bang centuries before the discovery of galaxies. Galen had, of course, missed the actual cause of cancer. There was no black bile clogging up the body and bubbling out into tumors in frustration. But he had uncannily captured something essential about cancer in his dreamy and visceral metaphor. Cancer was often a humoral disease. Crablike and constantly mobile, it could burrow through invisible channels from one organ to another. It was a “systemic” illness, just as Galen had once made it out to be.
Dyeing and Dying

Those who have not been trained in chemistry or medicine may not realize how difficult the problem of cancer treatment really is. It is almost—not quite, but almost—as hard as finding some agent that will dissolve away the left ear, say, and leave the right ear unharmed. So slight is the difference between the cancer cell and its normal ancestor.

—William Woglom

Life is... a chemical incident.
—Paul Ehrlich
as a schoolboy. 1870

A systemic disease demands a systemic cure—but what kind of systemic therapy could possibly cure cancer? Could a drug, like a microscopic surgeon, perform an ultimate pharmacological mastectomy—sparing normal tissue while excising cancer cells? Willy Meyer wasn't alone in fantasizing about such a magical therapy—generations of doctors before him had also fantasized about such a medicine. But how might a drug coursing through the whole body specifically attack a diseased organ?

Specificity refers to the ability of any medicine to discriminate between its intended target and its host. Killing a cancer cell in a test tube is not a particularly difficult task: the chemical world is packed with malevolent poisons that, even in infinitesimal quantities, can dispatch a cancer cell within minutes. The trouble lies in finding a selective poison—a drug that will kill cancer without annihilating the patient. Systemic therapy without specificity is an indiscriminate bomb. For an anticancer poison to become a useful drug, Meyer knew, it needed to be a fantastically nim-

ble knife: sharp enough to kill cancer yet selective enough to spare the patient.

The hunt for such specific, systemic poisons for cancer was precipitated by the search for a very different sort of chemical. The story begins with colonialism and its chief loot: cotton. In the mid-1850s, as ships from India and Egypt laden with bales of cotton unloaded their goods in English ports, cloth milling boomed into a spectacularly successful business in England, an industry large enough to sustain an entire gamut of subsidiary industries. A vast network of mills sprouted up in the industrial basin of the Midlands, stretching through Glasgow, Lancashire, and Manchester. Textile exports dominated the British economy. Between 1851 and 1857, the export of printed goods from England more than quadrupled—from 6 million to 27 million pieces per year. In 1784, cotton products had represented a mere 6 percent of total British exports. By the 1850s, that proportion had peaked at 50 percent.

The cloth-milling boom set off a boom in cloth dyeing, but the two industries—cloth and color—were oddly out of technological step. Dyeing, unlike milling, was still a preindustrial occupation. Cloth dyes had to be extracted from perishable vegetable sources—rusty carmines from Turkish madder root, or deep blues from the indigo plant—using antiquated processes that required patience, expertise, and constant supervision. Printing on textiles with colored dyes (to produce the ever-popular calico prints, for instance) was even more challenging—requiring thickeners, mordants, and solvents in multiple steps—and often took the dyers weeks to complete. The textile industry thus needed professional chemists to dissolve its bleaches and cleansers, to supervise the extraction of dyes, and to find ways to fasten the dyes on cloth. A new discipline called practical chemistry, focused on synthesizing products for textile dyeing, was soon flourishing in polytechnics and institutes all over London.

In 1856, William Perkin, an eighteen-year-old student at one of these institutes, stumbled on what would soon become a Holy Grail of this industry: an inexpensive chemical dye that could be made entirely from scratch. In a makeshift one-room laboratory in his apartment in the East End of London ("half of a small but long-shaped room with a few shelves for bottles and a table") Perkin was boiling nitric acid and benzene in smuggled glass flasks and precipitated an unexpected reaction. A chemical had formed inside the tubes with the color of pale, crushed violets. In an era obsessed with dye-making, any colored chemical was considered a
potential dye—and a quick dip of a piece of cotton into the flask revealed the new chemical could color cotton. Moreover, this new chemical did not bleach or bleed. Perkin called it aniline mauve.

Perkin’s discovery was a godsend for the textile industry. Aniline mauve was cheap and imperishable—vastly easier to produce and store than vegetable dyes. As Perkin soon discovered, its parent compound could act as a molecular building block for other dyes, a chemical skeleton on which a variety of side chains could be hung to produce a vast spectrum of vivid colors. By the mid-1860s, a glut of new synthetic dyes, in shades of lilac, blue, magenta, aquamarine, red, and purple flooded the cloth factories of Europe. In 1857, Perkin, barely nineteen years old, was inducted into the Chemical Society of London as a full fellow, one of the youngest in its history to be thus honored.

Aniline mauve was discovered in England, but dye making reached its chemical zenith in Germany. In the late 1850s, Germany, a rapidly industrializing nation, had been itching to compete in the cloth markets of Europe and America. But unlike England, Germany had scarcely any access to natural dyes: by the time it had entered the scramble to capture colonies, the world had already been sliced up into so many parts, with little left to divide. German cloth millers thus threw themselves into the development of artificial dyes, hoping to rejoin an industry that they had once almost given up as a lost cause.

Dye making in England had rapidly become an intricate chemical business. In Germany—goaded by the textile industry, cosseted by national subsidies, and driven by expansive economic growth—synthetic chemistry underwent an even more colossal boom. In 1883, the German output of alizarin, the brilliant red chemical that imitated natural carmine, reached twelve thousand tons, dwarfing the amount being produced by Perkin’s factory in London. German chemists rushed to produce brighter, stronger, cheaper chemicals and muscled their way into textile factories all around Europe. By the mid-1880s, Germany had emerged as the champion of the chemical arms race (which presaged a much uglier military one) to become the “dye basket” of Europe.

Initially, the German textile chemists lived entirely in the shadow of the dye industry. But emboldened by their successes, the chemists began to synthesize not just dyes and solvents, but an entire universe of new molecules: phenols, alcohols, bromides, alkaloids, alizarins, and amides, chemicals never encountered in nature. By the late 1870s, synthetic chemists in Germany had created more molecules than they knew what to do with. “Practical chemistry” had become almost a caricature of itself: an industry seeking a practical purpose for the products that it had so frantically raced to invent.

Early interactions between synthetic chemistry and medicine had largely been disappointing. Gideon Harvey, a seventeenth-century physician, had once called chemists the “most impudent, ignorant, flatulent, fleshy, and vainly boasting sort of mankind.” The mutual scorn and animosity between the two disciplines had persisted. In 1849, August Hofmann, William Perkin’s teacher at the Royal College, gloomily acknowledged the chasm between medicine and chemistry: “None of these compounds have, as yet, found their way into any of the appliances of life. We have not been able to use them . . . for curing disease.”

But even Hofmann knew that the boundary between the synthetic world and the natural world was inevitably collapsing. In 1828, a Berlin scientist named Friedrich Wöhler had sparked a metaphysical storm in science by boiling ammonium cyanate, a plain, inorganic salt, and creating urea, a chemical typically produced by the kidneys. The Wöhler experiment—seemingly trivial—had enormous implications. Urea was a “natural” chemical, while its precursor was an inorganic salt. That a chemical produced by natural organisms could be derived so easily in a flask threatened to overturn the entire conception of living organisms: for centuries, the chemistry of living organisms was thought to be imbued with some mystical property, a vital essence that could not be duplicated in a laboratory—a theory called vitalism. Wöhler’s experiment demolished vitalism. Organic and inorganic chemicals, he proved, were interchangeable. Biology was chemistry: perhaps even a human body was no different from a bag of busily reacting chemicals—a beaker with arms, legs, eyes, brain, and soul.

With vitalism dead, the extension of this logic to medicine was inevitable. If the chemicals of life could be synthesized in a laboratory, could they work on living systems? If biology and chemistry were so interchangeable, could a molecule concocted in a flask affect the inner workings of a biological organism?

Wöhler was a physician himself, and with his students and collaborators he tried to backpedal from the chemical world into the medical one. But his synthetic molecules were still much too simple—mere stick figures
of chemistry where vastly more complex molecules were needed to intervene on living cells.

But such multifaceted chemicals already existed: the laboratories of the dye factories of Frankfurt were full of them. To build his interdisciplinary bridge between biology and chemistry, Wöhler only needed to take a short day-trip from his laboratory in Göttingen to the labs of Frankfurt. But neither Wöhler nor his students could make that last connection. The vast panel of molecules sitting idly on the shelves of the German textile chemists, the precursors of a revolution in medicine, may as well have been a continent away.

It took a full fifty years after Wöhler’s urea experiment for the products of the dye industry to finally make physical contact with living cells. In 1878, in Leipzig, a twenty-four-year-old medical student, Paul Ehrlich, hunting for a thesis project, proposed using cloth dyes—aniline and its colored derivatives—to stain animal tissues. At best, Ehrlich hoped that the dyes might stain the tissues to make microscopy easier. But to his astonishment, the dyes were far from indiscriminate darkening agents. Aniline derivatives stained only parts of the cell, silhouetting certain structures and leaving others untouched. The dyes seemed able to discriminate among chemicals hidden inside cells—binding some and sparing others.

This molecular specificity, encapsulated so vividly in that reaction between a dye and a cell, began to haunt Ehrlich. In 1882, working with Robert Koch, he discovered yet another novel chemical stain, this time for mycobacteria, the organisms that Koch had discovered as the cause of tuberculosis. A few years later, Ehrlich found that certain toxins, injected into animals, could generate “antitoxins,” which bound and inactivated poisons with extraordinary specificity (these antitoxins would later be identified as antibodies). He purified a potent serum against diphtheria toxin from the blood of horses, then moved to the Institute for Sera Research and Serum Testing in Steglitz to prepare this serum in gallon buckets, and then to Frankfurt to set up his own laboratory.

But the more widely Ehrlich explored the biological world, the more he spiraled back to his original idea. The biological universe was full of molecules picking out their partners like clever locks designed to fit a key: toxins clinging inseparably to antitoxins, dyes that highlighted only particular parts of cells, chemical stains that could nimbly pick out one class of germs from a mixture of microbes. If biology was an elaborate mix-and-match game of chemicals, Ehrlich reasoned, what if some chemical could discriminate bacterial cells from animal cells—and kill the former without touching the host?

Returning from a conference late one evening, in the cramped compartment of a night train from Berlin to Frankfurt, Ehrlich animatedly described his idea to two fellow scientists, “It has occurred to me that... it should be possible to find artificial substances which are really and specifically curative for certain diseases, not merely palliatives acting favorably on one or another symptom... Such curative substances—a priori—must directly destroy the microbes responsible for the disease; not by ‘action from a distance,’ but only when the chemical compound is fixed by the parasites. The parasites can only be killed if the chemical compound has a particular relation, a specific affinity for them.” By then, the other inhabitants of Ehrlich’s train compartment had dozed off to sleep. But this rant in a train compartment was one of medicine’s most important ideas in its distilled, primordial form. “Chemotherapy,” the use of specific chemicals to heal the diseased body, was conceptually born in the middle of the night.

Ehrlich began looking for his “curative substances” in a familiar place: the treasure trove of dye-industry chemicals that had proved so crucial to his earlier biological experiments. His laboratory was now physically situated near the booming dye factories of Frankfurt—the Frankfurter Anilinfarben-Fabrik and the Leopold Cassella Company—and he could easily procure dye chemicals and derivatives via a short walk across the valley. With thousands of compounds available to him, Ehrlich embarked on a series of experiments to test their biological effects in animals.

He began with a hunt for antimicrobial chemicals, in part because he already knew that chemical dyes could specifically bind microbial cells. He infected mice and rabbits with Trypanosoma brucei, the parasite responsible for the dreaded sleeping sickness, then injected the animals with chemical derivatives to determine if any of them could halt the infection. After several hundred chemicals, Ehrlich and his collaborators had their first antibiotic hit: a brilliant ruby-colored dye derivative that Ehrlich called Trypan Red. It was a name—a disease juxtaposed with a dye color—that captured nearly a century of medical history.
Galvanized by his discovery, Ehrlich unleashed volleys of chemical experiments. A universe of biological chemistry opened up before him: molecules with peculiar properties, a cosmos governed by idiosyncratic rules. Some compounds switched from precursors into active drugs in the bloodstream; others transformed backward from active drugs to inactive molecules. Some were excreted in the urine; others condensed in the bile or fell apart immediately in the blood. One molecule might survive for days in an animal, but its chemical cousin—a variant by just a few critical atoms—might vanish from the body in minutes.

On April 19, 1910, at the densely packed Congress for Internal Medicine in Wiesbaden, Ehrlich announced that he had discovered yet another molecule with "specific affinity"—this one a blockbuster. The new drug, cryptically called compound 606, was active against a notorious microbe, Treponema pallidum, which caused syphilis. In Ehrlich's era, syphilis—the "secret malady" of eighteenth-century Europe—was a sensational illness, a tabloid pestilence. Ehrlich knew that an antisypilotic drug would be an instant sensation and he was prepared. Compound 606 had secretly been tested in patients in the hospital wards of St. Petersburg, then tested in patients with neurosyphilis at the Magdeburg Hospital—each time with remarkable success. A gigantic factory, funded by Hoechst Chemical Works, was already being built to manufacture it for commercial use.

Ehrlich's successes with Trypan Red and compound 606 (which he named Salvarsan, from the word salvation) proved that diseases were just pathological locks waiting to be picked by the right molecules. The line of potentially curable illnesses now stretched endlessly before him. Ehrlich called his drugs "magic bullets"—bullets for their capacity to kill and magic for their specificity. It was a phrase with an ancient, alchemic ring that would sound insistently through the future of oncology.

Ehrlich's magic bullets had one last target to fell: cancer. Syphilis and trypanosomiasis are microbial diseases. Ehrlich was slowly inching toward his ultimate goal: the malignant human cell. Between 1904 and 1908, he rigged several elaborate schemes to find an anticancer drug using his vast arsenal of chemicals. He tried amides, anilines, sulfon derivatives, arsenics, bromides, and alcohols to kill cancer cells. None of them worked. What was poison to cancer cells, he found, was inevitably poison to normal cells as well. Discouraged, he tried even more fantastical strategies. He thought of starving sarcoma cells of metabolites, or tricking them into death by using decoy molecules (a strategy that would presage Subbarao's antifolate derivatives by nearly fifty years). But the search for the ultimate, discriminating anticancer drug proved fruitless. His pharmacological bullets, far from magical, were either too indiscriminate or too weak.

In 1908, soon after Ehrlich won the Nobel Prize for his discovery of the principle of specific affinity, Kaiser Wilhelm of Germany invited him to a private audience in his palace. The Kaiser was seeking counsel: a noted hypochondriac afflicted by various real and imagined ailments, he wanted to know whether Ehrlich had an anticancer drug within reach.

Ehrlich hedged. The cancer cell, he explained, was a fundamentally different target from a bacterial cell. Specific affinity relied, paradoxically, not on "affinity," but on its opposite—on difference. Ehrlich's chemicals had successfully targeted bacteria because bacterial enzymes were so radically dissimilar to human enzymes. With cancer, it was the similarity of the cancer cell to the normal human cell that made it nearly impossible to target.

Ehrlich went on in this vein, almost musing to himself. He was circling around something profound, an idea in its infancy: to target the abnormal cell, one would need to decipher the biology of the normal cell. He had returned, decades after his first encounter with aniline, to specificity again, to the bar codes of biology hidden inside every living cell.

Ehrlich's thinking was lost on the Kaiser. Having little interest in this cheerless disquisition with no obvious end, he cut the audience short.

In 1915, Ehrlich fell ill with tuberculous, a disease that he had likely acquired from his days in Koch's laboratory. He went to recuperate in Bad Honnburg, a spa town famous for its healing carbonic-salt baths. From his room, overlooking the distant plains below, he watched bitterly as his country pitched itself into the First World War. The dye factories that had once supplied his therapeutic chemicals—Bayer and Hoechst among them—were converted to massive producers of chemicals that would be turned into precursors for war gases. One particularly toxic gas was a colorless, blistering liquid produced by reacting the solvent thioglycol (a dye intermediate) with boiling hydrochloric acid. The gas's smell was unmistakable, described alternatively as reminiscent of mustard, burnt garlic, or horse-radishes ground on a fire. It came to be known as mustard gas.

On the foggy night of July 12, 1917, two years after Ehrlich's death, a
volley of artillery shells marked with small, yellow crosses rained down on
British troops stationed near the small Belgian town of Ypres. The liquid
in the bombs quickly vaporized, a “thick, yellowish green cloud veiling
the sky,” as a soldier recalled, then diffused through the cool night air. The
men in their barracks and trenches, asleep for the night, awoke to a nau-
seatingly sharp smell that they would remember for decades to come: the
acid whiff of horseradishes spreading through the chalk fields. Within
seconds, soldiers ran for cover, coughing and sneezing in the mud, the
blind scrambling among the dead. Mustard gas diffused through leather
and rubber, and soaked through layers of cloth. It hung like a toxic mist
over the battlefield for days until the dead smelled of mustard. On that
night alone, mustard gas injured or killed two thousand soldiers. In a sin-
gle year, it left thousands dead in its wake.

The acute, short-term effects of nitrogen mustard—the respiratory
complications, the burnt skin, the blisters, the blindness—were so amply
monstrous that its long-term effects were overlooked. In 1919, a pair of
American pathologists, Edward and Helen Krumhhaar, analyzed the effects
of the Ypres bombing on the few men who had survived it. They found that
the survivors had an unusual condition of the bone marrow. The normal
blood-forming cells had dried up; the bone marrow, in a bizarre mimicry
of the scorched and blasted battlefield, was markedly depleted. The men
were anemic and needed transfusions of blood, often up to once a month.
They were prone to infections. Their white cell counts often hovered per-
sistently below normal.

In a world less preoccupied with other horrors, this news might have
caus ed a small sensation among cancer doctors. Although evidently poi-
sonous, this chemical had, after all, targeted the bone marrow and wiped
out only certain populations of cells—a chemical with specific affinity. But
Europe was full of horror stories in 1919, and this seemed no more remark-
able than any other. The Krumhhaars published their paper in a second-
tier medical journal and it was quickly forgotten in the amnesia of war.

The wartime chemists went back to their labs to devise new chemi-
cals for other battles, and the inheritors of Ehrlich’s legacy went hunting
elsewhere for his specific chemicals. They were looking for a magic bullet
that would rid the body of cancer, not a toxic gas that would leave its vic-
tims half-dead, blind, blistered, and permanently anemic. That their bul-
et would eventually appear out of that very chemical weapon seemed like
a perversion of specific affinity, a ghoulish distortion of Ehrlich’s dream.

Poisoning the Atmosphere

What if this mixture do not work at all? . . .
What if it be a poison . . . ?
—Romeo and Juliet

We shall so poison the atmosphere of the first act that no
one of decency shall want to see the play through to the
end.
—James Watson, speaking about
chemotherapy, 1977

Every drug, the sixteenth-century physician Paracelsus once opined, is a
poison in disguise. Cancer chemotherapy, consumed by its fiery obsession
to obliterate the cancer cell, found its roots in the obverse logic: every po-
ison might be a drug in disguise.

On December 2, 1943, more than twenty-five years after the yellow-
crossed bombs had descended on Ypres, a fleet of Luftwaffe planes flew by
a group of American ships huddled in a harbor just outside Bari in southern
Italy and released a volley of shells. The ships were instantly on fire.
Unbeknown even to its own crew, one of the ships in the fleet, the John
Harvey, was stockpiled with seventy tons of mustard gas stowed away for
possible use. As the Harvey blew up, so did its toxic payload. The Allies
had, in effect, bombed themselves.

The German raid was unexpected and a terrifying success. Fishermen
and residents around the Bari harbor began to complain of the whiff of
burnt garlic and horseradishes in the breeze. Grimy, oil-soaked men,
mostly young American sailors, were dragged out from the water seiz-
ing with pain and terror, their eyes swollen shut. They were given tea and
wrapped in blankets, which only trapped the gas closer to their bodies. Of
the 617 men rescued, 83 died within the first week. The gas spread quickly over the Bari harbor, leaving an arc of devastation. Nearly a thousand men and women died of complications over the next months.

The Bari “incident,” as the media called it, was a terrible political embarrassment for the Allies. The injured soldiers and sailors were swiftly relocated to the States, and medical examiners were secretly flown in to perform autopsies on the dead civilians. The autopsies revealed what the Krumbhaar had noted earlier. In the men and women who had initially survived the bombing but succumbed later to injuries, white blood cells had virtually vanished in their blood, and the bone marrow was scorched and depleted. The gas had specifically targeted bone marrow cells—a grotesque molecular parody of Ehrlich’s healing chemicals.

The Bari incident set off a frantic effort to investigate war gases and their effects on soldiers. An undercover unit, called the Chemical Warfare Unit (housed within the wartime Office of Scientific Research and Development) was created to study war gases. Contracts for research on various toxic compounds were spread across research institutions around the nation. The contract for investigating nitrogen mustard was issued to two scientists, Louis Goodman and Alfred Gilman, at Yale University.

Goodman and Gilman weren’t interested in the “vesicant” properties of mustard gas—it’s capacity to burn skin and membranes. They were captivated by the Krumbhaar effect—the gas’s capacity to decimate white blood cells. Could this effect, or some etiolated cousin of it, be harnessed in a controlled setting, in a hospital, in tiny, monitored doses, to target malignant white cells?

To test this concept, Gilman and Goodman began with animal studies. Injected intravenously into rabbits and mice, the mustards made the normal white cells of the blood and bone marrow almost disappear, without producing all the nasty vesicant actions, dissociating the two pharmacological effects. Encouraged, Gilman and Goodman moved on to human studies, focusing on lymphomas—cancers of the lymph glands. In 1942, they persuaded a thoracic surgeon, Gustaf Lindskog, to treat a forty-eight-year-old New York silversmith with lymphoma with ten continuous doses of intravenous mustard. It was a one-off experiment but it worked. In men, as in mice, the drug produced miraculous remissions. The swollen glands disappeared. Clinicians described the phenomenon as an eerie “softening” of the cancer, as if the hard carapace of cancer that Galen had so vividly described nearly two thousand years ago had melted away.

But the responses were followed, inevitably, by relapses. The softened tumors would harden again and recur—just as Farber’s leukemias had vanished then reappeared violently. Bound by secrecy during the war years, Goodman and Gilman eventually published their findings in 1946, several months before Farber’s paper on antifolates appeared in the press.

Just a few hundred miles south of New York, at the Burroughs Wellcome laboratory, biochemist George Hitchings had also turned to Ehrlich’s method to find molecules with a specific ability to kill cancer cells. Inspired by Yella Subbarao’s anti-folates, Hitchings focused on synthesizing decoy molecules that were taken up by cells killed them. His first targets were precursors of DNA and RNA. Hitchings’s approach was broadly disdained by academic scientists as a “fishing expedition.” “Scientists in academia stood disdainfully apart from this kind of activity,” a colleague of Hitchings’s recalled. “[They] argued that it would be premature to attempt chemotherapy without sufficient basic knowledge about biochemistry, physiology, and pharmacology. In truth, the field had been sterile for thirty-five years or so since Ehrlich’s work.”

By 1944, Hitchings’s fishing expedition had yet to yield a single chemical fish. Mounds of bacterial plates had grown around him like a molding, decrepit garden with still no sign of a promised drug. Almost on instinct, he hired a young assistant named Gertrude Elion, whose future seemed even more precarious than Hitchings’s. The daughter of Lithuanian immigrants, born with a precocious scientific intellect and a thirst for chemical knowledge, Elion had completed a master’s degree in chemistry from New York University in 1941 while teaching high school science during the day and performing her research for her thesis at night and on weekends. Although highly qualified, talented, and driven, she had been unable to find a job in an academic laboratory. Frustrated by repeated rejections, she had found a position as a supermarket product supervisor. When Hitchings found Trudy Elion, who would soon become one of the most innovative synthetic chemists of her generation (and a future Nobel laureate), she was working for a food lab in New York, testing the acidity of pickles and the color of egg yolk going into mayonnaise.

Rescued from a life of pickles and mayonnaise, Gertrude Elion leapt into synthetic chemistry. Like Hitchings, she started off by hunting for chemicals that could block bacterial growth by inhibiting DNA—but
then added her own strategic twist. Instead of sifting through mounds of unknown chemicals at random, Elion focused on one class of compounds, called purines. Purines were ringlike molecules with a central core of six carbon atoms that were known to be involved in the building of DNA. She thought she would add various chemical side chains to each of the six carbon atoms, producing dozens of new variants of purine.

Elion’s collection of new molecules was a strange merry-go-round of beasts. One molecule—2,6-diaminopurine—was too toxic at even low doses to give the drug to animals. Another molecule smelled like garlic purified a thousand times. Many were unstable, or useless, or both. But in 1951, Elion found a variant molecule called 6-mercaptopurine, or 6-MP.

6-MP failed some preliminary toxicological tests on animals (the drug is strangely toxic to dogs), and was nearly abandoned. But the success of mustard gas in killing cancer cells had boosted the confidence of early chemotherapists. In 1948, Cornelius “Dusty” Rhoads, a former army officer, left his position as chief of the army’s Chemical Warfare Unit to become the director of the Memorial Hospital (and its attached research institute), thus sealing the connection between the chemical warfare of the battlefields and chemical warfare in the body. Intrigued by the cancer-killing properties of poisonous chemicals, Rhoads actively pursued a collaboration between Hitchings and Elion’s lab at Burroughs Wellcome and Memorial Hospital. Within months of having been tested on cells in a petri dish, 6-MP was packaged off to be tested in human patients.

Predictably, the first target was acute lymphoblastic leukemia—the rare tumor that now occupies the limelight of oncology. In the early 1950s, two physician-scientists, Joseph Burchenal and Mary Lois Murphy, launched a clinical trial at Memorial to use 6-MP on children with ALL.

Burchenal and Murphy were astonished by the speedy remissions produced by 6-MP. Leukemia cells flickered and vanished in the bone marrow and the blood, often within a few days of treatment. But, like the remissions in Boston, these were disappointingly temporary, lasting only a few weeks. As with Farber’s anti-folates, there was only a fleeting glimpse of a cure.

The Goodness of Show Business

The name “Jimmy” is a household word in New England
...a nickname for the boy next door.
—The House That “Jimmy” Built

I’ve made a long voyage and been to a strange country,
and I’ve seen the dark man very close.
—Thomas Wolfe

Flickering and feeble, the leukemia remissions in Boston and New York nevertheless mesmerized Farber. If lymphoblastic leukemia, one of the most lethal forms of cancer, could be thwarted by two distinct chemicals (even if only for a month or two), then perhaps a deeper principle was at stake. Perhaps a series of such poisons was hidden in the chemical world, perfectly designed to obliterate cancer cells but spare normal cells. The fingerling of that idea kept knocking in his mind as he paced up and down the wards every evening, writing notes and examining smears late into the night. Perhaps he had stumbled upon an even more provocative principle—that cancer could be cured by chemicals alone.

But how might he jump-start the discovery of these incredible chemicals? His operation in Boston was clearly far too small. How might he create a more powerful platform to propel him toward the cure for childhood leukemia—and then for cancer at large?

Scientists often study the past as obsessively as historians because few other professions depend so acutely on it. Every experiment is a conversation with a prior experiment, every new theory a refutation of the old. Farber, too, studied the past compulsively—and the episode that pivotally fascinated him was the story of the national polio campaign. As a student at Harvard in the 1920s, Farber had witnessed polio epidemics
THE EMPEROR OF ALL MALADIES

sweeping through the city, leaving waves of paralyzed children in their wake. In the acute phase of polio, the virus can paralyze the diaphragm, making it nearly impossible to breathe. Even a decade later, in the mid-1930s, the only treatment available for this paralysis was an artificial respirator known as the iron lung. As Farber had rounded on the wards of Children’s Hospital as a resident, iron lungs had continuously huffed in the background, with children suspended within these dreaded contraptions often for weeks on end. The suspension of patients inside these iron lungs symbolized the limbo-like, paralytic state of polio research. Little was known about the nature of the virus or the biology of the infection, and campaigns to control the spread of polio were poorly advertised and generally ignored by the public.

Polio research was shaken out of its torpor by Franklin Roosevelt in 1937. A victim of a prior epidemic, paralyzed from the waist down, Roosevelt had launched a polio hospital and research center, called the Warm Springs Foundation, in Georgia in 1927. At first, his political advisers tried to distance his image from the disease. (A paralyzed president trying to march a nation out of a depression was considered a disastrous image; Roosevelt’s public appearances were thus elaborately orchestrated to show him only from the waist up.) But reelected by a staggering margin in 1936, a defiant and resurgent Roosevelt returned to his original cause and launched the National Foundation for Infantile Paralysis, an advocacy group to advance research on and publicize polio.

The foundation, the largest disease-focused association in American history, galvanized polio research. Within one year of its launch, the actor Eddie Cantor created the March of Dimes campaign for the foundation—a massive and highly coordinated national fund-raising effort that asked every citizen to send Roosevelt a dime to support polio education and research. Hollywood celebrities, Broadway stars, and radio personalities soon joined the bandwagon, and the response was dazzling. Within a few weeks, 2,680,000 dimes had poured into the White House. Posters were widely circulated, and money and public attention flooded into polio research. By the late 1940s, funded in part by these campaigns, John Enders had nearly succeeded in culturing poliovirus in his lab, and Sabin and Salk, building on Enders’s work, were well on their way to preparing the first polio vaccines.

Farber fantasized about a similar campaign for leukemia, perhaps for cancer in general. He envisioned a foundation for children’s cancer that would spearhead the effort. But he needed an ally to help launch the foundation, preferably an ally outside the hospital, where he had few allies.

Farber did not need to look far. In early May 1947, while Farber was still in the middle of his aminopterin trial, a group of men from the Variety Club of New England, led by Bill Koster, toured his laboratory.

Founded in 1927 in Philadelphia by a group of men in show business—producers, directors, actors, entertainers, and film-theater owners—the Variety Club had initially been modeled after the dining clubs of New York and London. But in 1928, just a year after its inception, the club had unwittingly acquired a more active social agenda. In the winter of 1928, with the city teetering on the abyss of the Depression, a woman had abandoned her child at the doorstep of the Sheridan Square Film Theater. A note pinned on the child read:

Please take care of my baby. Her name is Catherine. I can no longer take care of her. I have eight others. My husband is out of work. She was born on Thanksgiving Day. I have always heard of the goodness of show business and I pray to God that you will look out for her.

The cinematic melodrama of the episode, and the heartfelt appeal to the “goodness of show business,” made a deep impression on the members of the fledgling club. Adopting the orphan girl, the club paid for her upbringing and education. She was given the name Catherine Variety Sheridan—her middle name for the club and her last name for the theater outside which she had been found.

The Catherine Sheridan story was widely reported in the press and brought more media exposure to the club than its members had ever envisioned. Thrust into the public eye as a philanthropic organization, the club now made children’s welfare its project. In the late 1940s, as the boom in postwar moviemaking brought even more money into the club’s coffers, new chapters of the club sprouted in cities throughout the nation. Catherine Sheridan’s story and her photograph were printed and publicized in club offices throughout the nation. Sheridan became the club’s unofficial mascot.

The influx of money and public attention also brought a search for other children’s charity projects. Koster’s visit to the Children’s Hospital in Boston was a scouting mission to find another such project. He was
escorted around the hospital to the labs and clinics of prominent doctors. When Koster asked the chief of hematology at Children's for suggestions for donations to the hospital, the chief was characteristically cautious: “Well, I need a new microscope,” he said.

In contrast, when Koster stopped by Farber’s office, he found an excitable, articulate scientist with a larger-than-life vision—a messiah in a box. Farber didn’t want a microscope; he had an audacious telescopic plan that captivated Koster. Farber asked the club to help him create a new fund to build a massive research hospital dedicated to children’s cancer.

Farber and Koster got started immediately. In early 1948, they launched an organization called the Children’s Cancer Research Fund to jump-start research and advocacy around children’s cancers. In March 1948, they organized a raffle to raise money and netted $45,456—an impressive amount to start, but still short of what Farber and Koster hoped for. Cancer research, they felt, needed a more effective message, a strategy to catapult it into public fame. Sometime that spring, Koster, remembering the success with Sheridan, had the inspired idea of finding a “mascot” for Farber’s research fund—a Catherine Sheridan for cancer. Koster and Farber searched Children’s wards and Farber’s clinic for a poster child to pitch the fund to the public.

It was not a promising quest. Farber was treating several children with aminopterin, and the beds in the wards upstairs were filled with miserable patients—dehydrated and nauseated from chemotherapy, children barely able to hold their heads and bodies upright, let alone be paraded publicly as optimistic mascots for cancer treatment. Looking frantically through the patient lists, Farber and Koster found a single child healthy enough to carry the message—a lanky, cherubic, blue-eyed, blond child named Einar Gustafson, who did not have leukemia but was being treated for a rare kind of lymphoma in his intestines.

Gustafson was quiet and serious, a precociously self-assured boy from New Sweden, Maine. His grandparents were Swedish immigrants, and he lived on a potato farm and attended a single-room schoolhouse. In the late summer of 1947, just after blueberry season, he had complained of a gnawing, wrenching pain in his stomach. Doctors in Lewiston, suspecting appendicitis, had operated on his appendix, but found the lymphoma instead. Survival rates for the disease were low at 10 percent. Thinking that chemotherapy had a slight chance to save him, his doctors sent Gustafson to Farber’s care in Boston.

Einar Gustafson, though, was a mouthful of a name. Farber and Koster, in a flash of inspiration, rechristened him Jimmy.

Koster now moved quickly to market Jimmy. On May 22, 1948, on a warm Saturday night in the Northeast, Ralph Edwards, the host of the radio show Truth or Consequences, interrupted his usual broadcast from California and linked to a radio station in Boston. “Part of the function of Truth or Consequences,” Edwards began, “is to bring this old parlor game to people who are unable to come to the show. . . . Tonight we take you to a little fellow named Jimmy.

“We are not going to give you his last name because he’s just like thousands of other young fellows and girls in private homes and hospitals all over the country. Jimmy is suffering from cancer. He’s a swell little guy, and although he cannot figure out why he isn’t out with the other kids, he does love his baseball and follows every move of his favorite team, the Boston Braves. Now, by the magic of radio, we’re going to span the breadth of the United States and take you right up to the bedside of Jimmy, in one of America’s great cities, Boston, Massachusetts, and into one of America’s great hospitals, the Children’s Hospital in Boston, whose staff is doing such an outstanding job of cancer research. Up to now, Jimmy has not heard us. . . . Give us Jimmy please.”

Then, over a crackle of static, Jimmy could be heard.

Jimmy: Hi.

Edwards: Hi, Jimmy! This is Ralph Edwards of the Truth or Consequences radio program. I’ve heard you like baseball. Is that right?

Jimmy: Yeah, it’s my favorite sport.

Edwards: It’s your favorite sport! Who do you think is going to win the pennant this year?

Jimmy: The Boston Braves, I hope.

After more banter, Edwards sprung the “parlor trick” that he had promised.

Edwards: Have you ever met Phil Masi?

Jimmy: No.

Phil Masi (walking in): Hi, Jimmy. My name is Phil Masi.
Edwards: What? Who's that, Jimmy?
Jimmy (gasping): Phil Masi!
Edwards: And where is he?
Jimmy: In my room!
Edwards: Well, what do you know? Right here in your hospital room—Phil Masi from Berlin, Illinois! Who's the best home-run hitter on the team, Jimmy?
Jimmy: Jeff Heath.
(Heath entered the room.)
Edwards: Who's that, Jimmy?
Jimmy: Jeff... Heath.

As Jimmy gasped, player after player filed into his room bearing T-shirts, signed baseballs, game tickets, and caps: Eddie Stanky, Bob Elliott, Earl Torgeson, Johnny Sain, Alvin Dark, Jim Russell, Tommy Holmes. A piano was wheeled in. The Braves struck up the song, accompanied by Jimmy, who sang loudly and enthusiastically off-key:

Take me out to the ball game,
Take me out with the crowd.
Buy me some peanuts and Cracker Jack,
I don't care if I never get back

The crowd in Edwards's studio cheered, some noting the poignancy of the last line, many nearly moved to tears. At the end of the broadcast, the remote link from Boston was disconnected. Edwards paused and lowered his voice.

"Now listen, folks. Jimmy can't hear this, can he?... We're not using any photographs of him, or using his full name, or he will know about this. Let's make Jimmy and thousands of boys and girls who are suffering from cancer happy by aiding the research to help find a cure for cancer in children. Because by researching children's cancer, we automatically help the adults and stop it at the outset.

"Now we know that one thing little Jimmy wants most is a television set to watch the baseball games as well as hear them. If you and your friends send in your quarters, dollars, and tens of dollars tonight to Jimmy for the Children's Cancer Research Fund, and over two hundred thousand dol-

"OF BLACKE CHOLOR, WITHOUT BOYLING"

lars is contributed to this worthy cause, we'll see to it that Jimmy gets his television set."

The Edwards broadcast lasted eight minutes. Jimmy spoke twelve sentences and sang one song. The word swell was used five times. Little was said of Jimmy's cancer: it lurked unmentionably in the background, the ghost in the hospital room. The public response was staggering. Even before the Braves had left Jimmy's room that evening, donors had begun to line up outside the lobby of the Children's Hospital. Jimmy's mailbox was inundated with postcards and letters, some of them addressed simply to "Jimmy, Boston, Massachusetts." Some sent dollar bills with their letters or wrote checks; children mailed in pocket money, in quarters and dimes. The Braves pitched in with their own contributions. By May 1948, the $20,000 mark set by Koster had long been surpassed; more than $231,000 had rolled in. Hundreds of red-and-white tin cans for donations for the Jimmy Fund were posted outside baseball games. Cans were passed around in film theaters to collect dimes and quarters. Little League players in baseball uniforms went door-to-door with collection cans on sweltering summer nights. Jimmy Days were held in the small towns throughout New England. Jimmy's promised television—a black-and-white set with a twelve-inch screen set into a wooden box—arrived and was set up on a white bench between hospital beds.

In the fast-growing, fast-consuming world of medical research in 1948, the $231,000 raised by the Jimmy Fund was an impressive, but still modest sum—enough to build a few floors of a new building in Boston, but far from enough to build a national scientific edifice against cancer. In comparison, in 1944, the Manhattan Project spent $100 million every month at the Oak Ridge site. In 1948, Americans spent more than $126 million on Coca-Cola alone.

But to measure the genius of the Jimmy campaign in dollars and cents is to miss its point. For Farber, the Jimmy Fund campaign was an early experiment—the building of another model. The campaign against cancer, Farber learned, was much like a political campaign: it needed icons, mascots, images, slogans—the strategies of advertising as much as the tools of science. For any illness to rise to political prominence, it needed to be marketed, just as a political campaign needed marketing. A disease needed to be transformed politically before it could be transformed scientifically.
If Farber’s antifolates were his first discovery in oncology, then this critical truth was his second. It set off a seismic transformation in his career that would far outstrip his transformation from a pathologist to a leukemia doctor. This second transformation—from a clinician into an advocate for cancer research—reflected the transformation of cancer itself. The emergence of cancer from its basement into the glaring light of publicity would change the trajectory of this story. It is a metamorphosis that lies at the heart of this book.

The House That Jimmy Built

Etymologically, patient means sufferer. It is not suffering as such that is most deeply feared but suffering that degrades.

—Susan Sontag, Illness as Metaphor

Sidney Farber’s entire purpose consists only of “hopeless cases.”

—Medical World News, November 25, 1966

There was a time when Sidney Farber had joked about the smallness of his laboratory. “One assistant and ten thousand mice,” he had called it. In fact, his entire medical life could have been measured in single digits. One room, the size of a chemist’s closet, stuffed into the basement of a hospital. One drug, aminopterin, which sometimes briefly extended the life of a child with leukemia. One remission in five, the longest lasting no longer than one year.

By the early months of 1951, however, Farber’s work was growing exponentially, moving far beyond the reaches of his old laboratory. His outpatient clinic, thronged by parents and their children, had to be moved outside the hospital to larger quarters in a residential apartment building on the corner of Binney Street and Longwood Avenue. But even the new clinic was soon overloaded. The inpatient wards at Children’s had also filled up quickly. Since Farber was considered an intruder by many of the pediatricians at Children’s, increasing ward space within the hospital was out of the question. “Most of the doctors thought him conceited and inflexible,” a hospital volunteer recalled. At Children’s, even if there was space for a few of his bodies, there was no more space for his ego.
THE EMPEROR OF ALL MALadies

Isolated and angry, Farber now threw himself into fund-raising. He needed an entire building to house all his patients. Frustrated in his efforts to galvanize the medical school into building a new cancer center for children, he launched his own effort. He would build a hospital in the face of a hospital.

Emboldened by his early fund-raising success, Farber devised ever-larger drives for research money, relying on his glitzy retinue of Hollywood stars, political barons, sports celebrities, and moneymakers. In 1953, when the Braves franchise left Boston for Milwaukee, Farber and Koster successfully approached the Boston Red Sox to make the Jimmy Fund their official charity.

Farber soon found yet another famous recruit: Ted Williams—a young ballplayer of celluloid glamour—who had just returned after serving in the Korean War. In August 1953, the Jimmy Fund planned a “Welcome Home, Ted” party for Williams, a massive fund-raising bash with a dinner billed at $100 per plate that raised $150,000. By the end of that year, Williams was a regular visitor at Farber’s clinic, often trailing a retinue of tabloid photographers seeking pictures of the great ballplayer with a young cancer patient.

The Jimmy Fund became a household name and a household cause. A large, white “piggy bank” for donations (shaped like an enormous baseball) was placed outside the Statler Hotel. Advertisements for the Children’s Cancer Research Fund were plastered across billboards throughout Boston. Countless red-and-white collection cans—called “Jimmy’s cans”—sprouted up outside movie theaters. Funds poured in from sources large and small: $100,000 from the NCI, $5,000 from a bean supper in Boston, $111 from a lemonade stand, a few dollars from a children’s circus in New Hampshire.

By the early summer of 1952, Farber’s new building, a large, solid cube perched on the edge of Binney Street, just off Longwood Avenue, was almost ready. It was lean, functional, and modern—self-consciously distinct from the marbled columns and gargoyles of the hospitals around it. One could see the obsessive hand of Farber in the details. A product of the 1930s, Farber was instinctively frugal (“You can take the child out of the Depression, but you can’t take the Depression out of the child,” Leonard Lauder liked to say about his generation), but with Jimmy’s Clinic, Farber pulled out all the stops. The wide cement steps leading up to the front foyer—graded by only an inch, so that children could easily climb them—were steam-heated against the brutal Boston blizzards that had nearly stopped Farber’s work five winters before.

Upstairs, the clean, well-lit waiting room had whirring carousels and boxes full of toys. A toy electric train, set into a stone “mountain,” chugged on its tracks. A television set was embedded on the face of the model mountain. “If a little girl got attached to a doll,” Time reported in 1952, “she could keep it; there were more where it came from.” A library was filled with hundreds of books, three rocking horses, and two bicycles. Instead of the usual portraits of dead professors that haunted the corridors of the neighboring hospitals, Farber commissioned an artist to paint full-size pictures of fairy-book characters—Snow White, Pinocchio, and Jimmy Cricket. It was Disney World fused with Cancerland.

The fanfare and pomp might have led a casual viewer to assume that Farber had almost found his cure for leukemia, and the brand-new clinic was his victory lap. But in truth his goal—a cure for leukemia—still eluded him. His Boston group had now added another drug, a steroid, to their antileukemia regimen, and by assiduously combining steroids and antifolates, the remissions had been stretched out by several months. But despite the most aggressive therapy, the leukemia cells eventually grew resistant and recurred, often furiously. The children who played with the dolls and toy trains in the bright rooms downstairs were inevitably brought back to the glum wards in the hospital, delirious or comatose and in terminal agony.

One woman whose child was treated for cancer in Farber’s clinic in the early fifties wrote, “Once I discover that almost all the children I see are doomed to die within a few months, I never cease to be astonished by the cheerful atmosphere that generally prevails. True, upon closer examination, the parents’ eyes look suspiciously bright with tears shed and unshed. Some of the children’s robust looks, I find, are owing to one of the anti-leukemia drugs that produces a swelling of the body. And there are children with scars, children with horrible swellings on different parts of their bodies, children missing a limb, children with shaven heads, looking pale and wan, clearly as a result of recent surgery, children limping or in wheelchairs, children coughing, and children emaciated.”

Indeed, the closer one looked, the more sharply the reality hit. Enconced in his new, airy building, with dozens of assistants swirling around him, Farber must have been haunted by that inescapable fact. He was trapped in his own waiting room, still looking for yet another drug
to eke out a few more months of remission in his children. His patients—having walked up the fancy steamed stairs to his office, having pranced around on the musical carousel and immersed themselves in the cartoonish gleam of happiness—would die, just as inexorably, of the same kinds of cancer that had killed them in 1947.

But for Farber, the lengthening, deepening remissions bore quite another message: he needed to expand his efforts even further to launch a concerted battle against leukemia. “Acute leukemia,” he wrote in 1953, has “responded to a more marked degree than any other form of cancer . . . to the new chemicals that have been developed within the last few years. Prolongation of life, amelioration of symptoms, and a return to a far happier and even a normal life for weeks and many months have been produced by their use.”

Farber needed a means to stimulate and fund the effort to find even more powerful antileukemia drugs. “We are pushing ahead as fast as possible,” he wrote in another letter—but it was not quite fast enough for him. The money that he had raised in Boston “has dwindled to a disturbingly small amount,” he noted. He needed a larger drive, a larger platform, and perhaps a larger vision for cancer. He had outgrown the house that Jimmy had built.