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

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

—Susan Sontag, *Illness as Metaphor*

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

The notion of cancer as an affliction that belongs paradigmatically to the twentieth century is reminiscent, as Susan Sontag argued so powerfully in her book *Illness as Metaphor*, of another disease once considered emblematic of another era: tuberculosis in the nineteenth century. Both diseases, as Sontag pointedly noted, were similarly "obscene—in the original meaning of that word: ill-omened, abominable, repugnant to the senses." Both drain vitality; both stretch out the encounter with death; in both cases, *dying*, even more than death, defines the illness.

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

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

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

Like the normal cell, the cancer cell relies on growth in the most basic, elemental sense: the division of one cell to form two. In normal tissues, this process is exquisitely regulated, such that growth is stimulated by specific signals and arrested by other signals. In cancer, unbridled growth gives rise to generation upon generation of cells. Biologists use the term *clone* to describe cells that share a common genetic ancestor. Cancer, we now know, is a clonal disease. Nearly every known cancer originates from one ancestral cell that, having acquired the capacity of limitless cell division and survival, gives rise to limitless numbers of descendants—Virchow's *omnis cellula e cellula e cellula* repeated ad infinitum.

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

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

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

In 1862, Edwin Smith—an unusual character: part scholar and part huckster, an antique forger and self-made Egyptologist—bought (or, some say, stole) a fifteen-foot-long papyrus from an antiques seller in Luxor in Egypt. The papyrus was in dreadful condition, with crumbling, yellow pages filled with cursive Egyptian script. It is now thought to have been written in the seventeenth century BC, a transcription of a manuscript dating back to 2500 BC. The copier—a plagiarist in a terrible hurry—had made errors as he had scribbled, often noting corrections in red ink in the margins.

Translated in 1930, the papyrus is now thought to contain the collected teachings of Imhotep, a great Egyptian physician who lived around 262[illegible] BC. Imhotep, among the few nonroyal Egyptians known to us from the Old Kingdom, was a Renaissance man at the center of a sweeping Egyptian renaissance. As a vizier in the court of King Djozer, he dabbled in neurosurgery, tried his hand at architecture, and made early forays into astrolo[illegible]y and astronomy. Even the Greeks, encountering the fierce, hot blast of his intellect as they marched through Egypt centuries later, cast him as [illegible]n 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 pockmarks on the face of Ramses V in the twelfth century BC. Tuberculosis rose and ebbed through the Indus valley like its seasonal floods. But if cancer existed in the interstices of these massive epidemics, it existed in silence, leaving no easily identifiable trace in the medical literature—or in any other literature.

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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 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.

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

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

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

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

Aufderheide 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 archaeologist who dug up Lucy, one of the earliest known human skeletons, also discovered a jawbone dating from 4000 BC 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.

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The most striking finding, though, is not that cancer existed in the distant past, but that it was fleetingly rare. When I asked Aufderheide 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 prevalent in certain populations until the late nineteenth century, likely the result of several carcinogens found in pickling reagents and preservatives and exacerbated by endemic and contagious infection with a bacterium that causes stomach cancer. With the introduction of modern refrigeration (and possibly changes in public hygiene that have diminished the rate of endemic infection), the stomach cancer epidemic seems to have abated. In contrast, lung cancer incidence in men increased dramatically in the 1950s as a result of an increase in cigarette smoking during the early twentieth century. In women, a cohort that began to smoke in the 1950s, lung cancer incidence has yet to reach its peak.

The consequence of these demographic and epidemiological shifts was, and is, enormous. In 1900, as Roswell Park noted, tuberculosis was by far the most common cause of death in America. Behind tuberculosis came pneumonia (William Osler, the famous physician from Johns Hopkins University, called it "captain of the men of death"), diarrhea, and gastroenteritis. Cancer still lagged at a distant seventh. By the early 1940s, cancer had ratcheted its way to second on the list, immediately behind heart disease. In that same span, life expectancy among Americans had increased by about twenty-six years. The proportion of persons above sixty years—the age when most cancers begin to strike—nearly doubled.

But the rarity of ancient cancers notwithstanding, it is impossible to forget the tumor growing in the bone of Aufderheide's mummy of a thirty-five-year-old. The woman must have wondered about the insolent gnaw of pain in her bone, and the bulge slowly emerging from her arm. It is hard to look at the tumor and not come away with the feeling that one has encountered a powerful monster in its infancy.

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 *tuphon*, the father of winds—a word that also gives rise to the modern *typhoon*. *Influenza* emerged from the Latin *influentia* because medieval 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 uncontrolled 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 Archaemedes 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 apogee. 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 Bertipaglia, 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 discomforted 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, rasped ivory, hulled 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

Rackt 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, collaborating 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, και ειυ—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 □α□ □□□ 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 intemal . . . 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 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 lolled 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 elusively 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.

* Hunter used this term both to describe metastatic—remotely disseminated—cancer and to argue that therapy was useless.

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 happed 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 academic achievement, drew the attention of his teachers and mentors. He wandered into the world of surgery almost by accident, attending medical 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 surgical 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 orifice 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 convulsions ceased." Another doctor, prescribing a remedy for lung cancer, wrote, "Small bleedings give temporary relief, although, of course, they cannot often be repeated." At Bellevue, the "internes" ran about in corridors 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 scalpels dangling from their pockets. If a tool fell on the blood-soiled floor, it was dusted off and inserted back into the pocket—or into the body of the patient on the operating table.

In October 1877, leaving behind this gruesome medical world of purgers, bleeders, pus-pails, and quacks, Halsted traveled to Europe to visit the clinics of London, Paris, Berlin, Vienna, or Leipzig, where young American surgeons were typically sent to learn refined European surgical techniques. The timing was fortuitous: Halsted arrived in Europe when cancer surgery was just emerging from its chrysalis. In the high-baroque surgical amphitheaters of the Allgemeines Krankenhaus in Vienna, Theodor Billroth was teaching his students novel techniques to dissect the stomach (the complete surgical removal of cancer, Billroth told his students, was merely an "audacious step" away). At Halle, a few hundred miles from Vienna, the German surgeon Richard von Volkmann was working on a technique to operate on breast cancer. Halsted met the giants of European surgery: Hans Chiari, who had meticulously deconstructed the anatomy of the liver; Anton Wolfler, who had studied with Billroth and was learning to dissect the thyroid gland.

For Halsted, this whirlwind tour through Berlin, Halle, Zurich, London, and Vienna was an intellectual baptism. When he returned to practice in New York in the early 1880s, his mind was spinning with the ideas he had encountered in his journey: Lister's carbolic sprays, Volkmann's early attempts at cancer surgery, and Billroth's miraculous abdominal operations. Energized and inspired, Halsted threw himself to work, operating on patients at Roosevelt Hospital, at the College of Physicians and Surgeons at Columbia, at Bellevue, and at Chambers Hospital. Bold, inventive, and daring, his confidence in his handiwork boomed. In 1882, he removed an infected gallbladder from his mother on a kitchen table, successfully performing one of the first such operations in America. Called urgently to see his sister, who was bleeding heavily after childbirth, he withdrew his own blood and transfused her with it. (He had no knowledge of blood types; but fortunately Halsted and his sister were a perfect match.)

In 1884, at the prime of his career in New York, Halsted read a paper describing the use of a new surgical anesthetic called cocaine. At Halle, in Volkmann's clinic, he had watched German surgeons perform operations using this drug; it was cheap, accessible, foolproof, and easy to dose—

PART FIVE

"A DISTORTED VERSION OF OUR NORMAL SELVES"

It is in vain to speak of cures, or think of remedies, until such time as we have considered of the causes . . . cures must be imperfect, lame, and to no purpose, wherein the causes have not first been searched.

—Robert Burton,
The Anatomy of Melancholy, 1893

You can't do experiments to see what causes cancer. It's not an accessible problem and it's not the sort of thing scientists can afford to do.

—I. Hermann,
cancer researcher, 1978

What can be the "why" of these happenings?

—Peyton Rous,
1966, on the mystery
of the origin of cancer

"A unitary cause"

It is the spring of 2005—a pivot point in the medical oncology fellowship. Our paths are about to divide. Three of us will continue in the clinic, with a primary focus in clinical research and in the day-to-day care of patients. Four will explore cancer in the laboratory, retaining just a minor presence in the clinic, seeing just a handful of patients every week.

The choice between the two paths is instinctual. Some of us inherently perceive ourselves as clinicians; others primarily as scientists. My own inclinations have changed little since the first day of my internship. Clinical medicine moves me viscerally. But I am a lab rat, a nocturnal, peripatetic creature drawn to the basic biology of cancer. I mull over the type of cancer to study in the laboratory, and I find myself gravitating toward leukemia. I may be choosing the laboratory, but my subject of research is governed by a patient. Carla's disease has left its mark on my life.

Even so, in the fading twilight of my full-time immersion in the hospital, there are disquieting moments that remind me how deeply clinical medicine can surprise and engage me. It is late one evening in the fellows' room, and the hospital around us has fallen silent save for the metallic clink of cutlery being brought up for meals. The air outside is heavy with impending rain. The seven of us, close friends by now, are compiling lists of patients to pass on to the next class of fellows when Lauren begins to read her list aloud, calling out the names of those in her care who have died over our two-year fellowship. Suddenly inspired, she pauses and adds a sentence to each name as a sort of epitaph.

It is an impromptu memorial service, and it stirs something in the room. I join in, calling out names of my patients who have died and appending a sentence or two in memory.

Kenneth Armor, sixty-two, an internist with stomach cancer. In his final days, all he wished for was a vacation with his wife and time to play with his cats.

Oscar Fisher, thirty-eight, had small-cell lung cancer. Cognitively impaired since birth, he was his mother's favorite child. When he died, she was threading rosaries through his fingers.

That night I sit alone with my list, remembering the names and faces late into the evening. How does one memorialize a patient? These men and women have been my friends, my interlocutors, my teachers—a surrogate family. I stand up at my desk, as if at a funeral, my ears hot with emotion, my eyes full of tears. I look around the room at the empty desks and note how swiftly the last two years have reshaped all seven of us. Eric, cocksure, ambitious, and smart, is humbler and more introspective. Edwin, preternaturally cheerful and optimistic in his first month, talks openly about resignation and grief. Rick, an organic chemist by training, has become so infatuated with clinical medicine that he doubts that he will return to the laboratory. Lauren, guarded and mature, enlivens her astute assessments with jokes about oncology. Our encounter with cancer has rounded us off; it has smoothed and polished us like river rocks.

❧

A few days later, I meet Carla in the infusion room. She is casually chatting with the nurses, as if catching up with old friends. From a distance, she is barely recognizable. The sheet-white complexion I recall from her first visit to the hospital has warmed up several degrees of red. The bruises in her arm from repeated infusions have vanished. Her children are back in their routine, her husband has returned to work, her mother is home in Florida. Carla's life is nearly normal. She tells me that her daughter occasionally wakes up crying from a nightmare. When I ask her if this reflects some remnant trauma from Carla's yearlong ordeal with illness, she shakes her head assertively: "No. It's just monsters in the dark."

It has been a little more than a year since her original diagnosis. She is still taking pills of 6-mercaptopurine and methotrexate—Burchenal's drug and Farber's drug, a combination intended to block the growth of any remnant cancer cells. When she recalls the lowest points of her illness, she shudders in disgust. But something is normalizing and healing inside her. Her own monsters are vanishing, like old bruises.

When her blood counts return from the lab, they are stone-cold normal. Her remission continues. I am astonished and exalted by the news, but I bring it to her cautiously, as neutrally as I can. Like all patients, Carla smells overenthusiasm with deep suspicion: a doctor who raves disproportionately about small victories is the same doctor who might be preparing his patient for some ultimate defeat. But this time there is no reason to be suspicious. I tell her that her counts look perfect, and that no more tests are required today. In leukemia, she knows, no news is the best kind of news.

❧

Late that evening, having finished my notes, I return to the laboratory. It is a beehive of activity. Postdocs and graduate students hover around the microscopes and centrifuges. Medical words and phrases are occasionally recognizable here, but the dialect of the lab bears little resemblance to the dialect of medicine. It is like traveling to a neighboring country—one that has similar mannerisms but speaks a different language:

"But the PCR on the leukemia cells should pick up the band."

"What conditions did you use to run this gel?"

"Agarose, four percent."

"Was the RNA degraded in the centrifugation step?"

I retrieve a plate of cells from the incubator. The plate has 384 tiny wells, each barely large enough to hold two grains of rice. In each well, I have placed two hundred human leukemia cells, then added a unique chemical from a large collection of untested chemicals. In parallel, I have its "twin" plate—containing two hundred normal human blood-forming stem cells, with the same panel of chemicals added to every well.

Several times each day, an automated microscopic camera will photograph each well in the two plates, and a computerized program will calculate the number of leukemia cells and normal stem cells. The experiment is seeking a chemical that can kill leukemia cells but spare normal stem cells—a specifically targeted therapy against leukemia.

I aspirate a few microliters containing the leukemia cells from one well and look at them under the microscope. The cells look bloated and grotesque, with a dilated nucleus and a thin rim of cytoplasm, the sign of a cell whose very soul has been co-opted to divide and to keep dividing with pathological, monomaniacal purpose. These leukemia cells have come into my laboratory from the National Cancer Institute, where they were grown and studied for nearly three decades. That these cells are still growing with obscene fecundity is a testament to the terrifying power of this disease.

The cells, technically speaking, are immortal. The woman from whose body they were once taken has been dead for thirty years.

Under the Lamps of Viruses

Unidentified flying objects, abominable snowmen, the Loch Ness monster and human cancer viruses.

—*Medical World News*, 1974,
on four "mysteries" widely reported
and publicized but never seen

The biochemist Arthur Kornberg once joked that the discipline of modern biology in its early days often operated like the man in the proverbial story who is frantically searching for his keys under a streetlamp. When a passerby asks the man whether he lost his keys at that spot, the man says that he actually lost them at home—but he is looking for the keys under the lamp because "the light there is the brightest."

In the predawn of modern biology, experiments were so difficult to perform on biological organisms, and the results of manipulations so unpredictable, that scientists were severely constrained in their experimental choices. Experiments were conducted on the simplest model organisms—fruit flies, sea urchins, bacteria, slime molds—because the "light" there was the brightest.

In cancer biology, Rous's sarcoma virus represented the only such lamplit spot. Admittedly, it was a rare virus that produced a rare cancer in a species of chicken. But it was the most reliable way to produce a real cancer in a living organism. Cancer researchers knew that X-rays, soot, cigarette smoke, and asbestos represented vastly more common risk factors for human cancers. They had heard of the odd Brazilian case of a family that seemed to carry retinoblastoma cancer in its genes. But the capacity to *manipulate* cancer in an experimental environment was unique to the Rous virus, and so it stood center stage, occupying all the limelight.

The appeal of studying Rous virus was further compounded by the formidable force of Peyton Rous's personality. Bulldogish, persuasive, and inflexible, Rous had acquired a near paternal attachment to his virus, and he was unwilling to capitulate to any other theory of cause. He acknowledged that epidemiologists had shown that exogenous carcinogens were *correlated* with cancer (Doll and Hill's study, published in 1950, had clearly shown that smoking was associated with an increase in lung cancer), but this had not offered any mechanistic explanation of cancer causation. Viruses, Rous felt, were the only answer.

By the early 1950s, cancer researchers had thus split into three feuding camps. The virologists, led by Rous, claimed that viruses caused cancer, although no such virus had been found in human studies. Epidemiologists, such as Doll and Hill, argued that exogenous chemicals caused cancer, although they could not offer a mechanistic explanation for their theory or results. The third camp, of Theodor Boveri's successors, stood at the farthest periphery. They possessed weak, circumstantial evidence that genes internal to the cell might cause cancer, but had neither the powerful human data of the epidemiologists nor the exquisite experimental insights of the chicken virologists. Great science emerges out of great contradiction, and here was a gaping rift slicing its way through the center of cancer biology. Was human cancer caused by an infectious agent? Was it caused by an exogenous chemical? Was it caused by an internal gene? How could the three groups of scientists have examined the same elephant and returned with such radically variant opinions about its essential anatomy?

In 1951, a young virologist named Howard Temin, then a postdoctoral researcher, arrived at the California Institute of Technology in Pasadena, California, to study the genetics of fruit flies. Restless and imaginative, Temin soon grew bored with fruit flies. Switching fields, he chose to study Rous sarcoma virus in Renato Dulbecco's laboratory. Dulbecco, a suave, exquisitely mannered Calabrian aristocrat, ran his lab at Caltech with a distant and faintly patrician air. Temin was a perfect fit: if Dulbecco wanted distance, Temin wanted independence. Temin found a house in Pasadena with several other young scientists (including John Cairns, the future author of the *Scientific American* article on the War on Cancer) and spent his time cooking up unusual meals in heavy communal pots and talking volubly about biological riddles late into the night.

In the laboratory, too, Temin was cooking up an unusual experiment that was virtually guaranteed to fail. Until the late fifties, Rous sarcoma virus had been shown to cause tumors only in live chickens. Temin, working closely with Harry Rubin, wanted to study how the virus converted normal cells into cancer cells. To do this, they needed a vastly simplified system—a system free of chickens and tumors, and analogous to bacteria in a petri dish. And so Temin imagined creating *cancer* in a petri dish. In 1958, in his seventh year in Dulbecco's lab, Temin succeeded. He added Rous sarcoma virus to a layer of normal cells in a petri dish. The infection of the cells incited them to grow uncontrollably, forcing them to form tiny distorted heaps containing hundreds of cells that Temin called foci (the plural of *focus*). The foci, Temin reasoned, represented cancer distilled into its essential, elemental form: cells growing uncontrollably, unstoppably—pathological mitosis. It was the sheer, driving power of Temin's imagination that allowed him to look at a tiny heap of cells and reimagine that heap as the essence of the diffuse systemic disease that kills humans. But Temin believed that the cell, and its interaction with the virus, had all the biological components necessary to drive the malignant process. The ghost was out of the organism.

Temin could now use his cancer-in-a-dish to perform experiments that would have been nearly impossible using whole animals. One of his first experiments with this system, performed in 1959, produced an unexpected result. Normally, viruses infect cells, produce more viruses, and infect more cells, but they do not directly affect the genetic makeup, the DNA, of the cell. Influenza virus, for instance, infects lung cells and produces more influenza virus, but it does not leave a permanent fingerprint in our genes; when the virus goes away, our DNA is left untouched. But Rous's virus behaved differently. Rous sarcoma virus, having infected the cells, had *physically* attached itself to the cell's DNA and thereby altered the cell's genetic makeup, its genome. "The virus, in some structural as well as functional sense, becomes part of the genome of the cell," Temin wrote.

This observation—that a DNA copy of a virus's genes could structurally attach itself to a cell's genes—intrigued Temin and Dulbecco. But it raised an even more intriguing conceptual problem. In viruses, genes are sometimes carried in their intermediary RNA form. Certain viruses have dispensed with the original DNA copy of genes and keep their genome in the RNA form, which is directly translated into viral proteins once the virus infects a cell.

Temin knew from work performed by other researchers that Rous sarcoma virus is one such RNA virus. But if the virus genes *started* as RNA, then how could a copy of its genes convert into DNA? The central dogma of molecular biology forbade such a transition. Biological information, the

"deciphered"—i.e., converted into an intermediate RNA message. The RNA message, in turn, instructs the eye cells to build the red pigment protein, thus giving rise to red-eyed flies of the next generation. Any interruption in this information flow might disrupt the transmission of the red eye trait—producing flies with colorless eyes.

This unidirectional flow of genetic information—DNA → RNA → protein—was found to be universal in living organisms, from bacteria to slime molds to fruit flies to humans. In the mid-1950s, biologists termed this the "central dogma" of molecular biology.

An incandescent century of biological discovery—spanning from Mendel's discovery of genes in 1860 to Monod's identification of the RNA copy of genes in the late 1950s—illuminated the inner workings of a normal cell. But it did little to illuminate the workings of a cancer cell or the cause of cancer—except in two tantalizing instances.

The first came from human studies. Nineteenth-century physicians had noted that some forms of cancer, such as breast and ovarian cancer, tended to run in families. This in itself could not prove a hereditary cause: families share not just genes, but also habits, viruses, foods, exposures to chemicals, and neurotic behaviors—all factors, at some time or another, implicated as causes of cancer. But occasionally, a family history was so striking that a hereditary cause (and, by extension, a *genetic* cause) could not be ignored. In 1872, Hilário de Gouvêa, a Brazilian ophthalmologist practicing in Rio, treated a young boy with a rare cancer of the eye called a retinoblastoma by removing the eye surgically. The boy had survived, grown up, and married a woman with no family history of cancer. The couple had several children, and two of the daughters developed their father's retinoblastoma in both eyes—and died. De Gouvêa reported this case as a puzzling enigma. He did not possess the language of genetics, but to later observers, the case suggested an inherited factor that "lived" in genes and caused cancer. But such cases were so rare that it was hard to test this hypothesis experimentally, and de Gouvêa's report was largely ignored.

The second time scientists circled around the cause of cancer—almost hitting the nerve spot of carcinogenesis—came several decades after the strange Brazilian case. In the 1910s, Thomas Hunt Morgan, the fruit fly geneticist at Columbia, noticed that mutant flies occasionally appeared within his flock of flies. In biology, mutants are defined as organisms that differ from the normal. Morgan noticed that an enormous flock of flies with normal wings might occasionally give birth to a "monster" with rough or scalloped wings. These mutations, Morgan discovered, were the results of alterations in genes and the mutations could be carried from one generation to the next.

But what caused mutations? In 1928, Hermann Joseph Muller, one of Morgan's students, discovered that X-rays could vastly increase the rate of mutation in fruit flies. At Columbia, Morgan had produced mutant flies spontaneously. (When DNA is copied during cell division, a copying error occasionally generates an accidental change in genes, thus causing mutations.) Muller found that he could accelerate the incidence of these accidents. Using X-rays to bombard flies, he found that he could produce hundreds of mutant flies over a few months—more than Morgan and his colleagues had produced using their vast breeding program over nearly two decades.

The link between X-rays and mutations nearly led Morgan and Muller to the brink of a crucial realization about cancer. Radiation was known to cause cancer. (Recall Marie Curie's leukemia, and the tongue cancers of the radium-watch makers.) Since X-rays also caused mutations in fruit fly genes, could cancer be a disease of *mutations*? And since mutations were changes in genes, could genetic alterations be the "unitary cause" of cancer?

Had Muller and Morgan, student and mentor, pitched their formidable scientific skills together, they might have answered this question and uncovered this essential link between mutations and malignancy. But once close colleagues, they became pitted and embittered rivals. Cantankerous and rigid with old age, Morgan refused to give Muller full recognition for his theory of mutagenesis, which he regarded as a largely derivative observation. Muller, in turn, was sensitive and paranoid; he felt that Morgan had stolen his ideas and taken an undue share of credit. In 1932, having moved his lab to Texas, Muller walked into the nearby woods and swallowed a roll of sleeping pills in an attempted suicide. He survived, but haunted by anxiety and depression, his scientific productivity lapsed in his later years.

Morgan, in turn, remained doggedly pessimistic about the relevance of the fruit fly work in understanding human diseases. In 1933, Morgan received the Nobel Prize in Physiology or Medicine for his far-reaching work on fruit fly genetics. (Muller would receive the Nobel Prize independently in 1946.) But Morgan wrote self-deprecatingly about the medical relevance of his work, "The most important contribution to medicine that genetics has made is, in my opinion, intellectual." At some point far in the future, he imagined a convergence between medicine and genetics. "Possibly," he speculated, "the doctor may then want to call in his geneticist friends for consultation!"

But to oncologists in the 1940s, such a "consultation" seemed far-fetched. The hunt for an internal, genetic cause of cancer had stalled since Boveri. Pathological mitosis was visible in cancerous tissue. But both geneticists and embryologists failed to answer the key question: what caused mitosis to turn so abruptly from such an exquisitely regulated process to chaos?

More deeply, what had failed was a kind of biological imagination. Boveri's mind had so acrobatically leapt from sea urchins to carcinomas, or Morgan's from pea plants to fruit flies, in part because biology itself was leaping from organism to organism, finding systematic cellular blueprints that ran deeply through all the living world. But extending that same blueprint to human *diseases* had turned out to be a much more challenging task. At Columbia, Morgan had assembled a fair collection of fruit fly monsters, but none that even remotely resembled a real human affliction. The notion that the cancer doctor might call in a "genetic friend" to help understand the pathophysiology of cancer seemed laughable.

Cancer researchers would return to the language of genes and mutations again in the 1970s. But the journey back to this language—and to the true "unitary" cause of cancer—would take a bewildering detour through the terrain of new biology, and a further fifty years.

As early as 1858, Virchow recognized this power of proliferation. Looking at cancer specimens under the microscope, Virchow understood that cancer was cellular hyperplasia, the disturbed, pathological growth of cells. But although Virchow recognized and described the core abnormality, he could not fathom its cause. He argued that inflammation—the body's reaction to a harmful injury, characterized by redness, swelling, and immune-system activation—caused cells to proliferate, leading to the outgrowth of malignant cells. He was almost right: chronic inflammation, smoldering over decades, does cause cancer (chronic hepatitis virus infection in the liver precipitates liver cancer), but Virchow missed the essence of the cause. Inflammation makes cells divide in response to injury, but this cell division is driven as a reaction to an external agent such as a bacteria or a wound. In cancer, the cell acquires *autonomous* proliferation; it is driven to divide by an internal signal. Virchow attributed cancer to the disturbed physiological milieu around the cell. He failed to fathom that the true disturbance lay within the cancer cell itself.

Two hundred miles south of Virchow's Berlin laboratory, Walther Flemming, a biologist working in Prague, tried to uncover the cause of abnormal cell division, although using salamander eggs rather than human cells as his subject. To understand cell division, Flemming had to visualize the inner anatomy of the cell. In 1879, Flemming thus stained dividing salamander cells with aniline, the all-purpose chemical dye used by Paul Ehrlich. The stain highlighted a blue, threadlike substance located deep within the cell's nucleus that condensed and brightened to a cerulean shade just before cell division. Flemming called his blue-stained structures *chromosomes*—"colored bodies." He realized that cells from every species had a distinct number of chromosomes (humans have forty-six; salamanders have fourteen). Chromosomes were duplicated during cell division and divided equally between the two daughter cells, thus keeping the chromosome number constant from generation to generation of cell division. But Flemming could not assign any further function to these mysterious blue "colored bodies" in the cell.

Had Flemming moved his lens from salamander eggs to Virchow's human specimens, he might have made the next crucial conceptual leap in understanding the root abnormality in cancer cells. It was Virchow's former assistant David Paul von Hansemann, following Flemming's and Virchow's trails, who made a logical leap between the two. Examining cancer cells stained with aniline dyes with a microscope, von Hansemann noticed that Flemming's chromosomes were markedly abnormal in cancer. The cells had split, frayed, disjointed chromosomes, chromosomes broken and rejoined, chromosomes in triplets and quadruplets.

Von Hansemann's observation had a profound corollary. Most scientists continued to hunt for parasites in cancer cells. (Bennett's theory of spontaneous suppuration still held a macabre fascination for some pathologists.) But von Hansemann proposed that the real abnormality lay in the structure of these bodies internal to cancer cells—in chromosomes—and therefore in the cancer cell itself.

But was it cause or effect? Had cancer altered the structure of chromosomes? Or had chromosomal changes precipitated cancer? Von Hansemann had observed a correlation between chromosomal change and cancer. What he needed was an experiment to causally connect the two.

The missing experimental link emerged from the lab of Theodor Boveri, yet another former assistant of Virchow's. Like Flemming, who worked with salamander cells, Boveri chose to study simple cells in simple organisms, eggs from sea urchins, which he collected on the windswept beaches near Naples. Urchin eggs, like most eggs in the animal kingdom, are strictly monogamous; once a single sperm has entered the egg, the egg puts up an instant barrier to prevent others from entering. After fertilization, the egg divides, giving rise to two, then four cells—each time duplicating the chromosomes and splitting them equally between the two daughter cells. To understand this natural chromosomal separation, Boveri devised a highly unnatural experiment. Rather than allowing the urchin egg to be fertilized by just one sperm, he stripped the outer membrane of the egg with chemicals and forcibly fertilized the egg with two sperms.

The multiple fertilization, Boveri found, precipitated chromosomal chaos. Two sperms fertilizing an egg results in three of each chromosome—a number impossible to divide evenly. The urchin egg, unable to divide the number of chromosomes appropriately among its daughter cells, was thrown into frantic internal disarray. The rare cell that got the right combination of all thirty-six sea urchin chromosomes developed normally. Cells that got the wrong combinations of chromosomes failed to develop or aborted development and involuted and died. Chromosomes, Boveri concluded, must carry information vital for the proper development and growth of cells.

This conclusion allowed Boveri to make a bold, if far-fetched, conjecture about the core abnormality in cancer cells. Since cancer cells possessed striking aberrations in chromosomes, Boveri argued that these chromosomal abnormalities might be the cause of the pathological growth characteristic of cancer.

Boveri found himself circling back to Galen—to the age-old notion that all cancers were connected by a common abnormality—the "unitary cause of carcinoma," as Boveri called it. Cancer was not "an unnatural group of different maladies," Boveri wrote. Instead, a common feature lurked behind all cancers, a uniform abnormality that emanated from abnormal chromosomes—and was therefore *internal* to the cancer cell. Boveri could not put his finger on the nature of this deeper internal abnormality. But the "unitary cause" of carcinoma lay in this disarray—not a chaos of black bile, but a chaos of blue chromosomes.

Boveri published his chromosomal theory of cancer in an elegant scientific pamphlet entitled "Concerning the Origin of Malignant Tumors" in 1914. It was a marvel of fact, fantasy, and inspired guesswork that stitched sea urchins and malignancy into the same fabric. But Boveri's theory ran into an unanticipated problem, a hard contradictory fact that it could not explain away. In 1910, four years before Boveri had published his theory, Peyton Rous, working at the Rockefeller Institute, had demonstrated that cancer in chickens could be caused by a virus, soon to be named the Rous sarcoma virus, or RSV.

The central problem was this: as causal agents, Rous's virus and Boveri's chromosomes were incompatible. A virus is a pathogen, an external agent, an invader exogenous to the cell. A chromosome is an internal entity, an endogenous structure buried deep inside the cell. The two opposites could not both claim to be the "unitary cause" of the same disease. How could an internal structure, a chromosome, and an external infectious agent, a virus, both create cancer?

In the absence of concrete proof for either theory, a viral cause for cancer seemed far more attractive and believable. Viruses, initially isolated in 1898 as minuscule infectious microbes that caused plant diseases, were becoming increasingly recognized as causes for a variety of animal and human diseases. In 1909, a year before Rous isolated his cancer-causing virus, Karl Landsteiner implicated a virus as the cause for polio. By the early 1920s, viruses that caused cowpox and human herpes infections had been isolated and grown in laboratories, further cementing the connection between viruses and human and animal diseases.

Undeniably, the belief in cause was admixed with the hope for a cure. If the causal agent was exogenous and infectious, then a cure for cancer seemed more likely. Vaccination with cowpox, as Jenner had shown, prevented the much more lethal smallpox infection, and Rous's discovery of a cancer-causing virus (albeit in chickens) had immediately provoked the idea of a therapeutic cancer vaccine. In contrast, Boveri's theory that cancer was caused by a mysterious problem lurking in the threadlike chromosomes, stood on thin experimental evidence and offered no prospect for a cure.

While the mechanistic understanding of the cancer cell remained suspended in limbo between viruses and chromosomes, a revolution in the understanding of normal cells was sweeping through biology in the early twentieth century. The seeds of this revolution were planted by a retiring, nearsighted monk in the isolated hamlet of Brno, Austria, who bred pea plants as a hobby. In the early 1860s, working alone, Gregor Mendel had identified a few characteristics in his purebred plants that were inherited from one generation to the next—the color of the pea flower, the texture of the pea seed, the height of the pea plant. When Mendel intercrossed short and tall, or blue-flowering and green-flowering, plants using a pair of minute forceps, he stumbled on a startling phenomenon. Short plants bred with tall plants did not produce plants of intermediate height; they produced tall plants. Wrinkle-seeded peas crossed with smooth-seeded peas produced only wrinkled peas.

The implication of Mendel's experiment was far-reaching: inherited traits, Mendel proposed, are transmitted in discrete, indivisible packets. Biological organisms transmit "instructions" from one cell to its progeny by transferring these packets of information.

Mendel could only visualize these traits or properties in a descriptive sense—as colors, texture, or height moving from generation to generation; he could not see or fathom what conveyed this information from one plant to its progeny. His primitive lamplit microscope, with which he could barely peer into the interior of cells, had no power to reveal the mechanism of inheritance. Mendel did not even have the name for this unit of inheritance; decades later, in 1909, botanists would christen it a gene. But the name was still just a name; it offered no further explanation about a gene's structure or function. Mendel's studies left a provocative question hanging over biology for half a century: in what corporal, physical form was a "gene"—the particle of inheritance—carried inside the cell?

In 1910, Thomas Hunt Morgan, an embryologist at Columbia University in New York, discovered the answer. Like Mendel, Morgan was a compulsive breeder, but of fruit flies, which he raised by the thousands on rotting bananas in the Fly Room on the far edge of the Columbia campus. Again, like Mendel, Morgan discovered heritable traits moving indivisibly through his fruit flies generation upon generation—eye colors and wing patterns that were conveyed from parents to offspring without blending.

Morgan made another observation. He noted that an occasional rare trait, such as white eye color, was intrinsically linked to the gender of the fly: white eyes were found only in male flies. But "maleness"—the inheritance of sex—Morgan knew, was linked to chromosomes. So genes had to be carried on chromosomes—the threadlike structures identified by Flemming three decades earlier. Indeed, a number of Flemming's initial observations on the properties of chromosomes began to make sense to Morgan. Chromosomes were duplicated during cell division, and genes were duplicated as well and thus transmitted from one cell to the next, and from one organism to the next. Chromosomal abnormalities precipitated abnormalities in the growth and development of sea urchins, and so abnormal genes must have been responsible for this dysfunction. In 1915, Morgan proposed a crucial advance to Mendel's theory of inheritance: genes were borne on chromosomes. It was the transmission of chromosomes during cell division that allowed genes to move from a cell to its progeny.

The third vision of the "gene" emerged from the work of Oswald Avery, a bacteriologist at the Rockefeller University in New York. Mendel had found that genes could move from one generation to the next; Morgan had proved that they did so by being carried on chromosomes. In 1926, Avery found that in certain species of bacteria, genes could also be transmitted *laterally* between two organisms—from one bacterium to its neighbor. Even dead, inert bacteria—no more than a conglomeration of chemicals—could transmit genetic information to live bacteria. This implied that an inert chemical was responsible for carrying genes. Avery separated heat-killed bacteria into their chemical components. And by testing each chemical component for its capacity to transmit genes, Avery and his colleagues reported in 1944 that genes were carried by one chemical, deoxyribonucleic acid, or DNA. What scientists had formerly disregarded as a form of cellular stuffing with no real function—a "stupid molecule," as the biologist Max Delbruck once called it dismissively—turned out to be the central conveyor of genetic information between cells, the least stupid of all molecules in the chemical world.

By the mid-1940s, three decades after biologists had coined the word, the molecular nature of the gene had come into focus. Functionally, a gene was a unit of inheritance that carried a biological trait from one cell to another or from one generation to the next. Physically, genes were carried within the cell in the form of chromosomes. Chemically, genes were composed of DNA, deoxyribonucleic acid.

But a gene only carries information. The functional, physical, and chemical understanding of the gene begged a mechanistic understanding: How did genetic information become manifest inside the cell? What did a gene "do"—and how?

George Beadle, Thomas Morgan's student, switched from Morgan's fruit flies to an even more primitive organism, the slime mold, to answer these questions. Collaborating with the biochemist Edward Tatum at Stanford University in California, Beadle discovered that genes carried instructions to build proteins—complex, multidimensional macromolecules that were the workhorses of the cell.

Proteins, researchers found in the 1940s, carry out the bulk of cellular functions. They form enzymes, catalysts that speed up biochemical reactions vital to the life of the cell. Proteins are receptors for other proteins or molecules, responsible for transmitting signals from one cell to the next. They can create structural components of the cell, such as the molecular scaffolding that allows a cell to exist in a particular configuration in space. They can regulate other proteins, thus creating minuscule circuits inside the cell responsible for coordinating the life cycle of the cell.

Beadle and Tatum found that a gene "works" by providing the blueprint to build a protein. A protein is a gene realized—the machine built from a gene's instructions. But proteins are not created directly out of genes. In the late 1950s, Jacques Monod and François Jacob, working in Paris, Sydney Brenner and Matthew Meselson at Caltech, and Francis Crick in Cambridge, discovered that the genesis of proteins from genes requires an intermediary step—a molecule called ribonucleic acid, or RNA.

RNA is the working copy of the genetic blueprint. It is through RNA that a gene is translated into a protein. This intermediary RNA copy of a gene is called a gene's "message." Genetic information is transmitted from a cell to its progeny through a series of discrete and coordinated steps. First, genes, located in chromosomes, are duplicated when a cell divides and are transmitted into progeny cells. Next, a gene, in the form of DNA, is converted into its RNA copy. Finally, this RNA message is translated into a protein. The protein, the ultimate product of genetic information, carries out the function encoded by the gene.

An example, borrowed from Mendel and Morgan, helps illustrate the process of cellular information transfer. Red-eyed flies have glowering, ruby-colored eyes because they possess a gene that bears the information to build a red pigment protein. A copy of this gene is created every time a cell divides and it thus moves from a fly to its egg cells, and then into the cells of the offspring fly. In the eye cells of the progeny fly, this gene is

dogma proposed, only travels down a one-way street from DNA to RNA to proteins. How on earth, Temin wondered, could RNA turn around acrobatically and make a DNA copy of itself, driving the wrong way down the one-way street of biological information?

Temin made a leap of faith; if the data did not fit the dogma, then the dogma—not the data—needed to be changed. He postulated that Rous sarcoma virus carried a special property, a property unprecedented in any other living organism: it could convert RNA back into DNA. In normal cells, the conversion of DNA into RNA is called transcription. The virus (or the infected cell) therefore had to possess the reverse capacity: *reverse* transcription. "Temin had an inkling, but his proof was so circumstantial—so frail—that he could barely convince anyone," the virologist Michael Bishop recalled twenty-five years later. "The hypothesis had earned him little but ridicule and grief."

At first, Temin could barely even convince himself. He had made a bold proposition, but he needed proof. In 1960, determined to find experimental proof, Temin moved his lab to the McArdle laboratory in Wisconsin. Madison, unlike Caltech, was a frozen, faraway place, isolated both physically and intellectually, but this suited Temin. Standing unknowingly at the edge of a molecular revolution, he wanted silence. On his daily walk along Lakeshore path, often blanketed in dense snow, Temin planned experiments to find evidence for this reverse flow of information.

RNA into DNA. Even the thought made him shiver: a molecule that could write history backward, turn back the relentless forward flow of biological information. To prove that such a process existed, Temin would need to isolate in a test tube the viral enzyme that could reverse transcription and prove that it could make a DNA copy out of RNA. In the early 1960s, pursuing the enzyme, he hired a Japanese postdoctoral student named Satoshi Mizutani. Mizutani's task was to purify this reverse transcription enzyme from virus-infected cells.

Mizutani was a catastrophe. Never a cell biologist at heart, as a colleague recalled, he contaminated the cells, infected the cultures, and grew out balls of fungi in the petri dishes. Frustrated, Temin moved Mizutani to a project involving no cells. If Mizutani couldn't manipulate cells, he could try to purify the enzyme out of chemical extracts made from virus-infected cells. The move played to Mizutani's natural skills: he was an incredibly gifted chemist. Overnight, he picked up a weak, flickering enzymatic activity in the cellular extracts of the Rous virus that was capable of converting RNA into DNA. When he added RNA to this cellular extract, he could "see" it creating a DNA copy—reversing transcription. Temin had his proof. Rous sarcoma virus was no ordinary virus. It could write genetic information backward: it was a *retro*virus.

At MIT, in Boston, another young virologist, David Baltimore, had also picked up the hint of an RNA → DNA conversion activity, although in a different retrovirus. Brilliant, brash, and single-minded, Baltimore had met and befriended Howard Temin in the 1940s at science summer camp in Maine, where Temin had been a teaching assistant and Baltimore a student. They had parted ways for nearly a decade, yet their intellectual paths had kept crisscrossing. As Temin was exploring reverse transcription in Rous sarcoma virus in Madison, Baltimore had begun to amass evidence that his retrovirus also possessed an enzyme that could convert RNA into DNA. He, too, was steps away from isolating the enzyme.

On the afternoon of May 27, 1970, a few weeks after he had found initial evidence for the RNA → DNA converting enzyme in his lab, Temin caught a flight to Houston to present his work at the Tenth International Cancer Congress. The next morning, he walked to the cavernous auditorium at the Houston Civic Center. Temin's talk was entitled "The Role of DNA in the Replication of RNA Viruses," a title left intentionally bland. It was a short, fifteen-minute session. The room was filled mainly with tumor virus specialists, many already dozing off to sleep.

But as Temin began to unfold his findings, the importance of his talk dawned on the audience. On the surface, as one researcher recalled, "It was all very dry biochemistry. . . . Temin spoke in his usual nasal, high-pitched monotone, giving no indication of excitement." But the significance of the work crystallized out of the dry biochemical monotone. Temin was not just talking about viruses. He was systematically dismantling one of the fundamental principles of biology. His listeners became restive, unnerved. By the time Temin reached the middle of the talk, there was an awestruck silence. Scientists in the audience were feverishly taking notes, filling page after page with harrowed scribbles. Once outside the conference room, Temin recalled, "You could see people on the telephone. . . . People called people in their laboratories." Temin's announcement that he had identified the long-sought-after enzyme activity in the virus-infected cells left little doubt about the theory. RNA could *generate* DNA. A cancer-causing virus's genome could become a physical part of a cell's genes.

Temin returned to Madison the next morning to find his laboratory inundated with phone messages. The most urgent of these was from David Baltimore, who had heard an inkling of Temin's news from the meeting. Temin called him back.

"You know there is [an enzyme] in the virus particles," Baltimore said.

"I know," said Temin.

Baltimore, who had kept his own work very, very quiet, was stunned. "How do you know?"

"We found it."

Baltimore had also found it. He, too, had identified the RNA → DNA enzymatic activity from the virus particles. Each laboratory, working apart, had converged on the same result. Temin and Baltimore both rushed their observations to publication. Their twin reports appeared back-to-back in *Nature* magazine in the summer of 1970.

In their respective papers, Temin and Baltimore proposed a radical new theory about the life cycle of retroviruses. The genes of retroviruses, they postulated, exist as RNA outside cells. When these RNA viruses infect cells, they make a DNA copy of their genes and attach this copy to the cell's genes. This DNA copy, called a provirus, makes RNA copies, and the virus is regenerated, phoenixlike, to form new viruses. The virus is thus constantly shuttling states, rising from the cellular genome and falling in again—RNA to DNA to RNA; RNA to DNA to RNA—ad infinitum.

It is surely a sign of the prevailing schizophrenia of the time that Temin's work was instantly embraced as a possible mechanistic explanation for cancer by cancer scientists, but largely ignored by clinical oncologists. Temin's presentation in Houston was part of a mammoth meeting on cancer. Both Farber and Frei had flown in from Boston to attend. Yet, the conference epitomized the virtually insurmountable segregation between cancer therapy and cancer science. Chemotherapy and surgery were discussed in one room. Viral carcinogenesis was discussed in another. It was as if a sealed divider had been constructed through the middle of the world of cancer, with "cause" on one side and "cure" on the other. Few scientists or clinical oncologists crossed between the two isolated worlds. Frei and Farber returned to Boston with no significant change in the trajectories of their thoughts about curing cancer.

Yet for some scientists attending the conference, Temin's work, pushed to its logical extreme, suggested a powerful mechanistic explanation for cancer, and thus a well-defined path toward a cure. Sol Spiegelman, a Columbia University virologist known for his incendiary enthusiasm and relentless energy, heard Temin's talk and instantly built a monumental theory out of it—a theory so fiercely logical that Spiegelman could almost conjure it into reality. Temin had suggested that an RNA virus could enter a cell, make a DNA copy of its genes, and attach itself to a cell's genome. Spiegelman was convinced that this process, through a yet unknown mechanism, could activate a viral gene. That activated viral gene must induce

the infected cell to proliferate—unleashing pathological mitosis, cancer.

It was a tantalizingly attractive explanation. Rous's viral theory of the origin of cancer would fuse with Boveri's internal genetic theory. The virus, Temin had shown, could *become* an endogenous element attached to a cell's genes, and thus both an internal aberration and an exogenous infection would be responsible for cancer. "Spiegelman's conversion to the new religion [of cancer viruses] took only minutes," Robert Weinberg, the MIT cancer biologist recalled. "The next day [after Temin's conference] he was back in his lab at Columbia University in New York City, setting up a repeat of the work."

Spiegelman raced off to prove that retroviruses caused human cancers. "It became his single-minded preoccupation," Weinberg recalled. The obsession bore fruit quickly. For Spiegelman's schema to work, he would need to prove that human cancers had retrovirus genes hidden inside them. Working fast and hard, Spiegelman found traces of retroviruses in human leukemia, in breast cancer, lymphomas, sarcomas, brain tumors, melanomas—in nearly every human cancer that he examined. The Special Virus Cancer Program, launched in the 1950s to hunt for human cancer viruses, and moribund for two decades, was swiftly resuscitated: here, at long last, were the thousands of cancer viruses that it had so long waited to discover. Money poured into Spiegelman's lab from the SVCP's coffers. It was a perfect folie à deux—endless funds fueling limitless enthusiasm and vice versa. The more Spiegelman looked for retroviruses in cancer cells, the more he found, and the more funds were sent his way.

In the end, though, Spiegelman's effort turned out to be systematically flawed. In his frenzied hunt for human cancer retroviruses, Spiegelman had pushed the virus-detection test so hard that he saw viruses or traces of viruses that did not exist. When other labs around the nation tried to replicate the work in the mid-1970s, Spiegelman's viruses were nowhere to be found. Only one human cancer, it turned out, was caused by a human retrovirus—a rare leukemia endemic in some parts of the Caribbean. "The hoped-for human virus slipped quietly away into the night," Weinberg wrote. "The hundreds of millions of dollars spent by the SVCP . . . could not make it happen. The rocket never left its launching pad."

Spiegelman's conjecture about human retroviruses was half-right and half-wrong: he was looking for the right kind of virus but in the wrong kind of cell. Retroviruses would turn out to be the cause of a different disease—not cancer. Spiegelman died in 1983 of pancreatic cancer, having heard of a strange illness erupting among gay men and blood-transfusion recipients in New York and San Francisco. One year after Sol Spiegelman's death in New York, the cause of that disease was finally identified. It was a human retrovirus called HIV.

"The hunting of the sarc"

For the Snark was *a Boojum, you see.*

—Lewis Carroll

Sol Spiegelman had got hopelessly lost hunting for cancer-causing retroviruses in humans. His predicament was symptomatic: cancer biology, the NCI, and the targeted Special Virus Cancer Program had all banked so ardently on the existence of human cancer retroviruses in the early 1970s that when the viruses failed to materialize, it was as if some essential part of their identity or imagination had been amputated. If human cancer retroviruses did not exist, then human cancers must be caused by some other mysterious mechanism. The pendulum, having swung sharply toward an infectious viral cause of cancer, swung just as sharply away.

Temin, too, had dismissed retroviruses as the causal agents for human cancer by the mid-1970s. His discovery of reverse transcription had certainly overturned the dogma of cellular biology, but it had not pushed the understanding of human *carcinogenesis* far. Viral genes could attach themselves to cellular genes, Temin knew, but this could not explain how viruses caused cancer.

Faced with yet another discrepancy between theory and data, Temin proposed another bold conjecture—again, standing on the thinnest foundation of evidence. Spiegelman and the retrovirus hunters, Temin argued, had conflated analogy with fact, confused messenger with message. Rous sarcoma virus could cause cancer by inserting a viral gene into cells. This proved that genetic alterations could cause cancer. But the genetic alteration, Temin proposed, need not originate in a virus. The virus had merely brought a message into a cell. To understand the genesis of cancer, it was that culprit *message*—not the messenger—that needed to be identified. Cancer virus hunters needed to return to their lamplit virus again, but this time with new questions: What was the viral gene that had unleashed pathological mitosis in cells? And how was that gene related to an internal mutation in the cell?

In the 1970s, several laboratories began to home in on that gene. Fortuitously, RSV possesses only four genes in its genome. In California, by then the hotbed of cancer virus research, the virologists Steve Martin, Peter Vogt, and Peter Duesberg made mutants of the Rous virus that replicated normally, but could no longer create tumors—suggesting that the tumor-causing gene had been disrupted. By analyzing the genes altered in these mutant viruses, these groups finally pinpointed RSV's cancer-causing ability to a single gene in the virus. The gene was called *src* (pronounced "sarc"), a diminutive of *sarcoma*.

Src, then, was the answer to Temin's puzzle, the cancer-causing "message" borne by Rous sarcoma virus. Vogt and Duesberg removed or inactivated *src* from the virus and demonstrated that the *src*-less virus could neither induce cell proliferation nor cause transformation. *Src*, they speculated, was some sort of malformed gene acquired by RSV during its evolution and introduced into normal cells. It was termed an oncogene,[‡] a gene capable of causing cancer.

A chance discovery in Ray Erikson's laboratory at the University of Colorado further elucidated *src*'s function. Erikson had been a graduate student in Madison in the early 1960s when Temin had found retroviruses. Erikson had followed the discovery of the *src* gene in California and had been haunted by the function of *src* ever since. In 1977, working with Mark Collett and Joan Brugge, Erikson set out to decipher the function of *src*. *Src*, Erikson discovered, was an unusual gene. It encoded a protein whose most prominent function was to modify other proteins by attaching a small chemical, a phosphate group, to these proteins—in essence, playing an elaborate game of molecular tag.[‡] Indeed, scientists had found a number of similar proteins in normal cells—enzymes that attached phosphate groups to other proteins. These enzymes were called the "kinases," and they were soon found to behave as molecular master switches within a cell. The attachment of the phosphate group to a protein acted like an "on" switch—activating the protein's function. Often, a kinase turned "on" another kinase, which turned "on" another kinase, and so forth. The signal was amplified at each step of the chain reaction, until many such molecular switches were thrown into their "on" positions. The confluence of many such activated switches produced a powerful internal signal to a cell to change its "state"—moving, for instance, from a nondividing to a dividing state.

Src was a prototypical kinase—although a kinase on hyperdrive. The protein made by the viral *src* gene was so potent and hyperactive that it phosphorylated anything and everything around it, including many crucial proteins in the cell. *Src* worked by unleashing an indiscriminate volley of phosphorylation—throwing "on" dozens of molecular switches. In *src*'s case, the activated series of proteins eventually impinged on proteins that controlled cell division. *Src* thus forcibly induced a cell to change its state from nondividing to dividing, ultimately inducing accelerated mitosis, the hallmark of cancer.

By the late 1970s, the combined efforts of biochemists and tumor virologists had produced a relatively simple view of *src*'s ability to transform cells. Rous sarcoma virus caused cancer in chickens by introducing into cells a gene, *src*, that encoded a hyperactive overexuberant kinase. This kinase turned "on" a cascade of cellular signals to divide relentlessly. All of this represented beautiful, careful, meticulously crafted work. But with no human cancer retroviruses in the study, none of this research seemed relevant immediately to human cancers.

Yet the indefatigable Temin still felt that viral *src* would solve the mystery of human cancers. In Temin's mind, there was one riddle yet to be solved: the evolutionary origin of the *src* gene. How might a virus have "acquired" a gene with such potent, disturbing qualities? Was *src* a viral kinase gone berserk? Or was it a kinase that the virus had constructed out of bits of other genes like a cobbled-together bomb? Evolution, Temin knew, could build new genes out of old genes. But where had Rous sarcoma virus found the necessary components of a gene to make a chicken cell cancerous?

At the University of California in San Francisco (UCSF), in a building perched high on one of the city's hills, a virologist named J. Michael Bishop became preoccupied with the evolutionary origin of viral *src*. Born in rural Pennsylvania, where his father had been a Lutheran minister, Bishop had studied history at Gettysburg College, then drastically altered his trajectory to attend Harvard Medical School. After a residency at Massachusetts General Hospital, he had trained as a virologist. In the 1960s, Bishop had moved to UCSF to set up a lab to explore viruses.

UCSF was then a little-known, backwater medical school. Bishop's shared office occupied a sliver of space at the edge of the building, a room

* Other cancer-causing viruses, such as SV40 and human papillomavirus (HPV), would eventually be discovered in 1960 and 1983, respectively.
* Temin's statement was speculative, but it bore his unerring biological instinct. Formal proof of the structural attachment of RSV genes into the cellular genome would only come years later.
* The term *retrovirus* was coined later by virologists.

so cramped and narrow that his office-mate had to stand up to let him through to his desk. In the summer of 1969, when a lanky, self-assured researcher from the NIH, Harold Varmus, then on a hiking trip in California, knocked on Bishop's office door to ask if he might join the lab to study retroviruses, there was hardly any standing room at all.

Varmus had come to California seeking adventure. A former graduate student in literature, he had become enthralled by medicine, obtained his M.D. at Columbia University in New York, then learned virology at the NIH. Like Bishop, he was also an academic itinerant—wandering from medieval literature to medicine to virology. Lewis Carroll's *Hunting of the Snark* tells the story of a motley crew of hunters that launch an agonizing journey to trap a deranged, invisible creature called the Snark. That hunt goes awfully wrong. Unpromisingly, as Varmus and Bishop set off to understand the origins of the *src* gene in the early 1970s, other scientists nicknamed the project "the hunting of the sarc."

Varmus and Bishop launched their hunt using a simple technique—a method invented, in part, by Sol Spiegelman in the 1960s. Their goal was to find cellular genes that were distantly similar to the viral *src* gene—and thus find *src*'s evolutionary precursors. DNA molecules typically exist as paired, complementary strands, like yin and yang, that are "stuck" together by powerful molecular forces. Each strand, if separated, can thus stick to another strand that is complementary in structure. If one molecule of DNA is tagged with radioactivity, it will seek out its complementary molecule in a mixture and stick to it, thereby imparting radioactivity to the second molecule. The sticking ability can be measured by the amount of radioactivity.

In the mid-1970s, Bishop and Varmus began to use the viral *src* gene to hunt for its homologues, using this "sticking" reaction. *Src* was a viral gene, and they expected to find only fragments or pieces of *src* in normal cells—ancestors and distant relatives of the cancer-causing *src* gene. But the hunt soon took a mystifying turn. When Varmus and Bishop looked in normal cells, they did not find a genetic third or fifth cousin of *src.* They found a nearly identical version of viral *src* lodged firmly in the normal cell's genome.

Varmus and Bishop, working with Deborah Spector and Dominique Stehelin, probed more cells, and again the *src* gene appeared in them: in duck cells, quail cells, and geese cells. Closely related homologues of the *src* gene were strewn all over the bird kingdom; each time Varmus's team looked up or down an evolutionary branch, they found some variant of *src* staring back. Soon, the UCSF group was racing through multiple species to look for homologues of *src.* They found *src* in the cells of pheasants, turkeys, mice, rabbits, and fish. Cells from a newborn emu at the Sacramento zoo had *src.* So did sheep and cows. Most important, so did human cells. "*Src,*" Varmus wrote in a letter in 1976, ". . . is everywhere."

But the *src* gene that existed in normal cells was not identical to the viral *src.* When Hidesaburo Hanafusa, a Japanese virologist at Rockefeller University in New York, compared the viral *src* gene to the normal cellular *src* gene, he found a crucial difference in the genetic code between the two forms of *src.* Viral *src* carried mutations that dramatically affected its function. Viral *src* protein, as Erikson had found in Colorado, was a disturbed, hyperactive kinase that relentlessly tagged proteins with phosphate groups and thus provided a perpetually blaring "on" signal for cell division. Cellular *src* protein possessed the same kinase activity, but it was far less hyperactive; in contrast to viral *src,* it was tightly regulated—turned "on" and turned "off"—during cell division. The viral *src* protein, in contrast, was a permanently activated switch—"an automaton," as Erikson described it—that had turned the cell into a dividing machine. Viral *src*—the cancer-causing gene—was cellular *src* on overdrive.

A theory began to convulse out of these results, a theory so magnificent and powerful that it would explain decades of disparate observations in a single swoop: *perhaps* src, *the precursor to the cancer-causing gene, was endogenous to the cell.* Perhaps viral *src* had *evolved* out of cellular *src.* Retrovirologists had long believed that the virus had introduced an activated *src* into normal cells to transform them into malignant cells. But the *src* gene had not originated in the virus. It had originated from a precursor gene that existed in a cell—in *all* cells. Cancer biology's decades-long hunt had started with a chicken and ended, metaphorically, in the egg—in a progenitor gene present in all human cells.

Rous's sarcoma virus, then, was the product of an incredible evolutionary accident. Retroviruses, Temin had shown, shuttle constantly out of the cell's genome: RNA to DNA to RNA. During this cycling, they can pick up pieces of the cell's genes and carry them, like barnacles, from one cell to another. Rous's sarcoma virus had likely picked up an activated *src* gene from a cancer cell and carried it in the viral genome, creating more cancer. The virus, in effect, was no more than an accidental courier for a gene that had originated in a cancer cell—a parasite parasitized by cancer. Rous had been wrong—but spectacularly wrong. Viruses did cause cancer, but they did so, typically, by tampering with genes that originate in cells.

Science is often described as an iterative and cumulative process, a puzzle solved piece by piece, with each piece contributing a few hazy pixels of a much larger picture. But the arrival of a truly powerful new theory in science often feels far from iterative. Rather than explain one observation or phenomenon in a single, pixelated step, an entire field of observations suddenly seems to crystallize into a perfect whole. The effect is almost like watching a puzzle solve itself.

Varmus and Bishop's experiments had precisely such a crystallizing, zippering effect on cancer genetics. The crucial implication of the Varmus and Bishop experiment was that a precursor of a cancer-causing gene—the "proto-oncogene," as Bishop and Varmus called it—was a normal cellular gene. Mutations induced by chemicals or X-rays caused cancer not by "inserting" foreign genes into cells, but by activating such *endogenous* proto-oncogenes.

"Nature," Rous wrote in 1966, "sometimes seems possessed of a sardonic humor." And the final lesson of Rous sarcoma virus had been its most sardonic by far. For nearly six decades, the Rous virus had seduced biologists—Spiegelman most sadly among them—down a false path. Yet the false path had ultimately circled back to the right destination—from viral *src* toward cellular *src* and to the notion of internal proto-oncogenes sitting omnipresently in the normal cell's genome.

In Lewis Carroll's poem, when the hunters finally capture the deceptive Snark, it reveals itself not to be a foreign beast, but one of the human hunters sent to trap it. And so it had turned out with cancer. Cancer genes came from *within* the human genome. Indeed the Greeks had been peculiarly prescient yet again in their use of the term *oncos.* Cancer was intrinsically "loaded" in our genome, awaiting activation. We were destined to carry this fatal burden in our genes—our own genetic "oncos."

Varmus and Bishop were awarded the Nobel Prize for their discovery of the cellular origin of retroviral oncogenes in 1989. At the banquet in Stockholm, Varmus, recalling his former life as a student of literature, read lines from the epic poem *Beowulf,* recapitulating the slaying of the dragon in that story: "We have not slain our enemy, the cancer cell, or figuratively torn the limbs from his body," Varmus said. "In our adventures, we have only seen our monster more clearly and described his scales and fangs in new ways—ways that reveal a cancer cell to be, like Grendel, a distorted version of our normal selves."

* The term *oncogene* had been coined earlier by two NCI scientists, Robert Huebner and George Todaro, in 1969, although on scant evidence.
† Art Levinson, in Mike Bishop's lab at UCSF, also discovered this phosphorylating activity; we will return to Levinson's discovery in later pages.

The Wind in the Trees

The fine, fine wind that takes its course through the chaos of the world
Like a fine, an exquisite chisel, a wedge-blade inserted . . .

—D. H. Lawrence

The developments of the summer of 1976 drastically reorganized the universe of cancer biology, returning genes, again, to its center. Harold Varmus and Michael Bishop's proto-oncogene theory provided the first cogent and comprehensive theory of carcinogenesis. The theory explained how radiation, soot, and cigarette smoke, diverse and seemingly unrelated insults, could all initiate cancer—by mutating and thus activating precursor oncogenes within the cell. The theory made sense of Bruce Ames's peculiar correlation between carcinogens and mutagens: chemicals that cause mutations in DNA produce cancers because they alter cellular proto-oncogenes. The theory clarified why the same kind of cancer might arise in smokers and nonsmokers, albeit at different rates: both smokers and nonsmokers have the same proto-oncogenes in their cells, but smokers develop cancer at a higher rate because carcinogens in tobacco increase the mutation rate of these genes.

But what did human cancer genes look like? Tumor virologists had found *src* in viruses and then in cells, but surely other endogenous proto-oncogenes were strewn about in the human cellular genome.

Genetics has two distinct ways to "see" genes. The first is structural: genes can be envisioned as physical structures—pieces of DNA lined up along chromosomes, just as Morgan and Flemming had first envisioned them. The second is functional: genes can be imagined, à la Mendel, as the inheritance of traits that move from one generation to the next. In the decade between 1970 and 1980, cancer genetics would begin to "see" cancer-causing genes in these two lights. Each distinct vision would enhance the mechanistic understanding of carcinogenesis, bringing the field closer and closer to an understanding of the core molecular aberration in human cancers.

Structure—anatomy—came first. In 1973, as Varmus and Bishop were launching their initial studies on *src*, a hematologist in Chicago, Janet Rowley, saw a human cancer gene in a physical form. Rowley's specialty was studying the staining patterns of chromosomes in cells in order to locate chromosomal abnormalities in cancer cells. Chromosome staining, the technique she had perfected, is as much an art as a science. It is also an oddly anachronistic art, like painting with tempera in an age of digital prints. At a time when cancer genetics was zooming off to explore the world of RNA, tumor viruses, and oncogenes, Rowley was intent on dragging the discipline back to its roots—to Boveri's and Flemming's chromosomes dyed in blue. Piling anachronism upon anachronism, the cancer she had chosen to study was chronic myelogenous leukemia (CML)—Bennett's infamous "suppuration of blood."

Rowley's study was built on prior work by a duo of pathologists from Philadelphia who had also studied CML. In the late 1950s, Peter Nowell and David Hungerford had found an unusual chromosomal pattern in this form of leukemia: the cancer cells bore one consistently shortened chromosome. Human cells have forty-six chromosomes—twenty-three matched pairs—one inherited from each parent. In CML cells, Nowell found that one copy of the twenty-second chromosome had its head lopped off. Nowell called the abnormality the Philadelphia chromosome after the place of its discovery. But Nowell and Hungerford could not understand where the decapitated chromosome had come from, or where its missing "head" had gone.

Rowley, following this study, began to trace the headless chromosome in her CML cells. By laying out exquisitely stained photographs of CML chromosomes enlarged thousands of times—she typically spread them on her dining table and then leaned into the pictures, hunting for the missing pieces of the infamous Philadelphia chromosome—Rowley found a pattern. The missing head of chromosome twenty-two had attached itself elsewhere—to the tip of chromosome nine. And a piece of chromosome nine had conversely attached itself to chromosome twenty-two. This genetic event was termed a translocation—the flip-flop transposition of two pieces of chromosomes.

Rowley examined case after case of CML patients. In every single case, she found this same translocation in the cells. Chromosomal abnormalities in cancer cells had been known since the days of von Hansemann and Boveri. But Rowley's results argued a much more profound point. Cancer was not disorganized chromosomal chaos. It was *organized* chromosomal chaos: specific and identical mutations existed in particular forms of cancer.

Chromosomal translocations can create new genes called chimeras by fusing two genes formerly located on two different chromosomes—the "head" of chromosome nine, say, fused with the "tail" of a gene in chromosome thirteen. The CML translocation, Rowley postulated, had created such a chimera. Rowley did not know the identity or function of this new chimeric monster. But she had demonstrated that a novel, unique genetic alteration—later found to be an oncogene—could exist in a human cancer cell, revealing itself purely by virtue of an aberrant chromosome structure.

In Houston, Alfred Knudson, a Caltech-trained geneticist, also "saw" a human cancer-causing gene in the early 1970s, although in yet another distinct sense.

Rowley had visualized cancer-causing genes by studying the physical structure of the cancer cell's chromosomes. Knudson concentrated monastically on the function of a gene. Genes are units of inheritance: they shuttle properties—traits—from one generation to the next. If genes cause cancer, Knudson reasoned, then he might capture a pattern in the inheritance of cancer, much as Mendel had captured the idea of a gene by studying the inheritance of flower color or plant height in peas.

In 1969, Knudson moved to the MD Anderson Cancer Center in Texas, where Freireich had set up a booming clinical center for childhood cancers. Knudson needed a "model" cancer, a hereditary malignancy whose underlying pattern of inheritance would reveal how cancer-causing genes worked. The natural choice was retinoblastoma, the odd, rare variant of eye cancer that de Gouvêa had identified in Brazil with its striking tendency to erupt in the same family across generations.

Retinoblastoma is a particularly tragic form of cancer, not just because it assaults children but because it assaults the quintessential organ of childhood: the tumor grows in the eye. Afflicted children are sometimes diagnosed when the world around them begins to blur and fade. But occasionally the cancer is incidentally found in a child's photograph when the eye, lit by a camera flash, glows eerily like a cat's eyes in lamplight, revealing the tumor buried behind the lens. Left untreated, the tumor will crawl backward from the eye socket into the optic nerve, and then climb

into the brain. The primary methods of treatment are to sear the tumor with high doses of gamma radiation or to enucleate the eye surgically, leaving behind an empty socket.

Retinoblastoma has two distinct variants, an inherited "familial" form and a sporadic form. De Gouvêa had identified the familial form. Children who suffer from this familial or inherited form may carry strong family histories of the disease—fathers, mothers, cousins, siblings, and kindred affected—and they typically develop tumors in both eyes, as in de Gouvêa's case from Rio. But the tumor also arises in children with no family history of the disease. Children with this sporadic form never carry a history in the family and always have a tumor in only one eye.

This pattern of inheritance intrigued Knudson. He wondered whether he could discern a subtle difference in the development of cancer between the sporadic and the inherited versions using mathematical analyses. He performed the simplest of experiments: he grouped children with the sporadic form into one cohort and children with the familial form in a second. And sifting through old hospital records, Knudson tabulated the ages in which the disease struck the two groups, then plotted them as two curves. Intriguingly, he found that the two cohorts developed the cancers at different "velocities." In inherited retinoblastoma, cancer onset was rapid, with diagnosis typically two to six months after birth. Sporadic retinoblastoma typically appeared two to four years after birth.

But why did the same disease move with different velocities in different children? Knudson used the numbers and simple equations borrowed from physics and probability theory to model the development of the cancer in the two cohorts. He found that the data fit a simple model. In children with the inherited form of retinoblastoma, only one genetic change was required to develop the cancer. Children with the sporadic form required two genetic changes.

This raised another puzzling question: why was only one genetic change needed to unleash cancer in the familial case, while two changes were needed in the sporadic form? Knudson perceived a simple, beautiful explanation. "The number two," he recalled, "is the geneticist's favorite number." Every normal human cell has two copies of each chromosome and thus two copies of every gene. Every normal cell must have two normal copies of the retinoblastoma gene—*Rb*. To develop sporadic retinoblastoma, Knudson postulated, both copies of the gene needed to be inactivated through a mutation in each copy of the *Rb* gene. Hence, sporadic retinoblastoma develops at later ages because two independent mutations have to accumulate in the same cell.

Children with the inherited form of retinoblastoma, in contrast, are born with a defective copy of *Rb*. In their cells, one gene copy is already defective, and only a single additional genetic mutation is needed before the cell senses the change and begins to divide. These children are thus predisposed to the cancer, and they develop cancer faster, producing the "rapid velocity" tumors that Knudson saw in his statistical charts. Knudson called this the two-hit hypothesis of cancer. For certain cancer-causing genes, two mutational "hits" were needed to provoke cell division and thus produce cancer.

Knudson's two-hit theory was a powerful explanation for the inheritance pattern of retinoblastoma, but at first glance it seemed at odds with the initial molecular understanding of cancer. The *src* gene, recall, requires a single activated copy to provoke uncontrolled cell division. Knudson's gene required two. Why was a single mutation in *src* sufficient to provoke cell division, while two were required for *Rb*?

The answer lies in the function of the two genes. *Src activates* a function in cell division. The mutation in *src*, as Ray Erikson and Hidesaburo Hanafusa had discovered, creates a cellular protein that is unable to extinguish its function—an insatiable, hyperactive kinase on overdrive that provokes perpetual cell division. Knudson's gene, *Rb*, performs the opposite function. It *suppresses* cell proliferation, and it is the inactivation of such a gene (by virtue of two hits) that unleashes cell division. *Rb*, then, is a cancer *suppressor* gene—the functional opposite of *src*—an "anti-oncogene," as Knudson called it.

"Two classes of genes are apparently critical in the origin of the cancers of children," he wrote. "One class, that of oncogenes, acts by virtue of abnormal or elevated activity. . . . The other class, that of anti-oncogenes [or tumor suppressors], is recessive in oncogenesis; cancer results when both normal copies have been mutated or deleted. Some persons carry one such mutation in the germline and are highly susceptible to tumor because only one somatic event is necessary. Some children, even though carrying no such mutation in the germline, can acquire tumor as a result of two somatic events."

It was an exquisitely astute hypothesis spun, remarkably, out of statistical reasoning alone. Knudson did not know the molecular identity of his phantasmic anti-oncogenes. He had never looked at a cancer cell to "see" these genes; he had never performed a biological experiment to pin down *Rb*. Like Mendel, Knudson knew his genes only in a statistical sense. He had inferred them, as he put it, "as one might infer the wind from the movement of the trees."

By the late 1970s, Varmus, Bishop, and Knudson could begin to describe the core molecular aberration of the cancer cell, stitching together the coordinated actions of oncogenes and anti-oncogenes. Cancer genes, Knudson proposed, came in two flavors. "Positive" genes, such as *src*, are mutant *activated* versions of normal cellular genes. In normal cells, these genes accelerate cell division, but only when the cell receives an appropriate growth signal. In their mutant form, these genes are driven into perpetual hyperactivity, unleashing cell division beyond control. An activated proto-oncogene, to use Bishop's analogy, is "a jammed accelerator" in a car. A cell with such a jammed accelerator careens down the path of cell division, unable to cease mitosis, dividing and dividing again relentlessly.

"Negative" genes, such as *Rb*, suppress cell division. In normal cells, these anti-oncogenes, or tumor suppressor genes, provide the "brakes" to cellular proliferation, shutting down cell division when the cell receives appropriate signals. In cancer cells, these brakes have been inactivated by mutations. In cells with missing brakes, to use Bishop's analogy again, the "stop" signals for mitosis can no longer be registered. Again, the cell divides and keeps dividing, defying all signals to stop.

Both abnormalities, activated proto-oncogenes and inactivated tumor suppressors ("jammed accelerators" and "missing brakes"), represent the core molecular defects in the cancer cell. Bishop, Knudson, and Varmus did not know how many such defects were ultimately needed to cause human cancers. But a confluence of them, they postulated, causes cancer.

A Risky Prediction

They see only their own shadows or the shadows of one another, which the fire throws on the opposite wall of the cave.

—Plato

The philosopher of science Karl Popper coined the term *risky prediction* to describe the process by which scientists verify untested theories. Good theories, Popper proposed, generate risky predictions. They presage an unanticipated fact or event that runs a real risk of not occurring or being proven incorrect. When this unanticipated fact proves true or the event does occur, the theory gains credibility and robustness. Newton's understanding of gravitation was most spectacularly validated when it accurately presaged the return of Halley's comet in 1758. Einstein's theory of relativity was vindicated in 1919 by the demonstration that light from distant stars is "bent" by the mass of the sun, just as predicted by the theory's equations.

By the late 1970s, the theory of carcinogenesis proposed by Varmus and Bishop had also generated at least one such risky prediction. Varmus and Bishop had demonstrated that precursors of oncogenes—proto-oncogenes—existed in all normal cells. They had found activated versions of the *src* proto-oncogene in Rous sarcoma virus. They had suggested that mutations in such internal genes caused cancer—but a crucial piece of evidence was still missing. If Varmus and Bishop were right, then mutated versions of such proto-oncogenes must exist *inside cancer cells*. But thus far, although other scientists had isolated an assortment of oncogenes from retroviruses, no one had isolated an activated, mutated oncogene out of a cancer cell.

"Isolating such a gene," as the cancer biologist Robert Weinberg put it, "would be like walking out of a cave of shadows. . . . Where scientists had previously only seen oncogenes indirectly, they might see these genes, in flesh and blood, living inside the cancer cell."

Robert Weinberg was particularly concerned with getting out of shadows. Trained as a virologist in an era of great virologists, he had worked in Dulbecco's lab at the Salk Institute in the sixties isolating DNA from monkey viruses to study their genes. In 1970, when Temin and Baltimore had discovered reverse transcriptase, Weinberg was still at the bench, laboriously purifying genes out of monkey viruses. Six years later, when Varmus and Bishop had announced the discovery of cellular *src*, Weinberg was still purifying DNA from viruses. Weinberg felt as if he was stuck in a perpetual penumbra, surrounded by fame but never famous himself. The retrovirus revolution, with all its mysteries and rewards, had quietly passed him by.

In 1972, Weinberg moved to MIT, to a small laboratory a few doors down from Baltimore's lab to study cancer-causing viruses. "The chair of the department," he said, "considered me quite a fool. A good fool. A hardworking fool, but still a fool." Weinberg's lab occupied a sterile, uninspiring space at MIT, in a sixties-style brutalist building served by a single creaking elevator. The Charles River was just far enough to be invisible from the windows, but just near enough to send freezing puffs of wind through the quadrangle in the winter. The building's basement connected to a warren of tunnels with airless rooms where keys were cut and machines repaired for other labs.

Labs, too, can become machines. In science, it is more often a pejorative description than a complimentary one: an efficient, thrumming, technically accomplished laboratory is like a robot orchestra that produces perfectly pitched tunes but no music. By the mid-1970s, Weinberg had acquired a reputation among his colleagues as a careful, technically competent scientist, but one who lacked direction. Weinberg felt his work was stagnating. What he needed was a simple, clear question.

Clarity came to him one morning in the midst of one of Boston's infamously blinding blizzards. On a February day in 1978, walking to work, Weinberg was caught in an epic snowstorm. Public transportation had ground to a halt, and Weinberg, in a rubber hat and galoshes, had chosen to plod across the blustering Longfellow Bridge from his home to his lab, slowly planting his feet through the slush. The snow blotted out the landscape and absorbed all sounds, creating a silent, hypnotic interior. And as Weinberg crossed the frozen river, he thought about retroviruses, cancer, and human cancer genes.

Src had been so easy to isolate and identify as a cancer-causing gene, Weinberg knew, because Rous sarcoma virus possesses a measly four genes. One could scarcely turn around in the retroviral genome without bumping into an oncogene. A cancer cell, in contrast, has about twenty thousand genes. Searching for a cancer-causing gene in that blizzard of genes was virtually hopeless.

But an oncogene, by definition, has a special property: it provokes unbridled cellular proliferation in a normal cell. Temin had used this property in his cancer-in-a-dish experiment to induce cells to form "foci." And as Weinberg thought about oncogenes, he kept returning to this essential property.

Of the twenty thousand genes in a cancer cell, Weinberg reasoned the vast majority were likely normal and only a small minority were mutated proto-oncogenes. Now imagine, for a moment, being able to take all twenty thousand genes in the cancer cell, the good, the bad, the ugly, and transferring them into twenty thousand normal cells, such that each cell receives one of the genes. The normal, unmutated genes will have little effect on the cells. But an occasional cell will receive an oncogene, and, goaded by that signal, it will begin to grow and reproduce insatiably. Reproduced ten times, these cells will form a little clump on a petri dish; at twelve cell divisions, that clump will form a visible "focus"—cancer distilled into its primordial, elemental form.

The snowstorm was Weinberg's catharsis; he had rid himself of retroviruses. If activated oncogenes existed within cancer cells, then transferring these genes into normal cells should induce these normal cells to divide and proliferate. For decades, cancer biologists had relied on Rous sarcoma virus to introduce activated *src* into cells and thereby incite cell division. But Weinberg would bypass Rous's virus; he would determine if cancer-causing genes could be transferred *directly* from cancer cells to normal cells. At the end of the bridge, with snow still swirling around him, he found himself at an empty intersection with lights still flashing. He crossed it, heading to the cancer center.

Weinberg's immediate challenge was technical: how might he transfer DNA from a cancer cell to a population of normal cells? Fortunately, this was

one of the technical skills that he had so laboriously perfected in the laboratory during his stagnant decade. His chosen method of DNA transfer began with the purification of DNA from cancer cells, grams of it precipitated out of cell extracts in a dense, flocculent suspension, like curdled milk. This DNA was then sheared into thousands of pieces, each piece carrying one or two genes. To transfer this DNA into cells, he next needed a carrier, a molecule that would slip DNA into the interior of a cell. Here, Weinberg used a trick. DNA binds to the chemical calcium phosphate to form minuscule white particles. These particles are ingested by cells, and as the cells ingest these particles, they also ingest the DNA pieces bound to the calcium phosphate. Sprinkled on top of a layer of normal cells growing in a petri dish, these particles of DNA and calcium phosphate resemble a snowglobe of swirling white flakes, the blizzard of genes that Weinberg had so vividly imagined in his walk in Boston.

Once that DNA blizzard had been sprinkled on the cells and internalized by them, Weinberg envisioned a simple experiment. The cell that had received the oncogene would embark on unbridled growth, forming the proliferating focus of cells. Weinberg would isolate such foci and then purify the DNA fragment that had induced the proliferation. He would thus capture a real human oncogene.

In the summer of 1979, Chiaho Shih, a graduate student in Weinberg's lab, began to barrel his way through fifteen different mouse cancer cells, trying to find a fragment of DNA that would produce foci out of normal cells. Shih was laconic and secretive, with a slippery, quicksilver temper, often paranoid about his experiments. He was also stubborn: when he disagreed with Weinberg, colleagues recalled him thickening his accent and pretending not to understand English, a language he spoke with ease and fluency under normal circumstances. But for all his quirks, Shih was also a born perfectionist. He had learned the DNA transfection technique from his predecessors in the lab, but even more important, he had an instinctive feel for his cells, almost a gardener's instinct to discriminate normal versus abnormal growth.

Shih grew enormous numbers of normal cells in petri dishes and sprinkled them weekly with genes derived from his panel of cancer cells. Plate after plate of transfected cells piled up in the laboratory. As Weinberg had imagined in his walk across the river, Shih soon stumbled upon a crucial early result. He found that transferring DNA from mouse cancer cells invariably produced foci in normal cells, proof that oncogenes could be discovered through such a method.*

Excited and mystified, Weinberg and Shih performed a bolder variant of the experiment. Thus far they had been using mouse cancer cell lines to obtain their DNA. Changing tactics and species, they moved on to human cancer cells. "If we were going to trap a real oncogene so laboriously," Weinberg recalled, "we thought that we might as well find it in real human cancers." Shih walked over to the Dana-Farber Cancer Institute and carried back a cancer cell line derived from a patient, Earl Jensen, a long-term smoker who had died of bladder cancer. DNA from these cells was sheared into fragments and transfected into the normal human cell line. Shih returned to his microscope, scouring plate after plate for foci.

The experiment worked yet again. As with the mouse cancer cell lines, prominent, disinhibited foci appeared in the dishes. Weinberg pushed Shih to find the precise gene that could convert a normal cell to a cancer cell. Weinberg's laboratory was now racing to isolate and identify the first native human oncogene.

He soon realized the race had other contenders. At the Farber, across town, Geoff Cooper, a former student of Temin's, had also shown that DNA from cancer cells could induce transformation in cells. So had Michael Wigler at the Cold Spring Harbor Lab in New York. And Weinberg, Cooper, and Wigler had yet other competitors. At the NCI, a little-known Spanish researcher named Mariano Barbacid had also found a fragment of DNA from yet another cancer cell line that would transform normal cells. In the late winter of 1981, all four laboratories rushed to the finish line. By the early spring, each lab had found its sought-after gene.

In 1982, Weinberg, Barbacid, and Wigler independently published their discoveries and compared their results. It was a powerful, unexpected convergence: all three labs had isolated the same fragment of DNA, containing a gene called *ras*, from their respective cancer cells.‡ Like *src, ras* was also a gene present in all cells. But like *src* again, the *ras* gene in normal cells was functionally different from the *ras* present in cancer cells. In normal cells, the *ras* gene encoded a tightly regulated protein that turned "on" and "off" like a carefully modulated switch. In cancer cells, the gene was mutated, just as Varmus and Bishop had predicted. Mutated *ras* encoded a berserk, perpetually hyperactive protein permanently locked "on." This mutant protein produced an unquenchable signal for a cell to divide—and to keep dividing. It was the long-sought "native" human oncogene, captured in flesh and blood out of a cancer cell. "Once we had cloned a cancer gene," Weinberg wrote, "the world would be at our feet." New insights into carcinogenesis, and new therapeutic inroads would instantly follow. "It was," as Weinberg would later write, all "a wonderful pipe dream."

In 1983, a few months after Weinberg had purified mutant *ras* out of cancer cells, Ray Erikson traveled to Washington to receive the prestigious General Motors prize for his research on *src* activity and function. The other awardee that evening was Tom Frei, being honored for his advancement of the cure for leukemia.

It was a resplendent evening. There was an elegant candlelit dinner in a Washington banquet hall, followed by congratulatory speeches and toasts. Scientists, physicians, and policymakers, including many of the former Laskerites,* gathered around linen-covered tables. Talk turned frequently to the discovery of oncogenes and the invention of curative chemotherapy. But the two conversations seemed to be occurring in sealed and separate universes, much as they had at Temin's conference in Houston more than a decade earlier. Frei's award, for curing leukemia, and Erikson's award, for identifying the function of a critical oncogene, might almost have been given to two unconnected pursuits. "I don't remember any enthusiasm among the clinicians to reach out to the cancer biologists to synthesize the two poles of knowledge about cancer," Erikson recalled. The two halves of cancer, cause and cure, having feasted and been feted together, sped off in separate taxis into the night.

The discovery of *ras* brought one challenge to a close for cancer geneticists: they had purified a mutated oncogene from a cancer cell. But it threw open another challenge. Knudson's two-hit hypothesis had also generated a risky prediction: that retinoblastoma cancer cells contained two inactivated copies of the *Rb* gene. Weinberg, Wigler, and Barbacid had proved Varmus and Bishop right. Now someone had to prove Knudson's prediction by isolating his fabled tumor suppressor gene and demonstrating that both its copies were inactivated in retinoblastoma.

This challenge, though, came with an odd conceptual twist. Tumor suppressor genes, by their very nature, are asserted in their *absence*. An oncogene, when mutated, provides an "on" signal for the cells to grow. A tumor suppressor gene when mutated, in contrast, removes an "off" signal for growth. Weinberg and Chiaho Shih's transfection assay had worked because oncogenes can cause the normal cells to divide uncontrollably, thus forming a focus of cells. But an anti-oncogene, transfected into a cell, cannot be expected to create an "anti-focus." "How can one capture genes that behave like ghosts," Weinberg wrote, "influencing cells from behind some dark curtain?"

In the mid-1980s, cancer geneticists had begun to glimpse shadowy outlines behind retinoblastoma's "dark curtain." By analyzing chromosomes from retinoblastoma cancer cells using the technique pioneered by Janet Rowley, geneticists had demonstrated that the *Rb* gene "lived" on chromosome thirteen. But a chromosome contains thousands of genes. Isolating a single gene from that vast set—particularly one whose functional

presence was revealed only when inactive—seemed like an impossible task. Large laboratories professionally equipped to hunt for cancer genes—Webster Cavenee's lab in Cincinnati, Brenda Gallie's in Toronto, and Weinberg's in Boston—were frantically hunting for a strategy to isolate *Rb*. But these efforts had reached a standstill. "We knew where *Rb* lived," Weinberg recalled, "but we had no idea what *Rb* was."

Across the Charles River from Weinberg's lab, Thad Dryja, an ophthalmologist-turned-geneticist, had also joined the hunt for *Rb*. Dryja's laboratory was perched on the sixth floor of the Massachusetts Eye and Ear Infirmary—the Eyeball, as it was known colloquially among the medical residents. The ophthalmological infirmary was well-known for its clinical research on eye diseases, but was barely recognized for laboratory-based research. Weinberg's Whitehead Institute boasted the power of the latest technologies, an army of machines that could sequence thousands of DNA samples and powerful fluorescent microscopes that could look down into the very heart of the cell. In contrast, the Eyeball, with its proud display of nineteenth-century eyeglasses and lenses in lacquered wooden vitrines, was almost self-indulgently anachronistic.

Dryja, too, was an unlikely cancer geneticist. In the mid-1980s, having completed his clinical fellowship in ophthalmology at the infirmary in Boston, he had crossed town to the science laboratories at Children's Hospital to study the genetics of eye diseases. As an ophthalmologist interested in cancer, Dryja had an obvious target: retinoblastoma. But even Dryja, an inveterate optimist, was hesitant about taking on the search for *Rb*. "Brenda [Gallie] and Web [Cavenee] had both stalled in their attempts [to clone *Rb*]. It was a slow, frustrating time."

Dryja began his hunt for *Rb* with a few key assumptions. Normal human cells, he knew, have two copies of every chromosome (except the sex chromosomes), one from each parent, twenty-three pairs of chromosomes in all, a total of forty-six. Every normal cell thus has two copies of the *Rb* gene, one in each copy of chromosome thirteen.

Assuming Knudson was right in his two-hit hypothesis, every eye tumor should possess two independent inactivating mutations in the *Rb* gene, one in each chromosome. Mutations, Dryja knew, come in many forms. They can be small changes in DNA that can activate a gene. Or they can be large structural deletions in a gene, stretching over a large piece of the chromosome. Since the *Rb* gene had to be *inactivated* to unleash retinoblastoma, Dryja reasoned that the mutation responsible was likely a deletion of the gene. Deleting a sizable piece of a gene, after all, is perhaps the quickest, crudest way to paralyze and inactivate it.

In most retinoblastoma tumors, Dryja suspected, the two deletions in the two copies of the *Rb* gene would lie in different parts of the gene. Since mutations occur randomly, the chance of both mutations lying in precisely the same region of the gene is a little akin to rolling double sixes in dice that have one hundred faces. Typically, one of the deletions would "hit" the front end of the gene, while the other deletion might hit the back end (in both cases, the functional consequences would be the same—inactivating *Rb*). The two "hits" in most tumors would thus be asymmetric—affecting two different parts of the gene on the two chromosomes.

But even hundred-headed dice, rolled many times, can yield double sixes. Rarely, Dryja knew, one might encounter a tumor in which both hits had deleted exactly the same part of the gene on the two sister chromosomes. In that case, that piece of chromosome would be completely missing from the cell. And if Dryja could find a method to identify a completely missing piece of chromosome thirteen in a retinoblastoma tumor cell, he would instantly land on the *Rb* gene. It was the simplest of strategies: to hunt the gene with absent function, Dryja would look for absence in structure.

To identify such a missing piece, Dryja needed structural mileposts along chromosome thirteen—small pieces of DNA called probes, which were aligned along the length of the chromosome. He could use these DNA probes in a variant of the same "sticking" reaction that Varmus and Bishop had used in the 1970s: if the piece of DNA existed in the tumor cell, it would stick; if the piece did not exist, the probe would not stick, identifying the missing piece in the cell. Dryja had assembled a series of such probes. But more than probes, he needed a resource that he uniquely possessed: an enormous bank of frozen tumors. The chances of finding a shared deletion in the *Rb* gene in both chromosomes were slim, so he would need to test a vast sample set to find one.

This, then, was his crucial advantage over the vast professional labs in Toronto and Houston. Laboratory scientists rarely venture outside the lab to find human samples. Dryja, a clinician, had a freezer full of them. "I stored the tumors obsessively," he said with the childlike delight of a collector. "I put news out among patients and doctors that I was looking for retinoblastoma cases. Every time someone saw a case, they would say, 'Get that guy Dryja.' I would then drive or fly or even walk to pick up the samples and bring them here. I even got to know the patients by name. Since the disease ran in families, I would call them at home to see if there was a brother or sister or cousin with retinoblastoma. Sometimes, I would know [about a tumor] even before doctors knew."

Week after week, Dryja extracted the chromosomes from tumors and ran his probe set against the chromosomes. If the probes bound, they usually made a signal on a gel; if a probe was fully missing, the signal was blank. One morning, having run another dozen tumors, Dryja came to the lab and held up the blot against the window and ran his eyes left to right, lane after lane automatically, like a pianist reading a score. In one tumor, he saw a blank space. One of his probes—H3-8, he had called it—was deleted in both chromosomes in that tumor. He felt the brief hot rush of ecstasy, which then tipped into queasiness. "It was at that moment that I had the feeling that we had a gene in our hands. I had landed on retinoblastoma."

Dryja had found a piece of DNA missing in tumor cells. Now he needed to find the corresponding piece present in normal cells, thus isolating the *Rb* gene. Perilously close to the end, Dryja was like an acrobat at the final stretch of his rope. His one-room lab was taut with tension, stretched to its limit. He had inadequate skills in isolating genes and limited resources. To isolate the gene, he would need help, so he took another lunge. He had heard that researchers in the Weinberg lab were also hunting for the retinoblastoma gene. Dryja's choices were stark: he could either team up with Weinberg, or he could try to isolate the gene alone and lose the race altogether.

The scientist in Weinberg's lab trying to isolate *Rb* was Steve Friend. A jovial, medically trained molecular geneticist with a quick wit and an easy manner, Friend had casually mentioned his interest in *Rb* to Dryja at a meeting. Unlike Dryja, working with his growing stash of tumor samples, Friend had been building a collection of normal cells—cells in which the *Rb* gene was completely intact. Friend's approach had been to find genes that were present in normal retinal cells, then to try to identify ones that were abnormal in retinoblastoma tumors—working backward toward Dryja.

For Dryja, the complementarity of the two approaches was obvious. He had identified a missing piece of DNA in tumors. Could Friend and Weinberg now pull the intact, full-length gene out of normal cells? They outlined a potential collaboration between the two labs. One morning in 1985, Dryja took his probe, H3-8, and virtually ran across the Longfellow Bridge (by now, the central highway of oncogenesis), carrying it by hand to Friend's bench at the Whitehead.

It took Friend a quick experiment to test Dryja's probe. Using the DNA "sticking" reaction again, Friend trapped and isolated the normal cellular gene that stuck to the H3-8 probe. The isolated gene "lived" on chromosome thirteen, as predicted. When Dryja further tested the candidate gene through his bank of tumor samples, he found precisely what Knudson had hypothesized more than a decade earlier: all retinoblastoma cells

contained inactivations in both copies of the gene—two hits—while normal cells contained two normal copies of the gene. The candidate gene that Friend had isolated was indisputably *Rb.*

In October 1986, Friend, Weinberg, and Dryja published their findings in *Nature.* The article marked the perfect complement to Weinberg's *ras* paper, the yin to its yang—the isolation of an activated proto-oncogene (*ras*) and the identification of the anti-oncogene (*Rb*). "Fifteen years ago," Weinberg wrote, "Knudson provided a theoretical basis for retinoblastoma tumorigenesis by suggesting that minimally two genetic events are required to trigger tumor development." Weinberg noted, "We have isolated [a human gene] apparently representing one of this class of genes"—a tumor suppressor.

What *Rb* does in normal cells is still an unfolding puzzle. Its name, as it turns out, is quite a misnomer. *Rb*, retinoblastoma, is not just mutated in rare eye tumors in children. When scientists tested the gene isolated by Dryja, Friend, and Weinberg in other cancers in the early nineties, they found it widely mutated in lung, bone, esophageal, breast, and bladder cancers in adults. Like *ras*, it is expressed in nearly every dividing cell. And it is inactivated in a whole host of malignancies. Calling it retinoblastoma thus vastly underestimates the influence, depth, and prowess of this gene.

The retinoblastoma gene encodes a protein, also named Rb, with a deep molecular "pocket." Its chief function is to bind to several other proteins and keep them tightly sealed in that pocket, preventing them from activating cell division. When the cell decides to divide, it tags Rb with a phosphate group, a molecular signal that inactivates the gene and thus forces the protein to release its partners. Rb thus acts as a gatekeeper for cell division, opening a series of key molecular floodgates each time cell division is activated and closing them sharply when the cell division is completed. Mutations in *Rb* inactivate this function. The cancer cell perceives its gates as perpetually open and is unable to stop dividing.

The cloning of *ras* and *retinoblastoma*—oncogene and anti-oncogene—was a transformative moment in cancer genetics. In the decade between 1983 and 1993, a horde of other oncogenes and anti-oncogenes (tumor suppressor genes) were swiftly identified in human cancers: *myc, neu, fos, ret, akt* (all oncogenes), and p53, VHL, APC (all tumor suppressors). Retroviruses, the accidental carriers of oncogenes, faded far into the distance. Varmus and Bishop's theory—that oncogenes were activated cellular genes—was recognized to be widely true for many forms of cancer. And the two-hit hypothesis—that tumor suppressors were genes that needed to be inactivated in both chromosomes—was also found to be widely applicable in cancer. A rather general conceptual framework for carcinogenesis was slowly becoming apparent. The cancer cell was a broken, deranged machine. Oncogenes were its jammed accelerators and inactivated tumor suppressors its missing brakes.

In the late 1980s, yet another line of research, resurrected from the past, yielded a further bounty of cancer-linked genes. Ever since de Gouvêa's report of the Brazilian family with eye tumors in 1872, geneticists had uncovered several other families that appeared to carry cancer in their genes. The stories of these families bore a familiar, tragic trope: cancer haunted them generation upon generation, appearing and reappearing in parents, children, and grandchildren. Two features stood out in these family histories. First, geneticists recognized that the spectrum of cancers in every family was limited and often stereotypical: colon and ovarian cancer threading through one family; breast and ovarian through another; sarcomas, leukemias, and gliomas through a third. And second, similar patterns often reappeared in different families, thereby suggesting a common genetic syndrome. In Lynch syndrome (first described by an astute oncologist, Henry Lynch, in a Nebraskan family), colon, ovarian, stomach, and biliary cancer recurred generation upon generation. In Li-Fraumeni syndrome, there were recurrent bone and visceral sarcomas, leukemias, and brain tumors.

Using powerful molecular genetic techniques, cancer geneticists in the 1980s and 1990s could clone and identify some of these cancer-linked genes. Many of these familial cancer genes, like *Rb*, were tumor suppressors (although occasional oncogenes were also found). Most such syndromes were fleetingly rare. But occasionally geneticists identified cancer-predisposing gene alterations that were quite frequently represented in the population. Perhaps the most striking among these, first suggested by the geneticist Mary Claire-King and then definitively cloned by Mark Skolnick's team at the pharma company Myriad Genetics, was BRCA-1, a gene that strongly predisposes humans to breast and ovarian cancer. BRCA-1 (to which we will return in later pages) can be found in up to 1 percent of women in selected populations, making it one of the most common cancer-linked genes found in humans.

By the early 1990s, the discoveries of cancer biology had thus traversed the gap between the chicken tumors of Peyton Rous and real human cancers. But purists still complained. The crusty specter of Robert Koch still haunted the genetic theory of cancer. Koch had postulated that for an agent to be identified as the "cause" of a disease, it must (1) be present in the diseased organism, (2) be capable of being isolated from the diseased organism, and (3) re-create the disease in a secondary host when transferred from the diseased organism. Oncogenes had met the first two criteria. They had been found to be present in cancer cells and they had been isolated from cancer cells. But no one had shown that a cancer gene, in and of itself, could create a bona fide tumor in an animal.

In the mid-1980s, a series of remarkable experiments allowed cancer geneticists to meet Koch's final criteria. In 1984, biologists working on stem cells had invented a new technology that allowed them to introduce exogenous genes into early mouse embryos, then create a living mouse out of those modified embryos. This allowed them to produce "transgenic mice," mice in which one or more genes were artificially and permanently modified. Cancer geneticists seized this opportunity. Among the first such genes to be engineered into a mouse was *c-myc*, an oncogene discovered in lymphoma cells.

Using transgenic mouse technology, Philip Leder's team at Harvard altered the *c-myc* gene in mice, but with a twist: cleverly, they ensured that only breast tissue in the mouse would overexpress the gene. (*Myc* could not be activated in all cells. If *myc* was permanently activated in the embryo, the embryo turned into a ball of overproliferating cells, then involuted and died through unknown mechanisms. The only way to activate *myc* in a living mouse was to restrict the activation to only a subset of cells. Since Leder's lab was studying breast cancer, he chose breast cells.) Colloquially, Leder called his mouse the OncoMouse. In 1988, he successfully applied for a patent on the OncoMouse, making it the first animal patented in history.

Leder expected his transgenic mice to explode with cancer, but to his surprise, the oncomice sprouted rather mousy cancers. Even though an aggressive oncogene had been stitched into their chromosomes, the mice developed small, unilateral breast cancers, and not until late in life. Even more surprisingly, Leder's mice typically developed cancers only after pregnancy, suggesting that environmental influences, such as hormones, were strictly required to achieve full transformation of breast cells. "The active *myc* gene does not appear to be sufficient for the development of these tumors," Leder wrote. "If that were the case, we would have expected the uniform development of tumor masses involving the entire bilateral [breast] glands of all five tumor-bearing animals. Rather, our results suggest at least two additional requirements. One of these is likely to be a further transforming event. . . . The other seems to be a hormonal environment related to pregnancy that is only suggested by these initial studies."

To test the roles of other oncogenes and environmental stimuli, Leder created a second OncoMouse, in which two activated proto-oncogenes, *ras* and *myc*, were engineered into the chromosome and expressed in breast cells. Multiple tumors sprouted up in the breast glands of these mice in months. The requirement for the hormonal milieu of pregnancy was partially ameliorated. Still, only a few distinct clones of cancer sprouted out of

the *ras-myc* mice. Millions of breast cells in each mouse possessed activated *ras* and *myc*. Yet, of those millions of cells, each endowed with the most potent oncogenes, only a few dozen turned into real, living tumors.

Even so, this was a landmark experiment: cancer had artificially been created in an animal. "Cancer genetics," as the geneticist Cliff Tabin recalls, "had crossed a new frontier. It was not dealing with just genes and pathways and artificial lumps in the lab, but a real growing tumor in an animal." Peyton Rous's long squabble with the discipline—that cancer had never been produced in a living organism by altering a defined set of cellular genes—was finally laid to its long-overdue rest.

* In fact, the "normal" cells that Weinberg had used were not exactly normal. They were already growth-adapted, such that a single activated oncogene could tip them into transformed growth. Truly "normal" cells, Weinberg would later discover, require several genes to become transformed.

† In fact, *ras*, like *src*, had also been discovered earlier in a cancer-causing virus—again underscoring the striking capacity of these viruses to reveal the mechanisms of endogenous oncogenes.

* The Laskerites had largely been disbanded in the aftermath of the 1971 National Cancer Act. Mary Lasker was still involved in science policy, although with nowhere near the force and visceral energy that she had summoned in the sixties.

* Although cancer is not universally caused by viruses, certain viruses cause particular cancers, such as the human papilloma virus (HPV), which causes cervical cancer. When the mechanism driving this cancer was deciphered in the 1990s, HPV turned out to inactivate *Rb*'s and p53's signal—underscoring the importance of endogenous genes in even virally induced cancers.

The Hallmarks of Cancer

I do not wish to achieve immortality through my works. I wish to achieve immortality by not dying.

—Woody Allen

Scurrying about in its cage in the vivarium atop Harvard Medical School, Philip Leder's OncoMouse bore large implications on small haunches. The mouse embodied the maturity of cancer genetics: scientists had created real, living tumors (not just abstract, etiolated foci in petri dishes) by artificially manipulating two genes, *ras* and *myc*, in an animal. Yet Leder's experiment raised further questions about the genesis of cancer. Cancer is not merely a lump in the body; it is a disease that migrates, evolves, invades organs, destroys tissues, and resists drugs. Activating even two potent proto-oncogenes had not recapitulated the full syndrome of cancer in every cell of the mouse. Cancer genetics had illuminated much about the genesis of cancer, but much, evidently, remained to be understood.

If two oncogenes were insufficient to create cancers, then how many activated proto-oncogenes and inactivated tumor suppressors *were* required? What were the genetic steps needed to convert a normal cell into a cancer cell? For human cancers, these questions could not be answered experimentally. One could not, after all, proactively "create" a human cancer and follow the activation and inactivation of genes. But the questions could be answered retrospectively. In 1988, using human specimens, a physician-scientist named Bert Vogelstein at Johns Hopkins Medical School in Baltimore set out to describe the number of genetic changes required to initiate cancer. The query, in various incarnations, would preoccupy Vogelstein for nearly two decades.

Vogelstein was inspired by the observations made by George Papanicolaou and Oscar Auerbach in the 1950s. Both Papanicolaou and Auerbach, working on different cancers, had noted that cancer did not arise directly out of a normal cell. Instead, cancer often slouched toward its birth, undergoing discrete, transitional stages between the fully normal and the frankly malignant cell. Decades before cervical cancer evolved into its fiercely invasive incarnation, whorls of noninvasive premalignant cells could be observed in the tissue, beginning their first steps in the grisly march toward cancer. (Identifying and eradicating this premalignant stage before the cancer spreads is the basis for the Pap smear.) Similarly, Auerbach had noted, premalignant cells were seen in smokers' lungs long before lung cancer appeared. Colon cancer in humans also underwent graded and discrete changes in its progression, from a noninvasive premalignant lesion called an adenoma to the highly invasive terminal stage called an invasive carcinoma.

Vogelstein chose to study this progression in colon cancer. He collected samples from patients representing each of the stages of colon cancer. He then assembled a series of four human cancer genes—oncogenes and tumor suppressors—and assessed each stage of cancer in his samples for activations and inactivations of these four genes.

Knowing the heterogeneity of every cancer, one might naively have presumed that every patient's cancer possessed its own sequence of gene mutations and its unique set of mutated genes. But Vogelstein found a strikingly consistent pattern in his colon cancer samples: across many samples and many patients, the transitions in the stages of cancer were paralleled by the same transitions in genetic changes. Cancer cells did not activate or inactivate genes at random. Instead, the shift from a premalignant state to an invasive cancer could precisely be correlated with the activation and inactivation of genes in a strict and stereotypical sequence.

In 1988, in the *New England Journal of Medicine*, Vogelstein wrote: "The four molecular alterations accumulated in a fashion that paralleled the clinical progression of tumors." He proposed, "Early in the neoplastic process one colonic cell appears to outgrow its companions to form a small, benign neoplasm. During the growth of [these] cells, a mutation in the *ras* gene . . . often occurs. Finally, a loss of tumor suppressor genes . . . may be associated with the progression of adenoma to frank carcinoma."

Since Vogelstein had preselected his list of four genes, he could not enumerate the total number of genes required for the march of cancer. (The technology available in 1988 would not permit such an analysis; he would need to wait two decades before that technology would become available.) But he had proved an important point, that such a discrete genetic march existed. Papanicolaou and Auerbach had described the pathological transition of cancer as a multistep process, starting with premalignancy and marching inexorably toward invasive cancer. Vogelstein showed that the *genetic* progression of cancer was also a multistep process.

This was a relief. In the decade between 1980 and 1990, proto-oncogenes and tumor suppressor genes had been discovered in such astonishing numbers in the human genome—at last count, about one hundred such genes—that their abundance raised a disturbing question: if the genome was so densely littered with such intemperate genes—genes waiting to push a cell toward cancer as if at the flick of a switch—then why was the human body not exploding with cancer every minute?

Cancer geneticists already knew two answers to this question. First, proto-oncogenes need to be activated through mutations, and mutations are rare events. Second, tumor suppressor genes need to be inactivated, but typically two copies exist of each tumor suppressor gene, and thus two independent mutations are needed to inactivate a tumor suppressor, an even rarer event. Vogelstein provided the third answer. Activating or inactivating any single gene, he postulated, produced only the first steps toward carcinogenesis. Cancer's march was long and slow and proceeded though many mutations in many genes over many iterations. In genetic terms, our cells were not sitting on the edge of the abyss of cancer. They were dragged toward that abyss in graded, discrete steps.

While Bert Vogelstein was describing the slow march of cancer from one gene mutation to the next, cancer biologists were investigating the functions of these mutations. Cancer gene mutations, they knew, could succinctly be described in two categories: either activations of proto-oncogenes or inactivations of tumor suppressor genes. But although dysregulated cell division is the pathological hallmark of cancer, cancer cells do not merely divide; they migrate through the body, destroy other tissues, invade organs, and colonize distant sites. To understand the full syndrome of cancer, biologists would need to link gene mutations in cancer cells to the complex and multifaceted abnormal behavior of these cells.

Genes encode proteins, and proteins often work like minuscule molecular switches, activating yet other proteins and inactivating others, turning molecular switches "on" and "off" inside a cell. Thus, a conceptual diagram can be drawn for any such protein: protein A turns B on, which turns C on and D off, which turns E on, and so forth. This molecular cascade is termed the signaling pathway for a protein. Such pathways are constantly active

in cells, bringing signals in and signals out, thereby allowing a cell to function in its environment.

Proto-oncogenes and tumor suppressor genes, cancer biologists discovered, sit at the hubs of such signaling pathways. Ras, for instance, activates a protein called Mek. Mek in turn activates Erk, which, through several intermediary steps, ultimately accelerates cell division. This cascade of steps, called the Ras-Mek-Erk pathway—is tightly regulated in normal cells, thereby ensuring tightly regulated cell division. In cancer cells, activated "Ras" chronically and permanently activates Mek, which permanently activates Erk, resulting in uncontrolled cell division—pathological mitosis.

But the activated *ras* pathway (Ras→ Mek → Erk) does not merely cause accelerated cell division; the pathway also intersects with other pathways to enable several other "behaviors" of cancer cells. At Children's Hospital in Boston in the 1990s, the surgeon-scientist Judah Folkman demonstrated that certain activated signaling pathways within cancer cells, *ras* among them, could also induce neighboring blood vessels to grow. A tumor could thus "acquire" its own blood supply by insidiously inciting a network of blood vessels around itself and then growing, in grapelike clusters, around those vessels, a phenomenon that Folkman called tumor angiogenesis.

Folkman's Harvard colleague Stan Korsmeyer found other activated pathways in cancer cells, originating in mutated genes, that also blocked cell death, thus imbuing cancer cells with the capacity to resist death signals. Other pathways allowed cancer cells to acquire motility, the capacity to move from one tissue to another—initiating metastasis. Yet other gene cascades increased cell survival in hostile environments, such that cancer cells traveling through the bloodstream could invade other organs and not be rejected or destroyed in environments not designed for their survival.

Cancer, in short, was not merely genetic in its origin; it was genetic in its entirety. Abnormal genes governed all aspects of cancer's behavior. Cascades of aberrant signals, originating in mutant genes, fanned out within the cancer cell, promoting survival, accelerating growth, enabling mobility, recruiting blood vessels, enhancing nourishment, drawing oxygen—sustaining cancer's life.

These gene cascades, notably, were perversions of signaling pathways used by the body under normal circumstances. The "motility genes" activated by cancer cells, for instance, are the very genes that normal cells use when they require movement through the body, such as when immunological cells need to move toward sites of infection. Tumor angiogenesis exploits the same pathways that are used when blood vessels are created to heal wounds. Nothing is invented; nothing is extraneous. Cancer's life is a recapitulation of the body's life, its existence a pathological mirror of our own. Susan Sontag warned against overburdening an illness with metaphors. But this is not a metaphor. Down to their innate molecular core, cancer cells are hyperactive, survival-endowed, scrappy, fecund, inventive copies of ourselves.

By the early 1990s, cancer biologists could begin to model the genesis of cancer in terms of molecular changes in genes. To understand that model, let us begin with a normal cell, say a lung cell that resides in the left lung of a forty-year-old fire-safety-equipment installer. One morning in 1968, a minute sliver of asbestos from his equipment wafts through the air and lodges in the vicinity of that cell. His body reacts to the sliver with an inflammation. The cells around the sliver begin to divide furiously, like a minuscule wound trying to heal, and a small clump of cells derived from the original cell arises at the site.

In one cell in that clump an accidental mutation occurs in the *ras* gene. The mutation creates an activated version of *ras.* The cell containing the mutant gene is driven to grow more swiftly than its neighbors and creates a clump within the original clump of cells. It is not yet a cancer cell, but a cell in which uncontrolled cell division has partly been unleashed—cancer's primordial ancestor.

A decade passes. The small collection of *ras*-mutant cells continues to proliferate, unnoticed, in the far periphery of the lung. The man smokes cigarettes, and a carcinogenic chemical in tar reaches the periphery of the lung and collides with the clump of *ras*-mutated cells. A cell in this clump acquires a second mutation in its genes, activating a second oncogene.

Another decade passes. Yet another cell in that secondary mass of cells is caught in the path of an errant X-ray and acquires yet another mutation, this time inactivating a tumor suppressor gene. This mutation has little effect since the cell possesses a second copy of that gene. But in the next year, another mutation inactivates the second copy of the tumor suppressor gene, creating a cell that possesses two activated oncogenes and an inactive tumor suppressor gene.

Now a fatal march is on; an unraveling begins. The cells, now with four mutations, begin to outgrow their brethren. As the cells grow, they acquire additional mutations and they activate pathways, resulting in cells even further adapted for growth and survival. One mutation in the tumor allows it to incite blood vessels to grow; another mutation within this blood-nourished tumor allows the tumor to survive even in areas of the body with low oxygen.

Mutant cells beget cells beget cells. A gene that increases the mobility of the cells is activated in a cell. This cell, having acquired motility, can migrate through the lung tissue and enter the bloodstream. A descendant of this mobile cancer cell acquires the capacity to survive in the bone. This cell, having migrated through the blood, reaches the outer edge of the pelvis, where it begins yet another cycle of survival, selection, and colonization. It represents the first metastasis of a tumor that originated in the lung.

The man is occasionally short of breath. He feels a tingle of pain in the periphery of his lung. Occasionally, he senses something moving under his rib cage when he walks. Another year passes, and the sensations accelerate. The man visits a physician and a CT scan is performed, revealing a rindlike mass wrapped around a bronchus in the lung. A biopsy reveals lung cancer. A surgeon examines the man and the CT scan of the chest and deems the cancer inoperable. Three weeks after that visit, the man returns to the medical clinic complaining of pain in his ribs and his hips. A bone scan reveals metastasis to the pelvis and the ribs.

Intravenous chemotherapy is initiated. The cells in the lung tumor respond. The man soldiers through a punishing regimen of multiple cell-killing drugs. But during the treatment, one cell in the tumor acquires yet another mutation that makes it resistant to the drug used to treat the cancer. Seven months after his initial diagnosis, the tumor relapses all over the body—in the lungs, the bones, the liver. On the morning of October, 17, 2004, deeply narcotized on opiates in a hospital bed in Boston and surrounded by his wife and his children, the man dies of metastatic lung cancer, a sliver of asbestos still lodged in the periphery of his lung. He is seventy-six years old.

I began this as a hypothetical story of cancer. The genes, carcinogens, and the sequence of mutations in this story are all certainly hypothetical. But the body at its center is real. This man was the first patient to die in my care during my fellowship in cancer medicine at Massachusetts General Hospital.

Medicine, I said, begins with storytelling. Patients tell stories to describe illness; doctors tell stories to understand it. Science tells its own story to explain diseases. This story of one cancer's genesis—of carcinogens causing mutations in internal genes, unleashing cascading pathways in cells that then cycle through mutation, selection, and survival—represents the most cogent outline we have of cancer's birth.

In the fall of 1999, Robert Weinberg attended a conference on cancer biology in Hawaii. Late one afternoon, he and Douglas Hanahan, another cancer biologist, trekked through the lava beds of the low, black mountains until they found themselves at the mouth of a volcano, staring in. Their conversation was tinged with frustration. For too long, it seemed, cancer had been talked about as if it were a bewildering hodgepodge of chaos. The biological characteristics of tumors were described as so multifarious as to defy any credible organization. There seemed to be no organizing rules.

Yet, Weinberg and Hanahan knew, the discoveries of the prior two decades had suggested deep rules and principles. Biologists looking directly into cancer's maw now recognized that roiling beneath the incredible heterogeneity of cancer were behaviors, genes, and pathways. In January 2000, a few months after their walk to the volcano's mouth, Weinberg and Hanahan published an article titled "The Hallmarks of Cancer" to summarize these rules. It was an ambitious and iconic work that marked a return, after nearly a century's detour, to Boveri's original notion of a "unitary cause of carcinoma":

"We discuss . . . rules that govern the transformation of normal human cells into malignant cancers. We suggest that research over the past decades has revealed a small number of molecular, biochemical, and cellular traits—acquired capabilities—shared by most and perhaps all types of human cancer."

How many "rules," then, could Weinberg and Hanahan evoke to explain the core behavior of more than a hundred distinct types and subtypes of tumors? The question was audacious in its expansiveness; the answer even more audacious in its economy: six. "We suggest that the vast catalog of cancer cell genotypes is a manifestation of six essential alterations in cell physiology that collectively dictate malignant growth."

1. *Self-sufficiency in growth signals:* cancer cells acquire an autonomous drive to proliferate—pathological mitosis—by virtue of the activation of oncogenes such as *ras* or *myc*.
2. *Insensitivity to growth-inhibitory (antigrowth) signals:* cancer cells inactivate tumor suppressor genes, such as retinoblastoma (*Rb*), that normally inhibit growth
3. *Evasion of programmed cell death (apoptosis):* cancer cells suppress and inactivate genes and pathways that normally enable cells to die.
4. *Limitless replicative potential:* cancer cells activate specific gene pathways that render them immortal even after generations of growth.
5. *Sustained angiogenesis:* cancer cells acquire the capacity to draw out their own supply of blood and blood vessels—tumor angiogenesis.
6. *Tissue invasion and metastasis:* cancer cells acquire the capacity to migrate to other organs, invade other tissues, and colonize these organs, resulting in their spread throughout the body.

Notably, Weinberg and Hanahan wrote, these six rules were not abstract descriptions of cancer's behavior. Many of the genes and pathways that enabled each of these six behaviors had concretely been identified—*ras, myc, Rb*, to name just a few. The task now was to *connect* this causal understanding of cancer's deep biology to the quest for its cure:

"Some would argue that the search for the origin and treatment of this disease will continue over the next quarter century in much the same manner as it has in the recent past, by adding further layers of complexity to a scientific literature that is already complex almost beyond measure. But we anticipate otherwise: those researching the cancer problem will be practicing a dramatically different type of science than we have experienced over the past 25 years."

The mechanistic maturity of cancer science would create a new kind of cancer medicine, Weinberg and Hanahan posited: "With holistic clarity of mechanism, cancer prognosis and treatment will become a rational science, unrecognizable by current practitioners." Having wandered in the darkness for decades, scientists had finally reached a clearing in their understanding of cancer. Medicine's task was to continue that journey toward a new therapeutic attack.

* In 1988, the precise identity of only one gene—*ras*—was known. The other three were suspected human anti-oncogenes, although their identity would only become known later.

PART SIX

THE FRUITS OF LONG ENDEAVORS

We are really reaping the fruits of our long endeavors.

—Michael Gorman
to Mary Lasker, 1985

The National Cancer Institute, which has overseen American efforts on researching and combating cancers since 1971, should take on an ambitious new goal for the next decade: the development of new drugs that will provide lifelong cures for many, if not all, major cancers. Beating cancer now is a realistic ambition because, at long last, we largely know its true genetic and chemical characteristics.

—James Watson, 2009

The more perfect a power is, the more difficult it is to quell.

—Saint Aquinas, attributed

"No one had labored in vain"

Have you met Jimmy? . . . Jimmy is any one of thousands of children with leukemia or any other form of cancer, from the nation or from around the world.

—Pamphlet for the Jimmy Fund, 1963

In the summer of 1997, a woman named Phyllis Clauson, from Billerica, Massachusetts, posted a letter to the Dana-Farber Cancer Institute. She was writing on behalf of "Jimmy," Farber's mascot. It had been nearly fifty years since Jimmy had arrived at Farber's clinic in Boston from upstate Maine with a diagnosis of lymphoma of the intestines. Like all his ward-mates from the 1950s, Jimmy was presumed long dead.

Not true, Clauson wrote; he was alive and well. Jimmy—Einar Gustafson—was her brother, a truck driver in Maine with three children. For five decades, his family had guarded the knowledge of Jimmy's identity and his survival. Only Sidney Farber had known; Christmas cards from Farber had arrived each winter, until Farber himself had died in 1973. Every year, for decades, Clauson and her siblings had sent in modest donations to the Jimmy Fund, divulging to no one that the silhouetted face on the solicitation card for contributions was their brother's. But with the passage of fifty years, Clauson felt she could no longer keep the secret in good conscience. "Jimmy's story," she recalled, "had become a story that I could not hold. I knew I had to write the letter while Einar was still alive."

Clauson's letter was nearly thrown into the trash. Jimmy "sightings," like Elvis sightings, were reported often, but rarely taken seriously; all had turned out to be hoaxes. Doctors had informed the Jimmy Fund's publicity department that the odds of Jimmy's having survived were nil, and that all claims were to be treated with great skepticism. But Clauson's letter contained details that could not be waved away. She wrote of listening to the radio in New Sweden, Maine, in the summer of 1948 to tune in to the Ralph Edwards broadcast. She recalled her brother's midwinter trips to Boston that often took two days, with Jimmy in his baseball uniform lying patiently in the back of a truck.

When Clauson told her brother about the letter that she had sent, she found him more relieved than annoyed. "It was like an unburdening for him, too," she recalled. "Einar was a modest man. He had kept to himself because he did not want to brag." ("I would read in the papers that they had found me someplace," he said, "and I would smile.")

Clauson's letter was spotted by Karen Cummings, an associate in the Jimmy Fund's development office, who immediately understood its potential significance. She contacted Clauson, and then reached Gustafson.

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A few weeks later, in January 1998, Cummings arranged to meet Jimmy at a truck stop outside a shopping center in a suburb of Boston. It was six in the morning on a bone-chilling winter day, and Gustafson and his wife piled into Cummings's warm car. Cummings had brought a tape of Jimmy from 1948 singing his favorite song. She played it:

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.

Gustafson listened to his own voice with tears in his eyes. Cummings and Jimmy's wife sat in the car, their eyes also welling with silent tears.

Later that month, Cummings drove up to New Sweden, a brutally beautiful town in northern Maine with austere angular houses set against an even more austere landscape. Old-timers in the town also recalled Gustafson's trips to Boston for chemotherapy. He had hitchhiked to and from Boston in cars and trucks and delivery vans anytime someone from the town had driven up or down the coast; it had taken a village to save a child. As Cummings sat in Gustafson's kitchen, he crept upstairs and returned with a cardboard box. Wrapped inside was the battered baseball uniform that the Boston Braves had given Jimmy on the night of the Edwards broadcast. Cummings needed no further proof.

And so it was in May 1998, almost exactly fifty years after he had journeyed from small-town Maine to the Children's Hospital to meet the odd, formal doctor in a three-piece suit, that Jimmy returned with full fanfare to the Jimmy Fund. His wardmates from the hospital—the Sandler twin with his recalcitrant leukemia engorging his spleen, the blond girl in plaits by the television, little Jenny with leukemia—had long ago been buried in small graves in and around Boston. Gustafson walked into the Jimmy Fund Building, up the low, long steps to the room where the clockwork train had run through the mountain tunnel. Patients, survivors, nurses, and doctors milled around him. Like a latter-day Rip van Winkle, he found the present unfathomable and unrecognizable. "Everything has changed," Clauson recalled him saying. "The rooms, the patients, the drugs." But more than anything, survivorship had changed. "Einar remembered the cancer ward as a place with many curtains," she continued. "When the children were well, the curtains would be spread open. But they would soon close the curtains, and there would be no child when they were opened again."

Here Gustafson was, fifty years later, back in those long hallways with the faded cartoon paintings on the walls, his curtains thrown apart. It is impossible to know whether Jimmy had survived because of surgery, or chemotherapy, or because his cancer had been inherently benign in its behavior. But the facts of his medical history are irrelevant; his return was symbolic. Jimmy had unwittingly been picked to become the icon of the child with cancer. But Einar Gustafson, now sixty-three years old, had returned as the icon of a man beyond cancer.

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The Italian memoirist Primo Levi, who survived a concentration camp and then navigated his way through a blasted Germany to his native Turin, often remarked that among the most fatal qualities of the camp was its ability to erase the idea of a life outside and beyond itself. A person's past and his present were annihilated as a matter of course—to be in the camps was to abnegate history, identity, and personality—but it was the erasure of the future that was the most chilling. With that annihilation, Levi wrote, came a moral and spiritual death that perpetuated the status quo of imprisonment. If no life existed beyond the camp, then the distorted logic by which the camp operated became life as usual.

Cancer is not a concentration camp, but it shares the quality of annihilation: it negates the possibility of life outside and beyond itself; it subsumes all living. The daily life of a patient becomes so intensely preoccupied with his or her illness that the world fades away. Every last morsel of energy is spent tending the disease. "How to overcome him became my obsession," the journalist Max Lerner wrote of the lymphoma in his spleen. "If it was to be a combat then I had to engage it with everything I had—knowledge and guile, ways covert as well as overt."

For Carla, in the midst of the worst phase of her chemotherapy, the day-to-day rituals of survival utterly blotted out any thought of survivorship in the long run. When I asked a woman with a rare form of muscle sarcoma about her life outside the hospital, she told me that she spent her days and nights scouring the Internet for news about the disease. "I am in the hospital," she said, "even when I am outside the hospital." The poet Jason Shinder wrote, "Cancer is a tremendous opportunity to have your face pressed right up against the glass of your mortality." But what patients see through the glass is not a world outside cancer, but a world taken over by it—cancer reflected endlessly around them like a hall of mirrors.

I was not immune to this compulsive preoccupation either. In the summer of 2005, as my fellowship hurtled to its end, I experienced perhaps the singularly transformative event of my life: the birth of my daughter. Glowing, beautiful, and cherubic, Leela was born on a warm night at Massachusetts General Hospital, then swaddled in blankets and brought to the newborn unit on the fourteenth floor. The unit is directly across from the cancer ward. (The apposition of the two is hardly a coincidence. As a medical procedure, childbirth is least likely to involve infectious complications and is thus the safest neighbor to a chemotherapy ward, where any infection can turn into a lethal rampage. As in so much in medicine, the juxtaposition between the two wards is purely functional and yet just as purely profound.)

I would like to see myself at my wife's side awaiting the miraculous moment of my daughter's birth as most fathers do. But in truth I was gowned and gloved like a surgeon, with a blue, sterile sheet spread out in front of me, and a long syringe in my hands, poised to harvest the maroon gush of blood cells from the umbilical cord. When I cut that cord, part of me was the father, but the other part an oncologist. Umbilical blood contains one of the richest known sources of blood-forming stem cells—cells that can be stored away in cryobanks and used for a bone marrow transplant to treat leukemia in the future, an intensely precious resource often flushed down a sink in hospitals after childbirth.

The midwives rolled their eyes; the obstetrician, an old friend, asked jokingly if I ever stopped thinking about work. But I was too far steeped in the study of blood to ignore my instincts. In the bone-marrow-transplant rooms across that very hallway were patients for whom I had scoured tissue banks across the nation for one or two pints of these stem cells that might save their lives. Even in this most life-affirming of moments, the shadows of malignancy—and death—were forever lurking on my psyche.

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But not everything was involuting into death. Something transformative was also happening in the fellows' clinics in the summer of 2005: many of my patients, whose faces had so fixedly been pressed up against the glass of their mortality, began to glimpse an afterlife beyond cancer. February, as I said before, had marked the midpoint of an abysmal descent. Cancer had reached its full, lethal bloom that month. Nearly every week had brought news of a mounting toll, culminating chillingly with Steve Harmon's arrival in the emergency room and his devastating spiral into death thereafter. Some days I dreaded walking by the fax machines outside my office, where a pile of death certificates would be waiting for my signature.

But then, like a poisonous tide receding, the bad news ebbed. The nightly phone calls from the hospitals or from ERs and hospice units around Boston bringing news of yet another death ("I'm calling to let you know that your patient arrived here this evening with dizziness and difficulty breathing") suddenly ceased. It was as if the veil of death had lifted—and survivors had emerged from underneath.

Ben Orman had been definitively cured of Hodgkin's lymphoma. It had not been an effortless voyage. His blood counts had dropped calamitously during the midcycle of chemotherapy. For a few weeks it had appeared that the lymphoma had ceased responding—a poor prognostic sign portending a therapy-resistant, fatal variant of the disease. But in the end the mass in his neck, and the larger archipelago of masses in his chest, had all melted away, leaving just minor remnants of scar tissue. The formality of his demeanor had visibly relaxed. When I last saw him in the summer of 2005, he spoke about moving away from Boston to Los Angeles to join a law firm. He assured me that he would visit to follow up, but I wasn't convinced. Orman epitomized the afterlife of cancer—eager to forget the clinic and its bleak rituals, like a bad trip to a foreign country.

Katherine Fitz could also see a life beyond cancer. For Fitz, with the lung tumor wrapped ominously around her bronchus, the biggest hurdle had been the local control of her cancer. The mass had been excised in an incredibly meticulous surgery; she had then finished adjuvant chemotherapy and radiation. Nearly twelve months after the surgery, there was no sign of a local relapse. Nor was there any sign of the woman who had come to the clinic several months earlier, nearly folded over in fear. Tumor out, chemotherapy done, radiation behind her, Fitz's effervescence poured out of every spigot of her soul. At times, watching her personality emerge as if through a nozzle, it seemed abundantly clear why the Greeks had thought of disease as pathological blockades of humors.

Carla returned to see me in July 2005, bringing pictures of her three growing children. She refused to let another doctor perform her bone marrow biopsy, so I walked over from the lab on a warm morning to perform the procedure. She looked relieved when she saw me, greeting me with her anxious half-smile. We had developed a ritualistic relationship; who was I to desecrate a lucky ritual? The biopsy revealed no leukemia in the bone marrow. Her remission, for now, was still intact.

I have chosen these cases not because they were "miraculous" but because of precisely the opposite reason. They represent a routine spectrum of survivors—Hodgkin's disease cured with multidrug chemotherapy; locally advanced lung cancer controlled with surgery, chemotherapy, and radiation; lymphoblastic leukemia in a prolonged remission after intensive chemotherapy. To me, these were miracles enough. It is an old complaint about the practice of medicine that it inures you to the idea of death. But when medicine inures you to the idea of life, to survival, then it has failed utterly. The novelist Thomas Wolfe, recalling a lifelong struggle with illness, wrote in his last letter, "I've made a long voyage and been to a strange country, and I've seen the dark man very close." I had not made the journey myself, and I had only seen the darkness reflected in the eyes of others. But surely, it was the most sublime moment of my clinical life to have watched that voyage in reverse, to encounter men and women *returning* from the strange country—to see them so very close, clambering back.

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Incremental advances can add up to transformative changes. In 2005, an avalanche of papers cascading through the scientific literature converged on a remarkably consistent message—the national physiognomy of cancer had subtly but fundamentally changed. The mortality for nearly every major form of cancer—lung, breast, colon, and prostate—had continuously dropped for fifteen straight years. There had been no single, drastic turn but rather a steady and powerful attrition: mortality had declined by about 1 percent every year. The rate might sound modest, but its cumulative effect was remarkable: between 1990 and 2005, the cancer-specific death rate had dropped nearly 15 percent, a decline unprecedented in the history of the disease. The empire of cancer was still indubitably vast—more than half a million American men and women died of cancer in 2005—but it was losing power, fraying at its borders.

What precipitated this steady decline? There was no single answer but rather a multitude. For lung cancer, the driver of decline was primarily

prevention—a slow attrition in smoking sparked off by the Doll-Hill and Wynder-Graham studies, fueled by the surgeon general's report, and brought to its full boil by a combination of political activism (the FTC action on warning labels), inventive litigation (the Banzhaf and Cipollone cases), medical advocacy, and countermarketing (the antitobacco advertisements).

For colon and cervical cancer, the declines were almost certainly due to the successes of secondary prevention—cancer screening. Colon cancers were detected at earlier and earlier stages in their evolution, often in the premalignant state, and treated with relatively minor surgeries. Cervical cancer screening using Papanicolaou's smearing technique was being offered at primary-care centers throughout the nation, and as with colon cancer, premalignant lesions were excised using relatively minor surgeries.

For leukemia, lymphoma, and testicular cancer, in contrast, the declining numbers reflected the successes of chemotherapeutic treatment. In childhood ALL, cure rates of 80 percent were routinely being achieved. Hodgkin's disease was similarly curable, and so, too, were some large-cell aggressive lymphomas. Indeed, for Hodgkin's disease, testicular cancer, and childhood leukemias, the burning question was not how *much* chemotherapy was curative, but how *little:* trials were addressing whether milder and less toxic doses of drugs, scaled back from the original protocols, could achieve equivalent cure rates.

Perhaps most symbolically, the decline in breast cancer mortality epitomized the cumulative and collaborative nature of these victories—and the importance of attacking cancer using multiple independent prongs. Between 1990 and 2005, breast cancer mortality had dwindled an unprecedented 24 percent. Three interventions had potentially driven down the breast cancer death rate—mammography (screening to catch early breast cancer and thereby prevent invasive breast cancer), surgery, and adjuvant chemotherapy (chemotherapy after surgery to remove remnant cancer cells). Donald Berry, a statistician in Houston, Texas, set out to answer a controversial question: How much had mammography and chemotherapy *independently* contributed to survival? Whose victory was this—a victory of prevention or of therapeutic intervention?

Berry's answer was a long-due emollient to a field beset by squabbles between the advocates of prevention and the proponents of chemotherapy. When Berry assessed the effect of each intervention independently using statistical models, it was a satisfying tie: both cancer prevention and chemotherapy had diminished breast cancer mortality equally—12 percent for mammography and 12 percent for chemotherapy, adding up to the observed 24 percent reduction in mortality. "No one," as Berry said, paraphrasing the Bible, "had labored in vain."

These were all deep, audacious, and meaningful victories borne on the backs of deep and meaningful labors. But, in truth, they were the victories of another generation—the results of discoveries made in the fifties and sixties. The core conceptual advances from which these treatment strategies arose predated nearly all the significant work on the cell biology of cancer. In a bewildering spurt over just two decades, scientists had unveiled a fantastical new world—of errant oncogenes and tumor suppressor genes that accelerated and decelerated growth to unleash cancer; of chromosomes that could be decapitated and translocated to create new genetic chimeras, of cellular pathways corrupted to subvert the death of cancer. But the *therapeutic* advances that had led to the slow attrition of cancer mortality made no use of this novel biology of cancer. There was new science on one hand and old medicine on the other. Mary Lasker had once searched for an epochal shift in cancer. But the shift that had occurred seemed to belong to another epoch.

Mary Lasker died of heart failure in 1994 in her carefully curated home in Connecticut—having removed herself physically from the bristling epicenters of cancer research and policymaking in Washington, New York, and Boston. She was ninety-three years old. Her life had nearly spanned the most transformative and turbulent century of biomedical science. Her potent ebullience had dimmed in her last decade. She spoke rarely about the achievements (or disappointments) of the War on Cancer. But she had expected cancer medicine to have achieved more during her lifetime—to have taken a more assertive step toward Farber's "universal cure" for cancer and marked a more definitive victory in the war. The complexity, the tenacity—the sheer magisterial force of cancer—had made even its most committed and resolute opponent seem circumspect and humbled.

In 1994, a few months after Lasker's death, the cancer geneticist Ed Harlow captured both the agony and the ecstasy of the era. At the end of a weeklong conference at the Cold Spring Harbor Laboratory in New York pervaded by a giddy sense of anticipation about the spectacular achievements of cancer biology, Harlow delivered a sobering assessment: "Our knowledge of . . . molecular defects in cancer has come from a dedicated twenty years of the best molecular biology research. Yet this information does not translate to any effective treatments nor to any understanding of why many of the current treatments succeed or why others fail. It is a frustrating time."

More than a decade later, I could sense the same frustration in the clinic at Mass General. One afternoon, I watched Tom Lynch, the lung cancer clinician, masterfully encapsulate carcinogenesis, cancer genetics, and chemotherapy for a new patient, a middle-aged woman with bronchoalveolar cell cancer. She was a professor of history with a grave manner and a sharp, darting mind. He sat across from her, scribbling a picture as he spoke. The cells in her bronchus, he began, had acquired mutations in their genes that had allowed them to grow autonomously and uncontrollably. They had formed a local tumor. Their propensity was to acquire further mutations that might allow them to migrate, to invade tissues, to metastasize. Chemotherapy with Carboplatin and Taxol (two standard chemotherapy drugs), augmented with radiation, would kill the cells and perhaps prevent them from migrating to other organs to seed metastases. In the best-case scenario, the cells carrying the mutated genes would die, and her cancer would be cured.

She watched Lynch put his pen down with her quick, sharp eyes. The explanation sounded logical and organized, but she had caught the glint of a broken piece in the chain of logic. What was the connection between this explanation and the therapy being proposed? How, she wanted to know, would Carboplatin "fix" her mutated genes? How would Taxol know which cells carried the mutations in order to kill them? How would the mechanistic explanation of her illness connect with the medical interventions?

She had captured a disjunction all too familiar to oncologists. For nearly a decade, practicing cancer medicine had become like living inside a pressurized can—pushed, on one hand, by the increasing force of biological clarity about cancer, but then pressed against the wall of medical stagnation that seemed to have produced no real medicines out of this biological clarity. In the winter of 1945, Vannevar Bush had written to President Roosevelt, "The striking advances in medicine during the war have been possible only because we had a large backlog of scientific data accumulated through basic research in many scientific fields in the years before the war."

For cancer, the "backlog of scientific data" had reached a critical point. The boil of science, as Bush liked to imagine it, inevitably produced a kind of steam—an urgent, rhapsodic pressure that could only find release in technology. Cancer science was begging to find release in a new kind of cancer medicine.

* Jimmy began chemo in the Children's Hospital in 1948, but was later followed and treated in the Jimmy Fund Building in 1952.
* Surgery's contribution could not be judged since surgery predated 1990, and nearly all women are treated surgically.

New Drugs for Old Cancers

In the story of Patroclus
No one survives, not even Achilles
Who was nearly a god.
Patroclus resembled him; they wore
The same armor
—Louise Glück

The perfect therapy has not been developed. Most of us believe that it will not involve toxic cytotoxic therapy, which is why we support the kinds of basic investigations that are directed towards more fundamental understanding of tumor biology. But . . . we must do the best with what we nowhave.

—Bruce Chabner to Rose Kushner

In the legend, Achilles was quickly dipped into the river Styx, held up only by the tendon of his heel. Touched by the dark sheath of water, every part of his body was instantly rendered impervious to even the most lethal weapon—except the undipped tendon. A simple arrow targeted to that vulnerable heel would eventually kill Achilles in the battlefields of Troy.

Before the 1980s, the armamentarium of cancer therapy was largely built around two fundamental vulnerabilities of cancer cells. The first is that most cancers originate as local diseases before they spread systemically. Surgery and radiation therapy exploit this vulnerability. By physically excising locally restricted tumors before cancer cells can spread—or by searing cancer cells with localized bursts of powerful energy using X-rays—surgery and radiation attempt to eliminate cancer en bloc from the body.

The second vulnerability is the rapid growth rate of cancer cells. Most chemotherapy drugs discovered before the 1980s target this second vulnerability. Antifolates, such as Farber's aminopterin, interrupt the metabolism of folic acid and starve all cells of a crucial nutrient required for cell division. Nitrogen mustard and cisplatin chemically react with DNA, and DNA-damaged cells cannot duplicate their genes and thus cannot divide. Vincristine, the periwinkle poison, thwarts the ability of a cell to construct the molecular "scaffold" required for all cells to divide.

But these two traditional Achilles' heels of cancer—local growth and rapid cell division—can only be targeted to a point. Surgery and radiation are intrinsically localized strategies, and they fail when cancer cells have spread beyond the limits of what can be surgically removed or irradiated. More surgery thus does not lead to more cures, as the radical surgeons discovered to their despair in the 1950s.

Targeting cellular growth also hits a biological ceiling because normal cells must grow as well. Growth may be the hallmark of cancer, but it is equally the hallmark of life. A poison directed at cellular growth, such as vincristine or cisplatin, eventually attacks normal growth, and cells that grow most rapidly in the body begin to bear the collateral cost of chemotherapy. Hair falls out. Blood involutes. The lining of the skin and gut sloughs off. More drugs produce more toxicity without producing cures, as the radical chemotherapists discovered to their despair in the 1980s.

To target cancer cells with novel therapies, scientists and physicians needed new vulnerabilities that were unique to cancer. The discoveries of cancer biology in the 1980s offered a vastly more nuanced view of these vulnerabilities. Three new principles emerged, representing three new Achilles' heels of cancer.

First, cancer cells are driven to grow because of the accumulation of mutations in their DNA. These mutations activate internal proto-oncogenes and inactivate tumor suppressor genes, thus unleashing the "accelerators" and "brakes" that operate during normal cell division. Targeting these hyperactive genes, while sparing their modulated normal precursors, might be a novel means to attack cancer cells more discriminately.

Second, proto-oncogenes and tumor suppressor genes typically lie at the hubs of cellular signaling pathways. Cancer cells divide and grow because they are driven by hyperactive or inactive signals in these critical pathways. These pathways exist in normal cells but are tightly regulated. The potential dependence of a cancer cell on such permanently activated pathways is a second potential vulnerability of a cancer cell.

Third, the relentless cycle of mutation, selection, and survival creates a cancer cell that has acquired several additional properties besides uncontrolled growth. These include the capacity to resist death signals, to metastasize throughout the body, and to incite the growth of blood vessels. These "hallmarks of cancer" are not invented by the cancer cell; they are typically derived from the corruption of similar processes that occur in the normal physiology of the body. The acquired dependence of a cancer cell on these processes is a third potential vulnerability of cancer.

The central therapeutic challenge of the newest cancer medicine, then, was to find, among the vast numbers of similarities in normal cells and cancer cells, subtle differences in genes, pathways, and acquired capabilities—and to drive a poisoned stake into that new heel.

It was one thing to identify an Achilles' heel—and quite another to discover a weapon that would strike it. Until the late 1980s, no drug had reversed an oncogene's activation or a tumor suppressor's inactivation. Even tamoxifen, the most specific cancer-targeted drug discovered to that date, works by attacking the dependence of certain breast cancer cells on estrogen, and not by directly inactivating an oncogene or oncogene-activated pathway. In 1986, the discovery of the first oncogene-targeted drug would thus instantly galvanize cancer medicine. Although found largely serendipitously, the mere existence of such a molecule would set the stage for the vast drug-hunting efforts of the next decade.

The disease that stood at the pivotal crossroads of oncology was yet another rare variant of leukemia called acute promyelocytic leukemia—APL. First identified as a distinct form of adult leukemia in the 1950s, the disease has a distinct characteristic: the cells in this form of cancer do not merely divide rapidly, they are also strikingly frozen in immature development. Normal white blood cells developing in the bone marrow undergo a series of maturational steps to develop into fully functional adult cells. One such intermediate cell is termed a promyelocyte, an adolescent cell on the verge of becoming functionally mature. APL is characterized by the malignant proliferation of these immature promyelocytes. Normal promyelocytes are loaded with toxic enzymes and granules that are usually released by adult white blood cells to kill viruses, bacteria, and parasites. In promyelocytic leukemia, the blood fills up with these toxin-loaded promyelocytes. Moody, mercurial, and jumpy, the cells of APL can

release their poisonous granules on a whim—precipitating massive bleeding or simulating a septic reaction in the body. In APL, the pathological proliferation of cancer thus comes with a fiery twist. Most cancers contain cells that refuse to stop growing. In APL, the cancer cells also refuse to grow up.

Since the early 1970s, this maturation arrest of APL cells had prompted scientists to hunt for a chemical that might force these cells to mature. Scores of drugs had been tested on APL cells in test tubes, and only one had stood out—retinoic acid, an oxidized form of vitamin A. But retinoic acid, researchers had found, was a vexingly unreliable reagent. One batch of the acid might mature APL cells, while another batch of the same chemical might fail. Frustrated by these flickering, unfathomable responses, biologists and chemists had turned away after their initial enthusiasm for the maturation chemical.

In the summer of 1985, a team of leukemia researchers from China traveled to France to meet Laurent Degos, a hematologist at Saint Louis Hospital in Paris with a long-standing interest in APL. The Chinese team, led by Zhen Yi Wang, was also treating APL patients, at Ruijin Hospital, a busy, urban clinical center in Shanghai, China. Both Degos and Wang had tried standard chemotherapy agents—drugs that target rapidly growing cells—to promote remissions in APL patients, but the results had been dismal. Wang and Degos spoke of the need for a new strategy to attack this whimsical, lethal disease, and they kept circling back to the peculiar immaturity of APL cells and to the lapsed search for a maturation agent for the disease.

Retinoic acid, Wang and Degos knew, comes in two closely related molecular forms, called cis-retinoic acid and trans-retinoic acid. The two forms are compositionally identical, but possess a slight difference in their molecular structure, and they behave very differently in molecular reactions. (Cis-retinoic acid and trans-retinoic acid have the same atoms, but the atoms are arranged differently in the two chemicals.) Of the two forms, cis-retinoic acid had been the most intensively tested, and it had produced the flickering, transient responses. But Wang and Degos wondered if trans-retinoic acid was the true maturation agent. Had the unreliable responses in the old experiments been due to a low and variable amount of the trans-retinoic form present in every batch of retinoic acid?

Wang, who had studied at a French Jesuit school in Shanghai, spoke a lilting, heavily accented French. Linguistic and geographic barriers breached, the two hematologists outlined an international collaboration. Wang knew of a pharmaceutical factory outside Shanghai that could produce pure trans-retinoic acid—without the admixture of cis-retinoic acid. He would test the drug on APL patients at the Ruijin Hospital. Degos's team in Paris would follow after the initial round of testing in China and further validate the strategy on French APL patients.

Wang launched his trial in 1986 with twenty-four patients. Twenty-three experienced a dazzling response. Leukemic promyelocytes in the blood underwent a brisk maturation into white blood cells. "The nucleus became larger," Wang wrote, "and fewer primary granules were observed in the cytoplasm. On the fourth day of culture, these cells gave rise to myelocytes containing specific, or secondary, granules . . . [indicating the development of] fully mature granulocytes."

Then something even more unexpected occurred: having fully matured, the cancer cells began to die out. In some patients, the differentiation and death erupted so volcanically that the bone marrow swelled up with differentiated promyelocytes and then emptied slowly over weeks as the cancer cells matured and underwent an accelerated cycle of death. The sudden maturation of cancer cells produced a short-lived metabolic disarray, which was controlled with medicines, but the only other side effects of trans-retinoic acid were dryness of lips and mouth and an occasional rash. The remissions produced by trans-retinoic acid lasted weeks and often months.

Acute promyelocytic leukemia still relapsed, typically about three to four months after treatment with trans-retinoic acid. The Paris and Shanghai teams next combined standard chemotherapy drugs with trans-retinoic acid—a cocktail of old and new drugs—and remissions were prolonged by several additional months. In about three-fourths of the patients, the leukemia remission began to stretch into a full year, then into five years. By 1993, Wang and Degos concluded that 75 percent of their patients treated with the combination of trans-retinoic acid and standard chemotherapy would never relapse—a percentage unheard of in the history of APL.

Cancer biologists would need another decade to explain the startling Ruijin responses at a molecular level. The key to the explanation lay in the elegant studies performed by Janet Rowley, the Chicago cytologist. In 1984, Rowley had identified a unique translocation in the chromosomes of APL cells—a fragment of a gene from chromosome fifteen fused with a fragment of a gene from chromosome seventeen. This created an activated "chimeric" oncogene that drove the proliferation of promyelocytes and blocked their maturation, thus creating the peculiar syndrome of APL.

In 1990, a full four years after Wang's clinical trial in Shanghai, this culprit oncogene was isolated by independent teams of scientists from France, Italy, and America. The APL oncogene, scientists found, encodes a protein that is tightly bound by trans-retinoic acid. This binding immediately extinguishes the oncogene's signal in APL cells, thereby explaining the rapid, powerful remissions observed in Shanghai.

The Ruijin discovery was remarkable: trans-retinoic acid represented the long-sought fantasy of molecular oncology—an oncogene-targeted cancer drug. But the discovery was a fantasy lived backward. Wang and Degos had first stumbled on trans-retinoic acid through inspired guesswork—and only later discovered that the molecule could directly target an oncogene.

But was it possible to make the converse journey—starting *from* oncogene and going *to* drug? Indeed, Robert Weinberg's lab in Boston had already begun that converse journey, although Weinberg himself was largely oblivious of it.

By the early 1980s, Weinberg's lab had perfected a technique to isolate cancer-causing genes directly out of cancer cells. Using Weinberg's technique, researchers had isolated dozens of new oncogenes from cancer cells. In 1982, a postdoctoral scientist from Bombay working in Weinberg's lab, Lakshmi Charon Padhy, reported the isolation of yet another such oncogene from a rat tumor called a neuroblastoma. Weinberg christened the gene *neu*, naming it after the type of cancer that harbored this gene.

Neu was added to the growing list of oncogenes, but it was an anomaly. Cells are bounded by a thin membrane of lipids and proteins that acts as an oily barrier against the entry of many drugs. Most oncogenes discovered thus far, such as *ras* and *myc*, are sequestered inside the cell (*ras* is bound to the cell membrane but faces into the cell), making them inaccessible to drugs that cannot penetrate the cell membrane. The product of the *neu* gene, in contrast, was a novel protein, not hidden deep inside the cell, but tethered to the cell membrane with a large fragment that hung outside, freely accessible to any drug.

Lakshmi Charon Padhy even had a "drug" to test. In 1981, while isolating his gene, he had created an antibody against the new *neu* protein. Antibodies are molecules designed to bind to other molecules, and the binding can occasionally block and inactivate the bound protein. But antibodies are unable to cross the cell membrane and need an exposed protein outside the cell to bind. *Neu*, then, was a perfect target, with a large portion, a long molecular "foot," projected tantalizingly outside the cell membrane. It would have taken Padhy no more than an afternoon's experiment to add the *neu* antibody to the neuroblastoma cells to determine the binding's effect. "It would have been an overnight test," Weinberg would later recall. "I can flagellate myself. If I had been more studious and more focused and not as monomaniacal about the ideas I had at that time, I would have made that connection."

Despite the trail of seductive leads, Padhy and Weinberg never got around to doing their experiment. Afternoon upon afternoon passed. Introspective and bookish, Padhy shuffled through the lab in a threadbare coat in the winter, running his experiments privately and saying little about them to others. And although Padhy's discovery was published in a high-profile scientific journal, few scientists noticed that he might have stumbled on a potential anticancer drug (the *neu*-binding antibody was buried in an obscure figure in the article). Even Weinberg, caught in the giddy upswirl of new oncogenes and obsessed with the basic biology of the cancer cell, simply forgot about the *neu* experiment.

Weinberg had an oncogene and possibly an oncogene-blocking drug, but the twain had never met (in human cells or bodies). In the neuroblastoma cells dividing in his incubators, *neu* rampaged on monomaniacally, single-mindedly, seemingly invincible. Yet its molecular foot still waved just outside the surface of the plasma membrane, exposed and vulnerable, like Achilles' famous heel.

* In 1986, Jeffrey Drebin and Mark Greene showed that treatment with an anti-*neu* antibody arrested the growth of cancer cells. But the prospect of developing this antibody into a human anticancer drug eluded all groups.

A City of Strings

In Ersilia, to establish the relationships that sustain the city's life, inhabitants stretch strings from the corners of the houses, white or black or gray or black-and-white according to whether they mark a relationship of blood, of trade, authority, agency. When the strings become so numerous that you can no longer pass among them, the inhabitants leave: the houses are dismantled.

—Italo Calvino

Weinberg may briefly have forgotten about the therapeutic implication of *neu*, but oncogenes, by their very nature, could not easily be forgotten. In his book *Invisible Cities*, Italo Calvino describes a fictional metropolis in which every relationship between one household and the next is denoted by a piece of colored string stretched between the two houses. As the metropolis grows, the mesh of strings thickens and the individual houses blur away. In the end, Calvino's city becomes no more than an interwoven network of colored strings.

If someone were to draw a similar map of relationships among genes in a normal human cell, then proto-oncogenes and tumor suppressors such as *ras, myc, neu*, and *Rb* would sit at the hub of this cellular city, radiating webs of colored strings in every direction. Proto-oncogenes and tumor suppressors are the molecular pivots of the cell. They are the gatekeepers of cell division, and the division of cells is so central to our physiology that genes and pathways that coordinate this process intersect with nearly every other aspect of our biology. In the laboratory, we call this the six-degrees-of-separation-from-cancer rule: you can ask any biological question, no matter how seemingly distant—what makes the heart fail, or why worms age, or even how birds learn songs—and you will end up, in fewer than six genetic steps, connecting with a proto-oncogene or tumor suppressor.

It should hardly come as a surprise, then, that *neu* was barely forgotten in Weinberg's laboratory when it was resurrected in another. In the summer of 1984, a team of researchers, collaborating with Weinberg, discovered the human homolog of the *neu* gene. Noting its resemblance to another growth-modulating gene discovered previously—the Human EGF Receptor (HER)—the researchers called the gene *Her-2*.

A gene by any other name may still be the same gene, but something crucial had shifted in the story of *neu*. Weinberg's gene had been discovered in an academic laboratory. Much of Weinberg's attention had been focused on dissecting the molecular mechanism of the *neu* oncogene. *Her-2*, in contrast, was discovered on the sprawling campus of the pharmaceutical company Genentech. The difference in venue, and the resulting difference in goals, would radically alter the fate of this gene. For Weinberg, *neu* had represented a route to understanding the fundamental biology of neuroblastoma. For Genentech, *Her-2* represented a route to developing a new drug.

Located on the southern edge of San Francisco, sandwiched among the powerhouse labs of Stanford, UCSF, and Berkeley and the burgeoning start-ups of Silicon Valley, Genentech—short for *Gene*tic *En*gineering *Tech*nology—was born out of an idea imbued with deep alchemic symbolism. In the late 1970s, researchers at Stanford and UCSF had invented a technology termed "recombinant DNA." This technology allowed genes to be manipulated—engineered—in a hitherto unimaginable manner. Genes could be shuttled from one organism to another: a cow gene could be transferred into bacteria, or a human protein synthesized in dog cells. Genes could also be spliced together to create new genes, creating proteins never found in nature. Genentech imagined leveraging this technology of genes to develop a pharmacopoeia of novel drugs. Founded in 1976, the company licensed recombinant DNA technology from UCSF, raised a paltry $200,000 in venture funds, and launched its hunt for these novel drugs.

A "drug," in bare conceptual terms, is any substance that can produce an effect on the physiology of an animal. Drugs can be simple molecules; water and salt, under appropriate circumstances, can function as potent pharmacological agents. Or drugs can be complex, multifaceted chemicals—molecules derived from nature, such as penicillin, or chemicals synthesized artificially, such as aminopterin. Among the most complex drugs in medicine are proteins, molecules synthesized by cells that can exert diverse effects on human physiology. Insulin, made by pancreas cells, is a protein that regulates blood sugar and can be used to control diabetes. Growth hormone, made by the pituitary cells, augments growth by increasing the metabolism of muscle and bone cells.

Before Genentech, protein drugs, although recognizably potent, had been notoriously difficult to produce. Insulin, for instance, was produced by grinding up cow and pig innards into a soup and then extracting the protein from the mix—one pound of insulin from every eight thousand pounds of pancreas. Growth hormone, used to treat a form of dwarfism, was extracted from pituitary glands dissected out of thousands of human cadavers. Clotting drugs to treat bleeding disorders came from liters of human blood.

Recombinant DNA technology allowed Genentech to synthesize human proteins de novo: rather than extracting proteins from animal and human organs, Genentech could "engineer" a human gene into a bacterium, say, and use the bacterial cell as a bioreactor to produce vast quantities of that protein. The technology was transformative. In 1982, Genentech unveiled the first "recombinant" human insulin; in 1984, it produced a clotting factor used to control bleeding in patients with hemophilia; in 1985, it created a recombinant version of human growth hormone—all created by engineering the production of human proteins in bacterial or animal cells.

By the late 1980s, though, after an astonishing growth spurt, Genentech ran out of existing drugs to mass-produce using recombinant technology. Its early victories, after all, had been the result of a *process* and not a product: the company had found a radical new way to produce old medicines. Now, as Genentech set out to invent new drugs from scratch, it was forced to change its winning strategy: it needed to find targets for drugs—proteins in cells that might play a critical role in the physiology of a disease that might, in turn, be turned on or off by other proteins produced using recombinant DNA.

It was under the aegis of this "target discovery" program that Axel Ullrich, a German scientist working at Genentech, rediscovered Weinberg's gene—*Her-2/neu*, the oncogene tethered to the cell membrane. But having discovered the gene, Genentech did not know what to do with it. The drugs that Genentech had successfully synthesized thus far were designed to treat human diseases in which a protein or a signal was absent or low—insulin for diabetics, clotting factors for hemophiliacs, growth hormone for dwarfs. An oncogene was the opposite—not a missing signal, but a signal in overabundance. Genentech could fabricate a missing protein in bacterial cells, but it had yet to learn how to inactivate a hyperactive

protein in a human cell.

In the summer of 1986, while Genentech was still puzzling over a method to inactivate oncogenes, Ullrich presented a seminar at the University of California in Los Angeles. Flamboyant and exuberant, dressed in a dark, formal suit, Ullrich was a riveting speaker. He floored his audience with the incredible story of the isolation of *Her-2*, and the serendipitous convergence of that discovery with Weinberg's prior work. But he left his listeners searching for a punch line. Genentech was a drug company. Where was the drug?

Dennis Slamon, a UCLA oncologist, attended Ullrich's talk that afternoon in 1986. The son of an Appalachian coal miner, Slamon had come to UCLA as a fellow in oncology after medical school at the University of Chicago. He was a peculiar amalgam of smoothness and tenacity, a "velvet jackhammer," as one reporter described him. Early in his academic life he had acquired what he called "a murderous resolve" to cure cancer, but thus far, it was all resolve and no result. In Chicago, Slamon had performed a series of exquisite studies on a human leukemia virus called HTLV-1, the lone retrovirus shown to cause a human cancer. But HTLV-1 was a fleetingly rare cause of cancer. Murdering viruses, Slamon knew, would not cure cancer. He needed a method to kill an oncogene.

Slamon, hearing Ullrich's story of *Her-2*, made a quick, intuitive connection. Ullrich had an oncogene; Genentech wanted a drug—but an intermediate was missing. A drug without a disease is a useless tool; to make a worthwhile cancer drug, both needed a cancer in which the *Her-2* gene was hyperactive. Slamon had a panel of cancers that he could test for *Her-2* hyperactivity. A compulsive pack rat, like Thad Dryja in Boston, Slamon had been collecting and storing samples of cancer tissues from patients who had undergone surgery at UCLA, all saved in a vast freezer. Slamon proposed a simple collaboration. If Ullrich sent him the DNA probes for *Her-2* from Genentech, Slamon could test his collection of cancer cells for samples with hyperactive *Her-2*—thus bridging the gap between the oncogene and a human cancer.

Ullrich agreed. In 1986, he sent Slamon the *Her-2* probe to test on cancer samples. In a few months, Slamon reported back to Ullrich that he had found a distinct pattern, although he did not fully understand it. Cancer cells that become habitually dependent on the activity of a gene for their growth can amplify that gene by making multiple copies of the gene in the chromosome. This phenomenon—like an addict feeding an addiction by ramping up the use of a drug—is called oncogene amplification. *Her-2*, Slamon found, was highly amplified in breast cancer samples, but not in all breast cancers. Based on the pattern of staining, breast cancers could neatly be divided into *Her-2* amplified and *Her-2* unamplified samples —*Her-2* positive and *Her-2* negative.

Puzzled by the "on-off" pattern, Slamon sent an assistant to determine whether *Her-2* positive tumors behaved differently from *Her-2* negative tumors. The search yielded yet another extraordinary pattern: breast tumors that amplified Ullrich's gene tended to be more aggressive, more metastatic, and more likely to kill. *Her-2* amplification marked the tumors with the worst prognosis.

Slamon's data set off a chain reaction in Ullrich's lab at Genentech. The association of *Her-2* with a subtype of cancer—aggressive breast cancer—prompted an important experiment. What would happen, Ullrich wondered, if *Her-2* activity could somehow be shut off? Was the cancer truly "addicted" to amplified *Her-2*? And if so, might squelching the addiction signal using an anti-*Her-2* drug block the growth of the cancer cells? Ullrich was tiptoeing around the afternoon experiment that Weinberg and Padhy had forgotten to perform.

Ullrich knew where he might look for a drug to shut off *Her-2* function. By the mid-1980s, Genentech had organized itself into an astonishing simulacrum of a university. The South San Francisco campus had departments, conferences, lectures, subgroups, even researchers in cutoff jeans playing Frisbee on the lawns. One afternoon, Ullrich walked to the Immunology Division at Genentech. The division specialized in the creation of immunological molecules. Ullrich wondered whether someone in immunology might be able to design a drug to bind *Her-2* and possibly erase its signaling.

Ullrich had a particular kind of protein in mind—an antibody. Antibodies are immunological proteins that bind their targets with exquisite affinity and specificity. The immune system synthesizes antibodies to bind and kill specific targets on bacteria and viruses; antibodies are nature's magic bullets. In the mid-1970s, two immunologists at Cambridge University, Cesar Milstein and George Kohler, had devised a method to produce vast quantities of a single antibody using a hybrid immune cell that had been physically fused to a cancer cell. (The immune cell secreted the antibody while the cancer cell, a specialist in uncontrolled growth, turned it into a factory.) The discovery had instantly been hailed as a potential route to a cancer cure. But to exploit antibodies therapeutically, scientists needed to identify targets unique to cancer cells, and such cancer-specific targets had proved notoriously difficult to identify. Ullrich believed that he had found one such target. *Her-2*, amplified in some breast tumors but barely visible in normal cells, was perhaps Kohler's missing bull's-eye.

At UCLA, meanwhile, Slamon had performed another crucial experiment with *Her-2* expressing cancers. He had implanted these cancers into mice, where they had exploded into friable, metastatic tumors, recapitulating the aggressive human disease. In 1988, Genentech's immunologists successfully produced a mouse antibody that bound and inactivated *Her-2*. Ullrich sent Slamon the first vials of the antibody, and Slamon launched a series of pivotal experiments. When he treated *Her-2* overexpressing breast cancer cells in a dish with the antibody, the cells stopped growing, then involuted and died. More impressively, when he injected his living, tumor-bearing mice with the *Her-2* antibody, the tumors also disappeared. It was as perfect a result as he or Ullrich could have hoped for. *Her-2* inhibition worked in an animal model.

Slamon and Ullrich now had all three essential ingredients for a targeted therapy for cancer: an oncogene, a form of cancer that specifically activated that oncogene, and a drug that specifically targeted it. Both expected Genentech to leap at the opportunity to produce a new protein drug to erase an oncogene's hyperactive signal. But Ullrich, holed away in his lab with *Her-2*, had lost touch with the trajectory of the company outside the lab. Genentech, he now discovered, was abandoning its interest in cancer. Through the 1980s, as Ullrich and Slamon had been hunting for a target specific to cancer cells, several other pharmaceutical companies had tried to develop anticancer drugs using the limited knowledge of the mechanisms driving the growth of cancer cells. Predictably, the drugs that had emerged were largely indiscriminate—toxic to both cancer cells and normal cells—and predictably, all had failed miserably in clinical trials. Ullrich and Slamon's approach—an oncogene and an oncogene-targeted antibody—was vastly more sophisticated and specific, but Genentech was worried that pouring money into the development of another drug that failed would cripple the company's finances. Chastened by the experience of others—"allergic to cancer," as one Genentech researcher described it—Genentech pulled funding away from most of its cancer projects.

The decision created a deep rift in the company. A small cadre of scientists ardently supported the cancer program, but Genentech's executives wanted to focus on simpler and more profitable drugs. *Her-2* was caught in the cross fire. Drained and dejected, Ullrich left Genentech. He would eventually join an academic laboratory in Germany, where he could work on cancer genetics without the fickle pressures of a pharmaceutical company constraining his science.

Slamon, now working alone at UCLA, tried furiously to keep the *Her-2* effort alive at Genentech, even though he wasn't on the company's payroll. "Nobody gave a shit except him," John Curd, Genentech's medical director, recalled. Slamon became a pariah at Genentech, a pushy, obsessed

gadfly who would often jet up from Los Angeles and lurk in the corridors seeking to interest anyone he could in his mouse antibody. Most scientists had lost interest. But Slamon retained the faith of a small group of Genentech scientists, scientists nostalgic for the pioneering, early days of Genentech when problems had been taken on precisely *because* they were intractable. An MIT-educated geneticist, David Botstein, and a molecular biologist, Art Levinson, both at Genentech, had been strong proponents of the *Her-2* project. (Levinson had come to Genentech from Michael Bishop's lab at UCSF, where he had worked on the phosphorylating function of *src;* oncogenes were stitched into his psyche.) Pulling strings, resources, and connections, Slamon and Levinson convinced a tiny entrepreneurial team to push ahead with the *Her-2* project.

Marginally funded, the work edged along, almost invisible to Genentech's executives. In 1989, Mike Shepard, an immunologist at Genentech, improved the production and purification of the *Her-2* antibody. But the purified mouse antibody, Slamon knew, was far from a human drug. Mouse antibodies, being "foreign" proteins, provoke a potent immune response in humans and make terrible human drugs. To circumvent that response, Genentech's antibody needed to be converted into a protein that more closely resembled a human antibody. This process, evocatively called "humanizing" an antibody, is a delicate art, somewhat akin to translating a novel; what matters is not just the content, but the ineffable essence of the antibody—its form. Genentech's resident "humanizer" was Paul Carter, a quiet, twenty-nine-year-old Englishman who had learned the craft at Cambridge from Cesar Milstein, the scientist who had first produced these antibodies using fused immune and cancer cells. Under Slamon's and Shepard's guidance, Carter set about humanizing the mouse antibody. In the summer of 1990, Carter proudly produced a fully humanized *Her-2* antibody ready to be used in clinical trials. The antibody, now a potential drug, would soon be renamed Herceptin, fusing the words *Her-2*, *intercept*, and *inhibitor*.

Such was the halting, traumatic birth of the new drug that it was easy to forget the enormity of what had been achieved. Slamon had identified *Her-2* amplification in breast cancer tissue in 1987; Carter and Shepard had produced a humanized antibody against it by 1990. They had moved from cancer to target to drug in an astonishing three years, a pace unprecedented in the history of cancer.

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In the summer of 1990, Barbara Bradfield, a forty-eight-year-old woman from Burbank, California, discovered a mass in her breast and a lump under her arm. A biopsy confirmed what she already suspected: she had breast cancer that had spread to her lymph nodes. She was treated with a bilateral mastectomy followed by nearly seven months of chemotherapy. "When I was finished with all that," she recalled, "I felt as if I had crossed a river of tragedy."

But there was more river to ford: Bradfield's life was hit by yet another incommensurate tragedy. In the winter of 1991, driving on a highway not far from their house, her daughter, twenty-three years old and pregnant, was killed in a fiery accident. A few months later, sitting numbly in a Bible-study class one morning, Bradfield let her fingers wander up to the edge of her neck. A new grape-size mass had appeared just above her collarbone. Her breast cancer had relapsed and metastasized—almost certainly a harbinger of death.

Bradfield's oncologist in Burbank offered her more chemotherapy, but she declined it. She enrolled in an alternative herbal-therapy program and bought a vegetable juicer and planned a trip to Mexico. When her oncologist asked if he could send samples of her breast cancer to Slamon's lab at UCLA for a second opinion, she agreed reluctantly. A faraway doctor performing unfamiliar tests on her tumor sample, she knew, could not possibly affect her.

One afternoon in the summer of 1991, Bradfield received a phone call from Slamon. He introduced himself as a researcher who had been analyzing her slides. Slamon told Bradfield about *Her-2*. "His tone changed," she recalled. Her tumor, he said, had one of the highest levels of amplified *Her-2* that he had ever seen. Slamon told her that he was launching a trial of an antibody that bound *Her-2* and that she would be the ideal candidate for the new drug. Bradfield refused. "I was at the end of my road," she said, "and I had accepted what seemed inevitable." Slamon tried to reason with her for a while, but found her unbending. He thanked her for her consideration and rang off.

Early the next morning, though, Slamon was back on the telephone. He apologized for the intrusion, but her decision had troubled him all night. Of all the variants of *Her-2* amplification that he had encountered, hers had been truly extraordinary; Bradfield's tumor was chock-full of *Her-2*, almost hypnotically drunk on the oncogene. He begged her once again to join his trial.

"Survivors look back and see omens, messages they missed," Joan Didion wrote. For Bradfield, Slamon's second phone call was an omen that was not missed; something in that conversation pierced through a shield that she had drawn around herself. On a warm August morning in 1992, Bradfield visited Slamon in his clinic at UCLA. He met her in the hallway and led her to a room in the back. Under the microscope, he showed her the breast cancer that had been excised from her body, with its dark ringlets of *Her-2* labeled cells. On a whiteboard, he drew a step-by-step picture of an epic scientific journey. He began with the discovery of *neu*, its rediscovery in Ullrich's lab, the struggles to produce a drug, culminating in the antibody stitched together so carefully by Shepard and Carter. Bradfield considered the line that stretched from oncogene to drug. She agreed to join Slamon's trial.

It was an extraordinarily fortunate decision. In the four months between Slamon's phone call and the first infusion of Herceptin, Bradfield's tumor had erupted, spraying sixteen new masses into her lung.

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Fifteen women, including Bradfield, enrolled in Slamon's trial at UCLA in 1992. (The number would later be expanded to thirty-seven.) The drug was given for nine weeks, in combination with cisplatin, a standard chemotherapy agent used to kill breast cancer cells, both delivered intravenously. As a matter of convenience, Slamon planned to treat all the women on the same day and in the same room. The effect was theatrical; this was a stage occupied by a beleaguered set of actors. Some women had begged and finagled their way into Slamon's trial through friends and relatives; others, such as Bradfield, had been begged to join it. "All of us knew that we were living on borrowed time," Bradfield said, "and so we felt twice as alive and lived twice as fiercely." A Chinese woman in her fifties brought stash after stash of traditional herbs and salves that she swore had kept her alive thus far; she would take oncology's newest drug, Herceptin, only if she could also take its most ancient drugs with it. A frail, thin woman in her thirties, recently relapsed with breast cancer after a bone marrow transplant, glowered silently and intensely in a corner. Some treated their illness reverentially. Some were bewildered, some too embittered to care. A mother from Boston in her midfifties cracked raunchy jokes about her cancer. The daylong drill of infusions and blood tests was exhausting. In the late evening, after all the tests, the women went their own ways. Bradfield went home and prayed. Another woman soused herself with martinis.

The lump on Bradfield's neck—the only tumor in the group that could be physically touched, measured, and watched—became the compass for the trial. On the morning of the first intravenous infusion of the *Her-2* antibody, all the women came up to feel the lump, one by one, running their hands across Bradfield's collarbone. It was a peculiarly intimate ritual that would be repeated every week. Two weeks after the first dose of the antibody, when the group filed past Bradfield, touching the node again, the change was incontrovertible. Bradfield's tumor had softened and visibly

shrunk. "We began to believe that something was happening here," Bradfield recalled. "Suddenly, the weight of our good fortune hit us."

Not everyone was as fortunate as Bradfield. Exhausted and nauseous one evening, the young woman with relapsed metastatic cancer was unable to keep down the fluids needed to hydrate her body. She vomited through the night and then, too tired to keep drinking and too sick to understand the consequences, fell back into sleep. She died of kidney failure the next week.

Bradfield's extraordinary response continued. When the CT scans were repeated two months into the trial, the tumor in her neck had virtually disappeared, and the lung metastases had also diminished both in number and size. The responses in many of the thirteen other women were more ambiguous. At the three-month midpoint of the trial, when Slamon reviewed the data with Genentech and the external trial monitors, tough decisions clearly needed to be made. Tumors had remained unchanged in size in some women—not shrunk, but static: was this to be counted as a positive response? Some women with bone metastasis reported diminished bone pain, but pain could not objectively be judged. After a prolonged and bitter debate, the trial coordinators suggested dropping seven women from the study because their responses could not be quantified. One woman discontinued the drug herself. Only five of the original cohort, including Bradfield, continued the trial to its six-month end point. Embittered and disappointed, the others returned to their local oncologists, their hopes for a miracle drug again dashed.

Barbara Bradfield finished eighteen weeks of therapy in 1993. She survives today. A gray-haired woman with crystalline gray-blue eyes, she lives in the small town of Puyallup near Seattle, hikes in the nearby woods, and leads discussion groups for her church. She vividly remembers her days at the Los Angeles clinic—the half-lit room in the back where the nurses dosed the drugs, the strangely intimate touch of the other women feeling the node in her neck. And Slamon, of course. "Dennis is my hero," she said. "I refused his first phone call, but I have never, ever, refused him anything since that time." The animation and energy in her voice crackled across the phone line like an electrical current. She quizzed me about my research. I thanked her for her time, but she, in turn, apologized for the distraction. "Get back to work," she said, laughing. "There are people waiting for discoveries."

Drugs, Bodies, and Proof

Dying people don't have time or energy. We can't keep doing this one woman, one drug, one company at a time.

—Gracia Buffleben

It seemed as if we had entered a brave newworld of precisely targeted, less toxic, more effective combined therapies.

—*Breast Cancer Action Newsletter*, 2004

By the summer of 1993, news of Slamon's early-phase trial had spread like wildfire through the community of breast cancer patients, fanning out through official and unofficial channels. In waiting rooms, infusion centers, and oncologists' offices, patients spoke to other patients describing the occasional but unprecedented responses and remissions. Newsletters printed by breast cancer support groups whipped up a frenzy of hype and hope about Herceptin. Inevitably, a tinderbox of expectations was set to explode.

The issue was "compassionate use." *Her-2* positive breast cancer is one of the most fatal and rapidly progressive variants of the disease, and patients were willing to try any therapy that could produce a clinical benefit. Breast cancer activists pounded on Genentech's doors to urge the release of the drug to women with *Her-2* positive cancer who had failed other therapies. These patients, the activists argued, could not wait for the drug to undergo interminable testing; they wanted a potentially lifesaving medicine *now*. "True success happens," as one writer put it in 1995, "only when these new drugs actually enter bodies."

For Genentech, though, "true success" was defined by vastly different imperatives. Herceptin had not been approved by the FDA; it was a molecule in its infancy. Genentech wanted carefully executed early-phase trials—not just new drugs entering bodies, but carefully monitored drugs entering carefully monitored bodies in carefully monitored trials. For the next phase of Herceptin trials launched in 1993, Genentech wanted to stay small and focused. The number of women enrolled in these trials had been kept to an absolute minimum: twenty-seven patients at Sloan-Kettering, sixteen at UCSF, and thirty-nine at UCLA, a tiny cohort that the company intended to follow deeply and meticulously over time. "We do not provide . . . compassionate use programs," Curd curtly told a journalist. Most doctors involved in the early-phase trials agreed. "If you start making exceptions and deviating from your protocol," Debu Tripathy, one of the leaders of the UCSF trial, said, "then you get a lot of patients whose results are not going to help you understand whether a drug works or not. All you're doing is delaying . . . being able to get it out into the public."

Outside the cloistered laboratories of Genentech, the controversy ignited a firestorm. San Francisco, of course, was no stranger to this issue of compassionate use versus focused research. In the late 1980s, as AIDS had erupted in the city, filling up Paul Volberding's haunted Ward 5B with scores of patients, gay men had coalesced into groups such as ACT UP to demand speedier access to drugs, in part through compassionate use programs. Breast cancer activists saw a grim reflection of their own struggle in these early battles. As one newsletter put it, "Why do women dying of breast cancer have such trouble getting experimental drugs that could extend their lives? For years, AIDS activists have been negotiating with drug companies and the FDA to obtain new HIV drugs while the therapies were still in clinical trials. Surely women with metastatic breast cancer for whom standard treatments have failed should know about, and have access to, compassionate use programs for experimental drugs."

Or, as another writer put it, "Scientific uncertainty is no excuse for inaction. . . . We cannot wait for 'proof.'"

Marti Nelson, for one, certainly could not afford to wait for proof. An outgoing, dark-haired gynecologist in California, Nelson had discovered a malignant mass in her breast in 1987, when she was just thirty-three. She had had a mastectomy and multiple cycles of chemo, then returned to practicing medicine in a San Francisco clinic. The tumor had disappeared. The scars had healed. Nelson thought that she might have been cured.

In 1993, six years after her initial surgery, Nelson noticed that the scar in her breast had begun to harden. She waved it away. But the hardened line of tissue outlining her breast was relapsed breast cancer, worming its way insidiously along the scar lines and coalescing into small, matted masses in her chest. Nelson, who compulsively followed the clinical literature on breast cancer, had heard of *Her-2*. Reasoning presciently that her tumor might be *Her-2* positive, she tried to have her own specimen tested for the gene.

But Nelson soon found herself inhabiting a Kafkaesque nightmare. Her HMO insisted that because Herceptin was in investigational trials, testing the tumor for *Her-2* was useless. Genentech insisted that without *Her-2* status confirmed, giving her access to Herceptin was untenable.

In the summer of 1993, with Nelson's cancer advancing daily and spewing out metastases into her lungs and bone marrow, the struggle took an urgent, political turn. Nelson contacted the Breast Cancer Action project, a local San Francisco organization connected with ACT UP, to help her get someone to test her tumor and obtain Herceptin for compassionate use. BCA, working through its activist networks, asked several laboratories in and around San Francisco to test Nelson's tumor. In October 1994, the tumor was finally tested for *Her-2* expression at UCSF. It was strikingly *Her-2* positive. She was an ideal candidate for the drug. But the news came too late. Nine days later, still awaiting Herceptin approval from Genentech, Marti Nelson drifted into a coma and died. She was forty-one years old.

For BCA activists, Nelson's death was a watershed event. Livid and desperate, a group of women from the BCA stormed through the Genentech campus on December 5, 1994, to hold a fifteen-car "funeral procession" for Nelson with placards showing Nelson in her chemo turban before her death. The women shouted and honked their horns and drove their cars through the manicured lawns. Gracia Buffleben, a nurse with breast cancer and one of the most outspoken leaders of the BCA, parked her car outside one of the main buildings and handcuffed herself to the steering wheel. A furious researcher stumbled out of one of the lab buildings and shouted, "I'm a scientist working on the AIDS cure. Why are you here? You are making too much noise." It was a statement that epitomized the vast and growing rift between scientists and patients.

Marti Nelson's "funeral" woke Genentech up to a new reality. Outrage, rising to a crescendo, threatened to spiral into a public relations disaster. Genentech had a narrow choice: unable to silence the activists, it was forced to join them. Even Curd admitted, if somewhat begrudgingly, that the

* Ullrich actually found the human homolog of the mouse *neu* gene. Two other groups independently discovered the same gene.
* The drug is also known by its pharmacological name Trastuzumab; the "ab" suffix is used to denote the fact that this is an *anti*body.

BCA was "a tough group [and] their activism is not misguided."

In 1995, a small delegation of Genentech scientists and executives thus flew to Washington to meet Frances Visco, the chair of the National Breast Cancer Coalition (NBCC), a powerful national coalition of cancer activists, hoping to use the NBCC as a neutral intermediary between the company and the local breast cancer activists in San Francisco. Pragmatic, charismatic, and savvy, Visco, a former attorney, had spent nearly a decade immersed in the turbulent politics of breast cancer. Visco had a proposal for Genentech, but her terms were inflexible: Genentech had to provide an expanded access program for Herceptin. This program would allow oncologists to treat patients outside clinical trials. In return, the National Breast Cancer Coalition would act as a go-between for Genentech and its embittered and alienated community of cancer patients. Visco offered to join the planning committee of the phase III trials of Herceptin, and to help recruit patients for the trial using the NBCC's extensive network. For Genentech, this was a long-overdue education. Rather than running trials *on* breast cancer patients, the company learned to run trials *with* breast cancer patients. (Genentech would eventually outsource the compassionate-access program to a lottery system run by an independent agency. Women applied to the lottery and "won" the right to be treated, thus removing the company from any ethically difficult decision-making.)

It was an uneasy triangle of forces—academic researchers, the pharmaceutical industry, and patient advocates—united by a deadly disease. Genentech's next phase of trials involved large-scale, randomized studies on thousands of women with metastatic *Her-2* positive cancer, comparing Herceptin treatment against placebo treatment. Visco sent out newsletters from the NBCC to patients using the coalition's enormous Listservs. Kay Dickersin, a coalition member and an epidemiologist, joined the Data Safety and Monitoring board of the trial, underscoring the new partnership between Genentech and the NBCC, between academic medicine and activism. And an all-star team of breast oncologists was assembled to run the trial: Larry Norton from Sloan-Kettering, Karen Antman from Columbia, Daniel Hayes from Harvard, and, of course, Slamon from UCLA.

In 1995, empowered by the very forces that it had resisted for so long, Genentech launched three independent phase III trials to test Herceptin. The most pivotal of the three was a trial labeled 648, randomizing women newly diagnosed with metastatic breast cancer to standard chemotherapy alone versus chemotherapy with Herceptin added. Trial 648 was launched in 150 breast cancer clinics around the world. The trial would enroll 469 women and cost Genentech $15 million to run.

In May 1998, eighteen thousand cancer specialists flocked to Los Angeles to attend the thirty-fourth meeting of the American Society of Clinical Oncology, where Genentech would unveil the data from the Herceptin trials, including trial 648. On Sunday, May 17, the third day of the meeting, an expectant audience of thousands piled into the stuffy central amphitheater at the convention center to attend a special session dedicated to *Her-2/neu* in breast cancer. Slamon was slated to be the last speaker. A coil of nervous energy, with the characteristic twitch in his mustache, he stood up at the podium.

Clinical presentations at ASCO are typically sanitized and polished, with blue-and-white PowerPoint slides depicting the bottom-line message using survival curves and statistical analyses. But Slamon began—relishing this pivotal moment—not with numbers and statistics, but with forty-nine smudgy bands on a gel run by one of his undergraduate students in 1987. Oncologists slowed down their scribbling. Reporters squinted their eyes to see the bands on the gel.

That gel, he reminded his audience, had identified a gene with no pedigree—no history, no function, no mechanism. It was nothing more than an isolated, amplified signal in a fraction of breast cancer cases. Slamon had gambled the most important years of his scientific life on those bands. Others had joined the gamble: Ullrich, Shepard, Carter, Botstein and Levinson, Visco and the activists, pharma executives and clinicians and Genentech. The trial results to be announced that afternoon represented the result of that gamble. But Slamon wouldn't—he couldn't—rush to the end point of the journey without reminding everyone in the room of the fitful, unsanitized history of the drug.

Slamon paused for a theatrical moment before revealing the results of the trial. In the pivotal 648 study, 469 women had received standard cytotoxic chemotherapy (either Adriamycin and Cytoxan in combination, or Taxol) and were randomized to receive either Herceptin or a placebo. In every conceivable index of response, women treated with the addition of Herceptin had shown a clear and measurable benefit. Response rates to standard chemotherapy had moved up 150 percent. Tumors had shrunk in half the women treated with Herceptin compared to a third of women in the control arm. The progression of breast cancer had been delayed from four to seven and a half months. In patients with tumors heavily resistant to the standard Adriamycin and Cytoxan regimen, the benefit had been the most marked: the combination of Herceptin and Taxol had increased response rates to nearly 50 percent—a rate unheard of in recent clinical experience. The survival rate would also follow this trend. Women treated with Herceptin lived four or five months longer than women in the control group.

At face value, some of these gains might have seemed small in absolute terms—life extended by only four months. But the women enrolled in these initial trials were patients with late-stage, metastatic cancers, often heavily pretreated with standard chemotherapies and refractory to all drugs—women carrying the worst and most aggressive variants of breast cancer. (This pattern is typical: in cancer medicine, trials often begin with the most advanced and refractory cases, where even small benefits of a drug might outweigh risks.) The true measure of Herceptin's efficacy would lie in the treatment of treatment-naive patients—women diagnosed with early-stage breast cancer who had never received any prior treatment.

In 2003, two enormous multinational studies were launched to test Herceptin in early-stage breast cancer in treatment-naive patients. In one of the studies, Herceptin treatment increased breast cancer survival at four years by a striking 18 percent over the placebo group. The second study, although stopped earlier, showed a similar magnitude of benefit. When the trials were statistically combined, overall survival in women treated with Herceptin was increased by 33 percent—a magnitude unprecedented in the history of chemotherapy for *Her-2* positive cancer. "The results," one oncologist wrote, were "simply stunning . . . not evolutionary, but revolutionary. The rational development of molecularly targeted therapies points the direction toward continued improvement in breast cancer therapy. Other targets and other agents will follow."

On the evening of May 17, 1998, after Slamon had announced the results of the 648 study to a stunned audience at the ASCO meeting, Genentech threw an enormous cocktail party at the Hollywood Terrace, an open-air restaurant nestled in the hills of Los Angeles. Wine flowed freely, and the conversation was light and breezy. Just a few days earlier, the FDA had reviewed the data from the three Herceptin trials, including Slamon's study, and was on the verge of "fast-tracking" the approval of Herceptin. It was a poignant posthumous victory for Marti Nelson: the drug that would likely have saved her life would become accessible to all breast cancer patients—no longer reserved for clinical trials or compassionate use alone.

"The company," Robert Bazell, the journalist, wrote, "invited all the investigators, as well as most of Genentech's *Her-2* team. The activists came too: Marilyn McGregor and Bob Erwin [Marti Nelson's husband] from San Francisco and Fran Visco from the National Breast Cancer Coalition."

The evening was balmy, clear, and spectacular. "The warm orange glow of the setting sun over the San Fernando Valley set the tone of the festivities. Everyone at the party would celebrate an enormous success. Women's lives would be saved and a huge fortune would be made."

Only one person was conspicuously missing from the party—Dennis Slamon. Having spent the afternoon planning the next phase of Herceptin trials with breast oncologists at ASCO, Slamon had jumped into his run-down Nissan and driven home.

A Four-Minute Mile

The nontoxic curative compound remains undiscovered but not undreamt.

—James F. Holland

Why, it is asked, does the supply of newmiracle drugs lag so far behind, while biology continues to move from strength to strength . . .? There is still the conspicuous asymmetry between molecular biology and, say, the therapy of lung cancer.

—Lewis Thomas,
The Lives of a Cell, 1978

In the summer of 1990, as Herceptin entered its earliest trials, another oncogene-targeted drug began its long journey toward the clinic. More than any other medicine in the history of cancer, more even than Herceptin, the development of this drug—from cancer to oncogene to a targeted therapy and to successive human trials—would signal the arrival of a new era in cancer medicine. Yet to arrive at this new era, cancer biologists would again need to circle back to old observations—to the peculiar illness that John Bennett had called a "suppuration of blood," that Virchow had reclassified as *weisses Blut* in 1847, and that later researchers had again reclassified as chronic myeloid leukemia or CML.

For more than a century, Virchow's *weisses Blut* had lived on the peripheries of oncology. In 1973, CML was suddenly thrust center stage. Examining CML cells, Janet Rowley identified a unique chromosomal aberration that existed in all the leukemia cells. This abnormality, the so-called Philadelphia chromosome, was the result of a translocation in which the "head" of chromosome twenty-two and the "tail" of chromosome nine had been fused to create a novel gene. Rowley's work suggested that CML cells possess a distinct and unique genetic abnormality—possibly the first human oncogene.

Rowley's observation launched a prolonged hunt for the mysterious chimeric gene produced by the 9:22 fusion. The identity of the gene emerged piece by piece over a decade. In 1982, a team of Dutch researchers in Amsterdam isolated the gene on chromosome nine. They called it *abl*.[1] In 1984, working with American collaborators in Maryland, the same team isolated *abl*'s partner on chromosome twenty-two—a gene called *Bcr*. The oncogene created by the fusion of these two genes in CML cells was named *Bcr-abl*. In 1987, David Baltimore's laboratory in Boston "engineered" a mouse containing the activated *Bcr-abl* oncogene in its blood cells. The mouse developed the fatal spleen-choking leukemia that Bennett had seen in the Scottish slate-layer and Virchow in the German cook more than a century earlier—proving that *Bcr-abl* drove the pathological proliferation of CML cells.

As with the study of any oncogene, the field now turned from structure to function: what did *Bcr-abl* do to cause leukemia? When Baltimore's lab and Owen Witte's lab investigated the function of the aberrant *Bcr-abl* oncogene, they found that, like *src*, it was yet another kinase—a protein that tagged other proteins with a phosphate group and thus unleashed a cascade of signals in a cell. In normal cells, the *Bcr* and *abl* genes existed separately; both were tightly regulated during cell division. In CML cells, the translocation created a new chimera—*Bcr-abl*, a hyperactive, overexuberant kinase that activated a pathway that forced cells to divide incessantly.

In the mid-1980s, with little knowledge about the emerging molecular genetics of CML, a team of chemists at Ciba-Geigy, a pharmaceutical company in Basel, Switzerland, was trying to develop drugs that might inhibit kinases. The human genome has about five hundred kinases (of which, about ninety belong to the subclass that contains *src* and *Bcr-abl*). Every kinase attaches phosphate tags to a unique set of proteins in the cell. Kinases thus act as molecular master-switches in cells—turning "on" some pathways and turning "off" others—thus providing the cell a coordinated set of internal signals to grow, shrink, move, stop, or die. Recognizing the pivotal role of kinases in cellular physiology, the Ciba-Geigy team hoped to discover drugs that could activate or inhibit kinases selectively in cells, thus manipulating the cell's master-switches. The team was led by a tall, reserved, acerbic Swiss physician-biochemist, Alex Matter. In 1986, Matter was joined in his hunt for selective kinase inhibitors by Nick Lydon, a biochemist from Leeds, England.

Pharmaceutical chemists often think of molecules in terms of faces and surfaces. Their world is topological; they imagine touching molecules with the tactile hypersensitivity of the blind. If the surface of a protein is bland and featureless, then that protein is typically "undruggable"; flat, poker-faced topologies make for poor targets for drugs. But if a protein's surface is marked with deep crevices and pockets, then that protein tends to make an attractive target for other molecules to bind—and is thereby a possible "druggable" target.

Kinases, fortuitously, possess at least one such deep druggable pocket. In 1976, a team of Japanese researchers looking for poisons in sea bacteria had accidentally discovered a molecule called staurosporine, a large molecule shaped like a lopsided Maltese cross that bound to a pocket present in most kinases. Staurosporine inhibited dozens of kinases. It was an exquisite poison, but a terrible drug—possessing virtually no ability to discriminate between any kinase, active or inactive, good or bad, in most cells.

The existence of staurosporine inspired Matter. If sea bacteria could synthesize a drug to block kinases nonspecifically, then surely a team of chemists could make a drug to block only certain kinases in cells. In 1986, Matter and Lydon found a critical lead. Having tested millions of potential molecules, they discovered a skeletal chemical that, like staurosporine, could also lodge itself into a kinase protein's cleft and inhibit its function. Unlike staurosporine, though, this skeletal structure was a much simpler chemical. Matter and Lydon could make dozens of variants of this chemical to determine if some might bind better to certain kinases. It was a self-conscious emulation of Paul Ehrlich, who had, in the 1890s, gradually coaxed specificity from his aniline dyes and thus created a universe of novel medicines. History repeats itself, but chemistry, Matter and Lydon knew, repeats itself more insistently.

It was a painstaking, iterative game—chemistry by trial and error. Jürg Zimmermann, a talented chemist on Matter's team, created thousands of

variants of the parent molecule and handed them off to a cell biologist, Elisabeth Buchdunger. Buchdunger tested these new molecules on cells, weeding out those that were insoluble or toxic, then bounced them back to Zimmermann for resynthesis, resetting the relay race toward more and more specific and nontoxic chemicals. "[It was] what a locksmith does when he has to make a key fit," Zimmermann said. "You change the shape of the key and test it. Does it fit? If not, you change it again."

By the early nineties, this fitting and refitting had created dozens of new molecules that were structurally related to Matter's original kinase inhibitor. When Lydon tested this panel of inhibitors on various kinases found in cells, he discovered that these molecules possessed specificity: one molecule might inhibit *src* and spare every other kinase, while another might block *abl* and spare *src.* What Matter and Lydon now needed was a disease in which to apply this collection of chemicals—a form of cancer driven by a locked, overexuberant kinase that they could kill using a specific kinase inhibitor.

In the late 1980s, Nick Lydon traveled to the Dana-Farber Cancer Institute in Boston to investigate whether one of the kinase inhibitors synthesized in Basel might inhibit the growth of a particular form of cancer. Lydon met Brian Druker, a young faculty member at the institute fresh from his oncology fellowship and about to launch an independent laboratory in Boston. Druker was particularly interested in chronic myelogenous leukemia —the cancer driven by the *Bcr-abl* kinase.

Druker heard of Lydon's collection of kinase-specific inhibitors, and he was quick to make the logical leap. "I was drawn to oncology as a medical student because I had read Farber's original paper on aminopterin and it had had a deep influence on me," he recalled. "Farber's generation had tried to target cancer cells empirically, but had failed because the mechanistic understanding of cancer was so poor. Farber had had the right idea, but at the wrong time."

Druker had the right idea at the right time. Once again, as with Slamon and Ullrich, two halves of a puzzle came together. Druker had a cohort of CML patients afflicted by a tumor driven by a specific hyperactive kinase. Lydon and Matter had synthesized an entire collection of kinase inhibitors now stocked in Ciba-Geigy's freezer in Basel. Somewhere in that Ciba collection, Druker reasoned, was lurking his fantasy drug—a chemical kinase inhibitor with specific affinity for *Bcr-abl.* Druker proposed an ambitious collaboration between Ciba-Geigy and the Dana-Farber Cancer Institute to test the kinase inhibitors in patients. But the agreement fell apart; the legal teams in Basel and Boston could not find agreeable terms. Drugs could recognize and bind kinases specifically, but scientists and lawyers could not partner with each other to bring these drugs to patients. The project, having generated an interminable trail of legal memos, was quietly tabled.

But Druker was persistent. In 1993, he left Boston to start his own laboratory at the Oregon Health and Science University (OHSU) in Portland. Unyoked, at last, from the institution that had forestalled his collaboration, he immediately called Lydon to reestablish a connection. Lydon informed him that the Ciba-Geigy team had synthesized an even larger collection of inhibitors and had found a molecule that might bind *Bcr-abl* with high specificity and selectivity. The molecule was called CGP57148. Summoning all the nonchalance that he could muster—having learned his lessons in Boston—Druker walked over to the legal department at OHSU and, revealing little about the potential of the chemicals, watched as the lawyers absentmindedly signed on the dotted line. "Everyone just humored me," he recalled. "No one thought even faintly that this drug might work." In two weeks, he received a package from Basel with a small collection of kinase inhibitors to test in his lab.

The clinical world of CML was, meanwhile, reeling from disappointment to disappointment. In October 1992, just a few months before CGP57148 crossed the Atlantic from Lydon's Basel lab into Druker's hands in Oregon, a fleet of leukemia experts descended on the historic town of Bologna in Italy for an international conference on CML. The location was resplendent and evocative—Vesalius had once lectured and taught in these quadrangles and amphitheaters, dismantling Galen's theory of cancer piece by piece. But the news at the meeting was uninspiring. The principal treatment for CML in 1993 was allogeneic bone marrow transplantation, the protocol pioneered in Seattle by Donnall Thomas in the sixties. Allo-transplantation, in which a foreign bone marrow was transplanted into a patient's body, could increase the survival of CML patients, but the gains were often so modest that massive trials were needed to detect them. At Bologna, even transplanters glumly acknowledged the meager benefits: "Although freedom from leukemia could be obtained only with BMT," one study concluded, "a beneficial effect of BMT on overall survival could be detected only in a patients' subset, and . . . many hundreds of cases and a decade could be necessary to evaluate the effect on survival."

Like most leukemia experts, Druker was all too familiar with this dismal literature. "Cancer is complicated, everyone kept telling me patronizingly —as if I had suggested that it was not complicated." The growing dogma, he knew, was that CML was perhaps intrinsically a chemotherapy-resistant disease. Even if the leukemia was initiated by that single translocation of the *Bcr-abl* gene, by the time the disease was identified in full bloom in real patients, it had accumulated a host of additional mutations, creating a genetic tornado so chaotic that even transplantation, the chemotherapist's bluntest weapon, was of no consequence. The inciting *Bcr-abl* kinase had likely long been overwhelmed by more powerful driver mutations. Using a kinase inhibitor to try to control the disease, Druker feared, would be like blowing hard on a matchstick long after it had ignited a forest fire.

In the summer of 1993, when Lydon's drug arrived in Druker's hands, he added it to CML cells in a petri dish, hoping, at best, for a small effect. But the cell lines responded briskly. Overnight, the drug-treated CML cells died, and the tissue-culture flasks filled up with floating husks of involuted leukemia cells. Druker was amazed. He implanted CML cells into mice to form real, living tumors and treated the mice with the drug. As with the first experiment, the tumors regressed in days. The response suggested specificity as well: normal mouse blood cells were left untouched. Druker performed a third experiment. He drew out samples of bone marrow from a few human patients with CML and applied CGP57148 to the cells in a petri dish. The leukemia cells in the marrow died immediately. The only cells remaining in the dish were normal blood cells. He had cured leukemia in the dish.

Druker described the findings in the journal *Nature Medicine.* It was a punchy, compact study—just five clean, well-built experiments—driving relentlessly toward a simple conclusion: "This compound may be useful in the treatment of *Bcr-abl* positive leukemias." Druker was the first author and Lydon the senior author, with Buchdunger and Zimmermann as key contributors.

Druker expected Ciba-Geigy to be ecstatic about these results. This, after all, was the ultimate dream child of oncology—a drug with exquisite specificity for an oncogene in a cancer cell. But in Basel, Ciba-Geigy was in internal disarray. The company had fused with its archrival across the river, the pharma giant Sandoz, into a pharmaceutical behemoth called Novartis. For Novartis, it was the exquisite specificity of CGP57148 that was precisely its fatal undoing. Developing CGP57148 into a clinical drug for human use would involve further testing—animal studies and clinical

trials that would cost $100 to $200 million. CML afflicts a few thousand patients every year in America. The prospect of spending millions on a molecule to benefit thousands gave Novartis cold feet.

Druker now found himself inhabiting an inverted world in which an academic researcher had to beg a pharmaceutical company to push its own products into clinical trials. Novartis had a plethora of predictable excuses: "The drug . . . would never work, would be too toxic, would never make any money." Between 1995 and 1997 Druker flew back and forth between Basel and Portland trying to convince Novartis to continue the clinical development of its drug. "Either get [the drug] into clinical trials or license it to me. Make a decision," Druker insisted. If Novartis would not make the drug, Druker thought he could have another chemist take it on. "In the worst case," he recalled, "I thought I would make it in my own basement."

Planning ahead, he assembled a team of other physicians to run a potential clinical trial of the drug on CML patients: Charles Sawyers from UCLA, Moshe Talpaz, a hematologist from Houston, and John Goldman from the Hammersmith Hospital in London, all highly regarded authorities on CML. Druker said, "I had patients in my clinic with CML with no effective treatment options remaining. Every day, I would come home from the clinic and promise to push Novartis a little."

In early 1998, Novartis finally relented. It would synthesize and release a few grams of CGP57148, just about enough to run a trial on about a hundred patients. Druker would have a shot—but only one shot. To Novartis, CGP57148, the product of its most ambitious drug-discovery program to date, was already a failure.

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I first heard of Druker's drug in the fall of 2002. I was a medical resident triaging patients in the emergency room at Mass General when an intern called me about a middle-aged man with a history of CML who had come in with a rash. I heard the story almost instinctively, drawing quick conclusions. The patient, I surmised, had been transplanted with foreign bone marrow, and the rash was the first blush of a cataclysm to come. The immune cells in the foreign marrow were attacking his own body—graft-versus-host disease. His prognosis was grim. He would need steroids, immunosuppressives, and immediate admission to the transplant floor.

But I was wrong. Glancing at the chart in the red folder, I saw no mention of a transplant. Under the stark neon light of the examining room when he held out his hand to be examined, the rash was just a few scattered, harmless-looking papules—nothing like the dusky, mottled haze that is often the harbinger of a graft reaction. Searching for an alternative explanation, I quickly ran my eye through his list of medicines. Only one drug was listed: Gleevec, the new name for Druker's drug, CGP57148.

The rash was a minor side effect of the drug. The major effect of the drug, though, was less visible but far more dramatic. Smeared under the microscope in the pathology lab on the second floor, his blood cells looked extraordinarily ordinary—"normal red cells, normal platelets, normal white blood cells," I whispered under my breath as I ran my eyes slowly over the three lineages. It was hard to reconcile this field of blood cells in front of my eyes with the diagnosis; not a single leukemic blast was to be seen. If this man had CML, he was in a remission so deep that the disease had virtually vanished from sight.

By the winter of 1998, Druker, Sawyers, and Talpaz had witnessed dozens of such remissions. Druker's first patient to be treated with Gleevec was a sixty-year-old retired train conductor from the Oregon coast. The patient had read about the drug in an article about Druker in a local newspaper. He had called Druker immediately and offered to be a "guinea pig." Druker gave him a small dose of the drug, then stood by his bedside for the rest of the afternoon, nervously awaiting any signs of toxicity. By the end of the day there were no adverse effects; the man was still alive. "It was the first time that the molecule had entered a human body, and it could easily have created havoc, but it didn't," Druker recalled. "The sense of relief was incredible."

Druker edged into higher and higher doses—25, 50, 85, and 140 mg. His cohort of patients grew as well. As the dose was escalated in patients, Gleevec's effect became even more evident. One patient, a Portland woman, had come to his clinic with a blood count that had risen to nearly thirtyfold the normal number; her blood vessels were engorged with leukemia, her spleen virtually heaving with leukemic cells. After a few doses of the drug, Druker found her counts dropping precipitously, then normalizing within one week. Other patients, treated by Sawyers at UCLA and Talpaz in Houston, responded similarly, with blood counts normalizing within a few weeks.

News of the drug spread quickly. The development of Gleevec paralleled the birth of the patient chat room on the Internet; by 1999, patients were exchanging information about trials online. In many cases, it was patients who informed their doctors about Druker's drug and then, finding their own doctors poorly informed and incredulous, flew to Oregon or Los Angeles to enroll themselves in the Gleevec trial.

Of the fifty-four patients who received high doses of the drug in the initial phase I study, fifty-three showed a complete response within days of starting Gleevec. Patients continued the medicine for weeks, then months, and the malignant cells did not visibly return in the bone marrow. Left untreated, chronic myeloid leukemia is only "chronic" by the standards of leukemia: as the disease accelerates, the symptoms run on a tighter, faster arc and most patients live only three to five years. Patients on Gleevec experienced a palpable deceleration of their disease. The balance between normal and malignant cells was restored. It was an *unsuppuration* of blood.

By June 1999, with many of the original patients still in deep remissions, Gleevec was evidently a success. This success continues; Gleevec has become the standard of care for patients with CML. Oncologists now use the phrases "pre-Gleevec era" and "post-Gleevec era" when discussing this once-fatal disease. Hagop Kantarjian, the leukemia physician at the MD Anderson Cancer Center in Texas, recently summarized the impact of the drug on CML: "Before the year 2000, when we saw patients with chronic myeloid leukemia, we told them that they had a very bad disease, that their course was fatal, their prognosis was poor with a median survival of maybe three to six years, frontline therapy was allogeneic transplant . . . and there was no second-line treatment. . . . Today when I see a patient with CML, I tell them that the disease is an indolent leukemia with an excellent prognosis, that they will usually live their functional life span provided they take an oral medicine, Gleevec, for the rest of their lives."

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CML, as Novartis noted, is hardly a scourge on public health, but cancer is a disease of symbols. Seminal ideas begin in the far peripheries of cancer biology, then ricochet back into more common forms of the disease. And leukemia, of all forms of cancer, is often the seed of new paradigms. This story began with leukemia in Sidney Farber's clinic in 1948, and it must return to leukemia. If cancer is in our blood, as Varmus reminded us, then it seems only appropriate that we keep returning, in ever-widening circles, to cancer *of* the blood.

The success of Druker's drug left a deep impression on the field of oncology. "When I was a youngster in Illinois in the 1950s," Bruce Chabner wrote in an editorial, "the world of sport was shocked by the feat of Roger Bannister. . . . On May 6, 1954, he broke the four-minute barrier in the mile. While improving upon the world record by only a few seconds, he changed the complexion of distance running in a single afternoon. . . . Track records fell like ripe apples in the late 50s and 60s. Will the same happen in the field of cancer treatment?"

Chabner's analogy was carefully chosen. Bannister's mile remains a touchstone in the history of athletics not because Bannister set an unbreachable record—currently, the fastest mile is a good fifteen seconds under Bannister's. For generations, four minutes was thought to

represent an intrinsic physiological limit, as if muscles could inherently not be made to move any faster or lungs breathe any deeper. What Bannister proved was that such notions about intrinsic boundaries are mythical. What he broke permanently was not a limit, but the idea of limits.

So it was with Gleevec. "It proves a principle. It justifies an approach," Chabner continued. "It demonstrates that highly specific, non-toxic therapy is possible." Gleevec opened a new door for cancer therapeutics. The rational synthesis of a molecule to kill cancer cells—a drug designed to specifically inactivate an oncogene—validated Ehrlich's fantasy of "specific affinity." Targeted molecular therapy for cancer was possible; one only needed to hunt for it by studying the deep biology of cancer cells.

A final note: I said CML was a "rare" disease, and that was true in the era before Gleevec. The incidence of CML remains unchanged from the past: only a few thousand patients are diagnosed with this form of leukemia every year. But the *prevalence* of CML—the number of patients presently alive with the disease—has dramatically changed with the introduction of Gleevec. As of 2009, CML patients treated with Gleevec survive an average of thirty years after their diagnosis. Based on that survival figure, Hagop Kantarjian estimates that within the next decade, 250,000 people will be living with CML in America, all of them on targeted therapy. Druker's drug will alter the national physiognomy of cancer, converting a once-rare disease into a relatively common one. (Druker jokes that he has achieved the perfect inversion of the goals of cancer medicine: his drug has increased the prevalence of cancer in the world.) Given that most of our social networks typically extend to about one thousand individuals, each of us, on average, will know one person with this leukemia who is being kept alive by a targeted anticancer drug.

The Red Queen's Race

"Well, in our *country," said Alice, still panting a little, "you'd generally get to somewhere else—if you ran very fast for a long time, as we've been doing."*

"A slow sort of country!" said the Queen. "Now, here, *you see, it takes all the running* you *can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"*

—Lewis Carroll,
Through the Looking-Glass

In August 2000, Jerry Mayfield, a forty-one-year-old Louisiana policeman diagnosed with CML, began treatment with Gleevec. Mayfield's cancer responded briskly at first. The fraction of leukemic cells in his bone marrow dropped over six months. His blood count normalized and his symptoms improved; he felt rejuvenated—"like a new man [on] a wonderful drug." But the response was short-lived. In the winter of 2003, Mayfield's CML stopped responding. Moshe Talpaz, the oncologist treating Mayfield in Houston, increased the dose of Gleevec, then increased it again, hoping to outpace the leukemia. But by October of that year, there was no response. Leukemia cells had fully recolonized his bone marrow and blood and invaded his spleen. Mayfield's cancer had become resistant to targeted therapy.

Now in the fifth year of their Gleevec trial, Talpaz and Sawyers had seen several cases like Mayfield's. They were rare. The vast proportion of CML patients maintained deep, striking remissions on the drug, requiring no other therapy. But occasionally, a patient's leukemia stopped responding to Gleevec, and Gleevec-resistant leukemia cells grew back. Sawyers, having just entered the world of targeted therapy, swiftly entered a molecular world beyond targeted therapy: how might a cancer cell become resistant to a drug that directly inhibits its driving oncogene?

In the era of nontargeted drugs, cancer cells were known to become drug-resistant through a variety of ingenious mechanisms. Some cells acquire mutations that activate molecular pumps. In normal cells, these pumps extrude natural poisons and waste products from a cell's interior. In cancer cells, these activated pumps push chemotherapy drugs out from the interior of the cell. Spared by chemotherapy, the drug-resistant cells outgrow other cancer cells. Other cancer cells activate proteins that destroy or neutralize drugs. Yet other cancers escape drugs by migrating into reservoirs of the body where drugs cannot penetrate—as in lymphoblastic leukemia relapsing in the brain.

CML cells, Sawyers discovered, become Gleevec-resistant through an even wilier mechanism: the cells acquire mutations that specifically alter the structure of *Bcr-abl*, creating a protein still able to drive the growth of the leukemia but no longer capable of binding to the drug. Normally, Gleevec slips into a narrow, wedgelike cleft in the center of *Bcr-abl*—like "an arrow pierced through the center of the protein's heart," as one chemist described it. Gleevec-resistant mutations in *Bcr-abl* change the molecular "heart" of the *Bcr-abl* protein so that the drug can no longer access the critical cleft in the protein, thus rendering the drug ineffective. In Mayfield's case, a single alteration in the *Bcr-abl* protein had rendered it fully resistant to Gleevec, resulting in the sudden relapse of leukemia. To escape targeted therapy, cancer had changed the target.

To Sawyers, these observations suggested that overcoming Gleevec resistance with a second-generation drug would require a very different kind of attack. Increasing the dose of Gleevec, or inventing closely related molecular variants of the drug, would be useless. Since the mutations changed the structure of *Bcr-abl*, a second-generation drug would need to block the protein through an independent mechanism, perhaps by gaining another entry point into its crucial central cleft.

In 2005, working with chemists at Bristol-Myers Squibb, Sawyers's team generated another kinase inhibitor to target Gleevec-resistant *Bcr-abl*. As predicted, this new drug, dasatinib, was not a simple structural analogue of Gleevec; it accessed *Bcr-abl*'s "heart" through a separate molecular crevice on the protein's surface. When Sawyers and Talpaz tested dasatinib on Gleevec-resistant patients, the effect was remarkable: the leukemia cells involuted again. Mayfield's leukemia, fully resistant to Gleevec, was forced back into remission in 2005. His blood count normalized again. Leukemia cells dissipated out of his bone marrow gradually. In 2009, Mayfield still remains in remission, now on dasatinib.

Even targeted therapy, then, was a cat-and-mouse game. One could direct endless arrows at the Achilles' heel of cancer, but the disease might simply shift its foot, switching one vulnerability for another. We were locked in a perpetual battle with a volatile combatant. When CML cells kicked Gleevec away, only a different molecular variant would drive them down, and when they outgrew that drug, then we would need the next-generation drug. If the vigilance was dropped, even for a moment, then the weight of the battle would shift. In Lewis Carroll's *Through the Looking-Glass*, the Red Queen tells Alice that the world keeps shifting so quickly under her feet that she has to keep running just to keep her position. This is our predicament with cancer: we are forced to keep running merely to keep still.

In the decade since the discovery of Gleevec, twenty-four novel drugs have been listed by the National Cancer Institute as cancer-targeted therapies. Dozens more are in development. The twenty-four drugs have been shown to be effective against lung, breast, colon, and prostate cancers, sarcomas, lymphomas, and leukemias. Some, such as dasatinib, directly inactivate oncogenes. Others target oncogene-activated pathways—the "hallmarks of cancer" codified by Weinberg. The drug Avastin interrupts tumor angiogenesis by attacking the capacity of cancer cells to incite blood-vessel growth. Bortezomib, or Velcade, blocks an internal waste-dispensing mechanism for proteins that is particularly hyperactive in cancer cells.

More than nearly any other form of cancer, multiple myeloma, a cancer of immune-system cells, epitomizes the impact of these newly discovered targeted therapies. In the 1980s, multiple myeloma was treated by high doses of standard chemotherapy—old, hard-bitten drugs that typically ended up decimating patients about as quickly as they decimated the cancer. Over a decade, three novel targeted therapies have emerged for myeloma—Velcade, thalidomide, and Revlimid—all of which interrupt activated pathways in myeloma cells. Treatment of multiple myeloma today involves mixing and matching these drugs with standard chemotherapies, switching drugs when the tumor relapses, and switching again when the tumor relapses again. No single drug or treatment cures myeloma outright; myeloma is still a fatal disease. But as with CML, the cat-and-mouse game with cancer has extended the survival of myeloma patients—strikingly in some cases. In 1971, about half the patients diagnosed with multiple myeloma died within twenty-four months of diagnosis; the other half died by the tenth year. In 2008, about half of all myeloma patients treated with

Abl, too, was first discovered in a virus, and later found to be present in human cells—again recapitulating the story of *ras* and *src*. Once more, a retrovirus had "pirated" a human cancer gene and turned into a cancer-causing virus.

* Gleevec, the commercial name, is used here because it is more familiar to patients. The scientific name for CGP57148 is imatinib. The drug was also called STI571.

the shifting armamentarium of new drugs will still be alive at five years. If the survival trends continue, the other half will continue to be alive well beyond ten years.

In 2005, a man diagnosed with multiple myeloma asked me if he would be alive to watch his daughter graduate from high school in a few months. In 2009, bound to a wheelchair, he watched his daughter graduate from college. The wheelchair had nothing to do with his cancer. The man had fallen down while coaching his youngest son's baseball team.

In a broader sense, the Red Queen syndrome—moving incessantly just to keep in place—applies equally to every aspect of the battle against cancer, including cancer screening and cancer prevention. In the early winter of 2007, I traveled to Framingham in Massachusetts to visit a study site that will likely alter the way we imagine cancer prevention. A small, nondescript Northeastern town bound by a chain of frozen lakes in midwinter, Framingham is nonetheless an iconic place writ large in the history of medicine. In 1948, epidemiologists identified a cohort of about five thousand men and women living in Framingham. The behavior of this cohort, its habits, its interrelationships, and its illnesses, has been documented year after year in exquisite detail, creating an invaluable longitudinal corpus of data for hundreds of epidemiological studies. The English mystery writer Agatha Christie often used a fictional village, St. Mary Mead, as a microcosm of all mankind. Framingham is the American epidemiologist's English village. Under sharp statistical lenses, its captive cohort has lived, reproduced, aged, and died, affording a rare glimpse of the natural history of life, disease, and death.

The Framingham data set has spawned a host of studies on risk and illness. The link between cholesterol and heart attacks was formally established here, as was the association of stroke and high blood pressure. But recently, a conceptual transformation in epidemiological thinking has also been spearheaded here. Epidemiologists typically measure the risk factors for chronic, noninfectious illnesses by studying the behavior of individuals. But recently, they have asked a very different question: what if the real locus of risk lies not in the behaviors of individual actors, but in social *networks*?

In May 2008, two Harvard epidemiologists, Nicholas Christakis and James Fowler, used this notion to examine the dynamics of cigarette smoking. First, Fowler and Christakis plotted a diagram of all known relationships in Framingham—friends, neighbors, and relatives, siblings, ex-wives, uncles, aunts—as a densely interconnected web. Viewed abstractly, the network began to assume familiar and intuitive patterns. A few men and women (call them "socializers") stood at the epicenter of these networks, densely connected to each other through multiple ties. In contrast, others lingered on the outskirts of the social web—"loners"—with few and fleeting contacts.

When the epidemiologists juxtaposed smoking behavior onto this network and followed the pattern of smoking over decades, a notable phenomenon emerged: circles of relationships were found to be more powerful predictors of the dynamics of smoking than nearly any other factor. Entire networks stopped smoking concordantly, like whole circuits flickering off. A family that dined together was also a family that quit together. When highly connected "socializers" stopped smoking, the dense social circle circumscribed around them also slowly stopped as a group. As a result, smoking gradually became locked into the far peripheries of all networks, confined to the "loners" with few social contacts, puffing away quietly in the distant and isolated corners of the town.

The smoking-network study offers, to my mind, a formidable challenge to simplistic models of cancer prevention. Smoking, this model argues, is entwined into our social DNA just as densely and as inextricably as oncogenes are entwined into our genetic material. The cigarette epidemic, we might recall, originated as a form of metastatic behavior—one site seeding another site seeding another. Soldiers brought smoking back to postwar Europe; women persuaded women to smoke; the tobacco industry, sensing opportunity, advertised cigarettes as a form of social glue that would "stick" individuals into cohesive groups. The capacity of metastasis is thus built into smoking. If entire networks of smokers can flicker off with catalytic speed, then they can also flicker on with catalytic speed. Sever the ties that bind the nonsmokers of Framingham (or worse, nucleate a large social network with a proselytizing smoker), and then, cataclysmically, the network might alter as a whole.

This is why even the most successful cancer-prevention strategies can lapse so swiftly. When the Red Queen's feet stop spinning even temporarily, she does not maintain her position; the world around her, counter-spinning, pushes her off-balance. So it is with cancer prevention. When antitobacco campaigns lose their effectiveness or penetrance—as has recently happened among teens in America or in Asia—smoking often returns like an old plague. Social behavior metastasizes, eddying out from its center toward the peripheries of social networks. Mini-epidemics of smoking-related cancers are sure to follow.

The landscape of carcinogens is not static either. We are chemical apes: having discovered the capacity to extract, purify, and react molecules to produce new and wondrous molecules, we have begun to spin a new chemical universe around ourselves. Our bodies, our cells, our genes are thus being immersed and reimmersed in a changing flux of molecules—pesticides, pharmaceutical drugs, plastics, cosmetics, estrogens, food products, hormones, even novel forms of physical impulses, such as radiation and magnetism. Some of these, inevitably, will be carcinogenic. We cannot wish this world away; our task, then, is to sift through it vigilantly to discriminate bona fide carcinogens from innocent and useful bystanders.

This is easier said than done. In 2004, a rash of early scientific reports suggested that cell phones, which produce radio frequency energy, might cause a fatal form of brain cancer called a glioma. Gliomas appeared on the same side of the brain that the phone was predominantly held, further tightening the link. An avalanche of panic ensued in the media. But was this a falsely perceived confluence of a common phenomenon and a rare disease—phone usage and glioma? Or had epidemiologists missed the "nylon stockings" of the digital age?

In 2004, an enormous British study was launched to confirm these ominous early reports. "Cases"—patients with gliomas—were compared to "controls"—men and women with no gliomas—in terms of cell phone usage. The study, reported in 2006, appeared initially to confirm an increased risk of right-sided brain cancers in men and women who held their phone on their right ear. But when researchers evaluated the data meticulously, a puzzling pattern emerged: right-sided cell phone use *reduced* the risk of *left-sided* brain cancer. The simplest logical explanation for this phenomenon was "recall bias": patients diagnosed with tumors unconsciously exaggerated the use of cell phones on the same side of their head, and selectively forgot the use on the other side. When the authors corrected for this bias, there was no detectable association between gliomas and cell phone use overall. Prevention experts, and phone-addicted teenagers, may have rejoiced—but only briefly. By the time the study was completed, new phones had entered the market and swapped out old phones—making even the negative results questionable.

The cell phone case is a sobering reminder of the methodological rigor needed to evaluate new carcinogens. It is easy to fan anxiety about cancer. Identifying a true preventable carcinogen, estimating the magnitude of risk at reasonable doses and at reasonable exposures, and reducing exposure through scientific and legislative intervention—keeping the legacy of Percivall Pott alive—is far more complex.

"Cancer at the *fin de siècle,*" as the oncologist Harold Burstein described it, "resides at the interface between society and science." It poses not one but two challenges. The first, the "biological challenge" of cancer, involves "harnessing the fantastic rise in scientific knowledge . . . to conquer this ancient and terrible illness." But the second, the "social challenge," is just as acute: it involves forcing ourselves to confront our customs, rituals, and behaviors. These, unfortunately, are not customs or behaviors that lie at the peripheries of our society or selves, but ones that lie at their

definitional cores: what we eat and drink, what we produce and exude into our environments, when we choose to reproduce, and how we age.

Thirteen Mountains

"Every sickness
is a musical problem,"
so said Novalis,
"and every cure
a musical solution."
—W. H. Auden

The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease.
—Bert Vogelstein

When I began writing this book, in the early summer of 2004, I was often asked how I intended to end it. Typically, I would dodge the question or brush it away. I did not know, I would cautiously say. Or I was not sure. In truth, I was sure, although I did not have the courage to admit it to myself. I was sure that it would end with Carla's relapse and death.

I was wrong. In July 2009, exactly five years after I had looked down the microscope into Carla's bone marrow and confirmed her first remission, I drove to her house in Ipswich, Massachusetts, with a bouquet of flowers. It was an overcast morning, excruciatingly muggy, with a dun-colored sky that threatened rain but would not deliver any. Just before I left the hospital, I glanced quickly at the first note that I had written on Carla's admission to the hospital in 2004. As I had written that note, I recalled with embarrassment, I had guessed that Carla would not even survive the induction phase of chemotherapy.

But she had made it; a charring, private war had just ended. In acute leukemia, the passage of five years without a relapse is nearly synonymous with a cure. I handed her the azaleas and she stood looking at them speechlessly, almost numb to the enormity of her victory. Once, earlier this year, preoccupied with clinical work, I had waited two days before calling her about a negative bone marrow biopsy. She had heard from a nurse that the results were in, and my delay had sent her into a terrifying spiral of depression: in twenty-four hours she had convinced herself that the leukemia had crept back and my hesitation was a signal of impending doom.

Oncologists and their patients are bound, it seems, by an intense subatomic force. So, albeit in a much smaller sense, this was a victory for me as well. I sat at Carla's table and watched her pour a glass of water for herself, unpurified and straight from the sink. She glowed radiantly, her eyes half-closed, as if the compressed autobiography of the last five years were flashing through a private and internal cinema screen. Her children played with their Scottish terrier in the next room, blissfully oblivious of the landmark date that had just passed for their mother. All of this was for the best. "The purpose of my book," Susan Sontag concluded in *Illness as Metaphor*, "was to calm the imagination, not to incite it." So it was with my visit. Its purpose was to declare her illness over, to normalize her life—to sever the force that had locked us together for five years.

I asked Carla how she thought she had survived her nightmare. The drive to her house from the hospital that morning had taken me an hour and a half through a boil of heavy traffic. How had she managed, through the long days of that dismal summer, to drive to the hospital, wait in the room for hours as her blood tests were run, and then, told that her blood counts were too low for her to be given chemotherapy safely, turn back and return the next day for the same pattern to be repeated?

"There was no choice," she said, motioning almost unconsciously to the room where her children were playing. "My friends often asked me whether I felt as if my life was somehow made abnormal by my disease. I would tell them the same thing: for someone who is sick, this *is* their new normal."

Until 2003, scientists knew that the principal distinction between the "normalcy" of a cell and the "abnormalcy" of a cancer cell lay in the accumulation of genetic mutations—*ras, myc, Rb, neu*, and so forth—that unleashed the hallmark behaviors of cancer cells. But this description of cancer was incomplete. It provoked an inevitable question: how many such mutations does a real cancer possess in total? Individual oncogenes and tumor suppressors had been isolated, but what was the comprehensive set of such mutated genes that exists in any true human cancer?

The Human Genome Project, the full sequence of the normal human genome, was completed in 2003. In its wake comes a far less publicized but vastly more complex project: fully sequencing the genomes of several human cancer cells. Once completed, this effort, called the Cancer Genome Atlas, will dwarf the Human Genome Project in its scope. The sequencing effort involves dozens of teams of researchers across the world. The initial list of cancers to be sequenced includes brain, lung, pancreatic, and ovarian cancer. The Human Genome Project will provide the normal genome, against which cancer's abnormal genome can be juxtaposed and contrasted.

The result, as Francis Collins, the leader of the Human Genome Project describes it, will be a "colossal atlas" of cancer—a compendium of every gene mutated in the most common forms of cancer: "When applied to the 50 most common types of cancer, this effort could ultimately prove to be the equivalent of more than 10,000 Human Genome Projects in terms of the sheer volume of DNA to be sequenced. The dream must therefore be matched with an ambitious but realistic assessment of the emerging scientific opportunities for waging a smarter war." The only metaphor that can appropriately describe this project is geological. Rather than understand cancer gene by gene, the Cancer Genome Atlas will chart the entire territory of cancer: by sequencing the entire genome of several tumor types, *every* single mutated gene will be identified. It will represent the beginnings of the comprehensive "map" so hauntingly presaged by Maggie Jencks in her last essay.

Two teams have forged ahead in their efforts to sequence the cancer genome. One, called the Cancer Genome Atlas consortium, has multiple interconnected teams spanning several labs in several nations. The second is Bert Vogelstein's group at Johns Hopkins, which has assembled its own cancer genome sequencing facility, raised private funding for the effort, and raced ahead to sequence the genomes of breast, colon, and pancreatic tumors. In 2006, the Vogelstein team revealed the first landmark sequencing effort by analyzing thirteen thousand genes in eleven breast and colon cancers. (Although the human genome contains about twenty thousand genes in total, Vogelstein's team initially had tools to assess only

thirteen thousand.) In 2008, both Vogelstein's group and the Cancer Genome Atlas consortium extended this effort by sequencing hundreds of genes of several dozen specimens of brain tumors. As of 2009, the genomes of ovarian cancer, pancreatic cancer, melanoma, lung cancer, and several forms of leukemia have been sequenced, revealing the full catalog of mutations in each tumor type.

Perhaps no one has studied the emerging cancer genome as meticulously or as devotionally as Bert Vogelstein. A wry, lively, irreverent man in blue jeans and a rumpled blazer, Vogelstein recently began a lecture on the cancer genome in a packed auditorium at Mass General Hospital by attempting to distill the enormous array of discoveries in a few slides. Vogelstein's challenge was that of the landscape artist: How does one convey the gestalt of a territory (in this case, the "territory" of a genome) in a few broad strokes of a brush? How can a picture describe the essence of a place?

Vogelstein's answer to these questions borrows beautifully from an insight long familiar to classical landscape artists: negative space can be used to convey expanse, while positive space conveys detail. To view the landscape of the cancer genome panoramically, Vogelstein splayed out the entire human genome as if it were a piece of thread zigzagging across a square sheet of paper. (Science keeps eddying into its past: the word *mitosis*—Greek for "thread"—is resonant here again.) In Vogelstein's diagram, the first gene on chromosome one of the human genome occupies the top left corner of the sheet of paper, the second gene is below it, and so forth, zigzagging through the page, until the last gene of chromosome twenty-three occupies the bottom right corner of the page. This is the normal, unmutated human genome stretched out in its enormity—the "background" out of which cancer arises.

Against the background of this negative space, Vogelstein placed mutations. Every time a gene mutation was encountered in a cancer, the mutated gene was demarcated as a dot on the sheet. As the frequency of mutations in any given gene increased, the dots grew in height into ridges and hills and then mountains. The most commonly mutated genes in breast cancer samples were thus represented by towering peaks, while genes rarely mutated were denoted by small hills or flat dots.

Viewed thus, the cancer genome is at first glance a depressing place. Mutations litter the chromosomes. In individual specimens of breast and colon cancer, between fifty to eighty genes are mutated; in pancreatic cancers, about fifty to sixty. Even brain cancers, which often develop at earlier ages and hence may be expected to accumulate fewer mutations, possess about forty to fifty mutated genes.

Only a few cancers are notable exceptions to this rule, possessing relatively few mutations across the genome. One of these is an old culprit, acute lymphoblastic leukemia: only five or ten genetic alterations cross its otherwise pristine genomic landscape. Indeed, the relative paucity of genetic aberrancy in this leukemia may be one reason that this tumor is so easily felled by cytotoxic chemotherapy. Scientists speculate that genetically simple tumors (i.e., those carrying few mutations) might inherently be more susceptible to drugs, and thus intrinsically more curable. If so, the strange discrepancy between the success of high-dose chemotherapy in curing leukemia and its failure to cure most other cancers has a deep biological explanation. The search for a "universal cure" for cancer was predicated on a tumor that, genetically speaking, is far from universal.

In contrast to leukemia, the genomes of the more common forms of cancer, Vogelstein finds, are filled with genetic bedlam—mutations piled upon mutations upon mutations. In one breast cancer sample from a forty-three-year-old woman, 127 genes were mutated—nearly one in every two hundred genes in the human genome. Even within a single type of tumor, the heterogeneity of mutations is daunting. If one compares two breast cancer specimens, the set of mutated genes is far from identical. "In the end," as Vogelstein put it, "cancer genome sequencing validates a hundred years of clinical observations. Every patient's cancer is unique because every cancer genome is unique. Physiological heterogeneity is genetic heterogeneity." Normal cells are identically normal; malignant cells become unhappily malignant in unique ways.

Yet, characteristically, where others see only daunting chaos in the littered genetic landscape, Vogelstein sees patterns coalescing out of the mess. Mutations in the cancer genome, he believes, come in two forms. Some are passive. As cancer cells divide, they accumulate mutations due to accidents in the copying of DNA, but these mutations have no impact on the biology of cancer. They stick to the genome and are passively carried along as the cell divides, identifiable but inconsequential. These are "bystander" mutations or "passenger" mutations. ("They hop along for the ride," as Vogelstein put it.)

Other mutations are not passive players. Unlike the passenger mutations, these altered genes directly goad the growth and the biological behavior of cancer cells. These are "driver" mutations, mutations that play a crucial role in the biology of a cancer cell.

Every cancer cell possesses some set of driver and passenger mutations. In the breast cancer sample from the forty-three-year-old woman with 127 mutations, only about ten might directly be contributing to the actual growth and survival of her tumor, while the rest may have been acquired due to gene-copying errors in cancer cells. But while functionally different, these two forms of mutations cannot easily be distinguished. Scientists can identify some driver genes that directly goad cancer's growth using the cancer genome. Since passenger mutations occur randomly, they are randomly spread throughout the genome. Driver mutations, on the other hand, strike key oncogenes and tumor suppressors, and only a limited number of such genes exist in the genome. These mutations—in genes such as *ras, myc*, and *Rb*—recur in sample upon sample. They stand out as tall mountains in Vogelstein's map, while passenger mutations are typically represented by the valleys. But when a mutation occurs in a previously unknown gene, it is impossible to predict whether that mutation is consequential or inconsequential—driver or passenger, barnacle or engine.

The "mountains" in the cancer genome—i.e., genes most frequently mutated in a particular form of cancer—have another property. They can be organized into key cancer pathways. In a recent series of studies, Vogelstein's team at Hopkins reanalyzed the mutations present in the cancer genome using yet another strategy. Rather than focusing on individual genes mutated in cancers, they enumerated the number of *pathways* mutated in cancer cells. Each time a gene was mutated in any component of the Ras-Mek-Erk pathway, it was classified as a "Ras pathway" mutation. Similarly, if a cell carried a mutation in any component of the *Rb* signaling pathway, it was classified as "Rb pathway mutant," and so forth, until all driver mutations had been organized into pathways.

How many pathways are typically dysregulated in a cancer cell? Typically, Vogelstein found, between eleven and fifteen, with an average of thirteen. The mutational complexity on a gene-by-gene level was still enormous. Any one tumor bore scores of mutations pockmarked throughout the genome. But the same core pathways were characteristically dysregulated in any tumor type, even if the specific genes responsible for each broken pathway differed from one tumor to the next. *Ras* may be activated in one sample of bladder cancer; *Mek* in another; *Erk* in the third—but in each case, some vital piece of the Ras-Mek-Erk cascade was dysregulated.

The bedlam of the cancer genome, in short, is deceptive. If one listens closely, there are organizational principles. The language of cancer is grammatical, methodical, and even—I hesitate to write—quite beautiful. Genes talk to genes and pathways to pathways in perfect pitch, producing a familiar yet foreign music that rolls faster and faster into a lethal rhythm. Underneath what might seem like overwhelming diversity is a deep genetic unity. Cancers that look vastly unlike each other superficially often have the same or similar pathways unhinged. "Cancer," as one scientist recently put it, "really is a pathway disease."

This is either very good news or very bad news. The cancer pessimist looks at the ominous number thirteen and finds himself disheartened. The dysregulation of eleven to fifteen core pathways poses an enormous challenge for cancer therapeutics. Will oncologists need thirteen independent drugs to attack thirteen independent pathways to "normalize" a cancer cell? Given the slipperiness of cancer cells, when a cell becomes resistant to one combination of thirteen drugs, will we need an additional thirteen?

The cancer optimist, however, argues that thirteen is a finite number. It is a relief: until Vogelstein identified these core pathways, the mutational complexity of cancers seemed nearly infinite. In fact, the hierarchical organization of genes into pathways in any given tumor type suggests that even deeper hierarchies might exist. Perhaps not all thirteen need to be targeted to attack complex cancers such as breast or pancreatic cancer. Perhaps some of the core pathways may be particularly responsive to therapy. The best example of this might be Barbara Bradfield's tumor, a cancer so hypnotically addicted to *Her-2* that targeting this key oncogene melted the tumor away and forced a decades-long remission.

Gene by gene, and now pathway by pathway, we have an extraordinary glimpse into the biology of cancer. The complete maps of mutations in many tumor types (with their hills, valleys, and mountains) will soon be complete, and the core pathways that are mutated fully defined. But as the old proverb runs, there are mountains beyond mountains. Once the mutations have been identified, the mutant genes will need to be assigned functions in cellular physiology. We will need to move through a renewed cycle of knowledge that recapitulates a past cycle—from anatomy to physiology to therapeutics. The sequencing of the cancer genome represents the genetic anatomy of cancer. And just as Virchow made the crucial leap from Vesalian anatomy to the physiology of cancer in the nineteenth century, science must make a leap from the molecular anatomy to the molecular physiology of cancer. We will soon know what the mutant genes *are.* The real challenge is to understand what the mutant genes *do.*

This seminal transition from descriptive biology to the functional biology of cancer will provoke three new directions for cancer medicine.

The first is a direction for cancer therapeutics. Once the crucial driver mutations in any given cancer have been identified, we will need to launch a hunt for targeted therapies against these genes. This is not an entirely fantastical hope: targeted inhibitors of some of the core thirteen pathways mutated in many cancers have already entered the clinical realm. As individual drugs, some of these inhibitors have thus far had only moderate response rates. The challenge now is to determine which combinations of such drugs might inhibit cancer growth without killing normal cells.

In a piece published in the *New York Times* in the summer of 2009, James Watson, the codiscoverer of the structure of DNA, made a remarkable turnabout in opinion. Testifying before Congress in 1969, Watson had lambasted the War on Cancer as ludicrously premature. Forty years later, he was far less critical: "We shall soon know all the genetic changes that underlie the major cancers that plague us. We already know most, if not all, of the major pathways through which cancer-inducing signals move through cells. Some 20 signal-blocking drugs are now in clinical testing after first being shown to block cancer in mice. A few, such as Herceptin and Tarceva, have Food and Drug Administration approval and are in widespread use."

The second new direction is for cancer prevention. To date, cancer prevention has relied on two disparate and polarized methodologies to try to identify preventable carcinogens. There have been intensive, often massive, human studies that have connected a particular form of cancer with a risk factor, such as Doll and Hill's study identifying smoking as a risk factor for lung cancer. And there have been laboratory studies to identify carcinogens based on their ability to cause mutations in bacteria or incite precancer in animals and humans, such as Bruce Ames's experiment to capture chemical mutagens, or Marshall and Warren's identification of *H. pylori* as a cause for stomach cancer.

But important preventable carcinogens might escape detection by either strategy. Subtle risk factors for cancer require enormous population studies; the subtler the effect, the larger the population needed. Such vast, unwieldy, and methodologically challenging studies are difficult to fund and launch. Conversely, several important cancer-inciting agents are not easily captured by laboratory experiments. As Evarts Graham discovered to his dismay, even tobacco smoke, the most common human carcinogen, does not easily induce lung cancer in mice. Bruce Ames's bacterial test does not register asbestos as a mutagen.

Two recent controversies have starkly highlighted such blind spots in epidemiology. In 2000, the so-called Million Women Study in the United Kingdom identified estrogen and progesterone, prescribed in hormone-replacement therapy to women to ease menopausal symptoms, as major risk factors for the incidence and fatality from estrogen-positive breast cancer. Scientifically speaking, this is an embarrassment. Estrogen is not identified as a mutagen in Bruce Ames's test; nor does it cause cancer in animals at low doses. But the two hormones have been known as pathological activators of the ER-positive subtype of breast cancer since the *1960s.* Beatson's surgery and tamoxifen induce remissions in breast cancer by blocking estrogen, and so it stands to reason that exogenous estrogen might incite breast cancer. A more integrated approach to cancer prevention, incorporating the prior insights of cancer biology, might have predicted this cancer-inducing activity, preempted the need for a million-person association study, and potentially saved the lives of thousands of women.

The second controversy also has its antecedents in the 1960s. Since the publication of Rachel Carson's *Silent Spring* in 1962, environmental activists have stridently argued that the indiscriminate overuse of pesticides is partially responsible for the rising incidence of cancer in America. This theory has spawned intense controversy, activism, and public campaigns over the decades. But although the hypothesis is credible, large-scale human-cohort experiments directly implicating particular pesticides as carcinogens have emerged slowly, and animal studies have been inconclusive. DDT and aminotriazole have been shown to cause cancer in animals at high doses, but thousands of chemicals proposed as carcinogens remain untested. Again, an integrated approach is needed. The identification of key activated pathways in cancer cells might provide a more sensitive detection method to discover carcinogens in animal studies. A chemical may not cause overt cancer in animal studies, but may be shown to activate cancer-linked genes and pathways, thus shifting the burden of proof of its potential carcinogenicity.

In 2005, the Harvard epidemiologist David Hunter argued that the integration of traditional epidemiology, molecular biology, and cancer genetics will generate a resurgent form of epidemiology that is vastly more empowered in its ability to prevent cancer. "Traditional epidemiology," Hunter reasoned, "is concerned with correlating exposures with cancer outcomes, and everything between the cause (exposure) and the outcome (a cancer) is treated as a 'black box.' . . . In molecular epidemiology, the epidemiologist [will] open up the 'black box' by examining the events intermediate between exposure and disease occurrence or progression."

Like cancer prevention, cancer screening will also be reinvigorated by the molecular understanding of cancer. Indeed, it has already been. The discovery of the BRCA genes for breast cancer epitomizes the integration of cancer screening and cancer genetics. In the mid-1990s, building on the prior decade's advances, researchers isolated two related genes, BRCA-1 and BRCA-2, that vastly increase the risk of developing breast cancer. A woman with an inherited mutation in BRCA-1 has a 50 to 80 percent chance of developing breast cancer in her lifetime (the gene also increases the risk for ovarian cancer), about three to five times the normal risk. Today, testing for this gene mutation has been integrated into prevention efforts. Women found positive for a mutation in the two genes are screened more intensively using more sensitive imaging techniques

such as breast MRI. Women with BRCA mutations might choose to take the drug tamoxifen to prevent breast cancer, a strategy shown effective in clinical trials. Or, perhaps most radically, women with BRCA mutations might choose a prophylactic mastectomy of both breasts and ovaries before cancer develops, another strategy that dramatically decreases the chances of developing breast cancer. An Israeli woman with a BRCA-1 mutation who chose this strategy after developing cancer in one breast told me that at least part of her choice was symbolic. "I am rejecting cancer from my body," she said. "My breasts had become no more to me than a site for my cancer. They were of no more use to me. They harmed my body, my survival. I went to the surgeon and asked him to remove them."

The third, and arguably most complex, new direction for cancer medicine is to integrate our understanding of aberrant genes and pathways to explain the *behavior* of cancer as a whole, thereby renewing the cycle of knowledge, discovery, and therapeutic intervention.

One of the most provocative examples of a cancer cell's behavior, inexplicable by the activation of any single gene or pathway, is its immortality. Rapid cellular proliferation, or the insensitivity to growth-arresting signals, or tumor angiogenesis, can all largely be explained by aberrantly activated and inactivated pathways such as *ras, Rb*, or *myc* in cancer cells. But scientists cannot explain how cancers continue to proliferate endlessly. Most normal cells, even rapidly growing normal cells, will proliferate over several generations and then exhaust their capacity to keep dividing. What allows a cancer cell to keep dividing endlessly without exhaustion or depletion generation upon generation?

An emerging, although highly controversial, answer to this question is that cancer's immortality, too, is borrowed from normal physiology. The human embryo and many of our adult organs possess a tiny population of stem cells that are capable of immortal regeneration. Stem cells are the body's reservoir of renewal. The entirety of human blood, for instance, can arise from a single, highly potent blood-forming stem cell (called a hematopoietic stem cell), which typically lives buried inside the bone marrow. Under normal conditions, only a fraction of these blood-forming stem cells are active; the rest are deeply quiescent—asleep. But if blood is suddenly depleted, by injury or chemotherapy, say, then the stem cells awaken and begin to divide with awe-inspiring fecundity, generating cells that generate thousands upon thousands of blood cells. In weeks, a single hematopoietic stem cell can replenish the entire human organism with new blood—and then, through yet unknown mechanisms, lull itself back to sleep.

Something akin to this process, a few researchers believe, is constantly occurring in cancer—or at least in leukemia. In the mid-1990s, John Dick, a Canadian biologist working in Toronto, postulated that a small population of cells in human leukemias also possess this infinite self-renewing behavior. These "cancer stem cells" act as the persistent reservoir of cancer—generating and regenerating cancer infinitely. When chemotherapy kills the bulk of cancer cells, a small remnant population of these stem cells, thought to be intrinsically more resistant to death, regenerate and renew the cancer, thus precipitating the common relapses of cancer after chemotherapy. Indeed, cancer stem cells have acquired the behavior of normal stem cells by activating the same genes and pathways that make normal stem cells immortal—except, unlike normal stem cells, they cannot be lulled back into physiological sleep. Cancer, then, is quite literally trying to emulate a regenerating organ—or perhaps, more disturbingly, the regenerating *organism*. Its quest for immortality mirrors our own quest, a quest buried in our embryos and in the renewal of our organs. Someday, if a cancer succeeds, it will produce a far more perfect being than its host—imbued with both immortality and the drive to proliferate. One might argue that the leukemia cells growing in my laboratory derived from the woman who died three decades earlier have already achieved this form of "perfection."

Taken to its logical extreme, the cancer cell's capacity to consistently imitate, corrupt, and pervert normal physiology thus raises the ominous question of what "normalcy" *is*. "Cancer," Carla said, "is my new normal," and quite possibly cancer is *our* normalcy as well, that we are inherently destined to slouch towards a malignant end. Indeed, as the fraction of those affected by cancer creeps inexorably in some nations from one in four to one in three to one in *two*, cancer will, indeed, be the new normal—an inevitability. The question then will not be *if* we will encounter this immortal illness in our lives, but *when*.

but also Atossa's journey, the long arc of scientific discovery—and embedded in that journey, the animus, so inextricably human, to outwit, to outlive and survive.

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Late one evening in the spring of 2005, toward the end of the first year of my fellowship, I sat in a room on the tenth floor of the hospital with a dying woman, Germaine Berne. She was a vivacious psychologist from Alabama. In 1999, she had been struck by nausea, a queasiness so sudden and violent that it felt as if it had been released from a catapult. Even more unsettling, the nausea had been accompanied by a vague sense of fullness, as if she were perpetually stuck devouring a large meal. Germaine had driven herself to the Baptist Hospital in Montgomery, where she had undergone a barrage of tests until a CAT scan had revealed a twelve-centimeter solid mass pushing into her stomach. On January 4, 2000, a radiologist had biopsied the mass. Under the microscope, the biopsy had revealed sheets of spindlelike cells dividing rapidly. The tumor, which had invaded blood vessels and bucked the normal planes of tissue, was a rare kind of cancer called a gastrointestinal stromal tumor, or simply, a GIST.

The news quickly became worse. Her scans showed spots in her liver, swellings in her lymph nodes, and a spray of masses peppering the left lung. The cancer had metastasized all over her body. A surgical cure was impossible, and in 2000, no chemotherapy was known to be effective against her kind of sarcoma. Her doctors in Alabama cobbled together a combination of chemotherapeutic drugs, but they were essentially biding their time. "I signed my letters, paid my bills, and made my will," she recalled. "There was no doubt about the verdict. I was told to go home to die."

In the winter of 2000, handed her death sentence, Germaine stumbled into a virtual community of cosufferers—GIST patients who spoke to each other through a website. The site, like most of its bloggers, was a strange and moribund affair, with desperate folks seeking desperate remedies. But in late April, news of a novel drug began to spread like wildfire through this community. The new drug was none other than Gleevec—imatinib—the same chemical that Druker had found to be active against chronic myelogenous leukemia. Gleevec binds and inactivates the *Bcr-abl* protein. But serendipitously, the chemical inactivates another tyrosine kinase, called *c-kit*. Just as activated *Bcr-abl* drives cancer cells to divide and grow in CML, *c-kit* is a driver gene in GIST. In early trials, Gleevec had turned out to be remarkably clinically active against *c-kit*, and hence against GIST.

Germaine pulled strings to get enrolled in one of these trials. She was, by nature, effortlessly persuasive, able to cajole, badger, wheedle, pester, beg, and demand—and her illness had made her bold. ("Cure me, Doc, and I'll send you to Europe," she told me once—an offer that I politely declined.) She worked her way into a teaching hospital where patients were being given the drug on trial. Just as she was being enrolled, Gleevec had turned out to be so effective that doctors could no longer justify treating GIST patients with a placebo pill. Germaine started on the drug in August 2001. A month later, her tumors began to recede at an astonishing rate. Her energy returned; her nausea vanished. She was resurrected from the dead.

Germaine's recovery was a medical miracle. Newspapers in Montgomery picked up the story. She doled out advice to other cancer victims. Medicine was catching up on cancer, she wrote; there was reason for hope. Even if no cure was in sight, a new generation of drugs would control cancer, and another generation would round the bend just as the first one failed. In the summer of 2004, as she was celebrating the fourth anniversary of her unexpected recovery, the cells of Germaine's tumor suddenly grew resistant to Gleevec. Her lumps, having remained dormant for four years, sprouted vengefully back. In months, masses appeared in her stomach, lymph nodes, lungs, liver, spleen. The nausea returned, just as powerfully as the first time. Malignant fluid poured into the cisterns of her abdomen.

Resourceful as usual, Germaine scoured the Web, returning to her makeshift community of GIST patients for advice. She discovered that other drugs—second-generation analogues of Gleevec—were in trial in Boston and in other cities. In 2004, on a telephone halfway across the country, she enrolled in a trial of one such analogue called SU11248 that had just opened up at the Farber.

The new drug produced a temporary response, but did not work for long. By February 2005, Germaine's cancer had spiraled out of control, growing so fast that she could record its weight, in pounds, as she stood on the scales every week. Eventually her pain made it impossible for her to walk even from her bed to the door and she had to be hospitalized. My meeting with Germaine that evening was not to discuss drugs and therapies, but to try to make an honest reconciliation between her and her medical condition.

As usual, she had already beaten me to it. When I entered her room to talk about next steps, she waved her hand in the air with a withering look and cut me off. Her goals were now simple, she told me. No more trials. No more drugs. The six years of survival that she had eked out between 1999 and 2005 had not been static, frozen years; they had sharpened, clarified, and cleansed her. She had severed her relationship with her husband and intensified her bond with her brother, an oncologist. Her daughter, a teenager in 1999 and now a preternaturally mature sophomore at a Boston college, had grown into her ally, her confidante, her sometime nurse, and her closest friend. ("Cancer breaks some families and makes some," Germaine said. "In my case, it did both.") Germaine realized that her reprieve had finally come to an end. She wanted to get to Alabama, to her own home, to die the death that she had expected in 1999.

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When I recall that final conversation with Germaine, embarrassingly enough, the objects seem to stand out more vividly than the words: a hospital room, with its sharp smell of disinfectant and hand soap; the steely, unflattering overhead light; a wooden side table on wheels, piled with pills, books, newspaper clippings, nail polish, jewelry, postcards. Her room, wallpapered with pictures of her beautiful house in Montgomery and of her daughter holding some fruit picked from her garden; a standard-issue plastic hospital pitcher filled with a bunch of sunflowers perched on a table by her side. Germaine, as I remember her, was sitting by the bed, one leg dangling casually down, wearing her usual eccentric and arresting combination of clothes and some large and unusual pieces of jewelry. Her hair was carefully arranged. She looked formal, frozen and perfect, like a photograph of someone in a hospital waiting to die. She seemed content; she laughed and joked. She made wearing a nasogastric tube seem effortless and dignified.

Only years later, in writing this book, could I finally put into words why that meeting left me so uneasy and humbled; why the gestures in that room seemed larger-than-life; why the objects seemed like symbols; why Germaine herself seemed like an actor playing a part. Nothing, I realized, was incidental. The characteristics of Germaine's personality that had once seemed spontaneous and impulsive were, in fact, calculated and almost reflexive responses to her illness. Her clothes were loose and vivid because they were decoys against the growing outline of the tumor in her abdomen. Her necklace was distractingly large so as to pull attention away from her cancer. Her room was topsy-turvy with baubles and pictures—the hospital pitcher filled with flowers, the cards tacked to the wall—because without them it would devolve into the cold anonymity of any other room in any other hospital. She had dangled her leg at that precise, posed angle because the tumor had invaded her spine and begun to paralyze her other leg, making it impossible to sit any other way. Her casualness was studied, the jokes rehearsed. Her illness had tried to humiliate her. It had made her anonymous and seemingly humorless; it had sentenced her to die an unsightly death in a freezing hospital room thousands of miles away from home. She had responded with vengeance, moving to be always one step ahead, trying to outwit it.

operation; for the latter, "remote sympathy."

When Atossa reemerges in the nineteenth century, she encounters a new world of surgery. In Halsted's Baltimore clinic in 1890, Atossa's breast cancer is treated with the boldest and most definitive therapy thus far—radical mastectomy with a large excision of the tumor and removal of the deep chest muscles and lymph nodes under the armpit and the collarbone. In the early twentieth century, radiation oncologists try to obliterate the tumor locally using X-rays. By the 1950s, yet another generation of surgeons learns to combine the two strategies, although tempered by moderation. Atossa's cancer is treated locally with a simple mastectomy, or a lumpectomy followed by radiation.

In the 1970s, new therapeutic strategies emerge. Atossa's surgery is followed by adjuvant combination chemotherapy to diminish the chance of a relapse. Her tumor tests positive for the estrogen receptor. Tamoxifen, the antiestrogen, is also added to prevent a relapse. In 1986, her tumor is further discovered to be *Her-2* amplified. In addition to surgery, radiation, adjuvant chemotherapy, and tamoxifen, she is treated with targeted therapy using Herceptin.

It is impossible to enumerate the precise impact of these interventions on Atossa's survival. The shifting landscape of trials does not allow a direct comparison between Atossa's fate in 500 BC and her fate in 1989. But surgery, chemotherapy, radiation, hormonal therapy, and targeted therapy have likely added anywhere between seventeen and thirty years to her survival. Diagnosed at forty, say, Atossa can reasonably be expected to celebrate her sixtieth birthday.

In the mid-1990s, the management of Atossa's breast cancer takes another turn. Her diagnosis at an early age and her Achaemenid ancestry raise the question of whether she carries a mutation in BRCA-1 or BRCA-2. Atossa's genome is sequenced, and indeed, a mutation is found. She enters an intensive screening program to detect the appearance of a tumor in her unaffected breast. Her two daughters are also tested. Found positive for BRCA-1, they are offered either intensive screening, prophylactic bilateral mastectomy, or tamoxifen to prevent the development of invasive breast cancer. For Atossa's daughters, the impacts of screening and prophylaxis are dramatic. A breast MRI identifies a small lump in one daughter. It is found to be breast cancer and surgically removed in its early, preinvasive stage. The other daughter chooses to undergo a prophylactic bilateral mastectomy. Having excised her breasts preemptively, she will live out her life free of breast cancer.

Move Atossa into the future now. In 2050, Atossa will arrive at her breast oncologist's clinic with a thumb-size flash drive containing the entire sequence of her cancer's genome, identifying every mutation in every gene. The mutations will be organized into key pathways. An algorithm might identify the pathways that are contributing to the growth and survival of her cancer. Therapies will be targeted against these pathways to prevent a relapse of the tumor after surgery. She will begin with one combination of targeted drugs, expect to switch to a second cocktail when her cancer mutates, and switch again when the cancer mutates again. She will likely take some form of medicine, whether to prevent, cure, or palliate her illness, for the rest of her life.

This, indubitably, is progress. But before we become too dazzled by Atossa's survival, it is worthwhile putting it into perspective. Give Atossa metastatic pancreatic cancer in 500 BC and her prognosis is unlikely to change by more than a few months over twenty-five hundred years. If Atossa develops gallbladder cancer that is not amenable to surgery, her survival changes only marginally over centuries. Even breast cancer shows a marked heterogeneity in outcome. If Atossa's tumor has metastasized, or is estrogen-receptor negative, *Her-2* negative, and unresponsive to standard chemotherapy, then her chances of survival will have barely changed since the time of Hunter's clinic. Give Atossa CML or Hodgkin's disease, in contrast, and her life span may have increased by thirty or forty years.

Part of the unpredictability about the trajectory of cancer in the future is that we do not know the biological basis for this heterogeneity. We cannot yet fathom, for instance, what makes pancreatic cancer or gallbladder cancer so markedly different from CML or Atossa's breast cancer. What is certain, however, is that even the knowledge of cancer's biology is unlikely to eradicate cancer fully from our lives. As Doll suggests, and as Atossa epitomizes, we might as well focus on prolonging life rather than eliminating death. This War on Cancer may best be "won" by redefining victory.

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Atossa's tortuous journey also raises a question implicit in this book: if our understanding and treatment of cancer keep morphing so radically in time, then how can cancer's past be used to predict its future?

In 1997, the NCI director, Richard Klausner, responding to reports that cancer mortality had remained disappointingly static through the nineties, argued that the medical realities of one decade had little bearing on the realities of the next. "There are far more good historians than there are good prophets," Klausner wrote. "It is extraordinarily difficult to predict scientific discovery, which is often propelled by seminal insights coming from unexpected directions. The classic example—Fleming's discovery of penicillin on moldy bread and the monumental impact of that accidental finding—could not easily have been predicted, nor could the sudden demise of iron-lung technology when evolving techniques in virology allowed the growth of poliovirus and the preparation of vaccine. Any extrapolation of history into the future presupposes an environment of static discovery—an oxymoron."

In a limited sense, Klausner is right. When truly radical discoveries appear, their impact is often not incremental but cataclysmic and paradigm-shifting. Technology dissolves its own past. The speculator who bought stock options in an iron-lung company before the discovery of the polio vaccine, or the scientist who deemed bacterial pneumonias incurable just as penicillin was being discovered, were soon shown to be history's fools.

But with cancer, where no simple, universal, or definitive cure is in sight—and is never likely to be—the past is constantly conversing with the future. Old observations crystallize into new theories; time past is always contained in time future. Rous's virus was reincarnated, decades later, in the form of endogenous oncogenes; George Beatson's observation that removing ovaries might slow the growth of breast cancer, inspired by a Scottish shepherds' tale, roars back in the form of a billion-dollar drug named tamoxifen; Bennett's "suppuration of blood," the cancer that launches this book, is also the cancer that ends this book.

And there is a subtler reason to remember this story: while the content of medicine is constantly changing, its *form*, I suspect, remains astonishingly the same. History repeats, but science reverberates. The tools that we will use to battle cancer in the future will doubtless alter so dramatically in fifty years that the geography of cancer prevention and therapy might be unrecognizable. Future physicians may laugh at our mixing of primitive cocktails of poisons to kill the most elemental and magisterial disease known to our species. But much about this battle will remain the same: the relentlessness, the inventiveness, the resilience, the queasy pivoting between defeatism and hope, the hypnotic drive for universal solutions, the disappointment of defeat, the arrogance and the hubris.

The Greeks used an evocative word to describe tumors, *onkos*, meaning "mass" or "burden." The word was more prescient than they might have imagined. Cancer is indeed the load built into our genome, the leaden counterweight to our aspirations for immortality. But if one looks back even further behind the Greek to the ancestral Indo-European language, the etymology of the word *onkos* changes. *Onkos* arises from the ancient word *nek*. And *nek*, unlike the static *onkos*, is the active form of the word *load*. It means to carry, to move the burden from one place to the next, to bear something across a long distance and bring it to a new place. It is an image that captures not just the cancer cell's capacity to travel—metastasis—

Atossa's War

We aged a hundred years and this descended
In just one hour, as at a stroke
—Anna Akhmatova,
"In Memoriam, July 19, 1914"

It is time, it is time for me too to depart. Like an old man who has outlived his contemporaries and feels a sad inner emptiness, Kostoglotov felt that evening that the ward was no longer his home, even though . . . there were the same old patients asking the same old questions again and again as though they had never been asked before: . . . Will they cure me or won't they? What other remedies are there that might help?

—Aleksandr Solzhenitsyn, *Cancer Ward*

On May 17, 1973, seven weeks after Sidney Farber's death in Boston, Hiram Gans, an old friend, stood up at the memorial service to read some lines from Swinburne's "A Forsaken Garden":

Here nowin his triumph where all things falter,
Stretched out on the spoils that his own hand spread,
As a god self-slain on his own strange altar,
Death lies dead.

It was—careful listeners might have noted—a peculiar and deliberate inversion of the moment. It was *cancer* that was soon to be dead—its corpus outstretched and spread-eagled ceremonially on the altar—death lying dead.

The image belongs very much to Farber and his era, but its essence still haunts us today. In the end, every biography must also confront the death of its subject. Is the end of cancer conceivable in the future? Is it possible to eradicate this disease from our bodies and our societies forever?

The answers to these questions are embedded in the biology of this incredible disease. Cancer, we have discovered, is stitched into our genome. Oncogenes arise from mutations in essential genes that regulate the growth of cells. Mutations accumulate in these genes when DNA is damaged by carcinogens, but also by seemingly random errors in copying genes when cells divide. The former might be preventable, but the latter is endogenous. Cancer is a flaw in our growth, but this flaw is deeply entrenched in ourselves. We can rid ourselves of cancer, then, only as much as we can rid ourselves of the processes in our physiology that depend on growth—aging, regeneration, healing, reproduction.

Science embodies the human desire to understand nature; technology couples that desire with the ambition to control nature. These are related impulses—one might seek to understand nature in order to control it—but the drive to intervene is unique to technology. Medicine, then, is fundamentally a technological art; at its core lies a desire to improve human lives by intervening on life itself. Conceptually, the battle against cancer pushes the idea of technology to its far edge, for the object being intervened upon is our genome. It is unclear whether an intervention that discriminates between malignant and normal growth is even possible. Perhaps cancer, the scrappy, fecund, invasive, adaptable twin to our own scrappy, fecund, invasive, adaptable cells and genes, is impossible to disconnect from our bodies. Perhaps cancer defines the inherent outer limit of our survival. As our cells divide and our bodies age, and as mutations accumulate inexorably upon mutations, cancer might well be the final terminus in our development as organisms.

But our goals could be more modest. Above the door to Richard Peto's office in Oxford hangs one of Doll's favorite aphorisms: "Death in old age is inevitable, but death before old age is not." Doll's idea represents a far more reasonable proximal goal to define success in the War on Cancer. It is possible that we are fatally conjoined to this ancient illness, forced to play its cat-and-mouse game for the foreseeable future of our species. But if cancer deaths can be prevented before old age, if the terrifying game of treatment, resistance, recurrence, and more treatment can be stretched out longer and longer, then it will transform the way we imagine this ancient illness. Given what we know about cancer, even this would represent a technological victory unlike any other in our history. It would be a victory over our own inevitability—a victory over our genomes.

To envision what such a victory might look like, permit a thought experiment. Recall Atossa, the Persian queen with breast cancer in 500 BC. Imagine her traveling through time—appearing and reappearing in one age after the next. She is cancer's Dorian Gray: as she moves through the arc of history, her tumor, frozen in its stage and behavior, remains the same. Atossa's case allows us to recapitulate past advances in cancer therapy and to consider its future. How has her treatment and prognosis shifted in the last four thousand years, and what happens to Atossa later in the new millennium?

First, pitch Atossa backward in time to Imhotep's clinic in Egypt in 2500 BC. Imhotep has a name for her illness, a hieroglyph that we cannot pronounce. He provides a diagnosis, but "there is no treatment," he says humbly, closing the case.

In 500 BC, in her own court, Atossa self-prescribes the most primitive form of a mastectomy, which is performed by her Greek slave. Two hundred years later, in Thrace, Hippocrates identifies her tumor as a *karkinos*, thus giving her illness a name that will ring through its future. Claudius Galen, in AD 168, hypothesizes a universal cause: a systemic overdose of black bile—trapped melancholia boiling out as a tumor.

A thousand years flash by; Atossa's entrapped black bile is purged from her body, yet the tumor keeps growing, relapsing, invading, and metastasizing. Medieval surgeons understand little about Atossa's disease, but they chisel away at her cancer with knives and scalpels. Some offer frog's blood, lead plates, goat dung, holy water, crab paste, and caustic chemicals as treatments. In 1778, in John Hunter's clinic in London, her cancer is assigned a stage—early, localized breast cancer or late, advanced, invasive cancer. For the former, Hunter recommends a local

* Thus far, the full sequencing of ALL genomes has not been completed. The alterations described are deletions or amplifications of genes. Detailed sequencing may reveal an increase in the number of mutated genes.
* Mce filter out many of the carcinogenic components of tar. Asbestos incites cancer by inducing a scar-forming, inflammatory reaction in the body. Bacteria don't generate this reaction and are thus "immune" to asbestos.

It was like watching someone locked in a chess game. Every time Germaine's disease moved, imposing yet another terrifying constraint on her, she made an equally assertive move in return. The illness acted; she reacted. It was a morbid, hypnotic game—a game that had taken over her life. She dodged one blow only to be caught by another. She, too, was like Carroll's Red Queen, stuck pedaling furiously just to keep still in one place.

Germaine seemed, that evening, to have captured something essential about our struggle against cancer: that, to keep pace with this malady, you needed to keep inventing and reinventing, learning and unlearning strategies. Germaine fought cancer obsessively, cannily, desperately, fiercely, madly, brilliantly, and zealously—as if channeling all the fierce, inventive energy of generations of men and women who had fought cancer in the past and would fight it in the future. Her quest for a cure had taken her on a strange and limitless journey, through Internet blogs and teaching hospitals, chemotherapy and clinical trials halfway across the country, through a landscape more desolate, desperate, and disquieting than she had ever imagined. She had deployed every morsel of energy to the quest, mobilizing and remobilizing the last dregs of her courage, summoning her will and wit and imagination, until, that final evening, she had stared into the vault of her resourcefulness and resilience and found it empty. In that haunted last night, hanging on to her life by no more than a tenuous thread, summoning all her strength and dignity as she wheeled herself to the privacy of her bathroom, it was as if she had encapsulated the essence of a four-thousand-year-old war.

—S.M., June 2010