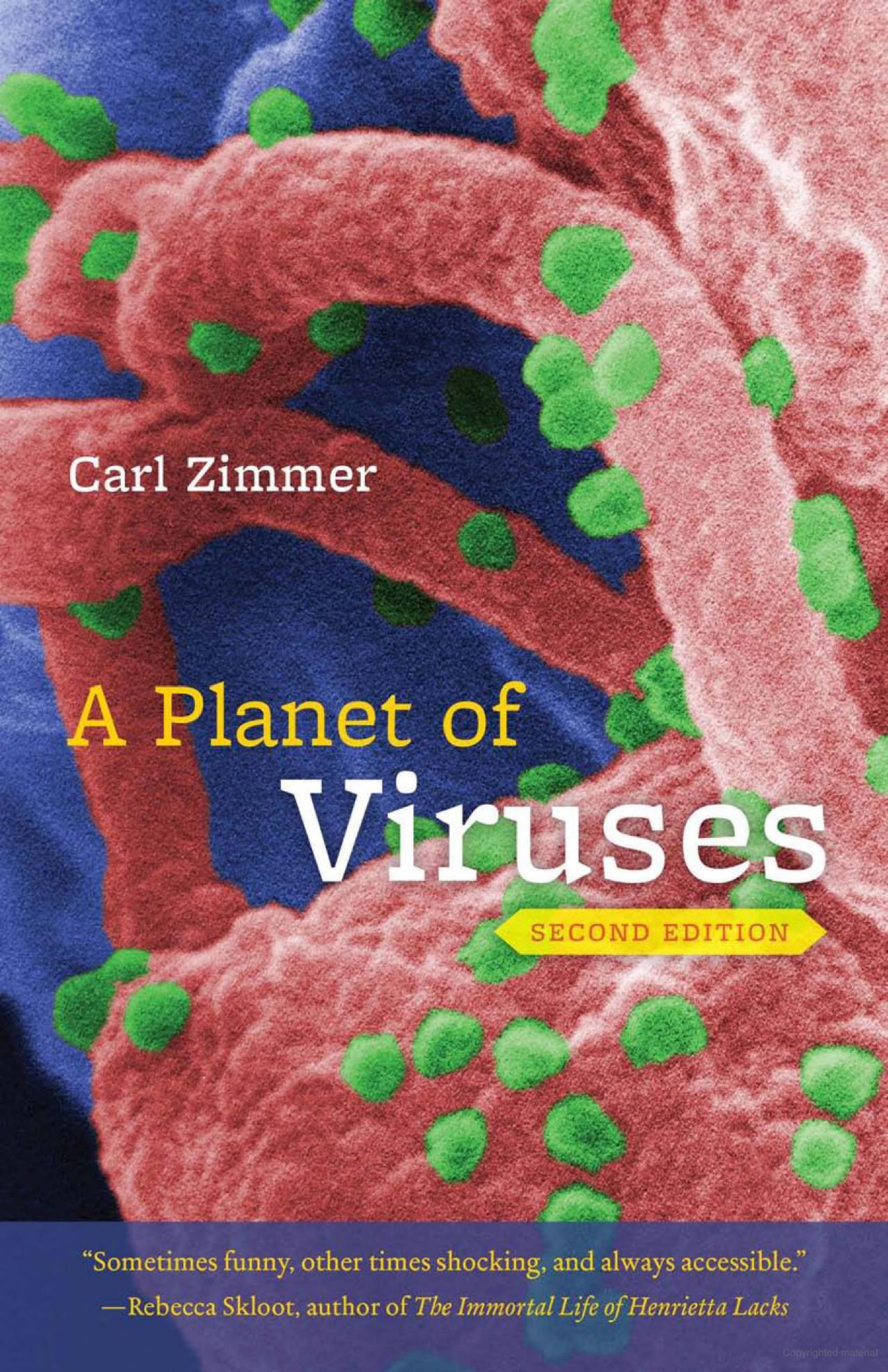

Carl Zimmer

A Planet of Viruses

SECOND EDITION

"Sometimes funny, other times shocking, and always accessible."
—Rebecca Skloot, author of *The Immortal Life of Henrietta Lacks*

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Foreword

Viruses wreak chaos on human welfare, affecting the lives of almost a billion people. They have also played major roles in the remarkable biological advances of the past century. The smallpox virus was humanity's greatest killer, and yet it is now one of the few diseases to have been eradicated from the globe. New viruses, such as HIV, continue to pose new threats and challenges.

Viruses are unseen but dynamic players in the ecology of Earth. They move DNA between species, provide new genetic material for evolution, and regulate vast populations of organisms. Every species, from tiny microbes to large mammals, is influenced by the actions of viruses. Viruses extend their impact beyond species to affect climate, soil, the oceans, and fresh water. When you consider how every animal, plant, and microbe has been shaped through the course of evolution, one has to consider the influential role played by the tiny and powerful viruses that share this planet.

After the first edition of *A Planet of Viruses* was published in 2011, viruses continued to surprise us all. The Ebola virus, once limited to small flare-ups in remote parts of Africa, exploded into a massive outbreak in cities like Freetown and Conakry, and, for the first time, spread to other continents. New viruses, like MERS, leapt from animals to humans. But scientists also discovered new ways to harness the amazing diversity of viruses for our own benefit. Carl Zimmer has drawn on all these developments to produce this second edition of *A Planet of Viruses*.

Zimmer originally wrote these essays for the World of Viruses project as part of a Science Education Partnership Award (SEPA) from the National Center for Research Resources (NCRR) at the National Institutes of Health (NIH). World of Viruses was created to help people understand more about viruses and virology research through radio documentaries, graphic stories, teacher professional development, mobile phone and iPad applications, and other materials. For more information about World of Viruses, visit http://worldofviruses.unl.edu.

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INTRODUCTION

"A Contagious Living Fluid"

Tobacco Mosaic Virus and the Discovery of the Virosphere

Fifty miles southeast of the Mexican city of Chihuahua is a dry, bare mountain range called Sierra de Naica. In 2000, miners worked their way down through a network of caves below the mountains. When they got a thousand feet underground, they found themselves in a place that seemed to belong to another world. They were standing in a chamber measuring thirty feet wide and ninety feet long. The ceiling, walls, and floor were lined with smooth-faced, translucent crystals of gypsum. Many caves contain crystals, but not like the ones in Sierra de Naica. They measured up to thirty-six feet long apiece and weighed as much as fifty-five tons. These were not crystals to hang from a necklace. These were crystals to climb like hills.

Since its discovery, a few scientists have been granted permission to visit this extraordinary chamber, known now as the Cave of Crystals. Juan Manuel García-Ruiz, a geologist at the University of Granada, was one of them. On the basis of his research, he was able to determine the age of the crystals. They formed 26 million years ago, when volcanoes began to form the mountains. Subterranean chambers took shape inside the mountains and filled with hot mineral-laced water. The heat of the volcanic magma kept the water heated to a scalding 136 degrees F, the ideal temperature for the minerals to settle out of the water and form crystals. Somehow the water stayed at that perfect temperature for hundreds of thousands of years, allowing the crystals to grow to surreal sizes.

In 2009, another scientist, Curtis Suttle, paid a visit to the Cave of Crystals. Suttle and his colleagues scooped up water from the chamber's pools and brought it back to their laboratory at the University of British Columbia to analyze. When you consider Suttle's line of work, his journey might seem like a fool's errand. Suttle has no professional interest in crystals, or minerals, or any rocks at all for that matter. He studies viruses.

There are no people in the Cave of Crystals for the viruses to infect. There are not even any fish. The cave has been effectively cut off from the biology of the outside world for millions of years. Yet Suttle's trip was well worth the effort. After he prepared his samples of crystal water, he gazed at them under a microscope. He saw viruses—swarms of them. There are as many as 200 million viruses in every drop of water from the Cave of Crystals.

That same year, another scientists named Dana Willner led a virus-hunting expedition of her own. Instead of a cave, she dove into the human body. Willner had people cough up sputum into a cup, and out of that fluid she and her colleagues fished out fragments of DNA. They compared the DNA fragments to millions of sequences stored in online databases. Much of the DNA was human, but many fragments came from viruses. Before Willner's expedition, scientists had assumed the lungs of healthy people were sterile. Yet Willner discovered that, on average, people have 174 species of viruses in the lungs. Only 10 percent of the species Willner found bore any close kinship to any virus ever found before.

The other 90 percent were as strange as anything lurking in the Cave of Crystals.

Just about wherever scientists look—deep within the Earth, on grains of sand blown off the Sahara, in hidden lakes a mile below the Antarctic ice—they are discovering viruses faster than they can make sense of them. And the science of virology is still young. For thousands of years, we knew viruses only from their effects in sickness and death. Until recently, we did not know how to join those effects to their cause.

The very word *virus* began as a contradiction. We inherited the word from the Roman Empire, where it meant, at once, the venom of a snake or the semen of a man. Creation and destruction in one word.

Over the centuries, *virus* took on another meaning: it signified any contagious substance that could spread disease. It might be a fluid, like the discharge from a sore. It might be a substance that traveled mysteriously through the air. It might even impregnate a piece of paper, spreading disease with the touch of a finger.

Virus began to take on its modern meaning only in the late 1800s, thanks to an agricultural catastrophe. In the Netherlands, tobacco farms were swept by a disease that left plants stunted, their leaves a mosaic of dead and live patches of tissue. Entire farms had to be abandoned.

In 1879, Dutch farmers came to Adolph Mayer, a young agricultural chemist, to beg for help. Mayer carefully studied the scourge, which he dubbed tobacco mosaic disease. He investigated the environment in which the plants grew—the soil, the temperature, the sunlight. He could find nothing to distinguish the healthy plants from the sick ones. Perhaps, he thought, the plants were suffering from an invisible infection. Plant scientists had already demonstrated that fungi could infect potatoes and other plants, so Mayer looked for fungus on the tobacco plants. He found none. He looked for parasitic worms that might be infesting the leaves. Nothing.

Finally Mayer extracted the sap from sick plants and injected drops into healthy tobacco. The healthy plants turned sick. Mayer realized that some microscopic pathogen must be multiplying inside the plants. He took sap from sick plants and incubated it in his laboratory. Colonies of bacteria began to grow. They became large enough that Mayer could see them with his naked eye. Mayer applied these bacteria to healthy plants, wondering if they would trigger tobacco mosaic disease. They did nothing of the sort. And with that failure, Mayer's research ground to a halt. The world of viruses remained unopened.

A few years later, another Dutch scientist named Martinus Beijerinck picked up where Mayer left off. He wondered if something other than bacteria was responsible for tobacco mosaic disease—something far smaller. He ground up diseased plants and passed the fluid through a fine filter that blocked both plant cells and bacteria. When he injected the clear fluid into healthy plants, they became sick.

Beijerinck filtered the juice from the newly infected plants and found that he could infect still more tobacco. Something in the sap of the infected plants—something smaller than bacteria— could replicate itself and could spread disease. In 1898, Beijerinck called it a "contagious living fluid."

Whatever that contagious living fluid carried was different from any other kind of life biologists knew about. It was not only inconceivably small but also remarkably tough. Beijerinck could add alcohol to the filtered fluid, and it would remain infective. Heating the fluid to near boiling did it no harm. Beijerinck soaked filter paper in the infectious sap and let it dry. Three months later, he could dip the paper in water and use the solution to sicken new plants.

Beijerinck used the word *virus* to describe the mysterious agent in his contagious living fluid. It was the first time anyone used the word the way we do today. But in a sense, Beijerinck simply used it to define viruses by what they were *not*. They were not animals, plants, fungi, or bacteria. What exactly they were, Beijerinck could not say.

It soon became clear that what Beijerinck had discovered was just one kind of virus among many. In the early 1900s, other scientists used the same method of filters and infections to trace other diseases to other viruses. Eventually, they learned how to cultivate some viruses outside of living animals and plants, using nothing more than colonies of cells growing in dishes or flasks.

Yet these scientists *still* couldn't agree about what viruses actually were. Some argued viruses were simple chemicals. Others thought viruses were parasites that grew inside cells. The confusion over viruses was so profound that scientists could not even agree if viruses were living or dead. In 1923, the British virologist Frederick Twort declared, "It is impossible to define their nature."

That confusion began to disperse with the work of a chemist named Wendell Stanley. As a chemistry student in the 1920s, Stanley learned how to combine molecules into repeating patterns, forming crystals. Crystals could reveal things about substances that they otherwise kept secret. Scientists could shoot X-rays at the crystals, for example, and observe the directions that the reflected rays bounced away. The patterns produced by the X-rays offered clues to the molecules inside the crystals.

In the early 1900s, crystals helped solved one of biology's biggest mysteries: what enzymes are made of. Scientists had long known that enzymes were produced by animals and other living things to carry out different jobs, such as breaking down food. By making enzyme crystals, scientists discovered they are made of protein. Stanley wondered if viruses were proteins as well.

To find out, he starting trying to make crystals out of viruses. He chose a familiar species for his attempt: tobacco mosaic virus. Stanley collected the juice of infected tobacco plants and then passed it through fine filters, as Beijerinck had done four decades earlier. To allow the viruses to crystallize in pure form, Stanley tried to remove every type of compound from that contagious living fluid except for proteins.

After he had prepared his purified concoction, Stanley watched tiny needles form inside it. They grew into opalescent sheets. For the first time in history, a person could see viruses with the naked eye.

These virus crystals were at once as rugged as a mineral and as alive as a microbe. Stanley could store them away for months like table salt in a pantry. When he then added the crystals to water, they turned back into invisible viruses that could infect tobacco plants as viciously as before.

Stanley's experiment, which he published in 1935, dazzled the world. "The old distinction between death and life loses some of its validity," declared the *New York Times*.

But Stanley had also made a small but profound mistake. The British scientists Norman Pirie and Fred Bawden discovered in 1936 that viruses were not pure protein, but only 95 percent. The other 5 percent consisted of another molecule, a mysterious strand-shaped substance called nucleic acid. Nucleic acids, scientists would later discover, are the stuff of genes, the instructions for building proteins and other molecules. Our cells store their genes in double-stranded nucleic acids, known as deoxyribonucleic acid, or DNA for short. Many viruses have DNA-based genes as well. Other viruses, such as tobacco mosaic virus, have a single-stranded form of nucleic acids, called ribonucleic acid, or RNA.

Four years after Stanley crystallized tobacco mosaic viruses, a team of German scientists finally saw the individual viruses themselves. In the 1930s, engineers invented a new generation of microscopes able to see objects far smaller than had ever been seen before. Gustav Kausche, Edgar Pfannkuch, and Helmut Ruska mixed crystals of tobacco mosaic viruses into drops of purified water and put them under one of the new devices. In 1939, they reported that they could see minuscule rods, measuring about 300 nanometers long. No one had ever seen a living thing anywhere near so small. To contemplate the size of viruses, tap out a single grain of salt onto a table. Stare at the tiny cube. You could line up about ten skin cells along one side of it. You could line up about a hundred bacteria. And you could line up a thousand tobacco mosaic viruses, end to end, alongside that same grain of salt.

In the decades that followed, virologists went on to dissect viruses, to map their molecular geography. While viruses contain nucleic acids and proteins like our own cells, scientists found that differences between the structures of viruses and cells are many. A human cell is stuffed with millions of different molecules that it uses to sense its surroundings, crawl around, take in food, grow, and decide whether to divide in two or kill itself for the good of its fellow cells. Virologists found that viruses, as a rule, were far simpler. They typically were just protein shells holding a few genes.

Virologists discovered that viruses can replicate themselves, despite their paltry genetic instructions, by hijacking other forms of life. They inject their genes and proteins into a host cell, which they manipulate into producing new copies of themselves. One virus goes into a cell, and within a day a thousand viruses may come out.

By the 1950s, virologists had grasped these fundamental facts. But that understanding did not bring virology to a halt. For one thing, virologists knew little about the many different ways in which viruses make us sick. They didn't know why papillomaviruses can cause horns to grow on rabbits and cause hundreds of thousands of cases of cervical cancer each year. They didn't know what made some viruses deadly and others relatively harmless. They had yet to learn how viruses evade the defenses of their hosts and how they evolve faster than anything else on the planet. In the 1950s they did not know that a virus that would later be named HIV had already spread from chimpanzees and gorillas into our own species, or that thirty years later it would become one of the greatest killers in history. They could not have dreamed of the vast number of viruses that exist on Earth; they could not have guessed that much of life's genetic diversity is carried in viruses. They did not know that viruses help produce much of the oxygen we breathe and help control the planet's thermostat. And they certainly would not have guessed that the human genome is partly composed from thousands of viruses that infected our distant ancestors, or that life as we know it may have gotten its start four billion years ago from viruses.

Now scientists know these things—or, to be more precise, they know *of* these things. They now recognize that from the Cave of Crystals to the inner world of the human body, Earth is a planet of viruses. Their understanding is still rough, but it is a start.

So let us start as well.

OLD COMPANIONS