# A Walk Through the Biotoxin Protocol

The Evidence-Based Way to Treat
Chronic Inflammatory Response Syndrome

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# CIRS: A Walk Through the Biotoxin Protocol

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## INTRODUCTION

One of the great principles of medicine is that if we're deficient in something our bodies need, we can learn how to make it or put it back in. And if something is there that shouldn't be and is hurting us, we take it out and repair the damage.

Simple enough, but identifying those things we need and those things that hurt us can be a monumental challenge. We are grateful to scientists who've gone before us who've discovered vitamins, minerals, essential fatty acids and the like. We're also indebted to those who identify environmental things that hurt us.

One such scientist is Ritchie C Shoemaker, MD, who almost singlehandedly worked out the pathways through which certain biotoxins do us harm.

For Dr. Shoemaker, a big step in the journey to discover these biotoxins began in the late 90s. In the summer and fall of 1997, thousands of fish died in the Pocomoke River in Maryland near his home and practice. It turned out that many locals were getting sick with a variety of symptoms that included headaches, myalgias, fatigue, muscle and joint pains, brain fog, memory loss and diarrhea. Typical laboratory tests were coming back negative. Dr. Shoemaker offered one woman suffering from severe diarrhea cholestyramine, a bile acid sequestrant that can be helpful with secretory diarrhea (1).

A few days later, a very grateful patient called him back to thank him, reporting that her diarrhea was gone … and all her other symptoms were remarkably better as well. Dr. Shoemaker was astonished. How could this be? Cholestyramine isn't absorbed and doesn't affect chemical reactions outside of the intestinal tract. How could it make all those other systemic symptoms better? Since it wasn't absorbed it didn't put anything into the system, so he surmised that perhaps it was taking something harmful out.

As it happened, there had been some fish kills caused by a dinoflagellate called *Pfiesteria* in North Carolina earlier that decade. Dr. Shoemaker theorized that the Maryland fish kills might have had the same cause. He collaborated with University of North Carolina experts. Led by a

prodigious curiosity as well as intellect, the challenge consumed him. His meticulous work in exploring why his patient's symptoms improved so drastically led to more investigations and then more expertise in the environmental factors that influence illness (1, 2, 3). He subsequently was consulted by the State of Florida to explore the idea that these biotoxins could cause illness in people affected by a blue green algae (cyanobacteria, e.g. Cylindrospermopsis and Microcystis) bloom (4). His practice extended to ciguatera poisoning (5) and to biotoxins as contributing to the pathology of Lyme Disease (6, 7) and, most importantly, to illness that comes from being exposed to the indoor environment of water-damaged buildings (8).

What happens in these biotoxin illnesses is that the biotoxins disrupt various parts of the endocrine and immune systems. Those disruptions lead to massive illness in some of our patients. This process often leads to misdiagnoses including depression, somatization, ME/CFS, fibromyalgia, Post Traumatic Stress Disorder, and Post Lyme Syndrome.

To emphasize the point that it's not a "mold infection" but an immunologic and endocrine response that makes people sick, Dr. Shoemaker coined the term Chronic Inflammatory Response Syndrome (CIRS). It's a rather clever name, obviously reminiscent of Systemic Inflammatory Response syndrome (SIRS).

SIRS is a medical term used in the Intensive Care Unit, describing a final common pathway of 2 or more of the following:

- Temperature > 100.4 or < 96.8
- Heart rate > 90
- Respiratory rate > 20 (or PCO2 < 32) and
- WBC >12 or < 4.

Classically, we think of it as a response to infection. In that case, we call it sepsis, but it also could be from ischemia, trauma or other kinds of inflammation. Similarly, CIRS is a final common pathway to multiple different exposures.

CIRS criteria includes (9):

- Exposure to water-damaged building, Lyme, cyanobacteria, ciguatera, or Pfiesteria
- Multi-system, multi-symptom illness
- Tests/lab markers consistent with CIRS
- Absence of cofounders
- Response to treatment

**MEET JIM**

How do we know patients have a biotoxin illness, and how can we help them? A recent conversation in my office went like this:

"Hi, Jim. I see you came from quite a distance. I appreciate how far you've come. Tell me what's been going on."

"Well, doc," Jim explains, "for the last year I've got no get-up-and-go. I'm achy all over and I've got headaches almost every day. I know some people get migraines. My wife, Leslie, has had them since her teen years but I've never been a headache guy… until now."

"And this all began a year ago?"

"Yeah, about that. And what's more, I can't remember anything. I've gained 20 pounds, and my stomach hurts sometimes."

"Do you ever find that you're leery of touching metal doorknobs?"

"Yes, I get shocked! How did you know?"

"I know because that's one of a series of symptoms associated with CIRS (*see Appendix A.*) Here's a list, Jim. Let's go through them together and see how many you have."

As we get to the end of the list, Jim becomes more concerned. "I've got 23 of those things, doc. I must be a really bad case," he says.

I tell him, "Actually, Jim, that's about what people with this illness have, at least if biotoxins are the cause." (10)

I ask about possible mold in his home or workplace. "Mold? No our house doesn't have mold. I thought of that, but if we had mold, Leslie would be sick, too. She's fine. It's got to be something else."

## DIAGNOSING BIOTOXIN ILLNESS/CIRS-WDB

While mold biotoxin illness is still a just a candidate at this point, Leslie's wellness does not eliminate the possibility of biotoxin illness in Jim because people have variable sensitivities to biotoxins based partly on past exposure to water-damaged buildings and partly on genetics.

In analyzing people diagnosed with CIRS, Dr. Shoemaker has identified a series of HLA haplotypes that make certain people increasingly sensitive to mold, Lyme Disease, both, and other causes of CIRS (11). *See Appendix B.*

### Exposure

With the possibility of mold exposure still on the table, we need to ask about exposure, which could mean:

- Seeing mold
- Smelling mold, such as musty smells
- Significant results from an ERMI or HERTMI-2 test.

The Environmental Relative Moldiness Index (ERMI) test was originally developed in 2006 by the Environmental Protection Agency (EPA). In contrast to air spore trapping tests, which can be rather hit or miss, the ERMI is a Quantitative Polymerase Chain Reaction (QPCR) test of

accumulated dust. It measures the DNA of dust samples from Group 1 molds, which are more toxigenic and associated with water-damaged buildings, and compares them to other molds in Group 2, which are not toxigenic. By comparing these results, we generate an ERMI score, which ranges from -10 (great) to +20 (terrible). Generally, people who are genetically susceptible need an environment with an ERMI < 2.

Since its development, a subset of the ERMI called the Health Effects Roster of Type Specific (Formers) of Mycotoxins and Inflammagens, Version 2 was developed. It's commonly referred to as HERTMI 2, and it is an analysis of the DNA of 5 mold species in particular: *Aspergillus penicilloides, Aspergillus versicolor, Chaetomium globosum, Stachybotrys chartarum, and Wallemia sebi*. The amount of these organisms' DNA is translated into points for each category. A genetically susceptible person generally needs to be in an environment with a HERTSMI -2 score < 11 (*See Appendix C*). The sensitivity of the HERTSMI-2 rivals that of the ERMI and has been found to be even more specific. What's more, it's less costly (12). While a professional can do these tests, they can also both be ordered as kits directly from Mycometrics, at http://www.mycometrics.com.

**OTHER CONDITIONS**

While we're checking for exposure to water-damaged buildings, we need to consider other possibilities as well. Has Jim had a tick bite with a subsequent rash or flu-like illness? Has he been tested for or diagnosed with Lyme Disease? Has he become ill after eating fish, especially in the tropics (ciguatera) or been in a lake with blue-green algae (cyanobacteria toxins), or a river or estuary, especially after a fish kill (Pfiesteria)? These can all generate a CIRS.

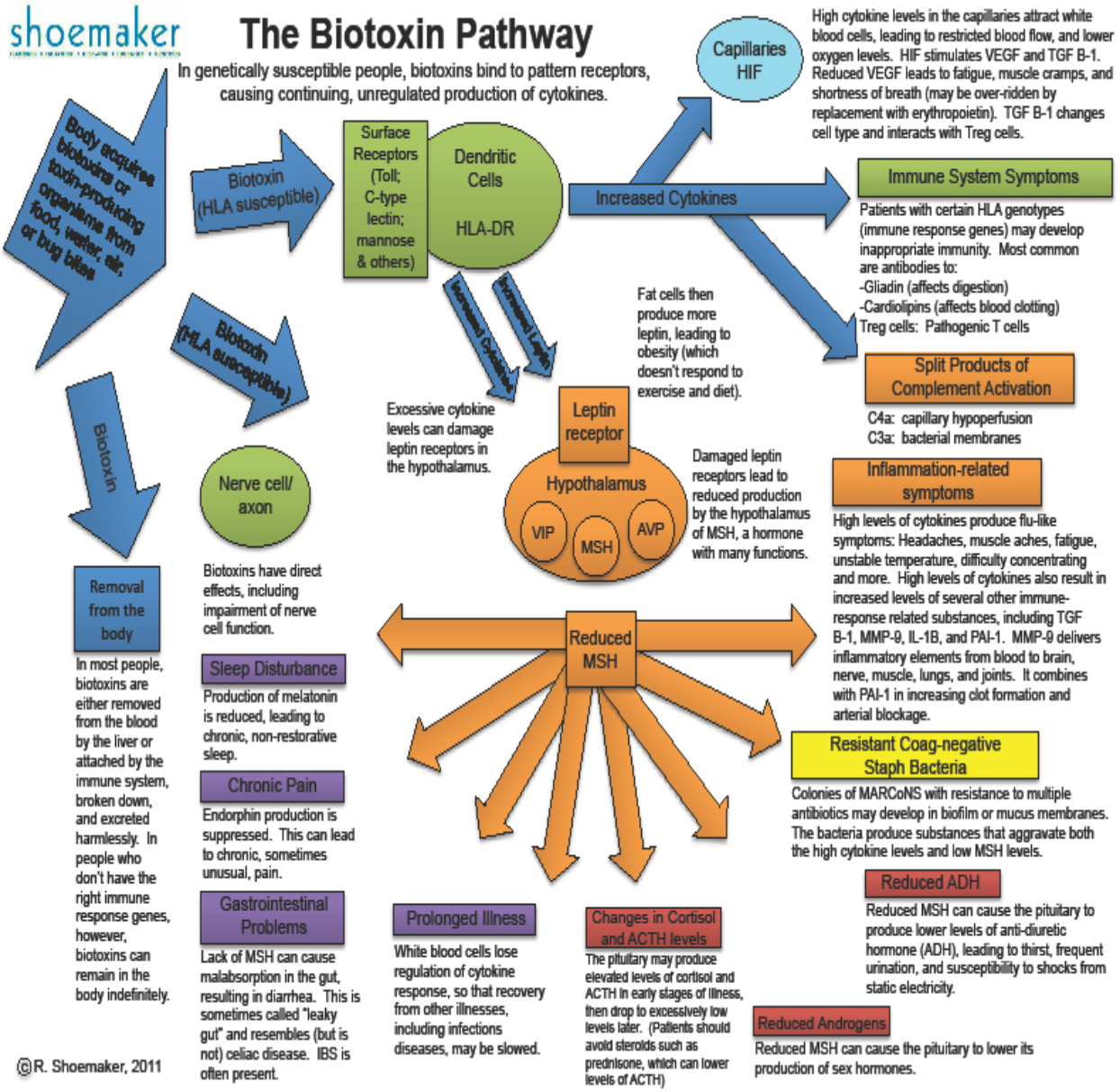
Does he have any other known toxic exposures, such as chemicals at work, or has he been diagnosed with Gulf War Syndrome? What about an endocrine disorder like uncontrolled hypothyroid, diabetes or Addison's, or a neurologic disorder like Parkinsons Disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Attention Deficit Disorder (ADD) or an autism spectrum disorder?

**FURTHER TESTING**

At this point, given all of Jim's symptoms, we begin with some testing. The battery of possible tests consists of the Mycometrics tests noted above, a specific vision test, conventional lab tests, a test of the deep nasal passages, a brain imaging test, and a specialty genomics test.

**Visual contrast test (VCS)**

Jim can do a VCS test at home (at http://www.survivingmold.com), or even better, it can be verified in a physician's office using a hand-held device. To do this test correctly, you need a visual acuity of 20/50 or better. It's not a test of visual acuity but rather the ability to detect the contrast between gray and white lines of variable thickness. This test is highly associated with neurotoxin effects on the brain, as 92% of people with biotoxin illness fail this test, while only 1% of those without biotoxin illness fail this test. Eight percent of people with biotoxin illness still pass this test. This group tends to be teens, especially teenaged girls, as well as people whose baseline visual contrast was excellent to begin with, such as baseball or tennis players, artists, photographers, or others with "keen eyes."




**HLA DR DQ via Labcorp**

In the top left of the Biotoxin Pathway above, you'll see that people are stratified into two groups: 1) those who have the genetics to make an immune response that can successfully usher biotoxins out of the body (76% of people) and 2) the other 24% of the population who don't. (13). The HLA test gives the information we need to stratify people by their genetics. (*See Appendix B*, as well as *Mold Warriors* Appendix 6 for more details in interpreting this test.)

**Lab tests**

These tests don't test for mold, Lyme, ciguatera or other causes of biotoxin illness directly. They test the body's response to biotoxins and, in the case of HLA, its susceptibility to a more dramatic response, i.e. the Biotoxin Pathway.

Melanocyte Stimulating Hormone, MSH (35-81 pg/ml)*[1] via Labcorp
In biotoxin illness, MSH will be too low in more than 95% of patients. This is a hypothalamic regulatory neuropeptide hormone that regulates many other hormones, inflammation pathways, and immune function. A low MSH is associated with lower endorphin production, leading to chronic pain. Low MSH means increased susceptibility to mold illness, ongoing fatigue, pain, hormone abnormalities, mood swings, and much more. *See also leptin, below.*

Multiple Antibiotic Resistant Coagulase Negative Staph (MARCoNS) via MicrobiologyDx
Staphylococci are characteristically divided into 2 camps: coagulase positive, such as Staph aureus, and coagulase negative staph, such as staph epidermidis. While in recent years, Staph aureus — particularly MRSA — has garnered more attention in the public eye, in biotoxin illness Multiple Antibiotic Resistant Coagulase Negative Staph (MARCoNS) infections are the problem. This is a slow growing, biofilm producer that lives deep inside the nasal cavities. One of MSH's roles is to help mucous membrane-based immune defenses. When MSH is low, it allows the growth of MARCoNS. MARCoNS secretes exotoxins A and B, which cleave MSH into small pieces. This becomes a vicious cycle, with the lack of MSH allowing the MARCoNS and the MARCoNS further depleting MSH.

Unfortunately, if you culture the MARCoNS using typical means, the other germs in the nose may outgrow the MARCoNS in the culture plate. The lab needs to use a special API-STAPH culture to grow the MARCoNS. The culture can be ordered through Microbiology Dx (http://www.microbiologydx.com/).

Anti-Gliadin (0-19 units) via LabCorp
Low MSH can result in T regulatory cell dysregulation, which can affect the tight junctions in the intestinal tract, which leads to intestinal hyperpermeability. Gliadins are indigestible fragments of gluten that are more likely to be absorbed in the presence of intestinal permeability. If the anti-gliadin antibody is high, it suggests that the already hypersensitive immune system is stimulated by gluten.

Dr. Shoemaker's research shows that anti-gliadin antibodies, while present in many people with CIRS-WDB, are even more common (58%) in children with CIRS (14).

Leptin (Male: 0.5-13.8 ng/mL; Female: 1.1-27.5 ng/mL) via LabCorp

[1] Traditionally, MSH has had 35-81 pg/ml as a normal range from the medical literature. After it got more popular as a test, in no small part because of doctors using the biotoxin protocol, in 2006, LabCorp changed the reference range to 0-40 pg/ml because they said, "so many people were low." (*Surviving Mold*, p. 48). They were low, in fact, because they were biotoxin patients. Any quoted reference range in this paper similarly is an optimal range, which often but not always matches the lab's reference range.

This is not always included in the panel but it's good to talk about because the test explains part of what Jim is going through and reflects a lot of what's going on in the Biotoxin Pathway.

As you review the Biotoxin Pathway chart above, you'll note that in the CIRS patient, the inflammatory response disrupts normal binding of leptin to its receptor. In response, the body makes more leptin, trying remedy the situation. Leptin increases the storage of fatty acids in fat, which is why Jim has gained 20 lbs. in the last year. As long as leptin stays high, diet and exercise will be less effective in helping him lose weight.

Furthermore, the leptin was supposed to have bound to the now damaged leptin receptor, which would have caused a signal to make proopiomelanocortin (POMC), which, in turn, was supposed to be cleaved into MSH and endorphins. But now that the biotoxins have damaged the leptin receptor, less MSH is being made and you've got less endorphins, which means more pain.

Transforming Growth Factor Beta 1 TGF beta 1 (< 2380 pg/ml) via Cambridge Biomedical

TGF beta 1 is a natural cytokine in our bodies that plays a role in fetal development, control of growth and differentiation, induces fibrosis and scar formation and suppression of the immune response, and is involved in angiogenesis, the development of tumors and inflammatory processes (15). Its increase is thought to be associated with fibrosis generally and, more specifically, it leads to increased endothelial cell remodeling (endothelial to mesenchymal transformation, or EMT), which leads to increased airway reactivity. This can result in a restrictive lung disease and CIRS patients' lungs becoming stiffer and more fibrotic. The American Thoracic Society reports that after an extended period of time, the lungs of people with asthma remodel. TGF beta 1 is part of that process (16).

When too high, TGF beta 1 can also activate an imbalance between T regulatory cells CD4+CD25++ cells and TH-17 cells. This imbalance can lead to autoimmunity.

Matrix Metallopeptidase 9, MMP9 (85-332 ng/ml) via Esoterix, a division of LabCorp

MMP9 is an enzyme produced by cytokine-stimulated neutrophils and macrophages. Cytokines involved include IL-1, IL2, TNF, IL-1B, and interferons alpha and gamma. MMP9 is involved in breakdown of tissue barriers, which is helpful in normal processes including embryonic development, angiogenesis, bone development, and wound healing. It can tunnel through endothelial and matrix tissue barriers including the basement membranes and the blood brain barrier, so when it's too high, any inflammatory molecules in CIRS can enter even more places in the body, including muscles, joints, lungs, and the peripheral nervous system and brain (17). It's been specifically implicated in the pathogenesis of Chronic Obstructive Pulmonary Disease (COPD) by impairing lung elastin. It's also been thought to play a role in rheumatoid arthritis, cardiomyopathy and aortic aneurysms. It is further thought to contribute to atherosclerosis when it combined with PAI-1, which allows oxidized low-density lipoprotein (LDL) to get into the sub endothelial space easier.

DHEA, and testosterone (ranges vary based on age and gender) via LabCorp
While not specific to biotoxin illness, these androgens are abnormal about 40-50% of the time (18). Dr. Shoemaker reports that aromatase which converts testosterone to estrogen is upregulated in CIRS (18). Consequently testosterone may be low at it is over converted into estrogen. VIP therapy may correct testosterone levels. Dr. Shoemaker infers from this that low vasoactive intestinal peptide is a contributing mechanism for aromatase upregulation. (19)

Plasma Vascular Endothelial Growth Factor, VEGF (31-86 pg/ml) via Quest
This polypeptide biomarker helps enhance blood flow in the capillaries and stimulates blood vessel formation. High levels of cytokines attract white blood cells into the capillaries, leading to hypoperfusion and lower oxygen levels. Hypoxia triggers hypoxia inducible factor (HIF), which should lead to the release of more VEGF and erythropoietin.

Two situations can derail this process. The first is that VEGF may initially run high but eventually become depleted. The second is that sometimes a high TGF beta 1 can lead to dysregulation of both VEGF and erythropoietin (20, 21). Also, even if the body could make more for a while, it can't keep it up in the face of the onslaught of these biotoxins, so it then starts running low in both. If Jim's VEGF is low, he just won't be able to do much manual labor or get much physical work done.

Knowing this can be validating to Jim, as some people have told him to "just pull yourself up by your bootstraps." Because this illness is not well understood by most medical professionals or the public, a proper diagnosis and information about CIRS is often validating for patients and can be an important part of the recovery process.

It's noteworthy that this test needs to be done on plasma, not serum, as serum levels can be falsely elevated.

Antidiuretic Hormone (ADH), Arginine vasopressin (AVP) (1.0-13.3 pg.ml), Osmolality (280-300 mOsm) Quest Laboratories
Once again, as you review the Biotoxin Pathway chart, you'll see how VIP, MSH and AVP are all produced in the hypothalamus. As noted in the Biotoxin pathway graphic above, biotoxins lead to the production of cytokines, which affect the hypothalamus through the leptin receptor. This creates dysregulation of ADH (partly through dysregulation of regulatory hormone, MSH).

The body is constantly regulating blood concentration (osmolality). If the osmolality is high, for example, an osmoreceptor senses that and triggers the release of antidiuretic hormone (ADH). A diuretic makes you urinate. Antidiuretic hormone helps you hold onto free water.

But suppose that because of these biotoxins, you can't make ADH and it's lower than it should be for a given osmolality. Well, now you can't hold on to free water. One way

your body might respond would be to get rid of a little extra salt by sweating it onto your skin. With all the extra chloride, skin will conduct electricity even better. That's why Jim experiences the static shocks.

Getting an osmolality level is important because it helps us interpret the significance of the ADH. If the Osmolality and AHD are both relatively low that's normal, but if the Osmolality is high and the ADH is low or even barely normal, that's reflective of dysregulation.

Complement split products: C3a (54.0-202 ng/ml), C4a (0-2830 ng/ml) National Jewish Hospital Lab

The Biotoxin Pathway chart shows that C3a and C4a can both be elevated. The mechanism by which biotoxins can lead increased complement split products is through the immune system. Components of the immune system include:

- Adaptive immunity involving the B cell line, which helps to make antibodies
- Innate immunity involving the T cell line, also called cellular immunity.
- The complement system, which involves a heat labile component of normal plasma that augments the opsonization by antibodies and allows antibodies to kill some bacteria. As it complements the antibacterial activity of the antibody, it was called the complement system but, in fact, it plays an important role in the innate immune system also.

C3 is an immune system protein and may split into C3a (and C3b). C3a however, is more likely to rise specifically in the presence of bacterial membranes, so when that is high, it offers more evidence for bacteria (eg, Lyme Disease) as the cause of the biotoxin illness.

C4a is more commonly elevated and indicates capillary hypoperfusion. It is an innate immune system activity marker and it is one of the better labs for reflecting the severity of disease.

Within the complement system, there are multiple pathways: the classical pathway, the alternative pathway and the lectin pathway.

C4a can be produced from either the classical pathway or the lectin pathway, which are homologous to each other except that the classical pathway begins when a molecule called C1q (the first protein in the complement cascade) binds to IgM or IgM complexed with an antigen. The lectin pathway uses the opsonin mannose bind lectin (MBL) and ficolins instead of C1q. This leads to the activation of MBL-associated serine proteinases (MASPs), which split C4 to C4a and C4b. Dr. Shoemaker's research indicates the lectin pathway is the one involved in the elevation of C4a in biotoxin illness (22).

C4a can rise as early as four hours after exposure to the toxigenic components in a water-damaged building. With repeated exposure, it can continue to rise.

In fact, if the C4a is especially high, we should rethink how safe we want the building to be. The ERMI needs to be $\leq$ -1 if the C4a is > 20,000 and the HERTSMI 2 will likely need to be better than the usually quoted < 11.

Vasoactive Intestinal Peptide, VIP (23-63 pg/ml) via Quest Laboratories

Like MSH, VIP is a neuroregulatory peptide made in the hypothalamus (suprachiasmatic nucleus). Like the other hormones of the Biotoxin Pathway, MSH and ADH, it is routinely low in CIRS patients. VIP regulates blood flow and distribution. It regulates cytokine responses and inflammation as well as pulmonary artery pressures and helps the body make T reg cells. Low VIP leads to poor regulation of inflammatory (cytokine) responses (17), chemical sensitivity and deficiency, and is especially seen in those with dyspnea on exertion.

NeuroQuant

This is a fascinating computer analysis of a standard non-contrast brain MRI done using a 3D T1 technique. This analysis can detect small changes in the sizes of brain organs that might be imperceptible to a radiologist. Based on the analysis, we can tell if the brain fits a CIRS-WDB pattern or a CIRS-Lyme pattern. If a standard brain MRI can be justified from the patients' symptoms, this extra processing can be helpful in addressing both diagnosis and treatment concerns. Some radiology companies, such as CDI or Northwest Radiology, will do NeuroQuant, but it's quite convenient to obtain the CD and send it to Whole World Heath Care in Roswell, New Mexico, where experienced CIRS clinician Scott McMahon will do the analysis for $150.

PAX gene analysis

Of all the tests that can be done, this is the most cutting edge. As noted above, HLA is a genetic test showing susceptibility; PAX gene analysis measures how strongly certain genes relative to biotoxin illness are expressed. Dr. Shoemaker and colleagues are generating a database of differential gene activation that will be a fingerprint for biotoxin illness and will help differentiate the root cause precipitating the Biotoxin Pathway.

## GETTING BETTER

"Look, doc," said Jim. "I feel terrible. When do you think I'll feel better? What happens next?"

"Jim, I can't tell you exactly how long it's going to take to get better, but there are well identified steps along the way. Let's look at some of them."

### STEP 1: Removal from exposure

A) Get out or remediate

This step is not just first in the sequence, it's also first in importance. As discussed above, exposure could be a water-damaged building, Lyme Disease, a dinoflagellate (ciguatera or Pfiesteria) or blue green algae (cyanobacteria). For most, though, it will be biotoxins from a water-damaged building. If a patient finds evidence of water damage, the first decision is, "Will I fix this or move?" If they live in an apartment and the lease is up or they can get out of the lease that might make the most sense. If remediation is called for, then patients have to find a company to help them successfully remediate the mold. The quality of the work then needs to be verified by not seeing mold, not having a musty smell and by

a HERTSMI-2 score < 11 (or an ERMI score < 2). If you're sensitive, the longer you're in the water-damaged building, the more it will damage you. The more exposures you have, the worse each can become.

B) Possessions
Everything in the water-damaged building can be contaminated. Non-porous items—those that particles can't get through, like things made of finished wood, metal and plastic—can be cleaned with Sporicidin or a quaternary ammonium compound. Then vacuum with a HEPA vacuum. If it's porous, like books, carpets, or clothing, you won't be able to clean it and you have to throw it away. Sometimes clothes can be salvaged with dry cleaning. Leather, if finished and not rough, can often be treated like a non-porous item.

C) Continued vigilance in new space.
You can contaminate a new residence by bringing things in from the old, contaminated residence, as well as by bringing things into the new space from outside contaminated areas. Paula Vetter, R.N., MSN, FNP-C talks about this extensively in her book *Surviving and Thriving: A Recovery Manual for Patients and Fammilies Impacted by CIRS*.

D) Other places
If the offending building is a workplace or a school, things get even trickier, as you can request remediation but without a legal challenge, you cannot insist on it. Thus, getting better could involve changing jobs or schools.

**STEP 2: Getting toxins out of the body**

"So if I've got mold I can't get rid of doc, how do I kill it?"

"Jim this isn't really about mold getting inside you. It's about all the toxins that go along with the mold and the other bugs in a building. You can't kill the toxins which were never alive."

The vast majority —some 95% of the people who suffer from CIRS—simply don't have the genetic instructions for their adaptive immune system to make the antibodies to get rid of these biotoxins. So we have to help the body accomplish that task. By far, the best toxin binder is a well-established cholesterol medicine, cholestyramine, CSM. CSM doesn't create systemic side effects other than those of the intestinal tract like constipation, bloating or reflux. Toxins are negatively charged molecules that reversibly bind ions and can diffuse across cell membranes, so they don't need the bloodstream to get around.

As a detox organ, the liver captures and releases them into the small intestine, but because they're intrinsically good at getting across cell membranes, they can get reabsorbed there. CSM's job is to prevent that from happening.

Each dose of CSM essentially gets into the body, sacrifices itself to bind the toxins and gets out, so you need to take it four times a day to see its magic work best. And because it's such a good binder, you can't take CSM with other food, medicine or supplements. You need to take it at least a half hour before or an hour after food and an hour away from medicines or supplements.

For certain meds like Coumadin, thyroid hormones and thiazide diuretics, you need to take 2 hours after CSM. Most people take it a half hour before breakfast, lunch, dinner, and at bedtime. You mix it with 6 oz. of water and follow it with 4-6 additional ounces after taking it.

There are three types of CSM:

1. "regular," which has 3.5 grams of sugar per dose and a few additives
2. "light," which has aspartame, felt by many to be worse than sugar, and
3. "pure resin," which has no sugar, aspartame or additives. While it's better, it's also significantly more expensive — at the time of this writing, upwards of $378 per month, which is usually not covered by insurance.

One last thing about CSM: Sometimes it can cause an intensification reaction if the patient also has Lyme Disease; that is, it can make Lyme feel worse. If Jim says he feels worse while taking CSM, that doesn't prove he has Lyme, but if his MMP 9 gets worse and his VCS test also worsens on row E and perhaps on Row D, it's evidence toward that possibility. Further, if you know or are suspicious the patient has Lyme Disease, you can load him up on high-dose fish oil and begin a low-amylose diet 5 days before taking CSM. Then continue the fish oil and low-amylose diet at least 5 days into taking the CSM.

Welchol, another cholesterol medicine, is another toxin binder, but it's a lot easier to take at 2 pills three times each day. But it only has a quarter of the charge of the cholestyramine and is about one fourth as powerful.

"You know, doc, I don't like taking meds," said Jim. "How 'bout I just take bentonite clay? I heard it binds toxins fine."

"That question really illustrates a principle about walking down this road," I tell him. I personally honor being natural, but the fact is this is a data-driven pathway. Not everything has been studied, of course, but we've found that things like activated charcoal and bentonite clay don't get these biotoxins out of the body well enough to make people feel better, so until we find something that we know is as good as CSM or Welchol, that's what we'll use. This is a war. That's why Dr. Shoemaker's earlier book on mold was called *Mold Warriors.* In a war, you have to win, and to win, we must use our best weapons."

**STEP 3: Eradicate MARCoNS**

We explained earlier why having CIRS predisposes people to MARCoNS growth, and also that it makes toxins itself that lower MSH and perpetuate the illness. Indeed, CIRS isn't primarily an infection, but MARCoNS is part of the problem. If it's there, we need to get rid of it first, in order to move ahead to the next steps in the protocol. After the first month of CSM treatment, we use a compounded nasal spray that consists of EDTA/Silver 0.5% / 25ppm with 15% MucoLox, 2 sprays in each nostril three times per day.

The traditional nasal spray had been another spray called BEG, which stands for Bactroban 0.2%, EDTA 1%, and Gentamicin 0.025%. Biofilm is a sticky substance that results in a better defense for the germs from our immune system. EDTA is a biofilm buster, while the other two

are antibiotics. BEG spray was used 2 sprays TID each nostril. Rifampin 300 mg twice a day has also been used for resistant cases, though it is now falling out of favor.

If someone does get more systemic symptoms, that can be from the MARCoNS dying off. If that happens, stop the BEG spray and prescribe high-dose fish oil (2.4g EPA, 1.8 of DHA) with a low amylose diet for 5 days (*See Appendix D*). Five days later, resume BEG spray. The medicine Actos can also help. Treatment is for 50 days, then culture for MARCoNS again. Thus far, EDTA/Silver spray has had great results, but if MARCoNS is still an issue, consider the other treatments noted above.

**STEP 4: Lowering gliadin antibodies**
MSH is a regulator of hormones and the immune system. When it's low, the T reg cells become dysregulated. The T regs help keep tight junction in the gastrointestinal tract intact. Consequently, when they're low, it can lead to intestinal hypopermeability, which can lead to IgG and IgA antibodies to gluten that can be picked up with the antigliadin antibody. If this test result comes back high, do a celiac work up, including TTG IgA and duodenal biopsy, if necessary. If the patient has celiac disease, he should be off gluten for life. Otherwise, if it's a high anti-gliadin, removing gluten from the diet for 3 months is still necessary. Retest after three months.

**STEP 5: Correct androgens**
For the first time, we're talking about correcting a hormone. The hope is that the body will correct itself once the toxins are removed, but sometimes we add a little help first, and look forward to the body taking over this regulation when it's safe from biotoxins. As we said before, MSH is a hormonal regulator and when it's low, we see problems in androgen hormones about 40%-50% of the time. When deficient in MSH, there can be a disruption of LH and FSH, the pituitary hormones meant to stimulate testosterone. The problem with just giving testosterone is, that also inhibits luteinizing hormone (LH) and follicle-stimulating hormone (FSH). So Jim would feel better for a little while but you've ultimately made the problem worse. Further, aromatase, which converts testosterone to estrogen, is upregulated in inflammatory illness, so if you artificially make testosterone too high, you get even more estrogen.

So give DHEA up to 25 mg TID, which can funnel into testosterone but doesn't cause the LH/FSH suppression directly. You can also give beta hCG 125 mg per week SQ to boost the body's own testosterone production. Clomid might work, but I stay away from it, as it seems that it's associated with higher estrogen levels (23). You'd think that aromatize inhibitors (ie, Arimadex/anastrazole) would be a good idea but they actually cause CIRS symptoms in people with low MSH (24).

It's great if this therapy restores the androgens faster. If not, then perhaps more time out of a toxic environment and binding the toxins will do the job. The vasoactive intestinal peptide (VIP) stage of the protocol can also help blocking aromatase while reversing CIRS symptoms (18).

**STEP 6: Correct ADH/osmolality**
As explained above, ADH is crucial in regulating osmolality, ie, blood concentration. So if the ADH is low relative to the osmolality, we can support it with DDAVP (Desmopressin). This not

only helps the body regulate osmolality, but ADH interacts with VIP and MSH. They all work together. People might also need to urinate more often, as they can't hold the fluids they drink. They might have orthostatic hypotension or headaches from dehydration with high osmolality. The treatment is DDAVP 0.2 mg every other night for 5 doses. After the fifth dose, test serum osmolality and electrolytes (as this medicine can lower sodium). If they're both normal and symptoms remain, go to 0.2 every day and test osmolality and electrolytes again. Some people need 0.2 mg twice a day. Children can use DDAVP nasal spray 1-4 sprays per night.

**STEP 7: Correct matrix metalloproteinase 9 (MMP-9)**
Biotoxins lead to elevated cytokines, which trigger the release of this enzyme from neutrophils and macrophages. MMP9 then allows for even great distribution of inflammatory molecules. We've got to lower it, and if just getting rid of the biotoxins with a toxin binder like CSM isn't doing it fast enough, we want to offer additional help.

It turns out that if we upregulate a peroxisome proliferator-activated receptor (PPAR gamma), this lowers MMP9. Omega 3 fatty acids—specifically a total daily dose of EPA 2.4 g and DHA 1.8—can do this in combination with a low amylose diet (*See appendix D*).

In combination with the low-amylose diet, the diabetes medicine Actos (45 mg) also can do it as well, and works faster. If you use it, however, note a few caveats. First, this is a 30-day treatment, as long-term Actos use has been associated with bladder cancer. Of course, you should mention that to anyone you prescribe it to, even though they will be taking it for a short time. Secondly, biotoxins often hit the leptin receptor, which causes higher leptin. Actos can lower leptin and a pleasant side benefit is that in combination with a low amylose diet, it can contribute powerfully to weight loss (25). That said, if the biotoxins don't raise leptin and the level is < 7 or the patient is < 18 years old or just can't take Actos, use fish oil.

If the person makes it to the last step of the protocol, VIP also helps decrease MMP9 (18).

**STEP 8: Correct VEGF**
These two steps are sometimes considered together, as the treatment above also helps lower VEGF. Graded exercise can help correct VEGF.

- Start with cardio exercises for 5 minutes daily, working up to 15 minutes daily by increasing only 1 minute a day.
- Then add 5 minutes of floor exercises daily and work up to 15 minutes daily, by increasing only 1 minute a day.
- Then add 5 minutes of free weights daily, working up to 15 minutes daily, increasing by 1 minute each day.
- After reaching 45 minutes of total exercise, go back to each exercise and increase intensity as tolerated.

If the person makes it the last step of the protocol, VIP also helps correct VEGF (18).

**STEP 9: Correct C3a**
C3a doesn't increase too often in CIRS-WDB. If it does, we think of Lyme because usually the trigger includes the involvement of a bacterial cell membrane. So if it's increased, reconsider

Lyme. Was there a tick bite, a bulls-eye rash, an HLA DR suggesting higher risk, or a bad response to CSM? Lyme tests help, but often this is like court case, and you're trying to generate evidence for or against the defendant, in this case *Borrelia burgdorferi*. One of the mechanisms for what has been called Chronic Lyme or Post Lyme Syndrome is that a person with a genetic difficulty in getting rid of biotoxins got Lyme and is having an especially hard time shepherding those biotoxins out of the body. The diagnosis and treatment of Lyme is beyond the scope of this paper but if Lyme disease is diagnosed, of course treat it appropriately.

The protocol for lowering C3a uses high-dose statin drugs (80 mg of lovastatin, pravastatin, rosuvastatin, atorvastatin or fluvastatin). In some circles, statins are a bit vilified, but when you've got a high C3a, the risk is worth the benefit, as use will be short term. Also use at least 150 mg a day of Co Q 10 beginning 10 days before the statin use and continue it for the duration of the statin use.

**STEP 10: CORRECT C4a**

C4a levels reflect the overall severity of disease. In years past, if removing from exposure, taking binders and progressing through the other earlier steps in this protocol did not result in a good C4a level, the protocol called for Procrit (erythropoietin), which lowers C4a. The dose was 8000 units SQ twice a week for 5 doses, along with aspirin 81 mg. Procrit use in the protocol has fallen out of favor because of a black box warning about its use (at higher doses) in cancer and renal patients, and because of increased medical board scrutiny. Further, insurance companies are reluctant to pay the approximately $4200 cost. VIP, the last step, also corrects C4a.

**STEP 11: Correct Transforming Growth Factor Beta 1 (TGF Beta 1)**

Again, this is the biomarker involved in "transforming" tissue. High levels are what make asthma exacerbations even harder to treat if it's high enough, long enough. It causes fibrosis in many tissues, and it's associated with autoimmunity. We can lower it with the blood pressure medicine Losartan (Cozaar). This angiotensin receptor blocker has a metabolite called EXP 3179 (24). A typical adult dose for blood pressure would be 50-100 mg. In CIRS, we begin 12.5 mg once a day and titrate up to 25 mg twice a day as tolerated. For children, prescribe 0.6-0.7 mg/kg/day in divided doses. If patients don't tolerate it, VIP can also help here.

**STEP 12: VIP**

"Hey, doc, the VIP sounds pretty good. Why don't you just give it to me right now? Don't you think I'm a Very Important Person?"

VIP is indeed a very special medicine. It's powerful, and as noted by Shoemaker and House (19), it can lower pulmonary artery systolic pressure in response to exercise (27), blocks peripheral innate immune activation (28), and raises VEGF (29). It restores circadian rhythm (30), regulates dendritic cells (31), regulates T17 function in autoimmunity (32), enhances IL 10 production (33), raises CD4+ CD25+ T regs (34), and inhibits TGF beta 1 (35). It's also been shown to reverse the brain volume changes seen on NeuroQuant (36).

Certain conditions must be met before use:

1) The patient has to be in a safe environment. This means the residence or and any other suspected place of exposure has to have an ERMI score < 2 or a HERTSMI 2 < 11.

2) VCS must have normalized.
3) MARCoNS must be eradicated.
4) We've walked through the other steps of the pathway, correcting what we can.
5) A baseline lipase must be normal.

One role of VIP is to regulate pulmonary artery pressure responses to exercise. Low levels are associated with an abnormally high pulmonary artery pressure at rest (> 30 mmHg) or an increase over 8 mmHg in response to exercise. While VIP levels are important, getting a baseline stress/rest echocardiogram with special attention to the pulmonary artery systolic pressure (PASP) serves as a functional test of the VIP.

Since getting the PASP at baseline and in response to exercise is a top reason for getting the stress echo, it's helpful to remind the radiologist of that, so that he or she pays special attention to it.

To calculate PA pressure, the radiologist adds the right atrial pressure to 4 times the square of the tricuspid jet number [$RA + 4(TR^2)$. If this number exceeds 30, there is pulmonary hypertension at rest.

Either a rest PASP > 30 mmHg or a raise > 8 mmHg validates the need for VIP.

If appropriate, give VIP to the patient in the office, one spray in one nostril. After 15 minutes draw VEGF, C4a and TGF beta 1. Watch especially the TGF beta 1. If that rises over 5000 after VIP therapy, it can be a sign of covert, ongoing mold exposure.

After a month of VIP at 1 spray QID, repeat labs, including a lipase. The lipase needs to be repeated each month as long as the patient is on VIP.

If the patient continues to pass the VCS test and the TGF beta 1 is going down, VIP may be lowered to one spray BID.

Notes: Pancreatitis is a potential reaction to VIP. Stop VIP if during the course of therapy lipase rises or the patient get abdominal pain, hypotension or a rash.

"This sounds like a lot, doc. How long's it going to take to get better if I do all this?"

"If your environment is really safe and you adhere to the protocol, it will go faster. But it's variable how long until you feel back to normal. For some, it's weeks. For others, it's many months. In one paper (23), all but two of the biomarkers were returned to normal over an 18-month study period, and the other two — MSH and VIP — got better. It's like Frodo's journey in the *Lord of the Rings*, at times seeing challenges and triumphs and at other times setbacks, but always with an eye toward victory in the end."

I tell patients it's not a walk in the park. It's a walk through the biotoxin protocol.

# APPENDIX A

*One proposed symptom criteria is at least one symptom from 8 of these 13 clusters*

| | |
|---|---|
| 1 | Fatigue |
| 2 | Weak,<br>Decreased assimilation of new knowledge,<br>Aches,<br>Headaches,<br>Light sensitivity |
| 3 | Memory impairment<br>Decreased word finding |
| 4 | Difficulty concentrating |
| 5 | Joint pain<br>Morning stiffness<br>Cramps |
| 6 | Unusual skin sensitivity<br>Tingling<br>Tremors<br>Unusual pain |
| 7 | Shortness of breath<br>Sinus congestion |
| 8 | Cough<br>Excessive thirst<br>Confusion |
| 9 | Appetite swings<br>Difficulty regulating body temperature<br>Increased urinary frequency |
| 10 | Red eyes<br>Blurred vision<br>Night sweats<br>Mood swings<br>Ice pick pain |
| 11 | Abdominal pain<br>Diarrhea<br>Numbness |
| 12 | Tearing of eyes<br>Disorientation metallic taste |
| 13 | Static shocks<br>Vertigo |

# APPENDIX B (37)

**HLA Susceptibilities**

| | DRB1 | DQ | DRB3 | DRB4 | DRB5 |
|---|---|---|---|---|---|
| Multi-susceptible | 4 | 3 | | 53 | |
| | 11/12 | 3 | 52B | | |
| | 14 | 5 | 52B | | |
| Mold Susceptible | 7 | 2/3 | | 53 | |
| | 13 | 6 | 52A, B, C | | |
| | 17 | 2 | 52A | | |
| | 18* | 4 | 52A | | |
| | | | | | |
| Borrelia, post Lyme Syndrome | 15 | 6 | | | 51 |
| | 16 | 5 | | | 51 |
| Dinoflagellates | 4 | 7/8 | | 53 | |
| Multiple Antibiotic Resistant Coagulase Negative Staph (MARCoNS) | 11 | 7 | 52B | | |
| No recognized significance | 8 | 3, 4, 6 | | | |
| Low-risk Mold | 7 | 9 | | 53 | |
| | 12 | 7 | 52B | | |
| | 9 | 9 | | 53 | |

For help interpreting this test from LabCorp, see *Mold Warriors*, Appendix 6.

Specific Relative risks
Susceptible genotypes (41)

| | | RR |
|---|---|---|
| Fungal only | 7-2-53 | 4.6 |
| | 13-6-52A,B,C | 3.4 |
| | 17-2-52A | 3.5 |
| Multiple | 4-3-53 | 2.1 |
| | 11/12-3-52B | 4.6 |
| | 14-5-52B | 2.0 |
| Post Lyme | 15-5-51, 15-6-51, 16-5-51 | 2.1 |
| Dinoflagellate | 4-8-53 | 2.6 |

# APPENDIX C

HERTMI 2 Scoring: Goal < 11

10 points are assigned for

| | |
|---|---|
| Aspergillus penicilloides | ≥500 |
| Aspergillus versicolor | ≥500 |
| Chaetomium globosum | ≥125 |
| Stachybotrys chartarum | ≥125 |
| Wallemia sebi | ≥2500 |

6 points are assigned for

| | |
|---|---|
| Aspergillus penicilloides | 100-499 |
| Aspergillus versicolor | 100-499 |
| Chaetomium globosum | 25-124 |
| Stachybotrys chartarum | 25-124 |
| Wallemia sebi | 500-2499 |

4 points are assigned for

| | |
|---|---|
| Aspergillus penicilloides | 10-99 |
| Aspergillus versicolor | 10-99 |
| Chaetomium globosum | 5-24 |
| Stachybotrys chartarum | 5-24 |
| Wallemia sebi | 100-499 |

# APPENDIX D

THE NO-AMYLOSE DIET *

AVOID

- All foods that grow beneath ground (only onions and garlic are OK)
- Most common root vegetables
- Sweet potatoes/yams
- Regular (white) potatoes
- Carrots
- Parsnips
- Beets
- Turnips
- Rutabaga
- Jerusalem artichokes
- The cereal grains are the biggest problem foods: wheat, rice, oats, barley and rye (Corn has a natural inhibitor of amylase, so it's OK).
- Amylose free is naturally gluten free.

**ALLOWED FOODS**

Allowed foods include basically anything that is not on the list of forbidden foods including:

- Corn.
- Onions.
- Garlic.
- All vegetables that grow above the ground including lettuce, tomatoes, beans of all types, peas, cucumbers, and celery.
- All fruits except bananas.
- Meat, fish, and poultry.
- Condiments (avoid low-fat varieties as they usually contain added sugar).
- Spices.
- Eggs.
- Nuts (except peanuts)
- Sunflower, pumpkin, and squash seeds.
- Caffeine drinks (coffee/tea)
- Popcorn and baked corn chips; tortilla chips always safe
- Dairy *

While dairy is OK as far as amylose, so many people have reactions, I recommend proceeding with caution.

** This is just a bit of advice from the diet originally proposed in "Lose the Weight You Hate," also by Ritchie Shoemaker and available as an e-book at http://www.survivingmold.com/store1/books.*

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