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and the

Holtorf Updated Peptide Protocol

for the

Rapid Treatment of CIRS (HUPPRTOC)

Kent Holtorf, MD

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Mold Illness

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This chapter is dedicated to detailing new, evidence-based treatments for mold illness and explaining how to effectively diagnose and treat mold-related disease and chronic inflammatory response syndrome (CIRS).

The chapter will review the groundbreaking work and current standard of care, the Shoemaker protocol for CIRS (CSCSPC), and demonstrate how peptides can augment and replace many aspects of this protocol to achieve faster recovery and superior efficacy. This chapter will also cover the symptoms and consistent pathophysiology associated with mold illness, illustrating the multisystem pathophysiology seen with mold patients, emphasizing the diagnosis and treatment of immune dysfunction, a hallmark of CIRS. In addition, this section will review the literature on effective methods of mold remediation and explain the use of peptides to treat mold illness, as well as the correlation between the degree of immune dysfunction, specifically the severity of T cell exhaustion, immunosenescence, and the Th1/Treg to Th2/Th17 shift and the severity of this multisystem condition, CIRS.

Aims and Goals

- Understand how to identify the symptoms of mold exposure and mold illness and differentiate them from other types of fatiguing conditions.
- Understand how mold-associated illness and CIRS have a common immune dysfunction as the underlying pathophysiology that results in a pathological vicious cycle that leads to multi-system disease.
- Understand that an updated multi-system approach that directly targets the underlying dysfunctions, including the immune dysfunction, is currently the most effective and rapid treatment strategy for mold illness and should now be considered the standard of care.
- Understanding that immune modulators, including peptides, effectively address the core abnormality of immune dysfunction, including a Th1 to Th2/Th17 immune shift, natural killer cell dysfunction, abnormal mast cell activation, T cell exhaustion, and immunosenescence, should be the first step in treatment. ***(Continued on Page 4.)***

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Aims and Goals (Cont'd)

- Common pathophysiology seen as a result of the immune dysfunction in mold illness/CIRS includes pineal-hypothalamic-pituitary-hormone dysfunction (despite having so-called "normal "hormone levels), mitochondrial dysfunction, inability to suppress reactivating viral, bacterial, fungal and parasitic infections, immune activation of coagulation, autonomic dysfunction, diminished detoxification capacity, thymic dysfunction, gastrointestinal abnormalities (including dysbiosis, SIBO, "leaky gut," and "leaky brain" via the gut-brain axis), natural killer cell dysfunction, cognitive dysfunction, sleep and mood disorders, cardiovascular abnormalities, pain syndromes, and multiple neurologic pathologies.
- With a greater understanding of the pathophysiology of CIRS, beneficial alterations to the current standard Shoemaker protocol for CIRS that utilizes immune modulators and pathology-specific peptides, and other therapies can significantly increase the effectiveness of the present protocol.
- Therapies that protect the body from the toxic effects of myco and other endotoxins can replace the use of binders, the core therapy of the Shoemaker protocol, which is marginally beneficial, fraught with numerous side effects, poorly tolerated, and often prescribed for many months or years without benefit.

Introduction

Mold is a much more common household toxin than most people realize. According to the World Health Organization (WHO), it builds up in homes and other buildings due to water damage and persistent indoor dampness, affecting between 9-and 70% percent of indoor environments worldwide.[MD1, MD2, MD5] It is not only found in basements, but mold can also permeate walls, floors, and ceilings, often going undetected until the health problems it causes become more than the body's immune system can cope with. While some types of mold are detectable by their color, fuzzy appearance, and/or musty odor, other types of mold can be invisible. As a result, people can be exposed to mold inhalation through skin contact and, in some cases, ingestion.

Inhalation is the most common mechanism of exposure in indoor environments. Harmful mold in homes continuously releases spores and mycotoxins as airborne inhalants, especially in electric and magnetic fields (EMFs).[EMF76-78] It has been reported that 25 percent of people cannot detoxify from mold on their own once they are exposed, making them exceptionally susceptible to mold-triggering chronic fatigue and other serious diseases, but this is far from proven. What is documented is that most individuals suffering from mold-related illness have additional conditions, such as "chronic Lyme disease (including coinfections and reactivating infections)," chronic illness, and significant physiologic stress, that make them more sensitive to the potentially toxic effects of mold due to their preexisting immune dysfunction. Subsequently, the synergistic poisonous effect blamed on toxic mold exposure is actually due to a combination of the entities. Often, when one of these immunotoxic effects is eliminated, and the immune system is normalized or optimized, the patient no longer gets sick from the mold exposure.

Another little-known fact about mold is that many of the mycotoxins produced are more harmful to the human body than any other human-made toxins except for certain radioactive elements. They are also fat-soluble, enabling them to accumulate in the body's fat cells, cell walls, and tissues while causing immune dysfunction. Because they are fat-soluble, mycotoxins in the body are difficult to eliminate on one's own. Additionally, EMFs will stimulate mold growth, but EMFs can also stimulate mold and fungi to secrete thousands of times more mycotoxins than they usually would.[EMF76-78]

- With the expanded use of biomarker testing, a greater understanding of the underlying abnormalities present in each case can be obtained and used to provide more directed, rapid-acting therapeutic strategies that have improved outcomes compared to the current treatment protocols.
- The Holtorf Updated Peptide Protocol for the Rapid Treatment of CIRS (HUPPRTOC) will almost always make using the misunderstood peptide vasoactive intestinal peptide (VIP) unnecessary. Also, with a greater understanding of VIP's mechanism of action, risks, and side effects, it becomes clear that the use of VIP may be helpful in the short term but has long-term adverse effects and significantly hinders long-term resolution of symptoms and mold sensitivity.
- Most all mold illness/CIRS patients have pre-existing immune dysfunction that makes them dramatically more likely to suffer from toxic effects of mold and mycotoxin exposure that has little impact on those with a healthier immune system. Genetic predisposition is far from proven.

Current Method of Diagnosis

Mold illness is also known as mold sickness or toxicity, biotoxin illness, immunologic disease, water-damaged building (WDB) sickness, and environmentally acquired illness. Regardless of how it is termed, it is rarely considered by most conventionally trained physicians as a primary cause or related source of their patients' presenting symptoms. Most physicians do not even recognize mold illness, either because they are unaware of the various ways it can present in the body or are not up-to-date on the science documenting the significant health risks that molds, mycotoxins, and other related contaminants pose. Therefore, it is impossible to accurately estimate how many people suffer from mold illness, though the figure is likely to be in the millions of patients worldwide.

Additionally, the multiple severe symptoms triggered by mold illness are often mistaken by physicians as allergic reactions, blamed on emotional stress, or explained away as being psychosomatic, especially if the patient is female. Frequently, it is a chronic inflammatory condition within the broader category of CIRS.

The leading CIRS and mold illness expert Ritchie Shoemaker, MD. defines CIRS as "*an acute and chronic, systemic inflammatory response syndrome acquired following exposure to the interior environment of a water-damaged building with resident toxigenic organisms, including, but not limited to fungi, bacteria, actinomycetes, and mycobacteria, as well as inflammagens, such as endotoxins, beta-glucans, hemolysins, proteinases, mannans and possibly spirocyclic drimanes; as well as volatile organic compounds.*"[MD1] Shoemaker also coined the term "CIRS-WDB (CIRS water-damaged building)" and recommends a symptom cluster analysis and a triple-tiered diagnosis system to distinguish mold illness/CIRS-WDB from other illnesses.

Symptom Cluster Analysis

While mold illness/CIRS symptoms can initially present in random sequences, Shoemaker's analysis of patients suffering from these conditions revealed thirteen distinct symptom clusters associated with mold illness/CIRS-WDB.[MD2]

CIRS patients suffer from many more multi-system symptoms than listed above in the CSCSPC, so I have not found the symptom clusters very helpful. Given that the above symptoms in each of these clusters are common in other health conditions and, in my opinion, that this cluster mix misses many symptoms suffered by those stricken with CIRS, it doesn't seem very helpful in the diagnosis of mold illness/CIRS nor does it seem to help differentiate CIRS patients from many other multi-system fatiguing conditions. Therefore, I would add the additional symptoms, including but not limited to sleep disorders, anxiety, palpitations, headaches (migraine or pressure), vertigo/dizziness, depression, appetite loss, dyspepsia, epigastric pain, gastrointestinal dysfunction, tinnitus, various neurologic symptoms, cognitive dysfunction (brain fog), weight gain, leptin and insulin resistance, PCOS, chronic cough, temperature intolerance, chest tightness, bruising, shortness of breath (SOB), rhinorrhea, rhinosinusitis, post-exertional fatigue, low libido, brittle nails, feeling overwhelmed, stress, and anxiety.

According to the CSCSPC, the most common misdiagnoses are allergies, anxiety, depression, attention deficit hyperactivity disorder (ADD/ADHD), chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel disorder (IBS), post-traumatic stress disorder (PTSD), and somatic symptom disorder (somatization). Still, these diagnoses are not mutually exclusive, and CFS, FM, IBS, and PTSD share the same pathophysiology and will often have the same symptoms and biomarkers used to diagnose CIRS. It comes down to the fact that it doesn't matter what you call it; the goal is to fix it and end the

Symptom Cluster Analysis

The unique clusters of symptoms are:

- Abdominal pain, diarrhea, numbness
- Shortness of breath, congested sinuses
- Impaired memory, difficulty recalling words
- Heightened skin sensitivity, tingling sensations, "pin and needles."
- Watery eyes, metallic taste, disorientation
- Weakness, body aches, headache, sensitivity to light, trouble grasping new concepts
- Night sweats, blurred vision, mood swings, red or bloodshot eyes, "ice pick" pain
- Morning stiffness, joint pain, muscle cramps
- Severe, persistent fatigue
- Difficulty concentrating
- Static shocks, dizziness
- Persistent cough, extreme thirst, confusion
- Frequent urination and fluctuating body temperature

patient's suffering. Shoemaker notes that adult patients experiencing symptoms in eight or more clusters (six in children) almost certainly (greater than 95 percent likelihood) are affected with mold illness/CIR-WDB.[MD2]

As just mentioned, while the syndrome of CIRS appears to be a unique entity with a unique set of symptoms, it shares a common multi-system underlying pathophysiology seen with chronic infections, including Lyme and associated infections, chronic fatigue syndrome (CFS), fibromyalgia, MCAS, PTSD, mast cell activation syndrome (MCAS), autoimmunity, neurodegenerative diseases, and chronic age-related diseases. Thus, CIRS will respond to new innovative immune-modulating and other therapies that have been developed for the above conditions with a few caveats unique to CIRS. As these newly developed therapies have resulted in the ability to see benefits in chronic Lyme patients in months rather than following the standard "enlightened" therapy of antibiotics for extended periods, often years, the Updated Peptide Protocol for the Rapid Treatment of CIRS (UPPRTOC), which doctors often refer to as the Holtorf Updated Protocol for the Rapid Treatment of CIRS (HHUPPRTOC), can result in rapid improvement in CIRS patients instead of the usual time frame of years that it typically takes to see progress with the current protocol used for CIRS by doctors trained in this condition.

A greater understanding of the pathophysiology of CIRS, combined with new therapies directed at modification and normalization of the dysfunctional systems, improvement, and resolution of CIRS can be achieved much quicker than following the current stepwise CIRS protocol that, while revolutionary and groundbreaking, fails to address numerous vital aspects of the dysfunctions seen with this condition.

Testing For Mold Illness/CIRS

The triple-tiered system of diagnosis Shoemaker developed to diagnose mold illness/CIRS consists of a combination of visual, genetic, and biomarker tests and analysis of MRI brain scans using NeuroQuant®, an FDA-approved software program, and most recently, a transcriptomics test. A brief description of each of Shoemaker's recommended tests follows.

Visual Contrast Sensitivity (VCS) Testing

Research shows that mold and other biotoxins, in addition to causing CIRS, also negatively impact nerves, resulting in various nerve dysfunctions and subsequent neurological symptoms. For example, a common nerve dysfunction in mold illness/CIRS patients is impaired visual contrast sensitivity (VCS), characterized by a diminished ability to detect visual patterns. Shoemaker posits that diminished VCS is caused by reduced red blood cell flow velocity into the eye structures that transmit visual information to the brain via the optic nerve.

VCS testing involves showing patients images designed to evaluate their ability to detect visual patterns. Patients affected with mold illness/CIRS typically score low on VCS tests. VCS testing has been stated to accurately determine mold illness/CIRS in 92 percent of cases, with an estimated eight percent of cases resulting in false-negative readings.[MD3] VCS testing is performed at the initial patient visit and then repeated at follow-up consultations to evaluate the patient's response to treatment. Loss of VCS is not, however, exclusive to CIRS patients.

Genetic Testing: Human Leukocyte Antigen (HLA) Test

The specific gene test used to determine a person's genetic susceptibility to mold illness/CIRS is the human leukocyte antigen (HLA) test. In the body, the HLA system is comprised of genes in chromosome 6. These genes encode cell-surface proteins that play an essential role in the immune system, helping to recognize foreign cells in the body. Therefore, patients in the HLA type category are more likely than other patients to develop CIRS when exposed to mold and other biotoxins.

After reviewing international gene registries matched by case-controlled studies, Shoemaker reported that approximately 25 percent of the population is "mold susceptible" because of their HLA haplotype, making them more susceptible to developing persistent mold illness/CIRS when exposed to mold and related biotoxins.[MD4] With that said, many patients with CIRS do not have a genetic predisposition, so this test cannot rule out someone from having CIRS or be used to diagnose CIRS.

NeuroQuant® Analysis of MRI Tests

NeuroQuant® is an FDA-approved software program used to detect evidence of brain injury. Most patients with mild to moderate traumatic brain injury (TBI) have normal MRI scans. NeuroQuant® can analyze a properly run MRI of the brain and assess volumes of fifteen different brain areas. These data are then compared to MRI data from normal control subjects to determine possible structural brain damage and brain volume atrophy. NeuroQuant® can detect brain atrophy in specific brain structures, which may be linked to particular biotoxins, but is not specific for CIRS.

Shoemaker Protocol Biomarker Tests

The biomarker tests recommended by Shoemaker to screen for or rule-in mold illness/CIRS are transforming growth factor beta-1 (TGF beta-1), C4a, matrix metallopeptidase 9 (MMP-9), leptin, vascular endothelial growth factor (VEGF), anti-gliadin antibodies (AGA), melanocyte-stimulating hormone (MSH), anti-diuretic hormone (ADH), adrenocorticotropic hormone (ACTH), plasminogen activator inhibitor-1 (PAI-1), anti-cardiolipin antibodies (ACA), Von Willebrand factor, and vasoactive intestinal peptide (VIP). I do not disagree with these biomarkers, but I have found that with about double the amount of biomarker tests, which can usually be obtained at standard commercial labs, and an understanding of the limitations of each test, the accuracy, specificity, and sensitivity of the diagnosis is dramatically increased. More importantly, it will give the treating physician a better understanding and direction of treatment based on the abnormalities instead of following a treatment algorithm. The expanded biomarkers also provide a much better objective measure of treatment success.

TGFbeta-1

The biomarker TGF beta-1 (TGFb) plays a vital role in regulating the immune system in chronic infections and illnesses. While potentially beneficial early on in a disease, it becomes a significant player in perpetuating chronic illness.

Chronically elevated TGFb levels occur when there is an overactive Th2/Th17 immune response that is seen in cases of mold illness/CIRS, but also with chronic Lyme disease, parasitic infections, toxin exposure, CFS, fibromyalgia, multiple sclerosis, mast cell activation syndrome (MCAS), IBS, autoimmune disease, immune activation of coagulation, fibrosis; chronic age-related illnesses, such as cardiovascular disease, cancer, and infertility, and neurodegenerative diseases, such as Alzheimer's, Parkinson's, ALS, and other inflammatory conditions.

Elevated levels are consistent with T cell exhaustion, immunosenescence, a Th1/Treg to Th2/Th17 immune shift, and a highly aged immune system where Th1 is low and Th2/Th17 is high. The immune system is like a seesaw with an unhealthy immune system having low Th1/Treg immunity and high Th2/Th17 immunity and is a hallmark of CIRS, aging, and chronic illness and disease severity (See figure 1)[TGF1-7]

Elevated TGFb also stimulates type III deiodinase, inactivating thyroid hormone (lower T3 and free T3) and increasing reverse T3.[TGF9,15] TGFb stimulates myostatin, which inhibits muscle growth (myogenesis) and promotes the differentiation of MSCs into fat cells. This makes patients with mold toxicity and CIRS often have difficulty losing weight and have an increased incidence of obesity, muscle weakness, cardiomyopathy, sleep disorders and deep sleep, low vitamin D, reduced growth hormone, reduced acetylcholine formation, Crohn's disease, scleroderma, loss of muscle mass (sarcopenia), fatigue, allergies, osteopenia/osteoporosis, kidney and liver fibrosis, capillary leakiness (edema), cognitive dysfunction, insulin resistance, diabetes, hypercholesterolemia, cardiovascular disease, and overall mortality.[TGF10] Elevated TGFb also reduces Treg and NK cell activity, increasing the risk of autoimmunity, inability to fight intracellular pathogens, inability to detoxify mycotoxins and other environmental and enterotoxins, and have a reduced ability to fight cancer with increased metastasis.[TGF10,11,16]

Figure 1

Th1/Treg to Th2/Th17 Immune Shift

New cellular laboratory techniques show that T cell exhaustion (TCE) and immunosenescence are the core underlying pathophysiologic processes causing CIRS. TCE is associated with progressive loss of effector functions of T cells (CD4 and CD8), dysfunctional Th1 immunity, as indicated by low NK cell function, IL-2, IL-12, and low TNF-alpha in late stages, and an elevated hTGFb, C4a, IL-6, and IL-10, along with the Th1 to Th2/Th17 immune shift. (see *Immune Dysfunction and CIRS* below)[TGF1-3, 5]

Thus, targeted therapy that addresses this core immune dysfunction, which includes a variety of immune-modulating peptide therapies, will help normalize the immune system, the resultant multisystem dysfunctions, and subsequently the symptoms of CIRS, allowing the potential for a much more rapid improvement than is seen with current CIRS protocols.

C4a

Biomarker C4a, like TGF-beta, is a marker of a dysfunctional immune system that is shifted from a healthy Th1/Treg dominant immune system, exemplified in young, healthy individuals, to a Th2/Th17 dominant immune system that is displayed in aged and chronically ill individuals. It helps activate a specific inflammatory process of the innate immune system known as a complement cascade. As a biomarker, C4a correlates with the degree of illness and can help serve as an objective measure of disease and improvement with treatment. [C4A1-3]

An elevated C4a can occur with multiple infections and reactivating infections associated with immune dysfunction, CFS, fibromyalgia, MCAS, autoimmune disease, and many diseases of aging. Again, elevated C4a levels, demonstrating a Th1/Treg to Th2/Th17 shift, can trigger immune activation of coagulation, breathing difficulties, fatigue, impaired detoxification, and cognitive function, all of which are hallmarks of mold illness/CIRS. Still, they are not specific for mold illness or CIRS. Shoemaker reports that mold illness/CIRS patients with high C4a levels suffer from decreased blood flow into the capillaries, which would be expected to be the case with many chronic illnesses and potentially a contributing cause of cognitive dysfunction, as is common in CIRS and other chronic immune-related diseases.[C4A3]

A robust Th1 immunity is required to detox from mycotoxins. For instance, Lyme patients with low Th1 immunity function cannot convert weak IgM antibodies to more powerful complement-activating IgG antibodies. On a personal note, I originally only had a single Lyme Western blot IgM 41 kd band, which is technically a negative test. After modulating my immunity and improving Th1 activity, I converted to having seven IgG antibodies on the Lyme western blot (a clear positive). With low Th1 immunity, the mycotoxins are not recognized via pattern recognition receptors and are not eliminated, along with the lack of tagging and elimination by IgG antibodies and phagocytic cells. Also, the immune-induced mitochondrial dysfunction results in cells that do not have enough cellular energy to eliminate intracellular and transmembrane heavy metals and mycotoxins.[C4A1, 4]

Matrix Metallopeptidase 9

Biomarker Matrix Metallopeptidase 9 (MMP-9) is a general inflammatory marker that helps break down cell membranes in the walls of blood vessels, enabling inflammatory compounds to travel from the blood vessel walls to various organs and tissues, including in the brain, lungs, joints, and muscles, and peripheral nerves. With mold illness/CIRS-WDB, cytokines cause various white blood cells to dump MMP-9 into the bloodstream, increasing inflammatory

biochemicals in the tissues and causing inflammation throughout the body. MMP-9 is an enzyme activated by macrophages inducing inflammatory cytokines that destroys the basement membrane of endothelial cells, which serves as a barrier between substances in the blood, allowing inflammatory compounds to penetrate tissue.[MMP1] It is also shown to increase blood-brain barrier permeability, allowing inflammatory substances, cytokines, and cells to enter the brain.[MMP2] High MMP-9 contributes to the destruction of connective tissues and increases Lp(a), increasing the risk of immune activation of coagulation, cardiovascular disease, and cardiomyopathy. Cytokine testing can be problematic. A prechilled SST tube is essential to use. Following the lab draw, the specimen should be immediately centrifuged and frozen. This step will prevent the release of MMP9 from the white blood cells into the blood specimen, which can double or triple at room temperature in as little as 30 minutes. Unfortunately, this is often not done in a busy commercial lab, making MMP9 an unreliable marker.

Leptin

Fat cells produce the Biomarker Leptin to help regulate hunger and fat stores. With increased fat storage, increased leptin is secreted, which should feedback on the hypothalamus and tell the body to decrease appetite, increase metabolism, burn fat, and increase thyroid production. In cases of excess inflammation, whether from mold, chronic infection, or diabetes, the inflammatory cytokines block the leptin receptors, so the brain thinks the body is starving and tells the body to store fat, increase hunger, and decrease metabolism and thyroid levels. A number of chronic illnesses and aging can result in leptin resistance.

Much like the elevated levels of insulin seen in patients with insulin resistance, elevated leptin levels indicate leptin resistance. The normal range for leptin in men is listed as 0.5-13.8 ng/ml and 1.1-27.5 ng/ml in women, but these laboratory ranges include obese people and those with chronic illnesses who have significant leptin resistance. A healthy leptin level should be between 1 and 10 ng/ml. Levels above 10 ng/ml are leptin resistance markers and are often seen in people who have difficulty losing weight. Leptin is also needed for the pituitary to produce and secrete TSH. Thus, with leptin resistance, the TSH is not a reliable marker to determine the presence of hypothyroidism. It is also a marker for low thyroid despite having a normal TSH and is often seen in those with insulin resistance. Still, a person can suffer from significant leptin resistance without having any insulin resistance. [LEP1,2]

Vascular Endothelial Growth Factor

Biomarker Vascular Endothelial Growth Factor (VEGF) is a signaling protein. It plays a vital role in cells responsible for growing new blood vessels needed to supply oxygen to tissues during diminished blood circulation. Under normal conditions, when capillary blood flow decreases, the resulting reduction in oxygen levels triggers the release of hypoxia-inducible factor (HIF). HIF, in turn, aids in the production of VEGF and erythropoietin (EPO). VEGF increases blood flow by creating new blood vessels, while EPO increases the production of red blood cells. Together, they work to improve the oxygen supply to the cells.[VEG2]

In patients with mold illness/CIRS, VEGF is suppressed due to high cytokine levels. The result is diminished oxygen supply to the tissues, leading to muscle cramps, which Shoemaker feels is the cause of extreme exhaustion following exercise or physical activity. While it very well may play a part, post-exertional fatigue has been shown to mainly be a function of mitochondrial dysfunction and immune activation of coagulation, resulting in a premature anaerobic

threshold, which is a hallmark of CIRS, chronic Lyme, CFS, FM, neurodegenerative diseases, and most every age-associated illness.[VEG1] The normal range of VEGF is 31-86 pg/ml. Bartonella will stimulate VEGF.

As a side note: my VEGF was off the chart when I was diagnosed with Bartonella in addition to Lyme and Babesia. Due to this elevated VEGF, my vessels were grotesquely enlarged all over my body. They were not varicose veins, just huge. I got them sclerosed for cosmetic reasons, but after I rid my body of Bartonella, I scarcely had a visible vein to draw blood from or to start an IV.

Anti-Gliadin Antibodies

Biomarker Anti-Gliadin Antibodies (AGA) are produced in the body as a reaction to gliadin, a compound contained in gluten. AGA is one of the factors that cause celiac disease. Under normal circumstances, gliadin is broken down into various amino acid chains (peptides). To utilize these peptides, specific epithelial and endothelial cells in the intestines known as tight junctions (because they resemble a tightly sealed interlocking gateway) need to open to allow the peptides to pass through. Once the nutrient or signaling peptide has passed, the tight junctions immediately close in healthy people. In some patients with mold illness/CIRS or other chronic illnesses (as well as patients with celiac disease), the gliadin protein trigger inflammatory and immune reactions that keep the tight junctions from completely closing, resulting in "leaky gut." The normal range for AGA is 0-19 units. AGA levels above this range can be another nonspecific indicator of mold illness/CIRS because it occurs in many chronic diseases, and "leaky gut" is a significant problem for so many chronic diseases due to the associated immune dysfunction discussed later in this chapter.[AGA1-4]

Rather than just checking for anti-gliadin antibodies, it is straightforward and inexpensive to check for a hundred or more food sensitivities (IgG antibodies, not IgE, which is an allergy). If you test positive for a significant number of foods, it demonstrates that these large food proteins are getting absorbed when they should not. This shows that the tight junctions in the gut are damaged, which is called leaky gut. If you have a leaky gut, you can be sure that your blood-brain barrier is also leaky. The good news is that there is a combination of peptides that heal inflammatory gut issues, dysbiosis, IBS, GERD, and specifically heal the tight junctions and leaky gut (discussed later in this paper).[AGA1-17]

Melanocyte-Stimulating Hormone

Biomarker Melanocyte-Stimulating Hormone (MSH) helps regulate many other hormones and plays an essential role in the body's inflammation responses to foreign pathogens. It is one of the most anti-inflammatory substances produced in the body.[MSH 1]

Unlike steroids, however, MSH and its analogs, such as the MSH fragment KPV, do not lower the body's ability to fight infections; rather, they significantly enhance the body's immunological defense against invading organisms and also have potent broad-spectrum antimicrobial effects against bacteria, viruses, mold, parasites, and fungi (discussed later in this chapter).[MSH4-5] Thus, low levels of MSH will result in multisystem inflammation (i.e., CIRS) and an inability to fight many infections, with MARcONS infection of the sinuses being a specific example. MSH acts as a guardian of the skin and mucous membranes, killing fungi and coagulase-negative staphylococci. With normal MSH, MARCoNS is unlikely to survive.[MSH2-4]

MSH and leptin have reciprocal stimulating effects on each other. Under normal conditions,

increased leptin levels result in a corresponding increase in MSH and vice versa. However, inflammatory cytokines interfere with leptin receptors, causing leptin resistance and high leptin levels, which is associated with low MSH because the leptin signal does not reach the receptors in the brain. Low levels of MSH are evident in patients with mold illness/CIRS and can remain low even after treatment. When this happens, leptin production increases without a corresponding rise in MSH levels, resulting in leptin resistance and unhealthy weight gain. A rise in leptin levels in healthy people would trigger the brain to create more MSH, which does not occur in CIRS patients.

MSH is also involved in the opening and closing of tight junctions in the intestinal tract. Diminished MSH levels can prevent tight junctions from closing correctly, leading to a leaky gut.[MSH1-2] In addition, some research has reported that approximately 80 percent of patients with low MSH levels also have MARCoNS (multiple antibiotic resistant coagulase negative staph, usually concentrated in the sinuses). This creates a vicious cycle because MARCoNS produces toxins that suppress MSH production.[MSH 1-2] Treating MARCoNS can be necessary to restore MSH levels to normal levels.

There are, however, much better ways to deal with and treat low MSH and MARCoNs than what is recommended for this in the CCSCP, as we will see.

Anti-Diuretic Hormone

Biomarker Anti-Diuretic Hormone (ADH), also known as vasopressin, is produced by specialized nerve cells in the hypothalamus. It helps maintain blood pressure, blood volume, and tissue water content by controlling the amount of water your kidneys reabsorb as they filter out waste from your blood. ADH signals the kidneys to conserve water and produce a more concentrated urine, diluting your blood, lowering the blood's osmolality (particle concentration), increasing blood volume, and increasing blood pressure. Conversely, suppose you produce too little ADH. In that case, your body loses too much water in the urine, potentially resulting in excessive blood osmolarity, frequent urination, dehydration, low blood pressure, increased thirst, fatigue, mental confusion, muscle aches and pains, frequent migraines, and postural orthostatic tachycardia syndrome (POTS), whereby your blood pressure drops and heart races when standing, and which is associated with high blood sodium levels. This is called diabetes insipidus.[ADH1] Such patients will often "drink like a fish and pee like a racehorse."

If your body produces too much ADH, water is retained, producing highly concentrated urine, high blood volume and blood pressure, and low serum sodium levels. This is called the syndrome of inappropriate ADH (SIADH). Symptoms can include nausea, headaches, disorientation, and tiredness or lethargy.

CIRS patients will typically have low ADH levels due to inflammation or damage in the hypothalamus, hippocampus, or amygdala.[ADH2] The normal range for ADH is 1.0-13.3 pg/ml, and normal blood osmolality is 275-298 mOsm/kg. You can order the blood osmolarity level via a blood test, or it can be easily calculated by using several websites where you enter your lab values for sodium, BUN, and glucose. In CIRS patients, there will often be a high normal blood osmolarity, with ADH being low normal.

Adrenocorticotropic Hormone

Biomarker Adrenocorticotropic Hormone (ACTH) plays a vital role in how the body responds to stress. ACTH is produced in the pituitary gland, and its production stimulates the production and release of cortisol from the adrenal glands. In healthy people, cortisol levels rise during the early morning, usually peaking by 8 am, and then decrease during the evening.

However, this process is negatively impacted by chronic inflammation and chronic illness, including mold illness/CIRS. Under such circumstances, cortisol production is interfered with, diminishing the body's ability to deal with stress.

In a state of good health, the production of ACTH is adjusted in response to the rising or lowering of cortisol levels. But in patients with mold illness/CIRS and other immune-related diseases, this process is often disrupted, causing fatigue, interfering with healthy sleep, and triggering a variety of other symptoms, including hypoglycemia (low blood sugar), fatigue, nausea, weakness, dizziness, weight loss, muscle aches, diarrhea, irregular periods, and inability to handle stress.[ACTH2] The normal range for ACTH is 8-37 pg/ml, and the normal ranges for cortisol are 4.3-22.4 ncg/dl (morning) and 3.1-16.7 ncg/dl (evening).

Inflammation induces the secretion of corticotropin-releasing factor (CRH) from the hypothalamus, which then stimulates the pituitary to produce ACTH, which stimulates the adrenals to make cortisol. The problem is that the pituitary can become resistant to CRH and cause ACTH resistance in the adrenals with significant inflammation. This results in high levels of CRH, which is a potent stimulator of inflammation and mast cell activation, but it may not stimulate cortisol due to ACTH resistance.[ACTH1] This results in low cortisol, further increasing inflammation and mast cell activation and an inability to handle physiological stress.

In addition, there can also be suppression of CRH in the hypothalamus, which results in low levels of ACTH and cortisol, resulting in increased inflammation and mast cell activation and an inability to handle stress.

Plasminogen Activator Inhibitor-1, Anti-cardiolipin Antibodies, and Von Willebrand Factor

Biomarkers Plasminogen Activator Inhibitor-1 (PAI-1), Anti-cardiolipin Antibodies (ACA), and Von Willebrand Factor (VWF) comprise the standard coagulation panel recommended in the current CIRS treatment algorithm but are inadequate to consistently identify those who are hypercoagulable and have immune activation of coagulation. Only doing these three tests according to the CSCSPC will miss up to 90% of CIRS patients that suffer from immune activation of coagulation, which is shown to occur in up to 90% of CIRS patients, depending on the sensitivity of the testing panel done.[PAV1]

The common understanding of CIRS holds that PAI-1, ACA, and VWF can cause blood clots and are biomarker indicators of abnormal bleeding conditions. Mold illness/CIRS and other inflammatory diseases cause PAI-1 to rise, increasing blood clotting and the risk of fibrosis. ACA antibodies target normal body tissues, negatively impacting phospholipid proteins in cell membranes. Elevated ACA levels are involved in connective tissue disorders such as scleroderma and lupus and can cause miscarriages. PAI-1 and ACA, in combination, are significant risk factors for heart attack, stroke, and deep vein thrombosis (DVT). Mold illness/CIRS patients are also at risk for a type of acquired Von Willebrand Syndrome, a condition that prevents proper blood clotting and which can result in frequent or heavy nosebleeds and, in women, excessive bleeding during menstruation.[PAV2-3]

The HUPPRTOC recommends a much more extensive and comprehensive hypercoagulation panel because the standard hypercoagulation panel recommended in the current CIRS protocol will miss 60-90% of those suffering from immune activation of coagulation. Missing this abnormality will often result in multiple levels of treatment failure and a frustrating protracted illness (see Immune Activation of Coagulation later in this chapter).[PAV4]

Vasoactive Intestinal Peptide

Biomarker Vasoactive Intestinal Peptide (VIP) is a neuropeptide produced in the hypothalamus, pancreas, gastrointestinal tract, and other places in the body. VIP is an interesting substance; it has many beneficial anti-inflammatory effects but can vigorously promote immune dysfunction. VIP plays a vital role in regulating the body's inflammatory responses; however, studies are inconsistent, with some showing a worsening of inflammation and autoimmunity and others showing anti-inflammatory effects.[VIP1-2]

VIP is also involved in regulating blood flow and the response of the pulmonary artery during exercise. Low VIP levels are thought to cause pressure to build in the pulmonary artery during exercise and strenuous physical activity, resulting in shortness of breath. I have found that immune activation of coagulation is likely a more frequent cause of shortness of breath or air hunger and that symptoms resolve with treatment. Both scenarios can, however, certainly be contributing symptomatically. Shoemaker has reported that nearly all (98 percent) mold illness/CIRS patients have low VIP levels.[VIP4] This may be influenced by the fact that this test requires complicated processing and to immediately be placed in dry ice, which is often not done correctly at standard labs. If not processed correctly, which frequently happens, it becomes undetectable. This is often mistaken for a suppressed VIP level due to mold toxins.[VIP3]

Problems With the Standard Treatment of Mold Illness/CIRS

The biggest problem with any treatment of mold illness/CIRS is that most physicians never look for this condition, or they use inappropriate treatments intended for other conditions based on symptomatic treatment, such as antidepressants and antianxiety, antiseizure, and pain medications. As a result, unless patients are aware of or suspect their symptoms are due to mold or other biotoxin exposures and seek out knowledgeable physicians in this area, they will typically suffer for months and even years without their symptoms being adequately addressed. At the same time, their overall health continues to worsen. Even if a mold patient finds a doctor knowledgeable about mold-associated illness and CIRS, the current standard of care, the CSCSPC, often takes months or years to see improvement, if any.

The few physicians in the U.S. who recognize, screen for, and treat mold illness/CIRS, usually do so by following the CSCSPC. It consists of the following twelve steps, which need to be administered in sequential order and do not directly address the core dysfunctions of CIRS, but rather utilize a prolonged, expensive, and inefficient therapy that has a high rate of side effects and failure or often only results in partial improvement. The HHUPPRTOC immediately addresses the underlying core dysfunctions seen with CIRS and mold-associated illnesses, as well as directly protecting the body from the toxic effects of the myco- and other enterotoxins.

The CSCSPC process often requires multiple years to achieve improvement, if it does at all. Additionally, much like the diagnosis of Lyme disease, the diagnosis of CIRS is not precise. While Shoemaker has done significant work and research regarding the diagnosis, pathophysiology, and treatment of CIRS, he has tried to piece together a diagnosis based on visual contrast and Neuroquant® testing, genetic susceptibility, biomarker analysis, symptom grouping, and most recently, genomic analysis. While a detailed review and critique of each of these modalities are beyond the scope of this chapter, it is clear that many of these modalities

are either difficult to get, expensive, complicated, and most importantly, not specific for CIRS. This is not surprising, as the underlying pathophysiology of CIRS is not specific, although most doctors think of mold when they think of CIRS.

This is not an attack on Dr. Shoemaker or the CSCSPC because it suffers from the same lack of sensitivity and specificity as the diagnosis of chronic Lyme disease. While I diagnose many patients with chronic Lyme disease, I try to explain that Lyme (*Borrelia burgdorferi*) may very likely be present and a significant cause of their symptoms, but the actual cause of their condition and reason for their symptoms is multifactorial. While Shoemaker clarifies that chronic Lyme disease can cause CIRS, I argue that mold can be a significant contributing cause of the symptoms of Lyme disease, and mold may need to be addressed to be able to treat many patients with chronic Lyme disease successfully. Much like the problem with chronic Lyme disease, it is often a mixture of unknown infections and external and internal etiologies that result in a vicious multi-system dysfunction cycle. The same is true of CIRS, and no wonder the method of diagnosis is imprecise.

The good news is that they all have common pathophysiology, which Shoemaker agrees with. The immune dysfunction then results in a vicious cycle of multisystem illness, which can be detected with a high degree of certainty. If a patient appears to have both mold and Lyme disease, the peptides can usually treat both simultaneously, so you don't have to decide which to treat first. The even better news is that with a greater understanding of the underlying pathophysiology associated with CIRS, HUPPRTOC addresses more of the underlying physiologic abnormalities of both conditions than the old CSCSPC, so you often see significant improvement much more quickly than with the current method of treatment, and it is effective when the current protocol is not. HUPPRTOC does not, however, throw the baby out with the bathwater. It is an enhanced protocol that builds on the CSCSPC, usually leading to a much faster and more effective recovery than with the CSCSPC.

Based on the common pathophysiology, so many conditions can be looked at as variations of the same processes that involve chronic, often unknown infections (primary and reactivating), immune dysfunction, including T cell exhaustion, immunosenescence, and Th1 to Th2/Th17 shift, thymic and pineal involution, mitochondrial dysfunction, excessive mast cell activation, pineal-hypothalamic-pituitary-hormone axis abnormalities (including thyroid deficiency not detected by standard blood tests and other hormone deficiencies), immune activation of coagulation, cancer, rapid aging, GI dysfunction, leaky gut and blood-brain barrier, brain inflammation, obesity, cognitive dysfunction, insulin resistance, endothelial dysfunction, inflammation, autoimmune disease, neurodegenerative disease, cardiovascular disease, toxic overload, abnormal temperature and vascular regulation, anxiety or irritability, sensitivities, sleep disturbances, muscle or joint pain, CFS, fibromyalgia, chronic stress, depression, migraines, diabetes, PCOS, PMS, neuropathies, chronic kidney disease, and potentially a number of often unexplained or misdiagnosed symptoms and conditions. The population may be living longer, but it is also sicker. In 2013, just one in twenty people (4.3%) had no health problems, with a third of the population experiencing more than five ailments.[PD1]

People lose more "years of healthy life" to illness now than they did in the 1990s; the Global Burden of Disease Study published in The Lancet showed that older Americans are sicker compared to ten other high-income counties despite the universal coverage that Medicare provides. Older Americans had the highest rate of having three or more chronic conditions and required help with activities of daily living (36% in the U.S to a low of 13% in New Zealand.[PD2]

On a personal note, during a particularly stressful period of my life, I became progressively sicker to the point of being mostly bedbound for

months with severe fatigue, anxiety, panic attacks, a severe sleep disorder, profuse sweating, neuropathy, complete inability to handle stress, allodynia (skin hurts with regular touch), along with many other symptoms. I then went into heart failure and intermittent a-fib. I could not stand upright or walk upstairs, and I developed autoimmune kidney disease and antiphospholipid syndrome. I was diagnosed with Lyme disease, Babesia, Bartonella, and a number of reactivating viruses and mold toxicity. I initially tried massive doses of antibiotics and the CSC-SPC, doing four to seven intravenous antibiotics simultaneously at many times the maximal doses for close to four years, and yet had no improvement. My immune system was barely functioning (my natural killer cell function ran between 0 and 3 LU (normal is > 30 LU); no wonder the antibiotics didn't work. I remember being in the ICU with sepsis and overheard the nurses talking outside my room, stating, *"This is the AIDS patient that keeps coming up negative for HIV."* I luckily found the power of immune modulation and directed pathophysiologic treatment with peptides.

After trying peptides, I felt different within a few days, and by the six-month mark, I was a different person. To the astonishment of my cardiologist, I walked into his office and was shown to have a normal cardiac function test about a year later after he said that I could maybe improve 10% in 10 years if I did intense cardiac rehab. He had never seen such a recovery. I also found a number of therapies that were very synergistic with the peptides, including LDN, T3, ozone, stem cells, plasmapheresis, IVIG, and oligonucleotide therapy.

Diagnosis of CIRS

One can certainly use the CSCSPC for the diagnosis of CIRS, but we have found that simple antibody levels to toxic molds, which is a straightforward test to get from standard commercial laboratories and an inexpensive method to determine exposure to toxic molds, is shown to have a high sensitivity and specificity. This can also be done at a number of specialty labs. A significant number of studies show that this simple test is accurate, sensitive, and specific, especially when combined with positive symptoms and biomarkers.[DC1-4] These tests can easily be ordered by standard labs and done at a fraction of the cost and time called for by the standard CIRS protocol. It has also been shown that all patients with mold exposure (positive antibodies to toxic molds) also have autoantibodies to neurologic tissues, with over 80% showing abnormal nerve conduction studies.[DC3] The most specific neural autoantibodies need to be done at specialty labs.

Most CIRS patients, especially those who have Lyme disease, will also have antibodies against brain structures called PANS.[DC4] This is associated with significant neuro-psychiatric dysfunction that seldom gets correctly diagnosed. The combination of symptoms and toxic mold antibodies and/or a simple, inexpensive home or business mold testing (can do more expensive versions); an expanded group of biomarker testing that includes the Shoemaker biomarkers plus additional easily obtained (but rarely ordered) tests, along with a number of the following symptoms can make the diagnosis much quicker and more accessible and much less expensively than what the current protocol calls for. The symptoms include significant fatigue, sleep disturbance, post-exertional fatigue, memory or cognitive dysfunction, ADD/ADHD, OCD, addictions, GI disturbance, flushing, excessive sweating, light sensitivity, unexplained weight gain or loss, excessive thirst or urination, joint pain, headaches, rashes, muscle pain or weakness, anxiety or depression, neurologic symptoms, including neuropathy, numbness or tingling, shooting pains, sensitivities, shortness of breath or poor endurance, histamine intolerance, static shocks, arrhythmias or palpitations, chronic cough, mast cell activation symptoms, or diagnosis of chronic Lyme disease or associ-

ated infection, CFS, fibromyalgia, PTSD, bipolar disorder, infertility, regional pain syndrome, POTS, PANS or PANDAS, Ehlers-Danlos syndrome (EDS), yeast overgrowth, leaky gut, seizers, severe periodontal disease, chronic sinusitis, SIBO, IBS, IBD, any autoimmune or neurodegenerative disease, and anything not clearly explained by another underlying condition. In a review of 119 patients exposed to mold in water-damaged buildings with positive antibodies to toxic molds and associated symptomatic peripheral neuropathy, 99 out of the 119 mold-exposed patients had confirmatory abnormal nerve conduction studies, and more importantly, all of the patients had highly significant increases in autoantibodies against neural antigens compared to healthy controls.[DC3] Of the nine antineuronal autoantibodies tested, the most significant were anti-myelin basic protein, myelin-associated glycoprotein, anti-tubulin, and anti-neurofilament antigen.[DC3]

Immune Dysfunction and CIRS

Most adults are infected with numerous persistent infections, such as Epstein-Barr Virus (EBV), Varicella-Zoster Virus, cytomegalovirus (CMV), Borrelia burgdorferi, Bartonella, toxoplasmosis, H-Pylori, Human Papillomavirus (HPV), tapeworms, roundworms, helminths, and many more. A healthy person with adequate Th1 immunity will be able to suppress these infections, and they will remain dormant. If, however, anything suppresses the Th1 immunity, including aging, an acute or additional chronic infection, stress, toxin exposure, such as mycotoxins, metabolic or mitochondrial dysfunction, chronic illness, etc., the dormant infections can reactivate, further suppressing the Th1 immune system. For instance, in a study published in Science Express entitled *Fighting Parasitic Infection Inadvertently Unleashes Dormant Viruses*, the scientists identified specific signals in mice that mobilize the immune system to fight tapeworms, roundworms, and other helminths, parasites that infect nearly a quarter of all humans. The same signals cause an inactive herpes virus infection in the mice to begin replicating again.[ICD97,100]

Numerous viral and bacterial infections, such as COVID causing reactivation of toxoplasmosis, EBV, or Lyme disease, and Lyme disease-causing reactivation of EBV and HHV6, can also induce reactivation of latent infections, as well.[ICD12,97-98] This can result in a vicious cycle leading to numerous diseases, including autoimmunity, neurodegenerative disease, diabetes, "chronic Lyme disease," CFS, fibromyalgia, cardiovascular disease, cancer, and much more. A hallmark of all of these "inflammatory diseases and diseases of aging" are significant immune dysfunction, which includes T cell exhaustion and immunosenescence with resultant Th1 to Th2/Th17 immune shift, elevated HTGFb, and C4a, and a reduction of natural killer cell (NK cell) activity. CIRS is a quintessential example of an immunological-based multi-system illness.[ICD78-82] In a review article entitled "The Neurological Significance of Abnormal Natural Killer Cell Activity in Chronic Toxigenic Mold Exposures," the authors state:

"In the light of this review, it is concluded that chronic exposures to toxigenic mold could lead to abnormal NKC activity with a wide range of neurological consequences, some of which were headache, general debilitating pains, fever, cough, memory loss, depression, mood swings, sleep disturbances, anxiety, chronic fatigue, and seizures. Depression, psychological stress, tissue injuries, malignancies, carcinogenesis, chronic fatigue syndrome, and experimental allergic encephalomyelitis could be induced at very low physiological concentrations by mycotoxin-induced NKC activity..It appears that an abnormal immunoregulatory response based on environmental mycotoxic damage to T cells is fundamental to the production of symptoms of mycotic illness."[ICD78]

Numerous studies have confirmed that the core

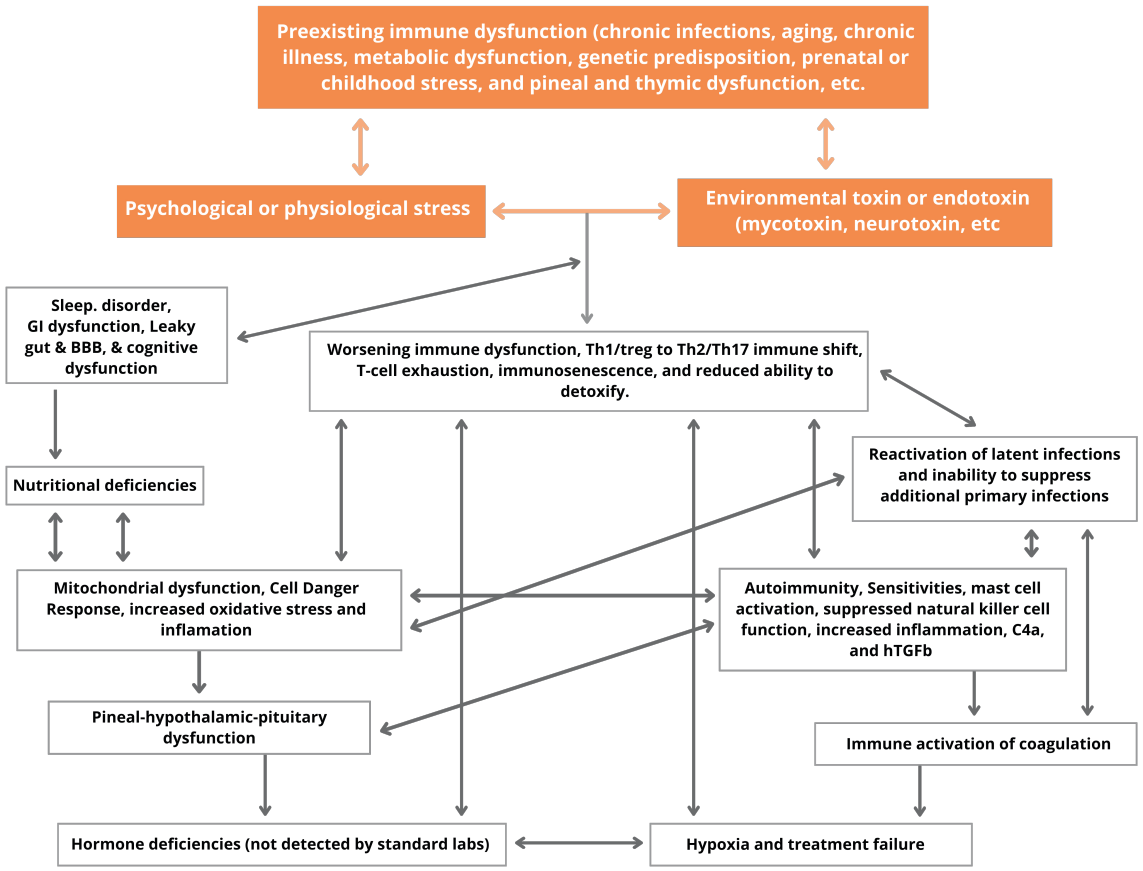


Figure 2 Kent Holtorf, MD, 2022®

damaging effect of mold and mycotoxin illness is on the immune system, which sets off a vicious cycle of dysfunction, resulting in multisystem illness. Thus, it stands to reason that the primary therapeutic target should be to reverse the mold-induced immune dysfunction. Low NKC activity is also an objective marker for severe disability in patients with CFS and is associated with worse overall symptoms and increased cancer risk in CIRS patients.[ICD1-2,4,3I,78,83] Most labs test CD57 NK cells, which are more mature but less active than CD56 NK cells. An elevated CD57 NK cell number may be a marker for immunosenescence. It is always better to check the activity rather than the number, as the cells may be there, but they have poor surveillance and cytotoxic activity.[IDC 1-3] We recommend getting the natural killer cell function through Quest (special send out) and a total CD57 and CD56 as part of an extensive immune panel, or CD56 and CD57 number from LabCorp. Also, Cyrex Laboratories has a test panel called the Lymphocyte MAP that can be very helpful in determining immune dysfunction. CIRS patients have an increased incidence of autoantibodies to neural structures, including but not limited to microtubule-associated protein-2, myelin basic protein, tau, glial fibrillary acidic protein, tubulin, and S-100B. The mycotoxins also directly inhibit thymic, NK cell, and mitochondrial function.[IDC1-4]

NK cells are thought of as cytotoxic lymphocytes critical to the innate immune system and function as a marker for Th1 immunity, but they also serve immunoregulatory functions, with low NK cell activity being associated with significant atopy and IgE levels and clinically worse autoimmunity, inflammation, and the multisystem symptoms of CIRS, chronic Lyme disease, CFS, fibromyalgia, neurodegenerative disease, MCAS, and diseases of aging.[ICD78] It makes sense, as NK cell function is an accurate down-

Mold can exacerbate sensitivities and conditions in at least eleven main ways:

One: Mold components, including spores, mycelium molecules, B-1,3 glucans, glycoproteins, and hyphal fragments, have been shown to act as allergens, increasing inflammation and sensitivities via the increased production of histamine, mast cells, and IgE antibodies.[ICD1-4]

Two: Direct and epigenetic immune-modulating effects of mycotoxins previously discussed, including suppression of NK cell function, thymic function, pineal-thymus axis, Th1 immunity, IL-2, IL-12, MSH, and VIP, stimulation of thymic involution, Th2/Th17 immunity, and subsequent inflammatory cytokines TGFb, C4a, C3a, IL-6, MMP-9, and others. Mycotoxins inhibit IL-12 production by dendritic cells, leading to impaired Th1 cell differentiation, and promoting Th2/Th17 driven inflammatory and autoimmune diseases.[ICD102,1-4]

Three: The stimulation of autoantibodies, including a wide range of antineuronal, antimitochondrial, and many other autoantibodies. Mold and mycotoxins can trigger and worsen PANS, and most autoimmune disorders.[ICD1-4]

Four: Mycotoxins have direct and indirect toxic effects on mitochondria.[ICD4]

Five: Direct damage to mucosal and other tissue barrier functions, including gastric, pulmonary, and BBB integrity and the function of tight junctions.[ICD1-4]

Six: Mycotoxins alter the gastrointestinal microbiota, causing dysbiosis via direct antimicrobial effects, mucosal inflammation, effects on the enteric immune system, and altering gastrointestinal function, secretions, and immunity.[ICD4]

Seven: Suppression of the pineal-hypothalamic-pituitary-(multi-hormone axis), including adrenal, thyroid, gonadotropins, growth hormone, ADH, estrogen, progesterone, aldosterone, DHEA, melatonin, oxytocin, MSH, etc.

Eight: Immune activation of coagulation (more on this to follow).[ICD2,3,78]

Nine: Direct and indirect activation of mast cells by fungi and mycotoxins[ICD 101]

Ten: Direct and indirect nephrotoxic, carcinogenic, teratogenic, mutagenic, immunotoxic, hepatotoxic, and neurotoxic effects on the central and peripheral nervous system.[ICD4]

Eleven: Stimulation of ROS and oxidative stress and the depletion of antioxidants, such as glutathione, further stimulating a Th1 to Th2/Th17 immune shift.[ICD103]

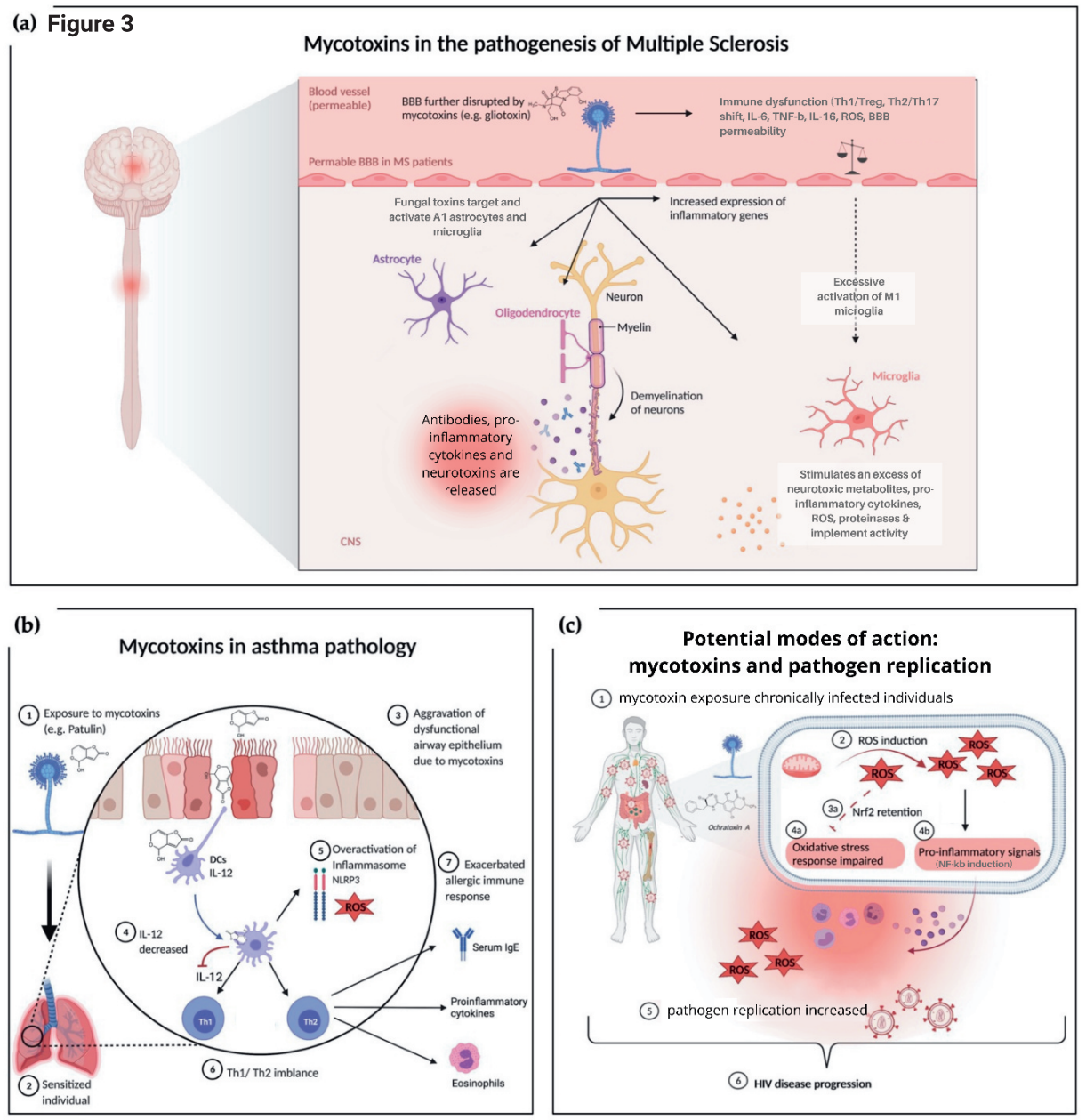
stream marker of Th1 immunity, so a low Th1 immunity would be expected to be associated with worse Th2/th17 inflammation and autoimmunity.[ICD4,78,83]

In an extensive review article entitled "Molecular and cellular insight into T cell exhaustion," published in the journal Nature Reviews: Immunology, the authors concluded, "*In chronic infections and cancer, T cells are exposed to persistent antigen and/or inflammatory signals. This scenario is often associated with the deterioration of T cell function: a state called 'exhaustion.' Exhausted T cells lose robust effector functions, express multiple inhibitory receptors, and are defined by an altered transcriptional program. T cell exhaustion is often associated with inefficient control of persisting infections and tumors.*"[VIP1,TGF2]

Exhausted T cells cannot eradicate intracellular pathogens or mycotoxins or repair toxin-induced damage due to immune-induced mitochondrial dysfunction and other damaging mycotoxin effects while causing excessive inflammation. This sets off a vicious cycle of immune dysfunction, causing mitochondrial

damage, which excretes excessive ROS and inflammation and creates more damage and immune suppression, which then causes more mitochondrial damage. The severity of TCE correlates with the level and length of antigen stimulation and the amount of thymic dysfunction. TCE is reversible (distinct subsets of T cells can have different potentials of having the possibility of regaining function) and typically occurs in a few weeks to months, while immunosenescence is not reversible (must eliminate the senescence cells as should naturally happen if the Th1 immunity, such as NK cell function, is robust enough to eliminate them). This generally takes longer to occur (months to years) than TCE. Although most of the data suggest that TCE and senescence are distinct mechanistic processes, there can be a blurring of characteristics. Both processes can coincide and often do.[TGF3]

This immune dysfunction results in numerous additional vicious cycles that include pineal-hypothalamic-pituitary-hormone dysfunction; mitochondrial dysfunction, GI abnormalities, cognitive dysfunction, sleep disorders, increased permeability of the gut ("leaky gut") and the blood-brain-barrier, immune activation of coagulation (hypercoagulability), leptin and



insulin resistance, mast cell activation, dysfunctional detoxification, and other multisystem abnormalities.[TGF2-4] (See figure 2)

In an extensive review article entitled "The Neurological Significance of Abnormal Natural Killer Cell Activity in Chronic Toxigenic Mold Exposures" by Anyanwu EC, et al. states, "*In various published studies, it is reported that patients presenting with toxigenic mold exposures show immune system dysfunctions to which abnormal natural killer cells (NKCs) are consistently observed. It is concluded that chronic exposures to toxigenic mold could lead to abnormal NKC activity with a wide range of neurological consequences...*"[ICD3] Extremely low levels of mycotoxins, lower than 0.000000000005 mol/l, or .05 ppb, were shown to have significant immunosuppressive effects on NK cells.[ICD95] NKC activity is shown to inversely correlate with sleep disturbances, thymic dysfunction, HPA dysfunction, depression by either subjective report or EEG assessment, anxiety, psychological stress, reduced IL-2, intracellular cyclic AMP, inositol-phospholipid signaling, cAMP messenger systems, the risk of malignancy and susceptibility to fungal, viral, bacterial and parasitic infections. Numerous mycotoxins have direct and indirect synergistic toxicological and carcinogenic effects. The suppression of NK cell activity further facilitates the development of abnormal immune responses and carcinogenesis.[ICD3, 83, 96]

A large multicenter investigation of patients with multiple health complaints attributable to confirmed exposure to mixed-molds infestation in water-damaged buildings. The study found significant abnormally high levels of multiple neurologic and other autoantibodies, multiple health problems involving the CNS and immune system, altered Th1/Th2 profile, and increased inflammation. The authors propose the term "mixed mold mycotoxicosis" for the multisystem illness observed in these patients.[ICD1]

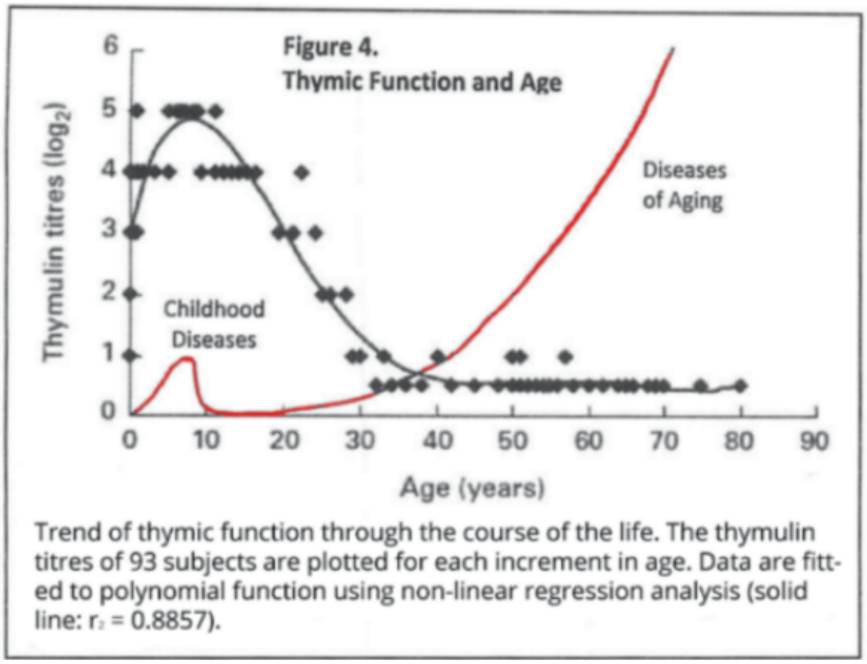
There is almost always a combination of the triad of chronic stress, chronic infection, and chronic toxin exposure in those suffering from mold-associated illness/CIRS.[ICD4, 78] Most CIRS patients have a predisposing cause, a chronic infection (such as Lyme disease), physiologic stress, or an environmental factor (or factors) that make them dramatically more sensitive to the toxic effects of mold, mycotoxins, or other enterotoxins. It is rare, except in extreme cases of sizeable toxic exposure, for a previously healthy person with a robust, balanced immune system to suffer from mold sensitivities or CIRS.[ICD4,78] It appears that the majority of CIRS patients were predisposed to CIRS because of an already compromised immune system, with a low NKC function, mitochondrial dysfunction, T cell exhaustion, or immunosenescence, or suffer from immune-related conditions, such as autoimmunity, chronic Lyme disease or other infection, CFS, fibromyalgia, sleep disorder, physiologic stress, autoimmunity, obesity, MCAS, neurodegenerative diseases, atopy, aging, depression, diabetes, and any age-related or inflammatory condition.[ICD4, 78]

In a recent review entitled "Mold, Mycotoxins and a Dysregulated Immune System: A Combination of Concern?" the authors conclude, "*Recent observations indicate a particular importance of mold/mycotoxin exposure in individuals with pre-existing dysregulation of the immune system, due to exacerbation of underlying pathophysiology including allergic and non-allergic chronic inflammatory diseases, autoimmune disorders, and even human immunodeficiency virus (HIV) disease progression.*

There is growing evidence that mycotoxins are of specific concern for individuals with pre-existing immune system impairment."[ICD4] This further exemplifies the core dysfunction in mold-associated illness/CIRS and why immune-modulatory peptides and other immune-modulatory therapies are the critical first-line therapy for CIRS. The current CIRS treatment protocol fails to adequately address the core immune dysfunction. It only addresses this dysfunction indirectly by trying to remove the toxin, which is difficult and very slow in the presence of immune dysfunction.[ICD18-83] (See figure 3)

T Cell Exhaustion and Immunosenescence

When T cells are exposed to persistent antigen and inflammatory signals, such as the case with chronic infections, cancer, chronic mycotoxin, or other toxic exposure, you can see a deterioration of T cell function: a state called T cell exhaustion. "Exhausted" T cells (ETC) lose inefficient effector functions, express multiple inhibitory receptors, and are defined by an altered transcriptional program. TCE is often associated with inefficient control of persisting infections and tumors, but the revitalization of exhausted T cells can reinvigorate immunity.[ICD5] As stated, TCE is associated with progressive loss of effector functions of T cells (CD4 and CD8) and phenotypic and functional defects, thymic dysfunction and involution, dysfunctional Th1 immunity, as indicated by a low NK cell function (activity), low IL-2, and elevated hTGFb, C4A, IL-10, and IL-6 (high Th2/Th17), and immune activation of coagulation.[ICD4-7,78-83]



Trend of thymic function through the course of the life. The thymulin titres of 93 subjects are plotted for each increment in age. Data are fitted to polynomial function using non-linear regression analysis (solid line: $r_2 = 0.8857$).

Exhausted T cells lose their ability to kill pathogens and proliferative capacity first; then, they lose the ability to secrete a number of cytokines. The severity of TCE correlates with the level and length of antigen stimulation. Again, TCE is reversible (distinct subsets of T cells can have different potentials of having the possibility of regaining function) and typically occurs in a few weeks to months, while immunosenescence is not reversible (must eliminate the senescence cells, which should naturally occur but does not with chronic inflammation and many chronic illnesses) and occurs in months to years. Although most of the data suggest that TCE and senescence are distinct mechanistic processes, there can be a blurring of characteristics.

Both processes can occur and often do at the same time.[ICD6,7] Exhaustion develops more rapidly, and the responding T cells do not recover function if the infectious loads are not contained, or the toxic exposure is not eliminated. TCE and its multisystem vicious cycle of repercussions, such as mitochondrial dysfunction, immune activation of coagulation, pineal-hypothalamic-pituitary-hormone axis dysfunction, etc., make the body unable to eliminate the chronic infection or eliminate the toxic burden.[ICD5,6]

As a side note, T cell exhaustion occurs with COVID, particularly Long Covid.[IDC8-11] Researchers in the United States and Turkey found that two-thirds of patients with Long-COVID have a reactivated Epstein-Barr infection due to (TCE) compared to only 10% of controls.[ICD12] Similarly, other researchers have shown reactivation of Lyme disease, Bartonella, Mycoplasma, and Toxoplasmosis in Long COVID patients secondary to TCE.[ICD12,13]

Cellular senescence is defined as a stable growth arrest induced when cells reach the end of their replicative potential or are exposed to significant cellular stress or insult, DNA damage, inflammation, metabolic stress, or tissue damage signals. Cellular senescence, especially immunosenescence (immune aging), is a significant determinant of the degree and level of physiologic

aging and disease. Immunosenescence contributes to the progressive inability to defend against infectious diseases, cancer development, autoimmunity, inflammation, and cardiovascular and neurodegenerative diseases.

A significant cause of immunosenescence is the progressive involution of the thymus from about age ten until it functions at less than 10% in your 40s.[ICD14-15] (See figure 4.) It is not a coincidence that diseases of aging start accelerating after the nadir of thymic function. The immune system is usually balanced between the division that fights intracellular infections, called Th1, which enables self-tolerance, called Treg. The division that fights extracellular infections and induces inflammation is called Th2 and Th17.

Excess Th2 and Th17 lead to excess inflammation, autoimmunity, degenerative diseases, diseases of aging, multisystem illness, and rapid aging. T cell exhaustion and immunosenescence are also synonymous with a Th1 to Th2/Th17 immune shift, which in normal aging is primarily caused by the lack of thymus function and thymic peptides. This establishes a vicious cycle of cause and effect with immune dysfunction and chronic illness.

Mycotoxins are shown to suppress thymic function directly, cause thymus involution, suppress IL-2, IL-12, and natural killer cell function, and stimulate inflammation, Th2 and Th17immunity, IL-6, and TGFbeta. ICD79, ICD83 Giving thymic, immune-modulatory, and pineal peptides, including thymosin alpha 1, thymogen/vilon (Thymogen alpha 1), thymosin beta-4 (TB4), TB4 active frag, BPC-157, KPV, epitalon, pinealon, as well as DSIP, LDN, mitochondrial peptides, and Cerebrolysin, are shown to reverse and prevent mycotoxin induced thymic involution and loss of thymic effect and subsequent immune dysfunction, inflammation and damage, thus protecting the body from and reversing these damaging effects of mycotoxins.[ICD18-88; BPC1-73; EP1-12]

The mold and mycotoxin-induced abnormal immune balance promote immuno- and cellular senescence, resulting in poorly functioning cells and senescent cells that secrete significant amounts of reactive oxygen species and inflammatory mediators, which recruit additional senescent cells, causing rapid aging and multisystem illness and diseases. This worsens the immune imbalance, causing progressive illness and deterioration rather than repair and rejuvenation. It becomes a "chicken or the egg" conundrum: does immunosenescence result in the inability to clear senescent cells, resulting in an accumulation of senescent cells and inflammatory secretions with associated inflammation, or does the excess accumulation of senescent inflammasome suppress the immune system, resulting in immunosenescence, which then results in the inability to clear the senescent cells and the accumulation of senescent cells with resulting inflammaging?

According to the U.S. Center for Disease Control (CDC), approximately 80 % of aged individuals are afflicted with at least one chronic disease due to declining thymic-related immune function.ICD 14-15 (See figure 3.) Many things negatively affect thymus involution, pineal dysfunction, and subsequent immunity, including age, genetics, inflammation, lifestyle, obesity, EMFs, diet, exercise, stress, pregnancy, toxins, hypothyroidism, low growth hormone, chronic infections, and zinc deficiency.ICD 14-16 EMFs are shown to dramatically speed up thymic and pineal dysfunction and involution, resulting in rapid multisystem aging and an increased risk for CIRS, other multisystem diseases, and neurodegeneration, previously felt to be diseases of aging.[ICD17]

Knowing this, one would not think it to be a giant leap to assume, "*Why not give back the missing thymic and pineal peptides causing the core dysfunction of CIRS that occur with age and cause or contribute to almost all diseases of aging?*" Yet, that is precisely what integrative, functional, and precision medicine doctors are doing. Such supplementation can reverse T cell exhaustion and immunosenescence, proving to be the core abnormality of most chronic inflammatory illnesses.

Thymic and Other Immune Modulatory Peptides for CIRS

Immune modulatory therapies are proving to be ideal therapies for CIRS, which include thymosin alpha 1 (the TA1 replacement is considered by many to be oral vilon/thymogen "Thymogen alpha-1"), thymosin beta 4 (TB4), TB4 frag (AC-SDKP), thymulin, BPC-157, KPV, mitochondria peptides, Cerebrolysin (oral CerebroPep), epitalon, pinealon, stem cells, exosomes, LDN, glutathione, NAC, zinc, ozone, and vitamin D. All are significant immune-modulators that can reverse the core dysfunction that results in numerous multi-system diseases, including CIRS.[ICD18-86] (See TabLe 1A.)

Additionally, the short peptide bioregulators thymogen/vilon (Thymogen alpha 1), TB4 active frag (Ac-SDKP), and KPV are shown to be particularly effective at suppressing a core issue in the underlying immune dysfunction present in CIRS, an elevated TGFb.[ICD59-71] (See Table 1B.) The nice thing is that supplementation with thymic and other peptides has been shown to be extremely safe, with studies unable to find a toxic dose, even at 1000 times the usual therapeutic amount. This is unheard of and in contrast to the small therapeutic window typical of medications.[ICD72,88]

TCE can be reversed, and immuno- and cellular senescence cells can be eliminated, which naturally occurs with a healthy Th1 immune system. When that is not the case, peptides and other T cell stimulators and modulators can achieve the same result by restoring thymic function, blocking upregulated inhibitory receptors, such as PD-1, giving specific senolytic therapies (not addressed due to the limited scope of this chapter), and reducing the Th2 and Th17 associated cytokines, IL-10, IL-6, IL-7, and hTGFb.[ICD18,18-71,84] Immune modulatory peptides are ideal for this role, resulting in subsequent improvement in most all of the biomarkers and symptoms of CIRS much faster and more efficaciously than utilizing the current CIRS protocol (CSSCP), which only indirectly and minimally affects the impaired functioning. Thus, the standard protocol only slowly normalizes the physiologic abnormalities over an extended period of time.ICD 18-86. Simply removing antigen does not reverse TCE or restart the memory T cell differentiation process unless it happens early in the process.[ICD5,7] (See Table 1C)

Several thymic and pineal peptides modulate immunity to establish a healthy, balanced Th1/Treg-Th2/Th17 immune system, but they have differing effects. Thymosin alpha-1 (TA1) is approved in over 30 countries for various infections and cancer therapy. To achieve a broad overview of thymic peptides, think of TA1, thymogen, and vilon as increasing Th1/Treg immunity, thymosin beta 4 (TB4), thymulin, and TB4 active frag (Ac-SDKP) as increasing Th1 and reducing Th2/Th17 immunity along with providing additional rejuvenating properties. In contrast, BPC-157, KPV, GHK, and DSIP (not

Table 1.

Thymic and Other Immune Modulatory Peptides for CIRS

A. Thymosin alpha 1 (TA1 replacement, is considered by many to be oral Vilon/Thymogen 'Thymogen alpha-1'), Thymosin beta 4 (TB4), TB4 frag, thymulin, BPC-157, KPV, mitochondria peptides, Cerebrolysin (oral CerebroPep), epitalon, pinealon, stem cells, exosomes, LDN, glutathione, NAC, zinc, ozone, vitamin D, herbal products and supplements.[ICD18- 86]

B. Vilon and TB4 frag (Ac-SDKP) and KPV are shown to be potent immune modulators and are particularly effective at suppressing hTGFb.[ICD59-71]

C. Simply removing antigen does not reverse TCE or restart the memory T cell differentiation process unless it happens early in the process. [ICD5,7]

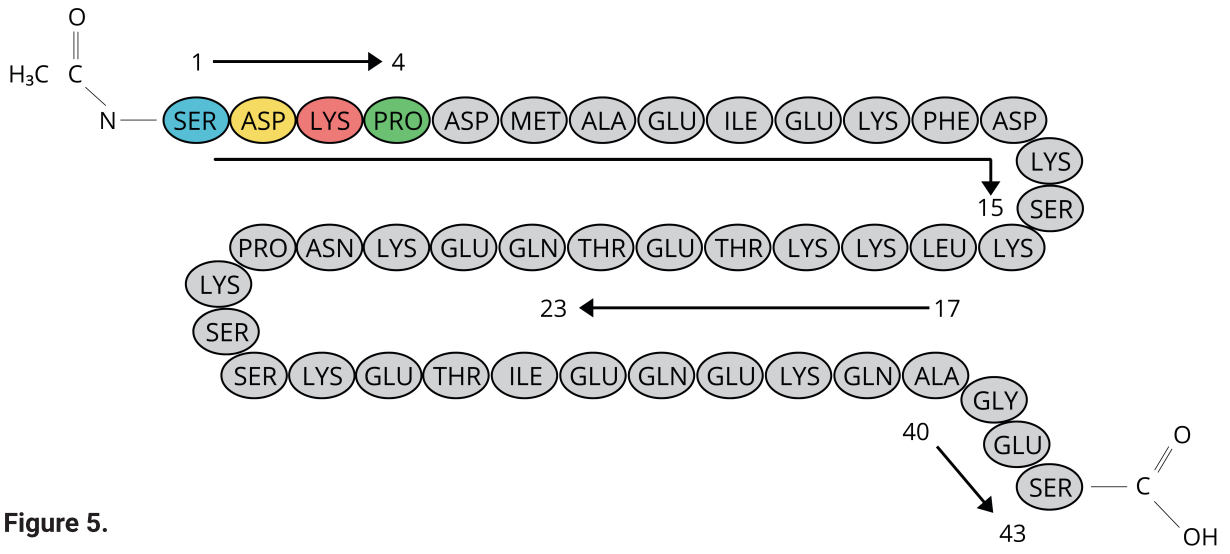


Figure 5.

thymic peptides) reduce Th2/Th17 with additional healing, anti-inflammatory, rejuvenating, and antiaging effects, acting directly on tissues and through the gut-brain-immune axis.[ICD18-86]

TB4 active fragment (Ac-SDKP) is a small part of the TB4 peptide that provides the majority of healing and immune-modulatory effects and removes a part (domain) of TB4 that can have a negative impact of stimulating mast cells, which cause inflammation.[ICD87] (See figure 5.) The full-length TB4 is 43 amino acids long, so it cannot be absorbed orally. In comparison, TB4 active fragment (Ac-SKDP) is only four amino acids in length and is orally bioavailable, being orally absorbed intact. It is also approximately ten times as potent per weight as the full-length TB4 and is available as a supplement. It is a potent inhibitor of TGF-beta 1, a central player in CIRS.[ICD59-63] (See table 1A.) Thymosin alpha-1 (TA1) was shown to be very safe and effective for COVID treatment, so the FDA banned it despite hundreds of studies confirming its safety and effectiveness and that it is approved in over thirty countries worldwide. The combination of thymogen/vilon (Thymogen Alpha-1) are potent immune-modulators and is considered an oral replacement for TA1 based on their mechanism of action and effects (potent Th1 stimulators) with confirmatory metabolomic testing.[ICD25,27,28,35,64-70]

In one study, seventy-six five-month-old female rats were divided into two groups and were treated with only 5 mcg per rat of thymogen (44 rats) or saline (32 rats) five times per week for 12 months. The animals were monitored up to their natural death, and all the tumors discovered were studied microscopically. The study found that the maximal life span of thymogen treated group was 4.6 months longer than the control group and slowed aging from 0.007082 days-1 to 0.004123 days-1. The occurrence of tumors and malignant neoplasia was 1.5 and 1.7 times lower, respectively. The authors concluded, "The ability of thymogen to inhibit spontaneous carcinogenesis and prolong life span has been established."[ICD27] Thymogen has consistently slowed aging, extended lifespan, normalized immune dysfunction, reduced inflammation, and prevented and treated inflammatory diseases, infectious diseases, and carcinogenesis.[ICD19,26,27,28,65,66,68,69,70,71]

Oral vilon is also a potent Th1 stimulating immune modulator, much like thymosin alpha-1, and is shown to suppress and prevent malignancy, reduce inflammation, and prevent and

treat inflammatory conditions, chronic infections, autoimmunity, and atopy.[ICD29] As stated, vilon, as are TB4 active frag (AC-SDKP) and KPV, is a particularly potent inhibitor of TGF-beta, a main biomarker and core issue with CIRS.[ICD59,60,62 63,64] (See table 1B.) Vilon can also normalize multiple hormones and neurotransmitters, leading to improved sexual and thyroid function, fertility, and resistance to emotional stress.ICD 42,28 Vilon can also inhibit hypertrophy of the adrenals, involution of the thymus, and raises plasma albumin levels, which is a biomarker for overall health.[ICD45, 69, 76, 77]

Both vilon and BPC-157 tend to have a homeostatic effect on the body's systems. They both tend to lower blood pressure if it is high but will raise it if it is low, which works well for POTS and other conditions associated with mast cell activation and autonomic dysfunction. In a study looking at the thymomimetic effects of vilon on the immune status and coagulation hemostasis in elderly patients with type I diabetes, who, almost without exception, suffer from various degrees of immune dysfunction and hypercoagulability, the authors summarized their results: "It was found that the administration of vilon resulted in optimization of coagulation hemostasis, which was manifested in the increased content of natural anticoagulants: antithrombin II, and protein C, as well as the stimulation of fibrinolysis."[ICD89]

They also noted a reduction in the amount of insulin needed and a normalization of T and B lymphocytes and IgA levels, pointing to a stabilizing hemostasis effect.[ICD89 TB4] active frag, thymogen/vilon (Thymogen alpha-1), BPC-157, and KPV are orally bioavailable using unique oral delivery methods and available as supplements with strict manufacturing and regulatory requirements in conjunction with the production of extensive quality and safety data. Injectable peptides are available at specialty compounding pharmacies with a valid prescription.

Peptides

What is a Peptide?

If you've investigated ways to improve your health, you've probably come across the term "peptide" and wondered what it is. A peptide is a compound composed of two or more amino acids linked in a chain. Essentially, peptides are short chains of amino acids linked together. By definition, if the chain is longer than 40 amino acids (AAs), it is called a protein. If it has fewer than 40 AAs, it is called a peptide. You may also hear the term "oligopeptide," which is sometimes used for short peptides with fewer than twenty AAs. The simplest peptides are dipeptides (two AAs), followed by tripeptides (three AAs), tetrapeptides (four AAs), and so on. Meanwhile, a polypeptide is a long, continuous unbranched peptide chain.

Peptides control and modulate most systems in your body in a tissue and cell-specific manner, including hormone production, immune function, the sleep cycle, the production of inflammatory mediators, DNA replication, cell division and renewal, cancer cell destruction and apoptosis, libido, and sexual arousal, weight loss, lean muscle gain, mitochondrial function, cognitive function, mood, energy and other metabolic activities, tissue healing and specific biological functioning of the brain, skin, eyes,

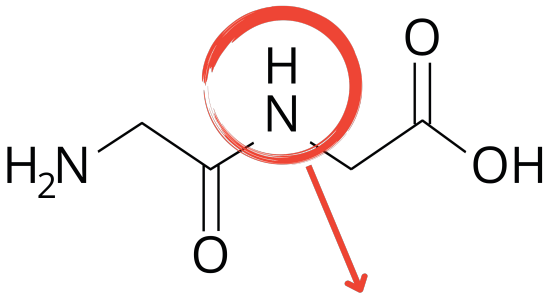


Figure 6.

urinary and reproductive systems, aging and longevity, and many more.

Compared to medications and hormones, peptides tend to be more selective and less likely to be associated with serious adverse side effects. Peptides are generally cell surface signaling molecules that indirectly affect cellular activity via a cascade of secondary messengers. (See Figure 7.) Hormones work on specific receptors in the nucleus, affecting protein synthesis, generally being slow on and slow off, less selective, and, in general, higher risk. Peptides have pleiotropic effects (no single effect) that are generally like those of supplements but more potent and selective and are quick on and quick off but can have lasting epigenetic changes. Peptides are very synergistic with other peptides, supplements, hormones, antibiotics, and most other therapies.

Small natural peptides have a long history of safety and effectiveness, being used in European countries for over 40 years, having hundreds of thousands of patient-years (hundreds of thousands of patients using for almost half a decade) that demonstrate their excellent safety and effectiveness. However, despite the many obvious clinical advantages, including unprecedented safety and efficacy and decades of commercial successes in Europe, the full potential of peptide therapeutics has yet to be unleashed in the United States. A significant reason is that they have surpassed their patent potential, making them undesirable to the pharmaceutical industry. In addition, the high cost of manufacturing has hindered their widespread use.

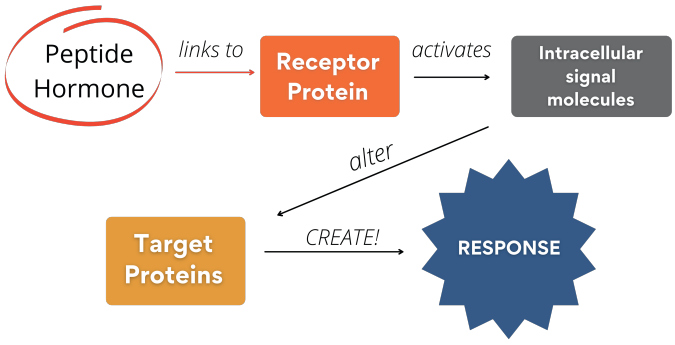


Figure 7.

Peptides are naturally produced in the body by linking amino acid residues together through peptide bonds in an end-to-end fashion; each amino acid carries a unique functionality that adds a specific property to the peptide. (See Figure 7.) The different amino acid residues target specific physiologic effects. As a result of their being bioidentical to what the body produces, the peptides are used to target and optimize particular physiologic functioning of the body's systems as "optimization and replacement therapies" that add back or supplement peptide levels in cases where endogenous levels are inadequate or absent. This is much like the incredible breakthrough in the 1920s, where the isolation and therapeutic use of the peptide/protein insulin was used in people with diabetes.

Based on peptides' extensive track record of safety and effectiveness over decades and the fact that it has finally been realized that they have significant advantages over most drugs and protein therapeutics (including their small size, which gives them the ability to penetrate cell membranes, the blood-brain barrier, biofilms, mitochondria, gastrointestinal membranes, avascular tissue, and much more), their therapeutic potential has seen a significant explosion of interest. They also have high potency, specificity, activity, and affinity. In addition, they have a huge therapeutic index (the effective dose divided by the toxic dose), which is many-fold higher than even over-the-counter medications and supplements.

Peptides have an incredibly low likelihood of drug or supplement interactions other than positive synergistic effects. Furthermore, being small and water-soluble, they are naturally degraded by the body and don't accumulate in specific organs, such as the kidney or liver, further increasing their safety profile. In addition, many popular peptides have no known toxic level, meaning researchers have not been able to elicit any toxicity effects no matter how high the dosage (consult your physician).

Table 2.

Peptide and small molecule classification by location of origin and main activity

Immune modulating peptides (thymic (from thymus gland) and gut-brain axis peptides)
- Thymosin Beta 4 (Tβ4),
- TB4 Active Frag (Ac-SDKP)
- Vilon/Thymogen (Thymogen alpha-1)
- BPC-157
- KPV
- Thymosin Alpha 1 (TA1)
- TB4 Active Frag (AGES)
- Zn-thymulin
- Delta Sleep Inducing Peptide (DSIP)
- GHK-Cu
- Cerebrolysin (IV and oral)(CerebroPep)

Pineal gland peptides (Modulate thymus, increase telomere length, modulate immunity, sleep, and the hypothalamic-pituitary-hormone axes)
- Epithalon
- Pinealon
- Delta sleep-inducing peptide (DSIP)
- Testagen
- Melatonin

Gastrointestinal/Leaky Gut/Inflammatory Bowel Disease/Gut-Brain Axis Peptides
- BPC-157
- TB4 Active Frag (Ac-SDKP)
- KPV
- Delta sleep-inducing peptide (DSIP)
- GHK-Cu
- LL-37
- Tuftsin
- Livagen
- Larazotide

Brain peptides (Improve memory, depression, anxiety, brain injury, cognitive function, etc.)
- Cerebrolysin (IV and oral)(CerebroPep)
- Semax
- Selank
- BPC-157
- TB4 Active Frag (Ac-SDKP)
- Delta Sleep Inducing Peptide (DSIP)
- KPV
- Humanin
- SS-31
- MOTSc
- 5-Amino-1Mq
- GHK-Cu
- PE 22-28
- P21
- Methylene Blue
- ARA-290
- Cortexin
- Dihexa

Antimicrobial peptides
- LL-37 (effective against Lyme cysts, viruses, fungal, parasites)
- BPC-157
- TB4/Active Fragment (Ac-SDKP)
- KPV
- GHK-Cu
- Methylene Blue

Mitochondrial peptides (Increase mitochondrial function, energy production, and repair)
- MOTSc
- SS-31
- Humanin
- 5-amino 1MQ
- BPC-157
- TB4 Active Frag (Ac-SDKP)
- Small-humanin-like peptides (SHLP)
- Delta sleep-inducing peptide (DSIP)
- T3
- Melatonin
- PQQ
- MitoQ
- Methylene Blue

Rejuvenation/Pain/Anabolic/Healing peptides
- BPC-157
- TB4/ TB4 Active Fragment (Ac-SDKP)
- Vilon
- Epitalon
- Pinealon
- DSIP
- AOD-9604 (fragment of growth hormone)
- GHK-Cu
- KPV
- Cerebrolysin (IV and oral)(CerebroPep)
- FOX 04-DRI
- Follistatin
- ACE-031
- ARA-290
- Cardiogen
- Carnosine

GHRH/GHRP (Growth hormone-releasing hormones and growth hormone-releasing peptides-stimulate growth hormone production)
- Sermorelin, CJC-1295, Tesamorelin, Ipamorelin, Hexarelin, Ibutamoren (MK-677), Others

Sleep Peptides/ Anti-anxiety
- DSIP
- Epitalon
- Pinealon
- Growth Hormone
- GHRH/RGRP
- AOD
- Selank
- BPC-157
- KPV

General Classes of Peptides

A detailed review of all the different classes of peptides is well beyond the scope of this chapter, but, in general, perhaps the best way to classify peptides and small molecules are by location of origin and main activity. (See Table 2)

Immune Modulating Peptides

Immune modulating peptides are secreted by or affect the pineal-thymic-immune axis and, ultimately, the immune system. These peptides, almost without exception, help normalize a dysfunctional immune system, which is consistently shown to be a shift from a healthy Th1/Treg dominant system to an unhealthy Th2/Th17 dominant system that is dominated by inflammation; autoimmunity; mitochondrial dysfunction; inability to fight intracellular infections and convert IgM antibodies to IgG; thymic dysfunction; T cell exhaustion; cellular and immunosenescence; inability to detoxify; low adrenal, thyroid, and growth hormone levels and effects even though standard lab tests look normal; and low or low-normal levels of the sex hormones, antidiuretic hormone, MSH, and VIP. This multifactorial immune dysfunction usually involves three things: stress, chronic infections, and significant toxic exposure.

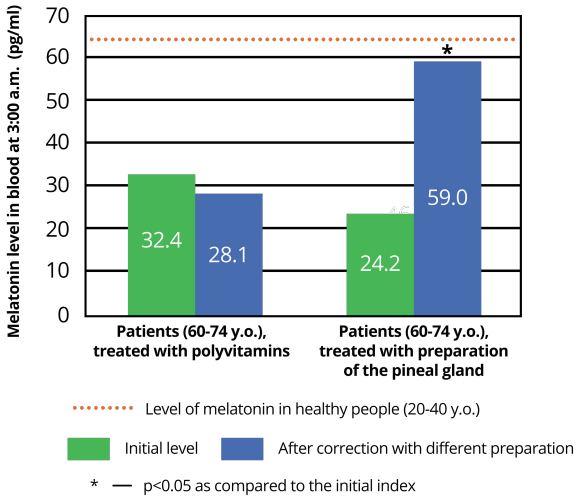
This results in a vicious cycle that can involve a multitude of multi-system diseases, including CIRS, CFS, FM, autoimmune disease, allergies and sensitivities, excessive mast cell activation, sleep and mood disorders, fatigue, neurodegenerative diseases, GI disorders, cognitive disorders, rapid aging, and much more. These peptides include thymosin Alpha 1 (TA1), vilon/thymogen (Thymogen alpha-1), thymosin Beta 4 (Tβ4), TB4 active frag (Ac-SDKP), BPC-157, KPV, TB4 active frag (AGES), and Zn-thymulin. (See table 3.)

Pineal Peptides

Pineal peptides include epitalon, pinealon, melatonin, and delta sleep-inducing peptide (DSIP). These potent antiaging peptides modulate thymus function, increase telomere length, and modulate immunity, sleep, and the hypothalamic-pituitary-hormone axes. These peptides, especially when combined with the thymic peptides listed earlier, have significant antiaging properties, increasing lifespan and healthspan, preventing malignancy formation and spread, and preventing and treating most of the all-too-common age-related diseases. The synergistic combination of thymic immune-modulators and pineal peptides protect against a wide range of toxic insults, whether from a drug overdose or an environmental toxin, including heavy metals and myco- and other enterotoxins.

Amazingly, pinealon, epitalon, BPC-157, TB4 active frag, KPV, DSIP, SS-31, GHK, and Cerebrolysin will protect the brain and other tissues from the toxic effects of excitotoxins, such as myco- and other endotoxins. Short regulatory peptides were studied under

Figure 8.
Poinealon an Epitalon restore melatonin secretion in aged individuals to that of healthy controls (multivitamins hand no effect)



Anisimo VN et al. Effects of pineal peptide preparation epitalon on free-radical processes in humans and animals. Neuroendocrinology Lett 2001;22:9–18

oxidative stress conditions caused in animals by hypobaric hypoxia. The authors concluded, "*Our results suggest that pinealon has a pronounced antihypoxic effect. The pinealon capability of increasing the neuronal resistance to hypoxic stress is complex; it is based not so much on the inhibition of ROS increase in cells in response to stress as on limiting the excitotoxic effect of NMDA. The pinealon effect on brain metabolism in stress-sensitive animals is expected to be the most pronounced.*"[EP14]

Removal of the pineal gland results in the destruction of the thymus gland and impairment of the immune system accompanied by wasting diseases.EP1 Given that the pineal peptides epitalon and pinealon can reset and reverse the damaged pineal-hypothalamus-pituitary-hormone axis that is so commonly seen in CIRS, chronic Lyme disease, and many chronic illnesses and diseases of aging. They, incredibly, can even normalize thyroid hormone levels in hypophysectomized (lacking a pituitary) animals.[EP4] Being that the pineal-thymus axis is bidirectional, thymic peptides, in turn, influence the pineal gland secretions, including melatonin, and the circadian rhythm.

The pineal peptides epitalon and pinealon and the thymic bioregulator vilon are shown to increase telomere length, melatonin levels (see table 5 & figure 8), exercise tolerance, mental working capacity, and prolong life span.[EP5] Vilon and epitalon reduced the HER-2/neu (breast cancer) gene expression by 2.0-3.6-fold in transgenic mice.[EP9] As stated, the oral use of pinealon increases telomere length, but it also stimulates serotonin production and promotes normalization of the antioxidant system, improves exercise tolerance, promotes and maintains a "trained status," and improves energy metabolism in athletes.

Table 3.

Thymic Peptide Effects

- Improved tissue repair and healing
- Improved host defense to infection
- Reverse immunosuppression of chronic infection (Lyme)
- Increases antioxidant and glutathione production
- Boost NK function
- Stimulates ligament, tendon, and muscle repair.
- Prevents and reverses fibrosis
- Effective in sepsis
- Improves dry eye disorders
- Can improve hair growth
- Accelerates wound healing
- Effective against fatty liver (NAFLD and NASH)
- TH2-TH1 immune modulation (infections, cancer, herxheimer, autoimmune)
- Protect against toxins, including neuro/myco (mold), and endotoxins
- Cardiac regeneration and protection post-MI, CHF, etc.
- Neurologic protection and regeneration post-stroke, TBI, Lyme disease, Alzheimer's, neuropathy, Parkinson's, etc.
- Improves memory
- Stimulate stem cell activity and proliferation
- Increases longevity
- Have almost non-existent side effects at 100-fold dose+ excess1
- Excellent safety profile with a large therapeutic window (over 1000-fold)
- Boosts mitochondrial function
- Reduces microglial activation (brain inflammation) to toxins and infections
- Cardiac regeneration
- Effective treatment of biofilms, especially smaller fragments, such as TB4 Active Fragment
- Improve allergies and mast cell activation • Improves insulin resistance and prevents and reverses diabetic complications, such as kidney and heart disease and neuropathy.
- Heals the tight junctions in the gastrointestinal mucosa with leaky gut and stabilize a leaky blood-brain barrier.
- Is antimicrobial against bacteria, viruses, parasites and fungi
- Breaks down biofilms

Table 4.

BPC-157 Effects

- Protects and promotes healing in the liver
- Prevents and reverses inflammatory and autoimmune diseases, such as rheumatoid arthritis, Lupus and Hashimoto's
- Modulates pain pathways
- Has neuroprotective and neuro-regulatory effects, particularly related to gut-brain interaction
- Repairs the gastrointestinal tract and is shown to be more effective than H2-blockers (Zantac), proton pump inhibitors (omeprazole) and gastric coating agents (sucralfate)
- Promotes muscle, tendon, and ligament healing
- Promotes wound healing in the corneal epithelium
- Accelerates bone healing and is effective for diseases such as periodontitis
- Has anti-inflammatory effects
- Is shown to increase serotonin secretion in a number of areas in the brain and is shown more effective for depression than antidepressants and is shown to help to handle chronic and acute stress
- Counteracts the damaging effects of NSAIDs on the gastrointestinal tract
- Protects against numerous toxins, including alcohol, NSAIDS, Clostridium difficile (C. diff) toxin, mycotoxins (toxins from mold) and other neurotoxins (toxins affecting the brain) and enterotoxins (gastrointestinal toxins)
- Shown to be effective in traumatic brain injury, Parkinson's and multiple sclerosis
- Shown to normalize lower esophageal and pyloric sphincter pressures, which are common causes of gastric reflux
- Effective for multiple diseases of the gastrointestinal tract, including gastritis and inflammatory bowel diseases
- Enhances the healing effects of growth hormone
- Shown to be effective both orally, rectally and parenteral (injection or intravenous)
- BPC-157 is shown to prevent and reverse a wide range of stimulated arrhythmias, including A-Fib, A-V Block, ventricular tach, A-V block, premature atrial contractions and premature ventricular contractions, as well as other cardiac arrhythmias.

There is evidence that one mechanism that pinealon and vilon realize their geroprotective and exercise-stimulating effects is by upregulating the irisin gene.[EP5] The pineal gland is smaller in obese significant environmental toxin exposure. The patients, insomniacs, and those with significant amounts of calcifications in the pineal gland "brain sand" correlates with pineal malfunction and is associated disorders, such as Alzheimer's disease, MS, schizophrenia, and other pathological conditions.[EP3] with various neurodegenerative

The pineal gland can also directly stimulate thyroid secretion. Surprisingly, the highest amounts of melatonin are produced in the GI tract, but the thymus gland and the spleen also secrete it. In turn, melatonin also stimulates thymocyte maturation and thymic peptide release.

Melatonin also stimulates SIRT1, leading to further anti-inflammatory and antioxidant effects, as well as protecting mitochondria and modulating mitophagy via mitochondria melatonin receptors. Based on the current literature and safety profile, the combination of a pineal and a thymic peptide appears to be a potentially potent option to protect against mold and mycotoxin exposure and an insurance policy against rapid aging, chronic illness, and the disorders that accompany the aging process. Further well-done clinical trials are needed in this exciting area to elucidate such therapies better.

In one study, the geroprotective effects of thymic and pineal peptides were investigated over six to eight years in 266 elderly patients after be-

ing treated for two to three years. The authors concluded: "*The obtained results convincingly showed the ability of the bioregulators to normalize the functions of the human organism, i.e. to improve the indices of cardiovascular, endocrine, immune and nervous systems, homeostasis and metabolism. Homeostasis restoration was accompanied by a 2.0-2.4-fold decrease in acute respiratory disease incidence, reduced incidence of the clinical manifestations of ischemic heart disease, hypertension disease, deforming osteoarthrosis and osteoporosis as compared to the control. Such a significant improvement in the health state of the peptide-treated patients correlated with decreased mortality rate during observation: 2.0-2.1-fold in the thymosin-treated group; 1.6-1.8-fold in the epitalon-treated group and a 2.5-fold in the patients treated with thymalin plus epitalon as compared to the control.*"[ICD41]

A separate group of patients was treated with the peptides annually for six years; their mortality rate decreased 4.1 times the rate of the controls.[ICD41] Pinealon and epitalon were shown to restore melatonin secretion in aged individuals to that of healthy controls, with multivitamins having no effect.[ICD43] (see table 5 & figure 9) A major part of the vicious cycle of CIRS is that the immune dysfunction causes mitochondrial dysfunction, which then feeds back, causing more immune dysfunction, pineal-hypothalamic-pituitary-thyroid, and other hormone deficiencies, which further contribute to the downward spiral.

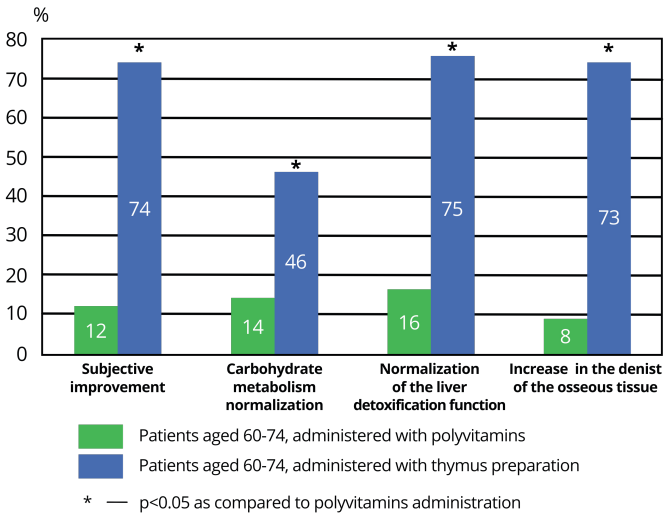
The key is to target the underlying abnormalities and stop or rewind the vicious cycles that are causing such difficult-to-treat multi-system illnesses such as CIRS. The combination of vilon and epitalon changed the expression of five of thirteen mitochondrial genes, improving mitochondrial function by increasing the expression two to sixfold in four of the genes and reducing one by 55%. The combination also inhibited pro-oncogenic genes and activated anticarcinogenic genes.[ICD38]

Gastrointestinal/Leaky Gut/Inflammatory Bowel Disease/ Gut-Brain Axis Peptides

BPC-157 is a naturally occurring peptide in human gastric fluid. It has enhanced stability compared to other peptides, is resistant to enzymatic hydrolysis and stomach acid breakdown, and is orally bioavailable, which is surprising due to its size (15 amino acids in length). It is the most popular peptide and is undoubtedly considered the "go-to" peptide for treating gut issues.

BPC-157 has a wide range of healing, rejuvenating, and antiaging effects, which include the up-regulation of growth factors and genes involved with proangiogenic effects (stimulates capillary formation to deliver more oxygen and nutrients to tissues), modulation of nitric oxide (NO) synthesis, modulation of the serotonergic and dopaminergic systems, as well as exerting significant beneficial effects on leaky gut, the gut-brain axis, and the microbiome. It has

Figure 9.
Effects of Thymus and Pineal Preparation vs Polyvitamins on Subjective Improvement, Dysfunctional Metabolism, and Detoxification Increase Bone density and Melatonin Levels P{patients 60-70 YO



Kavionson V. Peptides. and aging. neuroendocrinology letters 2002;23(3):11-144

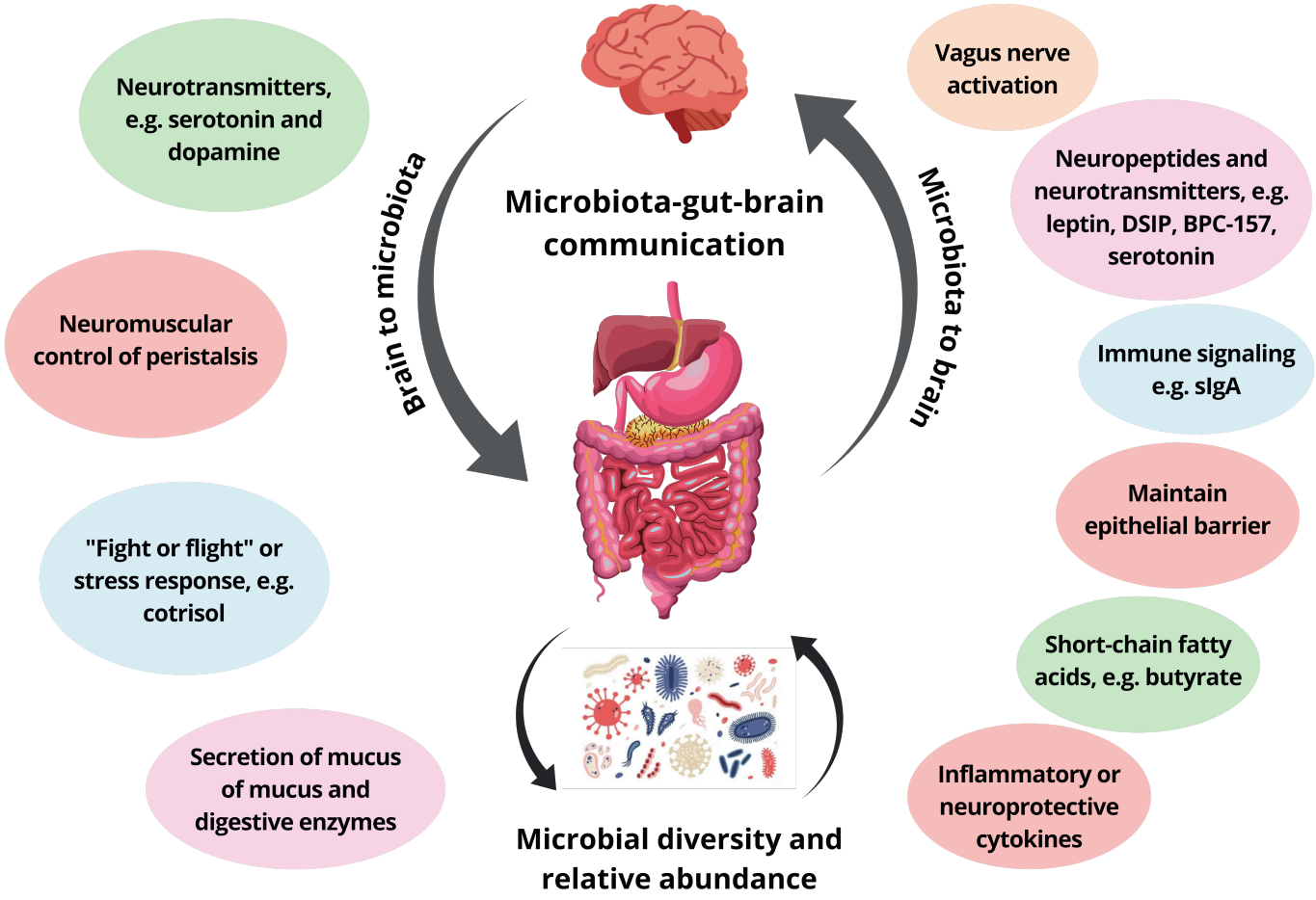


Figure 10.

similar effects as TB4, TB4 active fragment, and KPV, but it has a different mechanism. This makes them very synergistic and a powerful rejuvenation combination.[BPC1-73] (see table 4)

BPC-157 reduces inflammation and promotes healing in most tissues and systems in the body, including the gut (it probably has the best track record for leaky gut, but TB4 active frag and KPV are key combinations with BPC-157), the brain (improves mood, cognitive function, traumatic brain injury), skin, muscle, degenerative joints, the heart (prevents and treats arrhythmia, heart failure, and Lyme myocarditis), peripheral nerves (neuropathic pain), the bladder (incontinence), the immune system (inflammatory conditions, mast cell activation, and autoimmunity) and is protective against neuro-, myco- (mold) and endotoxins, improves insulin resistance and is antimicrobial, outperforming the antiviral acyclovir for the herpes class of viruses at 1/1000th the dose, making it an ideal therapy for CIRS.[BPC1-73]

While many physicians consider oral BPC-157 to be a gut-healing peptide, it has been demonstrated to protect and heal a wide range of both gastrointestinal and systemic tissues and organs. It is clearly shown to be equally efficacious and equipotent when injected for systemic conditions as when given orally (i.e., a dose given orally or via injection is equally effective for systemic disorders).[BPC1,35,47,53,55]

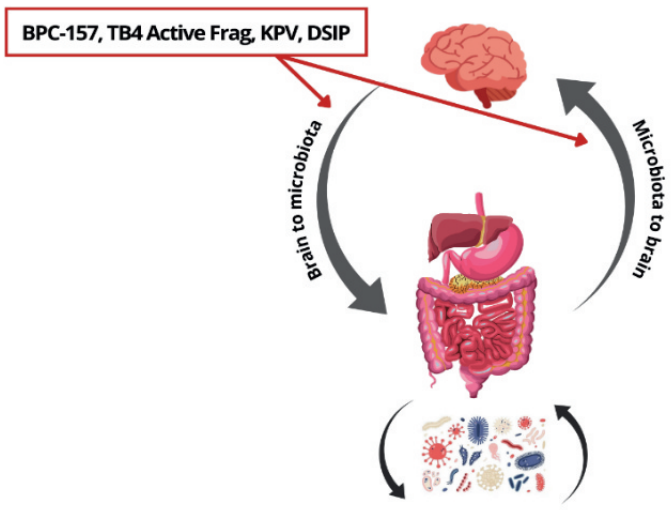
Every study that has tested the oral form against injectable BPC-157 for systemic conditions, such as MS, muscular-skeletal damage, central and peripheral nervous system damage, metabolic issues, and other body systems, has shown that oral administration works equally well at the same dose. There might be a slightly better result if injecting intraarticular, but other than that,

the studies show that oral BPC-157 will have the same efficacy as an injectable for systemic issues. We have found that some people prefer capsules, mouth sprays, or oral strips, while others prefer injectables. We also do it intravenously.

TB4 active frag (Ac-SDKP) is also resistant to enzymatic degradation and absorbs whole, as does the melanocyte-stimulating hormone MSH fragment KPV. They both have a selectivity of the tight junctions in the GI mucosa, the pulmonary mucosa, and the blood-brain barrier, making the BPC-157, TB4 active frag, and KPV trio an effective therapy for GI issues, including leaky gut, dysbiosis, IBS, inflammatory bowel disease, and SIBO (especially when the antimicrobial peptide, LL-37, is added). DSIP is produced in the gut and where its highest levels are found. It is also very anti-inflammatory and appears to absorb sublingually, but I have not directly tested it. In a recent study, oral antimicrobial peptide LL-37 was shown to significantly improve COVID symptoms compared to placebo.[ICD93,94]

One key aspect of treating the gut with the peptides listed above is that they work on the gut-brain and brain-gut axes. It is a bidirectional system. For instance, treating SIBO with antibiotics often results in relapse because the systemic condition causing an unhealthy gut via the brain-gut axis is not addressed. Peptides treat both sides of this loop. I usually add a good spore-based probiotic, oral IgG, and sometimes butyrate or digestive enzymes.

Mycotoxins destroy the gut mucosa and damage the tight junctions throughout the body, causing significant inflammation with the immune dysfunction, as discussed above, directly and indirectly, damaging mitochondria, causing pineal-hypothalamic-pituitary-hormone axis dysfunction, immune activation of coagulation, inability to detox, autoimmunity, and a multitude of other dysfunctions. One of the many nice things about peptide therapy for CIRS is that the peptides protect the body from the toxic effects of mold and mycotoxin exposure while



they also correct the dysfunctions and stimulate healing and rejuvenating.

In an extensive review of BPC-157's effects on the gastrointestinal tract, the authors summarized their findings, "*Pentadecapeptide BPC 157 is an anti-ulcer peptidergic agent, safe in inflammatory bowel disease clinical trials and wound healing, stable in human gastric juice, and has no reported toxicity. Particularly, it has a prominent effect on alcohol-lesions (i.e., acute, chronic) and NSAIDs-lesions (interestingly, BPC 157 both prevents and reverses arthritis)… and acts as a free radical scavenger and exhibits neuroprotective properties.*"[ICD72]

There are two critical aspects of the GI system that influence health and disease pathogenesis: the microbiome's effects on the neurologic system, inflammation, and health, and the brain's influence on the microbiome and overall GI functioning (intestinal mobility, mucous secretion, secretory functions, blood flow, etc.). Additionally, a "leaky gut" means there is a "leaky brain" (the blood-brain barrier (BBB) is not able to keep out toxins, infectious agents, and inflammatory molecules and cells). There is also brain inflammation due to this gutbrain connection if there is gut inflammation. (See Figure 10.)

Numerous studies show that BPC-157, TB4 active frag, KPV, and DSIP reduce gut inflammation and promote healing of the gut, the brain, BBB, and other tissues in the body. Additionally, TB4 active frag and KPV promote healing of the

GI and BBB tight junctions, which are core abnormalities that result in leaky gut and leaky brain, making them a powerful combo for leaky gut and cognitive, mood, and neurodegenerative diseases. The power of the effectiveness of these peptides in the treatment of leaky gut and diseases of the central nervous system is that they have the rare ability to work on both sides of the gut-brain axis, positively affecting the gut's health and its influence on brain health and the brain's health and its impact on gut health, and their influence on the overall body's inflammation and functioning via the gut-brain-immune-inflammatory connection.

Additionally, these peptides will also bind to mycotoxins and protect the body against the effects of numerous toxins, including mycotoxins, making them an ideal therapy for CIRS. Additional immune-modulatory peptides, including vilon/thymogen (Thymogen alpha-1) and thymulin, will further reduce the inflammation caused by a leaky gut, which prevents the system-wide damage caused by leaky gut and will subsequently help heal excessive brain inflammation and leaky brain. This will, in turn, help heal the leaky gut and GI dysfunction via the brain-gut axis and all of the body's inflammation and functioning via the gutbrain-immune-inflammatory connection.

EMFs and CIRS

There has been a massive increase in electromagnetic radiation (EMF) exposure in the last few decades, which continues to increase exponentially. We are exposed to 1018 more EMFs (1,000,000,000,000,000,000) than we experienced as recently as 1917.[EMF1-3] Over the last twenty years, a robust body of independent science has emerged showing significant negative biological impacts from exposure to EMFs, including evidence of developmental delay, neurological and cognitive dysfunction, neurodegenerative diseases, heart abnormalities, thyroid, and other hormone deficiencies, reproductive effects, accelerated aging, diabetes, autoimmunity, fatigue, cancer, and much more.[EMF1-8] EMFs cause increased ROS and inflammation, immune dysfunction, mitochondrial dysfunction, epigenetic disruption, abnormal activation of voltage-gated ion channel, leaky gut, and BBB, among other serious health problems.[EMF1-8]

EMFs, in particular, are shown to dramatically speed up thymic and pineal dysfunction and involution, resulting in rapid multi-system aging and increased risk for multisystem diseases and degeneration previously felt to be diseases of aging.[13] This was well recognized very early in the seventies by Dr. Robert O. Becker (twice nominated for Nobel Prize), who said, "*I do not doubt in my mind that, at the present time, the greatest polluting element in the earth's environment is the proliferation of electromagnetic fields (EMFs).*"[EMF8] EMFs significantly increase brain inflammation, including the hypothalamus, hippocampus, and amygdala, causing significant neurologic and cognitive defects and neurodegeneration. EMF sensitivity is common in CIRS, chronic Lyme disease, CFS, fibromyalgia, neurodegenerative diseases, autoimmunity, chronic Lyme disease, mast cell activation syndrome (MCAS), and many diseases of aging. They share the same immunological phenotype: Th1/Treg to Th2/Th17 shift with mitochondrial dysfunction, pineal-hypothalamic-pituitary-hormone dysfunction, leaky gut and BBB, immune activation of coagulation, GI dysfunction, brain inflammation, and neurodegenerative diseases, and other diseases of aging, all set off by immune dysfunction. Calcium-gated channels are located throughout the body, especially in the gut, heart, and brain. They are a core component of the Cell Danger Response (CDR), which causes immune dysfunction, abnormal cell signaling, pathological mitochondrial metabolism, significant inflammation, cell toxicity, and death.[VG1-11] EMF toxicity occurs in everyone to different degrees.[EMF63] (see figure 11.)

The good news is that peptide combinations, such as thymogen/vilon (Thymogen alpha 1),

Figure 11.

Physiologic Effects of EMFs

Behavioral Psychological

- Anxiety/Depression
- ADD/OCD
- Stress/Emotional

Neurologic Effects

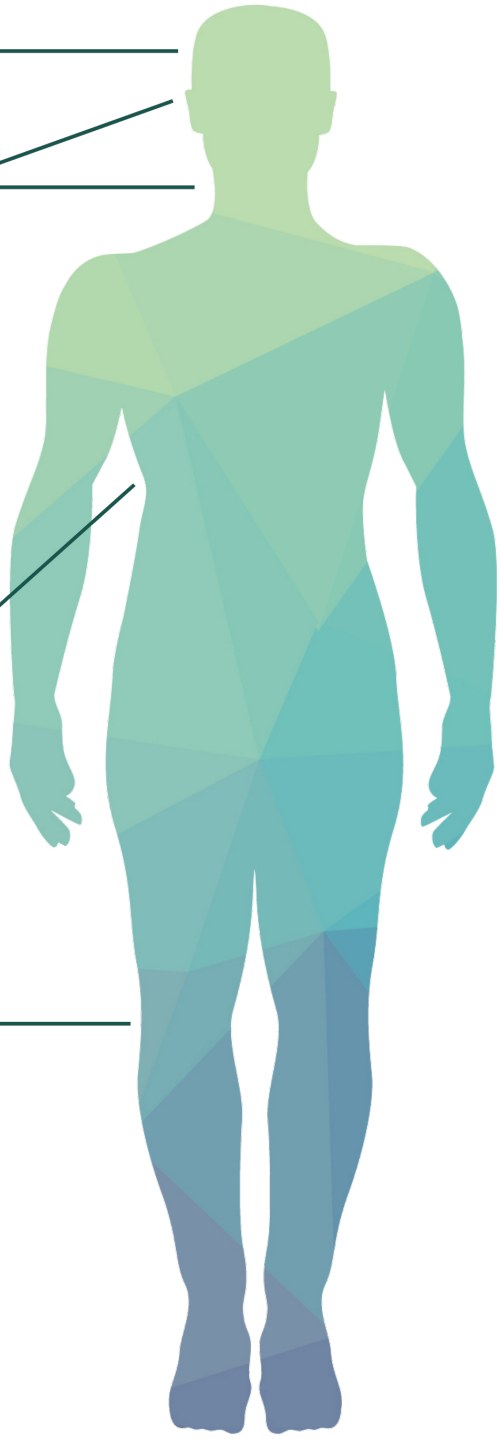
- Alzheimer's/Neurodegenerative diseases
- Cognitive dysfunction
- Learning/Memory
- Hypothalamic-Pituitary-Hormonal dysfunction
- Pineal/Thymus gland dysfunction
- Sleep disorders/Insomnia
- Brain tumors
- Tinnitus/Eye problems
- BBB disruption
- Microglial inflammation
- Headaches

Immunological Effects

- Inflammation/Aging (Inflammaging)
- Imbalance (Th1/Treg-Th2/Th17 shift)
- Mast cell activation
- Stimulates pathogens
- Synergistic with toxins
- Autoimmunity

Cellular Effects

- Metabolic dysfunction/Insulin resistance
- Mitochondrial dysfunction
- Cardiovascular dysfunction/HTN
- Fatigue/Weakness/Pain
- Cancers
- DNA damage/Epigenetic changes
- "Leaky gut"
- Infertility
- EMF sensitivity syndrome



The following are a few studies that demonstrate the potential hazards of the typical levels of EMF exposure experienced by most people in the United States, which is greatly enhanced with CIRS and other chronic illnesses secondary to preexisting abnormalities.

- Prenatal exposure to 900 Mhz EMFs resulted in offspring with a high degree of a dysfunctional thymus and spleen, as well as mitochondrial and immune dysfunction (thymic dysfunction and T cell exhaustion with Th1/Treg-Th2/Th17 shift), decreased glutathione and SOD, reduced NK cell function and number, gut dysbiosis, increased GI and BBB (brain) permeability, pineal-hypothalamic-pituitary-hormone dysfunction (resulting in multiple hormonal deficiencies that are not detected by standard blood tests.[EMF1-75]
- Aldad et al. exposed pregnant mice in utero to a mobile phone on active call mode throughout gestation. The offspring were shown to have memory impairment and hyperactive behavior compared to unexposed mice.[EM 64]
- Tang et al. chronically exposed rats to 28 days of mobile phone EMFs. They found significantly altered neurobehavioral performances, impaired spatial memory, and damaged BBB permeability by activating the mkp-1/ERK pathways. It was also shown that the rats experienced impaired special learning and reference memory. Morphologic changes were found in the rats' hippocampus.[EMF65]
- Saikhedkar et al. exposed rats to cell phone radiation for 4 hrs/day for 15 days, which induced deficits in learning and memory. They also found hippocampal neuronal degeneration.[EMF66]
- Pregnant rats exposed to cellphone RF-EMF throughout gestation drastically affected learning acquisition and memory retention, EM67, and further study also showed hippocampal morphological changes.[EMF68]
- Numerous studies have shown that rats exposed to cellular phone EMFs for various periods results in increased long-standing subsequent anxiety. One study found reduced GABA and aspartic acid in the cortex and hippocampus.[EMF68, 69]

BPC-157, TB4 frag, KPV, Selank, Semax, MOTSc, humanin, SS-31, GHK-Cu, and Cerebrolysin (IV and oral-available as a supplement) can mitigate and prevent a significant amount of EMF toxicity. BPC-157 is shown to block the abnormal activation of voltage-gated ion channels caused by EMFs.[BPC18,23,45,61,66] BPC-157, and thymosins modulate the immune system to maintain a healthy a Th1/Treg-Th2/Th17 as opposed to the pathogenic, inflammatory TH2/Th17/Th9 immune system caused by many things, including EMFs.[ICD19,35,40,41,66,67,87]

Thymic and immune-modulatory peptides, such as TB4 active frag, thymogen/vilon (Thymogen alpha-1), BPC-157, KPV, GHK, and oral Cerebrolysin (CerebroPep) have a wide range of mechanisms that protect the body against the damage of EMFs. This includes a general decrease in EMF-induced inflammatory cytokines; an increase in the EMF induced reduction in endothelial nitric oxide production; the ability to block the abnormal activation voltage-gated ion channels; inhibiting EMF-induced IL-6; helping to normalize the EMF induced immune and mitochondrial dysfunction; stimulating EMF suppressed phagocytosis and autophagy; reversing EMF induced reduction of antioxidant and glutathione production; stimulating EMF suppressed stem cell activity and proliferation; maintain healthy GI mucosa and blood-brain barrier permeability by maintaining tight junction integrity; healing EMF tight junction damage in the gut and BBB and blocking abnormal activation of the voltage-gated channels; reducing EMF, toxin and infection stimulated microglial activation; blocking the detrimental effects of EMF and neuro and endotoxins

throughout the body; and boosting EMF and vaccine-induced suppression of NK function.[ICD25-29,28,29,31,32,34,63,66,67,34-38,40-42,80,82,91,111,116,117]

The nanoparticular size of BPC-157, TB4 frag, KPV, and LL-37 allow these peptides to break down fungal and bacterial biofilms and granulomas, allowing them to effectively destroy these organisms and outperform most standard and common alternative antifungals and antibiotics. This makes them effective and very non-toxic antifungals and antimicrobials against toxic molds and pathogenic bacteria in the gut, nasal passages, and lungs.[AGA2,15, MSH3,4, ICD70,71,86,95] In one study, mice inoculated with aspergillus nasally, those given TB4 for 14 days found that TB4 had direct anti-fungal effects along with the induction of mucosal barrier protection and reduction of lung inflammation. (100% of controls died vs. 50% of treated mice)[AGA2]

Biomarkers

TGF beta-1, C4a, and MMP-9 are markers of a high Th2/Th17. As stated, the immune system is like a seesaw in that one side usually dominates; high Th1 immune activity suppresses Th2 and Th17 immunity, while elevated Th2 and Th17 immunity suppress Th1 immunity-depending on the condition and health of the system. The typical immune abnormalities seen with CIRS are not specific to CIRS but are extremely important. Because immune dysfunction lies at the core of CIRS, additional testing should be done. This should include NK cell function testing as a send out through Quest Diagnostics, though not all draw stations perform the test, and even then, they often only do it at particular times of the day. For instance, approximately 75% of CFS patients have low NK cell function, and 25% have low NK cell numbers. Other recommended tests that demonstrate immune dysfunction include CD4/CD8 ratio (< 2.5), NK cell function <30 LU, increased hTGFb-1 (TB4 frag, KPV, and vilon are potent suppressors of TGFb-1), increased C4a, tT3/rT3 < 12, tT3/T4 ratio < 3, leptin > 12, immune activation of coagulation, autoimmunity, toxic mold antibodies, low DHEA, AM cortisol < 12 with an ongoing chronic infection, low vitamin D, low pregnenolone, low testosterone, low GH or estrogen, increased CMV, EBV or H-pylori titers, low IgG subclasses (adequate Th1 immunity is required to convert IgM antibody to IgG), hyperlipidemia, high (high normal) eosinophil cationic protein (ECP), ACE > 30, and a low WBC (this can be useful, and is, of course, very easy to get, but it is not very sensitive).[TBM1, TCM2, 1 LEP, TGF1-8] Conditions associated with immune dysfunction include ongoing chronic infections, SIBO, IBS, PMS, cardiovascular disease, kidney disease, cognitive dysfunction, CFS, fibromyalgia, PTSD, traumatic brain injury, diabetes, obesity, hypothyroidism, chronic dieting, depression, osteoporosis, MCAS, frailty, depression, CIRS, allergic conditions, autoimmunity, aging, stress, anxiety, neurodegenerative diseases, inflammatory diseases, and most chronic illnesses.[1 LEP, ACTH1, TGF1-8]

You will find that close to all CIRS patients have significant immune dysfunction. Treatment usually entails TB4 frag, thymogen/vilon (Thymogen alpha-1), BPC-157, and KPV as a starting point, generally pairing a thymosin peptide or peptide combination along with a modulator and suppressor of Th2/Th17, which would be BPC-157 as a staple and KPV as a great choice, especially if the patient has any mast cell activation issues. I would then consider adding pinealon or epitalon to improve the immune dysfunction and the pineal-hypothalamic-pituitary-hormone axis, which will enhance hormone production, including thyroid and other hormones. Other effective therapies include GHK, Selank, DSIP, Cerebrolysin, stem cells, exosomes, glutathione, NAC, zinc, ozone, ozone plasmapheresis, vitamin D, and others. If sleep is an issue, the combination of a pineal peptide, growth hormone (GH) or a GH secretagogue and DSIP would be a good choice, as this combination can be dramatically beneficial for resetting sleep disorders.

While both the CSCSPC and the HUPPRTOC recommend that patients remove themselves from the mold source is a common-sense first step, the peptides BPC-157, TB4 active frag, KPV, GHK-Cu, epitalon, pinealon, oral Cerebrolysin, MOTSc, and SS-31 are essential at protecting the body against the toxic effects of the myco- and enterotoxins. You can use sequestrants (binders), but a properly functioning detoxification system will be able to eliminate the mycotoxins. However, if there is low cellular energy (mitochondrial dysfunction), another major issue with CIRS, the body cannot eliminate the toxins. The same is true for heavy metals. Due to the damaged pineal-hypothalamic-pituitary-thyroid axis and systemic inflammation, all but a small percent of CIRS patients will have low tissue levels of thyroid even though the standard thyroid function tests, including the TSH, look normal. They will usually have a low normal TSH, a normal or high-normal free T4, a low normal free T3, a high normal reverse T3, and an SHBG level less than 80 in women and 30 in men.[1 LEP, 3-7LEP] Supplementing with T3, in addition to immune modulators and mitochondrial peptides (such as MOTSc and SS-31), is shown to significantly improve mitochondrial function and cellular energy and reverse the dysfunctional mitochondrial cell danger response.[1LEP, 3-7 LEP] The increased cellular energy will facilitate the ability of the cells to detoxify and eliminate mycotoxins. It will also enable cellular and tissue resistance to the toxic effects of mycotoxins and heavy metals. I believe oral and intravenous phosphatidylcholine and poly-MVA outperform cholestyramine (CSM) for biotoxin removal if combined with the above.

ACTH, Cortisol, and Stress

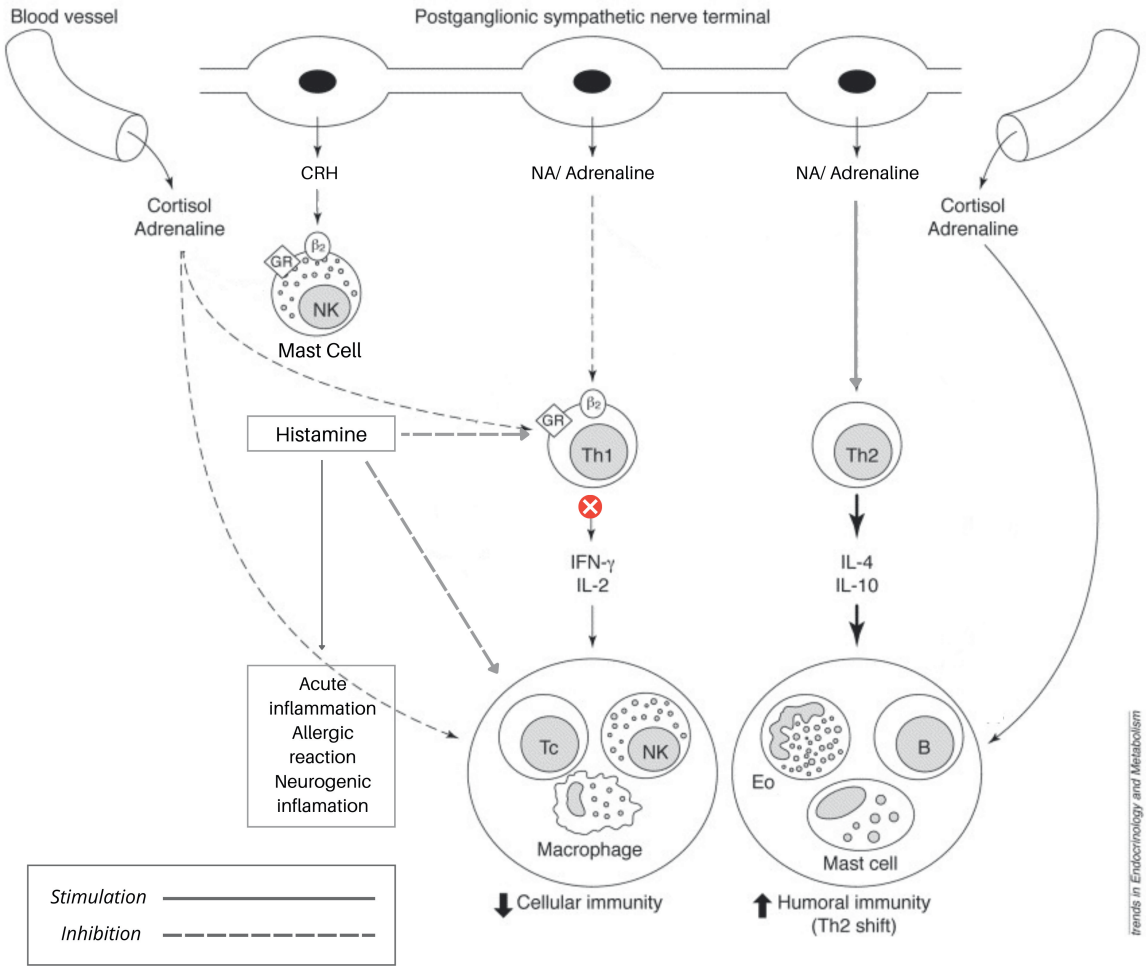
Stress and CIRS can result in significant mast cell activation (MCAS). As stated above, both conditions stimulate CRH, which is a potent stimulator of mast cells. When this is combined with the stress of CIRS, T cell exhaustion, and immunosenescence-induced immune dysfunction, MCAS is often a significant problem. (see figure 12) While direct mast cell inhibitors, the standard protocol for MCAS, can be helpful, upstream regulation via reversing the out-of-balance immune system, which includes reversing the Th1 to Th2/Th17 shift with pinealon, epitalon, TB4 frag, thymogen/vilon (Thymogen alpha-1), BPC-157 and KPV, is a much more effective method as a sole therapy or in combination with direct mast cell inhibitors for controlling excess mast cell activation.[ICD83,86,87,90,96, MSH1,4-6, BPC22,26,28,36,38]

I would then consider the pineal peptides, pinealon, or epitalon, and KPV and DSIP. Many of the biomarkers improve as the immune dysfunction improves and the pineal gland, the hypothalamus, and pituitary inflammation decrease. Cerebrolysin (IV or oral), Selank, Semax, DSIP, and humanin reduce activation of microglial (brain mast cells) and brain inflammation.[ICD87, 90, MSH4-6]

Using ACTH and centrally acting agents for cortisol stimulation tests, a study published in the Brazilian Journal of Infectious Diseases demonstrated that HPA axis dysfunction could be determined accurately using basal cortisol levels in individuals with chronic infections. They found that a basal cortisol below 11.5 ug/dl had a 94% specificity for HPA axis dysfunction. It is not uncommon for such patients to have a high ACTH, which correlates with a high CRH.[ACTH1] Also, any condition associated with inflammation or stress, including EMF-induced inflammation, will result in the Th1/Treg to Th2/Th17 shift, increasing the risk of MCAS, autoimmunity, and most every disease of aging. This HPA axis dysfunction should be treated with physiologic doses of cortisol 5-15 mg/day to optimize the cortisol level in physiologically stressed individuals and bring down CRH, a potent stimulus of mast cells and associated with a significant Th1/Treg to Th2/Th17 shift.

Figure 12.

Stress, TH1/Treg-Th2/Th2/Th17 Shift, Aging and Mast Cell Activation



1. Mast cell activation is a major concern for Lyme, CFS, fibromyalgia, CIRS, MCS, and MCAS (of course) patients, especially with POTS and other mast cell-related symptoms

2. Due to a dysfunctional, out of balance, immune system (not abnormal mast cells)

3. Direct mast cell inhibitors are the mainstay of treatment, **but upstream regulation can be much more successful** treatment of mast cell activation syndrome (MCAS)

4. Restoring and supporting normal immune balance (normal Th1/Treg-Th2/Th17 balance) with LDN and peptides inhibit mast cell activation by upstream and direct inhibition of mast cell activation. 73

97. Clerici M, Shearer, GM. The Th1-Th2 hypothesis of HIV infection: new insights. Immunology Today 1994; 15(12):575-581

In a review article that I published, entitled Diagnosis and Treatment of Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysfunction in Patients with Chronic Fatigue Syndrome (CFS) and Fibromyalgia (FM), it was demonstrated that while both CFS and FM patients are shown to have central HPA dysfunction, the dysfunction in CFS is at the pituitary-hypothalamic level. In contrast, the dysfunction in FM is more related to dysfunction at the hypothalamic and supra-hypothalamic levels.ACTH 1 Because treatment with low physiologic doses of cortisol (<15 mg) is safe and effective, and routine dynamic ACTH testing does not have adequate diagnostic sensitivity, it is reasonable to give a therapeutic trial of physiologic doses of cortisol to the majority of patients with CFS and FM, especially to those who have symptoms that are consistent with adrenal dysfunction, such as low blood pressure or have baseline cortisol levels in the low or low-normal range.[ACTH1]

Peptides were unavailable when the review article was published, so it describes the appropriate treatment as giving cortisol if a patient's morning cortisol level is below 12. Now, this can be rectified through the use of peptides. Some cortisol may be beneficial for some patients for a time. Most specialists in the treatment of mast cell disorders strictly focus on direct mast cell inhibitors and don't understand how it is a disease of immune dysfunction, not mast cells. The mast cells are not abnormal; they are being inappropriately stimulated. Thus, while direct mast cell inhibitors have benefits, treating the upstream cause of the mast cell activation is more appropriate and effective. While most of the peptides will improve MCAS and associated symptoms, BPC-157 and KPV (a fragment of MSH) have potent anti-inflammatory effects, including mast cell inhibition. [ICD83,86,87,90,96, MSH1,4,5, BPC22,26,28,36,38]

MSH and KPV

MSH is one of the most anti-inflammatory substances produced in the body. The tripeptide fragment of MSH, KPV, is about a hundred-fold more potent anti-inflammatory and mast cell inhibitor by weight than MSH. Also, KPV does not stimulate melanocytes, so there is no risk of hyperpigmentation. Its small size and stability make it orally bioavailable, whereas the large MSH peptide is not orally absorbable. Additionally, it has significant broad-spectrum antimicrobial activity. It is not practical to give MSH due to its poor bioavailability and short half-life. Commercially available MSH analogs have been developed, including Melanotan I & II and PT-141. Melanotan I & II have been known as the "Barbie Doll" peptide because it stimulates weight loss, libido, and activation of skin melanocytes (in other words, it makes you tan). However, tanning is a double-edged sword, as it works well for younger individuals, but older individuals will often develop dark spots as areas of sun damage darken. PT-141 works for erectile dysfunction in men and is FDA approved for sexual dysfunction in women. While effective, it has a significant side effect of nausea and vomiting and can stimulate skin melanocytes, although less than Melanotan I & II.

It has recently been found that the C-terminal tripeptide of MSH, KPV, is orally bioavailable, while MSH is not; it promotes healing of the gut and numerous other organ systems; is organoprotective; prevents cellular stress-induced toxicity; is very effective for excess activation of mast cells, as in mast cell activation syndrome (MCAS) and activated microglia in the brain (neuroinflammation); results in no stimulation of skin melanocytes; is very non-toxic; and has a broad spectrum of antimicrobial and antibiofilm properties, having both direct antimicrobial effects against fungi, mold, bacteria, viruses, and parasites, as well as indirect effects mediated through the immune system, being more potent and effective against fungi, yeast, viruses, and bacteria than fluconazole and commonly used antimicrobials even at very low (picomolar), concentrations.[MSH1-5] (see figures 13 & 14)

Figure 13.
KPV (MSH 11-13) Out-Performed Fluconazole on Inhibition of C. Albicans Viability

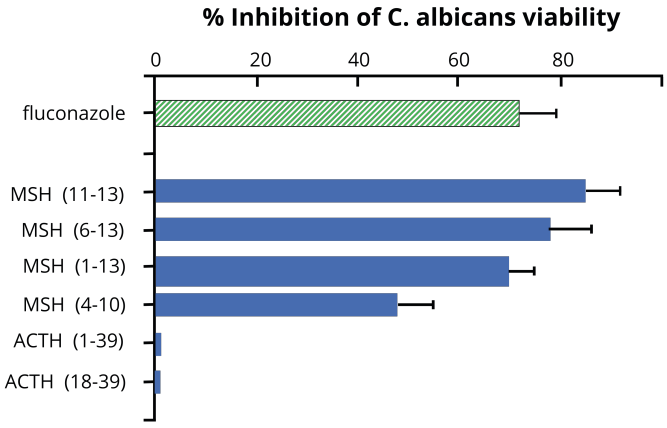


Fig. 4. Comparison of candidacidal activity of melanocortin peptides and fluconazole (all 10 M)

Figure 14.
Alpha MSH Peptides that Combine Antimicrobial, antipyretic, and anti-inflammatory effect could be very useful in the treatment of infections."[119]

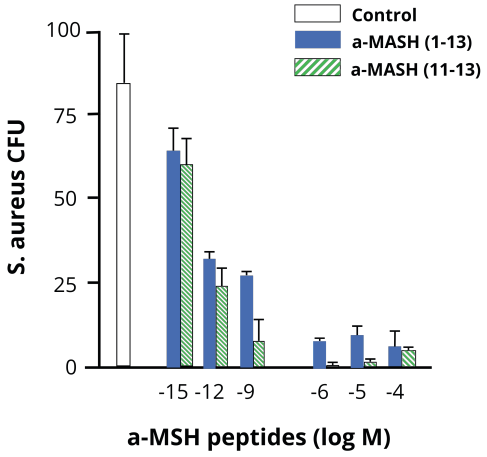


Fig. 1. Influence of 0i-MSH (1-13) and (11-13) on S.sureus colony -forming units. Scores are means ±SEM

A review article examining MSH fragment KPV's direct and indirect antimicrobial and immune-modulatory effects and its fragments found that MSH and its C-terminal fragment demonstrated potent antifungal, antibacterial, and immune-modulatory effects, stating, *"The C-terminal region (KPV) of α-MSH demands special attention for several reasons. It exhibits in vitro and in vivo anti-inflammatory activity similar to that of the parent peptide without the metabotropic effect. Moreover, this essential anti-inflammatory sequence, C-terminal tripeptide (KPV) of α-MSH, is also essential for its direct antimicrobial efficacy. Therefore, this short molecule KPV appears to have tremendous potential to be developed as a therapeutic agent as it is more suitable for clinical use…"*[MSH4]

PAI-1, ACA, and VWF

Plasminogen Activator Inhibitor-1 (PAI-1), Anticardiolipin Antibodies (ACA), and Von Willebrand Factor (VWF) comprise the standard coagulation panel recommended in the current CIRS treatment algorithm. The HUPPRTOC recommends a much more extensive and comprehensive hypercoagulation panel because the standard panel will miss 60-90% of those suffering from immune activation of coagulation. Missing this abnormality will often result in multiple levels of treatment failure and protracted illness.

There are over 60,000 miles of blood vessels in the body, of which 80% are capillaries. Inflammation from mold, bacteria, parasites, viruses, mycotoxins and other toxins, mast cells, and immune and mitochondrial dysfunction can trigger the clotting cascade, causing fibrin to be laid down on the capillary walls and thick, sluggish blood. This combination causes the body to suffer from diminished ability to deliver nutrients, medications, and oxygen to the cells and remove waste products from the cells. (see figure 15 & 16)

The internal width of a capillary is 8-10 microns (a human hair is 50-100 microns in diameter), and a red blood cell is about 7 microns wide. The sludge-like fibrin layer formed during a hypercoagulable state is about 1 micron thick. The red blood cells are also less flexible, making it difficult to flow through the narrowed capillaries. The fibrin-coated capillary walls also impair the

ability of nutrients, supplements, and medications to penetrate the cells and the capability of waste products to exit the cells. This often leads to treatment resistance in patients and is one cause of thyroid resistance.

The oxygen that usually takes approximately two seconds to diffuse into the cells can take up to 5 minutes to penetrate the thickened capillary walls, potentially causing cellular hypoxia, mitochondrial dysfunction, and extensive need to utilize anaerobic metabolism with even minimal physical or mental stress or stimulation. In addition, with fibrin coating the vessel walls, the endothelial cells can no longer release heparins, the body's natural blood thinner, perpetuating the cycle. Typical symptoms include air hunger, shortness of breath, poor endurance, fatigue, muscle pain, and POTS. The fibrin-coated vessels result in endothelial dysfunction, and the capillaries become stiff and unable to compensate to positional changes quickly. Patients may sometimes notice mottled (blotchy), lacelike purple discoloration under the skin (often on thighs and lower legs), called livedo reticularis. This is most commonly seen with Bartonella infections but can occur with other causes of immune activation of coagulation.

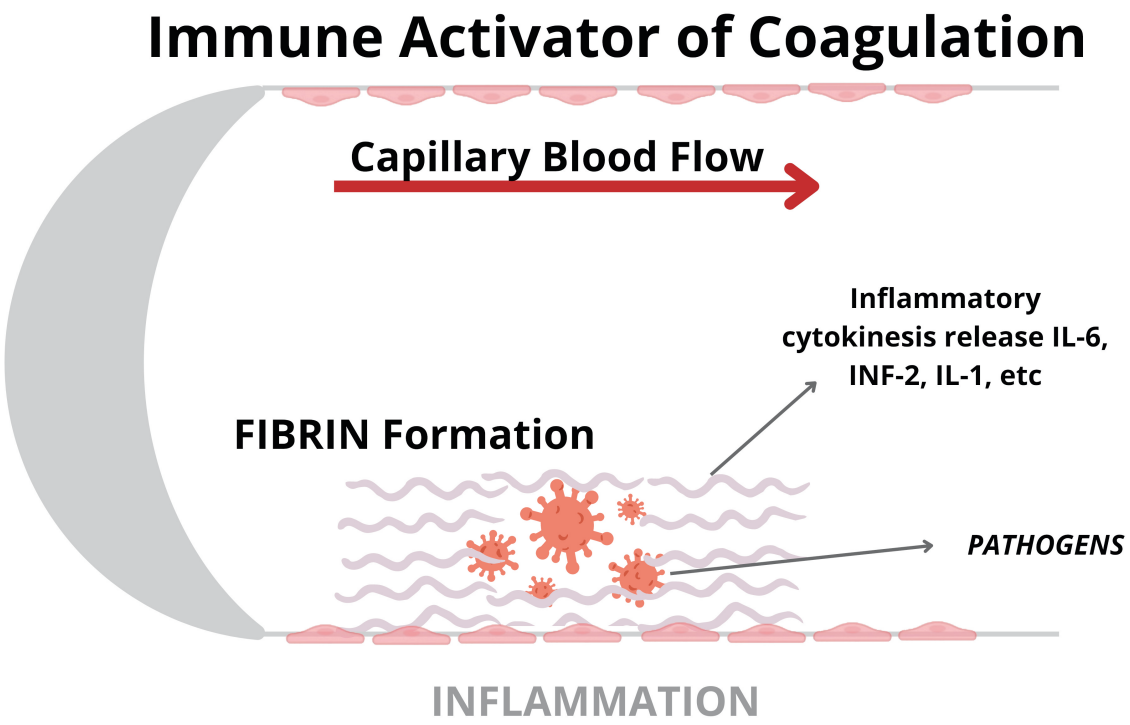
The coagulation system can also contribute to the innate immune system by trapping invading organisms and secreting antimicrobial peptides into the space between and below the platelet aggregates-fibrin fibers and red blood cell complex.PAV10 However, certain molds and bacteria have developed ways to use this stimulation of coagulation to increase virulence. The invading organism can either secrete substances that can activate clotting or hinder the coagulation pathway at the fibrin monomer formation state to hide under and amongst the fibrin monomers or by encasing themselves in a shield of fibrin that effectively blocks phagocytosis.[PAV4]

A study investigated the interplay of the complement and coagulation systems in host defenses. They write, "*Borrelia burgdorferi expresses a variety of plasminogen receptors on their surface, including the outer surface proteins (OspA and OspC) and Erp proteins (ErpA, ErpC, ErpP), to establish plasmin formation during all stages of infection,*" This allows Bb to break down and be free of any potentially entrapping fibrin monomers.[PAV10]

Like many processes in the body, immune activation of coagulation is initially beneficial, but as it continues, it becomes detrimental, which is often the case with unresolved chronic infections, including Lyme disease and other bacteria, viruses, parasites, and mold. Toxins can also induce coagulopathy, including mycotoxins and heavy metals. This is often seen in cases of CIRS, CFS, fibromyalgia, chronic inflammation, autoimmunity, GI dysfunction, and many chronic illnesses. A number of studies have found that 60-90% of CIRS, CFS, fibromyalgia, Gulf War syndrome, and Lyme disease patients have abnormal immune activation of the clotting system. In comparison, 75% have a genetic predisposition for thrombophilia, a fourfold increase over the general population.[PAV4]

The HUPPRTOC Immune Activation of Coagulation Panel is much more extensive than the one used in the CSCSPC. The HUPPRTOC panel includes D-dimer, soluble fibrin monomer (SFM), fibrinogen, prothrombin fragment 1+2, thrombin antithrombin (TAT) complex, factor II activity, PAI-1, anti-Xa, anti-phospholipid antibodies, lupus anticoagulant, anti-B2GPI antibodies, Sed rate < 5, low normal PTT, elevated fibrinogen, increased LP(a), PAI-1 4G/5G genetic polymorphism, an elevated or high-normal eosinophil cationic protein (especially when provocated with an antiparasitic, this has a high sensitivity for the detection of Babesia and associated hypercoagulability), factor V Leiden deficiency, and elevated homocysteine. This panel is exponentially more sensitive at detecting abnormal coagulation. If you miss immune activation of coagulation, which is so common with CIRS, and fail to treat the hypercoagulation, the patient is less likely to respond to therapy. A study examined the relationship between the level of activated partial thromboplastin time

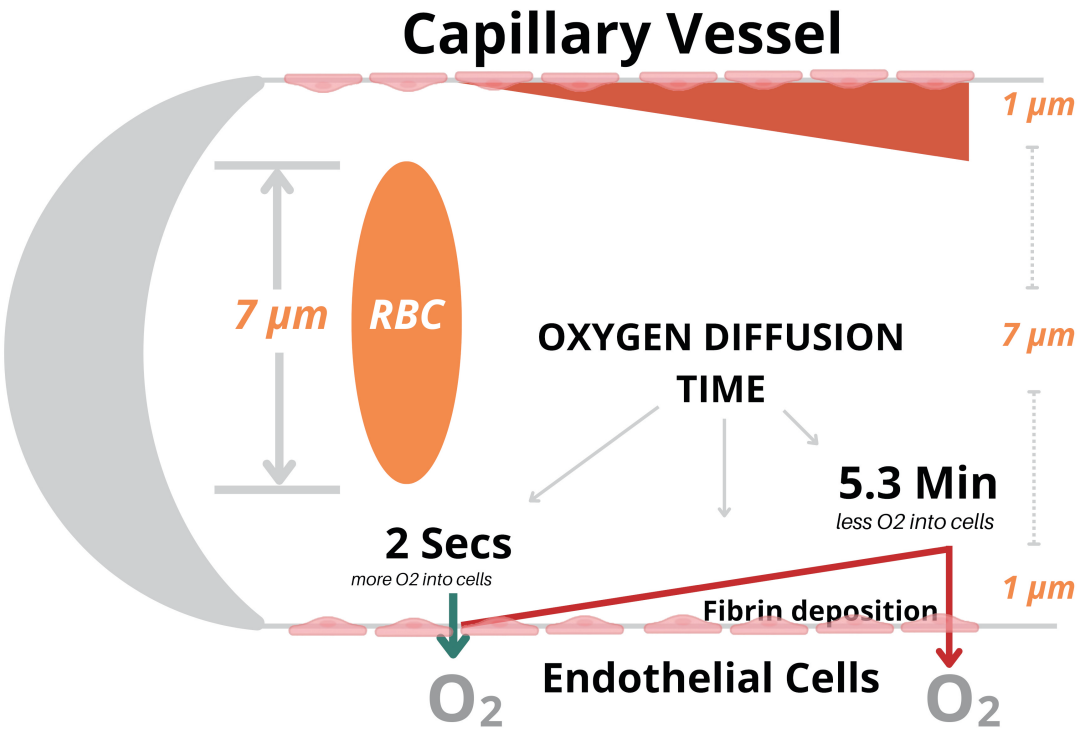
Figure 15.



Berg D, The Role of Hypercoagulation and Biofilm in Chronic Illness. April, 2011

Soluble Fibrin Protofibrils are generated to isolate invading pathogen

Figure 16.



1. **Y Nemerson. ISTH, Birmingham, ENG, July 2003**

Oxygen diffusion time increases with the amount of Fibrin deposition (increasing hypoxia, fatigue, weakness, poor endurance, and air hunger with a reduced anaerobic threshold)

(PPT) within the normal range and the risk of venous thromboembolism in 13,880 individuals over 13 years. The study found a 5.5-fold increased risk of idiopathic venous thromboembolism for those with a PTT level below the mean. The authors concluded, *"A single determination of the activated partial thromboplastin time below the median increased the risk of future venous thromboembolism. Findings were independent of coagulation factor levels, and a low activated partial thromboplastin time added to the risk associated with other risk factors."* PAV11

Studies in Germany and Scotland have found that fibrinogen levels are the top risk factor for cardiovascular diseases (CVD). The Prospective Cardiovascular Münster (PROCAM) study followed 5389 men for ten years. It found that *"the incidence of coronary events in the top third of the plasma fibrinogen levels was 2.4-fold higher than in the bottom third. Individuals in the top third of levels of low-density lipoprotein (LDL) cholesterol who also had high plasma fibrinogen concentrations had a 6.1-fold increase in coronary risk. Unexpectedly, individuals with low plasma fibrinogen had a low incidence of coronary events even when serum LDL cholesterol was high."*PAV14

In the Scottish Heart Health Study, 10,359 men and women were followed for two years; *"Fibrinogen was the single most powerful risk factor for CVD risk or death and more predictive than lipoprotein cholesterol. The increase in (relative risk) between the highest and lowest fibrinogen levels was*

Immune Activation of Coagulation (Hypercoagulation)

Treatment includes:

- Low dose heparin is typically started and titrated up to 5000 iu SQ bid (safer than aspirin). Heparin also binds inflammatory cytokines and is an immune modulator. Low dose heparin binds extracellular histones produced in sepsis and CIRS, blocking their cytotoxic effects, it blocks Babesia's entry into the red blood cell, and its immune-modulatory effect lowers inflammation, helps with herxheimer reactions, and stimulates NK cell activity that is synergistic with IL-2, which are all separate benefits apart from heparin's anticoagulatory effects. Of clinical note, it can artificially raise the level of free T3 and free T4.PAV7-9, 12
- Lumbrokinase 400,000 LU twice daily on an empty stomach. This directly activates TPA, degrades fibrin, works intravascular and in the intracellular space, and reduces Lp(a)).
- Nattokinase 1000 FU twice daily on an empty stomach. This indirectly acts on TPA and degrades fibrin only in the intravascular space. You can get both in Fibrinix.
- Melatonin 20 mg per night is a much higher dose than usually given. It is shown to improve hypercoagulability in a dose-dependent manner.PAV6.
- BPC-157 500-1000 mcg orally twice daily. It breaks down fibrin and clots and treats hypercoagulation. At the same time, it also reduces bleeding time in hypocoagulation and in heparin overdose (without affecting heparin effects), reduces mortality in heparin, warfarin, and aspirin overdose, and prevents heparin-induced thrombocytopenia.PAV5
- GHK downregulates the beta chain of fibrinogen by -475%. Since equal amounts of all three polypeptide chains are needed to produce fibrinogen, when the synthesis of one of the chains of fibrinogen is suppressed, it will have an overall inhibitory effect on fibrinogen synthesis [44]. Fibrinogen is well known for its ability to form blood clots. However, it also is a major determinant of blood viscosity, and it is associated with red blood cell "stacking," known as rouleaux formation, which severely limits capillary blood flow because capillaries can only accept free-flowing or singular RBCs.PAV13

301% for men and 342% for women (CVD death) and 259% for men and 220% for women (death from any cause).” GHK also suppresses the production of Interleukin-6, a main positive regulator of fibrinogen production, both in cell cultures and in mice.[PAV14]

Immune-modulatory peptides such as TB4/TB4 frag, thymosin, thymogen/vilon (Thymogen Alpha-1), KPV, DSIP, Thymosin alpha 1, epitalon, and pinealon improve hypercoagulability through their immune-modulatory effects and their ability to stimulate melatonin levels.

The response to treatment can be dramatic; treatments that previously had no effect become effective, as the therapeutics, oxygen, and nutrients can now enter the cells much easier, and waste products can more readily be removed. Heparin, BPC-157, TB4 frag, KPV, and vascular enzymes are biofilm busters and immune modulators. Heparin, BPC-157, TB4 frag, GHK, and KPV are significantly antimicrobial (heparin inhibits Babesia invasion of erythrocytes).[PAV7,13] The newer anticoagulants and warfarin don’t work very well for this type of hypercoagulation), though low molecular heparin is okay.

VIP

The CSCSPC considers normalizing VIP levels essential for helping CIRS patients to fully recover. It must be given only after all other parts of the CSCSPC are successfully completed in their entirety, which can take years, if ever.[VIP3, 4] VIP can be beneficial, but it has a high failure rate and can make someone chronically worse and more difficult to treat. In a low inflammatory environment, VIP has potentially beneficial pleiotropic immune-modulatory effects, but if there is any inflammation present, such as in the presence of C4a and especially hTGFb (major hallmarks of CIRS), VIP will drive the immune system into more of a T cell exhaustion, immunosenescent and aged immune system phenotype, further stimulating inflammatory Th2, and Th17 immunity while suppressing Th1 immunity.[VIP1, 7] This is the opposite of what you want when treating CIRS, chronic Lyme disease, CFS, fibromyalgia, autoimmune disease, and any chronic disease of aging.[VIP1,5,7]

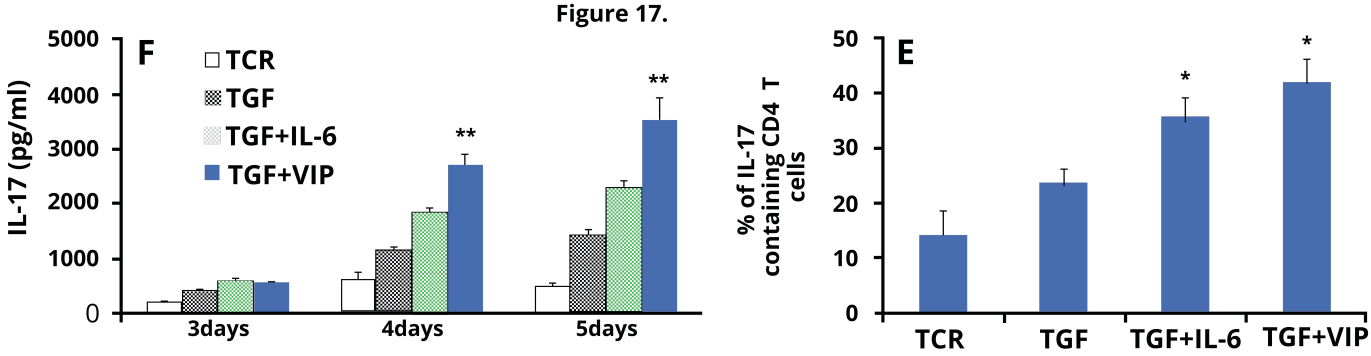
This is why Dr. Shoemaker states (and very astutely, I might add) that VIP should not be given unless you have dramatically cleaned up the immune dysfunction and all the inflammation.[VIP3] This also explains why some people feel better from it while others worsen and become sicker and more difficult to treat. It has also been shown to reduce metabolism and suppress NK cell activity.[VIP7] Thus, you dramatically inhibit your body’s ability to destroy pathogens and toxins. This reduction in killing may make you feel better for a short time, as inflammatory cytokine levels may temporarily be reduced, but you will be at risk of worsening symptoms, an inability to fight off pathogens, and cancer. VIP can make you more prone to adverse effects of toxic exposure, as your ability to eliminate these substances is diminished.

There is concern that VIP stimulates breast and prostate cancer, potentially due to the suppression of NK cell function. Cancers are shown to have upregulated VIP receptors; as such, VIP significantly stimulates the growth of many cancers. VIP antagonists are currently being developed for clinical anti-cancer use.[VIP7, 17] In a study entitled Vasoactive Intestinal Peptide (VIP) Induces Malignant Transformation of Human Prostate Epithelial Cell Line, VIP was shown to increase MMP-9 and PSA and cause the transformation of normal prostate cells into malignant cells. Numerous studies have also demonstrate that VIP induces breast cancer via a variety of mechanisms.[VIP19] VIP also stimulates substance P, a potent inflammatory marker associated with allergies and suppression of NK cell function.[VIP8] A 2022 study in the Journal of Immunology, concluded, *“Down-regulation of IL-21 by VIP could also diminish differentiation and activation of NK cells whose cytotoxic activity is augmented in the presence of IL-21*"[VIP7]

Considering the potential stimulation of sub-

VIP induced IL-17 and Th17 phenotypical cells from CD4 cells in the presence of TGF-beta[VIP7]

Figure 17.



stance P, the stimulation of Th2/Th17, and the suppression of NK cell function and Th1 immunity by VIP, it is not surprising that the CSCSPC takes a long-time to see beneficial effects and that patients never seem to recover fully, and they usually remain hypersensitive to future exposures to mold.[VIP7, 8] While VIP can have seemingly beneficial anti-inflammatory effects at a particular time, it must be given at the correct time, not too early, and not too late because its underlying immune-modulatory effect is opposite to that is what is needed for a speedy and complete recovery and may have the opposite effect you want or are expecting.

VIP will usually normalize with immune-modulatory treatment and lowering hypothalamic inflammation; effective peptide therapies include, TB4/TB4 frag, thymogen/vilon (Thymogen alpha-1), BPC-157, KPV, epitalon, pinealon, DSIP, AOD, growth hormone, and growth hormone secretagogues. Additionally, you don't have to wait until the other aspects of CIRS are successfully treated with the peptide therapy above, as is required with the current CIRS treatment algorithm; it can be done as initial therapy. As briefly discussed above, VIP has a dark side if given with TGF-beta or inflammation.

As stated, VIP stimulates Th17 and down-regulates NK cells in the presence of TGFb-1. One study found that the combination of VIP and TGFb-1 resulted in a thirtyfold increase in the T cell production of IL-17, resulting in a vicious cycle of autoimmunity and T cell exhaustion, which is precisely what you don't want for long-term resolution.[VIP7] Pointing out this fact, the authors of one study state, *"These results indicate that VIP plays an unanticipated permissive and/or proinflammatory role in propagating the inflammatory response in the CNS, a finding with potential therapeutic relevance in autoimmune neuroinflammatory diseases such as multiple sclerosis. Thus, enhancement of the relative contribution of VIP-VPAC1 axis signaling can skew the CD4 T cell response toward a Th17-rich proinflammatory type."*[VIP9]

VIP stimulates mast cell degranulation of histamine via the VIP receptor on mast cells, VPAC1. An extensive review article entitled Recent Advances in Vasoactive Intestinal Peptide Physiology and Pathophysiology: Focus on the Gastrointestinal System discusses how VIP may symptomatically improve colitis, but also how it perpetuates the disease and underlying immunopathology. The authors discuss how VIP stimulates colon cancer, with the VIP receptor VPAC1 being overexpressed in 35% of well-differentiated, 65% of moderately differentiated, and 87% of poorly differentiated colon cancer.[VIP20]

VIP treatment substantially reduces the number of CD4 cells producing IL-2 and TNF-alpha and increases IL-10 and TGFb-1, converting Th1 into Th2 cells, all of which are major drivers of TCE.

[VIP1,7,9,11,16] An additional concern is that while the half-life of VIP is only two minutes, but the physiologic results, such as TCE are long-lived.VIP 16 VIP is essentially transforming T cells into the dysfunctional immobilized state of TCE.[VIP5, 16] This short-term gain of reduced inflammation and symptom relief is associated with a longer-term worsening of the condition.

New cellular laboratory techniques show that T cell exhaustion (TCE) is a significant issue with many chronic illnesses, infections, and cancer. You typically see TCE with continued antigen exposure and/or inflammation, especially chronic infections and cancer. TCE is associated with progressive loss of effector functions of T cells (CD4 and CD8) and phenotypic and functional defects, sustained upregulation and co-expression of multiple inhibitory receptors, lack of availability of CD4 T cell help, increased levels of CD43, altered expression of key transcription factors, metabolic derangements, and failure to acquire antigen-independent memory and responsiveness, dysfunctional Th1 as indicated by low NK cell function, low IL-2 and low TNF-alpha in late stages, and elevated hTGFb and IL-10, with a high Th2/Th17.[VIP5,6,7,11]

Earlier, we discussed the core dysfunction of CIRS being an elevated hTGFb, a Th1/Treg to Th2/Th17 shift, and a low NK cell function. It is no surprise that giving VIP in the presence of hTGFb is a bad idea. It will dramatically increase the potent proinflammatory cytokine responsible for most autoimmune diseases. In addition, if given with an elevated TGFbeta-1, VIP appears to induce a particular T cell phenotype of long-term immunosuppression defined as T cell exhaustion, which is associated with the inability to clear chronic infections, toxins, and cancer with an increased risk of autoimmunity. (See figure 17)

The immune-modulatory peptides listed above will lower inflammation and normalize the abnormalTh1 to Th2/Th17 immune shift. TB4 active frag, KPV, and vilon are, in particular, ideal therapeutics for CIRS, as they directly address the core components of CIRS immune dysfunction and inflammation. They are potent inhibitors of TGFb and stimulate NK cell function, Th1 immunity, IL-2, and TNF-alpha, reversing T cell exhaustion. They can also be used to reverse those who have suffered from negative immunologic aspects of VIP.[VIP12-14] With TCE being the likely core pathophysiology of CIRS, which leads to a vicious cycle of multi-system dysfunction, these peptides should be an initial first-line therapy for CIRS. Treatment can potentially prevent or reverse the subsequent abnormalities slowly treated over time with the CSCSPC. Additional peptides are shown to protect the body from the damage caused by myco- and other enterotoxins, which can be given along with the immune-modulatory peptides discussed above, being a much better strategy than the CSCSPC. Patients will not likely need VIP, but if there appears to be a need to use VIP, patients should be treated with these peptides before starting VIP. They can also be given concomitantly with VIP to help prevent VIP therapy's potential long-term adverse effects.

There are numerous clinical trials underway investigating ways to reverse TCE because it is a significant reason individuals cannot clear chronic infections and cancer and suffer from autoimmune disease and most of the inflammatory diseases of aging. The good news is that some of the new therapies introduced in this chapter are shown to be able to reverse TCE. While VIP can improve CIRS patients' symptoms for some time under the right conditions (i.e., low TGFb) by causing paralysis to parts of the immune system, caution should be used if using VIP at any time for extended periods or in anyone with a chronic infection.[VIP1,5-7,9,10]

Supplementing with VIP, as recommended as the final and ultimate step in the Shoemaker Protocol for CIRS, is however associated with adverse consequences and can prevent long-term improvement and an inability to become symptom free.

Anti-Diuretic Hormone (ADH)

The old CIRS protocol recommends using DDAVP, an analog of ADH, which can be used. With immune-modulatory and directed therapy to reduce inflammation of the hypothalamus, hippocampus, and amygdala, ADH abnormalities will often significantly improve or resolve. Those who suffer from POTs usually respond well to such therapy This includes the use of oral, sublingual, or nasal BPC-157, TB4 frag, thymogen/vilon (Thymogen alpha-1), oral Cerebrolysin (CerebroPep), delta sleep-inducing peptide (DSIP), epitalon or pinealon, or even better, a combination of the above from a doctor knowledgeable in the use of peptide therapy.

Testosterone and Other Hormones

For CIRS and many chronic illnesses and inflammatory conditions, including aging, all the hormones need to be evaluated with the understanding that, as discussed, the pineal-hypothalamic-pituitary-hormone axis is dysfunctional secondary to the immune and mitochondrial dysfunction seen in many chronic illnesses, which results in multiple hormonal deficiencies that are not detected by standard blood tests because 95% of endocrinologists and other doctors do not take into account the suppressed hormonal axis and just assume that it is healthy despite hundreds of studies to the contrary. For instance, such patients can have deficient tissue levels of thyroid throughout the body, but the standard measure of hypothyroidism, an elevated level of thyroid-stimulating hormone (TSH), doesn't happen because TSH secretion is suppressed, This results in a misdiagnosis of normal thyroid activity greater than 95% of the time.

Adhering to this oversimplistic view of thyroid function because it is simple is intellectually wrong and immoral. It leaves so many patients misdiagnosed as euthyroid (normal thyroid) when their lives can be profoundly changed for pennies a day. In CIRS and with many chronic illnesses, doctors rely on a diagnosis based on TSH secretion from a suppressed and physiologically dysfunctional pineal-hypothalamus-pituitary axis to appropriately sense low tissue thyroid levels and then properly respond with the secretion of increased levels of TSH from the pituitary. Therefore it is low, not high, which is the standard simplistic definition used by most endocrinologists and other doctors as the gold standard for diagnosis despite its glaring well-documented shortcomings and the hundreds or thousands of published peer-reviewed journal articles demonstrating such.[LEP1-7]

For CIRS and many chronic illnesses and inflammatory conditions, including aging, potential sources of stress, and environmental toxin exposure should be investigated; the presence of immune, gastrointestinal, mitochondrial, neurological, cognitive, sleep, coagulation, detoxification, and pineal-hypothalamic-pituiatry-hormone dysfunction all need to be extensively evaluated; the identification of likely infections, including bacterial, viral, parasitic, and fungal, along with the presence of endotoxins, immune activation of coagulation, autoimmunity, autoimmunity and autonomic dysfunction, need to be rigorously perused in order to provide a comprehensive picture of this multisystem illness so a comprehensive, cutting-edge, multisystem treatment program can be implemented.

CSCSPC/Shoemaker Protocol

This section will summarize the Shoemaker protocol and compare and contrast it with the HUPPRTOC.

Step 1. Remove the Patient from the Exposure Source.

This is a vital step in both protocols. If the patient is not removed from the source of mold (most often water-damaged buildings), the other efforts will, at best, only provide limited symptom relief and, at worst, fail altogether. In some cases, mold exposure occurs in both the patient's home and place of work. In cases where water damage is not apparent in the home or workplace, testing by an accredited lab may be necessary. You can pay for expensive testing, but I have found that inexpensive plates can be purchased online, which after being placed around the house for an hour, then closed and left to sit for a few days per directions, can be sent in for identification. More sophisticated tests can be used, or a mold specialist could be enlisted. One that is worth considering is the Environmental Relative Mold Index (ERMI) test kit, which scientists at the Environmental Protection Agency originally developed. Current versions of the ERMI test use DNA testing to detect over 36 mold and other fungal species and provide rapid and accurate results. These tests are available from EMSL Analytics, Inc. (see their website for more information, including how to order). If mold is present, a mold remediation specialist should be utilized to repair the problem and assess the indoor air quality.

The adage "better safe than sorry" certainly applies to mold in your home. Therefore, it is highly advisable to regularly inspect indoor environments for mold, especially in homes and other buildings that have been subject to water leaks or further water damage. Examine basement walls and areas around sinks, bathtub and shower, washing machine, and dishwasher for visible mold. Touch these areas with your hands, feeling for moisture or cold spots, indicating hidden moisture.

Step 2. Use Binders to Lower the Circulating Toxic Burden.

This is the primary, most vital, lengthy, and cumbersome step in the Shoemaker protocol. However, with the HUPPRTOC, this step usually becomes unnecessary and is replaced with immune-modulatory and mycotoxin protection therapies discussed earlier. With such treatment, the body is protected from the toxic effects. It can naturally remove the toxins with improved immune function, reduce inflammation and cellular stress, suppress Cell Danger Response, increase cellular energy and mitochondrial function, improve hormone levels and gastrointestinal function, rescue T cell exhaustion and elimination of immunosenescence, inhibit immune activation of coagulation with a renewed ability to suppress chronic infections, improved brain, and cognitive function, and a return to homeostasis. Also, it should be noted that, like mycotoxins, thyroid hormones undergo enterohepatic circulation, so giving binders will also bind up and eliminate thyroid hormone, whether or not you are on supplemental thyroid replacement. Thus, thyroid levels should be overseen if on binders, and a knowledgeable doctor should consider judicious use of T3 replacement. Binders are so efficient at lowering thyroid levels we use them as first-line therapy to stabilize patients with hyperthyroidism, such as Grave's disease until we can treat the underlying cause.

Step 3. Eradicate MARCoNs.

The replacement of low MSH with KPV and improvement in immune function from peptide and other therapies will almost always eradicate the MARCoNs. If not, a combination of nasal KPV, BPC-157, TB4 frag, and the antimicrobial peptide LL-37 will usually finish off any residual cases. Nasal ozone can also be effective.

Step 4. Correct Anti-Gliadin (AGA) Antibodies.

It is easy and inexpensive to check for a hundred or more food sensitivities (IgG antibodies, not IgE, which is an allergy). If you test positive for a significant number of foods, that demonstrates that these large food proteins are getting absorbed and should not be. The combination of BPC-157, TB4 active frag, and KPV is the most effective therapy for gut inflammation and leaky gut, with TB4 active frag and KPV specifically targeting dysfunctional tight junctions. This will also help heal a leaky blood-brain barrier. The addition of oral IgG, LDN, and a potent spore-based probiotic can also be beneficial, as can avoiding gluten and taking high dose digestive enzymes with betaine to improve stomach acid. It is a good idea to check for H-pylori and intestinal parasites.

Step 5. Correct Abnormal Androgens.

This step should be called Correcting All the Hormones, which are generally low secondarily to the pineal-hypothalamic-pituitary-hormone axis, as discussed in this chapter. The thyroid is probably the most important and can reap the most significant benefit with proper treatment even if the TSH is normal. T3 is the treatment of choice (see review articles listed in this chapter). Also, consider growth hormone or growth hormone secretagogues, low dose cortisol, injectable testosterone, and the nonaromatizable androgen, nandrolone, which does not convert to estrogen or DHT, is less androgenic, so it has fewer side effects than testosterone. You can adjust the ratio to keep the estrogen level optimal. Giving the pineal peptides pinealon and/or epitalon will often repair this dysfunctional axis and bring the hormone levels back to normal levels except for the thyroid. It will improve thyroid levels, but there are additional thyroid transport problems into the cells in the periphery, so T3 should also be given. Fixing the immune system and the inflammation will usually fix the issue of excessive aromatase activity. Shoemaker recommends DHEA and HCG, which I do not because it will likely dramatically increase estrogen levels.

Step 6. Correct Antidiuretic Hormone (ADH) and Osmolality Problems.

Shoemaker recommends that treatment with desmopressin (DDAVP) be a synthetic form of ADH. However, this is seldom needed, as this is corrected (along with POTS if present) with the therapy discussed in this section.

Step 7. Correct Matrix Metallopeptidase 9 (MMP-9).

This step involves normalizing MMP-9 levels. Elevated levels of MMP-9 are an indication of chronic inflammation. To reduce MMP-9, Shoemaker recommends the omega-3 essential fatty acids and a no amylose diet. This is very difficult to maintain and usually doesn't have a significant effect. MMP-9 will come down with the therapies discussed in this section. GHK is shown to specifically lower elevated MMPs.

Step 8. Correct Low Vascular Endothelial Growth Factor (VEGF).

The standard protocol was once erythropoietin (EPO) to increase VEGF, but that is no longer recommended due to the risk of side effects. As mentioned in the previous step, Shoemaker recommends using omega-3 fatty acids and following a no amylose diet. Again, this is unlikely to improve VEGF levels. However, several peptides are shown to be potent stimulants of VEGF, and

activation and upregulation of VEGF receptors without the side effects of VIP, including TB4, TB4 active fragment (Ac-SDKP), and BPC-157 (modulates).ICD 92, VEG 3, BPC 5 These peptides modulate the immunity beneficially, as opposed to VIP, and are shown to be extremely safe even at doses 1000 times the typical therapeutic doses. Vitamin D, melatonin, baicalin, and exercise also stimulate VEGF.

Step 9. Correct Elevated Levels of C3a.

This is a marker of immune dysfunction. Shoemaker recommends using statin drugs in conjunction with Co-Enzyme Q-10 (Co-Q10). However, statin drugs are toxic to the mitochondria. Because mitochondrial dysfunction is a core abnormality in the overwhelming majority of CIRS patients, taking a statin doesn't make sense. This can result in muscle pain and weakness, fatigue, memory loss, diabetes, leptin resistance, neuropathy, neurologic issues, heart failure, rhabdomyolysis (muscle breakdown), and hormone abnormalities. All of which is not good for anyone, let alone a CIRS patient. The immune-modulatory therapy discussed earlier will lower the C3 and C4 levels.

Step 10. Correct Elevated Levels of C4a.

This is a marker of immune dysfunction. In the past, Shoemaker recommended using the drug Procrit (erythropoietin) to correct C4 levels. However, since the FDA gave the drug a black box warning, he now recommends that patients and their physicians follow the rest of his protocol, including vasoactive intestinal peptide (VIP), having to wait until step 12 of the protocol. As discussed, immune dysfunction is the core abnormality in CIRS and is addressed very quickly with HUPPRTOC, which will lower both C4a and C3a.

Step 11. Lowering Transforming Growth Factor Beta-1 (TGF-beta-1).

TGF-beta-1 is a vital issue, if not the most critical, with CIRS. This is addressed early in HUPPRTOC. Shoemaker recommends using losartan, an angiotensin II receptor antagonist drug (brand name Cozaar), for 30 days. Since losartan's primary use is for treating hypertension, patients must be monitored to ensure their blood pressure levels do not fall too low. Early treatment that utilizes the peptides that lower TGFb, including TB4 active frag, thymogen/vilon (thymogen Alpha 1), and KPV will usually significantly lower hTGFb in days or weeks instead of months or years, as is the case when utilizing the CSCSPC.

Step 12. Use Vasoactive Intestinal Peptide (VIP) To Restore Immune Balance and Regulation.

As stated previously, addressing immune dysfunction is the cornerstone of successful treatment of CIRS and is handled very early with the HUPPRTOC instead of waiting until the last step, which is the CSCSPC. Unfortunately, many people never make it to this step because they continue to suffer from significant inflammation even though this step is considered to be "the pinnacle of the pyramid." The CSSCP makes VIP seem like the nirvana that you have to reach, but the truth is that some people find symptomatic relief with it as long as there is no inflammation. However, especially if there is a significant amount of hTGFb, it also makes things worse. It is undoubtedly a mixed bag that provides some beneficial effects, but at the same time, potentially makes a full recovery much less likely. The problems associated with using VIP become abundantly clear with a careful examination of its physiologic effects. While it can improve the situation for some time, just looking at its not-so-positive effects, one should be concerned about its routine or long-term use in these multisystem patients. I have found that many patients who are doing reasonably well and attribute their success to VIP are usually very likely to relapse, sometimes worse than before, remain sensitive to mold, or don't feel quite as good as they convince themselves they do.

New Therapy for Mold Illness/CIRS-WPD

The Holtorf Updated Protocol for the Rapid Treatment of CIRS (HUPPRTOC)

The latest research demonstrates that chronic exposure to a toxic mold infection or mycotoxins causes TCE and immunosenescence with a Th1/Treg to Th2/Th17 immune shift with additional direct suppression of NK cell, thymic and mitochondrial function, setting off a deep vicious cycle of multi-system illness. Many CIRS patients have preexisting T cell exhaustion due to stress, chronic Lyme or other infection, autoimmune disease or other chronic illness, other toxic exposures, etc. This makes such patients much more prone to established mold, fungus, viral, bacterial, and parasitic infections because their immune system is too weak to fight the infection and unable to detoxify the mycotoxins. This makes them much more likely to develop severe sensitivities and excessive mast cell activation with excessive production of reactive oxygen species (ROS) and inflammation with a mold exposure that wouldn't bother a healthy person. This further contributes to a vicious cycle of progressive illness and deterioration rather than reverting to a repair and rejuvenation mode.

The current standard of care protocol for CIRS hopes to ultimately fix the immune system via a lengthy 3 phase (12 steps) process that tries to treat the various associated biomarkers that all have their origin in mycotoxin-induced T cell exhaustion rather than directly treating the immune dysfunction, which then corrects the resultant abnormalities. Patients can get better much faster by addressing the core abnormality early in the treatment protocol. With the current CIRS protocol, doctors are taught to address each dysfunction caused by T cell exhaustion. Only then should they use a weak immune-modulating peptide, VIP, to try and finally normalize the immune system and hopefully see significant symptomatic improvement. Doctors with substantial knowledge of specific immune-modulating peptides and other immune-modulating therapies, including immune-modulating, anti-inflammatory, pineal-pituitary-hypothalamic-hormone axis normalizing (including thyroid, adrenal, estrogen, progesterone, testosterone, MSH, melatonin, ADH, growth hormone, oxytocin, neurotransmitters, secondary messengers, and gastrointestinal), mitochondria, endorphin, brain nootropics, sleep inducers, mood and pain center modulators, antimicrobial, and much more), LDN, ozone and other IV therapies, ozone plasmapheresis, photodynamic therpay, stem cells, and exosomes, will usually understand how targeting the core abnormality, T cell exhaustion, will be much more likely for CIRS patients to see improvement with therapy. They will often see CIRS patients get better in weeks or months, not months to years, as with the current CIRS protocol.

Knowing this, you might ask, "Why not give back the suboptimal thymic and other peptides that occur with age and cause or contribute to almost all of the diseases of aging?" Thankfully, the concept of peptide and small molecule supplementation and optimization to reverse this immunosenescence is catching on. It had always been assumed to be an inevitable part of aging

with resultant disease and degeneration. The nice thing is that supplementation with thymic peptides is extremely safe, with studies unable to find a toxic dose, even when 1000 times the average therapeutic amount. This is unheard of and in contrast to the small therapeutic window typical of medications. Water would be lethal at such dosing extremes.

As with other poorly understood conditions, such as chronic fatigue syndrome (CFS) and fibromyalgia (FM), mold illness/CIRS-WDB is frequently ignored or misdiagnosed, leaving the vast majority of patients who suffer from this condition helpless to find effective resolutions for their problems.

It is well established that molds and mycotoxins negatively impact the immune system because of their immunotoxic and cytotoxic effects. America is getting sicker and sicker each generation. The people in charge of our health are failing us and, in turn, blame the population for their "made up conditions" or blame the patient for having a poor lifestyle. Let me reassure you that it is not your fault that you are sick, and I know you are sicker than you dare tell others for fear of being mocked. Or you start to believe the so-called experts in the top hospitals that have little to no knowledge in mold-related illness and CIRS. They often justify their unwillingness even to consider what you are saying, claiming that they can't treat "your psychological illness" (hint: it is always psychological if they don't understand it or can't treat it).

We are all under constant environmental attack-each by itself being a minor threat. While most people seemingly tolerate the constant environmental insults without effort, that is not the case with you. I am here to tell you that there are wonderfully caring, brilliant doctors who have the courage to think outside the box, even though it often means being ridiculed by the "conventional medical establishment." I know these doctors who are not only passionate about learning and the practice of medicine but are even more passionate about helping you get better. You don't deserve a doctor who doesn't believe you or care enough to try to learn enough to help you.

Dr. Shoemaker has provided excellent service for the many patients suffering from CIRS and mold-related illnesses. He has done a tremendous amount of research to prove (to those who will listen) that this is a significant problem and not due to some psychological issue, which is felt to be the case by the majority of "highly respected conventional doctors" who feel beyond reproach. Unfortunately, CIRS and mold-related illnesses will, in my opinion, likely skyrocket due to the increasing exposure to immunosuppressing environmental substances combined with the expansion of 5G, which will significantly stimulate the growth and toxicity of the majority of toxic molds.

You must understand that standard physicians work in a very flawed medical system. The insurance system is set up so that doctors have to see a tremendous number of patients per day, and there are a lot of incentives for them to do nothing for you. Most conventional doctors are taught not to "waste time" trying to figure out

...there are very knowledgeable and caring doctors out there that have a passion for learning, teaching, and helping those with complex, poorly treated illnesses. They are there for you.

what is going on with complex, multi-system patients, so don't get mad at your doctor; instead, realize that you need to take control of your health and don't be a passive participant. If you have made it through this boring chapter, my hat goes off to you. Your chances just got dramatically better that you will find a way to feel great again.

I hope you found this chapter helpful on your road to recovery from CIRS. If you are a healthcare practitioner, I hope it helps you understand the pathophysiology of CIRS better and gives you additional practical tools to combat this multi-system illness and other illnesses. While it may seem impossible after seeing multiple "standard physicians" who have little to no knowledge of mold-related illness, CIRS, or other multi-system conditions, there are very knowledgeable and caring doctors out there that have a passion for learning, teaching, and helping those with complex, poorly treated illnesses. They are there for you. I hope you found this chapter exciting or, at least, helpful in changing the way you look at CIRS and other inflammatory illnesses. Finally, I hope you derived some benefit from your time spent reading this book.

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