Post Covid-19 Syndrome

Threat versus Safety Physiology

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Abstract

SARS CoV-2 causes an acute viral infection. However, for many a SARS CoV2 infection represents more than a simple acute illness. In those who have significant comorbidities or have suffered a severe course during an acute infection, the symptoms associated with this event may not disappear in short order. The explanation for this protracted syndrome has not been made clear to date.[1]

If we look to the pathophysiology of an acute SARS CoV-2 infection we can gain insight into the multitude of changes in our physiology, cells, tissues, and organs with the potential for chronicity that accounts for this syndrome. However, we must look wider and deeper to fully understand the complexity of this illness as those who suffer more and have worse outcomes not only have biologic and physiologic differences, but also psychologic and sociologic differences to account for this disparity.

Introduction

Indeed, just as the SARS CoV-2 pandemic represents a complex sociopsychobiologic phenomenon Post Covid-19 Syndrome (PC19S) also exists as a complex sociopsychobiologic syndrome.[2] This article hopes to shed some light onto the syndrome and purpose a comprehensive treatment approach for enhancing rehabilitation and recovery from PC19S.

Common complaints and symptom associated with PC19S include but are not limited to the following.[3]

- Fatigue
- Shortness of Breath
- Cough
- Rapid or Irregular Heart Rate
- Dizziness
- Rashes
- Kidney impairment
- Poor Appetite
- Nausea or Queasiness
- Loose Stools
- Loss of Taste and Smell
- Numbness and Tingling
- Weakness

- Headaches
- Brain Fog
- Anxiety
- Depression
- Insomnia
- Aches and Pains
- High Blood Sugars

Fundamentals of PC19S

In general, the medical community remains somewhat perplexed with this constellation of symptoms that can persist long after SARS CoV-2 has been eliminated from our bodies. This lack of clarity has led to great uncertainty as to how to treat the PC19S.[4,5,6]

Here, PC19S will be looked at through the lens of threat versus safety and the body's defense network in terms of viral load with inflammatory and immune responses and cytokine load with inflammatory and metabolic responses. The lens of threat versus safety illuminates that illness and disease is fundamentally caused by our total threat load and the associated physiologic changes associated with this threat load. Conversely, wellness and health are contingent on our level of safety and the physiologic changes associated with this safety load.[7]

It is notable that the fourth fundamental function of life beyond a boundary from the other, a metabolic network, and a reproductive process is defense from threat – a threat response. Every species is on a constant and incessant course of searching the external and internal environment for signals of threat versus safety.[8] We avoid threat to survive and we seek safety to thrive.

The cytokine network, an intercellular peptide communication network, is an excellent set of biomarkers for understanding the status of the entire system. We purpose that the pro-inflammatory and catabolic cytokines, or threat cytokines (TCs), are a measure of the system's perceived threat. Conversely, the anti-inflammatory and anabolic cytokines, or safety cytokines (SCs), are a measure of the system's perceived safety. Therefore, much attention will be placed on the cytokine network as a key network in the overall communication of threat versus safety. It is well documented that pro-inflammatory and catabolic cytokines, TCs, are elevated in acute SARS CoV-2 infections and that multiple tissue, organ injuries, shock and death are associated with cytokine "storms".[9,10] In PC19S the TCs and their sequela remain elevated, as well.[11]

It is our contention that ongoing threat with persistent elevations in TCs, as well as ongoing threat associated genomic transcription and translation resulting in other threat signaling, are at the root of PC19S.[12] It is also, our contention that the threat network extends beyond the boundaries of the individual's own biologic and physiologic mechanisms to also engage, or disengage, psychologic and sociologic mechanisms that directly affect healing and recovery.

Rehabilitation strategies must use a holistic single-system approach to be successful in alleviating PC19S and pull patients from the depths of illness and disease back to wellness and health.

Foundation: (viewed through the lens of threat versus safety)

- PC19S patients suffer from more premorbid physical, emotional, social, mental and spiritual comorbidities.
- PC19S patients have significant elevations in premorbid threat load and threat triggering thus higher threat signaling in the acute and post-acute phases of infection.
- PC19S patients threat load and threat signaling remain high after the acute infection has resolved.
- PC19S patients suffered from more inflammation, coagulation, third spacing, fibrosis, catabolism, and mitochondrial and cellular "dysfunction".
- PC19S patients who have higher threat signaling during an acute infection have more MTOI.
- PC19S recovery time is dependent on the level of MTOI from the acute infection and the delay in healing associated with persistently elevated threat signaling.
- PC19S patients require focused efforts to shift physiology from threat signaling to safety signaling.
- PC19S patients require more time and precise rehabilitation efforts to recover.

Treatment Approach:

- Attend to the etiologies of baseline elevations threat signaling.
- Attend to the etiologies for persistent elevations in threat signaling.
- Attend to physiologic, including metabolic, changes associated with an acute SARS CoV-2 infection.
- Attend to the MTOIs.
- Utilize the body's own resources to counteract and reduce threat signaling and to recruit safety signaling.
- Optimize the body's recovery though nutrition, vitamins, trace elements, sleep, exercise, parasympathetic stimulation, emotional support, cognitive support and safe social connection.
- Use progressive pharmacological interventions with minimal risk for maximal benefit.

Keys to recovery:

- Properly controlling the threat signaling along the spectrum of a SARS CoV-2 infection from preexposure through recovery.

Infection

SARS CoV2 infections present a unique challenge to human physiology. In addition to activating the immune defense network, the virus activates the inflammation, coagulation, and metabolic defense networks, and engages autonomic reflexes in multiple ways that can escalate and lead to poor outcomes and bring us ever closer to the edge of death, if not death. There are two key factors that occur simultaneously and in reaction to each other in a threat or defense response to SARS CoV-2 that create the total stress on our system:

- Viral load – the viral inoculation, replication, and survival within the body Threat load – total
- threats that dictate the body's response including the threat imposed by the virus

Each of these loads needs to be simultaneously mitigated to successfully navigate a SARs Cov-2 infection and to minimize any post infection symptoms.

The current emphasis in our global response to Covid-19 is primarily to mitigate the viral load. We have been distancing, isolating, masking, practicing good hygiene, trialing antiviral medications, and

bringing online successful vaccines. However, as we design and bring pharmacologic interventions on-line the virus mutates to evade our interventions. In addition, we are struggling to get both our national and global population adequately immunized. We have yet to fully embrace antiviral treatments in the early phase of infections.

Secondarily, are the multiple on-going trials to mitigate the TC levels. These trials mainly focus on immunological pharmaceutical interventions and not on more basic interventions including accessing and integrating our own inborn immune, recovery and healing responses.

Nor are we examining and countering the primary source of our high-risk comorbidities and our overall poor general health – chronic threat. It is chronic threat that places us at risk for hospitalization, morbidity, death and PC19S from SARS CoV-2.

To be clear people are not being disabled or dying from the viral load alone. They are primarily dying from an elevated threat response and high TC levels. Certainly, the viral load plays a significant part in creating a TC "storm", but there are many other factors in someone's total threat load that place them at risk for cell, tissue and organ injury, and death, and place them at risk for PC19S.

Preexisting chronic medical, emotional, social, mental and spiritual disorders, addictions, and nutritional deficiencies contribute to threat load. Exposure to toxins including air pollution increase threat load.[13] Past traumas, physical or emotional, contribute to threat load.[14] Living in isolation, crowding, disenfranchisement, discrimination, injustice, and poverty elevate the threat load.[15] Social and political unrest contribute to threat load. Environmental disasters contribute to threat load. Even disconnection from the natural world increases our threat load.[16] Cultural constructs that lead to spiritual atrophy and existential angst contribute to our threat load.[17]

A high threat load associated with high threat signaling places people at increased risk for severe SARS CoV-2 infections and PC19S.

Acute Infection Threat Load = Pre-existing Threat Signaling + Viral Induced Threat Signaling

PC19S Threat Load = Pre-existing Threat Signaling + Residual Acute Infection Threat Signaling + New Threat Signaling

(New threat signaling = new physical, emotional, social, mental, financial, and/or spiritual burdens)

Note that all these risk factors shift the regulation of our physiological state into a defensive mode at great expense to the support and regulation of the processes that support healing, health and wellness. The immunologic network in partnership with other regulatory circuits including metabolic, endocrinologic and autonomic networks shift their functional strategies from support and surveillance states to a defensive and at times a deconstructive and even destructive state when dealing with threat. Certainly, the immunologic network isn't running wild as cellular immunity is faltering during severe protracted infections and with PC19S.[18] However, inflammation and catabolism do seem to be persistent during the course of severe infections and continue to be elevated in PC19S.

Consider, a TC "storm' may actual represent a relatively normal virally induced TC level, but in a person with a high baseline threat load with a quick TC trigger and chronically elevated TCs from other factors the summation may lead to a shock syndrome, MTOIs and death. The compounding loads can push the afflicted over a threshold into shock - collapse, tissue injury, organ failure and death. The baseline TC levels may reset to a new elevated baseline post severe infections due to the combined

physical, emotional, social, mental, financial, and spiritual traumas inflicted throughout the course of the infection and treatment.

If all factors are not treated, then elevated threat signaling and associated disease and illness can endure long after the virus has been extinguished (PC19S). Mitigating threat and thus threat signaling needs to be the primary focus of not only stopping the destruction and devastation of this virus during an acute infection, but to promote the healing and recovery from the infection and associated injuries. To do this we should treat all threats. To do this we have to turn over some rocks and dig deeper to uncover all the threats, but even more importantly we have to see the threats that are hiding in plain sight.

If we learn to successfully mitigate threat loads and threat signaling, the viral infection and recovery become relative non-events. Plus, the strategies for successfully mitigating high threat signaling will be available to us for all future pandemics, epidemics, shock syndromes and post-illness syndromes, unlike the viral focused interventions with an ever-changing target.

This healing process will not become obsolete as vaccines and antivirals do as a virus mutates. This is where the solution lies for returning to wellness and health, and returning life to normal. This plan mitigates the threat load and threat signaling to facilitate recovery and a return to health and wellness.

Finally, it must be noted that the state of spiritual, political, financial, mental, social, emotional, and physical health in the US, and the associated high levels of threat signaling, is so poor that it is difficult to fully heal and recover from an acute SARS CoV-2 infection, let alone be healthy in general. A successful national or global recovery from this pandemic may require addressing everything that is wrong in all these areas. Our lack of investment in public spiritual, financial, mental, social, emotional and physical health, and our global and national political and civil unrest, have truly come home to roost.

Covid-19 may serve as a proxy for all of the afflictions of the US and the World today. The rehabilitation and recovery pathways for all these afflictions will be similar.

The Cytokine Network

The origins of the human cytokine network are at least a billion years old, and the roots of the cytokine may be as old as the first bacteria and archaea that appeared on earth 4 billion years ago. Cytokines are small bits of protein (~100-200s amino acid sequences) that allow primarily paracrine but also autocrine and endocrine communication between cells. There are cytokine receptors on the surface of every cell in the body. Cytokines effect neurotransmission, are key in hormonal expression, regulate metabolism and influence genetic transcription and translation.[19] Cytokines are a major factor in the expression of the immune network, both stimulating immune cell activation and inflammation.

Cytokines tend to be over looked in their role in a healing response. Similarly, they are overlooked in their significance and influence over the metabolic network. The TCs induce catabolism and promote fuel production in a response to a threat such as an attack by a virus.[20]

The cytokines are numerous and have been classified by their source of production, target of action, effect, and/or their connection with disease states.[21,22] For the focus of this discussion, they have

been categorized by function - warding off threat and facilitating a defense state (TCs), or promoting healing, regeneration, recovery, reproduction, and a sense of safety (SCs).

Examples (IL = Interleukin, TNF = Tumor Necrosis Factor, TGF = Tissue Growth Factor)

TCs - Pro-inflammatory/Catabolic	**SCs – Anti-inflammatory/Anabolic**
Primary - IL1 beta, IL2, IL6, TNF alpha	Primary – IL4, IL10, Irisin, TGF beta
Others - IL 8, IL17, IL18	Others – IL13, IL37, IL38, other GFs

Our cells are all cousins with various areas of specialization. All having evolved from ancient archaea with endosymbiotic bacteria into a large multicellular, multiorganed, multinetworked and coordinated single system called a human. Our leukocytes produce cytokines, but so do epitheliocytes, endotheliocytes, fasciocytes, myocytes, osteocytes, hepatocytes, nephrocytes, gliocytes, and neurons. All of our cells communicate with the cytokine network.

From an evolutionary standpoint this peptide network in multicellular organisms well proceeded neural or vascular networks and neural and hormonal signaling. In this respect the cytokine network should be considered to super-cede these networks, especially in defense states, however communication is bidirectional within these networks. (Of note the purine-pyridimine signaling network may be older than the cytokine network.[23])

The intercellular cytokine network is a fundamental communication system within our bodies and brains having major governance over our physical, emotional, social, mental, behavioral and spiritual states. The TCs dictate defensive, inflammatory, catabolic and degenerative states. The SCs dictate the healing, anti-inflammatory, anabolic and regenerative states.

The cytokine network is much more than an adjunct of the immune network and controls more than just inflammation. The cytokine network is a fundamental communicator via intercellular transmission, neural transmission and/or hormonal like transmission, for the body and brain that results in the dissolution of any separation of “systems” and the mind-body duality. The cytokine network integrates the autonomic, neurologic, cardiac, gastroenterologic, endocrinologic, immunologic, psychologic, and sociologic networks.[24] These networks exist within the same soma and the same soup.

The cytokines create a single coordinated system – one system.

Threat

Chronic threat signaling is the underpinnings of chronic physical illnesses and diseases. This signaling is, also, the underpinnings of all of mental illnesses and diseases, including addictions. TCs are elevated from toxic exposures including air pollution. In addition, the TCs are elevated in those who suffer physical, emotional, social, mental and spiritual illness and disease.[25] The TC trigger is sensitized and TC levels are frequently elevated in those who have suffered significant past traumas.

Threat comes in many forms - physical, emotional, social, mental, financial, spiritual - and even from genetic and neural coding below the level of awareness.[26] Threat can be historical, remembered, predicted, potential, real, imagined, and/or relative.

With progressive elevations in our threat load, signaling and TCs we see the phenotypic changes with the progression from fight to flight to falter to faint physiology.[27]

Under the influence of the threat signaling and TCs, we become catabolic, inflamed, irritable, reactive, selfish, asexual, antisocial-asocial, disconnected and dissociated.[28] Our cellular immune response is activated within these early defense states.

With progressively higher threat signaling and TCs, or prolonged exposures to the threat signaling and TCs, we continue to be catabolic and inflamed, but progressively disconnected, isolated, depressed and dissociated, and can even progress into a state of both physical and emotional collapse.[29]

Chronically elevated threat signaling is responsible for systemic tissue and organ dysfunction, autonomic dysregulation, sickness behavior, helplessness, and hopelessness. At this far end of the threat spectrum we have poor cellular immunity ("immunoparalysis" or "exhaustion") and are at increased risk for more severe and chronic illnesses and diseases including degenerative disorders, chronic infections and cancers. Chronic threat signaling is associated with all of the symptoms of PC19S.

The combined acute effects of a SARS CoV-2 infection include catabolism, inflammation, coagulopathies, fibrosis, and other destructive defensive changes, can result in significant collateral damage, cell death, tissue loss, residual scar and organ dysfunction (MTOI). An effective healing response prevents the formation of fibrotic tissue and restores mitochondrial, cellular, tissue and organ functions. Unfortunately, the healing process is sometimes incomplete or non-existent when patients are stuck in threat physiology. This can leave people with senescent mitochondria, hypoactive cells, fibrotic tissues and damaged organs, and chronic impairment and disability.[30]

In addition to threat signaling influences over our coagulation, inflammation, and immune functions, the TCs also dictate our metabolism through complex pathways. TCs activate threat related metabolic states and fuel production by inducing strategic and organized breakdown of tissues for the fight and fever state of an infection. TCs are catabolic. Tumor necrosing factor was first known as a hormone, cachectin, because it was noted to cause cachexia (wasting).[31]

Furthermore, the TCs shift mitochondrial and cellular functions from the high energy production and anti-inflammatory metabolic state of oxidative phosphorylation to the lower energy producing and pro-inflammatory metabolic state of glycolysis.[32] The oxygen spared from mitochondrial oxidative phosphorylation is diverted to the mitochondrial production of reactive oxygen species and inflammation to fight the virus. Fats are diverted from cell structures, anabolic and sex hormones, and oxidative fuel production, to the production of stress hormones and pro-inflammatory molecules in a threat response.

The combination of chronic inflammation, chronic metabolic "dysfunction" (catabolism, mitochondrial defense state) and MTOIs results in a stunted, or sluggish, and prolonged recovery with delays in repairing tissues and restoring normal physiology, and perhaps an incomplete recovery.[33,34] Recovery cannot be achieved as long as the threat load, threat signaling and TCs remain high.

Threat load, threat signaling, and TCs determine our physiologic status by not only affecting fuel choices, metabolism (catabolism), coagulation, inflammation, and immunity, but also determining the extent of cell, tissue, and organ downregulation, deconstruction, destruction and injury. Additionally, chronic threat can act as an impediment to rehabilitation and recovery after a SARS CoV-2 infection.

We cannot adequately nor fully rehabilitate, recover and heal until we replace threat signaling with safety signaling.[35]

Safety

Safety signaling is the underpinning of health and wellness. With the elevations of safety signaling the states of breed, feed, digest, and rest are activated. It is here where we are anti-inflammatory, anabolic, regenerative, restorative, connected, cooperative, sexual, reproductive, intellectual, and creative. We also have strong cellular surveillance immunity. Our immune cells change phenotypes when in safety and become active in not only immunity but are fundamental to the regeneration, recovery and healing process.[36] We must get to this state to fully heal. High parasympathetic tone, free emotional expression, and safe social connection are imperative to healing.[37] Humans are dependent on connecting with others and the coregulation of others to induce the physiology of healing. We are energized and we feel well when fully safe, seen, and secure.

Defense

We purpose, our defensive repertoire contains two basic phenotypes that are expressed from a genomic, molecular, mitochondrial, cellular, physical, emotional, social, mental and to a spiritual level.

The first phenotype, Threat1 (T1), has been characterized as fight or flight and is expressed by activation of the TCs and sympathetic nervous network (with suppression of the parasympathetic network) with a mobilization response and an associated progressive dissolution response from evolutionary newer to older functions including significant neuropsychological dissociations.[38,39] The mobilized state provides an efficient platform for fight and flight behaviors. This state is notable for hypermetabolism, and feelings of irritability and anger and/or fear and anxiety.

When the T1 mobilization responses do not successfully move an individual into a safe context and/or resources are waning, then the system can shift into a second phenotype, Threat2 (T2), falter and faint, is an immobilized state with associated hypometabolism, further dissolution and neuropsychological dissociation, and submission, withdrawal, surrender, syncope, death feigning, and even death can be seen.

When the T2 state becomes chronic it presents with increasing sickness behaviors, loss of purpose, social isolation, depression, helplessness, hopelessness, despair, and at times psychosis. Cellular immunity is poor in this state as the immune cells reflect the general physiology and characteristics of the T2 phenotype.[40]

Both the T1, mobilization, and the T2, immobilization, phenotypes have value in defensing and protecting an individual. Both are catabolic and proinflammatory. Both interfere with interpersonal interactions, accessibility, trust, co-regulation, and feeling safe with another person.[41] In addition to impairment in social connection, higher level cognition, declarative memory, symbolic language, and attention and concentration are also strategically impaired when in chronic threat.

Thus, two defensive states emerge, one aggressive, reactive and combustive, T1, and the other submissive, paralytic and perseverative, T2, from different molecular, mitochondrial, cellular, metabolic, neural, cardiovascular, gastrointestinal, endocrine, and immune threat related phenotypes and physiologies. Both states, T1 and T2, evolved to assist with survival. Simultaneously, the capacity to

down-regulate our degenerative threat physiology through coregulation with another safe and trusted individual is compromised.

Conversely, this implies that in the presence of safety signaling, cues of predictable safe social interactions, the social engagement network, can down regulate threat signaling.

The flip side to reducing threat signaling is to stimulate safety signaling. These approaches adjust our physiologic status to optimal protective immunity with low inflammation and catabolism, and high anabolism, regeneration and healing.

Understanding all of these interactions allows us to calibrate threat versus safety on an individual level. With information on threat versus safety, there can be a better understanding of the foundational pathways through which the virus can have minor versus devastating consequences and rapid versus slow or incomplete recovery. This knowledge allows us to better prescribe the treatments needed to minimize infection, reduced injury, morbidity, and mortality to hasten healing and recovery.

Our ability to find safety and restore safety physiology is our resilience and the essence of healing. Healing cannot occur when catabolic and inflamed within threat physiology.

Discussion of Symptoms of PC19S

Fatigue – Fatigue can be multifactorial. In general, high levels of TCs will cause withdrawal, isolation, sickness behavior and even depression. It does not take a chronic infection to cause chronic fatigue; simply elevated TCs. At a neural transmission level one can see blocking of the production of the energetic adrenergic neurotransmitters, dopamine, and noradrenaline, as well as the feel-good neurotransmitters, serotonin, and acetylcholine.

Dopamine and noradrenaline production are down regulated at tyrosine in favor of tyrosine's metabolic role as a fuel source and other roles in a defense.[42] Serotonin production is down regulated at tryptophan in favor of the production of kynurenic and quinolinic acid, both excitatory to NMDA receptors, similar to glutamate.[43] Quinolinic acid inhibits the acetylation of choline resulting in a fall in available acetylcholine transmission.

In addition, TCs change the functions of mitochondria biasing them away from oxidated phosphorylation resulting in a marked reduction in ATP production, as the cells become dependent on aerobic glycolysis for fast energy production (an 18-fold drop in ATP production).[44] In higher concentrations the TCs can cause relative dormancy of mitochondria and cells.

TCs reduce hormone production including thyroid hormones if concentrations are high enough.[45] The threat physiology associated with high or chronic levels of TCs is one of preservation and energy conservation from a molecular, mitochondrial, cellular, hormonal, to a neural level that we experience as a state of fatigue if not depression.

Shortness of breath – This is a multifactorial phenomenon with SARs CoV-2 infections. SARS CoV-2 infects cells by sticking the Spike Protein into angiotensin converting enzyme 2 receptors (ACE2Rs) on our cells. Primarily, SARs CoV-2 attacks ACE2Rs on pulmonary, gastrointestinal and genitourinary epithelial, and vasculature and renal endothelial cells. This causes direct cell injury and death. There is clearly extensive endothelial/vascular and epithelial/alveolar lung tissue injury from direct viral cellular invasion and the inflammatory destructive immune response to the invasion that effects both blood

flow and gas exchange within the lungs.[46] These injuries can take time to heal and at times viable tissue is not restored and fibrotic tissue replaces it. Shortness of breath may be experienced for weeks to months during recovery and repair of these tissues.

Secondarily, dyspnea is from the threat load, TCs, and its sequelae. This can start with the disruption of mitochondrial function with a threat induced shift from oxidative phosphorylation metabolism to less efficient aerobic glycolytic metabolism and a loss in total ATP production. Our ability to respire is compromised. This process can resolve quickly with the reduction in TCs and the restoration of SCs.

In addition, the TCs facilitate third spacing of fluid, interstitial edema, and effusions resulting in fluid, protein and cell infiltration of tissues and accumulation around organs, particularly the lungs This can make gas exchange and ventilation difficult. This process should resolve within weeks to months but is also dependent on dropping TCs and increasing SCs.[47]

Poor intravascular protein status can perpetuate this fluid pooling process by allowing persistent leaking of fluid from the blood vessels. Good nutrition with adequate protein replacement is essential to hasten the resolution of these accumulated fluids.

Breathwork not only helps to regulate the system and set the autonomic network with a higher healing PNS tone, but also the rhythmical increases in intrathoracic pressure with breathwork act as a pump to push these fluids into the lymphatic drainage system. Breathing becomes easier and shortness of breath improves.

General deconditioning can also play a role in shortness of breath. Gradual reconditioning through a monitored exercise stimulates recovery and is essential to resolution of these symptoms. Exercise directly increases SC production. Muscle is an endocrine organ that produces anti-inflammatory and catabolic cytokines. Conditioning effects take time and adequate recovery between sessions, but they begin almost immediately at the molecular, mitochondrial and cellular levels.

The repair of the tissues takes the longest and may not be complete for over a year. However, with the correct plan and compliance there can be a steady progression with gradual resolution of being short of breath.

Rapid or irregular heart rate and dizziness – Rapid heart rate can be associated with deconditioning, but in PC19S there is likely much more going on. With SARS CoV-2 infections there is known direct viral invasion of the cardiac endotheliocytes (lining cells) and myocytes (muscle cells) with associated inflammation, irritability, dysfunction, and possible destruction of these cells.

It is felt that over 60% of all SARS CoV-2 patients suffer from some level of myocarditis and over 20% will show elevations in troponins, heart muscle cell enzymes, indicating some degree of significant heart muscle cell injury.[48] This kind of injury can be reflected in poorer pump function with varying symptoms from fatigue, shortness of breath, impaired endurance to frank heart failure depending on the severity of the injury. Excessive activity may induce excess strain on the heart leading to rapid heart rate and/or arrhythmias.

In addition, there can be a thromboembolic phenomenon with restrictions or occlusions of blood flow to the muscle cells, myocardium, and intrinsic neural network of the heart, neurocardium, resulting in hypoxic and metabolic strain on the heart and its conduction network that can lead to rapid heart rate and/or arrhythmia.

Perhaps more significantly is the role of TCs on the heart. Elevations in threat cytokines modulate the autonomic network first increasing the sympathetic tone with loss of parasympathetic tone thus predisposing to tachyarrhythmias. Then at higher concentrations with not only loss parasympathetic tone, but also loss sympathetic tone the risk for blocked conduction and arrhythmias, including bradycardia increases. This loss of top-down regulation over the neurocardium can lead to variable sinoatrial or atrioventricular arrhythmias and/or episodic rapid or slowed heart rate.[49]

In addition, TCs are known to increase the repolarization interval, QT interval, and predispose to arrhythmias. This is especially concerning in patients on multiple medications for treatment of SARS CoV-2, AC19S and PC19S as many of these medications may also increase the QT interval. Prolonged QT intervals can place patients at risk for arrhythmias, syncope, and sudden death.[50]

TCs signals to the brainstem and neurocardium result in faint physiology with low heart rate, low heart contractility, low blood pressure and poor postural response, all leading to dizziness with standing and a desire to remain supine, if not fetal.[51]

Control over threat signaling is essential to not only endothelial and myocardial rehabilitation and recovery, but, also, to the regulation of both the extrinsic and intrinsic cardiac conduction networks to reduce the risk for further cardiac complications from the disease and to facilitate this component of the rehabilitation and recovery process.

Kidney impairment **-** Direct viral effects on the kidney from SARS-CoV-2 include endothelial damage from viral entry and complement activation, local inflammation/cytokine release, and collapsing glomerulopathy.[52] The indirect effects of COVID-19 that can lead to acute kidney injury include volume depletion, hypotension/shock, rhabdomyolysis, as well as the common causes of in-hospital acute kidney injury, such as nephrotoxin exposure and sepsis.[53] In patients who suffer an AKI only 2% were found to have new-onset CKD 4 months later. This suggests that the vast majority of patients with COVID-19 induced AKI who survive will recover kidney function.[54]

Rashes – Threat signaling not only increase TCs but also histamines. Rashes are not uncommon with Covid-19 infections.[55] Persistent elevations in TCs and histamines post Covid-19 infection may lead to a variety of vascular and skin disorders.[56]

Poor appetite – Elevation in threat signaling at the hypothalamus and brainstem can cause a decrease in appetite. When under threat it is not a time for eating let alone digesting a meal. Resource allocation thus demands that networks like the gastrointestinal network (and for similar reason it is not a time for bonding and breeding, the reproductive network) go off-line. In addition, in this physiology, gastrointestinal motility is slowed down. The stomach may empty slowly, the bowels may be slow to move. Gastric acid and digestive enzymes are also reduced. Bloating, or even frank obstipation and constipation may be observed.[57]

Nausea – In addition to the relative inactivity of the gastrointestinal tract the TCs also stimulate the nausea center (area postrema) in the brainstem leaving people queasy if not nauseous or even vomiting.[58]

Loose stools – The epithelial cells of the gut have ACE2Rs making them prime targets for SARS CoV-2 attack and infection. As well, TCs induce inflammation in the gut and loosen intercellular junctions between the endothelial and epithelial cells, thus allowing leaking of fluid, proteins and cells into the

intestines resulting in loose stools. This can present as irritable bowel syndrome or frank colitis.[59] This is not a hypermotility issue. Medications to slow the colon further, especially anticholinergic medications, can exacerbate the problem and slow recovery.

Lost taste and smell – Covid-19 is associated with a variety of neurologic changes associated with threat signaling and threat cytokines.[60] The nose serves as the main entrance into the body for SARs CoV-2. The olfactory receptors are buried in the epithelial cells of the sinuses above and behind the nose. The olfactory epithelium has the highest density of ACE2Rs of any tissue in the respiratory tract. It is no wonder that loss of smell is one of the first symptoms of a SARS CoV-2 infection. The olfactory epithelial cells are likely to be the first infected and injured, but it is possible the olfactory sensory neurons themselves may also get infected and injured. The injury to the neurons would likely account for a more prolonged loss of smell while epithelial injury alone would be expected to recover faster.[61]

The loss of smell can affect the sensitivity of taste, but the epithelium of the tongue also has a high density of ACE2Rs and infection and injury of these cells most likely accounts for the majority of the loss of taste. It appears the taste buds themselves do not have a high density of ACE2Rs therefore it is assumed that the local epithelial damage and associated inflammation and edema is enough to interfere with the sense of taste. It has also been proposed that TCs themselves may inhibit taste bud neurotransmission as the taste buds have high levels of TC receptors.[62]

It has also been postulated that direct infection of the CNS cells could account for some loss of taste and smell, but more probable is the elevation of TCs acting at brainstem centers and the hypothalamus could not only down regulated gastrointestinal functions, but also the drive for food including the sensitivities of taste and smell.

Numbness and tingling – ACE2Rs are abundant on neuron cell bodies and less so on their axons and dendrites. Direct viral attack, infection and destruction of neurons is a concern in both the central and peripheral neurons.

TCs and high sympathetic tone can result in peripheral nerve inflammation and catabolism resulting in both poor conduction in nerves from loss of the insulation around the nerves, as well as, disintegration of the axons, or the wires, in the nerves. This Critical Illness Neuropathy has been documented and described in Covid-19 patients.[63] The loss of insulation can take weeks to months to fully repair. The loss of the axons can take even longer to repair and frequently this repair is incomplete thus leaving people with some level of permanent impairment.

Weakness – Skeletal myocytes also have ACE2Rs which have been thought to be protective against sarcopenia, or the loss of muscle mass. The presence of these receptors raises the concern for direct myocyte attack, infection, and destruction. The loss of viable ACE2Rs can cause increasing sarcopenia.[64]

In addition, the TCs (see TNFa and cachectin) and the glucocorticoids are both catabolic and directly cause muscle wasting. This Critical Illness Myopathy has been documented and described in Covid-19 patients.[65] The net effect of all of these mechanisms is a loss of muscular endurance and a generalized weakness (loss of force and power production).[66]

High levels of cytokines can inhibit dopaminergic pathways in the brain involved in not only actions, movement, facial expression and posture, but with emotions and reward seeking as well. In addition,

postural reflex mechanisms can be altered leading to a slumped posture and a feeling of being “weak kneed”.

As describe previously, acetylcholine availability and transmission can be impaired at the level of the neuromuscular junction leading to decreased recruitment of muscle cells and a loss of force and power production.

These combined effects lead to generalized, nonfocal, weakness.

Headaches – (See Aches and Pain below.) As noted above neuron cell bodies have ACE2Rs that make them susceptible to direct infection and associated cerebritis or encephalitis that can cause headaches. The meningeal tissue can also be involved, and viral meningitis can be another source of headaches and neck pain. In addition, endothelial cells of the cerebral vasculature are also loaded with ACE2Rs, and cerebral vasculitis can be associated with headaches. The TCs can influence vasomotor responses in the brain and induce inflammation within blood vessels to precipitate migraine type headaches. The TCs while inducing inflammation in the parenchyma of the brain can loosen intercellular junctions in the blood brain barrier resulting in edema of the brain.[67]

Brain fog – Certainly direct central nervous system (CNS) cell infection and injury of both neurons and glial cells, or viral encephalitis, is a possibility for persistent brain fog post SARS CoV-2 infections. However, this acute viral encephalitis is relatively rare (<0.05%)[68] with SARS CoV-2 infections, and even with a clinical picture of encephalitis there still may be sterile encephalitis, or encephalopathy without viral infection, induced by the high levels of TCs and the cascade of catabolic, coagulation, inflammation, mitochondrial and cellular changes, and the destructive immune response of SARS CoV-2 infections.

Microvascular injury, coagulation and strokes can occur with acute infections.[69] In addition, the TCs cause leakiness at the blood-brain barrier with fluid, protein and cellular infiltration and edema. Cerebral edema can slow cellular and conduction functions in the brain leading to brain fog. The best treatments for this edema are TC reduction, SC elevation, good sleep - when the glymphatic pump is most active - and good proteins in the diet to prevent further leakage of fluid, proteins and cells into the brain tissues. Certainly, all these acute processes outlined can lead to significant organ dysfunction, in this case the brain, and a prolong cognitive recovery from a SARS CoV2 infection.

Elevated threat signaling down regulates (or causes dissociation/dissolution of) newer cortical structures making sustained attention and concentration, executive functions, higher level language, declarative memory and interpersonal engagement challenging. This process is a strategic and selective resource allocation for the fight, flight and fever as these structures and functions are not necessary for defeating a virus, nor a tiger. As threat signaling increases even further, then lower older cortical structures are down regulated and working and sense of connection to the world, the body, and our sense of being will start to falter. This down regulation at its extreme can result in agitation, delirium, hallucinations, and frank psychosis.[70]

If threat signaling remains too high for too long, the down regulating of these cortical structures and functions as a resource utilization strategy extends to frank catabolism of these structures. The deconstructed components of these tissues will be reallocated for the defense of the system. This is likely a fundamental mechanism for prolonged brain fog in PC19S, as well as schizophrenia, dementias and other neurodegenerative diseases.[71]

A common pattern of threat signaling is strategic evolutionary dissolution, or down-regulation, followed by organized deconstruction, and rarely frank destruction. The PC19S threat signaling and TC levels thus determine the recovery as much as the acute infection processes. GCS, especially dexamethasone, will amplify this detrimental effect.[72,73] Rest, protein and good fats are helpful in the repair and re-insulation of neurons.

Anxiety – Anxiety is associated with moderate elevations in threat signaling and TCs and a significant elevation in the sympathetic tone that is consistent with flight physiology. Essentially, anxiety is a chronic mobilization fear response characterized by a protective posture, guardedness, restlessness, reactiveness, impulsiveness, vigilance and at times paranoia. Parasympathetic tone, GABA, acetylcholine, serotonin, and melatonin run low. Dopamine is also low while noradrenaline, adrenaline and glutamate are dominant in this state. Agitation can be present, but dopamine driven approach behavior, frank aggression, and fight is fleeting to absent. There is some cortical dissociation/dissolution especially from newer, more distinctly human, cortical functions.[74]

Depression – Depression is associated with even higher levels of threat signaling and TCs and diminished sympathetic tone that is consistent with immobilization faltering physiology. Essentially, depression is a chronic immobilization surrender response characterized by a submissive posture, withdrawal, isolation, helplessness, hopelessness and at times both physical and emotional collapse. In this state all neurotransmitters are in decline with glutamate being the most robust. There is more advanced dissociation/dissolution of cortical and subcortical functions that can be characterized as a loss of connection with the environment, others, and even of self. Delirium is a hallmark of severe acute infections and severe persistence of PC19S can result in depression, emotional numbing and even psychosis.[75]

Insomnia – Threat signaling and TCs at lower levels increase sympathetic activity and adrenergic transmission creating a state of arousal, reactivity, and vigilance. As mentioned previously acetylcholine production and transmission in the parasympathetic network is impaired, and GABA and serotonin production and transmission are also impaired.

Serotonin is an intermediate step in the synthesis of melatonin from tryptophan. As noted previously, under the influences of TCs tryptophan is shunted into the kynurenine pathway, so serotonin and melatonin levels can go very low.

At higher TC concentrations the adrenergic transmission can also be impaired and glutaminergic transmission becomes more dominant. TCs will block the formation of gamma alpha butyric acid, GABA, from glutamine-glutamate in favor of glutamate and glutaminolysis for fuel.

The absence of GABA, acetylcholine, serotonin, and melatonin make rest, relaxation and sleep difficult to find.[76]

Restorative sleep is essential to rehabilitation and recovery. It is as essential as social connection to the human species. A single night of lost sleep will be associated with a rise in TCs, simply exacerbating the problem into a downward spiral. Whereas restorative or recovery sleep is associated with a decrease in TCs and an elevation in SCs, as well as restoration of parasympathetic tone.[77]

Whether in the preventative phase through the later phases of infection and recovery, attention to sleep is imperative. This can be challenging when in the hospital and particularly when in an ICU with excessive activity, lights, noises, and interruptions.

Maintenance of circadian rhythms and attention to sleep hygiene needs to be practiced in all settings and in all phases of an infection for optimal recovery and health maintenance.

PTSD – Up to 30% of patients who have suffered a severe Covid-19 infection qualify for a diagnosis of posttraumatic stress disorder. PTSD can be considered a spectrum disorder encompassing anxiety, depression, and insomnia, and is associated with increased threat load, threat signaling and TCs.[78,79]

Aches and Pains – Threat signaling and TCs also amplify pain pathways peripherally and centrally. The TCs activate an inflammatory response by activating arachidonic acid, leukotriene, and prostaglandin pathways, as well as increasing substance P and CGRP. Beta oxidation of fatty acids is impaired in threat states and the fatty acids can be diverted to support inflammation within these pathways. Inflammation is an essential part of our innate immune response to a pathogen. This allows for an increase in blood flow to affected tissues which brings an army of destructive phagocytic immune cells to attack the pathogen. However, long after the pathogen has been defeated the total threat load and threat signaling can keep TCs elevated leaving PC19S patients with chronic inflammation, and aches and pains.[80,81]

Hyperglycemia/Diabetes – Worsening of diabetes as well as new onset of diabetes has been reported with SARS CoV-2 infections. As the islet cells (beta > alpha) of the pancreas have ACE2Rs, direct injury to the cells in a SARS CoV-2 infection is possible.[82] Vascular endothelial involvement may also contribute to acute pancreatitis and additional tissue injury with SARS CoV-2 infections. The combined effects of these injuries would result in beta cell injury and a decrease in insulin production consistent with Type 1 Diabetes Mellitus (T1DM).

In addition, the threat state preferentially down regulates beta cells and insulin production while upregulating alpha cells and glucagon production for support of glucose levels in the fight and flight.

It is well known that obesity, insulin resistance and T2DM are risk factors for severe SARS CoV-2 infections and PC19S. Adipocytes produce TCs, likely in greater quantities when storage of fat is approaching a maximum, that directly cause insulin resistance and subsequently Type 2 Diabetes Mellitus (T2DM). Therefore, the obese have higher baseline TCs placing them at risk for severe infections, PC10S and poorer outcomes. As long as TCs remain elevated there will be insulin resistance, and potential hyperglycemia and T2DM.[83]

This is not pathological physiology; this is logical physiology. We have to look to the root to understand disease. Threat and threat physiology when chronic become “pathologic” physiology. We know glucose is the preferred fuel for the fight, flight and fever of an attack.

TCs reduce insulin production and secretion and induce glucagon production and secretion, gluconeogenesis, and insulin resistance in many cells, to ensure the delivery of fuel to the cells (myocytes, leukocytes, etc.) that are necessary for the fight, flight and fever.[84]

Increases in insulin resistance, hyperglycemia and Diabetes Mellitus are predictable in this disease. Restoration of euglycemia will be dependent on the up regulation and recovery of pancreatic islet beta

cells and their function, and the resolution of threat, threat signaling and lower of TCs, and the elevation of safety, safety signaling and SCs.

Interdisciplinary Recovery Strategies to Systematically Treat PC19S

To evaluate patients fully, a thorough History and Examination and an expansive Review of System **and** Review of Threat is required. We must see our patients beyond vital signs, blood values and imaging studies. We must see the complexity of our systems including past (include generational) and current spiritual, financial, mental, social, emotional, and physical threats and traumas.

Recovery strategies require treating the entire system even from beyond the borders of body. Health and wellness are inclusive of the sense of safety and belonging in the world. The social engagement system is foundational to healing. The cytokine and autonomic neural networks are biologic markers for **the system** and have direct implications in the management of PC19S.

Safety is the cure to illness and disease – everything else is just a tool.

Tool Kit

Cellular/mitochondrial Support

Cellular and mitochondrial support includes healthy fluids and nutrition, normalized circadian rhythms, healthy activities and exercise, and adequate periods of recovery including restorative sleep.

Intake

Water, teas, and coffee are recommended over more processed fluids (Caffeine is a good phosphodiesterase inhibitor and lowers TCs).

Dietary recommendations are very simple – eat whole unprocessed foods with lots of colors, spices, herbs and variety.

That is it.

This results in a reduction in sugary simple carbohydrates, or starchy foods, and adequate intake of healthy oils, fats, proteins, vitamins, and prebiotic and probiotic supporting foods.

Whole, organic, unprocessed foods suppress TCs and increase SCs – food is medicine.

A 10-12 hour overnight fast is recommended to support nocturnal ketosis. Ketones deplete TCs enhance SC production thus stimulating growth, repair, regeneration, reproduction and recovery.[85]

Specific anti-inflammation, mitochondrial and immune supporting supplements can be used, especially, if there are any nutritional challenges or deficiencies that may slow a rehabilitation and recovery process.

Food is medicine.

Exercise

A minimum of four supervised sessions are recommended during the initiation of an exercise program.

A monitored daily progressive strength and endurance training program with attention to recovery markers is recommended. These biomarkers include a subjective inventory, morning HR, HRV (heart rate variability, which inversely correlates with cytokine profile[86]), BP – (postural BP if indicated) and O2 saturations. These markers can be referenced to adjust and modify the program for maximal effectiveness.

Loss of HRV is associated with threat signaling, falling parasympathetic tone and an increase in TC levels. HRV is also relatively easy to measure versus TC levels. Therefore, it is felt to be the best biomarker to monitor threat signaling, parasympathetic tone and TC levels to avoid an over training syndrome.

The exercise program can be supplemented with nature walks, restorative yoga, or slow restorative martial arts as long as there are no indications of over training.

Exercise reduces obesity and adipokines – TCs, and increases muscle mass and myokines – SCs, restoring mitochondrial and cellular functions and an anti-inflammatory, anabolic and regenerative state.[87] We feel good.

Exercise is medicine.

Rhythms

Maintaining physiologic circadian rhythms is essential for normal cellular functions and wellbeing. Getting real daylight during the days and solid darkness at night is mandatory for healing. Avoid screens at least two hours prior to bed.

Take Vitamin D in the morning and melatonin 2 hours prior to bed to help re-enforce circadian rhythms and decreased inflammation.[88] Melatonin 5-15 mg in the evening helps induce sleep and is a strong anti-inflammatory that suppress TCs. [89] Consider low dose trazadone (or mirtazapine) if sleep remains difficult.

Herbal teas (passionflower, chamomile, valerian, lavender, cinnamon, spearmint, peppermint, ginger, licorice, or lemongrass) in the evening can also help with relaxation and sleep, reduce TCs, and have anti-inflammatory properties.

Restorative sleep is a key to healing and recovery. A goal should be for 7-8 hours/night. A single night of lost sleep will be associated with a rise in TCs, and recovery sleep is associated with a decrease in TCs, an elevation in SCs, as well as restoration of parasympathetic tone.[90]

Allow a sustained period at night without food to create a relative ketosis to reduce TCs and elevate SCs.

Sunshine and sleep are medicine.

Autonomic Support

The autonomic nervous system has influences throughout the body and regulates the cytokine system and visa-versa. It is a bidirectional flow. Enhancing parasympathetic tone is a priority in recovery.

Breathwork is perhaps the best way we can directly influence our parasympathetic tone. There are many choices of breathing techniques, and all appear to be effective. In general, slow exhalations especially linked with deep shorter inhalations may enhance the vagal tone.[91,92,93]

Examples include:

- Relaxed slow breathing – 4 count in, 6 count out
- Soft belly and diaphragmatic breathing
- Alternate nostril breathing
- Square breathing – 4-10 count in, 4-10 count hold, 4-10 count out, 4-10 count hold
- Resonance frequency breathing

Cues of safety are important to the restoration of parasympathetic tone. Every measure should be taken to ensure feeling safe, seen, and secure. This can be done through safe socialization, and expressions, gestures, postures, intonations, and vocalizations that gives cues of safety.

Avoiding isolation and conflicting relationships will enhance recovery, but more importantly, maybe the key to recovery is staying connected to safe people and the world around us.

Parasympathetic, or vagal, stimulation can be achieved through safe social engagement and breathwork. However, when conditions demand isolation and/or breathwork is not effective there are other mechanisms to increase parasympathetic tone. Things like a washcloth to the forehead, or massage to the temples and ears, neck, shoulders, back, buttocks and feet, or acupuncture, especially to the ear lobe can increase parasympathetic tone.

Technology can also have a role. Acoustical vagal stimulation and direct electrical vagal nerve stimulating devices are other options for recovery treatment.[94,95]

Sensory support

Somatic awareness and integration are important to our health and wellness. It is important to be present with both the pleasant and unpleasant feelings.

This rehabilitation and recovery model links unpleasant bodily sensations and autonomic shifts with systemic threat and defense physiology. This response can be both autoregulated and coregulated (if needed with a therapist's guidance) to bring patients to a place of safety and restorative physiology.

Primary to healing is re-embodiment and being present with any sensations without the need to react to the sensations. This can be done both one on one and in safe groups.

Pleasant somatic sensations can be helpful in recovery (touch, warmth (bath with magnesium salts and therapeutic oils (eucalyptus, lavender, rosemary, tea tree, etc.)), vibration, massage, and/or visceral and/or fascial physical therapy).

Pleasant smells will enhance recovery. The smells of certain types of plant oils can reduce threat cytokines and increase parasympathetic tone (eucalyptus, lavender, rosemary, tea tree, etc.).[96]

Pleasant tastes are also helpful for recovery. Good food, especially with spices that also reduce threat cytokines (ginger, mint, cinnamon, clove, turmeric, curcumin, chili pepper, cayenne pepper, etc.), are preferred to salt or sugar for flavor.[97]

Pleasant and soothing sounds can promote healing. Relaxing music or acoustical vagal stimulation is recommended.

Even pleasant visuals, visualization therapy including virtual reality, can promote recovery.

Emotional Support

Emotional awareness and integration are also important to our health and wellness.[98] It is important to be present with both pleasant and uncomfortable emotional feelings. This rehabilitation and recovery model links threat, trauma and stress to avoidance, suppression or repression, of aversive emotions resulting in physical, emotional, social, and mental symptoms.

Expression also allows for movement and action which is a natural desire if in T1, fight or flight, physiology. Meditation can be therapeutic and help to regulate the autonomic network, and may be preferred if in T2 physiology, but at times it is in conflict with our physiologic drive to move. In addition, meditation doesn't allow for a full release of inhibited emotions from the shadows of the soul.

Free expression is best done first while alone without others to advise, criticize, judge, or reconstruct and without the emotions of shame or embarrassment. There is no goal nor permanence to the exercise of free expression other than the exercise itself. It is an opportunity to express unrecognized thoughts and emotions to become comfortable with them without having to react to or apologize for them.

One particularly effective intervention is using expressive writing where you freely write down your thoughts and immediately destroying the writings. There are also many other forms of expression and the exact best technique for a given person is unclear. However, there is extensive peer-reviewed research documenting the effectiveness of expressive writing in improving mood, performance, and physical symptoms.[99]

The extensions of this process can be play, art, music, dance, theater, prose, or poetry, all best done from a place of freedom. This is done not with intentions or goals, but simply for the sake of doing.

If a drawing or a writing is produced, it can be shredded and discard when completed. The practice of nonattachment and letting go helps with recognizing that energy flows, and sensations, emotions and thoughts are impermanent physiologic states that come and go, and not a rigid definition of who we are. This can give comfort and calm, a good state for healing.

The counterbalance to suppression and repression is expression. It is important to free the unexpressed feelings that we don't even know are within us.[100,101]

Examples of therapeutic activities include:

- Free movement
- Free drawing
- Free speech
- Free writing
- Free drumming - rhythms, vibrations
- Free playing
- Free laughing
- Free crying

No criticizing or judging – just let go!

Acute emotions are useful to get us to move, act and connect with others, or redirect and protect from others. Some emotions (anger, fear, sadness, grief, guilt, shame, and embarrassment) if held onto for too long perpetuate a chronic defensive state and chronic threat physiology.

Proverb – "Let Go or Be Dragged"

Thought Support

Once the system has been regulated, education and cognitive behavioral therapies are now accessible and useful. Individual and group sessions can cover a variety of topics that can help with recovery, health and wellness. Included in this process is practicing gratitude, forming healthy narratives, setting boundaries, and letting go of things, ideas, people, and illusions of control that prevent physical and spiritual health and wellness.

Education and cognitive training can be a big part of recovery from physical illness, as well as, emotional and mental illness. Much of this type of therapy involves the recognition that in different physiologic states we have different emotions, thoughts, and behaviors – that we are not a constant. The physiologic states of threat or safety can determine who we are more than our cortical control can determine who we are. This is especially true when under threat as our higher centers of control are not accessible to us.

In threat our thoughts are biased towards sensing danger, and we are asocial-antisocial, reactive, impulsive, aggressive, and judgmental. In fact, our epigenetic and predictive codes make us more prejudgmental or prejudiced. We are prone to cognitive distortions, negative and false narratives and constructs, and paranoia.

Reality is harder to find when in threat. We are prone to identifying malintent in others when none is present. We are prone to the creation of false stories, narratives and beliefs.

Regressing, rationalizing, intellectualizing, denying, suppressing, repressing, displacing, projecting, catastrophizing, criticizing, labeling, shaming, blaming, judging, gossiping, manipulating, and controlling

are common maladaptive behaviors seen when under chronic threat. These all create the bars to the prison that keep us ill.

Awareness, mindfulness, and presence help to ground us, but in threat we are physiologically biased towards reactivity, and negative predictions, emotions and thoughts. For survival purposes we are a predictive organism looking towards the past to predict the future. Presence only occurs when we feel safe.

In addition, many of the things we do to quell our distress give us an illusion of control while not actually giving us control nor making us safer. This is frequently done in an effort to protect the self. The ego is an illusion that may block us from having a clear understanding of all the issues around a given situation. These strategies, these illusions of control, lead to maladaptive behaviors that eventually lead to further distress and dysfunction.

Awareness of our illusions is essential to health and wellness. In other words, you have to become aware of being unaware before you can let awareness emerge.[102]

Social Support

Isolation is deadly and service heals.[103] Altruism is healthy for us.[104] It is biologically difficult for us if we feel threatened, but altruism also has the ability to push back the threat response. The system is bidirectional. Service is a feed forward mechanism that improves social connection, compassion, cooperation, cognition, creativity, physical health, mental health, and gives a sense of meaning and purpose. Dissipating threat physiology and promoting safety physiology makes social connection, empathy, compassion, cooperation, cognition, creativity and health and wellness even more accessible to us, thus this physiology builds on itself.

When we move towards these things, the physiology we are building in ourselves is simultaneously stimulating it in others. We are all one big system. Zero sum ideologies and behaviors can destroy this system. Altruism can spread by multiple degrees into exponential growth to not heal the individual but to heal the globe. It can happen spontaneously, but can also be facilitated with intent through prescribed service as a healing modality.

Service to “The Good” includes acts of kindness and compassion and the provision of safety to others. Service activates the brain areas associated with pleasure, connection, and trust. This response heals, prevents illness and disease, and delays aging.

Cooperation and Compromise

Our cultural reverence for competition and conflict is unfounded and our sense that cooperation and compromise signify weakness may be our demise and can certainly lead to ill health. In addition, in threat physiology we are cognitively more rigid and less flexible and cling to cultural constructs.[105] Life has unavoidable threats and conflict. These are best handled when one is fit and resilient, but threat, conflict and competition need not be the norm nor chronic. We are our best when we are together, and this requires the ability to adapt, cooperate and compromise, all physiologically brought forward when we are safe, seen and secure.

Evolution has demonstrated not just surviving, but thriving, is more dependent on adaptation than domination. We are social animals. Choose our social nature to help with recovery, health, and wellness.

Meaning and Purpose

During our time on Earth, it is helpful to have a sense of meaning and purpose for the life we are given. The simplest concept to give one a sense of meaning and purpose in this world is to try to have a life that spreads safety and love, not threat and hate.

Don't be the virus on the planet.

Summary and Conclusions

SARS CoV-2 causes an acute viral infection. However, for many a SARS CoV-2 infection represents more than a simple acute viral infection. For those who have significant comorbidities or have suffered a severe course of infection the symptoms associated with these events may not disappear in short order. This has been described as "Long Haulers Syndrome" or "Long Covid." This syndrome has been further characterized here as Post Covid-19 Syndrome (PC19S). The explanation for this syndrome has been outlined above through the exploration of the pathophysiology of acute SARS CoV-2 infections in combination with an individual's pre- and post-infection threat load. The TCs serve as biomarkers for this threat load. Measures such as a Review of System and a Review of Threat give insight into the systemic effects of a threat load and from where this threat load may be coming. The threat load extends well beyond the viral load and is an assessment of an individual's overall level of illness and disease versus wellness and health – physical, emotional, social, mental and spiritual.

PC19S is a complex sociopsychobiologic syndrome that reflects not only an individual's health but the health of society as a whole.

This begs the question:

Why are we willing to chase a virus and yet refuse to chase health and wellness?

This is not to imply we shouldn't chase the virus, but why are we willing to put such enormous resources into chasing the virus, when for so long we have under resourced
taking care of our health. Healthy people don't die from SARS Cov-2 infections. If we are healthy and people aren't dying from the virus then we all have the potential to live fully.

We can simultaneously chase a virus and pursue health. It is time to pursue wellness through safety, which is the definitive solution for this pandemic. It should be reinforced that better baseline health and better management of acute infections will decrease not only PC10S, but also deaths.

There is a fundamental theme for all healing – when we move people from threat to safety, threat physiology to safety physiology, we suffer fewer infections, fight infections better, and recover from infections more quickly. In fact, we suffer fewer overall illnesses and diseases, heal faster, and are more resilient in general.

Recovery (physical, emotional, social, mental, financial, spiritual) from PC19S will parallel the removal of threats and the reduction of the physiology of threat. Moving people to safety and safety physiology will benefit not just PC19S patients, but all society.

This is the task at hand.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Attachment

Review of Threat

- Do you have a history of a major illness or major surgery?
- Do you have a history of a mold, toxin or radiation exposure?
- Do you have a history of a chronic infection (viral, bacterial, fungal, other)?
- Do you have a history of substance use (alcohol, opioids, methamphetamines, other)?
- Do you lack a secure home or healthy food supply?
- Do you have a history of a major accident with injury?
- Do you have a history of a physical attack or abuse?
- Do you have a history of a sexual attack or abuse?
- Do you have a history of a major emotional (psychological) accident with injury?
- Do you have a history of a major emotional (psychological) attack or abuse?
- Do you experience unpleasant memories frequently?
- Do you have nightmares frequently?
- Do you feel you have difficulty freely expressing yourself?
- Do you feel people don't respect you or your personal boundaries?
- Do you feel your needs are unmet?
- Do you feel you have excessive or insurmountable debt?
- Do you feel you lack an adequate income?
- Do you feel you lack meaning or purpose?
- Do you feel disenfranchised or disconnected from opportunities?
- Do you feel discriminated against or suffer from injustice?
- Do you feel unsafe at home?
- Do you feel unsafe at school, work or in your community?
- Do you feel lonely or isolated?
- Do you feel you lack friends, family or community?
- Do you feel irritable or angry for no clear reason?

- Do you feel worried or anxious for no clear reason?
- Do you feel you are conflicted or stuck for no clear reason?
- Do you feel sad or desperate for no clear reason?
- Do you feel numb, empty or exhausted for no clear reason?
- Do you ever feel suicidal?

Total Score _____/30

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