CONSENSUS STATEMENT
Part 1

Medically sound investigation and remediation of water-damaged buildings in cases of CIRS-WDB

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ABSTRACT

Evidence supports a cause-effect relationship between exposure to the air and dust in water-damaged buildings (WDBs) and a chronic inflammatory response syndrome (CIRS) that is linked to certain HLA haplotypes. CIRS-WDB is mediated by an over-reactive innate immune response to the toxins, antigens, and inflammagens found in the interior environment of WDBs. Dose-response relationships in this condition are neither linear nor threshold in nature; the immune response depends on multiple variables in the human host. For patients with CIRS, current methods of WDB investigation and remediation are often not sufficient to prevent relapse of symptoms with re-exposure. CIRS-WDB is a growing public health hazard best addressed by a team of experts in medicine with specialized training in CIRS-WDB, indoor air quality, remediation, and construction working together to develop a collaborative plan that ensures ongoing safe habitation. Assessments of human health effects before and after remediation are mandatory to ensure adequacy of remediation efforts.

BACKGROUND

Scientific data support a cause-effect relationship between indoor air in water damaged buildings (WDBs) and chronic inflammatory response syndromes (CIRS-WDB) [1-3]. The first step in treatment of patients with CIRS-WDB is removal from exposure to the interior environment of WDB. Such removal may include either physical removal of patients; or removal of toxins, antigens and inflammagens found inside the affected building. Current standards regarding the investigation and remediation of WDBs fail to take satisfactory account of the health needs of occupants affected by CIRS-WDB. Long held practices, such as use of air sampling to determine safety of occupancy, are well documented to have no significant role in day-to-day management of CIRS-WDB patients and to have no role in assessment of remediation [2]. Given individual genetic susceptibility and adverse effects of prior innate immune disorders initiated by prior CIRS-WDB, including markedly abnormal differential gene activation seen in cases of CIRS-WDB compared to controls, reliance on older approaches alone no longer are medically tenable to guide remediation efforts. Proper evaluation of CIRS-WDB

patients demands application of far more stringent criteria to clear a building as safe for re-occupancy.

In *Recognition, Evaluation, and Control of Indoor Mold*, published in 2008 by the American Industrial Hygienists Association (AIHA), J. David Miller described the ongoing challenge for indoor air experts in their efforts to promote human health [4]:

> "The challenge is to apply existing techniques and knowledge in a prudent and reasonable manner to manage and prevent disease. Unfortunately, instrument readings alone may never be able to locate hidden damage and help define safe levels of exposure. Although this is not a comfortable situation, it is nothing new for industrial hygienists to be called on to make decisions without having all the desired information. As more is learned about mold damage in the built environment, some recommendations made today inevitably will be superseded."

Miller's words anticipated the challenge for today's indoor environmental professionals (IEPs). As we will show in our discussion, there is now scientific consensus that the diverse mixtures of toxins, antigens and inflammagens contained within reservoirs found within WDB are capable of triggering systemic inflammation. IEPs will need to reevaluate methods and standards for judging safe levels of exposure to all individual components found within air, dust and other reservoirs within WDB when occupants have, or may be at-risk for development of CIRS-WDB.

Given the variables involved with host susceptibility, currently identified based on the genetics of immune response genes (HLA DR/DQ) and prior CIRS episodes, the toxicological aphorism, the "*dose makes the poison*" alone simply never applies. In CIRS-WDB, environmental exposures trigger biologically complex host responses to toxins antigens, and inflammagens, including but not limited to endotoxins [5]. In a 1972 article in the New England Journal of Medicine, Lewis Thomas, speaking of endotoxins, anticipated the challenge for today's physicians [6]:

> "The reaction of sensing is the clinical disease… we are in danger from so many defense mechanisms that we are in more danger from them than from the invaders… *the response of the host makes the disease (*emphasis added)."

Chronic or repeated exposures to the mixture of toxins, antigens and inflammagens found in these buildings sets off a magnified host response resulting in a multi-symptom, multisystem inflammatory illness that *does not* typically involve allergy or asthma [7]. New methods for investigating and remediating WDBs are warranted following acute and/or chronic water intrusion events when occupants experience the onset of multiple symptoms, including new symptoms, or the exacerbation of pre-existing symptoms.

We are aware of published reports that conclude that the air within damp buildings is incapable of causing an inflammatory syndrome in humans [8-10]. But these reports contain flawed analyses that have been sharply criticized by objective scientists and by the U.S. Government Accountability Office GAO [1,11]. These papers have been withdrawn or amended with disclaimers. One of the reports was the subject of a Wall Street journal exposé on author bias [12]. Conversely, we are aware of a multitude of peer-reviewed articles that support a chronic inflammatory response in the genetically predisposed human host after chronic exposure to the interior of WDBs [13].

OBJECTIVES

We will present a brief review of the evidence concerning the etiology, pathophysiology, diagnosis and treatment of CIRS-WDB, as well as the evidence concerning the toxins, antigens and inflammagens found in WDBs. This evidence grounds our call for a collaborative consensus on medically sound methods of investigation and remediation in cases of CIRS-WDB. By sharing what experts have learned in the field of diagnosis and treatment of patients with CIRS-WDB, we intend to enhance awareness of actions that impact on remediation efforts.

DISCUSSION

The etiology and pathophysiology of CIRS-WDB

Scientific evidence supports an increasingly detailed description of the etiology and pathophysiology of CIRS [14-21]. The CIRS-WDB subset of CIRS variants requires exposure to the admixture of toxins, antigens and inflammagens found in WDBs. The innate immune systems of mammals contain highly conserved genetic sequences that respond rapidly to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) [22].

Evidence indicates that some of the PAMPs found in WDBs can activate pattern recognition receptors in the mannose binding lectin (MBL) pathway, thus activating MBL-associated serine proteases 1 and 2 (MASP-1 and MASP-2) [23]. C-type lectin receptors (CLRs), especially the dectin-1 and dectin-2 clusters of CLR family, recognize fungal-derived beta-glucans as well as molecular patterns associated with gram-positive bacteria, gram-negative bacteria, mycobacteria, viral particles, and parasites [24,25]. Fungal and bacterial fragments make up part of the antigenic component of the "chemical stew" found in WDBs. The MBL pathway also has the potential for marked amplification of the pro-inflammatory product C4a compared to the classical pathway [26]. In the HLA CIRS-susceptible, C4a levels are known to increase as a result of exposure to the air and dust of WDBs [14,20].

Practice data show that CIRS patients aged less than 19 years-old average 19.3 of 37 symptoms; those aged 19 and above average 25 of 37 symptoms; healthy controls averaged 3 of 37 symptoms [19]. For a full listing of symptoms presenting in at least 30% of patients with CIRS of any kind, see Table 1.

Table 1

The 37 most frequent symptoms seen in cases of CIRS-WDB [14,19]		
Fatigue	**Shortness of breath**	**Mood swings**
Weakness	**Abdominal pain**	**Appetite swings**
Aches	**Diarrhea**	**Sweats - especially at night**
Cramps	**Joint pain**	**Poor temperature regulation**
Unusual pain	**Morning stiffness**	**Excessive thirst**
Ice pick pain	**Memory**	**Increased urination**
Headache	**Focus/concentration**	**Static shocks**
Light sensitivity	**Word-finding**	**Numbness**
Red eyes	**Poor learning consolidation**	**Tingling**
Blurred vision	**Confusion**	**Vertigo**
Tearing	**Disorientation**	**Metallic taste**
Sinus	**Skin sensitivity**	**Tremors**
Cough	Each symptom seen in 30% or more of patients with CIRS of any kind.	

Practice data also indicate that the elements that set off C4a elevation are associated with others that, in turn, set off a cascade of innate immune system inflammation mediated by vascular endothelial growth factor (VEGF), transforming growth factor beta-1 (TGF beta-1), and matrix metalloproteinase-9 (MMP9). Should exposure be prolonged, the pro-inflammatory cytokine antagonism of hypothalamic leptin receptors can lead to decreased production of hypothalamic regulatory neuropeptide hormones [27]. These neuropeptides include alpha-MSH [28], antidiuretic hormone (ADH) [29], and vasoactive intestinal polypeptide (VIP) [30].

Inflammatory disruption of hypothalamic pathways can also adversely impact the production of other melanocortins including adrenocorticotrophic hormone, (ACTH) [31]. Shoemaker and Ryan have shown that transcriptomic signatures support the involvement of VIP pathways in patients with CIRS [15].

In addition, volumetric analyses of brain MRIs using an FDA-cleared software program (NeuroQuant®) in patients with CIRS-WDB compared to healthy controls showed atrophy of the caudate nucleus as well as microscopic interstitial edema of forebrain parenchyma, cortical grey and pallidum [32]. Experimental evidence shows that exposures to air and/or dust in WDBs trigger symptoms that correlate with changes in C4a, leptin, VEGF, TGF beta-1, and MMP-9 [12,20].

Serial exposure studies demonstrate commonalities in symptoms and lab parameters seen across groups and across studies, including commonalities in the temporal dynamics of post-exposure lab changes [14,20].

Contaminants Found in WDBs

Defining *sufficiently clean and safe* is the main challenge facing attempts to set standards for medically sound inspection and remediation in cases involving CIRS-WDB. This is because *many* types of contaminants have been found in WDBs. [33-40]. See Table 2.

Table 2

Range of toxins, inflammagens, and microbes found in WDBs		
Mycotoxins[33]	**Gram-negative bacteria**[38,40-42]	**Hemolysins**[13,35]
Bioaerosols[34]	**Gram-positive bacteria**[38,40-42]	**Proteinases**[13,35]
Cell fragments[35]	**Actinomycetes**[43]	**Chitinases**[13]
Cell wall components[35]	**Nocardia**[38]	**Siderophores**[13]
Hyphal fragments[36]	**Mycobacteria**[44]	**Microbial VOCs**[46-49]
Conidia[36]	**Protozoa**[43]	**Building material VOCs**[46]
Beta Glucans[35,37]	**Chlamydia**[45]	**Coarse particulates**[13]
Mannans[13,38]	**Mycoplasma**[45]	**Fine particulates**[13]
Spirocyclic drimanes[35]	**Endotoxins**[37,38]	**Ultrafine particulates**[57,58]
Inorganic xenobiotics[39]	**Lipopolysaccharides**[40]	**Nano-sized particulates**[57,58]

Studies have linked exposure to toxins and inflammagens in WDBs to various forms of inflammation [13,50-53]. The neurotoxic effects of trichothecene mycotoxins are well documented [54-56]. Concern is emerging about the enhanced toxicity of ultrafine and nanoparticles, whose collective surface area creates untold opportunities to bind and disrupt molecular mechanism- [57,58]. Multiple pathogens, antigens, toxic metabolites, inflammagens, and other particulates are present in the air and dust of WDBs. In the indoor environment of a damp building any combination of these contaminants can initiate inflammatory cascades, invalidating the unsupported idea of specific causation, often used as a legal defense in cases involving WDBs and CIRS-WDB. Because any permutation of noxious incitants could be present in a given WDB, legal demands to prove a specific causative factor of CIRS-WDB are fundamentally flawed.

The United States Government Accountability Office report from 2008 states [1]:

> "…specific causation doesn't exist. Even if not measured specifically, the multiple inflammagens and toxigens that can cause illness will be found in damp buildings."

Given that multiple PAMPs will be found in every WDB, we can be certain that when CIRS-susceptible occupants are exposed to these environments, their resultant inflammation and symptoms are the effects of complex causation and not specific causation. We must accept that pathogens, toxic metabolites, and particulates, both known and unknown, are playing causative roles in CIRS-WDB.

The 2008 US GAO report provides us with a working case definition of CIRS-WDB, later amplified in detail by the Expert Mold Treating Physicians' Consensus Report of 2010 [1].

1. There must be the potential for exposure to a building with water damage and subsequent amplified microbial growth. Amplified growth is documented by any of the following: (i) the presence of visible mold; (ii) the detection of musty odors; or (iii) commercial testing which demonstrates amplified mold growth by species known to flourish on damp indoor building materials.
2. There must be multiple symptoms involving multiple systems in a possible case of CIRS-WDB, similar to those seen in patients reported in peer-reviewed, published studies [14,18-20].
3. There must be laboratory abnormalities in a possible case that are similar to those seen in peer-reviewed, published studies [14,18-20].
4. There must be improvement with therapy similar to that reported in peer-reviewed, published studies [14, 18-20].

CIRS-WDB Treatment

A treatment protocol has been shown to produce predictably positive health outcomes [14,18-20]. The most comprehensive reporting of symptoms and laboratory abnormalities in CIRS-WDB included 1,829 cases and 500 healthy controls [19]. Yet the treatment process can be frustrated by uncertainties regarding what constitutes medically acceptable standards for the investigation and remediation of WDBs. Remediation to current industry standards may not be adequate to protect occupants with CIRS-WDB. Failed remediation delays treatment at great cost. There are no industry or governmental standards that take into account the special needs of occupants with CIRS-WDB.

In 1997, Shoemaker found a therapeutic role for cholestyramine (CSM) in biotoxin-mediated illness during a rural Maryland outbreak of *Pfiesteria* toxicity when a patient's headaches, memory impairment and severe diarrhea quickly resolved on CSM [59]. CSM is known to be of benefit in cases of the secretory diarrhea caused by *Clostridium difficile* [60].

A series of studies have shown benefit from CSM in a diverse range of biotoxin illnesses including *ciguatera* [18], *Pfiesteria* [61], and cyanobacterial illness [62, 63]. Multiple studies have shown therapeutic benefits of CSM in cases of CIRS-WDB [12,19], including a double-blinded, placebo-controlled clinical trial [19]. Additionally, multiple other studies have shown benefit from the mycotoxin-binding capacity of CSM [64-70].

CIRS-WDB treatment relies on the use of cationic polymers as anionic binding resins [71]. When taken according to specific directions, these polymers are able to bind and remove via the large bowel anion-ring forming compounds including heterocyclic

rings, polycyclic ethers, carboxylic acid ethers, ionophores, ampipathic toxins and inflammagens [14,19,20].

CSM and colesevelam are non-absorbable, FDA-approved cationic polymers for use as cholesterol absorption inhibitors and bile acid sequestrants. Both contain multiple quaternary ammonium groups whose positive charges attract and bind to anionic toxins and inflammagens. The mechanism of action of these bile acid sequestrants is the interruption of enterohepatic recirculation of ionophore and ampipathic compounds.

CSM has been used safely since the FDA approved it in 1973 for human use to reduce cholesterol. It not only reduces total cholesterol and LDL cholesterol but also reduces sudden death and cardiovascular death [72]. With the advent of use of statin drugs, use of CSM for cholesterol reduction has fallen.

While both CSM and colesevelam medications are considered to have excellent systemic safety profiles, correct timing of doses is needed to avoid decreasing the absorption of other medications and certain vitamins [73]. Side effects include constipation and gastroesophageal reflux.

Once treatment succeeds at binding, thereby allowing removal of toxins, antigens, and inflammagens from the body of a CIRS-WDB patient, the patient is at risk to become "sicker-quicker" from future exposures, such that even brief exposures may activate an amplified innate immune response that results in systemic symptoms—a sure sign that the response of the host, and not the dose, is what drives CIRS-WDB.

This commonly observed experience is managed with early removal from exposure and an additional short course of an anion binding resin as needed. The sicker-quicker phenomenon is found consistently in CIRS-WDB patients. The role of auto-activation of MASP2 [74] likely is a contributor factor to the "sicker-quicker" phenomenon. Inadequate remediation is a common cause of "sicker-quicker."

Treating CIRS-WDB is less beneficial when used prior to removal from ongoing exposure to a WDB. Treatment with binders is likely to fail or to progress more slowly unless the patient can be removed from the WDB, or the WDB undergoes successful remediation. When an ongoing accumulation of inhaled toxins, antigens and inflammagens exceeds the excretion achieved through anion binding, treatment will falter.

The first step in successful treatment thus depends on removal from ongoing exposure. In the absence of such removal, the supply of acceptably clean indoor air space falls far short of the demand for such space on the part of patients with CIRS-WDB. We again assert the need for collaboration between CIRS-WDB physicians, indoor environmental professionals (IEPs), remediators, and builders.

Unpublished Clinical Observations

While we have noted a robust published literature that represents the diversity of many significant features of CIRS-WDB, practicing physicians and remediators must recognize that the database on medical abnormalities in this field is much greater.

1. Measurement of VO2 max using a standard pulmonary stress test protocol in cases of CIRS-WDB routinely shows reduction to below 25 ml oxygen/kg/minute. These findings are also commonly seen in newly the renamed Chronic Fatigue Syndrome, SEID (Systemic Exertional Intolerance Disease) [75]. The objective evidence of capillary hypoperfusion that directly leads to reduction of VO2 max is paralleled by the symptom of the "push-crash" phenomenon, also called delayed recovery from normal activity. This symptom, called post-exertional malaise by the Centers for Disease Control and Prevention (CDC), is found in over 67% of cases of untreated adults with CIRS-WDB.
2. Presence of a rise in pulmonary artery systolic pressure (PASP) is seen in over 90% of adults with shortness of breath as part of their CIRS-WDB symptom complex and in nearly all pediatric patients with postural orthostatic tachycardia syndrome (POTS). The measurement of PASP in CIRS-WDB cases is derived from the nomogram of 4 times the square of velocity of tricuspid regurgitation plus the right atrial pressure. If PASP rises 8 mm Hg or more in near maximal exercise compared to rest, the CIRS-WDB patient has an acquired form of pulmonary hypertension that is often reversible with treatment. Measures of plasma VIP are complicated by the understanding that this neuropeptide regulatory hormone is commonly bound to tissue receptors. Whereas plasma VIP testing problematic, measurement of mRNA for VPAC2 receptors using NextGen DNA sequencing, is far more accurate. The finding of the excessive rise in PASP was so commonly seen it served as a biomarker for the VIP replacement study published in 2013 [19]. In step with VIP replacement, levels of mRNA for VPAC2 returned to normal and the PASP rise with exercise no longer exceeded 8 mm Hg.
3. Abdominal pain is often seen in CIRS-WDB (78% in one practice series). Symptoms of bloating, belching and acid taste suggest esophageal reflux but endoscopy rarely shows ongoing esophageal irritation. Treatment for bile acid reflux provides symptomatic relief in over 67% of cases.
4. Another gastrointestinal symptom of interest is prolonged post-prandial fullness associated with markedly reduced gastric emptying seen on nuclear scan imaging. These findings of gastroparesis are not uncommon in older diabetics with a history of poor control, but in non-diabetics, the incidence is less than 1 in 1000 adult patients. In adult cases of CIRS, the incidence of nuclear scan positive gastroparesis approaches 5%.
5. In 2007 Fisk and colleagues [76] reported that WDB account for 21% of all cases of asthma in the US. The pulmonary function tests used to diagnose repeated, reversible obstructive lung problems were not reported. In a single practice, a

review of over 4000 PFT procedures showed restrictive lung disease exceeded 33%, with obstructive disease seen in less than 10%. Sources of restrictive disease were more commonly seen in patients with elevated levels of TGF beta-1.

6. Levels of TGF beta-1 are highly associated with interstitial lung disease, with increasing fibrosis seen as well as mesenchymal to epithelial transformation. Additional observations of TGF beta-1 and fibrosis are not uncommon in CIRS with skin changes, liver changes and pulmonary findings most often observed. Additional changes related to elevated TGF beta-1 include hypermobility, catagen hair loss, and gadolinium-associated renal injury.
7. Reduced levels of T regulatory cells (T regs) are frequently associated with increased levels of TGF beta-1. Both thymus-derived T reg cells and acquired T regs are often reduced in CIRS-WDB cases; levels will rise into the normal range with treatment. Following signaling from TGF beta-1, T regs migrate into tissue to reduce inflammation and block the development of autoimmunity [77]. This anti-inflammatory property of TGF beta-1 is altered in the face of lower-than-normal levels of retinoic acid orphan receptors in tissue. There, T regs may plasticize to become T-effector cells that in turn increase tissue inflammation and drive up plasma levels of TGF beta-1 [78]. This condition of elevated TGF beta-1 and low levels of T regs is termed TH17/T reg imbalance [79]. The literature is rapidly expanding regarding illness states associated with this condition; much more likely will be learned in the near future. TH17/T reg imbalance is found in over 40% of CIRS-WDB cases.
8. As in acute sepsis, in CIRS-WDB coagulation abnormalities are commonly seen, particularly in von Willebrand's profiles. In 1701 cases of CIRS-WDB, 472 patients (27.7%) had lower than normal range values for Factor VIII, vWF antigen and ristocetin associated cofactor. 666 patients (39.1%) had *higher* than normal levels of the same values. Thirty-five of the same 1701 cases met criteria for acquired von Willebrand's Syndrome with lower than normal levels of both ristocetin associated cofactor and fibrin multimers. These findings of acquired von Willebrand's syndrome were associated with high levels of C4a. Acquired von Willebrand's syndrome is a rare hemorrhagic diathesis associated with lymphoproliferative disorders, myeloproliferative disorders, malignancy and cardiovascular illnesses. Less than 2% are associated with immune disorders. Incidence is unknown but as of 2000 there were 186 cases in the world's literature on the AvWS registry [80].
9. Hormonal abnormalities are often seen in CIRS. Dysregulation of normal feedback relationships of (i) ACTH/cortisol and (ii) ADH/osmolality are each seen in nearly 75% of cases. Abnormalities in androgens are seen in over 40% of cases.
10. Teens and adults present exclusively with multi-system, multi-symptom illness. Younger children often present with 1- or 2-system illness. The most common symptoms seen in children under 11 years of age are chronic headaches (70.7%), recurring abdominal "pains" (70.7%), or chronic fatigue (68.7%), which resist diagnosis using the standard pediatric work ups. Practice data reveal that 94.9%

of young CIRS-WDB patients presented with chronic headaches, abdominal issues and/or fatigue. Resolution of protracted symptoms and abnormal biomarkers following a short course of CSM occurs in almost all cases. Knowledge of the illness at a young age will likely prevent future long-term exposure-related health consequences. Additional problems seen more commonly in pediatric patients are findings of anti-gliadin antibodies, usually IgG, with negative TTG-IgA seen in 33% of cases with low MSH; and anticardiolipin antibodies, usually IgM, in 20% of cases.

The Need for Medically Sound Methods of Investigation and Remediation for Occupants with CIRS-WDB

The World Health Organization has estimated that up to fifty percent of built environments contain excessive dampness [2]. Analysis of EPA data indicated that thirty to fifty percent of built office environments in the U.S. have suffered from water damage [81]. The EPA's Building and Assessment and Survey Evaluation Study collected information on 100 representative office buildings in the 1990s. Statistics from this study showed that 34% had current water damage in occupied spaces and 71% had past water damage in occupied spaces [82]. Overall, 85% of the buildings had past water damage and 43% had current water damage. The economic and public health impacts of WDBs are considerable and warrant closer observations [83-85].

In addition to concerns about the causal links between WDBs and allergies, asthma and respiratory infection as discussed in the 2003 Institute of Medicine report [3], we advocate concern for the causal link between WDBs and CIRS. The implication for IEPs is clear: the investigation of WDBs should include answers to specific questions about the health of WDB occupants to assess the likelihood that one or more occupants may have CIRS-WDB.

Professional investigation of WDBs should not settle for questions about allergies and respiratory illnesses alone as literature over 12 years old would suggest. The presence of a multi-symptom, multisystem illness in one or more occupants warrants evaluation to see if the occupant meets the case definition for CIRS-WDB. However, not enough healthcare practitioners are skilled in the evaluating and managing CIRS-WDB. This barrier to easy access to expert care highlights both the importance of heightened awareness of CIRS-WDB within the medical and health professions as well as the growing need for education and training focused on this illness.

Effective indoor environmental practices are available for the control of allergies and asthma [86]. Yet a Cochrane review study found that there is only very low-quality evidence that remediation of dampness and mold in office buildings or schools can reduce asthma symptoms or respiratory infections in staff or children [87]. The review included eight studies totaling 6,538 participants. Because it found moderate-quality evidence for reduction of asthma and respiratory infections in houses affected by

dampness and mold, the implication is that occupant symptoms are less likely to subside when the WDB contains more cubic feet of air space and square feet of surface space to hold and distribute allergens. Larger indoor environments contain more dust and more people to import ultrafine particles from one location to another within the building. The investigation and remediation of WDBs is fast becoming a forensic discipline where the identified problems often relate building practices that neglect the moisture control imperative.

Given that brief low-dose exposures can initiate systemic inflammation in persons who are susceptible to CIRS-WDB, it stands to reason that remediation is likely to be more challenging when a WDB is occupied by one or more persons with CIRS-WDB when compared to WDBs whose occupants are healthy or who suffer only from allergies or asthma. Most pollen and intact spores can be trapped by HEPA filters; removing nano-particulates from the air is a more difficult challenge. CIRS-WDB patients raise the bar on what constitutes remediation to a safe exposure level. We may learn that the higher standard of post-remediation safety and cleanliness also applies to certain patients with treatment-resistant asthma.

The Need for a Consensus Statement on Medically Sound Investigation and Remediation of WDBs

The purpose of this brief review regarding the pathophysiology and the special treatment needs of patients with CIRS-WDB is to document the need for greater awareness on the part of medical, indoor air, remediation, and building professionals, policymakers, and the public at large regarding the wider implications of CIRS-WDB. The Indoor Air Consensus Statement that is paired with this review proposes the use of specific quantitative and qualitative methods to aid in the investigation and remediation of WDBs when occupants have, or are at-risk for CIRS-WDB. The health professionals who treat CIRS-WDB and the professionals who investigate and remediate WDBs, must collaborate and align their efforts with a new consensus on medically sound policies and procedures for investigating and remediating WDBs in cases of CIRS-WDB.

In addition to traditional methods of investigation and remediation when necessary there will be cases when small particle remediation methods are warranted for occupants affected by CIRS-WDB. Specific methods exist to remove small particles from the air, structural surfaces and other physical content in WDB spaces. These will be described in the Indoor Air Consensus Statement.

Given the life-altering issues created by CIRS-WDB, there is also a need for post-remediation maintenance planning to prevent future water intrusion, leaks, and condensation problems. This plan should include a way to index the mold propensity of a built environment. The companion Indoor Air Consensus Statement will describe a mold propensity index (MPI) as an empiric tool that can be included in assessing

building health. The MPI is based on consensus on remediation methods and monitoring indoor environmental conditions after remediation and cleaning.

Thus far, the WDB investigation method that best predicts successful treatment in a given space for patients/occupants with CIRS-WDB involves the use of MSQPCR (Mold-Specific Quantitative Polymerase Chain Reaction), also known as the Environmental Relative Moldiness Index (ERMI) [88]. A newer, more streamlined ERMI derivative—the Health Effects Roster of Type Specific (Formers) of Mycotoxins and Inflammagens, second version (HERTSMI-2), also predicts successful treatment in a given space [89]. ERMI scores were higher in homes with severely asthmatic children than in homes with non-asthmatic children [90].

Unfortunately, ERMI scores poorly correlate with air samples [91]. ERMI scores do not correlate well with measures of gram-positive and gram-negative bacterial cell wall components determined from the same dust samples [92]. These findings highlight the potential risks of relying on MSQPCR studies alone when investigating WDBs. ERMI scores based on standard dust samples have been used to help sort out whether air pollution *and* mold are causing health effects in occupants who live near busy roads [93]. Thus ERMI testing can be used to see if fungal exposure might account for symptoms being attributed to other kinds of airborne exposures.

The ERMI test currently is the best predictor as to whether or not a CIRS-WDB patient can get better on treatment in a given environment though unpublished data substantially favor the predictive power of HERTSMI-2. Yet in too many situations MSQPCR scores alone fall short of predicting safe post-remediation exposures. There is a need and an opportunity to develop more predictive and affordable methods of investigation and remediation to help CIRS-WDB sufferers determine when they have achieved safe levels of exposure in a post-remediation environment. Realization of such opportunities will not occur without collaboration between medical professionals and professionals with expertise in the adverse health effects of indoor air found in WDB and in methods of WDB investigation and remediation.

CIRS-WDB meets the epidemiological causality criteria described by Kundi in his revision of the principles proposed by Austin Bradford Hill in 1965 [94,95]. CIRS-WDB research meets Kundi's causality criteria by showing a consistency of demographics, genetics, environmental exposures and immune responses across all groups studied against controls.

The *most* upstream cause of CIRS-WDB has to do with building methods that fail to prevent water damage. Detailed methods for controlling moisture in built environments are available to builders [96]. Failure to adhere to moisture control standards during light or heavy construction can create hazards for future occupants who are susceptible to CIRS-WDB. Such failures create dilemmas for building owners and managers. In

addition to construction errors, poor building maintenance can result in undetected damage from weather, sump failures, and window or plumbing leaks.

Section 5(a)(1) of the *Occupational Safety and Health Act* of 1970, known as the General Duty Clause, indicates that each employer shall furnish to each of his employees a place of employment free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees [97]. CIRS-WDB causes physical harm and the proximate causal hazard(s) will be found in the indoor air and dust of water damaged buildings. CIRS-WDB is a potentially lethal and disabling building-related illness. The cause-effect relationship between the indoor air of WDBs and CIRS, and the damaging inflammatory results done to sufferers are no longer unclear.

CONCLUSIONS

A newly described form of systemic inflammation mediated by a dysregulated and uncontrolled innate immune response to PAMPs found in WDBs calls for new thinking by health care providers, builders, and by professionals who investigate or remediate WDBs. Occupants with CIRS-WDB are unusually sensitive to the toxins, antigens, inflammagens, nanoparticulates and volatile organic compounds (VOCs) found in WDBs. Minute exposures to these contaminants can result in a widely amplified innate immune system response in a subset of the population defined by symptoms, HLA haplotypes and laboratory data.

Physicians who treat CIRS-WDB are finding that traditional investigation and remediation methods often fail to produce post-remediation exposure conditions that are safe enough for CIRS-WDB patients to improve on treatment using an anion binding resin. The important question is raised of what constitutes a safe post-remediation exposure level for occupants who have been diagnosed with CIRS-WDB, as well as for those who would meet the case definition for CIRS but are not aware that their medically unexplained symptoms qualify for a CIRS-WDB diagnosis.

CIRS-WDB calls for collaboration between treating health professionals and experts in the construction of moisture-controlled buildings, in the investigation of indoor air quality, and in the effective remediation of WDBs. Interdisciplinary cooperation is needed to properly address this environmental health hazard. These issues call for a Consensus Statement from IEPs, remediators, and builders on what qualifies as medically sound investigation, correction, remediation, and prevention of WDBs based on the growing incidence of occupants who suffer, or may suffer, from CIRS-WDB.

Competing Interests
KB: none. RCS: Appearance as plaintiff expert in personal injury litigation.
SM: none. MA: none. SR: none. SG: none.

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