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LONG COVID: PREVENTION AND TREATMENT

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As Covid-19 becomes endemic, Long Covid may well become its major public health threat. A large study from the US Veterans Administration found that each time a person develops Covid-19, the risk of long-term complications increases, rather than decreases, regardless of vaccination status. A large international study found that 90% of people with persisting symptoms after Covid-19 had a mild illness to begin with.

Understanding the unique nature of Long Covid is essential for effective prevention and treatment. Despite what you may see in the press, we know a great deal about the causes of Long Covid and almost all can be reversed or treated.

I describe the complex relationships underlying Long Covid in the attached diagram, THE WEB OF LONG COVID. In the pages that follow, I'll describe practical steps I recommend to my patients to prevent and reverse Long Covid. The protocols work best the earlier they are implemented, but I've seen significant benefits even for people who have been suffering from Long Covid for two years.

Treatment of Long Covid and other late complications of Covid-19 cannot be done by formula; it must be individualized. The purpose of this document is to give you information that will allow you to pursue multiple avenues that may be needed to find solutions. All the data I'm presenting here is the result of scientific studies from all over the world; to keep this concise and easy to read, I'll save references for the appendix.

COVID-19

First, a brief introduction to what happens to your body when you first contract Covid-19. For any virus to make you sick, that virus must attach to your cells, enter them, and cause damage within them. In the case of Covid-19, the gateway is **ACE2**, a vital enzyme that is essential for health and recovery from illness. When the Covid virus (called SARS-CoV-2) attaches to ACE2 in your cells, it damagesACE2. Virtually all complications of Covid-19 can be traced to an ACE2 deficiency. ACE2 deficiency can cause damage to the heart and blood vessels, which in turn can cause blood clots, actual loss of blood vessels, and impairment of circulation to vital organs like the brain. Loss of ACE2 also increases inflammation and scarring that can affect any organ in your body – including your lungs, nervous system, digestive tract, heart, kidneys, liver, and skin. (For more information about ACE2, please see the section A Quick Deep Dive with ACE2 in APPENDIX E and Coronavirus Biology in APPENDIX D).

Once the virus destroys ACE2, the resulting inflammation impacts the mitochondria, tiny powerhouses inside your cells that generate 90% of the energy you need to live. Even after a mild Covid infection, mitochondrial distress can

continue for months. ACE2 deficiency and mitochondrial stress are the initial sources of nearly all the manifestations of Long Covid.

The good news is that the reverse is also true: restoring ACE2 and rescuing mitochondrial function are the foundation for protecting yourself and healing from Long Covid.

LONG COVID

It's not uncommon, after someone has recovered from any virus, to experience some lingering symptoms, which are medically labelled “post-viral syndromes.” But Long Covid is distinctly different from most other post-viral conditions, because it is more than just the persistence of symptoms that started with the initial infection. Covid enters your body as a respiratory infection, but it is essentially a circulatory disease, because the virus has a high affinity for the cells that line your blood vessels.

As I explain in a video created in June, 2021, Covid-19 is fundamentally a disease of these blood vessels. Once the virus attaches to the tissue that lines capillaries, veins, and arteries, it causes inflammation, and also causes microscopic blood clots that interfere with circulation, and therefore with the delivery of oxygen to your tissues. Every part of your body requires oxygen. This is why, even if Covid presented as an upper respiratory infection, similar to a cold, Long Covid can damage every part of your body – not just lungs, but also brain, heart, kidneys, liver, skin.

ACE2 depletion threatens more than circulation. A deficiency of intestinal ACE2 impairs the absorption of the essential amino acid tryptophan, causing a cascade of other gut-based problems including bacterial and/or fungal overgrowth, and a depletion of serotonin and certain vitamins. (More on this below and in APPENDIX F: The Gut Microbiome and Covid-19).

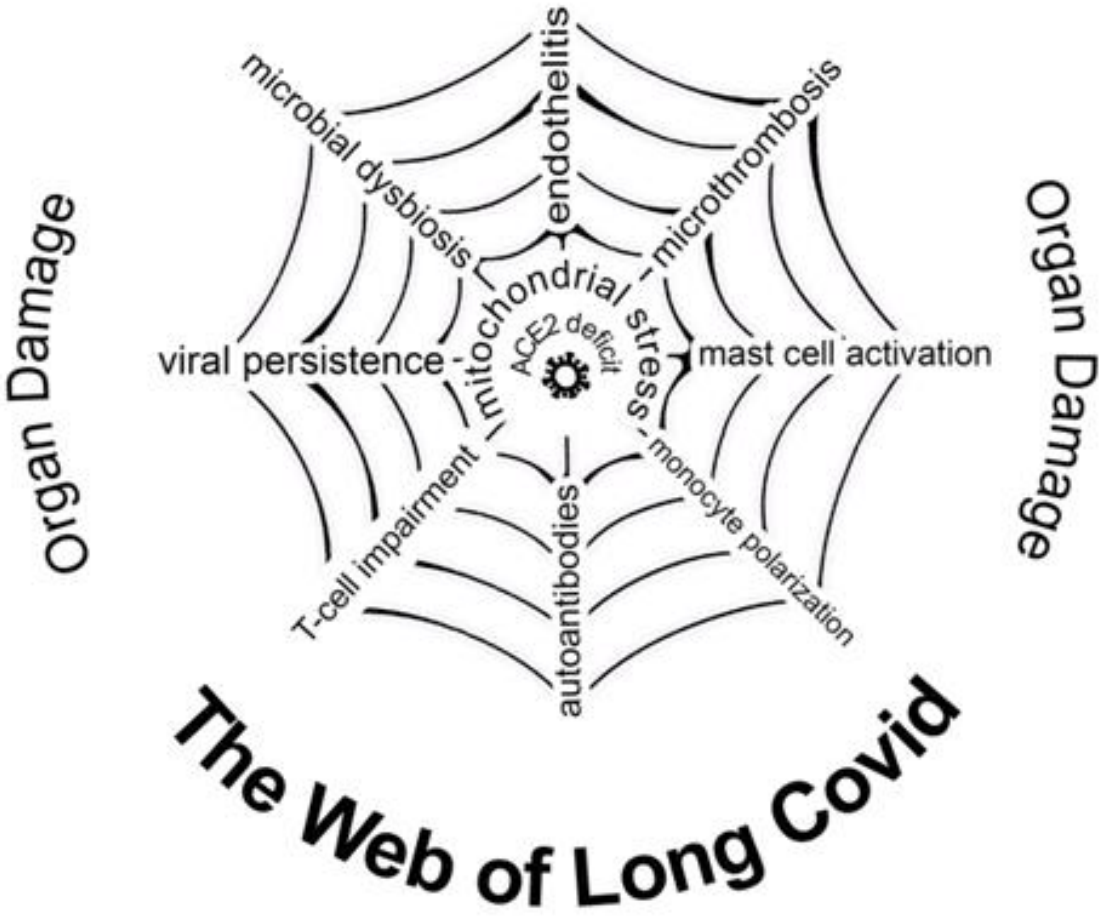
As I described earlier, Covid’s ability to “disarm” ACE2 results in damage to the mitochondria, the energy factories that power your cells. Mitochondrial damage can cause fatigue, brain dysfunction, muscle weakness, heart failure, and impaired immunity.

Instead of describing all the frightening complications of Long Covid, I want to go right to the steps I first recommend for my patients. I believe that implementing these steps can help prevent the late complications of Covid-19, including Long Covid. All the studies on Long Covid show a frequency of 5-30% among people who do not require hospitalization for acute Covid. Among people whom I have treated for Covid-19 from the start of their illness, the frequency of Long Covid has been under 1%. For people who already suffer from Long Covid, a more comprehensive program can help to cure it or relieve its effects.

Most writing about Long Covid starts with definitions: what is Long Covid, how do you know you have it. In fact, there are many different types of long-term problems that follow acute Covid-19. Some people get sick and don’t fully recover. Others appear to get well and then experience a relapse of their symptoms. For some people, a new set of symptoms emerges, either soon after acute Covid or

sometime later, after another acute illness, usually an apparent viral infection. For many others, the problem is the appearance of a new disease within 6 to 12 months of having acute Covid-19. Diabetes, high blood pressure, immune problems and neurological or psychiatric disorders are twice as likely to develop during the year after Covid-19 than would be expected. There are still others for whom Covid-19 leads to an aggravation of an underlying condition that was previously mild and is now much more severe. My approach has been to help doctors and patients understand the physiological changes that occur in the body when someone has Covid-19 and recognize how these may be contributing to the problem each individual has, whatever the symptoms or manifestations.

I think the metaphor that I call the Web of Long Covid is the best way to really understand these changes, Check out the diagram below:



At the center of this web is ACE2 deficiency caused by the virus entering your cells. This in turn causes mitochondrial distress. And this in turn leads to eight distinct dangers, each represented by a strand of the web, any of which can lead to organ damage. As in a real spider web, every strand is connected directly or indirectly, to every other strand. That's why Long Covid seems to be so complex. You have to look at the whole web, not just the strands, to understand it. Fortunately, when it comes to treatment, correcting a problem in one part of the web may also correct problems in other parts, so the treatment may be less complex than the analysis. But in order to understand the treatments, we have to start with the analysis.

I've described some of these strands already, but let's take a closer look at the whole web.

1. **ENDOTHELITIS**: this is inflammation of the cells that line your blood vessels, called the endothelium. This can actually lead to loss of the smallest blood vessels, called capillaries, and to stiffness of larger vessels like veins and arteries. Endothelitis may restrict blood flow and the delivery of oxygen to your tissues. It also leads to the second strand of the web, microthrombosis. Restoring ACE2 in and of itself can alleviate both endothelitis and microthrombosis, but sometimes further measures are needed. Almost all these are measures you can implement yourself.

2. **MICROTHROMBOSIS**: Tiny blood clots that can clog capillaries. Microthrombosis aggravates endothelitis, and further restricts blood flow. The mechanism of microthrombosis in Long Covid is not the same as the formation of an ordinary blood clot. That's why ordinary anti-clotting measures may not work.

3. **MAST CELL ACTIVATION:** Mast cells are primitive cells of the immune system, and are scattered throughout your tissues and organs. They do not circulate in your blood. Mast cells produce and secrete about 200 different chemicals, called mast cell mediators. The best known of these is histamine, which produces many symptoms of allergy. Mast cell mediators can cause constriction (narrowing) or dilation (widening) of blood vessels; they can also make blood vessels and membranes leaky, so that fluid escapes from them. Mast cell mediators may cause pain, swelling, redness, shortness of breath, diarrhea, high or low blood pressure. They contribute to migraine headaches, asthma and irritable bowel syndrome. In addition to causing symptoms on their own, mast cell mediators influence the function of more complex and evolved immune cells, like lymphocytes. Covid-19 can cause mast cell activation. In some people, once mast cells become activated, they do not "turn off" (i.e. they continue to release mediators that cause any of the above symptoms). Mast cell activation may contribute to microthrombosis and endothelitis. When patients I am treating for Long Covid have one of the problems listed above, or do not

respond as expected or have unusual adverse reactions to treatments that should be helping them, mast cell activation is usually the cause. I have written more about mast cell activation in APPENDIX C. There are a number of approaches to control of mast cell activation that can be self-administered. You can view an interview with me on Mast CellActivation in Long Covid at https://www.youtube.com/watch?v=WslPr1fVxBY

4. **MONOCYTE POLARIZATION**: Monocytes are a group of white blood cells involved in the immune response to Covid-19. Unlike mast cells, monocytes have a complex life cycle and change their functions as they move through it. Those functions are basically: attack, repair and patrol. (They attack anything that is perceived as a threat to the body; they repair the tissues that have been damaged; and they patrol to look for signs of danger.) Although most monocytes circulate in blood, some leave blood vessels to enter tissues, where they transform themselves into cells called macrophages. Polarization occurs when the normal life cycle is disrupted, shifting monocyte and macrophage function to create a disorganized immune response that favors chronic, unrelenting inflammation. You have probably read a lot about the chronic inflammation that creates Long Covid. Well, monocyte/ macrophage polarization plays a major role in maintaining that state. What's important to know about this complicated phenomenon is that ACE2 helps to regulate the monocyte and macrophage life cycles to prevent polarization. Restoring ACE2 is the first step in reversing chronic inflammation. Because monocytes and macrophages need a lot of energy to function properly, mitochondria play an important role in maintaining their normal life cycles. So, the second step in correcting monocyte/macrophage polarization and tamping down chronic post-Covid inflammation is mitochondrial support.

5. **AUTO-ANTIBODIES:** Antibodies are proteins produced under the direction of specialized white blood cells called B-lymphocytes. Their normal function is to bind to foreign molecules, like viral proteins, enabling their destruction and preventing them from doing damage. When you develop Covid-19, your immune cells produce antibodies that recognize several foreign proteins made by the virus, like the spike protein. For many people with Covid-19, the antibodies produced not only attack the virus, they also attack cells of your own body. These are called auto-antibodies and the illness created is an auto-immune disease. The mechanisms involved in auto-antibody production are complex and there are many different kinds of auto-antibodies produced during the course of Covid-19, some of them unique to Covid. Most of the covid-induced auto-antibodies only become active when there is inflammation and tissue damage. Decreasing inflammation is therefore the best protection against covid-induced autoimmunity.

[Covid vaccines are intended to induce your cells to make antibodies directed against the spike protein, to prevent the virus from attaching to ACE2 (these are called “neutralizing” antibodies). Vaccine induced antibodies have some similarities but many differences with natural Covid antibodies.]

6. **T-CELL IMPAIRMENT:** The generals of your immune system—the cells that coordinate all aspects of your immune response—are called T-lymphocytes. There are many kinds (or subsets) of T-lymphocytes, and one type may be able to morph into another type. Here’s what’s important to know: SARS-CoV-2 can directly invade T-lymphocytes and disable them. Impairment of T-lymphocytes makes it harder for you to eliminate the virus from your body, makes you more susceptible to repeat infection and also makes it more likely you will develop auto-antibodies. Restoration of T-cell function is an essential component of healing from Long Covid, and is especially important for resolving the next strand of the web, Viral Persistence. T-cells, like monocytes, have an intense need for energy. Mitochondrial dysfunction impairs T-cell function and, in particular, short-changes a critical type of T-cell called a T-effector memory (TEM) cell. TEM cell activity is essential for eradicating viral infections and for a robust response to vaccines. Some researchers have discussed re-activation of latent infections by other viruses as a result of Covid-19. Epstein Barr Virus (EBV, the cause of mononucleosis) lives sleeping in our B-lymphocytes for most of our lives and is often awakened by acute Covid-19. TEM cells keep EBV and other latent viruses under control in their dormant states. A detailed description of EBV in Long Covid is presented at the end of APPENDIX B. My conclusion is that EBV reactivation in Long Covid is the direct result of TEM cell dysfunction. TEM cell activity is strongly influenced by the nature of bacteria that live in your gastrointestinal tract (the gut microbiome). Restoring mitochondrial function and creating a healthy gut microbiome are mainstays of my protocol for enhancing TEM cell function after Covid-19.

7. **VIRAL PERSISTENCE:** For many people with LongCovid, persistence of the virus, SARS-CoV-2, in their bodies, appears to be driving the ongoing inflammatory reaction. Persistence of SARS-CoV-2 has been demonstrated in different parts of the body for many months after the initial infection. Most scientists who study this believe the main location of viral persistence is in the gastrointestinal tract, which ties this strand to the next one, Gut Microbial Dysbiosis.

8. **MICROBIAL DYSBIOSIS:** Dysbiosis is a disturbance in the body’s microbiome, the population of 100 trillion microorganisms

that cover every surface we have. About 99% of these organisms reside in the gastrointestinal tract, especially the large intestine. I've discussed the relationship between the gut microbiome and Long Covid in an interview available online and a presentation to the Long Covid Coalition

Here are the key facts:

(a) People who develop Long Covid have lost important beneficial gut bacteria before they develop long covid.
(b) These same people also show an overgrowth of potentially harmful gut bacteria.
(c) Butyrate, a chemical produced by many species of gut bacteria, is significantly reduced. Butyrate has potent healing powers throughout the body. Loss of butyrate has major implications for GI health and also for immune function and brain health. The reason for low butyrate appears to be loss of a keystone butyrate producer, a bacterial species called Faecalibacterium prausnitzii. (you cannot find this as a probiotic, so the name is not important).
(d) One of the dangerous bacteria that overgrows (Ruminococcus gnavus) produces a toxic metabolite called isoamylamine, which contributes to cognitive dysfunction and accelerates age-related cognitive decline.
(e) All these changes in the gut microbiome may contribute to a phenomenon called "leaky gut", in which the lining of the intestinal tract becomes porous, allowing gut-derived toxins to enter the body.

These findings make it likely that correcting the gut dysbiosis of Covid-19 will help recovery from Long Covid. The treatment protocol that I am using for prevention and treatment of Long Covid pays special attention to establishing a healthy gut microbiome.

The Web of Long Covid is more than just the center and the radial threads; the connecting threads are an essential component to understanding how Long Covid works, for these 8 dysfunctions magnify each other, strengthening the web. For instance: mast cell activation or monocyte/macrophage polarization may produce T-cell impairment; T-cell impairment allows viral persistence to run riot; autoantibodies may damage ACE2, making the GI tract even more vulnerable to dysbiosis; endothelitis and microthrombosis working together wreak havoc on circulation.

But fundamentally, it all starts with ACE2 depletion and mitochondrial distress. So let's look at tools for fixing these issues.

TREATMENT AND MITIGATION OF LONG COVID

Conventional treatments offered to people with Long Covid are basically designed to reduce symptoms. My goal is to address the causes of Long Covid that are described in the previous section, through self-care. Fortunately, most of these measures will also alleviate symptoms. The process starts with enhancing ACE2 activity and rescuing mitochondrial function. Everything I'm about to describe is in service to these goals. Basically, it comes down to a 5-part plan.

1. LIFESTYLE

Simply put: you need to sleep, hydrate, and exercise properly. I want to emphasize "properly" because lack of activity produces deconditioning – but for some people, even a little activity may be followed by a crash. There is no simple formula for exercise.

Sleep:
Sleep more than you think you need to, but do it on a regular schedule. If you're having difficulty sleeping, there are a number of natural sleep aids you can try, including melatonin, magnesium, theanine, and CBD. (see Appendix A for dosage and details)

Water:
Make sure you stay well-hydrated. Drink enough water to alleviate thirst. Unless you have high blood pressure, do not be afraid to use salt. Hydration is especially important for people who get fatigued, dizzy, or weak when standing or walking and feel much more comfortable lying down. This condition is called orthostatic intolerance. In people with Long Covid, it is usually a sign of damage to the autonomic nervous system, which regulates heart rate and blood pressure. There's more on how to determine if you have autonomic dysfunction in APPENDIX B, and if so, what to do about it.

Exercise:
Exercise is essential for recovery, but for some people even small amounts of exercise makes them much worse for days or weeks. To start with, try walking every day. How far can you walk before you have to rest? Is your need for rest due to fatigue, dizziness, or shortness of breath? If it's fatigue or dizziness, you can test yourself at home for orthostatic intolerance (see APPENDIX B). If it's shortness of breath, you might do the Six Minute Walk test described in APPENDIX B. If you do not get worse after exercise, try to walk every day; slowly and carefully increase the length of your walk and the speed with which you walk.

Watch out for a problem called Post-Exercise Malaise (PEM) which has long been recognized as a hallmark of Chronic Fatigue Syndrome. With PEM, exercise that exceeds a certain limit, which varies from person to person, will result in an aggravation of symptoms. If there is any hint of PEM, cut back immediately. If you cannot walk safely or comfortably, try exercising while lying down. Get resistance bands and use them to exercise your legs and upper-body, applying the same

cautions as I advise for walking (see APPENDIX B for some online guided workout routines with resistance bands). If exercise of any type is challenging, you should be tested for a condition called POTS (positional orthostatic tachycardia syndrome, the major cause of orthostatic intolerance in people with Long Covid). Self-testing for this is described in APPENDIX B, along with references to specific resources that can help overcome this problem.

2. NUTRITION

(and evidence-based nutritional supplementation)

DIET

Diet has a profound impact on ACE2 activity and on the outcome of Covid-19. A large-scale study at Johns Hopkins https://nutrition.bmj.com/content/4/1/257 found that a 40% increase in vegetable consumption produced a 70% decrease in the likelihood of severe or moderately severe illness in people with Covid-19. People eating more vegetables happened to be eating less sugar, but sugar is not what made the difference. A sub-group of people eating a low-carb, high-protein diet were almost 4 times likelier to get severely ill as people whose diet was mostly plant-based whole foods. The plant-based diet was not a true vegetarian diet. It included fish, eggs, and dairy products, and even a little meat. Just a lot more vegetables. Plant-based diets are high in fiber and in antioxidants called polyphenols. This kind of diet supports and enhances ACE2. It also improves the quality and diversity of your gut microbiome, so it helps recovery from Covid in at least 2 ways.

You also want to focus on eating anti-inflammatory foods, which are described in my book The Fat Resistance Diet. I'm making The Fat Resistance Diet available at no charge, just shipping, while copies last. You can request a copy at info@galland-health.com. No strings attached. Although The FRD was written as a weight loss book, Stage 3 (weight maintenance) works for people with no need or desire to lose weight.

If you already eat the way I described, there are three other dietary factors that can make a difference, although they are not helpful for everyone.

1. Including fermented foods in your diet can improve immune function and create a healthier gut microbiome. Eating foods like yogurt, sauerkraut and kimchi daily enhances activity of TEM cells, the lymphocytes so important for solidifying your body's ability to fight this virus.
2. Intermittent fasting is a dietary pattern in which you do not eat food for 12 or more hours of the day. Intermittent fasting has been shown to help balance the hormonal system in which ACE2 is such a critical component.
3. For people with mast cell activation, a low histamine diet may help to relieve symptoms, perhaps by reducing the body's burden of histamine, a chemical that can create inflammation and suppress immune function at the same time. If fermented foods aggravate your symptoms, you may be intolerant of histamine. I've included a Low Histamine Diet in APPENDIX C. More information is available online by searching

"histamine intolerance" and in a very dense book called Understanding Histamine Intolerance and Mast Cell Activation by Mariska van Wild Schotten.

SPICES AND HERBS can enhance ACE2 activity. The best studied are

ROSMARINIC ACID, found in rosemary, lemon balm, basil, sage, thyme, oregano, and spearmint.

CURCUMIN, a component of turmeric.

Both are available from food or as supplements.

SUPPLEMENTS FOR ACE2 ENHANCEMENT

Giving your body a high-quality, high-quantity dosage of certain nutrients sometimes calls for supplements. The appropriate dosage for the following can be found in APPENDIX A.

VITAMIN D increases the levels of ACE2 in your cells

CURCUMIN is a bioflavonoid found in the Indian spice turmeric. It has been extensively studied for its anti-inflammatory and anti-cancer effects. There are demonstrated protective effects of curcumin during acute Covid-19. Curcumin increases ACE2 activity. It also enhances brain recovery after injury and may have direct anti-viral activity.

OMEGA 3 FATTY ACIDS (EPA and DHA) are anti-inflammatory and neuroprotective. They stimulate ACE2 indirectly, by increasing activity of a group of hormones called apelins, which are potent promoters of ACE2. Omega-3 fats also prevent abnormal blood clotting, alleviate depression, and help brain recovery, enhancing cognitive function.

CBD (cannabidiol) is another potent apelin enhancer (and therefore potentially an ACE2 booster).

RESVERATROL is best known for its presence in red wine. It's the agent of the so-called French paradox (despite eating a lot of animal fat, French people have a relatively low rate of heart attacks). It's been studied for decades as an anti-aging supplement. Resveratrol directly enhances cellular ACE2 activity. Resveratrol has been shown to aid brain recovery after injury and to enhance immunity by stimulating formation of TEM cells. It may also have direct anti-viral and anti-bacterial effects.

ALPHA LIPOIC ACID is an anti-oxidant that complements omega-3 fats and has a special relationship with ACE2. It prevents the destruction of ACE2 when there is a high level of inflammation. It's been shown to preserve ACE2 activity in the brain. It also helps to repair damaged nerve tissue.

NAC (N-acetylcysteine) is another antioxidant that protects ACE2 from the destructive effects of inflammation. NAC has many beneficial actions: it helps lung function and is useful for treating asthma and bronchitis. It strengthens immune function and can ameliorate symptoms of influenza. It helps with detoxification and

protects the liver; NAC is the standard medical treatment for an overdose of acetaminophen (Tylenol).

ESTROGEN increases ACE2 activity. The largest subgroup of people with Long Covid are women over the age of 50, whose estrogen levels may be dropping. If that's you, ask your doctor whether hormone replacement therapy might be appropriate.

CORTISOL (the hormone from which cortisone is derived) enhances ACE2 activity. Studies have shown that cortisol levels are much lower in people with Long Covid than in people who have recovered fully from Covid-19. If you've been given steroids in any form during, before, or after Covid, your own adrenal glands may be slightly suppressed, and your cortisol may be sub-optimal. Ask your doctor if this should be investigated.

SUPPLEMENTS FOR MITOCHONDRIAL RESCUE

There are no drugs that enhance mitochondrial function, but there are supplements that have been shown to do so. The following information explains why each supplement works, but if that information is more than you can process right now, feel free to go directly to APPENDIX B to read about dosing.

COENZYME Q10 (CoQ10) tops the list because it's been studied the most. Unlike a vitamin or mineral, CoQ10 is a molecule your body can make, but may not make enough. A number of drugs interfere with its synthesis and high doses of vitamin E increase its breakdown. Coenzyme Q10 is the single supplement I have found to be most beneficial for reversing Covid-related fatigue.

B-VITAMINS are commonly used for mitochondrial rescue, especially vitamin B1 (thiamine), vitamin B2 (riboflavin), and vitamin B3 (niacin), which is probably the most important. There is more information about B-vitamins in the appendix. Both NAC and resveratrol support the ability of coenzymeQ10 and niacin to enhance mitochondrial function. Another natural substance that supports the mitochondrial benefits of niacin is Urolithin A, a substance formed when beneficial gut bacteria metabolize the polyphenols found in pomegranate and some other fruits.

L-CARNITINE, like CoQ10,is normally synthesized in your body, but may be depleted in states of fatigue. L-carnitine and its derivatives, like acetyl-L-carnitine, are often used for mitochondrial support and incorporated into various "mitochondrial cocktails" and formulas. I've seen mixed results with these, and I recommend that in the setting of LongCovid carnitine use be supervised by a health professional.

THE SPOKES OF THE WEB

Restoring ACE2 and supporting mitochondria should go a long way toward addressing the dangers I discussed in the spokes of the web. Additional treatments can address each spoke on its own.When describing each spoke, I went around the

web in a clockwise direction. In discussing treatments that can repair abnormal function, I'm going to travel counter-clockwise, starting with correction of Gut Microbial Dysbiosis, which is closely tied to Viral Persistence and T-cell Impairment. The most practical approach is to tackle all 3 of these spokes together, because they are so closely related.

RE-ESTABLISHING A HEALTHY GUT MICROBIOME

As I've described, consistent abnormalities of the gut microbiome have been described in people with Covid-19 and identified as predictors of development of Long Covid: specifically the loss of a diverse population of beneficial bacteria and an increase in undesirable, toxic or inflammatory bacteria. Fungal and yeast overgrowth may also occur. There's more information about this in APPENDIX F (The Gut Microbiome and Covid-19) and in these videos.

This type of imbalance is referred to as Dysbiosis, and correcting it is essential for recovery. The first step in its correction is restoration of ACE2, because ACE2 performs special functions in the gut that protect against dysbiosis. The next step is eradicating remnants of SARS-CoV-2 from the gut, because whether they are infectious or not, these viral remnants cause inflammation. Studies have shown that the virus may persist in the GI tract for months after acute Covid and that its proteins may be found in the cells lining the intestinal tract for a year or more. I've employed the following strategy to address gut microbial dysbiosis, viral persistence, and T-cell impairment as a triad in Long Covid. It works both for reversing Long Covid and for preventing it when a person is sick with acute Covid. Ibelieve that viral eradication is essential.

VIRAL ERADICATION is a two-step process.

1. The first step employs 3 natural antiviral, used together if possible for a period of 2 weeks. Dosage and more details are in the Appendix.
    1. Tollovid. Its active ingredient is a Chinese/Korean herb called red gromwell root (Lithospermium erythrorhizon), which has a high safety profile and has been used in Chinese medicine for a thousand years. Its chief mode of action is to inhibit a key viral enzyme called the main protease (more about the coronavirus main protease in Coronavirus Biology in APPENDIX D).
    2. The probiotic bacterial strain Bacillus subtitlis B-7092, available under the name Tundrex (www.tundrex.co), which has unique anti-viral activity.
    3. Vedicinals-9, a complex herbal antiviral from India that has been shown to increase the speed of viral clearance. Vedicinals-9, like Tollovid, also has numerous demonstrated anti-inflammatory effects.

2. After 2 weeks, the goal is to build a gut microbiome that will effectively support TEM cell activity and help the brain repair itself.
    1. A high fiber, plant-based diet, described above for restoring ACE2 activity, emphasizing fermented foods and berries, because of their specific benefits.
    2. Vitamin D and Resveratrol. Each of these aids TEM cell function.

3. A new probiotic, Lactobacillus plantarum, which is also found in fermented plant-based food like sauerkraut. This follows and replaces Bacillus subtilis B-7092.
4. To ensure adequate levels of butyrate, a prebiotic powder like arabinogalactan or galactooligosaccharides, or supplementation with butyrate itself.
5. Reishi mushrooms, available as capsules.
6. Zinc, which is important for T-cell function. Zinc accumulates within effector T-cells and is released when needed for its antiviral effects.

AUTO-ANTIBODY PRODUCTION:

The best defence against auto-antibody production is establishment of well-balanced T-lymphocyte activity. I am exploring treatment approaches that may specifically target auto-antibodies, but I don't have adequate experience with them as yet. This is definitely an area to discuss with your doctor.

MONOCYTE/MACROPHAGE POLARIZATION:

Enhancing ACE2 activity and mitochondrial function is the foundation for restoring monocyte and macrophage balance, which should then also improve T-cell function. Additional measures for correcting monocyte/macrophage polarization require prescription medications used off-label.

MAST CELL ACTIVATION:

This is a very complex area, which becomes extremely important for people who do not respond well to the measures I've described that enhance ACE2, mitochondria, and T-cell function or correct gut dysbiosis. A disorder called the mast cell activation syndrome (MCAS) is especially likely in people who have unpredictable adverse reactions to many parts of the treatment protocol I've outlined. It is also likely in people who develop asthma, migraines or POTS after Covid-19. There are specific steps that can alleviate MCAS, described in APPENDIX C. For those people in whom MCAS is pivotal, it can dominate the web, contributing to microthrombosis, endothelitis and T-cell impairment, so recognizing its presence and treating it directly is essential.

MICROTHROMBOSIS AND ENDOTHELITIS:

Microscopic blood clots (microthromboses) are very common with acute Covid-19 and often persist for weeks or months after recovery. Because it is so closely tied to endothelitis, I treat the two strands together. In the immediate aftermath of acute Covid, ACE2 restoration and mitochondrial support may be enough to reverse microthrombosis and endothelitis. In people sick for more than 3 months, additional measures will be needed.

Natural products that can prevent microthrombosis include two herbs derived from traditional Chinese medicine: Gingko biloba and Dan Shen. Gingko may also directly help cognitive function and Dan Shen is frequently used to support

circulation. I've found Dan Shen helpful in treating heartburn and other digestive complaints.

Quercetin, a bioflavonoid found in foods like apples and onions, has a specific effect on blood clotting. Quercetin prevents white blood cells called neutrophils from initiating the clotting process, and also can be very helpful in treating mast cell activation. Quercetin has been shown to reduce severity of acute Covid-19.

The enzyme nattokinase, derived from fermented soybeans (natto) has anti-thrombotic activity and can also heal the lining of blood vessels. One intriguing effect of nattokinase: it destroys the SARS-CoV-2 spike protein, and may help restore the lining of blood vessels by removing remnants of the spike protein attached to cells.

Natural products that can help to heal blood vessels or improve circulation are: Pycnogenol, an extract of the bark of the French maritime pine, which not only heals blood vessels, but also has beneficial effects in reducing mast cell activation, vinpocetin, an extract of periwinkle, long used for enhancement of brain function, and rhamnan sulfate extracted from the green seaweed Monostroma nitidum. This is available with a mix of herbal extracts in a product called Arterosil. Rhamnan sulphate works through a unique mechanism to heal the inner lining of blood vessels.

I've been particularly impressed by clinical responses to pycnogenol and vinpocetin, and I think they are each under-utilized in the treatment or prevention of Long Covid.

4. REPAIRING ORGAN DAMAGE

This is an area in which you will need help from a physician, usually a specialist. There are four specific areas in which self-care makes all the difference, so I've included discussions of them in APPENDIX B: POTS, brain fog, unexplained breathlessness and loss of taste and smell.

5. MENTAL AND EMOTIONAL HEALTH

The pandemic has taken a huge toll on our psyches. Isolation and fear create depression and anxiety. PTSD (post-traumatic stress disorder) affects many Covid survivors, and the emotional trauma itself can hinder recovery. Coverage of the pandemic and especially of Long Covid by the media is part of the problem. Social media platforms and chat rooms are two-edged swords. They may help you overcome isolation, but they can also subject you to bias, sensationalism, nihilism, and worst-case scenarios.

During 50 years of medical practice, I've found that what people need most is a clear understanding of the problems they have, information about what they can do to help themselves, and support in doing so from friends or family. Simply knowing that somebody is not only listening to you, but hearing your story and caring about it, makes a huge difference. Ask people in your support system to listen to you, to help you process some of this information (if you're having a hard time with it), and to help you stick with the steps needed to get better. DO NOT GIVE UP!

IN CONCLUSION

This is not a hopeless, mysterious disease that we're only barely beginning to understand. There has been a lot of science and a lot of research already applied to Long Covid, and it will continue. A review published in the journal Nature in January 2023 does an excellent job of describing that research, for scientists and health professionals.

APPENDIX A: NATURAL PRODUCTS AND DOSAGES

SLEEP AIDS:

-Melatonin, 3-10 mg at bedtime (because some people become very lethargic the next day, I recommend starting with 1 mg and working up as tolerated). Melatonin is also helpful for reducing inflammation and protecting mitochondrial function and may reduce heartburn.

-Magnesium glycinate 100-400 mg at bedtime. Be careful, as too much can cause diarrhea. I generally choose magnesium gycinate for sleep, because glycine by itself can help with sleep quality. Magnesium not only helps sleep, it can calm the nervous system, improve energy and relieve palpitations. If you have kidney disease, do not use magnesium as it can accumulate to toxic levels if your kidneys don't function well.

-Theanine, an amino acid found in green tea, comes as a pill in a dose of 200 mg. it may also relieve anxiety. It is fairly short-acting (effect lasts about 4 hours), so it is most useful for inducing sleep. Theanine often comes mixed with GABA (gamma-amino butyrate). The amount needed is usually 500-800 mg at one time.

-CBD (Cannabidiol, from hemp seed), ideally in products where it is partnered with CBN (cannabinol). CBD may relieve anxiety and pain. By elevating levels of peptides called apelins, CBD can restore depleted levels of ACE2. The dose needed varies considerably between people and depends on the preparation used. Safe doses are under 150 mg/day.

SUPPLEMENTS FOR ACE2 ENHANCEMENT:

Vitamin D 2000-6000 IU/day for adults, taken with food, needs fat for absorption

Omega 3 fats need to supply between 1200-2400 mg of EPA+DHA/day

- Omega-3's have broad anti-inflammatory effects and may help to protect the sense of smell
- Main side effects: diarrhea, heartburn, fish-oil burps

Resveratrol 200 to 1200 mg/day, taken with food in divided doses.

- Over 150 clinical trials have demonstrated positive effects of resveratrol at doses that vary from 75 to 2000 mg/day
- Also has anti-bacterial and anti-viral effects, inhibiting production of toxic bacterial metabolites that disrupt immune function

Curcumin 500 to 1000 mg/day (depending upon form of curcumin)

- Has broad anti-inflammatory effects

Rosmarinic acid, 150 mg/day

ALA (alpha lipoic acid), antioxidant 300 mg twice a day with food

- At 600 mg/day ALA helps to combat nerve damage, especially when paired with the omega-6 fatty acid, GLA (gamma-linolenic acid), found in primrose, borage and black currant seed oils
- At 600 mg/day, along with 2200 mg of EPA+DHA/day, ALA can improve cognitive function

NAC (n-acetylcysteine), an antioxidant. The dose ranges from 600-1200 mg taken 2-3 times a day, for a total dose of 1200-3600 mg/day.

- In human clinical trials, NAC has been shown to improve respiratory symptoms, support immune function in the elderly, prevent flu and (at the higher doses) relieve anxiety and obsessive-compulsive symptoms.

SUPPLEMENTS FOR RESTORING MITOCHONDRIAL FUNCTION:

Coenzyme Q10,at least 100 mg, 2-3 times a day with food. Available in 2 forms, ubiquinone and ubiquinol. Either form works, but ubiquinone may require a higher dose.

- CoQ10 may also repair “leaky gut” by improving tight junction integrity and can improve inflammation of blood vessels by restoring endothelial integrity

Vitamin B1 (thiamine) as lipotiamin,a fat soluble form, 100 mg once or twice a day

Vitamin B2 (riboflavin), 100 mg, 1 to 4 times a day.

- At 400 mg/day, riboflavin was shown to prevent migraine headaches, a disorder associated with mitochondrial dysfunction

Vitamin B3 (niacin), which comes in many forms. Covid-19 can deplete the body’s store of niacin, so this vitamin may play a special role in treatment of Long Covid. When supplied as NADH (a biochemically active cofactor form of niacin) 10mg twice a day, and combined with uniquinone 100 mg twice a day, vitamin B3 improved energy and mitochondrial function of people with Chronic Fatigue Syndrome, in a randomized clinical trial. Other forms of niacin require higher doses, which may produce unacceptable side effects, so that NADH is the safest form to use for self-treatment. It must be taken on an empty stomach with a glass of water or else under-the-tongue.

Urolithin A has been tested in a clinical trial, along with NAD+. The dose used was 500 mg 3 times a day.

USE VITAMIN C with caution: 1 gram/day of Vitamin C as a pill impairs mitochondrial regeneration in response to exercise.

NOTE: There are virtually no prescription drugs shown to enhance mitochondrial function, but hyperbaric oxygen, a treatment being studied for reversal of fatigue and brain fog in Long Covid, has mitochondrial stimulation as its major effect.

SUPPLEMENTS FOR ENHANCEMENT OF MEMORY T-CELLS

Lactobacilli, especially Lactobacillus plantarum, which as a probiotic supplement is best taken at the start of a meal, 2 or 3 times a day.

Butyric acid (butyrate), about 1000 mg/day, taken with meals. Because butyrate is produced by beneficial gut bacteria, it is called a post-biotic. The bacteria themselves are called probiotics and supplements that feed beneficial bacteria are called prebiotics. Butyrate absorbed from the gut circulates throughout the body and enters the brain

Prebiotics that increase production of butyrate in the gum include galactooligosaccharides and arabinogalactan. The dose needed is 2000-5000 mg/day, taken on an empty stomach. Black raspberry concentrate, 1 tablespoon daily, was shown to enhance TEM activity by increasing synthesis of butyrate by gut bacteria.

Reishi mushrooms, available as capsules (Host Defense 2 capsules twice a day) or as a tasteless powder (Health Ranger organic 1 tsp a day)

Zinc: this mineral is important for T-cell function. It accumulates within effector T-cells and is released when needed, for its anti-viral effects. Supplementation with 30 mg/day may be advisable.

- The main side effect of zinc is nausea.
- Excess zinc may produce a loss of trace minerals like copper and selenium, so higher doses of zinc should only be used under medical supervision.

SUPPLEMENTS FOR REVERSING MICROTHROMBOSIS AND ENDOTHELITIS

I generally recommend these when there is clinical or laboratory evidence of abnormal blood clotting and in people who experience abnormal breathlessness with physical activity.
Covid-19 damages the circulation to the lungs and can cause shortness of breath even when the lungs themselves are not damaged.

Gubgko Biloba 120 mg twice a day. The most studied Gingko preparation comes from New Zealand; it's called Tebonin.

- Ginko owes its anti-thrombotic effect to inhibition of blood platelets, which initiate clotting. It is synergistic with aspirin, although they use somewhat different mechanisms to achieve the same effect.
- Gingko has long been used for memory enhancement

Dan Shen is available from many sources. I've used it as an organic powder at a dose of 1 teaspoon a day (to dissolve it in water, the water must be very hot; it can then cool to room temperature and the powder will stay in solution).

- Dan Shen is used in traditional Chinese medicine to improve circulation.
- Like Gingko biloba, Dan Shen inhibits platelet activation.

Quercetin: a bioflavonoid derived from foods like apples and onions, the dose needed is between 1000 and 2000 mg/day, taken with food.

- Absorption of quercetin is enhanced when it is taken with lecithin.
- Quercetin is also a natural anti-histamine and can inhibit mast cell activation.
- In clinical trials, quercetin has been shown to prevent infection with SARS-CoV-2 among health care workers and to improve the outcome of Covid-19 if started as soon as symptoms began.
- Quercetin may owe its anti-thrombotic affect to inhibition of the inflammation that triggers abnormal blood clotting, which is initiated by white blood cells called neutrophils.

Vinpocetin: the dose used in human clinical trials is typically 20-30 mg twice a day.

- Vinpocetin has mostly been tested for its benefits in people with stroke
- It also improves circulation in the lungs and may improve breathlessness
- I've found vinpocetin helpful for people with a painful circulatory disturbance of the hands or feet called erythromelalgia, which can occur as a complication of covid-19

Nattokinase: 100 mg or about 2000 iu, twice a day, taken on an empty stomach (at least 30 minutes before eating).

- In addition to its benefits for circulation, nattokinase can destroy the SARS-CoV-2 spike protein, decreasing its ability to provoke inflammation

Arterosil as a source of rhamnan sulphate, a compound found in seaweed: the recommended dose is 1 pill twice a day.

Pycnogenol, a patented combination of bioflavonoids derived from the bark of the French maritime pine. Pycnogenol has been extensively studied in human clinical trials for its support of healthy circulatory function and for anti-inflammatory and anti-allergic effects. The dose shown to support endothelial healing after Covid-19 was 50 mg 3 times a day. In the past, I have used 100 mg twice a day for its anti-inflammatory effects, taken with food.

NOTE: Almost no drugs have been studied for healing endothelitis. An exception is pravastatin, a drug used to reduce cholesterol levels. Some protocols for long covid employ pravastatin at a relatively low dose, 10 mg/day. I've never seen this have any effect. I think the reason is that the dose of pravastatin shown to protect blood vessels in human clinical research is much higher, about 40 mg/day

DOSING FOR VIRAL ERADICATION

Tollovid from Todos Medical, 3 capsules 4 times a day for 10-15 days. The active ingredient is a Chinese herbal product called red gromwell root (Lithospermiumerythrorhizon), which has a very high safety profile and has been used in Chinese medicine for a thousand years. Its main mode of action is to inhibit a key viral enzyme called the main protease, which is also the target of the anti-viral drug Paxlovid (more about the coronavirus main protease in APPENDIX D, Coronavirus Biology). In addition, red gromwell root has numerous anti-inflammatory effects.

The probiotic strain, Bacillus subtitlis B-7092, available in the U.S. as Tundrex 1, through www.Tundrex.co, (not .com). This is a soil-derived bacterium, originally from Siberian tundra, which secretes alpha-interferon, a potent anti-viral protein. The dose recommended by the manufacturer is 1-2 capsules 5 times a day (take every 2 hours or so, with or without food, no need to refrigerate). Tundrex comes in easy to carry blister packs of 10 pills, which will each last for 1-2 days. Each box has 5 blister packs. If GI symptoms are present, the higher dose is usually needed; if no GI symptoms, then the lower dose is used. Tundrex, like Tollovid, is a short term treatment, typically 10 to 15 days. I have used Bacillus subtilis B-7092 for about 6 years for helping people recover from various types of GI infections and am now a consultant to the company.

Vedicinals-9, a complex herbal antiviral shown to increase the speed of viral clearance in a clinical trial. This must be ordered from overseas.

- Directions on use of Vedicinals: Recommended dosage : 1 box per person for Acute Covid, 3-5 boxes per person for established Long Covid. Each box contains 14 bottles. Take half a bottle after breakfast , half a bottle after evening meal , always on full stomach (never empty stomach). Never do water fasting / intermittent or any kind of Fasting or KETO diet together with Vedicinals 9. Keep the formulation in mouth for half a minute and swallow slowly (mixing with saliva is important). To open bottle, follow instructional video. You will need a pair of pliars.

  Each component of Vedicinals 9 has anti-viral effects of its own, but the entire mixture was designed to enhance the synergy of each component. Some people have problems taking the full mixture because of taste or components to which they have adverse reactions. Among the specific components of Vedicinals 9 that can be used as alternatives are the bioflavonoid quercetin (this is probably the least expensive of the products listed--taken at a dose of 300-600 mg 3 times a day) or the Chinese herb Scutellaria baicalensis (dose would depend on the formulation taken).

I USUALLY HAVE MY PATIENTS FOLLOW VIRAL ERADICATION WITH ACE-2 AND MICROBIOME SUPPORT AND THEN WITH TEMS ENHANCEMENT (DESCRIBED ABOVE) TO RESTORE NORMAL T-LYMPHOCYTE FUNCTION. FOR PATIENTS WITH POST-COVID FATIGUE, I ADD MITOCHONDRIAL SUPPORT AND FOR PATIENTS WITH CIRCULATORY DISTURBANCES OR

SHORTNESS OF BREATH, I ADD TREATMENT FOR ENDOTHELITIS AND MICROTHROMBOSIS. PEOPLE WITH BRAIN FOG MAY NEED SUPPORT IN ALL OF THESE AREAS. THAT PROBLEM IS ADDRESSED IN APPENDIX B.

APPENDIX B

(Resources and Special Topics)

RESISTANCE-BAND WORKOUTS:

1. https://ahc.aurorahealthcare.org/fywb/baycare/x36050bc.pdf
2. https://www.sralab.org/sites/default/files/2017-05/Upper%20Body%20Thera%20Band%20Exercise%20Program%20-%20Basic.pdf
3. https://workoutlabs.com/exercise-guide/resistance-band-lying-leg-extensions/

INTERMITTENT FASTING:

https://www.healthline.com/nutrition/intermittent-fasting-guide

BRAIN FOG (IMPAIRED COGNITIVE FUNCTION)
Problems with focus, memory, and executive function (the ability to process information and make decisions) are common with Covid-19. If this has happened to you, it is a real phenomenon. It is not just the result of anxiety or depression. A comparison of brain MRIs from patients pre-Covid and post-Covid showa a loss of brain cells in the parts of the brain that regulate spatial memory and complex decision making. Other studies have shown Covid's negative impact on problem-solving abilities and visual attention, indicating that these MRI changes have significant functional impact. The main cause of these deficits appears to be poor blood flow to spexific areas of the brain .Individual nerve cells (neurons) die out quietly and connections between nerve cells (synapses) are lost.

I discuss these events and their causes, along with possible treatments in several videos available on You Tube.

Your Brain After Covid-19, Power Point Presentation
https://youtu.be/HSgT_A38Q20

The brain after covid-119, interviews with the Long Covid Foundation (U.K.)
https://youtu.be/HU8QjMBCxMA
https://www.youtube.com/watch?v=8ugebwwv1AI

Restoring the Gut-Brain Axis after Covid-19, a presentation at the fourth colloquium of the Long Covid Coalition
https://www.youtube.com/watch?v=PsNSwuC-FFE

Many of the nutritional supplements I've already discussed enhance brain recovery and have been shown to improve cognitive function and enhance the brain's ability to recover from injury. These include curcumin, resveratrol, and omega-3 fats (especially when combined with alpha-lipoic acid), butyrate, B vitamins, Gingko biloba and vinpocetin. Appropriate dosages are all described in APPENDIX A. Vinpocetin specifically addresses the circulatory deficit that underlies Covid brain fog.

Three additional supplements that combine a high safety profile with evidence of clinical benefit for cognitive enhancement are:

- Luteolin, a bioflavonoid found in many vegetables, especially celery. The main problem with luteolin supplementation is low bioavailability, so I recommend using a liposomal preparation.Liposomes are tiny bubblers of lecithin that surround the substance being administered, in order to enhance absorption from the gut and transport in the body. The dose needed is about 300 mg/day.
- Fisetin, another bioflavonoid, most concentrated in strawberries. A cup of strawberries a day can supply enough fistein to enhance recovery from stroke.
- Phosphatidylserine (PS), a special form of lecithin.I've recommended PS to patients for enhancing memory over many years. The dose needed is 100 mg 3 times a day after eating. For each of these, the response may not be immediate. Allow 6 weeks before deciding if it's helpful.

SHORTNESS OF BREATH, POST-EXERTIONAL MALAISE AND THE SIX-MINUTE WALK TEST:

If shortness of breath limits your capacity for physical activity or if you are fatigued after brief exercise because of shortness of breath, there are three medical conditions that may be the cause, even if a cardiopulmonary evaluation is normal.

- The first is simple deconditioning, which would respond to an exercise conditioning program.
- The second is damage to the blood vessels that carry oxygen from your lungs. This creates what is known as a ventilation/perfusion imbalance. It appears to be a common complication of Covid-19, but is difficult to confirm with standard tests. Dr. William Li of the Angiogenesis Foundation has developed a computer algorithm for identifying this problem on a CT scan of the chest. Confirmation also comes from a special chest scan called a V/Q scan. Researchers at Duke University's Xenon MRI Center have made similar observations of loss of pulmonary blood flow after Covid-19. In my experience, people who have this problem often find that measures described

above for treating endothelitis and microthrombosis help to restore breathing capacity.

- A third possibility is microscopic scarring of the lungs, too subtle to be seen with an X-ray or CT scan. This is a condition called sub-clinical pulmonary fibrosis. There are medications called PDE inhibitors that can improve breathing capacity of people with mild pulmonary fibrosis. Mast cell activation can aggravate pulmonary fibrosis and ACE2 helps to prevent fibrosis, so attention to calming mast cell activation (see Appendix C) and supporting ACE2 activity may be helpful.

To better evaluate your own lung function, check your oxygen saturation using a fingertip pulse oximeter (available online or in pharmacies for about $35). If you can walk for 6 minutes without crashing, then try the 6 minute walk test.

Six minute walk test:

1. Put the pulse oximeter on the end of your finger, turn it on, and check your oxygen concentration. (Normal oxygen saturation is 94 to 99%.)
2. Walk for six minutes as fast as you can, then sit down and immediately check your oxygen concentration again.
3. If it's dropped, take the results to your doctor and ask for a test of oxygen diffusion capacity. If that's even mildly abnormal, ask your doctor about the possibility of either sub-clinical pulmonary fibrosis or a ventilation-perfusion imbalance.

- If you get short of breath when talking, not just with exercise, you may have a different condition called paradoxical vocal cord dysfunction. This diagnosis can only be confirmed by an ear, nose and throat specialist using a technique called video laryngoscopy. The treatment is not medical, however; it is voice therapy.

- If you cannot do a 6-minute walk test because even a small amount of walking causes you to feel worse for hours or days afterwards, you likely have a condition called post-exercise malaise (PEM). PEM is a hallmark of Chronic Fatigue Syndrome (also known as Myalgic Encepalomyelitis (CFS/ME). If that's the case, focus on ACE2 enhancement and mitochondrial rescue first, for several weeks, before you try any kind of exercise.

If you cannot improve your exercise intolerance with gradual conditioning, ACE2 enhancement and mitochondrial support, there are 2 conditions to look into: (1) POTS, the postural orthostatic tachycardia syndrome (more information about this below) or (2) small fiber neuropathy. Dr Ann Louise Oaklander of Harvard has long written about this kind of nerve damage as a cause of pain in people with fibromyalgia, and has more recently reviewed research indicating that small fiber neuropathy can cause post-exercise malaise by impairing blood flow to nerves and muscles. To confirm small fiber neuropathy, you will need to consult a neurologist. Natural products that have been most studied for treatment of neuropathy include alpha lipoic acid, N-acetylcysteine, B-vitamins and the mushroom known as lion's mane (Hericium erinaceus).

POTS, Positional Orthostatic Tachycardia Syndrome

This is a common complication of Covid-19. There are 3 different mechanisms for POTS. In Long Covid it's a direct result of ACE2 deficit impacting the brain and the autonomic nervous system, creating the hyperadrenergic form of POTS. If you experience weakness, fatigue, or dizziness when upright, and function best lying down, this may be your problem. If you cannot exercise because your heart races with minimal activity, POTS may be the cause. POTS can create a vicious cycle: the best way to reverse it is through physical conditioning, but the presence of POTS makes physical conditioning difficult and sometimes even hazardous.

a. To determine if you may have POTS, do the home test for orthostatic intolerance described here: https://www.wikihow.com/Diagnose-POTS
b. If your results are consistent with POTS, take that information to your physician. There are medications that can help control symptoms. The main value to these is that they allow you to exercise, so you can re-condition yourself and may no longer need these medications.
c. There appears to be an unusually high frerquency of mast cell activation among Long Covid patients with POTS. If you suffer from POTS as a manifestation of Long Clovid, check APPENDIX C; reducing mast cell activation may help your symptoms.
d. There are several self-care measures you can take to decrease the impact of POTS and many resources available online.
https://www.dysautonomiainternational.org/pdf/CHOP_Modified_Dallas_POTS_Exercise_Program.pdf
https://www.standinguptopots.org/node/107

   Mainstays of treatment include; hydrating with salt and fluid, avoidance of alcohol, the use of support hose and binders and graduated exercise.

   Be careful with exercise, however, as I have cautioned above, because POTS and PEM (post-exercise malaise) are not the same and exercise that benefits POTS may aggravate PEM.

e. Several studies have identified nutritional therapies that may slow the heart rate of people with POTS. These include (a) a gluten-free diet, even if you do not have celiac disease, (b) supplementation with thiamine (vitamin B1) or cobalamin (vitamin B12) or melatonin (dosages in Appendix A).
f. Eat small, frequent meals, because large meals may cause fluid to shift from your circulation into your intestines, reducing blood volume and aggravating POTS. Pay attention to the way your body responds to carbohydrates. Eating a high carb meal may increase the dumping of body fluids into the intestines, but very low carb diets are intrinsically dehydrating and may aggravate POTS. Be aware of how meals affect you and look for balance.

LOSS OF TASTE/SMELL:

This consequence of covid-19 can be life-altering. It results from damage to the nerves that regulate the senses of taste and smel. People with loss of smell from Covid-19 are at increased risk of developing brain fog and cognitive dysfunction. Taste is actually a very simple sense; the flavours associated with food and drink are mostly due to smell. There are only 4 tastes; salty, sweet, sour and bitter. If you think your sense of taste is impaired, you can test it this way:

Pour 4 glasses of water. Into one put a teaspoon of salt, into another a teaspoon of sugar, into the third a teaspoon of vinegar and into the fourth a teaspoon of lemon juice. Block your nose with a nose clip, so you cannot smell the drinks and just taste each, in sequence. If you can readily tell one drink from the other correctly, your sense of taste is intact and your apparent problem with taste is actually a problem of smell. (If taste is truly your problem, try supplementing with zinc, as described in Supplement A. The sense of taste is highly dependent on zinc.

Problems with smell come in two forms: loss of smell (anosmia) and distorted smells (parosmia). Anosmia appears to be caused by damage to the nerve that transmits smell to the brain (the olfactory nerve). Parosmia occurs as the nerve begins to heal. The new synapses being formed convey information that the brain does not yet know how to interpret.

The cause of nerve damage has been evident since early in the pandemic. When not associated with a stuffed nose, loss of smell is caused by swelling of an area at the top of the nose called the olfactory cleft[1]. Swelling is associated with viral invasion of a group of cells that surround and support the olfactory nerve,[2]. They're called sustenacular cells. Swelling in this area can damage the olfactory nerve in 2 ways: (1) There may be inflammatory chemicals (cytokines) released by the sustenacular cells that spill over and damage the nerve. (2) Local swelling may put pressure on the nerve, creating what is called a pressure neuropathy. It usually clears within days to weeks. Pressure neuropathies can be helped by the antioxidant alpha-lipoic acid, 600 mg/day[3], possibly in combination with gamma-linolenic acid (GLA), which is found in evening primrose and borage seed oils[4].

People recovering from anosmia sometimes develop a distorted sense of smell that varies and fluctuates in severity and in the nature of the distortions that occur. This is called parosmia. Parosmia may be associated with functional changes in the smell and taste centers of the brain[5]. The research suggests the following explanation: as damaged nerves begin to heal, they form new connections (synapses) that relay information between different parts of the brain. When first formed these synapses may present confusing information that creates baffling but intermittent neurological symptoms[6]. In the case of parosmia, training through aroma therapy may enhance recovery by supporting a phenomenon called neuroplasticity[7]. It is possible that other approaches to supporting the recovery of nerves may speed recovery of taste and smell.

A NOTE ABOUT EPSTEIN-BARR VIRUS (EBV)

EBV is a common virus that infects everyone in the world. It may cause acute mononucleosis, but most people don't even know they have it. Once it enters your body, it lives there for the remainder of your life, in a dormant state. Many people with Covid-19 experience transient re-activation of EBV infection. This finding has generated a lot of press and a fair amount of panic. The science of EBV and my professional experience have each convinced me that the focus on EBV as a cause of LongCovid is misguided. EBV is not the problem, and attempts to kill EBV with anti-viral drugs are rarely helpful. Blood tests that are believed to show EBV re-activation are actually measuring the impact of TEM lymphocyte impairment on antibody levels. If you've been told you have active EBV as a consequence of Covid-19, please read the paragraph below.

Although EBV lives in your B-lymphocytes, the virus stays suppressed, in what scientists call a latent state. B-cell infection makes it certain that you will show antibodies to EBV for life. The presence of some of these antibodies is to be expected and does not in and of itself indicate active EBV infection (which is called a "lytic" state, rather than a "latent" state). There are four specific EBV antibodies commonly measured. They are directed against different viral proteins (called antigens), specifically the VCA (viral capside antigen), EBNA (Epstein Barr nuclear antigen), and EA-D (early antigen diffuse). The type of antibodies measured are in a category called IgG (immunoglobulin G); these may be very long-lived antibodies. The presence of IgG antibodies to any microbe does not establish that there is an active infection, but only that you have been exposed to this microbe at some time in the past.

Because the virus usually presents the antigen EA-D to your cells for only a few months after infection, most people with a previous EBV infection will show IgG antibodies to the VCA and EBNA antigens and not to EA-D. Some doctors believe that elevated antibodies to EA-D are a sign of active infection; many researchers doubt that to be true. I've found that interpreting the significance of antibodies to EA-D requires understanding the context, looking at the entire clinical picture, not just reading antibody levels. The fourth antibody that is routinely measured is in a different antibody class called immunoglobulin M (IgM). IgM antibodies are formed soon after the onset of infection and usually disappear over a few months, being replaced by IgG antibodies. The presence of elevated IgM antibodies to any component of EBV is unusual and suggests recent acute infection or true re-activation; this needs to be taken seriously.

Many people with acute Covid-19 experience a surge in antibody production to EBV, including IgM antibodies, and may also have DNA from EBV circulating in their blood, a clear sign of re-activation. As acute Covid infection wanes, EBV DNA disappears from blood and IgM antibodies usually disappear. When acute Covid ends, the elevated IgG antibodies may persist for months and are often found in people with Long Covid. Their presence does not necessarily indicate that EBV has

switched from a latent to a lytic phase. It only shows evidence of immune dysregulation, which is common with Covid-19. I interpret it as a sign of TEM cell dysfunction.

Research done during the 1980's established that, for any individual, antibody levels to EBV can fluctuate widely over time and typically increase when T-lymphocyte function is impaired. Studies done with medical students at Ohio State University found that EBV antibody levels were highest after final exams and lowest after summer vacation, while T-cell responses to EBV showed the opposite pattern. So, if you've been told that you now have an active EBV infection on top of Covid-19, take a deep breath and challenge that assumption. The blood test may just be reflecting the T-cell impairment that is very common with Covid and the focus should be on restoring TEM function, not on killing EBV.

APPENDIX C:
Mast cell Activation Syndrome

Mast cells are primitive cells of the immune system that are sparsely distributed throughout the tissues of your body. They do not circulate in blood. Mast cells can release up to 200 different chemicals (called "mast cell mediators"), and they do so in response to a variety of internal or external triggers, which include food, drugs, temperature, environmental chemicals, physical exertion, and various types of physical trauma. Mast cells normally protect against infection, especially fungal or

parasitic infection, and they play a major role in acute allergic reactions. In a well-functioning immune system, mast cell activation subsides once the trigger is either neutralized or removed. Sometimes, however, once the mast cells are activated, they do not stop firing off chemicals. Like a machine gun with its trigger stuck, they create havoc and random damage, a condition called mast cell activation syndrome (MCAS). Because of all the variables at play, symptoms of MCAS vary greatly from person to person and are often misdiagnosed. For a general review of MCAS, read Never Bet Against Occam by Dr. Lawrence Afrin and colleagues.
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Researchers have been studying MCAS for just a few years and the underlying causes are not known. Mast cell activation is influenced by a number of genes, so one leading theory is that MCAS occurs in people who have inherited genes that produce hyperactive mast cells, which respond excessively to multiple minor or innocuous triggers.

The most common symptoms of people with MCAS are fatigue or pain and multiple allergies or sensitivities, followed in frequency by feelings of being cold or occasionally hot, often accompanied by sweats. Swelling and weight gain are common, but fluctuating weight or unexplained weight loss may occur. Brain fog, skin rashes, itching and gastrointestinal problems tend to occur intermittently.

A very wide range of environmental triggers may activate symptoms of MCAS, including drugs, insect stings, allergens, pressure, extremes of temperature (hot or cold), sunlight. In fact, any new environmental exposure may provoke symptoms of MCAS.

Because mast cells are found throughout the body and because they release so many mediators with such a variety of effects, potential symptoms of MCAS are numerous and vary greatly from person-to-person. They are listed in Table 1.

Table 1. Symptoms of MCAS

General symptoms	Fatigue, malaise, sweats, weight gain, lightheadedness, dizziness, weakness, brain fog, decreased libido
Skin	Rashes, itching, flushing, swelling, dryness, poor healing, sores, hair loss, striae (streaks on the skin)
Eyes	Irritation, redness, dryness or tearing, trouble focusing, twitching of eyelids
Ears	Change in hearing (hearing loss or excessive sensitivity to noise), ringing in the ears, increase in otosclerosis
Mouth and throat	Throat irritation or itching, burning mouth, mouth sores, swelling of tongue, lips, gums, cheeks, post-nasal drip
Lymph nodes	Enlarged lymph nodes, often tender to the touch
Respiratory	Nasal or sinus congestion, nosebleeds, cough, wheezing, trouble taking a deep breath
Gastrointestinal	Abdominal pain, bloating, diarrhea, constipation, heartburn
Urinary	Discomfort with urination, back or flank pain
Muscular	Diffuse or migrating muscle or soft tissue pain
Nervous system	Headache, numbness, tingling, tics, tremors, anxiety, depression, mood swings, memory problems, impaired focus or concentration, sleep disturbances

Immune system	Increased susceptibility to true allergic reactions and to infection; slow healing of infections
Circulatory system	Palpitations, rapid heart rate, fluctuating blood pressure, chest discomfort, abnormal blood clotting or bleeding

Aside from allergic and hypersensitivity disorders, conditions associated with MCAS include fibromyalgia, chronic fatigue syndrome, irritable bowel syndrome, migraine, vulvar vestibulitis syndrome, interstitial cystitis, endometriosis, autistic spectrum disorders, osteoporosis, hypothyroidism, micronutrient malabsorption, POTS (postural orthostatic tachycardia syndrome), and joint hypermobility syndromes. Researchers believe that chronic release of mast cell mediators may contribute to the formation of each of these conditions or to their symptoms.

Histamine, the best known mast cell mediator

Histamine causes the typical symptoms of acute allergies by activating cellular proteins called “histamine receptors”. This is a general pattern: release of chemical mediators activates specific receptors for those mediators, which then create the effects attributed to the mediators. Histamine may attach to and activate several different receptors, which have different effects, often complementary to one another, sometimes contradictory to one another. The first type of histamine receptor discovered is called the H1 receptor. H1 activation dilates blood vessels, producing redness and heat, and makes them leaky, so that blood plasma seeps out from the blood vessels into the surrounding tissues, causing swelling. H-1 activation causes many of the symptoms associated with classic allergic reactions, like sneezing and hives. Standard antihistamine drugs are H-1 receptor blockers. H-2 receptors also make blood vessels dilate but they are best known for increasing secretion of stomach acid. Drugs that are H-2 blockers are mostly used to reduce stomach acid but may have anti-allergic effects that are additive with those of H-1 antihistamines. Famotidine (Pepcid) is an H2 blocker that has been shown to be beneficial in the treatment of acute Covid and Long Covid. Both H1 and H2 blockers have shown benefits in Long Covid, not only through relieving symptoms but by enhancing T-lymphocyte function. They are first-line treatments for MCAS and for a separate condition called Histamine Intolerance.

Histamine intolerance is a separate syndrome, sometimes related to MCAS.

In addition to mast cells, there are several other sources of histamine in the body. Histamine is found in certain foods and may be produced by gut bacteria. Histamine is eliminated in 2 ways: (1) It is broken down by an enzyme called diamine oxidase (DAO), which uses copper as an essential co-factor. (2) It is inactivated by a process called methylation, and the resulting chemical, N-methylhistamine, is excreted in urine. People lacking adequate levels of DAO or sufficient capacity for methylation of histamine, may become symptomatic from levels of histamine that do not provoke symptoms in other people.

The symptoms of histamine intolerance overlap with the symptoms of MCAS. By increasing histamine secretion, MCAS can aggravate the symptoms of people with histamine intolerance. Because histamine intolerance is primarily caused by the inability to eliminate histamine, histamine intolerance can make MCAS much worse. Both H1 and H2 blockers can help symptoms of histamine intolerance, but MCAS and histamine intolerance are distinct from one another. MCAS always involves other mediators, not histamine alone. Histamine intolerance generally responds well

to a special diet (described in Table 2), which eliminates foods that contain histamine, liberate histamine from intestinal cells or block the activity of DAO. Taking DAO as an enzyme with meals, correcting copper deficiency if it is present, and using specific probiotic bacteria that break down histamine rather than secreting it, are therapeutic steps I have found very helpful for my patients with histamine intolerance. Seeking Health is a reliable source of these products.
https://www.seekinghealth.com/products/probiota-histaminx-60-capsules
https://www.seekinghealth.com/products/histamine-block

TABLE 2.DIET FOR HISTAMINE INTOLERANCE, FOODS TO AVOID

FOODS HIGH IN HISTAMINES:

- Alcohol, especially wine and beer
- Pickled or canned foods – sauerkraut, kimchi, etc.
- Vinegar
- Yogurt
- Aged cheeses
- Smoked or cured meat products – salami, ham, sausages….
- Shellfish
- Beans and pulses – especially chickpeas, soy beans, peanuts
- Soy sauce and tamari
- Nuts – especially walnuts, cashews
- Chocolates and other cocoa based products
- Most citrus fruits
- Wheat based products
- Vinegar
- Ready meals
- Salty snacks, sweets with preservatives and artificial colourings
- Fish, especially if it is aged or spoiled. The highest levels ogf histamine are found in bonito (skipjack), tuna and mahi mahi.

Histamine liberators:

- Most citrus fruits, especially lemon and lime, also kiwi, pineapple andplums…
- Cocoa and chocolate
- Nuts
- Papaya
- Beans and pulses
- Tomatoes
- Wheat germ
- Additives – benzoate, sulphites, nitrites, glutamate, food dyes

Diamine Oxidase (DAO) blockers.

- Alcohol
- Black tea
- Energy drinks
- Green tea

- Mate tea
  NB: More information on diet for histamine intolerance is available through several online sources and books https://www.amazon.com/s?k=histamine+intolerance+book&i=stripbooks&crid=25RFJSBHWHQEC&sprefix=histamine+inmtolerance%2Cstripbooks%2C69&ref=nb_sb_ss_sc_3_21 . These sources will contain information that adds to or expands on what I have presented.

Beyond Histamine: Other Mast Cell Mediators

Serotonin: Constricts blood vessels and increases motility of the gastrointestinal tract. It may cause abdominal cramps and diarrhea. In the brain, serotonin has numerous other effects on mood, sleep, appetite and cognitive function. Serotonin contributes to the pain of migraine.

Prostaglandin D2: Causes constriction of bronchial tubes and plays a key role in the wheezing of asthma. It also dilates blood vessels to cause flushing of the skin, slows hair growth and induces sleep.

Leukotrienes: Contribute to wheezing and runny nose. They are structurally related to prostaglandins. Sometimes, blocking prostaglandin synthesis makes symptoms worse, rather than better, because when prostaglandins go down, leukotrienes go up.

Cytokines: Groups of proteins that communicate signals between cells of the immune system. Many of the symptoms associated with infection or inflammation result from the activity of different cytokines.

Laboratory Tests for MCAS

These are all imperfect. Elevated levels of any mast cell mediator may be caused by mast cell activation, but the absence of abnormal test results does not eliminate mast cell activation as a cause of symptoms. The diagnosis of MCAS is not based on lab tests, but on the multiplex of symptoms and response to treatment.The tests most commonly ordered are serum tryptase (a mast cell enzyme), serum chronogranin A (a mast cell mediator), plasma levels of histamine and prostaglandin D2 and 24 hour urine for prostaglandin D2 or N-methylhistamine. Other blood test abnormalities associated with MCAS include abnormal blood cell counts, elevated liver or muscle enzymes, low or high iron (measured as ferritin), low magnesium and low copper. Copper is needed to break down histamine and low copper may play a role in histamine excess.

Treatment Options for MCAS

Treatment of MCAS is challenging, because people with MCAS are prone to adverse drugs reactions, even with drugs that should help their symptoms and even with natural products. Treatment is focused on mast cell mediators. Its purpose is to (1) inhibit production of mediators, (2) inhibit the release of mediators (this is called mast cell stabilization), (3) block the actions of mediators that are released and (4) hasten the breakdown of released mediators. These same principles apply whether drugs or natural products are used.

Each treatment needs to be used daily for at least a month to determine benefit and may need to be continued indefinitely if it is helpful. Multiple treatments

are usually needed. There is not one magic bullet. Any treatment that produces an adverse reaction should be stopped.

Many of the treatments for MCAS require a prescription from a specialist. There are two types of treatment you can implement yourself for control of MCAS:

(1) Over-the-counter drugs that might be helpful
    a. Standard antihistamines (H-1 blockers) like fexofenadine (Allegra), loratidine (Clariten), desloratidine(Clarinex), cetirizine (Zyrtec) or diphenhydramine (Benadryl)
    b. H-2 blockers (antihistamines used for reducing stomach acid, like ranitidine (Zantac), famotidine (Pepcid), and nizatidine (Axid). These may work well in concert with the H-1 antihistamines.
    c. Mast cell stabilizers like ketotifen and cromolyn. These are available over-the-counter as topical preparations (eye drops or nasal sprays), but doctors can prescribe systemically active forms.
    d. Aspirin, ibuprofen, naproxen and other non-steroidal anti-inflammatory drugs, which block synthesis of prostaglandin D2. The major warning with these drugs is that blocking prostaglandin production may increase leukotriene synthesis, increasing symptoms. Aspirin-sensitive asthma is one example of this effect, which can occur even in the absence of MCAS.

(2) Nutritional supplements and natural products: There are several natural products that have been shown to stabilize mast cells in laboratory experiments. Human data are limited, but I've seen beneficial effects from each of these. I have already described the use of most of these for treating other aspects of Long Covid.
    a. Quercetin, a bioflavonoid that occurs naturally in numerous fruits and vegetables, like apples and onions. [1] High doses may be needed, as much as 2000 milligrams a day.[2]
    b. Pycnogenol, an extract of the bark of the French maritime pine tree, prevents mast cell activation and histamine release[3].
    c. Luteolin, a bioflavonoid found in parsley and numerous herbs, like perilla leaves[4], which with significant anti-inflammatory and mast cell inhibition

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[1]Biocell. 2003 Aug;27(2):163-72.Role of mast cells in gastrointestinal mucosal defense.Penissi AB[1], Rudolph MI, Piezzi RS.

[2]Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans.Weng Z, Zhang B, Asadi S, Sismanopoulos N, Butcher A, Fu X, Katsarou-Katsari A, Antoniou C, TheoharidesTC.PLoS One. 2012;7(3):e33805.

[3]Pycnogenol inhibits the release of histamine from mast cells.Sharma SC, Sharma S, Gulati OP.Phytother Res. 2003 Jan;17(1):66-9

Pycnogenol inhibits immunoglobulin E-mediated allergic response in mast cells. Choi YH, Yan GH. Phytother Res. 2009 Dec;23(12):1691-5.

APPENDIX D. CORONAVIRUS BIOLOGY

THE VIRUS AND ITS VARIANTS

Corona viruses are a family of viruses made from RNA instead of DNA. There are many species that produce respiratory and gastrointestinal illness in humans and animals. Four strains cause the common cold. The pandemic corona virus, SARS-CoV-2, was first identified in Wuhan, China, in December 2019. It causes the disease named Covid-19. Under the electron microscope, the virus looks like a medieval weapon: a globe covered with spikes. The spikes are made of protein (the viral spike protein) and they are essential for viral entry into your cells. Mutations in the spike protein underlie emergence of all the variants that have made the virus increasingly more infectious. Numerous studies have shown that RNA viruses develop mutations at a much higher rate than other viruses. Each actively replicating SARS-CoV-2 virus will form a new mutation about once a week[8].

SARS-CoV-2 is almost identical to a corona virus that has inhabited bats for about 70 years, but had never been identified as a cause of disease in people. The closest human pathogen to SARS-CoV-2 is the corona virus that caused SARS (Severe Acute Respiratory Syndrome) in 2003. On an individual case basis, SARS was far more lethal than Covid-19, but it was also far less transmissible. Over a 2 year period, SARS sickened 8098 people worldwide and killed 774. Within 8 months, Covid-19 was already a thousand times more deadly than SARS. The genetic mutations that distinguish SARS-CoV-2 and that enable its high reproductive rate in humans are now well-known and form an important part of the debate over the origins of the virus: natural evolution in animals or accidental escape from the Wuhan Institute of Virology.

The spike protein is divided into two major segments called S1 and S2. S1 contains an area called the receptor binding domain (RBD), which is used by the virus to attach to a protein on
human cell membranes. That protein is called the cellular receptor. The initial mutation, which created the Wuhan strain and enabled the pandemic, placed a strong positive electrical charge very close to the RBD. This helps the spike protein stick to the outside of the human cell membrane in a way that increases the ability of the RBD to attach to the cellular receptor.

TRANSMISSION

SARS-CoV-2 is readily transmitted from person to person through respiratory droplets. Large droplets produced by a cough or sneeze may travel as far as 27 feet,

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[4] Anti-inflammatory and antipruritic effects of luteolin from Perilla (P. frutescens L.) leaves. Jeon IH, Kim HS, Kang HJ, Lee HS, Jeong SI, Kim SJ, Jang SI. Molecules. 2014 May 27;19(6):6941-51.

hurtling at a speed of up to 200 miles/hour and then coasting on turbulent airflow[9]. Breathing, talking, shouting and singing encase the virus within very small droplets that stay airborne as aerosols for up to 14 minutes if the air is totally still[10], longer if the air is moving. SARS-CoV-2 can be sustained in the air of a closed air conditioned bus for at least 30 minutes without losing infectivity[11]. A study from Wuhan found aerosolized SARS-CoV-2 in medical staff areas and unventilated bathrooms[12]. In the cold, stale air of a meat processing plant, the virus was able to infect people 26 feet away from its source[13].

Air conditioning can increase transmission by keeping the virus airborne longer through two mechanisms: (a) creating currents on which the droplets drift and (b) decreasing humidity, so that the droplets remain smaller and lighter[14]. Respiratory droplets absorb moisture from humid air to become larger and heavier, precipitating on to surfaces more quickly. Harvard researchers demonstrated that respiratory viruses are more likely to be spread within buildings when the relative humidity is low and recommend maintaining humidity in the range of 40-50%[15]. At higher levels of relative humidity, the growth of dust mites and of mold is increased, so the optimal range is quite narrow.

A study from South Korea traced 3 cases to a restaurant in which the infected person (the “index case”) infected other people at a distance of 20 feet with only 5 minutes of exposure; transmission was attributed to the pattern of air flow in the restaurant[16]. The Delta variant may require even less exposure time to create active infection.

Individuals vary in the number and quality of respiratory droplets they exhale. Researchers suspect that people who emit more droplets or whose droplets are naturally more viscous are more likely to transmit viral infections to others[17]. This may explain why some are super-spreaders and others do not even infect their spouses.

SARS-CoV-2 is mostly but not exclusively spread indoors. Open outdoor spaces allow dilution of viral particles, aided by wind. Summer sunlight inactivates 90 per cent of viral particles suspended in saliva within 7 minutes; on a dry surface it takes twice as long[18]. Winter conditions double the time required. Clusters of cases related to backyard barbecues and other outdoor activities where people were in close contact have been described[19] and outdoor transmission has been documented in China, so Covid-19 can clearly be acquired outdoors. Newer more transmissible variants may increase the risk of outdoor transmission

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THE KEY ROLE OF THE NOSE

The principle site of entry of SARS-CoV-2 is the lining of the nose. Here the virus replicates, increasing in number before aspiration into the lungs, where pneumonia occurs[20]. Having multiplied in the nose, SARS-CoV-2 is in a strong position to invade both the brain[21] and the blood vessels. The initial viral load in the nose is a key factor for determining the severity of infection[22], so that covering your nose with a mask—almost any mask—may protect you, in addition to preventing spread to others[23](More on this in ANTI-VIRAL HYGIENE). The role of the nose as an

incubator for Covid-19 suggests that an anti-viral nasal spray may help decrease transmission among individuals at high risk of exposure.[24] [25] [26] [27] [28]

Airborne virus will settle on solid surfaces and air vents and remain viable on these surfaces for varying periods of time[29]. This does not appear to be a major route of transmission, however. Passengers traveling by rail in China who occupied a seat that had just been vacated by a person with Covid-19 were no more likely to get sick than people in other parts of the train who had no contact with the infected person.[30]. The major determinants of risk on trains were proximity to the infected person and duration of travel together. Sitting next to a person with Covid-19 created a 3.5 per cent risk of infection that increased by 1.3 per cent for every hour of travel. (More about surface contamination in ANTI-VIRAL HYGIENE).

SARS-CoV-2 can attach to cells of the small and large intestines[31], appearing in bowel movements. Flushing a toilet with the lid open may then allow viral particles to become airborne. The virus frequently contaminates sewage. it persists in stool when respiratory swabs are negative[32] [33] [34] [35].

A small study demonstrated that when found in stool the virus is not only viable but infectious[36] Food-borne or water-borne infection is possible but still unproven[37] [38] [39].

VIRAL INFECTION: CELL ENTRY AND CELL DAMAGE

In order to cause disease, any virus must enter a human cell, replicate, and damage the cell, escaping to infect adjacent cells. Cell entry and cell damage can be controlled with strategies that are readily available now.

PART 1. Viral Entry, the Front Four

The entry of SARS-CoV-2 into human cells is a multistep process. For rapid spread, four steps seem to be essential. Addressing them is the core of an integrated management approach to stopping Covid-19 at the cellular level.

There are four human molecules that, working together, enable SARS-CoV-2 to quickly and efficiently enter your cells. I call them the Front Four because cellular entry is the gateway through which infection occurs. They are all found in or on the cell's external membrane (called the plasma membrane). Their names are heparan, furin, ACE-2, and TMPRSS2. Treatments that target each of these already exist and may prevent or limit viral entry and the damage it creates. They have been largely ignored in the trillion dollar race to develop antiviral drugs and vaccines.

- Step 1. Heparan is a complex sugar that coats the outside of all human cells. It is part of a structure called the glycocalix. A derivative of heparan called heparin is used in medicine as an anticoagulant drug, given by injection. The viral spike protein of SARS-CoV-2 sticks to heparan on the cell membrane, through a powerful electrical attraction[40]. Heparan holds the virus in place[41] so that the next substance, furin, can do its job.

- Step 2. Furin, like heparan, coats all human cells[42], but unlike heparan, it is an enzyme. Its role in Covid-19 is to split the viral spike protein in two, so that one part fits tightly into its cellular receptor, ACE-2, the way a key fits into a lock[43]. Without priming by furin, the viral spike protein forms a very weak attachment to the cellular receptor and the entry of virus into cells becomes slow and inefficient. The place on the viral spike protein that sticks to heparan (the heparan binding site) overlaps the place where it's split by furin (the furin cleavage site). <u>This relationship has enabled the pandemic, because it dramatically enhances the speed with which the virus enters human cells.</u>

  Genetic studies of the evolution of SARS-CoV-2 find that the predominant mutations separating SARS-CoV-2 from its relatives involve the furin cleavage site. They make the viral spike protein more susceptible to being cut by furin.

  The good news: Because furin plays a role in promoting cancer and certain well-known infectious diseases, like anthrax, there has been a lot of interest in furin inhibitors[44]. Two natural substances that inhibit furin are widely available:

  - Andrographis paniculata, an herb used in traditional Chinese medicine and Ayurveda. (The active ingredients are called andrographolides).
  - Luteolin, a bioflavonid found in celery, thyme, green peppers and chamomile tea, among other food sources.
  - Both Andrographis and luteolin have anti-inflammatory and anti-viral effects that are separate from furin inhibition. Their anti-inflammatory effects have been demonstrated in human clinical trials, not just laboratory studiesLuteolin is also a natural inhibitor of IL-13, the cytokine found to predict a need for mechanical ventilation in hospitalized patients, and of mast cells, which contribute to the cytokine storm of critically ill patients.

- Step 3. ACE-2, a protein embedded in the human cell membrane, is the centerpiece for viral entry, so it's called the cellular receptor. It attaches to the receptor binding domain of the viral spike protein. Unlike furin or heparan, ACE-2 is only found in certain types of cells, where it bridges the entire thickness of the membrane, from outside to inside. SARS-CoV-2 is most likely to infect cells that express ACE-2 in their membranes. This discovery has created a great deal of confusion about the role of ACE-2 in Covid-19. During the first few months of the pandemic, ACE-2 achieved undeserved notoriety as the villain that allows the virus to make us sick. Some researchers argued that people became sicker because they had an excess of ACE-2 in their cells. This idea has been proved totally wrong, but it continues to pop up in news articles and some research papers, because it seems so simple. It's

based on a superficial understanding of the complexity of ACE-2 and its multifaceted role healing.

ACE-2 is an enzyme that is vitally important for your health. It protects your blood vessels, your heart, your brain, your lungs, your kidneys and your bone marrow from many types of damage, inhibits inflammation, prevents abnormal blood clotting and enables healing without scarring. When a corona virus uses ACE-2 to enter cells, the protein loses its enzyme activity. ACE-2 is the victim not the cause of Covid-19 and loss of ACE-2 underlies all the terrible complications of Covid-19, including pneumonia, heart failure, blood clots, kidney failure, strokes, seizures, brain fog, purple toes, loss of lymphocytes, excessive inflammation and autoimmune disease.

Some scientists are attempting to develop drugs that prevent the viral spike protein from attaching to ACE-2. There is a natural product that does just that: quercetin, a bioflavonoid found in onions, apples and other fruits and vegetables. Quercetin is able to insert itself between ACE-2 and the receptor binding domain of the viral spike protein[45]. It's like a friendly bystander breaking up a fight. A small clinical trial from Turkey showed that health care workers taking quercetin 250 mg twice a day, along with vitamin C and bromelain (an enzyme found in pineapple stem) had a 92% reduction in acquiring antibodies to SARS-CoV-2, compared to health workers not taking quercetin[46]. This implies that these workers were far less likely to have become infected during the trial. Quercetin was considered to be the active ingredient. The intended role of vitamin C and bromelain was to increase quercetin absorption. The results of this study would be far more exciting if the participants had been randomly assigned to take quercetin or not, but instead they self-selected what they would do, which leaves considerable room for bias.

- Step 4. TMPRSS2 ("tempress-2"), like ACE-2, is an enzyme imbedded in human cell membranes. Like ACE-2, it is only found in certain types of cells. As the viral spike protein locks into ACE-2, TMPRSS2 cuts a wedge out of both, destroying the beneficial activity of ACE-2 and freeing the virus to fuse with the cell membrane. The cells that the virus can enter most quickly and efficiently are those few cell types that express both ACE-2 and TMPRSS2 in their membranes. The highest co-concentration of these two enzymes demonstrated so far occurs in cells that line the nose. Co-expression is also found in the lungs, the salivary glands, the lining of the heart and blood vessels, testicles and the small and large intestines. In these cells, it appears that the rate-limiting step for viral entry is the level of TMPRSS2, not the level of ACE-2, because TMPRSS2 speeds the rate of cell entry about one hundred fold. Depending on the type of cell, inhibition of TMPRSS2 can reduces viral entry by over 90%.

Expression of TMPRSS2 in the cells that carry it is quite variable. Two factors that increase its expression are male hormones (androgens) and the cytokine IL-13, which, according to one study, is associated with increased severity of illness in hospitalized patients. Interleukin 13, in fact, increases TMPRSS2 and decreases ACE2, a combination of effects that is likely to increase severity of Covid-19[47]. Increased levels of IL-13 in the lungs occurs in people with asthma. The effect of IL-13 may explain the results of large studies from South Korea, which found that people with non-allergic asthma were more than 4 times as likely to develop severe complications of Covid-19 than people without asthma[48] and that those who had experienced a flare-up of asthma within the past year had almost 3 times the fatality rate if hospitalized with Covid-19[49]. Asthma is also a major risk factor for severe Covid-19 among children[50]. [Other studies have shown that asthmatics are less likely to develop Covid-19. I believe that is due to asthmatics being extra cautious about exposure and also because many take inhaled steroids, which appear to have a protective effect].

- The good news: Inhibitors of TMPRSS2 exist, although none are readily available in the U.S. The safest of these is a cough medicine called bromhexine, which has been used in Europe, Asia and Latin America for decades. A randomized clinical trial in Iran found that addition of bromhexine to usual care at the time of hospitalization produced an 80% reduction in ICU admissions and the need for mechanical ventilation and reduced the death rate from 12% to zero[51].
- Researchers are looking at anti-androgen therapy for relieving severity of Covid-19. Two herbal extracts shown to decrease TMPRSS2 expression by inhibiting its activation through androgen signaling are baicalein (from the Chinese herb, Scutellaria baicalensis) and glycyrrhizin, the most active component of Chinese licorice. Both have additional anti-inflammatory and anti-viral effects.
- There are several natural inhibitors of IL-13. IL-13 plays an important role in asthma and allergies. It is secreted by several types of cells, including lymphocytes and mast cells. The high level of IL-13 in seriously ill patients with Covid-19 may be the result of the disease, but may also contribute to a heavy viral load by increasing levels of TMPRSS2. Foremost among these IL-13 inhibitors is the flavonoid luteolin, which we already met as an inhibitor of furin, and black cumin seed oil, an ancient health food used for medicinal and culinary purposes throughout the Middle East. The active ingredient in black cumin seed, thymoquinone, has demonstrated anti-inflammatory, anti-viral and anti-toxic properties and has a long history of safe human use. Both luteolin and black cumin seed oil have been proposed as treatments that might mitigate the symptoms of Covid-19.

In people who are sick with Covid-19, inflammation may create additional pathways through which the virus spreads from cell to cell. For acquiring the initial infection, however, the Front Four prevail.

PART 2. After Entry : the Role of NSP's (non structural proteins)

Once inside your cells, the corona virus takes over the normal cellular machinery to replicate itself. Its first act is to create a large complex poly-protein that rapidly splits itself into 16 smaller structures called non-structural proteins (nsp's) that function to evade your immune system, punch holes in your cells and enable the production of structural proteins. One of these, nsp-5, also known as the main protease or 3CL-protease, is essential for viral spreading because it acts like a scissor to break out 12 of the other nsp's. It works in tandem with nsp-3, also called papain-line protease, which releases two other segments of the poly-protein. Because 3-CL protease is so essential for viral growth, it's been called the "Achilles heel" of the corona virus family. In the laboratory, inhibition of 3CL-protease can totally block replication of SARS-CoV-2. Natural inhibitors are already known . They include:

- Shikonin, extracted from the Chinese and Korean herb Lithospermium erythrorhizon (red gromwell root)[52], which has several mechanism of antiviral activity against SARS-CoV-2[53]
- Andrographolides from the herb Andrographis paniculata, which has the ability to inhibit not only furin, but the coronavirus 3CL-protease and papain-like protease both[54] [55] [56] . Andrographis can potentially block Covid-19 entry at the cell membrane, limiting the initial viral load, and inhibit its activity inside your cells.
- Baicalein from Scutellaria baicalensis, which not only decreases synthesis of TMPRSS2, but can inhibit the corona virus 3CL protease.
- Polyphenols found in food, especially the flavonoids luteolin and quercetin. You've already met them both. Other flavonoids with potent 3CL protease inhibition in laboratory studies include herbacetin, which is primarily found in ground flax seed (not in flax seed oil but in the husk) and theaflavin gallates, which are abundant in black and puerh tea. Green tea and oolong tea were inactive in this study. Do not add milk to your tea, as milk interferes with theoflavin absorption.
- Elderberry fruit (Sambucus nigra)is a potent inhibitor of 3-CL protease in test tubes and in cells. Elderberry seems to be most effective if started before infection occurs. It may be contra-indicated in Phase Two of COVID-19, because of its immune boosting effects. Elderberries' 3CL protease inhibition is related to its content of flavonoids, especially those called anthocyanins, and its immune stimulating activity is related to its complex sugars (polysaccharides). (More about Elderbery, including a caution on its use, in THERAPEUTIC PROFILES.)

- Houttuynia cordata an herb that is widely used in traditional Chinese medicine. In addition to anti-microbial effects, it has also been shown to inhibit inflammation. It has generally served my symptomatic patients well.
- Melatonin
  Best known as a sleep-inducing hormone, melatonin has well-studied immune-boosting and anti-inflammatory effects, in addition to its potential for blocking 3-CL protease. Melatonin has been proposed for treatment and prevention of Covid-19. Its main side effect is drowsiness, which I find to be quite common among my patients. I restrict its use to patients who don't experience daytime lethargy when taking it.
- Zinc
  An essential mineral, zinc plays major roles in support of T-cell function and is frequently included in Covid-19 treatment protocols. In the test-tube, zinc has anti-viral effects, including inhibition of the coronavirus papain-like protease. I include zinc here for completeness, but a clinical trial of high dose zinc in outpatients with mild to moderate Covid-19 found no apparent benefits, when taken alone or combined with high doses of vitamin C[57]. I have concerns about the use of high dose zinc, which has been recommended by some physicians. I recommend zinc only for reversal of zinc deficiency (see THERAPEUTIC PROFILES).

- Probiotics. Spore-forming bacteria of the genus Bacillus produce at least 3 substances with the potential for inhibiting the Main Protease[58]. Bacillus species are part of a group of organisms normally found in soil that are being studied as human probiotics.

Another non-structural protein, nsp14, is also essential for replication of SARS-CoV-2 once it enters cells[59]. (Technically, it is called the nsp14-ExoN or nsp-14 endoribonuclease). Scientists are looking for ways to block the activity of nsp14-ExoN in order to curb Covid-19[60]. Definite inhibitors have not yet been demonstrated but baicalein, which also inhibits 3CL-protease, has emerged as a leading natural candidate, based on its molecular structure[61].

APPENDIX E. A QUICK DEEP DIVE WITH ACE2

The entry of SARS-CoV-2 into cells destroys the activity of its cellular receptor, ACE-2. Laboratory studies show that restoring ACE-2 dramatically reduces the severity of pneumonia in animals with many types of lung injury, infectious or toxic, including those infected with SARS CoV, a close relative of SARS-CoV-2. Administering ACE-2 intravenously or through ACE-2 secreting stem cells has been proposed as a treatment for people who are critically ill with Covid-19.

Many lifestyle factors influence ACE-2 activity in your body. Regular aerobic activity is good; high intensity interval training is even better. A whole foods diet rich in plant-based polyphenols is good. Herbs and spices like spearmint, sage, thyme, rosemary and oregano contain the polyphenol rosmarinic acid, which supports ACE-2 activity. High concentrations of fructose are bad. Avoid anything made with high fructose corn syrup; the fruit you eat should be flavonoid rich, like berries. The principles of an anti-inflammatory diet of the kind that supports ACE-2 activity are described in my book, The Fat Resistance Diet, written to help with weight loss but designed to combat inflammation for people with or without a weight problem.

I began advocating ACE-2 enhancement for protection against Covid-19 early in 2020, as soon as it became clear that ACE-2 is the cellular receptor for SARS-CoV-2. Confusion about the role of ACE-2 in Covid-19 created some pushback around my recommendations. The section below was written to eliminate the confusion. It's technical. You don't need to read it to understand the program, but it will help you cut through the misinformation that continues to seep into news media and press releases.

The most basic principle in biology is the balance of opposites: everything that happens triggers its opposite. Every stress response stimulates an anti-stress response. The road to inflammation creates a road back from inflammation. ACE-2 is part of that counter response. When the level of ACE-2 in cells goes up or the genes creating ACE-2 become more active, ACE-2 is responding to a stressor as part of the body's healing response. ACE-2 is also shed from the surface of cells and circulates in blood. When the rate of shedding is high, the levels of ACE2 on the cell surface go down.

Whether bound to cells or circulating in blood, ACE-2 is an enzyme that destroys two chemicals that play major roles in increasing severity of Covid-19: angiotensin-2 and desarg-9-bradykinin[62]. The names are not important. What is important is that people who are critically ill with Covid-19 have highly elevated levels of both these factors in their blood and in their lungs, because they have lost ACE-2 activity. When researchers state that ACE-2 levels are higher in certain states that increase the risk of Covid-19, they are missing the point. Elevated ACE-2 is not the cause of the risk, but the body's attempt to compensate for that risk. And elevated ACE-2 in blood may indicate loss of ACE-2 in cells.

In addition to breaking down substances that cause inflammation, blood clots, brain injury and circulatory problems, ACE-2 also produces a substance that on its own improves circulation, turns off inflammation, prevents blood clots, enhances healing, and protects the brain and the bone marrow. That substance is called angiotensin 1-7 (Ang 1-7).

Let's dive a little deeper. The cellular benefits of Ang 1-7 occur because Ang 1-7 activates a protein called the Mas Receptor. There are some substances that directly activate the Mas Receptor, by-passing ACE-2 and Ang 1-7. They are called "Mas Receptor agonists" (an agonist is the opposite of an antagonist) and they might compensate in part for loss of ACE-2. Two natural Mas Receptor agonists are widely used in traditional Chinese medicine: baicalein from Scutellaria baicalensis and Astragalus membranaceus (the active components are called Astragalus root polysaccharides).

For a more technical scientific profile of ACE-2, please view my presentation to the American Nutrition Association:
https://youtu.be/3hllO1dgUQA

APPENDIX F. THE GUT MICROBIOME IN COVID-19

Your body teems with microbes, tens of trillions of them. Collectively they are called the microbiome. They include bacteria, viruses, fungi, and –for most people in the world—worms and protozoa, like amebas. Bacteria have been the most studied; 99% of them are found in your large intestine. Because two-thirds of your lymphocytes make their home in the small intestine, there has been extensive investigation into the cross-talk between gut bacteria and immune function.

A lot's been published about the impact of gut bacteria on respiratory health[63] and on viral infections[64], so the early months of the pandemic saw considerable speculation about a link between gut microbes and Covid-19. Actual evidence began to emerge late in 2020. It derives from studies of patients in hospital and the numbers are small, but it presents a coherent picture.

First, people hospitalized with Covid-19 show profound changes in the bacterial microbiome as measured in stool specimens. Some of these changes may represent the impact of hospitalization, but there is a deeper connection. ACE2 has a special function in the small intestine. It acts as a chaperone for an enzyme that transports amino acids into the body. Damage to intestinal ACE2 creates amino acid deficiencies that impair gut immunity and barrier function[65], producing abnormalities in the microbiome (this state is called dysbiosis) and increased permeability of the intestinal lining (the so-called "leaky gut.")[66]. Intestinal leakiness in Covid-19 is associated with damage to the heart[67].

Covid-19 decreases diversity and richness of bacteria in the gut microbiome, with depletion of some beneficial species and overgrowth of others considered undesirable.[68] In contrast, Covid-19 increases the richness of yeasts and fungi in the gut (the mycobiome)[69]. The predominant fungal opportunists promoted by Covid-19 are the well-known yeast, Candida albicans, its scary cousin Candida auris (which has received global attention as an invasive drug-resistant species[70]), and the potent allergen, Aspergillus flavus. These organisms persist in stool even after respiratory symptoms have cleared and nose or throat swabs show no active viral infection.

To date, no one has studied the impact of fungi in Covid longhaulers, but I've been investigating, treating and teaching about yeast and fungal overgrowth for over 40 years and I've seen what they can do. Intestinal fungi can exert potent, often undesirable, effects on immunity, inflammation and metabolism that create symptoms in many body systems. Stool testing for bacteria and yeast should be considered in all people with persisting post-Covid symptoms.

Some researchers have attempted to correlate specific bacterial disturbances with severity of Covid-19. Two provocative findings have appeared. First, severity correlates with lower levels of a key anti-inflammatory species called Faecalibacterium prausnitzii. Loss of Faecalibacterium prausnitzii and its friends, the Bifidobacteria, persists for weeks after hospitalization, and correlates with increased severity of systemic inflammation[71] [72].

A study from the University of Massachusetts found that excessive growth of one species, Enterococcus faecalis, in fecal or oral specimens, was the best predictor of severe disease, more accurate than symptoms or underlying medical conditions[73]. The study's authors note that Enterococcus faecalis is a potent stimulator of inflammation. They believe it actively contributes to worse outcomes for people with Covid-19. Theirs is a reasonable theory, because the use of Enterococcus faecalis as a probiotic provokes the release of gamma-interferon[74], a major driver of the cytokine storm of severe Covid (mentioned above in IMMUNITY).

Possible support for the importance of the oral microbiome in Covid-19 comes from a study done in Bangladesh[75]. In a randomized controlled clinical trial, medical researchers told patients newly diagnosed with Covid 19, to use a povidone/iodine mouth wash (plus a nasal wash and eye drops) or use only warm water to flush their mouth, nose and eyes. The solutions were used every 4 hours for 4 weeks. Povidone iodine reduced the need for hospitalization and oxygen therapy by 84% and the death rate by 86%, compared to warm water. The researchers attributed the benefits to killing of the SARS-CoV-2 virus in the nose, mouth and throat, but by the time they were treated, these patients were already sick with Covid-19, making it likely that the infection was already systemic. Povidone/iodine kills bacteria as well as viruses and is quite effective at killing Enterococcus faecalis and other oral pathogens, so it is possible that eliminating pro-inflammatory bacteria from the mouth improved the outcome of disease in their patients.
So, here's the good news:

If an unbalanced microbiome creates sickness in people with Covid-19, restoring balance should lead to milder disease. Overgrowth of Enterococcus faecalis can be reversed. In addition to the use of an iodine-based gargle (which may only be needed once symptoms occur), there are several natural substances and dietary factors that can correct the specific microbiome imbalances described in Covid-19:

Resveratrol, a polyphenol that enhances activity of ACE2, inhibits the growth of Enterococcus faecalis[76] [77] and curcumin, another natural ACE2 enhancer, decreases bacterial virulence by breaking up biofilms that support the growth of Enterococcus faecalis[78] [79].

Ursolic acid is a dietary compound found in many fruits, vegetables, herbs and spices and is used as a muscle-building supplement by body builders. Ursolic acid has anti-inflammatory, anti-viral and cancer-fighting activity[80]. It also inhibits the growth of Enterococcus faecalis[81]. Dietary sources of ursolic acid include apple peel, cranberries, bilberries, blueberries, prunes, peppermint, rosemary, oregano, thyme, sage, and marjoram. Dried cranberries are an especially good source[82].. Human clinical trials of ursolic acid show anti-inflammatory effects at doses of 150 mg taken 1 to 3 times a day[83] [84]. Ursolic acid may also inhibit the SARS-CoV-2 Main Protease[85] [86] (The importance of this enzyme is described above in APPENDIX D).

Just as nutritional strategies can control colonization with the inflammatory organism Enterococcus faecalis, they can support growth of the anti-inflammatory Faecalibacterium prausnitzii, which is fed by fiber-rich foods[87], fiber supplements[88] [89], and certain prebiotics[90]. Daily consumption of chick peas[91] or of avocados[92] increases abundance of F prausnitzii in human volunteers.

Although probiotics based on F. prausnitzii do not exist, two commercial probiotics can increase its levels, according to human clinical trials. Bifidobacterium longum BB536 increases the growth of F. prausnitzii at the same time it relieves symptoms of pollen allergy in adults[93] or upper respiratory infection in young children[94]. Bacillus coagulans GBI-30, 6086 [GanedenBC(30)] was shown to increase growth of *F. prausnitzii* in men and women over the age of 65[95]. *Bacillus coagulans* pre-treatment also enhanced the effect of prebiotics in stimulating growth of *F. prausnitzii* in a clinical trial of older adults.[96]

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