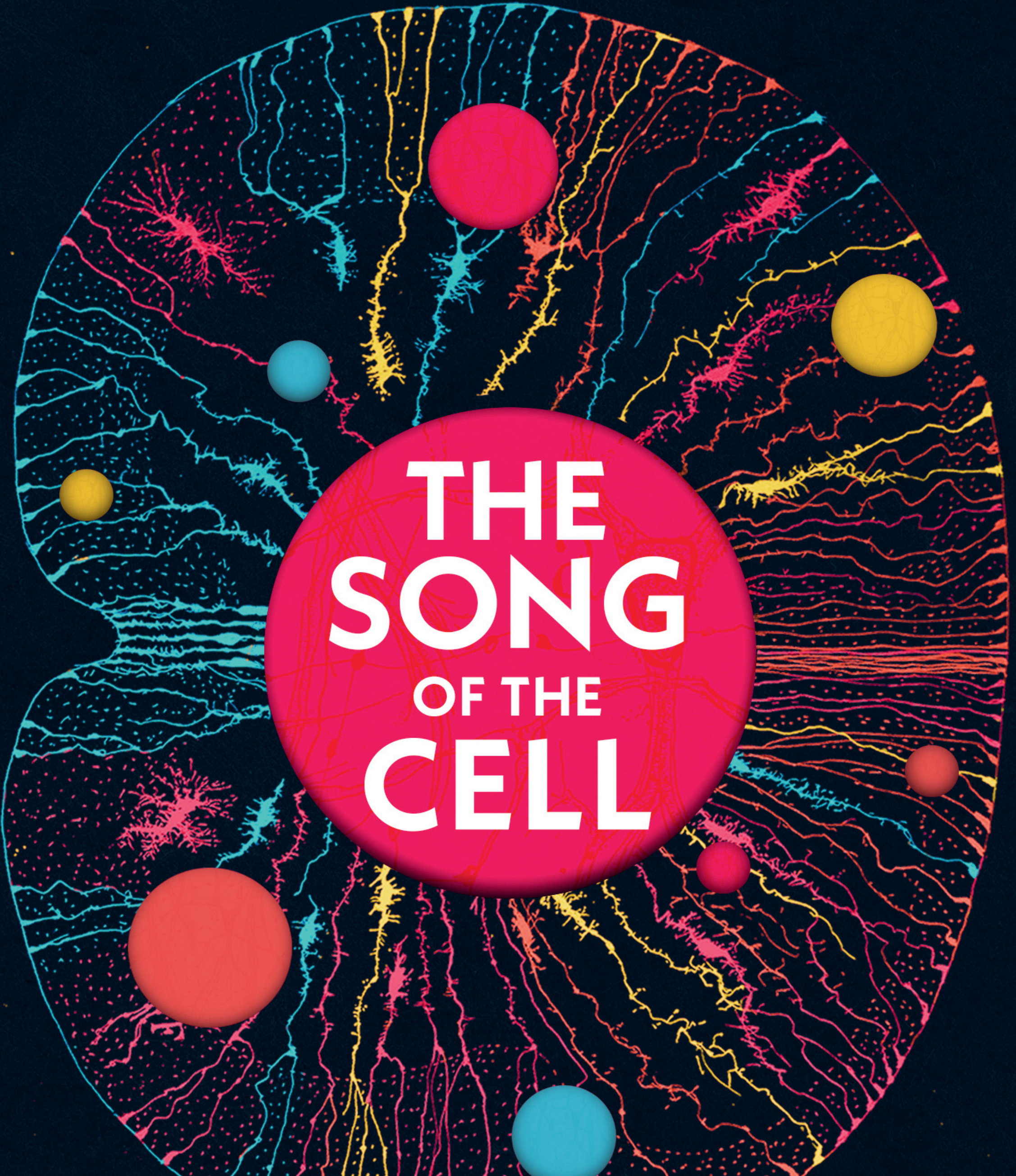

THE SONG OF THE CELL

AN EXPLORATION OF MEDICINE AND THE NEW HUMAN

SIDDHARTHA MUKHERJEE

AUTHOR OF *THE EMPEROR OF ALL MALADIES* AND *THE GENE*

THE SONG OF THE CELL

Also by Siddhartha Mukherjee

The Gene: An Intimate History

The Emperor of All Maladies: A Biography of Cancer

The Laws of Medicine: Field Notes from an Uncertain Science

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To W.K. and E.W.—among the first to cross

In the sum of the parts, there are only the parts.
The world must be measured by eye.

—Wallace Stevens

[Life] is a continuing rhythmic movement,
of the pulse, of the gait, even of the cells.

—Friedrich Nietzsche

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PRELUDE

"The Elementary Particles of Organisms"

"Elementary," he said. "It is one of those instances where the reasoner can produce an effect which seems remarkable to his neighbor, because the latter has missed the one little point which is the basis of the deduction."

—Sherlock Holmes to Dr. Watson,
in Sir Arthur Conan Doyle, "The Crooked Man"

The conversation took place over dinner in October 1837. Dusk had likely fallen, and the city's gas lamps had lit up the central streets of Berlin. Only scattered memories of the evening survive. No notes were taken, and no scientific correspondence ensued. What remains is the story of two friends—lab mates—discussing experiments over a casual meal, and the exchange of one crucial idea.* One of the two diners, Matthias Schleiden, was a botanist. He had a prominent, disfiguring scar across his forehead, the remnant blemish of a prior suicide attempt. The other, Theodor Schwann, a zoologist, had sideburns that descended to his jowls. Both worked under Johannes Müller, the eminent physiologist at the University of Berlin.

Schleiden, a lawyer turned botanist, had been studying the structure and development of plant tissues. He had been "hay gathering" ("*Heusammelei*"), as he called it, and collected hundreds of specimens from the plant kingdom: tulips, dog hobble, spruce, grasses, orchids, sage, linanthus, peas, and dozens of kinds of lilies. His collection was prized among botanists.

That evening, Schwann and Schleiden were discussing phytogenesis—the origin and development of plants. And what Schleiden told Schwann was this: in looking through all his plant specimens, he had found a "unity" in their construction and organization. During the development of plant

*Footnotes for the Prelude have been moved to the endnotes of the book.

tissues—leaves, roots, cotyledons—a subcellular structure, called the nucleus, became prominently visible. (Schleiden did not know the function of the nucleus but recognized its distinctive form.)

But perhaps more surprisingly, there was a deep uniformity in the construction of the tissues. Each part of the plant was built, bricolage-like, out of autonomous, independent units—*cells*. "Each cell leads a double life," Schleiden would write a year later, "an entirely independent one, belonging to its own development alone; and an incidental one, in so far as it has become part of a plant."

A life within a life. An independent living being—a unit—that forms a part of the whole. A living building block contained within the larger living being.

Schwann's ears pricked up. He, too, had noted the prominence of the nucleus, but in the cells of a developing *animal*, a tadpole. And he, too, had noted the uniformity in the microscopic construction of animal tissues. The "unity" that Schleiden had observed in plant cells was, perhaps, a deeper unity that ran through life.

An inchoate but radical thought—one that would swerve the history of biology and medicine—began to form in his mind. Perhaps that very evening, or soon after, he invited Schleiden (or dragged him, possibly) to the lab at the anatomical theater, where Schwann kept his specimens. Schleiden looked through the scope. The developing animal's microscopic structure, including the prominently visible nucleus, Schleiden confirmed, looked almost identical to that of the plant's.

Animals and plants—as seemingly different as living organisms could be. Yet, as both Schwann and Schleiden had noticed, the similarity of their tissues under the microscope was uncanny. Schwann's hunch had been right. That evening in Berlin, he would later recall, the two friends had converged on a universal and essential scientific truth: both animals and plants had a "common means of formation through cells."

In 1838, Schleiden collected his observations in an expansive paper entitled *Contributions to Our Knowledge of Phytogenesis*. A year later, Schwann followed Schleiden's work on plants with his tome on animal cells: *Microscopical Researches into the Accordance in the Structure and Growth of Animals and Plants*. Both plants and animals, Schwann posited, were similarly organized—each an "aggregate of fully individualized independent beings."

In two seminal works, published about twelve months apart, the living world converged to a single, sharp point. Schleiden and Schwann weren't the first to see cells, or to realize that cells were the fundamental units of living organisms. The acuity of their insight was in the proposition that a deep unity of organization and function ran through living beings. "A bond of union" connects the different branches of life, Schwann wrote.

Schleiden left Berlin for a position at the University of Jena in late 1838. And in 1839, Schwann left, too, for a position at the Catholic University in Leuven, Belgium. Despite their dispersal out of Müller's lab, they kept up a lively correspondence and friendship. Their seminal work on the foundations of cell theory is indubitably traced back to Berlin, where they had been intimate colleagues, collaborators, and friends. They had found, in Schwann's words, the "elementary particles of organisms."

This book is the story of the cell. It is a chronicle of the discovery that all organisms, including humans, are made of these "elementary particles." It's a story of how cooperative, organized accumulations of these autonomous living units—tissues, organs, and organ systems—enable profound forms of physiology: immunity, reproduction, sentience, cognition, repair, and rejuvenation. Conversely, it is the story of what happens when cells become dysfunctional, tipping our bodies from cellular physiology into cellular pathology—the malfunctioning of cells precipitating the malfunction of the body. And finally, it is a story about how our deepening understanding of cellular physiology and pathology has sparked a revolution in biology and medicine, leading to the birth of transformational medicines, and of human beings transformed by these medicines.

Between 2017 and 2021, I wrote three articles for the *New Yorker* magazine. The first was about cellular medicine and its future—in particular, about the invention of T cells reengineered to attack cancers. The second concerned a new vision of cancer centered on the idea of the *ecology* of cells—not cancer cells in isolation, but cancer in situ, and why specific locations in the body seem so much more hospitable to malignant growth than other organs do. The third, written in the early days of the Covid-19 pandemic, was about how viruses behave in our cells and bodies, and how that behavior might help us understand the physiological devastation caused by some viruses in humans.

I wondered about the thematic links among these three pieces. At the center of all of them, it seemed, was the story of cells and cellular reengineering. There was a revolution in the making, and a history (and future) that had been unwritten: of cells, of our capacity to manipulate cells, and of the transformation of medicine that is unfolding as this revolution unfolds.

From the seed of those three pieces, this book grew stalks, roots, and tendrils on its own. This chronicle begins in the 1660s and 1670s, when a reclusive Dutch cloth seller and an unorthodox English polymath, working independently, and about two hundred miles apart, looked down their handcrafted microscopes and discovered the first evidence of cells. It moves to the present—a time when human stem cells are being manipulated by scientists and infused into patients with chronic, potentially life-threatening diseases such as diabetes and sickle cell anemia, and electrodes are being inserted into cellular circuits of the brains of men and women with recalcitrant neurological illnesses. And it brings us to the precipice of an uncertain future, in which "maverick" scientists (one of whom was jailed for three years and has been permanently disbarred from performing experiments) are designing gene-edited embryos, and using cell transplantation to blur the boundaries between the natural and the augmented.

I draw from an array of sources: interviews; patient encounters; itinerant walks with scientists (and their dogs); visits to labs; visions through a microscope; conversations with nurses, patients, and doctors; historical sources; scientific papers; and personal letters. My purpose is not to write a comprehensive history of medicine or of the birth of cell biology. Roy Porter's *The Greatest Benefit to Mankind: A Medical History of Humanity,* Henry Harris's *The Birth of the Cell*, and Laura Otis's *Müller's Lab* are exemplary accounts. This, rather, is the story of how the concept of the cell, and our comprehension of cellular physiology, altered medicine, science, biology, social structures, and culture. It culminates in the vision of a future in which we learn to manipulate these units into new forms, or perhaps even create synthetic versions of cells, and parts of humans.

There are, inevitably, gaps and lacunae in this version of the story of the cell. Cell biology is inextricably linked with genetics, pathology, epidemiology, epistemology, taxonomy, and anthropology. Aficionados of particular niches in medicine or cell biology, legitimately partial to a particular cell type, might have viewed this history through a very different eyepiece; botanists, bacteriologists, and mycologists will doubtless miss adequate focus on the plants, bacteria, and fungi. To enter each of these fields in a non-desultory manner would be to enter labyrinths that fork into further labyrinths. I have moved many aspects of the story to footnotes and endnotes. I urge readers to read them seriously.

Throughout this journey, we will meet many patients, including some of my own. Some are named; others chose to be anonymous, with their names and identifying details removed. I feel an immeasurable gratitude to these men and women who have ventured into uncharted territories, entrusting their bodies and minds to an evolving and uncertain realm of science. And I feel an exhilaration, just as immeasurable, as I witness cell biology come to life in a new kind of medicine.

INTRODUCTION

"We Shall Always Return to the Cell"

No matter how we twist and turn,
we shall eventually come back to the cell.

—Rudolf Virchow, 1858

In November 2017, I watched my friend Sam P. die because his cells had rebelled against his body.

Sam had been diagnosed with a malignant melanoma in the spring of 2016. The cancer had first appeared as a coin-shaped mole, purple-black with a halolike aureole, near his cheek. His mother, Clara, a painter, had first noticed it during a late-summer vacation on Block Island. She had cajoled—and then begged and threatened—him to have it examined by a dermatologist, but Sam was a busy, active sportswriter for a big newspaper, with little time to worry about a pesky spot on his cheek. By the time I saw and examined him in March 2017—I was not his oncologist, but a friend had asked me to look at his case—the tumor had grown into a thumb-sized, oblong mass, and there was evidence of a metastasis in his skin. When I touched the growth, he winced in pain.

It is one thing to encounter a cancer, it is quite another to bear witness to its mobility. The melanoma had begun to travel across Sam's face toward his ear. If you looked closely, it had marked its progression like a ferry moving across the water, leaving a wake of stippled, purple dots behind it.

Even Sam, the sportswriter who had spent his life learning about speed, motility, and agility, was astonished by the pace of the melanoma's progression. How, he asked me insistently—*how, how, how*—had a cell that had sat perfectly still in his skin for decades suddenly acquired the properties of a cell capable of careening along his face while also dividing furiously?

But cancer cells don't "invent" any of these properties. They don't build anew, they hijack—or, more accurately, the cells that are fittest for survival, growth, and metasisis are naturally selected. The genes and proteins that cells use to generate the building blocks required for growth are appropriated from the genes and proteins that a developing embryo uses to fuel its fierce burst of expansion during the first days of life. The pathways used by the cancer cell to move across vast bodily spaces are commandeered from those that allow inherently mobile cells in the body to move. The genes that enable unfettered cell division are distorted, mutated versions of genes that allow cell division in normal cells. Cancer, in short, is cell biology visualized in a pathological mirror. And as an oncologist, I am, first, a cell biologist—except one who perceives the normal world of cells reflected and inverted in a looking glass.

In late spring 2016, Sam was prescribed a medicine to turn his own T cells into an army to fight the rebel army that was growing in his body. Consider this thought: for years, perhaps decades, Sam's melanoma and his T cells had coexisted, essentially ignoring each other. His malignancy was invisible to his immune system. Millions of his T cells had brushed past his melanoma every day and just moved on, bystanders that had turned their faces away from a cellular catastrophe.

The drug that Sam had been prescribed would hopefully uncloak the tumor's invisibility and make his T cells recognize the melanoma as a "foreign" invader and reject it, much as T cells reject microbe-infected cells. The passive bystanders would become active effectors. We were engineering the cells in his body to make visible what had previously been invisible.

The discovery of this "uncloaking" medicine was the culmination of radical advances in cellular biology that date back to the 1950s: an understanding of the mechanisms used by T cells to discriminate the self from the nonself, the identification of the proteins that these immune cells use to detect foreign invaders, the uncovering of pathways by which our normal cells resist being attacked by this detection system, the way cancer cells co-opt it to make themselves invisible, and the invention of a molecule that would strip the malignant cells of their cloak of invisibility—each insight, built atop an earlier insight and each dug by cell biologists out of hard, cold earth.

Almost immediately after Sam began his treatment, a civil war unfolded in his body. His T cells, shaken awake to the presence of the cancer, were pitched against his malignant cells, their vengeance provoking further cycles of vengeance. The crimson boil on his cheek turned hot one morning because the immune cells had infiltrated the tumor and unleashed a cycle of inflammation; then the malignant cells folded camp and left, leaving smoldering, dying campfires. When I saw him again a few weeks later, the oblong mass and the stipples behind it had vanished. Instead, there was just the dying remnant of a tumor, shriveled like a large raisin. He was in a remission.

We shared a coffee to celebrate. The remission had not just changed Sam physically; it had charged him psychologically. For the first time in weeks, I saw the creases of worry in his face relax. He laughed.

But then things turned: April 2017 was a cruel month. The T cells that attacked his tumor turned on his own liver, provoking an autoimmune hepatitis, an inflammation of the liver that could barely be controlled with immune-suppressive drugs. In October, we discovered that the cancer—in remission just weeks prior—had battened to his skin, muscles, and lungs, hidey-holing in new organs and finding new niches to survive the attack of his immune cells.

Sam maintained a steely dignity through these victories and setbacks. At times, his withering humor seemed like its own form of counterattack: *he would desiccate the cancer to death*. When I visited him at his desk in the newsroom one day, I asked if he'd like a private space—the men's bathroom, perhaps—where he could show me where the new tumors had arisen. He laughed breezily. "By the time we get to the bathroom, it will have moved to a new site. Better look at it while it's still here."

The doctors blunted the immune assault to control the autoimmune hepatitis, but then the cancer grew back. They restarted the immunotherapy to attack the cancer, and the fulminant hepatitis returned. It was like watching some kind of sport of bestial warfare: put the immune cells on a leash, and the animals would strain against their chains to attack and kill. Unleash them, and they would indiscriminately attack both the cancer and the liver. Sam died on a spring morning, about six months after I had first felt his tumor. In the end, the melanoma won.

On a blustery afternoon in 2019, I attended a conference at the University of Pennsylvania, in Philadelphia. Nearly a thousand scientists, doctors, and biotech researchers converged on a brick-and-stone auditorium on Spruce Street. They were there to discuss advances in a bold frontier in medicine: the use of cells, genetically modified and transplanted into humans, to cure diseases. There were talks on T cell modifications, on new viruses that could deliver genes into cells, and on the next major steps in cellular transplantation. The language, on and off stage, felt as if biology, robotics, science fiction, and alchemy had gotten together on an ecstatic evening and produced a precocious child. "*Reboot the immune system.*" "*Therapeutic cellular reengineering.*" "*Long-term persistence of grafted cells.*" It was a conference about the future.

But the present was also present. Sitting just a few rows ahead of me was Emily Whitehead, then fourteen, a year older than my elder daughter. She had tousled brown hair, wore a yellow-and-black shirt and dark pants, and was in her seventh year of remission from leukemia. "She was happy to miss a day of school," her father, Tom, told me. Emily smiled at the thought.

Emily was Patient No. 7, treated at the Children's Hospital of Philadelphia (CHOP). Nearly everyone in the audience knew her or knew of her: she had altered the history of cellular therapy. In May 2010, Emily had been diagnosed with acute lymphoblastic leukemia (ALL). Among the most rapidly progressive forms of cancer, this leukemia tends to afflict young children.

The treatment for ALL ranks among the most intensive chemo regimens ever devised: seven or eight drugs given in combination, some injected directly into the spinal fluid to kill any cancer cells hiding in the brain and spine. Although the collateral damage of the treatment—permanent numbness in the fingers and toes, brain damage, stunted growth and life-threatening infections, to name just a few—can be daunting, the treatment cures about 90 percent of pediatric patients. Unfortunately, Emily's cancer fell in the remnant 10 percent, proving unresponsive to standard therapy. She relapsed sixteen months into treatment. She was listed for a bone marrow transplant—the only option for a cure—but her condition worsened while she awaited a suitable donor.

"The doctors told me not to Google" her chances of survival, Emily's mother, Kari, told me. "So, of course, I did that right away."

What Kari found on the web was chilling: of the children who relapse early, or relapse twice, almost none survive. When Emily arrived at Children's Hospital in early March 2012, nearly every one of her organs was packed with malignant cells. She was seen by a pediatric oncologist, Stephan Grupp, a gentle, burly man with an expressive, ever-moving mustache, and then enrolled in a clinical trial.

Emily's trial involved infusing her body with her own T cells. But these T cells had to be weaponized, via gene therapy, to recognize and kill her cancer. Unlike Sam, who had received drugs to activate immunity *inside* his body, Emily's T cells had been extracted and grown *outside* her body. This form of treatment had been pioneered by the immunologist Michel Sadelain at the Sloan Kettering Institute in New York and by Carl June at the University of Pennsylvania, building on earlier work by the Israeli researcher Zelig Eshhar.

A few hundred feet from where we had been sitting was the cell therapy unit, a vault-like, enclosed facility with steel doors, sterile rooms, and incubators. There groups of technicians were processing cells collected from dozens of patients enrolled in the clinical studies and then storing them in vat-like freezers. Each freezer bore the name of a character from the animated TV sitcom *The Simpsons*; a fraction of Emily's cells were frozen in Krusty the Clown. Another portion of her T cells had been modified to express a gene that would recognize and kill her leukemia, cultured in the lab to increase their numbers exponentially and then returned to the hospital to infuse them back into Emily.

The infusions, which took place over three days, were largely uneventful. Emily sucked on an ice pop while Dr. Grupp dripped the cells into her veins. In the evenings, she and her parents went to stay with an aunt who lived nearby. The first two nights, she played games and got piggyback rides from her father. On the third day, though, she crashed: throwing up, and spiking an alarming fever. The Whiteheads rushed her back to the hospital. Things rapidly spiraled downward. Her kidneys failed. Emily drifted in and out of consciousness, verging on multi-organ system failure.

"Nothing made sense," Tom told me. His six-year-old daughter was moved to the intensive care unit, where her parents and Grupp kept an all-night vigil.

Carl June, the physician-scientist who was also treating Emily, told me candidly, "We thought she was going to die. I wrote an e-mail to the provost at the university, telling him that one of the first children with the treatment was about to die. The trial was finished. I stored the e-mail in my out-box but never pressed Send."

The lab technicians at Penn worked overnight to determine the cause of the fever. They found no evidence of infection; instead, they found elevated blood levels of molecules called cytokines—signals secreted during active inflammation. In particular, levels of a cytokine known as interleukin 6 (IL-6) were nearly a thousand times normal. As the T cells killed the cancer cells, they were releasing a storm of these chemical messengers, like a rioting crowd disgorging inflammatory pamphlets on a rampage.

By a strange twist of fate, however, June's own daughter had a form of juvenile arthritis, an inflammatory condition. He knew about a new drug, approved by the US Food and Drug Administration (FDA) just four months earlier, that blocks IL-6. As a last-ditch effort, Grupp rushed an application to the hospital pharmacy requesting permission to use the new therapy off-label. The board granted its approval for the IL-6–blocking drug that evening, and Grupp injected Emily with a dose in the ICU.

Two days afterward, on her seventh birthday, Emily woke up. "Boom," Dr. June said, waving his hands in the air. "Boom," he repeated. "It just melted away. We did a bone marrow biopsy twenty-three days later, and she was in a complete remission."

"I have never seen a patient that sick get better so quickly," Grupp told me.

The deft management of Emily's condition—and her startling recovery—saved the field of cell therapy. Emily Whitehead remains in that deep remission to this day. No cancer is detectable in her marrow or her blood. She is considered cured.

"If Emily had died," June told me, it's likely that the whole trial would have been shut down." It would have set back cellular therapy perhaps a decade or even longer.

During a pause in the sessions at the conference, Emily and I joined a tour of the medical campus led by Dr. Bruce Levine, one of Dr. June's colleagues. He is the founding director of the facility at Penn where T cells are modified, quality controlled, and manufactured, and was among the first to handle Emily's cells. The technicians here worked singly or in pairs, checking boxes, optimizing protocols, shuttling cells between incubators, sterilizing their hands.

The facility may as well have doubled as a small monument to Emily. Photographs of her were plastered on the walls: Emily at eight, in pigtails; Emily at ten, holding a plaque; Emily at twelve, with missing front teeth, smiling next to President Barack Obama. At a certain point during the tour, I watched the real Emily looking out the window at the hospital across the street. She could almost see into the corner ICU room where she had been confined for nearly a month.

The rain came down in sheets, streaking the windows with droplets.

I wondered how she felt, knowing that there were three versions of her in the hospital: the one here today, on a break from school; the one in the pictures, who had lived and almost died in the ICU; and the one frozen in the Krusty the Clown freezer next door.

"Do you remember coming into the hospital?" I asked.

"No," she said, looking out into the rain. "I only remember leaving."

As I watched the advance and retreat of Sam's illness, and the remarkable recovery of Emily Whitehead, I knew that I was also observing the birth of a kind of medicine in which cells were being repurposed as tools to fight illness—cellular engineering. But it was also the replay of a centuries-old story. We are built out of cellular units. Our vulnerabilities are built out of the vulnerabilities of cells. Our capacity to engineer or manipulate cells (immune cells, in both Sam's and Emily's cases) has become the basis of a new kind of medicine—albeit a kind of medicine that is still in midbirth. If we knew how to arm Sam's immune cells more effectively against his melanoma without unleashing the autoimmune attack, would he be alive today, spiral notebook in hand, writing sports pieces for a magazine?

Two new humans, examples of cellular manipulation and reengineering. Emily, for whom our understanding of the laws of T cell biology were seemingly sufficient to hold a lethal disease at bay for more than a decade, and, hopefully, for her lifetime. Sam, for whom we still seem to be missing some critical insight of how to balance a T cell's attack on cancer and an attack on the self.

What will the future bring? Let me clarify: I use the phrase "new human" throughout the book, and in its title. I mean it in a very precise sense. I explicitly do not mean the "new human" found in sci-fi visions of the future: an AI-augmented, robotically enhanced, infrared-equipped, blue-pill-swallowing creature who blissfully cohabitates the real and virtual worlds: Keanu Reeves in a black muumuu. Nor do I mean "transhuman," endowed with augmented abilities and capacities that transcend the ones we currently possess.

I mean a human rebuilt anew with modified cells who looks and feels (mostly) like you and me. A woman with crippling, recalcitrant depression whose nerve cells (neurons) are being stimulated with electrodes. A young boy undergoing an experimental bone marrow transplant using gene-edited cells to cure sickle cell disease. A type 1 diabetic infused with his own stem cells that have been engineered to produce the hormone insulin to maintain a normal blood level of glucose, the body's fuel. An octogenarian who, following multiple heart attacks, is injected with a virus that will home to his liver and permanently lower artery-clogging cholesterol, thus reducing his risk of another cardiac event. I mean my father, implanted with neurons, or a neuron-stimulating device, that would have steadied his gait so that he might not have suffered the fall that led to his death.

I find these "new humans"—and the cellular technologies used to create them—vastly more exciting than their imaginary sci-fi counterparts. We've altered these humans to alleviate suffering, using a science that had to be handcrafted and carved with unfathomable labor and love, and technologies so ingenious that they stretch credulity: such as fusing a cancer cell with an immune cell to produce an immortal cell to cure cancer; or extracting a T cell from a young girl's body, engineering it with a virus to weaponize it against leukemia, and then transfusing it back into her body. We will meet these new humans in virtually every chapter in this book. And as we learn to rebuild bodies and parts with cells, we will meet them in the present and in the future: in cafes, supermarkets, train stations, and airports; in neighborhoods; and in our own families. We will find them among our cousins and grandparents, our parents and siblings—and perhaps in our selves.

In a little less than two centuries—from the late 1830s, when the scientists Matthias Schleiden and Theodor Schwann proposed that all animal and plant tissues were made of cells, to the spring of Emily's recovery—a radical concept swept through biology and medicine, touching virtually every aspect of the two sciences, and altering both forever. Complex living organisms were assemblages of tiny, self-contained, self-regulating units—living compartments, if you will, or "living atoms," as the Dutch microscopist Antonie van Leeuwenhoek called them in 1676. Humans were ecosystems of these living units. We were pixelated assemblages, composites, our existence the result of a cooperative agglomeration.

We were a sum of parts.

The discovery of cells, and the reframing of the human body as a cellular ecosystem, also announced the birth of a new kind of medicine based on the therapeutic manipulations of cells. A hip fracture, cardiac arrest, immunodeficiency, Alzheimer's dementia, AIDS, pneumonia, lung cancer, kidney failure, arthritis—all could be reconceived as the results of cells, or systems of cells, functioning abnormally. And all could be perceived as loci of cellular therapies.

The transformation of medicine made possible by our new understanding of cell biology can be broadly divided into four categories.

The first is the use of drugs, chemical substances, or physical stimulation to alter the properties of cells—their interactions with one another, their intercommunication, and their behavior. Antibiotics against germs, chemotherapy and immunotherapy for cancer, and the stimulation of neurons with electrodes to modulate nerve cell circuits in the brain fall in this first category.

The second is the transfer of cells from body to body (including back into our own bodies), exemplified by blood transfusions, bone marrow transplantation, and in vitro fertilization (IVF).

The third is the use of cells to synthesize a substance—insulin or antibodies—that produces a therapeutic effect on an illness.

And most recently, there is a fourth category: the genetic modification of cells, followed by transplantation, to create cells, organs, and bodies endowed with new properties.

Some of these therapies, such as antibiotics and blood transfusion, have been so deeply entrenched in the practice of medicine that we hardly think of them as "cellular therapies." But they arose from our understanding of cell biology (germ theory, as we shall soon see, was an extension of cell theory). Some other therapies, such as immunotherapy for cancer, are twenty-first-century developments. Yet others, such as the infusion of modified stem cells for diabetes, are so new that they are still considered experimental. Yet all these—the old and the new—are "cellular therapies" because they depend critically on our understanding of cell biology. And each advance has changed the course of medicine and, equally, changed our conception of being human and living as humans.

In 1922, a fourteen-year-old boy with type 1 diabetes was resuscitated from a coma—born anew, as it were—by the infusion of insulin extracted from the pancreatic cells of a dog. In 2010, when Emily Whitehead received her infusion of CAR (chimeric antigen receptor) T cells, or twelve years later, when the first patients with sickle cell anemia are surviving, disease-free, with gene-modified blood stem cells, we are transitioning from the century of the gene to a contiguous, overlapping century of the cell.

A cell is the unit of life. But that begs a deeper question: What is "life"? It may be one of biology's metaphysical conundrums that we are still struggling to define the very thing that defines us. Life's definition cannot be captured by a single property. As the Ukrainian biologist Serhiy (or Sergey, as he was commonly known) Tsokolov put it: "Every theory, hypothesis, or point of view adopts life's definitions in accordance with its own scientific interests and premises. There are hundreds of working, conventional definitions of life within scientific discourse, but none has been able to achieve a consensus." (And Tsokolov, who unfortunately died in the prime of his intellectual life in 2009, would know, as it was the particular stone in his shoe. He was an *astro*biologist; his research involved finding life beyond Earth. But how can one find life if scientists are struggling to define the term itself?)

Life's definition, as it stands now, is akin to a menu. It is not one thing but a series of things, a set of *behaviors*, a series of processes, not a single property. To be living, an organism must have the capacity to reproduce, to grow, to metabolize, to adapt to stimuli, and to maintain its internal milieu. Complex, multicellular living beings also possess what I might call "emergent" properties: properties that emerge from systems of cells, such as mechanisms to defend themselves against injury and invasion, organs with specialized functions, physiologic systems of communication between organs and even sentience and cognition. And it is not a coincidence that all these properties repose, ultimately, in the cells, or systems of cells. In a sense, then, one might define life as having cells, and cells as having life.

The recursive definition is not nonsensical. Had Tsokolov met his first astrobiological being—say, an ectoplasmic alien from Alpha Centauri—and asked whether s/he/it is "living" or not, he might have asked whether this Being fulfills the menu of life's properties. But he might have also queried the Being: "Do you have cells?" It is difficult to imagine life without cells, just as it is impossible to imagine cells having no life.

Perhaps that fact outlines the importance of the story of the cell: we need to understand cells to understand the human body. We need them to understand medicine. But most essentially, we need the story of the cell to tell the story of life and of our selves.

What *is* a cell, anyway? In a narrow sense, a cell is an autonomous living unit that acts as a decoding machine for a gene. Genes provide instructions—code, if you will—to build proteins, the molecules that perform virtually all the work in a cell. Proteins enable biological reactions, coordinate signals within the cell, form its structural elements, and turn genes on and off to regulate a cell's identity, metabolism, growth, and death. They are the central functionaries in biology, the molecular machines that enable life.*

Genes, which carry the codes to build proteins, are physically located in a double-stranded, helical molecule called deoxyribonucleic acid (DNA), which is further packaged in human cells into skein-like structures called chromosomes. As far as we know, DNA is present inside every living cell (unless it has been ejected from the cell). Scientists have hunted for cells that use molecules other than DNA to carry their instructions—RNA, for instance—but so far, they've never found an RNA instruction-carrying cell.

By *decoding*, I mean that molecules within a cell *read* certain sections of the genetic code, like musicians in an orchestra reading their parts of a musical score—the cell's individual song—thereby enabling a gene's instructions to become physically manifest in the actual protein. Or, put more

*Genes provide the code to build ribonucleic acid (RNA) that, in turn, is deciphered to build proteins. But aside from carrying the code to make proteins, some of these RNAs carry out diverse tasks in cells, some of which are yet to be deciphered. RNA can also regulate genes and function in concert with proteins in some biological reactions.

simply, a gene carries the code; a cell deciphers that code. A cell thus transforms information into form; genetic code into proteins. A gene without a cell is lifeless—an instruction manual stored inside an inert molecule, a musical score without a musician, a lonely library with no one to read the books within it. A cell brings materiality and physicality to a set of genes. A cell *enlivens* genes.

But a cell is not merely a gene-decoding machine. Having unpacked the code by synthesizing a select set of proteins that is encoded in its genes, a cell becomes an integrating machine. A cell uses this set of proteins (and the biochemical products made by proteins) in conjunction with one another to start coordinating its function, its *behavior* (movement, metabolism, signaling, delivering nutrients to other cells, surveying for foreign objects), to achieve the properties of life. And that behavior, in turn, manifests as the behavior of the organism. The metabolism of an organism reposes in the metabolism of the cell. The reproduction of an organism reposes in the reproduction of a cell. The repair, survival, and death of an organism repose in the repair, survival, and death of cells. The behavior of an organ, or an organism, reposes in the behavior of a cell. The *life* of an organism reposes in the life of a cell.

And finally, a cell is a dividing machine. Molecules within the cell—proteins, again—initiate the process of duplicating the genome. The internal organization of the cell changes. Chromosomes, where the genetic material of a cell is physically located, divide. Cell division is what drives growth, repair, regeneration, and, ultimately, reproduction, among the fundamental, defining features of life.

I have spent a lifetime with cells. Every time I see a cell under a microscope—refulgent, glimmering, alive—I relive the thrill of seeing my first cell. On a Friday afternoon in the fall of 1993, about a week after I had arrived as a graduate student in Alain Townsend's lab at the University of Oxford to study immunology, I had ground up a mouse spleen and plated the blood-tinged soup in a petri dish with factors to stimulate T cells. The weekend passed, and on Monday morning, I switched on the microscope. The room was so dimly lit that it was not even necessary to pull down the curtains—the city of Oxford was *always* dimly lit (if cloudless Italy was a land made for telescopes, then foggy, dark England seemed custom-made for microscopes)—and I put the plate under the scope. Wading beneath the tissue culture medium were masses of translucent, kidney-shaped T cells that possessed what I can describe only as an inner glow and a luminous fullness—the signs of healthy, active cells. (When cells die, the glow dims, and they shrivel and turn granular, or pyknotic, to use the jargon of cell biology.)

"*Like eyes looking back at me,*" I whispered to myself. And then, to my astonishment, the T cell *moved*—deliberately, purposefully, seeking out an infected cell that it might purge and kill. It was alive.

Years later, then, it was nothing less than thrilling—mesmerizing—to watch the cellular revolution unfold in humans. When I first met Emily Whitehead, in a fluorescent-lit corridor outside the auditorium at the University of Pennsylvania, it was as if she had allowed me to enter a portal that linked the future and the past. I trained as an immunologist at first, then a stem cell scientist, and, finally, a cancer biologist before I became a medical oncologist.* Emily embodied all these past lives—not just mine, but, more importantly, the lives and labors of thousands of researchers, looking down thousands of microscopes, over thousands of days and nights. She embodied our desire to get to the luminous heart of the cell, to understand its endlessly captivating mysteries. And she embodied our aching aspiration to witness the birth of a new kind of medicine—cellular therapies—based on our deciphering the physiology of cells.

To encounter my friend Sam in his hospital room and watch his remission and relapse whiplash him week upon week, was to experience an opposite chill—not exhilaration but an apprehension of how much there was yet to learn and know. As an oncologist, I focus on cells that have gone rogue; cells that have marauded spaces where they should not exist; cells dividing out of control. These cells distort and overturn the very behaviors that I describe in this book. I try to understand why and how that happens. You might think of me as a cell biologist caught in an upside-down world. And so the story of the cell is one that is stitched into the very fabric of my scientific and personal lives.

As I wrote furiously from the early months of 2020 into 2022, the

*I even had a brief foray into neurobiology between 1996 and 1999, when I worked with Professor Connie Cepko at Harvard Medical School, studying the development of the retina. I studied glial cells long before they were in vogue in neurobiology. Cepko, a developmental biologist and geneticist, taught me the science and art of lineage tracing, a method that we will encounter later in this book.

Covid-19 pandemic continued wildfiring its way throughout the globe. My hospital, my adopted city of New York, and my homeland overflowed with the bodies of the sick and the dead. By February 2020, the ICU beds at Columbia University Medical Center, where I work, were full of patients drowning in their own secretions, with mechanical ventilators forcing air in and out of their lungs. The early spring of '20 was particularly bleak: New York turned into an unrecognizable, windblown metropolis of empty byways and avenues, where people hid from people. India's most lethal surge hit almost a year later in April and May 2021. Bodies were burned in parking lots, back alleyways, slums, and children's playgrounds. At the crematoria, the fires burned so often and so briskly that the metal grids holding the bodies corroded and melted.

I sat in a clinic room in the hospital at first, and then, when the cancer clinic itself was pared to its bare minimum, isolated with my family at home. Staring out the window at the horizon, I thought yet again about cells. Immunity and its discontents. The Yale University virologist Akiko Iwasaki told me that the central pathology caused by SARS-CoV2 (severe acute respiratory syndrome coronavirus 2) was "immunological misfiring"—a dysregulation of immune cells. I had not even heard the term before, but its immensity hit me: at its core, the pandemic, too, was a disease of cells. Yes, there was the virus, but viruses are inert, lifeless, without cells. Our cells had awoken the plague and brought it to life. To understand crucial features of the pandemic, we would need to understand not just the idiosyncrasies of the virus but also the biology of immune cells and their discontents.

For a while, then, it seemed as if every byway and avenue of my thinking and being led me back to cells. I am not sure how much I conjured this book into life, and how much this book demanded to be written.

In *The Emperor of All Maladies,* I wrote about the aching quest to find cures for cancer or to prevent it. *The Gene* was propelled by the quest to decode and decipher the code of life. *The Song of the Cell* takes us on a very different journey: to understand life in terms of its simplest unit—the cell. This book is not about hunting for a cure or deciphering a code. There is no single adversary. Its protagonists want to understand life by understanding a cell's anatomy, physiology, behavior, and its interactions with surrounding cells. A cell's music. And their medical quest is to seek cellular therapies, to use the building blocks of humans to rebuild and repair humans.

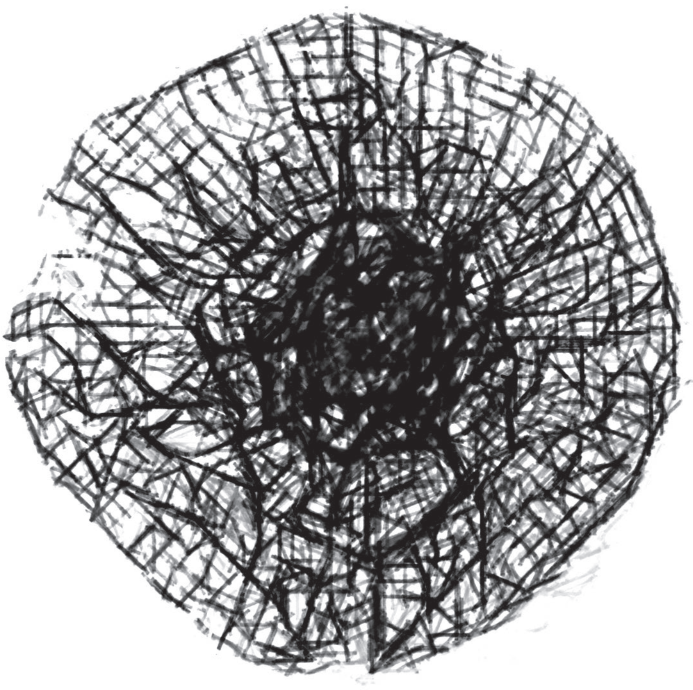
Rather than a chronological unfolding, then, I had to choose a very different structure. Each part of the book takes a fundamental property of complex living beings and explores its story. Each part is a mini history, a chronology of discovery. Each part illuminates a fundamental property of life (reproduction, autonomy, metabolism) that reposes in a particular system of cells. And each contains the birth of new cellular technology (say, bone marrow transplantation, in vitro fertilization [IVF], gene therapy, deep brain stimulation, immunotherapy) that arises from our understanding of cells and challenges our conceptions of how humans are built and how we function. The book is itself a sum of parts: history and personal history, physiology and pathology, past and future—and an intimate chronicle of my own growth as a cell biologist and doctor—spun together into a whole. The organization is cellular, if you will.

When I began this project in the winter of 2019, I chose initially to dedicate it to Rudolf Virchow. I was taken by this reclusive, progressive, soft-spoken German physician-scientist who, resisting the pathological social forces of his times, promoted free thinking, was a champion of public health, despised racism, published his own journal, carved a unique and self-assured path through medicine, and launched an understanding of the study of diseases in organs and tissues based on dysfunctions of cells—"cellular pathology," as he described it.

I returned, in the end, to a patient, a friend, being treated for cancer with a novel form of immunotherapy and Emily Whitehead—patients who had opened new inroads into our understanding of cells and cellular therapy. They were among the first to experience our early attempts to harness cells for human therapy and to transform cellular pathology into cellular medicine—partially successful and partially not. It is to them, and their cells, that this book is dedicated.

PART ONE

Discovery



Both of us, you and I, began as single cells.

Our genes are different, albeit marginally. The way our bodies develop are different. Our skin, our hair, our bones, our brains are all built differently. Our life experiences vary widely. I lost two uncles to mental illness. I lost a father to a deadly spiral following a fall. A knee to arthritis. A friend—so many friends—to cancer.

And yet, despite all the yawning gaps between our bodies and experiences, you and I share two features. First, we arose from a single-celled embryo. And second, from that cell came multiple cells—those that populate your body and mine. We are built of the same material units and are akin to two different nuggets of matter built from the same atoms.

What are we made of? Some ancients believed that we were created by menstrual blood that had congealed into bodies. Some believed we came preformed: mini-beings that just expanded over time, like human-shaped balloons blown up for a parade. Some thought humans were sculpted from mud and river water. Some thought we transformed gradually in the womb from tadpole-like beings to fish-mouthed creatures, and, finally, into humans.

But if you looked down a microscope at your skin and mine, or your liver and mine, you would find them strikingly alike. And you'd realize that all of us were, in fact, built out of living units: cells. The first cell gave rise to more cells, and then divided to form even more, until our livers and guts and brains—all the elaborate anatomical architectures in the body—were gradually formed.

When did we realize that humans were, in fact, composites of independent, living units? Or that these units are the basis of all the functions that the body is capable of—in other words, that our physiology reposes, ultimately, in cellular physiology? And conversely, when did we posit that our medical fates and futures were intimately linked to the changes in these living units? That our diseases are consequences of cellular pathology?

It is to these questions—and embedded within them, the story of a discovery that touched and radically transformed biology, medicine, and our conception of humans—that we first turn.

THE ORIGINAL CELL

An Invisible World

True knowledge is to be aware of one's ignorance.

—Rudolf Virchow, letter to his father, ca. 1830s

Let us give thanks, first, to the softness of Rudolf Virchow's voice. Virchow was born in Pomerania, Prussia (now split between Poland and Germany), on October 13, 1821. His father, Carl, was a farmer and a city treasurer. We know little of his mother, Johanna Virchow, née Hesse. Rudolf was a diligent and bright student—thoughtful, attentive, and clever with languages. He learned German, French, Arabic, and Latin, and earned distinctions for his academic work.

At the age of eighteen, he wrote his high school thesis, "A Life Full of Work and Toil Is Not a Burden but a Benediction," and began to prepare for a professional life in the clergy. He sought to become a pastor and preach to a congregation. But Virchow was anxious about the weakness of his voice. Faith emanated from the strength of inspiration, and inspiration from the strength of elocution. But what if no one could even *hear* him as he tried to project from the pulpit? Medicine and science seemed like more forgiving professions for a reclusive, studious, soft-spoken boy. Upon graduation in 1839, Virchow received a military scholarship and chose to study medicine at the Friedrich-Wilhelms Institute in Berlin.

The world of medicine that Virchow entered in the mid-1800s might have been divided into two halves—anatomy and pathology—one relatively advanced and the other still in a muddle, respectively. In the sixteenth century, anatomists began to describe the forms and structures of the human body with increasing precision. The best-known anatomist of all was the Flemish scientist Andreas Vesalius, a professor at Padua University in Italy. The son of an apothecary, Vesalius arrived in Paris in 1533 to study and practice surgery. He found surgical anatomy in absolute disarray. There were few textbooks and no systematic map of the human body. Most surgeons and their students depended, loosely, on the anatomical teachings of Galen, the Roman physician who lived between AD 129 and 216. Galen's centuries-old treatises on human anatomy were based on animal studies, had become badly outdated, and, frankly, were often incorrect.

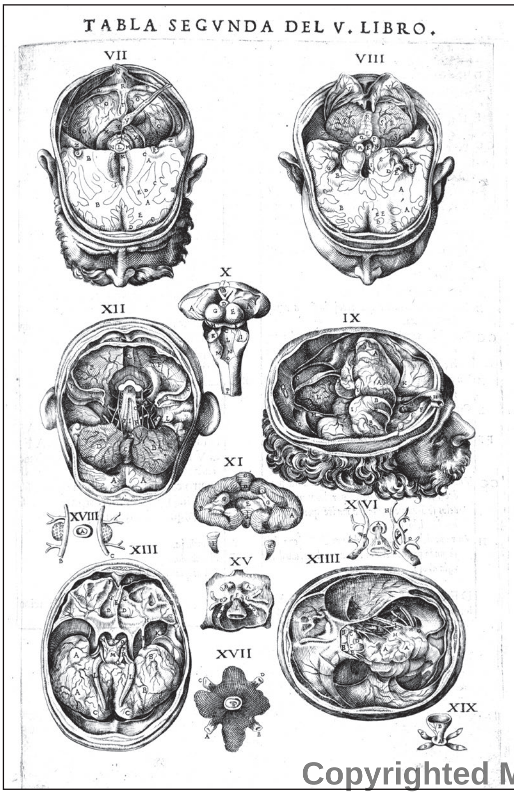
The basement of Paris's hospital Hôtel-Dieu, where decaying human cadavers were dissected, was a dingy, airless, badly lit space with half-feral dogs roaming underneath the gurneys to gnaw on the drippings—a "meat market," as Vesalius would describe one such anatomical chamber. The professors sat on "lofty chairs [and] cackle like jackdaws," he wrote, while their assistants hacked and tugged through the body at random, eviscerating organs and parts as if pulling out cotton stuffing from a toy.

"The doctors did not even attempt cutting," Vesalius wrote bitterly, "but those barbers, to whom the craft of surgery was delegated, were too unlearned to understand the writings of the professors of dissection. . . . They merely chop up the things which are to be shown on the instructions of the physician, who, having never put his hand to cutting, simply steers the boat from the commentary—and not without arrogance. And thus all things are taught wrongly, and days go by in silly disputations. Fewer facts are placed before the spectators in that tumult than a butcher could teach a doctor in his meat market." He concluded, grimly: "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."

Frustrated and confused, Vesalius decided to create his own map of the human body. He raided charnel houses near the hospital, sometimes twice a day, to haul specimens back to his laboratory. The graves at the Cemetery of the Innocents, often open to the air, with bodies ground to the bone, provided perfectly preserved specimens for skeletal drawings. And walking by Montfaucon, the massive, three-tiered gibbet of Paris, Vesalius spotted prisoners' corpses hanging from the gallows. He would secretly make off with the freshly hung bodies, their muscles, viscera, and nerves intact enough for him to flay them open layer by layer and map the locations of the organs.

The intricate drawings that Vesalius produced over the next decade transformed human anatomy. Occasionally, he cut the brain into horizontal sections, like a melon sliced down from its tip, to create the kind of images that a modern computerized axial tomography (CAT) scan might produce. Other times he overlaid the blood vessels above the muscles or opened the muscles into flaps, like a series of anatomical windows that one could imagine passing through to reveal the surfaces and layers beneath them.

He might draw the human abdomen visualized from the bottom up, like the fifteenth-century Italian painter Andrea Mantegna's perspective of Christ's body in *The Lamentation of Christ*, and cut the picture into slices, in the way that a magnetic resonance imaging (MRI) scan might visualize it. He collaborated with the painter and printmaker Jan van Kalkar to produce the most detailed and delicate drawings of human anatomy that existed. In 1543, he published his anatomical works in seven volumes entitled *De Humani Corporis Fabrica* (*The Fabric of the Human Body*). The word *Fabric* in the title was a clue to its texture and purpose: this was the human body treated like physical material, not mystery; made of fabric, not spirit. It was part medical textbook, with nearly seven hundred illustrations, and part scientific treatise, with maps and diagrams that would lay the foundation for human anatomical studies for centuries to come.



A plate from Vesalius's *De Humani Corporis Fabrica* (1543) demonstrating his method of cutting progressive slices through an anatomical structure to highlight the relationships between the substructures above and below it—akin to what a modern CT scanner might find. Books like *De Humani*, illustrated by Jan van Kalkar, revolutionized the study of human anatomy, but no comparably comprehensive textbook of physiology or pathology existed in the 1830s.

Coincidentally, it was published the same year that the Polish astronomer Nicolaus Copernicus would put out his "anatomy of the heavens," the monumental book *The Revolutions* (*On the Revolutions of Heavenly Spheres*), which featured a map of the heliocentric solar system that placed the Earth in orbit and the sun firmly at its center.

Vesalius had put human anatomy at the center of medicine.

But while anatomy, the study of structural elements of the human body, made radical advances, pathology—the study of human diseases, and their causes—had no such center. It was a mapless, dispersed universe. There was no comparable book of pathology, and no common theory to explain diseases—neither revelations, nor *Revolution*s. During the sixteenth and seventeenth centuries, most diseases were attributed to miasmas: poisonous vapors emanating from sewage or contaminated air. The miasmas carried particles of decaying matter called miasmata that somehow entered the body and forced it to decay. (A disease such as malaria still carries that history, its name created by joining the Italian *mala* and *aria* to form "bad air.")

Early health reformers thus concentrated on sanitary reform and public hygiene to prevent and cure illness. They dug sewage systems to dispense waste, or opened ventilation ducts in homes and factories to prevent the contagious fog of miasmata from accumulating indoors. The theory seemed to be fogged by an indisputable logic. Many cities, undergoing rapid industrialization and unable to deal with the influx of wageworkers and their families, were malodorous arenas of smog and sewage—and disease seemed to track the worst-smelling, most populated areas. Resurgent waves of cholera and typhus stalked the poorer parts of London and its vicinities, such as the East End (now glistening with shops and restaurants selling high-end linen aprons and expensive bottles of single-distillery gin). Syphilis and tuberculosis were rampant. Childbirth was a terrifying event, with a distinct likelihood of ending not in birth but in death—of the infant, the mother, or both. In the wealthier parts of town, where the air was clean, and sewage adequately discarded, health prevailed, while the poor, who lived in miasma-filled areas, inevitably succumbed to illness. If cleanliness was the secret to health, then disease must be a condition of uncleanliness or contamination.

But while the notion of vaporous contamination and miasmata seemed to carry a vague ring of truth—and provided perfect justification to further segregate rich and poor neighborhoods in cities—the understanding of pathology was riddled with peculiar puzzles. Why, for instance, did a woman who gave birth in one part of an obstetrics clinic in Vienna, Austria, have nearly three times the rate of postpartum death compared with a woman who gave birth in the adjacent clinic? What caused infertility? Why would a perfectly healthy young man suddenly succumb to a disease that racked his joints with the most excruciating pain?

Throughout the eighteenth and nineteenth centuries, doctors and scientists searched for a systematic way to explain human diseases. But the best they could achieve was an unsatisfactory surplus of explanations that ultimately relied on gross anatomy: each disease was the dysfunction of an individual organ. The liver. The stomach. The spleen. Was there some deeper organizing principle that connected these organs, and their diffuse and mystifying disorders? Could one even think of human pathology in a systematic manner? Perhaps the answer was not to be found in visible anatomy but rather in microscopic anatomy. Indeed, by analogy, eighteenth-century chemists had already begun to discover that the properties of matter—the combustibility of hydrogen or the fluidity of water—arose from the emergent properties of invisible particles, molecules, and atoms that comprised them. Was biology perhaps similarly organized?

Rudolf Virchow was a mere eighteen years old when he enrolled at the Friedrich-Wilhelms Institute of medicine in Berlin. The institute was designed to train medical officers for the Prussian army, and its work ethic was duly martial: students were expected to attend sixty hours of classes a week by day and memorize facts by night. (At the Pépinière, the surgical institute, senior military doctors often surprised students with "attendance drills." If a student was found missing from class, the entire section was punished.) "It goes on like this every day without a stop from six in the morning until eleven at night, except on Sunday," he wrote glumly to his father, "[. . .] and in this process you get so tired that in the evening you find yourself yearning for a hard bed—on which, having slept in half lethargy, you wake up in the morning almost as tired as before." They ate a daily ration of meat, potatoes, and watery soup, and lived in small, isolated, self-contained chambers. Cells.

Virchow learned facts by rote. Anatomy was taught reasonably: the gross map of the body had been slowly perfected since Vesalius's time by generations of vivisectors and thousands of autopsies. But pathology and physiology lacked fundamental logic. Why organs worked, what they did, and why they fell into dysfunction was pure speculation—spun, as if by martial dictum, from conjecture into fact. Pathologists had long been divided into schools that argued for various sources of disease. There were the miasmists, who thought that diseases originated in contaminated vapors; the Galenists, who believed disease to be a pathological imbalance among four bodily fluids and semifluids referred to as "humors"; and the "psychists," who argued that illness was a manifestation of a frustrated mental process. By the time Virchow entered medicine, most of these theories had become confusing or defunct.

In 1843, Virchow finished his medical degree and joined Berlin's Charité hospital, where he began to work closely with Robert Friorep, a pathologist, microscopist, and the curator of pathological specimens at the hospital. Liberated from the intellectual rigidity of his former institute, Virchow yearned to find a systematic way to understand human physiology and pathology. He delved into the history of pathology. "There is an urgent and far-reaching need to understand [microscopic pathology]," he wrote—but the discipline, he felt, had gone off track. Perhaps the microscopists were right: perhaps this systematic answer couldn't be found in the visible world. What if the failing heart or the cirrhotic liver were mere epiphenomena—emergent properties of a deeper underlying dysfunction invisible to the naked eye?

As he pored through the past, Virchow realized that there had been pioneers before him who had also visualized this invisible world. Since the late seventeenth century, researchers had found that plant and animal tissues were all built out of unitary living structures called cells. Might these cells sit at the heart of physiology and pathology? If so, where did they come from, and what did they do?

"True knowledge is to be aware of one's ignorance," Virchow had written in a letter to this father as a medical student in the 1830s. "[H]ow much and how painfully do I feel the gaps in my knowledge. It is for this reason that I do not stand still in any branch of science. . . . There is much that is uncertain and irresolute about me." In medical science, Virchow had found his footing at last, and it was as if an agitated pang in his soul had been soothed. "I am my own advisor," he wrote with newfound confidence in 1847. If cellular pathology did not exist, he would invent the field from scratch. Having acquired the maturity of a physician and a thorough knowledge of medical history, he could finally stand still and fill the gaps.

THE VISIBLE CELL

"Fictitious Stories About the Little Animals"

In the sum of the parts, there are only the parts.
The world must be measured by eye.

—Wallace Stevens

"The world must be measured by eye."

Modern genetics was launched by the practice of agriculture: the Moravian monk Gregor Mendel discovered genes by cross-pollinating peas with a paintbrush in his monastery garden in Brno. The Russian geneticist Nikolai Vavilov was inspired by crop selection. Even the English naturalist Charles Darwin had noted the extreme changes in animal forms created by selective breeding. Cell biology, too, was instigated by an unassuming, practical technology. Highbrow science was born from lowbrow tinkering.

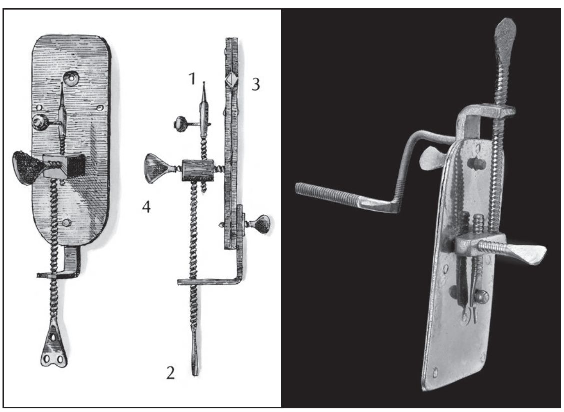
In the case of cell biology, it was simply the art of seeing: the world measured, observed, and dissected by the eye. In the early seventeenth century, a Dutch father and son team of opticians, Hans and Zacharias Janssen, placed two magnifying lenses on the top and bottom of a tube and found that they could magnify an unseen world.* Microscopes with two lenses would be eventually termed "compound microscopes," while those with single lenses were called "simple"; both relied on centuries of innovation in glassblowing that had made its way from the Arabic and Greek worlds to the workshops of Italian and Dutch glassmakers. In the second century BC, the writer Aristophanes described "burning globes": spheres of glass sold as baubles in the market to concentrate and direct beams of light; if you looked

*Some historians have argued that the Janssens' competitors, eyeglass makers Hans Lipperhey and Cornelis Drebbel, invented the compound microscope independently. The dates of all these inventions are in dispute, but likely occurred sometime between the 1590s and the 1620s.

carefully through a burning globe, you might see that same miniature universe magnified. Stretch that burning globe into an eye-sized lens, and you get the spectacle—invented supposedly by an Italian glassmaker, Amati, in the twelfth century. Mount it on a handle, and you have a magnifying glass.

The crucial innovation introduced by the Janssens was to fuse the art of glassblowing to the engineering of moving the pieces of glass on a mounted plate. By assembling one or two perfectly lucid pieces of lens-shaped glass on metal plates or tubes, with systems of screws and cogs to slide them, scientists would soon find their way into an unseen, miniature world—a whole cosmos previously unknown to humans—the obverse of the macroscopic cosmos observable through a telescope.

A secretive Dutch trader had taught himself to visualize this invisible world. In the 1670s, Antonie van Leeuwenhoek, a cloth merchant in Delft, needed an instrument to examine the quality and integrity of thread. Seventeenth-century Netherlands was a booming nexus of cloth merchandising—silks, velvets, wool, linen, and cotton came in swaths and bundles from ports and colonies, and were traded via the Netherlands throughout continental Europe. Building on the Janssens' work, Leeuwenhoek built himself a simple microscope, with a single lens secured on a brass plate, and a tiny stage to mount the specimens. At first, he used it to grade the quality of cloth. But his interest in his handmade instrument soon turned compulsive: he focused his lens on whatever objects he could find.



(a) (b)

(a) A schematic depicting one of Leeuwenhoek's early microscopes showing (1) the sample pin, (2) the main screw (3) the lens, and (4) the focus adjusting knob. (b) One of Leeuwenhoek's actual microscopes, mounted on a brass plate.

On May 26, 1675, the city of Delft was inundated by a storm. Leeuwenhoek, then forty-two, gathered some of the water from the drains of his rooftop, let it stand for a day, and then put a droplet under one of his microscopes and held it up to the light. He was instantly entranced. No one he knew had seen anything like it. The water was roiling with dozens of kinds of tiny organisms—"animalcules," he called them. Telescopists had seen macroscopic worlds—the blue-tinged moon, gaseous Venus, ringed Saturn, red-flecked Mars—but no one had reported a marvelous cosmos of a living world in a raindrop. "This was to me among all the marvels that I have discovered in nature the most marvelous among them all," he wrote in 1676. "No greater pleasure has yet come to my eye than these spectacle of the thousands of living creatures in a drop of water."*

He wanted to look more, to build finer instruments to visualize this captivating new universe of living beings. And so Leeuwenhoek purchased the highest-quality beads and globules of Venetian glass and then ground and polished them laboriously into perfectly lenticular shapes (some of his lenses, we now know, were made by stretching a rod of glass into a thin needle on a live flame, breaking the end, and then letting the needle "bubble" into a lens-shaped globule). He mounted these lenses on thin metal plates, crafted of brass, silver, or gold, each with an increasingly complex system of miniature armatures and screws to move parts of the instrument up and down and attain perfect focus. He made nearly five hundred such scopes, each a marvel of meticulous tinkering.

Were such creatures present in other samples of water as well? Leeuwenhoek entreated a man who was traveling to the seaside to bring him back a sample of ocean water in a "clean glass bottle." And again he found tiny single-celled organisms—"the body of a Mouse Color, clear towards the oval point"—swimming in the water. Eventually, in 1676, he recorded his findings and sent them to the most august scientific society of its time.

"In the year 1675," he wrote to the Royal Society of London, "I discover'd living creatures in Rain water, which had stood but few days in a new earthen pot. . . . When these animalcula or living atoms did move, they put forth two horns, continually moving themselves. . . . The rest of the body

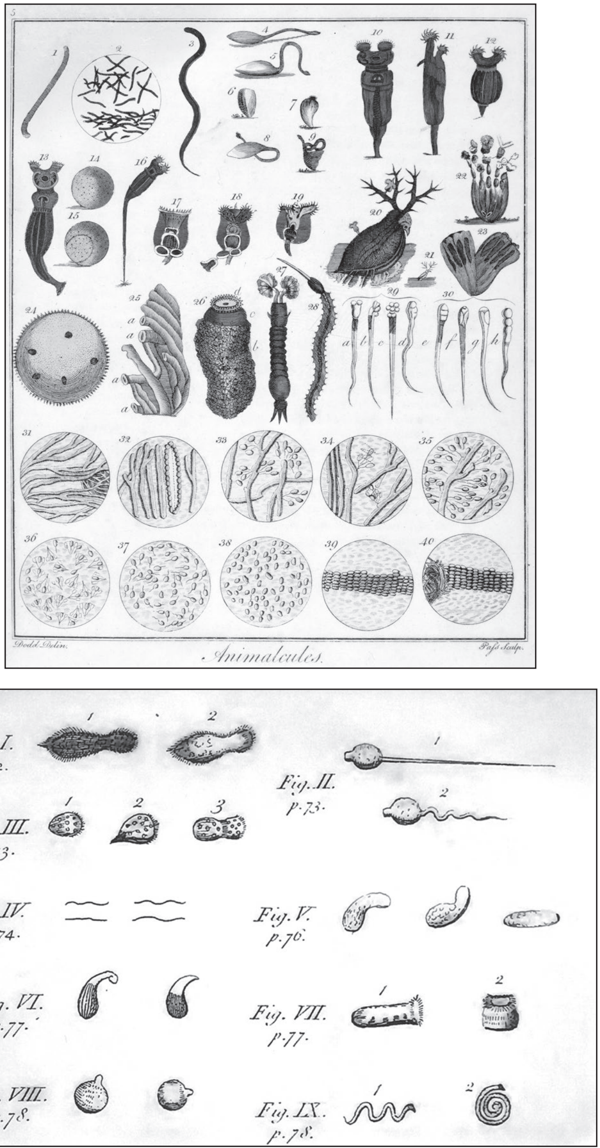
*Leeuwenhoek had observed the presence of microscopic, single-celled organisms as early as 1674, but his letter to the Royal Society, dated 1676, had the most vivid descriptions of such organisms in standing rainwater.

was roundish, sharpening a little toward the end, where they had a tail, nearly four times the length of the body."

By the time I'd finished writing that last paragraph, I was similarly obsessed: I wanted to look as well. Suspended in mid-pandemic limbo, I chose to build my own microscope, or at least the closest version that I could create. I ordered a metal plate and a turning knob, drilled a hole, and mounted the plate with the best tiny lens I could buy. It looked as much like a modern microscope as a bullock cart resembles, say, a spaceship. I trashed dozens of prototypes until I finally had one that might work. On a sunny afternoon, I placed a droplet of stagnant rainwater from a puddle on the mounting pin and held the apparatus up to the sunlight.

Nothing. Hazy forms, like shadows from a ghostly world, moved across my field of vision. A blur. Disappointed, I adjusted the focusing knob gently, as Leeuwenhoek would have. The anticipation made me feel each turn of the screw viscerally, as if the knob were, in fact, twisting its way up my spine. And suddenly I could see. The drop came sharply into view, and then a whole world within it. An amoeboid form flashed across the lens. There were branches of an organism I could not name. Then a spiral organism. A round, moving blob, surrounded by a halo of the most beautiful, the most tender filaments that I had ever seen. I could not stop seeing. *Cells*.

In 1677, Leeuwenhoek observed human spermatozoa, "a genital animalcule," in his semen as well as in a sample from a man with gonorrhea. He found them "moving like a snake or an eel swimming in water." Yet despite his ardor and productivity, the cloth merchant was notoriously reluctant to let observers or scientists examine his instruments. The suspicion was reciprocal, as scientists were often just as dismissive of him. Henry Oldenburg, the secretary of the Royal Society, implored Leeuwenhoek to "acquaint us with his method of observing, that others may confirm such Observations as these," and to provide drawings and confirmatory data, for of the roughly two hundred letters that Leeuwenhoek sent to the society, only about half offered evidence or used scientific methods considered fit for publication. But Leeuwenhoek would provide only vague details of his instruments or his methods. As the science historian Steven Shapin wrote, Leeuwenhoek was "neither a philosopher, a medical man, nor a gentleman. He had been to no university, knew no Latin, French, or English. . . . His claims [about microscopic organisms existing abundantly in water] strained existing schemes of plausibility, and his identity was of no help in securing credibility for those claims."



Some of the "animalcules" observed by Leeuwenhoek through his single-lensed microscope. Note the "Fig II" in the lower panel could either be a human spermatozoon or a bacterium with a flagellar tail.