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HOW THE CORONAVIRUS HACKS THE IMMUNE SYSTEM

At a laboratory in Manhattan, researchers have discovered how SARS-CoV-2 uses our defenses against us.

By **James Somers**

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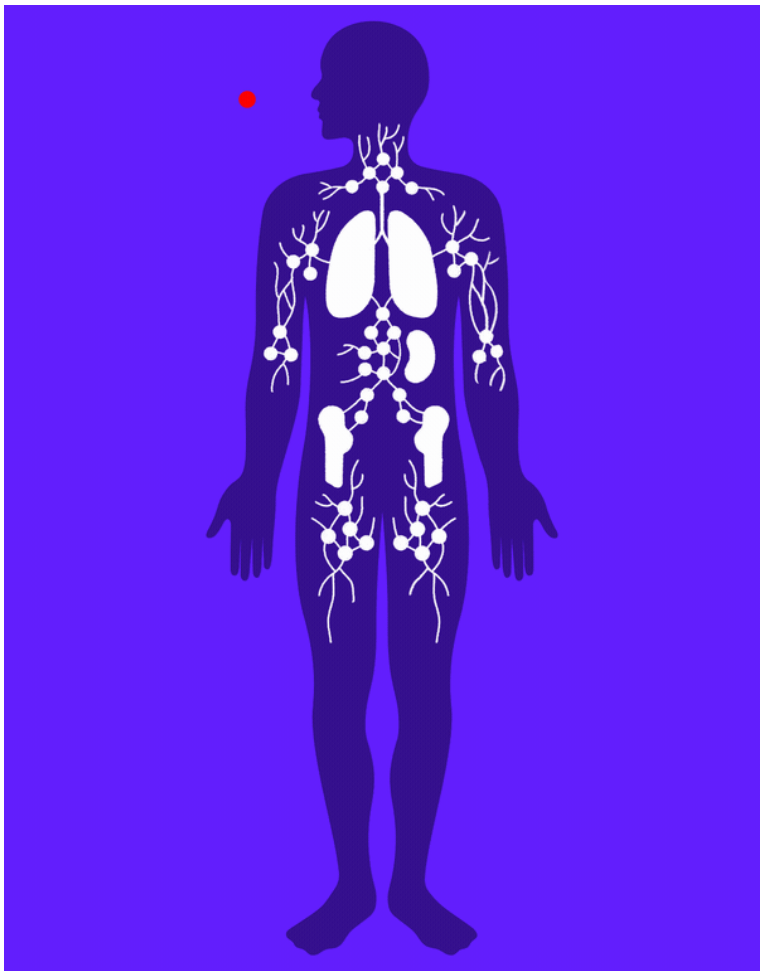

Dauntingly complex, human immunity has evolved over billions of years. Animation by Annie Jen

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Some four billion years ago, in the shallow waters where life began, our earliest ancestors led lives of constant emergency. In a barren world, each single-celled amoeba was an inconceivably rich concentration of resources, and to live was to be beset by parasites. One of these, the giant Mimivirus, masqueraded as food; within four hours of being eaten, it could turn an amoeba into a virus factory. And yet, as the nineteenth-century mathematician Augustus de Morgan said, "Great fleas have little fleas upon their backs to bite 'em, and little fleas have lesser

fleas, and so ad infinitum." The Mimivirus had its own parasites, which sometimes followed it as it entered an amoeba. Once inside, they crippled the Mimivirus factory. This trick was so useful that, eventually, amoebas integrated the parasites' genes into their own genomes, creating one of the earliest weapons in the immune system.

We tend to associate "survival of the fittest" with lions hunting antelope. But disease—the predation of parasites upon hosts—is actually the most potent force in evolution. "Every single phase of life has been selected to try to avoid parasitism," Stephen Hedrick, an immunologist at the University of California, San Diego, told me. "It's driven evolution as hard as it could be driven. Because it's life or death all the time. And it's a co-evolution." Whenever a host develops an immune defense, it perversely rewards the survival of the very parasites that can defeat it. Hosts, meanwhile, tend to be at an evolutionary disadvantage. "Bacterial or viral populations are truly vast in size," Robert Jack and Louis Du Pasquier write, in "Evolutionary Concepts in Immunology," and the wide variation among them gives natural selection many candidate organisms upon which to work. Viruses and bacteria also reproduce half a million times faster than we do. Given this "generation gap," Jack and Du Pasquier write, "one might well ask how on earth we could possibly have survived."

A clue comes from the amoeba *Dictyostelium discoideum*. It spends much of its life marauding alone, eating things. But, when food is scarce, it releases molecules that serve as a flocking signal to others of its kind; the amoebas merge, forming a superorganism of as many as a hundred thousand members. For this multicellular "slime mold" to be effective, almost all the amoebas must give up their ability to eat, lest they prey on one another. The few that retain it don't eat for themselves; rather, they swallow up debris and dispose of it to protect the organism. The other amoebas, freed from the burdens of offense and defense, form a "fruiting body" that releases spores for reproduction. Although none of the individuals would survive on their own, the collective thrives.

A human being is likewise a society of cells, with a coördinated defense. Our circulatory system doubles as a communications network; our blood vessels have an "endothelial" lining—a surface that is charged with the intelligent routing of immune cells. When ordinary cells are infected by a pathogen, they send signals to their neighbors, who pass them on until they reach the endothelial cells. In response, the blood vessels swell, creating off-ramps through which white blood cells,

which are part of the immune system's circulating defense force, can flow toward the site of infection. This is merely the beginning of our immune response.

Our bodies, like the United States government, make a startlingly large investment in defense. Our bone marrow produces billions of immune cells each day, and then discards most of them. Almost every one of our cells is perpetually scanning itself for evidence of invasion. The system is complex—ask a microbiologist about immunology and she'll whistle, wishing you luck. Those who describe it often resort to metaphor. Contemplating the enormous amounts of information that it collects and synthesizes throughout the body, Jack and Du Pasquier suggest that "the immune system can be regarded, above all else, as a computational device."

This device is so finely tuned that we seldom notice it at work. Our guts burble with foreign microbes outnumbering human cells roughly ten to one, but the good are seamlessly sorted from the bad; every day, some of our cells grow into cancers, but the immune system dispatches them before they become dangerous. On a recent camping trip, I was bitten three times by some kind of insect while putting my arm into a jacket sleeve. Who knows what entered my bloodstream. Almost immediately, three welts formed; a few minutes later, the welts came down. In moments like that, it is easy to assume that we hold the advantage over the parasites.

On Friday, March 6th, a purified sample of the novel coronavirus arrived at the laboratory of a virologist named Benjamin tenOever, at the Icahn School of Medicine, in East Harlem. Many virology labs focus on a single pathogen, but tenOever's studies dozens of viruses and how they change the cells they infect. During the winter, tenOever and his team were focussed on the flu. But, as the coronavirus pandemic began to escalate in the U.S., they initiated a side project, infecting lung cells in a dish with SARS-CoV-2, the virus that causes COVID-19, and studying the results. TenOever posted their preliminary analysis to Twitter on March 14th. Within a week, a program manager at the Defense Department e-mailed to ask about the research. Two weeks later, Defense gave tenOever a $6.3-million grant to find out what the new virus was doing to our immune systems.

Born to Dutch parents, tenOever grew up in rural Ontario. Now forty-three, he approaches his work with an amused, easy confidence. On March 26th, he gathered his team and they discussed

their plan. They would take half a dozen viruses—including SARS, MERS, and the new coronavirus—and induce infections in hosts, starting with cells in a petri dish and graduating to ferrets. They'd study the results to understand what made the new coronavirus unique. Their goal was to have results in three weeks.

The infections took place inside the lab's Biosafety Level-3 facility, a series of nested rooms in which each is kept at a lower pressure than the one surrounding it, so that air flows inward and up an exhaust chute containing sensitive filters. In the "warm zone," where there is always the danger of being exposed to a live virus, you must wear a gown, two sets of gloves, two sets of shoe covers, a respirator mask, a face shield, and a bouffant cap. You work with your arms under a hood, protected by an extra set of disposable sleeves. When you're finished with your experiment, you disinfect this gear and throw it into an autoclave—a kind of kiln—where it cooks for twenty minutes. To return to the "cold zone," you remove your shoe covers before stepping over a red line. In New York, at the end of March, these precautions had a whiff of the absurd: in a city where around three thousand new coronavirus cases were being diagnosed each day, you were more likely to be exposed to a highly pathogenic virus in your neighborhood.

A Ph.D. student named Daisy Hoagland, who had herself just recovered from a mild case of COVID-19, prepared the samples for analysis. Using a shaker machine and test tubes loaded with sand and ceramic pellets, she turned a suspension of ferret lung cells—some from infected animals, and others from members of the control group—into a homogeneous juice, then separated the solution in a centrifuge that generated fifteen thousand g's. It is painstaking work. ("I listen to a lot of podcasts," Hoagland said.) Using a pipette, she carefully transferred the topmost layer, a pink liquid, into another tube, which she centrifuged again, until she had a purified sample of RNA. This she handed off to her colleagues Rasmus Møller and Maryline Panis for sequencing. The process takes sixteen hours to complete, and Møller, who during the height of the pandemic lived in Greenpoint, Brooklyn, often biked home at dawn over the Pulaski Bridge.

Whereas the sequencing of DNA defined molecular biology in the early two-thousands, the sequencing of RNA defines it today. If you imagine a cell as a kind of computer, then your DNA contains all the software that it could possibly run. It is a somewhat astonishing fact of life that the exact same DNA is shared by every cell in your body, from the skin to the brain; those cells differ in

appearance and function because, in each of them, a molecular gizmo "transcribes" some DNA segments rather than others into molecules of single-stranded RNA. These bits of RNA are in turn used as the blueprints for proteins, the molecular machines that do most of a cell's work. If DNA is your phone's home screen, then transcription is like tapping an icon. By sampling the RNA present in a group of cells, researchers can see which programs those cells are running at that moment; by sampling it after the cells have been infected with a virus, they can see how that virus substitutes its own software.

TenOever's team quickly discovered that SARS-CoV-2 was uncannily good at disrupting cellular programming. A typical virus replaces less than one per cent of the software in the cells it infects. With SARS-CoV-2, tenOever said, about sixty per cent of the RNA in an infected cell is of viral origin—"which is the highest I've ever seen. Polio comes close." Among other things, the virus rewires the alarm system that cells use to warn others about infection. Normally, as part of what is known as the "innate" immune response—so called because it is genetically hardwired, and not tailored to a specific pathogen—a cell sends out two kinds of signals. One signal, carried by molecules called interferons, travels to neighboring cells, telling them to build defenses that slow viral spread. Another signal, transmitted through molecules called cytokines, gets a message to the circulatory system's epithelial lining. The white blood cells summoned by this second signal don't just eat invaders and infected cells; they also gather up their dismembered protein parts. Elsewhere in the immune system, these fragments are used to create virus-specific antibodies, as part of a sophisticated "adaptive" response that can take six or seven days to develop.

Usually, the viruses that humans care about are successful because they shut down both of these signalling programs. The coronavirus is different. "It seems to block only one of those two arms," tenOever told me. It inhibits the interferon response but does nothing about the cytokines; it evades the local defenses but allows the cells it infects to call for reinforcements. White blood cells are powerful weapons: they arrive on an inflammatory tide, destroying cells on every side, clogging up passages with the wreckage. They are meant to be used selectively, on invaders that have been contained in a small area. With the coronavirus, they are deployed too widely—a carpet bombing, rather than a surgical strike. As they do their work, inflammation distends the lungs, and debris fills them like a fog.

In late May, tenOever's team shared its findings in the biweekly journal *Cell*. In their article, they argued that it's this imbalanced immune response that gives severe COVID-19—which can sometimes cause blood clots, strange swelling in children, and ultra-inflammatory "cytokine storms"—the character of an autoimmune disorder. As the virus spreads unchecked through the body, it drags a destructive immune reaction behind it. Individuals with COVID-19 face the same challenge as nations during the pandemic: if they can't contain small sites of infection early—so that a targeted response can root them out—they end up mounting interventions so large that the shock inflicts its own damage.

The gears of the immune response that come apart in COVID-19 were discovered slowly, in a blundering way, as though science itself were recapitulating evolution. In a sense, there are several immune systems. In health, they coördinate with and balance each other. But a machine with so many moving parts is, inevitably, vulnerable.

Immunology as we know it began in earnest in 1882, at the Italian seaside. Ilya Metchnikoff, a Russian zoologist who would later help popularize yogurt in Western Europe, had developed an obsession with digestion, and with the process by which one cell eats another. In his memoir, Metchnikoff described the insight that would define his career. His family had gone to the circus, but he'd stayed home, "observing the life in the mobile cells of a transparent starfish larva" through his microscope. Suddenly, a thought occurred to him:

It struck me that similar cells might serve in the defense of the organism against intruders. Feeling that there was in this something of surpassing interest, I felt so excited that I began striding up and down the room and even went to the seashore in order to collect my thoughts. I said to myself that, if my supposition was true, a splinter introduced into the body of a starfish larva . . . should soon be surrounded by mobile cells.

Metchnikoff immediately performed the experiment, using a thorn from a rosebush in his garden. Sure enough, he saw cells surrounding the foreign body.

At the time, leading biologists, including Louis Pasteur, didn't think of hosts as actively defending themselves against pathogens. If it was often impossible to get diseases twice, then that was because we became inured to them, like alcoholics to liquor, or because some unknown quantity of illness

within us was "used up" as each disease ran its course. Immunology had advanced only haltingly since 1730, when the clergyman Thomas Fuller speculated that each person was born with "Ovula, of various distinct Kinds, productive of all the contagious, venomous Fevers we can possibly have." According to this theory, an infection was actually an impregnation; each "egg" could be fertilized only once.

Using dyes to distinguish cells under a microscope, Metchnikoff helped show that the body actively defended itself. In fact, specialized cells responded to intruders in a process he described as "phagocytosis," or cell-eating. One kind of cell-eater, called a "neutrophil"—because it can be stained only by pH-neutral dyes—swarmed to the site of the infection first. Larger cells called "macrophages" followed, absorbing both the invaders and the neutrophils into their "amoeboid protoplasm." Neutrophils and macrophages, Metchnikoff found, lived in tissues throughout the body—a standing army.

Metchnikoff's findings were promising: he had uncovered what would become known as "cellular" immunity. At the same time, other researchers seemed to be making progress in an entirely different direction. Emil von Behring and Shibasaburō Kitasato, two biologists working in Berlin, injected guinea pigs, goats, and horses with diphtheria and tetanus toxins. They found that, from the victims' blood, they could derive "antitoxins" capable of conferring protective immunity on other animals. (Von Behring won the first Nobel Prize in Physiology or Medicine for this work, in 1901.) It wasn't clear what these antitoxins, later called "antibodies," were made of. Still, von Behring and Kitasato had discovered what came to be known as "humoral" immunity, and it had nothing to do with cells eating other cells.

There came to be two camps: the cellularists, aligned with Metchnikoff, and the humoralists, aligned with von Behring. The feud over the origins of immunity was political and cultural as well as scientific. Metchnikoff was working at the Pasteur Institute, in Paris, and his followers, who believed that cell-eating was the basis of immunity, were mostly French. Von Behring's supporters, who focussed on antibodies, were German. The humoralists won the mainstream in 1897, when a biochemist named Paul Ehrlich published a theory explaining how antibodies might work. In his paper, Ehrlich drew a toxin as an amoeboid blob with small nubs jutting out of it, each differently shaped; the antibodies were like little tadpoles whose mouths sometimes fit exactly onto the nubs.

It was these variations in shape, Ehrlich argued, that allowed the antibody system to adapt to new pathogens and cripple them. For the first time, the elusive concept of immunity to specific diseases, so important and yet so poorly understood, felt tangible. "Helped in no small measure by the pictures which Ehrlich published," Arthur M. Silverstein writes, in "A History of Immunology," antibodies became "the principal object of interest to almost all immunologists." Although Ehrlich and Metchnikoff shared a Nobel Prize for their contributions to our understanding of immunity, Ehrlich's account eclipsed interest in Metchnikoff's cell-eaters for nearly fifty years.

As biologists grew expert in the distillation of "curative serums," the great quest in immunology became figuring out how antibodies were made, and how there could be so many kinds. It seemed that a person's antibody repertoire was limitless: biologists found that the immune system could quickly create antibodies to fit synthetic chemicals never before seen in nature.

For the first half of the twentieth century, the going theory was that the invading element—the "antigen"—served as a template around which a corresponding antibody was molded. Only in 1955 did scientists discover the much stranger truth. It turned out that the cells that produce antibodies —called B cells, because they were first discovered in the bursa of Fabricius, an organ that does for birds what bone marrow does for humans—can produce only one kind each. Its structure is random, and nearly every B cell is discarded unused. If, however, an antibody created by a B cell happens to match some part of an antigen, that B cell will not just survive but clone itself. The clone incorporates many mutations, which offer the possibility of an even better match. After a few generations, an antibody with the best fit is "constructed" through a process of mini-evolution that occurs continuously in our lymph nodes and spleen. (Our ancestors the bony fish adapted the machinery of the B-cell system from an even more ancient parasite.)

The vividness of this picture—a weapons factory deep in our bodies, working on the principles of Darwinian selection—further etched the formula "immunity equals antibodies" into the biological imagination. And yet problems remained that only the cellularists could solve. During the Second World War, severe burns treated with donor skin grafts became more common. But the donor skin was often rejected by the body. When scientists examined the site of a rejected graft, they didn't find antibodies. Instead, they saw swarms of a previously unknown kind of immune cell. Later, the attacking cells were shown to come from the thymus, a small, spongy organ, then thought to be

vestigial, that straddled the esophagus. They were named T cells as a result, and became an object of fascination. T cells were incredibly destructive but somehow selective. They knew the difference between self and other.

The balance between protection and self-destruction had always been a theme in immunology. Since Ehrlich's time, allergies had been seen as a misdirected immune response; in the nineteen-forties, scientists learned that certain precious parts of the body—the eyes, the reproductive organs, the brain—are actually walled off from much of the immune system. (Ehrlich himself discovered the "blood-brain barrier," a mesh too fine for phagocytes and even tiny antibodies to penetrate.) Now the question of how the body distinguished between foreign and domestic tissue focussed itself on skin grafts and T cells.

Earlier, in mice, researchers had identified genes that affected the success of organ transplants: they called this collection of genes the major histocompatibility complex, or MHC, from the Greek *histos*, for "tissue." In the sixties, a human version of the MHC was found. The genes turned out to be a blueprint for a remarkable system designed to distinguish self from non-self. Fragments of proteins built inside our cells are loaded onto tiny molecular rafts, which ferry them to the cell surface for inspection by T cells. Meanwhile, in the thymus, T cells are trained as inspectors: they are presented with rafts containing protein fragments, some of which are natural to the body. Any T cell that ignores its raft, or that goes on the attack in response to self-generated fragments, is destroyed. Competent inspectors are set loose to search for foreign material. They look for cells that display unfamiliar protein parts in their rafts and kill them.

This is how skin grafts are detected and rejected; how incipient cancers are disposed of; how cells that have been co-opted by viruses are rooted out. Together, B cells and T cells allow the human immune system to update itself as fast as our cells can replicate. But their power comes with risks. The immune system's adaptive weapons aren't always precise. Allergies affect somewhere between ten and forty per cent of the global population; as many as four per cent of people suffer from debilitating autoimmune diseases. And parasites could find ways to hack the system. "The invention of acquired immunity was like escalating a war with an omnipotent opponent," Hedrick, who is a T-cell expert, writes. Our new weapons could be turned against us.

By the late eighties, it no longer made sense to contrast cellularists and humoralists. They had both been right; it was just that they saw different parts of the immune system depending on where and when they looked. Phagocytes were often present at the moment of infection. Antibodies in the blood, which could take days to emerge, pursued invaders outside the body's cells, while T cells used MHC to peer inside those cells, destroying the ones that had been infected by viruses or corrupted by cancer.

Still, mysteries remained. At a 1989 symposium, the immunologist Charles Janeway described what he called the field's "dirty little secret": a vaccine containing an antigen designed to elicit antibodies wouldn't work unless an extra irritant, or "adjuvant"—usually a harmless chemical or bacterium—had been added. Why wasn't the antigen enough to jump-start the creation of antibodies? "To be quite honest, the answer is not known," Janeway said. His suspicion, though, was that the process couldn't begin unless the innate immune system—with its interferons, cytokines, and epithelial cells—had sounded its alarms first. Without marching orders, the standing army remained on call.

An innate system has to anticipate its enemies—a seemingly impossible task, given their stupendous variety. It wasn't until around 1997 that Janeway began to understand how such anticipation might be accomplished. About a decade earlier, a pair of biologists named Christiane Nüsslein-Volhard and Eric F. Wieschaus had found a gene that affected development in fruit flies. Nüsslein-Volhard had called it Toll, using the German word for "great." ("*Das ist ja toll!* " she exclaimed, upon making the discovery.) Another scientist, Jules A. Hoffmann, learned that the same gene was involved in the fruit-fly immune response; Janeway, with the help of Ruslan Medzhitov, showed that a version of it was also present in humans, and employed in some of the white blood cells that are the innate immune system's first responders. Through experiments with human cells, they showed that the gene coded for what came to be called a "Toll-like receptor," which could recognize a particular molecular motif—a building block of bacterial membranes. It was as if evolution had noticed that, while many cells built their houses out of oak or brick, dangerous bacteria always seemed to use pinewood. Why not make a pine detector?

Immunologists soon discovered a second Toll-like receptor, then a third; they started giving them names like TLR4 and TLR5. Whole new families of "pattern-recognition receptors" were found.

Each receptor, ingenious in its design, recognized some characteristic microbial or viral signature—a kink in a virus's RNA, a crenellation in a microbial cell wall.

At long last, a picture of the whole system was coming into focus. It was all interconnected. Innate immunity kicks off the immune response, as cells at the site of infection use their receptors to recognize and combat invaders, and release interferons and cytokines to raise the alarm. Various types of white blood cells respond, having been routed to the infection via the bloodstream. They identify and eat foreign cells, returning the digested bits, via the lymph nodes, to the thymus and the bone marrow, as intel. In the days that follow, antibodies and killer T cells—the weapons of adaptive immunity—are built to spec. Everything plays a double or triple role. Antibodies, for instance, don't just attach to invaders to block their entry into cells; they also tag them so that they'll be easier for white blood cells to find and eat. The innate and adaptive arms ramp up each other's destructive abilities.

Here, again, Hedrick sounds a cautious note. "Such a scheme should worry any systems analyst," he writes. "A potentially lethal mechanism controlled by positive feedback is a recipe for runaway destruction."

In late March, a thirty-two-year-old man of Dutch ancestry was admitted to a hospital in the Netherlands. He had difficulty breathing, and a CT scan showed an opaque haze spreading in his lungs. He was given a diagnosis of COVID-19, and spent sixteen days in intensive care; four days after he was moved out of the I.C.U., one of his lungs collapsed. He recovered enough to be sent home nine days later. His twenty-nine-year-old brother, who lived in a different house, got sick at roughly the same time, and died. Their parents had moderate symptoms.

When scientists learned that a second pair of young brothers—twenty-one and twenty-three years old, of African ancestry—had also had severe cases of COVID-19, they sought to study all four men. By sequencing the genomes of the men and their parents, the researchers hoped to find an anomaly that might explain why some young people, particularly men, had such bad outcomes.

The Dutch team found something that echoed tenOever's theory about the way in which SARS-CoV-2 rewires the cellular alarm system. The four men all had an ineffective variant of TLR7, a Toll-like receptor that recognizes viral RNA. When it works, TLR7 helps produce interferons,

which tell nearby cells to increase their antiviral efforts. When it doesn't, the alarm is silent, and the infection spreads. This genetic abnormality had made the virus's work dramatically easier. The raiders had come to an unlocked house.

This spring, a clinical trial in the U.K. gave interferon-beta, a synthetic version of the molecule, to a random selection of a hundred and one patients hospitalized with COVID-19. The trial found that those who received interferon early in their infection were seventy-nine per cent less likely to become seriously ill. Researchers agree that timing is crucial. In the early days of a coronavirus infection, an interferon boost might help your innate immune system contain the virus. Later, though, it might be harmful; at that point, your adaptive immune system could already be out of control, and you might need an immunosuppressant, such as the steroid dexamethasone. (Last month, President Trump received dexamethasone as part of his treatment for COVID-19; he was also given a drug that contained lab-engineered antibodies capable of fighting the virus alongside, or ahead of, his body's own adaptive response.)

The genes for TLR7 are on the sex-linked X chromosome. That could be a partial explanation for why men suffer from severe COVID-19 more often than women. But a TLR7 deficiency is likely to be rare—far rarer than the incidence of severe COVID-19 among young people. There are almost certainly other genetic or environmental factors that weaken the interferon response. In mid-September, research published in *Science* showed that some COVID-19 patients with bad outcomes had "autoantibodies" that were attacking their own interferon; another article published in the same issue outlined a genetic flaw related to TLR3, which is also involved in the interferon response. (As many as fourteen per cent of severe COVID-19 cases may be attributable to one of these two conditions.) The more researchers study our immune response to the virus, the more complexity they find. According to some theories, how things go for you could depend on how many viral particles you've inhaled, and on whether they reach your lungs when you breathe them in. If you've had a cold recently, it's possible that the T cells you developed to fight it could partially fit the coronavirus. Vitamin D levels might matter, because Vitamin D can help control inflammation. Harmful autoantibodies could be responsible for the persistent symptoms suffered by COVID-19 "long-haulers." All of this is still being explored.

The immune system uses feedback to stay balanced, like a gymnast on a beam. If a light breeze

blows, the gymnast might sway a bit; sensing this, she'll shift her weight to return to center. But, given a strong enough push, she's prone to overshoot with her reaction and, from the other side, overshoot again until she falls. Many factors contribute to the slip—a tight hip flexor, a strained calf, moisture in the air—each magnifying the force of the shove.

Older gymnasts tend to be less agile. The same goes for the immune system, which is why COVID-19 disproportionately affects the elderly. The already high case fatality rate for sixty-five- to seventy-four-year-olds more than triples in people seventy-five and older. This age distribution is unique to the coronavirus. Kids are more susceptible to the seasonal flu; children and young adults who had the swine flu in 2009 were hospitalized the most, while the pandemic flu of 1918 hit adults in their twenties and thirties the hardest. (Perhaps their immune systems overreacted, or older people had acquired immunity to similar strains.) "The difference of risk and profile, young versus old—I don't think anyone has seen an infectious agent behave quite like this before," Richard Hodes, the director of the National Institute on Aging, part of the National Institutes of Health, said, of the coronavirus.

The lopsidedness of the virus means that vaccines might not be as effective in older patients, even with double the dose, or after repeated inoculations. The beauty of a vaccine is that it relieves us of the task of completely understanding the virus; its package of antigens simply presses the On button of the great machine. Helping older people may require a more fine-tuned approach, tailored to the particular way this virus destabilizes the immune system. What we have learned so far suggests that it isn't just that being older makes you weak, and that COVID-19 preys on this weakness; the disease's mechanism of action is actually amplified in the aging body.

For this reason, about a month after beginning their coronavirus investigations, the researchers in tenOever's lab switched from ferrets to hamsters. Ferret immune systems are highly responsive, and the animals were getting better too quickly. "They look a lot more like kids," tenOever said. By contrast, some hamsters, when infected with the virus, "actually develop respiratory distress. We see a lot more infiltration in their lungs." In older hamsters, as in older people, innate immunity is less likely to contain the virus and adaptive immunity is slower to turn on and off. The hamster ends up wildly dysregulated. "The difference between these two outcomes really comes down to, as you get older—" TenOever paused. "Getting older sucks. Everything breaks down, even at the simplest of

levels."

As we age, our immune systems stiffen up. "If I had to respond to an insult—bacteria, a virus, a trauma, a lesion—the response is slower and is less strong," Luigi Ferrucci, who studies the aging process and the immune system at the National Institute on Aging, told me. But, at the same time, the system becomes chronically activated. Cytokines circulate at a constant, high level in the blood, as though the body were at all times responding to some attack. This is true no matter one's health. "Even in individuals that are extremely healthy, extremely well nourished, have no disease, and they're taking no drugs, there are some inflammatory markers whose concentration increases with aging," Ferrucci said. Think of the welt that rises with a bite, then imagine the same process —swelling, redness, stiffness, the accumulation of pus—slowly pervading the body. Your level of inflammation contributes to your "biological" age—which is not always in perfect lockstep with your chronological age—and increases your risk of developing cardiovascular disease, cancer, and dementia; it contributes to what geriatricians call "frailty."

A phenomenon known as cellular senescence is partly responsible for the body's increasing inflammation through time. As cells age and divide, small errors accrete in their DNA. These errors could lead to cancer, among other maladies. And so cells police themselves. When they detect decay in their DNA, they stop replicating and begin emitting cytokines, as though asking the immune system to inspect and destroy them. The accumulation of senescent cells may contribute to severe COVID-19: according to the current theory, Ferrucci said, they could "expand tremendously the cytokine storm," in which a runaway feedback loop leads to a sudden spike in inflammation throughout the body.

Adaptive immunity suffers with age, too, but for different reasons. The thymus itself atrophies. (On a restaurant menu, thymuses are called sweetbreads. "Sweetbreads come from young calves," Hedrick told me. "If you were to try to harvest the thymus from an old bull, you'd get . . . nothing.") When you're young, with a short history of exposure to pathogens, your thymus produces new T cells at an extravagant rate. But as you age production slows, and the cells differentiate. Some live indefinitely as "memory T cells," carrying with them a record of their defeated foes.

Certain viruses use up more T-cell memory than others. Around twenty per cent of an older adult's T-cell repertoire is devoted to fighting a single virus: human cytomegalovirus (HCMV), a strain of herpes that usually has no symptoms. It would be ironic if, in some small way, HCMV makes it harder to survive COVID-19. Unlike SARS-CoV-2, which spreads without hiding and so causes extensive damage, HCMV is a master of disguise. When infecting a cell, the virus turns off that cell's MHC system. No cellular raft delivers evidence of the infection to the surface. Still, this isn't enough to avoid detection. Our immune system has invented a weapon, the "natural killer" cell, that looks specifically for cells without functioning MHC systems. And so HCMV evolved to create a decoy MHC raft, designed to fool the natural killers.

As a parasite, HCMV is almost perfectly adapted to its host; able to spread without attracting attention, it does nothing but consume resources. The thymus is one place where such cleverness leaves its trace. The practice of science is another. Many of the workhorse tools employed by molecular biologists—including the enzymes used by tenOever's team to sequence RNA, and the CRISPR gene-editing system, perhaps the most important scientific discovery of our time—were once either weapons or defenses in the microbial arms race. It's there, at the crucible of life and death, that biological innovation happens fastest, leaving us with technology for mounting a new kind of defense.

The last time I spoke to tenOever, in late July, his team had begun a search for treatments. In the BSL-3 lab, Møller was infecting hamsters; the plan was to give the animals candidate drugs, sequencing their RNA through the entire process of infection and treatment. By examining patterns in the data, the team could find out which drugs were better at undoing the coronavirus's reprogramming. TenOever made use of a handy way of visualizing what was happening in the cells. He could turn the genetic analysis into an inkblot-like map, showing which parts of its genome each cell was activating. "You can build a landscape, if you will," tenOever said. If the coronavirus shifted the landscape to the northeast, they would look for drugs that pulled it southwest. They were testing four good candidates a week like this.

It was an impressionistic way to look at an immune system. But the system was not designed to be legible; it was, of course, not designed at all. For years, Robert Jack, one of the authors of "Evolutionary Concepts in Immunology," taught a class on immunology to students just beginning

their Ph.D.s. Bright and enthusiastic, the students struggled to untangle the immune system's feedback loops. Jack told me, "We tend to look at these systems and say, 'Wow, who would have thought of that? That's incredible. That's so fantastic. It does this incredibly complicated job, and it does it really well!' " He took a breath, then continued. "Whereas, in reality, the immune system has simply, in the face of pathogen attack, staggered from one emergency to the next. It just uses whatever is lying around. It is hoping against all possibilities to try to survive a little bit longer. Whatever crazy solution it comes up with—so long as it works, it will be accepted." The result is a system of great flexibility and power, which, pushed the right way, can be made to collapse upon itself. ♦

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