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**B**ack in April, as the pandemic was cresting over New York, Iris Navarro-Millán, a physician at Weill Cornell Medicine in Manhattan, treated a Covid-19 patient, a Hispanic woman in her 60s, who would prove to be a turning point in how she approached the disease. The woman was just a little short of breath when Navarro-Millán first saw her; a day later, she deteriorated so rapidly that she was rushed to intensive care, put on a ventilator and hooked up to a dialysis machine for her failing kidneys. Navarro-Millán feared that she would die. (She survived after spending two months sedated on the breathing machine.) When Navarro-Millán saw another Covid-19 patient soon after — a white man in his 60s already struggling to breathe — her first thought was, *Not again*. Believing that the prevailing standard of care — which, lacking drugs to directly fight the virus, consisted primarily of supportive measures like supplemental oxygen — was insufficient, she resolved to try something different, a treatment that was heretical in some circles but that she thought could save his life.

Navarro-Millán had unusual expertise for a hospitalist. Weill Cornell had asked her to move into that role when the pandemic hit, but she was a rheumatologist by training, a doctor whose specialty is autoimmune ailments in which the immune system, tasked with defending the self from invading pathogens, inexplicably turns on the body's own tissues. Now she drew on her experience to try to help this Covid-19 patient.

She suspected that the greatest danger here wasn't the coronavirus itself but an immune overreaction so severe that it could cause lungs to fill up with fluid and prompt organs to shut down, possibly killing the patient. Rheumatologists often describe this type of immune reaction as a “cytokine storm” or “cytokine release syndrome.” Cytokines are proteins released by cells in order to send messages to other cells — signaling, for instance, that a viral invasion is underway. The number of different cytokines is large, perhaps exceeding 100, and each one calls for a specific response. To save her patient, Navarro-Millán decided that she would have to calm his immune system and prevent that storm from getting started.

Early in her career, Navarro-Millán worked at the University of Alabama at Birmingham, where most of her patients had lupus, an autoimmune disease that can affect various parts of the body, including the kidneys, blood and even the brain. Its sufferers are especially prone to cytokine storms, which are often triggered by viral infections. What Navarro-Millán saw now in her Covid-19 patients wasn't, she thought, all that different from what she encountered in Alabama.

Illustration by John Karborn

FEATURE

# How Covid Sends Some Bodies to War With Themselves

Many Covid-19 patients may be dying from their immune response to the virus, not from the virus itself. Can science figure out how to save them?

By Moises Velasquez-Manoff

A major lesson learned from her years there was that saving patients from cytokine storms often required doctors to intervene early, preferably long before the patients landed in the I.C.U., when it was frequently too late to bring the immune system to heel. So, the sooner she treated her Covid patient by tamping down his inflammatory response, she figured, the better. At the same time, she was leery of subduing his immune system for too long or too profoundly, because that might hobble his body's ability to fight the virus that was making him sick in the first place.

An array of drugs was available to her, ranging from antibodies that target specific pathways in the immune system to molecules that have a more widespread effect on the body. One, called tocilizumab, blocked the cytokine interleukin-6, but it remained in the body for up to a month — too long, in her view. Steroids, which dampen the entire immune system, might open the door to other infections. (Hydroxychloroquine, an antimalarial drug that has been promoted by President Trump for its supposed coronavirus-fighting potential, also happens to suppress the immune system. But because this effect, which is mild, comes only after months of daily use, it is unlikely to be suitable as a way to quell an immune firestorm started by an infection. The evidence so far suggests that it doesn't work as an antiviral remedy, either, and that it can cause severe side effects.)

Navarro-Millán settled on anakinra, a drug originally developed to treat rheumatoid arthritis, an autoimmune condition. The drug targets a cytokine involved in fever called interleukin-1. As a biologic, anakinra mimics the body's own antibodies; unlike other biologics, however, it remains in the body for mere hours, not weeks. If her attempt at immune suppression here started to go awry — if some other infection took hold — it could be reversed quickly.

After her patient provided his consent, Navarro-Millán gave him the anakinra. His improvement was rapid. When she had first seen him, he was wearing nasal tubes that dispensed oxygen; by the next morning, his condition had deteriorated, and he needed a rebreather mask to get more oxygen. He received his first anakinra injection that day; the morning after, his breathing became less labored and he no longer needed the mask. Nose tubes were sufficient. A little more than a week later, he went home.

Navarro-Millán was not a lone pioneer in what she was doing. Horrified by the death toll among very ill patients, physicians around the world had already tried or were trying versions of her approach; as they battled the novel coronavirus, these doctors were trying to calm immune systems that they thought were out of control. Navarro-Millán thus belonged to a community of physicians who, eager to lower the mortality rates among their hospitalized Covid patients, were turning to still-unproven treatments directed at the immune system.

The idea of manipulating the immune system as a way to fight Covid-19 first arose last winter in China after physicians there observed that greater inflammation seemed to correlate with worse outcomes. In March, some Italian doctors turned to immune-modulating drugs as well, says Marco

Gattorno, head of the Center for Autoinflammatory Diseases and Immunodeficiencies at the Giannina Gaslini Institute in Genoa. So many intubated patients were dying, he told me, that physicians felt they had to try *something* to lower mortality rates. “They were rather desperate, because they realized that indeed it was a grave problem,” he says, referring to his colleagues on the front lines. “We were able to convince the people not to be too shy with glucocorticoids” — that is, steroids. And the death rate among I.C.U. patients at his hospital who received immune-modulating drugs seemed to decline.

It's probably no coincidence that those who have been most forcefully advocating to try Covid-19 therapies that rein in the immune system are often rheumatologists. Their specialty makes them quite familiar with the vagaries of the immune system and the drugs used to try to control it. But their willingness to use immune-modulating drugs in this pandemic without supporting evidence from robust studies is sometimes frowned upon by other specialists, many of whom worry about the consequences of deliberately weakening immune defenses while an infection is raging.

This proposed fix is something of a paradox. It posits that the best way to help some patients survive Covid-19 may not be to fortify the immune system, so that it can fight the virus with greater ferocity, but to subtly suppress the counterattack, so that the patient avoids self-destruction. The notion is controversial, not least because differentiating an appropriate immune response from a self-harming one can be difficult. An added wrinkle is the fact that SARS-CoV-2, the virus that causes Covid-19, may itself stifle aspects of the immune response, meaning that additional immune suppression could make things worse.

Each new study further complicates the picture of what exactly is going wrong with the immune system in severe Covid-19 cases. But the evidence continues to mount indicating that *something* is going awry, immunologically speaking. And in the absence of a vaccine, figuring out the best way to correct this dysfunction may prove crucial to helping patients survive the disease. This might be the case even if a course of treatment includes antiviral medicines. In a recently published preliminary report involving remdesivir, for example, some Covid-19 patients who received that antiviral drug experienced accelerated recovery times — remdesivir seemed to help, in other words. But the drug did not significantly lessen overall mortality rates. The very sick still died. One reason for this lack of improvement, according to Chaz Langelier, an infectious-disease specialist at the University of California, San Francisco, might be that the immune system, not the virus directly, is driving the disease in these instances. Helping those patients may require calming the immune system.

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While Langelier and other physicians recognize this enduring problem in medicine — the fact that the immune system can do us in — they still don't necessarily endorse the practice of giving immune-suppressing drugs to Covid-19 patients outside an actual trial. "It's treading in dangerous territory to practice without evidence-based principles," Langelier told me in early May. "I think it is just too early to know if that type of approach is really beneficial or it's just putting people at risk." Then he added, "We're obligated to do no harm."

Rheumatologists don't entirely disagree. But a global pandemic is a unique situation, several told me. In some situations, "letting disease kill the patient is also doing a kind of harm," says Randy Cron, a pediatric rheumatologist at the University of Alabama at Birmingham. "When people are dying in large numbers," he told me, "we don't have the time frame to wait."

**There is** a natural tension between what physicians themselves sometimes describe as the art and the science of medicine. Medicine's bedrock, its science, consists of treatments and protocols that have been tested rigorously and proven to work (better than placebos do). But in daily practice, as they try to help patients, none of whom are the same, doctors sometimes move slightly beyond what has been proven, particularly when established practices prove ineffective or when it's unclear what really ails a patient. They may draw on personal experience or case studies in the medical literature. They might prescribe drugs off-label, or for uses other than what they were approved for; and, within certain bounds, fiddle with dosages. As Navarro-Millán put it to me, "Nothing in medicine is fixed or precise, unlike other sciences."

The tension between the interpretive (or creative) and the conservative (or scientific), which is probably felt to some degree by every doctor, can escalate in times like the current moment. Doctors and scientists are facing a virus never seen before and are therefore figuring out how to treat it for the first time. Some doctors feel impelled to try new treatments in order to help their patients. But this may, as Langelier points out, end up in conflict with Hippocrates' injunction that physicians "do no harm." And certainly, there have been episodes in which doctors took action in a way that they thought should work but turned out to cause harm. For example, once scientists got around to thoroughly studying hormone-replacement therapy for postmenopausal women, beginning in the 1990s — a treatment that made sense in theory — they discovered a major downside: It increased the risk of breast cancer, heart disease and other ailments among certain groups of women.

That doesn't mean that physicians' experiences are useless or don't warrant attention. A recent opinion piece in *The Journal of the American Medical Association* noted the current "cacophony" of observational studies and pointed out that even these so-called weak studies can help advance Covid-19 treatments as long as they lead to well-designed follow-up trials. Stronger studies can test the ideas generated by weak studies (though the authors warn against publishing those weak studies in medical journals, so as not to unduly influence care).

In the United States, physicians' efforts to suppress the immune system in Covid-19 patients have been uncoordinated. Institutions formulate their own approaches. As Covid-19 overwhelmed New York, doctors at Montefiore Health System in the Bronx, a borough hit hard by the virus, convened a task force to develop a plan of care focused on the immune system. Over the course of months at New York University Langone Medical Center, critical-care doctors slowly increased their use of steroids, according to Sam Parnia, director of critical-care and resuscitation research. The gradual embrace of steroids stemmed in part from observations that patients seemed to improve when treated with them, and then worsen when the drugs were withdrawn.

Officials at Temple University Hospital in Philadelphia early on established a protocol for Covid-19 patients centered on aggressive immunomodulation. Roberto Caricchio, the head of rheumatology there, told me that the hospital, which serves a high-risk, mostly African-American and Hispanic population, immediately began giving steroids in low doses to everyone who tested positive for Covid-19 and who needed oxygen. Depending on the levels of various inflammatory indicators, patients might then be given anakinra — the short-acting drug that Navarro-Millán used — or tocilizumab, the longer-lasting drug that blocks the cytokine interleukin-6.

In Southern California, Thomas Yadegar, medical director of the I.C.U. at Providence Cedars-Sinai Tarzana Medical Center, says he changed how he cared for Covid-19 patients after a number of them suddenly and inexplicably deteriorated and several died. Starting in April, as soon as the oxygen in their blood began dropping — and before admission to the I.C.U. — Covid-19 patients at his hospital began receiving sarilumab, then, later, tocilizumab. He told me that the number of patients needing intubation has since declined greatly. "If you told me in January that you were coming into my I.C.U. to give immunomodulators, I would have called security and had you thrown out," he says.

At Weill Cornell, Navarro-Millán spent the April surge working with a team of internal-medicine doctors and rheumatologists, giving anakinra to Covid-19 patients who met certain criteria. (In June, she returned to rheumatology full time.) This summer, Navarro-Millán and her colleagues published a case series, or purely observational study, in the *Journal of Arthritis Rheumatology*. They detailed the outcomes for 11 of their hospitalized patients. Seven who were treated within 36 hours of the onset of symptoms — defined as worsening shortness of breath that didn't improve with supplemental oxygen — were able to avoid being put on ventilators and went home; four who were treated four or more days after symptoms began ended up on ventilators (one died). Although the

study wasn't designed to generate firm conclusions — among other shortcomings, it was tiny and contained no untreated comparison group — giving anakinra to patients early in their care seemed to produce better results, as Navarro-Millán anticipated. She is now seeking F.D.A. approval for a stronger trial involving multiple hospitals and doctors to test anakinra on Covid-19.

**It wasn't until** late June that a controlled study produced strong evidence suggesting that what so many doctors were already trying might actually work. That's when University of Oxford scientists released data from the best designed and largest trial to date — nearly 6,500 subjects took part — that has explored an immune-suppressing therapy for Covid-19 patients. The Recovery trial, which has since been published as a preliminary report in *The New England Journal of Medicine*, found that moderate doses of the steroid dexamethasone cut deaths by one-third among patients on ventilators and by one-fifth among those receiving oxygen who weren't on the breathing machines. This was a marked improvement in survival rates, and reason for hope. The findings included an important caveat, though: Mildly ill patients didn't fare any better when given steroids. In fact, in this subgroup, there was a trend toward worse outcomes.

One possible explanation for these divergent results is that suppressing the immune system in mildly ill patients actually delays, rather than helps, their recovery. For those who are beating back the virus just fine on their own, the treatment might hinder that process. If this is what's happening, it would support a criticism I heard often from skeptics, who oppose using immune-suppressing drugs outside trials: Not only might treatments expected to help patients end up doing them no good — they might do actual harm.

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One such critic is Carolyn Calfee, a critical-care specialist at the University of California, San Francisco, who opposes targeting the immune system unless it is done in trial settings. But even she refers to the Recovery results as “practice changing.” In late July, she said, experts at U.C.S.F. were discussing how to incorporate the study findings into the hospital's Covid-19 protocol. Some questions remained, but “this study has definitely changed my view,” she told me. “I think we have to take it very seriously.” (Chaz Langelier, too, found it convincing.) N.Y.U. also included dexamethasone in its official treatment plan after the study's results came out. Sam Parnia says, as did the hospital at the University of Alabama at Birmingham, where Randy Cron had pushed for months to give immune-modulating drugs to Covid-19 patients.

The results of the Recovery trial have not displaced the discomfort Calfee and others feel about giving immune-suppressing drugs to Covid-19 patients in situations other than well-designed trials, however. Suppressing the immune system to help patients survive infections has been tried before,

they point out. And it largely failed.

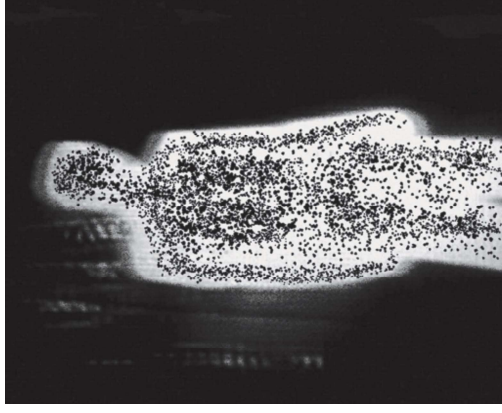


Illustration by John Karbom

Every year, nearly 200,000 Americans develop acute respiratory distress syndrome, or ARDS, from the flu and other infections or from massive trauma — car accidents, say, or burns. More than one-third of these patients die. Sepsis, a condition in which an overwhelming reaction to infection triggers blood-pressure loss and organ failure, contributes to 30 to 50 percent of all deaths in the hospital. (Other conditions that weaken the body, like cancer, can contribute to the development of sepsis in patients, meaning that sepsis may simply be the final diagnosis in a patient's long decline.) Even before Covid-19, lower-respiratory-tract infections were humankind's single greatest killer among communicable diseases, according to the World Health Organization.

If an overexuberant immune response is a major contributor to these conditions, as many suspect, then it's paramount to come up with methods to combat them by calming the immune system. That has proved to be easier said than done. “In both sepsis and ARDS, we haven't made the strides we wish we could have,” says Nuala Meyer, a critical-care physician and scientist at the University of Pennsylvania's medical school.

And some of the immune-modulating drugs now being tried against Covid-19 have failed to help sepsis and ARDS patients in the past. Researchers have been “trying for decades to find treatment without any success for ARDS,” Calfee told me. Advances have been made in non-drug-based management of the condition. Ventilators now pump smaller “breaths” for their patients than in the past, because studies have indicated that larger breaths cause spikes in inflammation. And patients with more inflammation fared worse. But, Calfee says, “there’s been absolutely zero success in pharmacological therapy.”

Today’s trials may have a better chance of succeeding, however, because scientists increasingly recognize that patients who appear to suffer from one affliction — ARDS, say — can be divided into smaller groups, defined by measurements of inflammation and other criteria. And some hope that these smaller, more clearly defined subsets of patients will benefit from treatments tailored to them. That’s one takeaway from Calfee’s own reanalysis of an old trial.

In 2018, she and an international team went back over data from a study originally conducted in the early 2010s that tested a statin, usually used to protect against heart disease, for ARDS. (Statins have anti-inflammatory properties.) The trial didn’t show a benefit when first published, but after Calfee sorted the patients according to how much inflammation they experienced, she discovered that, in fact, those who suffered the worst — 35 percent were in what she calls a “hyperinflammatory” state — were less likely to die if they received treatment instead of a placebo. Patients not in this inflamed state, however, did not benefit from the treatment. “Maybe there are actually patients within these groups responding,” Calfee told me. “But we can’t see them because there’s so much noise.” Randy Cron and his colleagues reached a similar conclusion after re-examining an old trial testing anakinra on sepsis, which was also initially deemed a failure. They found a subgroup of subjects with features of macrophage activation syndrome — a kind of cytokine storm that involves bleeding, clotting and liver dysfunction — who did, in fact, seem to improve after being treated.

Retrospective parsing of old studies can’t definitively prove that something works. Only large, well-designed trials that follow patients after treatment can. But these reanalyses hint at the existence of smaller groups within the broader syndromes that may respond to drugs directed at the immune system. And it may be possible to further subdivide these groups according to how exactly their immune systems have become unbalanced — too much of the cytokine IL-1 here, for example, or too much IL-6 there — and then to correct the unique imbalances of individual patients with specific drugs. This approach, which remains somewhat theoretical, highlights a concept that’s already a buzzword: “precision medicine,” the idea of tailoring care to the particular biology or unique dysfunction of a patient.

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#### The Coronavirus Outbreak

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Updated August 12, 2020

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For Calfee, the likely existence of differing, narrower types of disease within what have largely been thought of as single syndromes underscores why study design is so important — and why the dexamethasone treatment in the Recovery trial may have succeeded where previous trials testing steroids yielded contradictory findings. Earlier studies included ARDS or sepsis patients whose illness stemmed from a variety of causes. But the Recovery trial focused solely on Covid-19 patients. “We see much clearer results,” Calfee told me. The implication is that when scientists design trials, they should apply strict criteria in selecting study participants. “It’s possible that if we focus our trial on subsets of patients,” she says, “we may have a better chance of identifying effective therapies.”

Meyer, Calfee and Langelier hope that all the attention and energy now being brought to bear on the problem of immune overreaction, in response to coronavirus, will yield new remedies that work on lots of other medical conditions as well. Such treatments might not only save many thousands of ARDS and sepsis patients every year; they could serve us well during the next viral pandemic, which is also likely to be respiratory.

**The original source** of the novel coronavirus, thought to be horseshoe bats in China, may prove to be a source of therapeutic inspiration, too, when it comes to overcoming Covid-19. The only mammals that fly, bats are unusual in several ways. They live far longer than many other similarly sized mammals — decades, in some cases, compared with years. And they host, without apparent symptoms, a variety of viruses that are lethal to humans. So some scientists are asking how it is that bats carry their viruses without succumbing — and whether we can tweak the human immune system to make it more batlike.

One hypothesis follows from the animals’ adaptations to flight. Flapping wings requires immense amounts of energy, causing bat cells to spew out large quantities of a metabolic byproduct called reactive oxygen species, which might be thought of as cellular exhaust. In other animals, that

cellular waste, which bears some resemblance to a viral infection, might trigger overwhelming inflammation — a cytokine storm. But bats have evolved ways to keep that inflammation in check.

A consequence of such adaptation is that some viruses can establish long-term infections in their bodies. Yet to compensate for “turning down” one function of their immune system, bats have “turned up” another to prevent their bodies from being completely overrun by viral hangers-on. They produce unusual amounts of antiviral cytokines called interferons. In some species, even as one part of their immune system remains slow to rouse and relatively muted, another part, the front-line antiviral defenses, seems to engage readily and with force, tightly controlling viral infections.

It may be that fending off bat coronaviruses with batlike panache requires a strong initial antiviral response — interferon — followed by a cleanup crew, in essence, that works very softly, preventing a cytokine storm. Indeed, a few years ago, Stanley Perlman, a professor of microbiology and immunology at the University of Iowa, and his colleagues found that mice infected with the coronavirus SARS-CoV (which also came from bats originally) survived the infection if they quickly generated a strong interferon response. Animals that failed to produce interferon early, however, died not because the virus killed them but because they produced so much interferon *later* that their overreactive immune systems did them in. “If interferon comes up late, it causes really bad disease,” Perlman told me. “In most infectious diseases, the immune system is a major part of the problem.”

An immunological disposition that resembles what bats have could explain why children are less vulnerable to severe Covid-19 disease than adults. Children, whose immune systems are immature and developing, have naturally high levels of interferons and other cytokines circulating in their bodies. “Kids are just off the charts with inflammation — without symptoms,” says Paul Thomas, an immunologist at St. Jude Children’s Research Hospital in Memphis. Crucially, too, they have high levels of an anti-inflammatory cytokine called interleukin-10, which may play a role in preventing damage from the constant inflammation. This immune profile — an elevated baseline level of interferons and IL-10 — may be what helps children survive Covid-19. But it generally wanes as they reach early adulthood. (Nor are they invulnerable in the meantime: Some develop a multiorgan inflammatory condition from Covid-19 that resembles Kawasaki disease.)

Adults experience less inflammation and, as they enter old age, have a harder time mounting that interferon response at all, a problem called immune senescence. This deficiency may be why older people get so much sicker from Covid-19, Thomas told me. Aging immune systems may find themselves playing catch-up, increasing the chances that they will overdo it later and damage the self. A pre-existing immune imbalance may also be why people afflicted with conditions that often feature low-level, chronic inflammation — including heart disease, diabetes and obesity — fare worse when battling Covid-19. These diseases may tip their immune systems toward overreaction.

Tantalizing, if still inconclusive, evidence has begun to emerge that giving interferons could help in managing Covid-19. In July, the British biotech company Synairgen reported that inhaled interferon-beta, which would probably lessen the side effects that can accompany the drug in its injected form, greatly reduced severe illness in a small trial. (The company has yet to publish the actual data from the trial, as it plans to do, so its claims should be viewed with skepticism.) Recently, scientists in Hubei Province in China conducted a retrospective analysis of patients who were given antiviral medication plus an inhaled interferon, called IFN-alpha2b. They found that the interferon improved outcomes in a subset of patients. As seemed to be the case in Perlman’s studies with mice, timing mattered. Those who took the interferon earlier saw the most benefit compared with those who didn’t take it, while those who took it later seemed to fare worse.

These interferons are not acting as an immune suppressant, of course, but as a kind of immune stimulant. Still, they might pre-empt an excessive immune response by helping to bring a virus under control at the start of an infection, so that there is no reason to overreact later. Clearly this is the optimal outcome: Once an immune response to a pathogen has served its purpose, it shuts down to prevent damage and allow the organism to resume its normal functioning.

Janelle Ayres, a physiologist specializing in infectious diseases at the Salk Institute for Biological Studies, describes this concept as a “disease tolerance mechanism” — the ability, sometimes hard-wired, sometimes induced by environmental factors, to survive infections without falling ill. “Our traditional view has been: To survive an infection, you have to kill it,” she told me. “We have a very disease-centric approach to biology.” But infection doesn’t always equate to disease. Many of the most frightening pathogens — tuberculosis, cholera, polio and now the coronavirus — don’t cause illness in everyone they infect. Some people experience these infections with few if any symptoms. Their immune systems evidently handle the invasion with the perfect balance of aggression, restraint and repair — or tolerance — to stave off disease. The drugs of the future, Ayres hopes, will enable these native tolerance mechanisms that help some shrug off, with few ill effects, the diseases that sicken and kill others.

The Covid-19 pandemic has already prompted many physicians to bend in this direction. So few tools exist to reliably eliminate the virus from our bodies that they have, out of necessity, turned to the idea of prodding the immune system in various ways. They have shifted their focus in a manner that Ayres has long argued is necessary: from eradicating the pathogen to helping the patient survive the pathogen. They are, in a way, pinning their hopes on innate tolerance mechanisms.

**Dozens of trials** are currently underway that focus on the immune system. These involve everything from cheap, over-the-counter pain medication to expensive antibodies manufactured in living cells. The drugs they are testing include anakinra, used by Navarro-Millán; leroneimab, a drug with anti-inflammatory properties originally developed to treat H.I.V.; and drugs that block IL-6 (full disclosure: My wife works for Genentech, owned by Roche, which manufactures tocilizumab,

one of the IL-6 blockers). One study in Britain is testing high doses of a stomach-friendly formulation of the nonsteroidal anti-inflammatory ibuprofen, better known in the United States as Advil. (Don't try this at home.) Researchers are even looking into low-dose X-ray radiation as a way to calm the immune system, a method that was used in the early 20th century to treat pneumonia but has since fallen out of use.

There's an intriguing trial on an old drug originally developed to treat gout, a painful inflammatory condition of the joints, called colchicine. The drug, which was recently shown to offer protection against heart attacks, targets the very pathway — called NLRP3 inflammasome — that some scientists believe is naturally dampened in bats. Unlike biologics, which are given intravenously, colchicine can be taken in pill form. And while biologics can cost hundreds of dollars per dose, colchicine is dirt cheap. “We think that in the setting of this viral infection, NLRP3 gets activated aberrantly,” says Priscilla Hsue, a professor of medicine at U.C.S.F. and one of the physicians overseeing the trials. “And that leads to downstream badness.” The drug, it's hoped, will prevent the immune system from ever getting to the point where it becomes overly activated. The study aims to start treatment early by sending pills to the homes of patients who have tested positive for Covid-19. “The thought is, if we can intervene early with an anti-inflammatory agent, we can have an impact on slowing down progression and keeping patients off ventilators,” Hsue says.

It remains to be seen which, if any, drug will work best, and what might be the unforeseen consequences of suppressing the immune system in the midst of its battle with the coronavirus. Some trials are already showing failures. Despite promising results from early, weak studies, two of the strongest trials to date on the IL-6 blockers tocilizumab and sarilumab suggest no benefit. (The pharmaceutical companies running the studies, Roche and Regeneron, are continuing with other trials testing their IL-6 blockers.)

Or maybe the studies would have produced better results had they been designed differently. Thomas Yadegar, who thinks tocilizumab can be a lifesaver, if used in the right way, surmises that one study didn't employ stringent-enough criteria for choosing its study patients. Navarro-Millán thinks the trials tried to treat patients too late in the course of the disease. She likened these efforts to trying to cure Stage 4 metastatic cancer — probably doomed from the start.

Other researchers also raise this issue of timing — when doctors should administer drugs to curb immune responses — in a more general sense. Suppressing the immune system too soon after infection could be counterproductive because it might squelch the initial antiviral response and allow the coronavirus to proliferate, says Dawn Wahezi, a pediatric rheumatologist at Children's Hospital at Montefiore. Yet treating too late may make it impossible to quell the eventual immune overreaction. “Knowing when is the right time — I think that's one of the key components,” Wahezi told me. “There's a very delicate window where immunomodulators can help.”

**The debate over** study design parallels another disagreement, this one over the very term “cytokine storm.” Several non-rheumatologists told me that they found the phrase, which has been widely used to describe the immune overreaction that is suspected of taking place in severe Covid-19 cases, maddeningly imprecise and unhelpful. Their frustration partly comes from the fact that the term encompasses an array of syndromes with different causes, including trauma, burns, infections, cancer, genetic disorders, autoimmune diseases and more.

Adrienne Randolph, a professor of anesthesia and pediatrics at Harvard Medical School, told me that doctors and scientists who use the term “need to be specific about what they are defining as cytokine-storm syndrome, at what level.” She went on to say: “All of these patients have cytokines that are elevated, but what cytokines are you following, and for what? And which cytokines are most predictive?” That specificity is important, she and others argue, because it could dictate the pathways physicians will target and the drugs they'll use.

This complaint about terminology extends to the question of what levels of inflammation really qualify as a “storm.” Cytokine levels reported in many Covid-19 patients have been far below — sometimes by orders of magnitude — those seen in other conditions that prompt a strong inflammatory response, like ARDS. For these and other reasons, Calfee and Meyer have preferred to regard Covid-19 as a variation on the ARDS they see every flu season — one that can, if it progresses too far, kill people — rather than as the sort of systemic meltdown that can occur in sepsis patients.

As I spoke with doctors about these and other disagreements, it became clear that some of the differences in the willingness to use drugs off-label to modulate patients' immune systems, as well as embrace the term “cytokine storm” more generally, derive in part from an immersion in distinct scientific literatures. Intensivists and critical-care doctors, among others, operate in a discipline — and are familiar with that medical literature — in which treating the immune system has been tried for ARDS and sepsis and for the most part didn't work. But rheumatologists know another literature in which targeting the immune system seems to succeed. These are not always huge, robust studies. Individually, autoimmune diseases are relatively rare, which makes it hard to conduct large trials with hundreds of patients to study a given drug in, for example, the sliver of lupus patients who develop cytokine storms. The best available evidence sometimes comes from case series. As Navarro-Millán points out, anakinra is not F.D.A.-approved for treating cytokine storms. Even so, she and Cron and other rheumatologists consider its use standard care.

Everyone's immune system is different; how a given disease affects an individual patient can vary greatly. As a result, Navarro-Millán told me, she's always dealing with her patients' idiosyncrasies, always tinkering, always adjusting, always experimenting to some degree. Uncertainty, in other words, doesn't stop her from trying to help her patients. “We still treat it to the best of our

knowledge and with the best evidence we have at hand," she says. "We have done this for years with some successes and some failures." Why, she asks, shouldn't she take the same approach with sick Covid-19 patients?