CHRONIC INFLAMMATORY RESPONSE SYNDROME

Overview, Diagnosis, and Treatment

Keith Berndtson, MD

Park Ridge MultiMed
keith@parkridgemd.com
mobile (847) 404-4868

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This paper reviews a recently discovered chronic biotoxin illness that affects as many as one in four people in the United States and elsewhere. Most of what we know about this condition is the result of practice-based studies done by physician-researcher Ritchie Shoemaker. In a series of studies going back to 1998, Shoemaker developed an increasingly thorough description of an illness caused by poor clearance of biotoxins produced by certain dinoflagellates, algae, and molds. He named it *Chronic Inflammatory Response Syndrome* (CIRS), and he successfully developed methods to diagnose and treat it.

Shoemaker speculates that the neuroimmune, vascular, and endocrine dynamics present in CIRS may play roles in other forms of chronic illness including chronic fatigue syndrome (CFS), fibromyalgia (FM), post-treatment Lyme syndrome (PTLS), and multiple sclerosis (MS). This paper summarizes Shoemaker's protocol for CIRS diagnosis and treatment.

CIRS occurs when genetically susceptible people are exposed to certain *biotoxins*. This research dates back to 1997, when Ritchie Shoemaker, a family physician based in the rural coastal town of Pocomoke, Maryland, linked an illness to a toxin produced by a fish-killing dinoflagellate known as *Pfiesteria*.[1] Since then, Shoemaker and others have linked the same kind of illness to toxins from molds commonly found in water-damaged buildings—species of *Stachybotris, Aspergillus, Penicillium*, *Chaetomium*, *Wallemia*, and others[2]—and perhaps to toxins associated with tick-borne microbes (*Borrelia, Babesia*, *Bartonella, Anaplasma,* and *Ehrlichia*), though here the toxins involved have yet to be established by scientific consensus.

Other biotoxin producers include certain cyanobacteria (the freshwater blue-green algae *Cylindrospermopsis* and *Microcystis*, which can cause liver, neural, dermatological, and gastrointestinal complications), and a marine dinoflagellate that produces *Ciguatera* toxin, which moves up the ocean food chain into feeder fish and then to larger predator fish (such as red snapper, grouper, and barracuda)[3] can also cause CIRS. When humans eat contaminated finfish, they can develop an acute ciguatera syndrome with severe gastrointestinal and neurological symptoms.

In 1998, Shoemaker and Ken Hudnell were the first to link visual contrast deficits to *Pfiesteria* exposure. In 2001, they were the first to link improvement in visual contrast sensitivity to the use of the cholesterol-binding resin, cholestyramine (CSM).[4] Hudnell has been a principal investigator for the U. S. Environmental Protection Agency's (EPA) National Health and Environmental Effects Research Lab and is an expert on how neurotoxins affect the physiology of vision.

Shoemaker subsequently mapped out the pathways involved in CIRS and developed a case definition for the condition. The biotoxin-driven multisystem, multisymptom pathway imbalance persists until the culprit biotoxins are effectively cleared from the body and the neuroimmune, vascular, and endocrine imbalances are corrected (see Figure 1).[5] Among the sources of biotoxins that can produce CIRS, biotoxins from molds known to grow in water-damaged buildings (WDB) account for some 80% of the CIRS-related illness burden. In the case of mold toxins, recovery depends on continual effort to avoid re-exposure.

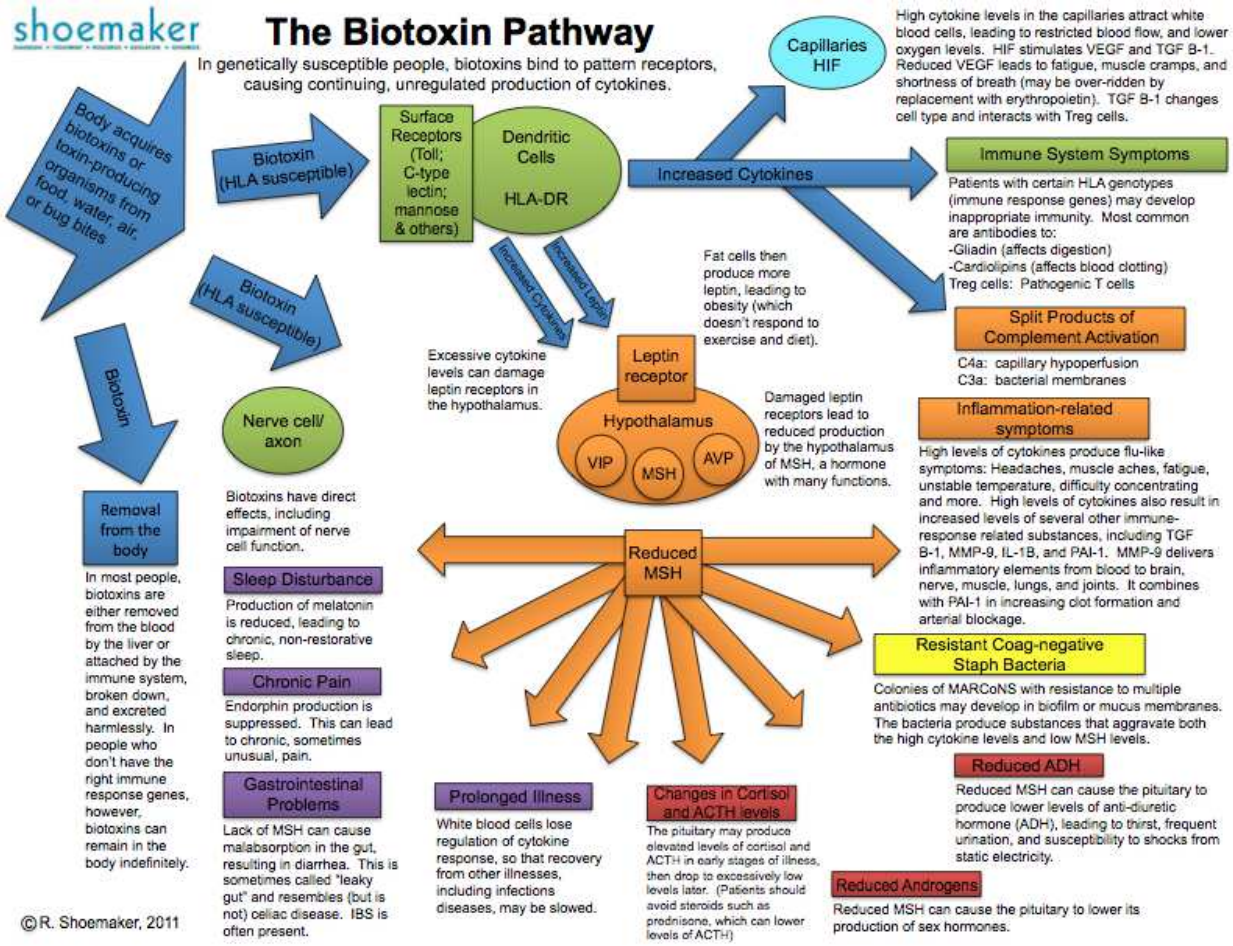

Figure 1

While assembling an increasingly detailed understanding of CIRS disease mechanisms, Shoemaker and colleagues developed a stepwise protocol to treat them. Researchers in the fields of toxicology and environmental systems biology are beginning to show serious interest in CIRS and its implications for health care, ecology, industry, agriculture, and the economy.

The CIRS Case Definition

To warrant a diagnosis of CIRS, the following criteria should be met:

1. History, signs, and symptoms consistent with biotoxin exposure. In cases of mold toxicity, history should include exposure to toxin-producing molds as documented by the EPA-approved ERMI test. In other cases (microcystin, ciguatera, etc.), history should include likely exposure or laboratory evidence of exposure.

2. A genetic predisposition to biotoxin-related illness based on identification of an HLA susceptible haplotype.

3. Abnormalities documented by Visual Contrast Sensitivity (VCS) testing.

4. Biomarkers consistent with the neuroimmune, vascular, and endocrine abnormalities that characterize CIRS. If you have a history consistent with biotoxin exposure, a susceptible genotype, and an abnormal VCS test, you are very likely to show the laboratory abnormalities seen in CIRS. Major and minor criteria are a work in progress.

CIRS Appears to Occur Only in the Genetically Predisposed

Roughly 25% of the population is genetically prone to develop CIRS if exposed to sufficient amounts of biotoxin. An estimated 2% of the population have genes that render them *highly* susceptible to disabling symptoms from prolonged or recurrent exposure to biotoxins.

Blood tests looking at HLA DRB and DQ haplotypes are used sort out the CIRS-susceptible patients from those who are not susceptible. Biotoxin exposure in HLA susceptible persons results in imbalanced responses between the innate and adaptive divisions of the immune system.

The Innate Immune Response

The innate immune system is factory installed and ready to go the minute you're born. Cells equipped with pattern recognition receptors are ready and waiting to respond to the presence of unfriendly toxins produced by the living things that our ancestors encountered during the long course of evolution. These toxins are then processed (in ways that depend on HLA genetics) and presented to naïve lymphocytes called T cells, the lead organizers of the adaptive immune response.

The Adaptive Immune Response

The newly exposed T cells then teach B cells how to recognize and respond to the most recognizable toxin parts. If again exposed to the same toxin, your B cells will produce antibodies to hunt them down.

The Basic Problem in Patients with CIRS

Though the exact mechanism of susceptibility remains unclear, patients prone to developing CIRS fail to mount an effective immune response to biotoxins. When this happens, the innate immune system shows signs of continuous but ineffective activation.

The Most Common Signs and Symptoms Seen in Patients with CIRS

Listed below are the most common of over 30 signs and symptoms that Shoemaker has documented in his patients suffering from exposure to biotoxins:

- Fatigue, weakness
- Post-exertional malaise
- Memory problems, difficulties with concentration and executive function
- Disorientation and confusion
- Headaches
- Vertigo, lightheadedness
- Muscle aches, cramping, joint pains without inflammatory arthritis
- Hypersensitivity to bright light, blurred vision, burning or red eyes, tearing
- Cough, asthma-like illness, shortness of breath, chronic sinus congestion
- Air hunger or unusual shortness of breath at rest
- Chronic abdominal problems including nausea, cramping, secretory diarrhea
- A propensity to experience static shocks

It takes more than a set of subjective symptoms and non-specific signs to separate CIRS from CFS, FM, or PTLS. Many patients with these diagnoses have a history and a set of biomarkers that are consistent with CIRS.

Historical Patterns in CIRS Cases

In cases that involve acute or chronic onsets of multisymptom, multisystem illness with symptoms like those listed above, the cause could be exposure to:

- *Worsening of multiple symptoms when in certain buildings or locations.* If so, history should explore the various structures the patient has lived, worked, or gone to school in over the years to assess the likelihood of exposure to biotoxin-producing molds. This is by far the most common presentation for CIRS.

- *The presence of Lyme disease and other tick-borne infections.* When these are suspected, testing is warranted but is seldom reliable. In some cases antibiotic treatment is offered despite negative tests. In HLA susceptible persons, antibiotics can eradicate the infection but any neurotoxins that remain in the system could be recycled for years, causing chronic signs and symptoms of an overactive innate immune response.

  A recent paper showed for the first time that differential binding of *Borrelia* antigens to pattern recognition receptors of the innate immune system can result in decreased CD38 expression and decreased migratory potential of dendritic cells. This would result in a less effective response to *Borrelia* infection, allowing more widespread infiltration of the tissues by certain *Borrelia* strains.[6]

  Combine a higher toxic burden with a genetically determined defect in protective antibody production, and we can expect to find Lyme patients who've been sicker longer, and who failed to improve after antibiotic therapy—the definition of (PTLS).

This occurs because the host innate immune system is stuck in an imbalanced position, while simultaneously hobbled for neuroimmune, vascular, and endocrine reasons. In such patients, the immune system would experience difficulty wrapping up infections even with proper antibiotic support.

- *Exposure to Dinoflagellates or blue-green algae biotoxin producers*. These are acute syndromes that start after waterborne, airborne, or ingested exposures to the respective biotoxins. Eating tropical ocean fish known to concentrate *Ciguatera* toxin should trigger a Shoemaker diagnosis and treatment protocol. A syndrome that starts after exposure to bodies of water associated with fish kills or overgrowth of blue-green algae should raise suspicion of exposure to *Pfiesteria*, *Cylindro*, *Microcystis*, or other as yet unidentified biotoxin-forming dinoflagellates or cyanobacteria.

- *Insidious or sudden CFS or FM*. In some cases, the patient will recall a potential triggering event. In other cases the onset is more gradual. The diagnoses of CFS and FM are merely labels Such patients should at least undergo HLA testing to see if they are susceptible to chronic illness from biotoxin exposures, and VCS testing to see if they are neurotoxic.

A history suspicious for CIRS warrants HLA and VCS testing to document susceptibility and exposure, respectively, ERMI testing to assess active environmental exposure, and a baseline look at the patient's pattern of CIRS biomarkers.

CIRS Biomarkers

1. **Visual contrast sensitivity deficits** as measured online or in the office correlate with the presence of biologically-derived neurotoxins.

2. **HLA DRB and DQ susceptible haplotypes** (gene markers that correlate with imbalanced innate immune responses and/or defective adaptive immune responses to biotoxins).

3. **Elevated C4a level** (an innate immune system activity marker). C4a elevations represent an excessive innate immune response to biotoxins. They have been associated with elevated levels of mannin-binding lectin serine protease 2 (MASP2) in patients with chronic fatigue syndrome.[7] Based on Shoemaker's analysis of biomarkers, targeting the cause of over-expressed MASP 2 activity could be the most beneficial way of intervening to keep CIRS signs and symptoms under control even in the face of re-exposures. High C4a levels are also seen in lupus and Lyme disease.

4. **Elevated MMP-9 level** (an innate immune system activity marker). In biotoxin-related illnesses, MMP-9 is a gelatinase enzyme that tunnels through endothelial and matrix tissue barriers. Higher levels of MMP-9 have been associated with increased tumor invasiveness,[8] and with increased permeability in the blood-brain barrier.[9]

5. **Reduced MSH level** (a marker of neuropeptide control of multiple functions including mucous membrane-based immune defenses). Alpha-MSH binding to receptors in the

brain and on white blood cells reduces inflammatory responses, including decreased production of pro-inflammatory cytokines.[10,11,12]

6. **Elevated leptin level** (a marker of inflammation-induced disruption of hypothalamic and peripheral leptin receptor function). Leptin receptors exist in the brain, where leptin signals help regulate the pro-opiomelanocortin pathway that also affects ADH levels. In the bloodstream and peripheral tissues, leptin binds to receptors on immune cells, affecting cytokine balance.[13] This marker has a relatively weak correlation to CIRS compared to the rest.

7. **Reduced ADH* and elevated osmolality levels** (a marker of disrupted MSH function). Reduced hypothalamic output of ADH in response to hyperosmolarity is associated with reduced VEGF production in response to low microcirculatory oxygen levels.[14] Genetically determined decreases in ADH receptor production are associated with autistic behaviors.[15] Low ADH receptor function is likely to result in lower ADH signaling in the amygdala. The low ADH levels found in CIRS patients could potentially account for the social avoidance tendencies described by some of these patients.

8. **Elevated TGF-beta 1 level** (a marker of an overactive immune system). TGF-beta 1 is a multifunctional cytokine in that it can inhibit the proliferation, differentiation, activation and effector functions of various immune cells. In addition to being a potent immune suppressor, TGF-beta 1 has several other roles as well, including tumor suppression and promoting tolerance to allergens and self-antigens.[16] TGF-beta 1 can also mediate pathology. It has been shown to promote immune evasion leading to chronic infections, and chronic elevations remodel various interstitial tissues resulting in fibrosis.

9. **Reduced VEGF level** (a marker of capillary hypoperfusion). A low level of skeletal muscle VEGF is associated with decreased muscle endurance.[17] Early in CIRS, VEGF can run high, a sign that it is trying to help compensate for low oxygen delivery to tissues. A low level indicates VEGF burnout.

10. **Reduced VIP level** (a marker of blood flow regulation and distribution). Low levels are associated with capillary hypoperfusion and abnormal pulmonary artery pressure at rest or in response to exercise). VIP helps determine which antigens the immune system will tolerate and is an important down-regulator of inflammation.[18]

11. **Elevated anti-gliadin antibodies** (markers of leaky gut and increased risk for autoimmune reactivity). Gliadins are indigestible fragments of gluten. In cases where intestinal hyperpermeability is present (more likely with a low MSH level), one of two forms of gluten reactivity may present: non-celiac gluten sensitivity (a milder but still problematic form of reactivity in those who are not genetically prone to celiac disease), and celiac permissive gluten sensitivity that can have more severe and wide-ranging complications).

12. **Exotoxin- and hemolysin-producing, multiply antibiotic resistant coagulase-negative staph (MRCoNS)** (a marker of low MSH). MRCoNS can be identified by nasopharyngeal culture. Biofilms produced by MRCoNS, other bacteria, and/or yeast form a barrier to immune defenses and anti-infective therapies. Researchers suspect that bacterial biofilms may account for some cases of chronic nasal and sinus congestion and inflammation.[19] MRCoNS release exotoxins that may damage MSH and thus impair its ability to coordinate dendritic cell responses within gut and respiratory mucous membrane compartments.[20] MRCoNS also release hemolysins, which disrupt red blood cell and endothelial cell membranes, increasing the risk of coagulation abnormalities and anti-phospholipid antibody activity.

13. **Markers of increased or decreased blood coagulation, demyelination**:

    1. **Anti-cardiolipin antibodies** (a marker of autoimmune activity).

    2. **PAI-1** (a marker of increased blood coagulation).

    3. **von Willebrand panel** (markers of increased blood thinning).

    4. **Myelin basic protein –** a marker that normalizes along with MRI scans in some patients treated with a CIRS protocol.

Adverse Biotoxin Effects are Due to Their Physical Structure

Many of the CIRS-causing biotoxins thus far identified show the structural form of *ionophores*.

Most cell membranes depend on ion channels to transport ions, such as potassium, sodium, and calcium, into and out of the cell space. Ionophores form ion channels that can disrupt cell electrodynamics. Their dipole structure makes them water-soluble on the inside and fat-soluble on the outside and able to nestle into the inner fatty compartment of a cell membrane where it can behave like a rogue ion channel. Such toxins can also move freely through cytoplasm and could directly or indirectly activate NFkappaB, increasing the expression of pro-inflammatory cytokines. Ionophore toxins can be highly potent despite their very small size.

Pore-forming toxins, on the other hand, create holes large enough to allow abnormal traffic of amino acids and nucleic acids in and out of cells. Pore-forming toxins are more likely to kill the cells whose membranes they have punctured. Research documents the presence of non-immune cellular defenses to pore-forming toxins.[21,22] Ionophore toxins disrupt cell functions without actually killing the cell. It is not clear what kinds of non-immune cellular defenses (apoptosis for example) exist to resist the disruptive effects of ionophore toxins.

While CIRS-causing biotoxins can take other forms, most are ionophores. They are drawn to the fatty components of tissues and cell membranes, especially nerve cell membranes. When they nestle into place, they disrupt normal cell function in two basic ways:

1. Creating an excess of voltage-dependent ion channels in cell membranes interferes with the electric "battery charge" at the cell's surface, usually reducing it to the point where

the cell is less able to do work with the energy derived from its ion pumps. The most likely mechanism is leakage of potassium ions out of the interior cell space.

2. As ion movement grows more chaotic, cell-signaling systems get disrupted. This triggers a defensive response, causing the affected cell to activate genes that code for an inflammatory response. In CIRS, the production of *pro-inflammatory cytokines* is superimposed on an already overdriven innate immune system response. TGF-beta 1 elevation is a sign that the body is trying harder to down-regulate the innate immune response and the T-cell driven inflammatory cytokine response, both of which are caused by biotoxins in the HLA susceptible.

Because CIRS-causing biotoxins track to fatty tissues and membrane structures, they function first and foremost as neurotoxins. Once inhaled, ingested, or absorbed through broken skin or mucous membranes, they circulate briefly before moving out of capillaries into cell neighborhoods. They seem more drawn to tissues with rich nerve supplies. The brain appears to be a common target. Due to their small size, ionophore neurotoxins may gain easy entry into the brain, perhaps more easily in the presence of weak spots in the blood-brain barrier.

Cardiovascular and gastrointestinal systems are also targets, perhaps due to their rich supply of autonomic nerve connections. Biotoxic ionophores are not easily dislodged from their locations outside of the circulation under ordinary circumstances. When the host immune system fails to produce an effective immune response upon exposure, you can imagine how the toxic burden would accumulate over time in cases of exposure to water-damaged buildings.

Inflammagens and Other Sources of Biotoxins

When toxic molds encounter man-made chemicals like those found in building materials such as particleboard, paneling, stained-wood surfaces, glues and other adhesives, the encounter triggers toxin release as a defensive response. The spores that contain these toxins also contain elements of such man-made chemicals. When such chemicals are able to trigger inflammatory response, they are viewed as inflammagens. In CIRS, the illness is related to the inflammatory response to both inflammagens and mold toxins.

A report appeared in 1999 that claimed to have identified a toxin produced by the Lyme spirochete, *Borrelia burgdorferi* (*Bb*).[23] Subsequent sequencing of *Bb's* chromosomal genome found no genes encoding for a toxin of any kind. Since *Bb* participates in horizontal gene transfer by means of plasmid conjugation, it is possible that toxin-encoding genes may find their way into any of its linear or circular plasmids but thus far, consensus as to whether *Bb* produces toxins is lacking. Part of the problem for people with CIRS may be one of ongoing internal exposure to as yet unidentified toxins produced by infectious agents. In CIRS, the mold toxin burden grows with each exposure. In the genetically vulnerable, this would occur *in addition* to a failure to clear biotoxins from other sources.

Though body may attempt to clear these toxins and inflammagens as they are mobilized, sending them out through the bile faucet accomplishes little if, as is suspected, the ionophore toxins are reabsorbed through the gut back into the system as a whole. This is why HLA DRB and DQ testing should be considered a routine part of the work-up for patients with CFS. If

positive, and if visual contrast deficits and CIRS biomarkers are present, Shoemaker's protocol could play a role, and perhaps a major one, in the treatment of CFS.

Proposed Types of CIRS

Shoemaker reports that a number of his patients who meet case definition criteria for CIRS also meet diagnostic criteria for CFS, FM, PTLS, and MS, and that his treatment approach is proving effective in some of these patients as well. These subtype patterns need more definition.

Rough estimates for the number of Americans affected by chronic inflammatory response syndromes of one type or another range between 10 and 20 million. The number is expected to grow because the syndrome is linked to chemical-induced environmental changes that cause more species to form toxins as part of their adaptive response to the threats posed to them by man-made chemicals. For practical purposes, CIRS can be separated into categories based on the source of the biotoxin participating. linked to CIRS thus far include:

- Neurotoxin producing *molds* present in water damaged buildings.
- Neurotoxins in fatty tissues commonly left behind after anti-infective treatment for tick-borne infections.
- *Pfiesteria* or *Ciguatera* neurotoxins produced by dinoflagellates.
- *Cylindro* or *Microcystis* neurotoxins produced by blue-green algae.

A preliminary way to think about CIRS subtypes based on Shoemaker's work:

Subtype 1: CIRS-WDB (for "water-damaged building" sources)

Shoemaker estimates that 75% OF CIRS cases are caused by repeated exposure to water damaged buildings. These cases are designated as CIRS-WDB. Symptoms can be intermittent but when the exposure is a home, school, or workplace, symptoms become chronic and worse over time, as each exposure trains the sufferer's innate immune response to work harder to make up for the lack of a protective antibody response.

In cases where CIRS-WDB is suspected, it is absolutely crucial to identify the environmental relative moldiness index (ERMI) score in buildings suspected as sources of toxin exposure. Recovery of balanced immune, vascular, and endocrine function depends on avoidance of spaces whose ERMI scores are above a score of 2.

Subtype 2: CIRS-LAD (for "Lyme and associated disease" sources)

This subtype may exist but it isn't clear whether *Bb* (the Lyme disease spirochete) possesses the ability to deploy toxins as a defense against the immune response of its hosts. Should *Bb* possess such a capability, it would make Lyme disease the next most common form is CIRS but statistically, CIRS-WDB may account for 80% of all CIRS cases.

For this reason, a majority of suspected CIRS-LAD cases may also be cases of CIRS-WDB. In this case, patients found non-responsive to treatment of suspected cases of persistent Lyme disease may a) not have persistent Lyme disease, or b) have undergone successful control of *Bb* but continue to report chronic symptoms. The latter group has been described as having *Post-Treatment Lyme Syndrome* (PTLS). because the CIRS-WDB has yet to be treated. In this situation,

clinicians may recognize what's known as the "two thumbtack principle." Namely, if you have two thumbtacks in your behind, and we remove one, odds are you won't feel 50% better. We need to treat both conditions.

A recent paper identified an antibody profile that distinguishes post-Lyme patients from successfully treated Lyme patients, but the reason for this difference is not yet understood.[24] If they are genetically predisposed to defective antibody responses and/or poor toxin clearance, they will be highly susceptible to CIRS.

Another paper found cerebrospinal fluid (CSF) protein profiles that distinguish patients with neurologic post-treatment Lyme disease syndrome (nPTLS) from patients with chronic fatigue syndrome.[25] These CSF proteome differences suggest that these syndromes have distinct pathobiologies. The data can therefore be used to separate these two groups in new research attempts to identify underlying mechanisms. Shoemaker's diagnostic and treatment framework for CIRS could well apply to both groups and all others that reasonably involve imbalanced immune reactions to toxins that remain in the system despite proper anti-infective therapies.

Where the malaria-like parasite, *Babesia*, is concerned, one or more as yet unidentified endotoxins likely drive the toxicity associated with this illness, which is less related to the endotoxins themselves than to the harmful mediators released by macrophages when activated by endotoxin—a response commonly known as the Jarisch-Herxheimer reaction.

Subtype 3: CIRS-DF/A (for "dinoflagellate/algal" sources)

Those suffering from neurotoxins produced by dinoflagellates suffer more acute syndromes. Exposure to *Pfiesteria* occurs when swimming or wading in affected bodies of water, or inhaling the vaporized air associated with contaminated waters.

Exposure to *Ciguatera* toxin occurs when eating marine fish that ate smaller fish that ate the dinoflagellate that produces the toxin. The acute syndrome can become chronic without repeated exposures because toxins excreted into bile are typically reabsorbed and re-circulated in an endless loop of internal re-exposure.

Swimming, wading, or inhaling freshwater containing the blue-green algae that produce *Cylindro*, *Microcystis*, or other toxins also cause toxicity syndromes that tend toward acute but become chronic as toxins marked for excretion in the bile get reabsorbed and redistributed into the fatty tissues of the body.

Domoic acid is a neurotoxin produced by a microscopic marine form of algae. It accumulates in exposed shellfish and finfish and is linked to Amnesic Shellfish Poisoning in humans.[26]The neurotoxic effects can produce irreversible damage in the animals and humans exposed to domoic acid. This biotoxin has yet to be linked to CIRS by means of a well-documented clinical case.

Proof of Concept

Shoemaker and House performed a time series analysis of 28 volunteers with CIRS-WDB that documented changes in symptoms and biomarkers at 5 different time points.[27] In this study, 13 participants agreed to a double-blinded, placebo-controlled trial of CSM therapy.

At time point 1, the group reported a average of 23 of 37 symptoms under study. All 28 participants showed low visual contrast sensitivity. MMP-9 levels were high in 22, leptin levels were high in 13, MSH levels were low in 25, and VEGF levels were low in 14 of the participants. Leptin levels were high and MSH levels low in 4 participants. At time point 2, after 2 weeks of CSM therapy, the average number of symptoms per person dropped to 4, and contrast sensitivity improved by 65% Moderate in improvements were seen in MMP-9 and VEGF levels.

These improvements were sustained after two weeks of mold avoidance without CSM therapy. After 3 consecutive days of re-exposure to mold-toxic building, all participants showed signs of relapse (time point 4), where the average number of symptoms per person increased to 15 and contrast sensitivity decreased by 42%. By time point 5, symptoms, visual contrast deficits, leptin and MSH levels again greatly improved on CSM therapy.

This ABB'AB design of this study linked symptoms and biomarker changes to toxic mold exposures and supported the utility of visual contrast sensitivity as a marker of neurotoxicity in these patients. The changes in leptin and MSH support the hypothesis that chronic inflammatory responses are disruption the pro-opiomelanocortin pathway in the hypothalamus.

The positive response to CSM demonstrate the utility of this unique adsorber that is able to bind both positively charged chemical toxicants and negatively charged biotoxins and thereby increase the clearance of toxins from the body via the bowel.

Growing Evidence On the Disruptive Effects of Biotoxins

Thousands of studies have documented the disruptive effects that biotoxins have on living systems. One recent study by Karunasena and colleagues describes a detailed human cell model by which mycotoxins found in water-damaged buildings can cause neurological damage.[28] In vitro research on the effects of tricothecenes, the class of toxins that make mold species like *Fusarium and Stachybotris* so dangerous, show that these toxins can slow the maturation rate of dendritic cells.[29]

Dendritic cells are among the first responders of the innate immune system. Sluggish maturation of these cells could result in defective antigen presentation, hampering host defense mechanisms against biotoxins. T-2 toxin (from *Stachybotris*) inhibits the differentiation of monocytes into macrophages and dendrite cells.[30] This blocked differentiation of immune cells could hobble antigen presentation to the adaptive immune system.

The *Fusarium* toxin, deoxynivalenol (DON), and the *Stachybotris* toxin, satratoxin G, have both been shown to amplify inflammatory responses to food-borne bacterial pathogens.[31] Endotoxins from gram negative bacteria sensitize macrophages, amplifying the innate immune response.[32] These lines of research indicates that toxic molds and pathogens can interact to create more inflammation and cell damage than either factor acting alone.

Fusarium toxins contaminate grains used for animal feeds and some grains produced for human consumption; they gain entry into the body by ingestion or inhalation. *Stachybotris* toxins are commonly in the air inside water-damaged buildings; they gain entry into the body mostly by inhalation. Chronic exposure to DON contaminated foods can damage gut barrier integrity, causing intestinal hyperpermeabilty that, in turn, can trigger chronic inflammatory responses in the gut wall.[33]

A Step-By-Step CIRS Diagnosis and Treatment Protocol

CIRS diagnosis relies on the combination of a focused history and examination along with a systematic conduction of lab tests. CIRS treatment follows this basic sequence: 1) remove from ongoing sources of exposure, 2) reduce toxin carriage in the home, office, or school as feasible, as well as in the body of the patient 3) eradicate MRCoNS if present, 4) normalize MSH, 5) normalize MMP-9, 6) normalize ADH/osmolality, 7) normalize VEGF, 8) normalize C4a, 8) normalize TGF beta-1, 9) normalize CD4+CD25+, 10) if symptoms persist despite scaling this pyramid, replace VIP.

The detailed protocol:

1. **Proper evaluation.** Undergo an intensive evaluation whose emphasis is on the history of how the patient's chronic illness infolded, looking for clues that would indicate a susceptibility to developing signs and symptoms related to biotoxin exposure.

2. **Visual contrast testing.** Check visual contrast sensitivity and monitor changes over the course of treatment.

3. **Check HLA susceptibility.** If the index of suspicion for CIRS is high, check all 12 of the top biomarkers at the same time to determine how advanced the immune, hormonal, and neuropeptide regulation problems are.

4. **Run ERMI test(s).** When toxic mold exposure is suspected, check the home, office, or school environments if these frequented buildings may reasonably serve as symptom triggers.

5. **Avoid exposure to toxic molds as best you can.** If ERMI tests document DNA from toxin-producing molds, get out and develop a strategy to prevent re-exposure to toxic molds including relocation where needed. This is the toughest step for almost everyone, yet it is perhaps the most crucial step toward full recovery.

6. **Pre-load with fish oil to prevent an intensification reaction to CSM and to reduce symptoms related to a high MMP-9.** In anticipation of an intensification reaction to cholestyramine (CSM) therapy, take purified fish oil 3 to 4 grams daily starting 3 days before CSM therapy. This will help block an inflammatory response to CSM-induced biotoxin mobilization, which seems especially strong early on in Lyme cases.

7. **Take CSM as directed.** CSM can bind positively charged industrial chemical toxins as well as negatively charged ionophore toxins, making it especially well suited to the task of toxin clearance, but it can also bind minerals in foods and supplements.Take a full packet of CSM 60 minutes after prescribed drugs and supplements, and 30 minutes before meals and at bedtime. Wait at least two hours after taking CSM to eat or ingest drugs or supplements. Symptoms typically abate with 3 to 4 weeks of toxin clearance in the stool. Avoid amylose in the diet because it can occupy binding sites on CSM that would otherwise bind toxins.

8. **Relieve constipation or bloating as needed.** Use 70% sorbitol (eg, Miralax) or anything else that works to resolve constipation or bloating should CSM cause these symptoms.

9. **Check for coag-negative staph in the nasal cavity if hypothalamic illness is suspected.** High leptin and osmolality with low MSH, ADH, ACTH and/or VIP = hypothalamic illness. Use corticosteroids with caution if at all. Patients showing these patterns must be screened for the presence of multiply resistant coagulase-negative staph (MRCoNS) deep in the nasal cavity. If MRCoNS is present, use a nasal spray combining EDTA with antibiotics for both gram positive and gram-negative bacteria (can be compounded). The use of Rifampin as well as nasally applied topical *Bactroban* can also help to eradicate this infection.

10. **Pull out all the stops to normalize a high TGF-beta 1 level.** High TGF-beta 1 levels represent widespread tissue involvement, more common in people with the highly susceptible 11-3-52B and 4-3-53 HLA types. To reduce TGF-beta 1 it is necessary to *minimize re-exposures to toxic molds*.

    a. If the anti-gliadin antibody tests suggest sensitivity, then the patient must avoid gluten and may need to support liver or gut function as needed. Both low and elevated GGT levels correlate with dysfunction in glutathione pathways.[34] The null genotype for glutathione S-transferase M1 correlates with HLA DRB markers for increased susceptibility to rheumatoid arthritis, suggesting metabolic linkages between HLA haplotypes and glutathione functional reserves.[35]

    b. An acquired von Willebrand syndrome (increased bleeding tendency driven by the effects of chronically elevated C4a levels in those so prone) can be addressed by lowering the C4a, which requires toxic mold avoidance. The drug, DDAVP, can also be used to control excessive bleeding while waiting for other markers to normalize.

    c. Unusual shortness of breath with post-exertional fatigue suggests the possibility of an acquired form of pulmonary hypertension (aPAH). This can be evaluated by doing a pulmonary function test looking for evidence of *restrictive* rather than obstructive airway disease. If restrictive signs are present, a pulmonary stress test can determine VO max, and a stress echocardiogram measuring the tricuspid jet and right atrial pressure can non-invasively estimate a pulmonary arterial pressure. A high pressure at rest is seen in some patients whose TGF-beta-1 is high and whose CD4+CD25+ Treg cells are low because T17 cells turn them into

pathologic T-cells. This can often be corrected with mold toxin avoidance, Losartan, and VIP nasal spray.

d. Try normalizing CD4+CD25+ using Losartan to prevent Th17 conversion of Treg cells into pathological effector T-cells, as this may correct the elevated TGF-beta-1 levels. Currently needed is a reliable commercial T-cell assay for CD4+CD25+ (both non-thymus and thymus derived).

As you move through the steps listed above, you should find yourself feeling much better over a period of a few months. If symptoms persist despite a normal VCS, a safe ERMI score, and absence of MRCoNS, or if your VIP continues to run low or your TGF beta-1 continues to run high, go to step eleven.

11. **For persistently low VIP or persistently elevated C4a, try compounded vasoactive intestinal peptide (VIP).** If you have followed the step-by-step protocol and continue to show signs of capillary hypoperfusion, including fatigue, unusual shortness of breath with exertion, and post-exertional malaise, consider a trial on the compounded form of VIP to put you over the top. If it effectively combats these problems, as long as your other biomarkers are normalizing and you are avoiding re-exposures to biotoxins, you should feel like yourself again. It will also allow you to tolerate exercise and gradually regain lean body mass, normal muscle function, and build stamina. You should have a normal VCS, an ERMI <2 or a HERTSMI-2 <10, and fully-cleared MRCoNS to qualify.

Will Ongoing Research Clarify Other CIRS Subtypes?

Of growing interest to patients who meet criteria for other chronic conditions including CFS, fibromyalgia (FM), and atypical forms of multiple sclerosis, the question is whether they suffer from a type of CIRS. Will research come to define a:

- CIRS-CFS type
- CIRS-FM type
- CIRS-MS type
- CIRS -? type related to never-before-seen biotoxins that emerge from the strange brew of defensive strains percolating through our air, soils, waters, and food chain

PAX genomics methodology allows for stabilization of mRNA and miRNA in serum samples, allowing investigators to analyze metabolic snapshots of cellular function based on RNA transcription patterns. Results from such analyses of cases versus controls may identify proteomic patterns specific to CIRS and its various current and future subtypes.

It is Time to Widen Our Research Paradigm for Chronic Illness

Finding the answers to these questions will be a matter of time and good research, but what kinds of research? It has been almost 30 years since the Lake Tahoe outbreak of CFS and satisfying answers have yet to emerge from epidemiological, basic, or clinical research. Randomized controlled trials aimed at answering CFS questions have been sparse and mostly cause for more confusion.

Shoemaker's research approach leans heavily on the use of inductive logic in a systems biology context to generate hypotheses that he then tests using practice-based outcomes research. It is a leading example of a new paradigm for making quick progress in the diagnosis and treatment of highly complex forms of chronic illness.

In the span of only a few years, Shoemaker linked otherwise unexplained patient symptoms and biomarker changes to specific toxic environmental exposures and a detailed diagnosis and treatment plan that works well in most cases and in some cases yields jaw-dropping successes.

His mind was prepared to synthesize disparate data from cell biology, microbiology, immunology, toxicology, and environmental science, and use it to generate flashes of insight that he could put to the test in the lab of human beings he was treating for these previously unexplained conditions. How many more unexplained elements of chronic illness might we better explain by using inductive logic in a context of practice-based outcomes research?

Dr. Shoemaker has set a wonderful example that many other doctors and medical teams would be happy to follow and perhaps build upon. America's health care system ought to cultivate this model of research – a new method that seems most capable of widening the path to progress and speeding up the translation of research findings into new clinical and cost-effective approaches to the care of many forms of chronic illness.

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