2011 Annual Scientific Conference: Update for Scientists, Clinicians & Health Officials

Co-sponsored by Columbia University & Lyme Disease Association, Inc.

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Conference Summary Prepared by Columbia University:

Scientific Chairs:
Brian Fallon, MD, Columbia University
Richard Marconi, PhD, Virginia Commonwealth University

This year's conference was once again an exciting and stimulating meeting bringing together researchers, clinicians, community leaders, patients, and public health officials. Below we summarize the talks for the benefit of those who were not able to attend.

Dr. J. William Costerton's riveting talk on "The Role of Biofilms in Chronic Bacterial Infections" reviewed the history of the discovery of biofilms, demonstrating that these biofilms enable micro-organisms to resist host defenses and antibiotics, enabling infections to become chronic. Biofilm forms when bacteria adhere to surfaces in moist environments by excreting a slimy, glue-like substance. Sites for biofilm formation include natural materials, metals, plastics, medical implant materials—even plant and body tissue. Biofilms are held together by sugary molecular strands, collectively termed "extracellular polymeric substances" or

“EPS.” The cells produce EPS and are held together by these strands, allowing them to develop complex three-dimensional, resilient, attached communities. Biofilms can be as thin as a few cell layers or many inches thick, depending on environmental conditions. Over 500 bacterial species have been identified in typical dental plaque biofilms. Dr. Costerton described how the capillary bed in the knee is a trap for bacteria, pointing out that septic arthritis in children settles in the knee (not the hip) and Treponema denticola (from periodontitis) also settles in the osteoarthritic knee (not the hip); this raises questions about the potential role of biofilms in chronic Lyme arthritis. Finally, emerging knowledge on biofilm dispersants was reviewed. For more information about biofilms, check out www.erc.montana.edu.

Dr. Eva Sapi’s talk on “Killing Borrelia – an impossible job?” addressed various mechanisms associated with Borrelia burgdorferi that may help it to survive despite antibiotic treatment. B. burgdorferi is a known pleomorphic species, able to adopt alternative, defensive morphologies to evade the immune response and perhaps to increase antibiotic resistance. One of these morphologies is a cyst form, which Dr. Sapi’s research suggests is resistant to the front line antibiotic treatment; alternative antibiotics were suggested. Another possible explanation for persistent symptoms might be the formation of a biofilm. Her group has employed several modes of microscopy to characterize biofilm morphology. Among optical microscopy techniques, dark field microscopy was used to observe the interaction of peripheral spirochetes with the biofilm, DIC microscopy revealed the heterogeneity of the biofilm matrix, and fluorescence microscopy enabled observation of the sessile internal biofilm population in a GFP-expressing population. A relatively new technique, atomic force microscopy, was used to directly scan the topography of the biofilm. The ability of B. burgdorferi to assume a biofilmic morphology may partly explain the continuing presence of symptoms in chronic Lyme sufferers. Dr. Sapi’s group is examining different agents that may help to reduce biofilms, such as the antibiotics doxycycline and tinidazole as well as the herb Banderol. Dr. Sapi concluded with the hypothesis that the B. burgdorferi biofilm likely provides a refuge for chronic Lyme infection, and offers an additional avenue of attack for potential treatments for Lyme disease.

Dr. Jason A. Carlyon’s talk focused on Anaplasma phagocytophilum, the agent of human granulocytic anaplasmosis (HGA). This emerging tick-borne pathogen demonstrates stealth trickery, enabling it to avoid and even subvert immune cells. In the United

States, HGA is endemic in the Northeast, the upper Midwest, and Northern California, where the disease's tick vector is prevalent. HGA presentation varies from sub-clinical to mild or severe disease. Though rare, HGA can be fatal. Symptoms include fever, chills, headache, myalgia, leucopenia, thrombocytopenia, and elevated serum levels of liver enzymes. The risk of mortality is increased when patients are elderly or, have complicating opportunistic infections or prior immunocomprise and when therapy is delayed. Patients generally respond to the antibiotic doxycycline, the treatment of choice. A. phagocytophilum is an obligate intracellular pathogen, which means that it cannot survive freely in the environment. Therefore, it must parasitize certain cells in its tick vector and in its mammalian/accidental human host to obtain nutrients. While the obligate intracellular lifestyle is shared among many bacterial species, A. phagocytophilum's chosen host cell in humans and animals – the neutrophil – makes it unusual. That A. phagocytophilum effectively invades and subverts the very cell meant to destroy microorganisms presents a striking paradox and brings forth the question of how it accomplishes this task. A major focus of Dr. Carlyon's laboratory is to understand the means by which A. phagocytophilummanipulates neutrophil functions to enable bacterial survival. Dr. Carlyon's lab has identified an Achilles' Heel that A. phagocytophilum exploits to convert its host cell into a Trojan Horse. Host cell proteins called Rab GTPAses are membrane traffic regulators that orchestrate the series of events that culminate in microbial killing machinery assembly on the phagosomal membrane as well as phagosome-lysosome fusion. These proteins also control the trafficking of cargo – nutrients, cellular components, and waste material – to their appropriate sub-cellular locations. After binding to the surface of a neutrophil or other host cell, A. phagocytophilum tricks the cell into engulfing it into a vacuolar compartment. Once inside, the pathogen selectively hijacks Rab GTPases that are involved in "recycling" cellular material. The bacterium redecorates its host cell-derived vacuolar membrane with the hijacked membrane traffic regulators as a means of molecular disguise. By masking itself as a "recycling compartment", the A. phagocytophilum-occupied vacuole is able to remain undetected within host cells. The organism also blocks the actions of membrane traffic regulators that would normally destine the engulfed bacterium for destruction. Thus, A. phagocytophilum remodels its host cell-derived vacuole from an inhospitable vessel marked for destruction to a protective safe haven for replication. Deciphering how A. phagocytophilum facilitates its survival inside neutrophils provides an avenue to better understand how different agents of disease manipulate their host cells to evade the immune response and cause disease. This knowledge has broad-reaching implications, as it

will aid in development of treatments and preventative measures for not only the agent of HGA, but also a battery of pathogens that employ similar intracellular survival mechanisms.

Dr. Richard Marconi's talk on "C-Di-GMP" described research demonstrating that the cyclic nucleotide, c-di-GMP, plays a critical role in regulating several important cellular processes. The levels of c-di-GMP in the cell were manipulated by deletion or overexpression of genes that encode proteins involved in c-di-GMP synthesis and breakdown. High levels of c-di-GMP inhibit the ability of B. burgdorferi to pass from ticks to mammals while low levels interfere with the passage of spirochetes from mammals to ticks. The molecular basis of the observed phenotypes was demonstrated to be due at least in part to aberrant motility and chemotaxis patterns. These studies provide unique insight into the molecular mechanisms that control the ability of the Lyme disease spirochetes to complete the enzootic cycle.

Dr. Chris Earnhart's talk described work developing a novel next-generation Lyme disease vaccine based on outer surface protein C. Osp C is expressed by all Bb species and strains and is expressed in the human host for several weeks before being down-regulated. The first generation OspA vaccine killed Bb in the mid-gut of the tick and was only 68-76% effective, requiring very high antibody titers in the human to maintain its effect, thus requiring frequent boosters. The OspA vaccine also raised considerable fears because of the putative autoimmunogenic T cell epitope that might trigger a type of arthritis. Other groups have tried to revise the OspA vaccine by changing amino acids within this immunogenic epitope. Dr. Earnhart then went on to report progress in developing an OspC polyvalent chimeric vaccine. This work appears highly promising and may soon lead to animal trials to test its effectiveness.

Dr. Robert S. Lane gave a brief overview of his research team's long-term studies of the ecology and epidemiology of Lyme disease in California, and then summarized some exciting recent findings regarding the genospecies and genotypes of Borrelia burgdorferi s. l. that infect the western black-legged tick and humans in this region. In particular, he and members of his research team reported in the March issue of the Journal of Clinical Microbiology that Borrelia bissettii-like spirochetes occasionally infect humans. This is the first time that this Lyme disease-group spirochete has been demonstrated to infect people in North America. Previously, it was known as a human pathogen only in central and southern Europe. Dr. Lane also pointed out that northwestern California is highly endemic for Lyme disease, that Ixodes pacificus has at least 108 vertebrate hosts, and that some of the highly invasive strains of Bb found in the Northeast were not detected in CA ticks.

Dr. Karen Newell Rogers presented a talk about novel ways to target chronic inflammation and chronic immune activation among patients with chronic Lyme disease. The primary controversy with Lyme disease has been whether the disease is the result of long-lasting bacterial infection or whether long-term symptoms result from a post-infectious, uncontrolled autoimmune response. By working with inbred strains of genetically identical mice, several researchers have found that mice with different genetic backgrounds display a broad range of symptoms when infected with the same amount of Borrelia. Recent studies have found that inflammation is involved in some symptoms of chronic Lyme disease, including Lyme arthritis. Some researchers would argue that chronic inflammation requires the continuous presence of bacteria, whereas others would suggest that continuous presence of bacteria does not always result in inflammation and that exacerbations of chronic symptoms could result from infection with a different organism—or that chronic symptoms could re-cur from unrelated pro-inflammatory events. Potentially reconciling these seemingly conflicting perspectives on the mechanism of Lyme disease may be the effect of Borrelia burgdoreri's bacterial by-products on Toll Like Receptors, (TLR)-mediated immune activation. TLR appear to be the "gate-keepers" of an inflammatory response. Bacteria, including Borrelia, produce products that, by binding to TLRs on the cell surface, promote leukocyte activation, cytokine production, and acute inflammation. In some genetic backgrounds of mice, acute inflammation is sufficient to fight off infection and resolve disease. In other mouse strains, the pathogens, or in this case the bacteria, get past TLR-induced inflammation and remain symptomatically undetectable in cells and tissues (Barthold, etc); Barthold et al. have found that no matter how severe or mild the disease in any of the genetically inbred strains of mice, there was no more inflammatory disease when the bacteria were eliminated. If bacteria find a new disguise, and then come out of hiding, does the process start over again, resulting in chronic, or relapsing remitting, symptoms of inflammation, until the pathogen finds a new disguise or a new hiding place? Or, even if the Borrelia remain dormant, does exposure to a different pathogen that also produces TLR agonists re-trigger the expansion of latent pro-inflammatory cells that were initially stimulated by Borrelia TLR binding proteins?

Dr. Newell's research is aimed at determining how Borrelia infection, accompanied either by acute response and resolution, or by chronic response and chronic inflammation, is influenced by TLR dependent activation of polyclonally expanded B cells and expression of an individual's immune response genes (specific Major Histo-compatibility Complex encoded gene products) (Newell et al. JLB, Oct. 2010).

Dr. Robert Yolken's talk on "Infections and Human Neuropsychiatric Diseases" focused on the Stanley Center's work at Hopkins which has examined infectious triggers of psychosis. He emphasized that schizophrenia is a major neuropsychiatric disorder with massive medical, social, and economic consequences. Epidemiological studies indicate a role for infectious agents contributing to many cases of schizophrenia, often in individuals who are susceptible due to genetic factors. Toxoplasma gondii in particular has a number of biological properties which suggest that it is one infectious agent contributing to schizophrenia risk. Of particular interest is that embedded within the genes of T. gondii is the code for tyrosine hydroxylase which leads to an increase in dopamine, thus providing one possible mechanism for the association between psychosis and T-gondii infection. He concluded by emphasizing that an increased understanding of the role of infectious agents might lead to new methods for the prevention and treatment of severe neuropsychiatric disorders, such as schizophrenia.

Dr. Josep Dalmau's talk on "The Clinical Spectrum and Cellular Mechanisms of Autoimmunity in NMDA and other synaptic receptors". His pioneering work studying anti-NMDA receptor encephalitis shows how an immune response triggered by a tumor (e.g., ovarian teratoma) or perhaps an infectious process, results in antibodies that can attack critical receptors and synaptic proteins in the Central Nervous System involved in memory, behavior, cognition, and psychosis. Dr. Dalmau's early work in this area was with patients who have cancer, and others who have benign tumors, who develop immune responses that attack the brain; these are called paraneoplastic syndromes. His recent work has led to the identification of new mechanisms of disease, as well as treatments for some previously untreatable diseases. Specifically his group demonstrated that there is a subgroup of patients with limbic encephalitis who have antibodies against the glutamate AMPA receptor, and that these antibodies modify the levels of this receptor – they are no longer on the cell surface, where they do their job, but are internalized or pushed away from the synapses to extrasynaptic sites; this had never been so clearly demonstrated before. Dr. Dalmau showed stunning videotapes of patients with limbic encephalitis with profound neurobehavioral disturbances (e.g., extreme terror) whose symptoms reversed after receiving treatment that interfered with the autoimmune process. He noted that the abnormal movements seen in these patients are not classifiable using currently accepted descriptions of defined movement disorders. Background on the NMDAR hypofunction hypothesis of schizophrenia may be helpful. The descending glutamatergic pathway projects from cortical pyramidal neurons to dopamine neurons,

and normally acts as a brake on the mesolimbic dopamine pathway by communicating through an inhibitory GABA interneuron. Antibodies that decrease the levels of NMDA receptors on GABA inhibitory interneurons may then lead to reduced GABA release. This could then disinhibit post-synaptic excitatory transmission and lead to the release of excessive glutamate in the prefrontal/subcortical structure. The resulting glutamate and dopamine dysregulation may contribute then to the symptoms of psychosis and unusual dyskinesias. Psychiatrists should be aware of these autoimmune encephalitides as 77% of these patients are first seen by psychiatrists (23% by neurologists); 88% are eventually admitted to the ICU and 90% have a CSF pleocytosis. Treatments vary, but include IV Ig, plasma exchange, cyclophosphamide, and rituximab (monoclonal Ab against CD20). This work may be of relevance in the field of Lyme disease given findings that patients with chronic Lyme disease have elevated levels of anti-neuronal antibodies which have been shown in vitro to target neurons in the cerebral cortex and dorsal root ganglia; it remains to be demonstrated however whether these antineuronal antibodies are associated with the chronic clinical symptoms in post-antibiotic treatment Lyme disease.

Dr. John Aucott's talk on "Early Lyme disease" reported from the SLICE prospective cohort and his Maryland studies. He indicated that 75% of patients with early Lyme disease will have the telltale skin lesion within the first 1-4 weeks of infection that lasts from days to weeks and expands in size. He emphasized that the classic description of a "bull's eye rash" occurs only 20% of the time – it is not the most common manifestation of the Lyme rash. Rather, a uniformly red or reddish-blue rash, round or oval in shape, with sharply demarcated borders is most common. Most often the rash develops in places such as the knee, groin, or arm pit, occurring at prime tick season, such as the late spring and early summer. The rash is usually accompanied by fever, chills, and muscular pain in the neck and extremities; these rashes are not extremely painful and are not markedly pruritic. Preliminary evaluation of immunologic responses to early infection with Borrelia show interesting patterns of cellular immune response. These may eventually shed light on the differing clinical outcomes that are seen during the two year study follow up after initial antibiotic therapy.

Dr. Reinhard K. Straubinger's talk on "Canine and Equine Lyme Borreliosis" focused on Lyme borreliosis in animals, especially in dogs and horses. There is no transfer of Borrelia from pets to humans. Epidemiological data generated with animal populations can help to monitor the geographical distribution of Lyme borreliosis (e.g., dogs are excellent sentinels). In experimentally induced infections, not all animals develop disease; for example, in one study up to 75 % of all infected dogs

developed disease, while none of the experimentally exposed ponies showed clinical signs. Regarding clinical disease in naturally infected dogs and horses, no broad epidemiological data are available so far. Contrary to common belief, the presence of serum antibodies does not correlate with clinical signs and infected dogs can seroconvert and stay asymptomatic. In dogs and horses the first signs of clinical disease are mild fever, general malaise, lameness and swelling of local lymph nodes; this stage may go unnoticed, waning after a few days. An erythema migrans has not been described in dogs and horses. With dissemination, local inflammatory reactions can cause pain, swelling and lameness. As shown after experimental tick exposure, dogs became lame 2 to 6 months post infection, with severe lameness lasting for 2 to 5 days (mono- or oligoarthritis). The lameness is an intermittent limping and sometimes recurs 2 to 3 weeks later in the same or another limb. In naturally infected dogs, a glomerulonephritis with protein loss has been described for certain breeds (Labrador Retrievers, Golden Retrievers or Bernese Mountain Dogs); progressive renal disease can also occur, with death or euthanasia 1 day to 8 weeks after onset of the disease without demonstration of viable Bb. Neuropathological findings in infected dogs and horses were described as an asymptomatic encephalitis, mild perineuritis or meningitis. The two-tiered ELISA and Immunoblotting system is the method of choice for LB serodiagnosis in dogs and horses using either whole-cell preparations of borrelial antigens or with recombinant antigen from borrelia. Whole-cell preparations provide intrinsic high sensitivity, but cross-reactivity with non-specific antibodies occurs frequently. The use of recombinant proteins, especially in commercial tests, is now well standardized. In veterinary medicine, IgM detection is not common and recommended, because clinical signs develop weeks after tick exposure when detectable IgG are already present. These IgG antibodies persisted for years; even after successful antibiotic treatment these antibodies were detectable for years in otherwise healthy individuals. The highly variable surface protein VlsE is, according to current knowledge, exclusively expressed in the mammalian host. The invariable region IR6, and even a shorter peptide sequence of IR6 called C6 were found having a high potential as specific antigenic components in serologic test systems. This was shown by evaluating sera from infected humans, dogs, monkeys and mice. In experimentally infected dogs, C6-specific IgG antibodies appeared 3 weeks post infection; hence almost one week earlier than antibodies detected with ELISA based whole-cell preparations. Additionally, another benefit became clear when testing sera of people and dogs before and after antibiotic treatment. Contrary to antibodies against whole-cell components, research demonstrates that C6-antibodies declined substantially a few months after treatment. However, in animals with low C6-antibody levels prior to treatment, the decline obviously was minimal post treatment. Despite their high specificity for borrelial contact, C6-antibodies do not necessarily correlate with clinical signs in dogs and false-positive results may result from maternal antibodies in puppies born to infected bitches. Treatment of C6-positive dogs independent of the presence of illness should be considered carefully. Still, the use of C6-antibody testing in veterinary practice is recommended in order to clarify whether lameness seen in patients is the result of an infection with B. burgdorferi or by other tick-transmitted organisms such as Anaplasma phagocytophilum.

Dr. James Moeller presented a talk on “Immunologic aspects of neuropsychiatric illness: Lyme disease as model”. In this talk, Dr. Moeller reported analyses demonstrating that the level of anxiety and depression among patients with chronic Lyme encephalopathy was highly correlated with a clinical index combining Bb-specific serologic & CSF status and brain metabolism. This represents the first time that psychiatric symptoms in Lyme disease have been directly linked to objective measures of Bb specific immunity & brain function.

Dr. Brian Fallon presented a talk on “Models of Chronic Lyme Disease”. The talk

started with a review of the terms that refer to chronic symptoms and recommendations on how the the IDSA's definition of Post-treatment Lyme Syndrome could be improved. This talk reviewed the evidence regarding models of persistent infection and/or persistent immune activation. This talk also described the results of a recent collaborative study conducted by Dr. Steven Schutzer (PloS-One, 2011) with Dr. Fallon's samples at Columbia, Dr. Nadelson's samples from NJ, and the Pacific Northwest Lab's Proteomics team (Tao Lui, Richard Smith, and Tom Angel) which revealed several important findings: a) that there are approximately 700 unique proteins distinguishing the patients with chronic neurologic post-Lyme syndrome from the patients with chronic fatigue syndrome, clearly demarcating them as different disorders; b) both PTLS and CFS had elevated levels of complement in the CSF proteome, highlighting what appears to be an aberrantly functioning immune system in both disorders, compared to normals; and c) compared to controls, PTLS patients had reduced levels of proteins considered important for the maintenance of CNS cellular architecture, such as axon, neurite, and dendritic spine growth and organization, supporting the neurologic basis for chronic Lyme encephalopathy. He highlighted that these discovery phase results require replication before conclusions can be drawn, but may lead to invaluable diagnostic and treatment marker insights. This talk concluded with reference to other chronic illnesses, such as chronic fatigue syndrome and fibromyalgia, discussing the close interplay with the neurologic, immune, and endocrine systems, and the potential importance of the emerging literature on "Central Sensory Sensitization" to patients with chronic symptoms.

Dr. Andrew Walter reported on Ehrlichiosis and Hemophagocytic Lymphohistiocytosis (HLH) in cases of children diagnosed in Delaware. Ehrlichiosis is an uncommon tick borne disease seen in the mid-Atlantic area and therefore clinicians need to maintain a heightened vigilance. Ticks in the MD/Delaware/PA area carry A. phagocytophilum which causes HGA. Amblyoma americanum ticks in the mid-west carry E chaffeenis and cause Human Monocytic Ehrlichiosis (HME). The elderly have the highest rate of illness due to Ehrlichiosis although more than 20% of children in endemic regions have evidence for past infection with TBRD. Doxycycline is the drug of choice for treatment of Ehrlichiosis since patients sick with Ehrlichiosis may be co-infected with other TBRD which are effectively treated by doxycycline. HLH is a rare complication of infectious diseases including Ehrlichiosis. Hemophagocytic lymphohistiocytosis (HLH) is a disease with major diagnostic and therapeutic difficulties. Primary HLH is an autosomal recessive illness that is fatal with a

median survival among infants of less than 2 months. Secondary HLH may result from a strong immunological reaction from a severe infection; most patients are not immunosuppressed. The most typical findings of HLH are fever, hepatosplenomegaly, lymphadenopathy, skin rash, jaundice, cytopenias, as well as hypertriglyceridemia, coagulopathy with hypofibrinogenemia, liver dysfunction, and elevated levels of ferritin and serum transaminases. Neurological symptoms may be associated with a spinal fluid hyperproteinemia and a moderate pleocytosis. Patients who are very ill with Ehlichiosis or other infection should be immediately screened for HLH with LFT, CBC, ferritin with other specialized tests to follow as needed.

Dr. Andrea Gaito provided an update on the clinical evaluation and treatment of Lyme Arthritis from an autoimmune perspective. Lyme arthritis occurs in sixty percent of patients with untreated Lyme disease .The arthritis may be mono,oligo or polyarticular and is frequently migratory in nature. The spirochete rapidly disseminates to joints by inducing the production of cytokines which then induce vascular permeability, allowing further infiltration of spirochetes into the synovial tissue. The presence of the bacteria can then trigger an autoimmune response in susceptible patients. The musculoskeletal evaluation of a patient with Lyme disease involves a physical exam focused on determining the mechanical and inflammatory state of the involved joint. Both serologic tests and diagnostic x-rays are often required to access the joint pathology. Evaluation of joint fluid for blood count, viscosity and cell type, along with testing for the presence of the Lyme bacteria is essential if an effusion is present. MRIs and synovial biopsies may be helpful in advanced cases. Many rheumatologic disorders may be associated with Lyme disease. These include Rheumatoid Arthritis, Systemic Lupus, Sjogren’s syndrome and hyperviscosity syndromes, such as antiphospholipid antibody disease. The management of autoimmune disorders in a Lyme patient may require additional therapy with disease modifying agents along with an antibiotic regimen. The use of steroids should be limited due to concerns of immunosuppression. Autoimmune disorders with accompanying inflammation should be considered and managed as aggressively as bacterial coinfections in a complex patient, as both can play a significant role in propagating the disease process.

Dr. Ingeborg Dziedzic presented an interesting (and at times entertaining) overview of how Lyme disease impacts the eye, emphasizing that the eye is in part like the skin and in part like the brain. Diseases, like Lyme disease, that affect skin and brain can thus potentially affect eyes. The embryonic connection between eyes and other ectoderm and mesoderm derived organs predisposes them to developmental disorders and infectious diseases. Lyme disease has many clinical forms but they are all related to it being firstly an infectious disease and secondly to inflammation. Eye manifestations that relate to infection with B.burgdoferi tend to be acute and can be recurrent conjunctivitis, keratitis, iritis, retinal vasculitis, retinitis, and optic neuritis. Presenting symptoms for “ITISES” are as follows. Keratitis: visual discomfort, gritty feeling, increased dry eye, cannot keep the eyes open, pain, glare. Iritis: photophobia and eye pain. Vasculitis: may be asymptomatic.

Retinitis: decreased vision. Optic neuritis: loss of peripheral vision first, central vision later or in more aggressive cases, acute loss of vision and it is an eye emergency. Lyme disease eye-related symptoms are as varied as they are seen systemically. These issues should be taken seriously & treated so the patient can function better & recover sooner.

Dr. Vijay Thadani presented an overview of seizures and non-epileptic seizures, showing videos of both. Brain infections such as Lyme disease can lead to the development of epilepsy. This happens as a result of inflammation of the surface of the brain and the formation of scar tissue. Such damaged areas of brain can act as foci from which seizures begin and spread through the brain. Epilepsy is not however a common complication of Lyme disease, and if it occurs it can usually be treated successfully with anti-epileptic drugs. Epilepsy that is resistant to drugs can occur, but when encountered should be investigated thoroughly to rule out other causes of seizures. These include lack of blood and oxygen, and metabolic problems such as low or high blood sugar. The consequences of any brain disease, or any traumatic life experience, include mental stress that can manifest as a conversion disorder with non-epileptic psychogenic seizures. About 25% of patients with seizures refractory to anti-epileptic medication do not have epilepsy but have non-epileptic psychogenic seizures. A few patients have both. Long-term video-EEG recording is the best way to capture events and make a definite diagnosis. Correct treatment depends on correct diagnosis.

Dr. Steve Bock addressed complementary and integrative medicine approaches to the treatment of chronic Lyme disease. Dr. Bock's talk started with the notion that most patients with chronic symptoms don't just suffer from Lyme disease but they also may have other diseases, perhaps triggered by other co-infections. Dr. Bock then proposed that the treatment needs to address multiple symptoms of the "Chronic Lyme Disease Complex" as well as the accompanying dysfunction. He then reviewed the "Wheel of Function" which included a multisystem assessment approach – inflammation, GI function, endocrinology, immune deficiency, nutritional deficiency, stress, sleep disturbance, neurotransmitter disturbance, food allergies, heavy metal toxicity, coinfections. Dr. Bock concluded by discussing various testing and treatment approaches.

Dr. Elizabeth Maloney addressed studies of antibiotic treatment of Lyme disease, providing a thoughtful and critical review of the literature to identify lessons, gaps, and future research needs. This presentation examined the evidence from

prospective studies conducted in the U.S. with regards to adequacy of design, success rates and lessons learned. The evidence from many clinical trials was found to be inadequate due to small sample sizes with high non-completion rates, poor trial designs and limited antibiotic regimens; success rates were unacceptably low. The review also found that the efficacy of prophylaxis studied in the single dose doxycycline trial pertained only to the development of an EM at the bite site; success rates in the EM trials ranged from 60 – 80%. The design of the largest of the chronic post-treatment Lyme trials (Klempner et al, 2001 study – reporting no benefit from retreatment) was limited in that the high bar set for clinical improvement increased the likelihood of a Type II error in a study sample of this size. Additionally, the review called attention to the fact that the retreatment trials by both Krupp and Fallon demonstrated positive treatment effects.