LONG COVID: PREVENTION AND TREATMENT

Leo Galland, M.D.

TIER 1

As Covid-19 has gone from pandemic to endemic, Long Covid has become its major public health threat, impacting at least 400 million people globally. 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. An 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 lingering conspiracy theories and other sources of misinformation, we know a great deal about the causes of Long Covid. This is a condition that can be treated rationally and systematically in most cases.

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 more than 3 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. Because it can be hard to find health practitioners with expertise in treating Long Covid, the emphasis here is on self-care.

This document is presented in tiers of increasing detail.

Tier 1 is very basic and intended for patients whose symptoms include fatigue or brain-fog. The purpose of this tier is simply to give you enough information to understand what's happening to you, and thus determine the best next steps to take.

TIER 2: is a more detailed version of what's in Tier 1, with the science behind the information and guidance. This is intended for patients to share with doctors and caregivers. It is also for people who want a deeper dive into understanding their illness.

The Appendices contain dosages of the supplements described, as well as details on the scientific studies behind the information in the most granular level of information, which may be of greatest interest to researchers and physicians (and interested patients/caregivers, of course). The Appendices also contain more comprehensive information and resources for some specific post-Covid conditions that may create considerable disability: fatigue, post-exertional malaise, autonomic dysfunction, breathlessness, loss of smell and taste, and mast cell activation.

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 appendices.

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 main gateway is ACE2, a vital enzyme that is essential for health and recovery from illness. When the Covid virus attaches to ACE2 in your cells, it damagesACE2. Virtually all complications of acute Covid-19 can be traced to an ACE2 deficiency.

As the virus is destroyingACE2, it's also damaging your mitochondria, tiny powerhouses inside your cells that generate 90% of the energy you need to live. Even after a mild Covid infection, mitochondrial dysfunction 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. The 5-part plan below is designed to help you do this.

LONG COVID

It's not uncommon, after someone has recovered from any virus, to experience some lingering symptoms, which are medically labeled “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 essentially becomes a circulatory disease, because the virus has a high affinity for the cells that line your blood vessels.

In Tier 2, you will find The Web of Long Covid, a useful visual metaphor for understanding the complicated interrelationships of elements of Long Covid.

But here, in Tier 1, 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.

PREVENTION AND MITIGATION OF LONG COVID

Conventional treatments offered to people with Long Covid are basically designed to reduce *symptoms*. My goal is to help address the *causes* of Long Covid 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 6-part plan: Lifestyle, Nutrition, Eliminating Viral Persistence, Restoring Normal Circulation, Repairing Organ Damage, and Mental/Emotional Health.

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. I cannot emphasize

enough that thoughtful self-management is essential for recovery from Long Covid. In Tier 2, you will find more detailed guidance about the following:

Sleep : Sleep more than you think you need to, but do it on a regular schedule.

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.

Exercise: Exercise is essential for recovery, but for some people even small amounts of exercise makes them much worse for days or weeks. Be aware of how your body responds to ordinary levels of activity. To start with, try walking every day. 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. If exercise of any type is challenging, you should be tested for a condition called POTS (postural orthostatic tachycardia syndrome). 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 has a profound impact on ACE2 activity and on the outcome of Covid-19. A large-scale study at Johns Hopkins found that a 40% increase in vegetable consumption produced a 70% decrease in the likelihood of severe or moderately severe illness in people with acute 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**.

If you already eat the way I describe, there are three other dietary factors that might 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. This includes foods such as yogurt, sauerkraut and kimchi. Note: If fermented foods *aggravate* your symptoms, you may be intolerant of histamine (see below).

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. Note: if fasting makes your symptoms worse, you may have a disturbance in mitochondrial function**.**

3. A **low-histamine diet** may help to relieve symptoms in people with mast cell activation. (More on Mast Cell Activation in Tier 2,and a Low Histamine Diet in APPENDIX C).

SPICES AND HERBS can enhance ACE2 activity. The best studied are: ROSMARINIC ACID, found in rosemary, lemon balm, basil, sage, thyme, oregano, and spearmint, and 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. More information on each of these is available in Tier 2, with dosages in the Appendices.

Vitamin D
Curcumin
Resveratrol
Alpha Lipoic Acid
NAC (N-acetyl-cysteine)
Omega 3 fatty acids (EPA and DHA)

SUPPLEMENTS FOR MITOCHONDRIAL RESCUE

There are no drugs that directly enhance mitochondrial function, but there is a cocktail of supplements that have been shown to do so in the setting of acute Covid. It's called Mito Support. Details about this can be found in Tier 2 and the Appendices. The most useful single supplement for mitochondrial support is Coenzyme Q10, which has been shown to help post-covid fatigue.

3. ELIMINATING VIRAL PERSISTANCE

Researchers at Harvard and other centers have observed persistence of viral proteins in the blood of Long Covid patients. Persistence of these viral proteins is associated with chronic inflammation that drives many of the symptoms of Long Covid. These viral proteins may be

found in the lining of the GI tract and also in blood vessels, including vessels that supply blood to the brain. They are often hidden within microscopic blood clots.

VIRAL ERADICTION :

It's important to eradicate remnants of the virus from the gut, because whether they are infectious or not, these viral remnants cause inflammation. Viral eradication is a 2-step process.

The first step employs a combination of herbal anti-viral polyphenols, used together for 2-4 weeks. Dosage and more details are in Appendix A.

The second step requires the use of probiotics, sometimes combined with proteolytic enzymes. For Long Covid, the probiotics that have worked best at viral clearance are soil-derived organisms. See Tier 2 and Appendix **A** for more information.

3. RE-ESTABLISHING A HEALTHY GUT MICROBIOME:

(There's more information about this in APPENDIX F).

After finishing the anti-viral protocol, the next phase is establishing a healthy gut microbiome. This involves 6 components.

1. A high fiber, plant-based diet, emphasizing fermented foods and berries
2. Continuing Vitamin D and Resveratrol (dosages in Appendix)
3. The probiotic *Lactobacillus plantarum*, found in fermented plant-based food like sauerkraut
4. Prebiotics that support the growth of the probiotic.
5. Zinc
6. Reishi mushrooms

4. RESTORING NORMAL CIRCULATION BY ADDRESSING DAMAGED BLOOD VESSELS (MICROTHROMBOSIS AND ENDOTHELITIS)

As I mentioned above, Covid-19 is a disease of the circulatory system. It damages the lining of blood vessels (the endothelium) and creates microscopic blood clots (microthromboses). Microthromboses are very common with acute Covid-19, and often persist for weeks or months after recovery. Because microthrombosis is so closely tied to endothelitis (inflammation in the endothelium of blood vessels), I treat them together. In the immediate aftermath of acute Covid, ACE2 restoration and mitochondrial support (above) may be enough to reverse microthrombosis and endothelitis. But in people sick for more than 3 months, additional measures will be needed. See Tier 2 for more on this. This may include treating a problem called mast cell activation syndrome.

ADDRESSING MAST CELL ACTIVATION:

This is a very complex area, but extremely important for people who do not respond well to the measures I've already described. 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 autonomic nervous system dysfunction after Covid-19. There are specific steps that can alleviate MCAS (see APPENDIX C). For those people in whom MCAS is pivotal, it can contribute to microthrombosis, endothelitis, and immune impairment, so recognizing its presence and treating it directly is essential.

5. REPAIRING ORGAN DAMAGE

This is an area in which you will need help from a physician, usually a specialist. There are five 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, fatigue, and loss of taste and smell.

5. MENTAL AND EMOTIONAL HEALTH

The pandemic took a huge toll on our psyches. Isolation and fear created depression and anxiety. PTSD (post-traumatic stress disorder) has affected many Covid survivors, and the emotional trauma itself can hinder recovery. Coverage of the pandemic and especially of Long Covid by the media was part of the problem. Social media platforms and chat rooms proved to be two-edged swords. They could help overcome isolation, but they were – and remain – rife with bias, sensationalism, nihilism, conspiracy theories, and worst-case scenarios.

Through more than 50 years of medical practice, I've found that what people need most is a clear understanding of the problems they have, accurate information about what they can do to help themselves, and support in doing so from friends or family. Simply knowing that somebody is listening to you, hearing your story and caring about you 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 encourage 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. Researchers have already learned a lot about the science of Long Covid, and continue to search for causes and cures.

TIER 2:

In this section, you will find a more detailed version of Tier 1. In addition to including everything described in Tier 1, there is added depth and information. Tier 2 also introduces The Web of Long Covid. This is a visual metaphor that will help explain how all elements of both the illness and its treatment are interconnected.

As Covid-19 has gone from pandemic to endemic, Long Covid has become its major public health threat, impacting at least 400 million people globally. 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 lingering conspiracy theories and other sources of misinformation, we know a great deal about the causes of Long Covid. This is a condition that can be treated rationally and systematically in most cases. 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 more than 3 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 main 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 damages ACE2. Virtually all complications of acute 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 APPENDIX E (A Quick Deep Dive with ACE2) and APPENDIX D **(**Coronavirus Biology).

As the virus is destroying ACE2, it is also damaging your mitochondria, tiny powerhouses inside your cells that generate 90% of the energy you need to live. Mitochondria are so important for the body's recovery from Covid-19, that scientists at the University of Pennsylvania were able to improve the outcome of acute Covid-19 in laboratory animals by giving them a cocktail of nutrients that support mitochondrial function. Even after a mild Covid infection, mitochondrial dysfunction 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. The 5-part plan below is designed to do this.

LONG COVID

It's not uncommon, after someone has recovered from any virus, to experience some lingering symptoms, which are medically labeled “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 essentially becomes a circulatory disease, because the virus has a high affinity for the cells that line your 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 initially 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, and 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).

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.

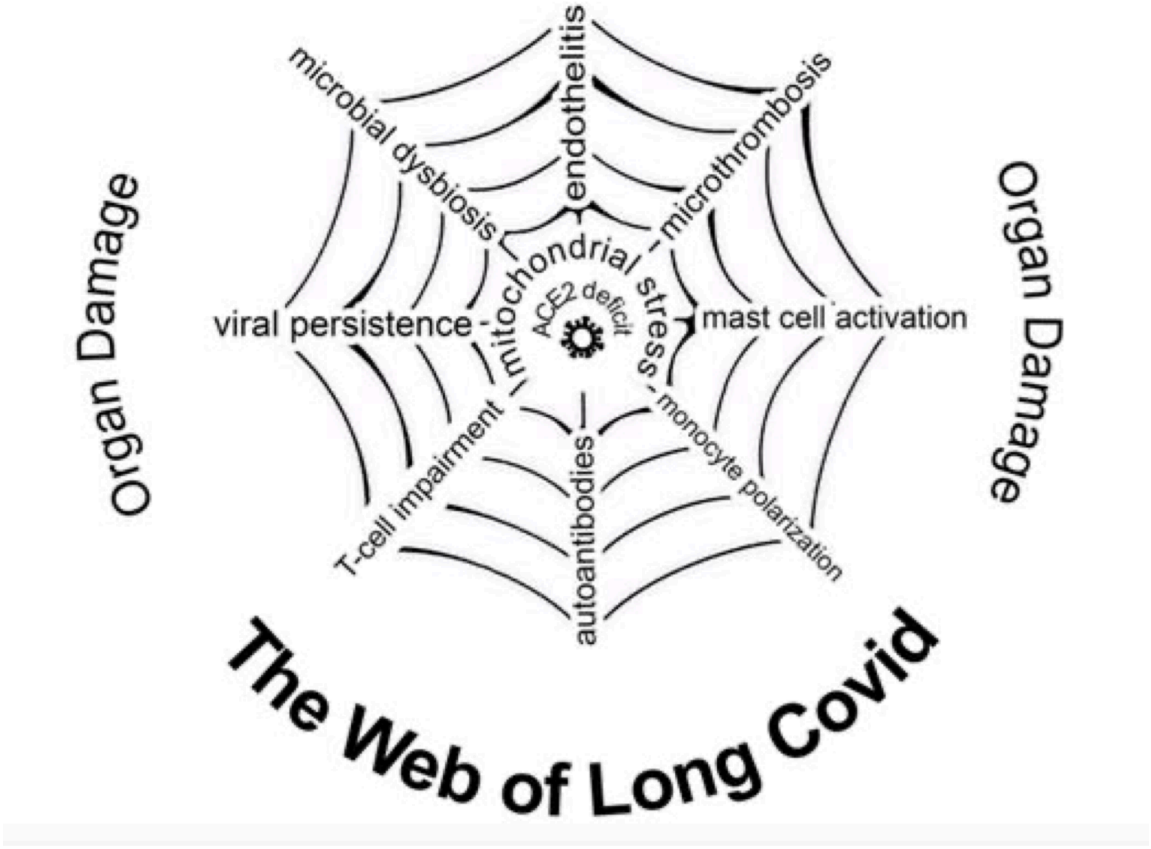
All the studies on Long Covid show that it occurs in 5-30% of people with mild to moderate infection. With each acute Covid infection, the probability that Long Covid will develop increases. Among people whom I’ve treated for Covid-19 from the start of their illness, the frequency of Long Covid has been under 1%. For people who already suffer from Long Covid, a more comprehensive program can help to cure it or relieve its effects. I believe that implementing the steps I recommend in this paper can help prevent and reverse the late complications of Covid-19, including Long Covid.

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 problems 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.

The next section describes the Web of Long Covid. Following this is a detailed section on Treatment and Mitigation of Long Covid, which appeared in Tier 1 in much simpler form.

THE WEB OF LONG COVID

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. Let's take a closer look at the 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** ***and*** **#D**: Mast cell activation is found in people whose systems are worsened by treatments that help others, or who become extremely sensitive to food or environmental conditions, or who develop migraine headaches, asthma, or apparent allergic reactions. This is such an important cause of prolonged, treatment-resistant Long Covid, that I have devoted an appendix to it. Here is a brief introduction.

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, and 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'm 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.

There are a number of approaches to control of mast cell activation that can be self-administered.

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. Monocytes play two critical roles in fighting Covid-19. First, they help your body attack the virus. Second, some monocytes leave the bloodstream and enter damaged tissues, where they change shape and become a new type of cell called a **macrophage**.

Macrophages play a critical role in cleaning up after infection. Failure of this clean-up function (the function is called “efferocytosis”) creates chronic inflammation and immune system dysregulation. The good news is that ACE2 plays an important role in helping monocytes attack viruses and then enter tissues and transition to the type of macrophages responsible for efferocytosis.

Polarization occurs when the normal cellular life cycle is disrupted, altering monocyte and macrophage function to create a disorganized immune response that favors chronic, unrelenting inflammation. You’ve probably read a lot about the chronic inflammation that creates Long Covid. Monocyte/ macrophage polarization plays a major role in maintaining that state of inflammation.

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.

But 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 autoantibodies, and the illness they create is an autoimmune disease. The mechanisms involved in autoantibody production are complex and there are many different kinds of autoantibodies produced during the course of Covid-19, some of them unique to Covid. Impairment of macrophage function is one mechanism that

results in auto-antibody production, so restoration of macrophage function through ACE2 enhancement should help diminish autoantibody production.

Furthermore, most of the Covid-induced autoantibodies only become active when there is inflammation and tissue damage. Decreasing inflammation is therefore the best protection against Covid-induced autoimmunity.

6. T-CELL IMPAIRMENT: T-lymphocytes are the generals of your immune system: the cells that coordinate all aspects of your immune response. 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 autoantibodies. Impairment of T-lymphocytes may also allow other viruses to make you sick. Most people over the age of 20 have been infected with a virus called Epstein-Barr Virus (EBV). Once infected with EBV, the virus remains in your body for the rest of your life, in a dormant state called "latency". T-cells keep the virus trapped in latency and T-cell impairment may allow EBV to become active, entering what is called the "lytic phase." There is no medication that will eradicate EBV from your cells, but restoring T-cell function pushes EBV back into latency.

Restoration of T-cell function is an essential component of healing from Long Covid. T-cells have an intense need for energy, and so their function can be significantly impacted by mitochondrial dysfunction.

7. VIRAL PERSISTENCE: For many people with Long Covid, 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 up to 2 years after the initial infection. In some studies, the virus appears to be actively growing, but most studies have demonstrated viral fragments that may be left over from the initial infection. There are no available tests for distinguishing between chronic infection with live SARS-CoV-2 and failure to clear the viral debris from a previous infection, so I have designed a protocol to deal with both possibilities. Most scientists who study viral persistence after Covid-19 believe the main

location of live virus or viral remnants 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.

Interview with the Microbiome Foundation:

https://microbiome-foundation.org/news/?lang=en

The gut and oral microbiome in Long Covid:

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

Here are the key facts:

(a) People who develop Long Covid had already lost important beneficial gut bacteria before they developed Long Covid.
(b) These same people also show an overgrowth of potentially harmful gut bacteria.
(c) Gut bacteria have several effects on your body that impact recovery from Covid-19:
-They affect activity of T-lymphocytes.
-They produce substances that are absorbed into your bloodstream and that may have beneficial or harmful effects on your organs, especially the brain.
-They affect the function of nerves in your intestinal tract and these nerves communicate directly with your brain.
-Gut bacteria may actually serve as a reservoir of SARS-CoV-2 virus or viral proteins.

If you develop gastrointestinal symptoms during or after Covid-19, gut microbial dysbiosis is a likely cause, but it can occur even when there are no gastrointestinal symptoms.

Restoring or creating a healthy gut microbiome is likely to be crucial for full recovery from Long Covid. It is so important that I have created an Appendix devoted to the gut microbiome and healing from Long Covid.

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 help you 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: Lifestyle, Nutrition, Eliminating Viral Presence, Repairing Organ Damage, and Mental/Emotional Health.

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. I cannot emphasize enough that thoughtful self-management is essential for recovery from Long Covid.

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, saffron (an extract of the spice) and CBD/CBN (extracted from Cannabis). Sleep has healing effects far beyond its impact on daytime energy. Research over the past decade reveals that during sleep the brain cleanses itself, washing away toxins that have accumulated during wakefulness through a set of recently discovered vessels called **glymphatics**. Covid-19 clogs glymphatics, interfering with this vital cleansing process. Sleep is important for its restoration. The duration of uninterrupted sleep has a significant impact on glymphatic function.

(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. This condition is called PEM (post-exertional malaise) or PESE (post-exertional symptom exacerbation). It is a major challenge for many people with Long Covid. I have seen many healthy young people who thought they were recovering from acute Covid-19 and attempted to return to their pre-Covid level of exercise too soon after the acute infection, and then crashed and did not recover.

Be aware of how your body responds to ordinary levels of activity. 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 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 (postural 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 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 acute 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 two 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 T-lymphocyte cells, the lymphocytes so important for solidifying your body's ability to fight this virus. Note: If fermented foods *aggravate* your symptoms, you may be intolerant of histamine (see below).

2. **Time-restricted eating (aka 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. If fasting aggravates your symptoms, especially fatigue or headache, do not attempt it. Intolerance of fasting might be a sign of mitochondrial dysfunction.

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.

SPICES AND HERBS can enhance ACE2 activity. The best studied are ROSMARINIC ACID, found in rosemary, lemon balm, basil, sage, thyme, oregano, and spearmint; and 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 has been shown to kill SARS-CoV-2 and its relative, Middle East Respiratory Syndrome (MERS) Virus. Resveratrol also directly enhances cellular ACE2 activity. Resveratrol has been shown to aid brain recovery after injury and to enhance immunity by stimulating T-lymphocyte function.

ALPHA LIPOIC ACID is an antioxidant that complements omega-3 fats, protects mitochondria, 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).

HORMONES:

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 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 directly enhance mitochondrial function, but there are supplements that have been shown to do so. As I mentioned, an earlier study done in mice showed a significant reduction in severity of Covid-19 and decreased inflammation, associated with improvement in mitochondrial function, when the cocktail below was given as a daily injection. The doses used can be found in Appendix A and are well within a dose range than can be taken by people.

Alpha-Lipoic acid
Coenzyme Q10
L-Arginine
Vitamin-B1/Thiamin
Vitamin-B2/Riboflavin
Vitamin-B7/Biotin
Vitamin-B9/Folic Acid
L-Carnitine
Creatine
Vitamin-B3/Niacin
Vitamin C
D-beta-hydroxybutyrate

3. THE SPOKES OF THE WEB: ELIMINATING VIRAL PERSISTANCE

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. If you are following the dietary practices described above and have

already taken steps to restore ACE2 function and support repair of mitochondria, then you will have gone a long way towards healing the gut. Whether or not you have gastrointestinal symptoms or continuing symptoms of Long Covid, re-establishing a healthy gut microbiome is really important for controlling inflammation and building a strong immune system.

Because the virus that causes Covid-19 infiltrates the lining of the GI tract, eradicating remnants of this virus from the gut is critical for re-establishing a healthy gut microbiome.

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.

VIRAL ERADICATION:

It's important to eradicate remnants of the virus from the gut, because, whether they are infectious or not, these viral remnants cause inflammation. This is a two-step process.

THE FIRST STEP employs a combination of natural antivirals, used together if possible for a period of 2 weeks. Dosage and more details are in the Appendix. A These include

1. Resveratrol. A study from Ohio State University found that patients with mild to moderate Covid-19 given resveratrol for 7 to 14 days were less likely to need emergency room care, hospitalization or to develop pneumonia.

2. A mixture of herbal polyphenols called Vedicinals-9, used for 14-28 days. Vedicinals-9 contains the bioflavonoids BAICALIN, QUERCETIN, LUTEOLIN, RUTIN, HESPERIDIN, CURCUMIN, EPIGALLOCATECHIN-GALLATE, plus PIPERINE (from black pepper, to enhance absorption) and GLYCYRRHIZIN (from licorice). In addition to anti-viral and anti-inflammatory effects, components of Vedicinals-9 help to heal the lining of the gastrointestinal tract and encourage the growth of a healthy gut microbiome.

THE SECOND STEP requires probiotics, specifically soil-derived bacteria, some of which, when tested in a placebo-controlled clinical trial of patients with Long Covid, were shown to significantly improve energy. Their specific function is viral eradication and healing the intestinal lining. They are not intended for long-term use; they are a prelude to the next phase.

RE-ESTABLISHING A HEALTHY GUT MICROBIOME :

After finishing the anti-viral protocol, the next phase is establishing a healthy microbiome that supports T-lymphocyte function and immune health. This involves 6 components:

1. **A high fiber, plant-based diet**, described above for restoring ACE2 activity, but now emphasizing fermented foods and berries consumed once or twice a day.

2. Continuing supplementation with **Vitamin D and Resveratrol**, but reduce the dose of resveratrol from its anti-viral level to a maintenance level of about 1200 mg/day.

3. A new probiotic, **Lactobacillus plantarum**, which is also found in fermented plant-based food like sauerkraut. A specific formula of Lactobacillus plantarum strains called AB21, has been shown to enhance anti-viral immunity and aid recovery from acute Covid 19

(https://www.ab21probiotic.com/;

study: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8757475/.

4. **Prebiotics that** support the growth of the probiotic. For most patients I recommend arabinogalactan or galactooligosaccharides, 1 teaspoon a day

5. **Zinc**, a mineral that is critical for healthy T-cell function. Zinc accumulates within T-cells and is released when needed for its antiviral effects. 30 mg/day may be advisable.

6. **Reishi mushrooms** (*Ganoderma lucidum*), which stimulates a balanced T-cell response and can control inflammation.

The protocol for establishing a healthy gut microbiome and supporting T-lymphocyte function can be continued indefinitely, as other components of the Web are addressed.

There's more information in APPENDIX F (The Gut Microbiome and Covid-19).

AUTO-ANTIBODY PRODUCTION:

The best defense against auto-antibody production is establishment of well-balanced T-lymphocyte activity. Other modes of treatment would need to be discussed 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 *and* #D:

This is a very complex area, which becomes extremely important for people who do not respond well to the measures I've already described. 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 autonomic nervous system dysfunction 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 antithrombotic activity and can also heal the lining of blood vessels.

Other 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 *Monostromanitidum*. 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 five specific areas in which self-care makes all the difference, so I've included discussions of them in APPENDIX B ***O *and* #16**: POTS; brain fog; unexplained breathlessness; fatigue (including PEM); 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 was part of the problem. Social media platforms and chat rooms proved to be two-edged swords. They could help overcome isolation, but they were – and remain – rife with bias, sensationalism, nihilism, and worst-case scenarios.

Through more than 50 years of medical practice, I've found that what people need most is a clear understanding of the problems they have, accurate information about what they can do to help themselves, and support in doing so from friends or family. Simply knowing that somebody is listening to you, hearing your story, and caring about you 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. Researchers have already learned a lot about the science of Long Covid and continue to search for causes and cures.

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 glycinate 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**, **usually 600-800 mg at one time.** 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). For people whose sleep is interrupted, a dose of theanine or theanine + GABA may help falling back to sleep. Should not be taken less than 4 hours before intended wake-up.

-**CBD** (Cannabidiol, from hemp seed). **Safe doses are under 150 mg/day**, 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.

Saffron extract: in my practice I use **Optimized Saffron from Life Extension, 2 pills taken at about 9 PM**. Controlled scientific studies have shown that saffron extracts improve sleep quality and decrease symptoms of anxiety and depression.

Magnolia Bark and **Ashwagandha**. Magnolia bark is a component of many traditional Chinese herbal formulas; Ashwagandha is a mainstay of Ayurvedic medicine. **Cortisol Manager**, a product that combines the two, at a dose of 1 capsule at bedtime has helped some of my patients improve sleep maintenance.

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 lipothiamine,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) 20mg twice a day**, and combined with **ubiquinone(a form of CoQ10) 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: 500 mg 3 times a day. This has been tested in a clinical trial, along with NAD+. (available over the Internet as Mitopure).

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.

As I mentioned earlier, a study done in mice at the University of Pennsylvania showed a significant reduction in severity of Covid-19 and decreased inflammation, associated with improvement in mitochondrial function, when the cocktail below was given as a daily injection. The doses used in mice were low enough, and the components well absorbed orally, that this formula is readily adapted for human use. There are so many ingredients, however, that I asked David Restrepo, RPh, who owns **VitaHealth Apothecary** in New York City (212-628-1110), to create a version of the product that would be convenient for people, and affordable. The product, a flavored powder, is called **Mito Support**.

Here's a link to the study:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC11287122/

If you are unable to obtain the VitaHealth product, but want to replicate the formula, the following will supply a daily dose of its ingredients:

Alpha-Lipoic acid 300 mg/day

Coenzyme Q10 200 mg/day

L-Arginine (an amino acid that improves blood flow) 800 mg/day

Vitamin-B1/Thiamine 100 mg/day

Vitamin-B2/Riboflavin 100 mg/day

Vitamin-B7/Biotin 5 mg/day

Vitamin-B9/Folic Acid 800 mcg/day

L-Carnitine 500 mg/day

Creatine 1000 mg/day

Vitamin-B3/Niacinamide 300mg/day

Vitamin-C 500 mg/day

D-Betahydroxybutyrate, a ketogenic fatty acid, 2500 mg/day (1 teaspoon x2 a day). This can be ordered online. The product used in the study was KetoneAid KE4.
https://www.amazon.com/KetoneAid-Worlds-Strongest-Exogenous-Caffeine/dp/B07PSP3ZJS

Please note: I have no financial interest in any of these products.

DOSING FOR VIRAL ERADICATION AND MICROBIOME SUPPORT *13 *and* #L

Tundrex1: The probiotic strain *Bacillus subtitlis B-7092,* is available in the U.S. 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 aday** (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 typically is taken for 10 to 15 days. I have used *Bacillus subtilis* B-7092 for about 10 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 can be ordered from. https://vedicinalsusa.com/.

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 pliers.

https://drive.google.com/file/d/152MvPrc-IWJYBuNEYt4BdmRQwSowXZBC/view?usp=sharing

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. Taken as directed on the bottle, Vedicinals-9 will supply a daily dose of the bioflavonoids BAICALIN (352mg), QUERCETIN (100mg), LUTEOLIN (200mg,) RUTIN (736mg), HESPERIDIN (667mg), CURCUMIN (1052mg), and EPIGALLOCATECHIN-GALLATE (EGCG) (889mg). Vedicinals-9 also contains PIPERINE (15mg) from black pepper, to enhance absorption, and GLYCYRRHIZIN (505mg), from Chinese licorice, as well as honey.

Baicalein, curcumin, quercetin, and gylcyrrhizin have been demonstrated to have anti-viral activity against SARS-CoV-2, and curcumin was shown to improve the outcome of Covid-19 in hospitalized patients. 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 - take at a dose of 300-600 mg 3 times a day), curcumin (500 – 1000 mg/day) or the Chinese herb *Scutellariabaicalensis* (the dose would depend on the formulation taken). Many of these ingredients have additional benefits in healing the lining of the gastrointestinal tract and helping to foster a healthier gut microbiome.

Resveratrol, a polyphenol, is a third anti-viral component, which you have already met because of its ability to restore ACE2 activity. Resveratrol was shown to speed recovery from acute Covid-19 in a double blind placebo-control trial. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9243086.

The dose used, 1000 mg 4 times a day, was calculated based on the concentration of resveratrol that kills the MERS virus, a relative of the SARS-CoV2 virus, and the amount of resveratrol the average adult would need to take to achieve that level in blood. Resveratrol would be used at that high dose for 7-14 days and taken with food.

The fourth step in viral eradication and microbiome support requires the use of a combination of probiotics and enzymes that were tested in a placebo-controlled clinical trial of patients with Long Covid and shown to improve energy: Immunoseb (the enzyme mixture) and BiomeUltra (a mixture of soil-derived organisms). I usually have patients start this after they finish Tundrex.

Study: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8472462/

To buy: https://www.amazon.com/ImmunoSEB-caps-Biome-Ultra-ProbioSEB/dp/B08WG1CL5L

The dose is 2 Immunoseb and 1 BiomeUltra taken with a full glass of water on an empty stomach twice a day for at least 14 days.

The mechanism of action of these products has not been identified, but the enzymes present in Immunoseb may break down viral debris and the microbes in BiomeUltra may pave the way for restoring a healthy gut microbiome.

Once the process of viral eradication and microbiome support is complete, it is time to focus on T-lymphocyte enhancement and restoring normal circulation.

SUPPLEMENTS FOR ENHANCEMENT OF T-LYMPHOCYTES

Lactobacilli, especially **Lactobacillus plantarum**, which as a probiotic supplement is best taken at the start of a meal. One product, **Probio7-AB21**, was shown to speed recovery from acute Covid-19. The dose would be 1 capsule twice a day This product needs to be ordered from https://probio7.com/.

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 gut include **galactooligosaccharides** and **arabinogalactan.**

The dose needed is **2000-5000 mg/day, taken on an empty stomach**.

Galactoligosaccharides: This can be ordered from Bimuno: **https://www.bimuno.com/about-bimuno.list)**

Black Raspberry Concentrate, 1 tablespoon daily, was shown to enhance T-lymphocyte activity by increasing synthesis of butyrate by gut bacteria. To purchase: Berrihealth.com. 888-761-8407; contact: Linda

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

GingkoBiloba: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). It is also available as a tincture.

- 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 (an extract of periwinkle): **typically 20-30 mg twice a day** when used in human clinical trials.

- 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).

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**.

For many people, the program described will help to restore them to their pre-Covid health. For those who do not get that benefit, there are specific problems that are addressed in Appendices B and C.

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

SPECIAL TOPICS

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 shows 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 specific 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-19," 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 bubbles 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 fisetin 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.

Famotidine (brand name **Pepcid**) is a drug available over the counter for treatment of heartburn. It has been used at higher than usual doses for the treatment of acute Covid-19 and was shown to help post-Covid brain fog in a controlled clinical study. The dose used was 40 mg twice a day, and the effect took about a month.

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, and if asthma or other lung problems have been ruled out by your doctor, 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 at sea level 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; 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-exertional malaise (**PEM**). PEM is a hallmark of Chronic Fatigue Syndrome, also known as MyalgicEncephalomyelitis (**CFS/ME**).

My experience with PEM in Long Covid patients has led me to the conclusion that it is the result of impaired circulation and mitochondrial dysfunction working together. Focus on treatments for endothelitis/microthrombosis and mitochondrial support for several weeks before trying any form of exercise and read the section on PEM below.

If you cannot improve your exercise intolerance with gradual conditioning, ACE2 enhancement, improvement in blood flow and mitochondrial support, there are 2 conditions to look into:

(1) **POTS, postural orthostatic tachycardia syndrome** (more information about this below)

(2) **Small fiber neuropathy**. Dr Ann Louise Oaklander of Harvard Medical School 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, **Postural 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. https://www.hopkinsmedicine.org/health/conditions-and-diseases/postural-orthostatic-tachycardia-syndrome-pots#:~:text=Hyperadrenergic%20POTS%20is%20a%20term,levels%20of%20blood%20(hypovolemia).

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 frequency of mast cell activation among Long Covid patients with POTS. If you suffer from POTS as a manifestation of Long Covid, 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.

Iron deficiency, even when mild, may aggravate POTS by creating a loss of red blood cell volume. Ask your doctor to test you for it by measuring ferritin and transferrin saturation.

POST-COVID FATIGUE AND POST-EXERTIONAL MALAISE

Fatigue is the most common symptom of people with Long Covid. It has many potential causes. If your fatigue is not associated with shortness of breath, POTS or nutritional deficiency, if it has persisted despite mitochondrial support, viral eradication and treatment of endothelitis and microthrombosis, there are 3 causes of fatigue to consider:

(1) **LACTIC ACID**

Lactic acid is created when your body uses carbohydrate for fuel. The main carbohydrate fuel is glucose, the sugar that circulates in your blood. A 10 step process converts glucose to pyruvic acid (pyruvate), the immediate precursor of lactic acid. Pyruvate undergoes 2 fates: some of it is converted to a substance called acetyl-CoA and enters mitochondria to begin the process by which mitochondria burn fuel for energy (more about acetyl-CoA later). The remainder is converted to lactic acid. *When formation of pyruvate exceeds the ability of mitochondria to use it, lactic acid is formed in excess and may accumulate in tissues*. Accumulating in tissues, lactic acid can create an excessively acid environment, which damages cell function, especially in the brain. But lactic acid is not simply a waste product. Mitochondria can take up lactic acid and when they do so, the mitochondrial metabolism of lactic acid creates intense mitochondrial oxidative stress, impairing mitochondrial function.

There are at least 4 ways to decrease lactic acid accumulation:

(a) Pace activity levels, as we've already discussed.
(b) Decrease consumption of sugar and starch, which limits the conversion of glucose to lactic acid.
(c) Stimulate the conversion of pyruvate to acetyl-CoA with the following supplements: L-carnitine, about 500 mg once or twice a day; alpha lipoic acid, 300 mg twice a day; vitamin B1(thiamine), 100 mg a day, and vitamin B2, (riboflavin) 100 mg/day.

(d) Take a probiotic that converts lactic acid to short chain fatty acids, which rapidly enter mitochondria and are burned for fuel quickly and efficiently. The probiotic shown to do this and tested in a clinical trial is V-nella (a strain of the bacterium *Veillonella*, that is normally found in the gut microbiome.) Information about V-nella can be found at https://fitbiomics.com/products/vnella-lactic-acid-metabolizer-for-fatigue-endura

nce?s I've been recommending this probiotic since its release during the summer of 2024 and have seen positive effects in Long Covid patients with severe fatigue.

(2)IMPAIRED FAT METABOLISM

Several researchers are finding that people with Long Covid do not efficiently burn fat for fuel and instead are forced to rely on carbohydrates for energy. Burning fat for fuel is a multistep process. Most fat, whether in tissues or circulating in blood, occurs in a form called triglycerides. The first step in breaking this fat down is conversion of triglycerides to its components, called fatty acids. Circulating fatty acids ("free fatty acids" or FFAs) are taken up by mitochondria, through a transport process that utilizes carnitine, and are then converted to acetyl-CoA by a process called fatty acid-beta oxidation.

This acetyl-CoA, just like the acetyl-CoA derived from pyruvate, enters a process called the Krebs cycle, which is an essential component of mitochondrial energy production. When you fast, about 70% of your body's energy production comes from fatty acid beta-oxidation, because the availability of glucose as a fuel is limited. The virus that causes Covid-19 can directly interfere with fatty acid beta-oxidation, at least in a test-tube. When this happens, not only do mitochondria function poorly, but free fatty acids can accumulate in blood, and these may be toxic, contributing to metabolic dysregulation.

The best treatment for this disturbance is likely to be a very low fat diet and supplementation with carnitine. The popular diet that comes closest to what is need for a disorder of fatty acid beta-oxidation is the Dean Ornish diet, which supplies 10% of calories from fat. It has been tested extensively in adults (I do not recommend it for children or adolescents) and its safety and potential benefits for prevention of heart attacks, cancer and Alzheimer's disease are established. [https://www.ornish.com/zine/smart-approach-vegetarian-diet/].

In summary, there are at least two potential dietary approaches to dealing with Post-Covid Fatigue when it is resistant to everything else you've tried:

- **A low-carbohydrate diet to reduce lactic acid, or**
- **A low-fat diet to reduce free fatty acids**.

If you do not have access to testing that can determine your metabolic needs, you need to explore both approaches to determine which approach works best for you.

NOTE: For some people, post-covid fatigue is a manifestation of mast cell activation, a condition that imposes its own specific dietary requirements. Treatment of this condition is described in detail in Appendix C.

(2) FATIGUE AND YOUR BRAIN

Several researchers have discovered that the source of fatigue for some Long Covid patients is their brain, not their muscles. There is hypersensitivity of brain regions that sense fatigability, either because of poor circulation or inflammation impacting those areas. Even when oxygen in your blood is normal, poor circulation and inflammation can deprive brain cells of oxygen. Lack of oxygen is medically called hypoxia. This is challenging to deal with on your own and may explain why medications like antidepressants can help Long Covid fatigue. If they help, it does not mean that you're just depressed. When they help, it is because they address a fundamental physiologic disturbance in brain function created by Covid-19.

A study done with the antidepressant drug Trintellix (Vortioxetine, a drug that increases serotonin in nerve endings) found a significant treatment improvement in cognitive function with the drug, but only in those Long covid patients who should elelvation of C-reactive protein (CRP), a marker of inflammation. In other words, the benefits of this antidepressant only occurred in the presence of inflammation. One important and treatable effect of hypoxia is reduced brain synthesis of creatine. Ordinarily associated with muscle function (95% of the body's creatine is stored in muscle), creatine plays an important role in brain function, which I explain below. In a randomized, placebo-controlled clinical

trial, creatine supplementation (8 grams/day as creatine monohydrate) was given to patients with Long Covid for 8 weeks. Creatine yielded a significant improvement in mental concentration, shortness of breath, headache, general malaise and body aches, which was associated with an increased concentration of creatine in two key brain regions detected on brain scans Other clinical trials of creatine supplementation for fatigue and cognitive function have used doses that range from 4 grams once a day to 5 grams 4 times a day.

BACKGROUND: CREATINE AND YOUR BRAIN. Creatine is made in your body from three amino acids: arginine, glycine, and methionine. Almost all creatine (95%) is stored in muscle as creatine phosphate, where it plays an essential role in maintaining the level of ATP, which is the immediate source of energy for virtually all cellular activity. Creatine phosphate plays the same critical role in your brain, especially when there is high metabolic demand due to sleep deprivation, stress or disease. Creatine phosphate generates ATP at a much faster rate than any other source, which is why it is so important for muscle and brain activity. Brain function depends on the connections between nerve endings, which are called synapses. Efficient synaptic activity requires rapid synthesis of ATP at the synaptic membrane, and neuronal

creatine phosphate is ideal for that purpose. Mitochondria, which supply over 90% of your body's total ATP, are too slow and too distant from nerve endings to support rapid synaptic activity. Under normal conditions, your brain makes all the creatine it needs, but if blood flow or oxygen is reduced, synthesis of creatine drops. Under those conditions, oral creatine supplementation can raise brain creatine concentration, improving cellular function, cognitive performance and brain health. Sleep deprivation aggravates stress-induced brain creatine deficiency. Creatine supplementation attenuates the impairment of executive function created by sleep deprivation and by lack of oxygen. Levels of creatine supplementation shown to be effective in human clinical trials range from about 4 grams to 20 grams a day (the latter is usually taken as 5 grams 4 times a day).

https://pmc.ncbi.nlm.nih.gov/articles/PMC8912287/ Forbes et al. Effects of Creatine Supplementation on Brain

Function and Health. Nutrients. 2022 Feb 22;14(5):921. doi: 10.3390/nu14050921. PMID: 35267907; PMCID:

PMC8912287.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6795258/. Turner et al. Creatine supplementation enhances

corticomotor excitability and cognitive performance during oxygen deprivation. J Neurosci. 2015 Jan

28;35(4):1773-80. doi: 10.1523/JNEUROSCI.3113-14.2015. PMID: 25632150; PMCID: PMC6795258.

ADDITIONAL IDEAS:

-Inflammation in the brain may be improved with a treatment called low dose naltrexone (LDN), which has shown benefit in the treatment of CFS/ME. You will need a physician and a compounding pharmacy to get this treatment. Here is one website with more information about it: https://ldnresearchtrust.org/what-is-low-dose-naltrexone-ldn.

-Circulation in the brain may be helped by a supplement called **PQQ**, or a medication called pentoxyphylline, which is presently being studied for treatment of Long Covid. They direct blood flow to the parts of the brain that need it.

PQQ: Two studies[1] have shown that PQQ 20 mg/day improves blood flow to the pre-frontal cortex, an area of the brain most impacted by Covid-19. In a study from Japan, PQQ specifically improved blood flow and oxygen delivery to an area called the right prefrontal cortex, which is where most of the post-covid brain hypoxia occurs[2].

Pentoxyphylline has been shown to improve blood flow to hypoxic regions of the brain. An herbal product called **vinpocetin** (derived from periwinkle) may do the same.

Pentoxyphylline is also anti-inflammatory (it blocks an inflammatory chemical called TNFalpha), enhances mitochondrial biogenesis (the creation of new mitochondria), decreases the abnormal stiffness of red blood cells that may occur with CFS or Long Covid, improves cardiac function, and inhibits the type of blood clotting that occurs because of inflammation. The effects of pentoxyphylline appear to be enhanced by vitamin E and the natural product resveratrol.

POST-EXERTIONAL MALAISE (PEM)

---

1 Itoh Y, Hine K, Miura H, Uetake T, Nakano M, Takemura N, Sakatani K. Effect of the Antioxidant Supplement Pyrroloquinoline Quinone Disodium Salt (BioPQQ™) on Cognitive Functions. Adv Exp Med Biol. 2016;876:319-325. doi: 10.1007/978-1-4939-3023-4_40. PMID: 26782228.

Nakano M, Murayama Y, Hu L, Ikemoto K, Uetake T, Sakatani K. Effects of Antioxidant Supplements (BioPQQ™) on Cerebral Blood Flow and Oxygen Metabolism in the Prefrontal Cortex. Adv Exp Med Biol. 2016;923:215-222. doi: 10.1007/978-3-319-38810-6_29. PMID: 27526146.]

Zhu BQ, Simonis U, Cecchini G, Zhou HZ, Li L, Teerlink JR, Karliner JS. Comparison of pyrroloquinoline quinone and/or metoprolol on myocardial infarct size and mitochondrial damage in a rat model of ischemia/reperfusion injury. J Cardiovasc PharmacolTher. 2006 Jun;11(2):119-28. doi: 10.1177/1074248406288757. PMID: 16891289.

Zhu BQ, Zhou HZ, Teerlink JR, Karliner JS. Pyrroloquinoline quinone (PQQ) decreases myocardial infarct size and improves cardiac function in rat models of ischemia and ischemia/reperfusion. Cardiovasc Drugs Ther. 2004 Nov;18(6):421-31. doi: 10.1007/s10557-004-6219-x. PMID: 15770429.

Tamakoshi M, Suzuki T, Nishihara E, Nakamura S, Ikemoto K. Pyrroloquinoline quinone disodium salt improves brain function in both younger and older adults. Food Funct. 2023 Mar 6;14(5):2496-2501. doi: 10.1039/d2fo01515c. PMID: 36807425.

Shiojima Y, Takahashi M, Takahashi R, Moriyama H, Bagchi D, Bagchi M, Akanuma M. Effect of Dietary Pyrroloquinoline Quinone Disodium Salt on Cognitive Function in Healthy Volunteers: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study. J Am Nutr Assoc. 2022 Nov-Dec;41(8):796-809. doi: 10.1080/07315724.2021.1962770. Epub 2021 Aug 20. Erratum in: J Am Nutr Assoc. 2022 Aug 2;:1. PMID: 34415830.

2

Post-exertional malaise, also called Post-Exertional Symptom Exacerbation (PESE) is probably the most disabling long-term complication of Covid-19; it is without a doubt the hardest to treat and the most controversial. The term PEM does not adequately describe this disorder. For many people, post-exertional agony is a more accurate name. As I said before, I've been treating patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) since 1982 and I find that the intensity of PEM and its impact on activities of daily living is much greater with Long Covid than I'd seen in the years before this pandemic. There are no established theories that adequately explain PEM, although the build-up of lactic acid or free fatty acids resulting from mitochondrial dysfunction (described above) is likely a part of the problem.

Because circulatory impairment is a cornerstone of Covid-19 and has been shown to persist in patients with Long Covid, I've researched the impact of impaired circulation on mitochondrial function and discovered something unique: *when mitochondria are compelled to supply energy but their blood supply is diminished, some of their essential enzymes actually run backward, creating toxic by-products.*

Here's my take. It's very technical and may be hard to follow, but it leads to concrete steps intended for people whose PEM has not been relieved by anything else.

First, the difference between fatigue and PEM (also called PESE, post-exertional symptom exacerbation)

- Fatigue limits your ability to perform physical or mental tasks.
- With PEM/PESE, performing those tasks and exceeding some limit, which varies greatly from person to person, will produce an increase in fatigue, pain or other symptoms that has its onset **after** stopping the activity to rest. The interval between finishing activity and the increase in symptoms may vary from a few minutes to as long as 24-48 hours.
    - Severity of PESE is often but not always proportional to the degree to which the exertion that provoked it exceeds your usual capacity for activity.
    - Duration of PESE is typically 2 days or longer and can be over 2 months.

There are no established theories as to the mechanisms of PESE, but the mechanism with which I am presently working is a concept called **ischemia-reperfusion**.

- *Ischemia* means lack of blood flow. It leads to hypoxia, diminished availability of oxygen in the tissues affected.
- Once the impairment of blood flow or the episode of hypoxia, clears, the return of normal oxygen levels can actually create more damage, which is known as *reperfusion injury*.
- Ischemia-reperfusion has been primarily studied in heart attacks and strokes. The initial injury with heart attacks and most strokes is ischemia, a blockage that creates lack of blood flow and therefore lack of oxygen delivery to specific tissues. This causes some damage, but much, even most, of the damage occurs with reperfusion, as blood flows back into the damaged area.

Here is my theory of how the concept of ischemia-reperfusion applies to PEM/PESE:

- With Long Covid, there can be mild, chronic ischemia of many tissues, especially muscle and brain, the result of inflammation that impacts the lining of blood vessels. This circulatory impairment has been well documented in Long Covid but may also occur in longstanding cases of CFS/ME.
- Physical or mental exertion activates cells being used in muscle or brain, increasing demand for oxygen and creating relative hypoxia (decreased oxygen tension) of the cells being activated. Then, with rest, the oxygen tension returns to normal, which simulates the effects of reperfusion.

Research on ischemia-reperfusion traces reperfusion injury to free radical damage and the source of free radicals to mitochondria.

There are several mechanisms through which ischemia-reperfusion interferes with normal mitochondrial function. The one that is embraced by this protocol is the observation that hypoxia actually causes some mitochondrial enzymes to run backwards, reversing their usual pattern of activity. This creates a build-up of metabolites that create free radicals (called reactive oxygen species or excited states of oxygen) during reperfusion.

The fulcrum of this disturbance is an enzyme called SDH/RC2 (succinate dehydrogenase/ respiratory complex 2), which is part of the Krebs cycle. Reverse activity of SDH creates an excess of succinate (an acid that increases inflammation) and also depletes cells of ubiquinol, the anti-oxidant form of Coenzyme Q10.

Laboratory experiments have shown that blocking the activity of SDH during hypoxia can prevent reperfusion injury. The protocol below is designed to inhibit SDH during exertion, and then to calm down hyperactive mitochondria during reperfusion.

PESE/PEM PROTOCOL

Before activity, whether it is exercise, mental work or stressful activities of daily living, take **oxaloacetate 500 mg** and **chrysin 1000 mg**.

Oxaloacetate is an important organic acid that shuttles through the Krebs cycle, of which SDH is part. Chrysin is a bioflavonoid found in many vegetables, fruits and herbs. Both oxaloacetate and chrysin inhibit SDH, and at the same time have a number of separate metabolic benefits, so they are not metabolic poisons; they have a specific short-lived function in this protocol.

Oxaloacetate is available via https://oxaloacetatecfs.com/

Chrysin can be ordered from Amazon as MRM Chrysin 500 mg #30 caps

They can be taken at **4-hour intervals** depending upon duration of activity and can be taken daily. There may be additional benefit from taking **ubiquinol** prior to exertion, in the form of **MitoQ10 (10-20 mg)**.

Following exertion (when resting, either at the end of the day or after a specific period of activity), take the following:

- **PQQ** (pyrolloquinoline quinine), which functions as a mitochondrial anti-oxidant, supports SDH activity, and has been shown to protect against ischemia-reperfusion injury. PQQ is naturally found in many vegetables and some fruits. A supplement of PQQ should contain 20-40 mg. Fresh PQQ can also be obtained (although at much lower dosage) through a green juice (recipe below).
- a Chinese herbal extract called **She Chuang Zi** (Cnidium fruit, available as a liquid from Hawaii Pharm), use 5 ml in water

- 4-8 ounces of **hydrogen water[3].** One source is Researched Nutritionals H2 Absorb, one tablet dissolved in the water. Another source of hydrogen water is available in cans from https://h2forlife.com/. You can also purchase a device that allows you to make your own hydrogen water: https://ionbottles.com/pages/our-technology

PQQ, She Chuan Zi, and hydrogen water have been shown to calm down hyperexcited mitochondria and prevent reperfusion damage.

Alpha-ketoglutarate (300 mg), another important substrate of the Krebs cycle, can help to restore mitochondrial function and reduce inflammation, once normal function of SDH has been established.

Red light therapy (near infrared and infrared primarily) may also be useful at calming mitochondria during reperfusion. The wavelengths matter. The ideal wavelengths for calming mitochondrial hyperactivity are 660 and 960 nm. An intermediate wavelength (810 nm) actually stimulates mitochondrial hyperactivity. Two commercial lamps that can be used for this effect are:

HOOGAHEALTH (intended for home use)
HG1000
https://hoogahealth.com/products/hooga-1000w-red-and-near-infrared-light-therapy-panel?mibextid=Zxz2cZ
HG 1500
https://hoogahealth.com/products/hg1500-red-light-therapy-device

MITO-RED LIGHT (intended for commercial use)
9319 N 94th Way #400

---

[3]
- Monocytes from asthmatic patients and lungs of ovalbumin-sensitized and challenged mice showed increased production of lactate and increased activity of glycolytic enzymes with decreased activity of mitochondrial complexes 1 and 3 and decreased production of ATP. Hydrogen-rich saline infusions reversed these changes in sensitized mice, but had no effect on control mice. Niu et al. Hydrogen Attenuates Allergic Inflammation by Reversing Energy Metabolic Pathway Switch. Sci Rep. 2020

- Hydrogen water protects against ischemic-reperfusion injury in laboratory models. Li et al. Metabolomics Analysis of the Effect of Hydrogen-Rich Water on Myocardial Ischemia-Reperfusion Injury in Rats. J BioenergBiomembr. 2020. Wu et al. Protective effects of hydrogen rich water on the intestinal ischemia/reperfusion injury due to intestinal intussusception in a rat model. Med Gas Res. 2017. Botek et al. Hydrogen Rich Water Consumption Positively Affects Muscle Performance, Lactate Response, and Alleviates Delayed Onset of Muscle Soreness After Resistance Training. J Strength Cond Res. 2022

- For untrained adults, drinking hydrogen water before exercise improves performance and VO2 max. Mikami et al. Drinking hydrogen water enhances endurance and relieves psychometric fatigue: a randomized, double-blind, placebo-controlled study [1]. Can J PhysiolPharmacol. 2019.

Scottsdale, AZ 85258
+1 866-861-6486
www.mitoredlight.com
Use settings 7 and 9

Sit in front of the light for 20-30 minutes after any significant exertion. If you are primarily impacted by cognitive effort rather than physical effort, you can select cheaper versions of these products that emit light for your head only, not your entire body. Infrared and near infrared light penetrate into the body (including the skull) to a depth of several inches.

This PEM protocol is a work in progress. If there is evidence of inflammation of blood vessels or microscopic blood clots, those need to be treated in addition.

Green Juice: High in Pyrroloquinoline Quinone (PQQ) (courtesy of James Sporandeo)

Juice and blend the following:

1 Green Apple
1 Kiwi Fruit
½ Lemon
1 Inch Piece of Fresh Ginger
¼ Head of Romaine Lettuce
¼ of a Peeled Cucumber
2 Ribs (Spears) of Celery
2 Spears of Asparagus
¼ Cup of Packed Parsley
¼ Cup of Red or Green kale
¼ Cup of Spinach

A NOTE ABOUT EPSTEIN-BARR VIRUS (EBV) AND POST-COVID FATIGUE

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 Long Covid 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 T lymphocyte impairment on antibody levels. **If you've been told you have active EBV as a consequence of Covid-19, please read the section 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 EBV proteins (called antigens), specifically the VCA (viral capsid 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 T 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 probably be restoring T-lymphocyte function, not on killing EBV.

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 smell. 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 flavors 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.

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[4]. Swelling is associated with viral invasion of a group of cells that surround and support the olfactory nerve[5]. They're called sustentacular cells. Swelling in this area can damage the olfactory nerve in 2 ways: (1) There may be inflammatory chemicals (cytokines) released by the sustentacular 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[6], possibly in combination with gamma-linolenic acid (GLA), which is found in evening primrose and borage seed oils[7].

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 *parosmia*. Parosmia may be associated with functional changes in the smell and taste centers of the brain[8]. 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

---

[4]https://www.medscape.com/viewarticle/933347?src=mkm_covid_update_200706_mscpedit_&uac=372244BT&impID=2448946&faf=1

[5]https://theconversation.com/coronavirus-scientists-uncover-why-some-people-lose-their-sense-of-smell-138898

[6]Memeo A, Loiero M. Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: a randomized, double-blind, comparative study. Clin Drug Investig. 2008;28(8):495-500. doi:10.2165/00044011-200828080-00004
https://pubmed.ncbi.nlm.nih.gov/18598095/

[7] Ranieri M, Sciuscio M, Cortese AM, et al. The use of alpha-lipoic acid (ALA), gamma linolenic acid (GLA) and rehabilitation in the treatment of back pain: effect on health-related quality of life. Int J ImmunopatholPharmacol. 2009;22(3 Suppl):45-50. doi:10.1177/03946320090220S309
https://pubmed.ncbi.nlm.nih.gov/19887043/

[8]https://www.medscape.com/viewarticle/944608?src=wnl_edit_tpal&uac=372244BT&impID=3156628&faf=1

intermittent neurological symptoms[9]. In the case of parosmia, training through aroma therapy may enhance recovery by supporting a phenomenon called neuroplasticity[10]. It is possible that other approaches to supporting the recovery of nerves may speed recovery of taste and smell.

[9]https://www.wsj.com/articles/damaged-sense-of-smell-in-covid-patients-holds-clues-to-how-recovery-might-work-11606140319

[10]https://www.webmd.com/lung/news/20201201/smell-training-might-speed-the-senses-return-after-covid?src=RSS_PUBLIC

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:

https://www.amazon.com/Never-Bet-Against-Occam-Activation/dp/0997319615/ref=sr_1_1?qid=1673826997&refinements=p_27%3ALawrence+B.+Afrin+M.D.&s=books&sr=1-1

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), and 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, light-headedness, 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, 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. For some people with POTS (link to above discussion on POTS), the use of antihistamines has been shown to slow the heart rate and relieve symptoms of orthostatic intolerance.**

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. As mentioned above, a placebo-controlled trial found that famotidine at a dose of 40 mg twice a day for a month improved mood and cognitive function in patients with Long Covid.

Anti-histamines and famotidine are first-line treatments for mast cell activation and a related condition called histamine intolerance.

NOTE: Histamine Intolerance is a separate syndrome, which may be related to MCAS.

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 below), which eliminates foods that contain histamine, liberate histamine from intestinal cells or block the activity of DAO.

Therapeutic steps I have found very helpful for my patients with histamine intolerance are:

- taking DAO as an enzyme with meals,

- correcting copper deficiency if it is present

- using specific probiotic bacteria that break down histamine rather than secreting it.

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

There is a very dense book called *Understanding Histamine Intolerance and Mast Cell Activation* by Mariska de Wild Schoten, with more detailed dietary advice.
https://www.amazon.com/Understanding-Histamine-Intolerance-Mast-Activation/dp/1481283669?dib=eyJ2IjoiMSJ9.9chssTRvdv47VhyQp0syz6omen5xjKhKYeLxPQqBZl8.SlzfpEHU4yzZCcL1pfS2B99VrnZ1T24n2KWNq7eMGy8&dib_tag=se&qid=1733168082&refinements=p_27%3AMariska+de+Wild-Scholten&s=books&sr=1-1

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.

Proteolytic enzymes like tryptase and carboxypeptidase

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 chromogranin A (a mast cell mediator), plasma levels of histamine and prostaglandin D2 and 24 hour urine for prostaglandin D2, leukotriene E4 and 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 drug 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, but only one treatment should be started at a time. 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. **However, 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), loratadine (Clariten), desloratadine(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[11]. 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.

---

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

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.

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.

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.

a. **Quercetin**, a bioflavonoid that occurs naturally in numerous fruits and vegetables, like apples and onions. High doses may be needed, as much as 2000 milligrams a day.
b. **Pycnogenol**, an extract of the bark of the French maritime pine tree, prevents mast cell activation and histamine release
c. **Luteolin**, a bioflavonoid found in parsley and numerous herbs, like perilla leaves, which has significant anti-inflammatory and mast cell inhibition.

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[12].

SARS-CoV-2 is almost identical to a corona virus that has inhabited bats for about 80years, 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, 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

[12] https://phys.org/news/2021-08-mutation-covid-virus-percent-higher.html

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, hurtling at a speed of up to 200 miles/hour and then coasting on turbulent airflow[13]. 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[14], 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[15]. A study from Wuhan found aerosolized SARS-CoV-2 in medical staff areas and unventilated bathrooms[16]. In the cold, stale air of a meat processing plant, the virus was able to infect people 26 feet away from its source[17].

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

[13] https://jamanetwork.com/journals/jama/fullarticle/2763852

Turbulent Gas Clouds and Respiratory Pathogen EmissionsPotential Implications for Reducing Transmission of COVID-19. Lydia Bourouiba, PhD[1] **JAMA.** 2020;323(18):1837-1838. doi:10.1001/jama.2020.4756

[14] https://www.pnas.org/content/early/2020/05/12/2006874117.long

The airbornelifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission. Stadnytskyi V[1], Bax CE[2], Bax A[3], Anfinrud P[3]. Proc Natl Acad Sci U S A. 2020 May 13. pii: 202006874. doi: 10.1073/pnas.2006874117.

[15] Stability and infectivity of coronaviruses in inanimate environments. Shi-Yan Ren, Wen-Biao Wang, Ya-Guang Hao, Hao-Ran Zhang, Zhi-Chao Wang, Ye-Lin Chen, and Rong-Ding Gao. World J Clin Cases. 2020 Apr 26; 8(8): 1391–1399. Published online 2020 Apr 26. doi: 10.12998/wjcc.v8.i8.1391PMCID: PMC7190947. PMID: 32368532

[16] Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Liu, Y. et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature https://doi.org/10.1038/s41586-020-2271-3 (2020)

[17] https://www.bloomberg.com/news/articles/2020-07-23/virus-can-jump-26-feet-at-cold-meat-plants-filled-with-stale-air

that the droplets remain smaller and lighter[18]. 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%[19]. 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[20]. The Delta variant required 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[21]. 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

[18] https://www.webmd.com/lung/news/20200708/air-conditioning-may-be-spreading-covid?ecd=wnl_spr_070820&ctr=wnl-spr-070820_nsl-LeadModule_cta&mb=Fj%40IeljkIwD8MMMwWGmG2a6Btkq86oGPjyPO8eteE2Y%3d

[19] https://www.forbes.com/sites/leahbinder/2020/12/24/scientists-say-this-one-move-could-beat-back-the-covid-19-surge-if-people-only-knew-about-it/?sh=592a246c6c49

[20] https://jkms.org/DOIx.php?id=10.3346/jkms.2020.35.e415

[21] https://www.nationalgeographic.com/science/2020/10/why-people-are-coronavirus-superspreaders-how-body-emits-infectious-particles/

suspended in saliva within 7 minutes; on a dry surface it takes twice as long[22]. 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[23] 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

Airborne virus will settle on solid surfaces and air vents, and remain viable on these surfaces for varying periods of time[24]. 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

---

[22] Shanna Ratnesar-Shumate, Gregory Williams, Brian Green, Melissa Krause, Brian Holland, Stewart Wood, Jordan Bohannon, Jeremy Boydston, Denise Freeburger, Idris Hooper, Katie Beck, John Yeager, Louis A Altamura, Jennifer Biryukov, Jason Yolitz, Michael Schuit, Victoria Wahl, Michael Hevey, Paul Dabisch, Simulated Sunlight Rapidly Inactivates SARS-CoV-2 on Surfaces, *The Journal of Infectious Diseases*, Volume 222, Issue 2, 15 July 2020, Pages 214–222, https://doi.org/10.1093/infdis/jiaa274https://watermark.silverchair.com/jiaa274.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAApMwggKPBgkqhkiG9w0BBwagggKAMIICfAIBADCCAnUGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQM1FfP53zlRhuIsAMcAgEQgIICRpFzcKUx4pIu3UcXTFp9mK1iwqw5rMpY-dNB8qQNY7DOTy67I1vkWP7cooK-8AYKDPSm9nSljKlQjqMroX25rI2dV3Y3EwdITr_mpc9gk5LSDQk8HWrkBJjZo7ISBAod79Dfk-OhXpOSuq-akbVTptuGhxJJYqgvG213bMYvIDqUdPLmwoHxxmSW7S19LfF4EP6I8RlqT9Ss23neMIEgMTc0v8kyMdquf2KrDI4dSneZ8CaPTgSoBXw4Xx8oRyuH2905a-VWEXV7GVwBdzhHfd0-8_ecoXvpEVkdm5JfXAvtIWDGgJH2jNbcoyQDlJlaAMOQlrRPfy-k7gQQyTqTruvpWjX1l3nm2H3ZR3qVJCCPlwbILKn1BWb_8e_4gPOu-e-NYFdq0z7Hx86KGAF04q230SHjVkXda1qN29M0ABLYl4N-xe7nHATGZZsI397jCNI25XwSQxsAKUTzXUUJU0VQkjRLBBNm7NOdgOHlrsVV-tpoofunbjZWCrWCfbCgEORvGk2QC_OimQPwkmZKsWRFM35juNrfuf-wj2IJIizJp2Rns7oztG5svwshw4-eRr8b1ShZXt1E1sVZfET3JVB4nUfnIW0eh6hlrZQSitlLfNDf6WsXgqV4X1OZVYQ7d6dEQ7-l3q3z2CaNoxVNsJKLCFRbeiIwlmKFYkWJvtgdSGblEso0LVG6-ifyflmKbIvDbnbRSNsrHtHl73KAFdWbFYl37S8NSLhVKoB9b_CCKe1IwyLnwoQGoi_xoUIUnSwXws56zA

[23]https://www.forbes.com/sites/karenrobinsonjacobs/2020/07/25/how-20-lifeguards-got-coronavirus-experts-say-gatherings-among-family-friends-spread-the-virus/#76a6b6b53963

[24] Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. Ong SWX[1], Tan YK[2], Chia PY[1], Lee TH[1], Ng OT[1], Wong MSY[2], Marimuthu K[1]. JAMA.2020 Mar 4. doi: 10.1001/jama.2020.3227.

train who had no contact with the infected person.[25]. The major determinants of risk on trains were proximity to the infected person and duration of travel together. During the initial stages of the pandemic, 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.

SARS-CoV-2 can attach to cells of the small and large intestines[26], 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[27][28][29][30].

---

[25]Maogui Hu, Hui Lin, Jinfeng Wang, Chengdong Xu, Andrew J Tatem, Bin Meng, Xin Zhang, Yifeng Liu, Pengda Wang, Guizhen Wu, Haiyong Xie, Shengjie Lai, The risk of COVID-19 transmission in train passengers: an epidemiological and modelling study, *Clinical Infectious Diseases*, , ciaa1057, https://doi.org/10.1093/cid/ciaa1057

https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa1057/5877944

[26]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095230/ Covid-19 and the digestive system. Wong SH, Lui RN, Sung JJ. J Gastroenterol Hepatol. 2020 May;35(5):744-748. doi: 10.1111/jgh.15047. Epub 2020 Apr 19. PMID: 32215956

[27] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7048229/

Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, Wang YY, Xiao GF, Yan B, Shi ZL, Zhou P. Emerg Microbes Infect. 2020 Feb 17;9(1):386-389. doi: 10.1080/22221751.2020.1729071. eCollection 2020. PMID: 32065057

[28] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7158584/

Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Lancet Gastroenterol Hepatol. 2020 May;5(5):434-435. doi: 10.1016/S2468-1253(20)30083-2. Epub 2020 Mar 20. PMID: 32199469

[29]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7172436/

COVID-19 Disease With Positive Fecal and Negative Pharyngeal and Sputum Viral Tests. Chen L, Lou J, Bai Y, Wang M. Am J Gastroenterol. 2020 May;115(5):790. doi: 10.14309/ajg.0000000000000610. PMID:32205644

[30]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095102/

Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. Xu Y, Li X, Zhu B, Liang H, Fang C, Gong Y, Guo Q, Sun X, Zhao D, Shen J, Zhang H, Liu H, Xia H, Tang J,

A small study demonstrated that when found in stool, the virus is not only viable but infectious.[31] Food-borne or water-borne infection is possible but still unproven[323334].

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 most 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, ACE2,** and **TMPRSS2.** *Treatments that*

Zhang K, Gong S. Nat Med. 2020 Apr;26(4):502-505. doi: 10.1038/s41591-020-0817-4. Epub 2020 Mar 13. PMID:32284613

[31]https://wwwnc.cdc.gov/eid/article/26/8/20-0681_article?deliveryName=USCDC_333-DM28664

[32]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7130008/

Enteric involvement of coronaviruses: is faecal-oral transmission of SARS-CoV-2 possible? Yeo C, Kaushal S, Yeo D. Lancet Gastroenterol Hepatol. 2020 Apr;5(4):335-337. doi: 10.1016/S2468-1253(20)30048-0. Epub 2020 Feb 20. PMID: 32087098

[33]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095230/

COVID-19: faecal-oral transmission? Hindson J. Nat Rev Gastroenterol Hepatol. 2020 May;17(5):259. doi: 10.1038/s41575-020-0295-

[34]https://www.ncbi.nlm.nih.gov/pubmed/32418307
Persistent viral shedding of SARS-CoV-2 in faeces - a rapid review. Gupta S, Parker J, Smits S, Underwood J, Dolwani S. Colorectal Dis. 2020 May 17. doi: 10.1111/codi.15138. [Epub ahead of print] PMID: 32418307

target each of these already exist and may prevent or limit viral entry and the damage it creates.

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[35]. Heparan holds the virus in place[36] so that the next substance, furin, can do its job.

Step 2. Furin, like heparan, coats all human cells[37], 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, ACE2, the way a key fits into a lock[38]. 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).**This relationship enabled the pandemic, because it dramatically enhances the speed with which the virus enters human cells.***

[35]SARS-CoV-2 Infection Depends on Cellular Heparan Sulfate and ACE2. Thomas Mandel Clausen etal. bioRxiv 2020.07.14.201616; doi: https://doi.org/10.1101/2020.07.14.201616

[36] Characterization of heparin and severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) spike glycoprotein binding interactions So YoungKim, et al. Antiviral Research 181 (2020) 104873

[37]Vidricaire G, Denault JB, Leduc R (1993) Characterization of a secreted form

of human furinendoprotease. BiochemBiophys Res Commun 195:

1011 – 1018

[38]Anwarul Hasan, Bilal Ahamad Paray, Arif Hussain, Fikry Ali Qadir, Farnoosh Attar, Falah Mohammad Aziz, Majid Sharifi, Hossein Derakhshankhah, Behnam Rasti, Masoumeh Mehrabi, KooroshShahpasand, Ali Akbar Saboury& Mojtaba Falahati(2020)A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin,Journal of Biomolecular Structure and Dynamics,DOI: 10.1080/07391102.2020.1754293

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**[39]. 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 studies.

Step *3. ACE2,* *a p*rotein 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, ACE2 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 ACE2 in their membranes. This discovery has created a great deal of confusion about the role of ACE2 in Covid-19. During the first few months of the pandemic, ACE2 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 ACE2 in their cells. This idea has been proved totally wrong. It's based on a superficial understanding of the complexity of ACE2 and its multifaceted role healing.

[39] Wu C, Yang Y, Liu Y, Zhang P, Wang Y, Wang Q, Xu Y, Li M, Zheng M, Chen L et al (2020b) Furin, a potential therapeutic target for COVID-19. chinaRxiv https://doi.org/10.12074/202002.00062

ACE2 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 ACE2 to enter cells, the protein loses its enzyme activity. *ACE2 is the victim not the cause of Covid-19 and loss of ACE2 underlies most of 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 ACE2. 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 ACE2 and the receptor binding domain of the viral spike protein[40]. 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[41]. 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 ACE2, is an enzyme imbedded in human cell membranes. Like ACE2, it is only found in certain types of cells. As the viral spike protein locks into ACE2, TMPRSS2 cuts a wedge out of both, destroying the beneficial activity of ACE2 and freeing the virus to fuse with the cell membrane. *The cells that the virus can*

[40] https://www.news-medical.net/news/20201123/Compounds-in-traditional-Chinese-medicine-herbs-may-inhibit-SARS-CoV-2-infection.aspx

[41] https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3682517

enter most quickly and efficiently are those few cell types which express both ACE2 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 ACE2, because TMPRSS2 speeds the rate of cell entry about one-hundred fold. Depending on the type of cell, inhibition of TMPRSS2 can reduce 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[42]. 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[43], 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[44].

Asthma is also a major risk factor for severe Covid-19 among children[45]. [Other studies have shown that asthmatics are *less* likely to develop Covid-19. I believe that is due to

---

[42] Kimura H, Francisco D, Conway M, et al. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. J Allergy Clin Immunol. 2020;146(1):80-88.e8. doi:10.1016/j.jaci.2020.05.004 https://pubmed.ncbi.nlm.nih.gov/32422146/

[43] https://www.jacionline.org/action/showPdf?pii=S0091-6749%2820%2931136-2

[44] https://www.nature.com/articles/s41598-020-77791-8

[45] https://www.medscape.com/viewarticle/945402

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[46].
- 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 signalling are baicalein (from the Chinese herb,*Scutellariabaicalensis)* 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.

As newer variants of the virus have emerged, some appear to be less dependent upon furin or TMPRSS2 for rapid cellular entry than were the early strains. As scientists learn more about how this virus enters tissues like the brain that do not express much ACE2, it is clear that other molecules on the cell surface can facilitate viral entry. In people who are sick with Covid-19, inflammation may create additional pathways through which the virus spreads from cell to cell.

[46]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7502909/

One gateway for viral entry into the brain is neuropilin-1 (NRP1). In some cells, NRP1 binds the spike protein after it has been cleaved by furin and then holds it in place so the RBD can attach to ACE2. In other cells, NRP1 may allow viral entry without a need for ACE2.

Whatever the new developments, infection for infection of the respiratory tract, the GI tract and blood vessels, the Front Four still 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 scissors 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. The drug Paxlovid works through inhibition of 3CL-protease.Natural inhibitors are already known . They include:

- **Shikonin**
  Extracted from the Chinese and Korean herb *Lithospermiumerythrorhizon*(red gromwell root)[47], which has several mechanism of antiviral activity against SARS-CoV-2[48]
- **Andrographolides**

[47]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7598899/

[48]Oh KK, Adnan M. Revealing Potential Bioactive Compounds and Mechanisms of *Lithospermum erythrorhizon* against COVID-19 via Network Pharmacology Study. Curr Issues Mol Biol. 2022 Apr 19;44(5):1788-1809. doi: 10.3390/cimb44050123. PMID: 35678652; PMCID: PMC9164027.

From the herb *Andrographis paniculata*, which has the ability to inhibit not only furin, but the coronavirus 3CL-protease and papain-like protease both[49][50][51] . *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 *Scutellariabaicalensis*, 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. In addition to its many anti-inflammatory effects, quercetin also blocks binding of the spike protein to NRP1.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 theaflavinabsorption.
- **Elderberry fruit (*Sambucus nigra*)**
  A potent inhibitor of 3-CL protease in test tubes and in cells,elderberry seems to be most effective if started before infection occurs. 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).
  Houttuynia cordata
  An herb 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

[49] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7212536/

[50] https://www.sciencedirect.com/science/article/pii/S0006291X20316831

[51] https://www.researchsquare.com/article/rs-35800/v1

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[52]. 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 or for improving T-lymphocyte function during recovery from Covid-19.
- **Probiotics**
  Spore-forming bacteria of the genus *Bacillus* produce at least 3 substances with the potential for inhibiting the Main Protease[53]. *Bacillus* species are part of a group of organisms normally found in soil that are being studied as human probiotics.

Another non-structural protein, nsp-14,is also essential for replication of SARS-CoV-2 once it enters cells[54]. (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[55]. 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[56].

---

[52] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776305

[53] Alam S, Sadiqi S, Sabir M, Nisa S, Ahmad S, Abbasi SW. *Bacillus* species; a potential source of anti-SARS-CoV-2 main protease inhibitors. J Biomol Struct Dyn. 2021 Jan 15:1-11. doi: 10.1080/07391102.2021.1873188. Epub ahead of print. PMID: 33446058; PMCID: PMC7814571. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7814571/

[54] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7654266/

[55] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7452913/

[56] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7476502/

APPENDIX E: A QUICK DEEP DIVE WITH ACE2

The entry of SARS-CoV-2 into cells destroys the activity of its main cellular receptor, ACE2. Laboratory studies show that restoring ACE2 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 ACE2 intravenously or through ACE2 secreting stem cells has been proposed as a treatment for people who are critically ill with Covid-19.

Many lifestyle factors influence ACE2 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 ACE2 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 ACE2 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 ACE2 enhancement for protection against Covid-19 early in 2020, as soon as it became clear that ACE2 is the cellular receptor for SARS-CoV-2. Confusion about the role of ACE2 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 I found it interesting.

The most basic principle in biology is the balance of opposites: everything triggers its opposite. Every stress response stimulates an anti-stress response. The road to inflammation creates a road back from inflammation. ACE2 is part of that counter response. When the level of ACE2 in cells goes up, or the genes creating ACE2 become more active, ACE2 is responding to a stressor

as part of the body's healing response. ACE2 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, the enzyme ACE2 destroys two chemicals that play major roles in increasing severity of Covid-19: angiotensin-2 and desarg-9-bradykinin[57]. 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 ACE2 activity. When researchers state that ACE2 levels are higher in certain states that increase the risk of Covid-19, they are missing the point. Elevated ACE2 is not the cause of the risk, but the body's attempt to compensate for that risk. And elevated ACE2 in blood may indicate loss of ACE2 in cells.

In addition to breaking down substances that cause inflammation, blood clots, brain injury, and circulatory problems, ACE2 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 ACE2 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 ACE2. Two natural Mas Receptor agonists are widely used in traditional Chinese medicine: **baicalein** from *Scutellariabaicalensis*and *Astragalusmembranaceus*(the active components are called **Astragalus root polysaccharides**).

For a more technical scientific profile of ACE2, please view my presentation to the American Nutrition Association:
https://youtu.be/3hllO1dgUQA

[57]Mahmudpour M, Roozbeh J, Keshavarz M, Farrokhi S, Nabipour I. COVID-19 cytokine storm: The anger of inflammation. Cytokine. 2020;133:155151. doi:10.1016/j.cyto.2020.155151
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260598/

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 amoebas. 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 has been published about the impact of gut bacteria on respiratory health[58] and on viral infections[59], 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[60], producing abnormalities in the microbiome (this state is called *dysbiosis*) and increased permeability of the intestinal lining (the so-called "leaky gut.")[61]. Intestinal leakiness in Covid-19 is associated with damage to the heart[62].

Covid-19 decreases diversity and richness of bacteria in the gut microbiome, with depletion of some beneficial species and overgrowth of others considered undesirable.[63]And at the same

---

[58]Zhang D, Li S, Wang N, Tan HY, Zhang Z, Feng Y. The Cross-Talk Between Gut Microbiota and Lungs in Common Lung Diseases. *Front Microbiol*. 2020;11:301. Published 2020 Feb 25. doi:10.3389/fmicb.2020.00301

[59]Li N, Ma WT, Pang M, Fan QL, Hua JL. The Commensal Microbiota and Viral Infection: A Comprehensive Review. *Front Immunol*. 2019;10:1551. Published 2019 Jul 4. doi:10.3389/fimmu.2019.01551

[60] Viana SD, Nunes S, Reis F. ACE2 imbalance as a key player for the poor outcomes in COVID-19 patients with age-related comorbidities - Role of gut microbiota dysbiosis. Ageing Res Rev. 2020 Sep;62:101123. doi: 10.1016/j.arr.2020.101123. Epub 2020 Jul 16. PMID: 32683039; PMCID: PMC7365123.

[61] Camargo SMR, Vuille-Dit-Bille RN, Meier CF, Verrey F. ACE2 and gut amino acid transport. Clin Sci (Lond). 2020 Nov 13;134(21):2823-2833. doi: 10.1042/CS20200477. PMID: 33140827.

[62]. Hoel H et al. Elevated markers of gut leakage and inflammasome activation in COVID-19 patients with cardiac involvement J Intern Med 2020 Sep 25. doi: 10.1111/joim.13178.

[63]Gu S, Chen Y, Wu Z, Chen Y, Gao H, Lv L, Guo F, Zhang X, Luo R, Huang C, Lu H, Zheng B, Zhang J, Yan R, Zhang H, Jiang H, Xu Q, Guo J, Gong Y, Tang L, Li L. Alterations of the Gut Microbiota in Patients with

time, it *increases* the richness of yeasts and fungi in the gut (the mycobiome)[64]. 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[65]), 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. A study from Boston found that fragments of fungal cell walls are often found circulating in the blood of people with Long Covid, although that research has not been confirmed by other groups.

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 reduced levels of a key anti-inflammatory species called *Faecalibacteriumprausnitzii.* Loss of

COVID-19 or H1N1 Influenza. Clin Infect Dis. 2020 Jun 4:ciaa709. doi: 10.1093/cid/ciaa709. Epub ahead of print. PMID: 32497191; PMCID: PMC7314193.

[64]Zuo T, Zhan H, Zhang F, et al. Alterations in Fecal Fungal Microbiome of Patients With COVID-19 During Time of Hospitalization until Discharge. *Gastroenterology*. 2020;159(4):1302-1310.e5. doi:10.1053/j.gastro.2020.06.048

[65] Lone SA, Ahmad A. Candida auris-the growing menace to global health. Mycoses. 2019 Aug;62(8):620-637. doi: 10.1111/myc.12904. Epub 2019 Jun 18. PMID: 30773703.

*Faecalibacteriumprausnitzii*and its friends, the Bifidobacteria, persists for weeks after hospitalization, and correlates with increased severity of systemic inflammation[6667].

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[68]. 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[69], 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[70]. 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

---

[66] Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, Zhan H, Wan Y, Chung A, Cheung CP, Chen N, Lai CKC, Chen Z, Tso EYK, Fung KSC, Chan V, Ling L, Joynt G, Hui DSC, Chan FKL, Chan PKS, Ng SC, Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization, Gastroenterology (2020), doi: https://doi.org/10.1053/j.gastro.2020.05.048.

[67] Yeoh YK, Zuo T, Lui GC-Y, et al. Gut Epub ahead of print: [please include Day Month Year]. doi:10.1136/ gutjnl-2020-323020….. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19

[68]https://www.medrxiv.org/content/10.1101/2021.01.05.20249061v1.full.pdf

[69] Molina MA, Díaz AM, Hesse C, Ginter W, Gentilini MV, Nuñez GG, Canellada AM, Sparwasser T, Berod L, Castro MS, Manghi MA. Immunostimulatory Effects Triggered by Enterococcus faecalis CECT7121 Probiotic Strain Involve Activation of Dendritic Cells and Interferon-Gamma Production. PLoS One. 2015 May 15;10(5):e0127262. doi: 10.1371/journal.pone.0127262. PMID: 25978357; PMCID: PMC4433276. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7814571/

[70] Effect of 1% Povidone Iodine Mouthwash/Gargle, Nasal and Eye Drop in COVID-19 patient. Bioresearch Communications, Volume 7, Issue 1, January 2021Md. Iqbal Mahmud Choudhury1, NilufarShabnam2, Tazin Ahsan3, Md. Saiful kabir4,

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*[71][72] and **curcumin**, another natural ACE2 enhancer, decreases bacterial virulence by breaking up biofilms that support the growth of *Enterococcus faecalis*[73][74].

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[75]. It also inhibits the growth of *Enterococcus faecalis*[76]. 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[77]. Human clinical trials of ursolic acid show anti-inflammatory effects at

---

[71] Chan MM. Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. BiochemPharmacol. 2002 Jan 15;63(2):99-104. doi: 10.1016/s0006-2952(01)00886-3. PMID: 11841782. https://pubmed.ncbi.nlm.nih.gov/11841782/

[72]Hu Y, Chen D, Zheng P, Yu J, He J, Mao X, Yu B. The Bidirectional Interactions between Resveratrol and Gut Microbiota: An Insight into Oxidative Stress and Inflammatory Bowel Disease Therapy. Biomed Res Int. 2019 Apr 24;2019:5403761. doi: 10.1155/2019/5403761. PMID: 31179328; PMCID: PMC6507241.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6507241/

[73]Sainudeen S, Nair VS, Zarbah M, Abdulla AM, Najeeb CM, Ganapathy S. Can Herbal Extracts Serve as Antibacterial Root Canal Irrigating Solutions? Antimicrobial Efficacy of *Tylophora indica*, *Curcumin longa*, *Phyllanthus amarus*, and Sodium Hypochlorite on *Enterococcus faecalis* Biofilms Formed on Tooth Substrate: *In Vitro* Study. J Pharm Bioallied Sci. 2020 Aug;12(Suppl 1):S423-S429. doi: 10.4103/jpbs.JPBS_127_20. Epub 2020 Aug 28. PMID: 33149499; PMCID: PMC7595561.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7595561/

[74]Neelakantan P, Subbarao C, Sharma S, Subbarao CV, Garcia-Godoy F, Gutmann JL. Effectiveness of curcumin against Enterococcus faecalis biofilm. Acta Odontol Scand. 2013 Nov;71(6):1453-7. doi: 10.3109/00016357.2013.769627. Epub 2013 Feb 11. PMID: 23394209.
https://pubmed.ncbi.nlm.nih.gov/23394209/

[75]https://pubmed.ncbi.nlm.nih.gov/29389599/

[76]https://pubmed.ncbi.nlm.nih.gov/28791824/

[77]https://www.jstage.jst.go.jp/article/fstr/19/1/19_113/_pdf

doses of 150 mg taken 1 to 3 times a day[7879]. Ursolic acid may also inhibit the SARS-CoV-2 Main Protease[8081] (The importance of this enzyme is described above inAPPENDIX D).

Just as nutritional strategies can control colonization with the inflammatory organism *Enterococcus faecalis,* they can support growth of the anti-inflammatory *Faecalibacteriumprausnitzii,* which is fed by fiber-rich foods[82], fiber supplements[8384], and

[78]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5709482/

[79] Ramírez-Rodríguez AM, González-Ortiz M, Martínez-Abundis E, Acuña Ortega N. Effect of Ursolic Acid on Metabolic Syndrome, Insulin Sensitivity, and Inflammation. J Med Food. 2017 Sep;20(9):882-886. doi: 10.1089/jmf.2017.0003. Epub 2017 Jun 9. PMID: 28598231.
https://pubmed.ncbi.nlm.nih.gov/28598231/

[80]https://www.tandfonline.com/doi/full/10.1080/07391102.2020.1772112

[81]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7284142/

[82] Medina-Vera I, Sanchez-Tapia M, Noriega-López L, Granados-Portillo O, Guevara-Cruz M, Flores-López A, Avila-Nava A, Fernández ML, Tovar AR, Torres N. A dietary intervention with functional foods reduces metabolic endotoxaemia and attenuates biochemical abnormalities by modifying faecal microbiota in people with type 2 diabetes. Diabetes Metab. 2019 Apr;45(2):122-131. doi: 10.1016/j.diabet.2018.09.004. Epub 2018 Sep 25. PMID: 30266575.
https://www.sciencedirect.com/science/article/pii/S1262363618301757?via%3Dihub

[83]Benus RF, van der Werf TS, Welling GW, Judd PA, Taylor MA, Harmsen HJ, Whelan K. Association between Faecalibacteriumprausnitzii and dietary fibre in colonic fermentation in healthy human subjects. Br J Nutr. 2010 Sep;104(5):693-700. doi: 10.1017/S0007114510001030. Epub 2010 Mar 29. PMID: 20346190.
https://core.ac.uk/reader/148232923?utm_source=linkout

[84]Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, Bindels LB, de Vos WM, Gibson GR, Thissen JP, Delzenne NM. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013 Aug;62(8):1112-21. doi: 10.1136/gutjnl-2012-303304. Epub 2012 Nov 7. PMID: 23135760; PMCID: PMC3711491.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711491/

certain prebiotics[85]. Daily consumption of chick peas[86] or of avocados[87] 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[88] or upper respiratory infection in young children[89]. *Bacillus coagulans*GBI-30, 6086 [GanedenBC(30)] was shown to increase growth of *F. prausnitzii*in men and women over the

[85] Ramirez-Farias C, Slezak K, Fuller Z, Duncan A, Holtrop G, Louis P. Effect of inulin on the human gut microbiota: stimulation of Bifidobacterium adolescentis and Faecalibacteriumprausnitzii. Br J Nutr. 2009 Feb;101(4):541-50. doi: 10.1017/S0007114508019880. Epub 2008 Jul 1. PMID: 18590586. https://pubmed.ncbi.nlm.nih.gov/18590586/

[86] Fernando WM, Hill JE, Zello GA, Tyler RT, Dahl WJ, Van Kessel AG. Diets supplemented with chickpea or its main oligosaccharide component raffinose modify faecal microbial composition in healthy adults. Benef Microbes. 2010 Jun;1(2):197-207. doi: 10.3920/BM2009.0027. PMID: 21831757. https://pubmed.ncbi.nlm.nih.gov/21831757/

[87] Avocado Consumption Alters GastrointestinalBacteria Abundance and Microbial MetaboliteConcentrations among Adults withOverweight or Obesity: A RandomizedControlledTrialSharon V Thompson,1Melisa A Bailey,1Andrew M Taylor,2Jennifer L Kaczmarek,1AnnemarieR Mysonhimer,2Caitlyn G Edwards,1Ginger E Reeser,3Nicholas A Burd,1,3Naiman A Khan,1,3,4and Hannah D Holscher, J Nutr2020;00:1–10.

[88]Odamaki T, Xiao JZ, Iwabuchi N, Sakamoto M, Takahashi N, Kondo S, Miyaji K, Iwatsuki K, Togashi H, Enomoto T, Benno Y. Influence of Bifidobacterium longum BB536 intake on faecal microbiota in individuals with Japanese cedar pollinosis during the pollen season. J Med Microbiol. 2007 Oct;56(Pt 10):1301-1308. doi: 10.1099/jmm.0.47306-0. PMID: 17893165. https://pubmed.ncbi.nlm.nih.gov/17893165/

[89] Lau AS, Yanagisawa N, Hor YY, Lew LC, Ong JS, Chuah LO, Lee YY, Choi SB, Rashid F, Wahid N, Sugahara H, Xiao JZ, Liong MT. Bifidobacterium longum BB536 alleviated upper respiratory illnesses and modulated gut microbiota profiles in Malaysian pre-school children. Benef Microbes. 2018 Jan https://pubmed.ncbi.nlm.nih.gov/29065707/

age of 65[90]. *Bacillus coagulans*pre-treatment also enhanced the effect of prebiotics in stimulating growth of *F. prausnitzii* in a clinical trial of older adults.[91]

The latest development in the study of gut bacterial dysbiosis in Long Covid comes from the work of Dr. Carlo Brogna and his colleagues at Craniomed in Milan. They have shown evidence that the virus causing Covid-19 (SARS-CoV2) not only infects human cells, but can enter into bacteria, where it is called a **bacteriophage**. Gut bacteria then become the principle reservoir for SARS-CoV-2 in the body, perhaps explaining the high frequency of viral persistence in the GI tract. Because bacteriophages often kill the bacteria they inhabit, infestation of the bacterial microbiome by SARS-Co2 may also explain the dysbiosis of Covid-19. Dr. Brogna combines antibiotics with probiotics in his treatment protocol. I have attempted to address the problem of gut viral persistence with methods that address restoration of a healthy gut microbiome, discussed in Tier 2 and Appendix A.

[90]Nyangale EP, Farmer S, Cash HA, Keller D, Chernoff D, Gibson GR. Bacillus coagulans GBI-30, 6086 Modulates Faecalibacteriumprausnitzii in Older Men and Women. J Nutr. 2015 Jul;145(7):1446-52. doi: 10.3945/jn.114.199802. Epub 2015 May 6. PMID: 25948780.
https://pubmed.ncbi.nlm.nih.gov/25948780/

[91]Nyangale EP, Farmer S, Keller D, Chernoff D, Gibson GR. Effect of prebiotics on the fecal microbiota of elderly volunteers after dietary supplementation of Bacillus coagulans GBI-30, 6086. Anaerobe. 2014 Dec;30:75-81. doi: 10.1016/j.anaerobe.2014.09.002. Epub 2014 Sep 16. Erratum in: Anaerobe. 2015 Aug;34:187. PMID: 25219857.
https://pubmed.ncbi.nlm.nih.gov/25219857/