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11/20/07

Dear Dr. Shane,

Thank you for the opportunity to address the NTP panel on the subject of human illness acquired following exposure to water-damaged buildings (WDB). It is my understanding that your group seeks to bring an objective, scientific approach to public health concerns regarding exposure to "mold" using tools of modern toxicology and molecular biology. I feel that my experience as a treating primary care physician, treating over 6600 patients exposed to biologically produced neurotoxins, including over 4500 people made ill following exposure to water-damaged indoor environments, is pertinent to your deliberations today. I have an extensive data base on those patients that our group has used to publish a series of academic papers on the subject of human illness acquired following exposure to WDB (1, 2, 3).

These peer-reviewed papers present a case definition of "mold illness;" a case control study; a roster of symptoms and lab abnormalities seen in affected patients; a double blinded, placebo controlled trial confirming benefit of treatment with cholestyramine (CSM); and assessment of sequential changes in inflammatory elements seen during treatment, re-exposure and re-treatment. These studies employ a 5-step, repetitive exposure study design (ABB`AB, see appendix 4) that includes prospective documentation of acquisition of illness. In the second paper in Neurotoxicology and Teratology (3), peer reviewers permitted us to say that the data presented were consistent with the hypothesis that exposure to WDB caused the illness.

My request to NTP is to investigate "mold illness" by recognizing that the illness is multi-factorial and that no single agent, especially mycotoxins, is the source of illness symptoms. We already have a large database collected prospectively (following informed consent) that demonstrates that the acute and chronic illness acquired following exposure to WDB is indeed *caused* by such exposure. We also know that the illness physiology can be demonstrated such that an organized approach to treatment can follow delineation of the abnormalities in innate immune response these patients have.

I have organized my presentation according to the following categories:

1) What do we know about symptoms seen in cases versus controls?
2) What objective parameters are present in all cases and found in no controls?
3) Treatment should correct parameters found in cases to equal those found in controls.
4) Hypothesis testing: prospective acquisition of illness after re-exposure in successfully treated patients will re-create baseline symptoms and objective parameters rapidly and reproducibly, independent of type of organisms found in the WDB (appendix 4).
5) Serial recording of objective parameters in blood (appendix 3) from innate immune responses will show differences according to a time course that is paralleled by gene activation (genomics work underway).
6) Presence or absence of particular haplotypes of HLA DR account for nearly all differences in individual susceptibility, given the same exposure.
7) Prior abnormalities in innate immune responses change the rate of response when previously affected patients are re-exposed.
8) First order or monotonic dose-response relationships do not apply to illnesses when differential activation of immune cascades is present and multiple potential toxigenic organisms and inflammagens are present simultaneously in a WDB.
9) Assessing the effects of one-time, massive exposures of rats or mice to a single type of inflammagen found in WDB to assess the potential for human illness acquisition is illogical. Given that WDB contain many different kinds of potential sources of inflammation, each must be looked at in an inhalant model of illness. Studies must be done in people.
10) Use of a case definition (appendix 1) and visual contrast testing (appendix 2) presents a rapid, inexpensive and reproducibly reliable method of screening exposed populations before lab testing is performed.
11) Defining problems for further research begins with an unbiased assessment of the potential human health risk given the number of buildings in the US with current or future water intrusion problems.

I will use the term, "mold illness," in this summary to save time: what I mean by the term "mold illness" is a chronic, biotoxin associated illness acquired following exposure to interior environments of WDB with resident toxigenic organisms, including but not limited to fungi, bacteria, mycobacteria and actinomycetes; as well as inflammagens such as beta glucans, VOCs, proteinases, hemolysins and particulates made by those organisms, and others as yet identified. Solely focusing on molds as a source of public health concern would be a serious error in assessment. Please look at WDB as the unit of exposure and not just molds!

BACKGROUND: I have attached a current CV. I continue to practice in a rural area of the Eastern Shore of Maryland, beginning in a NHSC clinic site at Pocomoke City, Maryland, 1980. My training was in molecular biology as Duke, including work here at NIEHS in the lab of Dr. Jud Spaulding in the early 1970's looking at the effects of pesticides on membrane-bound phospholipids. I chose Family Practice as a career, feeling that the union of primary care and clinical research in a medically underserved area was an ideal match for me.

My involvement with biotoxin associated illnesses was not due to choice but was instead due the unexpected outbreak of human illness in patients exposed to estuaries, beginning with the Pocomoke River, a tributary of the Chesapeake that flows past my office, that harbored resident toxigenic dinoflagellates, including *Pfiesteria*, beginning in 1997. Chance brought me an opportunity to treat some of my index patients with cholestyramine (CSM), with subsequent rapid reduction of symptoms and clinical improvement. I published the first papers in the world's literature on acquisition and treatment of Pfiesteria human illness acquired in the wild in 1997-1998 (4, 5), followed by papers in EHP in 2001 (6, 7). Application of the method of trial and error led to similar successful use of CSM in patients made ill by ciguatera, cyanobacteria, *Borrelia* species, apicomplexans and more, with no differences in lab abnormalities seen by location or duration of illness (see CV). My first "mold patients" were treated in 1998. Thanks to the pioneering work and teaching of Dr. Ken Hudnell (US EPA, NHEERL, RTP), who first used visual contrast sensitivity (VCS) testing in patients with biotoxin illnesses, I have been using VCS since 7/1998. Just like the symptoms and abnormalities in innate immune responses, the diagnostic deficits seen on VCS testing are essentially identical in all biotoxin-formers.

I define a biotoxin as a biologically produced, low molecular weight toxin, usually an ionophore that creates a molecular dipole or anion ring in three dimensions. These compounds have the potential to elicit a pro-inflammatory cytokine response by binding to membrane receptors, independent of their possible intracellular effects. These effects can be seen in isolated cell systems. We identify the illness from exposure to a biotoxin by the inflammatory effects of such exposures seen in affected patient. Not all patients exposed to biotoxins become ill: Individual susceptibility is not part of the definition of a biotoxin but is part of the definition of the illnesses caused by biotoxins.

My clinical research is accomplished through my private practice and a non-profit 501-c-3 organization, the Center for Research on Biotoxin Associated Illnesses (CRBAI).

Early in our group's work, we established that a series of illnesses, each of which would be present in a thorough differential diagnosis of symptoms acquired following exposure to WDB, *do not cause* the particular grouping of illness symptoms (identified by cluster analysis); *do not cause* abnormalities in innate immune responses; and *do not cause* VCS deficits. Combining these modalities in logistic regression provides an ability to classify patients with biotoxin illness compared to control with an extremely high degree of accuracy. Moreover, use of CSM does not correct other symptoms of systemic illnesses such as depression, stress, diabetes, high blood pressure, menopause, use of medications, lupus, asthma, nasal allergy, sensitivity to dust mites, sleep apnea and states such as deconditioning and obesity, among many others. Successful therapy with CSM in illnesses that don't self-heal, with say, removal from exposure, suggests that the mechanism of illness causation, corrected by CSM, involves the effects of a substance that is bound and removed by CSM.

I have included a lengthy list of references that reflect the explosion of publications that support the hypothesis that inflammatory processes are initiated in susceptible patients

following exposure to WDB (see attachment, Current References). The recent papers from the CDC (8) and EPA (9) show an evolution of opinion from Federal agencies on the potential for human illness and exposure to WDB. The comments of Bob Weinhold in EHP (10) regarding a mini-monograph on inhalational effects of mold also reflect a significant shift in opinion regarding the health effects of WDB. He concludes that, "…the overall recommendations of many organizations and agencies worldwide are reaching a common conclusion: Don't mess with mold. If you can see it or smell it-and especially *if health problems are occurring* (emphasis added)-clean it out, throw it out or get out."

Our data supports that conclusion. We want you to know that mold illness is readily identifiable, readily treatable and is a preventable cause of human misery.

1) **SYMPTOMS**: Biotoxin illnesses are typified by multiple acute and chronic symptoms from multiple organ systems. One would expect that more than one organ symptoms would be involved if a systemic inflammatory illness were present. Presence of one symptom compared to another has little significance, as the commonality of symptoms across the board in biotoxin illnesses is invariably found. Fatigue, cognitive effects, especially in executive cognitive functioning, respiratory effects, gastrointestinal symptoms, musculoskeletal symptoms, neurologic effects, headache and eye symptoms are routinely seen. In an average biotoxin illness patient, approximately 15-20 of 37 symptoms are the norm. Pediatric patients have fewer symptoms, averaging 10-12. Control patients will have fewer than 4 of the same symptom roster.

2) **OBJECTIVE PARAMETERS:** Standard lab testing is normal. CBC, CMP, TSH, ESR, CRP, ANA, immunoglobulin profiles, and more are not different in cases compared to controls. Testing of innate immune responses (see appendices of lab parameters) however is incredibly different. MSH deficiency, elevated MMP9, dysregulation of simultaneously measured ADH/osmolality and ACTH/cortisol jump off the page. VEGF deficiency, elevation of C4a and evidence of abnormalities of T-regulatory cell function are no less important: not found in controls with statistical significance, these abnormalities are nearly always present in cases. VCS deficits are found in 92% of cases and in 1% of controls, with errors in sensitivity and specificity that are less than 1.5%.

3) **TREATMENT EFFECTS:** As presented in multiple studies from our group and mirrored by multiple physicians employing our protocols across the country show that therapy with CSM, eradication of biofilm-forming commensals (11) found in case but not controls and correction of excessive cytokine responses as initial steps of treatment returns symptoms, labs and VCS found in cases to control values. Newer data, obtained in clinical trials (12, 13) with those not improved with the above protocols, show that reduction of refractory elevation of C4a with low-dose erythropoietin (epo) is of paramount importance in correcting central nervous system metabolic abnormalities of elevated lactate and depressed ratios of glutamate to lactate seen on magnetic resonance spectroscopy, cognitive effects

and peripheral symptoms. With re-exposure the CNS metabolic effects, symptoms and C4a elevation all rise within 24 hours.

4) **HYPOTHESIS TESTING:** We use a model of illness acquisition derived by treating and monitoring hundreds of patients. Much of this data is unpublished, but is mostly presented at academic conferences. If a sequential cascade of gene activation and gene product effects on downstream pathways is a player in human illness caused by exposure to WDB, then we should be able to re-create a long-term illness in an incredibly short period of time. Our repetitive exposure clinical trails confirm that essentially 95% of a long-term illness re-appears within three days or re-exposure. The "SAIIE index" presentation (14)), attached to this summary was the result of collation of a series of 50 cases and controls in which we could use the lab results of patients, previously affected, undergoing re-exposure, to create an index of illness that maintained a close correlation with the recent EPA index, ERMI, named for a building summary of fungal DNA. To date, we see a clear uniformity, within biological variation of the hyperacute markers of illness, including C4a, VEGF, MMP9, leptin, factor VIII, von Willebrand's' factor and ristocetin-associated antigen. While we feel that the bleeding, usually profuse epistaxis and hemoptysis seen in re-exposure trials and in mold illness patients, particularly children, is due to acquired on Willebrand's disease, our data sets are still building to assess statistical significance later.

5) **GENOMICS RULES THE WORLD!:** We feel that the genomic changes of hyperacute activation of genes predicted to be activated by our models, and shown by Dr James Ryan at NOAA in his ciguatoxin experiments (15), will be confirmed by ongoing testing using PAXgene testing. These data should be ready by 12/6/07 in an initial cohort. Costs of the 124-gene microarray are difficult to bear for a tiny, privately-funded non-profit group. We will be able to correlate lab results with gene activation in this ambitious project.

6) **HLA DR SAYS A LOT:** Each of us has two haplotypes of the immune response genes HLA DR found on chromosome 6. Large population studies (over 4000 patients, cases and controls) have shown a consistent increased presence of particular haplotypes in cases compared to controls. There are six separate haplotypes with an increased relative risk in cases of mold illness compared to controls. These haplotypes are in turn sub-divided by relative risk of development of profound, disabling chronic fatigue, with two uncommon haplotypes (DRB1-4, DQ-3, DRB4-53 and DRB1-11, DQ-3- DRB3-52B), found in 4% of the population actually representing 88% of cases of refractory CFS (16).

7) **SICKER, QUICKER**: Patients undergoing repetitive exposure protocols must not be those with any C4a that exceeds 20,000 (normal < 2830 ng/ml by RIA in Complement Lab, Dr. P. Giclas, at NJC, Denver, Colorado). They do poorly with re-exposure, with a correction rate following second treatment that is far less than those with C4a of < 20,000. In our data sets of C4a that exceed 2000 patients,

C4a elevation of this magnitude is not uncommon, found in over 10% of patients. Finding a C4a of over 20,000 in a screening sample of patients with exposure to a WDB should create a call for immediate action.

8) **WHAT DOES IT TAKE TO MAKE SOMEONE SICK?** Dose response relationships seen in illness caused by exposure of genetically susceptible patients to interior environments of water-damaged buildings (WDB) are not linear: there are so many variables of exposure and response that postulating a 1:1 relationship of total mass or number of spores required for a threshold exposure is nonsensical. Consider that an effect or response (X) is related in a linear fashion to dose. (X) will then be equal to the sum of routes of exposure (A) plus contaminants (B) plus length of time of exposure (C) plus individual genetic susceptibility (D) plus individual prior exposure and change of susceptibility from that exposure (E) plus amounts/types of microbial organisms, each potentially acting synergistically with another (F) plus the amount of inflammagens causing potentially exponential changes in c-type lectin receptors, especially dectin-1 and dectin-2 receptors (G). X then is equal to the combined effects of A through G, each of which can cause *amplification*, not additional, effects of innate immune responses. Moreover, the elements A through G are each themselves variable. It gets worse for the linear dose-response advocates: there are interactions of A through G, some of which are synergistic and some involve differential gene activation as well as epigenetic phenomena. It is impossible to assume that response or effect X will be linearly related to variables, each simultaneously expressed A through G. We cannot analyze one component of exposure, namely mold spores, and come to any meaningful conclusions from classical monotonic dose-response relationships.

9) **IS ONE SINGLE DOSE RAT STUDY ENOUGH TO BE ACCEPTED AS DEFINITIVE SCIENCE FOR ALL LOW DOSE EXPOSURES IN HUMANS?** I am aware that there are older consensus statements (17) about mold illness that relied on a single study of a single application of an unknown numbers of toxins on unknown number of spores into trachea of rats. The rats were seriously ill from this exposure, but the ACOEM statement authors concluded that the number of mycotoxins required to cause illness in people were insurmountably high. Some people actually think this bizarre mathematical speculation is good science. Our group presented an argument (3) that refutes the ACOEM position. Mold illness involves so many inflammagens and toxins, that trying to study the unique ecological niche that is a WDB with just one parameter doesn't make sense. Just two years ago, no one talked about mycolactone-forming mycobacteria and, quite frankly, mentions of c-type lectin receptors were discussed in just a small branch of immunology. Now c-type lectins, especially dectin-1 (and now dectin-*2, how many others?*!) receptors are recognized as critically important in generating an inflammatory response to beta glucans (see section in Current References). Even more important, the response of c-type lectins, recognizing glycoproteins, remains critical to understanding how low-dose erythropoietin (epo) reverses the ongoing activation of production of the

short-lived anaphylatoxin C4a. Epo lowers C4a and stops its regeneration. Does epo affect/stabilize c-type lectins?

10) **SCREENING:** This point is the thrust of my concerns for public health. In my experience, early case identification leads to far better outcomes from early intervention. Find the sick kid in school because the nurse does symptom recording and VCS testing on all third graders and that kid will be able to access definitive care more quickly. Find a bunch of sick kids from dry homes and the school gets evaluated for water intrusion and microbial growth. Early case finding leads to early remediation. No moisture, no mold and no more new cases of sick patients. As our data sets on MR spectroscopy grow (we have over 300 cases and 50 controls), we will be able to show statistical certainty of the presence of distinctive increases in lactate (i.e. lack of oxygen delivery from capillary hypoperfusion) that correlate with reduced production of the excitatory neurotransmitter glutamate compared to glutamine in long-standing cases, but increased glutamate to glutamine in shorter duration cases. MRS, however, isn't a good screening tool: VCS and symptoms screening take 5 minutes, yielding incredibly accurate results quickly (18). MR spectroscopy costs $1500 and requires 90 minutes of tech and machine time. While I am not suggesting routine measurements of HLA DR by PCR, MMP9, MSH and C4a in all people exposed to a WDB, we have used that approach at the request of employers in the past.

11) **FUTURE RESEARCH NEEDS:** NTP can best define its investigation by a multi-site, case/control study, adding treatment/outcome studies as their data set; small as it will be at onset, reaches statistical significance. Labs that reflect the basic disease mechanisms should be collected in all patients. PAXgene samples for mRNA analysis should be drawn and saved for future microarray assays. Investigation into the mechanism of C4a regeneration needs a prime position in analysis, as does the role of IL-4, IL-8 and IL-10, each of which could account for the reduced antigen recognition mechanism seen in previously affected patients (reduced presentation of HLA on monocytes??). Population studies of controls and cases need to be collated using a standard set of answers to questions obtained by a trained professional (**not** a checklist), with VCS testing, as performed currently according to a standard protocol by NIOSH, perhaps correlated with ERMI. Most importantly, NTP needs to support rigorous academic data collection by series of coordinated practices across the country. These practices are already identified.

Sincerely,

Ritchie C. Shoemaker, MD

Disclosure: The author has no competing financial interests. He has appeared as an expert in legal proceedings involving patients exposed to biotoxins, including mold illness, with testimony on behalf of plaintiffs and retention by Nationwide as an expert in mold defense litigation.

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APPENDICES

1. Case definition of mold illness

The case definition of an adult mold illness patient contains two tiers as follows: any diagnosis of environmentally acquired biotoxin illness, including that from mold, must include:

(1) the potential for exposure;
(2) the presence of a distinctive grouping of symptoms; and
(3) the absence of confounding diagnoses and exposures.

This first tier of the case definition is adopted from the initial CDC case definition of *Pfiesteria* cases from 1998. The second tier of objective factors includes three of six of the following:

(1) HLA DR by PCR showing susceptibility;
(2) reduced levels of melanocyte stimulating hormone (MSH) in a properly performed specimen;
(3) elevated levels in matrix metalloproteinase-9 (MMP9) in a properly prepared serum specimen;
(4) deficits in visual contrast sensitivity (VCS);
(5) dysregulation of ACTH/cortisol in simultaneously obtained specimens;
(6) dysregulation of ADH/osmolality in simultaneously obtained specimens.

This second tier is adapted from similar use of different parameters in illnesses such as systemic lupus erythematosis and rheumatic fever, among others. The case definition is derived from looking at what thousands of mold illness patients demonstrated that none of the control patients demonstrated.

For children, the case definition necessarily must exclude pituitary hormone abnormalities. What we have documented is an unusual increase in autoimmune factors in children with mold illness compared to control children. Our case definition for children must also account for the delay in maturation of the neurons involved with development of contrast. We include in our case definition in children five elements on the second tier, two of which must be present, including HLA DR, antigliadins, anticardiolipins, MMP9 elevation and MSH deficiency. This case definition was presented 12/16/05 at the ASTMH meetings in Washington, DC.

2. Visual Contrast Sensitivity

Testing

All subjects who normally wore corrective lenses for near-point viewing were asked to wear them during vision testing. The visual acuity and VCS tests were administered monocularly to each eye; an eye occluder was held over one eye while the other eye was tested. All vision tests were administered under illumination from a "daylight" illuminator (fluorescent source with a correlated color temperature of approximately = 6500E K; color rendering index > 90; intensity = 1150 lux; luminance approximately 70 foot-lamberts) in a clinical unit with normal background lighting. A light meter was used to insure that luminance remained constant throughout the test sessions. A test card holder, consisting of a face rest placed just under the cheek bones or chin as comfort provided, and connected by a calibrated rod to a card holder on the distal end, was used to position the acuity and VCS test cards at a constant distance, previously standardized, from the eyes (acuity - 36 cm (14 inches); contrast sensitivity - 46 cm (18 inches)).

Near Visual Acuity

The acuity test card (MIS Pocket Vision Guide, © 1997 MIS, Inc.) contained 10 rows of numbers in which the size of the numbers progressed from a larger size in the top row to a smaller size in the bottom row. Participants were asked to first read the numbers in a middle row. Testing proceeded to the next lower row if all numbers were correctly identified or to the next higher row if an error occurred. The Snellen visual acuity of the row (20/20 or 20/30, for example) with the smallest numbers each identified correctly was recorded as the visual acuity score. Two-tailed Student t-tests 0.05 were performed, using the mean score of each participant's two eyes, to determine if scores differed significantly between cohorts.

Contrast Sensitivity (VCS)

The contrast sensitivity test card (Functional Acuity contrast Test, (FACT), Stereo Optical Co., Chicago, IL, a Gerber-Coburn Co.) contained a matrix (5 x 9) of circles filled with sinusoidal gratings (dark and light bars). Spatial frequency (1.5, 3, 6, 12 and 18 cycles/degree of visual arc) increased from top to bottom, and contrast decreased from left to right in steps of approximately 0.15 log units. The grating bars were oriented

either vertically, or tilted 15 degrees to the left or right. As the investigator called out each circle from left to right, row by row, subjects responded by saying either: vertical, left, right or blank. Participants were encouraged to name an orientation if she had any indication that the bars could be seen. Participants were given the option to point in the direction to which the top of the grating was tilted if she felt any difficulty in verbalizing the orientation; none needed this assistance. The contrast sensitivity score for each row (spatial frequency) was recorded as the contrast of the last test patch correctly identified on that row following verification by repeated testing of that patch and the subsequent patch. The procedure was repeated for each row in descending order. The a priori criterion for the inclusion of data in analyses was that the eye has a visual acuity (Snellen Distance Equivalent Score) of 20:50 or better, in order to avoid confounding of the VCS results by excessive optical-refraction error. All eyes included in the data analyses met the visual acuity criterion.

Data Analysis

The units of analysis for the VCS test were the mean scores of the participant's two eyes at each spatial frequency. Standard error of the mean was calculated for each group of measurements. The VCS data were analyzed using multivariate analyses of variance (MANOVA, with the Wilks' lambda statistic) procedures suitable for repeated measures with $\pm = 0.05$. The factors in the model were group and spatial frequency. A factor for gender was not included since there aren't any gender differences in susceptibility to biotoxin-induced effects shown as yet, and no gender differences in VCS have been reported. Results that showed a significant group-by-spatial frequency interaction were further analyzed in the step-down, two-tailed Student t-tests ($\pm = 0.05$), the equivalent of a univariate ANOVA to determine which spatial frequencies accounted for the overall effect.

3. Laboratory studies

LabCorp, Inc. and Quest Diagnostics, each CLIA approved, high complexity, national laboratory facilities. Factors analyzed included:

MSH: Alpha melanocyte stimulating hormone (MSH) is a 13 amino acid compound formed in the ventromedial nucleus (VMN) of the hypothalamus, solitary nucleus and arcuate nucleus by cleavage of proopiomelanocortin (POMC) to yield beta-endorphin and MSH. MSH exerts inductive regulatory effects on production of hypothalamic endorphins and melatonin. MSH has multiple anti-inflammatory and neurohormonal regulatory functions, exerting regulatory control on peripheral cytokine release as well as on both anterior and posterior pituitary function. Deficiency of MSH, commonly seen in biotoxin-associated illnesses, is associated with impairment of multiple regulatory functions and dysregulation of pituitary hormone release. Symptoms associated with MSH deficiency include chronic fatigue and chronic, unusual pain syndromes. Normal values of MSH established in research labs and in commercial labs are 35-81 pg/ml. I note that the recent shift in normal range for MSH from LabCorp to 0-40 pg/ml was made following the receipt of so many low values of MSH. I have questioned both Dr. Andre

Valcour and Dr. Richard Marsella of LabCorp about this change; they have received case/control data sets from me and assure me that they will review the adjustment of normal ranges that were made only after lumping values for cases and control together. No lab, including LabCorp, can logically equate a case value of a test with a control value for a test.

Leptin: Leptin is a 146 amino acid adipocytokine produced by fat cells in response to rising levels of fatty acids. Leptin has peripheral metabolic effects, promoting storage of fatty acids, as well as central effects in the hypothalamus. Following binding by leptin to a long isoform of the leptin receptor in the VMN, a primordial gp-130 cytokine receptor, a JAK signal causes transcription of the gene for POMC, which is in turned cleaved to make MSH. Peripheral cytokine responses can cause phosphorylation of a serine moiety (instead of threonine) on the Leptin receptor, creating leptin resistance and relative deficiency of MSH production. Normal values in commercial labs show differences between males (5-8 ng/ml) and females (8-18 ng/ml), with levels of leptin correlated with BMI. In the presence of MSH deficiency, the relationship between body weight and leptin changes, as leptin elevation becomes disproportionate to weight.

ADH/osmolality: abnormalities in ADH/osmolality are recorded as absolute if ADH is < 1.3 or > 8 pg/ml; or if osmolality is >295 or <275 mOsm/kg. Abnormalities are recorded as relative if simultaneous osmolality is 292-295 and ADH $\leq$ 2.3; or if osmo is 275-278 and ADH $\geq$ 4.0. Symptoms associated with dysregulation of ADH include dehydration, frequent urination, with urine showing low specific gravity; excessive thirst and sensitivity to static electrical shocks; as well as edema and rapid weight gain due to fluid retention during initial correction of ADH deficits.

ACTH/cortisol: abnormalities in ACTH/cortisol are absolute if AM cortisol > 19 ug/ml or < 8 ug/ml; or if AM ACTH is >60 pg/ml or < 10 pg/ml. Abnormalities are recorded as dysregulation if simultaneous cortisol is > 15 and ACTH is > 15, or if cortisol is < 8 and ACTH <40. Early in the illness, as MSH begins to fall, high ACTH is associated with few symptoms; a marked increase in symptoms is associated with a fall in ACTH. Finding simultaneous high cortisol and high ACTH may prompt consideration of ACTH secreting tumors, but the reality is that the dysregulation usually corrects with therapy.

Androgens: total testosterone, androstenedione and DHEA-S provide measurements regarding the effectiveness of gonadotrophin secretion as influenced adversely by MSH deficiency. Normal ranges of these hormones in males are 75-205 ng/ml for androstenedione, 350-1030 ng/ml for testosterone and 70-218 ug/ml for DHEA-S. Normal values for pre-menopausal women are 60-245, 10-55 and 48-247, respectively. Post-menopausal normal ranges are 30-120, 7-40 and 48-247, respectively.

HLA DR by PCR: LabCorp offers a standard HLA DR typing assay of 10 alleles using a PCR sequence specific chain reaction technique. As opposed to serologic assays for the HLA DR genotypes, the PCR gives far greater specificity in distinguishing individual allele polymorphisms. Linkage disequilibrium is strong in these genotypes, with multiple associations made to inflammatory and autoimmune disease. These genes are part of the

human major histocompatibility complex (MHC), also called the HLA complex, and located on the short arm of chromosome 6. Relative risk was calculated, susceptible genotypes identified, compared within each group to location and exposure. The HLA doesn't by itself say that mold makes a patient sick: the increased relative risk in cases versus controls shows the increased individual susceptibility expressed as a statistical ratio,

MMP9: matrix metalloproteinase 9 (gelatinase B) is an extracellular zinc-dependent enzyme produced by cytokine-stimulated neutrophils and macrophages. MMP9 is involved in degradation of extracellular matrix; it has been implicated in the pathogenesis COPD by destruction of lung elastin, in rheumatoid arthritis, atherosclerosis, cardiomyopathy, and abdominal aortic aneurysm. Cytokines that stimulate MMP9 production include IL-1, IL-2, TNF, IL-1B, interferons alpha and gamma. MMP9 is felt to play a role in central nervous system disease including demyelination, by generation of myelin peptides, as it can break down myelin basic protein. MMP9 "delivers" inflammatory elements out of blood into subintimal spaces, where further delivery into solid organs (brain, lung, muscle, peripheral nerve and joint) is initiated. Normal ranges of MMP9 have a mean of 150, with range of 85-322 ng/ml.

C3a and C4a: Split products of complement activation, often called anaphylatoxins. Each activates inflammatory responses, with spillover of effect from innate immune response to acquired immune responses and hematologic parameters. These short-lived products are re-manufactured rapidly, such that an initial rise of plasma levels is seen within 12 hours of exposure and sustained elevation is seen until definitive therapy is initiated. The components increase vascular permeability, release inflammatory elements from macrophages, neutrophils and monocytes, stimulate smooth muscle spasm in small blood vessels and disrupt normal apoptosis. They also recruit additional inflammatory generators, such as chemokines, into action.

Anticardiolipins IgA, IgM and IgG: autoantibodies often identified in collagen vascular diseases such as lupus and scleroderma; often called anti-phospholipids. These antibodies in high titers are associated with increased intravascular coagulation requiring treatment with heparin and coumadin. Lower level titers are associated with hypercoagulability. An increased risk of spontaneous fetal loss in the first trimester of pregnancy is not uncommonly seen in women with presence of cardiolipin antibodies. This problem does not have the same "dose-response" relationship seen with levels of autoantibodies and illness, as does the antiphospholipid syndrome. Anticardiolipins are found in over 33% of children with biotoxin-associated illnesses.

Antigliadin IgA and IgG: Antibodies thought at one time to be specific for celiac disease. With the advent of testing for IgA antibodies to tissue transglutaminase (TTG-IgA), gliadin antibodies are most often seen in patients with low levels of MSH. Ingestion of gliadin, the 22-amino acid protein found in gluten (found in wheat, oats, barley and rye; often added to processed foods) will initiate a release of pro-inflammatory cytokines in the tissues lining the intestinal tract. This cytokine effect will often cause symptoms within 30 minutes of ingestion that mimic attention deficit disorder, often

leading to an incorrect diagnosis. Antigliadin antibodies are found in over 58% of children with biotoxin-associated illnesses.

Vasoactive intestinal polypeptide (VIP): neuroregulatory hormone with receptors in suprachiasmatic nucleus of hypothalamus. This hormone/cytokine regulates peripheral cytokine responses, pulmonary artery pressures and inflammatory responses throughout the body. VIP raises intracellular levels of cAMP, a vital secondary messenger of cell signaling. Deficiency is commonly seen in mold illness patients, particularly those with dyspnea on exertion.

4. ABB`AB protocol

The foundation of these conclusions includes the use of a repetitive exposure protocol, called ABB̀ AB. This protocol is widely used in assessment of causation in research, medicine and industry; it is one of the oldest and most used in all science. We accept the possibility that patients with exposure to toxigenic fungi and with multi-symptom, multisystem illnesses could potentially be due to many sources. The 5-step protocol answers this possibility and gives academic certainty to the cause of illness (*Figure 9*, p. 10). Our baseline **(Base)** evaluation, including symptoms, VCS, labs and exposures is compared to the same parameters measured after treatment with CSM **(AC-1).** After AC-1, the improvement of the patient is documented, with reduction of symptoms and VCS deficits; amelioration of the multiple biomarker abnormalities is also documented. Next, the patient is kept away from the affected environment for at least three days and medication is discontinued **(HOC).** Here, we look at the superficial argument often used by defense apologists that purports to say, "Why, that dastardly mold is everywhere; any exposure could cause the illness." Actually, amplified mold growth, the true source of illness, is rarely found in multiple environments for a given affected individual. Then, after documenting that nothing changed for the patient during HOC, he is re-exposed to the "suspect" environment **(BOC)** without use of CSM. The patient is re-evaluated in three days, ideally with symptom recording and lab evaluation done each of the three days.

Next, causation of the illness from exposure to indoor air in the contaminated residence is shown by recrudescence of symptoms and relapse in all the biomarkers (three days is all that is necessary: there is no dose-response relationship here, the genetic basis for susceptibility shows re-acquisition of the illness, complete with abnormalities in biomarkers with a short duration exposure isn't statistically different from that seen with long-term exposure). Representative VCS slides documenting graphically the results of the protocols we use are presented in Appendices Five 1-8.

The data from sequential monitoring during diagnostic re-exposure demonstrate a sequential activation of complement (C3a and C4a), cytokines (primarily IL-1B) on Day 1; followed by a rise in leptin on Day 2; and a rise of MMP9 and change in VEGF on Day 3. Symptoms usually begin to recur within hours of unprotected re-exposure, with a fall in VCS seen usually on Day 2 to Day 3. These data were presented at a February 2006 meeting of the American Society for Microbiology Conference on Biowarfare and Biodefense. Once the causative re-exposure occurs, clearly documented by temporal

association with the contaminated building, the patient is re-treated, with documentation of improvement **(AC-2).** For those who stay in the contaminated environment, and many must because of financial need, or for those who are primed for illness following exposure to other environments with amplified growth of mold, prophylaxis with CSM is offered.

The 5-step protocol has the scientific power to demonstrate causation, as shown in multiple studies in animals and humans. There is no known study design that can show greater power of causation: prospective acquisition in a time- and location-specific manner in a known affected, but healed individual. This approach is not novel; it has been routinely used outside litigation in animal and human research. It has its basis in the classic work by Dr. Robert Koch, as he developed Koch's Postulates for causation of illness by infectious agents.

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3. Islam Z, Amuzie CJ, Harkema JR, Pestka JJ. Neurotoxicity and inflammation in the nasal airways of mice exposed to the macrocyclic trichothecene mycotoxins roridin A: kinetics and potentiation by bacterial lipopolysaccharide co-exposure. ToxSci Advance Access May 2004.

4. Creasia DA, Thurman JD, Jones LJ, Nealley ML, York CG, Wannemacher RW, Bunner DL. Acute inhalation toxicity of T-2 mycotoxin in mice. Fundamental and Applied Toxicology 1987; 8: 230-235.

5. Rand TG, Flemming J, Miller JD, Womiloju TO. Comparison of inflammatory responses in mouse lungs exposed to atranones A and C from Stachybotrys chartarum. Journal of Toxicology and Environmental Health 2006; 69: 1-13.

6. van der Graff CAA, Netea MG, Verschueren I, van der Meer JWM, Kullberg BJ. Differential cytokine production and Toll-like receptor signaling pathways by Candida albicans blastoconidia and hyphae. Infection and Immunity 2005; 73(11): 7458-7464.

7. Rivera A, Van Epps HL, Hohl TM, Rizzuto G, Pamer EG. Distinct CD4+-T-cell responses to live and heat-inactivated Aspergillus fumigatus conidia. Infection and Immunity 2005; 73(11): 7170-7179.

8. Huttunen K, Hyvarinen A, Nevalainen A, Komulainen H, Hirvonen MR. Production of proinflammatory mediators by indoor air bacteria and fungal spores in mouse and human cell lines. Environmental Health Perspectives 2003; 111(1): 85-92.

9. Jiang H, Chess L. Regulation of immune responses by T cells. N Engl J Med 2006; 354: 1166-1176.

10. Kay AB. Natural Killer T cells and asthma. N Engl J Med 354(11): 1186-1188.

11. Akbari O, Faul JL, Hoyte EG, Berry GJ, Wahlstrom J, Kronenberg M, DeKruyff RH, Umestsu DT. CD4+ invariant T-cell-receptor+ natural killer T cells in bronchial asthma. N Engl J Med 2006; 354(11): 1117-1129.

12. Flemming J, Hudson B, Rand TG. Comparison of inflammatory and cytotoxic lung responses in mice after intratracheal exposure to spores of two different Stachybotrys chartarum strains. Toxicological Sciences 2004; 78: 267-275.

13. Stoeger T, Reinhard C, Takenaka S, Schroeppel A, Karg E, Ritter B, Heyder J, Schulz H. Instillation of six different ultrafine carbon particles indicates a surface area threshold dose for acute lung inflammation in mice. Environmental Health Perspectives 2006; 114(3): 328-333.

14. Veranth JM, Moss TA, Chow JC, Labban R, Nichols WK, Walton JC, Watson JG, Yost GS. Correlation of in vitro cytokine responses with the chemical composition of soil-derived particulate matter. Environmental Health Perspectives 2006; 114(3): 341-349.

15. Nurkiewicz TR, Porter DW, Barger M, Millecchia L, Rao MK, Marvar PJ, Hubbs AF, Castranova V, Boegehold MA. Systemic microvascular dysfunction and inflammation after pulmonary particulate matter exposure. Environmental Health Perspectives 2006; 114(3): 412-419.

16. Rand TG, Giles S, Flemming J, Miller JD, Puniani E. Inflammatory and cytotoxic responses in mouse lungs exposed to purified toxins from building isolated Penicillium brevicompactum dierckx and p. chrysogenum thom. Toxicological Sciences 2005; 87(1): 213-222.

17. Donohue M, Wei W, Wu J, Zawia NH, Hud N, De Jesus V, Schmechel D, Hettick JM, Beezhold DH, Vesper S. Characterization of nigerlysin c, hemolysin produced by Aspergillus niger, and effect on mouse neuronal cells in vitro. Toxicology 2006; 219: 150-155.

18. Rao CY, Burge HA, Brain JD. The time course of responses to intratracheally instilled toxic Stachybotrys chartarum spores in rats. Mycopathologia 2000; 149: 27-34.

19. Marc MM, Korosec P, Kosnick M, Kern I, Flezar M, Suskovic S, Sorli J. Complement factors C3a, C4a, and C5a in chronic obstructive pulmonary disease and asthma. American J of Respir Cell and Molecular Biology 2004; 31: 31-33.

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21. Kelk P, Claesson R, Hanstrom L, Lerner UH, Kalfas S, Johansson A. Abundant secretion of bioactive interleukin-1b by human macrophages induced by Actinobacillus actinomycetemcomitans leukotoxins. Infection and Immunity 2005; 73(1): 453-458.

22. Romani L. Immunity to fungal infections. Nature Reviews Immunology 2004; 4: 11-23.

23. Kohl J, Baelder R, Lewkowich IP, Pandey MK, Hawlisch H, Wang L, Best J, Herman NS, Sproles AA, Zwirner J, Whirsett JA, Gerard C, Sfyroera G, Lambris JD, Wills-Karp M. A regulatory role for the C5a anaphylatoxins in type 2 immunity in asthma. Journal of Clinical Investigation 2006; 116(3): 783-796.

24. Desjardins AE. Trichothecenes: from yellow rain to green wheat. ASM News 2003; 69(4): 182-185.

25. McCrae KC, Rand T, Shaw RA, Mason C, Oulton MR, Hastigns C, Cherlet T, Thliveris JA, Mantsch HH, MacDonald J, Scott JE. Analysis of pulmonary surfactant by Fourier-transform infrared spectroscopy following exposure to Stachybotrys chartarum (atra) spores. Chemistry and Physics of Lipids 2001; 110: 1-10.

26. Donohue M, Wei W, Wu J, Zawia NH, Hud N, De Jesus V, Schmechel D, Hettick JM, Beezhold DH, Vesper S. Nigerlysin, hemolysin produced by Aspergillus niger, causes lethality of primary rat cortical neuronal cells in vitro. 09/02/05; 1-16.

27. Vesper SJ, Vesper MJ. Possible role of fungal hemolysins in sick building syndrome. Advances in Applied Microbiology 2004; 55: 191-213.

28. Jussila JJ. Inflammatory responses in mice after intratracheal instillation of microbes isolated from moldy buildings. PhD dissertation 01/24/03 National Public Health Institute, Finland.

29. Vesper SJ, Vesper MJ. Stachylysin may be a cause of hemorrhaging in humans exposed to Stachybotrys chartarum. Infection and Immunity 2002; 70(4): 2065-2069.

30. Mason CD, Rand TG, Oulton M, MacDonald JM, Scott JE. Effects of Stachybotrys chartarum (atra) conidia and isolated toxin on lung surfactant production and homeostasis. Natural Toxins 1998; 6: 27-33.

31. Nikulin M, Reijula K, Jarvis BB, Veijalainen P, Hintikka EL. Effects of intranasal exposure to spores of Stachybotrys atra in mice. Fundamental and Applied Toxicology 1997; 35: 182-188.

32. Wilkins CK, Larsen ST, Hammer M, Poulsen OM, Wolkoff P, Nielsen GD. Respiratory effects in mice exposed to airborne emissions from Stachybotrys chartarum and implications for risk assessment. Pharmacology & Toxicology 1998; 83: 112-119.

Curriculum Vitae

10/29/07

Ritchie C. Shoemaker, M.D.
DOB: 06-13-51 Charlotte N.C. US Citizen
Home address: 2448 Lakeland Drive, Pocomoke, Maryland 21851

Current Employment
Ritchie C. Shoemaker MD. PA. DBA Chronic Fatigue Center
President, ChronicNeurotoxins, Inc
Medical Director, Center for Research on Biotoxin Associated Illnesses (501-c-3, non-profit corp.)

College: Duke University 1969-1973 Magna Cum Laude
Major in Molecular Biology, Zoology. Minor in Philosophy.

Theses:

- Microtubule control of phototactic responses in *Euglena*, 1971.
- Localization of DNA replication sites in *Tetrahymena* by electron microscopy, autoradiography and tritiated thymidine counts, 1972.

Medical School: Duke University 1973-77

Editor – "First Contact" Medical Student Primary Care Journal

Theses

- Molecular basis for muscle injury and repair 1974
- Ventilation-perfusion abnormalities in chronic lung disease 1975
- Epidemiology of *streptococci* 1976

Residency 1977-80
Family Practice Residency, The Williamsport Hospital, 777 Rural Ave, Williamsport, PA 17013

Board Certification ABFP 1980
MD License 1980 to present. D24924

Professional Memberships

- AMA 2001-present
- ACSM 1977-1996
- American Society of Bariatric Physicians 1998-2001
- American Academy of Family Physicians 1999-2001
- American Society for Microbiology 1999-present
- American College of Occupational and Environmental Medicine 2/6/05-2/6/06
- American Society of Tropical Medicine and Hygiene 11/05-present
- International Lyme and Associated Disease Society (ILADS) 2000-2003
- International Association for Chronic Fatigue Syndrome 4/05-present
- Maryland Medical Chirurgical Association (Med Chi) 1980-present
- Maryland Academy of Family Physicians 1999-2001

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Practice Experience

- 1980-1982 NHSC Pocomoke, Maryland.
- 1982 to present, Private Practice, Pocomoke, Maryland
  Outpatient Family Medicine
  1604 Market St 10/02-5/02
  500 Market Street, Suites 102,103 6/02-present
  Pocomoke City, Maryland 21851

Teaching Appointments

- Milton Hershey Medical School 1980-90, Physician Assistant Preceptor;
- Johns Hopkins Medical School 1981-86;
- Duke University Medical School 1983-85;
- Wilmington College Nurse Practitioner Program 1996-1997;
- University of Maryland Medical School 1997-present.

NB: These appointments are for community preceptorships only and are not salaried

Hospital Affiliation, Active Staff, McCready Hospital, Crisfield, Maryland 1980-1986, 1997-6/2003, courtesy 1986-1997; and 7/2003-present, pure outpatient practice (no demands to reduce privileges).

Medical Society

- President, Somerset County 1982-86
- Member, Worcester County 1986-1997
- President, Somerset County 1998-present

Credentialed By

- Medicare, Medicaid, BCBS, MDIPA, DHP, Alliance, Prudential, Principal, Aetna American Health Care, Infor Med, PHCS, Trigon, many others.
- Never denied credentials

Additional work experience

Shoemaker's Bench, Antique Refinishing and Restoration 1966-present. Historic Remodelers of the Eastern Shore 1981-present. Wetland Consultant 1983-present. Visiting Medical Lecturer 1991-present.

Website

www.chronicneurotoxins.com 4/00-present
www.moldwarriors.com 10/04-present

Books published

- Pandora Boxer (philosophy) 1972 (out of print)
- Hematology for Residents 1978 (out of print)
- Weight Loss and Maintenance; My Way Works, Does Yours?
  - First printing 1996; Second printing 1998.
- Pfiesteria: Crossing Dark Water
  - First printing 1997; Second printing 1998
- Desperation Medicine
  - 1/15/01 Second printing 6/06
- Lose the Weight You Hate
  - First printing 2/02; Second printing 10/05
- Mold Warriors 4/05
- Books in preparation:
  A Users Guide to Native Shrubs and Trees of the Eastern Shore
  From Farm to Estuary; A Chesapeake Bay Ecology Cookbook
  It's a Long Way From Pocomoke; This One's For You, Jack.
  Surviving Mold: Life in the Era of Dangerous Buildings

Columnist Worcester County Messenger weekly newspaper; "What's Cooking" 1994-2001

Editorials Published

Daily Times of Salisbury (many), Maryland Environmental Health Newsletter,
Outlook (op-ed) Washington Post, Baltimore Sun, Multiple Florida Newspapers,
Runoff Magazine, CCA Journal, Feature article with Duke Alumni Magazine,
Family Practice News, Internal Medicine News, OB-GYN News, Delmarva Farmer (many), Asbury (NJ) Press (Op-ed).

National television appearances

Good Morning America, BBC, Australian Broadcasting System, NBC News, CBS News, Discovery Health Channel: "Dangerous Catch" and "Is Your House out to Get You", CNN, ABC News

Local TV stations

Multiple: Salisbury, Md., Washington, DC, Baltimore, Md, Stuart, Florida, Philadelphia, Pa, Leesburg, Florida, New Orleans, Louisiana

Publications:

- "The Death of Edgar Allen Poe" What Really Happened MMJ 4/97
- Diagnosis of *Pfiesteria* Human Illness Syndrome, Maryland Medical Journal 1997; 46(10): 521-3.
- Treatment of Persistent *Pfiesteria* Human Illness Syndrome, MMJ 1998; 47(7): 64-66.
- Co-author, Grattan et al, Lancet 1998; 352: 532-41. Learning and memory difficulties after environmental exposure to waters containing *Pfiesteria* or *pfiesteria-like* dinoflagellates.
- Hippocrates 2000; February, Viewpoint Housecall: A crisis in the air restores a physician's faith in medicine
- Possible Estuary-Associated Syndrome, Environmental Health Perspectives 2001; 109(5): 539-545. Grand Rounds in Environmental Medicine
- Residential and Recreational Acquisition of Possible Estuarine Associated Syndrome: A New approach to Successful Diagnosis and Therapy, Environmental Health Perspectives, Special CDC *Pfiesteria* Supplement, 2001; 109S5; 791-796.
- How Sick is Your Building and What You can do About it, Filtration News, June, 2001
- Getting Inside Sick Building Syndrome, Filtration News, July, 2001
- American Diabetes Association, Diabetes 2002; 51(2) Supplement: A133. Use of pioglitazone to prevent intensification of persistent symptoms following cholestyramine treatment of patients with Post-Lyme syndrome
- A Primer in Sick Building Syndrome: Lessons from the Somerset County District Court, Filtration News June, 2002
- Lyme Times 2002; 33: 13-16. Lyme, an Infectious Disease and a Neurotoxin Illness.
- Lyme Times 2002; 33: 38-40. Someone Has to Tell; a patient's story.
- Environmental Health Perspectives 2002; 110: A121-A123, letter. Visual contrast sensitivity, response.
- Environmental Health Perspectives 2003; 111(1): A18-19, letter. Neuropsychologic Testing versus Visual Contrast Sensitivity: Response.
- Medical Conditions Arising From Environmental Conditions, interview, Filtration News, July 2003
- Moldy buildings: It's a jungle in there. Filtration News, Nov 2004
- Neurotoxicology and Teratology, January 2005. R. Shoemaker and D. House, A time-series of sick building syndrome; chronic, biotoxin-associated illness from exposure to water-damaged buildings. Neurotoxicology and Teratology 2005; 27(1) 29-46.
- Sick Building Syndrome in water-damaged buildings: Generalization of the chronic biotoxin-associated illness paradigm to indoor toxigenic fungi; 5/2005; Pg 66-77 in Johanning E. Editor, Bioaerosols, Fungi. Bacteria, Mycotoxins and Human Health. R Shoemaker, JM Rash, EW Simon.
- To Build a Safe House, Filtration News, June 2005
- Defining Sick Building Syndrome in adults and children in a case-control series as a biotoxin-associated illness: diagnosis, treatment and disorders of innate immune response, MSH, split products of complement. IL-1B, IL-10, MMP9, VEGF, autoimmunity and HLA DR; American Society of Tropical Medicine and Hygiene; 12/14/05

- C3a and C4a: complement split products identify patients with acute Lyme disease; ASTMH, 12/4/05
- MMP9, visual contrast sensitivity, C3a, C4a and HLA DR: New diagnostic aids in acute and chronic Lyme disease, ASTMH, 12/14/05
- Atovaquone plus cholestyramine in patients co-infected with *Babesia microti* and *Borrelia burgdorferi* refractory to other treatment, Advances in Therapy 2006; 23(1): 1-11. Shoemaker RC, Hudnell KH, House DE, van Kempen A, Pakes GE for the COL 40155 Study Team.
- American Society for Microbiology Biodefense Research meeting 2/16/06 Hyperacute physiological changes following prospective exposures to environmental sources of trichothecene toxins in water-damaged buildings (WDB): a Stealth toxin is revealed.
- SBS and exposure to water damaged buildings: time series study, clinical trial and mechanisms; submitted, Neurotoxicology and Teratology 3/27/06, accepted for publication 7/31/06. R Shoemaker, D House. Internet location: doi: 10.1016/j.ntt.2006.07.003. Published as NTT 2006; 28: 573-588.
- Mold Illness after Katrina: The truth you haven't heard. Filtration News, May, June 2006
- AAAAI; rebuttal to Bush position paper, endorsed by >100 PhD and MDs; submitted 5/06, accepted 7/8/06, JACI 2006; 118: 764-766. Co-authors: Harriett Ammann PhD; Richard Lipsey PhD; and Ed Montz PhD.
- ASTM International, Section D22, Boulder Colorado 7/27/06. Bringing science to bear on moisture and mold in the built environment. "Defining causality of a biotoxin-associated illness by exposure to water-damaged buildings: a case control series."
- ASTMH 11/06 (accepted) Defining chronic ciguatera illness by abnormalities in innate immune responses: final common pathways of biotoxin-associated illnesses
- ASTMH 11/06 (accepted) Eight year follow-up of patients with Possible Estuarine Associated Syndrome (PEAS): symptom reduction didn't result in cure
- International Association for Chronic Fatigue Syndrome 1/14/07. Treatment of elevate C4a in patients with CFS using low doses of erythropoietin safely reduces symptoms and lowers C4a: a prospective clinical trial.
- International Association for Chronic Fatigue Syndrome 1/14/07. Treatment of CFS patients with elevated C4a using low dose erythropoietin corrects abnormalities in central nervous system metabolites and restores executive cognitive functioning.
- International Association for Chronic Fatigue Syndrome 1/14/07. Treatment of CFS patients with low levels of vasoactive intestinal polypeptide (VIP) and shortness of breath with tadalafil improves exercise tolerance and pulmonary artery pressure responses to exercise.
- Inside Indoor air quality 4/15/07, with King-teh Lin PhD. Filtration News May/June 2007.
- 10/3/07 Allergy Clin Immunol Int: J World Allergy Org 2007 Supplement 2. C3a and C4a: Complement split products identify patients with hyperacute Lyme disease.
- 10/14/07 IAQA, Las Vegas, Nevada. Sequential activation of innate immune elements: a health index for people re-exposed to water-damaged buildings.
- ASTMH 11/07. Correction of central nervous system metabolic abnormalities, deficits in executive cognitive functioning and elevated C4a: a clinical trial using low dose erythropoietin in patients sickened by exposure to water-damaged buildings.
- ASTMH 11/07. Sequential upregulation of innate immune responses during acute acquisition of illness in patients exposed prospectively to water-damaged buildings.
- ASTMH 11/07. Defining mold illness in children: a chronic inflammatory illness with distinctive biomarkers.

Peer reviewer:

Environmental Health Perspectives; Special CDC Pfiesteria issue, 2001; comment on fungal illness 2007
Environmental Research; 2003, 2004
Journal of Nutritional and Environmental Medicine 2007 (small colony variants. MARCoNS)
Heart and Lung 2007 (Babesia as FUO)

Graduate degree examiner

University on Newcastle, Australia 10/04. Delta hemolysins production of long-term *Staphylococcus epidermidis* cultures. Hai Lin, Environmental and Life Sciences.

Presentations:

- **4/10/00** Regional Meeting American Society of Microbiology, Lewes, Delaware.
  A new approach to diagnosis and treatment of chronic Lyme disease: vision, cytokines, and cholestyramine.
- **5/10/00**- Chico, Calif. Lyme disease as a Neurotoxin and Cytokine-Mediated Illness
- **9/21/00** Lewes, Delaware. Center for the Inland Bays "*Pfiesteria* Human Illness Syndrome and Blue Green Algae Syndrome: Emerging Estuarine Health Threats"
- **9/24-25/00** Tallahassee, Florida. Florida Department of Environmental Protection Diagnosis and Treatment of a chronic neurotoxin-mediated illness from an unknown microbe at the Casteen Roads.
- **11/4/00**, Princeton, New Jersey. Annual Scientific Conference of the Lyme Disease Association Hypoperfusion of retina and neural rim of optic nerve head as biomarker for the chronic neurotoxin-mediated illness of Lyme disease.
- **10/25/00** American Psychiatric Association, Annual Meeting, Philadelphia, PA. Environmental Acquisition of Psychiatric Illness
- **10/30/00** Annual Meeting of American Society of Tropical Medicine and Hygiene, Houston, Texas.
  A new approach to diagnosis of chronic *ciguatera* illness and successful treatment with cholestyramine
- **6/01/01** Delaware Medical Society, Lewes, Delaware. Approach to Diseases Caused by Neurotoxins
- **11/09/01** Lyme Disease Association, Princeton, NJ. Acute Lyme Disease
- **11/10/01** ILADS. Princeton, NJ, Co-infection with apicomplexans and Lyme, role of extrachromosomal plastid DNA and persistent symptoms
- **11/30/01** International Society of Neurobiology, Seattle, Washington. Neurotoxins and solutions to questions raised by chronic fatiguing illnesses
- **2/14/02** American Academy of Environmental Medicine, St. Louis, Missouri, an 8 hour tutorial. Challenges to Clinical Paradigms: Cytokines, neurotoxins and vision
- **6/24/02 8th** International Symposium of Neurotoxicology, Brescia, Italy. Co-Chair (with Ken Hudnell, Ph.D.) of Biotoxin Session. Three lectures: Sick Building Syndrome: Possible Association with Exposure to Mycotoxins from Indoor Air Fungi (to date, the largest study on SBS in the world's literature, 103 patients and 43 buildings); Use of pioglitazone to prevent intensification of persistent symptoms following cholestyramine treatments of patients with Post-Lyme Syndrome: the multisite trial. Metallic Taste, a marker of neurotoxicity.
- **9/17/02** Environmental and Occupational Health Sciences Institute, Occupational Medicine Residency Program, Robert Wood Johnson Medical School, Piscataway, NJ; Neurotoxin mediated illnesses: A new approach to medically unexplained symptoms.
- **9/20/02** International College of Integrative Medicine, Grand Rapids, Michigan. Neurotoxins, hypothalamic hormones and chronic fatiguing illnesses
- **11/15/02 ASTMH** Denver, Colo, Use of atovaquone and cholestyramine in patients co-infected with *Borrelia burgdorferi* and *Babesia microti*, refractory to all antibiotic regimens (GlaxoSmithKline funded research).
- **12/6/02 Faculty** member, National panel, Wright State University, Michigan. Interim clinical guidelines for the diagnosis and treatment of mold associated medical disorders; presented, "A new paradigm for diagnosis and treatment of Sick Building Syndrome, a biotoxin associated illness."
- **2/20/03 Univ Connecticut,** Pathobiology seminar, "Biotoxins, vision, inflammatory cytokines and hypothalamic hormones in primary care medicine: From Post-Lyme Syndrome to Sick Building Syndrome, a new paradigm for medically uncertain symptoms.
- **7/11/03 Harris Chain of Lakes Restoration Commission,** Lake County, Florida. St. John's River Water Management District, invited lecture: Human health effects following exposure to toxigenic cyanobacteria: diagnosis, treatment and environmental implications
- **9/10/03 5th International Conference on Bioaerosols, Fungi, Bacteria, Mycotoxins and Human Health,** Saratoga Springs, NY (peer reviewed). Sick building syndrome in water damaged buildings: Generalization of the chronic biotoxin associated illness paradigm to indoor toxigenic fungi (156 patients in 150 buildings).
- **9/25/03 13th annual Environmental Information Association. Myrtle Beach, SC,** keynote. The clear link between mold exposure and human health: What you need to know

- **10/30/03 Mold 5 National Institute of Building Sciences, Building envelope and thermal environment committee,** San Diego, Cal, keynote, Human health effects from exposure to toxigenic fungi: The proof of causation is here.
- **11/25/03 Crossing boundaries: Medical Biodefense and Civilian/Military Medicine; First International conference, sponsored by George Mason University, National Center for Biodefense and Georgetown University,** Arlington, Va. Diagnosis and Treatment of Biotoxin Associated Illnesses: Learning for the future from Today's Example
- **12/02/03 Special Report to the Federal Research Committee on Gulf War Illness.** Gulf War Illness as a Biotoxin Illness: Report of a cohort of exposed veterans.
- **1/10/04 Invited speaker, National Center for Biodefense, George Mason University.** Physiology of chronic biotoxin illness.
- **4/30/04 American Society for Microbiology**, **Integrating Metabolism and Genomics**, Montreal, Quebec. Linkage disequilibrium of HLA DR genotypes, autoantibodies and wingspan/height ratios in patients with environmentally acquired toxigenic illness
- **5/25/04 104th General meeting of American Society for Microbiology,** New Orleans, Louisiana. Melanocyte Stimulating Hormone (MSH) Deficiency in Chronic Fatigue Syndrome Associated with Nasal Carriage of Coagulase Negative Staphylococci
- **6/22-23 2004 Mealey's National Mold Litigation Conference**, Orlando, Florida. Invited speaker, Emerging medical issues in mold illness.
- **10/8/04 American (now International) Association for Chronic Fatigue Syndrome,** Madison, Wisconsin. Chronic Fatigue Syndrome: Lessons from the Biotoxin Pathway
- **12/4/04 Johns Hopkins University, Occupational and Environmental Medicine Conference,** Chronic Illness from Water-Damaged Buildings: Just Another Stop Along the Biotoxin Pathway
- **12/9-10/04 Mealey's Construction Defect and Mold Litigation Conference, Las Vegas, Nevada,** Why the Institute of Medicine Report is Stale
- **9/6-10/05 International Symposium on Cyanobacteria and Harmful Algal Blooms, US EPA** Research Triangle Park, NC. Characterization of chronic human illness associated with exposure to cyanobacterial harmful algal blooms predominated by *Microcystis*
- **11/2/05 Mid-Shore Lyme Disease Association,** Acute and chronic Lyme disease: lessons from the Biotoxin Pathway. Easton, Maryland.
- **2/16/06 Drexel University School of Medicine, Philadelphia, Pa. Visiting professor series.** It's a Long Way from Pocomoke
- **3/4/06 CAM Expo East, NYC, NY.** Physiology of fibromyalgia and Chronic Fatigue Syndrome
- **3/25/06 Mid-Shore Lyme Disease Association**, Easton, Md. Rise of the innates; Lyme disease 2006:lessons from a billion years ago
- **4/1/06** Third Annual Mold Conference, Houston, Texas. Mold Illness: So What do We Really Know?
- **5/6/06** American College for Advancement in Medicine, Dallas Texas. Lyme disease update: Rise of the innates
- **6/28/07** Quarterly Medical Director's Conference; Department of Mental Health Services, State of Virginia, "Inflammatory central nervous system illness caused by environmental exposures presenting as psychiatric illness."
- **12/6/07** National Toxicology Program NIEHS, RTP, NC. Physiologic disturbances and causality in patients with illness acquired following exposure to water-damaged buildings
- **6/2/08** AIHA continuing education program Round Table, Minneapolis; Steve Vesper, Greg Boothe, Gil Cormier King teh Lin co-panelists. Integrating Field, Laboratory and Clinical data for the IAQ investigation.

Posters:

12/10/98 Georgetown Center for Food Policy, Washington, D.C.
1. *Pfiesteria*; Diagnosis and Treatment
2. Environmental Factors Contributing to *Pfiesteria* Blooms

6/15/99 Maryland Academy of Family Practice Annual Meeting
1. *Pfiesteria* Human Illness Syndrome
2. Use of Troglitazone in Treatment of Hyperinsulinemic Obesity

5/01/00 Association of Research in Vision and Ophthalmology, Fort Lauderdale, Florida.
1. Use of Contrast Sensitivity in Diagnosis of Chronic Neurotoxin-Mediated Illness

6/4/00 US EPA National Health and Environmental Effects and Research Lab
1. Human Health and Environmental Indicators
2. Possible Estuarine Associated Syndrome, Diagnosis and Treatment

10/18/00 CDC National Pfiesteria Conference Stone Mountain, Georgia
1. Evidence of Successful treatment of the chronic neurotoxin-mediated illness of Possible Estuarine Associated Syndrome
2. Possible *Cylindrospermopsis* Associated Human Illness Syndrome

6/20/01 81st Meeting of Endocrine Society, Denver, Colorado
1. Use of Rosiglitazone in Treatment of Hyperinsulinemic Obesity (SmithKlineBeecham funded research)

6/15/02 San Francisco, American Diabetes Association
1. Use of Pioglitazone to Prevent Intensification of Persistent Symptoms following Cholestyramine Treatment of Patients with the Post-Lyme Syndrome (Takeda Pharmaceuticals North America, funded research)

11/15/02 Denver, Colorado, ASTMH
1. Differential Association of HLA DR by PCR Genotypes with Susceptibility to Chronic, Neurotoxin-Mediated Illnesses

9/10-9/12/03 Saratoga Springs, NY 5th International Conference on Bioaerosols, Fungi. Bacteria, Mycotoxins and Human Health.
1. Sick Building Syndrome, diagnosis and treatment of a biotoxin associated illness with multiple biomarkers: prospective confirmation of causation in 156 patients from 150 buildings using 11 different biomarkers

10/8/04 American Association for Chronic Fatigue Syndrome, Madison, Wisconsin
1. Chronic Fatigue Syndrome: Lessons from the Biotoxin Pathway;

CME Speaker:

6/20/00 Maryland Academy of Osteopathic Physicians, Ocean City, Maryland Annual Meeting.
1. A physician's approach to diagnosis and treatment of chronic neurotoxin-mediated illnesses.

American Society of Bariatric Physicians:

4/10/99 Phoenix, Arizona Regional Meeting
1. Use of troglitazone in treatment of hyperinsulinemic obesity.

10/30/99 Las Vegas, Nevada. Annual Meeting
1. Rational use of the Glycemic Index

5/10/00 Portland, Oregon, Regional Meeting
1. Environmental acquisition of defects in insulin receptor physiology

10/4/00 Washington, D.C. Annual Meeting
1. Hypoperfusion, tumor necrosis factor alpha and environmental acquisition of diabetes and obesity

4/15/01 Houston, Texas.
1. Use of Rosiglitazone in treatment of Hyperinsulinemic Obesity in Non-Diabetics

4/15/99 WV Academy of Physician Assistants, Davis, WV.
1. The No-Amylose Diet

Congressional testimony: House of Representatives 9/22/04 staff briefing and press conference Member John Conyers; Health effects of exposure to water-damaged buildings; US Senate staff meeting 1/12/06, Human health effects of mold exposure, Senator Edward Kennedy.

Maryland Senate testimony: Commentary on indoor air quality task force at invitation of Senator Rob Garagiola 3/29/06

IRB Studies

a. SmithKline Beecham 9/99 IRB: Quorum
Use of rosiglitazone in treatment of hyperinsulinemic obesity.

b. Glaxo Wellcome 10/00 IRB: Copernicus Group
Use of Mepron (atovaquone) in patients with *Borrelia burgdorferi* coinfected with *Babesia microti* refractory to antibiotics and cholestyramine.
c. Protocol IND 63,993 Use of Melanocyte Stimulating Hormone in Patients with Chronic Fatigue
d. Protocol SBS 51326 Use of visual contrast sensitivity testing and cholestyramine therapy in diagnosis and treatment of environmentally-acquired, chronic, neurotoxin-mediated illness from indoor exposure IRB Copernicus 7/23/02
e. SPL-CFS 123 Treatment of Chronic Fatigue Syndrome in patients with nasal colonization of multiply antibiotic resistant, biofilm-forming species of coagulase negative Staph using nasal instillation of diluted Staphage Lysate® IRB Copernicus 11/27/03
f. Retrospective use of laboratory results in a report of group results: Complement split products C3a, C4a, MMP9 and visual contrast sensitivity are markers for acute acquisition of Lyme disease. IRB Copernicus Group, 9/8/05
g. Retrospective use of individual laboratory results in a report of group results: Defining Sick Building Syndrome in adults and children as a biotoxin-associated illness. IRB Copernicus Group 10/20/05
h. Retrospective use of individual laboratory results in a report of group results: Eight-year follow-up of Possible Estuarine Associated Syndrome cases and controls. IRB Copernicus Group 11/7/05

Lecturer Medical Mutual Insurance Company 2/00 Risk Management in Primary Care

Awards

- American Academy of Family Practice, Finalist, National Family Practice Physician of the Year, 2002
- Maryland Family Practice Doctor of the Year 2000, MAFP
- Maryland Governor's Volunteer of the Year for the Environment, 4/97
- Local Governor's Advisory Committee for Innovation and Restoration of Chesapeake Bay 1994
- State of Maryland Bill Jones Environmental Award 1995
- Maryland Dept. Agriculture Conservator of the Year 1994
- Good Neighbor Award 1993
- Dr. Henry P. and M. Page Laughlin Award for Distinguished Authorship/Editorial Award 5/98
    - (Maryland Medical Journal)

Commencement Speaker

- Malcolm Grow Medical Center (Andrews AFB 6/98)

CME Speaker

- Audio Digest Vol. 47 No. 22 6/99 Washington D.C.
- Audio Digest Vol. 48 No. 14 12/99 Washington D.C.

Internet links

- http://www.ImmuneSupport.com/library/showarticle.cfm/id/4291/searchtext/neurotoxins/.
- http:// www. ImmuneSupport.com/library/showarticle.cfm/id/3990/searchtext/neurotoxins/.

Patents applications, provisional

- PAI-1 and TNF as markers for the inflammatory basis of type II diabetes, obesity and atherosclerosis. US Provisional patent Serial no 60/356,541
- Use of alpha melanocyte stimulating hormone to treat patients with chronic fatigue syndrome. US Patent Provisional Serial no.: 60/356/539.
- Use of thiazolidinediones as an adjunct to diet in treatment of hyperinsulinemic obesity; importance of the No-Amylose diet. US Patent Provisional Serial no.: 60/356,690
- Pretreatment of patients with Post-Lyme Syndrome with pioglitazone before use of cholestyramine prevents intensification: Vision, neurotoxins and cytokines. US Patent Provisional Serial no.: 60/333,335

Completed Patent application

- "Methods for treating or inhibiting Sick Building Syndrome, Post-Lyme Syndrome, and/or Chronic Fatigue Syndrome." Inventors Ritchie Shoemaker MD and H. Kenneth Hudnell, Ph.D.
  PCT Patent application no PCT/US03/04137

Health Investigations and treatment, cohorts of patients exposed to toxigenic fungi (> 4 patients)

- Glenwood Springs, Colorado. Robert Cordova, leader of cohort. 7/28/06 14 patients.
- Fraternal Order of Police; Queen Anne's County, Maryland 5/06 8 patients
- St. Bernard Parish, Louisiana, on the Scotia Prince 2/06; conjoint investigation with Richard Lipsey, PhD; firefighters, homeless adults and children, Parish employees, ship's crew and health care workers 212 patients
- Residences at the Ritz; Ritz Carlton 1155 and 1111 23rd St NW Washington DC 8 patients
- Newmarket Courthouse, Toronto, Ontario, Canada. 12/04-present; 300 employees at risk
- International Marine Terminal, Portland, Maine. 11/05. 16 patients.
- Topsail (NC) School District. 9/04. 260 patients.
- Prince Georges County Fraternal Order of Police; Oxon Hill, Md. 6/03. 52 patients.
- Hampton Bays United Free Elementary School, Long Island, NY. 5/03. 44 patients.
- State Iowa Dept Corrections, Davenport, Iowa. 1/03. 10 patients.
- Baltimore-Washington Conference United Methodist Church, Columbia, Md. 12/02. 55 patients
- Eastern Correctional Institution, Westover, Md. 5/02. 11 patients.
- Accomack County (Virginia) Social Services Building. 4/02. 11 patients.
- Multi-Services Building 201 Baptist St., Salisbury, Md. 4/02. 20 patients.
- Police Department Berlin, Md. 4/02. 5 patients.
- Somerset County Library, Princess Anne, Md. 2/02. 13 patients.
- Somerset County Circuit Court, Princess Anne, Md. 10/01. 5 patients.
- Somerset County District Court, Princess Anne, Md. 6/01. 12 patients.
- Worcester County Board of Education Newark, Md. 5/99. 8 patients.
- Wicomico County Sheriffs Department, Salisbury, Md. 2/99. 25 patients.

Papers in preparation

- Biofilm formation makes multiply antibiotic resistant coagulase negative staphylococci pathogens in low MSH patients
- Pediatric mold illness: inflammatory links to autoimmunity
- HLA in illness and disease: equilibrium dissociation and biotoxin illness susceptibility

SAIIE: A HEALTH INDEX FOR PEOPLE RE-EXPOSED TO WATER-DAMAGED BUILDINGS

IAQA

10/14/07

Sequential Activation of Innate Immune Elements SAIIE

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Center for Research of Biotoxin Associated Illnesses
Pocomoke, Maryland

The Problems

- Use of spore counts alone to clear a building for re-occupancy doesn't make sense
- Symptoms, analyzed individually, won't be a reliable marker, especially in litigation
- Since safety for humans underlies testing for microbes and inflammagens in a water-damaged building, do we look at the microbes or do we look at the people?

Repeating IAQ history

- Indoor versus outdoor spores, total
- Indoor versus outdoor spores, by species
- Threshold levels of given kinds of spores
- Ahh, counting fungal particles is far more important than counting fungal spores
- ERMI is so much better!
- What about bacteria, mycobacteria, actinomycetes, VOCs and beta glucans?

How can you measure quality?

- Absence of bad things
- Threshold of bad implies a dose-response
- Dose-response isn't linear in inflammatory illnesses! And don't forget genetics!
- Presence of good things doesn't prevent
- How do you account for differential susceptibility based on genetics, previous exposures, illness, inflammatory status?

What is today's accepted approach?

- Maybe a few spore counts
- Maybe a symptom list
- Maybe a moisture reading
- Maybe a CO_2 reading
- Only a few use human health as a marker
- Welcome to the world of SAIIE!

Symptoms alone are subjective

- Check lists are full of bias, even if recorded by a trained third party
- An individual symptom means little without differential diagnosis
- Upgrade: Cluster analysis looks at grouping of symptoms; gives statistical certainty
- Mega-upgrade: Logistic regression provides much greater statistical certainty

Lab tests would help

- Before and after measures using a prospective design provides causation, *if:*
  - Patient is treated such that his lab results equal those of large numbers controls before re-exposure
  - No additional re-exposure activity elsewhere
  - No other change in health status
  - Patient becomes his own control

What labs are abnormal in WDB illness?

- If allergy is the problem, total IgE is a good start, but IgE doesn't rise with exposure
- Removal from exposure will reduce symptoms but not IgE
- Allergic responses are antibody mediated and as such are part of *acquired immune* response
- *Innate immune* responses have little to do with allergic responses: biotoxins affect innate immunity and not acquired immunity

Illness from WDB Is Not Allergy

Mean IgE, by illness, all patients

		Cases N=	IgE
Controls	No illness	305	38
Mold cases	Confirmed case	672	43
Asthma cases	Inhaled steroids + 1 other med, > 6 months/year	45	973
Nasal allergy	Nasal steroid + 1 other med, > 6 months/year	40	407

WHY NOT LOOK AT HEALTH EFFECTS AFTER RE-OCCUPANCY?

- This idea should be a no-brainer
- We know the genetic basis of susceptibility
- We can study human illness using prospective exposure protocols *if* adequate control of other, ongoing illness is present
- We can use prospective exposure trials only if we can first treat the illness!
- Treating docs have evidence-based data

PARAMETERS	ADULT	
	ILL	WELL
MSH, mean	15.3	23.2
MMP9, mean	506	225
VEGF % < 31	38	0
VEGF % >200	15	0
ADH/osmolality dysfunction	65%	14%
ACTH/cortisol dysfunction	44%	6%
MARCoNS +	80%	3%

PARAMETERS	ADULT	
	ILL	WELL
C3a	> 1100	285
C4a	7287	631
IL-10	10.2	0.5
IL-1B	5.9	0.8
Interferon alpha	398	14
Erythropoietin % < 7.3	25	3
Erythropoietin % > 27.7	9	3

New players in clinical evaluation

- Vasoactive intestinal polypeptide (VIP)
- Suprachiasmatic hypothalamic nuclear agonist
- Inputs from olfactory bulb and retina
- Regulates cytokines peripherally, pulmonary artery pressure responses to exercise
- Stimulates a rise in intracellular cAMP
- Low in >85% of CBAI
- Low in all MCS patients seen to date (N>500)

Von Willebrand's and VIII

- Acquired abnormalities in vWF invariably seen in those with mucus membrane bleeds
- Epistaxis and hemoptysis
- Factor VIII is acute phase reactant
- vWF and ristocetin associated factor fall after day 2-3
- Hemorrhage can be profuse-Rx with DDAVP

TGF-beta

- Part of hypoxia response
- Associated with abnormal collagen cross-linking and wingspan > height
- Major player in abnormalities in T-cell regulation
- Rx with low dose erythropoietin
- Assay not available commercially yet

IL-1ra

- Interleukin-1-receptor antagonist
- Compensatory rise after activation of IL-1
- IL-1beta often found to be elevated, rising in 12 hours, but measuring blood levels alone will ignore autocrine and paracrine activity
- IL-1ra correlates highly with clinical illness and may surpass MMP9 as best indicator of cytokine activity in WDB patients

What labs aren't abnormal?

- CBC, metabolic profile, ESR, CRP, TSH
- ANA, immunoglobulins (includes IgE)
- Lipid profiles, antibody profiles
- All complement except for anaphylatoxins
- All genetic testing except for HLA DR by PCR
- LH, FSH, SHBG, estradiol, estrone, prolactin

What studies show that labs change hyperacutely?

- ASM Biodefense cohort 2006
- NTT cohort 2006
- ISTM cohort 2006

- SAIIE 2007!

C4a-1

- Anaphylatoxin, released when C4 is activated
- Dr. Giclas says, “C4 is an element of complement that acts like it has a big sign on it: Activate me.”
- Stimulates smooth muscle contraction, increases vascular permeability
- Recruits chemokines, degranulates mast cells, basophils
- Normal is < 2830 ng/ml

C4a-2

- Release activated by cell wall components of essentially every pathogenic fungus (Kozel)
- Rises in 4 hours after exposure to WDB
- Rises in 12 hours after a tick bite in those with Lyme disease
- Elevated in CFS, fibromyalgia, dinoflagellate and cyanobacteria illnesses
- Rarely elevated in non-innate immune illnesses

C4a-3

- Highly correlated with symptoms of executive cognitive problems (CDC-IACFS, ASTMH)
- Highly correlated with elevated lactate and low ratio of glutamate to glutamine in frontal lobes and hippocampi
- Capillary hypoperfusion is the currency of C4a
- Correction of C4a corrects cognitive problems, total symptoms and CNS metabolites

Leptin-1

- Adipocytokine
- Agonist of POMC pathway in VLN hypothalamus; long-isoform receptor is primitive gp-130 cytokine receptor
- Inflammatory in its own right
- Disproportionate increase in leptin resistance will make patients fat
- If leptin resistant, forget weight loss by standard means!

Leptin-2

- Rise in leptin seen after 48 hours
- Tie unexplained weight gain to time of onset of MSH deficiency in WDB illness
- Lowered by pioglitazone and high dose omega three fatty acids; PPAR-gamma control
- Must avoid insulin rise to lower leptin pharmacologically; use no-amylose diet
- Dimorphic; levels in women higher than men

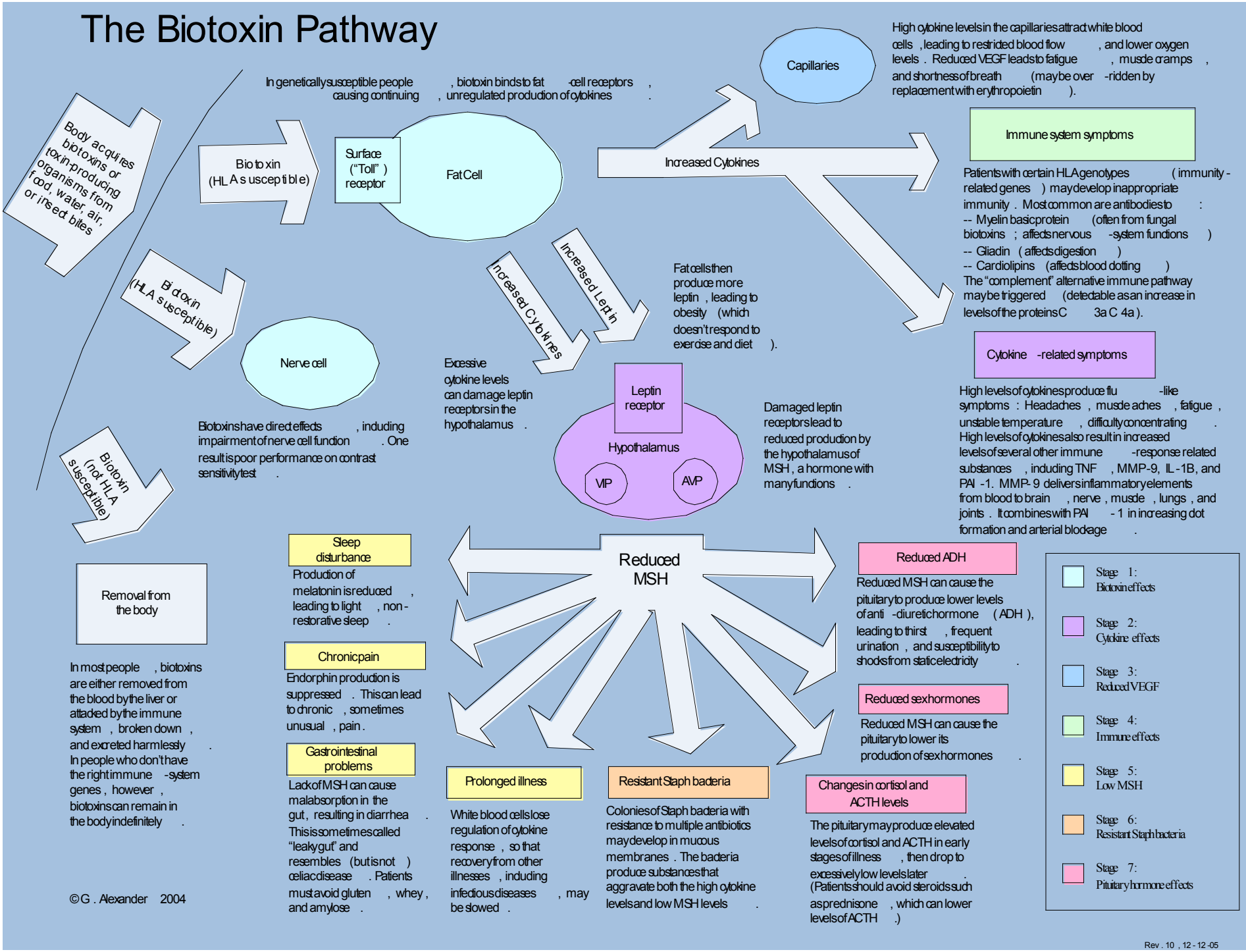
Matrix metalloproteinase-9

- MMP9 is the “delivery van” takes inflammatory elements out of blood and puts them into brain, joint, lung, nerve and muscle
- Normal range is 0-322; LabCorp range is wrong, still uses Esoterix range that combined cases and controls
- Freeze serum quickly after draw; don’t let tube clot!!
- Best measure of cytokine effect on endothelial cells and macrophages

Vascular endothelial growth factor

- Often low (< 31 ng/ml) in biotoxin illnesses
- Fumagillin was first antiangiogenic substance
- Clinical importance of high VEGF in cancer and atherosclerosis
- Response to hypoxia is initial transcription; expect levels to rise hyperacutely
- Second regulatory wave causes a fall of VEGF shortly thereafter

The Biotoxin Pathway



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Rev. 10, 12-12-05

Treatment of Biotoxin Illnesses

- Follow the innate immune responses
- Remove from exposure
- Cholestyramine protocol first
- Eradicate biofilm formers next
- Correct cytokines with Actos
- Correct hormones: ADH, androgens
- Correct VEGF/epo
- Correct autoantibodies
- Correct C3a, C4a
- Correct acquired pulmonary hypertension
- Correct CNS lactate; glutamate/glutamine

Now you are ready for SAIIE

- Collate symptoms and labs using 7 steps
- Baseline; After Rx (AC-1); Away from building off all meds three days (HOC); into WDB off mall meds three days (BOC-1, BOC-2, BOC-3); Re-Rx (AC-2)
- Used in hundreds of patients safely
- Patient provides informed consent
- Physician can forbid if C4a > 20,000

Time course of Biotoxin Pathway

- Initial detection: cytokines and C3a, C4a
- Binding to Toll, c-linked lectin and dectin receptors activates gene transcription, IL-1b
- Cytokines bind to long isoform of leptin receptor, compensatory rise in leptin at day 2
- Cytokines turn on second wave of gene transcription, MMP9 rises day 2-3
- VEGF rises on Day 1 and crashes on day 3

Case definition-1

FIRST TIER modeled on CDC *Pfiesteria* Case definition from 1998

- Potential for exposure
- Multisystem, multisymptom illness
- Absence of confounders
  - Differential diagnosis key feature here

Case definition-2

SECOND TIER

- Simply stated: what did cases have that controls didn't
- Genetic susceptibility; HLA DR by PCR
- Hypothalamic impairment; low MSH
- Neurotoxic illness; VCS deficit
- Cytokine activation; MMP9 elevation
- Pituitary and peripheral endocrine response dysregulation
  - ACTH/cortisol
  - ADH/osmolality

Case definition set the bar at 100%

- Over 4400 WDB patients
- Over 600 controls
- Given that nothing in biology is ever 100%
  - All cases met criteria
  - No controls met criteria
- Potential for incorrect classification
- Logistic regression shows that number is infinitesimally small

Does the sequence of innate immune events confirm the illness?

- Study design: identify cases and controls
- Treat cases to equal controls at baseline
- Controls don't have AC-1, HOC
- Record BOC 1, 2, 3 as % of baseline
- Subtract control % from case % BOC 1, 2, 3
- Establish illness effect by time of exposure
- Rate changes as % of 100, assign number 1-5

Using the SAIIE-1

- Prospective trial of 50 buildings
- Add indices from each category: symptoms, leptin, VEGF, MMP9 and C4a
- Cases average SAIIE was 17.1
- Controls 6.1
- Enables additional comparison of human health to environmental sampling
- Any ERMI > 2 was associated with acquisition of illness and SAIIE >13

Using the SAIIE-2

- If any C4a was > 20,000, however, illness recrudesced and SAIIE > 13 if ERMI was as low as NEGATIVE 1!
- No correlation of “safe” spore counts with any human health parameter (ie in the buildings that were cleared by spore counts)
- Not all patients have the identical pattern of response
- 50 buildings and 50 patients aren’t enough

Using the SAIIE-3

- Case in litigation
- Spore counts say the building is just peachy
- 3 volunteers, each met case definition and successfully treated
- Symptoms peak at day 3
- C4a peaks at Day 1, does not fall
- Leptin, VEGF and MMP9 show peaks on time
- Average SAIIE = 19.2

The future-1

- Add vWF and Factor VIII-difficult to get outlying labs to do specimen preparation right
- Genomics using PAX tubes
  - mMRA tells us which genes are activated and when
  - Other biotoxins (ciguatera, cholera) show same pattern
  - Assess gene activation as function of duration
- Use of genomics to assess illness at baseline

The future-2

- Link of SAIIE to ERMI will require much more data
- Early results are eerily similar, however
- If C4a > 20K means no exposure is safe, where do these patients live?
- How can the elevated IL-4, Il-8, IL-10 immuno-paralytic engine be stopped?

For more information

- www.chronicneurotoxins.com
- www.biotoxin.info
- www.moldwarriors.com
- Mold Warriors 2005, 2007
- Desperation Medicine 2001, 2006
- Lose the Weight You Hate 2002, 2005
- Surviving Mold Spring, 2008