GLOBAL CHALLENGES IN DIAGNOSING AND MANAGING LYME DISEASE—CLOSING KNOWLEDGE GAPS

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GLOBAL CHALLENGES IN DIAGNOSING AND MANAGING LYME DISEASE—CLOSING KNOWLEDGE GAPS

TUESDAY, JULY 17, 2012

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH,
AND HUMAN RIGHTS,
COMMITTEE ON FOREIGN AFFAIRS,
Washington, DC.

The subcommittee met, pursuant to notice, at 2:07 p.m., in room 2172, Rayburn House Office Building, Hon. Christopher H. Smith (chairman of the subcommittee) presiding.

Mr. SMITH OF NEW JERSEY. The hearing will come to order. Good afternoon, and welcome to our witnesses and to everyone who is joining us for this first ever congressional hearing examining the global challenges in diagnosing, treating, and managing Lyme disease.

My personal commitment to combating Lyme disease is longstanding, going back 20 years, when one of our witnesses, Pat Smith, attended one of my town hall meetings in Wall Township, New Jersey, and asked me to get involved. I did. On September 28, 1993, I offered an amendment to establish a Lyme disease program through the Environmental Hygiene Agency of the U.S. Department of the Army. It passed and became law.

On May 5, 1998, I introduced a comprehensive, bipartisan Lyme disease bill, H.R. 3795, the Lyme Disease Initiative Act of 1998, which had at its core the establishment of a task force, an advisory committee to comprehensively investigate Lyme with at least four major areas in mind: Protection, improved surveillance and reporting, accurate diagnosis, and physician knowledge. I reintroduced the bill again in 1999, 2001, 2004, 2005, 2007, 2009, and have a pending bill that I introduced in 2011.

I would note parenthetically that in 1998 I also introduced a comprehensive law to combat autism despite significant opposition in the Congress and at NIH and CDC that closely paralleled the Lyme bill's struggle. That became law in 2000. Last year, I authored the Combating Autism Reauthorization Act of 2011, which was signed into law in the fall with the support of—not opposition, but the support of NIH and CDC. If only we had done the same with Lyme disease legislation in the late 1990s; there has been a missed decade on Lyme.

As I have met scores of patients suffering the devastating effects of chronic Lyme who only got well after aggressive treatment by

Lyme-literate physicians, I have been dismayed and, frankly, angered by the unwillingness of some to take a fresh, comprehensive look at this insidious disease. My current bill, H.R. 2557, simply establishes a Tick-Borne Disease Advisory Committee, like we have been trying to do since 1998, with the requirement of ensuring diversity of valid scientific opinion, a "broad spectrum of viewpoints" to pull language out of the legislation, serving on the committee.

I would note to my colleagues that in Europe, Lyme disease syndromes were described as early as 1883, and by the mid-1930s, neurologic manifestations and the association with ticks were recognized. In the United States, Lyme disease was not recognized until the early 1970s, when a statistically improbable cluster of pediatric arthritis occurred in the region around Lyme, Connecticut. This outbreak was investigated by Dr. Allen Steere and others from Yale and stimulated intense clinical and epidemiologic research. In 1981, Dr. Willy Burgdorfer, an NIH researcher at the Rocky Mountain Laboratories, identified the spiral-shaped bacteria, or spirochetes, causing Lyme disease and made the connection to the deer or black-legged tick.

Lyme disease is the most common vector-borne illness in the United States and is also endemic in parts of Europe and Asia and recently has been confirmed to be endemic in the Amazon region of Brazil. In Europe, the highest rates are in Eastern and Central Europe. Recent surveillance studies have described growing problems in Australia and Canada.

In the United States, Lyme disease has been reported in 49 States—all except Hawaii—and is most common in the northeastern and north-central States and in northern California into Oregon. Over 30,000 confirmed cases were reported to the CDC in 2010, making it the sixth most common reportable disease in the U.S. and the second most reportable in the Northeast. CDC has estimated that actual new cases may be 10 times more than the reported number, indicating roughly 300,000 cases in 2010 alone. About 85,000 cases are reported annually in Europe as of 2006, according to the WHO, but that was recognized as a gross underestimate.

In North America, the only Borrelia species to cause Lyme disease is Borrelia burgdorferi. In Europe, Borrelia burgdorferi and at least four other species cause the disease. Different species are associated with different manifestations of the disease. There are numerous strains of Borrelia, which may affect the ability to evade the immune system, the ability to invade certain organs or tissues, and the response to antibiotics. Clinical manifestations of Lyme are usually divided into three stages, although the descriptions of the stages vary.

Few diseases have aroused such a high level of emotion and controversy among the public, physicians, and researchers than Lyme disease. There are two distinct views of Lyme disease, each citing specific scientific evidence to support its claims, while outcomes research is limited and conflicting.

One view, promoted by the Infectious Disease Society of America, is that the disease is "hard to catch and easy to cure" and denies the existence of chronic Lyme disease or persistent infection with the Lyme bacteria. Any treatment other than a short course of

antibiotics is considered too risky. Patients who do not fit the paradigm may have few options outside of psychiatric evaluation.

The alternative view, promoted by the International Lyme and Associated Disease Society and also by numerous academic researchers in the U.S. and around the globe, says that the science is too unsettled to be definitive, and there could be one or more causes of persistent symptoms after initial treatment in an individual who has been inflicted with the agent of Lyme disease. These causes include the possibility of persistent infection or postinfectious process or a combination of both.

These are not academic concerns, however, because the patient's health is at risk. Unfortunately, some academic researchers believe that some of their colleagues are more interested in winning arguments than moving the science forward. Three areas central to the controversy are: The quality of diagnostics, post-treatment, and available treatment options in light of clinical guidelines.

Current diagnostic tests commonly used to detect the spirochetes that cause Lyme disease rather than detect whether the patient has developed antibodies to these pathogen, CDC recommends a two-tier serological testing but cautions that the two-tier system could be used only for surveillance purposes and not for diagnosis. Part of the difficulty in clinically managing suspected Lyme disease is that the CDC protocol is frequently not only used but required for diagnosis.

A study in the Netherlands of eight commercially available ELISAs and five immunoblots found that they had widely divergent sensitivity and specificity and a very poor concordance and concluded that their "very high variable sensitivity and specificity further puts the much-advocated two-tier testing strategy into question." In addition, two of the authors of the July 3, 2007, article on an antibiotic resistance element were Julie Boylan and Frank Gherardini of NIAID's Rocky Mountain Laboratories. And they stated, "It is a multistage disorder that is difficult to diagnose at any stage of the disease, as well as being difficult to treat during the later symptoms."

Dr. Mark Eshoo, the head of new technology at the IBIS Biosciences Division of Abbott Laboratories, will tell us today some exciting information regarding the development of diagnostic tools that hopefully will move us past a lot of the controversy.

Then there is the issue of persistence. IDSA has repeatedly stated that there is no convincing evidence that the Lyme Borrelia persists after standard antibiotic treatment. "Convincing" is clearly a subjective term, however. There is substantial evidence of the persistence of it after treatment with antibiotics. There are numerous documented case studies of persistence in humans after antibody treatment, and our witnesses may comment on additional evidence for post-treatment persistence in humans.

Additionally, one of our speakers today, Dr. Stephen Barthold, one of the top experts in the country, and I am sure in the world, on animal models—Dr. Barthold will describe published and yet-to-be-published experimental studies that provide compelling evidence for the Borrelia burgdorferi persistence following an antibiotic treatment in animal model studies and their potential significance for human medicine.

Numerous studies have been conducted of the mechanism by which Borrelia may evade the immune system and antibiotics. Studies have suggested that resistance to antibiotics might be due to formation of different morphological forms of it, including cell wall deficient forms and biofilm-like colonies.

Contrary to the known scientific evidence, in a March 21, 2008, letter to Members of Congress, the Infectious Disease Society of America stated, "Not only is this assertion [that the notion that some spirochetes can persist despite conventional treatment courses] microbiologically implausible, there are no convincing published scientific data supporting the existence of chronic Lyme disease." It is problematic that the Infectious Disease Society of America would write to Congress trying to discourage support of legislation, saying that post-treatment persistence is microbiologically implausible.

Additionally, in an article, "A Chronic Appraisal of 'Chronic Lyme Disease'," published in 2007 in the New England Journal of Medicine, several IDSA physicians and a CDC colleague made the statement that "chronic Lyme disease"—and this is a quote—"which is equated with chronic B. burgdorferi infection is a misnomer." While this statement has been referred to repeatedly in other correspondence, calling chronic Lyme a misnomer does not seem reasonable or supportable since it goes far past expressing uncertainty. It seems clear that the intent of the statement was to firmly slam the door on the notion that there possibly could be chronic Lyme.

The final major area of controversy is the significance of the Infectious Disease Society of America's treatment guidelines, which directly impact patients and their ability to get treatment. Guidelines should be developed based on the best science, and there has been extreme controversy regarding the restrictive nature of the IDSA guidelines. The guidelines do not allow for the possibility of chronic infection and severely limit physician discretion on treating the disease.

Finally—and I would ask unanimous consent that my full statement be made a part of the record—I would point out to my colleagues that we did invite the Infectious Disease Society of America to be here, the NIH, as well as the Centers for Disease Control. We were told that the IDSA person who would have been here had a "scheduling conflict." And I would just make very clear at the outset of this hearing that I will reissue an invitation to them and fully expect that they will testify before our subcommittee at a date that will hopefully be very, very soon.

I would like to now yield to Ms. Bass for any opening comments she might have.

Ms. BASS. Thank you, Mr. Chair. I want to thank you for holding this hearing on Lyme disease.

And I also want to thank today's witnesses in research advocacy and other efforts to bring greater clarity to the nature of this disease. Your work has been critical to understanding the disease's continued emergence and what measures are needed to prevent new infections and treat those who are infected.

Mr. Chairman, I also want to commend you for your leadership on this issue. And, as you have noted, Lyme disease continues to

infect and affect a great number of North Americans, including our own citizens. We can and must do more to control its spread and work on new surveillance, control, and treatment efforts to mitigate future spread. I understand that you do have legislation that you mentioned that you have introduced several times, and I am happy to join as a cosponsor of that legislation.

I know that we have all heard stories of young people and even adults who suffer from extreme fatigue and joint pain due to Lyme disease. While Lyme disease is rarely fatal, symptoms can at times be debilitating. And as I know we will hear from our witnesses today, I, like others, know people who have suffered from this disease. And one of the things that has been very troubling to people I know is that the disease was not diagnosed at first.

And so I know CDC reports that there are a few cases in California. And I would actually question that and believe that it is probably underreported, especially in the Central Valley area of California. CDC just says there were 200 cases in 2010, and I would venture to say that I wonder if that is actually an undercount.

In June 2012, there was an article in The New York Times that says that we are all still trying to understand the transmission of Lyme disease. I wanted to quote from that article:

> "Deer ticks are aptly named, in a sense; a northeastern deer can carry over 1,000 of these ticks on its body. But as far as humans are concerned, the ticks might be more relevantly called mouse ticks. That is because white-footed mice and other small mammals, not deer, are now known by scientists to be major carriers of the disease."

While long thought that deer contribute greatly to Lyme disease transmission, other animals are now suspected, including birds.

I hope current research and data collection is leading to new possible solutions for areas in communities hardest hit but also on the front lines where we are seeing new cases. I would note that some studies suggest increasing temperatures and changes in precipitation patterns may be partially to blame for increased spread. If changes in weather patterns are to blame, I think we should take a look at the surge in cases in the U.S. and understand if there is a relationship. Surveillance and control is critically important in today's expanding field, where more and more States and counties are seeing new cases. I imagine some of the data that shows an increase in incidence is probably due to improved detection.

I welcome witnesses' recommendations on what can be done policy-wise to address Lyme disease and other similar diseases. As we move to control this disease, CDC and others report that the best way to prevent infection in the first place is really around awareness. Local health departments and agencies appear to be increasing awareness, raising efforts as the Nation enters the spring and summer months.

As we look at current and future funding, how can we effectively distribute limited resources to improve our Nation's response to this emerging disease?

And I know your legislation essentially would call for that. The task force that would be looking at it would look at the resources

and figure out the best way. I don't know if that is correct in my understanding in reading it.

It is my hope that as the U.S. continues to lead on Lyme disease that we can also work with the World Health Organization to prioritize the disease's continued emergence in other regions, including in Asia.

I thank you for today's hearing.

Mr. SMITH OF NEW JERSEY. Thank you, Ms. Bass.

I would like to now recognize, without objection, two Members—they are not members of the subcommittee, but very, very welcomed today, beginning with Mr. Gibson, the gentleman from New York.

Mr. GIBSON. Well, thank you, Mr. Chairman and to the ranking member. I want to begin by just thanking you for your leadership on this critical issue and for the way that you work together, which I think is so vitally important.

I want to also recognize Mr. Wolf. I know that all these Members here today have really been working this issue for Lyme awareness, diagnosis, treatment, and coverage from insurance companies very hard.

And I wanted to be here because, from listening to you, Mr. Chairman, I think that we have ended up here for the same reason. This has been constituent-driven. This is a major public health issue in upstate New York. And, you know, shortly after retiring from the Army and returning home a couple years ago, it was clear to me that—a couple things. One, there are so many folks in upstate New York that are suffering from this affliction and are confused—confused because they look to the medical community to get well, and we find the medical community divided.

We need to bring them together. And I think the task force is a great way to do it. We also appropriated last year in the Congress moneys for better research, awareness research toward diagnosis. But I also think it is vitally important that we follow up to make sure that those appropriations, those moneys, end up in the right place. Because I know that we have appropriated money in the past and ended up with the same results. So we have to make sure that we get the right folks that are doing the research on this.

But I am optimistic. I am optimistic because, coming out of the constituent-driven symposium that we held in upstate New York, we were beginning, I think, to find some common ground. We actually had participation from some of those on both sides. Insurance companies were there, as well. And perhaps most encouraging is research which I think will be published, perhaps in the next year, about really how co-infections, I think, can go a long way to explain the chronic illness that the constituents are incurring attendant to a tick-borne bite.

So, you know, toward that end, I will end where I began by thanking the chairman and the ranking member for holding this hearing. I look forward to hearing from the witnesses, and certainly want to stay engaged in moving us forward in a positive way.

And I yield back. Thank you.

Mr. SMITH OF NEW JERSEY. Thank you very much, Mr. Gibson. Thank you for your leadership.

I would like to yield to Chairman Frank Wolf.

Mr. WOLF. Thank you, Mr. Chairman. I want to thank you and the ranking member for the hearing.

This is a big issue in my congressional district, out in Loudoun Valley all the way out to the Shenandoah Valley, and we now see it spreading throughout the entire State of Virginia. For the longest period of time, you have long been a lone voice. And had it not been for you sort of crying in the wilderness, if you would, to force the different groups to come together—so I just want to second what was said and thank you for your leadership here.

I look forward to something very good whereby we can come to the day that there is a consensus on how we can treat Lyme and how we can diagnosis it, how we can treat it, but also how we can prevent it.

And, with that, I yield back.

Mr. SMITH OF NEW JERSEY. Thank you very much, Mr. Wolf.

I would like to now introduce our very distinguished panel, beginning first with Dr. Stephen Barthold, who is a professor of medical pathology at the University of California, Davis and director of the U.C. Davis Center for Comparative Medicine. He served as a captain in the U.S. Army Veterinary Corps and at the U.S. Army Research Institute of Environmental Medicine and was a professor of comparative medicine at the Yale School of Medicine. Dr. Barthold was elected to the National Academies' Institute of Medicine in 2001 and is the recipient of several career awards. His research has been funded continuously by the NIH for 35 years, including a focus on Lyme for the past 25 years.

We will then hear from Dr. Raphael Stricker, who received his medical degree and training in internal medicine at Columbia University in New York and is currently medical director of a multispecialty practice in San Francisco. Dr. Stricker is past president and currently vice president of the International Lyme and Associated Diseases Society. He is also a member of the Federation of Clinical Immunology Societies and the American Federation for Medical Research. He is a recipient of the American Medical Association Award for Physician Excellence and an Outstanding Reviewer Award from the Annals of Internal Medicine. Areas of special interest include tick-borne diseases.

We will then hear from Dr. Mark Eshoo, who earned his Ph.D. from the University of California, Davis and performed his postdoctoral studies at Stanford University. He has over 20 years of research experience in the field of genomics and genetic analysis. Dr. Eshoo's research has resulted in the testing of many thousands of ticks collected from the U.S. and Europe for a wide range of tick-borne pathogens. He has led the development of sensitive procedures to detect tick-borne pathogens from a variety of clinical specimens, and is the director of new technology development at IBIS Biosciences.

We will then hear from Pat Smith, who is in her 15th year as president of the national nonprofit Lyme Disease Association. She is a member of Columbia University's Lyme and Tick-Borne Diseases Research Advisory Committee, the Food and Drug Administration's PESP Partnership to promote avoidance of tick exposure, and an advisor to the Lyme Research Alliance. She is also former

chair of the New Jersey Governor's Lyme Disease Advisory Council and was the FDA's 2011 Lyme prevention conference session co-chair with the CDC. She has spent 27 years advocating for Lyme disease mitigation and combating this disease, raising money for both research and a children's fund.

We will then hear from Evan White, who has utilized his experience in recovery from chronic Lyme disease to serve as an advocate for the treatment rights of Lyme disease patients for nearly 20 years. Evan has testified before a U.S. Senate subcommittee on behalf of himself and Lyme disease patients nationwide and has been a featured speaker at numerous Lyme disease functions. Evan's story as a patient and advocate has been covered by several major news media. Evan currently lives in New York City with his wife Michelle, where he is a labor and employment attorney and co-founder of the firm White Harris.

Then we will hear—and this is by way of hookup with the UK—Ms. Stella Huyshe-Shires, who started her professional life as a plant pathologist before undertaking a research fellowship with IBM into the use of databases in plant research and moving into computing. She contracted Lyme disease in 1999 while working in her garden in Devon, United Kingdom, and was diagnosed 3 years later. She was retired from her IT job in the National Health Service on grounds of ill health. She joined Lyme Disease Action in 2007 and became its chairman in 2009. And we thank her for her willingness to join us at this hearing today from England.

I would like to now ask Dr. Barthold if you could proceed with your testimony.

STATEMENT OF STEPHEN W. BARTHOLD, PH.D., DISTINGUISHED PROFESSOR, DEPARTMENT OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY, CENTER OF COMPARATIVE MEDICINE, SCHOOL OF VETERINARY MEDICINE, UNIVERSITY OF CALIFORNIA, DAVIS

Dr. BARTHOLD. Well, thank you for the opportunity to speak to this subcommittee. I appreciate the recognition of what we have been doing.

As you pointed out, I have been working on Lyme disease for 25 years in animal model systems. And one of the things that has intrigued me the most is the fact that Borrelia persists in its immunologically competent hosts as the rule, not the norm, and so persistence is part of its biological behavior. And this has been shown in 100 percent of mice, rats, hamsters, guinea pigs, gerbils, dogs, and nonhuman primates—two different species of nonhuman primates.

And so, when you have an organism that is a professional at persisting and evading host immune clearance, you have a problem when you approach it with antibiotics. The antibiotics are likely to fail under some circumstances, if not many circumstances.

And so, this has been challenged. I find myself in a rather contentious field, at this point, coming out of the mainstream of Lyme disease research into one in which I am somewhat of a pariah, in terms of the established medical opinion.

In animal models, we know that early treatment during the preimmune phase of the infection, we can cure the animals. But dur-

ing persistent infection, 100 percent of the animals remain persistently infected after antibiotic treatment. And we are not alone. This has been described in a number of different laboratories: One in Finland, one in New York, one in Louisiana, one in Connecticut, and then in our own lab in California. It has been described in mice, in dogs, in nonhuman primates. It has been described with a number of different antibiotics, including ceftriaxone, doxycycline, tigecycline, amoxicillin, azithromycin.

And all of these studies have pointed to some commonality, some rather convincing evidence of spirochetes which are unusual in that they can no longer be cultured. We put clonal populations into a mouse, but we get these nonculturable forms out. And our naysayers have said this is residual DNA debris. But that "DNA debris" is transcribing RNA, which means it is a metabolically viable organism. We can acquire the infection feeding ticks upon the treated the animals, so-called xenodiagnosis. And we can look in the ticks and we see morphologically intact spirochetes that are viable. We can also look in the tissues of the animals that have been treated with antibiotics and we see morphologically intact spirochetal forms.

Ticks can acquire the infection. They can transmit the infection back into naive hosts. We can transplant the infectious material with tissues containing organisms from the treated mice to naive animals.

And in my written testimony, I have included some unpublished data, which we hopefully will get published in the next year or so, that shows after 12 months after treatment of mice we see resurgence of spirochetes in very large numbers, equivalent to numbers of wild-type infection in which the animals have not been treated with antibiotics.

So the significance of this remains to be determined. Are these pathogenic organisms? Everyone in this room is infected subclinically with a virus, bacteria, fungus, or all of the above, and under some circumstances those organisms can cause disease. And it varies from individual to individual.

So it remains to be determined, the significance of these persisting organisms, and they by no means indicate chronic Lyme disease or an example of post-Lyme disease syndrome. But, certainly, something unique is going on with Borrelia burgdorferi, and it needs further study.

And that is pretty much my testimony.

Mr. SMITH OF NEW JERSEY. Thank you very much, Doctor.

[The prepared statement of Dr. Barthold follows:]

Persistence of Non-Cultivable *Borrelia burgdorferi* Following Antibiotic Treatment:

Critical Need for Further Research

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Lyme disease, caused by a number of closely related members of the *Borrelia burgdorferi* sensu lato family (*B. burgdorferi* sensu stricto in the United States) that are transmitted by closely related members of the *Ixodes persulcatus* family (*I. scapularis* and *I. pacificus* in the United States) is endemic in many parts of the world, with particularly high prevalence in the United States and Europe. Prevalence of human disease continues to rise, as does the geographic distribution of endemic areas. These events are enhanced by perturbation of the environment by humans, as well as global climate change, which favor habitation of the environment by *Ixodes spp.* vector ticks and suitable reservoir hosts. Interest in Lyme disease is rising globally, as Lyme disease is increasing in southern Canada, where infected ticks and reservoir hosts are extending their range from the United States, as well as an increase in prevalence throughout Europe and Asia.

I have been engaged in Lyme disease research since its initial discovery in coastal Connecticut in the late 1970's/early 1980's. At that time, I was on the faculty of the Yale School of Medicine, and collaborated with Dr. Steere and others to develop an animal model for studying mechanisms of disease and vaccine development. I have continued Lyme disease research upon joining the faculty at the University of California at Davis in 1997. I have been actively funded by NIH in Lyme disease research for over 25 years.

During the course of my Lyme disease research career, I have become saddened by the negative discourse and division that exists among various factions of the Lyme disease community, including the lay community, the medical community, and the scientific community (the so-called "Lyme Wars"). In particular, debate has intensified regarding efficacy and appropriate regimens for antibiotic treatment. Central to this debate is the Infectious Disease Society of America (IDSA) position that this is a simple bacterial infection that is amenable to simple antibiotic treatment, while also recognizing that something is happening in patients after treatment, known as Post Lyme Disease Syndrome (PLDS).

Lyme disease is exceedingly complex in humans, and this poses major challenges to accurate diagnosis and measuring outcome of treatment. It has been known for years that the acute signs of Lyme disease (erythema migrans, cardiac conduction abnormalities, arthritis, etc.) spontaneously regress without benefit of antibiotics, but their resolution is accelerated by treatment. There is overwhelming evidence in a variety of animal species as well as humans that *B. burgdorferi* persists without treatment, but the crucial question is does it survive following treatment, and if so, do surviving spirochetes cause "chronic" Lyme Disease or PLDS? These questions cannot be answered by speculative and expensive human clinical trials motivated by firmly held dogmatism.

Something strange is happening with Lyme disease. *Borrelia burgdorferi* persistently infects a myriad of fully immunocompetent hosts as the rule, not the norm of its basic biology. When

such a situation occurs, antibiotics may fail, since it is generally accepted that antibiotics eliminate the majority of bacteria, and rely upon the host to "mop up" the rest. If the bacteria are able to evade host "mopping", then the logic of the scenario falters. It is not surprising, therefore, that experimental studies, using a broad spectrum of animal species (mice, dogs, monkeys) and a variety of antibiotics (doxycycline, amoxicillin, ceftriaxone, tigecycline) have all shown a failure to completely cure the animals of *B. burgdorferi* infection. What is surprising is that the surviving spirochetes can no longer be cultivated from tissues (culture is considered by some to be the gold standard for detecting viable *B. burgdorferi*), but their presence can be readily detected with a number of methods, including *B. burgdorferi*-specific DNA amplification (PCR), xenodiagnosis (feeding ticks upon the host and testing the ticks by PCR), detection of *B. burgdorferi*-specific RNA (indicating live spirochetes), and demonstration of intact spirochetes in tissues and xenodiagnostic ticks by labeling them with antibody against *B. burgdoreri*-specific targets. These surviving spirochetes are not simply "DNA debris" as some contend, but are rather persisting, but non-cultivable spirochetes. It remains to be determined if their persistence following treatment is medically significant. For example, humans are known to be persistently infected with a number of opportunistic pathogens, including viruses, bacteria, and fungi, which are held in abeyance by the immune response, without clinical symptoms. Their significance varies with individual human patients and their ability to keep them in check. Lyme disease is likely to be similar.

The following report is a bit technical, but provides a summary of documented evidence of published and yet to be published experimental studies that provide compelling evidence for *B. burgdorferi* persistence following antibiotic treatment in animal model systems. It remains to be determined if humans are different, but the wide range of animal species studied (including non-human primates) predicts commonality from which extrapolation to humans is logical. Because of firmly entrenched opinion within the medical scientific community, evidence of persisting viable but non-cultivable spirochetes is slow to be accepted, and research proposals submitted to NIH that feature persistence following treatment are likely to receive prejudicial peer review in the contentious environment of Lyme disease*. Negative comments by peer reviewers of grant applications in the current financially austere NIH climate result in unfundable scores, if they are scored at all (triaged). I have no personal stake in this issue any more, as I am retiring within a year.

In my opinion, for such important and controversial studies to go forward, NIH will need to publish a specific call for applications, known as a "Request for Applications" (RFA), that requests research on the biological significance of persisting spirochetes following antibiotic treatment.

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* a major weakness cited by a peer reviewer in a recent unfunded R01 application:

"The lay public that has so far denied the validity of scientific data will misunderstand the significance of...[persisting non-cultivable *Borrelia burgdorferi*]...and use it as additional evidence to support the idea of treatment-resistant Lyme disease."

Persistence of Non-Cultivable *Borrelia burgdorferi* Following Antibiotic Treatment:

Critical Need for Further Research

Background:

There is widespread consensus among the mainstream medical community that relatively short-term courses of antibiotics can eliminate objective signs of Lyme borreliosis in patients, with the assumption that patients have been cured of infection. This has been articulated in the *IDSA Guidelines* in 2006 [3] and reaffirmed by an expert Lyme disease review panel in 2010 [4]. The *IDSA Guidelines* are in agreement with position statements of other medical and scientific organizations, including the European Federation of Neurological Societies, The European Union of Concerted Action on Lyme Borreliosis, the American Academy of Neurology, the Canadian Public Health Network, the German Society for Hygiene and Microbiology, several expert panels in various different countries, the American Lyme Disease Foundation, the CDC and NIH. An *Ad Hoc International Lyme Disease Group* has also affirmed this position [5,6].

This consensus is based upon clinically objective criteria, in keeping with sound medical practice. However, it is well established that patients with objective criteria of Lyme borreliosis may also have widely varied and subjective manifestations that do not necessarily fit objective clinical criteria [7,8,9]. There is agreement that when objective clinical signs are persistent, a rare patient may have chronic Lyme disease, and when objective clinical signs return in a treated patient, a rare patient may have recurrent Lyme disease. Under both circumstances, repeated antibiotic treatment is advised. A principal area of continuing but unresolved debate involves patients who experience disabling subjective symptoms following completion of appropriate antibiotic therapy. This has been recognized by the term "post-Lyme disease syndrome" (PLDS). *IDSA Guidelines* state that there is "no well-accepted definition of the PLDS", and that "there is no convincing biologic evidence for the existence of systemic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease." [3] In the absence of objective clinical and diagnostic criteria, PLDS can never be proven to be, or not to be, associated with persistent infection with *B. burgdorferi*. Nevertheless, the vagaries of PLDS have promulgated a culture of "Lyme-literate physicians" (some literate, others not), emotionally charged lay support groups (well-intentioned, but often ill-informed), and speculative treatments, including scientifically unfounded and medically ill-advised long-term antibiotic regimens with outcomes that cannot be objectively proven. Therein lies the basis of what has been euphemistically termed the "Lyme Wars" [10]: a contentious debate that can never be won simply on strongly held conviction. What is needed is research on the basic biology of *B. burgdorferi*, including outcome after antibiotic treatment under controlled conditions in animal models. Animals are indeed different from humans, but knowledge gained with animal models lends credence to valid hypotheses that can then be rationally approached in human trials.

A basic feature of Lyme borreliosis (without antibiotics) **is that persistent infection is the rule, not the norm**. This occurs in *B. burgdorferi's* many reservoir hosts, and has been proven experimentally in Peromyscus mice [11], laboratory mice [12], rats [13], hamsters [14], gerbils [15], guinea pigs [16], dogs [17], and non-human primates [18]. Humans appear to be no different, as there are a number of documented case reports of persistent infection based on culture [19,20,21,22,23,24,25] and PCR [26,27,28,29,30]. *Borrelia burgdorferi* has evolved to persist in immunologically competent hosts as a survival strategy for maintaining its natural host-vector life cycle. Natural reservoir hosts and small laboratory animals are generally rodents. In such hosts, infection is generalized and persistent, including in the skin, wherein spirochetes can most efficiently interface with the vector tick. Both *in vivo* animal model studies

and *in vitro* studies have shown that *B. burgdorferi* spirochetes utilize an array of adhesins that engage virtually every component of the extracellular matrix to facilitate their dissemination [31], and sequestration within collagen as their preferred site of persistence [2,32,33]. Dissemination is also facilitated by bacteremia during early infection, which is generally cleared during the immune persistent phase of infection, and intermittent thereafter. Because humans are much larger, they experience localized infections, as evidenced by erythema migrans (EM), and sometimes disseminated, but randomly multifocal infection through bacteremia, which may result in pauciarticular arthritis, secondary EM, carditis, peripheral neuropathy, meningitis, and other objective clinical signs. It should be emphasized that Lyme disease in untreated humans (and experimental animals) is ephemeral, with "spontaneous" resolution (without antibiotic treatment) of EM, carditis, arthritis, and other signs [9,34]. Studies in animal models have shown that resolution of arthritis and carditis is mediated by the acquired humoral immune response of the host. Under these conditions, anatomically defined inflammation resolves, but infection persists [32,35,36]. Indeed, even during the pre-immune phase of infection, spirochetes populate many tissues with no evidence of inflammation (thus inflammation or "disease" does not necessarily correlate with spirochete presence). The random, multifocal nature of human infection, the ephemeral clinical signs, the myriad subjective symptoms, the clinical impracticality of culture or PCR, the insensitivity of culture, and the retrospective nature of serology all make objective diagnostic criteria for testing outcome of treatment in humans simply impossible. That is not the case with animal models.

In a recent critical review of studies involving antibiotic treatment of *B. burgdorferi*-infected animal models, it was stated that "in the treatment of other infections it is probably unrealistic to expect that antimicrobial therapy *per se* will eliminate every single microorganism from an infected host, and moreover, such an action would rarely if ever be required for a successful outcome...the role of antimicrobial therapy *in vivo* can be thought of in terms of "tipping the balance" in favor of the host's own defenses against a particular pathogen"[37].This may be true for "other infections" but when treating for *B. burgdorferi*, which persists in fully immunocompetent hosts as the rule of its natural behavior, "tipping the balance" in favor of the host poses a challenge.

In that regard, different laboratories, using various classes of antimicrobial drugs in different animal models, including mice [1,2,38,39,40], dogs [17,41,42], and non-human primates [43], have all demonstrated survival of *B. burgdorferi* following antibiotic treatment. What is unique about all of these studies is that spirochetes can be detected by PCR for *B. burgdorferi*-specific DNA (BbDNA), but not by culture. In mouse studies performed in this laboratory (see below), mice were treated with ceftriaxone, doxycycline, or tigecycline at various intervals of infection, and tissues were tested at intervals after treatment. Tissues remained BbDNA PCR-positive up to 12 months, but were consistently culture-negative. Morphologically-intact spirochetes could be visualized by immunohistochemistry in tissues from treated mice; ticks could acquire morphologically-intact *B. burgdorferi* and BbDNA from treated mice; ticks remained BbDNA-positive through molting into nymphs and adults; nymphs transmitted BbDNA to recipient immunodeficient (SCID) mice; allografts from treated mice transplanted into recipient SCID mice transferred BbDNA to recipient mice; and both tick- and transplant-inoculated mice had disseminated BbDNA. BbDNA-positive tissues were also positive for *B. burgdorferi*-specific RNA transcription. Furthermore, quantitative PCR indicated low-levels of replication during these various stages. The *IDSA Guidelines* have stated "the significance of continued PCR positivity needs to be better understood, but this phenomenon should not necessarily be construed to indicate persistence of viable *B. burgdorferi*" [3]. The above summarized behavior of PCR-positivity, RNA transcription, BbDNA transmission, BbDNA amplification, BbDNA dissemination, and morphologically intact spirochetes in both tissues and ticks strongly indicate the presence of persistent, viable, but uncultivable spirochetes.

IDSA Guidelines also state that "unless proven otherwise, culture should be regarded as the gold-standard to address viability of *B. burgdorferi*" [3]. Culture may indeed be a gold standard when it is positive, but it is often not. Having worked with *B. burgdorferi* for over 25 years, it is apparent that not all isolates or strains can be easily cultured, and this is especially apparent during long-term infection. Thus, culture cannot be relied upon as a gold standard of viability. As noted above, our studies and those of others in mice, dogs and non-human primates have all reached similar conclusions: spirochetes are persisting, but are paradoxically non-cultivable. In ongoing studies (see below), we have found resurgence of non-cultivable spirochetes in tissues of mice (and by xenodiagnosis) at 12 months after antibiotic treatment.

Because persistence of non-cultivable spirochetes has been shown to occur following treatment with several different classes of antibiotics, the phenomenon is likely explained by antimicrobial tolerance (in contrast to antibiotic resistance or inadequate antibiotic treatment), in which all classes of antibiotics fail to completely eliminate non-dividing or slowly-dividing subpopulations of a broad array of bacteria and fungi [44,45]. A possible explanation for these attenuated antibiotic-tolerant spirochetes may be because of plasmid loss, in which spirochetes have lost critical genetic material that favors robust growth. It has been known for decades that during *in vitro* passage, *B. burgdorferi* is highly prone to plasmid loss [46,47,48], and therefore plasmid loss is likely to also occur during the course of infection and increase over time. This may explain why treatment success in humans [3,8] and laboratory mice [2,38] appears to be most effective during early infection. Treatment success is inversely correlated with spirochete populations, since spirochete burdens in mouse (and human) tissues are highest during early infection [49], when antibiotics work best. The biological (in contrast to medical) significance of attenuated spirochetes is probably insignificant, in that robustly dividing-, genetically-intact spirochetes would be selectively favored upon tick acquisition, transmission, and survival in reservoir hosts. The medical significance of attenuated persisting spirochetes is another matter, and compels further investigation.

Animal Studies. Various studies have shown efficacy of antibiotics in curing laboratory rodents of *B. burgdorferi* infection, <u>based upon culture as the read out</u> [50,51,52,53] [54,55] [56,57]. With the advent of increasingly sensitive PCR analyses, we and others have repeatedly demonstrated in dogs [17,41,42], mice [1,2,38,39,40] and rhesus macaques [43] that non-cultivable spirochetes persist following antibiotic treatment. Straubinger, et al. [17,41,42] found that despite treatment of infected dogs for 1 month with ceftriaxone, doxycycline, or azithromycin, BbDNA continued to be detected as late as 12 months after therapy, but tissues were consistently culture-negative. This seminal observation prompted Bockenstedt's group in collaboration with our group to study mice infected with *B. burgdorferi* N40 and treated with ceftriaxone or doxycycline [1]. In that study, spirochetes could not be cultured from tissues of treated mice, but were detected by PCR in tissues for up to 9 months after treatment, and in ticks that fed upon treated mice at 3 months after treatment. Efforts to transmit spirochetes to naïve mice from infected ticks that fed upon treated mice were unsuccessful. However, <u>spirochetes could be visualized in midguts of ticks that fed upon treated mice</u> (**Fig. 1**). PCR analysis of spirochetes within the ticks suggested that they had lost one or more plasmids, based upon limited survey of gene targets on B31 lp25 and lp28-1, which are associated with potentially important virulence factors. It was concluded <u>that spirochetes in antibiotic-treated mice were viable, but non-infectious and genetically attenuated.</u>

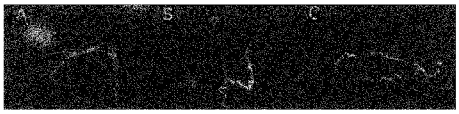

Fig. 1. *Direct fluorescence antibody labeling of B. burgdorferi within midguts of xenodiagnosis ticks that fed upon mice treated with saline (A), ceftriaxone (B) or doxycycline (C)* [1].

These studies prompted further investigation of *B. burgdorferi* persistence following antibiotic therapy by examining mice treated with ceftriaxone during the early (3 weeks) or late stage (4 months) of *B. burgdorferi* N40 infection [2], since we had found that there are significant shifts into, or preferential survival of spirochetes in collagen during chronic infection [32]. Commencing at 3 weeks or 4 months of infection, mice were treated with ceftriaxone or saline for 1 month (16 mg/kg b.i.d. for 5 days, s.i.d. for 25 days), and then necropsied at 1 or 3 months after treatment. Tissues of mice were tested by culture, PCR, and allograft (ear skin) transplantation into naïve mice, and mice were tested by xenodiagnosis, using larval ticks. As before, spirochetes could not be cultured, but low copy numbers of BbDNA were detected by real-time quantitative PCR (qPCR) in tissues of treated mice. Treatment commencing at 3 weeks of infection was more effective at curing mice of infection (including BbDNA) than commencing treatment at 4 months. Allograft (ear tissue) transmission could not be demonstrated, but a low percentage of xenodiagnosis ticks were BbDNA-positive, and nymphal ticks from those tick cohorts transmitted BbDNA to naïve SCID mice, in which multiple tissues became BbDNA PCR-positive, but were culture-negative. Thus, in contrast to the previous study [1], our study found that ticks could both acquire and transmit infectious, non-cultivable spirochetes. This study also detected lp25 and lp28-1 gene targets in BbDNA-positive ticks, thereby challenging the hypothesis that spirochetes were genetically attenuated. Furthermore, morphologically-intact *B. burgdorferi* were found by immunohistochemistry in collagenous tissues of antibiotic-treated, culture-negative mice (**Fig. 2**):

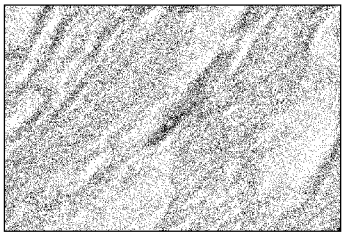

Fig. 2. *Immunohistochemical labeling of antigen-positive, morphologically-intact B. burgdorferi in a ligament of a mouse infected for 4 months, treated with ceftriaxone for 1 month, and then necropsied 1 month after completion of antibiotic treatment* [2]

Studies with tigecycline. A valid criticism of mouse studies utilizing ceftriaxone is that the serum half-life of ceftriaxone is extremely short in the mouse, compared to humans. This is not the case with tigecycline. Tigecycline is a new first-in-class antibiotic that is highly active and bactericidal *in vitro* against multiple strains of *B. burgdorferi* compared to ceftriaxone, reaches serum concentrations well above (70 times) therapeutic levels with a half life of 12 hours [58]. We evaluated high and low doses of tigecycline, ceftriaxone (comparison group), and saline (control group) treatment in mice, commencing at 1 week, 3 weeks, or 4 months of infection [38]. Infection status was evaluated at 3 months after completion of treatment by culture, qPCR of multiple tissues, xenodiagnosis, tick-borne transmission, and allograft transplantation of joint and heart tissue into SCID mice. Previous studies revealed no allograft transmission using ear punch tissue (which has been found to be usually BbDNA-negative following treatment), so this experiment utilized tissues that were the most consistently BbDNA-positive (joint and heart) for persisting spirochetes. Results found no difference in effectiveness between ceftriaxone and tigecycline. Results also confirmed previous studies, demonstrating persistence of non-cultivable spirochetes, based upon qPCR, particularly in the heart base and joint tissues. As previously found, antibiotic treatment during the early stage of infection was more effective than treatment during the later stages of infection. The viability of non-cultivable spirochetes in antibiotic-treated mice was confirmed by transmission to SCID mice by allograft transplantation, with dissemination to multiple tissues in the recipient mice, and by xenodiagnosis, including acquisition of BbDNA by ticks, transmission by ticks to SCID mice, and survival through molting

of larval ticks to nymphs, and then to adults. As before, gene target copy numbers were consistently low, but increased slightly, rather than being diluted, during each transmission stage, indicating low levels of replication. In addition, BbDNA-positive heart base tissue from antibiotic-treated mice revealed RNA transcription of several *B. burgdorferi* genes. Results extended previous ceftriaxone and doxycycline studies, indicating that antibiotic treatment is unable to clear persisting spirochetes, which remain viable and infectious, but are slowly dividing.

Persistence of multiple *B. burgdorferi* isolates following antibiotic treatment. We tested efficacy of ceftriaxone (vs. saline) in mice infected with *B. burgdorferi* N40, B31, 72a, 118a, or Bo126. In saline-treated mice, we were unable to culture 72a, and rarely 118a, yet tissues contained BbDNA at infection-level copy numbers and distribution, and mice seroconverted at a titer indicating active infection. There was no difference in sensitivity of any isolate to antibiotic, with all treated mice being positive for BbDNA. Results support the generality of spirochete persistence.

Resurgence of spirochetes at 12 months after treatment. It has been speculated that non-cultivable spirochetes would eventually die out following treatment [1,37]. We obtained supplemental funds from the National Research Foundation for Tick-Borne Diseases and from NIH/NIAID to support a long-term study, in which mice were followed for up to one year after completion of treatment. Mice were infected with *B. burgdorferi* cN40 for 30 days, treated with ceftriaxone for 30 days, and then necropsied at 2, 4, 8 and 12 months after treatment. Spirochetes could be cultured from inoculation site and urinary bladder of saline-treated mice, but could not be cultured from any of the antibiotic-treated mice at any interval. qPCR results (*flaB*) for saline-treated mice indicated widespread persistent infection in multiple tissues for up to 1 year after treatment:

flaB real-time Q-PCR and Xenodiagnosis Results in **Saline**-Treated Mice

Interval	Inoculation Site	Ear	Heart Base	Ventricular Muscle	Tibiotarsus	Quadriceps Muscle	XenoDx
2 mos	+	+	+	+	+	+	2/2
	+	+	+	+	+	+	2/3
	+	+	+	+	+	+	2/3
	+	+	+	+	+	+	2/2
4 mos	+	+	+	+	-	+	0/1
	+	+	+	+	-	+	NA
	+	+	+	+	-	+	NA
	+	+	+	+	-	+	NA
8 mos	+	+	+	+	-	+	NA
	+	+	+	+	-	+	NA
	+	+	+	+	-	+	2/2
	+	-	+	+	-	+	3/3
12 mos	+	+	+	+	+	+	5/5
	+	+	+	+	+	+	5/5
	+	+	+	+	-	+	4/5
	+	+	+	+	+	+	5/5
	+	-	+	+	+	+	4/5
	+	-	+	+	+	-	2/5
	+	-	+	+	+	+	2/5
	+	+	+	+	+	+	4/5

In contrast to saline-treated mice, remarkably different results were found in mice treated with antibiotic:

***flaB* real-time Q-PCR and Xenodiagnosis Results in Antibiotic-Treated Mice**

Interval	Inoculation Site	Ear	Heart Base	Ventricular Muscle	Tibiotarsus	Quadriceps Muscle	XenoDx
2 mos	- - -	- - -	- - -	- - -	+++	- - -	0/3
	- - -	+ - -	++ -	- - -	- - -	- - -	0/4
	- - -	- - -	- - -	+++	+ - -	- - -	0/2
	- - -	+ - -	- - -	- - -	+ - -	- - -	0/2
4 mos	- - -	- - -	- - -	- - -	- - -	- - -	NA
	- - -	- - -	- - -	- - -	- - -	- - -	NA
	- - -	- - -	+ - -	- - -	- - -	- - -	0/3
	- - -	- - -	- - -	- - -	++ -	- - -	NA
8 mos	- - -	- - -	- - -	- - -	+ - -	- - -	NA
	- - -	- - -	- - -	- - -	- - -	- - -	3/4
	- - -	- - -	- - -	- - -	- - -	- - -	1/2
	- - -	- - -	- - -	- - -	- - -	- - -	NA
	- - -	- - -	- - -	+ - -	- - -	- - -	0/3
	- - -	- - -	- - -	- - -	+ - -	- - -	1/6
	- - -	- - -	- - -	- - -	- - -	- - -	1/3
	- - -	- - -	- - -	- - -	- - -	- - -	2/2
12 mos	+ - -	- - -	+++	+++	+ - -	++ -	0/10
	+ - -	- - -	+++	+ - -	- - -	+++	1/10
	- - -	++ -	+++	+++	+++	++ -	1/10
	+++	+ - -	++ -	+ - -	+ - -	++ -	1/10
	+++	- - -	+++	+++	- - -	+++	1/10
	+++	+++	+++	+ - -	+++	+++	0/10
	+++	- - -	+++	+++	+++	+++	1/10
	+++	+++	+++	+++	+++	+++	1/10

Saline control tissues were tested as single samples, whereas antibiotic-treated mouse tissues were tested in triplicate, and expressed as such in the above table. Results revealed resurgence of spirochete distribution in tissues at 12 months. There was also an increase in *flaB* copy numbers in many samples from antibiotic-treated mice, with nearly 20% of the 12 month antibiotic samples containing 100 or more (up to 339) spirochetes/mg tissue (within range of saline-treated samples). Notably, although tissue samples were rarely positive at 8 months, xenodiagnosis at 8 months presaged resurgent activity prior to the 12 month interval.

Low Density Array (LDA) studies. LDA is a medium-throughput method based on a qPCR or a reverse transcription qPCR (RT-qPCR) platform. Forty three *B. burgdorferi* N40 genes were tested simultaneously, including genes associated with attachment, bacterial membrane, motility, metabolism, cellular processes, cell division, complement regulation, and metabolism (*General Methods*). Among 12 month samples, all gene targets were detected in 5 tissue samples from 4 saline-treated mice, whereas *B. burgdorferi* genomes in 16 tissue samples with high Bb DNA copy numbers from 6 antibiotic-treated mice were uniformly missing BBK32 (lp36), and variably missing *ospE*, various *erps* (cp32s), *vlsE* (located on N40 lp36), *arp* (located on N40 lp28-5), *bptA* (lp25), and *eppA* (cp9). Although preliminary, data suggest loss of small linear and circular plasmids in persisting spirochetes. Most notable was the uniform absence of lp36, loss of which significantly attenuates infectivity in mice, with markedly reduced, but detectable levels of infection [59]. Results also demonstrated amplification of multiple gene targets, thereby verifying the specificity of residual Bb DNA results. LDA was also utilized to detect RNA

transcription of various genes from cDNA-processed samples. Because of low copy numbers in samples, most gene transcripts were below detection levels in antibiotic-treated mice, but *dbpA* transcription was consistently found in most samples, and *bmpD*, *CRASP1*, *erp23* and *p23-T2* transcription were variably detected in samples at 12 months. Although preliminary, LDA analysis confirmed our previous findings [38] of RNA transcription by persisting spirochetes, indicating metabolic viability of non-cultivable spirochetes (in contrast to residual DNA debris).

This mouse study was repeated to confirm the findings of persistence and resurgence of non-cultivable spirochetes, with similar results of detection of non-cultivable spirochetes by PCR in tissues at 12 months following completion of ceftriaxone treatment. In addition, ticks were fed upon antibiotic-treated mice at 12 months after completion of antibiotic treatment, and found once again to be PCR-positive, as before. In addition, small numbers of spirochetes were visible by immunofluorescence within tick midgut preparations:

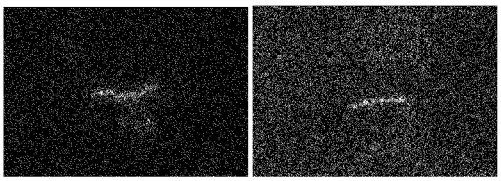

Fig. 4. *Immunoflourescence staining of B. burgdorferi spirochetes in the midgut of ticks that fed upon an saline-treated infected control mouse at 12+ months of infection (left image) and on a mouse infected with non-cultivable spirochetes at 12 months following completion of antibiotic treatment (right image).*

Tissues of mice infected with non-cultivable *B. burgdorferi* at 12 months following completion of antibiotic treatment were examined by immunohistochemistry for the presence of spirochetes. Rare, morphologically-intact spirochetes expressing immune-reactive antigen were found in heart tissue:

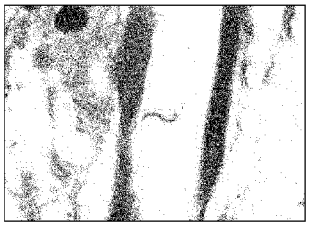

Fig. 5. *Immunohistochemical staining of B. burgdorferi spirochete entering a lymphatic vessel in the heart base of a mouse infected with non-cultivable spirochetes at 12 months following completion of antibiotic treatment.*

Persistence of non-cultivable spirochetes in antibiotic-treated rhesus macaques. In collaboration with Mario Philipp and Monica Embers at Tulane National Primate Research Center, we blindly analyzed tissues by qPCR from rhesus macaques treated with ceftriaxone and doxycycline [72]. Several tissues were confirmed to be BbDNA-positive. As in dog and mouse studies, animals were culture-negative and xenodiagnosis-positive. Morphologically-

intact spirochetes were observed by immunofluorescence in the ticks that fed upon treated animals:

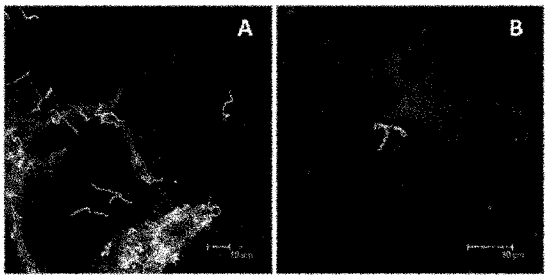

Fig 5. *Spirochetes recovered by xenodiagnosis from macaques treated with antibiotic. Images represent immunoflourescent staining of B. burgdorferi in xenodiagnostic tick midgut culture (A) or tick midgut preparation (B) from treated animals* [72].

Summary of Key Findings in Published and Preliminary (unpublished) Animal Studies

- Studies in mice, dogs and non-human primates have demonstrated persistence of non-cultivable spirochetes following treatment with several different bacteriostatic and bactericidal antibiotics.

- Non-cultivable spirochetes can be visualized as morphologically intact, antigen-positive spirochetes in ticks feeding upon antibiotic-treated mice and macaques, and in tissues of antibiotic-treated mice for 12 or more months after completion of antibiotic treatment.

- Non-cultivable spirochetes in antibiotic-treated mice can be acquired by ticks, transmitted by ticks, and survive molting of ticks from larvae to nymphs and to adults, confirming their viability.

- Non-cultivable spirochetes can be transmitted from antibiotic-treated mice to recipient SCID mice through tick-borne infection or transplantation of tissue allografts, and disseminate in recipient mice.

- Persisting non-cultivable spirochetes transcribe RNA, confirming their metabolic viability.

- Low copy numbers of target DNA of non-cultivable spirochetes are present in tissues of mice following antibiotic treatment, with evidence of very low but increasing levels of replication when acquired by ticks, transmitted by ticks, in different stages of ticks, and following transmission to recipient hosts.

- Non-cultivable spirochetes resurge at 12 months after antibiotic treatment, with increased BbDNA copy numbers and widespread dissemination in host tissues.

- Preliminary results suggest that resurgent non-cultivable spirochetes have lost small linear and circular plasmids, which may explain their attenuated, low-replicative behavior.

Conclusion:

"...the significance of continued PCR positivity needs to be better understood, but this phenomenon should not necessarily be construed to indicate persistence of viable *B. burgdorferi*." *IDSA Guidelines*

Persisting viable but non-cultivable *B. burgdorferi* is now a convincing phenomenon based upon a number of animal-based (mouse, dog and primate) studies using a number of different antibiotics, and the significance of continued infection indeed needs to be better understood. It is time to recognize that Lyme disease is not a simple bacterial infection.

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Mr. SMITH OF NEW JERSEY. Without objection, all of your full and very extensive testimonies will be made a part of the record.

Dr. Stricker?

STATEMENT OF RAPHAEL STRICKER, M.D., VICE PRESIDENT, INTERNATIONAL LYME AND ASSOCIATED DISEASES SOCIETY

Dr. STRICKER. Thank you, Mr. Chairman, members of the committee, honored guests.

First, let me take this opportunity to thank the committee for inviting me to speak about the growing international health threat of Lyme disease.

I am a practicing physician in San Francisco with a specialty in internal medicine. I am also vice president of the International Lyme and Associated Diseases Society, or ILADS, an international organization of medical providers with expertise in treating patients with Lyme disease and associated tick-borne illnesses. I currently have over 2,000 Lyme disease patients in my practice, and I have watched the number of patients with this disease grow exponentially over the past 15 years.

Patients come to me from all over the United States and around the world: From Connecticut to California, from Canada to Costa Rica, from Great Britain to Brunei, and from Germany to Japan, and, yes, even from New Jersey. Many of these patients have been ill for years, and, sadly, they have been unable to find a medical provider who can diagnose and treat them for Lyme disease.

My practice reflects the increasing rate of Lyme disease in the United States and around the world. This increase should not be a surprise to anyone; after all, Lyme disease is the most common tick-borne disease in the world today. It is caused by a spiral-shaped bacteria that is transmitted by the bite of a tick, as you have heard. Patients with Lyme disease develop a combination of muscle and joint symptoms, neurologic problems, and heart abnormalities that may be severe and debilitating.

Yet, in spite of the fact that the disease is so common, medical providers are often ignorant about how to diagnose and treat Lyme disease. There are a number of reasons for this ignorance. First, the telltale bullseye rash that is a classic sign of Lyme disease may be absent in more than half of Lyme disease patients. Absence of the classic Lyme rash makes the diagnosis of the disease much more difficult. Second, patients are often unaware of a tick bite. In many parts of the world, the black-legged tick that transmits Lyme disease may be no larger than a poppy seed and easily missed.

Third, Lyme disease may have a wide range of symptoms, and physicians are often unaware of the highly variable manifestations of the disease. Fourth, testing for Lyme disease remains problematic. For historical reasons, most laboratories around the world use tests that are unstandardized and insensitive, and these tests give negative results in about half the cases of Lyme disease. Fifth, treatment of Lyme disease has evolved in a haphazard fashion. The "standard of care" for treating Lyme disease put forth by specialty medical organizations, such as the Infectious Diseases Society of America, or IDSA, only addresses acute infection immediately following a tick bite. The IDSA standard ignores the more common

and severe chronic form of Lyme disease that many of my patients suffer from.

For all of these reasons, Lyme disease has become an international medical disaster. We have seen thousands of patients around the world who have suffered the dire consequences of undiagnosed and untreated Lyme disease. Their stories fill up pages and pixels in medical journals, newspaper articles, documentary films, YouTube videos, and online magazines. Yet our specialty medical organizations, such as IDSA, sit by and do nothing.

In California, we are grateful to the State legislature and the Department of Health Services for establishing the Lyme Disease Advisory Committee with the goal of educating medical providers and the public about Lyme disease. We have established mandatory laboratory reporting of positive Lyme disease tests directly to the Department of Health Services, just like the system for reporting syphilis, tuberculosis, HIV disease, and other public health threats. We also have a physician protection law that allows healthcare providers to care for Lyme disease patients in the most medically appropriate manner.

These essential steps should serve as a model for a national tick-borne disease program with a national Lyme disease advisory committee representing all stakeholders, a national and even international reporting system for positive tick-borne disease testing, and national legislation to protect healthcare providers who treat patients with the chronic form of Lyme disease.

Beyond these short-term goals, we need the Centers for Disease Control and Prevention, the CDC, and the National Institutes of Health, the NIH, to abandon their failed Lyme disease programs. We need the CDC and the NIH to promote targeted research to develop better diagnostic tests for tick-borne diseases, just as they did for AIDS. We need the CDC and the NIH to develop more effective treatments for patients who suffer from the chronic form of Lyme disease.

We cannot do this if specialty medical societies continue to turn their backs on these patients because those societies ignore the evidence that chronic Lyme disease exists. We need to get these organizations to look at the evidence, to discard dogmatic opinions that are out of date, and to start helping sick patients instead of contributing to the pain and suffering of those patients.

Above all, we need to listen to the voices of patients with Lyme disease. You will hear some of those voices today. The voices come from people in every walk of life, in every corner of our society, and in every corner of the world. Those voices need to be heard.

Almost 2 decades ago, a courageous physician named Joseph Burrascano testified at a Health Committee hearing of the United States Senate. The committee had just been reassured by prominent members of the medical establishment that Lyme disease was a trivial illness that was "hard to catch and easy to cure." Dr. Burrascano spoke these words:

> "The very existence of hundreds of Lyme support groups in the country and the tens of thousands of dissatisfied, mistreated, and ill patients whom these groups represent underscores the many problems that exist in the real world of Lyme disease."

Almost 2 decades later, those problems still exist in the real world of Lyme disease. We can and we must address those problems for the benefit of everyone in our international community.

Thank you very much for your attention.

Mr. SMITH OF NEW JERSEY. Thank you so very much, Dr. Stricker.

[The prepared statement of Dr. Stricker follows:]

Lyme Disease: The Hidden Epidemic

Raphael B. Stricker, M.D.
Vice President, International Lyme & Associated Diseases Society (ILADS)

House Committee on Foreign Affairs, Subcommittee on Africa, Global Health, and Human Rights
July 17, 2012

Summary

Lyme disease has reached epidemic proportions around the world. Recent animal and human studies have confirmed the potential for persistent infection with the corkscrew-shaped Lyme spirochete, *Borrelia burgdorferi*, as well as the complicating role of tick-borne coinfections associated with failure of short-course antibiotic therapy. Furthermore, renewed interest in the role of cell wall deficient (CWD) forms in chronic bacterial infection and progress in understanding the molecular mechanisms of biofilms has focused attention on these processes in chronic Lyme disease. Recognition of the importance of CWD forms and biofilms in tick-borne illness should stimulate pharmaceutical research into new antimicrobial agents that target these mechanisms of chronic infection with the Lyme spirochete. Concurrent clinical implementation of novel culture techniques and proteomic screening offers a chance to correct significant worldwide deficiencies in Lyme testing. Advances in these areas have the potential to revolutionize the diagnosis and treatment of Lyme disease in the future.

Introduction

Lyme disease is one of the most controversial illnesses in the history of medicine.[1,2] Over the past decade, two opposing camps have emerged in the controversy over this tick-borne illness. One camp is represented by the Infectious Diseases Society of America (IDSA), which maintains that Lyme disease is a rare illness localized to well-defined areas of the world.[3,4] According to IDSA, the disease is 'hard to catch and easy to cure' because the infection is rarely encountered, easily diagnosed in its early stage by means of accurate commercial laboratory tests and effectively treated with a short course of antibiotics over 2-4 weeks. Chronic infection with the corkscrew-shaped Lyme spirochete, *Borrelia burgdorferi*, is rare or non-existent.[3,4] The IDSA view is based on the work of a small group of researchers who have little or no contact with Lyme disease patients and use their limited research results to restrict clinical care for sick patients with persistent Lyme disease symptoms.

The opposing camp is represented by the International Lyme and Associated Diseases Society (ILADS), which argues that Lyme disease is not rare and, because its spread is facilitated by rodents, deer and birds, can be found in an unpredictable distribution around the world accompanied by other tick-borne coinfections that may complicate the clinical picture. According to ILADS, tickbites often go unnoticed and commercial laboratory testing for Lyme disease is inaccurate.[1,2,5] Consequently the disease is often not recognized and may persist in a large number of patients who are untreated or undertreated, requiring prolonged antibiotic therapy to eradicate persistent infection with the evasive Lyme spirochete.[1,2,5] The ILADS view is supported by independent clinicians and researchers around the globe who view the science of Lyme disease as unsettled and feel that decisions about the most appropriate treatment for patients with Lyme disease should be left in the hands of clinicians.

The controversy over Lyme disease came to a head in November 2006 when IDSA released new guidelines severely limiting treatment options for patients with persistent Lyme symptoms.[3] The guidelines were so restrictive that the Attorney General of Connecticut initiated an unprecedented investigation into potential anti-trust violations by IDSA, the dominant infectious disease society in the United States, in its formulation of the guidelines.[6-8] The investigation found significant conflicts of interest and suppression of data in the guidelines development process.[6,7] As a result, IDSA created a new scientific panel to review its Lyme guidelines under the guidance of a specialist in medical ethics. The review panel held a hearing in July 2009 that was broadcast live over the internet and featured more than 300 peer-reviewed articles and 1,600 pages of analysis supporting the concept of persistent infection despite short-course antibiotic therapy of 2-4 weeks in patients with persistent Lyme disease symptoms.[8,9] Despite this extensive evidence, the IDSA review panel voted unanimously to uphold the flawed Lyme guidelines.[8,9]

Advances and Contradictions

The unprecedented legal action against the IDSA Lyme guidelines reflected frustration over the widening gap between groundbreaking experimental evidence and entrenched clinical practices in Lyme disease.[8,9] The past decade witnessed significant advances in understanding the pathogenesis of *B. burgdorferi* infection.[10-16] The genome of *B. burgdorferi* was sequenced in its entirety, and the biologic and immunologic contribution of various genes was elucidated.[10-12] In particular, the mechanisms of "stealth pathology" utilized by the Lyme spirochete in evading the host immune response and establishing infection in diverse tissues was illuminated.[13-16] Animal models of Lyme disease in gerbils, hamsters, rats, mice, dogs, monkeys and horses provided evidence for persistent infection in various tissues following experimental transmission of *B. burgdorferi*.[17-30] In many of these models, infection persisted despite the equivalent of short-course antibiotic therapy.[19-27] (Table 1)

While progress was being made in research models of tick-borne disease, controversy raged over the clinical features of Lyme disease.[31-41] A growing number of studies highlighted persistent symptoms in patients following clinical infection with *B. burgdorferi*, but the pathologic mechanism of those symptoms remained murky.[31-36] The concepts of 'post-Lyme syndrome', 'post-treatment Lyme disease' and 'chronic Lyme disease' were hotly debated, and the issues of post-infectious autoimmunity versus persistent spirochetal infection remained unsettled despite numerous studies from Europe and the United States that documented failure of short-course antibiotic therapy and persistent *B. burgdorferi* infection in various tissues (Table 2).[33-36] The role of prolonged antibiotic therapy in patients with persistent Lyme symptoms was also debated based on conflicting study results involving a limited number of patients who had been symptomatic for long periods and had already failed similar treatment.[42-47] The statistical validity of these studies and generalizability to the majority of patients with persistent Lyme symptoms was also questioned.[46,47]

Evidence for Chronic Infection

The comprehensive review of the IDSA Lyme guidelines provided strong evidence for chronic spirochetal infection in animal models of Lyme disease[20-24] and patients with persistent Lyme symptoms (Tables 1 and 2).[48-58] This evidence underscores the importance of chronic infection in Lyme disease and further discredits the restrictive IDSA view of the disease that continues to harm

patients by denying appropriate treatment. It also raises many questions about the mechanism(s) and optimum therapy for persistent spirochetal illness.

Complementing the evidence in favor of chronic *B. burgdorferi* infection, clinical and experimental studies have shown that tick-borne coinfections may also have chronic phases.[59-67] In the past, reports of pathology due to *Babesia, Anaplasma, Ehrlichia* , *Bartonella* and *Rickettsia* species have focused on the fulminant acute forms of infection that are relatively easy to diagnose and often fatal in immunocompromised patients.[61,63,67] More recently, these organisms have been associated with chronic persistent infection in animal models and humans.[59-67] The presence of coinfecting organisms has been shown to enhance the symptoms and exacerbate the severity of Lyme disease.[68-73] Thus recognition of chronic coinfections supports the concept of unresolved illness due to persistent infection with the Lyme spirochete.

Renewed Interest in Cell Wall Deficient Bacterial Forms

Cell wall deficient (CWD) bacterial forms were first described in 1935 by Klieneberger, who named them L-forms after the Lister Institute where she worked.[74] Subsequent research by Dienes showed that various bacteria could form CWD colonies and then revert back to bacillary morphology under appropriate conditions.[75] An extensive review by Domingue and Woody highlighted the extent of CWD morphology in many bacterial strains and the potential role of these mutant bacteria to produce persistent infection and chronic diseases.[76] The confusing terminology used to describe CWD bacteria has hindered work in this field. While the term 'L-form' or 'spheroplast' describes CWD morphology in coccobacillary organisms, the term 'cyst' or 'round body' has been used to describe similar morphology in spirochetes.[76]

Margulis et al. described CWD spirochetal forms in 1993.[77] Subsequently Preac-Mursic and colleagues demonstrated the formation and cultivation of *B. burgdorferi* 'spheroplast-L-form variants',[78] and Brorson et al. showed that these forms, which he termed cysts or round bodies, could revert to viable spiral forms of the bacteria.[79,80] This observation has been confirmed by other investigators.[81-83] Although the pathogenicity of CWD borrelial forms has been questioned,[3] recent studies have suggested a link between CWD borrelia and neurodegenerative diseases including Alzheimer's disease,[84-86] and resistance of cystic forms to antibiotic therapy has been documented.[87-90] Recent advances in understanding molecular mechanisms of CWD bacterial formation has offered a glimpse at new treatment approaches to chronic Lyme disease.[90] Currently the only antibiotic that reliably targets the cyst form of *B. burgdorferi* is metronidazole or its derivatives,[87,88] while other agents have yielded negative or conflicting results with regard to cysts.[23,89,90] Given the potential importance of CWD forms in persistent *B. burgdorferi* infection, newer antibiotics aimed at this evasive mutant are desperately needed to eradicate chronic infection in Lyme disease.[85]

Biofilms

Another mechanism of chronic infection involves the formation of biofilms.[92-98] These adherent polysaccharide-based matrices protect bacteria from the hostile host environment and facilitate persistent infection. Biofilms are responsible for a number of chronic infections, including gum disease, ear infections, heart valve disease, gastrointestinal infection and chronic lung disease.[92-98] Sapi and MacDonald raised the possibility of biofilm formation by *B. burgdorferi*, and subsequent work has demonstrated these spirochetal formations in culture and in the tick gut.[99,100]

Combinations of borrelial cysts and putative biofilms have also been noted in patient skin biopsies using focus floating microscopy.[101] Biofilm formation is dependent on cyclic di-GMP expression,[102,103] and recent studies have shown that *B. burgdorferi* expresses this regulatory molecule.[104,105] Coordinated steps in the elaboration of biofilms have been demonstrated in other bacteria, and it remains to be seen whether similar molecular processes occur in borrelial strains and whether these processes play a role in persistent infection.[106,107]

To date no antibiotic treatment exists that targets biofilm formation. However elucidation of the regulatory steps in the biofilm process should allow development of "designer" antibiotics that interfere with this process.[106] It has recently been shown that mutations in genes that regulate biofilm development can interfere with the elaboration of new biofilms and also cause collapse of established biofilm colonies.[107] These findings indicate the potential effectiveness of newer antibiotics that target the biofilm regulatory process, suggesting a novel approach to treatment of Lyme disease and other chronic infections.[108,109]

Testing for Lyme Disease

Clinical testing for Lyme disease remains abysmal.[2,110-115] The two-tier algorithm recommended by the Centers for Disease Control and Prevention (CDC) utilizes a screening enzyme-linked immunosorbent assay (ELISA) or immunofluorescence assay (IFA) followed by a confirmatory Western blot. Although this approach has a high test specificity of 99% (ie, only 1% of tests yield false-positive results and a wrong diagnosis), the sensitivity of the two-tier approach in Lyme disease patients tested at least 4-6 weeks after infection is only 46% (ie, more than half the tests yield false-negative results and miss the diagnosis) (Table 3). This level of sensitivity is inadequate for a clinical diagnostic test and, by comparison, far below the 99.68% sensitivity of diagnostic HIV testing.[110,114,115] Furthermore, the misconception that two-tier testing is highly sensitive for Lyme disease patients with persistent arthritic or neurologic symptoms derives from a study that selected patients based on positive Lyme testing and then showed high levels of two-tier test positivity.[115] This circular reasoning is a systematic problem with the evaluation of Lyme testing.

There are a number of reasons for the inaccuracy of Lyme testing, including use of less antigenic laboratory spirochetal strains in the commercial test kits, elimination of important spirochetal target proteins from those kits and lack of standardization of the commercial Lyme assays.[111-113] Gender bias may also be a factor: while chronic Lyme disease is reportedly more common in women, the two-tier test system yields positive results more often in men.[116] Although a newer ELISA targeting the conserved VlsE or C6 peptide of *B. burgdorferi* has been developed, this test system does not appear to be more sensitive than the two-tier approach.[117,118] While molecular testing has been useful for diagnostic confirmation and treatment monitoring in other illnesses, molecular testing for *B. burgdorferi* has been unreliable, and newer molecular techniques targeting tickborne agents remain unproven and expensive.[119,120] Assays for more accessible surrogate markers of Lyme disease have yet to be accepted by the general medical community.[121-125] Thus testing for Lyme disease remains problematic.

A newer approach to Lyme testing involves the use of proteomics.[126,127] Based on the known genetic makeup of the spirochete, numerous proteins can be generated in vitro and tested for antigenicity using Lyme patient sera. In this manner, novel target proteins can be identified, and conceivably new test systems based on these proteins can be developed without even knowing the

function or location of the antigens within the spirochete.[126] Work on these proteomic-based test systems is already in progress, but extensive clinical validation will be required to bring those tests to market. Nevertheless the proteomic approach to Lyme testing holds great promise for more accurate serological diagnosis, and development of proteomic testing for tick-borne diseases provides a useful diagnostic model for other chronic and elusive infections. Beyond proteomics, novel test systems that exploit electromagnetic signals generated by bacterial DNA sequences may also prove to be effective in the diagnosis of chronic Lyme disease.[128,129] Novel culture techniques for *B. burgdorferi* are also being evaluated.[130]

Big Pharma is Watching

Until now, the pharmaceutical industry has steered clear of Lyme disease. There are a number of reasons for this avoidance, including the fear of entry into a controversial field and the perception that Lyme disease is easy to treat with short-course generic antibiotics. In simple terms, uncertainty about the disease and lack of profitable treatment options has limited pharmaceutical involvement in Lyme disease. This scenario is in stark contrast to the AIDS epidemic, where the prospect of billion-dollar antiviral drug sales propelled the pharmaceutical industry into a leading role in combatting the pandemic.[131] In a more recent example, the development of effective (and lucrative) drug therapy for fibromyalgia has boosted the status of that previously maligned diagnostic entity and fostered unprecedented awareness of the condition in the medical community and among the lay public.[132] The lack of a similar dynamic in Lyme disease has been a significant roadblock to progress in treating the tick-borne illness.

Progress in understanding the various aspects of Lyme disease outlined above should encourage the pharmaceutical industry to assume a more active role in the Lyme arena. The evidence for chronic infection with the Lyme spirochete and coinfecting organisms supports a greater need for antibiotic therapy in this disease beyond the 2-4 weeks specified in the discredited IDSA guidelines.[133-135] The need for more effective treatment of this chronic infection in turn supports the use of more complex (and lucrative) antibiotic regimens in Lyme disease. In a similar vein, targeting CWD forms of *B. burgdorferi* and biofilm formation offers the prospect of new antibiotic approaches to the disease, with an exciting opportunity for innovative therapeutics and increased profits. Development of antibiotic agents that target spirochetal CWD forms and biofilms may also provide valuable insight into the treatment of other chronic infections. The development of more reliable testing for Lyme disease based on proteomics and culture techniques will help to define the population in need of these innovative therapies. More reliable standardized testing will also assure reimbursement for newer Lyme therapies from third party payors.

Conclusions

In conclusion, extensive evidence now shows that persistent symptoms of Lyme disease are due to chronic infection with the Lyme spirochete in conjunction with other tick-borne coinfections. The mechanisms of chronic infection appear to involve CWD forms of the spirochete and biofilm formation, and these infectious processes are attractive targets for future drug development. Institution of more reliable Lyme testing based on culture techniques and proteomics should dispel uncertainty over the presence of the disease and facilitate identification of patients who require treatment. The opportunity for the pharmaceutical industry to develop new drugs targeting novel infectious processes in a well-defined patient population will lead to broader recognition and more effective treatment of Lyme disease in the future.

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Table 1: Evidence for Persistent Infection in Animal Models of Lyme Disease*

Study/Year/ Reference	Animal Origin	Persistence of *B. burgdorferi* Shown by	*B. burgdorferi* Detection**	Sample Source
1. Rodents				
Preac-Mursic et al, 1990[1]	Gerbils	Culture Histology	6 months	Joints, Skin, Spleen
Duray & Johnson, 1986[2]	Hamsters	Culture Histology	9 months	Spleen, Kidney, Eye
Schmitz et al, 1991[3]	Hamsters	Culture Histology	16 months	Synovium,
Moody et al, 1990[4]	Rats	Culture Histology	12 months	Spleen, Kidney, Joints
Malawista et al, 1994[5]	Mice	Culture, PCR	60 days †	Ear, Bladder
Moody et al, 1994[6]	Mice	Histology	90 days†	Joints, Heart
Bockenstedt et al, 2002[7]	Mice	PCR Xenodiagnosis	12 weeks†	Joints, Bladder
Hodzic et al, 2008[8]	Mice	PCR, Histology Xenodiagnosis	12 weeks†	Joints, Heart
Yrjänäinen et al, 2010[9]	Mice	PCR	30 weeks†	Joints
Barthold et al, 2010[10]	Mice	PCR, Histology Xenodiagnosis	12 weeks†	Joints, Heart, Muscle
Bockenstedt et al, 2012[11]	Mice	PCR, Histology Xenodiagnosis	12 weeks†	Joints
2. Dogs				
Straubinger et al, 1997[12]	Dogs	PCR Histology	3-6 months†	Skin, LN Joints
Straubinger, 2000[13]	Dogs	PCR	500 days†	Skin, Muscle Joints
3. Monkeys				
Roberts et al, 1995[14]	Monkeys	Culture, PCR Histology	6 months	Joints, Nerve
Roberts et al, 1998[15]	Monkeys	Culture, PCR Histology	46 months	Nerve
Pachner et al, 2001[16]	Monkeys	Culture, Histology PCR	3 months	Brain, Nerve, Heart
Cadavid et al, 2004[17]	Monkeys	Culture, Histology PCR	32 months	Heart
Miller et al, 2005[18]	Monkeys	PCR	3 months	Brain, Nerve Heart, Muscle Skin, Bladder
Embers et al, 2012[19]	Monkeys	Culture, Histology PCR, Xenodiagnosis	6-12 months†	Skin, Heart Bladder, Joints, Tendon, Spleen
4. Horses				
Chang et al, 2005[20]	Ponies	Culture	5 months†	LN, Joints, Muscle
Imai et al, 2011[21]	Horses	Histology, PCR	1-4 years†	Brain, Nerve

* PCR, polymerase chain reaction; LN, lymph node.
**Time from initial infection to final positive testing point.
†Detectable *B. burgdorferi* following antibiotic treatment.

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Table 2: Evidence for Persistent Human Infection Following Treatment of Lyme Disease*†

Study/Year/ Reference	Study Origin	Persistence of *B. burgdorferi* Shown by	Sample Source
Weber et al, 1988[1]	Europe	Histology	Brain, liver (Autopsy)**
Schmidli et al, 1988[2]	Europe	Culture	Synovial Fluid
Cimmino et al, 1989[3]	Europe	Histology	Spleen
Preac-Mursic et al, 1989[4]	Europe	Culture	Skin Bx, CSF
Pfister et al, 1991[5]	Europe	Culture	CSF
Strle et al, 1993[6]	Europe	Culture	Skin Bx
Preac-Mursic et al, 1993[7]	Europe	Culture	Iris Bx
Haupl et al, 1993[8]	Europe	Culture	Ligament Bx
Strle et al, 1996[9]	Europe	Culture	Skin Bx
Preac-Mursic et al, 1996[10]	Europe	Culture	Skin Bx, CSF
Oksi et al, 1996[11]	Europe	Culture	CSF
		PCR	Brain Bx
		PCR	Brain (Autopsy)
Priem et al, 1998[12]	Europe	PCR	Synovial Bx/Fluid
Oksi et al, 1999[13]	Europe	Culture, PCR	Blood
Breier et al, 2001[14]	Europe	Culture	Skin Bx
Hunfeld et al, 2005[15]	Europe	Culture	Skin Bx
Hudson et al, 1998[16]	Australia	Culture, PCR	Skin Bx
Steere et al, 1988[17]	USA	Histology	Synovial Bx
Kirsch et al, 1988[18]	USA	Histology	LN (Autopsy)
Liegner et al, 1993[19]	USA	Histology	Skin Bx
		PCR	Blood
Battafarano et al, 1993[20]	USA	Histology, PCR	Synovial Bx/Fluid
Chancellor et al, 1993[21]	USA	Histology	Bladder Bx
Nocton et al, 1994[22]	USA	PCR	Synovial Fluid
Shadick et al, 1994[23]	USA	Histology	Brain (Autopsy)
Masters et al, 1994[24]	USA	Culture	Blood
Lawrence et al, 1995[25]	USA	PCR	CSF
Bayer et al, 1996[26]	USA	PCR	Urine
Nocton et al, 1996[27]	USA	PCR	CSF

†Adapted from Reference 1.
*All patients had received a minimum of 2-4 weeks of antibiotic therapy. PCR, polymerase chain reaction; Bx, biopsy; CSF, cerebrospinal fluid; LN, lymph node.
**Mother treated with antibiotics during pregnancy; newborn died.

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Table 3: Sensitivity/Specificity of Commercial Two-Tier Testing for Convalescent/Late Stage Lyme Disease*

Study/Year**	Location	Patients/Controls	Sensitivity	Specificity
Schmitz et al 1993	USA	25/28	66%	100%
Engstrom et al 1995	USA	55/159†	55%	96%
Ledue et al 1996	USA	41/53	44%	100%
Tilton et al 1997	USA	23/23	45%	100%
Trevejo et al 1999	USA	74/38	29%	100%
Bacon et al 2003	USA	106/559	67%	99%
Binnicker et al 2008	USA	35/5	49%	100%
Steere et al 2008	USA	76/86††	18%	99%
TOTALS	**USA: 8**	**435/951**	**46%**	**99%**

* Adapted from Reference 2.
** Limited to studies from USA that included negative controls
† Non-commercial ELISA and Western blot
†† Non-commercial ELISA

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3. Ledue et al. *J Clin Microbiol*. 1996;34:2343-50.
4. Tilton et al. *Clin Infect Dis*. 1997;25(Suppl 1):S31-4.
5. Trevejo et al. *J Infect Dis*. 1999;179:931-8.
6. Bacon et al. *J Infect Dis*. 2003;187:1187-99.
7. Binnicker et al. *J Clin Microbiol*. 2008;46:2216-21.
8. Steere et al. *Clin Infect Dis*. 2008;47:188-95.

Mr. SMITH OF NEW JERSEY. Dr. Eshoo?

STATEMENT OF MARK ESHOO, PH.D., DIRECTOR, NEW TECHNOLOGY DEVELOPMENT, ABBOTT

Mr. ESHOO. Hello. Thank you for the invitation to address the committee. I represent IBIS Biosciences; we are a part of Abbott. And, obviously, our interest has been in developing better diagnostics for Lyme disease.

You know, as we heard earlier, Lyme disease is caused by a bacteria called Borrelia burgdorferi and is the most commonly reported vector-borne infectious disease in North America and is also found around Europe and Asia. The number of cases has been steadily increasing, and it is estimated that this disease is severely underreported.

Other tick-borne diseases are also very important, such as the protozoan parasite Babesia, which is found worldwide. And in many parts of the world, such as Africa, Babesiosis, the disease caused by Babesia, is frequently mistaken for malaria. In regions with Lyme disease, there are also a large number of other tick-borne pathogens that are typically present, leading to a high risk of co-infection with Lyme disease.

Now, in nature, Lyme disease is spread by ticks to mice, which act as the reservoir of the disease. The infected mice then infect more ticks, and then the ticks then infect more mice. Though these mice are infected, they don't die but, rather, become chronically or long-term infected. This is because if the mouse dies, so will the bacteria that cause Lyme disease.

To survive in the mice, these bacteria have evolved several clever tricks to evade the mouse's immune system. One of the ways they do this is by infecting the parts of the mouse's body where it is hard for the immune system to attack the infection—the skin, the joints, the nervous system. Now, when people become infected by a tick bite, the Lyme bacteria do the same things as they do in the mouse. The infections can be long-lasting or chronic. They can spread through the skin, which we see as a bullseye rash. They can invade the nervous system and cause neurological Lyme disease or infect the joints, causing Lyme arthritis.

The best time to treat Lyme disease is at the first sign of symptoms. The challenge is that the symptoms of early Lyme disease are varied and frequently mistaken for other illnesses. The most typical symptom of early Lyme disease includes the bullseye rash; however, this bullseye rash is present in a little over half of Lyme infections. The other symptoms of early Lyme disease are typically flu-like—fatigue, fever, and headache. Thus, early Lyme disease can be very difficult to clinically diagnosis by physicians who are not Lyme disease specialists.

The current diagnostic for Lyme disease is called the two-tiered test, and it does not directly detect Lyme bacteria but, rather, looks to see if the patient's immune system has developed antibodies against the bacteria.

There are three main problems with the current two-tiered test. The first is that it can take a Lyme patient 3 weeks or more after its infection with Lyme disease bacteria for the immune system to

develop enough to test positive. Thus, treatment could be delayed during the critical early period of the infection.

The interpretation of the two-tiered test results can be subjective, with essentially the same test from the same patient being performed by two separate labs reporting opposite results.

Thirdly, once a person has had Lyme disease, they will continue to test positive even after treatment due to the fact that the immune system remains active against the Lyme bacteria. Because of this fact, there is controversy over how much treatment is needed to cure Lyme disease, with some physicians recommending antibiotic treatment for a couple of weeks, with other physicians recommending treatment with antibiotics for months to years.

At Abbott Labs' IBIS division, we have applied our technology to detect a wide range of tick-borne pathogens based upon the detection of the pathogen's DNA, or directly looking for the pathogen's DNA. The challenge of Lyme disease tests is that there is very little Borrelia bacteria and its DNA circulating in the bloodstream of patients with early Lyme disease, making a sensitive direct assay very difficult.

To address this challenge, we have worked to improve the sensitivity of our Lyme assay by several means. First, we employ an assay that consists of eight independent tests for the Lyme disease-causing bacteria. This way, we have eight chances of finding the bacteria's DNA in the blood. Secondly, we use a very large volume of blood in the test, thereby increasing the chances of finding the bacteria in a given specimen.

And, thirdly, we employ a technique to increase the bacteria's DNA in the specimen. Initial results of this approach have been very, very encouraging. In a recent study of 21 patients with confirmed early Lyme disease, we detected Lyme disease in 62 percent of those patients' blood specimens at their first doctor's visit. We believe this work demonstrates it is possible to develop sensitive and direct tests for Lyme disease. However, there is a great deal of work needed to make this test suitable for use in clinical diagnostics.

Another area of interest for us and research has been looking at variations in the bacteria. Many pathogenic bacteria come in various strains, and these strains may determine the type and severity of disease that they cause. For example, E. coli comes in many strains, many of which are harmless but others that can cause serious illness. Worldwide, we have identified over 100 different strains of Lyme disease-causing bacteria in ticks. Knowing the roles of these strain differences may be important to knowing the potential types of Lyme disease to look for and how best to treat the infections.

There are three areas that we think are needed to fill the gaps. We believe we need more government research and funding in three key areas.

First, we believe that we need research and development to make a sensitive test that can directly detect the Lyme disease-causing bacteria. Such a test would enable detection of Lyme disease earlier in the infection before the bacteria are able to spread throughout the body. Such a test would then also enable the physician to monitor the responses to treatment.

We also need a better understanding of the roles and causes of post-treatment Lyme disease. Why don't the symptoms resolve following treatment for a large and significant number of Lyme disease patients? And, again, we believe a sensitive direct diagnostic may be instrumental into understanding the causes of these symptoms.

Lastly, many pathogenic bacteria come in these various strains and types, and we need increased research into the roles of the Borrelia strain differences in Lyme disease in humans.

Mr. SMITH OF NEW JERSEY. Thank you so very much, Dr. Eshoo.

[The prepared statement of Mr. Eshoo follows:]

Subcommittee on Africa, Global Health, and Human Rights
Christopher H. Smith (R-NJ)
Global Challenges in Diagnosing and Managing Lyme Disease—Closing Knowledge Gaps

July 17, 2012
Room 2172 of the Rayburn House Office Building

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The Need For Better Diagnostics For The Direct And Early Detection Of Lyme Disease And Other Tick-Borne Illnesses.

Lyme disease, caused by the tick-borne bacteria *Borrelia burgdorferi*, is the most commonly reported vector-borne infectious disease in North America. The number of yearly cases reported to the CDC has steadily increased since 1982 when case reporting began, with 20,000-30,000 cases now reported each year [1,2]. It is estimated that in endemic areas of the United States the disease is underreported. In addition, Lyme disease is also endemic to Europe and Asia. Other tick-borne illnesses, such as the protozoan parasite *Babesia*, are found worldwide, and in many parts of the world, such as Africa, Babesiosis is frequently mistaken for Malaria. In regions with Lyme disease other tick-borne pathogens are typically present leading to the risk of co-infection with Lyme disease.

Early Lyme is the period of time immediately following infection when the first symptoms of Lyme disease occur. If promptly diagnosed and correctly treated, outcomes for early Lyme disease are generally considered to be excellent. However, if undiagnosed and/or untreated, Lyme *Borrelia* can cause long-term chronic infections with the bacteria spreading to parts of the body such as the nervous system, the joints, or the heart where they can cause serious illness with the potential for long-term damage to the infected individual. As a result, infection with Lyme *Borrelia* can result in a wide range of disease symptoms and corresponding treatments, **Figure1**. To prevent these serious consequences of infection, Lyme disease is best treated early: at the first sign of Lyme symptoms. The challenge is that the symptoms of early Lyme infection are varied and frequently mistaken for other illnesses. The most typical symptoms for early Lyme disease include the Bull's eye rash also called eyrthema migrans (EM). However, these Bull's eye rashes are present in only a little over half of the Lyme infections[3,4]. Furthermore the Bull's eye rashes can be quite varied in their presentation so that the typical family physician may not recognize them as being Lyme disease even in endemic areas. Other symptoms of Lyme disease are typically Flu–like: fever, fatigue and headache. As a result early Lyme disease can be difficult to clinically diagnose by physicians who are not Lyme disease specialists.

Due to highly variable symptoms of Lyme disease and the benefits to treating the infection early before the bacteria can spread to other parts of the body, a diagnostic is needed that can detect the bacteria during the critical early part of the infection. As many patients, even after treatment, continue to suffer from a variety of Lyme disease symptoms, a diagnostic is also needed that can show that the infection has responded to the treatment.

The current diagnostic for Lyme disease does not test for the Lyme *Borrelia* bacteria directly, but rather looks to see if the patient's immune system has developed antibodies against the Lyme *Borrelia* bacteria (the two-tiered serological test). The two-tiered serological test looks for *Borrelia* antibodies in the patient's serum. There are several problems with the two-tiered serological test.

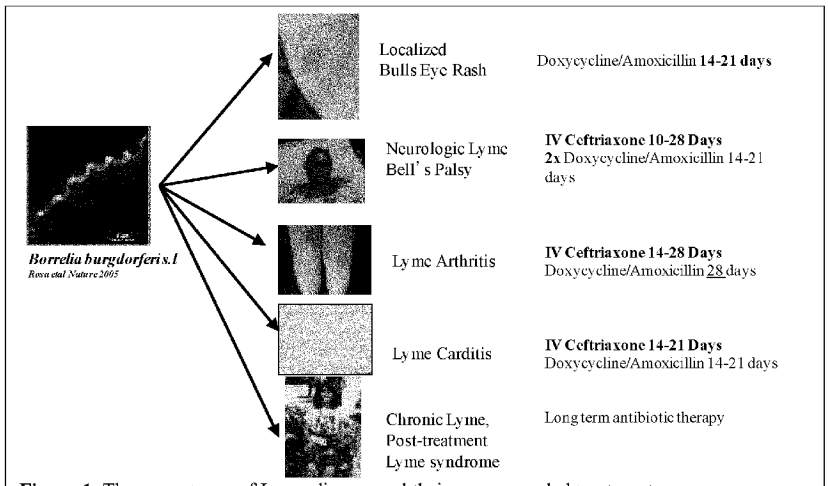

Figure 1. The many types of Lyme disease and their recommended treatments.

For most Lyme patients it can take three or more weeks of infection with the Lyme *Borrelia* bacteria for the immune system to develop sufficient response to test positive by the two-tiered serological test, thus treatment could be delayed during the critical early period of the Lyme infection and lead to the infection spreading to more sensitive and harder to treat parts of the body such as the nervous system or the joints.

Secondly, the interpretation of the two-tiered serological test results can be subjective with essentially the same test from the same patient being performed by two separate testing labs reporting opposite results. Results of this can lead to the treatment of patients who may not have Lyme disease but rather suffer from other illnesses.

Thirdly, once a person has had Lyme disease they will continue to test positive even after treatment due to the fact that the immune system remains active against the Lyme *Borrelia*

bacteria long after the infection has been cured. As a result there is no test that can show that the treatment for Lyme disease has cured the infection. Because of this fact there is controversy over how much treatment is needed to cure Lyme disease with some physicians treating with antibiotics for a couple of weeks while other physicians recommend treatment with antibiotics for months to years. Overuse of antibiotics can contribute to antibiotic resistance and may put the patient at risk for opportunistic infections, such as fungal infections, *Clostridium difficile*, etc.

The ideal diagnostic test for Lyme would directly detect the Lyme *Borrelia* bacteria in the blood from a patient while they were still early in the infection and identify active infection prior to the development of antibodies. Direct molecular tests for the Lyme *Borrelia* bacteria, such as those employing the polymerase chain reaction (PCR), look for the DNA of the bacteria and thus are not dependent on the patient's immune response. Furthermore, a direct molecular test by virtue of detecting the Lyme *Borrelia*'s DNA will only test positive while the bacteria are present, thus having the potential to be used to measure response to antibiotic treatment.

However, in the past, PCR based tests for Lyme disease have suffered from too low a sensitivity for their clinical use. This is due to the fact that there are very few Lyme *Borrelia* bacteria circulating in the blood stream in patients with Lyme disease. Importantly, this does not mean that there are NO Lyme *Borrelia* bacteria circulating in the blood stream. Studies have shown direct molecular detection of *B. burgdorferi* by PCR can be enhanced by culturing the blood specimen in growth medium prior to testing for Lyme *Borrelia* by PCR. This finding indicates that there is the presence of Lyme *Borrelia* bacteria in the bloodstream but that it's below the limits of detection by PCR [5]. In the past, direct PCR based assays for Lyme disease did not have the benefit of current advances in sample preparation [6] or DNA amplification techniques that could enable the detection of the very low levels of Lyme *Borrelia* bacteria in the bloodstream.

We have previously applied our direct molecular test based upon broad-range PCR and electrospray ionization mass spectrometry (PCR/ESI-MS) for the detection of a wide range of vector-borne pathogens such as *Ehrlichia, Rickettsia*, Powassan virus, *Babesia, Anaplasma* and canine heartworm [7,8,9]. The basis of this detection and identification is a multi-locus broad range PCR followed by the determination of the mass of the amplicons using automated electrospray ionization mass spectrometry. From the masses of the amplicons, the numbers of DNA base pairs A's, G's, C's and T's in each PCR amplicon are determined. By analysis of the base compositions of amplicons from all primer pairs, the organisms present in the sample can be identified from a database of all known base count signatures and quantified [10,11]. This technique has the advantage of rapidly identifying pathogens, genotyping pathogens and can identify new genetic variants.

To address the need for a better and sensitive diagnostic test for early Lyme disease we have improved the sensitivity of PCR/ESI-MS by several means. First we employ an assay that consists of eight independent targets to test for the Lyme *Borrelia* bacteria. This way we have eight chances of finding the bacteria's DNA in the blood specimen. Secondly we use a larger volume of blood in the test thereby increasing the chances of finding the Lyme *Borrelia* bacteria in a given specimen. Thirdly we employ a sensitive DNA amplification technique prior to the PCR to increase the amount of *Borrelia* DNA to levels above the limits of detection of PCR. Initial results of this approach have been very encouraging. In a recent study of 21 patients with

serologically confirmed early Lyme disease we detected early Lyme disease in 62% of the blood specimens collected from the patients at their first doctor visit [12].

Many pathogenic bacteria come in various strains and the strain may determine the risk of exposure and severity of disease. For example there are many genotypes or variants of *E. coli*, many of which are harmless but some can cause serious illness. Similarly there is a wide range of *Borrelia* species and genotypes world-wide that can cause Lyme disease. Our sensitive direct molecular test also yields a genotype for the Lyme *Borrelia* bacteria. These genotypes represents genetics differences in the bacteria that can be used to better understand roles of genetics differences and the type of illness in humans. Knowing the role of *Borrelia* genotypes for human illness may be critical in knowing how best to treat the infection. For example here in the United States, we have identified over 80 different genotypes of Lyme *Borrelia* in ticks. However when we look at the *Borrelia* genotypes found in patients with Lyme disease we find a much smaller representation of genotypes. This finding suggests that some genotypes may be more pathogenic for people. Furthermore, some genotypes could be associated with what type of Lyme disease the bacteria might cause: neurological Lyme or Lyme arthritis. A better understanding of the role of *Borrelia* genotypes and illness could help to direct the physician on how aggressively to treat the infection.

What's needed, Where are the gaps?

We believe increased government funding and research are needed in three key areas.

1) We believe that we need sensitive molecular tests that directly detect the DNA of the Lyme *Borrelia* bacteria and are not dependent upon the immune response. These tests would enable detection of Lyme disease earlier in the infection before the bacteria are able to spread throughout the body. A direct molecular test would also enable the physician to monitor the response to treatment. Though we have demonstrated the feasibility of a sensitive molecular test for early Lyme disease more work is needed to improve the sensitivity further and to get such a test approved by the FDA.
2) Better understanding of the role and causes of post-treatment Lyme and an understanding of why a significant number of Lyme disease patient's symptoms do not resolve with treatment. A sensitive direct molecular diagnostic test may be instrumental to understanding the causes of these symptoms.
3) Increased research into the roles of *Borrelia* genotypes and Lyme disease in humans. Studies are needed from many geographical regions looking at the prevalence of *Borrelia* genotypes in ticks, skin biopsies of patients with Eyrthema migrans, and other forms of Lyme disease.

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Mr. SMITH OF NEW JERSEY. Pat Smith, if you would proceed now.

STATEMENT OF MS. PATRICIA SMITH, PRESIDENT, LYME DISEASE ASSOCIATION

Ms. SMITH. Thank you for the opportunity to testify on a problem I have seen blossom from a regional into an international issue.

Twenty-seven years ago, I saw the devastation in my school district caused by an unknown disease affecting staff and students. To educate myself and my fellow school board members, I had to contact a nearby naval base, although many of my inquiries were answered with, "That's classified."

The past 20 years, I have traveled the country, 15 as president of the all-volunteer national nonprofit Lyme Disease Association, listening to patients, scientists, doctors, and government officials. Through the perspective of Lyme, I have found that some individuals charged with public welfare have lost their focus. Instead of solving the problems of humanity, some have abrogated their responsibilities, affecting people worldwide.

Over time, I have heard Lyme called a housewives disease; a yuppie disease; hard to catch, easy to cure; heard patients referred to as hysterical, faking, crazy, paranoid, even antibiotic-seeking; and heard Lyme advocates portrayed as crazed know-nothings responsible for mass hysteria over Lyme. Many U.S. organizations and others in the world have been victimized in peer-reviewed literature by noted researchers who don't agree that Lyme doctors should be permitted to use clinical judgment in treating Lyme, attacking those who are working tirelessly to raise research and education funds for Lyme disease—that is, the advocates and the patients. Many patients confide to me they would rather have cancer.

CDC and NIH have awarded grants to many of the same people, some for studies that rely on the strict CDC surveillance criteria for inclusion, including the use of the faulty nonsensitive tests. Thousands of patients have questioned this practice, and they ask for studies which can provide solutions to their dilemmas as chronic Lyme patients: "My doctor won't treat me when I am sick"; "No one believes my children and I are sick." A common refrain is, "Why isn't the government doing anything about Lyme?"

NIH funded several treatment studies, and the broad-brushed conclusions put a nail in the coffin of Lyme patients. One could possibly conclude from the studies that the specific treatments used by the study participants over the length of the study were not effective for the restrictive populations chosen for research purposes. However, instead, the conclusions became: No long-term treatment is effective for anyone with Lyme. Many doctors in mainstream medicine who had treated Lyme to date now turned a blind eye and a deaf ear to patients with Lyme.

The CDC Lyme surveillance system is in shambles. CDC criteria have become stricter, reducing the patient pool for reported cases. Lyme surveillance is very labor-intensive, including calling doctors to verify case reports. And human resources have been cut, forcing States to institute cost-savings measures involving changing case reporting methods, affecting national and regional numbers.

Officials continue to declare there is no Lyme in the South or the Midwest. And reasons given for that stance range from: "There are

no deer ticks in the South; if there are deer ticks there, they are not infected with Lyme because there are no reservoir hosts in the South," and those are small mammals that carry Lyme bacteria and transmit it to the ticks who infect people. "Deer ticks in the South feed on lizards, which do not transmit Lyme bacteria to ticks." "Deer ticks in the South behave differently." And, really, my favorite, "And deer ticks in the South do not bite people."

Scientific studies do not support those conclusions, yet many physicians still refuse to diagnose and treat Lyme in the South, forcing those patients to seek medical treatment in endemic areas of the country, adding to the already-overburdened medical practices there.

Compounding the problem, the very strict Lyme definitions, meant for surveillance only, are abused by mainstream medicine, insurance companies, pharmacists who won't even fill prescriptions for Lyme patients, and even public officials who are charging moms with Munchausen's-by-proxy. And believe it or not, in this day and age, they are taking away their children. And what is their crime? Having a licensed doctor prescribe an antibiotic for their children's Lyme.

On its Web site, CDC disclaims any responsibility, stating its criteria are for surveillance only. But its actions belie that position. CDC openly endorses IDSA guidelines, which are featured on its Web site—guidelines written by researchers, not clinicians who care about patient outcomes. For example, the IDSA guidelines recommend against any long-term treatment with antibiotics, they recommend against any alternative treatments, and they recommend against any supplements for Lyme patients. And patients have no treatment options open to them under these guidelines, even if they can find a doctor who is willing to treat under the threat of license removal for exercising clinical judgment in treating Lyme.

The CDC criteria form the basis of the IDSA guidelines. Intertwined, inseparable, like strands of a rope, they form a noose around the neck of Lyme patients, sometimes leaving them to die a very slow, painful death without medical treatment.

Even in death there is no rest for the Lyme victims and their families. A published study examined 114 death certificates listing Lyme as a cause, and the researchers concluded—and I have to quote this—"Most terminal events listed on death certificates for which Lyme was the underlying cause of death were inconsistent with the well-characterized complications of Lyme disease," leaving only one death record standing as Lyme disease—a conclusion, by the way, they reached without even conducting medical chart reviews.

Researchers have concluded Lyme causes more pain and suffering than osteoarthritis, myocardial infarction, and Type 2 diabetes. But they still have not let patients have any recourse, denying any clinical judgments in patients who otherwise have no treatment options.

Since Lyme often affects more than one family member and those at the highest risk are our children ages 5 to 9, mothers often have to forgo their own treatment to save their children. And these same moms are then accused of Munchausen's-by-proxy, a controversial

diagnosis which blames parents for making their own children sick. I have advocated for patients and children whose schools accuse them of faking illness, despite reputable research showing a drop in IQ of 22 points in children with Lyme rectified by antibiotic treatment. I have mourned with those families whose children committed suicide after leaving notes which said no one believed them to be sick and they could not bear the pain of the disease and the rejection.

And in conclusion, I want to say that this hearing has provided a public forum for Lyme issues to be discussed before an impartial audience with the ability to initiate and implement changes. Whatever our differing viewpoints today, we all came to testify to be part of that solution. I came today as a grandmother of four, trying to protect my granddaughters and others against the agonies of Lyme experienced by two of my very own daughters.

Yet, as I look around the room, I notice the absence of the key players in Lyme—CDC, NIH, IDSA—who were invited to be part of the solution. Instead, they chose consciously to remain part of the problem—at the least, abrogating their responsibilities; at the worst, violating a basic tenet of medicine: First, do no harm. They need to be brought to this table with patients, advocates, and treating physicians, who have before this time been locked out of the process, so that patients who suffer from Lyme can find treatment and the millions of potential victims worldwide can be spared the medical and political debacle we call Lyme disease.

Thank you.

Mr. SMITH OF NEW JERSEY. Ms. Smith, thank you so very much for your advocacy as well as your testimony here today.

[The prepared statement of Ms. Smith follows:]

House Committee on Foreign Affairs,
Subcommittee on Africa, Global Health, & Human Rights
July 17, 2012

Patricia V. Smith, President, Lyme Disease Association, Inc. (LDA)
www.LymeDiseaseAssociation.org

Overview of the Patients and Physicians in the US & Abroad in Managing Lyme Disease: Why Patients Worldwide Can't get Treated

HISTORY: From its murky beginnings 37 years ago to the present day, Lyme disease has presented researchers, clinicians and patients with innumerable challenges medically and politically. Lyme was first thought to be caused by a virus by someone who was later dubbed the "father of Lyme disease," rheumatologist Dr. Allen Steere, and some people thought it was something that did not require treatment. After continued research, he dubbed the condition Lyme arthritis, after the town in Connecticut where the investigation was triggered by a mother, Polly Murray, whose children were diagnosed with rheumatoid arthritis.

In 1982, noted National Institutes of Health (NIH) researcher Dr. Willy Burgdorfer published his studies of isolating the bacterium which causes Lyme disease, *Borrelia burgdorferi (Bb)*, which now bears his name. Much later, the disease was shown to cause cardiac and neurologic symptoms which required longer term treatment.

By the late 80s, some of the original researchers were postulating that Lyme disease was a persistent infection with considerable degree of complexity, producing varied multi-systemic symptoms which were not always eradicated by a short course of antibiotics.

But as research continued and funding dollars mounted up, researchers began to take sides, and the disease that was thought might be an arthritic disease, then also became a neurologic disease. At first they thought it required short-term antibiotic treatment, then longer-treatment for what they were now considering might be a chronic bacterial infection. In a still unexplained twist, researchers who had been concluding that the disease was a chronic infection seemed suddenly to do an about face in the very late 80s. Their description of Lyme became more narrow, fitting mostly people in the Northeast and portions of the upper Midwest, and patients who had been diagnosed with Lyme were finding they could no longer get treated, their symptoms did not fit a narrow enough criteria. Meanwhile, in spite of that narrowing view, cases in the US began to rise. In Europe, other strains of the bacteria were causing a rise in cases. The controversy which developed has followed the disease wherever it has spread, to now approximately 65 countries.

LYME PARADIGMS: In Lyme disease, there are two distinct disease paradigms, each providing science to support its claims. One paradigm (IDSA) views the disease as ``hard to catch and easy to cure" and denies the existence of chronic Lyme disease—persistent infection with *Borrelia burgdorferi*, the spirochete that causes the disease. Under this paradigm, the state of the science for patients with chronic Lyme disease is closed. Any treatment is considered too risky because practitioners are unable to determine the cause or extent of patient symptoms, or they view the subjective symptoms as insignificant and write off the patients' complaints as psychiatric in nature. This leaves seriously ill patients without any viable therapeutic avenues. It also shuts the door on future research necessary to get patients to a state of wellness.[1] Much of mainstream medicine, especially many rheumatologists and the Infectious Diseases Society of America (IDSA) have been taught that viewpoint, although a growing number of these doctors are beginning to recognize that patients continue to be sick or relapse after short courses of treatment for Lyme disease.

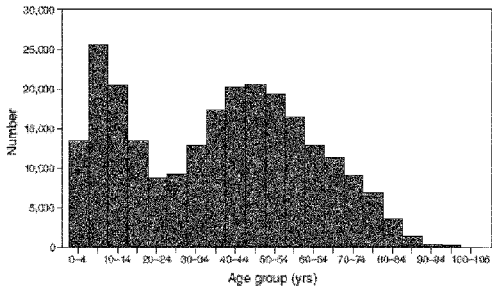
The alternative paradigm (ILADS) says that the science is too unsettled to be definitive, and there can be one or more causes of persistent symptoms after initial treatment in an individual who has been infected with the agent of Lyme disease. These causes include the possibility of persistent infection, or a post-infectious process, or a combination of both, with the Lyme bacterium itself driving the autoimmune process. This paradigm allows doctors the ability to exercise their clinical judgment and

provide therapies that are helping their patients. [2] This disease paradigm is held by some researchers, the International Lyme & Associated Diseases Society, (ILADS; doctors throughout the world who treat patients with chronic Lyme disease) and most Lyme-related organizations, including the national non-profit Lyme Disease Association, Inc. (LDA), and patients.

US CASE NUMBERS: Lyme disease statistics do not support the "hard to catch and easy to cure" version of Lyme disease. The Centers for Disease Control & Prevention (CDC) numbers themselves are underreported by a factor of ten.[3] In 2009, CDC's Morbidity and Mortality Weekly Report (MMWR) showed Lyme to be the 7th highest reportable disease per 100,000 of population at 12.71, higher than HIV at 12.13. Only sexually transmitted diseases, salmonella, strep, fungal disease, and the flu had higher incident rates.[4] Children are at the highest risk of acquiring Lyme disease according to CDC **(CDC-Fig.1)** and case numbers continue to rise, with CDC adding a "probable case" category **(CDC Fig. 2)** to count those who do not fall into the limited "confirmed" case definition (1995-2009).[5]

Centers for Disease Control & Prevention, CDC-Fig. 1

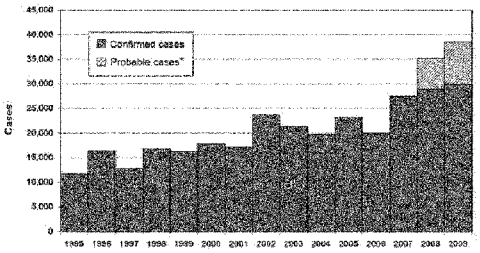
FIGURE 3. Number* of reported Lyme disease cases, by age group — United States, 1992–2006

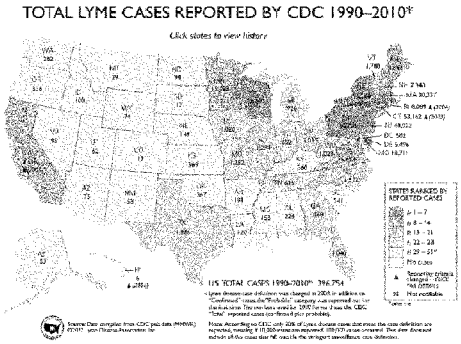


*N = 241,931.

Centers for Disease Control & Prevention CDC-Figure 2

Reported Lyme Cases 1995-2009





Lyme Disease Association LDA-Fig. 1

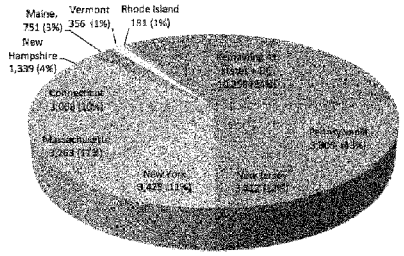
Lyme disease is often considered a problem only in the Northeast, and this perception frequently leads to patients' inability to be diagnosed and treated, as doctors and health officials sometimes deny that Lyme is present in their area, because little or no studies have been done in those areas.

The LDA has compiled case numbers on a US map **(LDA-Fig. 1)** using CDC reported cases from 1990 through 2010. (A user can click on each state and see a history of the numbers in that state on www.LymeDiseaseAssociation.org).

Additionally, LDA designed a pie graph **(LDA-Fig. 2)** which shows the percent of Lyme disease CDC-reported case numbers in nine Northeast states (66%) compared to the rest of US (34%) in 2010. Using the same comparisons in 2008, it was Northeastern States (76%), rest of US (24%). Lyme is not just a problem in the Northeast, although patients in other regions are often mistakenly told that when they get a tick bite and try to get diagnosed or treated.

Lyme Disease Association LDA-Fig. 2

2010 Lyme Disease % in Northeast States (66%) Compared to Rest of US (34%)



CHANGES IN REPORTING BY STATES: Besides the huge under-reporting, the numbers do not reflect the real prevalence of the disease for other reasons. States must use the CDC's surveillance criteria to have a case included for reporting purposes, but they can use various methods to report, which skewer state and national numbers, leading to a paper drop in case numbers which influences public policy, e.g., monies, and diagnostic and treating issues.

Connecticut (CT), which had been generally number 1 or 2 in reported case numbers nationally until 2002 with 4,631 reported cases, removed Lyme as a laboratory reportable disease in 2003, leaving only physicians to report disease cases. That year, CT reported a 70% drop in case numbers compared to the prior year. Over a three year period, 2003-05, without mandatory lab reporting requirements in place, CT's reported cases totaled 4,561— 70 cases lower than the single 2002 year total, the last year lab reporting was mandatory. [6]

CT's rationale for changing the reporting was lack of funding to verify the growing numbers of cases that are being reported. The State told concerned residents that it would be restored when electronic

reporting was instituted. In 2007, electronic reporting commenced; however, not all labs have the capability to report electronically, especially the smaller specialty labs which often receive samples from doctors treating Lyme disease patients, so the reported numbers never rose to original levels. According to then CT Attorney General Richard Blumenthal in a CT Lyme hearing in January 2004 (C-p.268), "…This disease now is prevalent, it's off the charts." … "But we still need the charts to do the counting because we won't know whether we've made a dent, let alone real significant progress in fighting it." Now US Senator Blumenthal continues to pursue the Lyme issue, sponsoring S-1381.

New York State (NYS) has traditionally been #1 in reported cases nationally for many years, and Pennsylvania (PA) now has moved to the top. Are NYS cases declining? No, but in 2010, seventeen New York counties investigated a sample of positive laboratory results, and the number of cases was extrapolated to generate estimates for total case numbers for those counties.[7] The 2010 number of CDC-reported cases for NYS (including NYC) was 3,425. NYS itself reported 6,316 Lyme cases including those 17 estimated county numbers. Why this dichotomy in case numbers between State and Federal Lyme reporting? The Council of State & Territorial Epidemiologists (CSTE), charged by Congress with surveillance, does not permit inclusion of estimated numbers to be reported in the CDC counts. Thus, NYS reported 6,316 Lyme cases including those 17 county numbers by State count, but CDC only reported a total of 3,425 Lyme cases for NYS.

Several states, including Maryland are moving in the same direction due to the labor intensive Lyme reporting system. They are "exploring alternative data sources, such as billing code datasets to serve as a source of Lyme disease case information." [8]

Last week, Wisconsin (WI), which had moved to #3 nationally in 2010 cases, announced that starting this summer, health officials are no longer required to investigate or report Lyme cases unless the patient has the characteristic bull's-eye rash. The bull's eye has been shown through research studies to be present in less than 50% of cases. Sometimes no rash develops, other times a different type of rash may occur. [9] WI still requires doctors and laboratories to report all positive test results to local health departments, but departments won't have to pursue cases if there is no rash.[10] WI cited increasing cases of whooping cough (WC; considered cyclical outbreaks in WI) on which they could now concentrate. In 2011, WC reported cases in WI were 1,192, while comparably reported Lyme cases were 3,609.[11] Lyme patients there are concerned that loss in Lyme case reporting will cause a further loss of focus on diagnosis and treatment, which many travel out of state for now.

In 2005, the Rhode Island (RI) Department of Health no longer prompted health care providers to report cases in response to positive lab reports.[12] RI numbers were artificially lower in 2005. Although RI had made some internal changes to its reporting system, it quickly understood the negative significance of the changes and promptly rectified its methods. [13] RI generally ranks at the top in incidence of Lyme in the US.

At the 2012 International Conference on Emerging Infectious Diseases organized by the CDC, CSTE, World Health Organization and others, a study was presented showing that in Maryland (MD), 4,768 Lyme case reports were in the 2009 state database; 2,029 (43%) were "Confirmed" or "Probable." However, local health departments (LHD) in MD did not enter an additional 5,722 Lyme disease reports in the state database that year. Seven (29%) of the LHDs lost Lyme surveillance staff in the past 2 years; one lost all staff and does not currently investigate Lyme. In 2008, 16 (75%) LHDs investigated each Lyme report, while 5 (21%) investigated only if sufficient laboratory evidence of infection.

In California (CA) in September 2005, laboratory reporting of Lyme disease was made mandatory by the Department of Public Health (DPH), because Lyme advocates were seeking legislation to make

changes and DPH did not want that to happen. CA Lyme case numbers went from 32 cases in 2004 to 174 cases in 2006.[14] With the exception of CA, these examples indicate that when states experience high numbers of reported cases, they devise methods which lower case reporting, affecting their own and national numbers.

SURVEILLANCE CRITERIA: Surveillance criteria are narrowly defined to compare "apples to apples" in the field. Clinical treatment criteria are broader to ensure that patients who are sick are able to receive care. CDC surveillance criteria by the current CDC/CSTE definition are as follows: Confirmed Case: A case of *erythema migrans* (EM) >= 5cm with a known exposure. A case of EM with laboratory evidence of infection and without a known exposure. A case in a patient with at least one late manifestation that has laboratory evidence of infection.

As mentioned earlier, less than 50% of people who develop Lyme disease get a bull's eye rash, and those who do may be in an area not considered to have Lyme (non-endemic, no known exposure). One can test negative and still have Lyme disease, and the CDC has tightly regulated what types of tests can be used, thus an antiquated serologic test such as the ELISA is used for the original screening for Lyme even though it is less than 50% sensitive. It may take 4-6 weeks or more for antibodies to build up to a testable level. Even when they do, research has shown that the antibodies often combine with the antigen, the protein on bacterial cell that stimulates antibody production, and the commercial ELISA test can only test for free antibody. Thus, one can test negative and still have Lyme disease.[15] If the test is negative and you do not have an EM rash, doctors will not proceed to the next test, the Western Blot (WB). If they try to proceed with a negative ELISA, some labs refuse to run the test, and often insurance companies will not pay. If the patient does have a positive ELISA, according to the 2-step testing process, the doctor should order a WB for confirmation purposes.

In a Dearborn, MI, 1994 meeting, the CDC decided that only a certain number of bands would be allowed to be used to determine a positive WB test for Lyme. "In a Western blot, the testing laboratory looks for antibodies directed against a wide range of Bb proteins. This is done by first disrupting Bb cells with an electrical current and then "blotting" the separated proteins onto a paper or nylon sheet. The current causes the proteins to separate according to their particle weights, measured in kilodaltons (kDa)."[16] There were researchers present who disagreed with the decision to exclude certain bands they felt were indicative of Lyme, and there was dissention on the floor.[17] According to treating physicians, two of the bands that were not included, the 31KD (OSP A) and 34 KD (OSP B) bands, are often found in chronic Lyme patients and the 31 and 34 are specific for Bb. By scrapping those bands and others, many patients remain undiagnosed and untreated as they may have 5 out of 10 bands, but 2 of the 5 may include the 31 and 34 bands which are not counted in a CDC positive.[18]

There are indications that the bands were only scrapped because a vaccine was in the pipeline,[19] and there was concern that tests would not be able to distinguish between a vaccinated and unvaccinated individual, since positive IgG results on Bands 31 or 34 may occur after vaccination in otherwise uninfected people. A person could be asked if he/she had been vaccinated. The only human Lyme vaccine has been off the market for more than 10 years now. Physicians, researchers and advocates have fought to include additional bands in the criteria as so many people are not being counted as positive with current band limitations. Many people are unable to be treated even though they have significant species specific bands.

In 2007, the CDC in Ft. Collins, Colorado (CO) invited me to speak with its Vector-Borne Diseases Division about Lyme problems, and I expressed concerns that a decision on the bands made with then 13 year-old data was condemning patients to a life of debility. CDC assured me they had new data supporting that banding decision. I then requested copies of it, but it has never been provided, and now, to my knowledge, Western Blot test results are based on data that is 18 years old.

Although the CDC criteria are only surveillance criteria, most doctors refuse to diagnose outside these criteria and insurance companies refuse to pay. Thirty-seven years after Lyme was recognized, sick patients cannot get diagnosed and not be treated because of antiquated, unsubstantiated tests which may pick up 50% of cases. HIV was identified as the cause of AIDS in 1984 and the screening test was developed in 1985, and the HIV screening test has a sensitivity of ~ 99%. In 1982, *Bb* was identified as the causative agent of Lyme and the screening test continues to lack sensitivity 30 years later: "...studies conducted by the group responsible for Lyme disease proficiency testing for the College of American Pathologists (CAP) concluded that the currently available ELISA assays for Lyme Disease do not have adequate sensitivity to be part of the two-tiered approach of the CDC/ASPHLD, where only ELISA-positive samples can be tested by Western blotting. [20]

CHANGES IN REPORTING BY CSTE/CDC: Changes in federal reporting criteria also significantly influence the numbers and the perceptions about the geographic spread of Lyme disease. In 2008, the CSTE who defines the surveillance reporting definitions added new categories of Lyme reporting, "probable" Lyme cases **(see CDC-Fig.2)** and "suspected" cases. However, despite concerns voiced by LDA and ILADS at the CSTE meeting where definition changes were presented, CSTE adopted a definition that only "confirmed" and "probable" cases are able to be reported out, not the "suspected" case numbers, which may be maintained by the states themselves. New Jersey (NJ), which ranked #2 nationally in total case numbers in 2010, shows the suspected number of cases[21] in its own reporting: Confirmed 3,320; Probable 392; Total: 3,712; Rate 42.2; Suspected 2,895. How and if these "suspected" numbers are used by anyone is unclear, since they are not factored into the national picture, surprising since the only significant funding for Lyme in most states, federal funds, apparently is number or incident based.

According to an NIH report, "Setting Research Priorities at the National Institutes of Health," [22] disease burden data is given serious consideration during NIH deliberations regarding funding allocations. They indicate that other factors are also considered and that data can be difficult to gather and assess. But the NIH considers the following as it sets its research priorities: the number of people affected, the number of deaths that result, the extent of disability produced, the effect on quality of life and productivity, the economic and social expenses generated, and the importance of halting its spread. Assessing any one of these should begin with mandatory laboratory reporting.

LYME IN THE SOUTH/MIDWEST/CANADA: Other significant changes were made to the surveillance criteria, changes which have significant impact on patient care, especially in specific regions of the US. *Ixodes scapularis*, the black legged tick (deer tick). transmits the Lyme disease bacteria in most of the country, and *Ixodes pacificus*, western black legged tick, transmits the disease on the West Coast. Another tick, *Amblyomma americanum*, the lone star tick, transmits a disease that looks, acts, and is treated the same as Lyme disease, now called Southern Tick-Associated Rash Illness (STARI; which is not confined to the South and does not necessarily include a rash). It is also known as Master's Disease, after a Midwestern doctor/researcher, the late Ed Masters, who did much of the research on it. STARI often does, however, produce a rash virtually indistinguishable from the Lyme EM rash. There is no commercially available test to detect STARI.

Scientific controversy surrounds STARI, which many think is Lyme caused by a different strain of the bacterium, *Borrelia lonestari*, but since its discovery in the mid 90s, the CDC has not confirmed it as the causative agent. Lone star ticks have been shown to have now broadened their range from the deep South to as far North as Maine and Iowa. People are being bitten by this aggressive species of ticks, get sick with the Lyme-like disease STARI, and need treatment. There is no accepted test for STARI, and prior to the Lyme surveillance criteria changes in 2008, patients bitten by a lone star who developed the EM rash were treated with antibiotics just as they were with Lyme disease. Now, many

doctors refuse to treat these patients because they say there is no Lyme in the South and Midwest (No Lyme), and thus they cannot treat an EM.

Originally, reasons used by some doctors, researchers and the CDC for the No Lyme theory were that there are no reservoir hosts (small mammals that carry the bacteria and are fed upon by ticks which then pick up the bacteria and bite people), there are no deer ticks there, there are no infected deer ticks, deer ticks in the South behave differently, deer ticks in the South do not bite people, deer ticks in the South feed upon lizards, which do not transmit *Bb* bacteria to the tick. Research has debunked those assertions, yet the No Lyme mantra has been repeated so often that the doctors in those regions often refuse to diagnose patients, and health department officials continue to deny the obvious or count reported cases.

The same type of scenario took place in Canada, a country which like others throughout the world, often follows CDC guidelines. For many years, the LDA received communications from hundreds of Canadians desperately seeking medical help in the US and also political help to prove that deer ticks were in Canada, were infected with Lyme and other TBDs, were biting people, and were transmitting Lyme disease. In 2008, Lyme problems became so blatant there that the Canadian Public Health Agency and others funded a study creating Canadian risk maps for Lyme disease. [23] The Canadian government has now held conferences on Lyme, some of the speakers have been US CDC officials and US and Canadian Lyme advocates. According to Canadian Lyme patients and advocates, CDC opinions on Lyme disease are often cited by the Canadian government.

According to CDC, "known exposure" to Lyme means one having been (≤ 30 days before onset of EM) in a wooded brushy or grassy area (i.e., potential tick habitats) in a county in which at least two confirmed cases have been acquired or in which established populations of a known tick vector are infected with Bb. A history of tick bite is not required. The problem with this surveillance criterion is that it is skewered so that it is almost impossible for a county which has not been declared endemic for Lyme to get that declaration. Few of the areas which are non endemic have the personnel or resources to perform studies to prove the ticks are infected with *Bb*. Additionally, many of those areas are locations where doctors refuse to diagnose cases, so cases are not reported, equaling no endemic county status. Thus the No Lyme in the South and Midwest continues to be perpetuated, and people continue to be sick without getting any medical help in those areas. Besides the patients' dilemma, go without treatment and let the disease progress, or travel at great expense long distances while sick to see doctors in other areas of the US, this issue also presents a physician dilemma. In endemic areas, the small number of physicians willing to treat are already overwhelmed with patients from their own region, and the influx of patients from non endemic US areas and from international patients strains their practices. Because of the treatment controversy, few new physicians are willing to participate in treating patients.

CDC clearly states that surveillance case definitions establish uniform criteria for disease reporting and are not to be used as the sole criteria for establishing clinical diagnoses, not to be used for determining the standard of care necessary for a particular patient and not to be used for setting guidelines for quality assurance, and not to be used for providing standards for reimbursement. The reality is, doctors are inappropriately requiring CDC surveillance criteria to diagnose patients, doctors are using it to determine the standard of care, and insurance companies are using the criteria to deny reimbursement. Bottom line: due to 'surveillance only" criteria, patients cannot get diagnosed, treated or reimbursed for Lyme disease.

IDSA LYME TREATMENT GUIDELINES: A critical aspect of patients' inability to get treatment is the development of clinical guidelines based on the CDC surveillance criteria by the IDSA. With the apparent blessing of the CDC, IDSA has a set of Lyme treatment guidelines which call for absolute

reliance upon either the presentation of an *Erythema migrans* rash or positive serologic blood tests to diagnose Lyme disease. The Guidelines recommend severely limited courses of antibiotic treatment when either a rash or a positive test are present. They have taken the place of a longstanding policy of deference to the clinical discretion of the treating physician in both diagnosing and treating the disease. The IDSA guidelines fail to explain the scientific justifications for their absolute reliance upon the rash and current blood testing to diagnose the disease in light of the numerous studies and medical opinions concluding that the typical rash is either not discovered by or present in many infected persons and that the serologic testing methods recommended by the IDSA are inherently unreliable because they do not even remotely approach a dispositive level of accuracy. Widespread adoption of these guidelines by practitioners, insurers, and government entities has caused real and egregious harm to many patients by inhibiting physicians who otherwise would be free to clinically diagnose and treat this disease.

The LDA has a petition on its website addressing the IDSA guidelines and currently has about 42,000 signatures opposed to the guidelines: "These guidelines fail to meaningfully address the needs of patients with chronic Lyme disease, who are now relegated to the pile of diseases with unknown etiology, like CFS and FMS, and who are provided with only symptomatic relief, while the underlying infectious disease is allowed to progress unabated. ...Failure to address the underlying infectious disease etiology keeps these patients sick, which is inhumane and immoral. There are no chronic Lyme disease patient studies supporting symptomatic therapies, which presumably would be necessary for life at considerable cost to insurers and society. Moreover, the IDSA rejected out-of-hand the requests by patients and their treating physicians to participate in the guideline development process. No medical society should be able to dictate patient healthcare through exclusionary guidelines that ignore considerable scientific evidence and fail to meet the basic goal of medicine—to improve the quality of life of the patient." [24]

Bottom line, the guidelines recommend against any long term treatments, listing numerous specific antibiotic classes not to be given to patients with Lyme, they recommend against alternative treatments (which they list and are many of the treatments patients seek when they cannot get antibiotic treatment) and even recommend against supplements for Lyme patients. Recommendations from the CDC itself encourage patients to speak to their health care providers about treating symptoms of Chronic Fatigue Syndrome (CFS) with vitamins and other nutritional and herbal supplements,[25] yet IDSA recommends against the use of the same approaches for Lyme patients. IDSA develops hundreds of guidelines for diseases, and these Lyme guidelines seem to be the only ones that are so anti patient and draconian in nature, consigning patients to an existence with no options and not a life.

IDSA and others like to point out that there are other Lyme treatment guidelines which independently corroborate the IDSA guidelines, referring to the *Practice parameter: treatment of nervous system Lyme disease (an evidence-based review), Report of the Quality Standards Subcommittee of the American Academy of Neurology (2007)*, by the American Academy of Neurology (AAN). These AAN guidelines actually shared several of the same panelists including the lead author of the IDSA guidelines, Gary Wormser, so they really cannot be considered independent corroboration.

The European Federation of Neurological Societies (EFNS) published guidelines on the diagnosis and management of European Lyme neuroborreliosis in 2010 based on an internet search of practice parameters proposed by the American Academy of Neurology (AAN) and the Infectious Diseases Society of America guidelines (IDSA), which formed the basis for the recommendations. As would be expected, European guidelines recommend the same limited treatment as their counterparts (AAN, IDSA), 2 weeks of antibiotics for treatment of all stages of Lyme disease, with the exception of the late stage, peripheral neuropathy and *acrodermatitis chronica atrophicans* (ACA),appearing more often in European Lyme disease. Treatments for these conditions are up to 3 weeks of antibiotics. [26]

In the Lyme & Tick-Borne Diseases CME scientific conference for physicians jointly sponsored by the Lyme Disease Association and Columbia University, researcher CW Ang, MD, PHD from the Netherlands will discuss *Serologic tests for Lyme disease - how reliable are they?* His recent paper on testing presented to the European Congress of Clinical Microbiology and Infectious Disease on comparing different ELISAs and immunoblots from different labs concluded: "ELISAs and immunobots for detecting *anti-Borrelia* antibodies have widely divergent sensitivity and specificity, and immunoblots for detecting *anti-Borrelia* antibodies have only limited agreement. Therefore the choice of ELISA-immunoblot combination severely influences the number of positive results, making the exchange of test results between laboratories with different methodologies hazardous. The widespread availability of more specific and sensitive assays for the detection of *anti-Borrelia* antibodies will open the way for reappraisal of 2 tier testing system." [27]

The following data was reported in a 2009 survey of Lyme disease patients by LymeDisease.org (previously CALDA) which had over 4,000 respondents. Subsequently, data from the survey was published in HealthCare 2011.[28]

Only 16% of those responding were diagnosed within 4 months of becoming infected with Lyme. The remainder were diagnosed much later when Lyme disease is much more difficult and expensive to treat. It took more than 6 years for 35% of patients to be properly diagnosed.
Only 13% were diagnosed using the IDSA-recommended two-tiered Lyme testing approach. 20% were diagnosed by western blot using CDC criteria, and 42% were diagnosed clinically with supporting lab tests that did not use CDC surveillance criteria.
90% had difficulty or extremely difficulty obtaining treatment from a knowledgeable physician to treat Lyme disease. 51% had traveled more than 100 miles to obtain treatment and 53% had been forced to travel out of state to obtain care.
54% had been treated and failed treatment under IDSA protocols. A resounding 81% stated that they would not consider being treated under IDSA protocols.
More than 60% of respondents who failed to improve under IDSA protocols improved with additional treatment.
41% of patients were not able to afford the medical care they needed.
88% had to cut back on work, school and household activities. 50% either had to quit work or school due to illness and another 11% went from full time to part time work or school.
65% had to cut back or quit work or school at some point. (Johnson 2011)
28% were unable to work for more than a year. (Johnson 2011)
50% see 7 or more physicians before diagnosis. (Johnson 2011) **30%** travel 100 or more miles for treatment. (Johnson 2011)
84% were not diagnosed within 4 months.
Over 40% of patients report substantial improvement with additional therapy and approximately 30% report some improvement with additional antibiotic therapy
65% have had to cut back or quit work or school
25% of those with chronic Lyme disease have been on disability. (Johnson 2011) • 75% of those on disability have been for more than 1 year. (Johnson 2011) • 37% of those on disability have been for more than 5 years. (Johnson 2011)

Many doctors across the country and the world have adopted a universal attitude about Lyme patients and Lyme disease based in part upon these guidelines which they espouse in lieu of treating the patient. An example occurred in a meeting in the Northeastern US recently at a forum with federal and state officials. An infectious disease physician who is the director of a Lyme clinic described the patients he

saw in three categories: the first group he described as patients with fatigue and brain fog who were treated for years with antibiotics and not helped. He said they had been diagnosed with chronic Lyme disease, that current research does not support long-term treatment, so they focus only on treating symptoms with these patients and no focus on Lyme disease, but they keep "an open mind." The second group he described were those who had a "fear" of Lyme disease. They were anxiety ridden. They try to focus those people on protection measures to prevent future tick bites, such as clothing sprays and most go away "at least with information." The third group he sees have a positive test. This is more difficult, he opined, as the 2-step test for Lyme relies on immune response, there are mis-interpretation of tests and probably cross reactions, so there are a lot of false positives.

Those who heard his remarks were left with the impression that Lyme patients are either anxiety ridden people, people with vague symptoms who are not able to be treated for Lyme, or are those with a positive test who don't really have the disease anyway, and he did not provide anything of substance to back up his remarks. The characterization was very demeaning to patients and contributory to the problems patients face getting diagnosed and treated, and not one official present corrected that perception. Bottom line: the perception is that there is no real Lyme disease problem, just hysteria.

On a daily basis, the LDA and other patient groups across the country hear the same stories repeated, of Lyme patients being sent to psychiatrists rather than treated for Lyme, of parents (usually mothers) being charged with Munchausen by Proxy for having their children treated with antibiotics by a licensed physician for Lyme disease, of people with EM rashes being refused treatment, of people who have positive tests denied treatment, of children being labeled in school systems as fakers when they are out long term due to Lyme symptoms.

LYME IN CHILDREN: Children are at the highest risk acquiring Lyme disease. Just dealing with the usual childhood issues of growing up can be very stressful, now factor in the effects of a chronic disease which can physically, mentally, and emotionally disable that child. Lyme attacks the central nervous system, and there is a study out of Columbia University in New York, showing a drop in IQ of 22 points before a student is treated for Lyme disease and a return to normal after IV treatment for Lyme disease. [29]

Another study from Columbia on children with Lyme disease showed that they had significantly more cognitive and psychiatric disturbances. Cognitive deficits were still found after controlling for anxiety, depression, and fatigue. Lyme disease in children may be accompanied by long-term neuropsychiatric disturbances, resulting in psychosocial and academic impairments. Parents indicated that 41% of children with LD had suicidal thoughts, 11% had made a suicide gesture.[30]

Children, as well as adults, experience tremendous brain fog, pain, memory loss and confusion, seizures, and may miss months or years of school. My own daughter was out of school for more than four years, on home instruction. The isolation alone was emotionally hard. Additionally, we had to fight with the school to get her Advanced Placement courses as she was a gifted student, but she and the many other Lyme students like her, were often discriminated against due to the stigma of having Lyme. Fortunately, I was on the Board of Education and understood the laws, and I advocated for her and for students like her throughout the country. Schools did not (and often still do not) believe Lyme could produce such a problem, since their doctors tell them how easy it is to cure.

My daughter was able to go on and graduate from Johns Hopkins and be successful in life, others I worked with have not been that fortunate. Some children with Lyme have been unable to graduate, others did not survive the disease, and quite a few committed suicide. "In one New Jersey case, the child felt no one understood her Lyme disease problems. In another, a young man stopped his medications after a psychiatrist told him he did not have Lyme, it was all in his head. He could not bear

the pain from the disease." [31] An NIH-sponsored study found that the impact of Lyme disease on physical health status was at least equal to the disability of patients with congestive heart failure or osteoarthritis, was greater than those observed in type 2 diabetes or a recent myocardial infarction. Chronic pain was an important contributor to the impairment of physical health and was similar to that reported by patients with osteoarthritis. [32]

Many advocates have had to help US families deal with charges of Munchausen by Proxy, where a parent is charged with causing a child's illness— a diagnosis that has largely been disputed by many in the medical community.[33] Often the situation is complicated by split families, where the father is charged with providing funding for care and the mother is charged with custody. These fathers attempt to shirk their financial responsibility by refusing to pay for healthcare and charging the mother with Munchausen by Proxy.

There have been cases where the mother was taking the child to a licensed physician for treatment, and the father called child protective services. In some cases, that child and other children have been taken away from the mother on the basis of the mother getting a child treatment with antibiotics for Lyme disease. Congressman Smith once intervened in NJ to help a mother in such circumstances to keep her children. A surge in the United Kingdom of mothers being charged for the same reason followed a number of US cases. [34]

Many of the doctors who developed the Guidelines have vested interests in Lyme testing and Lyme vaccines, which was recognized after the then CT Attorney General (AG) Richard Blumenthal took legal action against the IDSA. According to AG Blumenthal's settlement announcement "My office uncovered undisclosed financial interests held by several of the most powerful IDSA panelists…The IDSA's guideline panel improperly ignored, or minimized, consideration of alternative medical opinion and evidence regarding chronic Lyme disease, potentially raising serious questions about whether the recommendations reflected all relevant science…. The IDSA's 2006 Lyme disease guideline panel undercut its credibility by allowing individuals with financial interests — in drug companies, Lyme disease diagnostic tests, patents and consulting arrangements with insurance companies — to exclude divergent medical evidence and opinion."[35]

IDSA members and colleagues also sit as reviewers for many of the most significant medical journals. They have authored articles that blame Lyme advocates and patients for "Lyme hysteria," for being against a vaccine, for giving out faulty scientific information, information published in peer review, (read scientific information with which they do not agree), and for supporting clinical discretion for treating physicians, which is a tenant ostensibly held by CDC. From the CDC website: "No surveillance case definition is 100% accurate. There will always be some patients with Lyme disease whose illness does not meet the national surveillance case definition. For this reason, CDC has stated repeatedly that the surveillance case definition is not a substitute for sound clinical judgment. Given other compelling evidence, a physician may choose to treat a patient for Lyme disease when their condition does not meet the case definition." [36] Despite that statement, CDC only has the IDSA guidelines on their website as diagnostic guidelines, the IDSA guidelines which basically use the CDC surveillance criteria as their basis.[37]

The IDSA guidelines contain a disclaimer that clinical discretion can be used. However, members of the IDSA have played a role in testifying against doctors who do not subscribe to the IDSA Guidelines viewpoint and who have been brought up on charges by medical boards for treating Lyme patients.

One of the only pediatricians in the country treating and helping children with Lyme disease return to health and to the classroom is in his mid 80's. He has seen children with Lyme 6 and 7 days a week due to their inability to get care anyplace else. The CT medical board has been actively pursuing 3

cases against him—the State opened by saying the case had nothing to do with Lyme treatment, then proceeded to call several "expert" witnesses in Lyme disease. [38] At the end of 2011, the Connecticut Supreme Court agreed to hear his appeal. The doctor has continued to fight the very costly legal battle and still practices, despite having to pay for monitoring charges.

Since 1990, doctors across the US and recently in Canada and Europe have had similar situations where they have been investigated related to treatment of chronic Lyme patients, often in a sham peer review process. Charges range from long term treatment of Lyme, too much testing, not enough testing, not following the standard of care (despite the fact they were following one of the two standards of care), use of alternative therapies. Many time patients did not file any of the complaints, and were very unhappy with their charts being pulled and used in the case. Penalties in the US have ranged from suspending or removal of licenses, continuation of practice but not allowed to treat Lyme, to records keeping fines, and monitoring.

New York has experienced a high number of doctors facing Lyme-related charges over time. Here is an excerpt from testimony from Andy Schlafly, General Counsel, the American Association of Physicians & Surgeons, to the *New York State Assembly, Committees on Health, Higher Education, and Codes. January 31, 2002:*

> We have many physician members in New York who feel pressured and intimidated to protect their own licenses by altering their care to patients. They are faced with the choice between avoiding the wrath of insurance companies and delivering the best possible care to their patients. This intimidation interferes with the ethical practice of medicine, and ultimately hurts patients.
>
> Physicians feel threatened because they have fewer rights than almost anyone else in a judicial proceeding. Physicians can lose their license based on very little proof, and inadequate due process. Physicians are vulnerable to manipulation of the process for economic reasons, rather than true concern for patient health. For example, we see unexplained targeting of certain types of physicians for discipline. Physicians who treat Lyme Disease are frequent victims of investigations, but not due to any complaints by their patients. Third-party payers, who find the aggressive treatment of Lyme Disease costly, have too much influence over the disciplining of a physician.

In the mid 90s when areas of particular states starting to see a rise in reported cases, suddenly the doctors who were treating Lyme long term in those areas were targeted by the medical boards and charts were pulled and investigations opened into long-term Lyme treatment. That greatly affected Lyme reporting, doctors were afraid to report, and even today doctors are wary of reporting cases due to investigations.

In some cases doctors with hospital privileges had pressure applied to them by the hospital in relation to treatment of Lyme. Some hospitals became Lyme unfriendly. When my own daughter seized for 3 years, I never took her to a hospital because we knew by then that they were admitting these children to psychiatric facilities, as they said Lyme does not produce seizures, and patients were not permitted Lyme treatment while there. The same thing has happened to adults, and many of those people have become productive with long-term antibiotic Lyme treatment.

Most chronically ill Lyme patients today will not allow themselves to be hospitalized, and if they are for any reason, they often neglect to tell the hospital of their Lyme diagnosis. Patients labeled with Lyme disease are treated as second class citizens, as hysterics, fakers, mentally ill. Hospital personnel themselves are often thirsty for Lyme information. When I took care of my mom with cancer, arthritis,

Lyme, stenosis, other issues, she was hospitalized 8 different times. I would sleep in the hospital in the chair in her room, because she was so fragile. I did my Lyme charity work by phone in her room, and often nurses and aides would suddenly materialize and ask if I were the "Lyme Lady" that they heard was in the hospital. They begged me for info for themselves or family members but would not tell others in hospital they had Lyme. I was careful to indicate I could not provide any medical advice but did provide them access to resources and educational information.

On one of my mom's stays, I saw an engorged tick hanging from her leg, I rushed to get the oncologist who was just leaving, and he looked at it and told me it was a mole. I said, well then, it is the first mole I have seen with 8 legs. He gathered all staff around and made me remove the tick, said he had no idea how to do it. They brought me all kinds of supplies and gathered around and were amazed when I pulled out the tick remover I always carry and pulled it right off. To his credit, he agreed to give her a course of antibiotics as it was a fully engorged tick.

On another hospital stay, my mom was having upper GI problems. Tests indicated she may have ulcers. For various reasons, the doctor prescribed a biopsy for *H. pylori*, a bacterium which had been finally acknowledged to cause ulcers. I asked her doctor if while they did that, could they biopsy for *Bb*, now shown to be found in lesions in the GI tract.[39] He saw no problem, told me to go down with my mom and tell the doctor doing it that he concurred. That doctor at first refused, told me he never saw anyone in his practice who had that, and I opined it is difficult to find something you are not looking for. He did the tests, and a few days later, he came into the hospital room all excited at his good news: no *H. pylori*. I said what about *Bb*? He said well, that takes longer, and they were sending my mom home, and I could get results later.

Days after my mom was at home, I called his office and he refused to speak with me. I finally said I would have my attorney call. Then the office said he told them if I wanted the results, I would have to call the lab myself and get the results! I called the lab and had to beg to just get them to tell me that, yes, a test had been done for her prescribed by Dr. such and such. I said there is some mistake; he is not my mother's doctor. The lab said, that is who is listed as ordering the test. I called the listed doctor whom I knew—a pediatric doctor who was practicing at the hospital and also doing Lyme research. The first thing he said to me before I said anything is, this is crazy, I just got in a positive Lyme result for an 80 year-old woman I never heard of, and obviously I never prescribed for, since I work with children. I said, that person is my mother. That other doctor used his name on the test, because he was too afraid to put his own there, and here my mother had a positive result, Bb in the GI tract, and I would have never known had I not pursued it myself.

Lyme organizations and patients agree that doctors need to adhere to standards and that medical boards have the right to investigate claims, however, in the case of Lyme, there has appeared to be a clear cut pattern of witch hunts. A treating physician was asked to testify before the Senate in the early 90s, which he did. Not long after his testimony, his state medical board began to pull his charts on Lyme disease patients. For years to come, he was continuously harassed by them, as those cases are never really closed, and you cannot confront your accuser. Most of the patients whose records were used were furious, as they had not filed complaints and even held a press conference to indicate that, and felt they were progressing nicely on their treatments regimens. After many years, while he continued to treat and faced staggering legal bills, he was given a slap on the wrist for some trivial charge. He was considered by treating physicians and many researchers, and patients worldwide (many who flew in to avail themselves of his expertise) as one of the most knowledgeable Lyme disease treating physician in the world.

LYME IN THE US MILITARY, HOME & ABROAD: A US Army Centers for Health Promotion & Preventive Medicine (CHPPM; now Public Health Command) report states that ticks are among the

most important of all arthropod vectors of disease. There are over 850 recognized species worldwide. Ticks rank second only to mosquitoes in the number of life-threatening and debilitating diseases they transmit to humans. In the United States, ticks are responsible for more human disease than any other arthropod group. Tick-borne diseases represent potentially serious health threats to troops, their family members, DoD civilian employees, and other residents at military installations in many parts of the world.[40]

According to the Armed Forces Health Surveillance Center report,[41] confirmed cases of Lyme disease in the services were diagnosed at more than 120 locations worldwide. Medical facilities at the following locations accounted for nearly one-half of the total: West Point, NY; Heidelberg, GE; Walter Reed Army Medical Center, Washington; Camp Lejeune, NC; Vilseck, GE; Landstuhl Regional Medical Center, GE; Naval Health Clinic New England (branch clinics in Newport, RI; Groton, CT; Portsmouth, NH; Brunswick, ME; Saratoga Springs, NY); National Naval Medical Center, Bethesda, MD; Fort Knox, KY; Andrews Air Force Base, MD; Fort Meade, MD; and McGuire Air Force Base, NJ. 2008 had nearly 3 times more confirmed cases than 2004.

At a blood products advisory committee meeting on Babesia in the blood supply, Dr. Jesse Goodman, M.D., Director of FDA's Center for Biologics, made the observation, "I will say I just finished a month of clinical attending at the Naval hospital in the summer, and I was actually fairly shocked by the number of cases of disseminated Lyme disease that we are seeing. So I think that the notion that we have control over tick-borne disease…we don't really have a good hand on how many cases of primary infection[Lyme disease] there are."42

The LDA and other advocacy groups including Military Lyme often hear from military personnel who have Lyme disease. Many of them have been unable to get treatment for themselves or their families, despite the fact that military installations were being mapped for Lyme disease risk as far back as the late 80s.

The Lyme Disease Association presented written testimony to the Defense Health Board on a Lyme disease agenda item, September 4-5, 2008. In part, LDA recommended that "the Board should change the Lyme diagnosis and treatment policy to allow treatment under both the IDSA standard of care and the ILADS standard of care for Lyme and for all tick-borne diseases. The use of surveillance criteria to restrict diagnosis/treatment should not be permitted. Military insurance needs to include such provisions…. The military are at high risk for Lyme disease and they require and deserve prompt diagnosis and treatment. If physicians used by the military are not knowledgeable about tick-borne diseases, personnel should be able to avail themselves of knowledgeable treating physicians without penalty to prevent further long-term implications of Lyme disease. Physicians should be encouraged to attend CME conferences on tick-borne diseases."[43]

Air Force aeromedical concerns may require flyers to receive a waiver to fly if they have Lyme disease. "The symptoms during primary Lyme disease, included arthralgias, fatigue, headache, neck pain and possible fever are obviously not optimal in the flying environment. As with all infectious diseases, if recognized and treated early with full resolution of symptoms, return to flight status is appropriate. However, if untreated, then aeromedical concerns of this disease are its debilitating effects in regards to the neurologic, cardiovascular, and arthritides that may result. Neurocognitive impairment, cardiac arrhythmias and arthritic pain are all manifestations that could impact the safety of the individual and mission." [44]

"LDA has spoken about Lyme disease on several bases and presented a 2002 educational briefing for military officials at a DC meeting arranged by then House Veteran's Committee Chair, Congressman Christopher Smith (NJ). LDA provided noted clinicians who educated military officials from all

branches of the armed services about chronic Lyme disease and the problems faced by Lyme disease patients.... Military doctors indicated they faced the same set of "political" problems in treating their Lyme disease patients.

LDA has been invited twice to US Army Centers for Health Promotion & Preventive Medicine (CHPPM) [*now Public Health Command], Aberdeen Proving Grounds, where...CHPPM has shared its extensive work on identifying tick-borne disease organisms in various ticks found on military installations nationwide. CHPPM discussed its mapping of military installations for risks of Lyme disease and its plan to eventually beam that information to satellites which then will convey it to handheld devices, alerting troops to the presence of ticks. CHPPM shared development of technology which enables it to test ticks in the field for any known disease agent, so that troops can be treated immediately if bitten by infected ticks. CHPPM has been both a speaker and exhibitor at LDA's annual scientific conference for physicians on tick-borne diseases–conferences jointly sponsored with New York's Columbia University. The LDA's 9th annual scientific conference in San Francisco Oct. 17, 2008, has a speaker from the Armed Forces Institute of Pathology who will discuss the pathology of Lyme carditis....[Lyme can also produce palpitations, heart block, and valve prolapse.]" [45] NOTE: LDA's 13th international conference is upcoming in Philadelphia in September 2012.

DEATH BY LYME: Although most bacterial diseases can cause death, the establishment has added that to its unending list of things Lyme cannot do, since in their opinion, it is hard to catch and easy to cure. Rocky Mountain spotted fever (RMSF), another tick-borne disease carried by different types of ticks, is considered by experts to be a disease with a relatively high mortality rate. I have never seen that claim disputed. The CDC in their MMWR reported deaths from RMSF and Lyme from 2002 to 2007, and both RMSF and Lyme had the same number of deaths listed, 36.

Even those who die from Lyme disease when listed as a cause of death on death certificates are not left to rest in peace. In 2010, researchers did a study published in Clinical Infectious Disease where they reviewed 114 death records from 1999-2003, which listed Lyme disease as an underlying or multiple cause of death. Researchers concluded that only 1 record was consistent with clinical manifestations of Lyme disease and concluded that Lyme disease is rare as a cause of death in the United States.

These conclusions were reached despite the following comments taken from the study "Most importantly, we did not conduct medical chart reviews. Therefore, we were unable to confirm or deny the diagnosis of Lyme disease or the causal sequence leading to death....Most terminal events on death certificates for which Lyme disease was the underlying cause of death were inconsistent with the well-characterized complications of Lyme disease and the rare published case reports of Lyme disease-associated mortality. Additionally, the underlying causes of death when Lyme disease was listed as a multiple cause of death varied widely and also were inconsistent with the well-characterized complications of Lyme disease." [46]

The universal story of Lyme patients: no diagnosis, no treatment, no insurance reimbursement, no compassion, and no dignity even in death.

SOLVING THE PROBLEM: The Lyme surveillance system needs to be revamped so accurate numbers are obtained. More education is needed on Lyme and other tick-borne diseases. A full research agenda needs to be developed with patient and treating physician input. The following comes from the Congressional Record and was submitted by the Lyme Disease Association (LDA), CALDA (now LymeDisease.org) and Time for Lyme (now Lyme Research Alliance). It clearly expresses the need for more practical research which will help Lyme patient get diagnosed and treated in a timely fashion and will lead to physicians finally being able to treat Lyme patients appropriately.

"Patients with Lyme disease need a research agenda that reflects outcomes that matter to patients, namely effective diagnostic tools and effective treatments that restore them to health. The reason there are two disease paradigms in Lyme disease is because central pieces of the puzzle are missing or are inadequate. The first area of concern involves testing.

There are no reliable biomarkers of the disease.\1\ Current diagnostic tests commonly used do not detect the spirochete that causes Lyme disease, rather, they detect only whether the patient has developed antibodies to the pathogen. Antibody production, if it registers on the tests at all, takes weeks to appear, thus rendering the current tests ineffective in the earlier and more easily addressed stage. Additionally, the Lyme antibody has been shown to form a ``complex" with the bacterium itself--and tests cannot detect ``complex" antibodies. Once triggered, antibody reactions may remain long after an infection has been treated, also clouding the diagnostic and treatment picture.

A vast number of strains of Borrelia burgdorferi have been identified. Variation in strain may cause differing symptoms or severity of symptoms as well as determine the appropriate antibiotics and duration of treatment needed to clear the infection.\3\ Different strains may also express different proteins. Preliminary research shows that proteins need to be examined to find the ones most often expressed, then using microarray technology, doctors may be able to diagnose patients using a chip which contains the proteins.

Research is needed concerning the role of mutation on persistence. Some research indicates that bacteria can exchange genetic material, probably contributing to its ability to invade different systems in the body--some may have a proclivity for the heart muscle, others for the brain, and some for muscles and joints. By exchanging genetic material, bacteria may be able to form a symbiotic relationship to avoid detection by the immune response or to further invade the body.

To date, every NIH-funded treatment research study has been designed using the inaccurate diagnostic test results as part of the entry criteria. The entry criterion in these studies excluded the vast majority of Lyme patients and created sample sizes too small (less than 220 patients to date) to detect clinically important treatment effects or generalize to the clinical population. Moreover, Lyme has not attracted industry funding for treatment approaches, which places the disease at a considerable research disadvantage. To detect clinically relevant treatment effects requires much larger treatment trials with sample populations that reflect those seen in clinical practice.\4\

Patients want research which will restore their health. Their voice and the voice of the clinicians must be given the necessary weight to legitimize the research agenda and the research process. Truth in science can be achieved through open debate in an independent process free from bias and conflicts of interest. The scientific process fails when one side of a debate controls the arena and sets the rules to ensure that its viewpoint prevails. [47]

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[2] *Ibid*

[3] Dr. P. Meade, CDC epidemiologist, (NJ) Herald News 5-4-04

[4] MMWR http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5853a1.htm?s_cid=mm5853a1_w

[5] CDC http://www.cdc.gov/lyme/resources/brochure/508_LD_Brochure.pdf

[6] Centers for Disease Control & Prevention Lyme Disease Cases by State 1993-2005

[7] *NY State Dept of Health*

[8] Maryland DHMH letter, JUNE 5, 2012

[9] R. Smith et al Annals of Internal Medicine 2002;421:421-428, 477-479 ; A. Pachner Reviews of Infectious Diseases-Vol. II, supplement 6 - September-October 1989 Neurologic Manifestations of Lyme Disease, the new "Great Imitator"; J.M. Johnson, Ph.D., Chief, Public Health, NPS Ticks and Disease
[10] Beloit Daily News 7-5-12 (online ed.)
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[12] RI DOH Office of Communicable Diseases, Health Advisory 7/20/05
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[33] DSM IV term: *Factitious Disorder by Proxy (FDP, FDbP)* (U.S., 2000) American Psychiatric Association, DSM-IV-TR
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[37] IDSA indicates Ixodes species ticks- CSTE does not indicate a tick species. CSTE requires a "physician" diagnosed EM"- IDSA does not mention that. CSTE says- Laboratory confirmation is recommended for persons with no known exposure. IDSA does not say that directly. CSTE includes radiculoneuropathy in its late manifestations. IDSA does not.
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47 September 29, 2010 Congressional Record PATIENT PERSPECTIVES ON THE RESEARCH GAPS IN TICK BORNE DISEASES, Submitted by Time for Lyme (Diane Blanchard/Deb Siciliano), the national Lyme Disease Association (Patricia V. Smith), and the California Lyme Disease Association (Lorraine Johnson) on behalf of our patients across the United States, read into the Record by Congressman Christopher Smith

Mr. SMITH OF NEW JERSEY. I would like to now invite Evan White to testify from New York City. His wife just gave birth last week, so we congratulate him on a blessed event. So, Mr. White, if you could begin now by way of Skype.

STATEMENT OF MR. EVAN WHITE, LYME DISEASE PATIENT

[The following testimony was delivered via Skype.]

Mr. WHITE. Thanks again for having me by video. It is appreciated. I have been an advocate for Lyme disease for over the course of 20 years, and my advocacy for Lyme disease is really borne out of a very tragic and unfortunate case of chronic Lyme disease that I was subjected to because of a doctor's insistence on providing me with limited antibiotic treatment. At the other end of the spectrum, I am well, and I am able to be here with you today because of conscientious doctors that have provided me with careful, long-term treatment.

Today I am a father, husband, practicing attorney, business owner, employer, and advocate for the rights of Lyme disease patients. Now, I mention that to illustrate a point, not to be boastful. My point is that were it not for this long-term treatment by a careful and conscientious Lyme physician, none of this would be possible. And I raise that to illustrate the fact that so many of our Lyme constituents do not have the benefits that I had. Certainly by comparison, if they did, my belief is that they, too, would be able to live fulfilling, recovered lives and be contributing members of society.

So my story has a happy ending. That being said, I am here to fight for the same for all of my fellow Lyme constituents. Obviously the nature of roadblocks and obstacles in achieving that for everyone are these outdated and unduly limited treatment guidelines that, you know, turn a blind eye to what we as patients and people in the Lyme community know as effective treatment.

My personal story is really a real-life case study to illustrate these points, that short-term antibiotic treatment can be absolutely devastating, and then long-term treatment, conversely, can reverse these effects sometimes. In fact, that is what we are fighting for.

Now, my story begins over 21 years ago in the fall of 1991 as an 11-year-old going on 12, going into middle school, when I began to all of a sudden miss several days of school due to flulike symptoms. Unlike with the other Lyme patients, my physician was able to diagnose me properly with Lyme disease. Unfortunately, we—like so many physicians today, that was met with the improper and catastrophic response of insufficient treatment and approximately a week, 2 weeks of antibiotic treatment.

Now, the response to my not recovering after 2 weeks was one that is very common and unfortunate in the Lyme community, and that was to recommend a treatment of physical therapy and psychological therapy. As I was taken off medication and persisted with that course of treatment, I noticed daily that my condition was deteriorating. I had placed my faith in these physicians and, as a 12-year-old, knew nothing else other than to trust my doctor.

Lo and behold, after 6 months the deterioration was so severe that I was really having great difficulty performing any activities. I certainly hadn't been to school; I hadn't even had any home

schooling. Even simple tasks like getting out of bed became virtually impossible.

When we turned back to the blood tests, my doctors were surprised Lyme disease was still very present along with other co-infections in my blood. What we had learned there is an example of the devastating impact of untreated Lyme disease, and one that is met with what represents the current suggested treatment.

This 6-month layoff from Lyme treatment sent me in tailspin. It was a virtual nightmare for myself and my family as my condition vastly deteriorated, and I was really transformed over the course of the year from an active, healthy, athletic child to one that essentially couldn't even care for myself. I was about 60 pounds. This treatment had caused me to experience great muscle atrophy, as well as neurological defects, so just a drastic, striking contrast in my life that was absolutely devastating. For lack of a better term, by the time I was age 13, I was essentially a vegetable.

Doctors were really baffled and confused by my condition, by the severity of it. Their only solution at that time was to place me full time in children's rehabilitational care. What had ensued, fortunately, for me afterward was the type of brain scan that revealed that this unfortunate medical treatment had caused Lyme disease to penetrate the blood brain barrier, causing hypoperfusion within my brain, and this offered some explanation, some insight into why I was unable to essentially take care of myself, essentially perform even the most basic functions like reading, talking, communicating, things like that. That being said, I was still surrounded by doctors who were totally confused and confounded and had absolutely no idea what condition I was suffering from or why.

Shortly, after spending about 2 years bouncing from hospital to hospital, 6 months in a children's institution, I was sent home to receive outpatient treatment. And right around that time my parents, who were incredibly dedicated to assisting me and helping me recover, were able to arrange for an appointment with a very prominent Lyme disease physician. This person essentially got it. When I met with him, I finally felt understood. I mean, this person had their own personal experience with the disease to bring to the table, not to mention a day-in, day-out practice and a repetition and seeing and treating patients with the disease.

Now, I had a long road ahead of me to recovery, but what had transpired there was really a turning point for me and for my life entirely. This physician was able to treat me, put me on a long-term treatment program, long-term antibiotics, coupled with therapy and other essential supplements that he recognized as necessary. And it was a 2-year crawl, but if it even were a 10-year crawl to get me out of that unfortunate place that I was in, that would be just fine with me.

Through hard work and attentive treatment from this doctor, I was able to stop using a wheelchair, get out of bed, be able to function, take care of myself. My neurological symptoms began to dissipate. I began to be able to read, and communicate and converse. This was a very slow and long process, but ultimately, due to this physician's belief in me and treatment, he set me out on a trajectory that has allowed me to become the person that I am today.

And I am happy to be fully recovered from Lyme disease, and certainly hoping through this testimony that patients that are afflicted by Lyme disease are not deprived of what I had the opportunity to do, and that is certainly my mission as someone who has recovered from symptoms of chronic Lyme disease.

And in closing, what I am hoping that this subcommittee throws out there or people take away from my testimony is that my belief that the net effect of the current guidelines that are out there restricting treatment of Lyme disease patients ultimately deprived so many, if not all of them, who suffer as I have from the opportunity to have the healthcare option to seek long-term treatment that is effective, that is proven, and that has worked in allowing me and others who were fortunate enough to achieve normal, fulfilling, pain-free lives.

Thank you.

Mr. SMITH OF NEW JERSEY. Mr. White, thank you so very much for your eloquent statement and for showing a way, I think, for many other Lyme patients that there is hope if the right treatments are procured. So thank you so much.

[The prepared statement of Mr. White follows:]

Name: Evan J. White, Esq.

Title: Lyme Patient

Date: July 17, 2012

Committee/Subcommittee: House Committee on Foreign Affairs, Subcommittee on Africa, Global Health, and Human Rights

Re: *Testimony for Congressional Sub-Committee Hearing "Global Challenges in Diagnosing and Managing Lyme Disease – Closing Knowledge Gaps"*

First I would like to thank the Sub-Committee for accommodating me in arranging for me to testify by video conference. My wife was originally due to give birth to our first child this Friday so I was unable to make travel arrangements. Nevertheless, our son came last week and both he and Mom are doing great.

Now my becoming a new Dad brings me to a great point that underscores my entire testimony. My story has a happy ending, those that I am here representing do not have the opportunity to have a happy ending. Today I am able to appear before this sub-committee as a new father, husband, attorney, business owner, employer and advocate for the rights of Lyme Disease patients because I had the benefit of receiving medical treatment that is not currently recognized as a treatment option by the National Guidelines Clearinghouse as a treatment option for Lyme Disease sufferers—long term antibiotic treatment.

To be clear, if I hadn't received this course of treatment for my chronic Lyme disease symptoms, I would not be here today. Years of my life are now missing due to my bout with Lyme disease and my fate at one point appeared very grim, until my case was recognized as a

chronic form of Lyme disease and addressed by a physician with day to day, hands on experience in treating Lyme disease patients.

What I hope this subcommittee is able to take away from my testimony is that the net effect of the NGC's restrictive treatment guidelines is that it deprives the numerous chronic Lyme disease patients, who suffer just as I had, living normal fulfilling pain-free lives.

I offer my personal history as a real life case study, that like so many others individual cases, shows that chronic Lyme disease exists and but may be effectively treated if given the healthcare option to pursue the same long term treatment I received.

My story begins over 21 years ago, in the fall of 1990, as I was entering middle school, I became ill with flu-like symptoms and doctors were able to diagnose that I was suffering from Lyme disease however, for my course of treatment physicians made the same error so many make today when faced with the diagnosis—offered only four weeks of antibiotic treatment for my symptoms. This course of treatment proved to be catastrophic. After antibiotic treatment failed to alleviate Lyme symptoms including severe fatigue and headaches, due to the treatment guidelines in place that still remain in place, my doctors felt that the best course of treatment would consist of psychiatric and physical therapy.

Under this course of treatment, not only did my symptoms worsen, but I experienced new and different symptoms, that I simply couldn't grasp at the time. As I recall, performing everyday functions both mentally and physically became increasingly difficult and ultimately impossible. After nearly six months under this treatment my physicians threw their hands up in disbelief when my blood tests confirmed my suspicion, I was getting sicker due to the untreated Lyme disease. I was left in a position where like so many patients today, I felt, hopeless,

helpless and misunderstood. The oversight made by my initial treating physicians in offering only short-term treatment, as I said proved catastrophic, the result was four years of my life lost to battling this disease.

Over the course of a year, I was transformed, once an otherwise healthy, active, happy kid, I became unrecognizable, my Lyme symptoms worsened physically, to the extent I became bedridden, a wheelchair was my only mode of transportation by this point and my weight fell to 60 pounds. Neurologically I regressed the point where tasks like reading writing and even basic verbal communication seemed next to impossible. Whereas, in the fall of 1990 I was due to enter middle school, by fall of 1991, after diagnosis and improper medical treatment at age 13, my prospects for a normal life were as dim as ever. I had moved into a full time children's rehabilitation facility.

Shortly, thereafter new physicians discovered that the initial refusal to continue antibiotic treatment gave way for the disease to penetrate my blood brain barrier, causing hypo perfusion in my brain. While this discovery offered some insights as to my condition, Physicians at the children's hospital were simply confused and confounded by my case and could not offer me anything as far as relief of effective treatment was concerned. While living in the children's rehabilitation facility, due to the simple helpless ness of my situation my family and I faced, was this it? was this my life? would I ever be able to live a normal productive life again, let alone function?

After spending virtually two years in hospitals, I was sent home to receive outpatient treatment. Additionally, through the fortitude and determination of my family, they were able to secure an appointment with a physician who himself was a patient and who treated individuals

with Lyme disease, like me on a daily basis. In retrospect, this was the turning point, the opportunity that changed my fate. This physician clearly had a deep understanding of my condition. His treatment was methodical and effective and grounded in real life results--that is Lyme patients who through his, long term antibiotic treatment were able to experience relief from Lyme symptoms.

While I had a significant way toward full recovery, with this treatment, for the first time two years, I experienced progress. My ultimate recovery was very incremental and took another full two years of my life but it was clear that only upon the care of this Lyme physician, was I able to change course and undo the devastation caused by my earlier short term treatment.

Depriving Lyme disease patients of the option for effective long term medical treatment, through biased treatment guidelines is an injustice that has gone on far too long. Whereas the self-interested members have been steadfast in their opposition to long term treatment, their corresponding arguments fail to show chronic Lyme sufferers in the light which they hope, either medical anomalies or misdiagnosed individuals. The suffering Lyme constituency has only grown to prove those against proper long term treatment wrong, time and again. It's time for those with vested interests in the current guidelines to step aside, let down their opposition, recognize the Lyme community and make way for relevant treatment guidelines that provide our suffering constituency with the same opportunity given to me, the opportunity to have effective medical treatment, the opportunity to recover.

Mr. SMITH OF NEW JERSEY. I would like to now welcome Stella Huyshe-Shires, who is the chair of the Lyme Disease Action for the United Kingdom.

STATEMENT OF MS. STELLA HUYSHE-SHIRES, CHAIR, LYME DISEASE ACTION

[The following testimony was delivered via telephone.]

Ms. HUYSHE-SHIRES. Lyme Disease Action is a nonprofit organization striving to improve the understanding of Lyme disease in the UK on behalf of doctors, patients, careers, employers and healthcare providers.

In particular we have to improve the position of the doctors. If doctors are able to recognize, diagnose and treat Lyme disease, and have the means to do this, all other stakeholders will benefit.

The whole of Europe is affected by the polarization of views concerning Lyme disease that has arisen from the IDSA/ILADS controversy and it became apparent to Lyme Disease Action that UK doctors would not take us seriously without some official accreditation. We are therefore now accredited to our Department of Health Information Standard. This means that our information management processes have been verified to make correct, unbiased use of sources of evidence. There is disagreement on the incidence of European Lyme disease and the possible scale of the problem.

Papers and Web sites written by health professionals normally say that Lyme is overdiagnosed, but those written by members of the public say that Lyme disease is underdiagnosed. What is the evidence?

In the UK we don't know the incidence, as only positive blood tests are recorded; however, an audit at a highly aware GP practice has found an incidence 20 times that of the surrounding region. Extrapolating from this, it seems perfectly possible that the recorded figure for the UK of a mere 1,300 cases may actually be 26,000.

Is there evidence that Lyme disease is overdiagnosed? Well, a recent paper analyzed notes of all patients referred to a major infectious diseases clinic with possible Lyme disease. It reports that only 23 percent of the patients were diagnosed by the clinic as actually having Lyme disease, and 33 percent were diagnosed with chronic fatigue syndrome instead. The authors state these figures mirror similar studies in North America and voice their concerns that CFS patients are susceptible to misdiagnosis and inappropriate treatment.

So yes, Lyme disease may be misdiagnosed in some cases, but the number of patients in the whole 5-year period was 42. Say 12 similar clinics across the UK, this might mean about 100 people a year in the UK being misdiagnosed with Lyme disease. Contrast that with the possible 20,000 real Lyme disease cases misdiagnosed with something else.

Lyme disease isn't alone. A similar survey of patients referred to a specialist chronic fatigue syndrome clinic found that 40 percent of those patients have been misdiagnosed with chronic fatigue syndrome. The challenge there is for everyone to stop beating their own particular drum and ask why Lyme disease is difficult to diagnose and what can be done about it.

Diseases that are rare and difficult take doctors' time and effort. They need unequivocal tests and clear guidelines. Unfortunately, neither of those exist in the UK for Lyme disease. In this small country with a relatively low incidence, most doctors haven't seen enough cases to gain experience, so there is a heavy reliance on tests, and doctors are likely to telephone the laboratory for clinical advice.

The former head of the Health Protection Agency laboratory served as consultant to the IDSA panel in the development of 2006 guidelines, so it is understandable that the views of IDSA have prevailed in the UK.

The Health Protection Agency has also told doctors that Internet sources of information are unreliable, that the dangers to patients from misdiagnosis are considerable, and that tests from some laboratories are unreliable. All of this has an element of truth, but drawing attention to only this side of the coin is a misrepresentation of the state of affairs.

A small number of UK microbiologists have drawn up, under the British Infection Association, a position paper on Lyme disease. Despite its biased view of the literature, it is used by professionals to support the view that Lyme disease can be definitively diagnosed by serology and does not persist after recommended treatment. Unfortunately, European research shows otherwise, but doctors don't have time for critical reading, and understandably they trust that their peers would have done a good job of drawing up guidance.

Europe faces the challenge of more than one species of Borrelia burgdorferi, that has already been said, and this adds a complexity to serology tests. In Scotland the Lyme reference laboratory uses its own in-house Western blot, recording far more bands than are used in commercial test kits. No laboratory undertakes extra work like this without good reason.

When it comes to treatment, the UK follows IDSA despite European guidelines which point out that there have been no good-quality European trials on agent, dose or treatment length, but most treatment recommendations are, in fact, based on opinion, not evidence. It does seem to us that there are uncertainties, but we need to get other skeptical stakeholders to examine this possibility, very difficult in the current climate of suspicion and disbelief in patient views.

We have now started a process mediated by the James Lind Alliance which involves documenting doctors' and patients' uncertainties. To engage doctors in this has been taxing and only achievable because the British Infection Association, following our criticism of their paper, realized that that input was important. The collective uncertainties are now being examined against the published literature and systematic reviews, and this will result in a list of true uncertainties.

The biggest challenge we face globally is the recognition and agreement on the uncertainties. There are other positive signs over here. The Health Protection Agency, following the reorganization and move of the Lyme reference laboratory, has now also engaged with us. However, across Europe lies this polarization of opinions along the ILADS/IDSA fault line, as recently illustrated by several journal articles.

It can be hard not to see the collective publications that deny patient rationality as an orchestrated attempt to discredit an alternative view. It may, however, simply be a reluctance to climb out of an entrenched position.

Earlier this year we attended the European Congress of Clinical Microbiology and Infectious Diseases in London. Discussions with a lot of international delegates were revealing. Northern European doctors face similar problems to the UK, with doctors relying heavily on test results. In Central Europe, where incidence of Lyme disease is far higher, doctors have more experience, and they were telling us Lyme is a big problem, we don't have good enough tests, and we don't know how to treat.

To us here there seem to be two principle aspects to the Lyme disease problem: Politics and the uncertainties of the science. The politics drives patients to seek care away from the UK National Health Service, which is failing them. And it is politics which is preventing recognition of the uncertainties. Politics, prestige, and defense of positions should not obstruct patient care nor hamper the search for understanding.

Thank you for inviting Lyme Disease Action to testify.

Mr. SMITH OF NEW JERSEY. Ms. Huyshe-Shires, thank you very much for your testimony.

[The prepared statement of Ms. Huyshe-Shires follows:]

Stella Huyshe-Shires
Chairman, Lyme Disease Action, UK
July 17, 2012
Subcommittee on Africa, Global Health, and Human Rights

I would like to start by making clear that Lyme Disease Action does not regard itself solely as a patient advocacy group. We are a non-profit organisation striving to improve the prevention, diagnosis and treatment of Lyme disease in the United Kingdom. This is on behalf of everyone: doctors, patients, carers, employers and healthcare providers alike. To improve the position for patients, we have to improve the position for doctors: if doctors are able to recognise, diagnose and treat Lyme disease, and have the means to do this, all other stakeholders will benefit.

In the UK we are affected by the polarisation of views concerning Lyme disease that has arisen from and is epitomised by the IDSA/ILADS controversy. This controversy has, courtesy of the internet, washed across the Atlantic to Europe, affecting all countries but possibly the UK the most because of the common language.

It became apparent to Lyme Disease Action that UK doctors would not take a public group seriously without some sort of official accreditation. We are therefore now accredited to our Department of Health's Information Standard. This means that our information management processes have been verified to make correct, unbiased use of sources of evidence: where there are alternative opinions, or uncertainties regarding evidence, we say so. I shall therefore not just be presenting the patients' views of the challenges, but trying to portray where we feel the problems really lie.

Recorded incidence in mainland Europe is far higher than in the UK, and in E Europe higher than in the USA. This is partly because of better awareness but partly because of the history and epidemiology of the disease itself. However, every country has a different reporting mechanism and so all incidence figures are approximations only.

Across Europe it is notable that there is disagreement on the incidence of Lyme disease and the possible scale of the problem. Papers and websites written by health professionals normally say that <u>over</u> diagnosis occurs and "Public perceptions of the disease in Europe have been distorted by the media and by activist groups".[1] Papers and websites written by members of the public say that Lyme disease is <u>under</u> diagnosed.

Is Lyme disease underdiagnosed? In the UK we do not know the incidence of Lyme disease. Positive blood tests are recorded centrally and these have been rising steadily since records started but nobody knows how many are diagnosed in the early stages from an erythema migrans and no-one knows how many are undiagnosed. An audit at a highly aware GP Practice in Scotland has found an incidence of 370/100,000 population, based on clinical diagnosis of the erythema migrans rash, in contrast to the recorded (laboratory confirmed) 17/100,000 in the surrounding area. (Private communication) Although one practice is a small sample, it seems perfectly possible from this that 95% of cases are not entering our official statistics: a few because they are diagnosed without a blood test; the majority because they are simply not diagnosed at all. Applying this figure (of 95% possibly not being recorded) leads to an estimated 24,000 cases per year in the UK. The Health Protection Agency (HPA) estimates up to 3,000 diagnosed early with erythema migrans and this would leave about 20,000 cases of undiagnosed, untreated Lyme disease cases per year. This, for a disease that is treatable with cheap antibiotics, places a large unnecessary burden on state healthcare and benefit costs.

Is there evidence that Lyme disease is over diagnosed in the UK? A recent paper retrospectively analysed the case notes of all patients referred to a major infectious diseases clinic in the NW of England over a 5 year period (n=115) for consideration of possible Lyme disease.[2] The abstract reports that out of all the patients only 23% (n=27) were diagnosed by the clinic as having active or previous Lyme disease, whereas 33% (n=38) were diagnosed by

the clinic with Chronic Fatigue Syndrome (CFS). The authors state that these figures mirror similar studies in N America and voice their concern that patients with CFS are susceptible to misdiagnosis and inappropriate treatment, particularly in private settings. This analysis does appear to support the idea that Lyme disease is misdiagnosed in some cases in the UK, but it should be appreciated that the total number of patients was small and the number of patients found by the clinic to have been misdiagnosed with Lyme disease in the whole 5 year period was a mere 42.

Lyme disease is not alone: many diseases and conditions are misdiagnosed. Putting it in perspective, a similar survey of patients referred to a specialist CFS clinic in NE England found that over a single year 40% of the patients did not have CFS - 48 in one year. 47% of these were suffering from fatigue associated with a chronic disease.[3]

The challenge here is for everyone to stop beating their own particular drum and ask why Lyme disease is difficult to diagnose and whether anything can be done about it.

Because of the state funded National Health Service in the UK, money is less of a direct healthcare issue than in the USA. Doctors in the UK simply want to be able to diagnose and treat their patients effectively. Diseases and conditions that are rare and difficult to diagnose take doctors time and effort. They need unequivocal tests and clear guidelines so that they can do their job for their patients. Unfortunately neither of those exists in the UK for Lyme disease.

In a small country, with a relatively low incidence of Lyme disease, most UK doctors have not seen enough cases to gain much clinical experience and so there is heavy reliance on the tests. When a test result is returned, the doctor is likely to telephone the laboratory for advice and because the majority of confirmatory tests have until recently been conducted at one particular reference laboratory it is this laboratory which came to be seen as the expert source of knowledge in this country. The head of this HPA laboratory served as consultant to the IDSA panel in development of the 2006 guidelines and has collaborated with other IDSA authors in papers, and so it is understandable that the views of IDSA have prevailed in the UK.

The HPA has issued information packs and website pages with references encouraging doctors to believe that internet sources of information are unreliable, that the dangers to patients from misdiagnosis are considerable and that tests from non UK laboratories are unaccredited and therefore unreliable. All of this has an element of truth: some internet sources are not based on science at all, one patient has died from inappropriate treatment (in the USA) and some non-UK laboratories offer tests that are no more a specific indicator of Lyme disease than is a very swollen knee. These facts are a concern to all of us but drawing attention to only this side of the coin is a misrepresentation of the state of affairs.

A small number of UK doctors, led by microbiologists concerned that serology was being questioned, have drawn up under the auspices of their professional organisation the British Infection Association (BIA), a Position Paper on Lyme Disease and published this in their own journal.[4] This paper fails to take a balanced and unbiased view of the literature and is inadequately referenced. It is, however, referred to by the HPA and by doctors across the country to support the view that Lyme disease can be definitively diagnosed by serology and that it does not persist after "recommended" treatment: it attempts to reassure BIA members that there is not a problem.

Unfortunately, European research shows otherwise. Several studies have looked at various blood tests used in Europe and found differing results depending on which tests are used.[5] Doctors do not have time for critical reading, however, and understandably trust that their peers within the BIA will have done a good job of drawing up some guidance.

Europe faces the challenge of more than one species of *Borrelia burgdorferi* sensu lato and this adds a complexity to serology tests which rely on detection of heterogeneous antigens. The

Lyme reference laboratory in Scotland uses its own in-house Western blot, using native antigens and far more bands than are used in commercial test kits. In an acknowledgement that even the best test is not perfect, they also include response to treatment in the diagnostic path.[6] No laboratory undertakes extra work like this without good reason.

The clinical presentation may also be more complex in Europe. It has been shown that *Borrelia garinii* causes what, in Europe, is appreciated as typical early Lyme neuroborreliosis (Bannwarth syndrome), whereas the clinical features associated with *B. afzelii* are much less specific and more difficult to diagnose.[7] In the absence of a definitive test it is not surprising that many cases are un-diagnosed.

When it comes to treatment, the UK follows IDSA guidelines in asserting that there is no evidence of persistence following recommended antibiotics and refers to USA papers which have claimed no benefit for prolonged treatment. This is despite evidence to the contrary in UK case studies where patients have required more than one course[8] and European research studies showing survival of Borrelia in previously treated patients.[9] It also flies in the face of European guidelines for Neurological Lyme disease[10] which point out that there have been no good quality European trials on agent, dose or treatment length; that treatment recommendations are, in fact, based on opinion not evidence.

In most other diseases, if a patient relapses, there is no question of withholding a further course of treatment, even if the symptoms are subjective. In Lyme disease it appears that patients must prove, by objective signs, that they are still suffering: their word is not enough.

Following extensive and critical reading, it seems to us that there are uncertainties in the diagnosis and treatment of Lyme disease but we need to get other sceptical stakeholders to examine this possibility. A small organisation like ours can accomplish very little in the current climate of suspicion and disbelief in patients' views. To attempt to address this, we have started a process, mediated by an organisation funded by the National Institute for Health Research, the James Lind Alliance.

This process involves surveying doctors and patients to find out what uncertainties they have been faced with during consultations. To engage doctors in this has been taxing, to say the least, because many believe there are no uncertainties. It has only been achievable because the British Infection Association, following our criticism of their position paper, realised that their input was important. The collected uncertainties are currently being examined by an independent researcher against the published literature and systematic reviews. This will result in a list of true uncertainties: questions about diagnosis and treatment of Lyme disease to which research has not yet found an answer. This list will then be voted on to find which both doctors and patients agree are the top 10 priorities. Note that word: agree.

The biggest challenge we face globally is probably agreement on the uncertainties. Only then can we, together, prioritise research. There are positive signs that in the UK we are beginning to shake off the IDSA/ILADS shackles. Not only is the BIA working with us on prioritising uncertainties, but the HPA, following a reorganisation and a move of the Lyme disease reference laboratory, has also engaged with us in a joint research proposal. It will take time, but we are moving forward.

The situation of polarisation of opinions along the ILADS/IDSA fault line occurs in other European countries as recently illustrated by an editorial in the Netherlands Journal of Medicine.[11] The Lancet Infectious Diseases published an opinion piece claiming anti-science in patient organisations[12] and inclusion of a UK author will have reinforced the idea amongst readers that "anti-science activists" are causing problems in the UK.

It can be hard not to see the collective publications denying patient rationality as an orchestrated attempt to discredit an alternative view. It is probably, however, simply an

example of confirmation bias and the natural reluctance of people to climb out of an entrenched position.

Lyme Disease Action attended the European Congress of Clinical Microbiology and Infectious Diseases in London in April this year. Discussions with international delegates were revealing. Scandinavian and N European doctors face similar problems to the UK: doctors have little clinical experience and rely heavily on test results. When patients don't believe a negative test result they send to Germany for a CD57 test and believing that a positive result indicates Lyme disease, they demand treatment which may not be appropriate. In E Europe, where incidence of Lyme disease is far higher, doctors have more experience and were telling us "it is a big problem: we don't have good enough tests and we don't know how to treat."

This Congressional hearing is being held because it is perceived that there is a problem with Lyme disease. This is not just a medical problem due to the imperfect state of 21st century medicine, but a Problem with a capital P. A human problem, perhaps, which humans can therefore resolve; if, collectively, they have the will.

To us in the UK there seem to be two principal aspects to the Lyme disease problem: politics and the uncertainties of the science. The first is preventing recognition of the second. Politics, prestige and defence of positions should not obstruct patient care and should not hamper the search for understanding.

Stella Huyshe-Shires
Chairman, Lyme Disease Action, UK

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Mr. SMITH OF NEW JERSEY. And I thought I would start with you, if I could, on some questions and ask, perhaps, others to jump in.

Mr. White in his testimony talked about the short-term antibiotic treatment being devastating to him. And in a London Telegraph article on May 16, 2011, in which you spoke to the reporter about how you waited 3 years for confirmation that you had Lyme disease, and then you got a low-dose antibiotic for 2 weeks, standard treatment for Lyme, and it made absolutely no difference; then you went in the hospital for 2 weeks of intravenous antibiotics, you thought you would get better, but you got worse. If you just could speak to, you know, just what that was like to have the prescribed remedy seemingly inefficient and unavailing in your case.

You also point out that doctors in Britain follow the advice of the Health Protection Agency, which adheres to the guidelines set by the Infectious Diseases Society of America, and, of course, those guidelines say that patients should not take antibiotics for longer than 28 days. But you then made the comment that scientists have found that Lyme can survive a short course of antibiotics, something that has been debated in this subcommittee by our other witnesses, citing a recent paper from the London School of Hygiene and Tropical Medicine.

You might speak to that paper and some other data that you have come across. It would seem that the information being conveyed to at least the UK and perhaps the rest of the world by the Infectious Diseases Society of America is not just now affecting Americans, but people in other lands as well.

Ms. HUYSHE-SHIRES. Yes. As a patient who believes in the health service, to have a treatment that doesn't work is devastating. The worst thing is probably when people do not believe you; when patients with subjective symptoms are told, it is in your head, and it can be very hard. The IDSA recognizes that if you still have visible arthritis, then you may get some more treatment, but if you have invisible pain, then you cannot have further treatment.

The Health Protection Agency does follow IDSA guidelines. Individual doctors often, or do sometimes, take an individual clinical decision. The paper that you mentioned looking at case studies for the London School of Hygiene and Tropical Medicine followed—looked at the case studies of patients, I think, over a 4- or 5-year period, and they documented the fact that there were some patients who did not recover after their initial course of antibiotics, so they were given a second course of antibiotics, and, when that didn't work, they were given a third course of antibiotics. And between each course the patients were believed, but they also checked on the serology and found a rising antibody titer in the blood test.

Now, quite often people—doctors will not check the antibody level, will not check anything, and will just say, you have had adequate treatment, where "adequate" means conforms to some guidelines; "adequate" does not mean adequate to treat the disease.

Mr. SMITH OF NEW JERSEY. Thank you.

Doctor Barthold, if I could ask you, in your testimony you ask, "Does it survive following treatment, and if so, do surviving spirochetes cause chronic Lyme disease or post-Lyme disease syn-

drome?" You have also testified that "Research proposals submitted to NIH that feature persistence following treatment are likely to receive prejudicial peer reviews in the contentious environment of Lyme disease."

Could you elaborate on that? Are good, laudable proposals being rejected simply because they don't comport with, you know, an entrenched belief at the NIH?

Dr. BARTHOLD. Well, it is certainly not NIH that is at fault, it is peer review, and when peers are divided as everybody else in the Lyme community, then there is bound to be prejudice percolating into the review.

I have direct experience with such prejudicial statements in grant applications that I have submitted. There may be fault with the science, and that is fine, we can respond to that, but when there is prejudice in the reviewer's mind in terms of scoring the significance or the impact of this research, it is not going get over the barrier.

And right now NIH is really struggling to fund investigators. They are spreading the butter very thin, they are finding ways to cut here and there, pay lines are extremely high and very difficult hurdles to overcome. Young people are not entering science; old people like me are leaving. It is a difficult environment. It is going to take years to come out of. So in that environment it is a combination of things that anything controversial, be it Lyme disease or otherwise, is going to have difficulty getting funded.

Mr. SMITH OF NEW JERSEY. Thank you.

Dr. Barthold, you also have made a recommendation that NIH publish a call, a specific call, for applications that request research on the biological significance of persisting spirochetes following antibiotic treatment. In making that call, I am sure this isn't the first time—or maybe it is—has there been any openness to that suggestion?

Dr. BARTHOLD. The only suggestion is mine in this testimony.

Mr. SMITH OF NEW JERSEY. Okay.

Dr. BARTHOLD. Our system works. We scientists are always looking for money, and we follow the money. And when NIH puts out a request for applications with a devoted pot of money to support that kind of work, you will get response from the scientific community. I think we saw a good example of that with biodefense funding several years ago where people left their traditional fields and went over into biodefense research.

It is just a matter of opportunity. If NIH says, this is an important subject area that needs to be explored, then hopefully young people will gravitate to those opportunities.

Mr. SMITH OF NEW JERSEY. Let me ask you, Dr. Stricker, on page 2 of your testimony you point out that the investigation that was initiated by the attorney general of Connecticut, now Senator, Blumenthal found conflicts of interest and suppression of data in the guidelines development process. And then you point out that despite extensive evidence, IDSA review panel voted unanimously to uphold the flawed guidelines.

Could you elaborate on that? Because, you know, I was one of those who for years asked that there be an investigation to potential conflicts of interest. Finally the attorney general took it up, I

am sure because of local people and others who brought it to his attention.

But, you know, if there is not confidence in the process and the transparency, it does erode a belief that this a completely on-the-up process, and the outcomes then are suspect if it has not been. But suppression of data, that is a very serious conflict of interest. We knew what they were with the insurance companies. Would you elaborate on that if you would?

Dr. STRICKER. Well, the attorney general's investigation uncovered significant instances of suppression of data where only the IDSA viewpoint was accepted. Any conflicting or contrary viewpoint was rejected in terms of formulating the guidelines. And this was a systematic problem with these guidelines. The investigation—and the attorney general published his concerns, and that is available on the Web site of the attorney general.

What happened after that was that IDSA put together a hearing to review the guidelines, and that hearing was entirely under the control of IDSA. It was organized by IDSA. They picked the members of the review committee. They picked the individuals who testified before the committee. They had a medical ethicist who basically excluded treating physicians who treat Lyme disease, which biased the proceedings significantly. And for all those reasons the committee then came down with a decision that even though these guidelines were flawed, they were okay, and they were acceptable. And that has just been a travesty.

Mr. SMITH OF NEW JERSEY. In your testimony you say, clinical testing for Lyme disease remains abysmal. Are you encouraged at all by Dr. Eshoo's testimony and some of the things he is doing?

Dr. STRICKER. I am very encouraged. I think we need these kind of sophisticated laboratory tests. I think this advances the science of Lyme testing. We need the NIH and CDC to be supporting this type of advance, and I think—I am very encouraged by his work.

Mr. SMITH OF NEW JERSEY. You went into great detail in your written statement about renewed interest in cell wall-deficient bacterial forms and biofilms. And perhaps others on the panel might want to speak to those issues. Because you also point out that to date no antibiotic treatment exists that targets biofilm formation.

And, Dr. Barthold, in your statement you did talk about the issue of mopping up. I don't think that has been mentioned. You know, most lay people don't understand that the antibiotics don't take it all away; that the host, as you put it up, mops up those bacteria or whatever it might be. Could you elaborate on that, and you, too, Dr. Stricker?

Dr. BARTHOLD. So, using the biofilm analogy, biofilm is a population of microorganisms, some of which are dormant. This is kind of a universal survival mechanism among bacteria and fungi across the world. It is not just a biofilm of a human situation. So those dormant, nondividing bacteria are universally tolerant to the effects of antibiotics because they are not dividing, they are not metabolically active. And so this is a survival strategy that has been going on for eons among microbial communities.

So Borrelia is kind of akin to that in that we know during an early infection it is rapidly dividing and disseminating and quite

susceptible to antibiotics, and we see the same things in vitro or in a culture tube.

During persistent infection in the immune phase of the infection, there is a tenfold reduction of organisms in the hosts—and we are talking about animal model studies that are not human—and those organisms are nondividing and dormant. They are not necessarily in the formation of biofilms, but the analogy is there. They are not dividing, and, as a result, antibiotics can't touch them, and so they grow out and survive.

But what is unique about Lyme disease organisms is that they grow out, but they can't be cultured. So they are genetically attenuated in some way, but further work is needed there.

Dr. STRICKER. And I would add that there was an article on biofilms that was published last week that goes to the molecular mechanisms of that process, and Borrelia has the molecular machinery to make biofilms, and so that makes it very significant in terms of the survival of the spirochete.

I would add that was cell wall-deficient forms or cysts are another mechanism by which the bacteria can persist, because it basically becomes dormant and evades the immune system and antibiotics by taking this cell wall-deficient form. That is something that we need to do much more research on, and right now it is not being done.

Mr. SMITH OF NEW JERSEY. In your testimony, Dr. Stricker, you point out that big pharma is watching, and that hopefully at some point they get engaged, as they have in the HIV/AIDS pandemic. I am wondering, with Dr. Eshoo there, who is working overtime on a better way of discerning whether or not Lyme exists in the individual without resorting to the antibiotic antibody reaction in the host, how close are you, Dr. Eshoo, to coming up with this new test? And if you could, why, in your view, are the big pharmaceutical companies not getting further involved in this whole issue since it affects so many people?

Mr. ESHOO. Well, I think there are a couple of reasons here. One the reason for the big pharmaceutical companies is even though they still see this as a small-market opportunity, to get a test and a diagnostic approved through the FDA takes a lot of money, a lot of time and a lot of resources. And so that is a big barrier to entry right there.

You also have, as we have heard, you know, a lot of people in the community saying, well, the current tests are adequate enough. And so that also acts as a barrier.

I think we are getting closer to getting a diagnostic that we could—to push forward, you know, for a clinical setting, but there is a lot of work still to be done. We would like to increase the sensitivity even further. We think looking for the DNA or some other marker of the bacteria directly will help end a lot of the controversy, and particularly during that early treatment period, early in the infection, when the treatment with antibiotics seems to be the most successful. And if we could diagnose it—I mean, who wants to be infected with a bacteria for 3 weeks or more waiting for a test result to turn positive? So——

Mr. SMITH OF NEW JERSEY. Let me ask you, whoever would like to answer this, how many people at the Infectious Diseases Society

of America are actually controlling the guidelines? You know, I have seen the list, you know, what Attorney General Blumenthal did with each of those individuals. But are there people outside of that panel that have say as to the guidelines, or is that it? And do people like Dr. Collins, Francis Collins, a very distinguished individual, NIH Director, I mean, do he and others take it upon themselves to say, hey, "What is wrong here?" Why is this a persistent bone of contention, and so many reasonable people, heavily credentialed people like yourselves, who come forward and say, there is another view, and people are sick and not getting treatment they need?

Dr. STRICKER. The Blumenthal investigation showed that there was a small group of about 14 individuals who controlled the IDSA program on Lyme disease. And it really is a very small group. The rest of the organization, the other 9,000 members, defer to that group. And that has been a big problem. And other organizations like the NIH and CDC defer to that very small group, and that has been a huge problem with Lyme disease.

Mr. SMITH OF NEW JERSEY. Let me ask Pat Smith, if you could, does your organization and do other Lyme disease nonprofits have established scientific or medical review boards?

Ms. SMITH. Yes, we do.

Mr. SMITH OF NEW JERSEY. Could you explain a little bit?

Ms. SMITH. Okay. Basically our organization and most of the major organizations have either a separate scientific review board, or they might have—we have what is called a scientific and professional review board. And what our organizations for the most part that I am familiar with do is we don't pay those people. They don't pay us. Nothing is done like that. But if we have issues that we need to address, and it is in their area of expertise, or we are considering funding research—we fund a significant amount of research. As a matter of fact, our research has been published and acknowledged in 25 different peer-review journals. So what will happen if we get a project in, and we need expertise in the area, we might call upon some of those people. And the other organizations that I am familiar with, the CALDA, or lymedisease.org, Time for Lyme, which is now the Lyme Research Alliance, they also will do the same thing if we need people in the field to help us.

But we do not ourselves—our organizations are basically organizations, patients and families of patients, but we have the resources with these people, who kindly give of their time to help us to achieve our mission.

Mr. SMITH OF NEW JERSEY. Dr. Stricker, you testified that you have some 2,000 patients that you have taken under your wing and treated. What has been your takeaway from that huge patient number? And how far progressed are many of these people when they finally get to you?

Dr. STRICKER. I think one takeaway is that it shows that the number of Lyme disease patients far exceeds what the CDC reports, that the CDC reporting system is inadequate in terms of, you know, reporting all the patients with Lyme disease. They themselves admit it may be tenfold higher in terms of than what they report.

Many of my patients come to me with years of suffering and misdiagnosis, like you have heard from the other speakers. The gratifying issue for me as a physician is that about 70 percent of those patients—I know that about 70 percent will get better. And for a physician to have that kind of a response is really very, very gratifying, and it makes me sort of turn a deaf ear to the political controversy and go on and treat these patients, and it makes it a very rewarding thing to do.

Mr. SMITH OF NEW JERSEY. Could you elaborate a bit as to what that treatment entails?

Dr. STRICKER. Well, as you heard it, generally long-term antibiotics. These patients do not respond to short-term antibiotic treatment. Many of them have failed short-term antibiotics. When they come to me, many of them have not been diagnosed with Lyme disease, so they haven't even considered treatment, and generally it is long-term antibiotics.

We published a study last year of patients with neurologic Lyme disease required an average of 6 to 12 months of antibiotic therapy to improve, for their neurologic symptoms to improve. That gives you a general idea of what kind of treatment is needed.

Mr. SMITH OF NEW JERSEY. Mr. Gibson.

Mr. GIBSON. Well, thanks very much, Mr. Chairman, and I have certainly found this event here to be very informative.

I would like to take advantage of the panelists being here to seek their feedback. Clearly we are in wide agreement on everything here today. And so what I would ask is do any of the panelists know—or yourself—plan to apply for the money that we put in last year, the $8.75 million for research and for treatment and chronic Lyme is actually in the wording in the law. So I guess broadly I am interested in how we can be more effective.

Is there something about the way—obviously we want to have more money, we know that, but is there something in the way we are wording the law and the language for the report that could be improved? And what about the RFP process; how can we provide better oversight to make sure that we get these monies to the right place?

Dr. BARTHOLD. Well, as I said before, we in the scientific community chase the money, and if you simply enlarge the pot for Lyme disease research and spend it on large programs and so on that have already pretty much been done, we get nowhere. So if we recognize collectively, if NIH leadership recognizes, persistence after antibiotic treatment as an issue, then a focused call for applications looking at the biology will attract everybody and probably some new insight instead of the just the old-school club of people that feed off of Lyme disease. So a more narrowly focused call for applications is appropriate if NIH program people are willing to do that.

Mr. ESHOO. Yeah, I would just like to concur with that statement. Even our research has been almost all supported by government grants, and research foundations and private donors. So it is really—you know, the field needs this support right now to get off the ground. And I think targeted RFAs that are specifically targeting areas of need and carefully worded so that we don't see, you know, a better serological test, for example, would be very beneficial.

Ms. SMITH. I would like to say that, first of all, we would never apply per se for those monies because we don't perform research; however, I do believe it is extremely important that the wording has to be almost mandatory that these funds are going toward the chronic form of the disease no matter what it is called, because what has happened over the past number of years of my involvement is all the research funding, or a good percentage of it, is going to institutions and researchers who have basically addressed the same issues over and over, and they don't fit the patient population that needs the help.

The patient population, as you have heard today, are people, within quotes, "chronic Lyme disease." So we need to be able to define that in such a way that the moneys are—actually go for that type of study, and it isn't awarded, as has happened sometimes in the past, that says for chronic research, and it ends up being for post-Lyme syndrome, which is certainly a totally different issue.

Additionally I think that there is a pressing need for a Federal advisory committee. Most other major diseases have advisory committees on, by the way, which patients and advocates sit, and no one says anything bad about them. No offense, but they don't. And I think that their perspectives to this issue are very important. They are living these problems. They have a greater understanding, maybe not of the technical aspects, but how it is affecting them, and what kind of things need to be done to change that.

So I think that you have to have patients, you have to have advocates, you must have the treating physicians. It is abhorrent to me that clinicians—it means nothing that they went to medical school. It means nothing that they have treated 2,000 patients or 4,000 patients for this chronic Lyme disease. It is taken away. They don't have any validity.

This is wrong. They are seeing reality. What is on a piece of paper is not necessarily reality; that is just people's perceptions of what they think about this, it is not what is happening. And I see from my seat what is happening to patients.

And I think that the government can do this. I think they have done it with other diseases. It is not even difficult to do, it is not costly to do. And, quite frankly, I really don't understand why it hasn't been done, and it has not been for a lack of advocacy.

Mr. GIBSON. Thank you, and we will continue to work that, I can tell you.

And then for Dr. Stricker, I am interested in hearing from the role of a mentor how in California you influence and try to expand Lyme literacy, particularly among newer doctors, but really all doctors, sort of—for those that even may be in midcareer, expanding their—enlightening them and expanding their understanding.

Dr. STRICKER. Well, ILADS does have a preceptorship program where physicians can come and spend time in my practice and other ILADS doctors' practices to learn about diagnosis and treatment of Lyme disease and to learn how to treat these patients. That has been very successful. It is funded privately, and that has been a way of mentoring doctors who want to get involved with the disease.

But let me make one comment, and that is that I currently have a position in my practice for a Lyme-treating physician. I really

cannot find anyone who is willing to take that position, and the reason is that with all the controversy around Lyme disease, doctors are basically unwilling to get involved in that controversy. And that controversy has really had a chilling effect on the mentorship and the development of physicians who can treat the disease.

Mr. SMITH OF NEW JERSEY. Follow up on that. Is that because they might be censored by the State medical board?

Dr. STRICKER. Absolutely. There is always that fear. I mentioned that in California we do have a physician protection law, but certainly censorship by medical board, censorship by your colleagues and by infectious disease experts is definitely a deterring factor in terms of doing that.

Mr. SMITH OF NEW JERSEY. Let me ask the entire panel, if I could, how would you would react to that statement, and it was recently made, and it is very important if I could get your feedback from it: "There is no solid evidence despite many efforts that persistent infection occurs in humans following recommended treatment regimen."

Dr. STRICKER. Well, let me mention that in my written testimony there is a table that lists 27 studies that show exactly that persistence infection following accepted IDSA-type treatment for Lyme disease. And actually I realize that I hadn't updated that table in a couple of years, so there are probably more studies now that show that. It is table 2. And that complements the other table, which is studies in animal models, that Dr. Barthold can address, that show basically the same thing.

Mr. SMITH OF NEW JERSEY. Thank you.

Dr. BARTHOLD. I have little to add, but working and making guesses at how to treat people will only get us so far, and I am a believer in basic biology studies. We need to understand what is going on with Borrelia in the mammalian host, be it a mouse, or a dog, or a primate or a human. Human studies are very difficult to do, and so animals allow us to extrapolate those findings.

A lot of people are using the animal models, including the mouse model that I developed years ago, in their research, but they are all looking at the early phase of the infection when spirochetes are disseminating and causing acute inflammation and so on. And I am not aware of very many people that are looking at chronic persistent infection and the mechanisms by which Borrelia evades postimmune clearance. There may be less than five laboratories worldwide studying that phenomenon, and yet that is the most important aspect of this disease.

Mr. SMITH OF NEW JERSEY. Ms. Huyshe-Shires, did you want to comment on that?

Ms. HUYSHE-SHIRES. Just to corroborate what other witnesses have said, but there are well-documented cases of patients from whom Borrelia have been isolated after antibiotic treatment who were still symptomatic, still following further perhaps long-term antibiotics, then did recover. It is a very disputed area, and until, I think, everybody gets down together to actually decide on what facts we are uncertain, then we won't move forward.

Mr. SMITH OF NEW JERSEY. Thank you.

Ms. Huyshe-Shires, you mentioned in your testimony European guidelines for neurological Lyme disease; can you clarify where

those guidelines were developed? Are they more flexible that the Infectious Diseases Society of America guidelines, and are those guidelines accepted in the UK?

Ms. HUYSHE-SHIRES. The guidelines are accepted in the UK. They are not so much more flexible, but they state more clearly the uncertainties. So there are summary recommendations.

But the guidelines got drawn up by the European Federation of Neurological Societies. These guidelines state on what basis they are drawn up, and they make the point that for neurological Lyme, there have been no good-quality European trials more than 28 days. So although they recommend 21 to 28 days' treatment in neurological Lyme, they say that this is based on a good practice and opinion, because there haven't been any trials to say whether that it is better—whether a longer course, 35, 40 days, would be better.

And, in fact, the studies that they quote, or the trials that they quote, you can see that the response rate varies from about 20 percent, 30 percent to 100 percent. They are often trials which show a good recovery for that short period, but most of them around about in the 50-, 70-percent response. Now, often clinicians quote trials and say European trials show an excellent response rate. A patient would not consider 7 out of 10 people responding to treatment as being excellent.

Mr. SMITH OF NEW JERSEY. Thank you.

Ms. Smith, you mention in your testimony that children are at the highest risk of acquiring Lyme. Can you describe the consequences to children who contract it? I know your own children, two of them, have suffered the devastating impact of Lyme. Could you speak to that, please?

Ms. SMITH. Yes. The effects on children are I am going to say more devastating in some ways, because, first of all, they are kind of defenseless oftentimes, and they can't articulate the kinds of symptoms that they have. So what happens, not only do they have the medical complications which are obviously very serious, but they also are greatly impacted about what their peers, their schools, their teachers are saying about them.

My own daughter was out of school for over 4 years on home instruction, and I was a board of education member. And I am not going to tell you that it wasn't appalling to me at comments, you know, that were made that my daughter was trying to get out of school, that she wanted to stay home. And I finally said to someone, excuse me, but what 15-year-old wants to stay home with her mother for 4 years, and what mother wants to have her 15-year-old home for 4 years?

But I guess the bottom line is the research studies that we have seen out of Columbia and other institutions have shown that these children benefit greatly from long-term treatment, and that oftentimes the short-term treatment really doesn't help them, and sometimes maybe it hurts them, because it may stop immune response, they may not get a positive test, which then brings them down even further, because less people now believe them in the scheme of things. And so it is very hard for them, it is hard for their families.

And, you know, I mentioned the Munchausen's by proxy, and the reason I mentioned that is because I think that shows the extremes

that some people and physicians will go to to, you know, make a point that there is no chronic Lyme disease, that these moms should not be having their children treated by licensed physicians with antibiotics—we are not talking about other types of medications. And here what is happening in many States across the country has happened already where the local family services departments will come in—and I have seen this happen—where one child is being treated for chronic Lyme, yet they will take away all the children from the mother. And this is abhorrent to me, and I don't understand how in this century that this is still happening.

And I would be remiss if I didn't mention, Congressman Smith, that you intervened in New Jersey for us for a mom that was having that happen. So I think that you know personally that this is serious.

And our kids are psychologically damaged. That is why there is a high rate, relatively high rate, of suicides among Lyme patients in general and children—or I should say suicide attempts. Fortunately they are not always successful. But I have been there with those moms when their children—after they have committed suicide, and it is the saddest thing in the world to me that we have the tools, we have the knowledge in this great country that we could put a stop to this.

Mr. SMITH OF NEW JERSEY. Mr. Huyshe-Shires, can I just ask you when the Infectious Diseases Society of America came under fire from the attorney general from Connecticut, did that cause pause and perhaps some reflection on the part of Europeans as well as people in the UK about the accuracy of what their recommendations were all about? I mean, did people say, wait a minute, this small subgroup of people have been found to have conflicts of interests and suppression of evidence and information. Did that cause anyone to say, let's do our own work on this?

Ms. HUYSHE-SHIRES. Unfortunately not. There was a strong belief, as I have mentioned, that the expertise tended to be vested in really one, two or three people in the UK, and therefore people believe those few people. And because they have been engaged with the IDSA 2006 guidelines, they carried on supporting IDSA, and therefore everyone believed that there wasn't a problem with IDSA. And, in fact, when the panel reported that they recommended some changes to the IDSA guidelines, and that Europe should be considered slightly differently, this was reported in the UK as a confirmation that IDSA guidelines could not be changed.

So in this country, as far as the official NHS goes, there was no change at all, and no one recognized that IDSA had actually pointed out that there should be a few changes made.

Mr. SMITH OF NEW JERSEY. Let me ask Mr. White—and I just have two more questions, and anything anyone would like to say, and if you have any final questions or comments. What would be your advice to those who have chronic Lyme disease symptoms but have not located a doctor as yet? What do you recommend to them?

Mr. WHITE. Well, I think they actually need to do the same thing that my family did, and that is be as resourceful as possible, and dedicated to getting all the information that you can, and searching out the people like Pat Smith who can lead them to a knowledgeable physician that will give them effective treatment.

Mr. SMITH OF NEW JERSEY. Ms. Smith, you mentioned the importance of having an agency, interagency, a coordinating committee that would include patients, clinicians and the like. I started out this hearing noting that I introduced two bills almost at the same exact time that had very similar components, including one was for autism and one was for combating Lyme. The autism became law. We now have the IACC, or the Interagency Autism Coordinating Committee, led by Dr. Insel.

Just last week I joined others testifying before them, speaking to them about latest advances in combating autism. And you have patient groups, you have people of all walks in the room, diverse opinion, some who think that thimerosal is the cause of autism, and all of it is being treated very seriously to try to get to causation as well as the best way to mitigate that horrific developmental disorder.

I am shocked and dismayed by the inability to do the same, I introduced almost identical bills, put the bills side by side, we borrowed ideas from both, including a task force and interagency with people of diverse opinions to try to really get to the bottom of this. I will remind everybody, we invited the Infectious Diseases Society of America to be here to testify, as well as NIH and CDC. That invitation stands. Hopefully they will get back to us so that we can continue this dialogue. But why contrary opinion is so frowned upon is beguiling to me.

And I would just say parenthetically I served on the Veterans' Affairs Committee for most of my time in Congress. I have been in Congress for 32 years. The first amendment—it wasn't my amendment, but I was a cosponsor of it—that Tom Daschle offered was on Agent Orange, and it failed. And we know the evidence clearly supported service-connection presumption disability for those suffering from Agent Orange. Years later I am the one who held the hearings and offered legislation that became law on the Persian Gulf illness, which was attributed to stress rather than some other trigger which we know or believe is the cause.

This inability to say, welcome all sides, so that we can get to the bottom of this is, like I said, beguiling. If any of you want to speak to that, I would surely like it, and I would like to ask as well my good friend Mr. Gibson if he has anything, and then final words go to you.

Mr. GIBSON. Well, let me just wrap up by saying that, you know, I deeply appreciate your leadership. You have taken us far, very far, on these issues that you listed. I am the author of a bill right now to make sure that we get presumptive coverage to our Navy veterans who are serving offshore who have been exposed to Agent Orange and now have to fight to get that kind of coverage.

Now, we do win some of those cases. Even in the 1½ years I have been in the Congress, we have helped win these cases. But they should get presumptive coverage. And, in fact, through desalinization, they are exposed to 10 times more powerful from Agent Orange. That that was the kind of exposure they had from being offshore.

So the passion that you have brought to these afflictions that we bring forward and the treatment that is necessary is deeply appreciated. We are going to continue to work this. We will be indefati-

gable on this issue, and we will work to bring forward the appropriations necessary so we get the research so that we get a better test. If we get a better test, then we get better treatment and ultimately change the guidelines, the CDC definitions, because we know, or at least we have been told, that insurance companies will then follow. And that is part of this equation, as well.

So thank you. I appreciate all of the panelists for what they have contributed here today and, Mr. Chairman, for your leadership. I yield back.

Mr. SMITH OF NEW JERSEY. Mr. Gibson, thank you so very much for your leadership.

And if anyone would like to make a final comment or suggestion, this would be the time.

Dr. STRICKER. I would also like to echo the gratitude to the chairman for organizing this hearing, and just to say once again that we need a more comprehensive program for Lyme disease. We need better animal studies funded by the government. We need better diagnostic testing research. And we need better clinical trials to see how to treat Lyme disease, what the best way is to treat these patients.

Ms. SMITH. In closing, I would particularly—besides thanking the committee—I would like to address those agencies in absentia, if you will. And I just want to say that advocacy groups that I work with all across the country, you know, they are really not adversarial. They are not adversarial at all. The people involved in them are fighting for their very lives.

And so, these agencies forget. They are up there, and they are sometimes well-meaning; the bureaucracy gets in the way. I know, I was a school board president. I know about government bureaucracy. However, there comes a point in time when they have to stop, they have to look at the statistical data, they have to look at the reality, they have to talk to the treating physicians, they have to accept the patients and the advocates as being able to be part of this process, not as them being adversaries, but in sitting across the same table.

I don't have to agree with you. I have been married 44 years. I don't always agree with my husband. Once in a while, we disagree. And so the point being is, it is not about that. It is about sitting down and discussing, "Guys, what can we do about it? How can we help these suffering patients?"

And so that is why I came. That is why I have devoted most of my latter life, you know, to doing this. I don't have any agenda other than that. And I would ask that they recognize those things about the patients and advocates. And, please, you know, sit with us. Let's forget all this, and let's move forward as to how can we get help for patients in this country and across the world.

Thank you.

Mr. SMITH OF NEW JERSEY. Yes, Mr. Eshoo?

Mr. ESHOO. I would like to expand on a point. I think, you know, good science will really help bring this community together on the same page.

And, you know, I grew up in the San Francisco Bay area. And if you look back in the 1980s when the HIV outbreak was coming out, there was all kinds of hysteria associated with what was this

coming from, how was it transmitted, what were the causes and sources. And, really, what shed a lot of light was good diagnostics. Suddenly now we could reliably tell, who had it, how it was transmitted, and the science behind the various.

And I think that is really what Lyme disease needs, too. And I think, you know, some of the animal studies are especially relevant for these kinds of questions that we have in understanding the biology of this infectious agent. And good science will, I think, bring everybody together.

Dr. BARTHOLD. I just would like to summarize.

My career with Lyme disease started way back with Allen Steere in Connecticut. These are good people. People on the IDSA report are good people. The lay community are good people. But I am very saddened by the contentiousness that has evolved with this disease. People are backed into corners and protective. And I think we need to have open dialogue where everybody hugs and kisses and gets along. Because we all have the same goal, and that is to improve human health.

And, as a veterinarian, I will say veterinary species, as well, are afflicted with this disease.

Mr. SMITH OF NEW JERSEY. Mr. White or Ms. Huyshe-Shires, do you have any final comments before we conclude?

Ms. HUYSHE-SHIRES. I would just like to agree with what most of the witnesses have said. We do need to work together. We need to come out of any entrenched positions. And we do need to get to the bottom of the science. We are improving our science all the time. And there is a lot to learn about Lyme disease. We do not know it all.

Mr. WHITE. I would just like to add that, you know, I absolutely echo everyone's sentiments, but I just want to put it in context, the fact that this has been a long time running and so such of this sounds very familiar to me from when I was much younger. And I think that that shows that it is time, that it is time for people to kind of get together, for everyone to kind of show their cards and, really, to act in the best interest of the collective community.

I don't, like you, understand what the basis is for this contentiousness when, clearly, so many people are being harmed at this point.

Mr. SMITH OF NEW JERSEY. On that last word, thank you so very much.

The hearing is adjourned.

[Whereupon, at 4:08 p.m., the subcommittee was adjourned.]

APPENDIX

Material Submitted for the Hearing Record

SUBCOMMITTEE HEARING NOTICE
COMMITTEE ON FOREIGN AFFAIRS
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, D.C. 20515-0128

SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, AND HUMAN RIGHTS
Christopher H. Smith (R-NJ), Chairman

July 13, 2012

You are respectfully requested to attend an OPEN hearing of the Subcommittee on Africa, Global Health, and Human Rights, to be held in Room 2172 of the Rayburn House Office Building **(and available live via the Committee website at http://www.hcfa.house.gov)**:

DATE: Tuesday, July 17, 2012

TIME: 2:00 p.m.

SUBJECT: Global Challenges in Diagnosing and Managing Lyme disease - Closing Knowledge Gaps

WITNESSES:

Stephen W. Barthold, Ph.D.
Distinguished Professor
Department of Pathology, Microbiology and Immunology
Center of Comparative Medicine, School of Veterinary Medicine
University of California, Davis

Raphael Stricker, M.D.
Vice President
International Lyme and Associated Diseases Society

Mark Eshoo, Ph.D.
Director, New Technology Development
Abbott

Ms. Patricia Smith
President
Lyme Disease Association

Mr. Evan White
Lyme disease Patient

Ms. Stella Huyshe-Shires
Chair
Lyme Disease Action

By Direction of the Chairman

The Committee on Foreign Affairs seeks to make its facilities accessible to persons with disabilities. If you are in need of special accommodations, please call 202/225-5021 at least four business days in advance of the event, whenever practicable. Questions with regard to special accommodations in general (including availability of Committee materials in alternative formats and assistive listening devices) may be directed to the Committee

COMMITTEE ON FOREIGN AFFAIRS

MINUTES OF SUBCOMMITTEE ON *Africa, Global Health, and Human Rights* HEARING

Day *Tuesday* Date *July 17, 2012* Room *2172 Rayburn*

Starting Time *2:00 p.m.* Ending Time *4:08 p.m.*

Recesses [*0*] (____to ____) (____to ____) (____to ____) (____to ____) (____to ____) (____to ____)

Presiding Member(s)

Rep. Chris Smith

Check all of the following that apply:

Open Session [✓]
Executive (closed) Session [ ]
Televised [✓]

Electronically Recorded (taped) [✓]
Stenographic Record [✓]

TITLE OF HEARING:

Global Challenges in Diagnosing and Managing Lyme Disease: Closing Knowledge Gaps

SUBCOMMITTEE MEMBERS PRESENT:

Rep. Chris Smith, Rep. Karen Bass

NON-SUBCOMMITTEE MEMBERS PRESENT: *(Mark with an * if they are not members of full committee.)*

Rep. Christopher Gibson*, Rep. Frank Wolf*

HEARING WITNESSES: Same as meeting notice attached? Yes [✓] **No** [ ]
(If "no", please list below and include title, agency, department, or organization.)

STATEMENTS FOR THE RECORD: *(List any statements submitted for the record.)*

Prepared statement from the Infectious Diseases Society of America

TIME SCHEDULED TO RECONVENE _____
or
TIME ADJOURNED *4:08 p.m.*

Shari Ciddett
Subcommittee Staff Director

MATERIAL SUBMITTED FOR THE RECORD BY THE HONORABLE CHRISTOPHER H. SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY, AND CHAIRMAN, SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, AND HUMAN RIGHTS

Statement for the House Foreign Affairs Committee
Africa, Global Health and Human Rights Subcommittee's Hearing on
Global Challenges in Diagnosing and Managing Lyme Disease — Closing Knowledge Gaps
Submitted by the Infectious Diseases Society of America
July 17, 2012

Chairman Smith and Members of the Subcommittee, the Infectious Diseases Society of America (IDSA) appreciates the opportunity to submit a statement for the record for the Subcommittee's hearing, "Global Challenges in Diagnosing and Managing Lyme Disease—Closing Knowledge Gaps." IDSA represents nearly 10,000 physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases, including Lyme disease. IDSA is pleased to provide the following information on Lyme disease-related issues, including the latest scientific data, the need for new diagnostics and increased research, and evidence-based treatment recommendations. (The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America; *Clin Inf Dis*, Vol. 43, Issue 9, Pp. 1089-1134.) We hope you will find the information provided useful to you in your deliberations.

Prevention

During 2006–2009, the total number of Lyme disease cases reported to the Centers for Disease Control and Prevention (CDC) increased each year, albeit with no consistent trend across states. In 2010, however, confirmed cases decreased 25% and probable cases decreased 11% as compared with 2009. In addition, regional trends were apparent. Among 12 high-incidence states in the Northeastern and mid-Atlantic regions, all but Virginia reported a decrease in confirmed cases. Conversely, the number of confirmed cases increased >20% in Minnesota and Wisconsin. The reasons for these patterns are unknown. Given the observed regional consistencies, surveillance artifact is an unlikely explanation. (MMWR, Vol. 59, No. 53, June 1, 2012, page 15)

The risk of acquiring Lyme disease for people who live in endemic areas can be lessened by taking simple, preventative steps such as avoiding brushy areas when walking in wooded areas; wearing long pants, long-sleeved shirts; using insect repellents; and thoroughly checking for ticks after being outdoors. IDSA supports efforts to further educate the public about these prevention efforts.

Another strategy worthy of discussion is a vaccine for prevention of Lyme disease. As you may know, in 1998, a Lyme disease vaccine for humans was introduced and initially was popular. Unfortunately, vaccine opponents began making unsubstantiated claims about the vaccine's side effects. These claims were not backed up by clinical data. The trials had not shown such side effects. The Food and Drug Administration (FDA) and the CDC looked into the claims, and then continued to recommend that people in or around tick-infested areas get the vaccine. However, the damage to the vaccine's public image caused vaccine sales to plummet. SmithKline Beecham, the company that manufactured the vaccine, pulled it from the market. A second Lyme disease vaccine-maker, Pasteur Mérieux Connaught, perhaps because of the SmithKline Beecham experience, subsequently decided not to market its own product. Lyme vaccines

remain available for animals, but not humans. IDSA would be happy to participate in discussions with Congress, the Administration, and industry to determine if a Lyme disease vaccine would be a useful tool in preventing Lyme disease and, if so, how to ensure that a safe and effective vaccine reaches recommended populations.

The National Institute for Allergy and Infectious Disease (NIAID) at the National Institutes of Health (NIH) also is funding grants for research and development of a bait vaccine to immunize wildlife in Lyme-infested areas. This effort has the potential to reduce the transmission of Lyme disease by reducing the number of ticks capable of infecting humans. Although this product is still being tested, initial data are very promising. While not a foolproof solution, this effort could be combined with other prevention strategies to strengthen our defenses against Lyme disease. IDSA urges further support to continue this research.

New Diagnostics

IDSA believes that specific and more sensitive diagnostic tests for Lyme disease are needed. NIAID devotes about 20 percent of its funding for Lyme disease to research that relates directly or indirectly to diagnosis. Because of enormous advances in bioinformatics and molecular genetics, significant progress has been made in the development of new diagnostic tests. However, it must be noted that whenever any new diagnostic test is developed, it must be compared to existing diagnostic methods to ensure that it is indeed superior with respect to specificity and sensitivity before it can be widely used and applied.

Studies performed at different institutions may use a variety of experimental methods that make it impossible to compare results in a meaningful way. This is why IDSA strongly advocated for the establishment of a Serum Reference Repository with a computerized data base to accelerate the decision making process by applying uniform standards to a large number of patient cases. The NIH and CDC initiated this repository in 2008 and, at the end of 2011, began making Lyme disease and related serum samples for testing and comparison of new and current diagnostic tests with a common serum sample set for standardization available to the scientific community on a broad basis. The repository now can enable comparison of results of newly developed and existing diagnostic tests under identical conditions using the same panel of well-characterized reference specimens. Though the effort is still quite new, IDSA believes it has the potential to yield positive results in the development of new diagnostic tools for Lyme disease.

Post-Treatment Lyme Disease Syndrome

IDSA recognizes that Lyme disease can be painful and that the disease is not always properly identified or treated. The Society advocates for educational efforts and, as mentioned in the section above, development of improved diagnostics that will enable clinicians to accurately identify patients infected with *Borrelia burgdorferi* so appropriate treatment can be prescribed. We recognize that some patients may continue to experience prolonged Lyme disease symptoms even after a course of antibiotic therapy has killed the Lyme disease bacterium. We sympathize with these patients' suffering, but remain concerned that a diagnosis of so-called "chronic Lyme disease," suggesting that active infection is ongoing, is not supported by scientific evidence and,

more alarmingly, the treatment of long-term antibiotic therapy will do patients more harm than good.

There is no scientifically accepted case definition for "chronic Lyme disease." Standard courses of antibiotics (between 10-28 days depending on the manifestation of Lyme disease) have been proven effective to clear the infection in the vast majority of cases. IDSA recognizes that some patients continue to experience Lyme symptoms, such as arthritis, after the infection has been cleared by standard antibiotic therapy. According to peer-reviewed studies, these stubborn symptoms may be due to persisting inflammatory responses, by genetically predisposed individuals, to bacterial debris left in the body after the infection is cleared as well as joint damage caused by the initial infection. One study focusing on patients with antibiotic-refractory late Lyme arthritis, published in the *Annals of Internal Medicine*, found that these symptoms may persist for nine years, but the incidence and severity of these symptoms do decrease over time and eventually stop. During the first year following the first onset of illness, 90% of patients had bouts of arthritis, and the number of individuals who continued to have recurrences decreased by 10−20% each year. (Steere, A. C. *et al. Ann. Intern. Med.* 107, 725−731 [1987]).

Long-Term Antibiotic Therapy

Most cases of Lyme disease are successfully treated with 10-28 days of antibiotics. Using antibiotics for a very long time (months or years) does not offer superior results and can be dangerous, because it can cause potentially fatal complications and can promote the development of drug-resistant infections. Whether long-term antibiotics benefit patients with persistent symptoms of fatigue, musculoskeletal pains and neurocognitive dysfunction has been scrutinized using the highest level of scientific evidence: four placebo-controlled randomized trials do not support the use of long-term antibiotics as an appropriate treatment for Lyme disease. Though some patients report feeling better after this treatment, these results are largely anecdotal and study after study has failed to demonstrate any benefit of long-term antibiotic treatment over placebo. It should be noted that these randomized clinical studies reflected that approximately one-third of patients benefit from placebo. Hence, it is perhaps understandable why some patients and practitioners might mistakenly endorse long-term antibiotic therapy as helpful. This is precisely why it is important to perform well-designed clinical trials to distinguish if a therapeutic intervention has actual, beneficial effect in contrast to a resolution of symptoms which might merely happen on its own accord.

Further, no reliable evidence exists that supports the designation of Lyme disease as a chronic, actively infectious disease requiring ongoing antibiotic therapy. Two recent reviews -- one published in the *New England Journal of Medicine* (*N Engl J Med* 357:14; October 4, 2007) and the other in the *American Journal of Medicine* (2008) 121, 562-564 -- give evidence-based assessments of Lyme disease diagnoses and the recommended treatments that substantiate IDSA's position. Neither the diagnosis of so-called "chronic" Lyme disease, nor long-term antibiotic therapy are supported by the NIH, CDC, American Academy of Neurology, the American College of Physicians, and the American Academy of Pediatrics, or by an overwhelming majority of experts in the field of infectious diseases medicine in this country and abroad.

Specific to the issue of global aspects of Lyme disease, although the pathogen that causes Lyme disease in Europe is somewhat different from the one we face in the U.S., eliciting more neurological symptoms rather than the primarily arthritic symptoms Americans suffer, the same short-term course of antibiotics has been proven effective in clearing Lyme disease infections in Europe. European infectious diseases societies have endorsed IDSA's treatment guidelines for Lyme disease.

IDSA recognizes that medicine is continually evolving, and the Society's members do not claim to have all the answers. Given that long term antibiotic therapy has not been found to effectively treat symptoms that persist after the initial infection is cleared, IDSA supports additional research to determine safe and effective treatments for patients that experience such long-term symptoms. IDSA will continue to periodically review its Lyme disease guidelines and update them as needed to reflect the scientific literature.

Conclusion

Once again, IDSA thanks Chairman Smith and Members of the Subcommittee for their attention to this issue and their interest in IDSA's perspective. The Society looks forward to working with you on matters of importance to global health.

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