Chronic Inflammatory Response Syndrome Acquired After Exposure to Water-Damaged Buildings (CIRS-WDB)

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The current body of literature describing the multiple adverse health effects acquired following exposure to the interior environments of water-damaged buildings (WDB) is extensive. This body of literature is authored by both health care professionals actively involved in the patient care of those made ill by exposure to WDB and by other scientists who study environmental illness.

Exposure to indoor environments of WDB can cause a readily-identifiable illness characterized by specific metabolic disturbances that go beyond allergenic response. Contaminants and their metabolites found in the indoor environment of WDB include but are not limited to fungi, bacteria, actinomycetes, and mycobacteria and the toxic chemicals they produce; inflammagens from fungal fragments; beta glucans, mannans, hemolysins, spriocyclic drimanes, and microbial volatile organic compounds. These substances cause illness due to a lack of control of host inflammatory responses, genetic susceptibility, and abnormal inflammatory events resulting from exposure. The abnormalities, documented through labs and other means of objective testing, are both **biomarkers for the presence of illness and guides for therapy.** The illness acquired after exposure to WDB is referred to as "Chronic Inflammatory Response Syndrome acquired following exposure to the interior environment of Water-Damaged Buildings", or CIRS-WDB.

Thorough differential diagnosis is the key to linking the abnormal physiology seen to the cause of the illness.

Known Health Effects and Diagnosis

As identified by the US Government Accountability Office report (GAO, 2008) and the World Health Organization report (WHO, 2009), there are many compounds, toxigens and inflammagens present in the indoor air of a WDB that have been identified. These have been shown to be synergistic in producing an inflammatory stimulus. There is clear data showing the initiation of such a host response from these substances.

Furthermore, these data have been presented in multiple academic presentations and papers to show the illness is indeed treatable as shown by reduction of symptoms and improvement in signs of the illness.

These publications include the understanding that:

1. CIRS-WDB is a **multisystem, multisymptom illness syndrome** that is acquired after exposure to the indoor environment of WDB. A proven and consistent pattern of symptoms is demonstrated among published research findings in both human and animal studies.

2. CIRS-WDB is identified as **immunologic with inflammatory responses** seen

according to a) genetic susceptibility, and b) unique aspects of innate immune responses.

3. When defined by a) exposure, b) symptom evaluation, and c) epidemiologic similarities between studies of similar hosts and similar exposures, **CIRS-WDB is both identifiable and treatable.**

4. The process of diagnosis is supported by a) **symptom clusters** found in epidemiologic cohorts of affected patients, b) identification of **unique groupings of biomarkers**, such as genetic markers, neuropeptides, inflammatory markers, and autoimmune findings. CIRS-WDB consistently shows abnormalities in levels of regulatory neuropeptides melanocyte stimulating hormone (MSH) and vasoactive intestinal polypeptide (VIP); pro-inflammatory cytokines IL-1B, IL-6, 8, 12, 13 and others and matrix metalloproteinase 9 (MMP-9); split products of complement activation, especially C4a; responses of hypoxia-inducible factor, including but not limited to vascular endothelial growth factor (VEGF), erythropoetin, and transforming growth factor beta-1 (TGF beta-1); cellular immunity including T-regulatory cells, Th-17 immunity impacting IL-17 and -23 functions; and autoimmunity, primarily anti-gliadin and anti-cardiolipin antibodies. Additional problems commonly seen are hormonal dysregulation involving corticosteroids (via simultaneous serum adrenocorticotropic hormone [ACTH] and cortisol testing), regulation of body osmolality (identified when antidiuretic hormone [ADH] and osmolality are measured simultaneously), androgen disruption, and coagulation factors (seen on von Willebrand's profile).

5. Many tests commonly utilized in daily medical practice such as sedimentation rate, thyroid studies, c-reactive protein, lipid profiles, complete blood counts, and metabolic profiles are nearly always normal in CIRS-WDB and provide **pertinent negative findings** that rule out other potential causes of chronic symptoms and provide a differential diagnosis.

6. Patients with CIRS-WDB are often **incorrectly diagnosed** with depression, stress, allergy, fibromyalgia, and somatization but if those conditions are actually present they will not improve with therapies employed in CIRS-WDB. The symptom resolution and improvement of objective laboratory values following appropriate treatments aimed at CIRS-WDB not only prove this, but also show an additional clinical basis to distinguish CIRS-WDB from other diagnoses.

7. **Re-exposure trials** have been performed post-treatment in numerous instances and have demonstrated that patients again mount immunologic responses that cause a recurrence of symptoms and abnormal lab findings. Re-treatment with appropriate therapies used in CIRS-WDB returns both subjective and objective findings to baseline.

8. **Sequential treatment** of CIRS-WDB is necessary. No single intervention is likely to correct all the underlying abnormalities in the inflammatory and immunological

responses. These treatments and their outcomes have been well-documented.

To establish the presence of CIRS-WDB, there must have been **exposure** to the interior environment of a WDB. Microbial growth (bacteria, fungi, actinomycetes) begins approximately 48 hours after water intrusion and may include *Stachybotrys, Chaetomium*, *Aspergillus* and *Penicillium* species. In the absence of sophisticated PCR testing or ERMI (Environmental Relative Mold Index, using DNA amplification of mold species) testing confirmation of water damage can be documented by visible mold and/or musty smells. However, understanding that the sensitivity to smells varies from person to person, the absence of musty smells according to an individual is not adequate to rule out microbial growth.

Once there is evidence that a building is water-damaged, then there must be **epidemiologic similarity** of the findings from a given patient to those findings identified in published cohorts of CIRS-WDB patients. These include both symptom clusters and laboratory data. The illness is multisystem and multisymptom. The diagnosis of CIRS-WDB can be excluded if symptoms in at least 3 of 6 body systems is not found. Similarly, absence of laboratory abnormalities consistent with CIRS-WDB demonstrating that there is no reduction of regulatory neuropeptides or associated dysregulation of hormone physiology rules out the diagnosis. Proper testing must be done. Absence of testing does not mean that the test results are absent.

Support for diagnosis includes deficits found in visual contrast sensitivity (VCS), a neurotoxicologic test that is well-represented in published literature and is used by Federal agencies including EPA, NIOSH and the CDC. Finding the presence of particular HLA DR haplotypes adds weight to the differential diagnosis process but absence of such HLA DR does not rule out the diagnosis. Magnetic resonance spectroscopy (MRS) shows elevated lactate and low ratio of glutamate to glutamine in the brain and provides metabolic evidence of neural dysfunction following hypoperfusion that is correlated with cognitive dysfunction. Pulmonary artery pressure, measured using tricuspid regurgitation after exercise during stress echocardiography, is often abnormally high and is manifested by the decreased stamina and exercise intolerance of these individuals.

No single test can diagnose CIRS-WDB illness. **It is the constellation of laboratory findings that document the CIRS-WDB.**

Consensus Reports

Research studies done on humans have shown a **consistent pattern of symptoms** identified following exposure to the interior environment of WDB. Over 40 studies, including over 50,000 patients from 14 countries, show that the illness is recognized world-wide. Those who would disagree with the concept that exposure to WDB can cause illness are unable to provide evidence of even a single human research study that includes physiologic testing showing that no illness exists following exposure to WDB. The absence of any studies refuting the presence of illness (combined with the multiple studies demonstrating the presence of illness) show that **the arguments against human illness from WDB are**

unsubstantiated.

Moreover, **re-exposure trials** have been performed and document predictable illness from CIRS-WDB: Prospective studies have looked at patients with illness treated successfully with standard CIRS-WDB treatments who then were exposed to all other known environments in their day-to-day life other than the WDB with no evidence of change in symptoms, VCS or laboratory findings; then when evaluated each day for three consecutive days without use of protective medications following exposure to a known WDB show a sequential relapse in inflammatory markers, with C4a, a split product of complement activation, rising on day 1; leptin rising on day 2; MMP-9 rising between day 2 to day 3; VEGF rising on day 1 and falling by day 3; TGF beta-1 rising on day 1, though somewhat later than C4a; Factor VIII falling on day 1, but recovering by day 3; von Willebrand's factor and antigen falling by day 3, with bleeding (epistaxis or hemoptysis), if it occurs, seen as ristocetin-associated cofactor falls and von Willebrand's multimers decrease. TGF beta-1 rises rapidly with re-exposure and may remain elevated for weeks. Reacquisition of illness is shown by symptoms, VCS and laboratory findings to equal in three days what may have taken months or years to develop. Re-initiation of appropriate treatment returns patients to baseline. Furthermore, no changes in any lab parameters performed daily have been shown to occur in patients with prior mold illness who are not exposed to WDB.

Consensus statements regarding the human health effects of indoor environments associated with water damage must be evaluated for their thoroughness of inclusion, rigor of assessment of the science, scientific accuracy of statements made, inclusion of pertinent and current scientific literature in this rapidly moving field and absence of concealed conflict of interest. If a consensus panel does not meet each of these five criteria, then the opinion of the consensus must be devalued to the point of elimination.

Both the GAO and the WHO (see references) meet all five criteria as does the consensus statement by Shoemaker, Mark, and McMahon. **All three of these panels agree that humans can become ill from exposure to the toxic elements in a WDB**. Consensus statements not meeting the above criteria include the ACOEM statement of 2002; the AAAAI paper written by Bush et al in 2006; and the ACMT statement of 2007. As one might suspect, these three opinions are written by persons who are highly paid witnesses for defense in mold litigation. This failure to disclose conflicts of interests was decried in a Wall Street Journal expose written by David Armstrong January 9th, 2007. As one might expect, the three "defense-authored" consensus statements cite no human research and present no animal research to support their opinions.

There are hundreds of academic citations and the overwhelming unity of agency and impartial opinion to support the concepts (1) that WDB host inflammagens and toxigens that are **inhaled as the initiating event** in the acquisition of illness; (2) that human illness seen following inhalant exposure has **epidemiologic consistency** among multiple studies published in multiple diverse locations throughout the world; (3) that the inflammatory responses seen following inhalant exposure in affected patients are epidemiologically consistent and are **consistent with experimental data** seen in vitro, in both humans

and animals; (4) that **treatment of CIRS-WDB is shown to be effective** in peer-reviewed publications, including **double-blind, placebo-controlled clinical trials**, and is further supported by the **clinical experience of treating physicians**, (5) that **re-exposure of previously treated patients re-creates the illness** within three days with not only an increase in the magnitude of inflammatory host responses but also the speed at which those enhanced inflammatory host responses occurs and; (6) **prevention of illness** by use of replacement doses of VIP restores control of multiple physiologic abnormalities seen routinely in CIRS-WDB cases.

Treatment

There have been repeated observations showing that inflammatory changes acquired following exposure to WDB **will not resolve with simple removal from exposure**, remediation of the affected structure, or prevention of future exposures in those with genetic susceptibility to the inflammatory illness. The inflammatory injury caused by the WDB persists even though the inflammagens are removed.

The lessons learned from treating physicians are that CIRS-WDB must have specific **targeted therapies** to return ill patients to health. Shoemaker's data on over 6000 treated patients (with more than 2000 cases and 450 controls published) shows that, up until recently, a significant percentage of patients will have persistently lowered levels of the regulatory neuropeptides MSH (less than 35 pg/ml) or VIP (less than 23 pg/ml) despite all therapies. Control of inflammatory responses to the toxic milieu of interior environments of WDB demands adequate neuropeptide regulation of inflammation. Current data on use of replacement VIP, a relatively recent addition to the treatment protocol, has restored health to those for whom other treatments had been ineffective. VIP therapy has also resulted in significant reduction of the "sicker, quicker" phenomenon such that patients no longer have increased susceptibility to relapse with re-exposure.

Successful **correction of the series of abnormalities** of the systemic inflammatory and innate immune responses is mandatory before successful treatment of the illness can be accomplished. Correction of symptoms; neurotoxicologic deficits (i.e. VCS); inflammatory markers (C3a, C4a, MMP9, TGF beta-1); presence of commensal biofilm-forming bacteria (i.e. multiply antibiotic resistant coagulase negative staphylococci, or MARCoNS); and presence of autoimmune findings and VIP deficiency must take place to see resolution of illness. Given that not all patients have all such abnormalities, the patient must be assessed at baseline for these potential problems. Therefore, identification of all known physiological abnormalities provides both confirmation of the chronic inflammatory basis for the illness and also a a guide to therapeutic intervention.

In summary, treatment of this complex syndrome involves the **sequential** (1) removal from exposure; (2) correction of toxin overload, using VCS monitoring to assess endpoints; (3) eradication of biofilm-forming MARCoNS; (4) correction of elevated MMP-9; (5) correction antigliadin antibodies; (6) correction of ADH/osmolality (7) correction of low VEGF; (8) correction of elevated C4a (9) reduction of elevated TGF beta-1 and (10) replacement of low VIP. In the March 2013 publication of Health by Shoemaker, House and Ryan a VIP

replacement trial showed **100% resolution of symptoms and normalization of lab markers for all patients following this protocol.** These results are consistent with the clinical results of physicians across the country treating CIRS-WDB.

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