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The role of Borreliosis, tick-borne co-infections, and the 16 point MSIDS model in Lyme-like illness in Australia

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Senate Inquiry into Lyme Disease-like Illness in Australia

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Overview: I am a board certified internist living in one of the highest Lyme endemic areas of the United States, and have specialized in Lyme disease and tick-borne disorders due to the need to serve a population of extremely ill individuals for whom classical diagnostic and treatment paradigms have failed to provide answers. I am one of the founding members and past president elect of the International Lyme and Associated Diseases Society (ILADS), as well as past president of the International Lyme and Associated Educational Foundation (ILADEF), which is a non-for-profit organization dedicated to the education of health care professionals. I was one of the co-authors of the published peer review ILADS guidelines on the diagnosis and treatment of Lyme disease, and my experience is based on having seen over 12,000 chronically ill individuals over the past 29 years with clinically “unexplained syndromes” which have been labeled by other medical providers as Chronic Fatigue Syndrome/Systemic Exertional Intolerance Disease (CFS/S.E.I.D.), Fibromyalgia, autoimmune diseases including seronegative rheumatoid arthritis, MS, and Chronic Lyme disease. They come to see me from all over the United States, Europe, Canada, New Zealand and Australia, and I have found up to 16 different overlapping etiologies accounting for these patients “unexplained” symptoms of chronic fatigue, musculoskeletal pain syndromes, cognitive deficits, sleep and mood disorders. I have labeled this syndrome “MSIDS”, or Multiple Systemic Infectious Disease Syndrome, which is able to account for the broad variety of symptoms seen in this population of ill patients. The Australian patients who have come to see me have improved their health based on this model of diagnostic and treatment options. I will therefore

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provide an overview in this paper of the following three topics which are relevant to the diagnostic and treatment dilemma's facing the Australian community:

- Scientific articles on the insensitivity of Lyme and tick-borne testing
- The role of other borrelia species, co-infections and the 16 point MSIDS model in identifying overlapping etiologies in "Lyme-like illness"
- The need for long term antibiotics in some patients with Chronic Lyme Disease and overlapping co-infections

One of the first and most basic problems we face is in helping Australian patients is defining "chronic Lyme disease" or "Lyme-like illness". Patients with chronic symptoms who see me, either before or after classical treatment for Lyme disease, have multifactorial causes for their illness. I call this syndrome Lyme-MSIDS. MSIDS stands for Multiple Systemic Infectious Disease Syndrome, and represents sixteen potential overlapping medical problems contributing to persistent symptoms in the Lyme patient (Horowitz, R.I., Clinical Roundup: Selected Treatment Options for Lyme disease: Multiple Causative Factors in Chronic Disease. Alt and Compl Therapies. DOI:10.1089/act.2012.18407. Mary Ann Liebert, Inc. Vol 18, No.4 Aug 2012)

The first point on the MSIDS map is infections. Ticks are now containing multiple bacterial, viral and parasitic infections which can be transmitted simultaneously with *Borrelia burgdorferi*, the agent of Lyme disease. Patients infected with Lyme disease and associated co-infections are much sicker and resistant to standard therapies.

Patients with Lyme-MSIDS also have evidence of associated immune dysfunction, inflammation, environmental toxins and heavy metal burdens, detoxification problems, nutritional deficiencies, hormonal abnormalities, sleep disorders, mitochondrial dysfunction, food allergies and sensitivities, deconditioning and imbalances in their autonomic nervous system (adversely affecting the heart rate, blood pressure and digestive system). All of these factors can keep the patient chronically ill. There is a commonly held belief in medicine, called Pasteur's postulate that there is "one cause for one illness". This does not apply to patients with chronic Lyme symptoms or symptoms due to borreliosis and associated co-infections. The term "chronic Lyme disease" or "Lyme-like illness" needs to be redefined as Lyme-MSIDS to more accurately reflect the multiple underlying etiologies

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responsible for persistent symptoms. This will help you to overcome the problem that *Borrelia burgdorferi* has not been found in Australia, yet ticks are containing multiple other species.

Australian ticks that have been studied so far (*I. holocyclus* and *A. triguttatum*) have many different types of bacteria (Gofton et al. 2016b) which have been found to contain *Borrelia* (Relapsing Fever-like), as well as *Ehrlichia*, *Anaplasma* and *Neoehrlichia*. Conclusive evidence of tick-borne disease has also been reported in Australia for spotted fever diseases (Flinders Island Spotted Fever, Queensland Tick Typhus caused by *Rickettsia* spp.) and Q fever (caused by *Coxiella burnetii*), with many parasites (e.g. *Babesia*, *Theileria* and *Trypanosoma*) reported to be both widespread and common in Australian native animals. Some of the Australian patients that I have seen showed evidence of borreliosis (positive testing and positive borrelia specific bands on a Western blot) as well as co-infections including Babesiosis. Co-infections in ticks are the rule not the exception in the US and Europe (Moutailler S, et al. Coinfection of ticks: The rule rather than the exception. PLoS Negl Trop Dis 2016; 10(3): e0004539 doi:10.1371/journal.pntd.0004539

<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004539>) and they account for an increase in the severity and duration of symptoms (Krause, P.J., et al. Concurrent Lyme Disease and Babesiosis Evidence for Increased Severity and Duration of Illness. JAMA 1996; 275(21):1657-1660). There are many different species of piroplasms (parasites) related to *Babesia*, and not all of these are easily found on standard blood testing. This was the case in Australia two years ago. There was a confirmed Babesiosis case in Australia where a 56 year-old man died in 2011 (Senanayake et al., 2012) and the authors identified *Babesia microti* at the 18S ribosomal RNA (18S rRNA), and the beta-tubulin (β -tubulin) gene loci. They required using a novel PCR-based assay for the β -tubulin gene, which was developed to corroborate the results obtained from the analysis of the 18S rDNA. (Molecular confirmation of the first autochthonous case of human babesiosis in Australia using a novel primer set for the beta-tubulin gene. Papparini A, et al. Exp Parasitol. 2014 Mar 24).

The same problem exists for relapsing fever like borrelia found in Australian ticks. *Borrelia miyamotoi*, which has now spread across the US and Europe, is a common relapsing fever borrelia being found in a significant percentage of ticks. The standard two-tiered testing for Lyme disease will not pick up *Borrelia miyamotoi*, and specific PCR's are necessary to discover the organism.

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Four percent of people living in southern New England were recently found to have evidence of previous *B. miyamotoi* infection, and it was missed because of the insensitivity of standard testing.

The frequency of *B. miyamotoi* infection was comparable to that of other infections transmitted by *Ixodes scapularis*, such as Anaplasmosis and Babesiosis. This has been a major problem in the United States, and may explain symptoms in those with Lyme like syndromes, since the antibody test for *Borrelia burgdorferi* is not an effective tool for detecting *Borrelia miyamotoi*.

(<http://www.ecnmag.com/news/2014/05/yale-researchers-identify-extent-new-tick-borne-infection>, May 7 online Emerging Infectious Diseases)

There are over 100 species of *Borrelia* in the US and over 300 species worldwide. *B. miyamotoi* is the first borrelia species to be transmitted transovarially, as 6-73% of larvae from infected female deer ticks have been shown to be infected, which may cause a significant increase in the prevalence of borreliosis. Since *B. miyamotoi* usually does not cross react with *B. burgdorferi* tests (Branda JA, Rosenberg, E.S. *Borrelia miyamotoi*: A lesson in disease discovery. *Ann Intern Med* (2013) 159: 61-2; Lee SH, Vigliotti JS, Vigliotti VS, Jones W, Shearer DM. Detection of *Borreliae* in archived sera from patients with clinically suspect Lyme disease. *Int J Mol Sci* (2014) 15: 4284-98) patients may have “Lyme-like syndromes” due to relapsing fever borrelia species, combined with other species on bacteria. A sensitive and reliable DNA-based test is needed to support the diagnosis of Lyme disease and Lyme disease-like borreliosis, and researchers have only recently been able to identify and create more sensitive PCR testing, which is not commercially available worldwide (Lee, S.H., et al: *International Journal of Molecular Sciences* <http://www.mdpi.com/1422-0067/15/3/4284/>). Spirochetemia and persistence of both *B. burgdorferi* and *B. miyamotoi* is being found by PCR in patients with Lyme disease during winter months, after conventional antibiotic regimens (S. H. Lee, et al. Detection of *Borreliae* in Archived Sera from Patients with Clinically Suspect Lyme Disease. *Int. J. Mol. Sci.* 2014, 15(3), 4284-4298), so it is feasible that Australian patients with relapsing fever like borrelia may face the same problem of persistence after standard antibiotic treatments.

Relapsing fever borrelia generally have an incubation period between 5-15 days, and an acute onset involves non-specific symptoms that can be mistaken for a flu-like viral illness by medical practitioners. Fever can be up to 104 degrees Fahrenheit (which can be confused with other tick-

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borne infections like Babesia, Q-fever and Brucella with high fevers) with associated chills and sweats which can be drenching, and can have associated symptoms of headaches (also seen with Ehrlichia/Anaplasma and Q-fever), myalgias and arthralgias (seen with Ehrlichia, rickettsial species, and Q-fever), nausea/vomiting (seen with rickettsia, Ehrlichia, and tick-borne diseases like Tularemia in the typhoidal form), as well as patients presenting with an occasional conjunctivitis and cough. These symptoms are so non-specific, that most practitioners unless having a high level of suspicion and asking about a tick-bite (which may be missed) would be unable to make the diagnosis. Symptoms typically last 2-9 days then recur in relapsing fever borrelia, but there are also atypical symptoms, making relapsing fever borrelia similar to Lyme (that has been referred to as the "Great Imitator" like syphilis). Symptoms of relapsing fever borrelia can include G.I. symptoms of nausea, vomiting, abdominal pain; diarrhea, hepatitis with hepatosplenomegaly and jaundice (which could be confused with symptoms associated with rickettsia), cardiac manifestations of a myocarditis with arrhythmias, pulmonary symptoms resembling Acute Respiratory Distress Syndrome (ARDS) which is also seen with Babesia species, hematological manifestations including central nervous system manifestations of a facial nerve palsy, hearing loss, iritis, peripheral neuropathy, neuropsychiatric symptoms, stroke (CVA) with meningo-encephalitis and Disseminated Intravascular Coagulation (DIC). Neoehrlichia species found in Australian ticks can also cause similar atypical symptoms with hematological manifestations. It is a newly discovered bacteria in ticks and rodents in Europe (Sweden, Switzerland, Germany, and the Czech Republic), mimics B cell malignancies, and causes non-specific symptoms of fever, muscle and joint pain, vascular and thromboembolic events, including deep vein thrombosis (DVT), TIA's, pulmonary embolism (PE), and arterial aneurysms. It can be mistaken for recurrence of hematologic (B cell Lymphomas) or autoimmune diseases and/or unrelated arteriosclerotic vascular events (Grankvist, A. et al. Oxford University Press March 12, 2014) and therefore needs to be considered in the differential diagnosis of atypical "Lyme-like disease", as multiple organisms can be transmitted simultaneously with a tick bite, so that Borrelia, Ehrlichia, Neoehrlichia, rickettsial, Babesia and Theileria species may cause chronic illness.

We are underestimating the risk of Lyme disease worldwide and the spread of borreliosis due to the non-specific nature of symptoms, and the lack of a gold standard for diagnosis, which makes producing accurate statistics difficult. Some pathogenic strains belonging to the B. burgdorferi

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sensu lato complex have a worldwide distribution, yet they are rarely considered or tested for (Perronne C (2014) Lyme and associated tick-borne diseases: Global challenges of Lyme disease. Front. Cell. Infect. Microbiol. 4:74; Stanek G, Reiter M. The expanding Lyme Borrelia complex – clinical significance of genomic species? Clin Microbiol Infect (2011) 17: 487-93). How then can we make the diagnosis of Lyme and Lyme-like illness?

Lyme disease is first and foremost a clinical diagnosis. This is been established by both the FDA and the CDC. The CDC Surveillance Case Definition is

a) a case with EM or;

b) a case with at least one objective manifestation such as meningitis, cranial neuropathy, arthritis, or AV block, that is laboratory confirmed. In the words of the CDC:

“This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis.” Centers for Disease Control Prevention

MMWR56(23);573-576, June 15, 2007

http://www.cdc.gov/ncphi/diss/nndss/casedef/lyme_disease_2008.htm

How do we make that clinical diagnosis? The patient must have a reasonable history of tick exposure; have signs and symptoms consistent with the illness, and laboratory testing which helps confirm the diagnosis. Since MRI's, SPECT scans and PET scans of the brain are not able to definitively determine if a patient has neurological Lyme disease, physicians will occasionally perform a spinal tap and look at markers in the spinal fluid to determine if *Borrelia burgdorferi* has invaded the CNS.

Unfortunately, spinal taps also have their limitations. Although increased antibody production in the spinal fluid can be seen in early Lyme disease with a lymphocytic meningitis or encephalitis, in late stage neurological Lyme patients, patients can have normal cerebrospinal fluid (CSF) antibody studies. For example, Dr. Coyle and Dr. Schutzer studied 35 patients with specific Lyme Antigen (Osp A) in their cerebrospinal fluid, indicative of neurological Lyme disease. Of these patients studied, although the Lyme antigen was positive, 43% had no evidence of antibodies to Lyme in their CSF testing, and 47% had otherwise normal routine CSF analyses. 60% of these patients were also seronegative for Lyme disease when tested with standard blood tests, implying that a patient can have Lyme disease despite a negative blood test and a negative spinal tap. The

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authors concluded that, “neurologic infection by *B. burgdorferi* should not be excluded solely on the basis of normal routine CSF or negative CSF antibody analyses.”

- Coyle PK, Schutzer SE, Deng Z, Krupp LB, Belman AL, Benach JL, Luft BJ. Detection of *Borrelia burgdorferi*-specific antigen in antibody-negative cerebrospinal fluid in neurologic Lyme disease. *Neurology*. 1995 Nov;45(11):2010-5;

Patients may also be seronegative for Lyme disease because of sequestration of antibody in immune complexes.

- Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. *Lancet*. 1990 Feb 10;335(8685):312-5;

Patients will therefore not necessarily meet the CDC two step criteria to diagnose Lyme disease (a positive Elisa followed by a positive Western blot). Again, this surveillance case definition was developed for national reporting of Lyme disease, and was not intended to be used in clinical diagnosis:

<http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=752&DatePub=1/1/2011%2012:00:00%20AM>

Why do patients fail two tiered testing? The blood tests to diagnose Lyme are known to lack sufficient sensitivity and specificity to pick up all patients with the disease. **False seronegativity has been extensively reported in the peer review medical literature:**

1. Steere AC. Seronegative Lyme disease. *JAMA*. 1993 Sep 15;270(11):1369
2. Kaiser R. False-negative serology in patients with neuroborreliosis and the value of employing of different borrelial strains in serological assays. *J Med Microbiol*. 2000
3. Pikelj F, Strle F, Mozina M. Seronegative Lyme disease and transitory atrioventricular block. *Ann Intern Med* 1989 Jul 1;111(1):90. Oct;49(10):911-5.
4. Dejmkova H, Hulinska D, Tegzova D, Pavelka K, Gatterova J, Vavrik P. Seronegative Lyme arthritis caused by *Borrelia garinii*. *Clin Rheumatol*. 2002 Aug;21(4):330-4.
5. Brunner M. New method for detection of *Borrelia burgdorferi* antigen complexed to antibody in seronegative Lyme disease. *J Immunol Methods*. 2001 Mar 1;249(1-2):185-90.
6. Breier F, Khanakah G, Stanek G, Kunz G, Aberer E, Schmidt B, Tappeiner G. Isolation and polymerase chain reaction typing of *Borrelia afzelii* from a skin lesion in a seronegative patient with

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generalized ulcerating bullous lichen sclerosus et atrophicus. *Br J Dermatol.* 2001 Feb;144(2):387-92.

7. Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. *Lancet.* 1990 Feb 10;335(8685):312-5

8. Dattwyler RJ, Volkman DJ, Luft BJ, Halperin JJ, Thomas J, Golightly MG. Seronegative Lyme disease. Dissociation of specific T- and B-lymphocyte responses to *Borrelia burgdorferi*. *N Engl J Med.* 1988 Dec 1;319(22):1441-6

Finally, even the FDA has stated "...a patient with active Lyme disease may have a negative test result..." Brown SL, Hansen SL, Langone JJ. (FDA Medical Bulletin) Role of serology in the diagnosis of Lyme disease. *JAMA.* 1999 Jul 7;282(1):62-6.

One way to help confirm the clinical diagnosis, after ruling out other diseases, is to look at the bands on the Western Blot. The significance of these bands on the Western blot was described in the peer review medical article by Ma et al: Serodiagnosis of Lyme Borreliosis by Western Immunoblot: Reactivity of Various Significant Antibodies against *Borrelia burgdorferi*. *Journal of Clinical Microbiology*, Feb. 1992, p. 370-376.

"The significance of various antibodies against *Borrelia burgdorferi* was studied by Western blot (immunoblot) by using 578 human serum samples. The proteins regularly detected by using samples from patients with Lyme borreliosis were those with bands with molecular masses of 94, 83, 75, 66, 60, 55, 46, 41, 39, 34, 31, 29, 22, and 17 kDa. The detectable frequencies of most of these proteins appeared to be significantly different between the sera from patients with Lyme borreliosis and those from normal control individuals as well as from the group with syphilis"

There are therefore 2 divergent standards of care regarding the testing and treatment of Lyme disease in the United States: The IDSA and ILADS guidelines. These 2 standards of care vary in their diagnostic and treatment recommendations. Key points of the IDSA guidelines are that Lyme tests are held to be reliable, and patients with persistent Lyme symptoms after standard treatment have Post Treatment Lyme Disease ("PTLD") with possible autoimmune phenomenon driving chronic illness. The ILADS guidelines on the other hand state that Lyme tests are unreliable and that multiple factors may account for persistent symptoms. I was one of the authors of the evidence-based 2004 ILADS guidelines, published in *Expert Review of Anti Infective Therapy*

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(Evidence-based guidelines for the management of Lyme Disease. Cameron, Horowitz, et al. Expert Review of Anti Infective Therapy 2(1) 2004).

Physicians in the United States have a choice to follow either of these two evidence based guidelines, but there are known problems with the IDSA guidelines. There was a published scientific review in the Archives of Internal Medicine which analyzed the overall level of evidence behind the IDSA guidelines: Analysis of Overall Level of Evidence Behind Infectious Diseases Society of America Practice Guidelines, Dong Heun Lee, MD; Ole Vielemeyer, MD; Arch Intern Med. 2011;171(1):18-22

As per the conclusions of the authors: "We analyzed the strength of recommendation and overall quality of evidence behind 41 IDSA guidelines released between January 1994 and May 2010. Their conclusions: "More than half of the current recommendations of the IDSA are based on level III evidence only (opinion). Until more data from well-designed controlled clinical trials become available, physicians should remain cautious when using current guidelines as the sole source guiding patient care decisions".

The majority of physicians in the United States in fact do not follow IDSA guidelines (which have been taken off the government's web site of the National Guidelines Clearinghouse, because they were outdated). They treat for seronegative disease, and treat for extended periods of time. An article that was published in the journal Infection in 1996 by Dr Sam Donta highlighted the discrepancy, and showed that the majority of physicians do not treat according to IDSA guidelines: "For chronic Lyme disease, 57% of responders treat 3 months or more." (Ziska MH, Donta ST, Demarest FC. Physician preferences in the diagnosis and treatment of Lyme disease in the United States. Infection 1996 Mar-Apr;24(2):182-6). A recent study by the CDC confirmed the same data. The CDC surveyed a representative sample of people in the US and found that only 39% of those with Lyme disease were treated in accordance with blanket short term recommendations in the IDSA guidelines. The majority were treated for longer periods:

- Hook S, Nelson C, Mead P. Self-reported Lyme disease diagnosis, treatment, and recovery: Results from 2009, 2011, & 2012 Health Styles nationwide surveys. Presented at The 13th International Conference on Lyme Borreliosis and other Tick Borne Diseases, Boston, MA Aug 19, 2013. Available from: <http://archive.poughkeepsiejournal.com/assets/pdf/BK211780914.pdf>.

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The reason that the majority of physicians in the United States do not follow IDSA guidelines is because more than half of their recommendations are based on level III evidence only, and we know that the two-tier testing approach recommended by the IDSA does not always work in clinical practice. According to these guidelines, an immunoblot is not to be performed if the ELISA is negative, despite the poor sensitivity of ELISA tests ranging from 34 to 70.5%.

The effect of using the IDSA guidelines would be to miss roughly half of those suffering with Lyme disease:

- Marangoni, A. et al. Comparative evaluation of three different ELISA methods for the diagnosis of early culture-confirmed Lyme disease in Italy. *J. Med. Microbiol.* 54, 361-367 (2005);
- Ang, C.W., et al. T. Large differences between test strategies for the detection of anti-Borrelia antibodies are revealed by comparing eight ELISAs and five immunoblots. *Eur. J. Clin. Microbiol. Infect. Dis.* 30, 1027-1032 (2011).
- Wojciechowska-Koszko, et al. Serodiagnosis of borreliosis; *Arch. Immunol. Ther. Exp.* 59, 69-77 (2011).

John Hopkins University also found problems with the CDC two-tiered testing approach. In 2005, John's Hopkins did a study and found that the CDC two tiered testing missed up to 55% of positive Lyme cases (Coulter, et al., *J Clin Microbiol* 2005;43:5080-5084). A NYS DOH Study done in 1996 which was reported to the CDC, found the number of patients missed by the two-tiered protocol (without an EM rash) to be even higher: 81% of Non-EM Cases were not confirmed with present two tiered testing algorithms (CDC correspondence with NYS DOH, April 15th, 1996).

Inaccurate diagnostic tests—based on technology that is over 20 years old—create medical uncertainty in both the diagnosis and treatment of Lyme disease

- Stricker RB, Johnson L. Lyme disease diagnosis and treatment: lessons from the AIDS epidemic. *Minerva Med.* 2010 Dec;101(6):419-25

Understanding the role of laboratory testing in Lyme disease and other tick-borne diseases requires understanding that the 2 tiered protocol of using a Lyme ELISA followed by a Western Blot will miss approximately 1/2 of the patients secondary to the insensitivity of the ELISA test. The utility of the

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Western Blot is therefore based on understanding specific bands which reflect exposure to *Borrelia*:
23, 31, 34, 39, 83-93.

- Ma et al, Serodiagnosis of Lyme Borreliosis by Western Immunoblot: Reactivity of Various Significant Antibodies against *Borrelia burgdorferi*. Journal of Clinical Microbiology, Feb. 1992, p. 370-376.

PCR testing is an important diagnostic tool for seronegative patients, but many require multiple sets over time using serum, urine, spinal fluid, etc from reliable laboratories. We may fail to detect antibodies because of borrelia antibodies bound in circulating immune complexes:

- Coyle, et al. Detection of Bb antigens in CSF. Neurology 1993;43:1093-1097;
- Schutzer SE, Coyle PK, Belman AL, Golightly MG, Drulle J. Sequestration of antibody to *Borrelia burgdorferi* in immune complexes in seronegative Lyme disease. Lancet. 1990 Feb 10;335(8685):312-5;

We also have over 100 different strains of borrelia in the US, and over 300 strains worldwide, including the new relapsing fever borrelia, *Borrelia miyamotoi*, which cannot be found on standard two tiered testing. Standard testing for borrelia by most commercial laboratories only uses the B31 strain, and will therefore miss many borrelia species. Also, wild birds play key roles in the maintenance and movement of these zoonotic pathogens such as TBEV, *Borrelia*, *Bartonella* and *Rickettsia* spp worldwide, so that evaluating the tick population on a regular basis is necessary, as infections in tick populations keep changing, leading to new manifestations of chronic disease.

(Scott, J. et al. Infection Prevalence of *Borrelia burgdorferi* in Ticks Collected from Songbirds in Far-Western Canada. Open Journal of Animal Sciences, 2015, 5, 232-241; Hamer SA, et al., Wild birds and urban ecology of ticks and tick-borne pathogens, Chicago, Illinois, USA, 2005–2010. Emerg Infect Dis. 2012;18:1589–95.; *Bartonella henselae* and *B. koehlerae* DNA in Birds. Mascarelli PE, et al. EID, Volume 20, Number 3—March 2014; Elfving K, et al. Dissemination of spotted fever rickettsia agents in Europe by migrating birds. PLoS ONE. 2010;5:e8572)

Rationale for Long Term Treatment:

I have already outlined the extensive peer reviewed literature showing seronegativity for Lyme disease. Regarding treatment, some physicians believe that there is no reason to be treating patients beyond the 30-day course routinely recommended by the IDSA guidelines; however, there

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are high rates of treatment failure for all stages of Lyme disease. **According to the CDC, as many as 20% of patients remain ill after the short term treatment protocol recommended by the IDSA (<http://www.cdc.gov/lyme/treatment/>). Other studies suggest the treatment failure rate for early Lyme disease may be as high as 36%:**

- Aucott JN, et al. Post-treatment Lyme disease syndrome symptomatology and the impact on life functioning: is there something here? *Qual Life Res.* 2013 Feb;22(1):75-84

In late Lyme disease, treatment failure rates may exceed 50%:

- Cameron, D., Horowitz, R, et al: Treatment of Lyme disease: a medicolegal assessment. *Expert review of anti-infective therapy.* 2004 Aug;2(4):533-57

Why do patients fail short term therapy? The peer reviewed medical literature shows chronic persistent infection despite intensive antibiotics:

- Bradley JF, et al, The Persistence of Spirochetal Nucleic Acids in Active Lyme Arthritis. *Ann Int Med* 1994;487-9

- Bayer ME, Zhang L, Bayer MH. *Borrelia burgdorferi* DNA in the urine of treated patients with chronic Lyme Disease symptoms. A PCR study of 97 cases. *Infection* 1996. Sept-Oct;24(5):347-53

- Diringner MN, et al, Lyme meningoencephalitis- report of a severe, penicillin resistant case. *Arthritis & Rheum,* 1987;30:705-708

- Donta, ST, Tetracycline therapy in chronic Lyme disease. *Chronic Infectious Diseases,* 1997; 25 (Suppl 1): 552-56

- Fitzpatrick JE, et al. Chronic septic arthritis caused by *Borrelia burgdorferi*. *Clin Ortho* 1993 Dec;(297):238-41

- Georgilis K, Peacocke M, & Klempner MS. Fibroblasts protect the Lyme disease spirochete, *Borrelia burgdorferi*, from ceftriaxone in vitro. *J Infect Dis* 1992;166: 440-444

- Fallon BA, et al. Repeated antibiotic treatment in chronic Lyme disease, *Journal of Spirochetal and Tick-borne Diseases,* 1999; 6 (Fall/Winter):94-101

- Fraser DD, et al. Molecular detection of persistent *Borrelia burgdorferi* in a man with dermatomyositis. *Clinical and Exper Rheum.* 1992;10:387-390

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- Fried MD et al, *Borrelia burgdorferi* persists in the gastrointestinal tract of children and adolescents with Lyme Disease, *JNL of Spirochetal and Tick-borne Diseases*, Spring/Summer 2002; 9:11-15
- Girschick HJ, et al. Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatol Int* 1996;16(3):125-132
- Hassler D, et al. Pulsed high-dose cefotaxime therapy in refractory Lyme Borreliosis (letter). *Lancet* 1991;338:193
- Horowitz RI. Chronic Persistent Lyme Borreliosis: PCR evidence of chronic infection despite extended antibiotic therapy: A Retrospective Review. Abstract XIII Intl Sci Conf on Lyme Disease. Mar 24-26, 2000.
- Haupl T, et al. Persistence of *Borrelia burgdorferi* in ligamentous tissue from a patient with chronic Lyme borreliosis. *Arthritis Rheum* 1993;36:1621-1626
- Karma A, et al. Long term follow-up of chronic Lyme neuroretinitis. *Retina* 1996;16:505-509
- Keller TL, et al. PCR detection of *Borrelia burgdorferi* DNA in cerebrospinal fluid of Lyme neuroborreliosis patients. *Neurology* 1992;43:32-42
- Masters EJ, et al. Spirochetemia after continuous high-dose oral amoxicillin therapy. *Infect Dis Clin Practice* 1994;3:207-208
- Ma Y, et al. Intracellular localization of *Borrelia burgdorferi* within human endothelial cells. *Infect Immun* 1991;59:671-678
- Meier P, et al. Pars plana vitrectomy in *Borrelia burgdorferi* endophthalmitis. *Klin Monatsbl Augenheilkd* 1998 Dec;213(6):351-4
- Preac-Mursic V, et al. Survival of *Borrelia burgdorferi* in antibioticly treated patients with Lyme borreliosis. *Infection* 1989;17:355-359.
- Preac-Mursic V, et al. Persistence of *Borrelia burgdorferi* and Histopathological Alterations in Experimentally Infected Animals. A comparison with Histopathological Findings in Human Lyme Disease. *Infection* 1990;18(6):332-341
- Straubinger RK, et al. Persistence of *Borrelia burgdorferi* in Experimentally Infected Dogs after Antibiotic Treatment. *J Clin Microbiol* 1997;35(1):111-116
- Embers, M. et al. Persistence of *Borrelia burgdorferi* in Rhesus Macaques following Antibiotic treatment of Disseminated Infection. *PLoS ONE* 7(1): e29914. doi:10.1371/journal.pone

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Chronic persistent infection with Bb despite intensive antibiotics was also proven in two recent Xenodiagnosics studies. The first was in mice:

- Hodzic E, Barthold SW (2014) Resurgence of Persisting Non-Cultivable Borrelia burgdorferi following Antibiotic Treatment in Mice. PLoS ONE 9(1): e86907.

Results confirmed previous studies: Bb could not be cultured from tissues, but low copy numbers of Bb flaB DNA were detectable in tissues up to 8 months after completion of treatment & RNA transcription of genes was seen with visualized spirochetes.

In humans, a recent NIH study by Dr Marques showed that among ten patients who had high levels of antibodies against B. burgdorferi after antibiotic treatment, two of those patients had “indeterminate results”, and one patient with Post Treatment Lyme disease syndrome (PTLDS) had a positive result, confirming evidence of ongoing Borrelia DNA in these patients:

- Marques, A. et al. Xenodiagnosis to Detect Borrelia burgdorferi Infection: A First-in-Human Study. Clinical Infectious Diseases DOI: 10.1093/cid/cit939 (2014).

Some physicians feel that there is no evidence of prolonged antibiotics helping symptoms.

We know that short term antibiotics fail in 25%-71% of patients with late stage disease:

- Berglund J, Stjernberg L, Ornstein K, Tykesson-Joelsson K, Walter H. 5-y Follow-up study of patients with neuroborreliosis. Scand J Infec Dis. 2002;34(6):421-5.
- Valesová H, Mailer J, Havlík J, Hulínská D, Hercogová J. Long-term results in patients with Lyme arthritis following treatment with ceftriaxone. Infection. 1996 Jan-Feb;24(1):98-102

These frequent treatment relapses and failures with short term therapy are documented by other authors:

- Logigian (1990) : After 6 mo's of therapy, 10/27 patients treated with IV AB's relapsed or had treatment failure.
- Pfister (1991): 33 patients with neuroborreliosis were treated with IV AB's. After a mean of 8.1 months 10/27 were symptomatic and borrelia persisted in the CSF in 1 patient.
- Shadick (1994) : 10/38 pts relapsed (5 with IV) within 1 year of treatment, and had repeated AB treatment.
- Asch (1994) : 28% relapsed w/ major organ involvement 3.2 years after initial treatment

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Many doctors use IDSA guidelines to base their conclusions to not treat sick patients with long term antibiotics. However only three NIH-funded trials have been conducted on the treatment of chronic Lyme disease:

- Klemmner M, Hu L, Evans J, Schmid C, Johnson G, Trevino R, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *The New England journal of medicine*. 2001 Jul 12:85-92
- Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. *Neurology*. 2003 Jun 24;60(12):1923-30
- Fallon BA, Keilp JG, Corbera KM, Petkova E, Britton CB, Dwyer E, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. *Neurology*. 2008 Mar 25:992-1003

These were inadequate treatment trials as sample sizes were extremely small, ranging from 37 to 78 patients. Critics have pointed out that studies this small lack sufficient statistical power to measure clinically relevant improvement:

- Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. *Expert Review Anti-Infective Therapy*. 2014 Sep;12(9):1103-35.
- Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. Washington, DC: National Academies Press; 2011. Available from: http://books.nap.edu/openbook.php?record_id=1305

Nevertheless, two of the three clinical trials demonstrated that retreatment improved some patients' measures, such as fatigue and pain (Krupp, Fallon). Others have shown improvement in cognitive function, in those with Lyme encephalopathy (Fallon).

- Fallon BA, Petkova E, Keilp J, Britton C. A reappraisal of the U.S. clinical trials of Post-Treatment Lyme Disease Syndrome. *Open Neurology Journal*. 2012;6(Supp. 1-M2):79-87.

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- Delong et al. Antibiotic retreatment of Lyme disease in patients with persistent symptoms: A biostatistical review of randomized, placebo controlled, clinical trials. *Contemporary Clinical Trials* 33 (2012), 1132-1142

The recent PLEASE trial, published in the NEJM, based on treatment with IV Rocephin and oral antibiotics for borrelia species found in Europe, also showed short term benefit with antibiotics, but no long term benefit (Berende A, ter Hofstede HJM, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *New England Journal of Medicine*. 2016; 374(13):1209-20. <http://www.nejm.org/doi/full/10.1056/NEJMoa1505425>).

The medical literature however does in fact show a benefit to using longer treatment regimens for disseminated Lyme Disease:

- 1. Wahlberg, P. et al, Treatment of late Lyme borreliosis. *J Infect*, 1994. 29(3): p255-61 →31% improved w/ 14 days of Rocephin, 89% improved w/ Rocephin + 100d of Amoxicillin and Probenecid, 83% improved w/ Rocephin, then 100 days of cephadroxil
- 2. Donta, ST., Tetracycline therapy for chronic Lyme disease. *Clin Infect Dis*, 1997. 25 Suppl 1: p.S52-6. →277 pts with chronic LD treated between 1-11 months: 20% cured, 70% improved, 10% failed
- 3. Oksi, J et al., Comparison of oral cefixime and intravenous ceftriaxone followed by oral amoxicillin in disseminated Lyme borreliosis. *Eur J Clin Microbiol Infect Dis*, 1998. 17(10) :p 715-9 → 30 pts w/ chronic Lyme disease were treated for 100 days, and 90% had good or excellent responses
- 4. Oksi, J., et al. *Borrelia burgdorferi* detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. *Ann Med*, 1999. 31(3):p.225-32 →32/165 patients with disseminated Lyme were treated for 1 or more months of antibiotics, and showed that even more than 3 months of treatment may not eradicate the spirochete, and that longer term therapy may be necessary. This last study detected chronic persistent Lyme by both PCR and culture, the “gold standard” for proving chronic infection. As we showed earlier, relapsing fever borrelia, such as the ones found in Australia, nor all of the co-infections in ticks, may also not be found on standard testing, nor eradicated by standard courses of antibiotics.

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If the scientific literature shows unreliable blood tests, and persistence of borrelia despite short term treatment, what is the answer? Newer persistence studies have recently been published by John's Hopkins University and other researchers, showing evidence of bacterial persisters:

- *Borrelia burgdorferi*, the causative agent of Lyme disease, forms drug-tolerant persister cells. Sharma B, et al. *Antimicrobial Agents And Chemotherap*, pii: AAC/00864-15. Online first, 2015 May 26
- Identification of novel activity against *Borrelia burgdorferi* persisters using an FDA approved drug library, Zhang, Y. et al. *Emerging Microbes and Infections* (2014) 3, e49;
- Zhang, Y (2015) Drug Combinations against *Borrelia burgdorferi* Persisters In Vitro: Eradication Achieved by Using Daptomycin, Cefoperazone and Doxycycline. *PLoS ONE* 10(3): e0177207.
- Identification of new compounds with high activity against stationary phase *Borrelia burgdorferi* from the NCI compound collection. Zhang Y. *Emerging Microbes and Infections* (2015) 4,e31:anthracyclines (anti-cancer)++

Borrelia has also been shown to exist in biofilms and many refractory infections are attributable to biofilm colonies. Biofilms are made up of cells and extracellular polymeric substance (EPS), creating a matrix, constituting a sheltered environment. Prior work by Dr Eva Sapi had shown that biofilms in *Borrelia burgdorferi* protect the bacteria in chronic cutaneous borreliosis (Sapi E, Bastian SL, Mpooy CM, et al. Characterization of biofilm formation by *Borrelia burgdorferi* In vitro. *PLoS ONE* 2012; 7(10): e48277. doi:10.1371/journal.pone.0048277

<http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0048277>).

Biofilms allow for the exchange of genetic material which may also contribute to persistence. The PLEASE study, nor any of the prior double blind NIH trials, did not use newly discovered drugs that target bacterial persisters, nor address biofilm colonies. Other mechanisms allowing borrelia to evade the immune system include the organism's ability to create cystic forms in adverse environments, change its outer surface proteins, evade the complement system, and inhibit strongly induced protective borrelia-specific antibody responses upon entering into lymph nodes

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early on in the infectious process. Immune evasion also takes place as the bacteria enters tissues where antibiotics don't penetrate well, such as the fibroblasts of the skin, and the intracellular compartment (Girschick H.J., Huppertz H.I., Russmann H., Krenn V, Karch H. Intracellular persistence of *Borrelia burgdorferi* in human synovial cells. *Rheumatol Int* 1996;16(3):125-32. <http://www.ncbi.nlm.nih.gov/pubmed/8893378>). Many persister bacteria such as mycobacterial infections (TB and leprosy), persist as intracellular infections and in biofilms (Ehrlich GD, Hu FZ, Shen K, Stoodley P, Post JC. Bacterial plurality as a general mechanism driving persistence in chronic infections. *Clinical Orthopaedics and Related Research* 2005; 437: 20-4. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1351326>;) where prolonged courses of antibiotics like rifampin and Dapsone are required to effect a cure. These drugs were not also used in the PLEASE study or NIH trials. We have just received acceptance of publication a peer review journal article of 100 patients with chronic Lyme disease with associated Babesiosis who had failed classical antibiotics like Rocephin, doxycycline and Biaxin, who in our pilot study responded positively to mycobacterial "persister" drugs like Dapsone, which penetrates inside the intracellular compartment, and has associated anti-malarial activity. I have included a copy of the abstract for the article, which is due to be published in the *Journal of Clinical & Experimental Dermatology Research (Open Access)*, ISSN: 2155-9554, in April 2016:

OMICS PUBLISHING GROUP/Clinical

The Use of Dapsone as a Novel "Persister" Drug in the Treatment of Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome

Manuscript Number: CLINICALGROUP-16-246R1

Full Title: The Use of Dapsone as a Novel "Persister" Drug in the Treatment of Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome

Section/Category: *Journal of Clinical & Experimental Dermatology*

Keywords: Dapsone; rifampin; Post Treatment Lyme Disease Syndrome (PTLDS); biofilms; "persister bacteria"; Morgellon's syndrome; Multisystemic Infectious Disease Syndrome

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Abstract:

Dapsone (diaminodiphenyl sulfone, i.e., DDS) is commonly used to treat dermatological conditions including acne, dermatitis herpetiformis, and leprosy. *Mycobacterium leprae*, a known "persister" bacteria, requires long-term treatment with intracellular medications including rifampin and Dapsone. Other "persister" bacteria recently have been identified, including *Borrelia burgdorferi*, the agent of Lyme disease.

Objectives: We tested the efficacy of DDS in patients with chronic Lyme disease/Post Treatment Lyme Disease Syndrome (PTLDS) with tick-borne co-infections including Babesiosis, who failed commonly used antibiotic and antimalarial protocols.

Methods: 100 patients with Lyme disease, 56 of whom were *Babesia* positive, were placed on Dapsone and folic acid in combination with either one or two other intracellular drugs, including rifampin, tetracyclines, and/or macrolide antibiotics. Several patients also took cephalosporins, and all patients were on protocols to treat cystic forms of *Borrelia* and biofilms.

Results: Patients completed a symptom severity survey before beginning treatment with Dapsone and then again after at least one month of treatment scoring their complaints from 0 indicating "none" to 4 indicating "severe" for symptoms including fatigue, joint and/or muscle pain, disturbed sleep, and cognitive difficulties. Dapsone significantly improved all patients' clinical symptoms except for headache, where changes did not reach statistical significance. Dapsone, known to have anti-malarial effects, also helped resistant *Babesia* symptoms of sweats, chills, and flushing. Lyme positive, *Babesia* positive patients also demonstrated significant changes in pain, disturbed sleep, and cognitive difficulties. Side effects included macrocytic anemia and rare cases of methemoglobinemia, which resolved by either decreasing the dose of Dapsone or increasing folic acid.

Conclusion: Dapsone is a novel and effective "persister" drug for those with PTLDS and associated tick-borne co-infections who have failed classical antibiotic protocols. Further prospective trials must determine the DDS dose, length of treatment and best combination antibiotic therapy in order to effect a long-term health benefit.

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As we discussed, co-infections are the rule, not the exception, and Babesiosis is frequently transmitted simultaneously with borreliosis increasing the severity of symptoms. This may be the same in Australia since you have multiple parasitic organisms present in ticks. We effectively treated our chronically ill Lyme patients in our Dapsone pilot study with pulsed regimens addressing the cell wall forms, cystic forms and intracellular forms of borrelia while treating biofilms. The PLEASE study and prior NIH trials did not use such a broad spectrum approach, nor did they treat for tick-borne co-infections, which are a common source of treatment failures in our patient population.

Scientific studies on persisters and recent studies on biofilm formation in persistent infection, explain in part why prior peer reviewed clinical trials showed benefit of longer term antibiotic therapies (referenced above), but may not completely have eradicated the infection. Until better studies are available, it is therefore incumbent on the physician to use their best clinical judgement in treating sick patients based on the available scientific literature.

I would ask the Australian Senate to please consider all of the evidence referenced above to help sick and suffering patients in Australia. Tick-borne co-infections play a large role in keeping patients ill, and the tests for Lyme disease and co-infections are unreliable. These infections are routinely missed using standard blood tests, because the tests are not sensitive enough to pick up the presence of these organisms which can hide from the immune system. Patients also remain chronically ill because many of these tick-borne infections persist despite “seemingly adequate” antimicrobial therapies, leading to immune dysfunction and inflammation. These infections cause the release of inflammatory molecules called cytokines, such as Tumor Necrosis Factor alpha, interleukin-1, interleukin-6, interferon gamma as well as chemokines, which are responsible for many of the symptoms we see with Lyme disease and “Lyme-like illness” including fatigue, joint and muscle pain, memory and concentration problems, and mood disorders. Unless we simultaneously treat the three “I’s”: infection, immune dysfunction and inflammation, patients will not get better. Finally, most physicians are unaware of the concept of MSIDS, and that there are multifactorial causes for the patient’s illness, increasing the underlying inflammatory process,

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increasing cytokine formation. It is as if a patient came to the doctor with sixteen nails in their foot complaining of foot pain. Unless you pull out all of the nails, the patient is not going to feel better.

Thank you for taking the time to review this information. I hope that it is of benefit in helping the Australian people, and please let me know how I may also be of help.

Sincerely,

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Curriculum Vitae

Education:

Free University of Brussels Medical School, Brussels, Belgium

Doctor of Medicine, Graduated with Grand Honors, 1984

Bilingual, French and English

Northwestern University, Evanston, Illinois

Bachelor of Arts, Biology, Graduated with Departmental Honors in Biology, 1977

Post Graduate Training:

Mount Sinai City Hospital at Elmhurst, New York, New York

Internship and Residency in Internal Medicine, 1984-1987

Certifications:

American Board of Internal Medicine, 1987

New York State Flex, 1986; ECFMG, 1983

Associations:

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President NYEMA foundation (Nangchen/Yushu Educational Medical Foundation), 501 c3
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Board of Advisors Xymogen 2010-2016

ILADS: President-elect, International Lyme and Associated Diseases Society (ILADS) 2003-2007

Vice President, International Lyme and Associated Diseases Society (ILADS) 2007-2008-2010

President International Lyme and Associated Diseases Educational Foundation (ILADEF),

2009-2010

Professional /Research Experience:

Private practice, Internal Medicine, June 1988 – present

Co-founder Lyme Navigator LLC, development of an app for treatment of Lyme dx, 2014

Co-founder Be Well, LLC, development of an app for prevention/health, 2016

Founding and establishment of the Hudson Valley Healing Arts Center, Inc. for Integrative Health Care, including comprehensive treatment for Lyme disease and related tick-borne illnesses, June 1997.

Clinical research and literature studies in the diagnosis and treatment of Lyme & related Tick Borne Disease, 1992 - present

Vassar Brothers Hospital, Poughkeepsie, New York

Staff physician, Department of Emergency Medicine, 1987 - 1988

Attending Physician, 1987- 2001, Assistant Director of Medicine, 1993 - 2000

Saint Francis Hospital, Poughkeepsie, New York

Attending Physician; 1987-2001, Medical Quality Assurance Committee, Chair 2000

Adjunct faculty, Manchester Hospital residency training program, 2015

Consulting Experience:

Chinese government:

-Chinese CDC/ Ministry of Health, Beijing/Shanghai China 2011. Overview of Lyme Disease and Babesiosis. Special invitation from the Chinese government to present to

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top Government officials, Chinese CDC and the National Academy of Sciences on the difficulties of diagnosis and treatment of expanding tick-borne disorders

French government:

-Presentation on Lyme disease to the office of the Ministre de la Sante, Paris. September 2013.

Private meeting with government officials on tick-borne diseases in France regarding epidemiology, testing and treatment of Lyme disease and associated tick-borne co-infections

Belgian government:

-Presentation to the Belgium Senate in April 2014 by invitation of Belgian Senator Nele Lijnen regarding the world-wide epidemic of Lyme Disease and the MSIDS map

-Presentation to the Belgian Parliament in September 2015 on Lyme disease, co-infections, and the MSIDS map in the diagnosis and treatment of chronic disease

UK government:

-Discussion with Tim Brooks and UK Health Department, January 2016, regarding the creation of new guidelines for the diagnosis and treatment of Lyme disease and tick-borne disorders

US government:

-Presenter: Congressional Hearing on Lyme disease, Vermont House and Senate, April 2013. Lyme disease and MSIDS: Diagnosis and Treatment of Tick-Borne disorders

-Presenter: Congressional Public Forum on Lyme disease, May 2012. Senator Chris Gibson, Saratoga Springs, N.Y. Lyme disease and MSIDS: A New paradigm in treating chronic illness

-Presenter: Congressional Public Forum with Congresswoman Elise Stefanik and Congressman Chris Gibson. SUNY Adirondack, August 8th, 2015. Lyme disease, Co-Infections & the 16 Point MSIDS Model: Solutions for Diagnosing and Treating Chronic Illness

-Presenter: Congressional Hearing on Lyme disease, Rhode Island 2004. Lyme disease and co-infections: Diagnostic and Therapeutic Challenges.

Presentations:

Presenter, March 2nd, 2016: Belgian Lyme Conference, Wavre. How Can I Get Better? Updates on Diagnosing and Treating Tick-Borne Illness

Presenter, February 11th, 2016: Focus on Lyme, Scottsdale, Arizona. Lyme Disease, Co-infections and the 16 Point MSIDS model: Solutions for Diagnosing and Treating Chronic Illness

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Presenter: January 16th, 2016: Xymogen Experience, Orlando, Florida: From Symptoms to

Solutions: The 16 point MSIDS model in Chronic Disease

Presenter, December 4th-6th, 2015: Kripalu Yoga and Meditation Center: Beyond Lyme and Other Chronic Illness. Three-day workshop on the MSIDS model with meditation training.

Presenter, October 3rd, 2015: CISON Conference, Paris, France: The Lyme-MSIDS model in chronic disease, complementary/alternative therapies for health and wellness

Presenter, September 19th, 2015. Louvain La Neuve, Belgium: Formation Lyme-MSIDS for French speaking physicians/Public talk on the diagnosis and treatment of tick-borne diseases and the MSIDS model

Presenter, September 17th, 2015. Presentation to the Belgian Parliament/government on the diagnosis and treatment of Lyme and associated tick-borne disorders; use of the MSIDS model and questionnaire for resistant disease

Presenter, September 12-13, 2015. BBOW Lyme conference. Antwerp, Belgium. Four presentations: An introduction to Lyme and associated tick-borne diseases in the 21st century, The 16 point MSIDS model in chronic disease, Tick-borne co-infections: presentation, diagnosis and treatment, Clinical Studies and Treatment options in Lyme-MSIDS

Presenter, August 2015: Congressional Public Forum with Congresswoman Elise Stefanik and Congressman Chris Gibson. SUNY Adirondack, August 8th, 2015. Lyme disease, Co-Infections & the 16 Point MSIDS Model: Solutions for Diagnosing and Treating Chronic Illness

Presenter: June, 2015: Omega Institute: Living Well with Lyme disease. A 3 day workshop for health professionals and the public, discussing Lyme disease, co-infections, the 16 point MSIDS map for chronic disease, with case presentations

Presenter, May 2015: Ridgefield, Connecticut, Western Conn State University: Why Can't We Get Better? The Lyme-MSIDS map in chronic disease

Presenter, May 2015, SUNY Binghamton, Lyme Awareness Day: The Lyme-MSIDS Map in Chronic Disease: Reclaiming our Health and Well-being

Presenter, May 2015: Xymogen Lyme & Hormone Summit, NYC, N.Y., The Disruptive Effects of Lyme & Associated Tick-borne Infections: Presentation, Diagnosis, and Treatment.

Presenter, April, 2015, SUNY New Paltz, Preparing for the Health and Mental Health Consequences of Climate Change. "Lyme Disease and Co-infections: A Global Health Epidemic".

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Presenter, Kripalu, Lenox, Mass, December 2014: Weekend workshop: Beyond Lyme and Other Chronic Illnesses: Reclaiming our Health and Well-Being

Presenter, ILADS conference, Washington, D.C, October 2014: Tick-borne relapsing fever, Lyme and the MSIDS model in chronic disease, Lyme and co-infections

Presenter, CALRB conference, Hartford, CT, September 2014, Relapsing fever borrelia and the MSIDS model for chronic persistent disease

Presenter, Omega Institute, June 2014: Living Well with Lyme Disease. Weekend seminar on Lyme and associated tick-borne diseases, with Dr Tom Franscescott and Dr Katina Makris

Presenter, June 2014: Lyme Sans Frontier, JIDMT (Journee Internationale des Maladies a Tiques): 3 day conference for French health care professionals; One day teaching course for physicians on the Lyme-MSIDS model in Chronic Disease

Presenter, May 2014: Norvect Lyme conference, Oslo, Norway. Tick-borne co-infections and the Lyme-MSIDS model in Chronic Disease.

Presenter: Xymogen, April 2014. Modern Epidemics: The Lyme Epidemic. Hyatt Regency, Greenwich, CT

Presenter: IHS/Integrative Health Symposium, NYC Feb 2014. Lyme disease and Multiple Systemic Infectious Disease Syndrome (MSIDS): Answers for chronic fatiguing/musculoskeletal illness.

Presenter: Xymogen Experience, Orlando, Florida, Jan 2014. The Role of Inflammation and Detoxification in Lyme disease and Chronic Illness.

Presenter: Xymogen 2013 Vanguard Lyme Conference, Mohonk Mountain House, Nov 2013. Why Can't I Get Better? Solving the Mystery of Lyme and Chronic Illness.

Presenter: Harvard/Massachusetts Gen Hospital, Lyme disease and Tick-Borne Illness Community Conference, October 2013. "Lyme Disease and Multi-Systemic Infectious Disease Syndrome (MSIDS): A new paradigm for the diagnosis and treatment of chronic illness"

Presenter: JMT (Journee Maladie de Ticques), Paris, France (1 Day Infectious Disease Conference), September, 2013. Overview of Lyme disease and MSIDS in Chronic persistent disease

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Presenter: Minister of Health, France, September 2013. Private meeting with government officials on tick-borne diseases in France, regarding epidemiology, testing and treatment of Lyme disease and associated tick-borne co-infections

Presenter: JID'IMVT Strasbourg, France (2 Day Infectious Disease Conference). June, 2013. Why Can't I Get Better? Solving the Mystery of Lyme and Chronic Disease.

Presenter: ACAM, May 2013, Hollywood, Fla. Lyme Disease and Multi-Systemic Infectious Disease Syndrome (MSIDS): A new paradigm for the diagnosis and treatment of chronic illness

Presenter: LIA foundation webinar, May 2013: Lyme and MSIDS: Why Can't I Get Better? Diagnostic and Treatment Strategies in the chronically ill patient.

Presenter: Xymogen. Lyme disease and co-infections: Classical and Integrative Therapies. Mohonk Mountain House, New Paltz, N.Y. May 2103

Presenter: Congressional Hearing on Lyme disease, Vermont House and Senate, April 2013. Lyme disease and MSIDS: Diagnosis and Treatment of Tick-Borne disorders

Presenter: Integrative Health Symposium, NYC, March 2013. The Science and Practice of Meditation

Presenter: ILADS, Boston, 2012. Diagnosis and Treatment of Complex Patients with Tick-borne disorders.

Presenter: Congressional Public Forum on Lyme Disease, May 2012. Senator Chris Gibson, Saratoga Springs, N.Y. Lyme disease and MSIDS: A New paradigm in treating chronic illness

Presenter: American College for the Advancement of Medicine, San Diego, California, May 2102. Overview of Lyme Disease and Tick-Borne co-infections, Classical and Integrative approaches

Presenter: California Lyme disease association, San Diego, California, May 2012. New paradigms in diagnosis and treatment: MSIDS.

Presenter: Integrative Health Symposium, Feb 2012. Chronic pain syndromes and Lyme disease with MCIDS

Presenter: a4m, Las Vegas, 2011. Lyme Disease and MCIDS: Classical and Integrative therapies in chronic diseases

Presenter: ILADS 2011, Babesia: Updated Diagnostic Treatment & Protocols. Toronto, Canada

Presenter: ILADS 2011, 2nd International Lyme Conference, Aufsborg, Germany. Lyme and Co-

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-infections, Classical and Integrative Therapies, May 2011

Presenter: UNESCO, Paris, June 2011. Lyme Disease presenting as MCIDS

Presenter: JINI, National Infectious Disease Conference France, June 2011, Controversies in Lyme Disease

Presenter: Chinese CDC/ Ministry of Health, Beijing/Shanghai China 2011. Overview of Lyme Disease and Babesiosis. Special invitation from the Chinese government to present to top Government officials, CDC, and National Academy of Sciences on the difficulties of diagnosis and treatment of expanding tick-borne disorders

Presenter: IHS Symposium NYC March 2011: Integrative protocols for Lyme and co-infections

Presenter: Bioresource: California March 2011: Differential Diagnosis and Integrative treatment Protocols in tick borne disorders

Presenter: ILADS 2010, 1st International Lyme Conference in Europe: Lyme and co-infections

Presenter: ILADS 2010, Westin Jersey City, N.J. Lyme and Co-infections

Presenter: California Naturopathic Doctors Association, Los Angeles, Calif 2010. Overview of Protocols in the Complex Lyme patient

Presenter :Western Conn. State University-Lyme disease: New Diagnostic and Treatment Protocols, April 2010

Presenter: Xymogen, Integrative Medical Protocols for Lyme Disease and Associated Co-Infections, Double Tree Inn, Tarrytown, NY: March 2010

Presenter: Lyme and Autism, Crowne Plaza, NJ, May 2009

Presenter: ILADS: Oct 2009, Maryland: Differential Diagnosis in Lyme Disease and Co- Infections

Presenter: ILADS: Oct 2008, San Francisco, CA.: Nuts and Bolts of Lyme Disease

Presenter: Mercy Hospital, PA, Lyme Disease: A Scientific Overview, March 2008

Presenter: Western Connecticut State University, April 2008, Lyme Disease and Other Tick Borne Diseases; Classical and Complementary Therapies.

Presenter: Lyme in Autism Conference, Ft. Lee, NJ. April 2008. Herbs, Hormones and Heavy Metals.

Presenter: University of New Haven, May 2008. Classical and Integrative Medical Approaches in Chronic Lyme Disease: New Paradigms in Diagnosis and Treatment

Presenter: Lyme in Autism Conference , Palm Springs, California, June 2008. Classical and

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Integrative Medical Approaches in Chronic Lyme Disease

Presenter, Western Connecticut State University: Lyme Disease: A Scientific Overview. May 2007

Presenter, University of New Haven: The Role of Co-Infections in Chronic Lyme Disease. May 2007

Presenter, ILADS, Chronic Lyme Disease: A Symptom Complex of Multiple Co-infections.

Philadelphia, Pennsylvania, October 2006

Presenter, ILADS, Lyme Disease and Other TBDs: An Overview of Co-Infections and Their Role in Chronic Symptomology, Philadelphia, Pennsylvania, October 2005

Presenter, Southeastern Pennsylvania & Northern Massachusetts, Lyme Disease and Tick-Borne Diseases: A Scientific Update, November 2004

Presenter, Lyme Disease Association, Intravenous Glutathione: A Novel Approach for Treating Resistant Symptoms in Chronic Lyme Disease, October 2004

Presenter, 16th International Scientific Conference on Lyme Disease and Other Tick-Borne Disorders, Hartford, Connecticut, June 2003

Presenter, Educational Forum on Lyme Disease, United States Congress; Understanding the Role of Laboratory Testing in Lyme Disease and Other Tick-Borne Disorders, Rhode Island, August 2002

Presenter, Lyme & Other Tick-Borne Diseases: Lyme Disease Association, New Jersey, A 21st Century View, November 2001

Presenter, Lyme & Other Tick-Borne Diseases: Lyme Disease Association, New Jersey, Focus on Children & Adolescents, November 2000.

Presenter, Dutchess Community College, Lyme, Babesiosis and Ehrlichiosis for "Infectious Diseases- Past, Present and Future", Poughkeepsie, NY, March 26, 2001

Presenter, Lyme Disease Association, Inc., The Increasing Incidence of Co-Infections: Babesiosis and Ehrlichiosis@, Doral Forrestal, Princeton, New Jersey, November 14, 2000

Presenter, 13th International Scientific Conference on Lyme Disease and Other Tick -Borne Disorders, Hartford, Connecticut. March 25-26, 2000.

Presenter, Chronic Lyme Disease: A Symptom Complex of Multiple Co-Infections, New Diagnostic and Treatment Protocols@, Lyme Disease and Other Spirochetal and Tick-Borne Diseases: A Two

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Diplomate, American Board of Internal Medicine

Day Discussion of the Most Recent Developments in Research and Clinical Management, Bard College, Annandale-on-Hudson, NY, November 14, 1999.

Presenter, Michigan Lyme Disease Association, Current Clinical Approaches and Microbiology of Lyme Disease and Other Tick-borne Illnesses, September 25, 1999, Midland, Michigan.

Presenter, 12th Annual International Scientific Conference on Lyme Diseases & Other Spirochetal and Tick-Borne Disorders, April 1999, New York, NY.

Presenter, First International Tibetan Medical Conference; with His Holiness the Dalai Lama, November 1999, Washington, D.C.

Faculty Member, Marist College Certificate in Alternative Health Care; Lectures in Fundamentals of Alternative Healing, 1998;

Lecturer, Marist College Center for Lifetime Studies, 1998 & 2001.

New York State Dietetic Association Conference, May 1995:

Nutrition and Lyme Dutchess County Lyme Disease Conference, March 1995:

Current Overview & Treatment of Lyme Disease USCablevision/NewsChannel6, April 1994: Lyme Disease in Dutchess County >94

Presenter, Lyme Disease: A Community Public Health Challenge Conference, June 1994, Poughkeepsie, NY, Lyme Disease: The Local Medical Perspective

Media/ TV Appearances:

The Today Show, June 2015: Tick Talk with Kathie Lee and Hoda: The 6 things You Need to Know about Lyme

Fox News Health Talk with Dr Manny, May 2015, The Lyme Disease Debate: Can the condition be chronic?

People Magazine, April 2015 - Avril Lavigne Suffers from Lyme Disease: Things to Know about the Illness

The Today Show, July 2nd, 2014, Signs, symptoms, & prevention of Lyme disease

Fox and Friends, July 26th, 2014, Lyme disease risks, signs & symptoms

Katie Couric, ABC TV, October 9th, 2013: Chronic Lyme disease, Does it exist?

The New York Times, Room for Debate, Deconstructing Lyme disease, focusing on the co-infections, August 11, 2013

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The New Yorker, Annals of Medicine, July 2013: The Lyme Wars

NPR, Vermont Public Radio, April 3rd, 2013, Expert: Lyme disease just one part of tick-borne epidemic, testimony before the Vermont Joint House and Senate Health Committee

Oprah magazine: December 2009, Chronic Lyme Disease, Myth or Reality?

Publications /Abstracts

NY Times Science Best Seller: Why Can't I Get Better? Solving the Mystery of Lyme and Chronic Disease. Dr Richard I. Horowitz. St Martin's Press, NYC. Publication date November 2013

Why Can't I Get Better?

Richard Horowitz, M.D.

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In peer review, accepted for publication:

The Use of Dapsone as a Novel "Persister" Drug in the Treatment of Chronic Lyme Disease/Post Treatment Lyme Disease Syndrome. Horowitz, R.i. Freeman, P. Journal of Exper Derm, April 2016

Letters: Lyme disease: time to shift the paradigm

Approach to diagnosing Lyme disease misses a large proportion of cases, Dr Richard Horowitz

BMJ 2016; 352 doi: <http://dx.doi.org/10.1136/bmj.i1113> (Published 13 January 2016)

Cite this as: BMJ 2016;352:i1113

Clinical Roundup: Selected Treatment Options for Lyme disease: Multiple Causative Factors in Chronic Disease. Alt and Compl Therapies. DOI:10. 1089/act.2012.18407. Mary Ann Liebert, Inc Vol 18, No.4 Aug 2012

Human Babesiosis and Ehrlichiosis-Current Status. Shah, J., Horowitz, R., Eur Infect Dis, Vol 6, Issue 1, Spring 2012

Mycoplasma Species in Ticks. Sapi, E, Horowitz, R: Awaiting Publication

Controversy brewing over Lyme Disease testing. Phillips, Burrasano, Horowitz, Savely, Stricker. The Lancet, Vol 6 March 2006

Richard I. Horowitz, M.D.

Diplomate, American Board of Internal Medicine

Rash Discussions about STARI and Lyme Disease. Stricker, Horowitz, et. al. Clinical Infectious Disease, January 15, 2006 V42i2 p 306.

Lyme Disease: Scratching the Surface. Phillips, Harris, Horowitz, Johnson, Stricker. The Lancet. Vol. 2005 November 19

Evidence-based guidelines for the management of Lyme Disease. Cameron, Horowitz, et al. Expert Review of Anti Infective Therapy 2(1) 2004

Bartonella Henselae: Limitations of Serological Testing: Evaluation of Elisa and Polymerase Chain Reaction Testing In a Cohort of Lyme Disease Patients and Implications for Treatment. Horowitz R.I., M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

Borrellia Burgdorferi & Bartonella Henselae: A Study Comparing Tetracyclines In Combination with Quinolones in Co-Infected Patients. Horowitz R.I.,M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

Mycoplasma Infections in Chronic Lyme Disease: A Retrospective Analysis of Co-Infection and Persistence Demonstrated by PCR Analysis Despite Long Term Antibiotic Treatment. Horowitz R.I.,M.D. et.al. Abstract, 16th

International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

A Prospective Study of Heavy Metal Exposure Among Lyme Disease Patients with Chronic Persistent Symptomatology: Implications for Treatment. Horowitz R.I.,M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

Lyme Disease and Pregnancy: Implications of Chronic Infection, PCR Testing and Prenatal Treatment. Horowitz R.I. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

Effects of Shifting the Acid-Base Balance Among Lyme Patients during Jarish Herxheimer Flares: A Small Prospective Study. Horowitz R.I.,M.D. et.al. Abstract, 16th International Scientific Conference on Lyme Disease & Other Tick-Borne Disorders. Hartford, Connecticut, June 2003.

Richard I. Horowitz, M.D.

Diplomate, American Board of Internal Medicine

Lyme Disease and Babesiosis: New Therapeutic Options for Chronic Persistent Disease. Horowitz R.I.,M.D.. Abstract, 13th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders. Hartford, Connecticut, March 25-26,2000.

Mefloquinine and Artemesia: A Prospective Trial of Combination Therapy in Chronic Babesiosis Horowitz R.I.,M.D.. Abstract, 13th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders. Hartford, Connecticut, March 25-26,2000.

Chronic Persistent Lyme Borreliosis: PCR Evidence of Chronic Infection Despite Extended Antibiotic Therapy- A Retrospective Review Horowitz R.I.,M.D.. Abstract, 13th Annual International Scientific Conference on Lyme Disease and other Tick-Borne Disorders. Hartford, Connecticut, March 25-26,2000.

Chronic Lyme Disease: A Symptom Complex of Multiple Co-Infections: New Diagnostic & Treatment Protocols. Horowitz, R.I.,M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York.

Bicillin Therapy and Lyme Disease: A Retrospective Study of the Safety and Efficacy of High Dose Intramuscular Bicillin in the Treatment of Chronic resistant Lyme Disease. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

High Dose Trimethoprim-Sulfamethoxazole Therapy: A Useful Adjunct to Combination Therapy in the Treatment of Resistant Babesiosis. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

Metronidazole Therapy in the Treatment of Chronic Lyme Disease. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York.

Chronic Persistent Babesiosis after Acute Treatment with Cleocin and quinine, and Atovaquone and Azithromycin Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

Babesiosis in Upstate New York: PCR and RNA Evidence of Co-Infection with Babesia Microti Among Ixodidae Ticks in Dutchess County, NY. Horowitz, R.I., M.D. 12th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 9-10, 1999. New York, New York

Richard I. Horowitz, M.D.

Diplomate, American Board of Internal Medicine

Atovaquone and Azithromycin Therapy: A New Treatment Protocol for Babesiosis in Co-Infected Lyme Patients. Horowitz, R.I., M.D. 11th International Conference on Lyme Disease and Other Spirochetal and Tick-Borne Disorders, April 25-26, 1998. New York, New York.

Alternative Therapies, 5 (5), 30-31: Rainbow Healing Arts Center: Integrating the Science of Medicine with the Art of Healing. Horowitz, R.I., M.D., September 1999.

Developmental Genetics, Int. J. Insect Morphol Embryol, 7 (4), 359-375: A mutation that affects female and male germ cells differently in *Drosophila Melanogaster* Meign. King, Bahns, Horowitz, Larramendi. Pergamon Press, 1978.

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