Medically sound investigation and remediation of water-damaged buildings in cases of chronic inflammatory response syndrome.

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ABSTRACT

Evidence supports a cause-effect relationship between exposure to the air and dust in water-damaged buildings (WDBs) and chronic inflammatory response syndrome (CIRS). This syndrome has an increased relative risk associated with specific HLA genotypes. CIRS-WDB is mediated by a persistent innate immune inflammatory response to toxins, antigens, and inflammagenspresent in the interior environment of WDBs. Dose-response relationships in this condition are supralinear in nature. For patients with CIRS-WDB, current methods of WDB investigation and remediation are often not sufficient to prevent a relapse of symptoms with re-exposure. CIRS-WDB is a growing public health hazard best addressed by collaboration among experts in CIRS-WDB medicine, indoor air quality, remediation, and moisture-controlled building design and construction. Assessments of human health effects associated with exposure to WDBs 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 syndrome (CIRS-WDB) (Clark, Anderson et al. 2004, Stephenson, Ammann, et al. 2008, Afshari A, Anderson et al. 2009). The first step in the treatment of patients with CIRS-WDB is removal from exposure to indoor biocontaminants, followed by investigation and remediation without delay, where remediation may warrant small particle cleaning methods. 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 documented to have no significant role in day-to-day management of CIRS-WDB patients and to have little role in assessment of remediation adequacy (Afshari, Anderson, et al. 2009). In those who are genetically susceptible, WDB exposures result in poor clearance of inhaled biocontaminants, which causes and perpetuates systemic inflammation and multiple symptoms. Given that this susceptibility-exposure inflammation-symptoms relationship is supported by markedly abnormal differential gene activation seen in cases of CIRS-WDB compared to controls (unpublished data), reliance on older sampling approaches alone can no longer be considered a medically tenable guide to remediation efforts. Proper evaluation of CIRS-WDB patients demands application of 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 (AIHA 2008):

> "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). There is now scientific consensus that the diverse mixtures of toxins, antigens and inflammagens contained within reservoirs present in WDB are capable of triggering systemic inflammation in those who carry CIRS susceptible HLA genotypes.

Given the variables involved with host susceptibility, currently identified based on the genetics of immune response genes (HLA DR/DQ), the toxicological aphorism, the "dose makes the poison" simply never applies. In CIRS-WDB, environmental exposures trigger biologically complex host responses to toxins, antigens and inflammagens, including endotoxins (Calabrese 2005). In a 1972 article in the New England Journal of Medicine,

Lewis Thomas, speaking of endotoxins, anticipated the challenge for today's physicians (Thomas 1972): "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 may or may not be accompanied by allergy or asthma (Shoemaker 2010).

We are aware of published reports that allege that the air within damp buildings is incapable of causing an inflammatory syndrome in humans (Hardin, Kelman et al. 2003, Sudakin and Kurt 2007, Bush, Portnoy et al. 2006). However, these reports contained flawed analyses that have been sharply criticized by objective observers as well as the U.S. Government Accountability Office GAO (Craner 2008, Stephenson, Ammann 2008). The criticized papers have been either withdrawn or amended with disclaimers. One of the reports was the subject of a Wall Street journal exposé on author bias (Armstrong 2007). Conversely, we are aware of an extensive series of peer-reviewed papers that support the existence of a chronic inflammatory response in patients after chronic exposure to the interior of WDBs (Shoemaker 2010).

DISCUSSION

The etiology and pathophysiology of CIRS-WDB

Scientific evidence supports an increasingly detailed description of the etiology and pathophysiology of CIRS (Shoemaker and Hudnell 2001, Shoemaker and House 2005, Shoemaker and House 2006, Shoemaker, House et al. 2010, Shoemaker, House et al. 2013, Mustonen, Karvonen et al. 2015, Rosenblum, Lichtenstein, Hsu et al. 2015, Ryan, Wu et al. 2015). The CIRS-WDB subset of CIRS variants requires exposure to the admixture of toxins, antigens and inflammagens found in WDBs. These exposures result in adverse symptoms in the genetically susceptible. Clinical data from 1,829 CIRS cases show that patients aged less than 19 years-old average 19of 37 symptoms; those aged 19 and above average 25 of 37 symptoms; healthy controls averaged 3 of 37 symptoms (Shoemaker, House et al. 2013). For a full listing of symptoms presenting in at least 30% of patients with CIRS of any source (see Table 1). Experimental evidence shows that exposures to WDBs trigger symptoms that correlate with expected changes in C4a, leptin, VEGF, TGF beta-1, and MMP-9 (Shoemaker and House 2006, Shoemaker 2010).

The innate immune systems of mammals contain highly conserved genetic sequences for receptors that respond rapidly to pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs) (Tang, Kang et al. 2012).Evidence indicates that some of the PAMPs found in WDBs can activate bloodborne mannose-binding lectin (MBL) receptors, which immediately activates the MBL-associated serine proteases MASP-1 and MASP-2,(Heja, Kocsis et al. 2012) as well as downstream pathways in the complement system. 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 (Drummond and Brown 2013, Dambuza and Brown 2015). Fungal and bacterial fragments make up part of the antigenic component of the "chemical stew" found in WDBs. The MBL pathway results in marked amplification of the pro-inflammatory product C4a compared to the classical pathway (Rawal, Rajagopalan et al. 2008). In the HLA CIRS-susceptible, C4a levels are known to increase as a result of exposure to the air and dust of WDBs (Shoemaker and House 2005, Shoemaker and House 2006).

Should exposure be prolonged, the pro-inflammatory cytokine antagonism of hypothalamic leptin receptors can lead to decreased production of hypothalamic regulatory neuropeptide hormones (Fantuzzi 2006). These neuropeptides include alpha-MSH (Faulkner, Dowling et al. 2015), antidiuretic hormone (ADH) (Yamamoto, Morimoto et al. 1999), and vasoactive intestinal polypeptide (VIP) (Jones and Symes 2000).

Inflammatory disruption of hypothalamic pathways can also adversely impact the production of other melanocortins including adrenocorticotrophic hormone, (ACTH) (Manna, Sarkar et al. 2006). Shoemaker and Ryan have shown that transcriptomic signatures support the involvement of VIP pathways in patients with CIRS (Ryan, Wu et al. 2015). Hypothalamic dysregulation may play a role in the pattern of volumetric abnormalties when MRIs of the brain without contrast are analyzed using an FDA-

cleared software program (NeuroQuant®) in patients with CIRS-WDB. The CIRS-WDB pattern shows atrophy of the caudate nuclei as well asenlargementof forebrain parenchyma, cortical grey and pallida (Shoemaker, House et al. 2014).

Contaminants Found in WDBs

Defining sufficiently clean and safe challenges attempts to set standards for medically sound investigation and remediation in cases involving CIRS-WDB.

The problem is clear: many types of biocontaminants have been found inside WDB (see Table 2).

(Sorenson, Frazer et al. 1987, Smoragiewicz, Cossette et al. 1993, Saraf, Larsson et al. 1997, Butte and Heinzow 2002, Douwes, Thorne et al. 2003, Rao, Riggs et al. 2007, Pestka, Yike et al. 2008, Thrasher and Crawley 2009).

Studies have linked exposure to toxins and inflammagens in WDBs to multiple inflammatory pathways (Beijer, Thorn et al. 2003, Li and Yang 2004, Shoemaker 2010, Zhang, Sahlberg et al. 2012, Karottki, Spilak et al. 2015). The neurotoxic effects of trichothecenemycotoxins are well documented (Islam, Harkema et al. 2006, Karunasena, Larranaga et al. 2010, Arunachalam and Doohan 2013). An emerging concern stems from the enhanced toxicity of ultrafine and nanoparticles, whose collective surface areas create increased opportunities to bind and disrupt molecular mechanisms in cells and tissues (Oberdorster, Oberdorster et al. 2005, Rettig, Haen et al. 2010). 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 invoked in legal cases involving WDBs and CIRS-WDB. Because any permutation of noxious incitants could be present in a given WDB, demands to prove a specific causative factor of CIRSWDB are flawed.

The United States Government Accountability Office report from 2008 states (USGAO 2008):

> "…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 the mixtures of pathogens, antigens, toxic metabolites, microparticulates, and nanoparticulates–all of which act as inflammagens, are the basic elements causing CIRS-WDB.

The 2008 US GAO report provides a case definition of CIRS-WDB, later amplified in detail by the Expert Mold Treating Physicians' Consensus Report of 2010 (Shoemaker 2010).

- 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)mycological testing which demonstrates amplified mold growth by species known to flourish on damp indoor building materials and known to produce secondary metabolites with known toxigenic and inflammagenic effects on persons with HLA susceptibilities to poor processing and clearance of such innate immune system activators.

- 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 (Shoemaker 2010, Shoemaker, House et al. 2013, Shoemaker, House et al. 2014, Mustonen, Karvonen et al. 2015).
- There must be laboratory abnormalities in a possible case that are similar to those seen in peer-reviewed, published studies (Shoemaker 2010, Shoemaker, House et al. 2013, Shoemaker, House et al. 2014, Mustonen, Karvonen et al. 2015).
- There must be improvement with therapy similar to that reported in peer reviewed, published studies (Shoemaker 2010, Shoemaker, House et al. 2013, Shoemaker, House et al. 2014, Mustonen, Karvonen et al. 2015).

CIRS-WDB Treatment

A treatment protocol has been shown to produce predictably positive health outcomes (Shoemaker and House 2006, Shoemaker, House et al. 2010, Shoemaker, House et al. 2013). The most comprehensive reporting of symptoms and laboratory abnormalities in CIRS-WDB included 1,829 cases and 169healthy controls (Shoemaker, House et al. 2013). Yet the treatment process can be impeded by uncertainties regarding what constitutes medically acceptable standards for the investigation and remediation of

WDBs. Failed remediation delays treatment. 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 Maryland outbreak of Pfiesteriawhen a patient's headaches, memory impairment and severe diarrhea quickly resolved on CSM (Shoemaker 1998). CSM was then known to be of benefit in diarrhea caused by Clostridium difficiletoxin (McCoy, Klick et al. 2015).

A series of subsequent studies have shown benefit from CSM in a diverse range of biotoxin illnesses including ciguatera (Shoemaker, House et al. 2010), Pfiesteria (Hlavsa, Roberts et al. 2014), and cyanobacterial illness (Haselow, Brown et al. 2001, Stewart, Webb et al. 2006). Multiple studies have shown therapeutic benefits of CSM in cases of CIRS-WDB (Shoemaker 2010, Shoemaker, House et al. 2013), including a double-blinded, placebo-controlled clinical trial (Shoemaker and House 2006). Much of this benefit is likely derived from CSM'sanionic toxinbinding capacity (Humphrey, Condon et al. 1979, Dahlem, Hassan et al. 1989, Brouillard and Rateau 1990, Andersen, Andersen et al. 1993, Underhill, Rotter et al. 1995, Kerkadi, Barriault et al. 1998, Phibbs 1998).

CIRS-WDB treatment currently relies on the use of cationic polymers as anionic binding resins (Carmona-Ribeiro and de Melo Carrasco 2013). When taken according to specific directions, these polymers are able to bind and remove via the large bowel, small (less than 2000 daltons) anion-ring forming compounds including heterocyclic rings,

polycyclic ethers, carboxylic acid ethers, ionophores, amphipathic toxins and inflammagens (Shoemaker and House 2005, Shoemaker and House 2006, Shoemaker 2013).

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. In cases of CIRS-WDB, the mechanism of action of these bile acid sequestrants is the interruption of enterohepatic recirculation of ionophore and amphipathic 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 (Rifkind 1986). With the advent of use of statin drugs, use of CSM for cholesterol reduction has fallen. One can speculate that at least some of the death prevention benefits of CSM were related to the binding and removal of anionic toxins and inflammagens. While both CSM and colesevelammedications 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 (Jacobson, Armani et al. 2007). Side effects include constipation, gastroesophageal reflux, and mast cell activation.

Once treatment succeeds at binding and removinganionic 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. This is a reliable sign that the genetically modified innate immune inflammatory response of the host, and not the putative dose, is what drives CIRS-WDB.

The rapid onset of symptoms with re-exposure is routinely observed. Treatment includes both prompt removal from exposure and reinstitution of anion binding resins. The role of auto-activation of MASP1 and MASP2 (Heja, Kocsis et al. 2012) likely is a contributing factor.

Benefit from treatment of CIRS-WDB is reduced when used prior to removal from ongoing exposure to a WDB. Treatment with binders is likely to progress more slowly when the patient cannot be removed from the WDB, or the WDB cannot successfully be remediated to CIRS-WDB standards. When an ongoing accumulation of inhaled toxins, antigens and inflammagens exceeds the excretion achieved through anion binding, treatment will falter and inflammation-driven symptoms will persist.

The first step in successful treatment thus depends on removal from ongoing exposure. 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, IEPs, remediators and building performance experts.

Unpublished Clinical Observations Regarding CIRS-WDB

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, including practice-based data concerning the following:

- 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 Chronic Fatigue Syndrome, newly renamed Systemic Exertional Intolerance Disease. The objective evidence of capillary hypoperfusion that directly leads to reduction of VO2 max is paralleled by the symptom of the "pushcrash" phenomenon, also called delayed recovery from normal activity. This symptomis found in over 67% of cases of untreated adults with CIRS-WDB.
- 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 velocity of tricuspid regurgitation squared plus the right atrial pressure. If PASP rises8 mm Hg or more in near maximal exercise compared to rest, the CIRS-WDB patient has an acquired form of pulmonary hypertension. This condition invariably is corrected with treatment. 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 (Shoemaker, House et al. 2013). In step with VIP replacement, the PASP rise with exercise no longer exceeded 8 mm Hg.

- In 2007 Fisk and colleagues (Fisk, Lei-Gomez, et al. 2007) reported that WDB account for 21% of all cases of asthma in the US. 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.Levels of TGF beta-1 are highly associated with interstitial lung disease, with increasing fibrosis seen as well as epithelial to mesenchymal transitions (EMT). Additional observations of TGF beta-1 and fibrosis are not uncommon in CIRS with skin changes, liver changes, polyp development, and pulmonary findings most often observed. Additional changes related to elevated TGF beta-1 include hypermobility, catagen hair loss, and gadolinium-associated renal injury.
- 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 regsare 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 (Han, Li et al. 2012). 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(Hatton 2011). This condition of elevated TGF beta-1 and low levels of T regs is termed TH17/T reg imbalance (Noack and Miossec 2014). The literature is rapidly expanding regarding illness states associated with this condition. TH17/T reg imbalance is found in over 40% of CIRS-WDB cases.

- As in acute sepsis, coagulation abnormalities are commonly seen in CIRSWDB, particularly in von Willebrand's profiles. In 1,701 cases of CIRSWDB, 472 patients (28%) had lower than normal range values for Factor VIII, vWF antigen and ristocetin associated cofactor. 666 patients (39%) had higher than normal levels of the same values. Thirty-five of the same 1,701 cases met criteria for acquired von Willebrand's Syndrome (AvWS) with lower than normal levels of both ristocetin associated cofactor and fibrin multimers. These findings of AvWS were associated with high levels of C4a.AvWS is a rare hemorrhagic diathesis associated with lymphoproliferative disorders, myeloproliferative disorders, malignancy and cardiovascular illnesses. Less than 2% are associated with immune disorders. As of 2000 there were only 186 cases in the AvWS registry (Federici, Rand et al. 2000), with actual incidence in 2015 unknown.
- 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.

- Teens and adults present exclusively with multisystem, multi-symptom illness. Younger children often present with a 1- or 2-system illness. The most common symptoms (found in 70% of cases) seen in children under 11 years of age are chronic headaches, recurring abdominal "pains," or chronic fatigue, which resist diagnosis using the standard pediatric work ups. 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 Building Occupants with CIRS-WDB

The World Health Organization has estimated that up to fifty percent of built environments in developing countries have suffered damp conditions (Afshari, Anderson, et al. 2009). In an analysis of previously collected data on a nationwide sampling of office buildings, Mendell and Cozen found correlations between building conditions and worker symptoms that, if causal, "would suggest an increase in symptoms among the very large proportion of the U.S. workforce that is employed indoors" (Mendell and Cozen 2002). Another analysis of office building data indicated that thirty to fifty percent of built office environments in the U.S. have suffered from water damage (Mendell

2005). A separate analysis office building data found that 34% had current water damage in occupied spaces, 71% had past water damage in occupied spaces, and overall, 85% of the buildings had past water damage and 43% had current water damage (Cox-Ganser, Park 2011). The economic and public health impacts of WDBs are considerable and warrant closer observations (Mudarri, Fisk et al. 2002,).

As early as 2003, the Institute of Medicine reported finding causal links between WDBs and allergies, asthma and respiratory infection (Clark, Ammann, et al. 2003). We contend that there now needs to be concern for the causal link between WDBs and CIRS. Professional investigation of WDBs should not settle for questions about allergies and respiratory illnesses alone as older literature would suggest. The presence of a multi-symptom, multisystem illness in one or more occupants warrants referral for medical evaluation to see if the occupant meets the case definition for CIRS-WDB.

Given that brief, low-dose exposures can initiate systemic inflammation in susceptible people, 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 mild to moderate allergies or asthma. Most pollen and intact spores can be trapped by rated furnace and HEPA filters; removing micro- and nanoparticulates from the air is a 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 helps 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, as well as policymakers, stakeholders and the public regarding the wider implications 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. Given the life-altering issues created by CIRS-WDB, there is also a need for post-remediation maintenance plans designed to prevent future water intrusion, leaks, and indoor condensation problems.

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); the test most often used is the Environmental Relative Moldiness Index (ERMI)(Vesper 2011). A 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 by measuring the presence of the five most prevalent and toxigenic molds in WDBs based

on practice data sets (Shoemaker 2011). ERMI scores were higher in homes with severely asthmatic children than in homes with non-asthmatic children (Vesper, McKinstry et al. 2008).

Unfortunately, ERMI scores poorly correlate with air samples (Reponen, Singh, et al. 2010). ERMI scores do not cross-correlate well with measures of grampositive and gram-negative bacterial cell wall components determined from the same dust samples (Adhikari, Kettleson et al. 2014). 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 (Kamal, Burke, et. al. 2014). Thus ERMI testing can be used to see if fungal exposure might account for symptoms being attributed to other kinds of airborne exposures. Still, there is a need 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.

CIRS-WDB meets the epidemiological causality criteria described by Kundi in his revision of the principles proposed by Bradford Hill in 1965 (Kundi 2006, Hill 1965, Bliss,Jackson 2007). CIRS-WDB research meets Kundi's causality criteria by showing a consistency of demographics, genetics, environmental exposures and immune responses in 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 (OSHA 1970). 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. WDB biocontaminants are increasingly recognized as a serious health hazard able to produce physical harm by means of complex causation in a process can result in CIRS-WDB. Aninflammagenic admixture of airborne and settled biocontaminants is the proximate causal hazard. In the genetically prone, the cause-effect relationship between the indoor air of WDBs and chronic inflammatory response syndrome is clear.

CONCLUSIONS

A newly described form of systemic inflammation mediated by a dysregulated innate immune response to PAMPs found in WDBs calls for new thinking by health care providers, builders, and by professionals who investigate and remediate WDBs. Occupants with CIRS-WDB are unusually reactive to the biocontaminantspresent in

WDBs. Minute exposures to such contaminants triggers a widely amplified innate immune system response in a subset of the population defined by symptoms, HLA haplotypes and laboratory data. CIRS-WDB calls for collaboration between treating health professionals and experts in (i) building performance and moisture control; (ii) the investigation of indoor air quality; and (iii) methods of remediation adequate to the medical needs of occupants with chronic inflammatory response syndrome acquired by exposure to water-damaged buildings.

Competing Interests

KB: none. SWM: none. MA:none. SR:none.SG: none.

RCS:Appearance as plaintiff expert in personal injury litigation.

Acknowledgments

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Table 1

The 37 most frequent symptoms seen in cases of CIRS-WDB

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.	

Table 2 Range of biocontaminants found in WDBs

Mycotoxins[1]	Gram-negative bacteria[8-11]	Hemolysins[3,6]
Bioaerosols[2]	Gram-positive bacteria[8-11]	Proteinases[3,6]
Cell fragments[3]	Actinomycetes[12]	Chitinases[6]
Cell wall components[3]	Nocardia[8]	Siderophores[6]
Hyphal fragments[4]	Mycobacteria[13]	Microbial VOCs[15-19]
Conidia[4]	Protozoa[12]	Building material VOCs[15]
Beta Glucans[3,5]	Chlamydia[14]	Coarse particulates[6]
Mannans[6,7]	Mycoplasma[14]	Fine particulates[6]
Spirocyclicdrimanes[3]	Endotoxins[5,8]	Ultrafine particulates[20]
Inorganic xenobiotics[8]	Lipopolysaccharides[9]	Nano-sized particulates[20]

Table 2 References: 1: Smoragiewicz 1993 2: Douwes 2003 3: Pestka 2008 4: Sorenson 1987 5: Rao 2007 6: Shoemaker 2010 7: Thrasher 2009 8: Butte 9: Saraf 1997 10: Hirvonen 2005 11: Roponen 2001 12: Suikho 200913: Kettleson 2013 14: Yli-Pirila 2004 15:Claeson 2009 16: Bennett 2015 17: Li 2004 18: Korpi 199819: Beijer 2003 20: Oberdorster 2005

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