Smallpox was among the most fearsome diseases we have ever encountered and dates back tens of thousands of years, when it would routinely decimate large populations throughout Africa, China, and Europe. It may have been responsible for the death of the Egyptian pharaoh Ramses V, whose mummified head reveals classic smallpox scars. Later, smallpox scourged Western Europe, wiping out more people than the Black Plague, and landed in the United States along with European settlers. A century or so prior to a hint of the concept of vaccination, doctors in the seventeenth century found that scratching a bit of fresh material, or pus, from a smallpox pustule to an uninfected person under their skin, via a sharp lancet, would provide some protection against the illness. This was termed *inoculation*, from the Latin *inoculare*, meaning "graft."

When the English aristocrat and poet Lady Mary Wortley Montagu contracted smallpox in the early 1700s, she survived but was left severely disfigured. Her brother died from the disease. After she ordered that her children be inoculated, people who heard about the noble family's use of the technique started to think more positively about the concept of inoculation, though it would not be scientifically validated for about another half a century.

As is the case with many other groundbreaking discoveries, the smallpox vaccine, the first and most powerful of all, happened from a serendipitous and monumental observation. In the late 1700s, a small-town country doctor, Edward Jenner, noticed that farmers and milkmaids exposed to cowpox never seemed to suffer from smallpox during its frequent outbreaks. The milkmaids would retain their beautiful, blemish-free complexions after a brief bout with the illness, unlike those who either died from smallpox or suffered mightily and had a pockmarked face to show for it. Jenner began investigating if these workers were getting naturally vaccinated (*vacca* means "cow" in Latin) by exposure to the cowpox virus, which somehow provided protection against the smallpox virus.

Poxviruses are known to infect many animals, and cowpox was a

common disease among cattle at the time of Jenner's observations, but produced much milder symptoms than smallpox, its more deadly relative. In 1796, Sarah Nelms, a young dairymaid, went to Jenner with cowpox lesions on her hands. After noticing the pustules were on the part of Sarah's hands she used to milk cows, Jenner inquired about the health of the animals. In fact, Sarah told him, a cow named Blossom had recently been infected with cowpox. Back then, there was no requirement to get approval from an independent review board to experiment and test his theory. So Jenner obtained some of the material from Sarah's pockmarked hand and scratched it into the arm of an eight-year-old boy, named James Phipps, the son of his gardener.

About a week later, Phipps developed temporary symptoms that included chills, a fever, some generalized discomfort, and loss of appetite. Two months later, Jenner conducted a risky human challenge trial, when he purposely exposed the young child to smallpox material. Keep in mind, this was a known deadly infection at the time, and no one was certain this would work or that the boy wouldn't succumb to the illness. I can only imagine the wave of relief when the boy stayed well, and Jenner concluded that his subject was protected from the deadly smallpox. Still, his idea of vaccination, scratching a small amount of cowpox virus into healthy individuals, was not an easy sell initially. But eventually people accepted the pricks in the arm—a vaccine that was itself a living virus named vaccinia and was delivered via a bifurcated needle. Most people born before 1972 have the telltale roundish, semi-sunken scar on their upper arm to show for it.

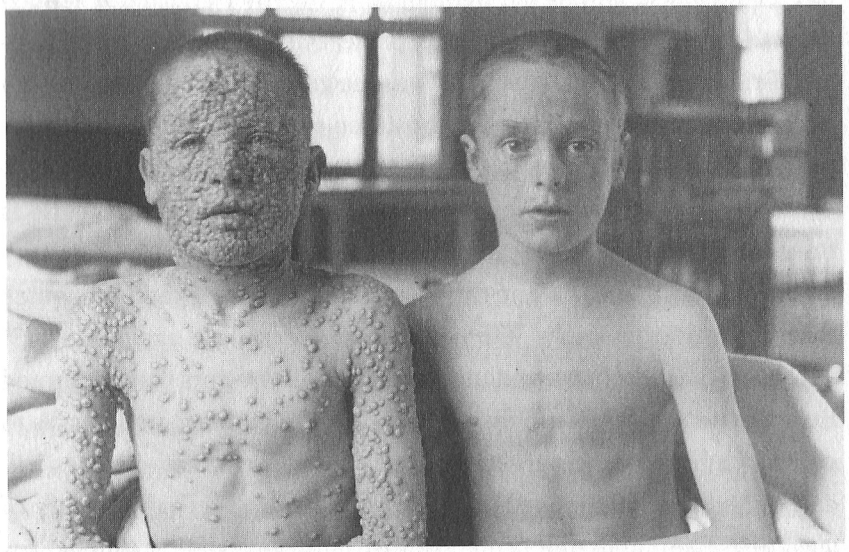
Unlike more modern vaccines, the smallpox pricks carried such a high viral load, injected just below the skin's surface, that a local infection of smallpox would occur, followed by the scar that could be up to an inch in diameter. After decades of worldwide vaccination, smallpox was declared eradicated in the United States in 1972, just a few years after I was born; in 1977 a single case of smallpox occurred in Somalia for the last time, and in 1980, the WHO considered smallpox to be eradicated worldwide.[3]

The story didn't quite end there, however. In recent years, rumors about the original vaccine coming from horses rather than cows have caused scientists to rethink the centuries-old story. Jenner himself had suspected that cowpox originated from horsepox and sometimes used material directly obtained from horses to inoculate against smallpox.

Not a lot is known about horsepox, and the virus seems to have become extinct, although it possibly remains circulating in an unknown reservoir. Studies mapping its genome show it to be very similar to some old vaccinia strains, bolstering the hypothesis that the vaccine could have been derived from horses. In a letter to the editor published in the *New England Journal of Medicine* in 2017, researchers said they discovered vials of smallpox vaccines from the nineteenth century that contained the horsepox virus.[4] And to add another layer of puzzlement, both horsepox and cowpox may originally have been rodent poxviruses that only occasionally infected livestock. At least one company today is revisiting a live, modified horsepox virus to develop a COVID vaccine, modifying it to target the COVID spike protein.

Dr. Larry Brilliant, a visionary epidemiologist, technologist, and philanthropist, had the privilege of seeing the last case of smallpox in the world during his crusade to end the "speckled monster" scourge in the 1970s while working in collaboration with the WHO. He is one of our generation's most decorated and celebrated public health experts with a sharp eye on ending pandemics as CEO of Pandefense Advisory and chair of the advisory board of the nongovernmental organization Ending Pandemics. Over the years, he has become a friend, and our communication is often in Hindi, which he knows quite well from all the time he spent in India. While he didn't choose his last name, I tell him that it suits him very well. It was while working in India, the last place on Earth where smallpox persisted, that Brilliant came across a young girl named Rahima Banu who had contracted the virus in October of 1975 at the age of two and survived. She was the last case in an unbroken chain of transmission of killer smallpox

that went all the way back to Pharaoh Ramses and beyond, probably 10,000 years.[5] "Billions of people died of smallpox," Brilliant reminds me. At one stage of the virus's treacherous march across Europe, it was the single biggest cause of death, killing 400,000 every year. In the Americas, it ravaged Native Americans and led to the collapse of



This photograph of two thirteen-year-old boys—one vaccinated and one not—was taken in the early 1900s by Dr. Allan Warner of the Isolation Hospital at Leicester in the United Kingdom. It was part of a series of photographs by Warner that were published in the Atlas of Clinical Medicine, Surgery, and Pathology *in 1901. Warner photographed a number of smallpox patients in order to study the disease. Both boys had been infected by the same smallpox source on the same day, but only one (on the right) had received a vaccination in infancy. Note that while the boy on the left is in the fully pustular stage, the boy on the right has had only two spots, which have aborted and have already scabbed. Apparently, the parents of the boy on the left were swept up by anti-vaccination fervor when they decided not to inoculate their child.* SOURCE: THE JENNER TRUST. THE PHOTO IS PART OF A COLLECTION HOUSED AT DR. JENNER'S HOUSE, MUSEUM AND GARDEN IN GLOUCESTERSHIRE, ENGLAND. FOR MORE, GO TO JENNERMUSEUM.COM.

entire cultures. It slaughtered around 30 percent of those who contracted it, leaving a third of survivors blind and almost all who did not die scarred for life. Medical historians have even suggested that we owe part of our longevity today—a doubling of life expectancy between 1920 and 2020—to the smallpox vaccine and eradication of the menace through activism and vaccination campaigns.[6]

"The miracle is that the people came together and did it [ended the pandemic]. The magic is the science, but the miracle is the people," Brilliant says. Smallpox was a unique germ in that it infected only humans. It didn't have any other hosts, so exterminating it was easier once we had the vaccine against it. COVID, however, will be a virus we chase as it mutates and circulates in other animals. Until the world is fully vaccinated, there will always be customers for COVID.

Ask Dr. Brilliant what he thinks about anti-vaxxers and he's quick to point out, amusingly, "Oh, you mean the people against cows?" Much of the vaccine avoidance among anti-vaxxers has stemmed from the notion that the only way to be protected from an illness is to contract a bit of the illness itself. Many people fear that vaccines will cause the illness against which they protect. But that's the beauty of vaccines: They offer the protection without devastating illness. Today's vaccines also have the benefits of modern science; they are exceedingly safe and rigorously tested (even the new COVID vaccines that gained emergency use authorization were tested in clinical trials on tens of thousands of individuals first, and adverse reactions attributed to the vaccines are exceedingly rare; according to data from the CDC, you're three times more likely to get struck by lightning than die from a COVID vaccine).[7]

Brilliant loves keeping anti-vaxx propaganda lying around, especially items from more than a century ago, like the cartoon at the start of this chapter. Such ridiculousness reminds him of how there's nothing new about the anti-vaxx movement. The distrust of doctors and the government that feeds the anti-vaccination movement might be considered recent, but its roots were put down well over a century

ago.[8] In the late nineteenth century, tens of thousands of people took to the streets in opposition to compulsory smallpox vaccinations. There were arrests and fines, and people were even sent to jail. Some of the rhetoric that anti-vaxxers used way back then is still employed today, but with greater force now that we have the Internet and social media platforms. People's soapboxes are bigger and their megaphones are louder. I happened to be working on a documentary about vaccine hesitancy prior to the pandemic, which my team and I fine-tuned and aired in April 2021 (interestingly, in 2019 the World Health Organization named vaccine hesitancy among the top ten threats to global health). When I spoke with Dr. Peter Hotez, a world-renowned virologist, researcher, and outspoken vaccine advocate, he called vaccines "the most powerful technology humankind has ever invented."[9] His group at Baylor College of Medicine produced one of the first SARS vaccines, and he continues to champion vaccine diplomacy—the global partnerships we must create among countries rich and poor to head off major health problems. From his perspective, the anti-vaxx movement of late gained oxygen and moved from the fringes to the mainstream around 2015. The movement was well shaped by targeted messaging, shrewd organization, and strong leadership—something that is not much seen in scientific circles, whose leaders tend to be siloed and usually silent. There is also a lot of money fueling the anti-vaccination movement in the form of books, live events, and medical products. I found it incongruous that many people will consume these products, which haven't undergone any safety or efficacy testing, but avoid vaccines, which have been through stringent and rigorous medical trials.

For far too long, scientists turned a blind eye to the antiscience folks under the thinking that by not paying attention to them, they'd go away or at least not be heard. But that has changed significantly now that the anti-vaccine community has established a following that perpetuates the disinformation. As much as we celebrate the remarkable science of these new COVID vaccines, their full utility won't

The title of this wood engraving by Sir E. L. Sambourne (1898) and owned by the Wellcome Collection in London is "Death as a Skeletal Figure Wielding a Scythe: Representing Fears concerning the Vaccination Act 1898, Which Removed Penalties for Not Vaccinating against Smallpox." The act had originally forced vaccination but introduced a clause allowing people to opt out for moral reasons. It was the first time "conscientious objection" was recognized in UK law. The growth of anti-vaccination sentiment reached full force in the 1890s with the National Anti-Vaccination League. The group organized protests and produced its own publications to distribute anti-vaccine propaganda. In this artwork, Death, adorned in a cloak and laurel wreath, is brandishing a roll of paper labeled "Bill" and "Anti vaccination." A coiled snake, an hourglass, and the Lancet *medical journal are scattered around the skeletal figure.* SOURCE: THE WELLCOME COLLECTION, LONDON.

be recognized until enough people take them. Science can rescue us only if we do our part.

The whole point of a vaccine is to teach the immune system what that pathogen—a virus, bacterium, fungus, or parasite—looks like. It gives the immune system a giant WANTED sign with the list of names and identifying details of the bad guys to look out for and attack if they show up. This can be done in several ways: inactivated vaccines, live-attenuated vaccines, toxoid vaccines, subunit/recombinant/conjugate vaccines, viral vector vaccines, and the newly developed messenger RNA (mRNA) vaccines.[10]

Inactivated vaccines do not contain live viruses or bacteria, but either whole killed germs or simply parts of these organisms. These microbial parts are DNA, protein, or specific molecules on the germ's surface. They allow your immune system to identify this as the enemy and obtain advance notice if that pathogen were to invade. Immune system cells then have a memory that allows them to recognize the organism when they next encounter it in order to produce antibodies to fight it. The immune cells remain circulating in your blood on guard, ready to stop an infection in its tracks if your body is later exposed to the real thing. It's armed and ready long before the invasion. Often these antibodies either don't loiter in your body for your whole lifetime or aren't enough to protect you after just one shot, which is why booster immunizations are recommended—for example, for whooping cough and rabies. Inactivated vaccines are also used to protect against hepatitis A and some types of influenza.

The smallpox vaccine was a live-attenuated vaccine. Other live-attenuated vaccines include the measles vaccine, the rotavirus vaccine, the chickenpox vaccine, and the yellow fever vaccine. A toxoid vaccine should not be confused with a "toxin." A toxoid is merely a form of vaccine that is an inactivated bacterial toxin. Examples include toxoids against diphtheria and tetanus. These types of vaccines enable the body to render the real toxin harmless if it were to show up in the future. Tetanus is exceedingly rare today (fewer than thirty

cases per year occur in the United States), and most doctors have never seen a case. Tetanus is not like other infections that can spread between people. It's a spore-forming soil bacterium and is transmitted by entering an open wound. Its spore can survive on surfaces, like a rusted nail, for long periods, only to start replicating in the unsuspecting person who steps on the nail. The spore produces a toxin that causes powerful and life-threatening muscle contractions, unless, of course, the person has been vaccinated.

Like inactivated whole-cell vaccines, subunit/recombinant/conjugate vaccines contain not live components of a pathogen but small fragments of its outer surface protein. This is what stimulates a protective immune response. Some examples of subunit/conjugate vaccines are those for hepatitis B, HPV, meningococcal disease, and some for influenza and shingles.

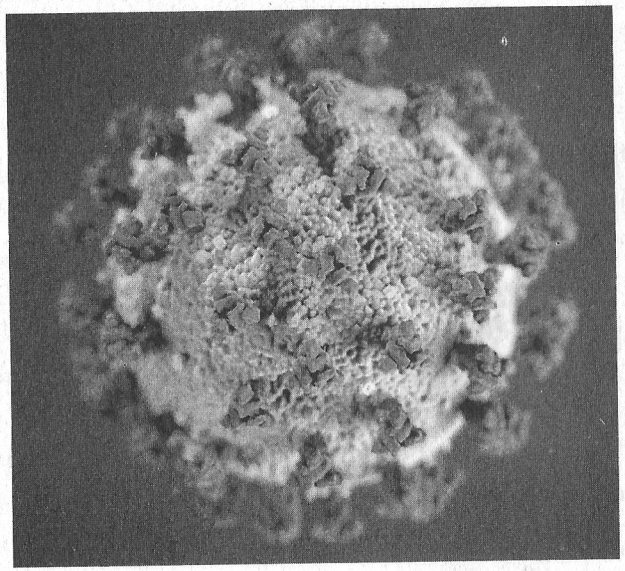
Viral vector vaccines use a modified version of a different virus as a means to deliver protection. For example, the Johnson & Johnson and AstraZeneca vaccines for COVID employ a harmless disabled adenovirus to convey the instructions for making antibodies. The adenovirus, which causes the common cold in activated form, is not at all related to the coronavirus but it triggers the immune system to respond without infecting the person. Viral vector vaccines have been used for Ebola outbreaks and are under study for Zika, flu, and HIV.

The new mRNA COVID vaccines represent a new class of vaccines because of their RNA technology, but the concept is the same: Introduce instructions to the body for making a protein that the immune system will tag as a bad guy so when the real bad guy shows up, the body is ready to effortlessly fight and take care of it (you probably won't even know it). I should state clearly and firmly that these mRNA vaccines do not contain the live virus that causes COVID. They contain only the code for a small portion of the virus, the spike protein. They do not affect or interact with your DNA whatsoever. In fact, mRNA never enters the nucleus of the cell, which is where our

DNA is kept. The cell breaks down and gets rid of the mRNA soon after it is finished using the message.

I like to think of vaccines as language instructors: They teach the human body a new language. If you're constantly speaking in that language, such as regular exposure to the virus, the immune system gets pretty good at communicating in this new language. As the virus starts to wither away, there's less conversation in this new language, and every now and then, a refresher course may need to be given in the form of a booster shot. That quickly reminds the body how to fight the virus, especially if it has had a slight wardrobe change since the original strain.

As previously noted, viruses contain a core of genes made of DNA or RNA wrapped in a coat of proteins; in the case of COVID, the virus



This illustration, created at the Centers for Disease Control and Prevention (CDC), reveals the ultrastructural morphology exhibited by coronaviruses. Note the spikes on the outer surface of the virus, which impart the look of a corona, or crown, surrounding the virion.
SOURCE: CDC.

is RNA based. To make its now iconic spike proteins, the RNA genes of the virus make messenger RNA that then leads to the production of the proteins. An mRNA of a specific structure makes a protein of a distinct structure.[11]

Again, it is important to remember that mRNA is a message, and in your body at this moment, there are thousands of such messages being delivered. They are messages that disappear or expire quickly like a Snapchat. The vaccine is a message for one particular coronavirus protein, not the dozens of proteins that make up the virus, so there is no way the mRNA could actually lead to the creation of a virus in your own body. For this reason, the antibodies from people who are vaccinated are different from the antibodies from those who have been infected. In those who have been vaccinated, the antibodies are specific to the spike (S) protein, while those who have been infected may also show antibodies to other parts of the virus, such as the nucleocapsid (N) protein. If you have antibodies to both, your immunity is likely from previous infection.

The first steps taken to make mRNA-based vaccines did not occur on day 1 of Operation Warp Speed. It was thirty years ago that scientists began exploring the possibility.[12] The question they raised: If you know the exact structure of the mRNA that makes the critical piece of a virus's protein coat, such as the spike protein of the COVID germ, could you make that mRNA easily and quickly in a lab setting? The concept seemed simple and doable: Manufacture the mRNA that holds the recipe for a certain virus's protein coat, then inject that mRNA into someone so it travels through the bloodstream and alerts immune system cells, then confers immunity. But it turns out that the feat was not easily achieved.

We first had to learn how to modify mRNA so that it did not produce violent immune system reactions that could be deadly on their own. Once we figured that out, we next had to become proficient in encouraging human cells to not only pick up the mRNA as it passed by in the blood and produced large quantities of the critical piece of

protein, but also generate antibodies to the protein. Finally, we had to learn how to enclose the mRNA inside microscopically small capsules to protect it from being destroyed by chemicals in our blood. That's a highly simplified version of the mRNA lesson plan that scientists executed as they worked to develop these new vaccines. Of course, they'd also come across some unexpected findings along the way, one of them being that mRNA vaccines trigger a stronger type of immunity than traditional vaccines. These new mRNA-based vaccines for COVID have the power to inflict a double whammy against the virus—they stimulate the immune system to make antibodies *and* immune system killer cells. That's like possessing two different kinds of ammo just in case one is not as effective.

I had the pleasure of speaking with two of the chief scientists behind the Pfizer/BioNTech mRNA vaccine that was the first to be approved for emergency use by the FDA on December 11, 2020. Of the thousands of conversations I've had while reporting on the pandemic, this may have been one of my favorites. Within minutes of the Chinese releasing the virus's genetic code in January, Drs. Uğur Şahin and Özlem Türeci got cracking ten thousand miles away in their German laboratory on designing an mRNA vaccine to hit the virus. It's where they'd been studying mRNA technology for cancer research but could easily pivot to tackle this new challenge. They had all the tools at their disposal as well as the competency and capacity. Previously, no new vaccine had been developed in less than four years. The race was on, though, with a raging pandemic that could not wait at least four years.

Şahin and Türeci are a married couple with Turkish roots who founded BioNTech in Germany in 2008; their love for each other is matched by their love for science and medicine: After their wedding ceremony in 2002, they immediately went back to their lab to work. "Translating science into survival was what we shared and why at some point we decided to do this journey together of translating science into drugs and vaccines," Şahin said.

As doctors who specialize in cancer treatments, they described for me "the sense of urgency that cancer brings to people's lives." And when Şahin read an article in the *Lancet* in January about the quickly spreading coronavirus in China, his gut instinct told him that a full-blown pandemic was upon us. Vacation plans at the company were canceled and Project Lightspeed was born.

Soon after they identified several promising vaccine candidates, they needed help testing them and bringing them to market. By March, they forged a relationship with Pfizer, and that "beautiful friendship and collaboration," as they described it, resulted in the world's first effective and safe COVID vaccine. Pfizer took no federal money from Trump's Operation Warp Speed to research and develop a vaccine but did land a supply contract to provide millions of doses. It was a big gamble with no guarantees, but one that ultimately paid off.

It's important to reiterate that these new breakthrough vaccines are built on many previous breakthroughs and innovations, from biological ones like understanding the structure and function of DNA and its mRNA offspring to purely technological ones such as the ability to transmit large bundles of information (e.g., sequencing data) around the world in seconds. Şahin describes some of the biology in elegant terms, referring to mRNA as the most fundamental way to transfer knowledge to cells. He calls mRNA an intracellular information molecule—the first biomolecule in life invented by nature to enable proteins to be produced based on a grand plan mastered in the DNA. It helps to think of DNA as the hard copy information and mRNA as the soft copy of this information to tell cells what to do next. As its name implies, mRNA are truly messengers—the body's couriers.

Already, mRNA technologies have been used to treat sickle cell disease, and they are also being tested for use against infectious agents such as Ebola, Zika virus, rabies, cytomegalovirus (CMV is a common herpes virus), and influenza. Şahin and Türeci expect the technology to revolutionize many areas of medicine, including cancer treatments and genetic diseases like cystic fibrosis, where mRNA technology could produce vital proteins that are missing in an individual. Even cancer cells make proteins that can be targeted by mRNA vaccines, though this is a more difficult challenge. For starters, not all cancers are the same. What makes curing cancer such an ambitious feat is the heterogeneity of the disease: Within a single cancerous colony of cells, for example, you have a diversity of cells with different markers. And cancers between different individuals are also unique. So imagine being able to personalize cancer treatment with an mRNA vaccine that can be designed to target those unique cancer cells. You figure out the molecular makeup of an individual's cancer, extract the information, and select the markers against which to use a custom-tailored mRNA vaccine. The versatility and speed with which you can perform this exercise using mRNA technology is breathtaking and potentially limitless.

Şahin and Türeci's success story has made them wealthy billions of dollars over, but they don't seem to have changed their lives much as a result. They continue to live with their teenage daughter in a modest apartment near their office. They don't even own a car; they ride bicycles to work. One of their star biochemists who was among the masterminds of mRNA technology, Hungarian-born researcher Katalin Karikó, also recalls the decades of adversity toiling in the lab and enduring serial demotions in academia. She and her longtime collaborator, immunologist Dr. Drew Weissman, figured out how to make the mRNA technology work. Karikó is a senior vice president at BioNTech overseeing its mRNA work now, having moved there from the University of Pennsylvania in 2013 when the school determined that she was "not of faculty quality."[13] The one thing she does struggle with today is comprehending the fact that her forty years of research are poised to change the lives of billions around the world.

Speed and versatility are important when it comes to chasing COVID with vaccines in the years ahead. Changes in the spike proteins drive the variant strains, but our vaccines can still meet the challenge.

As more mutations accumulate, tweaks to the vaccines will probably be necessary, like editorial tweaks to written copy to make it stronger and tighter. But we can be well prepared for COVID's iterations with enough disease surveillance and routine sequencing to keep track of the virus's evolving characteristics. In the meantime, preventing viral transmission through vaccination is essential to contain the virus and foil its natural tendency to refashion itself.

Immunology 101: The Beauty of Bs and Ts

I can't cover the benefits of vaccines without dishing out some basic biology about your body's immune system. It will help you complete the picture in your head about why vaccines are so vital.

The human immune system, which is tasked with keeping you healthy in the face of bacterial, viral, fungal, parasitic, and other invaders, has two main components: the innate immune system and the adaptive immune system.[14] The innate immune system is the first line of defense. Parts of it include physical barriers like your skin and mucosal membranes, which physically stop invaders from getting in. It also includes certain cells, proteins, and chemicals that do things like create inflammation and destroy invading cells. Whereas the innate immune system is immediate and nonspecific (it tries to stop anything from entering the body), the adaptive immune system is targeted against a specific and previously recognized invader, which takes a bit longer to kick into gear.

The adaptive immune system includes a type of white blood cell, called a B cell, that patrols the body looking for bad guys. Each B cell has a unique antibody that sits on its surface and can bind to a unique antigen (the technical name for the foreign invader) and stop it from entering a host cell. When it finds and binds to a bad guy, the B cell gets activated: It copies itself and churns out antibodies, eventually creating a mega-army of neutralizers for that particular invader.

That's where antibodies come from that are created by the immune systems of people who have had COVID. Unfortunately, concerns have risen from a few studies that antibodies to this particular coronavirus can fade away pretty quickly, especially in people who have had mild cases of COVID. This has worried many researchers because if the antibody response fades quickly, we don't know how long a person who has been infected with this virus will stay protected from a new infection. This is also worrisome since we are relying on vaccines to trigger an antibody response to help protect us, and we want that protection to last a long time.

Fortunately, antibodies aren't the only weapon our adaptive immune system uses to stave off an infection. Enter the T cell. T cells, which come in three varieties, are created by the body after an infection to help with future infections from the same invader. One of those T cells helps the body remember that invader in case it comes knocking again, another hunts down and destroys infected host cells, and a third helps out in other ways.

After you get an mRNA COVID vaccine, cells in your arm muscle pick up those tiny, fatty droplets that contain the mRNA. The cells start producing a spike protein, which makes your body think its muscle cells are infected with the coronavirus.[15] Because of this, your body will try to fight off the simulated infection in the cells with its innate immune system. That's what causes some of the inflammation that people experience—the sore arms, fevers, and/or muscle aches. What happens next is those cells that have replicated the COVID spike protein (RNA) are seized by immune cells that can communicate with the special cells that make antibodies. Through this exchange, antibodies specific for COVID are generated. This process takes place in your adaptive immune system.

In the case of other vaccines made with DNA, the outcome is the same: a delivery of instructions to the immune system to wake up to the COVID virus. The method of delivery, however, is not directly from an mRNA strand. Instead, a modified adenovirus is used. Adenoviruses are common viruses that typically cause colds or flu-like

symptoms. Scientists can deactivate these adenoviruses so they act as vehicles for transporting the coronavirus spike protein gene into cells, without the ability to replicate inside those cells (translation: they do not cause infection). After the vaccine goes into a person's arm, the adenoviruses bump into cells and latch onto proteins on their surface. The cell engulfs the virus in a bubble and pulls it inside. Once inside, the adenovirus breaks away from the bubble and travels to the nucleus where the cell's DNA is stored. There, the adenovirus inserts its DNA into the nucleus so those spike protein instructions can be read by the cell and copied into an mRNA that leaves the nucleus and begins assembling spike proteins. In turn, the proliferation of spike proteins alerts the immune system and promotes the same production of COVID-specific antibodies and activated B and T cells.

Many of these vaccines, both mRNA and DNA based, require two doses spaced a few weeks apart. People who feel lousy after the second dose for a day or so can thank their immune systems for showing signs that the vaccine is working. The first dose mimics an infection and organizes the troops, albeit weakly. The second shot riles up the troops and tells them this is serious, turbocharging your immunity against the virus to full capacity. People who experience a reaction after the first shot may attribute that to a previous exposure to COVID whether they were aware of it or not. But to be clear: People who have already gone through a natural infection with COVID should still receive the vaccine because it will boost their overall response to a possible future infection. Examples of other vaccines that require multiple doses include the measles-mumps-rubella (MMR) vaccine, vaccines against hepatitis A and hepatitis B, and the shingles vaccine.

As the United States ramped up its rollout of vaccines in spring 2021, I paid a visit to Pfizer's manufacturing plant in Kalamazoo, Michigan, and met with the president of global supply, Mike McDermott. Millions of doses were being manufactured every week, and they were on track to get to 2 billion doses by the end of the

year.[16] Their ability to scale up production tenfold has been a remarkable feat of awesome technology combined with improvements and innovations along the way. Although Pfizer could repurpose some of its equipment, most of what I saw did not exist the previous year. Before Pfizer even knew if they had a product that worked and long before clinical trials would start, the company had spent hundreds of millions of dollars—almost $2 billion by the time I was there.

Before Pfizer decided on its final vaccine candidate, it was looking into four options, which meant that McDermott and his team had to be ready to go in any direction. He described the dilemma to me as like trying to plan an amazing dessert but without knowing what you're supposed to make. So you start buying up all the raw ingredients to make a cake or brownies, but also a pie or ice cream. "Filling up this pantry," McDermott quipped, "was quite, quite expensive."

For McDermott and his team, one of the biggest hurdles that had the possibility of slowing things down was the availability of those raw materials and specifically lipids, the fatty substance that safely houses the mRNA until it can get to our cells. Lipid nanoparticles had not yet been used in a large commercial product, making lipid suppliers in high demand all of a sudden. Pfizer worked closely with these suppliers to build more lipid capacity and also began making lipids on-site.

Ultimately, the successful production of so many vaccines came down to a gizmo the size of a quarter. "The heart of this whole machine," McDermott showed me, "is what's called an impingement jet mixer," he said as he twirled it around his fingers. The impingement jet mixer, also known as the tea stirrer, works by simply pumping lipids in one side and mRNA in the other, forcing them together with around 400 pounds of pressure. That's what creates the lipid nanoparticle that is essentially the vaccine. These aren't just any lipids; the company had to design the right combination of four different lipids that would not only protect the mRNA on the way to cells

but then release the mRNA once it gets there. And while the process of creating lipid nanoparticles is not new, McDermott said the challenge was scaling up this process. The first time he saw the impingement jet mixer, McDermott thought, *You can't be serious?* His confidence was low. He could not fathom pushing billions of doses through the device. But they eventually solved that problem by replicating the quarter-sized mixers and putting technology in place to ensure efficiency. It was McDermott's moonshot.

"As a kid, my dad worked for NASA," McDermott told me. "He was lucky enough to be in mission control in Houston when Neil Armstrong stepped on the moon right at that amazing moment. I could never imagine having a moment like that in my life. Right? Like, what's the odds that something like that would ever happen again?"

When he shipped his first batch of vaccines from the facility on December 13, 2020, McDermott felt the moonshot moment rush over him.

On my tour of the plant, I saw the warehouse, the vaccine production area, and the freezer farm—the place where they store the vaccine at ultracold −80 degrees Celsius (your freezer is about −20 degrees Celsius, or −4 degrees Fahrenheit) while they're waiting to be tested. All of the purity testing, processing, and paperwork takes about thirty days, and then the vials are ready to ship. Now the race is on to keep production going and develop new variant-specific vaccines as necessary. I remember talking about the newly authorized vaccines on television one evening in December 2020. The anchor just asked me to reflect on the moment, which wasn't something I had really thought much about. I had been reporting more intently on the trial process, interpreting the data and manufacturing. After a second, I said, "The story of these vaccines will be told for generations to come," with the same reverence we have spoken of remarkable public health leaps of the past. Even beyond this pandemic, the pace of medical innovation has forever been changed by what happened this year.

It's like the story of Roger Bannister and the four-minute mile. In

1956, he was the first person in history to break that record, which many believed wasn't possible for a human to do. Shortly after that, however, someone else ran even faster, and now there are teenagers who can do it. Bannister was amazing for being first, but his legacy is more about showing us what is possible. The same is true of these vaccines.

My hope is that as people learn more about how these vaccines work and came into being, they will be universally embraced for the modern marvels they are rather than feared or, worse, shunned. As a doctor, I am often asked, "What would you do?" in a certain situation. I think it is a fair question because it requires me to put all the pieces of information together—big and small, clinical trial results and anecdotal case reports—and then make a decision. That is what I always do for my own patients and my family as well. As the only doctor in the family, it was my role long before I was ever reporting on television. And after doing all that homework, I elected to receive the vaccine and recommended it to my parents. As soon as my kids' age group opened up for vaccination, I made sure they got their shots too to protect them and help reduce overall viral spread. As I have often said about childhood vaccines, it's not just because I love my kids that I vaccinated them. It's because I love your kids as well.[17]

Top 10 Myths Debunked[18]

Myth: The vaccine will make me infertile, increase my risk for cancer and dementia, and who knows what else.

Truth: The COVID vaccine does not affect fertility. The COVID vaccine was falsely linked to infertility because of the syncytin-1 protein I defined earlier that is an important component of the placenta in mammals. It shares similar genetic instructions with part of the spike of the new coronavirus. If the vaccine causes the body to make antibodies against syncytin-1, it was argued, it might also cause the

body to attack and reject the protein in the human placenta, making women infertile. The similarities are not remotely close enough to make a match though. It's like two people with phone numbers that both include the number 5. They share a digit, but you couldn't dial one number to reach the other person.[19] Plus, if the infertility theory were true, we'd see a shift in fertility statistics among the tens of millions of people who've been infected or vaccinated. During the Pfizer vaccine trials, twenty-three women volunteers involved in the study became pregnant, and the only one who suffered a pregnancy loss had received not the actual vaccine but a placebo.

Myth: The vaccine will change my DNA.

Truth: Without an understanding of biochemistry, it's easy to think that injecting genetic material into the body will somehow mix with our DNA and change it. But that is not the case (and if it were, imagine what we'd be able to accomplish!). You are not a GMO after being vaccinated. Nor are these vaccines "gene therapy," another subject entirely unrelated to COVID. First, the mRNA vaccines act as messengers to cells without ever entering their nucleus. They hand-deliver a recipe for making those spike proteins, and then they are destroyed by the cell (they shoot the messenger). Viral vector vaccines that use DNA (e.g., adenovirus) do go into the cell's nucleus, but they do not integrate with your own DNA. These vaccines, which have fifty years of history, act like delivery shuttles to serve up the genes for making the same antigen COVID spike protein. Unlike retroviruses such as HIV, wild-type adenoviruses do not carry the enzymatic machinery necessary for integration into the host cell's DNA. That's exactly what makes them good vaccine platforms for infectious diseases.

Myth: People who take these new vaccines are guinea pigs. Researchers rushed the development of the COVID vaccine, so its effectiveness and safety cannot be trusted.

Truth: The vaccines were authorized quickly in part because red tape was cut, not corners. As noted, the mRNA vaccines were created with a method that has been in development for decades. The companies could start the vaccine development process early in the pandemic because they were at the ready to deploy this technology. The more traditional vaccines also came into being from decades of experience. The vaccine developers didn't skip any testing steps, but conducted some of the steps simultaneously to gather, and share, data faster. These vaccine endeavors had plenty of resources, as governments invested in research or paid for vaccines in advance, or both. Social media helped companies find and engage study volunteers, and millions of people have now proven the vaccines' success. Because COVID is so contagious and widespread, it did not take long to see if the vaccine worked for the participants who were vaccinated.

Myth: I never get flu shots because they give me the flu. Why would I get a COVID vaccine when it will also make me sick, from side effects to the illness itself?

Truth: None of the vaccines for COVID can give you the disease. The spike protein that stimulates your immune system to recognize and fight the virus does not cause infection of any sort. Any side effects from the vaccine are related to the immune system waking up and doing its job. And with regard to flu, you cannot contract influenza from a flu shot. People who feel sick from a flu shot can either blame their own immune system kicking into gear or blame an illness they contracted naturally before the flu shot had enough time to work. Similarly, these COVID vaccines also need time to work. Upon inoculation, you're not instantly immune to the virus. You reach full vaccination status two weeks after a single-dose vaccine like the J&J one, or two weeks after the second mRNA shot. And you don't want to miss that second mRNA shot. Although you do have some immunity a couple of weeks after the first jab, slightly over 50 percent, you

need the second jab to fill up your immunity cup to the 90 percent–plus level of protection. When people become COVID positive and develop symptoms soon after vaccination, they may have contracted the virus before the vaccine has time to deploy, or fall into the small percentage of people who don't achieve enough protection. And contrary to other reports, once vaccinated, you do not shed virus because of the vaccine.

Myth: I've already had COVID, so why bother with the vaccine? I'm immune naturally. And I have allergies, so . . .

Truth: It is true that your previous infection has offered you protective antibodies and likely revved up other parts of your immune system as well. Still, there may be a benefit to getting vaccinated because the vaccine appears to offer better protection against the emerging variants and stronger protection overall. While we haven't seen significant reinfection rates in the United States, other countries with emerging variants such as Brazil have been hit quite hard. Even people with severe allergies, including ones that require them to carry an EpiPen, can safely receive the vaccine and are encouraged to do so under special supervision in a health care setting. For people who have had COVID and go on to experience long-haul symptoms, getting vaccinated appears to significantly diminish or totally eliminate those symptoms in many patients.

Myth: The vaccines contain questionable substances, some of which could be used to monitor or control me—maybe even turn me into a zombie.

Truth: Contrary to misinformation swirling online about what's in these vaccines, they do not contain any suspicious ingredients or "toxins" as some say. They do not contain any dubious material, such as implants, microchips, or tracking devices. In addition to the main COVID-killing ingredient found in their genetic instructions, they

also contain a support staff of fats, salts, and a small amount of sugar. And they were not developed using fetal tissue.

Myth: Once I'm vaccinated, I'm bulletproof and can fully return to normal life.

Truth: Once vaccinated, you are very well protected against severe illness, breakthrough infections, and the possibility you could still be contagious. Still, we need to practice infection prevention precautions until a large percentage of the country—and world—is immunized. In areas of the world where there is still significant viral transmission, while unlikely, the odds are higher you could become an unwitting carrier, even after being vaccinated. It's as simple as that. Mask wearing may be recommended in certain situations and environments until enough people are immunized, which will likely coincide with a very low rate of new cases—when the average daily rate of people testing positive in a given area is much less than 5 percent. That number reflects a time when this coronavirus response could go from mitigation to containment. We could finally get our arms around this and test, trace, and isolate the last few embers of the disease. Even if the virus is out there at that point, it would be far less consequential.

Myth: Everyone around me has already been vaccinated, and the pandemic is under control, so why bother getting vaccinated? Can't I stay unvaccinated in the herd?

Truth: We do not know what level of immunity in the community confers "herd" immunity. The exact percentage required for community immunity for COVID is a moving target. Herd immunity for measles, which is highly contagious, requires around 95 percent of the population to be immunized. In spring 2021, based on the contagiousness of the virus, the target is close to 75 percent for COVID. New variants, however, continually change the community immu-

nity equation. The more contagious the virus becomes, the higher the percentage of people that need to get vaccinated. On top of that, the distribution of vaccines on a global scale is uneven, so pockets of unvaccinated communities may remain to fuel variants ready to hop on a plane and threaten those living in vaccinated areas. The imbalance between low-income countries and high-income nations, especially those that can produce their own vaccines, will likely continue until we have equitable global access through programs such as the Vaccine Alliance (known as Gavi) and the Coalition for Epidemic Preparedness Innovations (CEPI). Unlike other products of intellectual property, vaccines are not easily reproducible by lifting patents and sharing recipes. There's an art to developing vaccines, and it takes years of experience. Moreover, it's hard to set up a new manufacturing site quickly with all the equipment, infrastructure, and vaccine ingredients, not to mention bringing in an experienced staff to produce a large number of high-quality vaccines. Finally, keep in mind that adults make up roughly 75 percent of the population in the United States, but not all adults are willing to be vaccinated, and some may choose not to vaccinate their children that make up the other 25 percent. The more we encourage vaccination across all ages, the closer we get to community immunity.

Myth: The variants are going to come get us eventually and continually outpace the vaccines. Why be the recipient of a useless vaccine? They don't even prevent infection or transmission from what I've heard.

Truth: Combating the variants starts with aggressive vaccination to prevent the virus from replicating and changing. And the vaccines are not useless even when they are weakened by a variant. They are the bullets against the virus whether they hit the middle target or otherwise disable the fitness of the virus.

With regard to infection, Dr. Redfield highlighted a counterintuitive

detail to me about the virus-vaccine relationship that most people miss: Vaccines are not necessarily intended to prevent infection. What they do is modify the viral-host interaction. They tip the scales in favor of the host, making it less likely for the virus to cause disease. That means we can be vaccinated, be showered with viral particles by a nearby sneezer, and become infected. The virus can still get in, but the host is no longer a very hospitable environment, and that means the virus might not replicate as well, or enough, to cause symptoms. Powerful new strains like Delta, however, could potentially transmit from vaccinated individuals. So vaccines don't necessarily prevent infection, but they do a much better job at dampening transmission and illness. They also, not so unimportantly, are nearly 100 percent effective at keeping you from dying of the disease. Note too that you may not necessarily have to follow the same brand or type of vaccine for future booster shots. A mix-and-match approach may prove to be even more effective at protecting you.

Myth: I have a lot of underlying conditions, including chronic inflammation, allergies, and chemical sensitivities to a lot of environmental exposures. The vaccine is one giant exposure I know my body can't handle.

Truth: Having underlying conditions that can worsen and further complicate a COVID illness is all the more reason to get vaccinated. In fact, people with high-risk medical conditions, including cancer, autoimmune disease, and heart conditions, are prioritized for vaccines. The vaccine is not an "exposure" that will exacerbate an underlying illness. For those with serious concerns about their conditions and the potential side effects from the vaccine, it's a good idea to partner with a doctor to help you through the decision. But again, we cannot confuse serious adverse events with the expected side effects of getting the vaccine. About 10 to 15 percent of vaccine recipients can expect to experience side effects such as headache, arm pain, fatigue, and fever.

These clear up after a day or so. Again, it shows the vaccine is doing its job—preparing your immune system to fight against the coronavirus.

Sleeping Giants

The oldest virus ever directly sequenced belongs to an extinct lineage of hepatitis B.[20] It came from a man likely in his mid- to late twenties who lay down to die seven thousand years ago in a valley that is now in central Germany. He was probably a farmer. Our genetic tools today managed to lift a tantalizing clue from a tooth to explain his young death: a piece of viral DNA code that infected his liver. Although hepatitis B can be prevented now with vaccines, it continues to infect hundreds of millions of people around the world and remains a major global health problem. And while it targets and infects the liver, it also enters the bloodstream and circulates through the body, winding up in bones and teeth, where it can be preserved. The WHO is leading vaccination campaigns to immunize the world against this ancient plague.

It may feel disheartening to know that we may have to live with COVID—a newly emerging plague—in our environment for the rest of our lives. But that may be the least of our worries going forward as we pull through this pandemic and prepare for another one someday. Many pathogens, some much deadlier than COVID, lie in wait for a close encounter with our kind. Viruses in particular have an advantage over other pathogens because they are not alive, so they can theoretically hide out for as long as it takes to strike when the settings are right.

Case in point: A few years ago, scientists in France awakened a gigantic, ancient virus from its 30,000-year-long slumber in Siberian permafrost that's ready to infect again.[21] Now, this virus, dubbed *Pithovirus sibericum*, only infects single-celled amoebas (whew!). But the discovery has scientists wondering what other microbes are hidden in melting permafrost awaiting another chance to find a new host. If a 30,000-year-old virus can maintain its infectious abilities, other microbes are capable of revisiting humanity in catastrophic fashion, which is to say: There may be no such thing as total eradication of a virus. Devastating diseases like smallpox could come back to haunt us if we're not careful.

The good news is that we have modern science—and the lessons we've learned—on our side.