The Shoemaker Protocol: Diagnosis and Treatment of Chronic Inflammatory Response Syndrome (CIRS)

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Introduction: In the 1990's, Ritchie Shoemaker was "living the dream" as a family practice physician in Pocomoke, Maryland when his life became turned upside down. Increasing numbers of the local aquatic wildlife and eventually humans became sick with what appeared to be a new illness with significant multi-systemic symptoms that was apparently incurable. Symptoms included diarrhea, cough, muscle aches, cognitive issues, rashes, shortness of breath, unusual neurologic findings and more[1]. Many of the patients who came down with the symptoms never got better. Eventually the cause was discovered to be a dinoflagellate protist called Pfiesteria piscicida.

As the local family physician Dr Shoemaker was seeing many of the affected patients. As any good practitioner would do, he tried one after another of the "tricks" he had learned over the years to treat the symptoms. One of those was to use cholestyramine (a medication which binds bile in the bowels, typically used to lower cholesterol) to treat the secretory diarrhea. He was surprised to find that, in addition to treating diarrhea, it also helped resolve neurologic and other symptoms. It was with this simple observation that the Shoemaker Protocol was born.

Over time he found that the cholestyramine (CSM for short) helped many of the patients he treated to get a full recovery from an otherwise incurable illness. Later he was called to investigate other similar outbreaks, and found similar infectious causes, with the CSM helping these patients as well. Eventually he discovered that some people exposed to mold from Water Damaged Buildings (WDB) had similar symptoms, as well as improvement with cholestyramine. In addition, other conditions were found to cause similar symptoms and appeared to be affecting the same pathways. With the multifactorial causes and the multi-systemic symptoms, and with the biologic pathways only slowly coming into view, he called the condition Chronic Inflammatory Response Syndrome (CIRS) in 2010.

Unfortunately (though expectedly) the general medical community did not immediately understand the significance of Dr Shoemaker's finding, so for the last 20 plus years he has painstakingly done significant research into the etiology and treatment of CIRS, and along the way has become a prolific publisher of his scientific discoveries and theories. What follows is a synopsis of the current state of the Shoemaker protocol.

Background: While Chronic Inflammatory Response Syndrome (CIRS) can have a variety of etiologies (parasitic infections, Post-Lyme syndrome, recluse spider bites), the most common

cause evaluated and treated by Dr Shoemaker was that caused by water damaged buildings (WDB). Hence, frequently he refers to CIRS-WDB (Chronic Inflammatory Response Syndrome caused by exposure to Water Damaged Buildings). So what's the big deal with WDB's and why do they make people so sick?

CIRS-WDB appears to be a relatively recent phenomenon, with rapidly increasing numbers of cases. Symptoms are multifactorial, with several components of WDB's contributing to the symptoms. While it is true that water damaged buildings have been with us since the dawn of buildings, trends within the last 50 years or so have predisposed to the current problem. Building materials like gypsum or particle board provide the perfect medium for the inciting organisms to flourish. Mingle that with a desire for increased efficiency (or "air-tightness") of buildings, increased uniformity of indoor temperatures, as well as designing airflow going through crawlspaces, and you have an indoor environment that is very different from any appearing in nature[2].

Unfortunately, it doesn't take much to turn a building into a WDB. All it takes is water exposure (on carpets, wallboards, porous surfaces) for as little as 48 hours without being completely cleaned and dried, and you vastly increase the likelihood for damage to occur. Even if the area later dries, many of the mold and bacteria are already in the area and can continue to cause problems. Common suspect areas include: basements / crawl spaces, roofs, soffits, penetrating vent pipes, windows, doors, and pressure variables (negative pressure worse than positive pressure)[3].

It turns out that different organisms (ex. bacteria and molds) grow preferentially at certain temperatures and levels of humidity. In addition to the organisms themselves, there are also other things that can cause problems, including bacterial breakdown products, fungal cell wall fragments, hyphal fragments, bacteria, mycotoxins, endotoxins, microbial volatile organic compounds (MVOC's) and a host of others[4].

Table 1 describes some of the potential pathogens[5]:

Table 1: Causative Agents for CIRS

Bacteria	Molds / Fungi	Other
Actinomycetes (gram +)	Stachybotrys sp. "black mold"	Dinoflagellates
Mycobacteria (stronger walls making them more resistant)	Penicillium sp.	Endotoxins
Cyanobacteria	Aspergillus sp.	Beta Glucans
Borrelia burgdorfori and other non-WDB associated bacteria	Mycotoxins from various species	Hemolysins
Bacterial breakdown products	Fungal wall vs hyphae breakdown products	Microbial volatile organic compounds (MVOCs)
And many others...	And many others...	And many others...

Mechanism of causation: CIRS has multiple symptoms from several different organ systems in the body. Generally, however, it is believed that the underlying cause has to do with the immune system. When the interior of the body comes in contact with a new antigen (virus, bacteria, mold, or

other substance) it doesn't recognize it as "self" the immune system starts a generalized inflammatory reaction while trying to come up with antibodies to make a more targeted and specific attack. This initial generalized attack is considered to be part of "innate immunity" and the antibodies part of "adaptive immunity". Once antibodies are formed they become key players in taking care of the problem. At that time the innate immune reaction to that antigen calms down and the body can reach homeostasis again.

In the setting of CIRS, however, the body is unable to process the antigens in a way to be able to make the antibodies. Without the adaptive immune system turned on, the innate immune system keeps chugging away causing generalized inflammation for extended periods of time. Re-exposure to the antigens will increase the response.

Unfortunately, the "usual" labs looking for infection or inflammation (CBC, ESR, CRP, ANA, RF and others) in CIRS cases are normal, making the diagnosis much more difficult. The good news is that there are some more esoteric labs which are typically abnormal. For instance the hypothalamic produced hormone alpha melanocyte stimulating hormone (MSH - possibly the strongest anti-inflammatory agent in the body) is typically depressed. Matrix metallopeptidase 9 (MMP9, an agent that allows inflammatory cells to cross from the bloodstream into the lungs, brain and heart) is elevated. Complement 4a (C4a - part of the complement portion of the innate immune system) is often elevated, and can quickly elevate even more with re-exposure. In the case of chronic bacterial infection, complement 3a (C3a) can also be elevated. Leptin levels are often elevated, leading to leptin resistance and predisposing to obesity. These and other lab abnormalities will be discussed further later.

Because inflammation can go on for years, patients tend to have a multitude of symptoms causing significant difficulty in their lives, often leading to disability and possibly an early grave from cardiac, pulmonary and neurologic diseases.

Diagnosis of CIRS: Chronic Inflammatory Response Syndrome from Water Damaged Buildings (CIRS-WDB) can be presumptively diagnosed clinically if all three of the following criteria are met:

1: History of exposure to a Water Damaged Building (WDB),
2: An abnormal Visual Contrast Sensitivity (VCS) test, and
3: 8 or more of 13 symptom "clusters" (6 or more if the patients age is less than 11).

It has been shown that if you have all three of the above clinical criteria, you have a 98.5% chance of having CIRS.

Before getting to some more formal and rigorous diagnostic criteria, I would like to explain the preceding three categories.

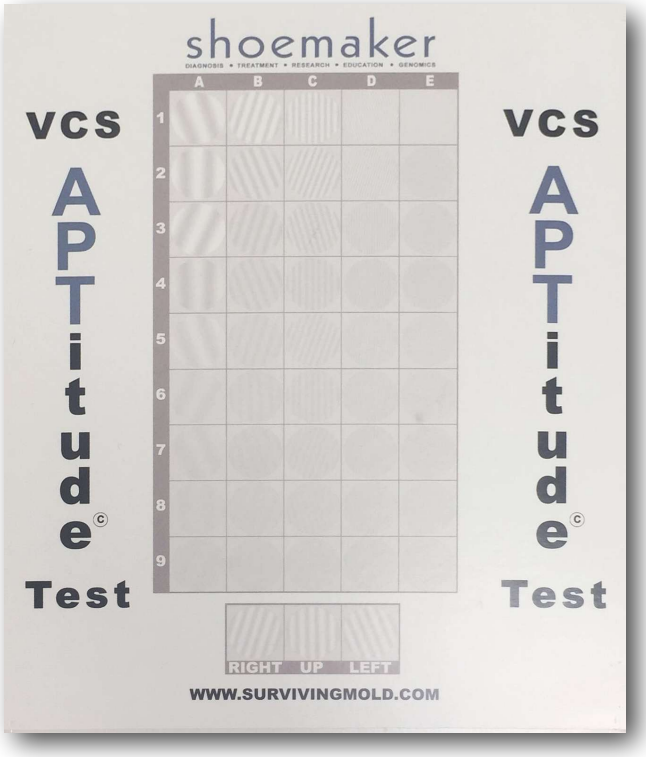
1: **Exposure to a water damaged building (WDB)**. Unfortunately any level of exposure to WDB's could potentially cause problems with susceptible individuals. Diagnosing the problem in the building could be as simple as seeing visible mold (not soot) or having a musty smell in the area. More formal diagnostics would include an Environmental Relative Moldiness Index (ERMI)[6] test which tests house dust for DNA from molds typically seen in water damaged buildings and compares them with common indoor molds, with the result being a ratio between the two. Lower numbers are safer and higher numbers more problematic. A ratio of < -4 is great, and 5-20 is bad (with higher being worse) and between -4 and 5 is intermediate.

A second (less expensive) test is the HERTSMI-2[7], which looks at the levels of five of the most problematic molds (Aspergillus penicilloides, Aspergillus versicolor, Chaetomium globusum, Stachybotrys chartarum and Wallemia sebi) and gives a cumulative score. Scores <11 are considered safe for people with CIRS, 11-15 are borderline and >15 are dangerous for CIRS patients. The HERTSMI-2 also tests house dust and this report is often included with the ERMI test.

A third test is to check for actinomycetes[8], another DNA test of house dust looking for actinomycete bacteria as well as mycobacteria. Both of these can make biotoxins which may be more clinically important than mycotoxins (mold toxins). This is scored similarly to the HERTSMI-2, with 10 or below being "indicative of a healthy building", 11-15 being "further investigation needed", and >15 being "suggestive of building-related illness."

2: **An abnormal Visual Contrast Sensitivity (VCS) test**[9]. Previously known as a Functional Acuity Contrast Test (F.A.C.T), this test is similar in some ways to a standard Snellen vision test. Instead of checking for visual acuity, however, you are testing for the ability of the eyes to detect changes in contrast. In order for the test to be valid you need to have a visual acuity of 20:50 or better, and overhead illumination of 70 foot-lamberts or more. The test card (or computer screen in the online version) is 18 inches from your eyes, and the test is read from the top down in each of 5 consecutive columns. Each column has a number of squares, each with gray lines with progressively less difference in contrast (see Figure 1).

Figure 1: Visual Contrast Sensitivity (VCS) test



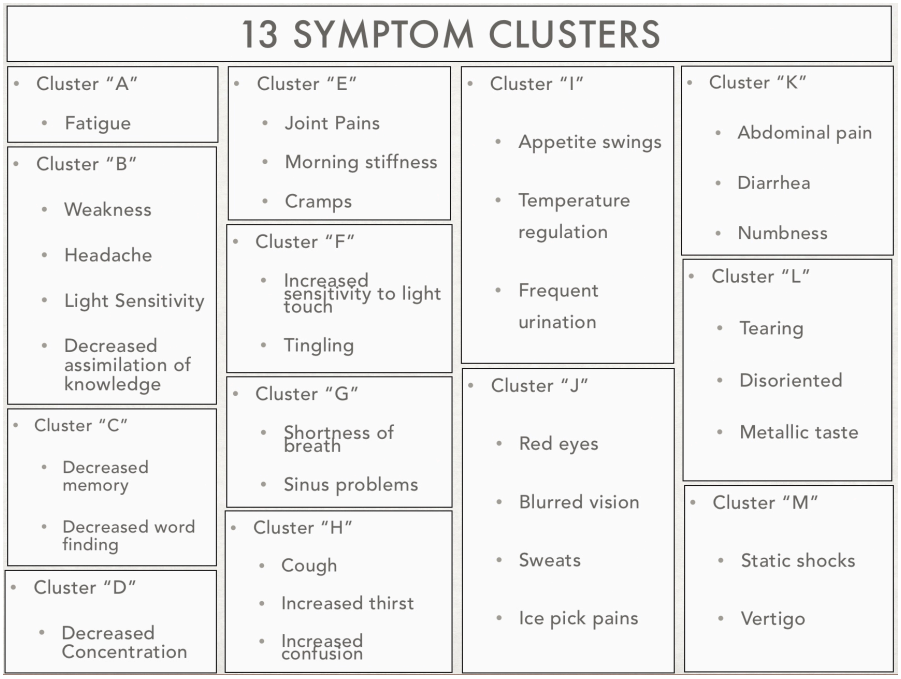
The highest attained score for each column is counted and compared against normals. Commonly people with CIRS will have abnormalities, particularly in columns C and D.

As the CIRS is treated, typically the VCS scores improve, giving a simple, inexpensive objective test of the efficacy of the treatment protocol.

3: **8 or more of 13 symptom "clusters"**. Because CIRS patients have a multitude of symptoms from several different organ systems, it can be difficult to ferret out whether a patient's symptoms are due to CIRS or a host of other different potential causes. Dr Shoemaker worked with some statisticians on figuring out the best way to use the symptoms as part of a diagnostic criteria. The most sensitive and specific way was to divide 31 symptoms into 13 groups or "clusters" (see figure 2).

If a patient complains of symptoms from 8 or more of the 13 clusters, chances are they have CIRS.

Figure 2: CIRS symptoms categorized into clusters



Case Definition:
While the above presumptive clinical diagnosis can be inexpensive and useful, there are plenty of CIRS patients who fail to meet all of the criteria. In addition, per Dr Shoemaker, it is important to have diagnostic labs for the following reasons[10]: a) ongoing differential diagnosis, b) labs show interval improvement due to therapy, c) labs show re-exposure, d) labs can objectively demonstrate physiology, e) labs allow further study.

The official case definition has changed over the years as knowledge in the field has grown. In September 2008, the Government Accounting Office (GAO) published a document entitled "INDOOR MOLD Better Coordination of Research on Health Effects and More Consistent Guidance Would Improve Federal Efforts."[11] Their recommendations were to have CIRS defined as having the following 4 items:

1: **There must be the potential for exposure to a damp indoor space.**
2: **There must be a multisystem, multi-symptom illness present with symptoms similar to those seen in peer-reviewed publications.**
3: **There must be laboratory testing results similar to those seen in peer-reviewed, published studies.**
4: **There must be documentation of response to therapy.**

We have already discussed the first two parts of the first tier, namely potential for exposure and symptom clusters.

With regards to laboratory testing, since 2008 there have been more tests added to the list of those published in peer-reviewed studies. Some of these (like NeuroQuant) aren't laboratory testing at all. Because of this, I prefer to think of the labs and other tests as objective biomarkers, and improvement in these as evidence of response to therapy. Following is a list of some of the well documented biomarkers that can be abnormal in CIRS.

1: **HLA-DR** is a genetic test looking at the human leukocyte antigen complex, DRB1, DQ, DRB3, DRB4 and DRB5. There is a strong correlation between certain HLA haplotypes and CIRS. The theory is that people with certain haplotypes either have decreased ability to recognize and/or make antibodies to certain antigens, leading to a CIRS scenario.

Table 2: HLA Haplotype Susceptibilities

Susceptibility	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B (02)		
	14	5	52B (02)		
Mold	7	2/3		53	
	13	6	52A,B,C (01,02,03)		
	17 (03)	2	52A (01)		
	18	4	52A (01)		
Borrelia, Post-Lyme Syndrome	15	6			51
	16	5			51
Dinoflagellates	4	7/8		53	
MARCoNS	11	7	52B (02)		
Low MSH	1	5			
No recognized significance	8	3,4,6			
Low-risk Mold	7	9		53	
	12	7	52B (02)		
	9	9		53	

Figure 3, from Dr Shoemaker's book "Surviving Mold"[12], shows some of the genetic susceptibilities for various HLA genetic types. In his experience, patients who fall in the "multisusceptible" category - 4-3-53, 11/3/52B, 12/3/52B, and 14-5-52B are much more likely to have significant symptoms and problems from WDBs. Only 5% of CIRS-WDB patients have HLA-DR haplotypes that do not fall in the high risk categories.

2: **Alpha Melanocyte Stimulating Hormone (MSH)**, as previously discussed, is produced in the hypothalamus. It is made from the breakdown of proopiomelanocortin, a molecule that ends up getting split to make three separate controlling molecules in the immune system: beta endorphins (and [Met]enkephalin)[13], MSH, and ACTH. While MSH *does* stimulate melanocytes to make melanin, it also has powerful anti-inflammatory and neuroregulatory effects. It is "involved in weight, appetite, mood, circadian rhythms, mucus membrane defenses, pulmonary responses, blood-based immunocyte response, gut tight junctions (don't say leaky gut in face of low MSH)[14]." It slows down the production of several different inflammatory cytokines[15]. Despite what the "normal" values from the laboratory say, optimal levels of MSH fall between 35 and 81 pg/mL. Levels below this are associated with CIRS.

3: **C4a (Complement 4a)** is part of the complement system which is in turn part of the innate immune system, which when activated in a CIRS type situation, can be hard to turn off. Normal levels are below 2830, but in CIRS they are often over 10000, and have been seen to rise over 190,000[16]! The best results for this lab are when it's run through National Jewish Center in Colorado (it needs to be placed on dry ice after drawing the blood).

4: **Matrix Metalloproteinase-9 (MMP9)**: The matrix metalloproteinases are enzymes which digest protein and can dissolve part of the basement membranes of the blood vessels. This can allow inflammatory cytokines to go from the bloodstream into multiple tissues including the brain, joints, nerves and lungs where they can cause damage. Normal levels are 85-332, with levels higher than that being associated with significant inflammation and CIRS.

5: **ADH/Osmolality dysregulation**: Antiduretic hormone (ADH, also known as Vasopressin, or arginine vasopressin (AVP)), functions, as it's name implies, to cut down on the amount of free water excreted in the urine by increasing water resorption in the nephrons. It is created in the posterior pituitary where it is released in response to hyperosmolality (or increased concentration) in the extracellular fluid[17]. In addition to effectively diluting the plasma, it has a pressor effect on the arterioles (hence the name "vasopressin"). Both effects help to keep blood pressure from going too low.

Table 3: 6 types of ADH/Osmolality

ADH lower than normal	ADH higher than normal
Osmolality lower than normal	Osmolality higher than normal
ADH low normal with osmality high normal	ADH high normal with osmolality low normal

ADH/osmolality dysregulation is frequently associated with low MSH, and is often associated with "chronic migraines." Because ADH levels rise in response to high osmolality and lowers in response to low osmolality, the ADH and osmolality levels should mirror each other.

6: **ACTH/Cortisol dysregulation**: Like MSH, adrenocorticotropic hormone (ACTH) is one of the cleavage products of proopiomelanocortin. It is produced and secreted by the anterior pituitary gland in response to stress. ACTH stimulates the production and release of cortisol by the adrenal cortex. In primary adrenal insufficiency the ACTH is elevated and cortisol is low. In secondary adrenal insufficiency the ACTH is low and cortisol is low and the corticotropin releasing hormone (CRH) is high (suggesting hypopituitarism). In tertiary adrenal insufficiency, hypothalamic insufficiency leads to CRH, ACTH and Cortisol deficiency[18]. In Cushing's disease the cortisol is elevated, usually due to an elevated ACTH (or the patient is taking long term exogenous steroids).

Table 4: 6 types of ACTH/Cortisol

ACTH lower than normal	ACTH higher than normal
Cortisol lower than normal	Cortisol higher than normal
ACTH low normal with cortisol low normal	ACTH high normal with cortisol high normal

In the case of CIRS, the basis for the dysregulation is different from other forms of adrenal insufficiency, it is caused by the disruption in the melanocortin physiology[19]. Because of this, use of exogenous steroids is highly discouraged in the treatment of CIRS due to an elevated risk of ACTH suppression[20].

Unlike the ADH/osmolality relationship, the correlation of ACTH to cortisol is inverse. When you have a high cortisol level you would expect a low ACTH (to bring it back down) and vice versa.

7: **Visual Contrast Sensitivity test (VCS)**: As mentioned above the Visual Contrast Sensitivity (VCS) test is an objective test that is frequently abnormal in CIRS. While this is very inexpensive to perform, improvements in VCS testing correlate well with improvement in other signs and symptoms.

8: **Physical Exam**: While this may seem obvious, unfortunately the art of physical exam is quickly becoming lost in medicine. A few findings that could be helpful in CIRS diagnosis could be height vs "wingspan", evaluating fine resting tremor with a sheet of paper over the outstretched hand, obesity (suggestive of leptin resistance), and dermatographia - common with elevated C4a. Bedside spirometry can also tell us if they have low forced vital capacity (FVC - suggestive of restrictive lung disease) or a low forced expiratory volume in 1 second (FEV-1) suggestive of obstructive lung disease.

9: **ERMI, HERTSMI-2, Actinomycetes**: This is a lab test not of the patient but of their environment. ERMI stands for the "environmental relative moldiness index", which uses DNA testing comparing the levels of common outdoor molds with certain toxin producing molds from WDB's. There is a total of 36 different mold species tested. The scoring is the difference between the WDB molds and the outdoor molds. The range is from -10 (really good) to +20 (really bad). Many people with CIRS cannot tolerate a score higher than +2 and often need to be in places with a score -1 or lower.

HERTSMI-2 stands for "health effects roster of type specific formers of mycotoxins and inflammagens - 2nd Version" and is a DNA test looking at the 5 most toxic molds: Aspergillus penicilloides, Aspergillus versicolor, Chaetomium globosum, Stachybotrys chartarum and Wallemia sebi. Higher points are assigned to higher levels of each mold, with a total score of <11 being considered safe, 11-15 borderline and >15 dangerous for people with CIRS - "do not enter".

The actinomycetes test is, as expected, a genetic testing for the levels of actinomycetes in the room vs building. This is the bacteria that causes the "musty smell" that can be found in many WDB's. It is a DNA sequencing test evaluating levels of 40 different Actinomycetes species. Scoring is Q1 (9 or below - indicative of a healthy building), Q2 (between 10 and 15 - further investigation needed), and Q3 (>15 - suggestive of building-related illness). In conjunction with the ERMI or HERTSMI-2 it can be a powerful test looking for likelihood of toxicity.

All three of the above tests can be collected with a "Swiffer" and sent to Envirobiomics.

10: **MARCoNS**: A nasal swab looking for MARCoNS ("Multiple Antibiotic Resistant Coagulase Negative Staphylococci") is done on each patient doing the CIRS protocol. These bacteria are frequently colonized in the nasal pharynx and harbor the ability to make biofilms, as well as creating MSH cleavage factors, potentially bringing MSH levels even lower.

11: **Transforming Growth Factor beta 1 (TGF beta 1)**: This has been called the "single most important proteomic test" by Dr Shoemaker and is often elevated in CIRS. High levels are associated with fibrosis in multiple organ systems including but not limited to the lung, liver, kidney and skin by dedifferentiating epithelial cells to become

mesenchymal cells. In the lung, the fibrosis can lead to interstitial lung disease. The levels tend to go highest in patients with HLA 11-3-52B as hypermobility (for example Ehlers-Danlos syndrome patients). Normal levels are less than 2380. Elevated levels are associated with chronic inflammation.

12: **Vascular Endothelial Growth Factor (VEGF)**: VEGF can be either elevated or low in CIRS, since it is induced by cytokine induced hypoxia. Levels that are too low can be associated with increased permeability of the blood-brain barrier leading to cognitive dysfunction. In addition, people with low levels can have shortness of breath, fatigue and muscle cramps[21].

13: **Anti-Gliadin Antibodies**: CIRS patients often have elevated levels of antigliadin antibodies, suggestive of a gluten sensitivity (worse cases with Celiac Disease). While CIRS patients aren't the only ones to get this, treating this with a gluten free diet for at least three months is an important part of the Shoemaker Protocol.

14: **Complement 3a (C3a)**: Closely associated with C4a (mentioned above), C3a is a part of the complement system that can go up quickly and potentially be elevated for long periods of time. The difference is that C3a tends to become elevated in the presence of bacterial membranes, so can be helpful to diagnose if there is any kind of ongoing bacterial infection.

15: **Vasoactive Intestinal Polypeptide (VIP)**: VIP is a neuroendocrine peptide that is in both the central and peripheral nervous systems. It functions not only in the bowels but in the skin, lungs, and central nervous system among others. Along with MSH and ADH it is considered a hypothalamic marker[22]. Depressed levels are associated with peripheral inflammation[23]. Dr. Shoemaker reports that all of the patients he's seen with Multiple Chemical Sensitivities (MCS) have low levels of VIP[24]. Normal levels are 23-63 pg/mL. CIRS patients tend to have depressed levels of VIP, and it has been shown that replacing VIP with an intranasal spray can have profound effects if it is given after other major symptoms and labs have been adequately addressed (see treatment section).

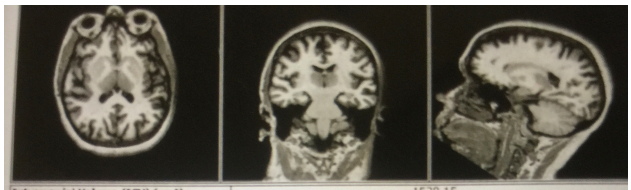
16: **Leptin**: Produced by the adipocytes, leptin can act as both a hormone and cytokine. As a cytokine, it reacts with the macrophages to produce pro-inflammatory cytokines (for example TNFa1, IL-1 and IL-6[25]). It acts as a hormone in the hypothalamus signaling to break down proopiomelanocortin to make MSH, ACTH and beta endorphins (discussed above). Unfortunately, several of the inflammatory cytokines can block the hypothalamic receptor for leptin, leading to leptin resistance and elevated leptin levels. This is associated with weight gain, obesity and inability to lose weight. Normal levels for males is 0.5-13.8 ng/mL, and for females is 1.1-27.5 ng/mL[26].

17: **von Willebrand's Profile**: Von Willebrand's disease (VWD) is the most common inherited clotting disorder, affecting 66-100 patients per million in the general population. Patients usually present with mucocutaneous bleeding. While it is generally a classical autosomal inherited disorder, an acquired von Willebrand's syndrome is generally felt to be rare, and associated with lymphoproliferative disorders, autoimmune disorders, aortic stenosis and other causes[27]. Dr Shoemaker found, however, that acquired VWD can be quite common in CIRS. The panel includes factor VIII, von Willebrand's antigen and ristocetin associated cofactor. Low levels of von Willebrand's multimers can be associated with excess bleeding (eg. nosebleeds that won't quit), while high levels can lead to excessive clotting in the microvasculature. Fortunately, if a

patient with CIRS gets a nosebleed taking oral DDAVP 0.1-0.2 mg can stop it within 5-10 minutes[28].

18; **NeuroQuant Testing**: One of the more exciting diagnostic tests to come along in years is the NeuroQuant from Cortechs Labs. The test takes a sagittal view from an MRI of the brain and uses computer software to measure the size of eleven different structures in the brain. It has been FDA approved since 2006. Statistical analysis of CIRS-WDB patients has shown an increased size in forebrain parenchyma, increased size of cortical gray matter, and a decrease in the size of the caudate nucleus. Post Lyme patients tend to have a small putamen and a large right thalamus (the left thalamus is normal).

Figure 3: Example of NeuroQuant



Intracranial Volume (ICV) (cm³)	1520.15				
Brain Structure	LH Volume (cm³)	LH Volume (% of ICV)	RH Volume (cm³)	RH Volume (% of ICV)	Asymmetry Index (%)
Forebrain Parenchyma	486.62	32.01	496.80	32.68	-2.07
Cortical Gray Matter	244.35	16.07	248.29	16.33	-1.60
Lateral Ventricle	10.01	0.66	10.95	0.72	-8.97
Inferior Lateral Ventricle	0.55	0.04	0.53	0.04	2.60
Hippocampus	4.02	0.26	4.04	0.27	-0.42
Amygdala	1.70	0.11	1.69	0.11	0.83
Caudate	2.79	0.18	2.95	0.19	-5.51
Putamen	5.19	0.34	4.86	0.32	6.55
Pallidum	0.71	0.05	0.69	0.05	2.29
Thalamus	7.53	0.50	7.33	0.48	2.67
Cerebellum	60.39	3.97	62.71	4.13	-3.77

It is believed that the change in size of different parts of the brain results from chronic inflammation changing permeability of the blood brain barrier leaving different parts of the brain to get more or less relative swelling. Treatment with the Shoemaker protocol has been shown to correct some of these abnormalities.

19: **Transcriptomics**: Evidence suggests that on the intracellular level mycotoxins and other agents cause damage by attacking the sarcin-ricin loop on ribosomes[29], cutting down on the ability for RNA transcription to occur. Since most of the mitochondria's DNA is housed in the nucleus, cutting down on the transcription of mitochondrial genes can significantly diminish its ability to produce ATP, an energy molecule used by the cell. The latest breakthrough in genomics is to check the levels of various RNA particles to see how many of individual nucleotides are being made. This can give a very accurate look into exactly what is going on, with the possibility in the future to tailor individual treatments to the precise problem intracellularly. While this technology and treatment is still in its infancy, the prospects for using this successfully in the future look very bright!

20: **Echocardiogram**: Patients with elevated TGF beta-1 and decreased VEGF are at high risk for having pulmonary hypertension. Often these people will have dyspnea on exertion. It can be evaluated with an echocardiogram looking for the pulmonary artery systolic pressure (PASP). This can be calculated using the following equation:

$$PASP = 4 * TR^2 + RA$$

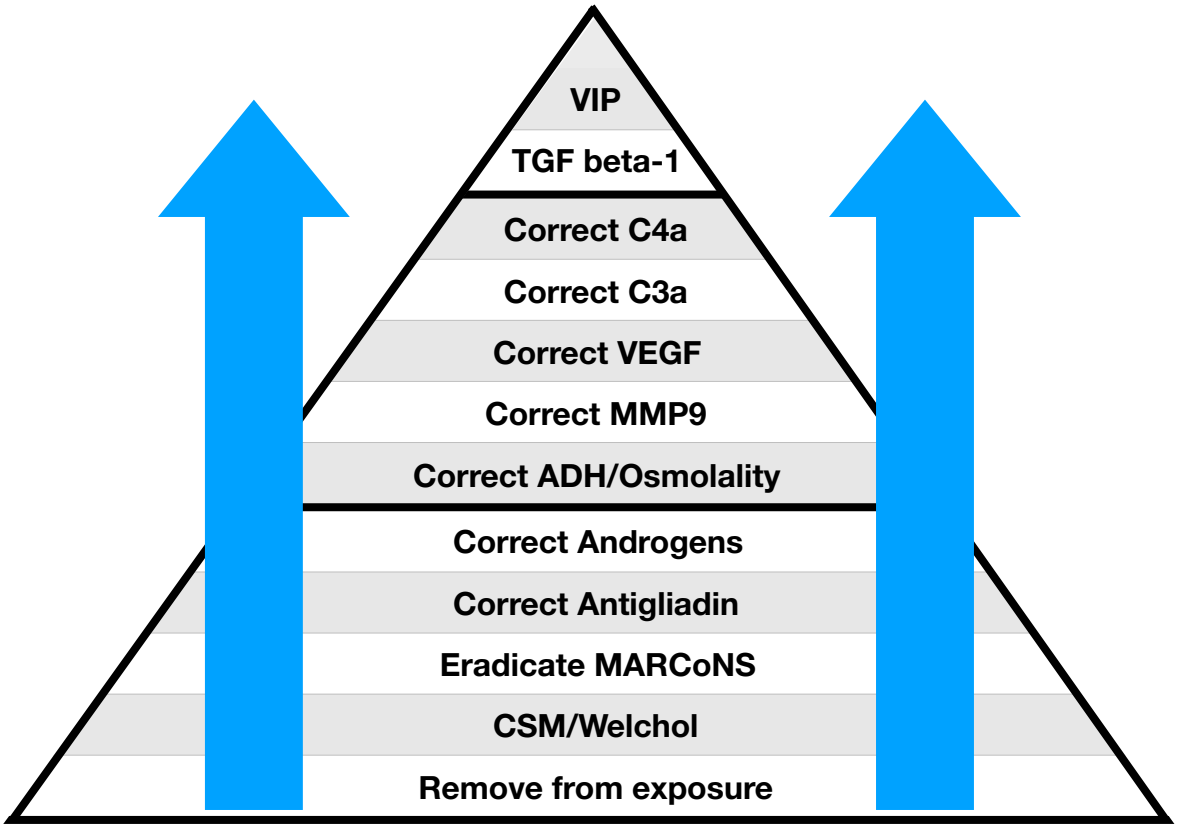
where TR = tricuspid regurgitation and RA = right atrial pressure. If the results are ≤ 30 and you are still clinically suspicious of pulmonary hypertension, a stress echo may need to be performed.

Treatment: Once you've made the diagnosis of CIRS, the next step is treatment. Dr Shoemaker's protocol has 12 steps, divided into 3 main groups and arranged like a pyramid[30] (see Figure 4). Treatment starts at the base and works up step by step.

Starting at the base, the treatment steps go as follows:

1: **Remove from exposure**: This is perhaps the most important step, since patients with prolonged exposure can get continued increased worsening of symptoms. That being said, it is not always easy to do. As noted above, part of making the diagnosis in the first place is having known exposure to WDB's. While you could make the diagnosis if you have verified visible mold, particularly with a musty odor, often times the actinomycetes plus ERMI or HERTSMI-2 are the best tests to do, and they can take 7-10 days to come back. The decision to do those tests in the first place can sometimes be a difficult one - do you find out if the house you own has mold and then be stuck with a possible six-figure bill for remediation and/or have to sell the house at a huge loss or do you sell the house right away not even knowing for sure if there's mold in it?

Figure 4: Treatment Steps in the Shoemaker Protocol



Fortunately, either way you CAN use HEPA filters throughout the house to try to cut down on the number of inciting particulates. While this is not a good permanent solution, hopefully it can calm things down enough to allow time to figure out whether you indeed have CIRS and to start the treatment protocols. Should a person indeed have CIRS-WDB, eventually either a full remediation and/or a move is a must.

2: **CSM/Welchol**: Cholestyramine (CSM) is the medication which has consistently worked for Dr Shoemaker ever since those early days 20+ years ago with Pfiesteria. CSM is a powder and is ideally taken at 1 scoop 4 x per day 30 minutes apart from meals and also apart from any medicines. In the general population the main side effect is constipation (remember, Dr Shoemaker initially used it for secretory diarrhea). To help prevent this side effect soluble fiber (for example prunes, apricots, cashews) is recommended.

Unfortunately, many CIRS patients can't initially tolerate a full dose of CSM, and need to start with MUCH smaller doses - maybe a fraction of a scoop every 1-3 days and SLOWLY work up from there. While the CSM binds toxins in the bile and prevents them from being resorbed into the body via the enterohepatic circulation, clinical experience leads us to suspect that in removing some of the toxins, it allows the body to release more of the stored toxins from the tissues for elimination. These additional toxins can potentially overwhelm the patient and make their symptoms temporarily worse! Low and slow is the game. If they are having worsening of the symptoms, cut back - there is nothing to be gained from a prolonged exacerbation.

The regular prescription of CSM does have sugar in it. There is a version "Questran Lite" that uses artificial sweeteners, and it is possible to get it compounded for people requiring something "cleaner."

Instead of cholestyramine, another similar medicine, Welchol (colesevolam) may be used. It has the advantage of being a tablet (675 mg), and the ability to take it with food. It is not as potent of a binder as is CSM, having only about 25% of the efficacy, but according to Dr Shoemaker in a conversation I had with him, "after a month, who cares?" Typical dosing is 2 tablets 3 x per day with meals. There is a powdered version also available. While side effects from Welchol are less than for CSM, they can still occur, and for extremely sensitive patients, Dr Shoemaker told me he will crush a tablet and mix it in 6 oz of water, and have the patient take 1 oz per day with meals and work up from there.

Welchol can also cause constipation (although not as much as CSM), so the recommendations for the soluble fiber also apply with this medicine.

For patients who are especially sensitive (eg those with high MMP9 or MARCoNS), taking omega 3's EPA/DHA 875/675 mg 3 x per day for 5 days before starting the medicine can be very helpful[31].

3: **Eradicate MARCoNS**: Many people with CIRS have nasal colonization of a bacteria called "Multiply Antibiotic Resistant Coagulase Negative Staphylococci" (MARCoNS for short). While this may not directly cause symptomatic sinusitis or pharyngitis, the bacteria tends to produce biofilm locally and elsewhere in the body. The biofilm can help protect not just the staphylococci but a host of other bacteria, fungi, and protists in a stew of organisms, with each one potentially swapping genetic fragments with each other, allowing for acceleration of antibiotic and treatment resistance to occur.

Because MARCoNS are by definition multiply antibiotic resistant, treatment with antibiotics is problematic at best. For years Dr Shoemaker and his associates used "BEG spray" (Bactroban (mupirocin) 0.2%, EDTA (Edetate Disodium) 1%, and gentamicin 0.025%) to treat it, but even that is not working as well as it has. The latest recommendation is to use a mixture of 0.2% EDTA as a nasal spray, 2 sprays each

nostril 3 x per day for 3-6 months[32]. The EDTA tends to break up biofilms as well as have antibacterial and antifungal activity.

4: **Correct Antigliadin**: Antigliadin Antibodies (IgA, IgG) are common in people with celiac disease as well as gluten sensitivity. IgA is more commonly elevated in celiac disease and IgG more in non-celiac gluten sensitivity. If the antibodies are positive, then patients are recommended to go on a strict gluten free diet for at least 3 months.

Various gluten free diet options exist. One that Dr Shoemaker has used with success is the Amylose free diet, although other gluten free diets (Paleo, Keto, Atkins, Wahl's, etc) should work fine.

5: **Correct Androgens**: While androgen deficiency is very common in non-CIRS patients, it is even more common in the CIRS population, with an incidence between 40 and 50%[33]. This is at least in part due to elevated aromatase levels (aromatase is an enzyme that transforms androgens into estrogens). Assuming the levels are low, testosterone replacement is not considered a good idea for two reasons: 1) exogenous use of androgens diminishes endogenous production and 2) elevated aromatase increases the transformation of what testosterone that is there into estradiol, the most potent estrogen in the body.

As a first line of treatment a patient may take DHEA 25 mg 3 x per day for 30 days. The second line treatment is HCG 125mg IM 1 x per week x 30 days. The third line treatment is VIP 1 spray alternating nostrils four times per day x 30 days.

It may be, however, that the low androgens cannot truly be corrected until you get to the last step, using VIP (which helps correct the underlying problem causing the elevated aromatase).

6: **Correct ADH/Osmolality**: As noted above, CIRS patients often have abnormalities in either ADH, osmolality, or the ratio between the two. Treatment of the dysregulation is to use DDAVP 0.2 mg every other day for ten days.

As DDAVP can cause low serum sodium, it is important to watch for peripheral edema, weight gain, elevated or lower blood pressure, serum osmolality and sodium levels in the blood.

7: **Correct MMP9**: As mentioned above, elevated levels of MMP9 can lead to significant inflammation in various organs. This is usually corrected with omega 3 fatty acids - EPA/DHA 875/675 mg three x per day for at least a month. Often this is given in conjunction with a low amylose diet.

A second line therapy would be VIP 1 spray in alternating nostrils 4 x per day for 30 days.

The other treatment that has worked well historically is 45 mg of Actos (pioglitazone) daily for 10 days. Actos works by lowering leptin[34], MMP9[35], raising VEGF[36] and improving insulin resistance and lowering systemic inflammation. Unfortunately Actos could potentially cause or exacerbate congestive heart failure (CHF), and longer term use has also been associated with increased risk of bladder cancer[37]. Also, do not use Actos in patients whose leptin level is less than 7[38].

8: **Correct VEGF**: Fortunately, the things that correct MMP9 also tend to correct VEGF, so treating with the omega 3's - EPA/DHA 875/675 mg three times per day for a least a month should be good. Actos can also help with this (although it's rarely used any more for the reasons mentioned above), as well as the low amylose diet.

The other potential treatment to raise depressed VEGF levels is to add daily exercise that barely gets to the anaerobic threshold then stop[39]. Continuing beyond that point will cause "push-crash" which can leave people more debilitated for the next 2-3 days while their body recovers.

9: **Correct C3a**: If the C3a is elevated it is likely from a bacterial infection as C3a rises in response to bacterial membranes. Treatment with antibiotics may be warranted in this setting.

First pretreat with CoQ10 200mg daily for 10 days, followed by high dose statins (80mg per day) for 30 days. Continue the CoQ10 while on the statins. This is believed to help protect against statin toxicity (including rhabdomyolysis).

10: **Correct C4a**: As mentioned above, complement 4a can be extremely elevated in CIRS. Hopefully by this point in the protocol the level will have fallen below 2830 (due to avoidance of exposure). If it is still elevated at that time, however, it can be treated with VIP nasal spray, 50 mcg/mL, using a single spray 4 x per day (see instructions for VIP use below).

An older treatment (not used currently due to a black-box warning) is to use erythropoietin (Procrit). Dosing was to 8,000 unit every 3 days for 5 doses. Because of potential concerns of increased blood clots, levels of D-dimer and hemoglobin were checked regularly, and the treatment was avoided in patients with clotting disorders, cancer, and kidney failure. This treatment reduced symptoms by 75% and corrected lactate and glutamate/glutamine ratios[40]. As noted above, this treatment is no longer used and is included as a historical reference only.

11: **Correct TGF beta-1**: Transforming growth factor beta-1 is easily corrected with the angiotensin receptor blocker (ARB) losartan (brand name Cozaar). The benefit comes not from the drug itself, but from one of its breakdown products EXP3179[41] which can significantly lower TGF beta-1 levels. Dosing is to start with 12.5 mg daily and work up as tolerated to 25 mg 2 x per day. Dosing may be limited by blood pressure (many CIRS patients have low blood pressure). Pediatric dosing is 0.6-0.7 mg/kg/day divided into two doses. Dosing is continued for 30 days.

If the losartan fails to bring the TGF beta-1 levels below 2380, then VIP nasal spray 4 x per day can be used (see below for dosing).

12: **VIP**: Vasoactive intestinal polypeptide therapy can be remarkably effective for getting rid of remaining symptoms, but will not work if the preceding 11 steps have not been taken. There is some evidence that it could potentially be curative.

People who could most benefit from VIP therapy include those who meet one or more of the following criteria:

- Decreased VIPR1 (vasoactive intestinal peptide receptor 1)
- Increased pulmonary artery systolic pressure (PASP) during rest or provocative testing

- Incomplete improvement with steps 1-11

In order to be eligible for VIP therapy, the following conditions must be met:

- No continued exposure (ERMI <2 or HERTSMI-2 $\leq$10)
- Negative MARCoNS
- Normalized VCS
- Normal lipase levels
- Normal GGT levels

Works well with:
- Poor recovery of energy (at least 70-90%)
- Poor recovery of cognitive function
  - Especially if NeuroQuant shows caudate atrophy
- Poor recovery of exercise tolerance
- Multiple Chemical Sensitivities (MCS)
- Nothing has helped
- Has had good response to the protocol but would like to get even better.

Dosing of VIP is 50 mcg/mL, 1 spray in one nostril 4 x per day. It can be obtained by prescription from various compounding pharmacies, most notably Hopkington Drug located in Hopkington, MA.

When giving the first dose, the patient needs to be in the office, and have levels of TGF beta-1 drawn before and 15 minutes after the first dose, and be monitored during that time for any improvement or worsening.

The therapy is continued at 4 x per day dosing for 3-4 months, then slowly discontinued as tolerated. During therapy monthly lipase levels need to be monitored and the patient watched closely for abdominal pain since VIP can increase the risk of gallstones.

VIP therapy can help correct any remaining abnormalities in C4a, TGF beta 1, VEGF, MMP9, estradiol, testosterone, and vitamin D3. If all goes well, the patient will feel fantastic and be symptom free, even off the medicine, and no longer exhibit the “sicker quicker” effect with repeat exposure. Of course, avoiding significant further exposure is always prudent.

Conclusion: Patients with Chronic Inflammatory Response Syndrome (CIRS) can be very sick, with few successful diagnostic or treatment options out there. The Shoemaker Protocol has the potential to help these patients enormously, with the potential for a sustained remission from their symptoms.

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