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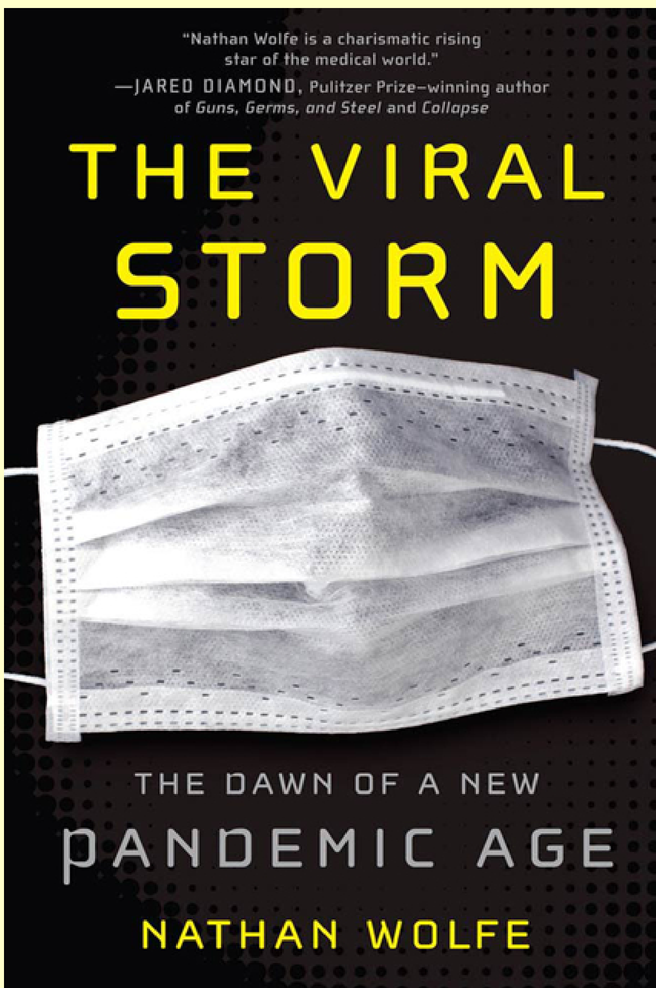

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THE VIRAL PLANET

Martinus Beijerinck was a serious man. In one of the few images that remain of him, he sits in his Delft laboratory in the Netherlands, circa 1921, just a few days before his reluctant retirement. Bespectacled and in a suit, he's presumably as he'd like to be remembered—among his microscopes, filters, and bottles of laboratory reagents. Beijerinck had some peculiar beliefs, including the idea that marriage and science were incompatible. According to at least one account, he was verbally abusive to his students. While rarely remembered in the history of biology, this strange and serious man conducted the pivotal studies that first uncovered the most diverse forms of life on Earth.

Among the things that fascinated Beijerinck in the late nineteenth century was a disease that stunted the growth of tobacco plants. Beijerinck was the youngest child of Derk Beijerinck, a tobacco dealer who went bankrupt due to crop losses caused by this blight. Tobacco mosaic disease causes discoloration in young tobacco plants, leading to a unique mosaic pattern on leaves and radically slowing the growth of the adult plants. As a microbiologist, Beijerinck must have been frustrated by the

Dr. Martinus Beijerinck.
(*Undated photo*)

unclear etiology of the disease that had wiped out his father's business. Despite the fact that it spread like other infections, microscopic analysis did not reveal a bacterial cause of disease. Curious, Beijerinck subjected the fluids of one of the diseased plants to intense filtration using a fine-grained porcelain filter. He then demonstrated that even after such filtration the fluids retained their capacity to infect healthy plants. The tiny size of the filter meant that bacteria, the usual suspects for transmissible disease at the time, would be too large to pass through. Something else must have caused the infection—something unknown and considerably smaller than everything else recognized to be alive in his time.

Unlike his colleagues, many of whom believed a bacteria would emerge as the cause, Beijerinck concluded that a new form of life must cause tobacco mosaic disease.* He named this

* There are some who consider Dmitri Ivanovski the "father of virology" because he did similar research with tobacco mosaic virus six years earlier. But perhaps because he wasn't the first to name the new entities (i.e., viruses) or did not as widely disseminate his findings as Beijerinck, he is not generally credited with their discovery.

new organism the *virus*, a Latin word referring to poison. The word *virus* had been around since the fourteenth century, but his use was the first to link it to the microbes to which it refers today.* Interestingly, Beijerinck referred to viruses as "contagium vivium fluidum," or "soluble living agent," and felt they were likely fluid in nature. That is why he used the term *virus*—or poison—to denote its "fluidity." It wasn't until later work with the polio and foot-and-mouth-disease viruses that the particulate nature of viruses was confirmed.

In Beijerinck's time a new microscopic perspective began revealing itself to scientists. Looking through microscopes and applying gradually smaller filters, these microbiologists realized something that continues to amaze us today: shielded from our human-scaled senses is a wide, teeming, startlingly diverse, unseen world of microbial life.

I teach a seminar at Stanford called Viral Lifestyles. The title was meant to evoke curiosity among prospective students but also describe one of the course's objectives: to learn to envision the world from the perspective of a virus. In order to understand viruses and other microbes, including how they cause pandemics, we need to first understand them on their own terms.

The thought experiment that I give my students on the first day is this: imagine that you have powerful glasses allowing you to perceive any and all microbes. If you were to put on such magical bug-vision specs, you would instantly see a whole

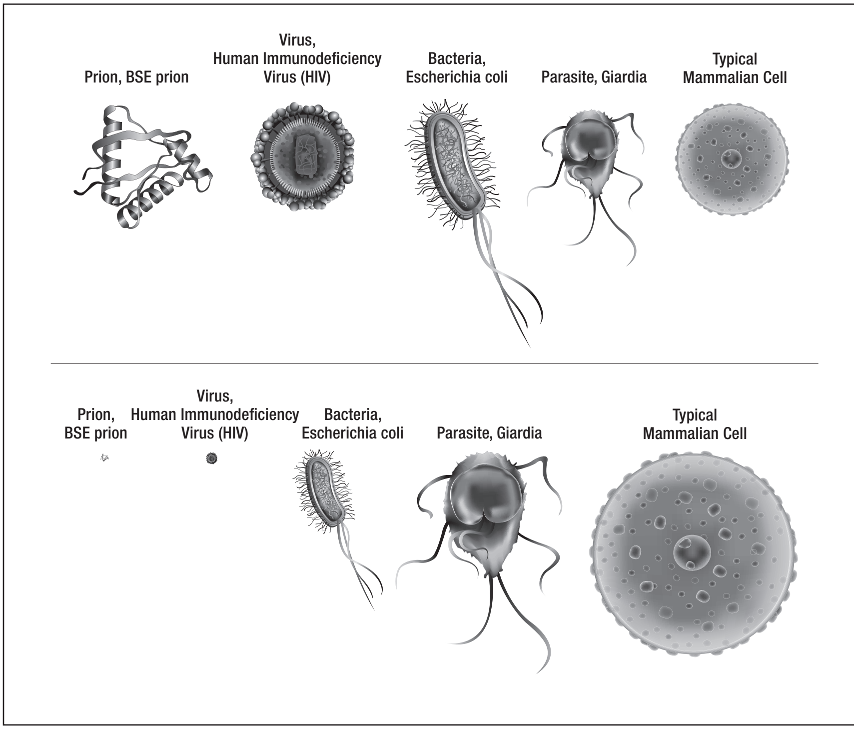
* In addition to his pivotal work as the first virus hunter, creating the foundations of what would later become the field of virology, Beijerinck remains an unsung hero for those studying the relationships between plants and bacteria. Among other notable findings, he discovered nitrogen fixation, whereby bacteria living in the roots of legumes make nitrogen available to plants through a set of biochemical reactions critical for the fertility of agricultural soil systems.

new, and very active, world. The floor would seethe, the walls would throb, and everything would swarm with formerly invisible life. Tiny bugs would blanket every surface—your coffee cup, the pages of the book on your lap, your actual lap. The larger bacteria would themselves teem with still smaller bugs.

This alien army is everywhere, and some of its most powerful soldiers are its smallest. These smallest of bugs have integrated themselves, quite literally, into every stitch of the fabric of earthly life. They are everywhere, unavoidable, infecting every species of bacterium, every plant, fungus, and animal that makes up our world. They are the same form of life that Beijerinck found in the late days of the nineteenth century, and they are among the most important of the microbial world. They are viruses.

Viruses consist of two basic components, their genetic material—either RNA or DNA—and a protein coat that protects their genes. Because viruses don't have the mechanisms to grow or reproduce on their own, they are dependent on the cells they infect. In fact, viruses *must* infect cell-based life forms in order to survive. Viruses infect their host cells, whether they are bacterial or human, through the use of a biological lock-and-key system. The protein coat of each virus includes molecular "keys" that match a molecular "lock" (actually called a receptor) on the wall of a targeted host cell. Once the virus's key finds a matching cellular lock, the door to that cell's machinery is opened. The virus then hijacks the machinery of that host cell to grow and propagate itself.

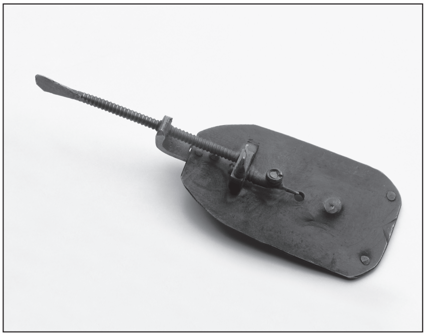
Viruses are also the smallest known microbes. If a human were blown up to the size of a stadium, a typical bacterium would be the size of a soccer ball on the field. A typical virus would be the size of one of the soccer ball's hexagonal patches. Though humans have always felt virus's effects, it's no wonder it took us so long to find them.



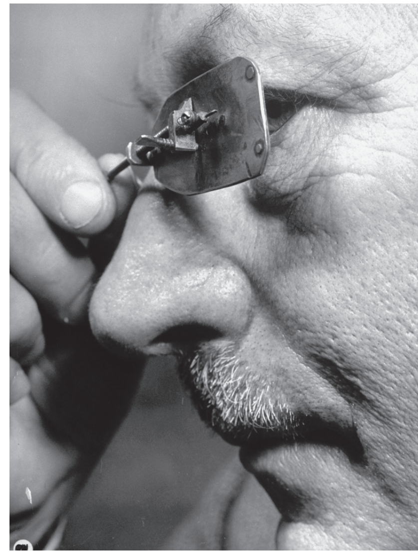
Microbes, Above: In detail; Below: To scale. (*Dusty Deyo*)

Viruses, the most diverse forms of life, remained completely opaque to humans until a meager one hundred years ago with Beijerinck's discovery. Our very first glimpses of bacteria came a little under four hundred years ago when Antonie van Leeuwenhoek adapted the looking glasses of textile merchants to create the first microscope. With it, he saw bacteria for the first time. This finding represented such an incredible paradigm shift that it took the British Royal Society another four years before it would accept that the unseen life forms were not merely artifacts of his unique apparatus.

Our scientific understanding of unseen life has proceeded pitifully slowly. Compared to some of the other major scientific breakthroughs over the last few thousand years, our understanding of the dominance of unseen life occurred only recently. By



L: Replica of van Leeuwenhoek's microscope, 17th century; R: van Leeuwenhoek's microscope in use. (*L: Dave King / Getty Images; R: Yale Joel / Getty Images*)



the time of Jesus, for example, we already understood critical elements of how the Earth rotated, its rough size, and its approximate distance to the sun and moon—all fairly advanced elements in understanding our place in the universe. By 1610 Galileo had already made his first observations using a telescope. Van Leeuwenhoek's microscope came fifty years after that.

It is hard to overstate the paradigm shift that van Leeuwenhoek's discovery represents. For thousands of years humans had recognized the existence of planets and stars. Yet our understanding of unseen life and its ubiquity began only a few hundred years ago with the invention of the microscope. The discovery of novel life forms continues to this day. The most recent novel life form to be uncovered is the unusual prion, whose discovery was acknowledged with a Nobel Prize in 1997. Prions are an odd microscopic breed that lack not only cells but also DNA or RNA, the genetic material that all other known forms of life on Earth use as their blueprint. Yet prions persist and can be spread, causing, among other things, mad cow disease. We would be arrogant to assume that there are no other life forms remaining to be discovered here on Earth, and they are most likely to be members of the unseen world.*

We can roughly divide known life on Earth into two groups: *noncellular* life and *cellular* life. The major known players in the noncellular game are viruses. The dominant cellular life forms on Earth are the prokaryotes, which include bacteria and their cousins, the archaea. These life forms have lived for at least 3.5 billion years. They have striking diversity and together make up a much larger percentage of the planet's biomass than the other more recognizable cellular forms of life, the eukaryotes, which include the familiar fungi, plants, and animals.

Another way of categorizing life is this: seen and unseen. Because our senses detect only the relatively large things on Earth, we are parochial in the way that we think about the richness of life. In fact, unseen life—which combines the worlds of bacteria, archaea, and viruses as well as a number of microscopic eukaryotes—is the truly dominant life on our planet. If some highly advanced extraterrestrial species were to land on Earth and put together an encyclopedia of life based on which things made up most of Earth's diversity and biomass, the majority of it would be devoted to the unseen world. Only a few slender volumes would be dedicated to the things we normally equate with life: fungi, plants, and animals. For better or worse, humans would make up no more than a footnote in the animal volume—an interesting footnote but a footnote at best.

Global exploration to chart the diversity of microbes on the

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* Among the most intriguing possibilities is that non-DNA/non-RNA forms of life, which originated completely independently of our own RNA/DNA-based life, might persist undetected on Earth. These life forms, referred to as shadow life, would almost certainly be microscopic. If discovered, they might best be described as aliens, and some believe that if we are to discover aliens within our lifetimes, looking on Earth will be our best shot.

planet remains in its infancy. Considering viruses alone gives some sense of the scale of what's unknown. It's thought that every form of cellular life hosts at least one type of virus. Essentially—if it has cells, it can have viruses. Every alga, bacterium, plant, insect, mammal. Everything. Viruses inhabit an entire microscopic universe.

Even if every species of cellular life harbored only one unique virus, that would by definition make viruses the most diverse known life forms on the planet. And many cellular life forms, including humans, harbor a range of distinct viruses. They are found everywhere—in our oceans, on land, deep underground.

The dominant forms of life on our planet, when measured in terms of diversity, are unambiguously microscopic.

The largest virus to be discovered is the still microscopic six-hundred-nanometer Mimivirus—viruses are by nature tiny. But the sheer number of viruses in our world leaves a significant biological impression. A groundbreaking paper published in 1989 by Oivind Bergh and his colleagues at the University of Bergen in Norway found up to 250 million virus particles per milliliter of seawater, using electron microscopy to count the viruses. Alternate, more comprehensive measurements of the biomass of viruses on Earth are even more unimaginably outsized. One estimate suggests that if all the viruses on Earth were lined up head to tail the resulting chain would extend 200 million light years, far beyond the edge of the Milky Way. Though often thought of as a pesky irritant or blight, viruses actually serve a role that goes far beyond, and has a much greater impact than, what was previously understood—a role that scientists are only just beginning to comprehend.

It's true that in order to complete their life cycle, viruses have to infect cellular forms of life, but their role is not necessarily destructive or harmful. Like any major component of the global ecosystem, viruses play a vital role in maintaining global equilibrium. The 20 to 40 percent of bacteria in marine ecosystems that viruses kill every day, for example, serves a vital function in the resulting release of organic matter, in the form of amino acids, carbon, and nitrogen. And though studies in this area are few, it is largely believed that viruses, in any given ecosystem, play the role of "trust busters"—helping to ensure that no one bacterial species becomes too dominant—thereby facilitating diversity.

Given the ubiquity of viruses, it would be surprising indeed if they were relegated to a destructive role. Further studies will likely reveal the profound ecological importance of these organisms not just in destroying but also in benefiting many of the life forms they infect. Since Beijerinck's discovery, the vast majority of research conducted on viruses has understandably focused on the deadly ones. In the same way, we know much more about venomous snakes, despite the fact that they represent a startlingly small percentage of snake diversity. As we consider the frontiers of virology in part III, we will explore the potential benefits of viruses in detail.

Viruses infect all known groups of cellular life. Whether a bacterium living in the high-pressure depths of the planet's upper crust or a cell in a human liver, for a virus, each is just a place to live and produce offspring. From the perspective of viruses and other microbes, our bodies are habitats. Just as a forest provides a habitat for birds and squirrels, our bodies provide the local environment in which these beings live. And survival in these environments presents a range of challenges. Like all forms of life, viruses compete with each other for access to resources.

Viruses face constant pressure from our immune systems, which have multiple tactics to block their entrance into the body or disarm and kill them when they manage to get in. They face constant life choices: should they spread, which risks capture by our immune systems, or remain in latency, a form of viral hibernation, which can provide protection but sacrifices offspring.

The common cold sore, caused by the herpes simplex virus, illustrates some of the challenges that viruses face in negotiating the complex habitats of our bodies. These viruses find refuge in nerve cells, which because of their privileged and protected positions in our bodies do not receive the same level of immune attention as the cells in our skin, mouth, or digestive tract. Yet a herpes virus that maintained itself within a nerve cell without spreading would hit a dead end. So herpes viruses sometimes spread down through the nerve cell ganglions to the face to create virus-loaded cold sores that provide them a route to spread from one person to the next.

How viruses choose when to launch themselves remains largely unknown, but they almost certainly monitor the environmental variables of their world when making these decisions. Many of the adult humans who are infected with herpes simplex virus know that stress can bring on cold sores. Some also have noted anecdotally that pregnancy seems to bring on active infections. While still speculation, it would not be surprising if viruses responded to environmental cues indicating severe stress or pregnancy by activating. Since severe stress can indicate the possibility of death, it may be their last opportunity to spread—a dead host is also a dead virus. A pregnancy, on the other hand, presents the opportunity for spread either through genital contact with the baby during childbirth or during the kissing that inevitably follows the birth of a baby.