COVID-19 & THE NEW CORONAVIRUSES

Seasonal coronaviruses have been infecting us for eons, with studies concluding that "coronaviruses appear to be an ancient viral lineage." While the early strains have remained relatively innocuous human pathogens, causing mild upper respiratory symptoms compatible with the common cold, in the last few years, things have changed.

The word "changed" doesn't seem to quite do it justice. Quantum leap might be a more accurate term. SARS was first discovered in Asia in 2003. With a 15 percent case fatality rate, terror gripped most of the continent and almost overnight, inhabitants of Asian countries started wearing surgical masks for protection. The World Health Organization's (WHO) official consensus statement straddled the fence on how the virus was spread, saying that airborne transmission was "plausible" and "could not be excluded." Unlike COVID, patients with SARS were not infectious before the development of symptoms, and by 2004, the pandemic was largely contained. SARS was demonstrated to be spread by airborne transmission in the analysis that followed the pandemic.

In 2012, another coronavirus, Middle East Respiratory Syndrome (MERS), sprang up in Saudi Arabia. The case fatality rate of this coronavirus was a staggering 35 percent. Fortunately, it proved to be less contagious than SARS and the worst of it was contained quickly, but it continues to smolder to this day, with small numbers of cases still occurring. Despite its reduced transmissibility, evidence of airborne transmission has also been demonstrated in MERS.

And then in 2020, when the now infamous third iteration from this same coronavirus lineage began ravaging us, theories as to its provenance began circulating in scientific circles. At first, COVID-19 was viewed as simply a severe upper respiratory virus with an average incubation period of 5 to 6 days (with a range of 2 to 14 days), but it quickly became clear that its clinical features were multi-systemic and alarmingly severe. Doctors were told to be on the lookout for fever, cough, and shortness of breath. They didn't know about the nausea and diarrhea, as well as a set of more ominous

features: heart failure with fatal arrhythmias, kidney failure, hepatitis, loss of taste and smell, heart attacks, strokes, and pulmonary embolisms. The medical community was left reeling.

One of the puzzling features of COVID-19 was that patients who had incredibly low blood oxygen saturations didn't feel short of breath. In ordinary pneumonias, patients with similarly low oxygen levels would be gasping for air. Doctors have called this "happy hypoxia," and it's mainly due to numerous small blood clots developing in the lungs.

We now know that vascular injury resulting in abnormal clotting is arguably the most significant part of COVID's ability to cause disease. When Dr. William Li, president and medical director of the Angiogenesis Foundation, looked at tissue from autopsies of people who died from COVID, what he found astounded him: "It wasn't just lung destruction, inflammation, and pneumonia. The virus was invading and infecting blood vessel cells in the lungs and every other organ in the body. We saw it in the brain, heart, the kidneys, testicles, lymph nodes. Seeing microscopic blood clots everywhere was really a Eureka moment to understanding how some of the damage that this disease causes is beyond simple pneumonia or respiratory distress."

The Long Haul

Today, there are a staggering number of reports on "recovered" COVID patients who are saddled with months of debilitating, chronic symptoms, many of which can be serious, even resulting in organ damage. There is also an ever-growing number of patients with "mild" cases that initially resolve, but who become extremely ill weeks or months later. The presence of such a latency period is eerily reminiscent of what happens in many Lyme+ infections, and it begs the question of whether acute COVID can turn into a chronic, insidious infection. A study of protracted illness after initial COVID documented a whopping 205 symptoms across ten body organs.

These patients have been referred to by an increasing group of monikers: “Long Haulers,” “long-COVID,” and “long-term COVID.” Some doctors refer to their condition as “post-COVID syndrome,” a name that implies, perhaps erroneously, that the virus is gone. The list of those affected, and their symptoms, is terrifying in both its breadth and randomness. Even young, healthy patients are being struck down.

So, how do we understand those who experience such an array of prolonged symptoms? From our perspective, the terms “post-viral syndrome,” “post-infectious syndrome,” and “post-COVID” are misleading. They leave patients floating in a sea of uncertainty, with no clear path back to health. Damage to the body from the acute infection is perhaps the easiest potential cause of long-term COVID for most of us to grasp, but it’s not the only one, and it wouldn’t explain people developing long-term symptoms after a latency period of feeling fine, or after mild cases.

We don’t claim to have all the answers, but as is often the case, missing links tend to hide in plain sight. As described in the book, there is precedent for chronic infections as the cause of ongoing symptoms in a multitude of chronic disease states. Aside from the vector-borne infections that have been the focus of this book, persistent infection has been documented as a potential root cause in illnesses ranging from ulcers to back pain. We’re concerned by the echo chamber in the medical community that defaults patients who develop chronic illness after an acute infection, to a “post-viral” or “post-infectious” syndrome, without deep exploration into the likelihood of ongoing infection. We fear that long-term COVID patients will be resigned to the same fate.

Many viruses, including coronaviruses, set up persistent infection in various cell lines, organs and body fluids, in some cases long after presumed recovery of the acute phase. For coronaviruses, this has been known since at least 1979. So, it’s not surprising that SARS-CoV-2 has been found not only within the brain, spleen, and many other sites distant from the lungs, but also that it’s been shown to persist for many months after apparent recovery from acute COVID infection. An immune-suppressed man experienced a series of multiple confirmed COVID relapses after thinking he was free of the virus, and he ultimately died from COVID after a grueling 154 days. All of this is deeply

troubling, especially when we realize that the pharmaceutical industry has succeeded in putting more of us on lifelong immunosuppressants than at any time in history. And to add salt to this wound, the virus itself also induces a degree of immunosuppression.

We expect that drug trials for long COVID will be a burgeoning field over the next few years. One drug being studied, leronlimab, is an immunomodulator. Accumulating data shows that SARS-CoV-2 can persist long after the acute phase of illness has resolved. So, in addition to drugs that work on the immune system, it would be logical to also study medications with direct anti-SARS-CoV2 activity. Given the institutional denial of the overwhelming evidence of active infection in chronic Lyme+, if persistent viral infection is a major cause of long-term COVID, we fear that history may repeat itself.

In addition to persistent infection with SARS-CoV2, another potential explanation for COVID long-haulers is that the insult from the initial infection upsets the immunologic apple cart, allowing other asymptomatic chronic infections to manifest as disease, which has already been documented with COVID. It's a hard notion to get your head around, that we're all walking around with a bunch of hidden infections. Lyme is a perfect example—random blood testing of healthy individuals in the northeastern US routinely reveals that almost 10 percent of the population has been infected with this organism, often unbeknownst to the infected healthy person. Studies from Italy demonstrate that 11 percent of healthy adults have been infected with Bartonella, another common but widely overlooked bacteria whose spectrum of illness, like Lyme, ranges from asymptomatic infection to debilitating and even deadly. Could a tip of the scales turn asymptomatic infection into symptomatic infection? Could this be the cause of chronic symptoms in a subset of COVID Long Haulers?

—**Ivermectin** is a cheap, old, safe, generic drug that won its discoverers the Nobel Prize in 2015. Referred to as a "wonder drug" with "potential[1] as an antibacterial, antiviral and anti-cancer agent," it began research as a potential COVID-19 treatment

when it was found[2] to inhibit replication of SARS-CoV2. It provides benefits against COVID-19 at all stages of exposure and disease. For pre-exposure prophylaxis[3], two doses spaced three days apart reduced new COVID-19 infections among healthcare workers by 73 percent over a month follow-up. A study of post-exposure[4] preventative treatment, same dose, reduced infections from 58 percent to percent over 14 days in household contacts of COVID-19 patients. A study[5] of doxycycline and ivermectin in 100 early COVID patients demonstrated 100 percent survival without any progressing to the point of requiring ICU care. Doxycycline, although an antibiotic, has antiviral[6] activity against SARS-CoV2. In late stage COVID-19, including ventilated patients, ivermectin[7] has been associated with more than a 50 percent reduction in mortality. A WHO-sponsored meta-analysis[8] of eleven randomized controlled trials demonstrated[9] an overall 83 percent reduction in COVID mortality.

Yet despite this evidence, the NIH states[10], "...there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19." Physicians are understandably frustrated. At a senate committee meeting evaluating outpatient COVID-19 treatments, Dr. Pierre Kory, pulmonary and critical care specialist, said[11], "I don't know how much longer I can do this. Especially knowing that it will all be needless death from here on out, given there is a readily available solution. A solution that cannot be dismissed or ignored. There is a critical need to inform health care providers in this country and the world."

—**Bromhexine** is used to thin out mucus and it's available without a prescription throughout much of the world but is not commonly available in the US. It was found that bromhexine works in a way that may inhibit[12] SARS-CoV2 from getting into cells. In a randomized controlled trial[13], it was demonstrated to improve COVID-19 outcomes in regard to ICU admission, ventilator usage, and survival, without significant side effects.

—**Hydroxychloroquine** is an antimalarial being studied for COVID-19. It's been FDA-approved since 1955 with a generally good safety profile. In a study[14] out of France using hydroxychloroquine (HCQ), and in a patient subset also azithromycin, benefits in viral clearance and mortality was demonstrated. Azithromycin, although an antibiotic, also has antiviral activity[15]. The study was criticized due to its small size and design flaws.

A series of studies were released which associated HCQ use with worse outcomes in COVID-19 patients. One was retracted[16] by The Lancet shortly after its publication, amidst a serious scandal[17] in regard to the legitimacy of its data. In another[18], the U.S. Veterans Health Administration was criticized[19] as only the sickest patients received HCQ, skewing results. In some studies[20], extremely high doses of HCQ were used late into the illness. There was concern of toxic[21] overdose causing poor outcomes in the HCQ treated groups, with legal[22] action brought against some researchers. Another study[23] diagnosed patients via an online questionnaire, none were evaluated in-person, and two-thirds had negative COVID tests. Concern has been raised about possible cardiac toxicity of HCQ, but a review[24] of the medical literature evaluating HCQ's cardiac toxicity over more than fifty years found only 12 deaths. Data[25] from three outpatient clinical trials using HCQ for COVID-19 confirmed a lack of any serious safety concerns.

A series of articles were released in which HCQ was associated with improved outcomes. A review article[26] supported HCQ's use against COVID-19 based on accumulating efficacy data. In a study of 2541 patients, hydroxychloroquine was associated with about a two-thirds reduction in mortality[27]. In a study[28] of 539 patients, azithromycin and HCQ was also associated with about a two-thirds reduction in mortality. In a study[29] of 3737 patients, of those treated with azithromycin and HCQ, mortality was very low at 0.5 percent. A meta-analysis[30] of chloroquine or HCQ for COVID-19 also demonstrated about a two-thirds reduction in mortality.

—**Zinc, Quercetin, & Bromelain**. Zinc has long been known to have antiviral[31] properties. Not only are lower blood levels of zinc[32] associated with worse outcomes in COVID-19, but zinc plus an ionophore[33] was associated with a 24 percent reduced mortality in hospitalized patients. It's difficult to achieve high levels of zinc within cells, but ionophores help it to cross into cells where it can exert its effect. The ionophore listed in the aforementioned study was HCQ. Interestingly neither zinc on its own nor HCQ without zinc was associated with a reduction of COVID mortality in late-stage, hospitalized patients, in that study. The dosage of zinc appears critical, with at least 100mg per day being required in the treatment of other coronaviruses and a small case report[34] suggesting similar dosing strategy in COVID-19. There can be detrimental[35] effects to taking long term high doses of zinc.

In addition to being a zine ionophore, quercetin also has direct antiviral[36] activity against SARS-CoV2. There is evidence which supports a mechanism for the combination of quercetin and vitamin C being synergistic[37] against COVID-19. Bromelain[38] is an enzyme found in pineapple which prevents SARS-CoV2 from entering cells. The combination of quercetin, bromelain, and vitamin C was shown in a study[39] to be protective against COVID-19 in at-risk healthcare workers. The control group had twelve times the risk of developing COVID-19 compared to those who took the combination supplement. Long term use of quercetin can negatively impact thyroid[40] function.

Antibody Treatments

—**Monoclonal antibodies** are lab-manufactured antibodies that block the "doors" that allow the SARS-CoV2 to hack into living cells. This treatment is expensive and needs to be administered in a clinical setting. Although there is data that monoclonal antibodies can decrease hospitalizations, statistically speaking, up to 10 to 20 people[41] may have to undergo treatment in order to prevent a single hospitalization.

—**Convalescent plasma**[42] is a blood component from recovered COVID-19 patients that contains antibodies against the virus. When infused into other patients, it's being evaluated as a treatment for COVID-19. Since antibody levels vary between patients, they vary between plasma samples as well. A study demonstrated improved survival among patients who have received convalescent plasma with higher[43] levels of antibodies. Of note, the use of these human blood products carry the potential risk for the transmission of blood-borne infections such as HIV and hepatitis C.

—**Famotidine**, sold under the brand name Pepcid, is available without a prescription and is widely used to treat heartburn. It first[44] came to researchers' attention when it was observed that patients on famotidine appeared to have improved survival. Famotidine has been associated with reduced COVID-19 mortality in some studies[45] but not others[46].

Immunologic Treatments

—Vitamin D

Vitamin D deficiency is associated with worse outcomes in many infections and in COVID-19 it's associated with an almost quadrupling[47] of mortality. A letter[48] from over 4,000 experts was sent to world leaders, imploring them to increase vitamin D intake recommendations in order to mitigate COVID-19. A randomized controlled trial[49] of vitamin D in early COVID-19 demonstrated improved viral clearance. A study[50] of hospitalized patients who started vitamin D upon admission, added on to azithromycin and HCQ, had a 25 times lower rate of requiring ICU care than those who didn't receive vitamin D. There were no deaths in the vitamin D treated group and two deaths in the group not receiving it. This difference, although suggestive, was not statistically significant.

—NAC, Liposomal Glutathione, Vitamin C, and Melatonin are over-the-counter supplements indirectly shown to improve COVID-19 patient outcomes. They are listed

here together because they share the ability to decrease activation of key inflammatory[51] steps which may lead to a hyper-inflammatory response, aka, a cytokine storm.

—**Steroids**, under certain circumstances appear to be beneficial. The COVID-19 Recovery trial demonstrated[52] that a moderate dose of dexamethasone (6 mg daily for 10 days) reduced mortality in hospitalized patients who had respiratory failure requiring oxygen, including those on mechanical ventilation, but also indicated that dexamethasone may increase mortality in hospitalized patients not requiring oxygen.

Anti-Clotting Treatments

—**Aspirin** can help reduce the abnormal clotting that is a major source of disability and death in COVID-19. This is due not only to vascular injury but also to activation of platelets[53]. Various anti-clotting strategies have been explored in the treatment of COVID-19 but at the time of this writing there is no uniformly agreed upon regimen. Preliminary data demonstrates that aspirin[54], with its anti-platelet effect, has been associated with more than a 60 percent reduction in COVID-19 mortality. Analysis[55] of data on studies of COVID-19 patients receiving blood thinners is ongoing. Given that bleeding risks, which can be serious, accompany anti-clotting medications, including aspirin, advice from a physician on this is particularly important.