

Waking Up the Nation,
One Reader at a Time...

PUBLIC HEALTH ALERT

Will Surviving Mold Mean Surviving Lyme?

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With Laura Mark, MD

NOTES FROM THE MOLD FRONTIER...

Take out a microscope and look under the in the kitchen cabinet right underneath the pin-hole leak in the water supply line. Is there something growing in the waster-damaged area? You bet: You'll surely see some filamentous fungi (AKA molds), but look too at the bacteria and actinomycetes. They are feasting on the simple food stuffs created by the extracellular digestive enzymes of the fungi. Free food! This habitat is a nice warm 65-72 degrees all day, every day, year round. Microbe paradise! Plenty of food, plenty of moisture and plenty of places to breed safely means plenty of microbial growth and plenty of secondary products of microbial metabolism.

Call the products toxins, inflammagens, cell wall fragments and beta glucans; they are all foreign antigens as far as our immune response is concerned. And they all cause intense inflammatory responses that are well-demonstrated in tests of innate immunity.

If you put those compounds in the nose or lung of someone with "increased susceptibility," you will see innate immune functions going nuts trying to defend against the invasion of these foreign antigens. The excessive host inflammatory response can become the enemy if levels of melanocyte stimulating hormone (MSH) are low or if there is a particular collection of immune response genes present. As it turns out, about 25% of the general population have these specific immune response genes (HLA DR).

Add to this exam-

ple of health hazards created by a leaky pipe some other sources of water intrusion that beget microbial growth like musty basements, crawlspaces with sagging flexible duct work, leaky roofs and slidshod construction in schools, homes and workplaces. You will see why in 2011 NIOSH says that **50% of our buildings** in the US are water-damaged.

Do you think that people with chronic illnesses *are helped* by being subjected to inflammatory stressors from within? No, they aren't. Don't forget, those chronic illnesses are altered in presentation and therapy by such exposure to toxigenic microbes.

This entire mold problem hasn't gone unnoticed. There are numerous reports from US agencies (some are just downright deceptive, however; don't believe it when you hear that mold



Dr. Ritchie C. Shoemaker

is a nice warm fuzzy co-habitant that doesn't make people sick unless they eat it), the Government Accountability Office and the World Health Organization all describe how moldy buildings sicken people. There are hundreds of academic papers published showing the diversity and intensity of the inflammatory responses found in people sickened by exposure to the interior environment of water-damaged buildings (WDB) even without other illnesses. We have accurate diagnostic tests

PUBLIC HEALTH ALERT

and our meticulous research has defined the abnormal physiology carefully. Such delineation led to published treatments that detail the step-by-step protocols used successfully by our group (and countless others) in thousands of patients. We aren't done; these illnesses continually show us that there is still much to learn.

Paralleling the march of science in the "mold" community has been a similar call in the Lyme community: to (1) establish better diagnostic tests, (2) identify accurate physiologic markers that define the illness; and then, (3) publish case control data on protocols (not anecdotes!) that work. We have these three defining parameters in the mold world but they are not yet in the world of Lyme. Indeed, some practitioners who focus on Lyme still don't acknowledge the devastating effect of exposure to the interior environment of WDB has on their patients. Lyme isn't just Lyme when a patient is moldy too. And to secure the diagnosis of Lyme, the illness must pass intact and unchallenged through the sieve of all other

CIRS, including mold.

Mold illness is **essentially identical to Lyme in symptoms and chronicity**. This observation is critical to understanding why some Lyme patients just don't get better with antibiotics. There can be no "clinical diagnosis" of Lyme simply based on the geography at the time of onset of illness or symptoms until mold has been considered and ruled out by careful environmental evaluation and sampling that includes DNA sampling. Mold illness doesn't get better with antibiotics.

Maybe some perspective will help bring understanding to treatment of the many patients suffering needlessly who are taking antibiotics for Lyme that haven't worked. The answers start with genetics, move on to loss of regulation of inflammation and then to the effects of unregulated inflammation (including silent colonization by commensal bacteria living in biofilms). Finally, correction of T regulatory cell (T regs) abnormalities must occur before return to normal health can be claimed. In the end, if the inflammatory elements that are invari-

ably abnormal in Lyme and mold, specifically C4a, TGF beta-1 and MMP9, aren't identified and corrected the patients won't get better. Said bluntly: **If these parameters aren't improving with a given therapy, the therapy isn't correct**. Clearly, what many physicians who treat mold illness use for therapy has direct application to the management of illnesses collectively called Post-Lyme Syndrome.

The reader may find complete discussions and up-to-date information on mold illness at www.survivingmold.com and by reading *Surviving Mold: Life in the Era of Dangerous Buildings*, by Ritchie C. Shoemaker MD, published 12/2010. Another useful resource is the peer-reviewed consensus statement, "The Expert Mold Treating Physicians Report," hosted by Policyholders of America (see www.survivingmold.com or www.policyholdersofamerica.com) and published in 7/2010. This consensus statement has the most complete set of references of any of the current mold reports. Additional information is found at www.globalindoorhealthnetwork.com.

So what is "Mold Illness?"

Long answer: The acute and chronic health conditions caused by exposure to the interior environment of a building with a history of, or ongoing, water intrusion in which there is amplified growth of microbes, including but not limited to fungi, bacteria, mycobacteria and actinomycetes; and presence of inflammagens in air and dust, including but not limited to beta-glucans, endotoxins, mycotoxins, mannans, proteinases, hemolysins, microbial volatile organic compounds (mVOCs) and spirocyclic drimanens. The illness is readily identified by a combination of health symptoms, visual contrast sensitivity (VCS) deficits and abnormalities shown in blood tests performed by high complexity, CLIA-approved laboratories. **These tests are eligible for insurance coverage and are all available to practicing physicians** (see www.survivingmold.com at the laboratory section).

Short answer: this is an incredibly common Chronic Inflammatory Response Syndrome from

PUBLIC HEALTH ALERT

Water-Damaged Buildings (CIRS-WDB). The lesson for the Lyme community is that Post-Lyme is a CIRS too.

The US Government Accountability Office (US GAO) conducted and published its own review of governmental agency efforts to look at CIRS-WDB. What they found wasn't pretty: no rigorous science, no coordination of research efforts and no involvement sought by agencies of people who actually treated the illness. At least the GAO provided an overview of the

inflammatory basis of the illness and a case definition. That definition superseded the one published by our group in 2003. The GAO looked for three elements: (1) similarity of symptoms of a given individual to those published (see roster of symptoms in Table 1) and a (2) similarity of lab abnormalities seen in published studies involving experimental animals and people (see roster of lab abnormalities in Table 2). Finally, the (3) GAO wanted to see improvement with treatments. The GAO reserved special criticism

for a paper published in 2006 from the American Academy of Allergy, Asthma and Immunology (AAAAI) that is routinely used by defense interests in mold litigation.

In July 2009, the World Health Organization (WHO) weighed in with a far more comprehensive assessment of the inflammatory basis for mold illness, with recognition of the diverse potential sources of inflammation found inside WDB.

The mold world is dominated by litigation, with outcomes of per-

sonal injury cases resting on decisions made by judges across the country that have a marked diversity of interests in the science involved in mold illness. The defense in these cases can only cite one or two papers that purport to show that mold illness can't possibly exist, especially the 2002 (and now 2011) consensus statement from the American College of Occupational and Environmental Medicine (ACOEM). This trivial contrivance has no data, no science and nothing even close to facts in it, and the newer

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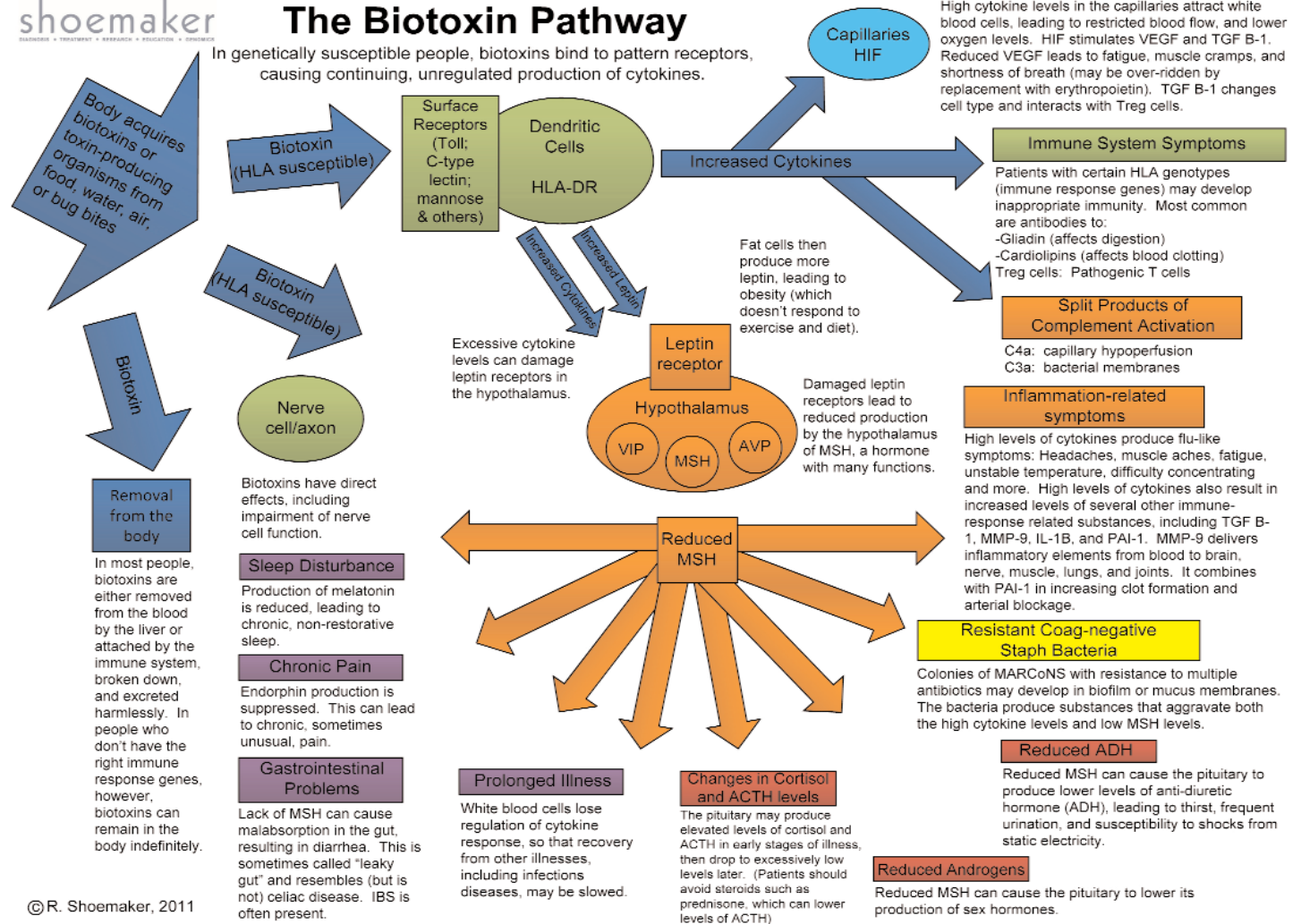
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DESIGNER • THERAPIST • EDUCATOR • AUTHOR • ORATOR

The Biotoxin Pathway

In genetically susceptible people, biotoxins bind to pattern receptors, causing continuing, unregulated production of cytokines.



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version added no new information and no new references despite the passage of nine years (see ACOEM: Ploys and Lies at www.survivingmold.com), yet there it is at every mold case, portrayed as the best science in the world. Unfortunately for the defense, however, the collusion and bastardization of science that underlies ACOEM was exposed by Dr. James Craner in 2008 (see link on

www.survivingmold.com) and the Wall Street Journal in 1/2007 in an expose` written by David Armstrong (see link on the same website). These battles sound eerily similar to what goes on in the Lyme world: the basic battle of patients and their physicians versus entrenched university types with their numerous conflicts of interest goes on, though I haven't heard of \$22 million judgments against the deer and

mouse community for fomenting tick-borne disease like I see in construction defect mold cases. Not surprisingly, the same strategies manipulated by Big Tobacco for years (see the Tobacco Legacy Library documents at UCSF) involved a tightly coordinated use of well-paid physicians who would opine that cigarette smoking never hurt a fly. In fact, the same docs who so often opine that mold won't hurt a

fly either are the same ones whose opinions were used by Big Tobacco to hide the truth about health risks associated with using tobacco. Actually, few of the physicians involved with mold cases are "insurance company whores." The research interests in the mold community are broad-based with good science being published constantly. International meetings help researchers share peer-

reviewed papers on a regular basis. Physicians affiliated with our group, for example, use the same template to collate and share data in an organized fashion.

Until the Lyme community can attain the same research collaboration from treating physicians, with many clinicians involved in publishing peer-reviewed papers based on hard data and solid statistics, the argument against Post Lyme Syndrome will continue to be a one-sided battle of university physicians with academic reputations (and an agenda) versus anecdote (but also with their own agenda). Organized data collection would end the arguments but even though I hear of attempts to bring such organization to the variety of Lyme docs out there, there is no position paper with authoritative references in favor of long-term antibiotics in Lyme patients not healed by three weeks of antibiotics. Even the studies of long-term antibiotics in Lyme don't sort the benefit of antibiotics alone by HLA haplotype (see below for why this lack of recognition is a major oversight). I recently looked over

some of the opinions I wrote in 1999 and 2000 for the Dr. Bransfield's LISTSERV about microbes and mental illness (mmi) calling for organized data collection; nothing has changed. No organized data collection is ongoing that has led to publication of multiple data-driven papers.

So what is a CIRS-WDB? (And what implications does this entity hold for Post-Lyme patients?)

The innate immune system directs inflammatory responses seen in both mold illness and Lyme disease. The host defenses are constantly prepared for battle with foreign antigens. Antigen detection is performed by specialized cell membrane-based receptors (Toll, c-linked lectin, dectin, mannose and many more) that when activated set off inflammatory responses characterized by release of preformed cytokines and complement. Such inflammatory responses lead to differential gene activation and suppression such that the exact time course of acute exposure/illness acquisition can be identified as a sequence of activation of innate immune

elements (SAIIE). These changes are easily seen in mold illness with re-exposure and in cyanobacterial illness (blue green algae syndromes), also with re-exposure. The exact time course has been delineated by our published research. What we see is complement activation with enhanced production of C4a on day 1; leptin rising on day 2 as cytokine responses block the activity of the leptin receptor in the hypothalamus creating temporary leptin resistance; MMP9 rising on day 2 to day 3 as endothelial cells are producing MMP14 from gene activation by cytokines and then MMP14 is cleaved to MMP9. VEGF rises on day 1 as cytokine responses create capillary hypoperfusion, generating tissue hypoxia. As VEGF rises, enhanced production of TGF beta-1 down-regulates VEGF, a well-documented feature of the day 3 labs. Factor VIII, an acute phase reactant, falls on day 1, recovering to baseline by day 3. von Willebrand's antigen and ristocetin associated co-factor fall by day 3, with such a nadir often associated with bleeding from lung

or nose. Interestingly, TGF beta-1 will rise later in day 1 and is well established by day 2. TGF beta-1 will initially cause a rise of T regs. This rise is difficult to catch unless there are two blood draws on day 1, as by the time the blood is drawn on day 2 the T reg levels are falling (!) as they are bound in tissue with many apparently are being converted to pathogenic T cells.

I only have a few acute Lyme patients who waited three days to start antibiotics specifically so that they could participate in clinical care by testing our research models. Their lab parameters demonstrated the exact same pattern as those seen in our mold patients, understanding that I have hundreds of mold patients recorded in acute exposure data sets.

The inflammatory response following antigen detection also activates immature dendritic cells (professional antigen-presenting cells) to then engulf (phagocytose) the antigen/receptor complex into a "bubble" inside the cell called an endosome. This endosome, if acidified, will fuse with a lysosome where a specific mole-

SPECIAL REPORT

cule of HLA DR will be attached. Further processing of the antigen/HLA complex occurs when the antigen complex is processed in the endoplasmic reticulum, finally leading to presentation of the finished antigen/HLA complex at the cell surface to a naïve T lymphocyte. If there are no blocking cells, activation of the T cell leads to presentation of the HLA-labeled antigen to a B cell. From then on, antibody production occurs. (See Figure 1, the Biotoxin Pathway.)

Here's the bottom line of the findings that both mold and Lyme communities must acknowledge: there are individual differences in response to Lyme and mold solely based on the immune response genes found on chromosome 6, HLA DR. Specific haplotypes are associated with a marked increase in incidence in cases of mold illness and Post-Lyme patients. The haplotypes overlap, with several being "multisusceptible," and in that group there are two types that (while uncommon) are wildly over-represented in those with the worst clinical illness. These are the "dreaded haplotypes," of

Table 1. Number of subjects reporting symptom by group and symptom

Symptom	GROUP		
	Control (n=132)	Mold (n=812)	P value**
Fatigue	22	742	<.0001
Weak	6	634	<.0001
Ache	10	601	<.0001
Cramp	4	501	<.0001
Unusual pain	0	446	<.0001
Ice pick pain	1	249	<.0001
Headache	27	596	<.0001
Light sensitivity	11	634	<.0001
Red eyes	4	460	<.0001
Blurred vision	9	515	<.0001
Tearing	12	401*	<.0001
Sinus	47	534	<.0001
Cough	28	449	<.0001
Shortness of breath	17	581	<.0001
Abdominal pain	18	361	<.0001
Diarrhea	3	300	<.0001
Joint pain	40	561	<.0001
Morning stiffness	5	438	<.0001
Memory	10	681	<.0001
Focus/concentration	6	647	<.0001
Word recall	9	652	<.0001
Decrease assimilation	6	647	<.0001
Confusion	1	561	<.0001
Disorientation	1	371	<.0001
Skin sensitivity	1	302*	<.0001
Mood swings	6	607	<.0001
Appetite	5	492	<.0001
Sweats	7	531	<.0001
Temp regulation	17	531	<.0001
Thirst	9	540	<.0001
Increased urination	11	537	<.0001
Static shocks	2	399	<.0001
Numbness	6	445	<.0001
Tingling	10	484	<.0001
Vertigo	4	463	<.0001
Metallic taste	2	339	<.0001

* n=811

**From testing hypothesis of no difference between groups

11-3-52B and 4-3-53, with the subtypes of 0401, 0402 and 0404 being the worst of the 12 identified subtypes of 4-3-53. Elegant research has shown why these HLA structures don't do well in antigen presentation.

Data on HLA DR haplotypes in over 7000 patients confirm that there are six separate haplotypes conferring increased relative risk (incidence in cases divided by incidence in controls) for mold illness and four haplotypes for Post-Lyme. For those with Lyme (don't guess!) who don't improve with antibiotics, expect to find one of these four haplotypes. Similarly, in those who become ill following exposure to the interior environment of a WDB, expect to find one of the six mold susceptible haplotypes. Understanding that essentially nothing in biology is guaranteed, there are some moldy patients without one of the six mold haplotypes and there are a few Post-Lyme people without one of the Lyme susceptible types. In the general population, the incidence of these mold susceptible haplotypes is 25% and for Post-Lyme susceptible is 21%.

The key point here is that when a patient continues to experience illness symptoms and is shown to have genetic susceptibility, it is mandatory to understand that defective antigen presentation is ongoing and that production of a protective antibody (ies) is **NOT** happening. The problem must then be re-defined - **persistent antigen stimulation of production of cytokines, TGF-beta-1 and complement factors have become the illness**, with all of the SAIE activity ongoing. Now that we know that there are inflammatory parameters that must be corrected in order for mold patients and Lyme patients alike to return to health, physicians and their patients need to be educated about fixing what is shown objectively to be wrong. Don't guess!

Differential diagnosis is never ending.

Since the clinical diagnosis of Post Lyme and mold illness are the same, how can one say the illness is one or the other? Without exposure, diagnosing neither illness would be supported, but with exposure, each illness could be

present (and many times both are!). What evidence could be used to convince a skeptic that mold illness could be present?

First, look for the moisture. There are many sources of water intrusion commonly seen in construction, both brand new and old. Crawl spaces and basements are the biggest offenders. Look for water coming through concrete walls (block and poured concrete are porous wicks for water). Check for in-ground water pressure against a subterranean wall, especially if the wall is at the bottom of a hill. When you hear about a sump pump or dehumidifier being used in the basement look out: water intrusion already confirmed! Musty smells should not be ignored. "Dry" soils in crawlspaces are always releasing water through transpiration and evaporation: that dry soil isn't benign! Whenever you see fiberglass ductwork in a crawlspace of basement, be very wary as it won't be long before the joints between sections of those ducts loosen and permit entry of air full of bioaerosols made by the crawlspace microbes into

the universal distributor, the HVAC system. That means the "dry soils" in the crawlspace just contaminated the whole house.

Bathrooms surprisingly aren't the common source of moisture most people think. Sure pinhole leaks in plumbing will contaminate wall cavities but the black fungal growth you see on grout lines and along condensation areas of windows usually isn't from the big-time illness causers. Always test: never guess.

Common disasters from construction defects include lack of flashing around doors and windows, venting exhaust pipes into the attic, failure to seal around roof boots and over-flowing condensation pans. This isn't an exhaustive list.

As it turns out, it makes no difference in determining the potential for exposure if we use DNA testing (ERMI, environmental relative mold index), observe mold growth or simply smell musty odors. Each of these indicators of impacted building health is correlated with human illness. What ERMI does is to provide a clear indicator of what organisms

SPECIAL REPORT

are present, something that air sample never can do thoroughly, and that make-up of the fungi tells us what levels of water saturation are going to be found. That information in turn tells us where to look to (1) fix the moisture; (2) tear out the wet building materials and clean reservoirs in air, possession and floor/wall/ceiling. Cleaning the reservoirs of microbial products is maddeningly demanding of attention to detail.

If one is considering a Lyme diagnosis, take a minute or two (that is all it takes) to ask the questions about water intrusion. If you have a problem, and NIOSH says over 50% of US buildings do, then the illness might not be Lyme. Or if Lyme really is there, it might be both Lyme and mold illness! Treating with antibiotics alone in the face of mold illness is illogical and potentially disastrous for the patient.

Tip-offs to presence of mold illness and not Lyme will be absence of elevated C3a at any time, especially after treatment for mold illness is completed. C4a will be high in both illnesses as will TGF beta-1. Sorting illness presenta-

tion by HLA DR is wonderfully instructive. When one sees a mismatch of HLA DR and illness, we need to re-consider the differential diagnosis. In fact, always challenge today's diagnosis tomorrow.

Each step along the sequential path of therapy includes an assessment of outcome from what the prior intervention. Treatment should be transparent, logical and plodding with one step at a time the rule. Repeated evaluations of the response to therapy help narrow the diagnostic process. Please remember that a sudden worsening of illness or a recurrence of prior symptoms will usually mean re-exposure to a WDB or there might be a new colonization of a MRCoNS.

Genomics

We have entered the world of genomics testing. This diagnostic advance, using microRNA and mRNA, has given a preliminary fingerprint to the genomic differences between controls and those with mold illness; between controls and Lyme patients defined before and after antibiotics; and between mold and Lyme. The genomics

of ciguatera has been established previously. We are working on defining the role of commensals, such as biofilm-forming, methicillin resistant coagulase negative staphylococci (MRCoNS), as agents that influence genomic changes in affected hosts. We know that eradication of such organisms is absolutely mandatory as one of the steps in therapy for both mold illness and Lyme, but now we are seeing just why that observation is correct. The future of this research is bright!

For those physicians interested in learning more about genomics, please contact the www.survivingmold.com website. Specialized testing tubes are used in phlebotomy for genomics assays; cost of these tubes is about \$15 each. After the tubes are filled with blood (we will provide instructions on specimen handling) and frozen the stabilized RNA can be analyzed electively. The website also offers the new seven-hour instructional videos in mold illness and Lyme, as well as the Physicians' Section where treating docs can share information, ask questions and comment on what they

have seen in their practices. The potential for cooperative interaction here is expanding rapidly, as new docs are being trained in protocols and collation of research data every day. Learning how to use an evidence-based and sequentially organized approach to diagnose and treat biotoxin illnesses opens a world to improve the health and lives of our patients.

This brief discussion is just an overview of the research basis of modern mold illness practice. Given the commonality of findings in mold illness and Lyme, clinicians need to consider if their data base is current. If not, we truly hope they will ask what can be done to bring their practice into the exciting new era of management of CIRS. Successful patient outcome depends on it.

We don't have to guess any more about complex illnesses. Use of physiologic and genomic parameters will bring order to the arguments that continue in the Lyme community, just as it has for mold illness.

ABOUT THE AUTHOR:

Ritchie

PUBLIC HEALTH ALERT

Shoemaker MD is a practicing physician in rural Pocomoke, Md where he has lived since 1980. Since the Pfiesteria outbreaks in the Chesapeake Bay in 1997, Shoemaker has dedicated his practice to unraveling the complex physiology of biotoxin-associated illnesses. To date he has treated over 8800 cases, including 6500 mold cases, maintaining a database that includes symptoms, labs, visual contrast scores and response to therapy.

Many of the tests

physicians now routinely use in the chronic fatigue/Lyme/mold communities (C3a, C4a, MSH, VIP, HLA DR, MMP9, TGF beta-1, VCS, CD4+CD25+, MARCoNS cultures) are spin-offs of Shoemaker's research on innate immunity in chronic inflammatory response syndromes (CIRS). While most of his work focuses on illnesses acquired following exposure to the interior environment of water-damaged buildings (WDB), Lyme and dinoflagellate illness are routinely treated in his prac-

tice. He has extensive experience in legal cases as a plaintiff's expert, having provided testimony in over 150 cases in the US, Canada and Caribbean. Shoemaker has published academic papers in peer-reviewed journals including papers on mold, Lyme, cyanobacteria, Pfiesteria and ciguatera. He is lead author (2010) of the Expert Treating Physicians Report on CIRS-WDB.

He has written eight books of which *Mold Warriors* (2005)

and *Surviving Mold* (2010) are must-reads. Much of Shoemaker's academic research is presented at www.survivingmold.com. His current focus is on therapeutic use of vasoactive intestinal polypeptide and unveiling the genomics of differential gene activation by step of diagnosis and therapy. *pha*

Table 1. Mean, standard error (SE), and sample size of controls and cases by parameter; p-value from testing hypothesis of no difference between controls and cases*.

Parameter	Cases			Controls			P
	Mean	SE	n	Mean	SE	n	
Age	47.8	0.46	812	50.3	0.94	132	0.0378
# Symptoms	22.7	0.27	812	2.9	0.17	132	<.0001
VIP	12.8	1.64	812	36.6	1.02	129	<.0001
MSH	13.1	0.62	799	41.2	1.22	130	<.0001
Leptin	19.4	2.66	697	17.9	2.15	126	0.8160
ADH	3.1	0.47	692	3.7	0.20	119	0.5436
Osmo	302	0.62	709	288	2.65	119	<.0001
ACTH	16.8	0.60	687	22.0	1.23	121	0.0007
Cortisol	13.0	0.35	689	21.7	5.86	124	0.0009
MMP-9	420	9.90	812	269	10.9	132	<.0001
PAI-1	7.0	0.63	636	6.3	0.57	116	0.6605
VEGF	62.2	2.88	756	67.9	2.34	132	0.4084
C3a	427	13.8	808	253	13.1	131	<.0001
C4a	9661	348.5	812	2303	99.3	132	<.0001
TGF-BET-1	6412	189.5	812	2365	84.7	132	<.0001

* One-way analysis of variance