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To the memory of Alice Mayhew and Carolyn Reidy.

What a joy it was to see them smile.

Introduction

Into the Breach

Jennifer Doudna couldn't sleep. Berkeley, the university where she was a superstar for her role in inventing the gene-editing technology known as CRISPR, had just shut down its campus because of the fast-spreading coronavirus pandemic. Against her better judgment, she had driven her son, Andy, a high school senior, to the train station so he could go to Fresno for a robot-building competition. Now, at 2 a.m., she roused her husband and insisted that they retrieve him before the start of the match, when more than twelve hundred kids would be gathering in an indoor convention center. They pulled on their clothes, got in the car, found an open gas station, and made the three-hour drive. Andy, an only child, was not happy to see them, but they convinced him to pack up and come home. As they pulled out of the parking lot, Andy got a text from the team: "Robotics match cancelled! All kids to leave immediately!"[1]

This was the moment, Doudna recalls, that she realized her world, and the world of science, had changed. The government was fumbling its response to COVID, so it was time for professors and graduate students, clutching their test tubes and raising their pipettes high, to rush into the breach. The next day—Friday, March 13, 2020—she led

a meeting of her Berkeley colleagues and other scientists in the Bay Area to discuss what roles they might play.

A dozen of them made their way across the abandoned Berkeley campus and converged on the sleek stone-and-glass building that housed her lab. The chairs in the ground-floor conference room were clustered together, so the first thing they did was move them six feet apart. Then they turned on a video system so that fifty other researchers from nearby universities could join by Zoom. As she stood in front of the room to rally them, Doudna displayed an intensity that she usually kept masked by a calm façade. "This is not something that academics typically do," she told them. "We need to step up."[2]

It was fitting that a virus-fighting team would be led by a CRISPR pioneer. The gene-editing tool that Doudna and others developed in 2012 is based on a virus-fighting trick used by bacteria, which have been battling viruses for more than a billion years. In their DNA, bacteria develop clustered repeated sequences, known as CRISPRs, that can remember and then destroy viruses that attack them. In other words, it's an immune system that can adapt itself to fight each new wave of viruses—just what we humans need in an era that has been plagued, as if we were still in the Middle Ages, by repeated viral epidemics.

Always prepared and methodical, Doudna (pronounced DOWD-nuh) presented slides that suggested ways they might take on the coronavirus. She led by listening. Although she had become a science celebrity, people felt comfortable engaging with her. She had mastered the art of being tightly scheduled while still finding the time to connect with people emotionally.

The first team that Doudna assembled was given the job of creating a coronavirus testing lab. One of the leaders she tapped was a postdoc named Jennifer Hamilton who, a few months earlier, had spent a day teaching me to use CRISPR to edit human genes. I was pleased, but also a bit unnerved, to see how easy it was. Even I could do it!

Another team was given the mission of developing new types of coronavirus tests based on CRISPR. It helped that Doudna liked

commercial enterprises. Three years earlier, she and two of her graduate students had started a company to use CRISPR as a tool for detecting viral diseases.

In launching an effort to find new tests to detect the coronavirus, Doudna was opening another front in her fierce but fruitful struggle with a cross-country competitor. Feng Zhang, a charming young China-born and Iowa-raised researcher at the Broad Institute of MIT and Harvard, had been her rival in the 2012 race to turn CRISPR into a gene-editing tool, and ever since then they had been locked in an intense competition to make scientific discoveries and form CRISPR-based companies. Now, with the outbreak of the pandemic, they would engage in another race, this one spurred not by the pursuit of patents but by a desire to do good.

Doudna settled on ten projects. She suggested leaders for each and told the others to sort themselves into the teams. They should pair up with someone who would perform the same functions, so that there could be a battlefield promotion system: if any of them were struck by the virus, there would be someone to step in and continue their work. It was the last time they would meet in person. From then on the teams would collaborate by Zoom and Slack.

"I'd like everyone to get started soon," she said. "Really soon."

"Don't worry," one of the participants assured her. "Nobody's got any travel plans."

What none of the participants discussed was a longer-range prospect: using CRISPR to engineer inheritable edits in humans that would make our children, and all of our descendants, less vulnerable to virus infections. These genetic improvements could permanently alter the human race.

"That's in the realm of science fiction," Doudna said dismissively when I raised the topic after the meeting. Yes, I agreed, it's a bit like *Brave New World* or *Gattaca*. But as with any good science fiction, elements have already come true. In November 2018, a young Chinese scientist who had been to some of Doudna's gene-editing conferences used CRISPR to edit embryos and remove a gene that produces a

receptor for HIV, the virus that causes AIDS. It led to the birth of twin girls, the world's first "designer babies."

There was an immediate outburst of awe and then shock. Arms flailed, committees convened. After more than three billion years of evolution of life on this planet, one species (us) had developed the talent and temerity to grab control of its own genetic future. There was a sense that we had crossed the threshold into a whole new age, perhaps a brave new world, like when Adam and Eve bit into the apple or Prometheus snatched fire from the gods.

Our newfound ability to make edits to our genes raises some fascinating questions. Should we edit our species to make us less susceptible to deadly viruses? What a wonderful boon that would be! Right? Should we use gene editing to eliminate dreaded disorders, such as Huntington's, sickle-cell anemia, and cystic fibrosis? That sounds good, too. And what about deafness or blindness? Or being short? Or depressed? Hmmm . . . How should we think about that? A few decades from now, if it becomes possible and safe, should we allow parents to enhance the IQ and muscles of their kids? Should we let them decide eye color? Skin color? Height?

Whoa! Let's pause for a moment before we slide all of the way down this slippery slope. What might that do to the diversity of our societies? If we are no longer subject to a random natural lottery when it comes to our endowments, will it weaken our feelings of empathy and acceptance? If these offerings at the genetic supermarket aren't free (and they won't be), will that greatly increase inequality—and indeed encode it permanently in the human race? Given these issues, should such decisions be left solely to individuals, or should society as a whole have some say? Perhaps we should develop some rules.

By "we" I mean *we*. All of us, including you and me. Figuring out if and when to edit our genes will be one of the most consequential questions of the twenty-first century, so I thought it would be useful to understand how it's done. Likewise, recurring waves of virus epidemics make it important to understand the life sciences. There's a joy that springs from fathoming how something works, especially when that

something is ourselves. Doudna relished that joy, and so can we. That's what this book is about.

The invention of CRISPR and the plague of COVID will hasten our transition to the third great revolution of modern times. These revolutions arose from the discovery, beginning just over a century ago, of the three fundamental kernels of our existence: the atom, the bit, and the gene.

The first half of the twentieth century, beginning with Albert Einstein's 1905 papers on relativity and quantum theory, featured a revolution driven by physics. In the five decades following his miracle year, his theories led to atom bombs and nuclear power, transistors and spaceships, lasers and radar.

The second half of the twentieth century was an information-technology era, based on the idea that all information could be encoded by binary digits—known as bits—and all logical processes could be performed by circuits with on-off switches. In the 1950s, this led to the development of the microchip, the computer, and the internet. When these three innovations were combined, the digital revolution was born.

Now we have entered a third and even more momentous era, a life-science revolution. Children who study digital coding will be joined by those who study genetic code.

When Doudna was a graduate student in the 1990s, other biologists were racing to map the genes that are coded by our DNA. But she became more interested in DNA's less-celebrated sibling, RNA. It's the molecule that actually does the work in a cell by copying some of the instructions coded by the DNA and using them to build proteins. Her quest to understand RNA led her to that most fundamental question: How did life begin? She studied RNA molecules that could replicate themselves, which raised the possibility that in the stew of chemicals on this planet four billion years ago they started to reproduce even before DNA came into being.

As a biochemist at Berkeley studying the molecules of life, she focused on figuring out their structure. If you're a detective, the most

basic clues in a biological whodunit come from discovering how a molecule's twists and folds determine the way it interacts with other molecules. In Doudna's case, that meant studying the structure of RNA. It was an echo of the work Rosalind Franklin had done with DNA, which was used by James Watson and Francis Crick to discover the double-helix structure of DNA in 1953. As it happens, Watson, a complex figure, would weave in and out of Doudna's life.

Doudna's expertise in RNA led to a call from a biologist at Berkeley who was studying the CRISPR system that bacteria developed in their battle against viruses. Like a lot of basic science discoveries, it turned out to have practical applications. Some were rather ordinary, such as protecting the bacteria in yogurt cultures. But in 2012 Doudna and others figured out a more earth-shattering use: how to turn CRISPR into a tool to edit genes.

CRISPR is now being used to treat sickle-cell anemia, cancers, and blindness. And in 2020, Doudna and her teams began exploring how CRISPR could detect and destroy the coronavirus. "CRISPR evolved in bacteria because of their long-running war against viruses," Doudna says. "We humans don't have time to wait for our own cells to evolve natural resistance to this virus, so we have to use our ingenuity to do that. Isn't it fitting that one of the tools is this ancient bacterial immune system called CRISPR? Nature is beautiful that way." Ah, yes. Remember that phrase: Nature is beautiful. That's another theme of this book.

There are other star players in the field of gene editing. Most of them deserve to be the focus of biographies or perhaps even movies. (The elevator pitch: *A Beautiful Mind* meets *Jurassic Park*.) They play important roles in this book, because I want to show that science is a team sport. But I also want to show the impact that a persistent, sharply inquisitive, stubborn, and edgily competitive player can have. With a smile that sometimes (but not always) masks the wariness in her eyes, Jennifer Doudna turned out to be a great central character. She has the instincts to be collaborative, as any scientist must, but ingrained in her character is a competitive streak, which most great innovators

have. With her emotions usually carefully controlled, she wears her star status lightly.

Her life story—as a researcher, Nobel Prize winner, and public policy thinker—connects the CRISPR tale to some larger historical threads, including the role of women in science. Her work also illustrates, as Leonardo da Vinci's did, that the key to innovation is connecting a curiosity about basic science to the practical work of devising tools that can be applied to our lives—moving discoveries from lab bench to bedside.

By telling her story, I hope to give an up-close look at how science works. What actually happens in a lab? To what extent do discoveries depend on individual genius, and to what extent has teamwork become more critical? Has the competition for prizes and patents undermined collaboration?

Most of all, I want to convey the importance of *basic* science, meaning quests that are curiosity-driven rather than application-oriented. Curiosity-driven research into the wonders of nature plants the seeds, sometimes in unpredictable ways, for later innovations.[3] Research about surface-state physics eventually led to the transistor and microchip. Likewise, studies of an astonishing method that bacteria use to fight off viruses eventually led to a gene-editing tool and techniques that humans can use in their own struggle against viruses.

It is a story filled with the biggest of questions, from the origins of life to the future of the human race. And it begins with a sixth-grade girl who loved searching for "sleeping grass" and other fascinating phenomena amid the lava rocks of Hawaii, coming home from school one day and finding on her bed a detective tale about the people who discovered what they proclaimed to be, with only a little exaggeration, "the secret of life."

Part One

The Origins of Life

The Lord God made a garden in the east, in Eden;
and there he put the man he had made.
Out of the ground the Lord God caused to grow
every tree that is beautiful and good for food;
the tree of life also in the midst of the garden,
and the tree of the knowledge of good and evil.

—Genesis 2:8–9

Jennifer in Hilo

Don Hemmes

Ellen, Jennifer, Sarah, Martin, and Dorothy Doudna

Chapter 1

Hilo

Haole

Had she grown up in any other part of America, Jennifer Doudna might have felt like a regular kid. But in Hilo, an old town in a volcano-studded region of the Big Island of Hawaii, the fact that she was blond, blue-eyed, and lanky made her feel, she later said, "like I was a complete freak." She was teased by the other kids, especially the boys, because unlike them she had hair on her arms. They called her a "haole," a term that, though not quite as bad as it sounds, was often used as a pejorative for non-natives. It imbedded in her a slight crust of wariness just below the surface of what would later become a genial and charming demeanor.[1]

A tale that became part of the family lore involved one of Jennifer's great-grandmothers. She was part of a family of three brothers and three sisters. Their parents could not afford for all six to go to school, so they decided to send the three girls. One became a teacher in Montana and kept a diary that has been handed down over the generations. It is filled with tales of perseverance, broken bones, working in the family store, and other frontier endeavors. "She was crusty and stubborn and had a pioneering spirit," said Jennifer's sister Sarah, the current generation's keeper of the diary.

Jennifer was likewise one of three sisters, but there were no brothers. As the oldest, she was doted on by her father, Martin Doudna,

who sometimes referred to his children as "Jennifer and the girls." She was born February 19, 1964, in Washington, D.C., where her father worked as a speechwriter for the Department of Defense. He yearned to be a professor of American literature, so he moved to Ann Arbor with his wife, a community college teacher named Dorothy, and enrolled at the University of Michigan.

When he earned his doctorate, he applied for fifty jobs and got only one offer, from the University of Hawaii at Hilo. So he borrowed $900 from his wife's retirement fund and moved his family there in August 1971, when Jennifer was seven.

Many creative people—including most of those I have chronicled, such as Leonardo da Vinci, Albert Einstein, Henry Kissinger, and Steve Jobs—grew up feeling alienated from their surroundings. That was the case for Doudna as a young blond girl among the Polynesians in Hilo. "I was really, really alone and isolated at school," she says. In the third grade, she felt so ostracized that she had trouble eating. "I had all sorts of digestive problems that I later realized were stress related. Kids would tease me every day." She retreated into books and developed a defensive layer. "There's an internal part of me they'll never touch," she told herself.

Like many others who have felt like an outsider, she developed a wide-ranging curiosity about how we humans fit into creation. "My formative experience was trying to figure out who I was in the world and how to fit in in some way," she later said.[2]

Fortunately, this sense of alienation did not become too ingrained. Life as a schoolkid got better, she developed a genial spirit, and the scar tissue of early childhood began to fade. It would become inflamed only on rare occasions, when some act—an end run on a patent application, a male business colleague being secretive or misleading—scratched deeply enough.

Blossoming

The improvement began halfway through third grade, when her family moved from the heart of Hilo to a new development of cookie-cutter

houses that had been carved into a forested slope further up the flanks of the Mauna Loa volcano. She switched from a large school, with sixty kids per grade, to a smaller one with only twenty. They were studying U.S. history, a subject that made her feel more connected. "It was a turning point," she recalled. She thrived so well that by the time she was in fifth grade, her math and science teacher urged that she skip ahead. So her parents moved her into sixth grade.

That year she finally made a close friend, one she kept throughout her life. Lisa Hinkley (now Lisa Twigg-Smith) was from a classic mixed-race Hawaiian family: part Scottish, Danish, Chinese, and Polynesian. She knew how to handle the bullies. "When someone would call me a f—king haole, I would cringe," Doudna recalled. "But when a bully called Lisa names, she would turn and look right at him and give it right back to him. I decided I wanted to be that way." One day in class the students were asked what they wanted to be when they grew up. Lisa proclaimed that she wanted to be a skydiver. "I thought, 'That is so cool.' I couldn't imagine answering that. She was very bold in a way that I wasn't, and I decided to try to be bold as well."

Doudna and Hinkley spent their afternoons riding bikes and hiking through sugarcane fields. The biology was lush and diverse: moss and mushrooms, peach and arenga palms. They found meadows filled with lava rocks covered in ferns. In the lava-flow caves there lived a species of spider with no eyes. How, Doudna wondered, did it come to be? She was also intrigued by a thorny vine called hilahila or "sleeping grass" because its fernlike leaves curl up when touched. "I asked myself," she recalls, "'What causes the leaves to close when you touch them?'"[3]

We all see nature's wonders every day, whether it be a plant that moves or a sunset that reaches with pink fingers into a sky of deep blue. The key to true curiosity is pausing to ponder the causes. What makes a sky blue or a sunset pink or a leaf of sleeping grass curl?

Doudna soon found someone who could help answer such questions. Her parents were friends with a biology professor named Don Hemmes, and they would all go on nature walks together. "We took excursions to Waipio Valley and other sites on the Big Island to look for mushrooms, which was my scientific interest," Hemmes recalls. After photographing the fungi, he would pull out his reference books

and show Doudna how to identify them. He also collected microscopic shells from the beach, and he would work with her to categorize them so they could try to figure out how they evolved.

Her father bought her a horse, a chestnut gelding named Mokihana, after a Hawaiian tree with a fragrant fruit. She joined the soccer team, playing halfback, a position that was hard to fill on her team because it required a runner with long legs and lots of stamina. "That's a good analogy to how I've approached my work," she said. "I've looked for opportunities where I can fill a niche where there aren't too many other people with the same skill sets."

Math was her favorite class because working through proofs reminded her of detective work. She also had a happy and passionate high school biology teacher, Marlene Hapai, who was wonderful at communicating the joy of discovery. "She taught us that science was about a process of figuring things out," Doudna says.

Although she began doing well academically, she did not feel that there were high expectations in her small school. "I didn't get the sense that the teachers really expected very much of me," she said. She had an interesting immune response: the lack of challenges made her feel free to take more chances. "I decided you just have to go for it, because what the hell," she recalled. "It made me more willing to take on risks, which is something I later did in science when I chose projects to pursue."

Her father was the one person who pushed her. He saw his oldest daughter as his kindred spirit in the family, the intellectual who was bound for college and an academic career. "I always felt like I was the son that he wanted to have," she says. "I was treated a bit differently than my sisters."

James Watson's The Double Helix

Doudna's father was a voracious reader who would check out a stack of books from the local library each Saturday and finish them by the following weekend. His favorite writers were Emerson and Thoreau, but as Jennifer was growing up he became more aware that the books he

assigned to his class were mostly by men. So he added Doris Lessing, Anne Tyler, and Joan Didion to his syllabus.

Often he would bring home a book, either from the library or the local secondhand bookstore, for her to read. And that is how a used paperback copy of James Watson's *The Double Helix* ended up on her bed one day when she was in sixth grade, waiting for her when she got home from school.

She put the book aside, thinking it was a detective tale. When she finally got around to reading it on a rainy Saturday afternoon, she discovered that she was right, in a sense. As she sped through the pages, she became enthralled with what was an intensely personal detective drama, filled with vividly portrayed characters, about ambition and competition in the pursuit of nature's inner truths. "When I finished, my father discussed it with me," she recalls. "He liked the story and especially the very personal side of it—the human side of doing that kind of research."

In the book, Watson dramatized (and overdramatized) how as a twenty-four-year-old bumptious biology student from the American Midwest he ended up at Cambridge University in England, bonded with the biochemist Francis Crick, and together won the race to discover the structure of DNA in 1953. Written in the sparky narrative style of a brash American who has mastered the English after-dinner art of being self-deprecating and boastful at the same time, the book manages to smuggle a large dollop of science into a gossipy narrative about the foibles of famous professors, along with the pleasures of flirting, tennis, lab experiments, and afternoon tea.

In addition to the role of lucky naïf that he concocted as his own persona in the book, Watson's other most interesting character is Rosalind Franklin, a structural biologist and crystallographer whose data he used without her permission. Displaying the casual sexism of the 1950s, Watson refers to her condescendingly as "Rosy," a name she never used, and pokes fun at her severe appearance and chilly personality. Yet he also is generous in his respect for her mastery of the complex science and beautiful art of using X-ray diffraction to discover the structure of molecules.

"I guess I noticed she was treated a bit condescendingly, but what mainly struck me was that a woman could be a great scientist," Doudna says. "It may sound a bit crazy. I guess I must have heard about Marie Curie. But reading the book was the first time I really thought about it, and it was an eye-opener. Women could be scientists."[4]

The book also led Doudna to realize something about nature that was at once both logical and awe-inspiring. There were biological mechanisms that governed living things, including the wondrous phenomena that caught her eye when she hiked through the rainforests. "Growing up in Hawaii, I had always liked hunting with my dad for interesting things in nature, like the 'sleeping grass' that curls up when you touch it," she recalls. "The book made me realize you could also hunt for the reasons why nature worked the way it did."

Doudna's career would be shaped by the insight that is at the core of *The Double Helix*: the shape and structure of a chemical molecule determine what biological role it can play. It is an amazing revelation for those who are interested in uncovering the fundamental secrets of life. It is the way that chemistry—the study of how atoms bond to create molecules—becomes biology.

In a larger sense, her career would also be shaped by the realization that she was right when she first saw *The Double Helix* on her bed and thought that it was one of those detective mysteries that she loved. "I have always loved mystery stories," she noted years later. "Maybe that explains my fascination with science, which is humanity's attempt to understand the longest-running mystery we know: the origin and function of the natural world and our place in it."[5]

Even though her school didn't encourage girls to become scientists, she decided that is what she wanted to do. Driven by a passion to understand how nature works and by a competitive desire to turn discoveries into inventions, she would help make what Watson, with his typical grandiosity cloaked in the pretense of humility, would later tell her was the most important biological advance since the double helix.

Darwin Mendel

Chapter 2

The Gene

Darwin

The paths that led Watson and Crick to the discovery of DNA's structure were pioneered a century earlier, in the 1850s, when the English naturalist Charles Darwin published *On the Origin of Species* and Gregor Mendel, an underemployed priest in Brno (now part of the Czech Republic), began breeding peas in the garden of his abbey. The beaks of Darwin's finches and the traits of Mendel's peas gave birth to the idea of the gene, an entity inside of living organisms that carries the code of heredity.[1]

Darwin had originally planned to follow the career path of his father and grandfather, who were distinguished doctors. But he found himself horrified by the sight of blood and the screams of a strapped-down child undergoing surgery. So he quit medical school and began studying to become an Anglican parson, another calling for which he was uniquely unsuited. His true passion, ever since he began collecting specimens at age eight, was to be a naturalist. He got his opportunity in 1831 when, at age twenty-two, he was offered the chance to ride as the gentleman collector on a round-the-world voyage of the privately funded brig-sloop HMS *Beagle*.[2]

In 1835, four years into the five-year journey, the *Beagle* explored

a dozen or so tiny islands of the Galápagos, off the Pacific coast of South America. There Darwin collected carcasses of what he recorded as finches, blackbirds, grosbeaks, mockingbirds, and wrens. But two years later, after he returned to England, he was informed by the ornithologist John Gould that the birds were, in fact, different species of finches. Darwin began to formulate the theory that they had all evolved from a common ancestor.

He knew that horses and cows near his childhood home in rural England were occasionally born with slight variations, and over the years breeders would select the best to produce herds with more desirable traits. Perhaps nature did the same thing. He called it "natural selection." In certain isolated locales, such as the islands of the Galápagos, he theorized, a few mutations (he used the playful term "sports") would occur in each generation, and a change in conditions might make them more likely to win the competition for scarce food and thus be more likely to reproduce. Suppose a species of finch had a beak suited for eating fruit, but then a drought destroyed the fruit trees; a few random variants with beaks better suited for cracking nuts would thrive. "Under these circumstances, favorable variations would tend to be preserved, and unfavorable ones to be destroyed," he wrote. "The results of this would be the formation of a new species."

Darwin was hesitant to publish his theory because it was so heretical, but competition acted as a spur, as often happens in the history of science. In 1858, Alfred Russel Wallace, a younger naturalist, sent Darwin a draft of a paper that proposed a similar theory. Darwin rushed to get a paper of his own ready for publication, and they agreed that they would present their work on the same day at an upcoming meeting of a prominent scientific society.

Darwin and Wallace had a key trait that is a catalyst for creativity: they had wide-ranging interests and were able to make connections between different disciplines. Both had traveled to exotic places where they observed the variation of species, and both had read "An Essay on the Principle of Population" by Thomas Malthus, an English economist. Malthus argued that the human population was likely to grow faster than the food supply. The resulting overpopulation would

lead to famine that would weed out the weaker and poorer people. Darwin and Wallace realized this could be applied to all species and thus lead to a theory of evolution driven by the survival of the fittest. "I happened to read for amusement Malthus on population, and . . . it at once struck me that under these circumstances favorable variations would tend to be preserved and unfavorable ones to be destroyed," Darwin recalled. As the science fiction writer and biochemistry professor Isaac Asimov later noted concerning the genesis of evolutionary theory, "What you needed was someone who studied species, read Malthus, and had the ability to make a cross-connection."[3]

The realization that species evolve through mutations and natural selection left a big question to be answered: What was the mechanism? How could a beneficial variation in the beak of a finch or the neck of a giraffe occur, and then how could it get passed along to future generations? Darwin thought that organisms might have tiny particles that contained hereditary information, and he speculated that the information from a male and female blended together in an embryo. But he soon realized, as did others, that this would mean that any new beneficial trait would be diluted over generations rather than be passed along intact.

Darwin had in his personal library a copy of an obscure scientific journal that contained an article, written in 1866, with the answer. But he never got around to reading it, nor did almost any other scientist at the time.

Mendel

The author was Gregor Mendel, a short, plump monk born in 1822 whose parents were German-speaking farmers in Moravia, then part of the Austrian Empire. He was better at puttering around the garden of the abbey in Brno than being a parish priest; he spoke little Czech and was too shy to be a good pastor. So he decided to become a math and science teacher. Unfortunately, he repeatedly failed his qualifying exams, even after studying at the University of Vienna. His performance on one biology exam was especially dreadful.[4]

With little else to do after his final failure at passing the exams, Mendel retreated to the abbey garden to pursue what had become his obsessive interest in breeding peas. In previous years, he had concentrated on creating purebreds. His plants had seven traits that came in two variations: yellow or green seeds, white or violet flowers, smooth or wrinkled seeds, and so on. By careful selection, he produced purebred vines that had, for example, only violet flowers or only wrinkled seeds.

The following year he experimented with something new: breeding together plants with differing traits, such as those that had white flowers with those that had violet ones. It was a painstaking task that involved snipping off each of the plant's receptors with forceps and using a tiny brush to transfer pollen.

What his experiments showed was momentous, given what Darwin was writing at the time. There was no blending of traits. Tall plants cross-bred with short ones did not produce medium-size offspring, nor did purple-flowered plants cross-bred with white-flowered ones produce some pale mauve hue. Instead, all the offspring of a tall and a short plant were tall. The offspring from purple flowers crossbred with white flowers produced only purple flowers. Mendel called these the dominant traits; the ones that did not prevail he called recessive.

An even bigger discovery came the following summer, when he produced offspring from his hybrids. Although the first generation of hybrids had displayed only the dominant traits (such as all purple flowers or tall stems), the recessive trait reappeared in the next generation. And his records revealed a pattern: in this second generation, the dominant trait was displayed in three out of four cases, with the recessive trait appearing once. When a plant inherited two dominant versions of the gene or a dominant and a recessive version, it would display the dominant trait. But if it happened to get two recessive versions of the gene, it would display that less common trait.

Science advances are propelled by publicity. The quiet friar Mendel, however, seemed to have been born under a vanishing cap. He presented his paper in 1865, in two monthly installments, to forty farmers and plant-breeders of the Natural Science Society in Brno, which

later published it in its annual journal. It was rarely cited between then and 1900, at which point it was rediscovered by scientists performing similar experiments.[5]

The findings of Mendel and these subsequent scientists led to the concept of a unit of heredity, what a Danish botanist named Wilhelm Johannsen in 1905 dubbed a "gene." There was, apparently, some molecule that encoded bits of hereditary information. Painstakingly, over many decades, scientists studied living cells to try to determine what molecule that might be.

Watson and Crick with their DNA model, 1953

Jews who were having trouble getting tenure on the East Coast, one of the nation's best genetic departments, starring the future Nobel Prize winner Hermann Muller and the Italian émigré Salvador Luria.

With Luria as his PhD advisor, Watson studied viruses. These tiny packets of genetic material are essentially lifeless on their own, but when they invade a living cell, they hijack its machinery and multiply themselves. The easiest of these viruses to study are the ones that attack bacteria, and they were dubbed (remember the term, for it will reappear when we discuss the discovery of CRISPR) "phages," which was short for "bacteriophages," meaning bacteria-eaters.

Watson joined Luria's international circle of biologists known as the Phage Group. "Luria positively abhorred most chemists, especially the competitive variety out of the jungles of New York City," said Watson. But Luria soon realized that figuring out phages would require chemistry. So he helped Watson get a postdoctoral fellowship to study the subject in Copenhagen.

Bored and unable to understand the mumbling chemist who was supervising his studies, Watson took a break from Copenhagen in the spring of 1951 to attend a meeting in Naples on the molecules found in living cells. Most of the presentations went over his head, but he found himself fascinated by a lecture by Maurice Wilkins, a biochemist at King's College London.

Wilkins specialized in crystallography and X-ray diffraction. In other words, he took a liquid that was saturated with molecules, allowed it to cool, and purified the crystals that formed. Then he tried to figure out the structure of those crystals. If you shine a light on an object from different angles, you can figure out its structure by studying the shadows it casts. X-ray crystallographers do something similar: they shine an X-ray on a crystal from many different angles and record the shadows and diffraction patterns. In the slide that Wilkins showed at the end of his Naples speech, that technique had been used on DNA.

"Suddenly I was excited about chemistry," Watson recalled. "I knew that genes could crystallize; hence they must have a regular structure that could be solved in a straightforward fashion." For the next couple

of days, Watson stalked Wilkins with the hope of cadging an invitation to join his lab, but to no avail.

Francis Crick

Instead, Watson was able, in the fall of 1951, to become a postdoctoral student at Cambridge University's Cavendish Laboratory, which was directed by the pioneering crystallographer Sir Lawrence Bragg, who more than thirty years earlier had become, and still is, the youngest person to win a Nobel Prize in science.[3] He and his father, with whom he shared the prize, discovered the basic mathematical law of how crystals diffract X-rays.

At the Cavendish Lab, Watson met Francis Crick, forming one of history's most powerful bonds between two scientists. A biochemical theorist who had served in World War II, Crick had reached the ripe age of thirty-six without having secured his PhD. Nevertheless, he was sure enough of his instincts, and careless enough about Cambridge manners, that he was unable to refrain from correcting his colleagues' sloppy thinking and then crowing about it. As Watson memorably put it in the opening sentence of *The Double Helix*, "I have never seen Francis Crick in a modest mood." It was a line that could likewise have been written of Watson, and they admired each other's immodesty more than their colleagues did. "A youthful arrogance, a ruthlessness, and an impatience with sloppy thinking came naturally to both of us," Crick recalled.

Crick shared Watson's belief that discovering the structure of DNA would provide the key to the mysteries of heredity. Soon they were lunching together on shepherd's pie and talking volubly at the Eagle, a well-worn pub near the labs. Crick had a boisterous laugh and booming voice, which drove Sir Lawrence to distraction. So Watson and Crick were assigned to a pale brick room of their own.

"They were complementary strands, interlocked by irreverence, zaniness, and fiery brilliance," the writer-physician Siddhartha Mukherjee noted. "They despised authority but craved its affirmation. They found the scientific establishment ridiculous and plodding, yet they

knew how to insinuate themselves into it. They imagined themselves quintessential outsiders, yet felt most comfortable sitting in the inner quadrangles of Cambridge colleges. They were self-appointed jesters in a court of fools."[4]

The Caltech biochemist Linus Pauling had just rocked the scientific world, and paved the way for his first Nobel Prize, by figuring out the structure of proteins using a combination of X-ray crystallography, his understanding of the quantum mechanics of chemical bonds, and Tinkertoy model building. Over their lunches at the Eagle, Watson and Crick plotted how to use the same tricks to beat Pauling in the race to discover the structure of DNA. They even had the tool shop of the Cavendish Lab cut tin plates and copper wires to represent the atoms and other components for the desktop model they planned to tinker with until they got all the elements and bonds correct.

One obstacle was that they would be treading on the territory of Maurice Wilkins, the King's College London biochemist whose X-ray photograph of a DNA crystal had piqued Watson's interest in Naples. "The English sense of fair play would not allow Francis to move in on Maurice's problem," Watson wrote. "In France, where fair play obviously did not exist, these problems would not have arisen. The States also would not have permitted such a situation to develop."

Wilkins, for his part, seemed in no rush to beat Pauling. He was in an awkward internal struggle, both dramatized and trivialized in Watson's book, with a brilliant new colleague who in 1951 had come to work at King's College London: Rosalind Franklin, a thirty-one-year-old English biochemist who had learned X-ray diffraction techniques while studying in Paris.

She had been lured to King's College with the understanding that she would lead a team studying DNA. Wilkins, who was four years older and already studying DNA, was under the impression that she was coming as a junior colleague who would help him with X-ray diffraction. This resulted in a combustible situation. Within months they were barely speaking to each other. The sexist structure at King's helped keep them apart: there were two faculty lounges, one for men

and the other for women, the latter unbearably dingy and the former a venue for elegant lunches.

Franklin was a focused scientist, sensibly dressed. As a result she ran afoul of English academia's fondness for eccentrics and its tendency to look at women through a sexual lens, attitudes apparent in Watson's descriptions of her. "Though her features were strong, she was not unattractive and might have been quite stunning had she taken even a mild interest in clothes," he wrote. "This she did not. There was never lipstick to contrast with her straight black hair, while at the age of thirty-one her dresses showed all the imagination of English bluestocking adolescents."

Franklin refused to share her X-ray diffraction pictures with Wilkins, or anyone else, but in November 1951 she scheduled a lecture to summarize her latest findings. Wilkins invited Watson to take the train down from Cambridge. "She spoke to an audience of about fifteen in a quick, nervous style," he recalled. "There was not a trace of warmth or frivolity in her words. And yet I could not regard her as totally uninteresting. Momentarily I wondered how she would look if she took off her glasses and did something novel with her hair. Then, however, my main concern was her description of the crystalline X-ray diffraction pattern."

Watson briefed Crick the next morning. He had not taken notes, which annoyed Crick, and thus was vague about many key points, particularly the water content that Franklin had found in her DNA samples. Nevertheless, Crick started scribbling diagrams, declaring that Franklin's data indicated a structure of two, three, or four strands twisted in a helix. He thought that, by playing with different models, they might soon discover the answer. Within a week they had what they thought was a solution, even though it meant that some of the atoms were crushed together a little too close: three strands swirled in the middle, and the four bases jutted outward from this backbone.

In a fit of hubris, they invited Wilkins and Franklin to come up to Cambridge and take a look. The two arrived the next morning and, with little small talk, Crick began to display the triple-helix structure. Franklin immediately saw that it was flawed. "You're wrong for the

following reasons," she said, her words ripping like those of an exasperated teacher.

She insisted that her pictures of DNA did not show that the molecule was helical. On that point she would turn out to be wrong. But her other two objections were correct: the twisting backbones had to be on the outside, not inside, and the proposed model did not contain enough water. "At this stage the embarrassing fact came out that my recollection of the water content of Rosy's DNA samples could not be right," Watson drily noted. Wilkins, momentarily bonding with Franklin, told her that if they left for the station right away, they could make the 3:40 train back to London, which they did.

Not only were Watson and Crick embarrassed; they were put in a penalty box. Word came down from Sir Lawrence that they were to stop working on DNA. Their model-building components were packed up and sent to Wilkins and Franklin in London.

Adding to Watson's dismay was the news that Linus Pauling was coming over from Caltech to lecture in England, which would likely catalyze his own attempt to solve the structure of DNA. Fortunately, the U.S. State Department came to the rescue. In the weirdness engendered by red-baiting and McCarthyism, Pauling was stopped at the airport in New York and had his passport confiscated because he had been spouting enough pacifist opinions that the FBI thought he might be a threat to the country if allowed to travel. So he never got the chance to discuss the crystallography work done in England, thus helping the U.S. lose the race to figure out DNA.

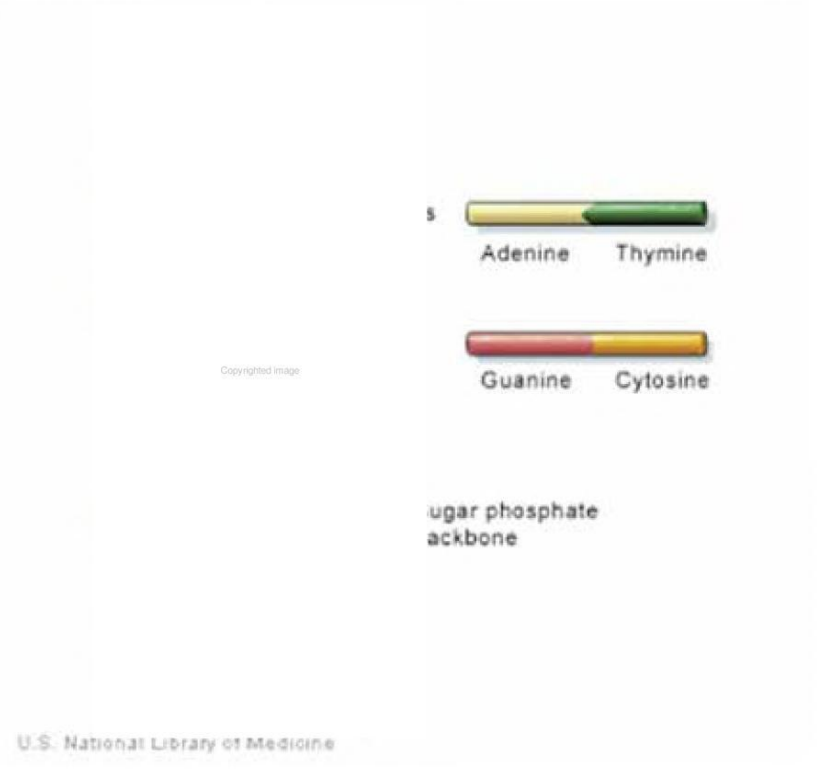
Watson and Crick were able to monitor some of Pauling's progress through his son Peter, who was a young student in their Cambridge lab. Watson found him amiable and fun. "The conversation could dwell on the comparative virtues of girls from England, the Continent, and California," he recalled. But one day in December 1952, young Pauling wandered into the lab, put his feet up on a desk, and dropped the news that Watson had been dreading. In his hand was a letter from his father in which he mentioned that he had come up with a structure for DNA and was about to publish it.

In the unheated train car back to Cambridge, Watson sketched ideas in the margins of his copy of *The Times*. He had to climb over the back gate into his residential college, which had locked up for the night. The next morning, when he went into the Cavendish lab, he encountered Sir Lawrence Bragg, who had demanded that he and Crick steer clear of DNA. But confronted with Watson's excited summary of what he had learned, and hearing of his desire to get back to model-building, Sir Lawrence gave his assent. Watson rushed down the stairs to the machine shop to set them to work on making a new set of components.

Watson and Crick soon got more of Franklin's data. She had submitted to Britain's Medical Research Council a report on her work, and a member of the council shared it with them. Although Watson and Crick had not exactly stolen Franklin's findings, they had appropriated her work without her permission.

By then Watson and Crick had a pretty good idea of DNA's structure. It had two sugar-phosphate strands that twisted and spiraled to form a double-stranded helix. Protruding from these were the four bases in DNA: adenine, thymine, guanine, and cytosine, now commonly known by the letters A, T, G, and C. They came to agree with Franklin that the backbones were on the outside and the bases pointed inward, like a twisted ladder or spiral staircase. As Watson later admitted in a feeble attempt at graciousness, "Her past uncompromising statements on this matter thus reflected first-rate science, not the outpourings of a misguided feminist."

They originally assumed that the bases would each be paired with themselves, for example, a rung that was made up of an adenine bonded to another adenine. But one day Watson, using some cardboard models of bases that he cut out himself, began playing with different pairings. "Suddenly I became aware that an adenine-thymine pair held together by two hydrogen bonds was identical in shape to a guanine-cytosine pair held together by at least two hydrogen bonds." He was lucky to work in a lab of scientists with different specialties; one of them, a quantum chemist, confirmed that adenine would attract thymine and guanine would attract cytosine.



There was an exciting consequence of this structure: when the two strands split apart, they could perfectly replicate, because any half-rung would attract its natural partner. In other words, such a structure would permit the molecule to replicate itself and pass along the information encoded in its sequences.

Watson returned to the machine shop to prod them to speed up production of the four types of bases for the model. By this point the machinists were infused with his excitement, and they finished soldering the shiny metal plates in a couple of hours. With all the parts now on hand, it took Watson only an hour to arrange them so that the atoms comported with the X-ray data and the laws of chemical bonds.

In Watson's memorable and only slightly hyperbolic phrase in *The Double Helix*, "Francis winged into the Eagle to tell everyone within hearing distance that we had found the secret of life." The solution

was too beautiful not to be true. The structure was perfect for the molecule's function. It could carry a code that it could replicate.

Watson and Crick finished their paper on the last weekend of March 1953. It was a mere 975 words, typed by Watson's sister, who was persuaded to do so by his argument that "she was participating in perhaps the most famous event in biology since Darwin's book." Crick wanted to include an expanded section on the implications for heredity, but Watson convinced him that a shorter ending would actually carry more punch. Thus was produced one of the most significant sentences in science: "It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material."

The Nobel Prize was awarded in 1962 to Watson, Crick, and Wilkins. Franklin was not eligible because she had died in 1958, at age thirty-seven, of ovarian cancer, likely caused by her exposure to radiation. If she had survived, the Nobel committee would have faced an awkward situation: each prize can be awarded to only three winners.

Two revolutions coincided in the 1950s. Mathematicians, including Claude Shannon and Alan Turing, showed that all information could be encoded by binary digits, known as bits. This led to a digital revolution powered by circuits with on-off switches that processed information. Simultaneously, Watson and Crick discovered how instructions for building every cell in every form of life were encoded by the four-letter sequences of DNA. Thus was born an information age based on digital coding (0100110111001 . . .) and genetic coding (ACTGGTAGATTACA . . .). The flow of history is accelerated when two rivers converge.

Chapter 4

The Education of a Biochemist

Girls do science

Jennifer Doudna would later meet James Watson, work with him on occasion, and be exposed to all of his personal complexity. In some ways he would be like an intellectual godfather, at least until he began saying things that seemed to emanate from the dark side of the Force. (As Chancellor Palpatine said to Anakin Skywalker, "The dark side of the Force is a pathway to many abilities that some consider to be unnatural.")

But her reactions when she first read his book as a sixth-grader were far simpler. It sparked the realization that it was possible to peel back the layers of nature's beauty and discover, as she says, "how and why things worked at the most fundamental and inner level." Life was made up of molecules. The chemical components and structure of these molecules governed what they would do.

The book also sparked the feeling that science could be fun. All of the previous science books she read had "pictures of emotionless men wearing lab coats and glasses." But *The Double Helix* painted a more vibrant picture. "It made me realize that science can be very exciting, like being on a trail of a cool mystery and you're getting a clue here and a clue there. And then you put the pieces together." The tale of Watson

In the lab at Pomona College

conducted by following a recipe. There was a rigid protocol and a right answer. "The work in Don's lab wasn't like that," she said. "Unlike in class, we didn't know the answer we were supposed to get." It gave her a taste of the thrill of discovery. It also helped her see what it would be like to be part of the community of scientists, making advances and piecing them together to discover the ways that nature worked.

When she returned to Pomona in the fall, she made friends, fit in better, and became more confident in her ability to do chemistry. As part of her work-study program, she had a series of jobs in the college chemistry labs. Most did not engage her because they did not explore how chemistry intersected with biology. But that changed after her junior year, when she got a summer position in the lab of her advisor Sharon Panasenko, a biochemistry professor. "It was more challenging for women biochemists at universities back then, and I admired her not only for being a good scientist but also for being a role model."[5]

Panasenko was studying a topic that aligned with Doudna's interest in the mechanisms of living cells: how some bacteria found in soil are able to communicate so that they can join together when they are starved for nutrients. They form a commune called a "fruiting body." Millions of the bacteria figure out how to aggregate by sending out chemical signals. Panasenko enlisted Doudna to help figure out how those chemical signals worked.

"I have to warn you," Panasenko told her, "that a technician in my lab has been working on growing these bacteria for six months, and he hasn't been able to make it work." Doudna began trying to grow the bacteria in large baking pans rather than the usual Petri dishes. One night she put her preparations in the incubator. "I came in the next day, and when I peeled back the foil on the baking dish that lacked nutrients, I was stunned to see these beautiful structures!" They looked like little footballs. She had succeeded where the other technician had failed. "It was an incredible moment, and it made me think I could do science."

The experiments yielded strong enough results that Panasenko was able to publish a research paper in the *Journal of Bacteriology*, in which

declared it wouldn't work. Doudna was stubborn and went ahead with her idea. "I did it my way and got the clone," she told him. He was surprised but supportive. It was a step in overcoming the insecurity that lurked inside her.

Doudna eventually decided to do her dissertation work in the lab of Jack Szostak, an intellectually versatile Harvard biologist who was studying DNA in yeast. A Canadian American of Polish descent, Szostak was one of the young geniuses then in Harvard's Department of Molecular Biology. Even though he was managing a lab, Szostak was still working as a bench scientist, so Doudna got to watch him perform experiments, hear his thought process, and admire the way he took risks. The key aspect of his intellect, she realized, was his ability to make unexpected connections between different fields.

Her experiments gave her a glimpse of how basic science can be turned into applied science. Yeast cells are very efficient at taking up pieces of DNA and integrating them into their genetic makeup. So she worked on a way to make use of this fact. She engineered strands of DNA that ended with a sequence that matched a sequence in the yeast. With a little electric shock, she opened up tiny passageways in the cell wall of the yeast, allowing the DNA that she made to wriggle inside. It then recombined into the yeast's DNA. She had made a tool that could edit the genes of yeast.

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