CHRONIC INFLAMMATORY RESPONSE SYNDROME

SHOEMAKER TREATMENT PROTOCOL

SCIENTIFIC SUPPORT

(As Of March 23, 2015)

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I. A person with a multisystem/multisymptom syndrome presents for evaluation.

In his work with greater than ten thousand patients with biotoxin illness, Dr. Shoemaker identified 37 symptoms found in cases with thirteen symptom clusters later identified. A positive cluster analysis for Chronic Inflammatory response syndrome (CIRS) was defined as a finding of eight or more of the thirteen clusters. This diagnostic criteria is the first requirement for the diagnosis of CIRS-water damaged building (CIRS-WDB), CIRS-post treatment Lyme disease (CIRS-PTLD), CIRS-post Ciguatera/Pfiesteria (or other toxin-producing dinoflagellate) exposure, CIRS-post Cylindrospermopsis or Microcystis (or other toxin producing blue-green algae) exposure and toxin exposure from the bite of a Brown Recluse spider. It is likely that additional toxic triggers will be identified as the research evolves. (1,2,3)

II. Past medical records are reviewed.

During this important step the thoroughness of prior screening and diagnostic evaluations of this patient is determined. Are recommended cancer screenings up to date? What specialties (i.e. rheumatology, neurology) have evaluated the patient and what were their findings? CIRS can be mistaken for, confused with or found in combination with other conditions. From this information the initial differential diagnosis list is constructed.(1,2,4)

III. A thorough history is obtained including any known tick born illness, history of tick bites and/or high risk activities (i.e. hunting, hiking, camping, landscaping, gardening, etc.) or spending time in an endemic area (i.e. Cape Cod &/or the off shore regional islands). Additionally, any history of exposure to water damaged buildings, toxin carrying fish and/or potentially toxic biologics is noted. Current review of systems and a physical exam are completed.

At the time of initial patient evaluation the CIRS event may have been triggered months, years or in some cases decades before. A central tenant to a CIRS diagnosis is that once triggered the condition will not resolve without toxin binding and removal. Therefore, a thorough and detailed history must be obtained regarding when exposure to a toxic trigger was likely to have occurred. Was an old school, workplace or residence known or suspected to

be water-damaged? Is there recollection of an acute febrile illness preceding the decline in health? This information becomes most important when current exposures are ruled out. In mold exposure, simply a recollection of a musty smell in a dwelling is enough to indicate that there was microbial growth (U.S. Government Accountability Office (GAO) Report, 2008; World Health Organization Report (WHO), 2009; Policyholders of America Report on Diagnosis and Treatment of CIRS Caused by Exposure to the Interior Environment of Water-Damaged Buildings, 2010).

There are no universal physical exam findings but many signs supportive of a CIRS diagnosis. Fatigue and/or poor endurance can be evidenced by noticeable exhaustion in the patient who has simply walked from the waiting room to the exam room. Neurologic impairment on exam can be evidenced by muscle weakness, tremor, abnormal gait, coordination or balance, flat/depressed or anxious affect, memory impairment, poor word retrieval, photosensitivity, hyperacusia and allodynia. Orthostatic hypotension can be present. Other signs of mild dehydration may be seen including resting tachycardia, dry skin and mucous membranes. Nonspecific skin rashes and lesions are not uncommon. It is important to document all initial findings in order to re-evaluate them at subsequent visits. More focused evaluation should be given to physical signs and observations that do not change with treatment of CIRS as another condition may have gone unrealized. (1,2,3,4,6)

IV. A differential diagnosis list is constructed which includes Chronic Inflammatory Response Syndrome (CIRS).

After review of past medical records, patient interview with review of systems and physical examination, it should be clear to the examiner what laboratory; imaging and consultative services are needed to fully evaluate the differential list. Dr. Shoemaker's experience with thousands of patients documented the increased prevalence of certain autoimmune illnesses in CIRS, therefore the presence or absence of Antigliadin and Anticardiolipin antibodies should be documented. (2,6)

V. Testing (i.e. lab studies, imaging) is ordered to rule in or out items on the differential diagnosis list. Testing should include HLA DRB 1,3,4,5 and DQ1 to determine genetic susceptibility to poor toxin clearance. Additionally a baseline Visual Contrast Sensitivity (VCS) is taken and repeated at every step of the treatment protocol if CIRS is ultimately the diagnosis. (6,8)

Based on findings in Steps II, III, and IV, specialty consultations, laboratory and imaging studies are ordered. HLADR studies and Visual Contrast Sensitivity testing must be done before a diagnosis of CIRS, as defined by Dr. Shoemaker, can be made.(2,6,8)

With few exceptions, genetic susceptibility to poor toxin clearance as evidenced by certain HLA DR haplotypes must be present for a CIRS diagnosis. Research associating HLA status and

illness is plentiful. The discovery by Dr. Shoemaker of those genetic markers for biotoxin illness brought to light the enormous potential burden of CIRS as the identified haplotypes can potentially cause illness in approximately twenty-four percent of the population. Repeated demonstration in peer reviewed literature of the presence of these genetics showing increased relative risk in cases versus controls solidifies the association. With genetic susceptibility comes defective antigen presentation resulting in the absence of antibody production and chronic activation of the innate immune system (CIRS) when a toxic trigger is encountered. Subsequent to peer review in 2003, Dr. Shoemaker and colleagues presented the HLA data which was later confirmed by independent researchers in 2006. (1,2,6,7)

In 1998, Dr. Shoemaker and Dr. Kenneth Hudnell first linked deficits in visual contrast sensitivity to Pfiesteria toxin exposure. Subsequent research found these deficits to correlate with the presence of the other biologic toxins and correction of VCS with the standard CIRS treatment. The Visual Contrast Sensitivity Test (VCS), a scientifically sound evaluative tool for neurotoxicity, was found to be highly sensitive in identifying the impact of biotoxins known to trigger CIRS in adults. Establishing a baseline score and serial testing is required in the management of a patient with biotoxin illness. Deficit scores found after prior correction is evidence of re-exposure to a toxin. (2,5,8)

VI. CIRS becomes the diagnosis when all other items are eliminated from the differential list although the differential list is re-examined at every step in the treatment protocol. Now the specific source of toxin(s) must be determined (i.e. mold and other toxins from a water damaged building, Lyme disease, spider bite, fish consumption). This can be a complex process as not everyone with Lyme disease knows they were bit by a tick and immune suppression may complicate antibody response on testing. Additional studies (i.e. C6 peptide, C3a & C4a, and MRI with NeuroQuant) can help identify Lyme disease that was never treated or undertreated. Previous history should have identified intake of reef dwelling fish and spider bites are rarely missed by the person bit. Fungal DNA in the home can easily be tested by securing an Environmental Relative Moldiness Index (ERMI) using collected dust sample(s) and interpreted based on the criteria developed for safe environments for persons with CIRS. However, determining mold in a school or workplace can be quite challenging. Attempts must be made to ERMI test these environments if no other source can be found and VCS results &/or biomarkers support the CIRS diagnosis. In these cases the student must temporarily be tutored at home or participate in on-line education through their school system and adults must attempt to change their workplace. If subsequent treatment is effective then these environments will cause relapse. Unfortunately, many never successfully get through this first step.

Identifying Lyme disease in persons presenting with multisystem-multisymptom syndromes is very challenging as confidence is lacking in available testing methods. However, there are a few tests not included in current diagnostic guidelines that can be helpful.

<u>C6 Peptide Enzyme Linked Immunosorbent Assay (ELISA)</u> has demonstrated improved specificity rates of 90-100% over the traditional Lyme ELISA test. Additionally, it will pick up infections by all Geno species of Borrelia Burgdorferi (including European strains) and can detect infection in persons vaccinated with Osp A Lyme vaccine. (9)

<u>Complement split product C3a and C4a</u> were found by Dr. Shoemaker and colleagues to be early markers of acute Lyme disease. (2,10)

<u>MRI (non-contrast) with Neuro Quant</u> is now used to identify distinctive and specific brain changes in treated and untreated Lyme disease and mold toxin illness. This "brain ruler" is reproducible and reliable. (11)

Despite the widespread use of air testing in the mold evaluation industry, science supports <u>Mold Specific Quantitative Polymerase Chain Reaction (MSAQPCR)</u> testing using the <u>Environmental Relative Moldiness Index (ERMI)</u>. This EPA approved test was developed by Dr. Stephen Vesper and colleagues at the Microbial Exposure Laboratories of the EPA (Cincinnati). It is a DNA based method of mold identification and quantification. Thirty-six species of mold were divided into 2 groups. Group 1 includes 26 species/clusters of molds associated with water-damaged buildings and Group 2 includes 10 common species/clusters not known to be identified with water-damaged buildings. The difference between Group1 and Group 2 is the ERMI score. For treated patients attempting to return to a remediated dwelling an abbreviated ERMI test (HERTSMI2) is utilized to determine safety for occupancy. The HERTSMI2 includes 5 species that represent molds that exist in varied degrees of water saturation. (2,12,13)

VII. If the presence of unacceptable levels of fungal DNA (ERMI score >2 or HERTSMI2 >10) are detected in the home the treatment plan options include: proper remediation of the home or alternative housing in a structure with an acceptable level of mold. When the *melanocyte stimulating hormone (MSH)* is <35 and the *C4a* is greater than 20,000 the acceptable ERMI level is reduced to <-1. If there is a delay in securing mold acceptable housing, adding dehumidification to a level of <45 % and high-efficiency particulate air (HEPA) filters in bedrooms & common living space that eliminate particles down to at least 0.3 microns may provide some assistance in the short term. Higher cost filters that not only remove particles down to 0.01 micron but also chemicals and volatile organic compounds effectively would be the ideal especially for those persons with multiple chemical sensitivities. The use of a fan to increase air circulation in a room with a filter can improve effectiveness of particulate removal. Using a HEPA vacuum will likely have some qualitative advantage over those without this feature. (2,16)

A 2011 review of the literature on the effectiveness of air filters in allergic respiratory diseases (Sublett) documented some benefit to HEPA filters in homes without heating,

ventilation, air conditioning (HVAC) systems. Factors found to qualitatively improve air cleaning with HEPA filters were: increasing room airflow exchange, regular maintenance of the filter, placement in the bedroom, and several units placed throughout the dwelling. (14)

Two Canadian studies in 2009 evaluated the effectiveness of HEPA vacuums. The first study focused on inhaled dust mite allergens, bacterial endotoxins and fungal glucans. The second one evaluated the change in air levels of mold spores in homes known to have mold. Both studies concluded that a vacuuming protocol that involves longer and more frequent vacuuming events removed significant amounts of CIRS triggers. Understanding that reducing environmental load will not impact recovery, it may still be helpful a moderating symptoms in some patients. (15)

VIII. The ill person along with family members and/or significant others returns for an in-depth discussion of CIRS. Diagnosis, environmental interventions required for recovery if necessary, treatment, and potential for cure versus recurrence are discussed at length. Antibiotics are given for Lyme infections and a recommendation to avoid reef dwelling fish consumption is given for persons with ciguatera. Eliminating exposure to water damaged buildings is required for CIRS induced by the microbial contents of these structures. Creative problem solving is undertaken to effectively approach environmental challenges at home, work, and/or school when appropriate. Referrals to CIRS literate inspectors are given for mold identification as are the names of competent remediators. ERMI or HERTSMI2 testing are the only acceptable methods of documenting a CIRS safe dwelling. All present are reminded that once the person with CIRS-WDB is secure in a mold free environment (i.e. home, work, school) any additional exposure during treatment will likely cause a back stepping in the treatment protocol and delay in their recovery. The need to avoid re-exposure during treatment must be emphasized. (2,16)

CIRS patients can be advised that a musty smell is all that is needed to determine that a structure is water damaged. History can be obtained regarding floods, leaking roofs or other water intrusions before moving to a new apartment, school or job. **(16)**

IX. Treatment can be initiated at this point in the process. Cholestyramine (CSM) or Welchol (colesevelam) are prescribed per dosing protocols. If a significant detox reaction is anticipated due to the severity of illness it is recommended to precede this treatment with a five day course of Omega 3 fatty acids (EPA 2.4 grams, DHA 1.8 grams per day) along with a low amylose diet. This regimen is continued after treatment is initiated for five additional days. The common side effects of constipation and gastro esophageal reflux are addressed up front with specific guidelines for interventions should either begin to develop. Once the person receives a passing score on the VCS test they may proceed to the next step unless they have not been able to totally remove themselves from the environment which brought on their illness. Appropriate serum biomarkers should be retested at the end of each treatment step.

There are many detoxification strategies employed by Functional and Environmental Medicine practitioners. However, research has established that for persons with the identified HLA haplotypes associated with CIRS, preventing re-absorption of bile from the small intestine into enterohepatic circulation is the method necessary for treatment of this condition. CSM, a non-absorbable bile acid sequestrant, is a highly positively charged anion exchange resin that binds to negatively charged anions such as bile salts. This binding activity replaces toxin removal by antibodies found in the genetically uncompromised individual. (1,2,5,6,8)

A double-blinded, placebo controlled study (Shoemaker & House,2006) documenting the efficacy of CSM in improving symptom & VCS scores and correcting leptin and MSH levels in CIRS patients was completed. A subsequent re-exposure to a mold toxic building after recovery trial documented relapse (increased symptoms & drop in VCS score) after three days of re-exposure. (17,18)

X. Eliminating biofilms containing multiple antibiotic resistant coagulase negative staphylococci (MARCoNS) is the next step in the process. The presence of MARCoNS in the nasopharynx impairs the body's ability to re-establish normal levels of Melanocyte Stimulating Hormone (MSH). Adequate MSH is required for recovery from biotoxin induced CIRS. Following the instructions from Diagnostic Laboratory Medicine (http://www.dimlabs.com) a deep nasal culture is obtained from adults and children age 14 and older. If coagulase negative staphylococci are present and resistance to more than one class of antibiotics is documented then treatment is required. A compounded nasal spray containing bactroban (Mupirocin), ethylenediaminetetraacetic acid (EDTA), and gentamicin (BEG spray) is prescribed for one month. Dosing for adults is 2 sprays each nostril three times a day and for children (14 and older) 1 spray twice a day alternating nostrils. High quality product is assured if purchased from Hopkinton Drug (Hopkinton, Massachusetts), the original developer of the prescription. Reculturing nasal passages is advisable if the baseline culture showed a large or moderate amount of bacteria.

An Australian research team led by Dr. Timothy Roberts first identified the pathological role that colonized coagulase negative staphylococcus (CNS) played in Chronic Fatigue Syndrome. What were thought to be simple planktonic forms of bacteria, highly susceptible to antimicrobials were subsequently found to be well defended organisms in biofilm. In CIRS patients, researchers found them to be in biofilm located in the nasopharynx. These opportunistic pathogens were also often found to be multiple antibiotic resistant (MARCoNS). As MARCoNS exist as a result of a drop in MSH, once MSH production levels normalize with successful CIRS treatment these opportunistic organisms should not return unless relapse occurs. (2,19)

XI. Testing for CIRS induced antigliadin antibodies (AGA) is necessary as some persons with biotoxin induced CIRS will temporarily acquire this autoimmune issue. The person who is

positive for AGA but negative for tissue transglutaminase antibodies (TTG) should simply remove gluten from their diet for a minimum of 3 months with an option to continue if they physically feel better with its elimination. Should the person have both types of antibodies they will need to stay off gluten permanently due to Celiac Disease. (2,6)

In research spanning two decades Dr. Shoemaker documented anti-gliadin antibodies (AGA) in 58% of children and a significant number of adults with CIRS-WDB. Risk was observed to increase with 17-2-52A and 7-2-53 haplotypes. As intestinal hyperpermeability increases in the presence of low MSH, indigestible fragments of gluten (gliadins) often create gluten reactivity in the following ways: 1.) non-celiac gluten sensitivity and/or inability to adequately digest gluten and 2.) worsening Celiac Disease evidenced by increase in both AGA and tissue transglutaminase antibodies (TTG). (2,6)

XII. Secondary androgen (testosterone, DHEA) deficiency is a common issue with CIRS due to upregulation of aromatase in these persons. Normalization of MSH production with successful treatment will ultimately correct this problem if no other cause is contributing to the reduction. If the DHEA (dihydroepiandrosterone) level is subnormal or low in the range then an appropriate short term strategy in adults is to recommend supplementation with DHEA.

Treatment with testosterone directly is ill advised due to the predictable conversion of testosterone to estrone and estradiol that occurs when aromatase is upregulated in CIRS. (2)

XIII. Commonly, CIRS causes a dysregulation in production of *antidiuretic hormone (ADH)* and a disproportionate serum osmolality. Symptoms often associated with this hormone disruption are those of mild dehydration: increased thirst, frequent urination, dizziness with position change, headache and increased incidence of static shocks. If ADH (also known as arginine vasopressin-AVP) levels are low then short term augmentation with prescription DDAVP (desmopressin) is the next step. For adults, desmopressin .2mg tablet every other night is prescribed. In children, DDAVP nasal spray is used with dose being weight and age dependent. Serum electrolytes and osmolality are checked after five doses. Appropriate ongoing clinical surveillance includes daily weights and weekly measurement of serum electrolytes and osmolality to identify possible hyponatremia. (2)

ADH/AVP deficiency is but another downstream effect of reduced MSH production. The synergistic relationship of ADH/AVP, Vasoactive Intestinal Polypeptide (VIP), and MSH in the suprachiasmatic nucleus of the hypothalamus is critical to optimal global neuro-hormonal regulation. (20)

XIV. *Matrix metalloproteinase 9 (MMP-9)* is an important enzyme providing both vital assistance to normal physiologic processes and pathological tissue destruction when it is produced inappropriately. Often elevated in CIRS, MMP-9 is responsible for a good deal of the disabling pain that results from this condition. Treatment of elevated MMP-9 involves high level

Omega 3 fatty acid supplementation with EPA 2.4 grams and DHA 1.8 grams daily along with a low amylose diet. (2,6)

As a marker for innate immune system activation, MMP-9 is associated with some of the most significant negative sequelae associated with CIRS. Its ability to tunnel through endothelial and matrix tissue results in weakening of the blood brain barrier (BBB). Compromising the integrity of the BBB results in the disabling neurologic symptoms (pain, cognitive dysfunction) found in some of the sickest CIRS patients. (6,21)

XV. Correcting an existing deficiency of *vascular endothelial growth factor (VEGF)* will improve capillary blood flow. Subsequently, improved tissue oxygenation can reduce pain and cognitive impairment. Treatment is the same high dose Omega 3 supplementation as in step XIV. (2)

VEGF plays a critical role in angiogenesis (creation of small vessels) and dilation of capillaries. Although inhibition of this process is thought to be important in cancer treatment, for the person with CIRS, deficiency of VEGF is responsible for a significant amount of disability. The persistent capillary hypoperfusion resulting causes diffuse cellular hypoxia. Symptoms associated with this deficiency state include: cognitive impairment, muscle pain and spasm, fatigue, shortness of breath with exertion and post-exertion exhaustion. (2,6,22)

XVI. Complement system proteins are integral to proper immune function however excess production can be deleterious to the host. *C3a*, a split product of complement activation, is elevated as a result of the presence of bacterial membranes as in Lyme disease. If Lyme disease has been treated adequately then treatment involves a high dose (80 mg) statin together with Coenzyme Q10 150mg daily. (2)

Since its role in the control of infection was identified a century ago, research of the past few decades has more clearly defined the intricate workings of the "complement" system. C3 is the most abundant of the 30 proteins in this system. Its split product, C3a, works in conjunction with antibodies to fight bacterial infections through phagocytosis and the inflammatory cascade. Despite this life saving role, unregulated production of C3a in response to undetected atypical bacterial infections can cause significant harm to the host by damaging blood vessels, kidney basement membrane, joint synovia and red blood cells. Research in 1989 (Glovsky et al) and 2008 (Shoemaker et al) documented elevated C3a levels in acute Lyme disease. A consistent elevation of C3a in persistent Lyme infections is yet to be definitively documented. Testing serial C3a levels in CIRS patients is advised as capturing elevated levels intermittently has been observed by clinicians who treat CIRS patients. (10,6,23)

XVII. *C4a* is the split product of complement activation associated with the highest level of inflammation from CIRS-WDB. Currently, specimens for testing should be sent exclusively to the National Jewish Hospital Lab in Denver. Any remaining elevation in C4a at this point in the

process will ultimately be addressed by treatment with VIP nasal spray once all steps have been completed. (2)

Like C3a, C4a is a split product of an activated innate immune system. Through its cytokine role with basophils and mast cells dysregulation is often evidenced by symptoms of histamine excess. Overproduction results in capillary hypoperfusion and unregulated inflammation causing diminished energy, lung function and cognition in the CIRS patient. Shoemaker and colleagues also found that the elevated C4a levels in CIRS patients often triggered acquired von Willebrands Syndrome by interfering with the polymerization process (the linking of vW antigens or monomers to form multimers). Ineffective clot formation then results in increased risk of bleeding especially from nasal mucosa. A vonWillebrands Panel should be included in the evaluation of all persons with CIRS. (2,6,10,23)

XVIII. *Transforming growth factor beta-1 (TGFB-1)* is another protein that supports many normal physiologic processes when it is produced appropriately in normal amounts. However, in excess it becomes destructive and disruptive. When TGFB-1 levels are still elevated at this step, treatment with losartan is given to help reduce the level. Dosing in adults is started at 25 mg daily until stability of blood pressure can be assured, then increased to 25mg BID for 30 days. Dosing for children is 0.6 – 0.7 mg/kg/day in divided doses 2 times/day. Special consideration must be given for persons already on antihypertensives and blood pressure monitoring should be part of this intervention. (2)

As with all markers of an activated immune system already discussed, TGFB-1 has both therapeutic and pathological potential. Research on both functions is extensive. Elevations have been documented in multiple cancers, fibrosis, inflammatory skin disorders, amyotrophic lateral sclerosis (ALS), and Alzheimer disease. Dr. Hal Dietz, a Johns Hopkins researcher, was the first to identify losartan as an agent effective at reducing the TGF beta1 elevations he found in patients with Marfans disease. Losartan, the first antihypertensive agent in the angiotensin II receptor blocker class, has a specific active ingredient thought to be responsible for this action. (25)

In 2008, Dr. Shoemaker worked with Cambridge Biomedical Laboratory to validate a test for TGF beta1. Once widely available the test has been instrumental in explaining many of the disabling symptoms associated with CIRS. Dr. Shoemaker and colleagues continued to study TGF beta1's influence on T-regulatory cells in biotoxin patients and were able to document various associated pathological immune responses. This work resulted in the development of a CIRS specific T-Regulatory Cell Panel (CD4+CD25++CD127 lo/-) used in the ongoing patient evaluation and an appreciation for the frequency at which autoimmune disease is triggered in biotoxin patients. (2,6,20)

XIX. *Vasoactive intestinal polypeptide (VIP)* is an important regulatory neuropeptide. At this step, persistently symptomatic persons; not residing, working or in school in an untreated water damage building (as demonstrated by a HERTSMI2 score </= 10 or ERMI score <2), not failing the VCS test, and already demonstrating negative MARCoNS should be offered VIP nasal spray compounded only by Hopkinton Pharmacy in Hopkinton, Massachusetts. Dosing for adults is 50 mcg (1 spray) intranasally QID. Dosing for children should be determined after consultation with Dr. Shoemaker. The first dose of VIP should be given in the office after a TGFB-1 is drawn. Fifteen minutes after this dose a TGFb-1 is drawn again. If the level is, found to rise then it is clear that there is an unidentified mold exposure which will require investigation before VIP spray can be continued. When prescribing VIP, if serum lipase levels rise, discontinuation should occur. Additionally, any new symptoms should trigger consideration of intolerance to VIP. (2) Finally all labs should be repeated to document resolution of CIRS.

The science supporting the role of VIP deficiency in CIRS is well established. Critical work by researchers Ganea and Delgado documented the important neuro-regulatory role played by VIP in vivo. In 2006, Shoemaker and colleagues documented the synergy between VIP, MSH, and ADH ("the hypothalamic regulatory triangle") in CIRS patients. The action of correcting one will indirectly assist in correcting the other two. (2,20,24)

The primary treatment goal for CIRS is restoration of neuro-hormonal regulation of the innate immune system. For some persons recovering, this goal will be met without the need for VIP supplementation. However, for those still affected at this step, the multi-symptom, multi-system syndrome associated with CIRS can finally be resolved with VIP nasal spray. Shoemaker and colleagues were able to demonstrate both efficacy and safety in an open label trial of 600 persistently symptomatic CIRS patients. (20)

XX. Finally, moving forward with sustained recovery will require ongoing avoidance of water damaged buildings. For some even brief re-exposures can acutely reactivate disabling illness evidenced by the "sicker quicker" phenomenon. Persons with history of CIRS-WDB must always be hyper vigilant regarding any symptoms that arise in a new structure. If they experience any GI or neurologic symptoms it should be a sign that the dwelling is not safe for them. (2)

Research by Shoemaker and colleagues documented through Sequential Activation of Innate Immune Elements (SAIIE) Trials that most successfully treated CIRS patients will be at risk for relapse if spending time in a structure with an ERMI score >2. For an unfortunate 2% of these persons this reactivation of the innate immune system can occur within 60 minutes after as little as five minutes of exposure. The "sicker, quicker" phenomenon is caused by auto activation of MASP2 (the enzyme that splits the C4 complement to C4a). (17,18,26)

XXI. In conclusion, prolific research documents the hazards to human health from multiple genera of organisms, inflammagens and toxins in water damaged buildings. The expansive work

of Shoemaker and colleagues to synthesize and expand this information has brought an end to suffering for thousands of affected persons and opened the gate of inquiry into many other chronic conditions and their possible association with a treatable chronic inflammatory state.

Shoemaker and Ryan's current work into the genomics of CIRS, preserving mRNA in patient's blood collected in PAX gene tubes for analysis, is the next great frontier in biotoxin illness research. It is the collective hope of those involved with this journey that the larger medical community will take the time to review this work and acknowledge its tremendous potential to improve the health status of millions on our planet.

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