The Diagnosis and Treatment of Chronic Inflammatory Response Syndrome "CIRS"

Caused by the Environment;

Frequently Overlooked and Misunderstood

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Introduction

It is generally expected that when a person becomes ill, a visit to see their primary care physician (PCP) would result in a diagnosis and treatment for the condition that they have. If the treatment plan did not prove to be effective or if the PCP felt a referral was needed, a referral to a "specialist" may be the next step. This cycle can become a vicious one when the patient does not get better. Many times, the patient will seek out multiple healthcare providers over a period of years trying to get answers. Meanwhile, after multiple prescriptions, diagnostic tests and even surgical procedures (sometimes unnecessary ones), the patient's health has continued in a downward spiral. No one, including the patient or any of the healthcare providers, has a clue as to what to do next. Unfortunately, this is not an uncommon scenario.

When it comes to treating patients with chronic illnesses that aren't responding to conventional therapies, today's practitioners have to consider the environment as a potential contributor and look to emerging evidence-based diagnostic and treatment approaches in order to find the root cause of their patients' health challenges. We have *to be willing to challenge what we think we know*. I certainly subscribe to this approach. Case in point, about 7 years ago, a patient presented with a severe cardiomyopathy, so severe that he was on the heart transplant list. After taking a thorough and detailed history, I was left with the question, *how does a perfectly healthy male with good eating habits and in great overall health suddenly develop a cardiomyopathy?* His history included working in the printing industry for 30 years. This fact combined with my overall curiosity led me to look for toxins that might be present in his environment which was the printing industry in this case. A few hours later, I had discovered that cobalt is used in certain inks as it helps the ink to dry faster. I had also discovered that it is actually fairly well-documented in the literature that cobalt toxicity can cause a cardiomyopathy. With some confirming information from the patient, it became clear that his cardiomyopathy was most likely caused by his exposure to cobalt and his inability to clear the related toxins. This diagnosis was further validated by the patient's progress once we got him removed from the environment (not an easy task) and treated the cobalt toxicity. A complete description of this case is beyond the scope of this paper but the common thread here is the

"environment". As in Chronic Inflammatory Response Syndrome (CIRS) cases, his illness was caused by his environment and his inability to clear the toxins from the cobalt.

Like the patient above, CIRS patients have typically been evaluated by numerous healthcare providers, and they have been told that their labs are normal and that there is nothing wrong. Or they have been misdiagnosed or worse yet, they are told that it is "all in their head", and they are sent to a psychiatrist or given an antidepressant or anti-anxiety drug. To a degree, there is some truth to the assessment of the illness being in their heads because CIRS affects multiple systems of the body including the brain. It has been characterized as a multisystem, multi-symptom illness. A one size fits all approach to these patients does not result in good outcomes. These patients can be very complex, and the approach to treating them is also complex and requires an understanding of immunology, genomics, toxicology, microbiology, neuroscience as well as a personalized, functional-medicine-based approach.

CIRS: Discovery and Definition

CIRS is also known as a Biotoxin-Associated Illness, Mold Illness and CIRS-WDB (water damaged buildings). CIRS was originally defined by Ritchie Shoemaker, M.D. in the late 90s as a result of inferences from a series of patient cases that are described below. Dr. Shoemaker was a family physician from the rural town of Pokomoke, MD. In October 1996, and again in the spring and summer of 1997, thousands of fish were killed along the Eastern Shore of the Chesapeake Bay due to a Pfiesteria outbreak. Pfiesteria is a dinoflagellate and is a single-celled organism that creates potent toxins. The fish that were killed were found to have unusual bloody lesions and sores. During the same time frame, Dr. Shoemaker began treating watermen who had a mysterious illness with symptoms that included cognitive issues, fatigue, weakness, aching, difficulty with word finding, difficulty with concentration, cough, shortness of breath, diarrhea, abdominal pain, numbness and tingling, confusion and disorientation. He made the connection between the Pfiesteria fish kill and human illness, and determined that this was the first of the biotoxin illnesses. However, at that point the mechanism and pathway of the illness was not at all clear.

Next, Dr. Shoemaker accidently discovered that cholestyramine (CSM) provided significant symptom improvement to these patients. Since that finding and years of research in understanding the biotoxin pathway and the role of binders like CSM, it is now one of the first steps to treating patients with biotoxin illnesses. This discovery was made when one of his Pfiesteria patients was experiencing chronic diarrhea, and he made the decision to treat her diarrhea with CSM. CSM is a cholesterol lowering drug (not a statin), but because of its effect on bile acids, it is sometimes prescribed as a treatment for chronic cases of diarrhea. What he was pleasantly surprised to discover was that not only did her diarrhea improve, but many of her other symptoms such as brain fog and memory issues improved.

He then applied the information that he gleaned from the Pfiesteria outbreak in Maryland to the outbreaks of blue-green algae in Florida. The pieces of the puzzle were beginning to come together, and he realized that there were other illnesses that presented with similar symptoms in patients. This included patients who had exposure to mold in water-damaged buildings.

In 1998, two years after Dr. Shoemaker treated his first Pfiesteria patient, he treated his first "mold" patient. The term "mold illness" is a subcategory of biotoxin illness. However, keep in mind that mold in a water-damaged building is not the only organism that produces illness that can eventually lead to CIRS. The definition for CIRS is as follows:

"*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*." [1]

Dr. Shoemaker goes on to say, *"You can also get a Chronic Inflammatory Response Syndrome illness from a brown recluse spider bite; from fish that have been contaminated with ciguatera; and from Borrelia burgdorferi, the bug that causes Lyme disease."* [1]

To simplify a very complex subject regarding biotoxins and their role in CIRS, there are four subtypes that are important. (1) Biotoxins are produced by living

organisms and can be found in water damaged buildings, (2) Lyme and other tick-borne diseases such as Babesia, (3) blue-green algae (cyanobacteria), and (4) dinoflagellates such as Pfiesteria, Ciguatera or Chattonella.

How is CIRS Diagnosed?

Initially, the Shoemaker case-definition criteria included only Tier One and Tier Two Criteria. All tier-one criteria had to be met, and three of six tier-two criteria had to be met to confirm a CIRS case. In 2006, the Shoemaker case definition for CIRS was updated to include tier-three criteria to incorporate validation of the CIRS case through successful treatment. Then in 2008, the Government Accountability Office (GAO) issued its case definition which has become the "defacto" case definition. Fortunately, the GAO case definition is well-aligned with the Shoemaker case definition and in fact relies heavily on the published of Shoemaker and associates.

Tier One Criteria – All three of the following criteria must be met

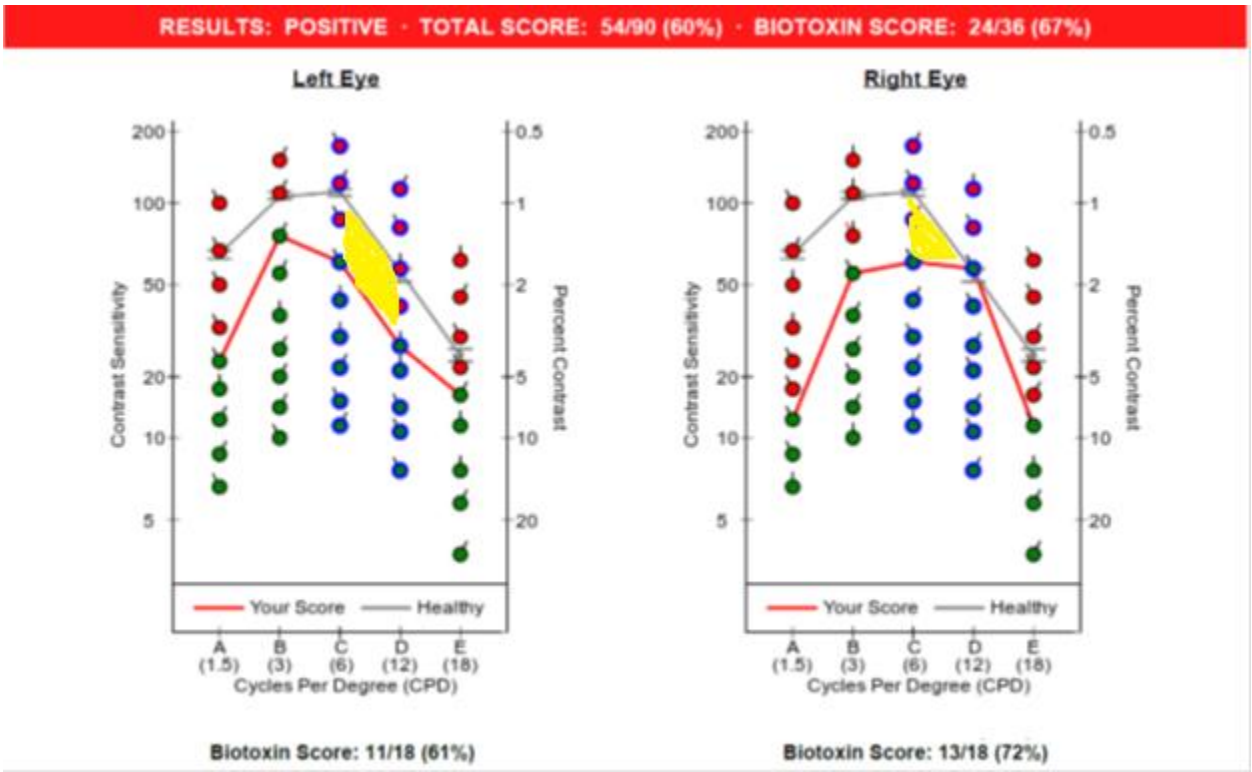
1. **Exposure.** The patient has a history of a biotoxin exposure. This could be from an exposure such as residing or working in a water-damaged building. Note that the National Institute for Occupational Safety and Health reported in 2011 that 50% of buildings have sustained water damage. Other exposures can result from biotoxins such as Borrelia, Babesia, ciguatera or blue green algae.
2. **Differential Diagnosis** rules other causes for the patient's illness.
3. **Symptoms.** The patient has at least one symptom in at least 6 of the 13 symptom clusters that comprise the 37 symptoms of mold exposure. If the patient has at least one symptom in 8 of 13 symptom clusters, this provides a high probability of CIRS diagnosis. See the figure below and note that each cluster has between 1 and 5 symptoms. The clusters were selected by a statistician in order to maximize their predictive capabilities.

Figure 1 - CIRS Symptom Clusters (13)

Fatigue	Unusual Skin Sensitivity	Red Eyes
Weak	Tingling	Blurred Vision
Decreased Assimilation of New Knowledge	Tremors	Night Sweats
Aches	Unusual Pain	Mood Swings
Headaches	Shortness of Breath	Ice-pick Pain
Light Sensitivity	Sinus Congestion	Abdominal Pain
Memory Impairment	Cough	Diarrhea
Decreased Word Finding	Excessive Thirst	Numbness
Difficulty Concentrating	Confusion	Tearing of Eyes
Joint Pain	Appetite Swings	Disorientation
A.M. Stiffness	Difficulty Regulating Body Tempera	Metallic Taste
Cramps	Increased Urinary Frequency	Static Shocks
		Vertigo

Tier Two Criteria - three of the following six criteria must be met.

1. **Abnormal VCS Test** – biotoxin exposure can impair the optic nerves and the patient's ability to see patterns is impaired. 98% of patients who fail the VCS test and have 8 of the symptoms clusters have a biotoxin illness.



The gray line represents the contrast sensitivity curve (average, both eyes) over the tested range of spatial frequencies among healthy individuals as published in Dr. Shoemaker's research, and the red line (lower line) is the curve formed by the highest level of contrast the patient was able to see in this test. The yellow highlight shows the gap between the patient's performance and the healthy control. Higher contrast sensitivity numbers are better, and if the red line is generally above the gray line, the patient outperformed Dr. Shoemaker's healthy research subjects. If, on the other hand, the red line dips substantially below the gray line at "6" and "12" CPD (as it does for the subject above), the patient may have a biotoxin illness.

2. **HLA DRB and DQ susceptible haplotypes** – HLA stands for Human Leukocyte Antigen. HLAs are found on the surface of nearly every cell in the human body. They provide instructions for making a group of related proteins known as the HLA complex which helps the immune system distinguish between the body's own proteins and proteins made by foreign invaders such as viruses and bacteria. The HLA DR test can determine a person's genetic predisposition to multiple illnesses including CIRS. Certain genetic haplotypes are susceptible to mold, others to multiple diseases (multisusceptible), and others have susceptibility to other specific diseases including Chronic Fatigue Syndrome, Post Lyme Syndrome and Multiple Sclerosis.

   According to the research, 76% of the population is not susceptible to CIRS and 24% of the population is susceptible, meaning that they do not have the genetic capability to clear biotoxins. The susceptible population makes up 95% of the CIRS patients. The remaining 5% of CIRS patients do not have the genetic susceptibility. In determining susceptibility, the differences in relative risk were assessed using incidence in cases to incidence in an established control population. Results were considered significant if the ratio exceeded 2.0. [2]

Figure 2 - HLA Susceptibility (Shoemaker, Survivingmold.com)

	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	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 Staph Epidermis (MARCoNS)	11	7	52B		
No recognized significance	8	3, 4, 6			
Low-risk Mold	7	9		53	
	12	7	52B		
	9	9		53	

3. **Elevated Matrix Metalloproteinase 9 (MMP-9)** – MMP-9 is an enzyme produced by activated immune cells. These cells are involved in the breakdown of the extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, in addition to disease processes. MMP-9 is elevated when the immune system is chronically stimulated, and is responsible for delivering inflammatory compounds out of the blood and into the lungs, brain, muscle tissue, peripheral nerve and joints.
   Normal range: 85 – 322 ng/mL

4. **Dysregulated ACTH/Cortisol –** ACTH (adrenocorticotropin hormone) and cortisol are both hormones that are used to assess hypothalamic regulation of adrenal function. In the early stages of CIRS, ACTH and cortisol levels are often elevated; however, later in the progression of the illness there is a decrease in ACTH and cortisol levels.
   Normal ranges: ACTH: 8-37 pg/mL; AM Cortisol: 4.3-22.4 ug/dl ;
5. **Dysregulated ADH/Osmolality** – Antidiuretic hormone (ADH) is also known as arginine vasopressin (AVP). It is a nine amino acid peptide that is produced by the hypothalamus in the brain, and it is stored in the posterior pituitary gland which is at the base of the brain. The most important role of ADH is to conserve body water by reducing the loss of water in the urine. ADH binds to receptors on cells in the collecting ducts of the kidney to promote reabsorption of water back into the systemic circulation. Serum osmolality is a measure of solutes that are present in the blood. ADH partly controls serum osmolality, and dysregulation of this system can lead to chronic dehydration with increased urinary frequency
   Normal range: ADH: 1.0 – 13.3 pg/ml; Osmolality: 280 - 300 mosmol
6. **Low MSH** – Alpha melanocyte stimulating hormone (MSH) is made in the hypothalamus and is the most potent anti-inflammatory compound in the body. It is responsible for regulating innate immune responses and is involved in numerous hormone pathways. Low levels of MSH lead to chronic fatigue, chronic pain as well as problems with leptin which can lead to leptin resistance. Leptin resistance can contribute to weight gain that does not respond to eating less and exercising more.
   Normal range: 35 – 81 pg/mL

Tier 3 Criteria

Tier 3 criteria are evaluated after treatment has begun and serve as the final validation of the CIRS case. Based on the 2010 Consensus CIRS report [3], improvement in the following areas is required to validate the CIRS case.

1. Symptoms and VCS Improve with treatment
2. Labs (leptin, MMP9) return to normal levels

GAO Case Definition Criteria

The GAO case-definition criteria are very similar to the current version of the Shoemaker case-definition criteria except that the GAO case definition focuses exclusively on WDB cases and does not extend to CIRS from sources other than WDB. The GAO case-definition criteria are summarized below.

1. Patient has been exposed to a WDB. A WDB is defined specifically as requiring "amplified microbial growth" [4] which can be verified by the presence of visible mold, detection of musty odors, or mycological testing.
2. Multiple symptoms from multiple systems similar to those found in peer-reviewed published research (i.e. Shoemaker research)
3. Laboratory abnormalities similar to those found in peer-reviewed published research (i.e. Shoemaker research)
4. Improvement with therapy similar to those found in peer-reviewed published research (i.e. Shoemaker research)

In summary, the GAO case definition criteria is aligned very well with the Shoemaker criteria except that the Shoemaker case definition recognizes CIRS other than from WTB. Further, the Shoemaker case definition has the specific parameters to make it operational.

Going back to the Shoemaker criteria, three of the tier-two criteria in addition to all of the Tier 1 criteria must be met to make the preliminary diagnosis of CIRS. Once the preliminary diagnosis is made, there are other proteomic markers (laboratory tests), MRI with NeuroQuant and environmental tests (ERMI – Environmental Relative Moldiness Index) that are important to confirm the diagnosis and help determine how to proceed through the 12 steps of the Shoemaker protocol treatment plan.

MRI with NeuroQuant (see image below)

NeuroQuant uses FDA-cleared computer-automated analysis to produce volumetric data on 11 different paired structures of the brain including the thalamus, forebrain, cortical gray matter, lateral ventricle, inferior lateral ventricle, amygdala, pallidum, hippocampus, caudate, cerebellum, and putamen. Patients with CIRS related issues are marked by a distinctive "fingerprint" that includes a significant enlargement in the forebrain, cortical gray and pallidum and

a marked decrease in volume of the caudate nucleus when compared to the control group [5]. On the other hand, patients with Lyme disease demonstrate a decrease in volume in the putamen and an increase in volume in the right thalamus [5]. This ability to directly support differential diagnosis between mold and Lyme makes the NeuroQuant particularly valuable. In addition, the NeuroQuant is also used to diagnose other neurological conditions including early detection of brain atrophy in dementia and Alzheimer's disease.

The capability of diagnosing CIRS using the NeuroQuant analysis is directly attributed to the work of Ritchie Shoemaker, Dennis House and James C. Ryan [5]. The following summary statement was taken from the landmark study referenced above, *"This study demonstrates, for the first time, a distinctive CNS finding of a structural and neurological injury in patients diagnosed with CIRS-WDB." "The presence of atrophy in the CN but enlargement in other areas of gray matter by itself seems a unique marker ".* Operationally, the findings are expressed in the table below:

KEY: THRESHOLD VALUES FOR SCORING L/R AVERAGES			
BRAIN AREAS	**THRESHOLD 1 (1 point)**	**THRESHOLD 2 (2 points)**	**RELATED TO**
Forebrain	>=31.9	>=32.5	Mold
Cortical Gray	>=16.3	>=17.0	Mold
Caudate	<=0.255	<=0.235	Mold
Pallidum	>=0.07	>=0.08	Mold
Putamen	<=0.345	<=0.335	Lyme
Right Thalamus	>=0.58	>=0.60	Lyme

To use the matrix above, compare the NQ outputs to the numbers above assigning 1 or 2 points to each brain area depending on score. 8 of 8 points provide the highest level of certainty but fewer points combined with labs and other measures may still confirm a CIRS diagnosis. In Shoemaker's research, no confirmed CIRS cases had less than 5 points and no controls had 3 or more points so this can be used as a guide to interpreting a NQ score that is less than 8 points.

NeuroQuant®
General Morphometry Report

CorTechs Labs, Inc.
4690 Executive Dr., Suite 250
San Diego, CA 92121
Tel: (858) 459-9700

PATIENT INFORMATION

Patient ID:	Patient Name:	Sex: M	Age: 85
Accession Number:	Referring Physician:	Exam Date:	

MORPHOMETRY RESULTS

ICV(cm³)	1625.48				
Brain Structure	**LH Volume (cm³)**	**LH Volume (% of ICV)**	**RH Volume (cm³)**	**RH Volume (% of ICV)**	**Asymmetry Index (%)***
Forebrain Parenchyma	501.31	30.84	504.50	31.04	-0.63
Cortical Gray Matter	227.62	14.00	230.30	14.17	-1.17
Lateral Ventricle	25.34	1.56	19.17	1.18	27.75
Inferior Lateral Ventricle	1.55	0.10	1.66	0.10	-7.22
Hippocampus	3.86	0.24	4.15	0.26	-7.07
Amygdala	1.82	0.11	1.74	0.11	5.00
Caudate	4.14	0.25	4.35	0.27	-5.07
Putamen	5.23	0.32	4.89	0.30	6.78
Pallidum	1.09	0.07	1.41	0.09	-25.89
Thalamus	9.51	0.58	9.12	0.56	4.21
Cerebellum	70.22	4.32	68.28	4.20	2.80

From a practical clinical perspective, the test is best used after further confirmation of CIRS with the additional proteomic markers listed below since there is typically the need to get pre-authorization of the test for nearly all insurance programs.

Further, without the additional testing that confirms the preliminary diagnosis, some patients may not readily submit to the MRI with NeuroQuant. The value of the test is unquestionable as it provides diagnosis, illustration of the injury and helps to direct therapy for the upcoming treatment. Practitioners should carefully explain this value to the patient to attempt to get their approval to proceed with the test.

The additional proteomic markers needed are:

- **C4a** – Complement C4a the inflammatory marker of greatest significance when looking at innate immune response for patients exposed to WDB. When C4a is elevated, it means that the innate immune system is in overdrive.
    - Normal range: 0 – 2830 ng/mL
- **TGF beta-1** – Transforming growth factor beta - 1 is a protein that causes cells to transform. It activates genes and turns on the production of TH-17 immune cells and T-regulatory cells. Together, these cells are responsible for preventing autoimmunity. High levels of TGF beta-1 can cause pulmonary remodeling and interstitial lung disease, which can lead to shortness of breath and even asthmatic symptoms. TGF beta-1 cause also cause tissue remodeling in the liver, heart, central nervous tissue and the kidney.
    - Normal range: < 2380 pg/mL
- **VEGF** – Vascular endothelial growth factor stimulates blood vessel growth. In patients with CIRS, elevated cytokine levels suppress VEGF production which leads to decreased oxygen delivery to the tissues.
    - Normal range: 31 – 86 pg/mL
- **VIP** – Vasoactive intestinal polypeptide is a hormone that is made in the nerve endings, gut, pancreas and the hypothalamus. In CIRS, VIP supports healthy hormone levels, decreases inflammation, regulates the immune system, restores the balance of vitamin D3, corrects genomic dysregulation and helps to heal the brain.
    - Normal range: 23 – 63 pg/mL
- **AGA IgA/IgG** – Antigliadin antibodies are produced in response to consuming gliadin. Gliadin is a protein that found in gluten. Elevated AGAs is just one of the many autoimmune responses that are seen with

CIRS. Autoimmunity occurs in CIRS as a result of elevated TGF beta-1 levels. If AGA levels are elevated, gluten must be avoided for 3 months and then reintroduced. If AGA levels normalize after reintroduction, then gluten is allowed. If the AGA levels show sensitivity, then a gluten free diet should be continued indefinitely.

- Normal Range: 0-19

Further, for patients that show sensitivity for AGA, it is advisable to rule out celiac disease by ordering a Tissue Transglutaminase (tTG) antibody, IgA (tTG-IgA test). If positive, an esophagogastroduodenoscopy (EGD) and biopsy should be performed on the small intestine with 4-6 samples, one including the duodenal bulb1. Practitioners may consider referral to a gastroenterologist in order to confirm celiac disease. Remember, a **normal, gluten-containing diet must also be maintained** in order for the histological testing to be accurate.

The following additional labs may be evaluated if indicated

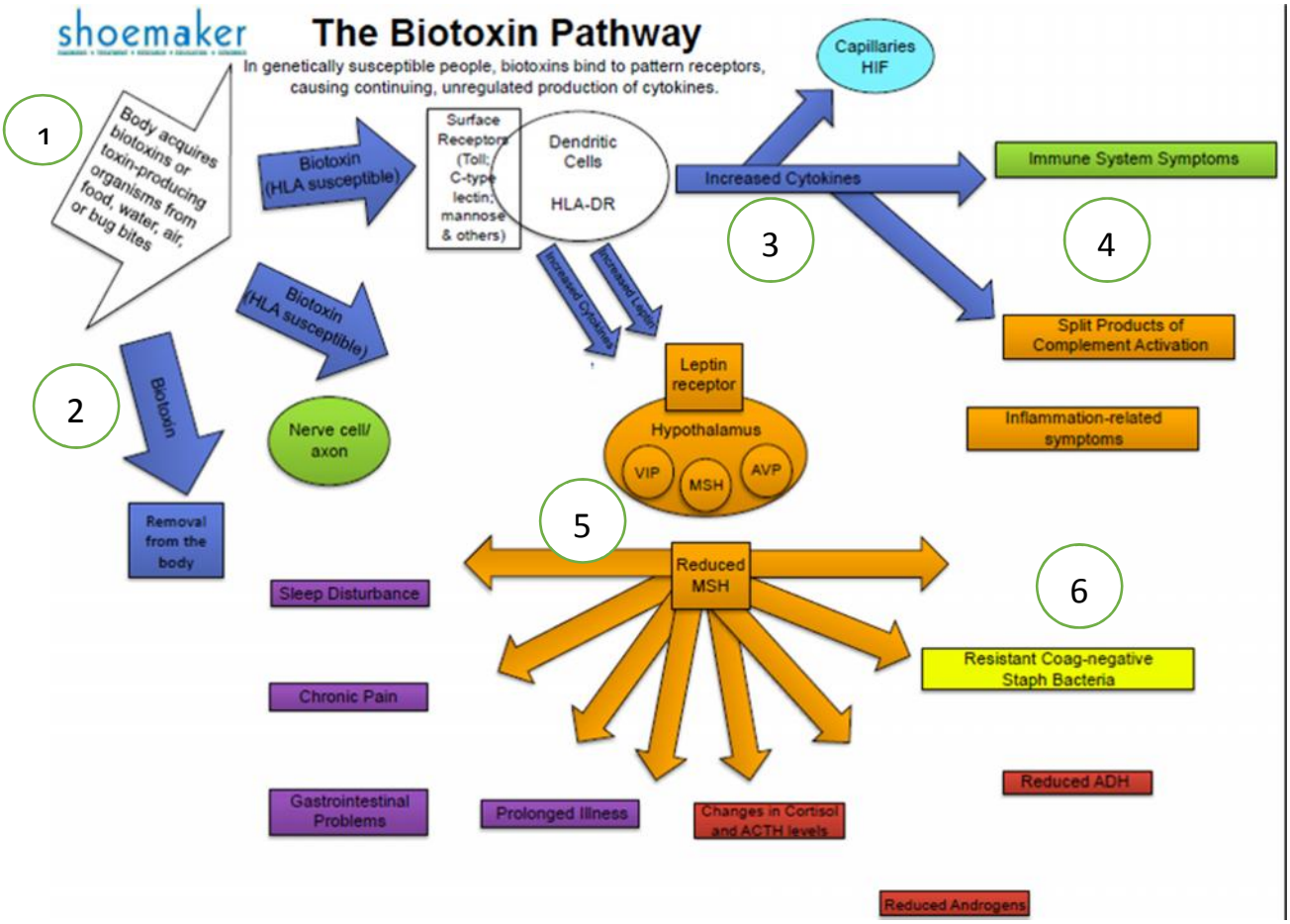
- **Leptin –** Leptin is a hormone made by adipose (fat) cells that plays a crucial role in appetite and weight control. Leptin crosses the blood-brain barrier and binds to receptors in the hypothalamus which regulate appetite. It also increases sympathetic nervous system activity which stimulates fatty tissue to burn energy. Increased cytokine levels are present in CIRS. Cytokines have the capacity to move throughout the body so that they can direct the immune response. Cytokines cross the blood brain barrier and bind to receptor sites in the hypothalamus that are normally reserved for leptin. This causes leptin resistance which leads to weight gain that is not easily managed by consuming fewer calories and increasing exercise.
  - Normal Range: Male: 0.5 – 13.8 ng/mL; female: 1.1 – 27.5 ng/mL
- **von Willebrand's Panel** - Acquired von Willebrand's Syndrome is caused by elevated C4a levels. Acquired von Willebrand disease (AvWD) is an acquired bleeding disorder which may suddenly manifest in individuals, usually in the absence of a personal or family history of bleeding and frequently in association with monoclonal gammopathies,

lymphoproliferative, myeloproliferative and autoimmune disorders. C4a must be lowered; DDAVP can be used to control bleeding.

- **PAI-1** – Plasminogen activator inhibitor, an inhibitor of fibrinolysis in situations where coagulation is needed, though elevated levels increase risk for blood clots. PAI-1 reduces the activity of MMPs (Matrix metalloproteinase), whose excess activity creates the need for PAI-1. PAI-1 levels must be checked if there is concern about coagulation issues, especially in diabetics. Further, in patients with elevated CVD risk factors or existing CVD, Lp(a) and the complete t-PA-PAI-1 complex should be evaluated since research shows that elevated levels of Lp(a) and the plasma t-PA-PAI-1 complex play an important role in the development of CVD by increasing clot formation and arterial blockage [6].
- **ACLA** – Anticardiolipin Antibodies when present are associated with miscarriages, cold hands and feet, stroke, heart attack, vascular problems and Lupus.

CIRS: The Biotoxin Pathway

This biotoxin pathway is very complex, but as per the image below, a broad overview shows that a biotoxin enters the body through air, water, food or a bug bite (1). There are two divisions of the immune system – the adaptive immune system and the innate immune system. Dr. Yvonne Berry has one of the best analogies to explain the differences between the adaptive and innate immune systems. She explains that the adaptive immune system is like a trained sniper, and it is very targeted and takes out the enemy very precisely and systematically. As it relates to a person having an exposure to a biotoxin, the adaptive immune response is what produces an antibody and removes it from the body. The toxin is then no longer able to cause harm because it was removed successfully. This process is illustrated by the short pathway on the far-left side of the chart below.(2)



She then explains that the innate immune system is like a blind folded soldier with a machine gun that senses trouble and is firing away non-stop. In the case of what happens in CIRS, the innate immune system is firing away at the biotoxin because it is detected to be a foreign invader. However, a lot a collateral damage occurs in the body because the innate immune system is not targeted in its approach. The remainder of the chart details the six stages of the Biotoxin Pathway as explained below.

Stage 1: Biotoxin effects

In people with the genetic haplotypes that are not able to rid their bodies of biotoxins, an increase in cytokines occurs, and this represents Stage 1 of the six stages of the "biotoxin pathway" (3). Increased cytokines cause a cascade of events in the body. The person can develop flu-like symptoms, headaches, fatigue and muscle aches. This is the type of response that is consistent with an increased production of proinflammatory cytokines. Then, 4 – 8 hours later there

is a compensatory anti-inflammatory cytokine response. When this happens, the regulatory T cells (T reg cells) produce IL-4, IL-8, IL-10 and IL-13 in an effort to reduce the level of proinflammatory cytokines including Th17. Now the T reg cells and the Th17 are competing, and in CIRS patients the altered regulation of this key developmental checkpoint may be tipping the balance toward inflammation. We can find support for this position in the paper, *"The Treg/Th17 Cell Balance: A New Paradigm for Autoimmunity".* [7] At this stage, people experience chills, fever and feel very shaky. In short, there is somewhat of a cytokine storm that occurs in the body. If the person has the ability to overcome the cytokine storm, in a few hours all of the symptoms subside. This is what occurs when the protective anti-inflammatory mechanisms worked.

But this is a short-term win, and the toxins are continuing to wreak havoc within the person's body by setting off a complex cascade of biochemical events. The biotoxin binds to surface receptors (Toll receptors and many more) in nearly every kind of cell in the body. This recognition and binding of the biotoxin causes a continual upregulation of multiple inflammatory pathways, including production of cytokines, split product of complement, and TGF beta-1. Biotoxins also directly affect nerve cell function, which is one of the reasons that the symptoms and visual contrast sensitivity (VCS) test are so useful in diagnosis.

Stage 2: Cytokine effects (3)

Cytokines in turn bind to their receptors, causing release of MMP-9 in blood. In the brain, cytokines bind to the leptin receptor, preventing its normal function in the hypothalamus. The blocked leptin receptor will no longer create the initiation of steps that lead to production of alpha melanocyte stimulating hormone (MSH). Elevated cytokines can produce many different symptoms including: headache, muscle aches, unstable temperature and difficulty concentrating. This problem is the disastrous effect of MSH deficiency. High levels of cytokines can also result in increased lymphocytes, neutrophils, monocytes and other cells, as well as clotting factors indicated by a von Willebrand's profile. Of importance in cardiovascular health, MMP-9 delivers inflammatory elements from the blood into sensitive tissues and can combine with PAI-1 to increase clot formation, arterial blockage and Lp(a).

As MSH continues to fall, leptin tries to increase MSH. The rise in leptin causes weight gain. Patients are told to exercise more and eat less, but this is an ineffective strategy. Also, as MSH declines, beta-endorphins decrease. This decrease in beta-endorphins can lead to chronic pain. It is a sad state of affairs at this point because this scenario leads to chronic pain, chronic fatigue and weight gain.

Stage 3: Reduced vascular endothelial growth factor

Cytokines are produced when innate immune defense are activated. Increased levels of cytokines trigger an accumulation of white blood cells in the capillaries. The result of this process is hypoperfusion and reduced oxygen delivery to the tissues. Vascular endothelial growth factor (VEGF) is released in response to poor oxygenation of peripheral tissue beds, and its role is to stimulate the formation of new capillaries to compensate for lower levels of oxygen. Initially, VEGF levels increase; however, the rise in VEGF triggers an increase in TGF beta-1. Paradoxically, TGF beta-1 then suppresses VEGF and oxygen delivery is further compromised. Reduced VEGF can lead to fatigue, muscle cramps, and shortness of breath.

Stage 4: Immune System Effects (4)

Patients with certain HLA genotypes (immunity related genes) may develop inappropriate immune responses which may include antibodies to: gliadin (gluten sensitivity), actin, ANCA (anti-neutrophil cytoplasmic antibodies), cardiolipins (affects blood clotting), and more. Most devastatingly of all, the complement system becomes chronically activated resulting in high levels of C4a.

Stage 5: Low MSH (5)

Low MSH levels also lead to sleep disturbances, gastrointestinal problems, changes in cortisol and ACTH levels, reduced reproductive hormone levels, reduced antidiuretic hormone (ADH) levels and MARCoNS (multiple antibiotic resistant coagulase negative staphylococci). It is clear to see how CIRS becomes a multisystem, multi-symptom illness.

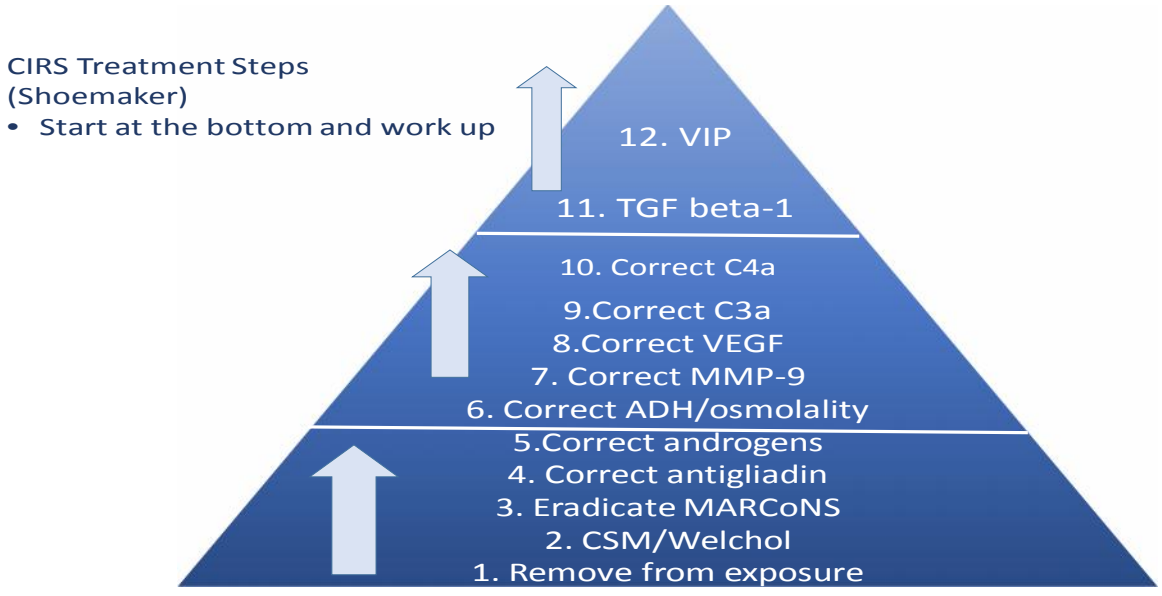
Step 6: Antibiotic Resistant Staph Bacteria (6)

Reduced MSH also allows resistant staphylococci (MARCoNS) to survive in biofilm on the mucous membranes. This bacteria further compounds MSH deficiency by

producing exotoxins A and B that cleave MSH which further decrease the MSH levels. At this point, the downward spiral starts to perpetuate itself.

How is CIRS treated?

Once a diagnosis of CIRS has been established, a 12-step treatment protocol developed by Dr. Shoemaker is implemented. It is important to follow the steps closely since many of the later steps in the protocol are most effective only if the earlier steps have been successfully completed. Going slightly beyond the specific requirements of the 12-step protocol, but following numerous references that provide guidance, I feel that diet is also a part of the treatment strategy. From the protocol, we know that a gluten-free diet is recommended in cases of elevated TGF beta-1 or elevated anti-gliadin antibodies. Further, an amylose free diet is recommended for patients with elevated MMP-9, and for patients with Lyme or other co-infections for 5 days prior to administering CSM. Given the importance and potential benefit from the amylose free diet for all patients, I feel that it is advisable to recommend the amylose free diet [8] for all CIRS patients. Even if patients don't strictly adhere, there are likely benefits from even a partial adoption of the diet, and there are no downsides.



Step 1 - Removal from ongoing toxin exposure

This can be the most challenging step for a patient with CIRS when the environmental toxin is the result of water damage in the primary residence. A

water damaged work place is also a challenge, but not to the extent that it is if a patient must completely uproot themselves from their home and completely relocate.

The first step in removing the patient from the exposure is to confirm the building that is responsible for the exposure. The ERMI (Environmental Relative Moldiness Index) test is the most widely recommended test used by practitioners who treat CIRS patients to determine the level of biotoxins in WDB. The ERMI test is a dust sampling analysis that uses a DNA-based method for identifying mold species. There are currently three labs that offer this test. They are EMSL Analytical (www.emsl.com), Mycometrics (www.mycometrics.com) and EMLab P&K (www.emlab.com). All three labs offer a vacuum canister method to obtain dust samples; however, Mycometrics is the only one of the three labs that also offers a Swiffer-type cloth to collect settled dust and the HERTSMI-2 (see below) score. Further, according to Dr. Shoemaker's research, Mycometrics produces the most accurate results. [10]

ERMI testing evolved by using EPA research and mold-specific quantitative polymerase chain reaction (MSQPCR) technology, and it isolates the DNA from a 36 different mold species found in dust. The ERMI test was validated in a published study in 2007. [11] The ERMI test report lists the mold score expressed as the number of mold spore equivalents per milligram of dust. The species of molds are divided into two categories, Group I and Group II. In Group I, there are 26 molds that are associated with molds that are commonly found in water-damaged buildings. The 10 molds that are in Group II are those that are commonly found outside. The report gives an overall score which is the difference between the sum of the Group 1 molds less the Group II molds.

The ERMI value is typically between -10 (lowest relative mold levels) and 20 (highest relative mold levels) This score must be correlated with the patient's proteomic (lab) test results to determine the safety of the home and/or work environment.

If a patient has been diagnosed with CIRS, an ERMI score of 2 or less is needed if the MSH is less than 35 and the C4a is less than 20,000. However, if the MSH is

less than 35 and C4a is greater than 20,000, the ERMI score needs to be less than -1.

Not only is the ERMI score important, but another test that is important to evaluate is the HERTSMI-2. HERTSMI-2 is an acronym for Health Effects Roster of Type Specific Formers of Mycotoxins and Inflammagens. The 5 species of molds (these molds are also included in the ERMI) that are included in the HERTSMI-2 are particularly detrimental to the health of a person who is genetically susceptible to develop CIRS. These molds included the following:

- Aspergillus penicillioides
- Aspergillus versicolor
- Chaetomium globosum
- Stachybotrys chartarum
- Wallemia sebi

There is a HERTSMI-2 scoring system that can be found at http://www.survivingmold.com/diagnosis/hertsmi-2. The calculated result helps to determine the safety of the environmental impact on the person's health:

- ≤10 - Safe
- 11-15 - Borderline - clean and retest
- ≥15 Dangerous for those with CIRS

Note that Mycometrics is the only company of the three that perform ERMI testing that offers a HERTMI-2 only analysis. This is particularly helpful as it offers a lower price point than an ERMI test, and it is a very helpful to retest an environment that has been remediated and to determine the safety of re-exposure to the building. On the latter point of post-remediation testing, the Indoor Environmental Professionals Panel of Surviving Mold Consensus Statement provides guidance to ensure a proper sample for ERMI/HERTSMI-2 testing. *"One method of collecting "new" dust for a HERSTMI-2 or ERMI test is to tape large black or green garbage bags on horizontal and vertical surface to attract new dust on them for a sample. This may take 3-5 weeks."* [12]

There is some controversy on the point of using ERMI/HERTSMI-2 since even Mycometrics states that ERMI testing may not be suitable for repeat testing

immediately after a mold remediation project. The statement is somewhat in line with the statement from the IEP Consensus paper referenced above in that both indicate that ERMI/HERTSMI-2 are not appropriate for immediate post-remediation testing. Mycometrics states: *"Another time to use the ERMI is before and after remediation. After fixing the water problem and removing the mold contaminated materials, it is important that the entire home be thoroughly cleaned. You can then repeat the ERMI sampling and analysis to ensure "post abatement verification". There should be a significant reduction in the ERMI value. However, it may take some weeks to months before the ERMI returns to pre-water-damaged mold levels."* [13]

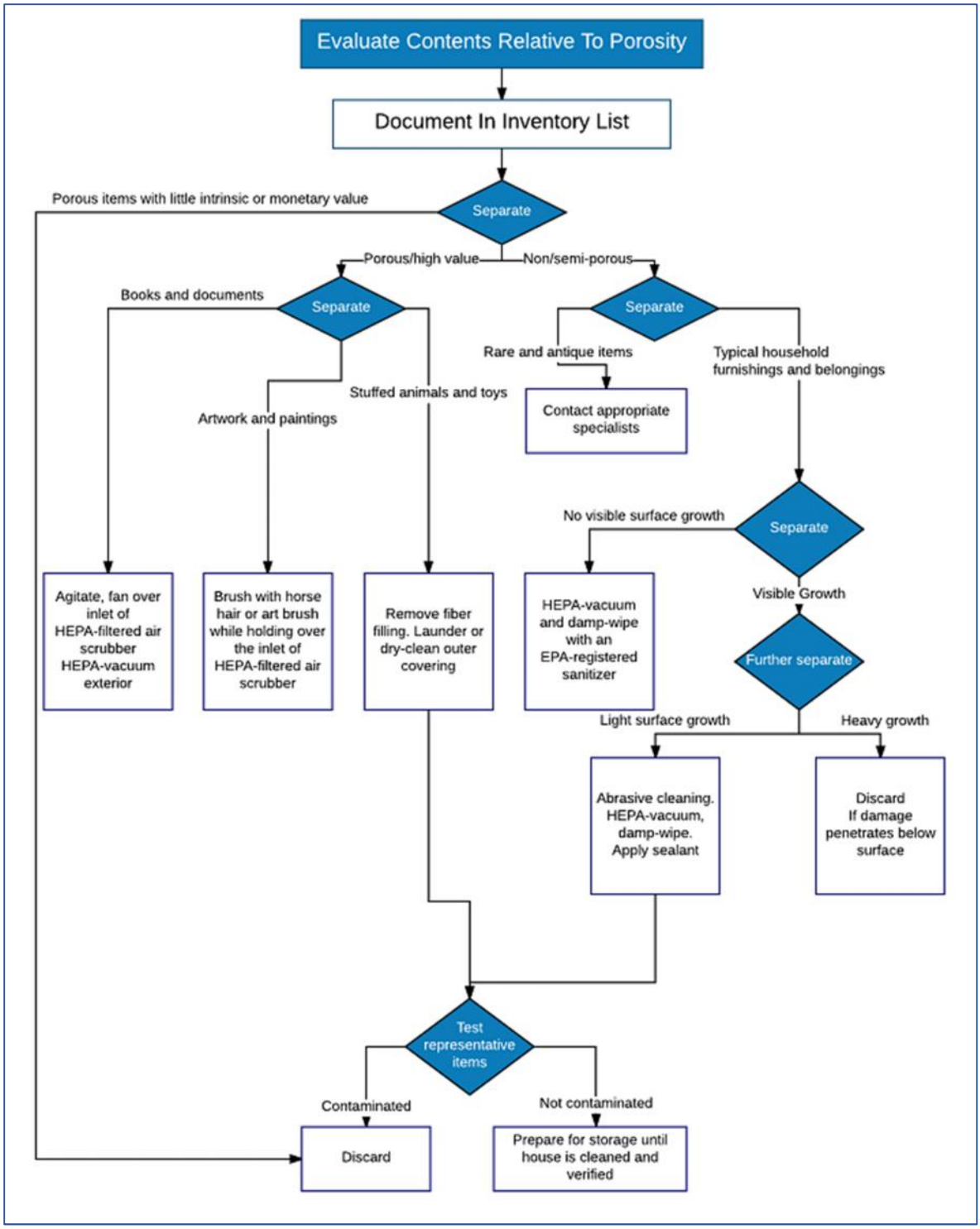
Notwithstanding the value of ERMI, it is just a starting point. All tests, including ERMI have limitations, pros, and cons and there is no single test that can assess all areas of a building. The indoor environment of a WDB is a complex mixture of microbes and toxins including MVOCs, beta-glucans, endotoxins, mycotoxins, actinomycetes, pathogenic bacteria and numerous other toxins, inflammagens and microbes.

Accordingly, prior to remediation, there is no substitute for a thorough physical assessment by an Indoor Environment Professional (IEP). This assessment will validate the ERMI findings, identify the specific source(s) of the mold contamination and help to identify what needs to be done to remediate the property. The remainder of this section sets forth at a high level, the steps needed to remove the person from the exposure.

Removal from exposure necessarily includes the home/building that has been identified as the source of the mold problem along with the contents. In a perfect world and for a home with severe contamination, a person would vacate the home and take no porous item with them. In a practical world, this rarely happens. People are attached to their "stuff" and leaving behind all soft goods such as furniture, draperies, photos and books isn't feasible for many people. Further, many people economically cannot vacate their home long term. At a minimum, however, people need to vacate the home long enough for a thorough remediation to take place and need to have non-porous items professionally cleaned and porous items discarded. This requires a detailed and thorough

assessment. Below is a sample of a flow chart that is used by some IEPs. This is indicative of the level of detail needed for a complete and safe "remediation".

Figure 3- Sample IEP Flowchart for Evaluating Contents of a WDB



Step 2 – Binders: cholestyramine/Welchol

It is essential for patients with CIRS to decrease the biotoxin load within the body. Biotoxins from molds, cyanobacteria, dinoflagellates and other inflammagens are very small negatively charged molecules that form anion rings called ionophores which are small amphipathic molecules. Due to the very small structure of these molecules, they have the capacity to readily cross cell membranes. These very small structures can be captured by the liver, secreted into the bile and stored in the gallbladder. Once a meal has been consumed, the gallbladder releases bile into the small intestine. However, rather than being excreted from the body through the gastrointestinal tract, these biotoxins are reabsorbed through the enterohepatic circulation and are not removed from the body. Without a mechanism put in place to effectively decrease the toxic load, the innate immune system is constantly "revved up" which causes a cascade of inflammation. The two most effective binders are cholestyramine (CSM) and Welchol. CSM and Welchol are both anion binding resins with a quarternary ammonium side chain which creates a positive charge. It is the shape and size of the positive charges on CSM and Welchol that allow them to bind to the negatively charged biotoxins.

CSM is the binder of choice for patients with CIRS. This medication is FDA-approved for lowering cholesterol, and prescribing it as a binder for CIRS patients is an "off-label" usage. CSM is a very safe medication in that it is not absorbed systemically. However, even though it is not absorbed and does not add anything to the body, patients can experience some annoying side effects. The primary side effects that occur with the use of CSM are gas, bloating, GERD, nausea and constipation. Also, patients with Lyme disease and various co-infections can experience intolerable side effects known as an intensification reaction. To minimize this occurrence, it is recommended that an amylose-free diet and high dose omega-3 fatty acids are used for 5 days prior to administering CSM.

CSM is available commercially at retail pharmacies. It is marketed under the brand name of Questran. The downside to Questran is that it contains sugar and other additives that can create side effects in some patients. There is another commercially available CSM alternative that contains aspartame instead of sugar called Questran Lite; however, many patients prefer not to consume sugar or aspartame and they opt for pure CSM which is made by a compounding

pharmacy. The recommended dosing for CSM is 4 grams mixed in 4-6 ounces of water, taken four times per day, 30 minutes prior to meals or 1 hour after meals. Note that when prescribing Questran, it takes 9 grams of medication (powder) to obtain 4 grams of CSM due to the additives. Additionally, other medications should be taken 1-2 hours before or 2-4 hours after CSM if at all possible since CSM interferes with the absorption of many drugs. See below for additional guidance regarding concurrent prescriptions.

Frequently, patients are unable to consume 4 grams of CSM four times per day for various reasons. It can be challenging to get the timing just right for taking CSM, given the before/after meals timing that is mentioned above. Also, certain medications such as thyroid hormones, Dilantin, theophylline and coumadin should be taken two hours before or two hours after CSM. As stated earlier, gastrointestinal discomfort can be challenging for many, and some patients just do not tolerate CSM very well. Sometimes it is necessary to reduce the dose and titrate up based upon patient response. Or, another option when these situations are encountered is to prescribe Welchol. It is in tablet form versus powder form, and it can be consumed with food which makes it less challenging to take. The downside with Welchol is that it is only 25% as effective at binding biotoxins as compared to CSM.

There are other binders that have been used by practitioners as an alternative to CSM and Welchol but none that are backed by published evidence validating their efficacy in restoring VCS and CIRS inflammatory markers to normal levels. These include activated charcoal, bentonite clay and chlorella. While there is some evidentiary support for the alternative binders in the removal of endotoxins, there are no peer-reviewed, published evidence showing their efficacy in treating CIRS.

CSM is safe to be used in pediatric and adolescent patients (<120 lbs or <18 years old). The dosing regimen is 60 mg/kg/dose to be mixed with 6 ounces of water. It should be taken three times per day 30 minutes before food.

CSM and/or Welchol should be taken until VCS test results have normalized, symptoms equal controls and lab tests are equal to controls. This is the reason why these parameters should be checked with each step of the treatment

process. Some patients take CSM for several months, and then switch over to Welchol as a preventive agent. Once a patient with CIRS is no longer ill and it has been determined that their home and work environments are safe, CSM and Welchol may no longer be necessary. On the other hand, if the person is going into an unknown environment, it is advisable to take Welchol prior to and after exposure until it has been determined that the environment is a safe one.

Step 3 – Eradicate MARCoNS (Multiple Antibiotic Resistant Coagulase Negative Staphylococcus)

MARCoNS is an antibiotic resistant staphylococcus bacteria that resides deep in the nasopharynx. MSH (Melanocyte Stimulating Hormone) levels are low in 95% of CIRS patients, and it is quite common to see positive MARCoNS nasal cultures in these individuals. Presence of these bacteria can cause the following:

- The release of exotoxins which split MSH and cause further damage to it.
- The production of a biofilm matrix which makes it difficult for the immune system to remove it and for antibiotics to treat it.
- Can make compounds that are genomically active which can change gene activation.
- Can make hemolysins that cleave MSH and lead to further inflammation due to an increased production of cytokines.

MARCoNS rarely cause symptoms such as runny nose, sinus congestion, post-nasal drainage or facial pain. However, a nasal culture is still indicated (especially in the presence of low MSH) to determine if treatment is necessary. Obtaining a nasal culture to test for MARCoNS is not a very comfortable procedure, but when performed properly it is completed in just a few seconds. A nasal swab must be inserted into one of the nares and placed in the nasopharynx (back of the throat area) three to four inches back. The swab is then rotated for three seconds, and once it is removed from the nose it is then placed into a TransPorter tube. It is then shipped by USPS to the lab for testing. The results are usually reported within 2 weeks. The preferred laboratory for this test is MicrobiologyDX, www.microbiologydx.com.

If the test result indicates that MARCoNS is present, treat with a prescription nasal preparation called BEG spray. BEG spray is not available at commercial

pharmacies and must be compounded. The standard BEG spray prescription is as follows:

- Bactroban (Mupirocin) 0.2%
- EDTA (Edetate Disodium) 1%
- Gentamicin 0.025%
- Consider the addition of a 15% Mucoadhesive Polymer Gel (MAPG) which helps the antibiotic to stay in the nasal cavity longer which makes it more effective

It is important to note that not all MARCoNS bacteria produce biofilms. A recent addition to Microbiology DX is biofilm testing on MARCoNS positive cultures. Having this information can help to determine the best course of treatment.

Step 4 – Correct Antigliadin Antibodies (AGA IgG/IgA)

Patients with CIRS frequently have low MSH levels which can lead to malabsorption in the gastrointestinal system (leaky gut). When this occurs, it is not unusual to see positive AGA levels. Gluten should be avoided for three months in patients who have positive AGA levels. After three months, gluten is then reintroduced and the AGA levels are retested. If the AGA levels are negative, then gluten can be added back into the diet. If additional testing indicates that celiac disease is present, then gluten should be avoided permanently.

Step 5 – Correct Androgen Levels

Low MSH levels can lead to decreased production of androgen levels due to a disruption of normal pituitary release of the gonadotropins LH (leutinizing hormone) and FSH (follicle stimulating hormone). Decreased androgen levels are seen in 40% of patients with CIRS. The reproductive hormone levels that are most important to test are total testosterone, DHEA-S and estradiol. CIRS patients usually also have increased levels of aromatase. Aromatase is an enzyme that converts testosterone into estradiol. This process causes the testosterone levels to fall which can lead to weight gain, fatigue, erectile dysfunction, decreased cognitive function as well as many other untoward symptoms.

It is not recommended that testosterone replacement therapy (TRT) be administered in CIRS patients until the inflammation has been corrected because of the rebound suppression of gonadotropin release and the up-regulation of

aromatase. What happens is that the patient initially feels better with TRT; however, since aromatase levels are elevated the testosterone is converted to estradiol. More and more testosterone is required for the patient to feel better, and thus a vicious cycle occurs. It is best to address decreased androgen levels in CIRS patients by addressing the underlying inflammation. It is acceptable in this situation to have the patient take precursor hormones such as DHEA, but it is not recommended to use aromatase inhibitors in these patients as they can cause significant adverse outcomes when MSH is decreased.

Step 6 - Correct ADH/Osmolality

In CIRS patients, the normal mechanism that increases ADH levels when osmolality increases can be impaired or dysregulated. When the osmolality is elevated and the compensatory increase in ADH does not occur, this can lead to increased levels of electrolytes within the body. Since the body is not able to conserve water, chronic dehydration occurs, which manifests as increased urinary frequency and excessive thirst. In extreme cases, this mechanism results in increased susceptibility to static shocks due to increased chloride levels on the skin.

Treatment is Desmopressin 0.2 mg every other night for 10 nights. Children can use Desmopressin nasal spray 1-4 sprays per night. Desmopressin is a replacement for endogenous ADH that will help the patient overcome the ADH dysregulation.

Step 7 – Correction of MMP-9

Treat with Actos (pioglitazone hydrochloride) in combination with high-dose Omega-3 fatty acids to correct the elevated MMP-9. Actos works by lowering leptin, lowering MMP-9, raising vascular endothelial growth factor, all while improving insulin resistance and lowering systemic inflammation by slowing cytokine amplifications that occur in these diseases. Actos is most effective if the patient is also on an amylose free diet. Start with 15 mg – 30 mg daily following the manufacturer's guidance and titrate to 45 mg daily if needed.

It should be noted that the FDA has issued a Black Box warning for Actos as the drug has been linked to an increased risk of bladder cancer [14]. Specifically, In June 2011, the U.S. Food and Drug Administration (FDA) published a "Drug Safety

Communication," *indicating that based on dose and duration of use, there exists a 40 percent increased risk of developing Actos bladder cancer*. The study supporting that announcement looked at patients that took Actos for more than 12 months.

Step 8 – Correction of VEGF

If the above steps have not corrected VEGF, then exercise can be added to lower VEGF. [15]

Add anaerobic exercise daily based on patient tolerance. Anaerobic exercise is defined as short duration, high intensity exercise lasting anywhere from merely seconds up to around two minutes. After two minutes, the body's aerobic system kicks in and this process is the catalyst for the mechanism to increase VEGF. Specifically, in response to exercise, blood vessels proliferate by sprouting from existing vessels (i.e. angiogenesis). Increased angiogenesis helps in maintaining perfusion and adequate nutrient supply. VEGF is secreted in response to the exercise and is a potent factor in angiogenesis. In this way, the right kind of exercise, anaerobic exercise in particular, is an excellent remedy to overcome the low VEGF condition.

Step 9 – Correction of C3a

Treat with high-dose statins (80 mg daily) to reduce elevated C3a levels. Statins lower Coenzyme Q 10 (CoQ10) levels, and it is recommended to have the patient take a minimum of 150 mg CoQ10 daily.

Step 10 – Correction of C4a

Treat with VIP nasal spray administered at 4 sprays per day. Procrit was used in the past, but has been eliminated due to a Black Box warning.

Step 11 – Reduction of TGF beta-1

Treat with Losartan 25 mg given orally twice daily for 30 days in adults. In children, Losartan can be given at a dose of 0.6–0.7 mg/kg/day divided into two doses.

Step 12 – Replacing low VIP

This is the final step of the treatment protocol pyramid. Most patients who have gotten to this step will have already experienced significant improvement in their baseline symptoms; however, some will still require additional intervention. VIP

is a peptide hormone that exerts a profound anti-inflammatory and immunomodulatory effect. The following protocol is recommended for this final step of the treatment program:

1. Recheck all abnormal levels
2. Ensure no significant exposure to WDB
3. Ensure normal VCS
4. Get a baseline lipase level prior to VIP administration
5. Consider a stress echocardiogram prior to commencing treatment if patient has poor exercise tolerance. A stress echo can estimate if there is abnormal pulmonary artery (PA) pressure response to exercise. Normally the PA pressure drops with exercise, allowing increased oxygenation, but in CIRS patients the PA pressure may increase, reducing the amount of oxygen absorbed into the blood during exercise, and therefore causing the poor tolerance.
6. Treat with VIP, 50 mcg/ml, 1 spray in alternating nostrils QID. For safety, the first dose should be administered at the physician's office. The possible side effects of VIP are:
    a. Increased lipase levels
    b. Abdominal pain
    c. Rash
    d. Hypotension
7. Recheck lipase, C4a and TGF beta-1 after 30 days. **Note that VIP should be stopped if lipase increases, patient experiences abdominal pain or hypotension, or develops a rash.**
8. Taper to twice daily and continue for 30 additional days if needed

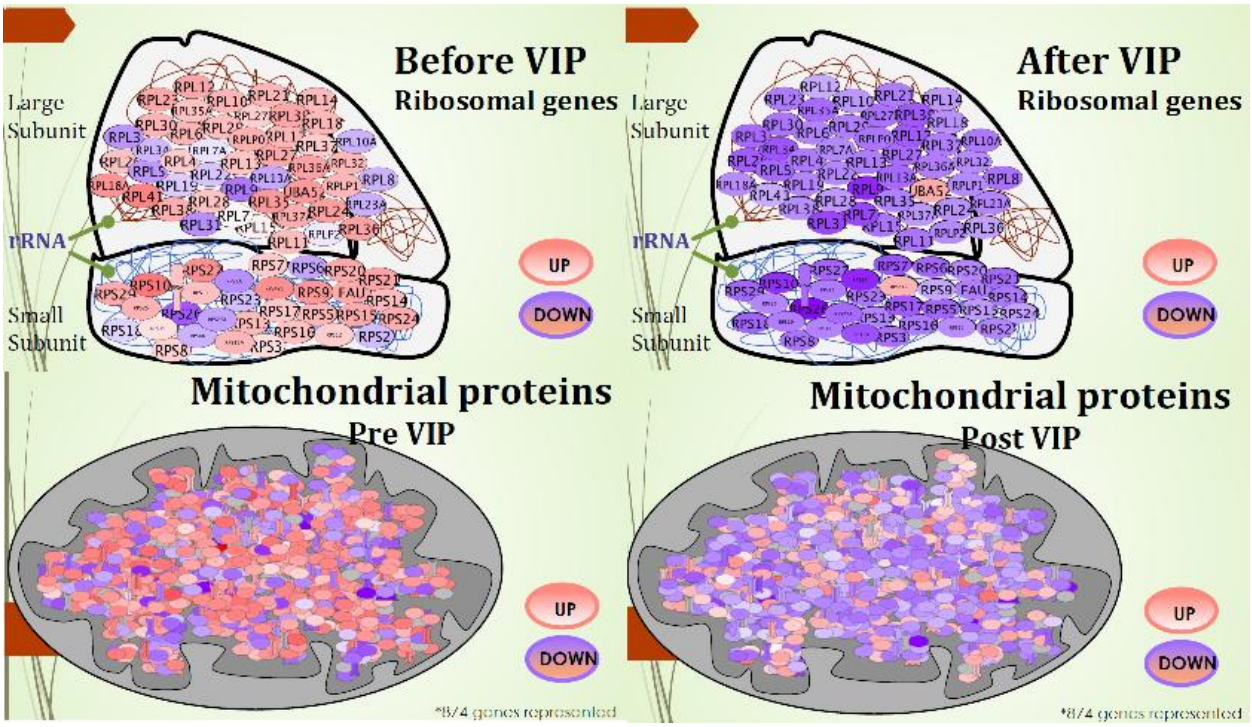
Repeat the Progene Dx CIRS genetic assay if a pre-treatment test was done. The emerging area of genomic testing is discussed in the Treatment Summary section below. Assuming that the test was given prior to treatment, the post-treatment test should clearly indicate the impact of the treatment as shown in the example illustration below.

CIRS Treatment Summary and additional considerations

The Shoemaker treatment protocol for CIRS is a very comprehensive, evidence-based approach to stopping the progression of the disease, stabilizing the patient,

reversing the negative markers and alleviating the symptoms. The protocol must be closely followed for the highest success. Yet, there are cases where practitioners have to evaluate and correct other factors. These were mentioned in the additional labs to evaluate if indicated in the CIRS diagnosis section above.

The area of genomics is an emerging area and represents the ultimate in diagnosing CIRS. Genomic testing allows us to look at gene expression which is the most reliable and promising way to look at DNA and It shows us patterns of gene expression and changes in gene regulation that can create illness. Illness is caused by the "lack of regulation" of regulation, and assessing DNA transcriptomics give us a phenomenal amount of information about a patient's risk factors for acquiring CIRS as well as other illnesses. Since the Progene Dx CIRS genetic assay is relatively expensive at this time ($1,750.00), practitioners will have to selectively use it with patients that can afford the high cost. I am hopeful that over time, genomic testing will become more affordable. The below images illustrate the power of genomic testing by showing gene expression and mitochondrial proteins before and after treatment with VIP [16].



Conclusion

As stated in the title of this paper, CIRS is frequently overlooked, misunderstood and misdiagnosed. Worse yet, many uninformed practitioners deny the existence of any disease that is the result of mold presence in a building. In my practice, I have actually had patients tell me horror stories about their provider having told them that mold related illnesses do not exist.

Fortunately for the body of suffering patients, Dr. Shoemaker has brought forward an emerging body of science and clinical validation that provides an evidence-based approach to understanding the disease process, diagnosing and treating it. Given the HLA research to date, 24% of the population is susceptible to developing CIRS. Further, according to www.survivingmold.com, more than 25% of all buildings are water damaged. In fact, some estimates are that 50% of the buildings are water-damaged. Putting these data together, we can easily see that CIRS is a pending "epidemic" of sorts since simple math using known population statistics yields the potential for 13.5 million or more susceptible adults that are living in water damaged buildings in the United States. That value is conservatively based on 300 million people, 73% adults 21 or over, 24% susceptible and 25% water-damaged buildings.

Understanding the biotoxin pathway is the key to understanding this multisystem, multi-symptom illness at the core level. It provides practitioners with a detailed analysis of the mechanism of the illness that helps to diagnose it, then helps in mapping out the steps to reverse the impacts of the disease. The Shoemaker approach provides practitioners with a data-driven formula that has actually been proven in clinical use, rather than only in an academic environment. The pathway when combined with the HLA testing also helps us to explain to patients how two people can have the same exposure, yet only one gets sick. Further, the "Biotoxin Pathway" illustrates an ongoing, amplifying cascade of events that starts with exposure to a biotoxin in those individuals who are genetically susceptible or in 5% of the cases, the same impacts can occur in non-genetically-susceptible individuals. In the susceptible individuals after the initial presentation, the biotoxin then binds to toll receptors, primarily in fat-cells and cells that line blood vessels, resulting in the production of proteins called cytokines which are involved in immune response and inflammatory processes. Cytokines recognize invaders

and recruit additional cytokines in response. This starts the biotoxin pathway and eventually leads to the multi-symptom multi-system illness that we have come to know.

Largely due to Dr. Shoemaker's research, including double-blind controlled studies, practitioners that choose to embrace this body of knowledge are well-positioned for effective differential diagnosis and treatment of CIRS and the imbalances that it causes. The combination of powerful screening tools that are easy to use like the VCS test, HLA susceptibility testing and the use of multiple confirming lab tests makes the CIRS diagnosis robust and literally non-controversial. Further, NeuroQuant itself is a brilliant piece of work that provides a strong piece of supporting diagnostic evidence and directly contributes to clarifying the distinction between Lyme disease and Mold illness, both of which are in fact biotoxin illnesses.

The emerging genomics research promises to provide the ultimate in CIRS diagnosis and treatment effectiveness by allowing us to directly see the pre-treatment gene expressions showing the disease impact in terms of up/down regulation of gene expression, and the post-treatment view showing that the gene expression has been returned to normal levels. This approach allows us to truly implement personalized medicine and provides the highest form of validation of the CIRS treatment protocol that can overcome even the most rigorous objections to the protocol.

Over time, given Dr. Shoemaker's passion for the CIRS body of knowledge and the growing certified practitioner base, the body of knowledge will continue to grow and it will be enhanced by higher volumes of patients, varying cases and presentations. The foundation is rock solid and practitioners are well-positioned to help patients return to health, respond to the "naysayers", and advance the body of knowledge to new levels.

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