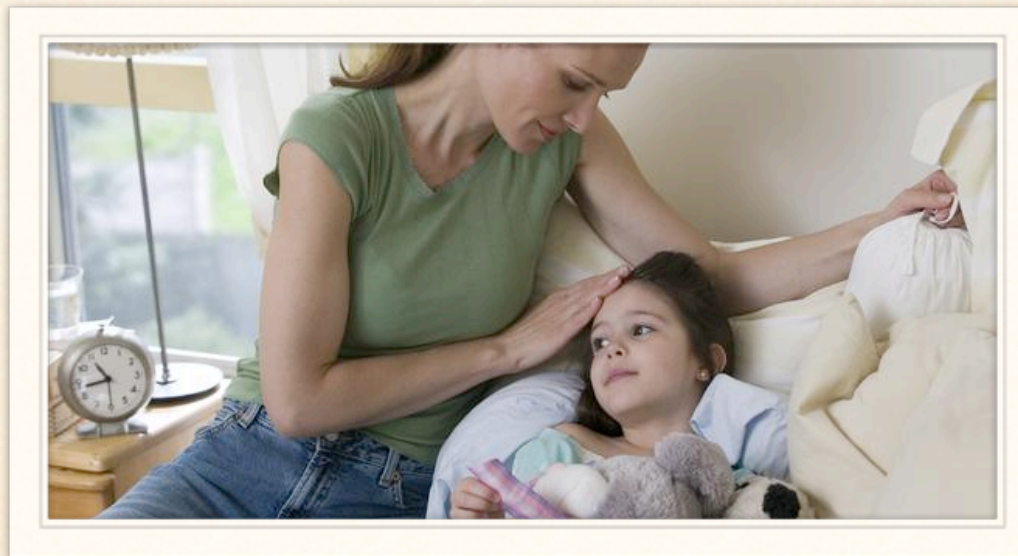


Mold Toxicity

A Chronic Inflammatory Response Syndrome



Keith Berndtson, MD



Chronic Inflammatory Response Syndrome:

CIRS is the adopted name that refers to the underlying pathophysiology of an increasingly well understood multi-symptom, multi-system illness.

Other Names for CIRS:

- *Biotoxin Illness*

Refers to the currently understood common denominator cause: toxins made by living things.

- *Mold Toxicity Syndrome*

Underplays the importance of inflammagens that combine with mold toxins to create indoor air capable of making susceptible people chronically ill. Sometimes called toxic mold sickness.

- *CIRS-WDB*

The mold-driven version of CIRS associated with .

Data suggest that 80 percent of human biotoxin illness is driven by indoor air contaminated with mold toxins and other inflammagens.

Shoemaker RC, Mark L, MacMahon S, Thrasher JD, Grimes C. Research committee report on diagnosis and treatment of chronic inflammatory response syndrome caused by exposure to the interior environment of water-damaged buildings. *Policyholders of America*. 2010.

Ritchie Shoemaker, MD

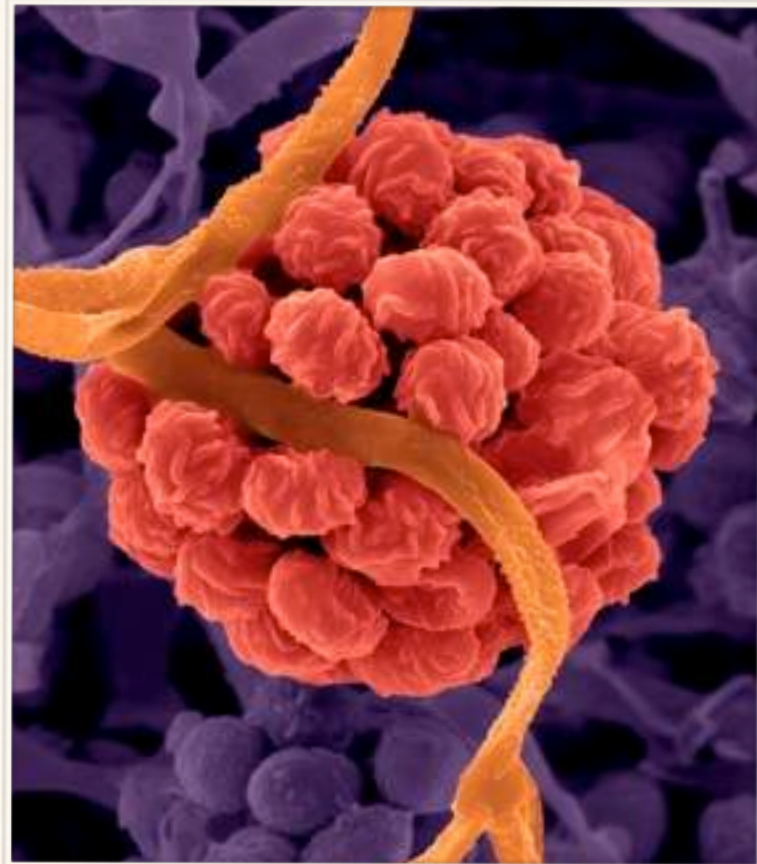
- First to link a toxin produced by *Pfiesteria* to the Mid-Atlantic outbreaks of human illness in the late 1990s. (1)
- First to determine that most cases of biotoxin illness are due to toxins produced by certain molds known to grow in water-damaged buildings. (2)
- First to clarify the underlying pathophysiology of biotoxin illness and to develop a stepwise protocol to treat it. (3)



1. Shoemaker R, Hudnell K. Possible Estuary-Associated Syndrome: symptoms, vision, and treatment. *Environmental Health Perspectives*. 2001;109:539-45.
2. Shoemaker R, Hudnell K, House D. Sick Building Syndrome in Water Damaged Buildings: Generalization of the Chronic Biotoxin-Associated Illness Paradigm to Indoor Toxigenic-Fungi Exposure. 9/2003 5th International Conference on Bioaerosols (conference peer review)
3. Shoemaker R, Hudnell D. A time-series study of sick building syndrome: chronic, biotoxin-associated illness from exposure to water-damaged buildings. *Neurotoxicology and Teratology* 2004; 1-18.

Stachybotrys: nature's solution to the human problem?

- Perhaps the most toxic mold of them all.
- Requires sustained moisture.
- Makes *tricothecene* toxins:
 - T2 toxin
 - Satratoxin H
- T2 toxin allegedly added to the chemical weapon known as *yellow rain* (this is disputed).
- Stachy toxins often found in heavily water-damaged buildings.



Stachybotrys chartarum

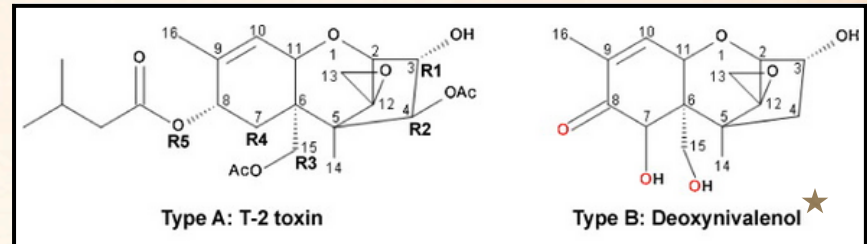
Tricothecenes: how toxic are they?

Mini review

Tricothecene toxicity in eukaryotes: Cellular and molecular mechanisms in plants and animals

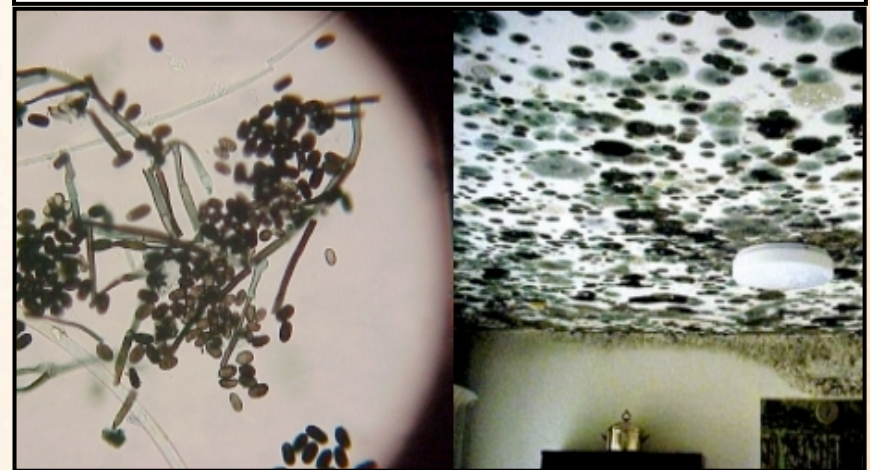
Chanemougasoundharam Arunachalam  , Fiona M. Doohan  

Molecular Plant-Microbe Interactions Group, School of Biology and Environmental Science, College of Life Sciences, University College Dublin, Belfield, Dublin 4, Ireland



Mechanisms of toxicity

- Cell-cycle arrest
- Mitosis disruption
- Protein synthesis inhibition
- Oxidative cell stress with DNA damage
- Cell membrane disruption and permeability
- Immunostimulatory *and* immunosuppressive
- Induction of apoptosis and programmed cell death
- Increased expression of inflammatory and apoptotic mRNAs
- Ribotoxic stress response producing MAPK induction of cytokine release
- Endoplasmic reticulum stress with protein misfolding and blocked unfolding



Stachybotrys micro- and macro-colonies

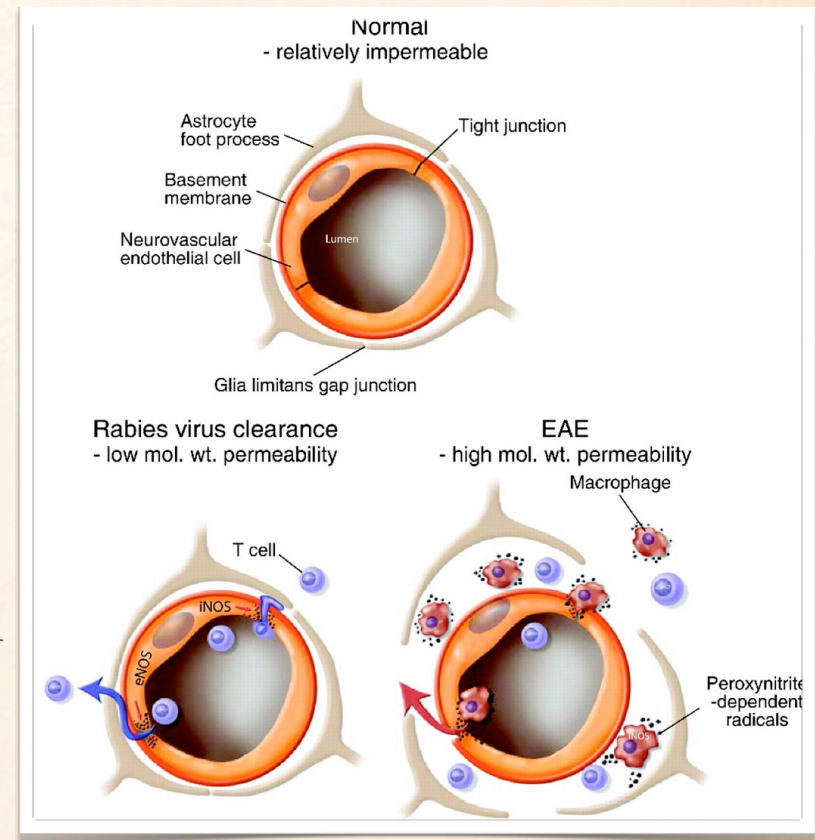
Toxicology Letters, 217(2):149-158.

★ Deoxynivalinol (DON) is ingested with wheat contaminated by *Fusarium* mold species.

Tricothecenes: brain damage anyone?

Satratoxin H (SH) causes a leaky blood-brain barrier. (1) BBB changes naturally vary depending on the nature of the situation. (2) A mouse experimental allergic encephalitis (EAE) model studied the effects of tricothecenes on neuroinflammation. Can SH cause brain interstitial microedema?

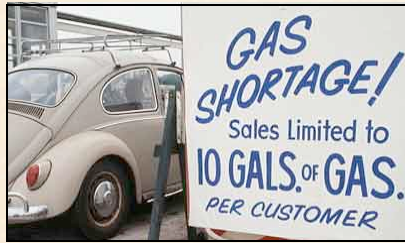
- SH disrupts brain endothelial cells and the integrity of the blood-brain barrier.
- SH induces an initial anti-inflammatory response from astrocytes. Chronic exposure results in local oxidative stress and neuronal apoptosis like that seen in lupus, multiple sclerosis, and Alzheimer's disease.
- Results suggest that a chronic immune response to inhaled SH could produce neuronal hypersensitivity and damage, which could be additive with exposure to other airborne toxins or inflammagens.



1. Karunasena E, Larranaga MD, Simoni JS, Douglas DR, Straus DC. Building-associated neurologic damage modeled in human cells: a mechanism of neurotoxic effects by exposure to mycotoxins in the indoor environment. *Mycopathologia*, 2010 Jun 13. PMID:22846391

2. Fabis MJ, Phares TW, Kean RB, Koprowski H, Hooper DC. Blood-brain barrier changes and cell invasion differ between therapeutic immune clearance or neurotrophic virus and CNS autoimmunity. *PNAS*. 2008 Oct 7;105(40):15221-15634. (Source of figure above)

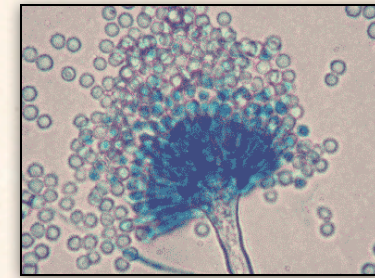
Sick Building Syndrome (SBS)



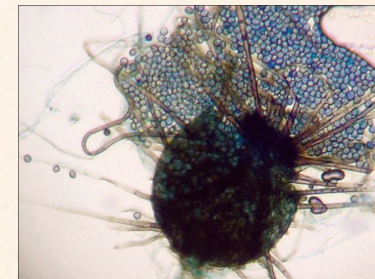
- Modern SBS began after the 1973 OPEC oil embargo prompted builders to seal the indoor environment off from the outdoors as a way to reduce energy consumption.
- This allowed even minor flooding or leaks to foster indoor fungal growth giving rise to new combinations of toxin-producing indoor molds.
- Molds release toxin-laden spores in response to contact with inflammatory man-made building chemicals. Inflammagens from gram-negative bacteria and mycobacteria can add to the toxic mix.
- The mold/bacterial/chemical mix can induce a chronic multi-symptom illness in people who are genetically susceptible to poor toxin clearance.

Common Toxin Producing Indoor Molds

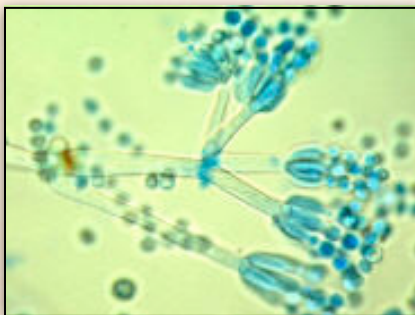
Mold species	Toxin types
<i>Aspergillus penicilloides</i>	aflatoxin, ochratoxin
<i>Aspergillus versicolor</i>	chaetosin
<i>Chaetomium globosum</i>	deoxynivalinol, T2 toxin
<i>Penicillium corylophilum</i>	gliotoxin
<i>Stachybotrys chartarum</i>	T2 toxin, satratoxin H
<i>Trichoderma viride</i>	T2 toxin, DAS
<i>Wallemia sebi</i>	walleminol



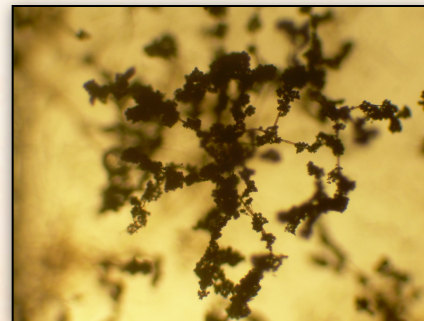
Aspergillus versicolor



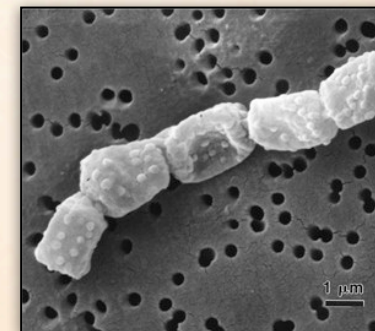
Chaetomium globosum



Penicillium corylophilum



Trichoderma viride

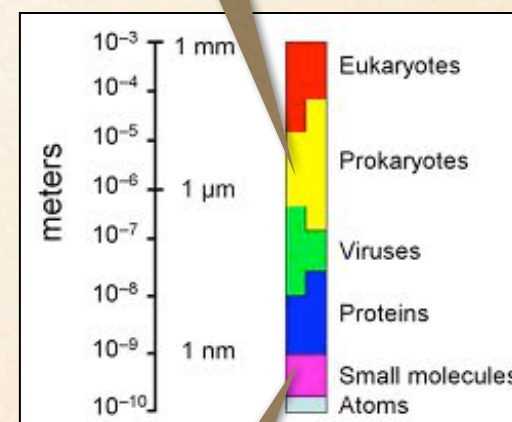


Wallemia sebi

Toxic Bioaerosol Dispersal

- Mold toxins are undetectable with conventional sampling methods due to their unusually small size (0.001 to 0.005 microns).
- Less than 2% of mold toxins are attached to mold spores (10 to 30 microns). The remainder are attached to fungal fragments or exist as free-floating particles. Like other aerosol particles, they are dispersed by vibration and air turbulence.
- Aerosolized mold toxins mixed with volatile organic compounds are major threats to indoor air quality and this warrants collaborative research. (1,2)

Mold
Spores

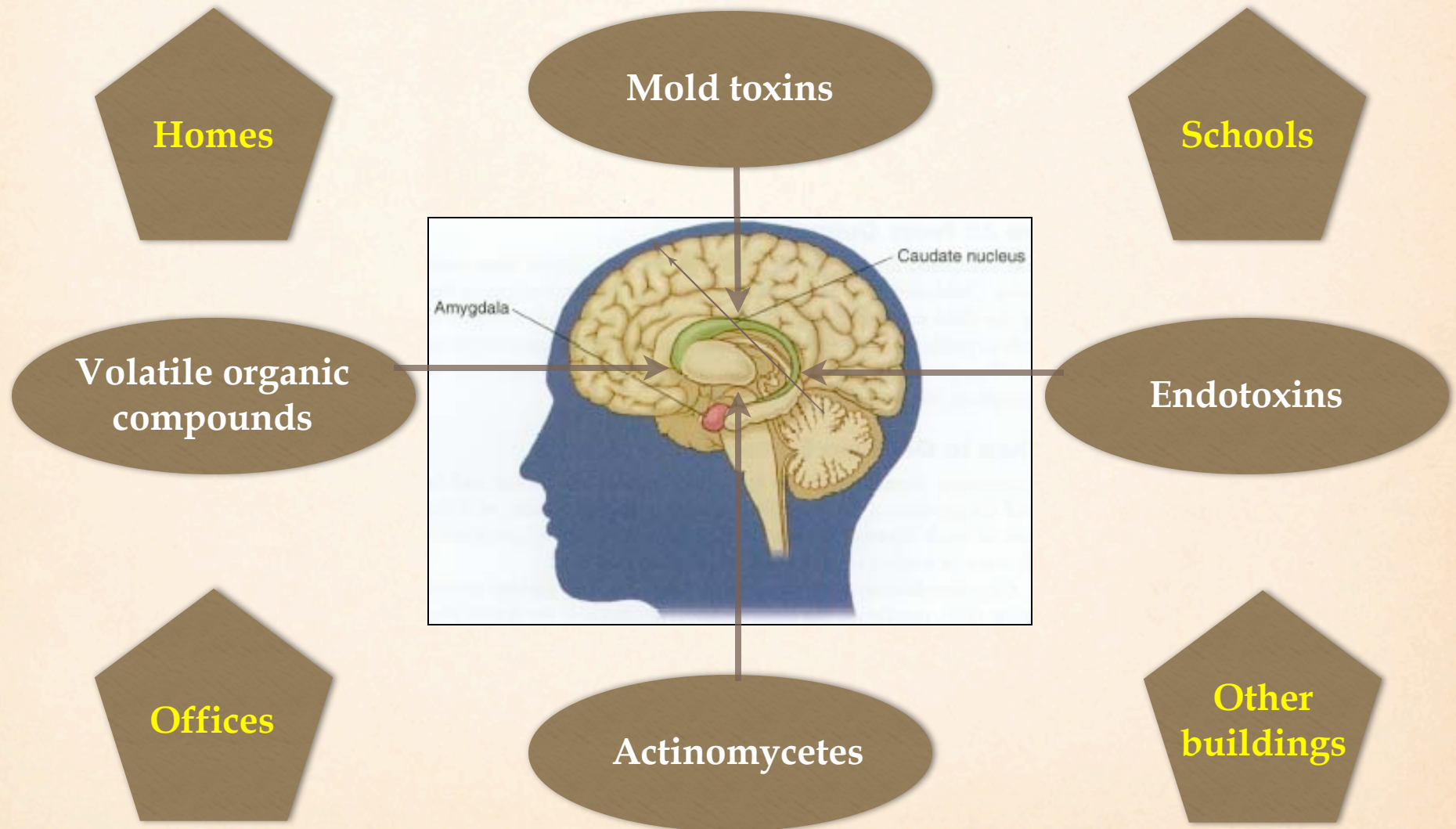


Mold
Toxins

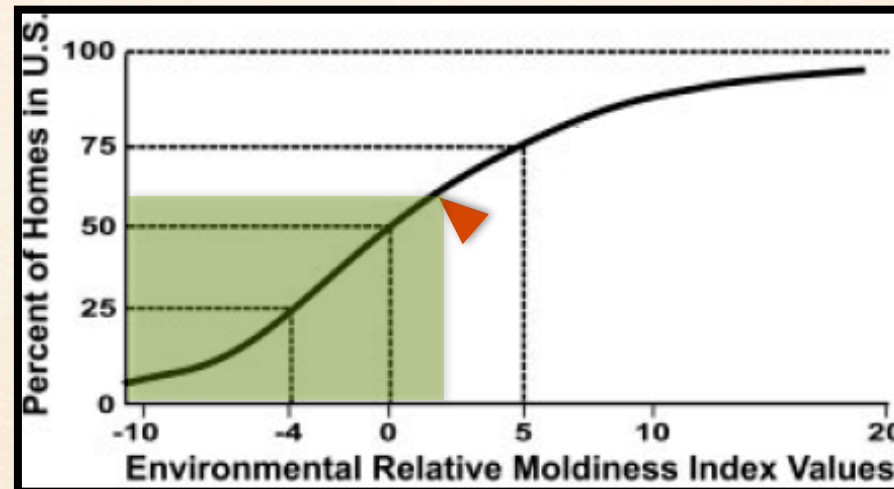
1. Rosen J, Heseltine E. WHO guidelines for indoor air quality: Dampness and Mould. Copenhagen: WHO; 2009:1-228.

2. Indoor mold: better coordination of research on health effects and more consistent guidance would improve federal efforts. United States Government Accountability Office; 2008:1-60.

Toxin-Inflammagen Synergism in the Air of Water Damaged Buildings



The Environmental Relative Moldiness Index Test (ERMI)



Recovery from mold toxicity syndrome is likely only if routinely visited building structures (home, office, and/or school) manifest ERMI scores *less than 2* on a scale from -10 to 20. The ERMI test is currently the only mold inspection method with predictive value concerning clinical recovery.

ERMI does not account for non-mold inflammagens including VOCs, endotoxins, actinomycetes, glucans, glycoproteins, and other noxious incitants.

Fungal ID \ Sample ID	EC1261 Basement
<i>Aspergillus flavus/oryzae</i>	4
<i>Aspergillus fumigatus</i>	28
<i>Aspergillus niger</i>	26
<i>Aspergillus ochraceus</i>	120
<i>Aspergillus penicilloides</i>	33000
<i>Aspergillus restrictus*</i>	63
<i>Aspergillus sclerotiorum</i>	21
<i>Aspergillus sydowii</i>	27
<i>Aspergillus unguis</i>	9
<i>Aspergillus versicolor</i>	680
<i>Aureobasidium pullulans</i>	130
<i>Chaetomium globosum</i>	97
<i>Cladosporium sphaerospermum</i>	170
<i>Eurotium (Asp.) amstelodami*</i>	830
<i>Paecilomyces variotii</i>	7
<i>Penicillium brevicompactum</i>	53
<i>Penicillium corylophilum</i>	260
<i>Penicillium crustosum*</i>	5
<i>Penicillium purpogenum</i>	4
<i>Penicillium spinulosum*</i>	1
<i>Penicillium variable</i>	19
<i>Scopulariopsis brevicaulis/fusca</i>	2
<i>Scopulariopsis chartarum</i>	18
<i>Stachybotrys chartarum</i>	51
<i>Trichoderma viride*</i>	32
<i>Wallemia sebi</i>	2100
Sum of the Logs (Group I):	43.30
<i>Acremonium strictum</i>	3
<i>Alternaria alternata</i>	30
<i>Aspergillus ustus</i>	77
<i>Cladosporium cladosporioides 1</i>	390
<i>Cladosporium cladosporioides 2</i>	73
<i>Cladosporium herbarum</i>	200
<i>Epicoecium nigrum</i>	1600
<i>Mucor amphibiorum*</i>	8
<i>Penicillium chrysogenum</i>	52
<i>Rhizopus stolonifer</i>	20
Sum of the Logs (Group II):	17.72
ERMI (Group I - Group II):	25.58

ERMI score: 25.58

Aspergillus penicilloides = 33,000 (10)

Aspergillus versicolor = 680 (10)

Chaetomium globosum = 97 (6)

Stachybotrys chartarum = 51 (6)

Wallemia sebi = 2,100 (6)

(HERTSMI-2 score: 38)

Get out ASAP!

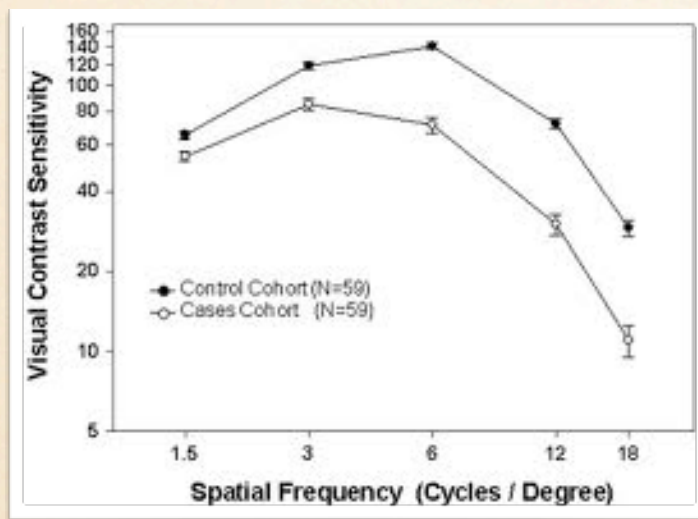
Case Criteria for a Diagnosis of Mold Toxicity Syndrome

1. Multiple unexplained or non-responsive symptoms.
2. Evidence for HLA genetic susceptibility.
3. Evidence for the documented pattern of abnormal findings seen in exposed HLA-susceptible patients.

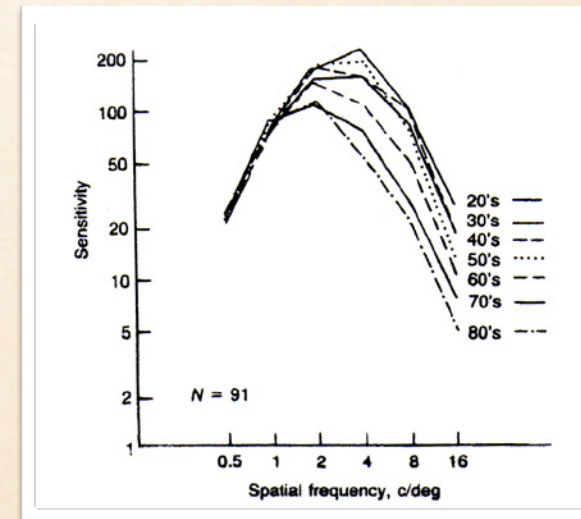
- Patient presents with multi-symptom, multi-system illness.
- Past history of exposure to a water damaged building (optional).
- Failed visual contrast sensitivity testing (8% false negative).
- Current ERMI Score >2 in home, office, and/or school.
- Markers for HLA genetic susceptibility (see *Rosetta Stone*).
- Pattern of abnormal findings seen in biotoxin illness.

Visual Contrast Sensitivity Testing

Most biotoxins are neurotoxic. The optic nerve's superolateral rim carries the fibers responsible for edge-detection needed for visual contrast sensitivity (VCS). For vascular supply reasons, this rim is more vulnerable to neurotoxic effects. Neurotoxicity thus causes a decrease in VCS that self-corrects with a sufficient reduction in toxin carriage. Age-related decreases in VCS are not reversible, or so it is assumed.



Biotoxin illness: *reversible*



Age-related: *irreversible?*

Who gets sick: HLA susceptibility to poor clearance of biotoxins.

The **Rosetta Stone** for interpreting HLA nomenclature in biotoxin illness:

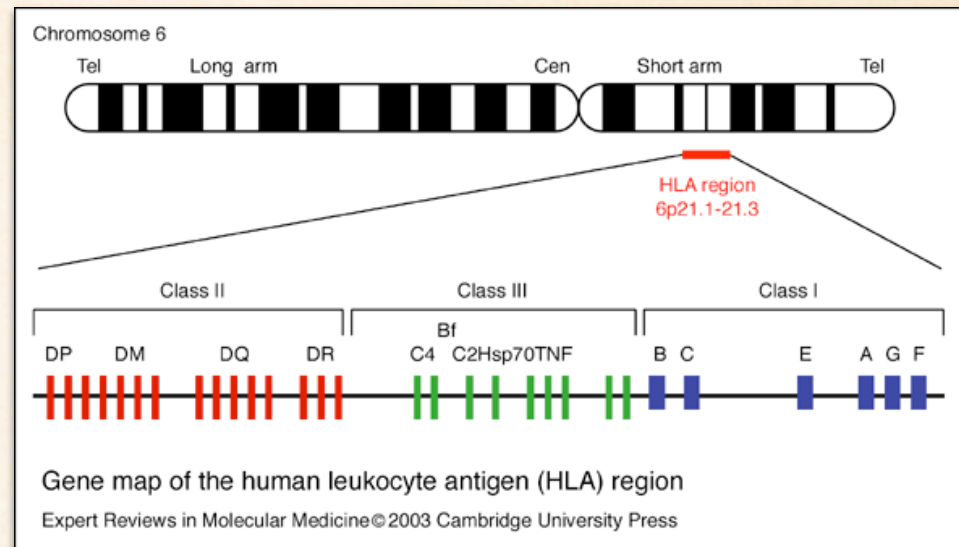
DRB1	DQB1	DRB3	DRB4	DRB5
4	3		53	
11/12	3	52B		
14	5	53B		
7	2/3		53	
13	6	52A,B,C		
17	2/3	52A		
18	4	52A		
15	6			51
16	5			51
11	7	52B		

HLA haplotypes in each row are associated with at least twice the risk of treatable biotoxin clearance susceptibility problems compared to controls.

Shoemaker R. Linkage disequilibrium in alleles of HLA DR: differential association with susceptibility to chronic illness following exposure to biologically produced neurotoxins. American Society of Microbiology 2003. (conference peer review).

Genes Load the Gun...

- Specific haplotypes affect susceptibility to poor clearance of biotoxins.
- More research needed to clarify relative risks of the homozygous 8-4 haplotype.



Exposures Pull the Trigger.

- Biotoxin exposures call out the genetic vulnerability to poor clearance.
- Molds, blue-green algae, and dinoflagellates are the main sources of biotoxin exposure.



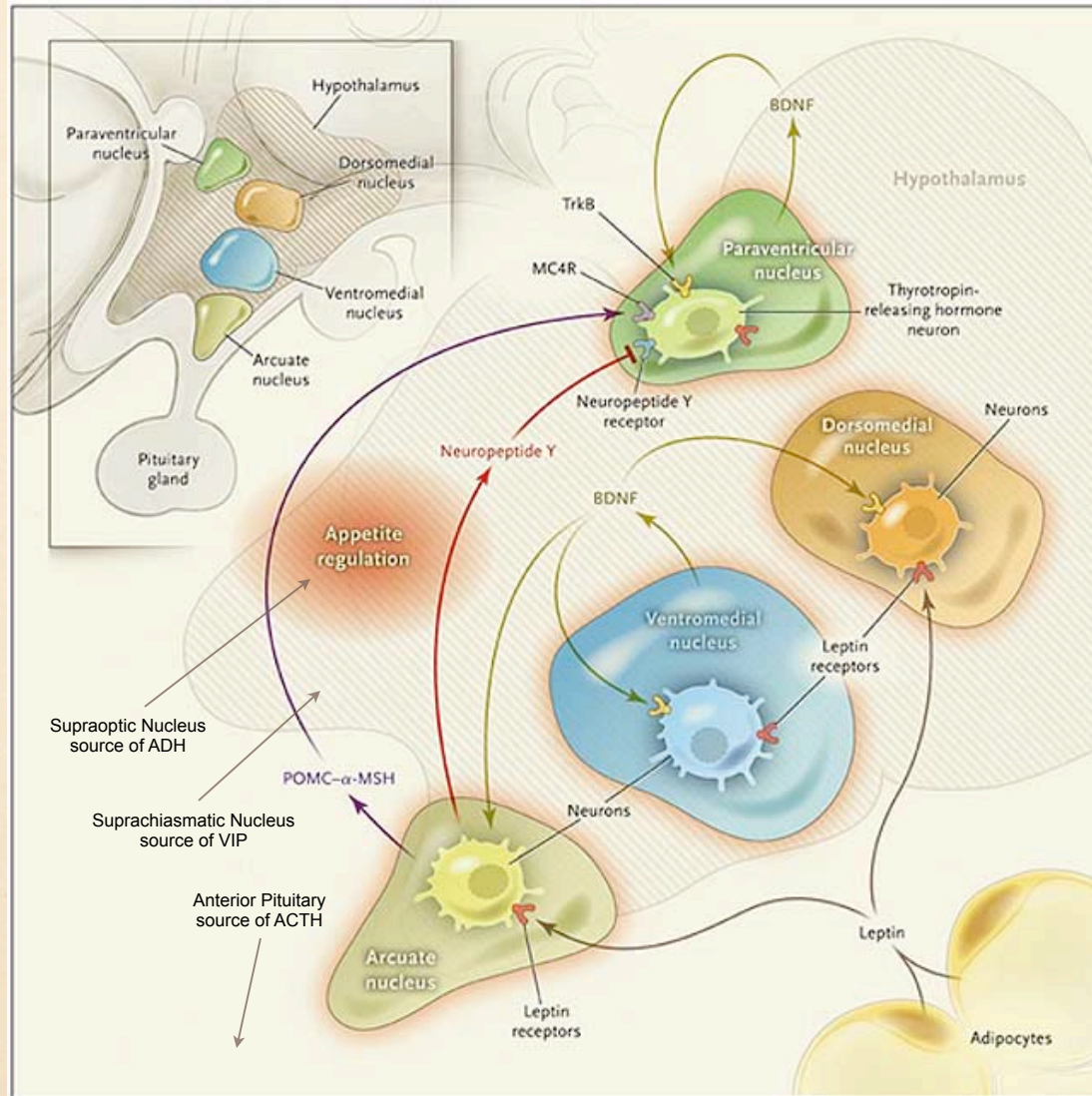
Key Biomarker Abnormalities in Mold Toxicity Syndrome

<i>Biomarkers</i>	<i>Physiology</i>	<i>What it Means</i>
High C4a, Low C3a	Innate immune system in overdrive due to toxins	A biotoxin burden is present.
High MMP-9	Tissue barrier disruption and remodeling	Neuroimmune stress and/or injury is likely.
High TGF beta-1	Immune suppression+activates Th17-driven inflammation	Imbalanced innate-adaptive immune response is likely.
Low MSH	Disrupted neuropeptide regulation of immune function	Impaired tissue-based immune defenses.
Low ADH	Dysregulation of ACTH and kidney water conservation	Impaired stress response, chronic dehydration.
Low or High VEGF	Chronic tissue hypoxia	Imbalanced response to capillary hypo-perfusion.
Low VIP	Poorly controlled inflammation and blood flow	Impaired regulation of multiple functions.
Low Treg cells	Poorly suppressed inflammation	Chronic inflammatory response syndrome.

References

High C4a, Low C3a	Zhou W. The new face of anaphylatoxins in immune regulation. <i>Immunobiology</i> . 2012;217(2):225-34 (C3a up-regulates Th2-driven antibody responses to foreign particles. We await more research into C4a-specific effects on the activation or inhibition of Th1, Th2, Th17, and/or T reg cell activities).
High MMP-9	Romi F, Helgeland G, Gilhus NE. Serum levels of matrix metalloproteinases: implications in clinical neurology. <i>European Neurology</i> . 2012;67(2):121-8 (MMP-9 levels correlate with multiple sclerosis activity and ALS neurodegenerative activity).
High TGF beta-1	Han G, Li F, Singh TP, Wolf P, Wang XJ. The pro-inflammatory role of TGF beta-1: a paradox? <i>International Journal of Biological Sciences</i> . 2012;8(2):228-35. (TGF beta-1 has both pro-inflammatory [Th17, Th2] and anti-inflammatory [Foxp3-induced CD4+CD25- T reg cells]).
Low MSH	Catania A, Lonati C, Sordi A, Carlin A, Leonardi P, and Gatti S. The melanocortin system in control of inflammation. <i>The Scientific World Journal</i> . 2010;10:1840-1853. (MSH and ACTH are melanocortin peptides. MSH reduces overactive immune responses in various tissues).
Low ADH	Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. <i>Regulatory Peptides</i> . 2000;96(1-20):23-9 (Low ADH [vasopressin] levels reduce stress adaptation capacity by lowering cortisol and kidney water conservation capacity).
Low or High VEGF	Mayer G. Capillary rarefaction, hypoxia, VEGF, and angiogenesis in chronic renal disease. <i>Nephrology, Dialysis, and Transplantation</i> . 2011;26(4):1132-7 (If VEGF-induced hypoxia counter-regulatory factors can exert beneficial or harmful effects in chronic kidney disease, they likely do so in other tissues as well).
Low VIP	Shoemaker RS, House D, Ryan JC. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. <i>Health</i> . 2013;5(3): 396-401 (VIP is a regulator of immune, oxygenation, and blood flow functions).
Low T reg cells	Goldstein JD, Perol L, Zaragoza B, Baeyens A, Marodon G, Piaggio E. Role of cytokines in thymus-derived vs. peripherally derived regulatory T cell differentiation and function. <i>Frontiers in Immunology</i> . 2013;4:155. (TGF-beta can shift activity from T regs to Th17 cells. C3a-C4a-C5a also play a role).

CIRS Reduces Levels of Key Regulatory Neuropeptides



Adrenocorticotrophic hormone (ACTH)

Pituitary ACTH induces release of cortisol. Low levels reduce inflammation control and stress resilience.

Alpha melanocyte stimulating hormone (MSH) Pituitary MSH coordinates mucous membrane-based immune defenses. Low levels may result in leaky barriers, low ADH, and chronic membrane inflammation.

Anti-diuretic hormone (ADH)

Hypothalamic ADH induces kidneys to conserve water. Low levels result in dehydration and osmolality changes that aggravate inflammation.

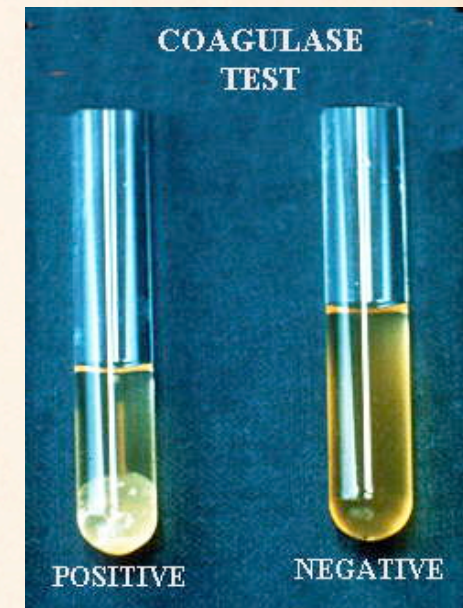
Vasoactive intestinal polypeptide (VIP)

Down-regulates Th1 responses, up-regulates tolerogenic dendritic cells and antigen-specific Treg cells, and improves microcirculatory blood flow.

Multidrug Resistant Coagulase Negative Staph (MRCoNS)

Long-considered non-pathogenic for lacking an enzyme that coagulates plasma, coagulase-negative staph (CoNS) are now considered pathogens for other reasons, including:

- Their *ability to participate in biofilm communities* that host a range of other bacteria and that may also include fungal and protozoal species.
- Their *ability to differentially active gene expression*.
- Their *ability to make and release hemolysins* - pore-forming toxins that can disrupt cell membranes membranes.
- Their *ability to make and release exotoxins* that interfere with host immune defenses that *can incapacitate MSH*.
- Their *ability to develop multidrug resistance* (MRCoNS).



If MSH is low, obtain deep nasal culture for MRCoNS!

Khosravi Y, Ling LC, Loke MF, et al. Determination of biofilm formation capacity of bacterial pathogens associated with ENT diseases in the Malaysian population. *Eur Arch Otorhinolaryngol*. 2013 Jul 24.

Zell C, Resch M, Rosenstein R, et al. Characterization of toxin production of coagulase negative staphylococci isolated from food and starter cultures. *Int J Food Microbiol*. 2008 Oct 31;127(3):246-51.

Rapidly Changing Markers of Biotoxin Exposure

Based on Re-exposure Trials

	day 1	day 2	day 3
C4a	<i>rises</i>		
TGFb1	<i>rises</i>		
VEGF	<i>rises</i>		<i>falls</i>
Leptin		<i>rises</i>	
MMP-9			<i>rises</i>

This 3-day Sequential Activation of Innate Immune Elements (SAIIE) panel is a CIRS health index that answers the question, "Did the building cause the patient's symptoms and abnormal biomarkers?" Results correlate well with ERMI results. As a test, SAIIE must be done in the genetically susceptible who achieved a healthy baseline by toxic mold avoidance and use of cholestyramine or welchol.

Shoemaker R, House D. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. Neurotoxicology and Teratology 2006; 573-588.

Interpreting C4a Levels

<i>Level</i>	<i>Clinical Significance</i>
2,380-5,000	concerning
5,000-10,000	worrisome
>10,000	needs prompt reduction
>20,000	indicates repeated exposures, “sicker, quicker” sensitivity, MASP1 + MASP2 activation

Shoemaker R, House D. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. *Neurotoxicology and Teratology* 2006; 573-588.

The Roles of C3a and C4a in Host Defenses

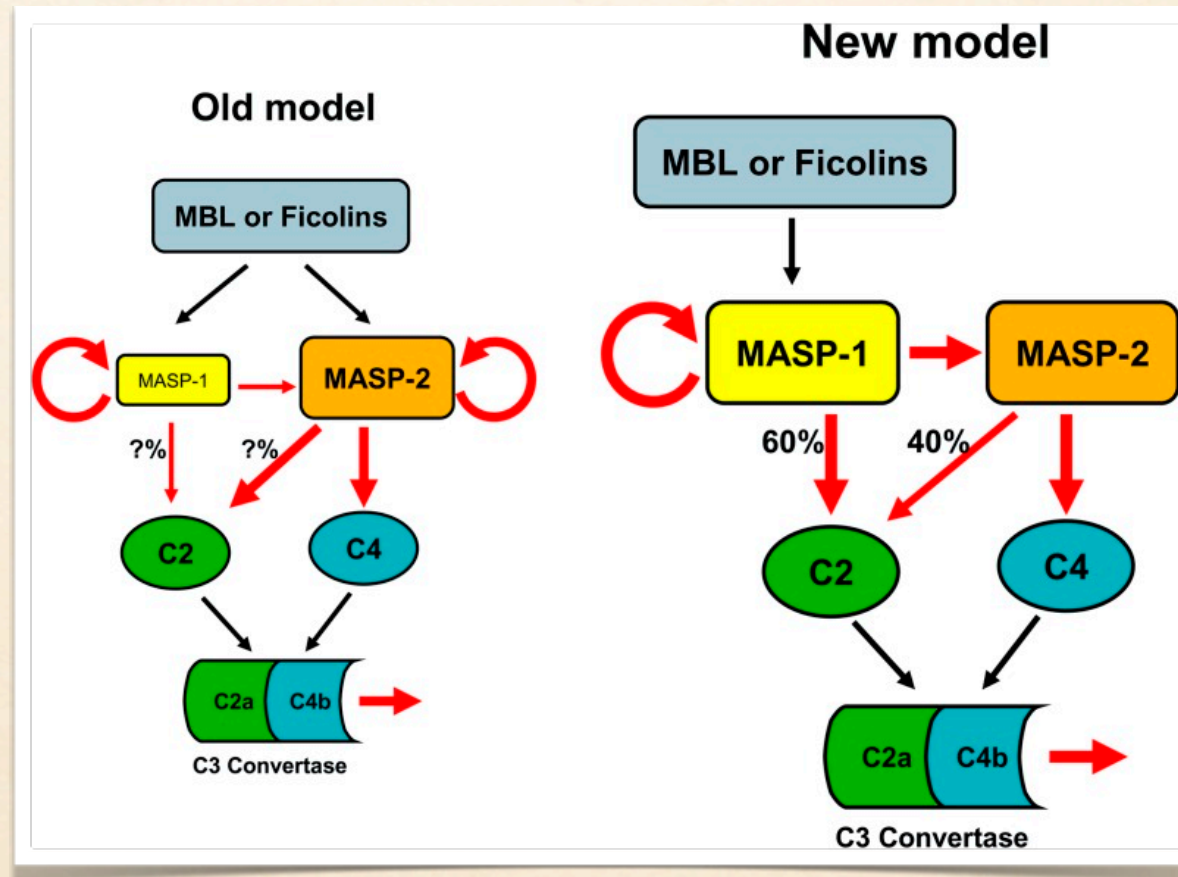
The lectin pathway of the complement system serves as a first line of defense against microbial intruders. The innate immune system recognizes danger signals presented by the pathogens (pathogen-associated molecular patterns) or altered host cells (damage-associated molecular patterns) by means of germline encoded cell-surface bound *or* soluble pattern recognition molecules. These pattern recognition molecules have evolved against evolutionarily conserved structures of microorganisms, such as carbohydrates and acetylated compounds.

The pattern recognition molecules do not act alone - they are associated with other proteins, mainly serine proteases. These serine proteases (MBL-Associated Serine Proteases), or MASPs, become activated to initiate the complement cascade when the recognition molecules bind to their target. Activation of the complement cascade culminates in the destruction and elimination of pathogens *or* dangerous molecules via direct cell lysis or opsonization, respectively.

C3a and C4a are anaphylatoxins. C3a reacts to bacterial membrane molecules. C4a reacts to biotoxins. Lyme disease can raise C3a and C4a levels. CIRS-WDB raises C4a and tends to lower C3a levels.

Heja D, Kocsis A, Dobo J, et al. Revised mechanism of complement lectin-pathway activation revealing role of serine protease MASP-1 as the exclusive activator of MASP-2. *Proc Natl Acad Sci USA*. 2012 Jun 26;109(26):10498-503.

How MASP-1 and MASP-2 are activated by the Mannose Binding Lectin (MBL)-Associated Complement Pathway



Heja D, Kocsis A, Dobo J, et al. Revised mechanism of complement lectin-pathway activation revealing role of serine protease MASP-1 as the exclusive activator of MASP-2. *Proc Natl Acad Sci USA*. 2012 Jun 26;109(26):10498-503.

The dual regulatory roles of TGF beta-1

Pro-inflammatory Th17 cells vs. Anti-inflammatory Treg cells

Activated Th17 cells supply their own TGFb1 to help maintain their pro-inflammatory posture in antigen-challenged tissues like mucous membranes. T reg cell-derived TGFb1 helps maintain the immune suppressing action of T reg cells in the body's periphery.

Th17 cells secrete cytokines IL-17, IL-21, and IL-22, shown to be more active in autoimmune and inflammatory disease.

T reg cells delete autoreactive T cells, induce tolerance, and dampen inflammation. Natural T regs are thymus-derived. Inducible T regs are present in the periphery. TGFb1 recruits both types.

Peterson RA. Regulatory T cells: diverse phenotypes integral to immune homeostasis and suppression. *Toxicologic Pathology*. 2012;40(2):186-204.

Hatton RD. TGF-b in Th17 cell development: the truth is out there. *Immunity*. 2011 Mar 25;34(3):288-90.

Han G, Li F, Singh TP, Wolf P, Wang XJ. The pro-inflammatory role of TGF beta-1: a paradox? *International Journal of Biological Sciences*. 2012;8(2):228-35.

Physical Effects of High C4a Levels

C4a reduces capillary perfusion, producing the following well-documented pathophysiological effects:

- Reduces VO₂ Max and thus lowers anaerobic threshold.
- Lowers ratio of glutamate/glutamine (G/G) as measured by magnetic resonance spectroscopy (MRS).
- Raises lactate as measured by magnetic resonance spectroscopy.

Neuronal cells synthesize glutamate from glutamine. Glutamate is a substrate for the neuronal TCA cycle. Thus, in addition to its excitatory neurotransmitter role, glutamate is involved in neuronal energy production. A reduced glutamate/glutamine ratio indicates capillary hypoperfusion, reduced neuronal energy, loss of glutaminergic excitatory activity, and possibly micro-interstitial edema in the brain. Correction of C4a levels correlates with improved VO₂ max, MRS G/G ratio, MRS lactate, and with improvements in cognitive function, tolerance for exertion, and other symptoms associated with CIRS.

Shoemaker R, Maizel M. Treatment of elevated C4a in patients with CFS using low doses of erythropoietin safely reduces symptoms and lowers C4a: a prospective clinical trial 2007, IACFS (conference peer review).

Lanz B, Gruetter R, Joao MN Duarte. Metabolic flux and compartmentation analysis in the brain *in vivo*. *Frontiers in Endocrinology (Cellular Endocrinology)*. doi: 10.3389/fendo.2013.00156

The role of C4a in Coagulation

In a diagnostic re-exposure trial, Ristocetin-associated factor, von Willebrand's (vW) antigen, and multimers of von Willebrand's antigen all fell by day 3.

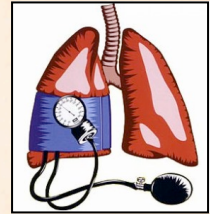
In cases where vW factors initially rose, they included factor VIII, von Willebrand's antigen, and ristocetin-associated factor.

Rising levels of C4a prevent the formation of the fibrin multimers that are needed to form the scaffolding for proper blood clotting. Without these multimers, mucosal bleeding becomes more likely.

The drug desmopressin (also known as DDAVP) helps correct the bleeding problem by enhancing the ability of fibrin monomers to form multimers.

Biotoxin Illness is a Cause of Pulmonary Hypertension.

Vasoactive Intestinal Polypeptide can Reverse It.



The pathophysiology of PAH:

Proliferation of pulmonary vascular endothelium resulting in elevation of right heart pressures and peripheral hypoxemia.

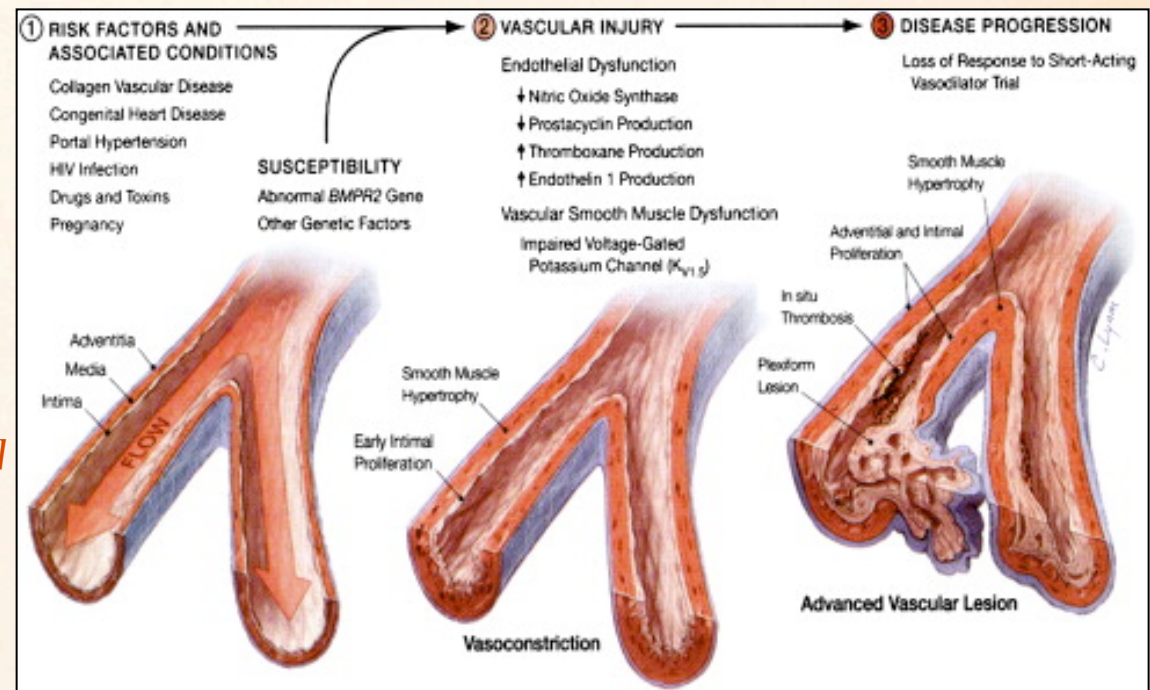
Non-invasive diagnosis of PAH:

Stress echo with calculation of right atrial pressure pre- and post-exertion:

[(tricuspid regurg) x 4 + right atrial pressure]

Treatment of CIRS-PAH with VIP:

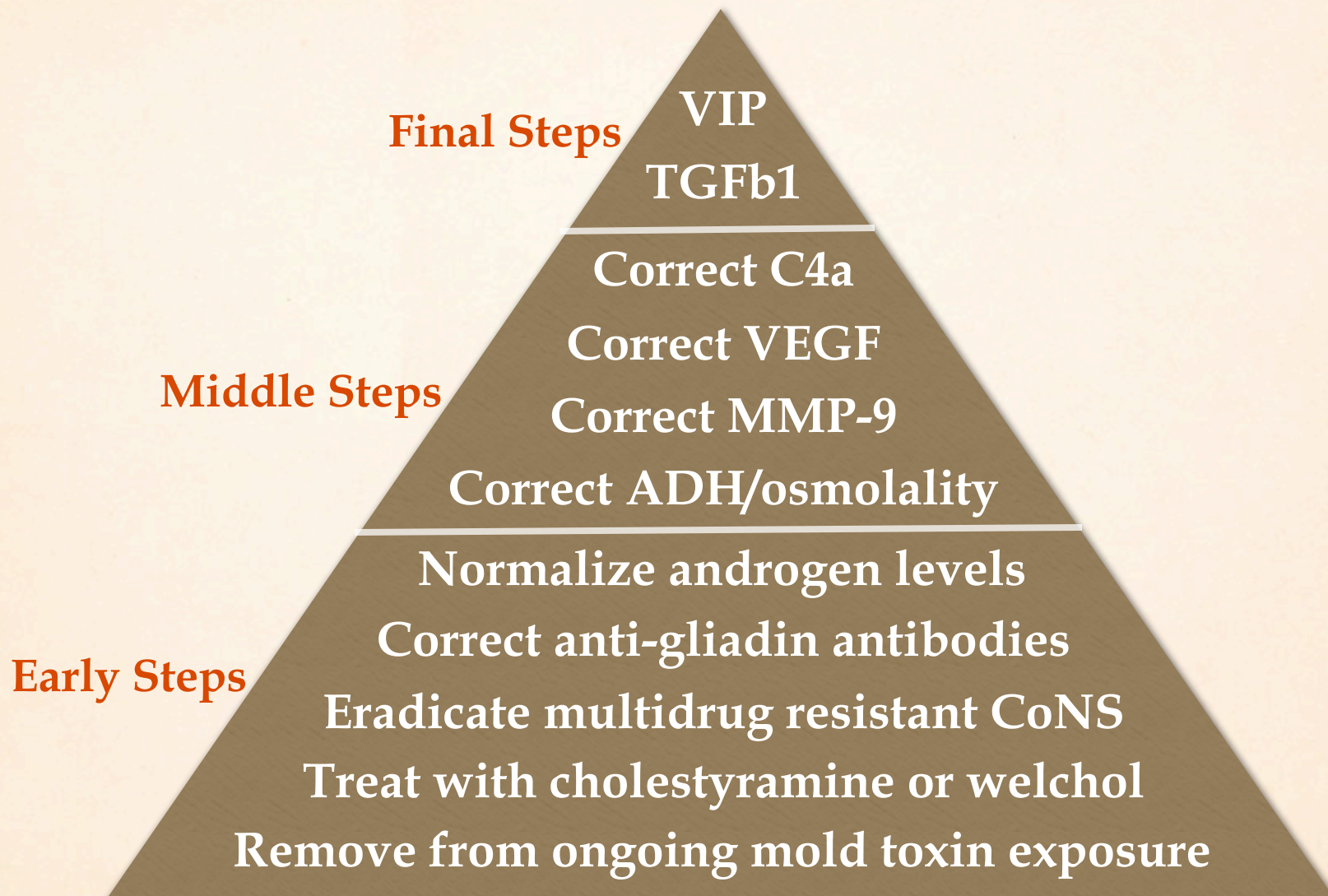
Nasally inhaled VIP, 4-6 times daily to reduce TGFb1-induced airway remodeling.



Shahzad GR, Shabaz MR. Treating pulmonary arterial hypertension: current treatments and future prospects. *Therapeutic Advances in Chronic Disease*. 2011 Nov;2(6):359-70.

Shoemaker RS, House D, Ryan JC. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. *Health*. 2013;5(3):396-401.

Stepwise Treatment Protocol for CIRS



Shoemaker RS, House D, Ryan JC. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. *Health*. 2013;5(3):396-401.

Early Treatment Steps for CIRS

Remove from ongoing mold exposure or the deal's off



The first step is often the most difficult because recovery is not possible without strict avoidance of exposure to toxic molds. To get well one must produce toxin egress while stopping toxin ingress.

Early Treatment Steps for CIRS

Treat with cholestyramine (CSM) or Welchol

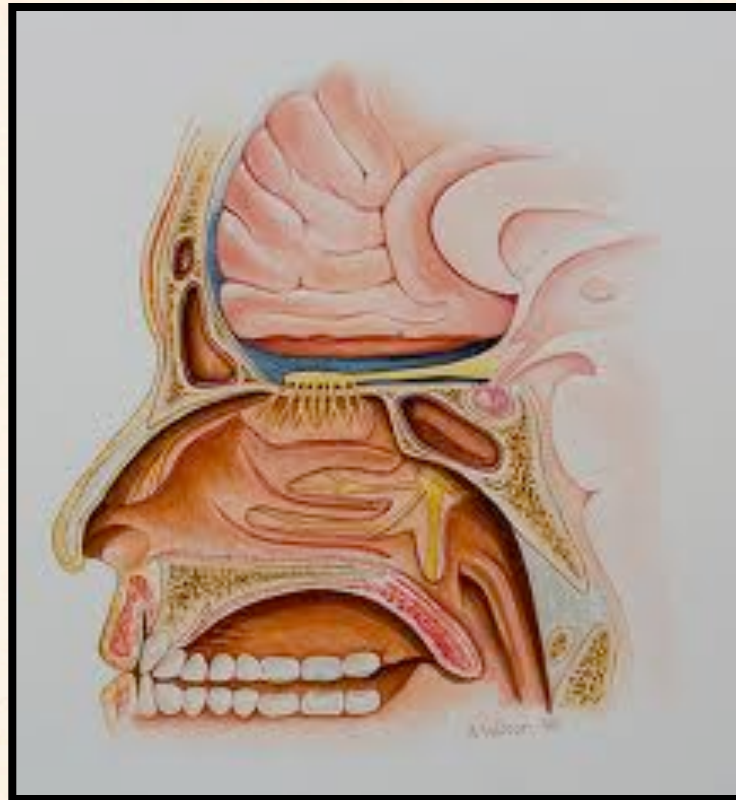


Patients must adhere to detailed guidelines in order to obtain the best possible results. Should be monitored by a physician with experience in the treatment of chronic inflammatory response syndrome.

Shoemaker R, House D. Sick building syndrome (SBS) and exposure to water-damaged buildings: Time series study, clinical trial and mechanisms. *Neurotoxicology and Teratology* 2006; 573-588.

Early Treatment Steps for CIRS

Test for MRCoNS and eradicate it's presence



MRCoNS and other biofilm-associated microbes in the deep nasal space cause various troubles for the immune system and the brain.

Shoemaker R, Hudnell K, House D, Domenico P. Association of nasal carriage of methicillin resistant and multiple antibiotic resistant coagulase negative staphylococci species with deficiency of alpha melanocyte stimulating hormone in Chronic Fatigue Syndrome: implication for expanded treatment options. American Society of Microbiology 2003 (conference peer review).

Early Treatment Steps for CIRS

**Hasten binder-mediated toxin clearance with
a gluten-free, amylose-free diet**

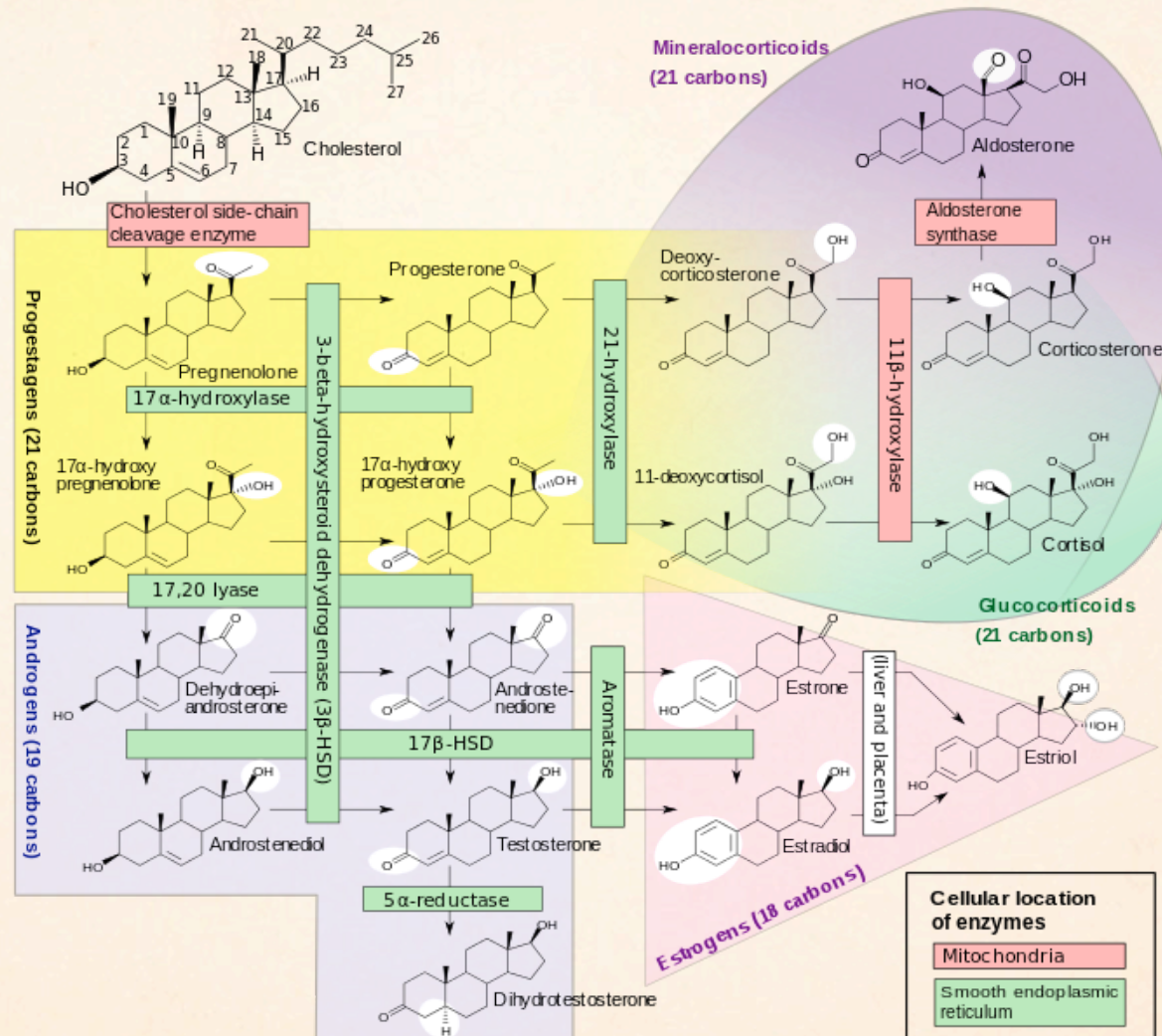


The Rosa Parks Bus - Henry Ford Museum

Strict adherence to dietary guidelines leaves more bus seats open for clearance of toxins. The Welchol bus is slower and smaller than the CSM bus but it's more user friendly.

Early Treatment Steps for CIRS

Androgen levels tend to self-correct with toxin clearance.

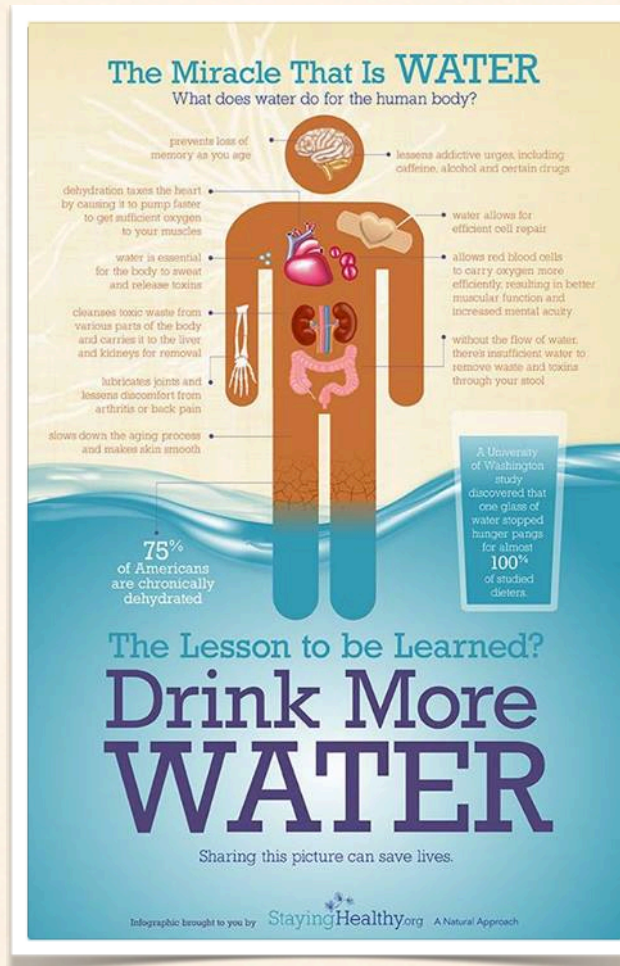


If estradiol is high an aromatase inhibitor may be indicated.
Testosterone replacement causes more problems than it solves.

Mid-Treatment Steps for CIRS

If ADH rise lags, consider additional measures.

Drinking more water doesn't work because the kidneys aren't able to conserve water when the ADH level is low.

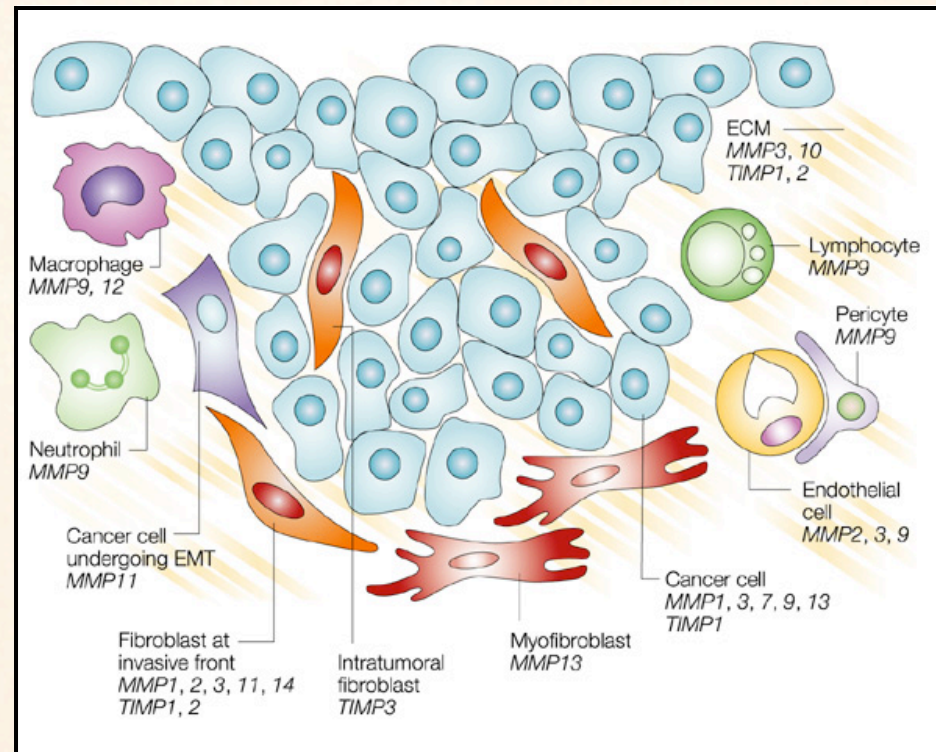


Dehydration alters blood viscosity, the delivery of oxygen and nutrition to cells, and tolerance for exertion.

Replete minerals when osmolality is low.
Use DDAVP (desmopressin) only with close physician supervision.

Mid-Treatment Steps for CIRS

If MMP-9 fall lags, consider additional causes for elevation.



Interacting MMPs and TIMPs* released by varied cell types in a Breast Ca tumor nodule.

MMPs and TIMPs engage in ongoing skirmishes in tissue inflammation zones.

MMP-9 is a gelatinase involved in collagen breakdown and tissue remodeling processes. If high despite reduced toxin carriage, consider the possibility of infectious, autoimmune, or neoplastic disease. VIP may succeed in lowering MMP-9.

*TIMPs = tissue inhibitors of metalloproteinases. *Nature Reviews Cancer* 2012;2:161-174.

Mid-Treatment Steps for CIRS

If VEGF or C4a correction lags,
consider other drivers for abnormal levels.



Lyme disease and lupus can elevate C4a levels. VEGF can remain high or low despite treatment when there are separate causes for capillary hypoperfusion.

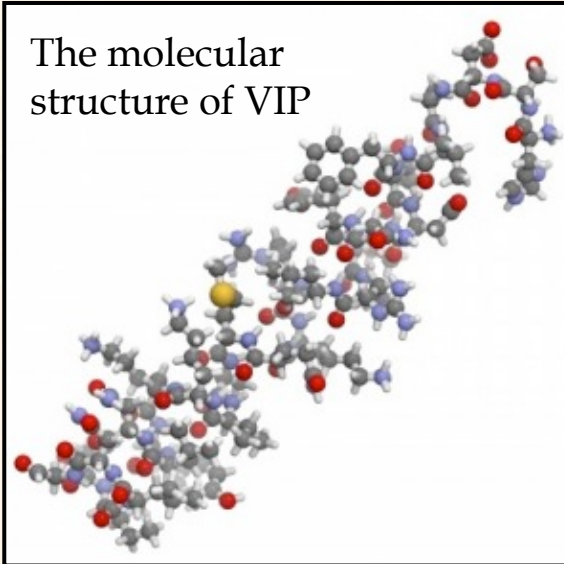
Shoemaker R, Giclas P, Crowder C, House D. Complement split products C3a and C4a are early markers of acute Lyme disease in tick bite patients in the United States. *International Archives of Allergy Immunol* 2008; 146: 255-261.

Stricker RB, Savely VR, Motanya NC, Giclas PC. Complement split products C3a and C4a in chronic Lyme disease. *Scandinavian Journal of Immunology*. 2009 Jan;69(1):64-9.

Final Treatment Steps for CIRS

If TGFb1 remains high or if symptoms persist despite normal VCS, clean ERMI, and (-) MRCoNS, treat with nasal VIP.

The molecular structure of VIP



Vasoactive Intestinal Peptide (VIP) is a neuropeptide, expressed by lymphoid as well as neural cells, which has diverse effects on the cellular mediators of inflammation and immunity and is also a potent neurotransmitter. As a neurotransmitter, VIP exerts a potent bronchodilatory and vasodilatory effect and also induces the house-keeping of mucus secreted by submucosal glands. It has immunomodulatory functions which include humoral immune response suppression and inhibition of vascular and bronchial remodeling.

- *modified excerpt from* Mathioudakis AG, et al. Vasoactive intestinal peptide inhaled agonists; potential role in respiratory therapeutics. *Hippokratia*. 2013 Jan-Mar;17(1):12-16.

Benefits and Side Effects of VIP

Beneficial Effects of VIP

- lowers high C4a
- lowers high TGFb1
- raises low VEGF
- lowers high VEGF
- lowers high MMP-9
- raises low vitamin D3
- lowers high vitamin D3
- raises thymus-derived and induced T reg cells
- reduces reactivity to WDB

Potential Side Effects of VIP

- may raise lipase levels
- may cause stomach or abdominal discomfort by reducing gastric hydrochloric acid secretion
- may cause excessively low blood pressure (is a vasodilator)
- may cause a rash

For use only with physician supervision. Stop use of VIP if lipase rises or if abdominal pain, hypotension, or rash occur(s).

How CIRS-WDB results in a multisymptom, multisystem illness *made worse* by usual medical care:

Mold toxins and inflammagens from sick indoor air trigger MBL-related MASP activation in the genetically susceptible, raising C4a, TGFb1, Leptin, and MMP-9 levels, producing a variety of symptoms.



Inflammatory cytokines disrupt the balance of regulatory neuropeptides, producing more symptoms. TGFb1 goes higher to suppress immune up-regulation, but balance may shift from T reg cells to pathogenic Th17 cells, producing more inflammation, making symptoms worse.



Patients present with a multisymptom, multisystem illness that persists despite “excellent” medical care from various specialists, at great expense. They have been told that there is nothing wrong, that “all is explained” by depression, that they need to get a life or exercise more. Some are discharged from care for being “chronic complainers” or “high maintenance.” Meanwhile, even the most well-intentioned specialists are guaranteed to keep missing the data they’re not looking for.

This needs to stop.

Estimated scope of the CIRS-WDB problem:

US population: 315 million

One in four = 80 million at risk for CIRS-WDB

NIOSH estimate of percent of US buildings with water damage: 50% = 40 million exposed to WDB

Conservative estimate of percent harboring toxic molds: 10% = 4 million with CIRS-WDB

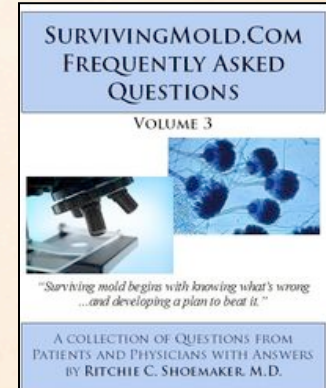
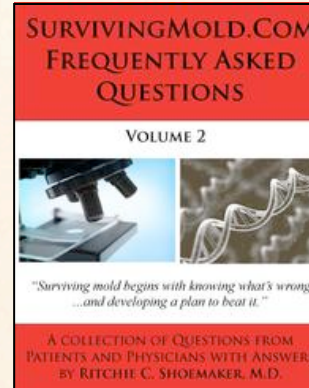
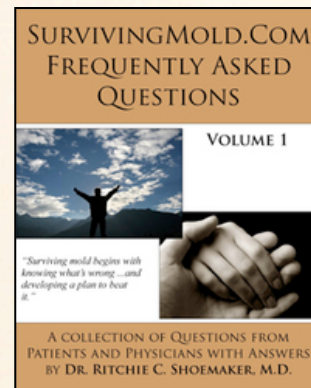
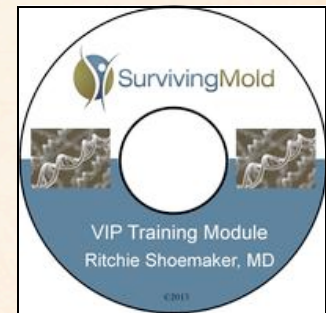
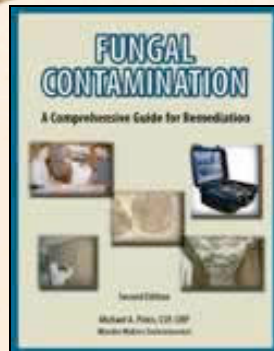
That's 40 Michigan Wolverine football stadiums filled with 100,000 people needlessly suffering from lack of access to competent medical care.

Thomas G, Burton NC, Mueller C, Page E. Comparison of mold exposures, work-related symptoms, and visual contrast sensitivity between employees at a severely water-damaged school and employees at a school without significant water damage. *CDC Workplace Safety and Health: Health Hazard Evaluation Report*. 2010.

Access to competent medical care for people with CIRS-WDB needs to be a national health care priority.

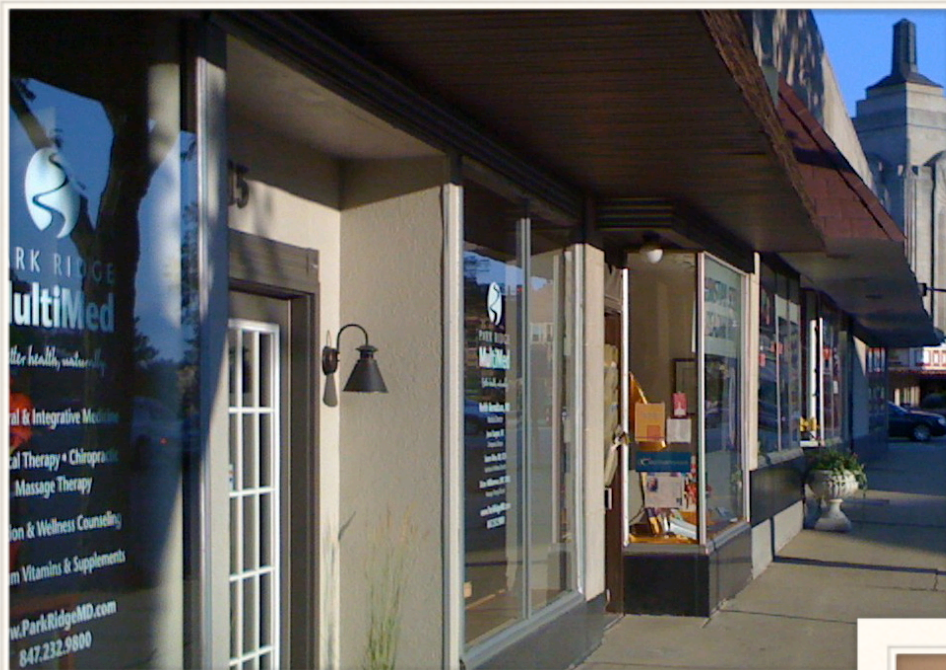
Calling all health care professionals!

Climb the CIRS-WDB learning curve with the resources below:



All of the above available for purchase through:

www.survivingmold.com



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