LYME DISEASE IN THE CAROLINAS

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This is a treatise on persistent Lyme disease, or more correctly, neuroborreliosis, and is written for the physician who wishes to learn about it.

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Section 1: Introduction

A most distinctive and disturbing epidemic is growing in America, and few can agree on what it is and how it should be tracked. Lyme Disease (LD) is caused by the tick-borne spirochete Borrelia burgdorferi (Bb) and is acknowledged as the most common vectorborne disease in the United States. According to a recent CDC report, 17,730 Lyme Disease (LD) cases were reported in year 2000 and there have been more than 100,000 cases overall (ref) - but there is a common perception among LD activists, LD patients, and students of this disease that LD is underreported by a factor of 10 or more. Furthermore, the most debilitating form of LD, the persistent or chronic form, often referred to as neuroborreliosis, is debunked, or at least felt to be grossly over-diagnosed

by powerful factions in academic medicine. Unfortunately, this attitude filters down to most treating physicians, especially in a low prevalence region for LD like the Carolinas, whose physicians thereby tend to trivialize or deny the existence of persistent LD, or neuroborreliosis.

For surveillance purposes, the CDC employs a definition for LD as the presence of a physician-diagnosed erythema migrans (EM) rash > 5 cm in diameter or at least one manifestation of musculoskeletal, neurologic, or cardiovascular disease with laboratory confirmation of Bb infection (ref). A number of confounding factors, ranging from physician or patient failure to recognize EM, to inaccurate laboratory testing, serve to disguise the true magnitude of this epidemic. In addition, there is growing evidence that coinfections with other microbes, such as Bartonella hanselae, Babesiosis microti, and Ehrlichiosis chafeensis may occur in as many as 25% of recognized LD cases (ref). Coinfection with any of these pathogens tends to confound the clinical course and present difficult treatment issues. In our experience, patients with a coinfected state tend to have more difficult and complicated illnesses.

Dr. Joseph Jemsek had diagnosed and treated an occasional patient with LD as early as 1985. Based on this experience, he became convinced that Bb infections could persist and cause chronic and/or recurrent symptoms. Since opening its doors in June 2000, the JEMSEK Clinic, which is known as a prominent HIV specialty clinic in the Carolinas with general medicine capabilities, has now become recognized as “Lyme literate”. The Clinic now follows over 600 patients from all over the Southeast with various manifestations of LD.

Dr. Jemsek draws many parallels between his more than 20 years of HIV/AIDS experience and his more recent exposure to LD sufferers…e.g. indifference and ignorance from his peers, and a lack of scientific data on which to base diagnosis and therapy.

The JEMSEK Clinic has made a strong commitment to LD patients. In the past two years, Dr. Jemsek has joined ILADS (International Lyme and Associated Diseases Society), the Lyme Disease Association group (LDA), and is in routine communication with prominent treaters of LD from around the country, as well as enjoying daily access to reviews of literature updates on LD. The Clinic actively works with the South Carolina Lyme Support Group in the Columbia, SC area, as well as the recently formed North Carolina Lyme Disease Foundation,Inc located in Raleigh, NC. Based on our interaction with members of these groups, as well as the growing experience at the JEMSEK Clinic, we hope to contribute to the Lyme literature in the near future. In only two years of intensive interaction with LD patients, the Clinic has garnered numerous testimonials attesting to the benefits of its programs. Furthermore, as the Clinic gains additional clinical experience and insight in LD, patient treatment protocols continue to evolve

(please see our section on Lyme treatment protocols in the main Lyme text – Spring 2003 newsletter).

In late 2002, Christie Roeske, FNP joined JEMSEK Clinic, with a significant portion of her duties dedicated to the care of patients with Lyme Disease. In 2003, Tanya Pusey, FNP joined the Jemsek Clinic to share treatment duties for patients with Lyme Disease. They join Angela Bud, R.N. and director of the LD service, Leslie Rudisell R.N., and Jacki Smith R.N., who together provide full time nursing support for our patients.

Section 2: Background in Borrelia burgdorferi and Lyme Disease

Lyme disease (LD) is a complex and potentially persistent or chronic condition that may affect the human host in many ways. LD is classically described as involving musculoskeletal, neurological (both brain and peripheral nervous system), and cardiac systems, and, while this is largely true, it only begins to tell the story. LD is caused through infection by a bacterium, Borrelia burgdorferi (Bb), which is a mobile, spiral-shaped bacterial organism (see photo below) called a spirochete. Bb consists of a cluster of genotypically and phenotypically divergent isolates collectively referred to as Borrelia burgdorferi sensu lato. In this cluster, three species, B. burgdorferi sensu stricto, B.afzelii, and B.garinii., have been identified as vectors for human illness. Bb sensu stricto is the only species known to exist in North America and hundreds of strains have been isolated (1,2,3,4,5,6,7).

Lyme disease was recognized in 1975 and the name derived from Lyme, Connecticut, the site of an epidemiological investigation of an outbreak of arthritis in adolescents at that time. The researchers included Dr. Allen Steere, a former CDC officer, who was working at Yale University in the Rheumatology section during that period. As cases accumulated and time passed, several parents, dissatisfied and alarmed with the diagnoses and treatments provided by their children's physicians, began to clamor for more definitive action. In large part due to their efforts, Steere and others were dispatched to Connecticut by the CDC to evaluate this outbreak of disabling arthritis. In time, the researchers suspected that an unidentified infectious agent was the culprit and reasoned that it may be tick-borne due to a recurring theme of patient reports of tick bites. In 1977, Dr. Steere and colleagues at Yale University published their work, describing children of that area who had recurrent joint swelling in this epidemic, and so termed this "new" clinical entity as "Lyme Arthritis"(8). By 1979, after further study, these researchers realized that there was a great deal more to this illness than just inflammatory arthritis. Specifically, they began to record the incidence of a characteristic expanding rash termed erythema migrans (EM), which occurred in most of their cases. Other symptoms, primarily neurological and cardiac, also became better recognized. On the basis of this information, Steere and colleagues decided to rename the clinical entity "Lyme Disease", and continued to claim it as a new clinical entity (9). Later, many European academicians would object to Steere's claim for primary discovery by stating that the clinical picture of "Lyme Disease" had been recognized on their continent for decades, perhaps centuries (10,11,12,13).

In 1981, Dr. “Willie” Burgdorfer at the National Institute of Allergy and Infectious Disease (NIAID) discovered the microbial spirochete which proved to belong to the genus Borrelia (hence the name Borrelia burgdorferi) and the family Spirochaetaceae (which also includes the agents for syphilis, leptospirosis, and relapsing fever, among others). A year later Bb was isolated from the deer tick at the Rocky Mountain laboratory of the NIAID (14). Subsequently, the genomic characteristics of Bb have been elucidated and revealed as a single chromosome and several plasmids, both linear and coiled variety (15,16). Important and highly immunogenic surface proteins termed OspA and OspC have been identified and these proteins are recognized to be highly variable and capable of changing or mutating under different conditions (17). OspA is a critical factor in survival in the tick gut, whereas OspC becomes the dominant antigen in the human.

The origin of Bb is unknown, although it is pertinent to note that Lyme-like dermatological lesions have been described for centuries in Europe (10,11). Some then speculate that Bb migrated to America from Europe on a stowaway rodent. Others doubt that Bb could have been here with the pilgrims because there is no record of erythema migrans, etc. In response, we suspect that colonial America was more concerned with the British and dysentery, not necessarily in that order. Undoubtedly, Bb has been around in various forms for centuries, although there may never be factual evidence to support this notion. As is the case with other zoonoses, the human is an accidental host, and is the worse for it.

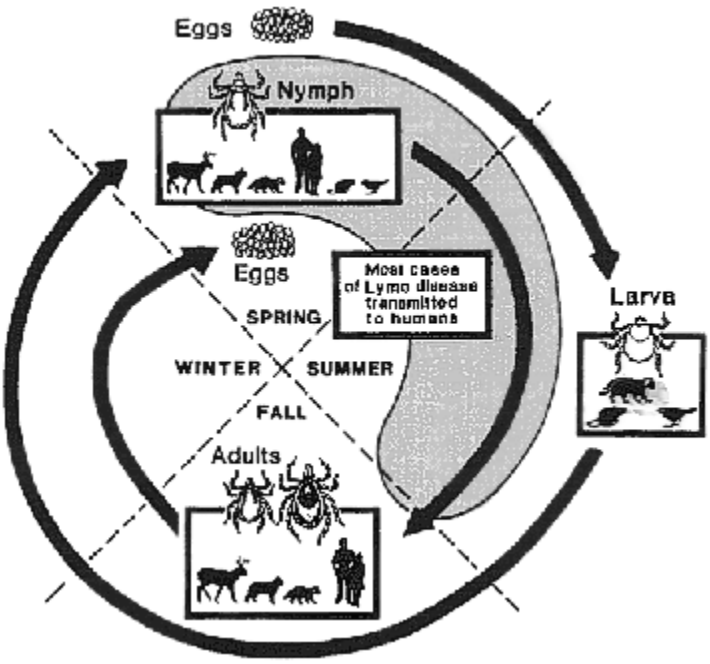
Over 100,000 cases of LD have been reported to the CDC. It is understood de facto that reports of various diseases to the CDC are underreported, but LD may be the all time winner for underreporting (18), so far as we are concerned. We believe that up to 90% of cases are unrecognized and/or unapparent to the host. By this, we do not mean to imply that these infections are insignificant, because chronic forms of Bb infection may follow and cause significant morbidity. When, in fact, Bb becomes chronic, or persistent, many authorities refer to the illness as neuroborreliosis, due to the acknowledged tropism of Bb for nervous tissue, whether it is glial cells or neurons (19,20). One impressive report stated that Bb presence in the cerebrospinal fluid after EM occurred in 67% of their cases (21). Not surprisingly, the eventual clinical presentation in persistent LD often portrays a major neurological disorder, undoubtedly the most severe manifestation of this illness. Some of these neurological syndromes mimic the pattern of findings one would expect to find in patients with multiple sclerosis (MS)(22,23)or amyotrophic lateral sclerosis (ALS) (see discussion below). In fact, it is well known that many neuroborreliosis victims have been mistaken for MS or, less commonly ALS, before the correct diagnosis was rendered. We have seen this clinical presentation on numerous occasions at the JEMSEK Clinic over the past three years.

Section 3: Life Cycle of Ioxodes Scapularis

In most cases, transmission of the spirochete Bb is by the Ixodes scapularis tick (I.scapularis), which is commonly known as the deer or mouse tick, or more correctly, the black legged tick. The Ixodes tick is very small in comparison to the more common dog

tick. To understand the transmission of the Bb spirochete, one must review the life cycle of the I. scapularis or “black legged” tick.

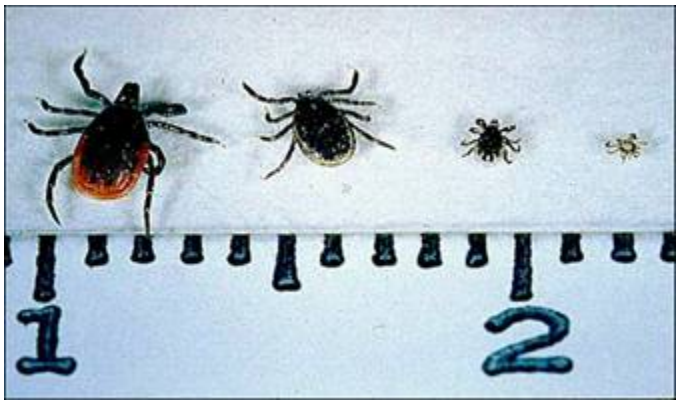
The Life Cycle of the Ixode Tick



The adult Ixodes tick lays eggs in the spring. The larvae develop in a month and by summer are ready to feed on mice, birds, rabbits and deer (many believe only the white tailed mouse and perhaps other rodents are intermediate hosts and that deer and other putative hosts merely provide temporary lodging and source of feeding). It is during this time that larva feeding on Bb infected mice acquire the Bb spirochete. In fall and winter the larva become dormant. As spring arrives the larva molt into a nymph form, which feed on deer, mice, rabbits and humans. It is during this spring and summer season (primarily May through September) that the infected nymph form of the tick transmits the spirochete to humans, as well as continuing the future spread of the spirochete by transmitting it to the white tailed mouse. By the fall, the nymph has transformed to an adult tick. Although adult ticks carry Bb, they seldom transmit the disease to humans because the adult forms are active during the fall and winter, a time when humans have a more limited outdoor exposure and wear more clothing when outdoors because of the elements. This is also a time in which the ticks are larger (see below illustration) and therefore more visible, a particularly germane point when one considers that the tick form may require up to 48-72 hours in order to transmit the Bb spirochete (see below).

Section 4: Risk for Transmission of Bb

Finding a tick on the skin does not equate to an infection. Once a tick crawls onto a human it will take at least 24 hours to find an appropriate site to feed. The most common sites are warm and moist areas, such as the genital and axillary areas, behind the knees, and on the neck or midriff. Once the tick has chosen a site, it inserts its barbed mouthparts. This usually goes undetected by the host. Next, the tick injects its saliva, which helps promote an optimal feeding opportunity for the tick. The saliva contains many active anti-inflammatory agents that render the body's natural response to the bite useless, but in some cases an allergic reaction occurs. This may become an advantage to the host who becomes aware of the tick at that time and is therefore able to remove it prior to engorgement. However, in most cases the bite remains unnoticed due to the minute size of the nymphal tick that has been likened to a tiny freckle. Upon attachment, the tick secretes a compound called cementum, a substance that adheres the tick directly to the skin. Once these steps are accomplished the tick will begin to feed. While it is commonly stated that the Ixodes tick must feed an average of 48-72 hours in order to become sufficiently engorged to transmit Bb, this may not necessarily be the case (24). As with many scientific statements that become dogma, the concept that transmission of Bb requires a minimum of 72 hours came from animal studies which are now criticized as being flawed (25). In all probability, it is likely that some Ixodes nymph forms require 72 hours or more to transmit Bb, while other nymph ticks do so in less time. In the end, we learn that one should not take comfort in a limited exposure to the Ixodes scapularis tick and related species.



Left to Right: Adult Female Ixodes Tick, Adult Male Ixodes Tick,
Nymph, And Larvae With A CM Ruler

The likelihood of contracting LD is dependent on many factors. As mentioned above, the duration of engorgement and the stage of the tick involved may be major factors. Only a minority percentage of ticks are infected with Bb (or other pathogens such as Babesiosis, Ehrlichiosis, or Bartonella), but the consensus among epidemiologists is that the absolute numbers are increasing, likely in part due to a succession of mild winters on the East coast, which have lead to increased survival rates for adult ticks (26). In addition, the recently described theory of dilution is an explanation by which Bb may proliferate (27). In short, this theory points out that the destruction of forested areas leads to elimination of some of the native species due to loss of habitat. Less discriminating and more enduring species like the white tailed mouse, a favorite host for Ixodes scapularis,

survive preferentially as they can exist almost anywhere. With less “competition” for a host, Ioxodes mediated infection with Bb naturally increases. In addition, it turns out that deforested sites which leave five acres or less, a common occurrence in urban America, also tend to favor species such as the white-tailed mouse, simply because other species require larger territories for survival and/or optimal propagation (28).

The description of “coinfections” with Bb by the aforementioned microorganisms is also becoming better recognized, and has important clinical implications for diagnosis and treatment. Unfortunately, the scope of this report does not allow for detailed descriptions of the epidemiology, clinical features and treatment of these important tick-borne infections. In future updates, we hope to provide this information. Until then, the reader is referred to the following sites (29,30,31,32,33,34,35).

In highly endemic areas for LD, such as certain counties in Connecticut, New York, and New Jersey, territories known as “hot pockets” have been identified, where the incidence of tick infection with Bb exceeds 25% of the population studied (36). Those living in these areas obviously have a greater risk of contracting LD, and communities now recognize this and therefore are responding with awareness campaigns (37). Unfortunately, no such information about tick infestation currently exists for the Carolinas or surrounding regions. We speculate that the number of cases of LD will increase over time in the Southeast, and we can only hope that this will lead to identification of high risk areas so that public officials, once they accumulate necessary information, will make the necessary changes for surveillance and referral.

Debate about the best approach to limit the epidemic is being conducted regularly (38). Broad based methods have been proposed, such as those aimed at limiting the acknowledged vectors, whether it be reduction of deer, rodent, or tick populations through an assortment of measures. Most of these suggestions appear doomed to failure, as they are intuitively impractical. Some of the more creative approaches, such as rodent traps which coat the animal’s fur with a long lasting insecticide, and thereby reduce the tick infestation, appear promising as a rational, targeted, and affordable (39).

Those living in areas of lower incidence for Bb infection are at increased risk during travel to endemic areas. These individuals and groups tend to be more vulnerable since they are not aware of the dangers of Bb and the necessary protective measures that are recommended to avoid tick bites. Please take note of the precautionary measures discussed later in our article in the section “An Ounce of Prevention”.

Finally, the issue of transmission of Bb that is not tick-borne must be acknowledged. Regrettably, it is proven that human vertical transmission, i.e. mother to child, exists and is more likely to occur when the mother is infected in the first trimester (40). Fortunately, the incidence of transmission is believed to be quite low. Additional risk factors for transmission, which are routinely identified in other models of infection, have not been studied in vertical Bb transmission. For example, we know nothing about the relative risk or characteristics of intrauterine transmission versus exposure in the birth channel, breast feeding, etc. However, we recognize that perinatal transmission of Bb can result in a

multisytemic illness which can prove fatal (18), although we do not have evidence for the converse situation, i.e. asymptomatic infection for a prolonged period. Even less well studied is the issue of sexual transmission. Borrelia species, including Bb, have been found in genital secretions (41). A close relative of Bb, treponema pallidum, was perhaps, until HIV happened, the most notorious sexually transmitted disease known to man. Barriers to recognition and diagnosis (see discussions to follow) present major impediments to understanding the epidemiological patterns of Bb. It is of interest that one of our colleagues, Dr. Bill Harvey in Houston, has begun to study his population of chronic fatigue patients, many of whom have proven to be serologically positive for Bb infection. In noting various demographic and social characteristics among his patients, he has begun to question whether all Bb infections represent a zoonoses (personal communication). He considers routine sexual transmission of Bb a distinct possibility, certainly one worthy of a longitudinal study. Again, such epidemiological information will be virtually impossible to gather without more verifiable means of recognition and diagnosis than are currently available. The implications Dr. Harvey's observation and theory are profound and deserve an assiduous scientific effort.

Section 5: Other Vectors - A New Syndrome?

More information has been recently forthcoming, which provides putative evidence to support the role of other ticks in the transmission of Bb and other microorganisms (42,43). For example, in North Carolina, the Lone Star Tick, or Ambylomma americanum, is more common than Ixodes scapularis (above referenced deer tick), and has been implicated in transmission of Bb. In the western US, another tick, Ixodes pacificus, is recognized as the vector for Bb, and behaves much like its counterpart in the eastern US, Ixodes scapularis. In contrast to the Ixodes scapularis tick, we know much less about the nature of transmission of Bb, when other vectors, like the Lone Star tick, are involved. It would seem unlikely that the Lone Star tick requires 48 to 72 hours of attachment in order to transmit Bb, since the human host would in most instances be expected to recognize the attached tick before that time. No one knows how transmission by a different vector such as Ambylomma americanum would influence the epidemiology and natural course of LD.

Another Lone Star tick borne illness, Southern Tick Associated Rash Illness, or STARI, has been described in the southeast and southern Midwest US (44,45,46). This syndrome bears a great clinical resemblance to LD, including the presence of a bull's eye rash. The organism responsible for this illness has not been positively identified, although Bb sensu lato is clearly not the agent, as multiple efforts to identify this pathogen from biopsies of the rash have been found negative (47). The presence of another spirochete, named Borrelia lonestari, which has been recovered from the tick midgut but not from clinical specimens in patients with STARI, is of considerable interest. Borrelia lonestari differs in DNA homology from Bb by about 5-7% (48). One important difference for B. lonestari is the absence of the OpsA gene, an important surface marker antigen for Bb (49). Until more is known, we cannot assume that this is a self-limited disease, as it is purported to be. For that matter, STARI may simply represent one of the many variant strains of Bb. A family practice physician residing in Missouri, Dr. Ed Masters, is credited with

recognizing and categorizing this tick borne illness. As a consequence, the infection is commonly referred to as “Masters Disease” as well as the older eponym STARI.

With Rocky Mountain spotted fever and now West Nile virus also firmly entrenched in the south, there is a much broader differential diagnosis list for the clinician to consider when one encounters flu like illness in warm weather months. The treating MD needs to be particularly mindful should they encounter a rash and/or any alteration of mental status, or encephalopathy, since failure to understand the potential severity of this process may lead to both serious short and long-term morbidity.

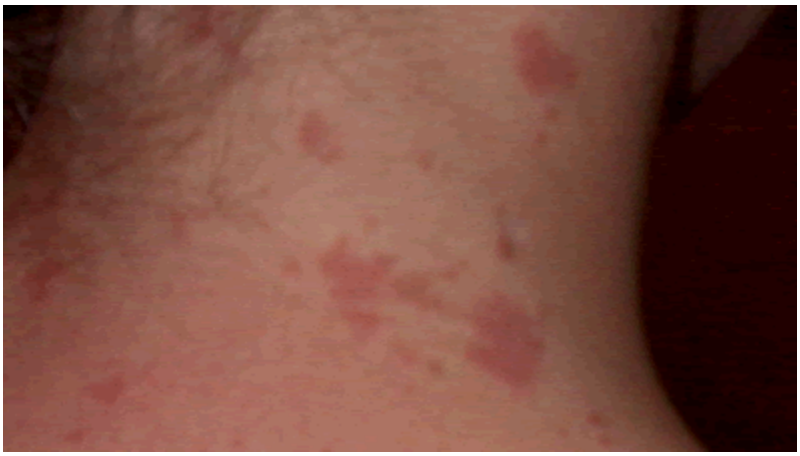
Section 6: Erythema Migrans

Generally the first symptom associated with LD is a dermal reaction at the site of the tick bite called erythema migrans (EM). The incubation period for transmission of Bb is broad but generally averages 7 to 10 days, and can present as early as 2 or 3 days after the tick is recognized (50). It is commonly stated that 60% to 80% of Americans with LD experience this initial cutaneous lesion, characterized as an erythematous target shaped rash, which should measure at least 5 cm in width to qualify as EM or bulls eye rash (see below). In fact, this percentage is clearly an overestimate, as a majority of patients do not recall a rash, certainly not a classic bulls eye form with central clearing. Recent reports confirm, that in most cases, one experiences a more amorphous flat, expanding rash rather than the target or bulls eye shape (51). As mentioned previously, an allergic reaction can occur due to the saliva injected by the tick and may be confused with EM. The salivary reaction is typically small, usually less than1 cm, and generally appears one day and disappears the next.

Erythema migrans, on the other hand, is a gradually expanding lesion, frequently taking the target or bulls eye form, which develops 7-10 days after the bite and can last for days to weeks (52). The characteristics of size, expansion, and chronicity of the rash are more important and consistent features with LD than the morphology of the rash. It has been noted that unusual, multiple simultaneous EM lesions can occur. Whether this represents a condition compatible with disseminated EM or, perhaps less likely, represents multiple simultaneous Bb bites, is not clear (53). We have had several patients describe and document this feature of the illness. Our record for disseminated Bb target lesions is 50 or so EM lesions noted at one time, reported by a female podiatrist who resides in the countryside just a few miles south of Charlotte, NC.

A little recognized fact about the EM rash is that it can and does recur, usually in the original site, with or without antibiotic therapy. We estimate that between 5-10% of patients demonstrate this phenomenon during their illness. Other patients remark that they have migratory rashes of moderate duration from time to time that remain unexplained, until a diagnosis of Bb infection is made. More commonly, however, is the presence of rash occurring after the onset of antimicrobial therapy. A subset of patients manifests a mildly pruritic, maculopapular eruption, often appearing in clusters, typically lasting for only a few days or so. We note that some patients erupt with rash repeatedly while on antibiotic therapy, often in different areas. Eventually this dissipates as the

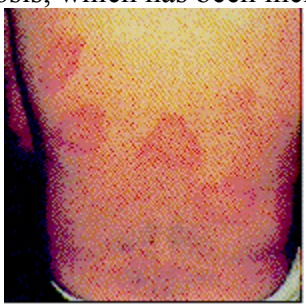
patient improves on antibiotic therapy. Pressure points may play a role in the appearance of the rash, but gravitational influence does not appear to play a role in terms of the site of eruption, i.e. as one would see in a vasculitic presentation characteristic of most drug reactions. The first appearance of rash has been reported as late as 6 months into therapy (personal observation). This has led to obvious diagnostic challenges when one is on antibiotic therapy and has to consider a drug reaction. However, we have come to recognize that the LD rash on treatment presents as flat or occasionally raised coalescent islands of erythema, in contrast to the classic generalized morbilliform rash caused by a drug reaction. When confronted with this clinical picture, the JEMSEK Clinic views this as a positive indication of therapeutic benefit, probably representing a dermal form of the "Herxheimer reaction", and so we generally proceed cautiously on with antibiotic therapy, usually with eventual resolution of the rash.

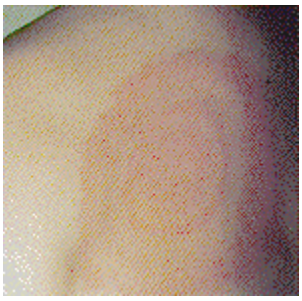


In the initial infection stage, or acute illness, a variety of flu like symptoms may occur a few days after the appearance of the rash. Specific symptoms may include fever, malaise, fatigue, joint pain, muscle pain, lymphadenopathy, and not uncommonly encephalopathy, or altered mental status, with or without headache. We believe that, consistent with the conventional doctrine, most cases of LD respond to relatively short courses of antibiotics. However, we prefer to treat at higher than usual doses for up to four weeks instead of 7 to 10 days, in the hope that we may prevent a few cases from going on to develop neuroborreliosis (see discussion below). We believe the benefit to risk ratio with this approach is extremely high. Unfortunately, given the lack of consensus on diagnosis of LD and issues on the validity of a persistent form of this infection, the clinical trials needed to confirm the value of our approach cannot easily be performed at this time. Nonetheless the Clinic has interviewed numerous individuals who present to us with a history of relapsing into a persistent set of symptoms after having been administered the standard 7 to 10 days of therapy for presumptive LD.

As was mentioned above, in many cases the symptoms of LD present in the absence of EM or any typical expanding rash. Occasionally this can be explained by the fact that the rash has occurred in the scalp, hairline, or in a posterior location where it may not have been easily visible. In persons of color, the obvious difficulties in identifying a rash

undoubtedly hold true here as well. In cases without rash, one may also wish to consider Ehrlichiosis, which has been increasingly referred to as “spotless fever”(54,55,56).





Section 7: Basic Issues in Understanding Lyme Disease

The protean characteristics of Bb disease are undoubtedly accounted for by several factors. First, several hundred Bb strains exist (7,57,58,59) and there is a limited, but growing, understanding about their significance in the clinical spectrum of LD, in either acute or chronic infection (2,3). At present, strain differentiation is strictly in the province of a research laboratory. Likewise, in vitro sensitivity data for various Bb strains is scarce and testing for antimicrobial sensitivity, as is done routinely on other bacterial pathogens, is unavailable except at a research level. In fact, most of the published information comes from Vera Preac-Mursic, who began reporting both in vitro and in vivo (gerbil model) data in the mid-80s (60). Her excellent research program includes a recent description of an animal model evaluating 20 strains of Bb, which compared responses to a range of antimicrobial therapies (61). Despite apparent similarities amongst the strains, her findings are disconcerting to LD treating practitioners because she noted wide discrepancies in antimicrobial sensitivities between strains in the response to the antibiotics selected. Naturally, the antibiotics studied were selected on the basis of conventional therapy at this time and included, among others, ceftriaxone, cefotaxime, amoxacillin, doxycycline, and azithromycin. While some Bb strains are non-pathogenic and the description of an experiment with gerbils may not parallel the human experience, Preac-Mursic’s work raises the serious question of potential antimicrobial failure in our patients due to drug resistance. A recent report suggests that markers for antibiotic resistance have been identified by researchers at New York Medical College (62). These findings will accelerate the understanding of genetic vectors that govern resistance patterns in Bb strains. This knowledge may ultimately translate into improved clinical management of Bb infections through a better understanding of drug resistance mechanisms and patterns.

Documentation of infection with multiple Bb strains in the same human host has now been reported (2). This begs the question about the clinical implications for persistent Bb infections in a particular host over time. Furthermore, the Bb organism has an astounding ability to alter its molecular structure even as it passes through the gut of the tick vector (63), and in the host where it can “morph” into an L form (lacking a cell wall) or, more significantly, into a cystic form which is antigentically dissimilar from the spirochetal form (64) (see photos below). This process occurs in reverse when it is advantageous to

Bb. Undoubtedly these are survival mechanisms developed by Bb. Whether all Bb strains have a like capacity to do this is not known, but strain variability in terms of propensity to develop the cyst form may theoretically explain some of the clinical differences observed in the treatment of individuals with persistent LD.

Likewise, strain variation in terms of the degree of oxygen tolerance, or the extent to which a strain is microaerophilic or tolerates oxygen, may explain observed differences among our patients' response to various therapies. In addition, in recognition of Bb's intolerance to higher oxygen partial pressures (65,66), interest in use of hyperbaric oxygen treatment (HBO) has emerged as an adjunctive program for difficult or poorly responsive cases of neuroborreliosis. While the JEMSEK Clinic has no personal experience with this treatment, we have discussed this approach with leaders in the field (personal communication with Mitch Hoggard). Given the current state of affairs, i.e. insufficient clinical trials for the treatment of neuroborreliosis, the JEMSEK Clinic has an open mind to the possibilities that HBO therapy presents.

It is interesting to speculate that metronidazole (flagyl), which is arguably the most potent anaerobic antimicrobial available, and which is used by LD treating physicians to eradicate the cystic form of Bb (see below), may actually be effectively treating some highly anaerobic Bb strains which ceftriaxone and other commonly used antimicrobials would not be expected to eradicate (see below) The venerable antibiotic clindamycin, which has excellent activity against both strict anaerobes and facultative anaerobes, may provide a therapeutic option not generally employed by others and certainly not recognized to date in the Lyme literature. At the JEMSEK Clinic, we have treated over 30 patients to date with either oral or IV clindamycin as adjunctive therapy to their main program (see treatment section below). In our more difficult cases where response to intensive combination antimicrobials was not forthcoming, we serendipitously discovered positive clinical responses whenever clindamycin was employed in therapy. Since then, we have been consistently and profoundly impressed by the clinical response to clindamycin therapy, particularly when administered intravenously. Thus, in our view, clindamycin may ascend to a role of first line intravenous therapy, alone or in combination with more conventional approaches such as ceftriaxone or imipenem.

Bb Transformation To Cyst Form

The host response is critical in any infection model. In the case of Bb, as with other infections, the host response may be influenced by the Bb inoculum, the diversity of infecting strains, and the presence of coinfecting organisms. At the JEMSEK Clinic, we have elicited several case histories in which the patient describes a single or multiple EM rash in the appropriate setting (e.g. deer hunting and skinning) without any recognizable immediate sequelae. However, months or years later, after experiencing a second or third EM outbreak, usually at different body site, the patient becomes acutely ill and may go on to develop chronic or persistent symptoms. We argue that these events represent recurrent, rather than reactivation episodes, perhaps caused by a different Bb strain(s). Alternatively, it is conceivable that multiple Bb infections simply overwhelm the immune system over time. Multiple strain infection with Bb has been described (67) but there are no incidence or prevalence data whatsoever which might provide insight into these issues. Intuitively speaking, it might be of considerable clinical import with regard to the recommended length and types of therapy one should offer, were we able to correlate or predict that, for example, simultaneous infection with multiple Bb strains led to a more serious illness. Likewise, in chronic neuroborreliosis, the identification of infection with multiple coexisting Bb strains could conceivably influence a clinician's approach to therapy. In fact, there are pertinent biologic correlates to support the notion that multiple strain infection has clinical implications. In recent news at the 10th Clinical Retrovirus and Opportunistic Infection conference, there were reports of well documented infection with two separate strains of HIV that led to accelerated and more severe symptoms (68). We now believe that some Bb infections which manifest EM may in fact simply represent the first known manifestation of Bb infection in previously infected patients, some of whom go on to develop persistent symptoms. We also speculate that infection with multiple Bb strains, whether it occurs through initial simultaneous infections or through repeated serial exposure, may have profound implications on immune response and disease expression. Inotherwords, when EM is identified with LD, one cannot assume that this is the first encounter for the human host for Bb infection. Only extensive epidemiologic prevalence studies using more sensitive serologic tests than are currently available, which logically ought to be done in known "hot pocket areas", can answer that question. Of course, in these cases, a coinfection would also need to be considered, as this likely occurs more than commonly appreciated and clearly correlates with more severe illness (29,30,31,32,33). Studies to clarify these issues are desperately needed.

In addition to an extracellular phase, Bb has been identified as an intracellular pathogen (69). The organism has been identified to reside in macrophages (69), fibroblasts (70,71), glial and neuron cells (19) and presumably many other sites. The capacity for an organism to exist in an intracellular habitat carries certain implications. For example, most persistent intracellular infections evoke a predominately Th-1, or cell-mediated, response from the immune system. Activation of Th-1 and the attendant cytokine release (see below) in a chronic infection state accounts for and generally leads to a number of debilitating symptoms. A model for this in humans is Mycobacterium tuberculosis, which manifests several of the properties we are attempting to ascribe to Bb, namely latency, slow replicative properties, reactivation, and escape from immune surveillence. Perhaps the conventional tuberculosis model for treatment, which in the past has consisted of

therapy for up to 18 months, is a good way to begin to think about the approach to neuroborreliosis therapy. We know that, with the proper antimicrobial molecule, we have the capability to eradicate intracellular pathogens (72), so it would be important to use antibiotics known to work by penetrating the cell and interfering with a specific crucial intracellular bacterial processes, which generally imply bacterial ribosomal or DNA sequencing interference (73). Examples of these agents include tetracyclines, quinolones, and macrolides which, incidentally, also work well on susceptible organisms outside the cell. In contrast, cell wall active agents, such as penicillins and cephalosporins, may work well against Bb in the extracellular state, but would have no effect in the intracellular compartment. To further complicate the treatment issue, while we do have some limited in vitro susceptibility data on Bb (60), we have no information about the organism's ability, if any, to develop drug resistance, a routine occurrence with almost all other bacterial pathogens. Acknowledging the capacity for Bb to alter its molecular structure inside the tick gut and elsewhere, we feel it is likely that Bb has the capacity to mutate against antibiotic pressure in vivo. In addition, we now assume that the neuroborreliosis patient may have multiple Bb strains, some of which may be resistant to conventional antimicrobial therapy. This then presents a presently unsolvable clinical conundrum in therapy when our patient on long term therapy fails to respond. We are then left with clinical empiricism as the only rational approach.

Patient-to-patient variability in the spectrum of host response is well accepted and may depend not only on the immune experience, but also on various unique individual immune markers such as HLA type, natural killer cell activity, lymphocyte subset profiles, and so forth. Inotherwords, we all respond in our individual way to an invading microbe. It is clear to us that a significant portion of our LD cases occur as a result of a reactivation phenomenon, which in turn implies that Bb is a dormant infection in these individuals. It is conceivable that many Bb infections, both recognized and inapparent, result in a latent infected state with the potential for reactivation whenever the proper circumstances occur, such as immune activation for any number of reasons. One could then theorize that there are individual predetermined immune sets whose variations account for one patient being able to suppress Bb infection indefinitely and another patient suffering the manifestations of Bb infection to varying degrees.

Unfortunately, the understanding of the immunologic response to LD is in the figurative "dark ages", especially when compared to dramatic increases in our fund of knowledge on the immune system and HIV/AIDS. Fortunately, some glimmer of hope for understanding the immune changes with Bb have recently been observed and reported by Dr. Raphael Stricker, a LD treating specialist who resides in San Francisco. He has made the very interesting observation that a certain lymphocyte subset, CD57, has been found to be depressed in patients with active persistent Bb infection, and that the CD57 levels return to a normal level when symptoms of disease come under control (74,75). CD57 cells are classified as a subset of natural killer cells which appear to be downregulated by Th-1 cytokines interferon-gamma, interleukin-2 and tumor necrosis factor-alpha. These cytokines are recognized to be increased in LD (76,77,78,79). In discussing these findings, he notes that other lymphocyte subsets appear to remain in normal range. While further study is needed, these findings suggest that CD57 may

become a useful laboratory marker in the treatment of neuroborreliosis, something LD treaters have never had before. We suspect that this finding will eventually be shown not to be specific for Bb alone, but at least for now this information opens a crack into the door behind which the secrets of Bb host specific immune response are kept. It would seem that the entire field of Bb infection and human immunologic response lies before us and that we need to begin to do systematic reviews on HLA haplotype status, analysis of T cell subsets, and other immunologic markers so that we can better understand the factors involved in primary response and chronic infection.

In a prospective unblinded treatment trial, Dr. Stricker describes 31 patients treated with either oral or IV antibiotics (orals used for predominant musculoskeletal symptoms and IV for predominant neurological symptoms) who experienced normalization of CD57 counts when symptoms remitted. Of considerable interest was his finding that restoration of CD57 counts required an average length of therapy of 5.4 +/- 3.3 months for those treated with oral antibiotics and 10.5 +/- 5.7 months in those patients on IV therapy (75). This finding represents a degree of affirmation for the use of long-term antibiotic therapy in our chronically ill LD patients.

In summary, regarding host-organism interaction, we espouse the view that Bb may be a true persistent infection in a significant number of cases, associated with persistent clinical symptoms in a small percentage of these cases, and lie dormant via “immune suppression” in the vast majority of these persistently infected individuals. We believe that persistence is more common in unrecognized or untreated cases versus those treated within the first 2-3 weeks of the EM rash or other symptoms, but that early treatment for Bb by no means guarantees that persistent LD, i.e. neuroborreliosis, will not develop.

We support this idea of latency or dormancy by describing a group of patients at JEMSEK Clinic who developed clinically consistent and laboratory confirmed cases of LD in a low incidence area (North Carolina) at the wrong time of year (winter). In addition, a significant number of our cases have provided a history of documented LD sometime in the past, as long as 15 years earlier, which had been treated according to the convention of the time and from which the patient had appeared to recover. Later, these patients present with clinical and laboratory evidence for neuroborreliosis, often in dramatic fashion. None of these cases suggested reexposure to Bb in the interim or “asymptomatic” periods, and several had actually moved from a high endemic area (northeast sector) to the Carolinas. In most of these cases, the patient had an easily identifiable “trigger”, such as a severe illness, e.g. documented parvovirus infection, or a severe and sustained emotional trauma that preceded the recurrence of Bb syndrome. This situation would then seem akin to what is described for chronic fatigue, or immune dysfunction syndrome (IDS), or for that matter, herpes simplex or herpes zoster reactivation infections. The immune system is “turned on”, or “activated” and a chronic endogenous or latent infection is reactivated. Since the immune system was not able to eradicate Bb in the first place, it cannot be expected to perform well in this reactivation event. Instead, what usually occurs is that one develops a persistent state of immune activation with its attendant cytokine barrage and cascade of immunologically active proteins or cytokines (76,78,79). These cytokines, which include tumor necrosis factor,

IL-6, IL-1, and others (see above), are well known to be associated with symptoms of fatigue, cognitive dysfunction, and abnormal muscle pain, just to name a few unpleasant symptoms (80). What is poorly understood and seems counterintuitive is the realization that, in the patient with reactivation Bb, the immune system was in fact able to suppress the infection for extended periods of time. Paradoxically, once this immune surveillance is lost, these patients can become quite ill for lengthy periods and present very difficult treatment challenges. It would appear that a fundamental shift in immune competence as it relates to Bb has occurred in these cases. Once again, there is a corollary with HIV infection where patients who are virologically stable inexplicately lose this state of viral suppression, a condition termed "viral escape"(81,82,83,84).

In neuroborreliosis, direct central nervous system (CNS) involvement with Bb is well recognized and documented, typically involving the leptomeninges (85,86). In addition to the well-described cytokine effect (see above), cognitive and other abnormal CNS reactions are purported to result from Bb associated neurotoxins which have been speculated to exist, but which remain unidentified and unproven (87). A currently popular theory exists for the handling of this unidentified neurotoxin, which suggests that a common resin such a cholestyramine may be successful in reducing levels of this toxin. The JEMSEK Clinic does offer products like cholestyramine to our patients, but always with the caveat that there is no scientific validation for this therapy and that therapy is optional. Quite honestly, we don't expect any scientific information to be forthcoming which will document the benefit of this approach. Our strong bias at the JEMSEK Clinic is that a neurotoxin theory is not necessary to explain cognitive deterioration in neuroborreliosis. We believe that the combination of immune dysregulation with its attendant cytokine barrage, influencing CNS function, as well as direct local effects caused by Bb infection in the leptomeninges (85,86), adequately accounts for these symptoms.

Finally, local CNS immune mediated inflammatory changes contribute to a significant and disabling component of the neuroborreliosis syndrome, the so-called "inflammatory headache". We have noted that chronic headache, as well as prominent signs of sensory aversion, e.g. photophobia, hyperacusis and tinnitus, are extremely common, but will eventually improve with therapy. Some of the symptoms are so intense that patients are unable to tolerate ambient light or noise and must remain withdrawn from light and sound sources in order to be comfortable. One of our patients put it aptly as follows, "when I walk in a room I have to be careful not to shut the door too hard or turn on the light, or else I throw up". This alarming group of symptoms relates to cerebral edema or "brain swelling" associated with the inflammatory process caused by Bb infection. This edema, however, is not recognized on an MRI or CT brain study, nor is elevated cerebrospinal fluid (CSF) pressure confirmed when measured during a lumbar puncture. Nonetheless, the cerebral edema due to inflammatory Bb CNS disease is sufficient to cause these symptoms, and is a consistent and predictable feature of advanced neuroborreliosis. In extreme cases, we have had some success in therapeutic lumbar punctures employed to reduce CSF pressure in patients who have intractable headache. More commonly, we prescribe a medication that has proven to be a reliable method for rapid relief for headache and the related sensory aversion symptoms. Acetazolamide (Diamox), a

carbonic anhydrase inhibiting diuretic, recognized to be useful in the treatment of headache associated with altitude sickness, has been very useful in providing relief to these tortured individuals. Side effects are common and usually transient, but when present, consist of paresthesias usually involving the face and distal extremities. Potassium wasting is inevitable with treatment and so serum potassium blood levels must be monitored closely.

Section 8: More on LD Symptom Complexes

LD sufferers may present with a myriad of symptoms, which reflect disseminated infection and the affinity of Bb for certain tissue types, notably the brain and peripheral nervous system, joint space and dermal tissues. In the textbook definition, acute illness is followed in some cases by early dissemination, which is sometimes characterized by peripheral neuropathies (mononeuritis multiplex), or cranial neuropathies (e.g. Bell's palsy). Depending on the nerve involved, the patient may complain of primarily sensory (i.e. burning, shooting pain or numbness) or motor symptoms (weakness, fatigue, tremor, etc). In persistent cases of LD, or neuroborreliosis, the neurological symptoms may wax and wane or even disappear, with or without therapy. In some individuals, however, these neurological complaints may become the predominant set of symptoms and, over time, may become severe and bizarre enough to mimic multiple sclerosis (MS) or amyotrophic lateral sclerosis (ALS). In fact, many of our advanced and severely ill patients have been diagnosed with MS or ALS (primarily MS) when they come to us, but very few actually meet the diagnostic criteria for MS or ALS when expert neurologists critically examine these cases. We believe that the neurologic symptoms in early disseminated and certainly persistent LD are so common and important that the absence of these symptoms may call the diagnosis of Bb infection into question. Many of our advanced and disabled patients have already had at least one extensive neurological evaluation and most have had at least one referral to a neurologist. Naturally, these workups include an MRI of the brain that invariably is non-specific for MS, but often shows non-specific enhancing "white lesions", usually in the subcortical regions. Interestingly, these are the same lesions found in some immune dysfunction cases where they have been whimsically referred to as "unidentified bright objects". Undoubtedly, these radiologic changes represent inflammation due to possible infection or changes in the glial cells (22,23), and perhaps the neuronal cells as well. Understanding that persistent Bb infection is capable of contributing to a diagnosis of immune dysfunction syndrome, or chronic fatigue, one has to wonder how many IDS cases have been incorrectly or incompletely diagnosed.

As stated, the vast majority of our patients describe symptoms of cranial or peripheral neuropathy. In our experience, the current protocols used by most neurologists for peripheral nerve conduction studies are relatively insensitive and fail to detect both the sublime and the obvious neurologic deficits in our LD patients. When we have had occasion to order nerve conduction studies, we have consistently found that the somatosensory modality was the most sensitive and helpful tool. Unfortunately, this modality is usually excluded from the standard report. Clinically, we commonly encounter mononeuropathies in the thoracoabominal or pelvic distribution, the symptoms of which have led to exhaustive and unrewarding workups for gall bladder, colon,

pleural, or pelvic disease by previous physicians. We usually have the benefit of these workups, of course, and so our efforts to reduce symptoms in these cases usually involve reassurance and treatment with a neuroleptic agent such as gabapentin. In most cases, this approach is successful but sometimes we require assistance from physical or occupational therapists, useful and important resources greatly appreciated for difficult cases.

Other patients with neuroborreliosis who are not labeled as having MS may exhibit great difficulty with balance, presumably as a result of peripheral or spinal cord associated neurological involvement affecting the lower extremities. Where cord involvement is concerned, we have now had three patients with documented neurogenic bladder that almost certainly reflects sacral plexus involvement.

Where balance issues are concerned, the root cause of these difficulties may lie in abnormalities of proprioreceptive dysfunction and/or muscle wasting associated with prolonged illness. In some cases there is also clearly a CNS or vestibular component contributing to imbalance. It is not unusual for these ailments to dominate the clinical picture and a significant number or our patients have come to us in wheelchairs or with other chronic ailments requiring the use of assistive devices.

Where LD is complicated by cranial nerve disease, the classic clinical cranial nerve malady linked with Bb infection is Bell's palsy, or 7th nerve paresis. Other common cranial neuropathies we have witnessed include direct eighth nerve (auditory) involvement causing maddening tinnitus and sometimes leading to deafness (88). Advanced neuroborreliosis can lead to brainstem pathology, which may cause optokinetic disturbances, or difficulty in tracking objects in motion. Holmes-Adie syndrome, or unilateral papillary dilatation due to 3rd nerve involvement, have been reported as well (89). Acute anosmia, or loss of smell, was the major complaint in a newly diagnosed Bb patient recently seen at the JEMSEK Clinic. Possibly the most common cranial neuropathic symptoms we detect are reports of a sensation of sharp or radicular facial pain, twitching of the facial muscles, or dysesthesias described as either numbness or itching "like something crawling all over my face". Obviously, these symptoms reflect inflammation of the 5th nerve. We always query our patients about these symptoms since many patients will fail to volunteer these complaints. They sheepishly state that the symptoms are so bizarre that no one believes them and so, out of embarrassment, they no longer discuss this issue. We believe that these cranial neuropathies, as well as other associated symptoms such as tremor, assorted tics and regional dysesthesias of the torso or extremities, are more common than realized in persistent Bb infection and reflect a generalized polyneuropathy syndrome. Hence, we feel this supports our preference to refer to persistent LD as neuroborreliosis. Interestingly, prolonged antibiotic therapy in this population often creates a flare of the neurological symptoms, akin to the dermal "Herxheimer" phenomenon mentioned previously. This can be highly unpleasant and the patient will require a great deal of reassurance and encouragement, as well as providing symptomatic relief with the therapies just mentioned.

In our experience, we have had the opportunity to identify and study at least three individuals with a narcolepsy-like syndrome associated with LD. None of these cases

came to diagnosis easily. In fact, all of them had extensive cardiac and endocrinologic evaluations without a diagnosis forthcoming. It took clinicians an average of 3 to 4 years before the link between borrelial brain involvement and the symptoms were connected. One of our patients was so severely affected that she began to wear a football helmet at home to prevent or minimize further skull trauma with potential brain injury. Genetic narcolepsy screening was negative in all of our subjects. In referring two of these patients to a sleep specialty clinic, after a seizure disorder had been ruled out, we learned that the differential diagnosis was either an atypical cataplectic event or postinfectious idiopathic central nervous system hypersomnia (personal communication). Certainly the latter diagnosis fits well with what is known about Bb and CNS disorders. For this reason, we believe that a narcolepsy-like syndrome, perhaps best described as postinfectious idiopathic hypersomnia, should be added to the litany of CNS disorders described in this disease.

We have observed that the vast majority of our patients with persistent LD have ongoing cognitive dysfunction, or chronic encephalopathy (see prior description). In some cases, this may be the only symptom, and in a significant number of patients it is the most prominent symptom and is often debilitating. Several of our persistent LD patients have undergone neuropsychiatric testing by professionals who document IQ scores well below the patient's historical levels, or at least grossly inconsistent with the academic or professional standing the patient had accomplished prior to their illness. We regret that this testing is not commonly available. Other validating procedures for the workup of chronic encephalopathy include brain SPECT scanning, which usually indicates abnormal blood flow in the encephalopathic Bb infected brain. Since this screening procedure is now more readily available, the JEMSEK Clinic has begun to utilize this procedure more often, recognizing that abnormal findings are non-specific. We look forward to the increased availability of PET scanning, which reflects metabolic activity in the brain and would be expected to offer more sensitive and specific information that brain SPECT scanning. We are hopeful that Dr. Brian Fallon's work will provide some answers to these questions (see below).

Experiencing acute encephalitis with acute LD is by no means a prerequisite to developing cognitive difficulties. However, in our clinical experience, if initial symptoms of confusion and disorientation fail to clear promptly, the prognosis for protracted CNS symptoms is high. Many patients tend to have variable courses in this regard, too often with progressive decline in cognitive abilities over the years. Still others demonstrate a reactivation or relapsing pattern in which encephalopathic symptoms can be severe and disabling. Specific cognitive problems include decreased ability to concentrate, recent memory deficits, mood disturbances, word-finding difficulties and geographic disorientation. These disturbing symptoms are often referred to as "brain fog" by our patients. The germane concern is whether or not irreversible CNS change occurs after a period of time, and one must assume that this is the case. Nonetheless, the JEMSEK Clinic feels that every patient deserves a trial of intensive treatment before all hope of improvement is abandoned.

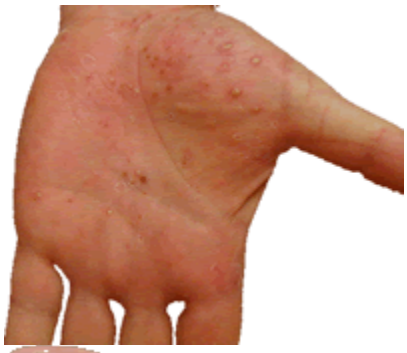
Mundane sleep disorders (see discussion on narcolepsy above) commonly accompany persistent LD and are one of the first items addressed in the initial visit at the JEMSEK Clinic. In fact, if problems are found, we attempt to deal with them prior to or in concert with the onset of LD therapy. Our philosophy is that no illness can be optimally treated until a proper sleep cycle has been restored. Our patients with LD often have severe sleep disturbances, especially if these patients happen to manifest immune dysfunction syndrome with fibromyalgia.

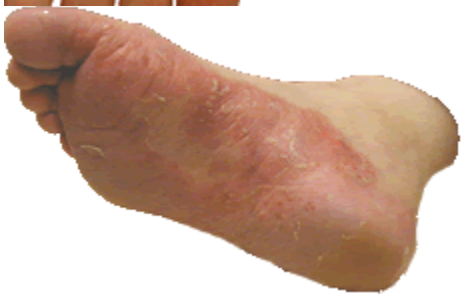
In addition to the role of Bb in organic CNS and peripheral nervous disease in neuroborreliosis, we firmly believe that various psychiatric and mood disorders result from Bb CNS involvement. We include a mental status evaluation in our initial and subsequent reports, along with all other symptoms and signs (90,91,92,93,94,95). Certainly cognitive issues related to Bb are well described in the literature (92) and we do all we can to address these issues with our patients. Dr. Brian Fallon, a psychiatrist well published in LD, works at Columbia University in New York City and has been awarded an NIH grant for the evaluation of neuropsychiatric manifestations of LD, using some of the latest imaging resources such as brain SPECT scanning and PET scanning. Dr. Fallon is currently actively recruiting patients. If you are interested and believe you may qualify for these trials, please contact our office for further instructions.

Cardiovascular manifestations of Lyme disease are seen in 5% of untreated patients and are largely described as transient mild atrial-ventricular block. However, a subset of our patients have had to undergo temporary pacing of the heart due to life threatening cardiac nerve conduction disturbances. In addition, at the JEMSEK Clinic we have recognized several individuals, mostly younger women, who manifested unexplained tachycardia, with heart rates in the nineties and in whom all cardiac and metabolic studies have been normal or non-diagnostic. In our limited experience with several individuals to date, after all the medical information has been processed, we find that antibiotic treatment over time tends to be associated with resolution of this problem. We would hypothesize that the events occur as a result of direct involvement of Bb at the sinus node or an extranodal site where excitation occurs due to pathologic neurogenic changes brought on by Bb infection.

Other reported LD associated cardiac conditions include neurocardiogenic syncope, myocarditis, myocardiomyopathy, and pericarditis (96,97,98).

We have already discussed the presence of multiple recurrent rash episodes in some patients, which can be a striking clinical feature. One of the more dramatic and interesting dermatological presentations is acrodermatitis chronica atrophicans (ACA), which was recently diagnosed in two of our patients with persistent LD (see photo).





We understand that Bb has been recovered from these lesions, according to previous reports (99). In fact, ACA was reported in Europe in the 19th century (10) and by the end of the century reported in the United States as well (100). One of our patients improved dramatically after about 4 weeks of combination IV/oral therapy, while the other is still symptomatic and waiting to begin more aggressive antimicrobial therapy.

Some less well recognized complications of LD that we have recorded at the JEMSEK Clinic include TMJ disease, chronic gingivitis, erosion of enamel and other dental changes, assorted tremors and tics, pressure-related neuropathic symptoms (e.g. an arm going to "sleep" while resting on a car door while driving), intensification of migraine syndromes, and the presence of palpable nodules in a peripheral nerve distribution, which we hypothesize represents glial hypertrophy of an affected nerve, mimicking a neurofibroma. Several of our patients describe a burning or "icy hot" feeling extending from their neck down the spine with certain movements, such as dorsiflexion of the neck. Some of these neuropathies mimic sinus disease or other chronic headache syndromes. Because of the frequency with which 5th nerve inflammation exists, we have found it helpful to add a novel physical test to our exam, namely tapping the pre-auricular area with the examiner's middle digit, to elicit a response of pain, numbness or tingling in the V2 or V3 distribution of the 5th nerve. It has been surprising to note how often this maneuver yields positive results.

In our neuroborreliosis population, many patients have musculoskeletal complaints, and occasionally these are the major and most debilitating problems, sometimes accompanied by fever and chills. Typically, large joints are involved and the arthralgias are migratory, which in fact fits the classic description for LD. In a few cases, actual arthritis is evident, although only rarely does this persist. When it does persist and comes to joint replacement surgery, we have anecdotal reports in which orthopedic surgeons, upon

opening the joint in question, discover a cheesy, fibrous exudate which is uncharacteristic for the usual bacterial infection and which proves to be negative or sterile on routine smears and cultures. This is the prototypical “Lyme joint” which almost no one in the operating arena ever recognizes. In fact, some surgeons stop there and refuse to go on, believing that their patient has an unusual and previously unrecognized infection that makes their job impossible. However, if the arthroplasty continues after these initial concerns are addressed, we have noted a high rate of success in joint replacement (personal experience).

In the past 3 years, we have treated 3 individuals who had ocular complaints as their presenting symptoms. Two of these cases presented as posterior uveitis and the other with Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE). One of the cases of uveitis was acute and the other chronic. The acute case was associated with symptoms of confusion, headache, and CSF lymphocytic pleocytosis, suggesting diffuse CNS involvement. Later, she would manifest more generalized symptoms such are arthralgias, fever, severe fatigue, and so forth. The chronic uveitis case appeared at first to have symptoms localized to the eye alone, but later systemic symptoms became prominent and included various dysesthesias, unexplained headache, photosensitivity, and arthralgias. Full testing for thyroid and connective tissue disorders, HIV and STDs, and all routine studies were negative in both cases. Both were treated with steroids initially, without clinical improvement. A diagnosis of Lyme disease was made through our clinic after referral. At this point, the ocular status is much improved on intravenous antibiotiotic therapy, although neither has had full resolution yet of their non-ocular complaints. The case of APMPPE is a self referred 81 y/o Caucasian male who had enjoyed excellent health until he suddenly developed problems with fatigue and “weak muscles”, “foggy brain”, and shortly thereafter developed bilateral visual problems that were ultimately diagnosed as APMPPE. In reviewing the differential diagnoses possibilities in the literature and on the internet, the patient came to the conclusion he probably had LD. He convinced a friend and local physician to commence therapy with oral antibiotics and the visual and systemic symptoms improved significantly over the next few weeks. However, whenever antibiotic therapy was withdrawn, symptoms have relapsed. Eventually a laboratory diagnosis for LD was made. He is currently stable and improving on a high dose oral combination antibiotic program, which fortunately he is able to tolerate. APMPPE is rare and was originally described by Gass in 1968 (101,102). The etiology of APMPPE is controversial and the argument basically consists of theories of direct invasion of the retinal pigment epithelium proposed by Gass versus involvement of the choriocapillaris with inflammation at this level caused by a hypersensitivity reaction to an external antigen (103). Certain HLA haplotypes have been shown to be associated with this disorder, with 56% of APMPPE patients reported to be HLA-DR2 positive in one series, whereas, in another series, 40% express HLA-B7. These MHC proteins may present viral or bacterial antigens to helper and cytotoxic T cells and activate the immune response leading to capillary and pigment epithelial cell inflammation (104). This information suggests that HLA haplotypes, and therefore individual immune makeup, may play a role in the immune response to LD, as it does in other disorders (see our previous discussion on LD and immunogic response). In fact, there was some limited

data on the predisposition of certain HLA haplotypes to arthritis with LD (105), but more needs to be done.

Curiously, we have noted that several of our LD patients test positive, sometimes at high titer, for rheumatoid arthritis. We consider these to be false positive serologic epiphenomenon associated with an activated immune system. In most, but certainly not all of these cases, classic measures of inflammation, e.g. sedimentation rate and C reactive protein, are normal. In reviewing our cases where C reactive protein levels are elevated, we can find no clinical patterns that would predict either disease severity or progression, but titers do tend to fall in response to treatment. This suggests that some neuroborreliosis cases may manifest inflammatory markers and activity not found in other cases. In evaluating all possibilities, we routinely test for lupus syndromes and have found no consistent pattern. However, one measure of widespread inflammatory change has been noted in our practice, namely the measurement of the anticardiolipin antibodies. We believe that up to 40% of our patients with active persistent LD will demonstrate positive tests to either IgG or IgM anticardiolipin antibodies. We consider this to be a secondary phenomenon that occurs as a result of widespread endothelial disturbance due to LD leading to an ensuing immune response. In fact, a positive anticardiolipin antibody test has become a very useful secondary laboratory marker for us in our pursuit of an LD diagnosis, where direct Bb testing remains negative. Only rarely have we documented true thrombotic events associated with these findings, but we generally recommend two baby aspirin in this circumstance regardless. We distinguish this acquired situation from the true antiphospholipid syndrome, whose cause itself, of course, remains unknown.

Finally, pervasive fatigue, often debilitating, is almost universally present in our more severe cases of persistent LD. The similarities to the classic description of Chronic Fatigue Immune Dysfunction Syndrome (CFIDS) are unmistakable and usually include relapsing fatigue, as well as lymphadenopathy and sore throat. Unlike CFIDS, treatment with antimicrobials should benefit the persistent LD patient, although response to these therapies is often slower and less certain in the group of patients with the longest history of symptoms. Key distinctions between persistent LD and classic CFIDS, even where LD is a cause for CFIDS, have to do with the presence or history of clinically significant neurological symptoms and/or joint pain or arthritis in those patients with LD. CFIDS is clearly often associated with fibromyalgia, which may be disabling in some cases. However, joint pain or overt arthritis are not features of CFIDS, but they are common in persistent LD. Other debilitating conditions, such as cognitive dysfunction and, to a lesser extent, CNS irritability, are present in both CFIDS and LD; these symptoms are probably mediated in similar fashion for both conditions by a dysregulated immune system (see above discussion).

In summary, as we take a complete history and physical on all new patients and constantly reevaluate all new or unexplained complaints, we focus on five symptom categories in our initial evaluation of persistent LD, or chronic neuroborreliosis. Later on, focusing on these symptom groupings during antibiotic treatment is of critical importance and benefit to patient care. These categories are 1) cognitive dysfunction, 2) CNS irritability, 3) B symptoms, 4) peripheral neurological symptoms/findings, 5) chronic

fatigue state. A typical clinic chart at JEMSEK Clinic will reflect periodic "grading" in these symptom/sign categories. As an example, with 1 being the worst and 10 the best or norm for the patient pre-illness, the patient is asked to grade their symptoms 1 to 10 in each category on their personal scale. Inotherwords, a rating of 10 reflects absence of symptoms in categories 1 through 4. Where the fatigue scale is concerned, 10 reflects that patient's usual state of well being pre-illness ---as an example

Category	Date Of Visit
1) Neurocognitive Function	5/10 (Short-term memory,word finding, etc.)
2) CNS Irritability	6/10 (Photophobia, hyperacusis)
3) B Symptoms/signs	8/10 (Muscle and joint pain)
4) Neurological	2/10 (Mononeuritis multiplex)
5) Fatigue	4/10 (compared to pre-illness)

In this theoretical case, our patient has prominent neurological symptoms that overshadow everything else. However, the patient's neurocognitive decline is severe enough to adversely impact job performance and interpersonal relationships to a significant extent. In almost all patients with these characteristics, one would expect major limiting fatigue and perhaps a mood disorder. The only area in which this patient is relatively spared is the absence of serious musculoskeletal complaints.

Assuming this is our baseline reading, once therapy is initiated we would periodically return to our survey and do updated comparisons. While this approach may appear overly simplistic, we have found it to be very useful in the monitoring of these complex patients.

Section 9: Endocrinopathy Syndromes in Neuroborreliosis

- to be added Summer 2003

Section 10: Laboratory Testing for Lyme Disease

The laboratory testing of Bb has been a source of great debate for as long as the tests have been available. Ideally, one would prefer to culture the organism from tissue or blood (the culture medium of choice is Barbour-Stoenner-Kelley medium), but this has proved highly impractical due to the low recovery rates typically observed, in part due to the paucity of organisms involved. A surrogate method, commonly used for other pathogens, is the polymerase chain reaction (PCR), which utilizes techniques to magnify limited amounts of antigen. While quite useful and specific when positive, this technique is also limited by the paucity of organisms in blood, urine and infected tissues. Other techniques for antigen capture, such as the PCR urine panel and Lyme Dot-Blot assay (LDA) from IgeneX Lab, are now under evaluation at the JEMSEK Clinic, possibly later will be used both for screening and confirmation of state of disease.

When dealing with antibody responses to Bb or any other infection, one is always at the mercy of the vagaries of the immune system response involved. Serologic or antibody testing has always been regarded as problematic at best, with the caveat that one may

"live or die" by the report. The basic variables in testing include the timing and degree of antibody response. To be useful to the clinician, these disease specific results must be easily quantitated and reported on a scale or measurement that embodies a meaningful correlation with a clinical entity or fact. In some systems like the Immunoblot assays, however, the test is either positive or negative depending on whether a certain marker is present. The important concept about serologic testing is that no test has intrinsic value in and of itself. It is the interpretation of the test report that makes things interesting, and often there is more art than science when guidelines are being drawn. After this deed is done, both clinicians and patients have to live with what has been decided, until the next revision happens.

In virtually all infections, the IgM class of antibody (immunoglobulin) appears first and therefore represents a marker for an early infection. In most immune models, the IgM antibody gives way to the well-known IgG antibody class, usually regarded as the major enduring antibody response in chronic infectious diseases or other immune models. In almost all infection models, after just a few weeks, the IgM antibody level wanes to the point of being non-detectable and does not recur. However, a confounding fact in Bb infections is that the IgM antibody may persist for years, a very unusual situation in most disease states. Logically, one would have to conclude that this reflects an ongoing reactivation or persisting and continually renewing infectious state of Bb infection. Most active diagnostic laboratories involved with LD tend to agree with this notion. Therefore, the JEMSEK Clinic requires that a positive IgM antibody be present in order to declare laboratory confirmation for an active LD case. As discussed below, this most likely will be a Western Blot test. The presence of either a positive IgG ELISA or a positive IgG Western Blot test does not confirm active disease, and may only signify dormant or inactive (suppressed) infection.

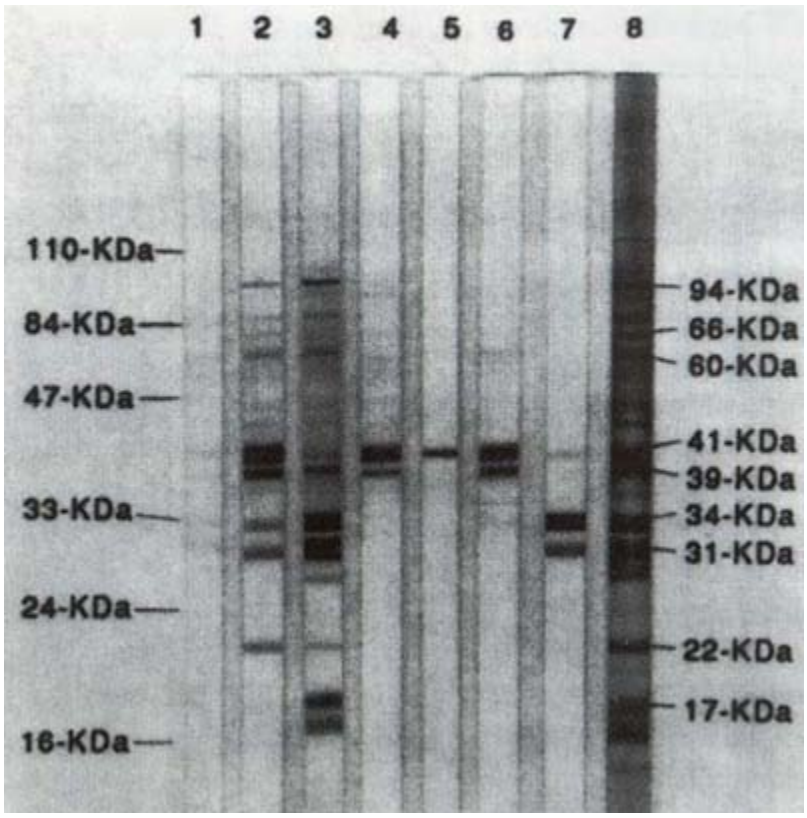
There are various techniques accepted for screening for both types of antibodies, most notably the ELISA or IFA (Enzyme Linked Immunosorbant assay and Indirect fluorescent antibody), known for their widespread applicability and high level of sensitivity. In contrast, the Immunoblot assays are generally regarded as insensitive but highly specific since a specific set of proteins are isolated from Bb (such as outer coat antigens Osp A and Osp C) and set up in an agar electrophoresis field to be mixed with serum from the host. A positive reaction to one of the proteins is called a "positive band" and requires visual interpretation of a line or band in the agar by the laboratory personnel. In LD, by protocol per the CDC and another group called the Association of State and Territorial Public Health Laboratory Directors (ASPHLD), there are 10 proteins set up for IgG testing and 3 proteins set up for IgM testing.

Based on this information, one would naturally conclude that the ELISA would make an excellent screening test for LD and that the Immunoblot Test, in this case, the Lyme Western Blot (WB) Test, would be an insensitive, but highly specific and confirmatory assay. This is precisely the case for other models of infection, a notable example being testing for the Human Immunodeficiency Virus (HIV), a retrovirus, where this two-tier system of screening with ELISA and confirming with Western Blot technology works beautifully. In 1995, a CDC/ASPHLD joint committee apparently felt the same approach

would apply for LD as they introduced a two-tier system for serologic confirmation, i.e. a positive ELISA or IFA followed by a confirmatory positive WB. Unfortunately, almost one/third of patients with LD are IgG seronegative during the first year and later the percent negative by ELISA only increases, up to 50% at two years. Clearly, the next generation ELISA test will need to increase sensitivity for Bb by incorporating more unique and specific antigens in their protocol, similar to what one finds in the WB analysis.

To compound matters further, this committee also deemed that, for a WB to be positive, 5 of the10 listed bands must be reactive (qualifying bands include 23-25, 39, 31, 41,45, among others) in order to be IgG positive, a situation that merely indicates that the subject was infected sometime in the past. In order to be positive for IgM WB testing, 2 of 3 listed bands positive for IgM (qualifying bands include 23,39,and 41) must be present. Of interest is the fact that bands 31(OspA), 34(OspB), and 93 are considered highly specific for Bb but are excluded as qualifying bands, according to current criteria. It is equally curious that the antigen for band 31(OspA) was included in the ill-fated LYMErix vaccine, but apparently does not merit any respect from the creators of the diagnostic criteria (106).

In our experience at the JEMSEK Clinic, we have discovered that these qualifying diagnostic standards are virtually impossible to satisfy in a large majority of our patients who otherwise fulfill clinical criteria for a LD diagnosis. In testing well over 200 patients for Bb, we can recall only one person who met the CDC criteria for 5 positive IgG Western Blot bands. We have fared considerably better in testing for IgM Western Blot through laboratories such as MDL in New Jersey, LabCorp, and IgeneX in California. Still, it often requires multiple tests at multiple laboratories before we retrieve a positive report. As was stated above, the three IgM bands selected for qualifying a Bb infection are 23, 39, and 41. It is widely recognized that band 41 is present in the general population at a high incidence and therefore is a common false positive. One then wonders why band 41 is included at all in this small group of antigens that qualify a Bb infection. On the other hand, both bands 23 and 39 are considered highly specific for Bb infection, yet we require at least 2 bands for a diagnosis. Since we feel that the specificity of either the 23 or 39 band is quite high for Bb infection, and therefore the false positive rate exceedingly low when one of these bands are present, we believe that the detection of only one of these antigens is highly probable for laboratory confirmation of active LD. In this way, we differ in a major way from the stated criteria of the currently establishing committee.



It is curious to note that some of our patients only convert to a laboratory positive after they have received antimicrobial therapy, whether it is oral, intravenous, or a combination of the two. We suspect this phenomenon stems from Bb die-off on therapy, with an ensuing boosted immune response. As we have stated, fully one-third or more of all patients with active Bb infection will test negative with current methods (far more will be undiagnosed employing Lyme disease illiterate MDs), and so, as much as those of us in Infectious Disease would like a positive or confirmatory laboratory diagnostic report to comfort us, and we will continue to strive for this piece of paper to "soothe our souls", neuroborreliosis still remains a clinical diagnosis.

Recently, critics of the two-tiered system have correctly pointed out that the current LD ELISA does not meet the criteria of a screening test (sensitivity > 95%), especially in a setting where prior antimicrobial therapy may blunt an antibody response. For this reason, the policy at JEMSEK CLINIC is to include the WB as a screening test for LD. We look forward to industry improvements in LD testing that are desperately needed. We also recognize that the biology of the spirochete Bb in human infection poses special problems in laboratory diagnosis. Indeed, for this reason, it may be many years before significant progress is made in this area.

Section 11: The Herxheimer Reaction

In a field in which clinical findings can be vague and imprecise, and where helpful monitoring laboratory tests are lacking, the Herxheimer reaction is an indispensable

clinical tool in the treatment of persistent LD, or neuroborreliosis. In theory, Herxheimer reactions occur when an administered antimicrobial agent has successfully led to lyses of certain organisms (107). By definition this phenomenon is not unique to Bb. Fortunately, however, the Herxheimer reaction appears to provide a highly reliable barometer of therapy in Bb, so much so that a treatment course which lacks the Herxheimer response places the diagnosis of persistent Bb in serious doubt.

The reaction was first described in 1895 by an Austrian dermatologist Jarisch Adolf Herxheimer, who was practicing in Vienna, and later confirmed by his brother Karl Herxheimer, who was also a dermatologist, practicing in Frankfort (108,109). During these times, both physicians were responsible for treating syphilitic lesions and employed various preparations of mercury, arsenic and bismuth in these therapies. The key observation noted by both physicians was that, shortly after treatment of syphilitic skin lesions had been administered, many of their patients developed fever accompanied by rigors, drenching sweats, and nausea and vomiting. In addition, they found that the syphilitic skin lesions flared and became larger before healing; results were best in the patients that experienced this reaction, which typically lasted for 2 to 3 days.

The debate about the cause and nature of this predictable reaction has raged on for decades. Various theories have ranged from a vascular reflex mediated by the autonomic nervous system (110) to a direct toxic effect of the antimicrobial on tissues (111). In 1943 Mahoney described the first Jarisch-Herxheimer reaction in syphilitic patients treated with the relatively new antibiotic penicillin (112). Classically, the Jarisch-Herxheimer reaction occurred when treating the secondary stage of syphilis, at a time when a widespread rash may occur and the spirochetal burden is high. Even today, medical students are taught that a Jarisch-Herxheimer reaction occurs as a result of treatment of secondary syphilis. Most physicians are not aware that the Herxheimer reaction occurs in Bb infections and has been described in a variety of other diseases, many of them caused by spirochetal organisms such as Treponema pallidum (syphilis) and Bb in LD. A short list of treated spirochetal infections noted to manifest Herxheimer reactions includes Relapsing Fever (Borrelia recurrentis), Yaws (a subspecies of Treponema pallidum), Rat Bite Fever (spirullum minus), and perhaps Vincents Angina (spirochetal mouth forms) (113). Non-spirochetal infections manifesting the Herxheimer event after treatment include Brucellosis, Glanders, Anthrax, and even Leprosy (mycobacterium leprae) (113).

In 1972 Gudjonsson reported on a summary of experiments that entailed almost a decade of work (114). He concluded that the Herxheimer effect was not allergic in nature and was likely caused by a leukocyte pyrogen released at the time of phagocytosis. Most now believe that the pyrogens in question are exogenous pyrogens, or endotoxins, derived from components of the bacterial cell wall. In the case of Bb, the pyrogen is most likely the lipoprotein moiety which comprises the outer coat of the organism. These lipoproteins, specifically OspA and Osp B, have been shown to have potent B cell mitogenic and cytokine-stimulatory properties (78). It is widely recognized that antibiotic therapy may promote endotoxin release by virtue of its microbicidal effect which leads to the disintegration of the bacterial organism and exposure, or presentation, of endotoxin. On recognition of the endotoxin, polypeptides such as IL-1, interferons, or tumor necrosis

factor (TNF), otherwise referred to as endogenous pyrogen (EP) or pyrogenic cytokines, are released by the monocyte/macrophage system(115). It should be pointed out that only minute quantities of EP are needed in order to generate fever and other systemic symptoms. In the extreme case, such as gram negative bacterial sepsis, high and persistent levels of endotoxin are present and lead to sepsis syndrome with capillary leak syndrome and vascular collapse. In the Bb model, with a relatively low number of organisms present and with limited and inconsistent die-off with each round of antibiotic therapy, one could conceive a model in which constitutional complaints, mediated by pyrogenic cytokines, are manifested in an ongoing and rather unpredictable manner. This then would represent the defining principle for the Herxheimer reaction in Bb infection. In predicting a pattern of response based on our knowledge of Bb infection, we would expect these symptoms to be worse initially, depending on die-off rates, and to not be life threatening, but likely to be life altering. Our clinical experience supports these precepts.

Published reviews have suggested a periodicity exists for Bb activity or replication, specifically that symptoms of fever and malaise, etc. occur at 4 week intervals (116). Others have created so called mathematical models to support this hypothesis. While we respect this author's opinion, we find it difficult to understand how there could be synchronicity in any given polymorphic Bb population (often consisting of multiple strains) in any given host. The matter merits further study and validation. In females, increased symptoms and increased urinary shedding of Bb has been documented in the perimenstrual period, suggesting a hormonal influence (personal communication Dr. Nick Harris), and so it would seem possible that periodicity may exist in menstruating females (although our more seriously ill female LD patients routinely develop menstrual irregularity).

In our clinic, prior to starting any antimicrobial therapy, especially if our patient is naïve to treatment, we emphasize to the patient that they may notice certain significant clinical events while on therapy. In the occasional patient in whom we have no firm diagnosis but where we are suspicious enough to offer short-term empiric oral therapy, we are intentionally a bit vague about providing information to the patient about the Herxheimer effect, as we do not wish to influence a response by suggestion. We have found the Herxheimer response in LD to be as myriad as the course of persistent LD itself. It is naïve for one to expect to witness simply a flu-like syndrome, although this certainly happens. Instead, generally one sees an intensification of pre-existing symptoms, e.g. increased brain fog or muscle/joint pain, where these symptoms were reported prior to therapy. On the other hand, it is equally common to take reports of new symptoms, e.g. headache in a patient who previously reported symptoms other than headache. In general, the Herxheimer reaction is worse in our most seriously ill patients and most violent at the onset of therapy. The Herxheimer response typically occurs within 3 to 5 days, but may take up to 2 weeks to appear. These symptoms may persist for days or weeks and often become a major management concern as our patient may suffer considerably in the process of treatment. Eventually, as therapy progresses, we tend to witness a dampening of the intensity of the Herxheimer response, as well as some reports of positive clinical gains. Introduction of new therapy, as we cycle antibiotics through our treatment schedule (see treatment program to follow), invariably leads to

intensification or new symptoms, all of which are unpleasant. In fact, if we do not observe a new response when therapy is added or substituted, we question the efficacy of our program. Later in this report, we refer to dermal or neurologic Herxheimer phenomena, which we feel reflect local manifestations of pyrogenic cytokines in response to treatment.

Regrettably, but not unexpectedly, we have treated a number of individuals whose Herxheimer experience is so intense and prolonged that continued treatment is virtually impossible. After exhausting all customary supportive and treatment measures, which incidentally never includes the use of systemic steroids, we have resorted to the off-label use of infliximab (Remicade) in these cases, with positive results in a significant majority of those treated. Therapy with infliximab is not continued if the initial treatment does not provide significant relief. Where relief is provided, however, we are convinced that judicious use of this approach, in the occasional situation where it may be needed, has allowed Bb treatment to continue. Undoubtedly, as other cytokine blockade therapies become available, we will evaluate their potential role in this setting as well.

The escalating headache symptoms experienced by some patients on intensive antibiotic treatment is a Herxheimer effect that merits special attention. This “Lyme” headache is thought to be linked to cerebral edema brought about by Bb die-off and the ensuing creation of inflammatory microfoci in the leptomeninges. In our experience, severe CNS symptoms, such as incapacitating headache, are more likely to occur when the patient has had prominent CNS symptoms or findings pre-therapy, e.g. encephalopathy, aseptic meningitis, optic neuritis, and so on. In 2-3% of our treated cases, we have had to resort to one or more therapeutic lumbar punctures to provide relief by lowering intracranial pressure.

Given the miserable experience which we may exact on our patients during therapy, we would perhaps be better off if we followed the advice of Russell McMillan, DDS, DPH, who wrote the Arthritis Trust of America in 1994 with his personal remedy for the Herxheimer reaction. “I take a saltz bath which consists of adding 1 cup salt, 1 cup soda, 1 cup Epsom salts, 1 cup aloe vera, to a hot bath which I remain in and keep hot for about 11/2 hours all the while consuming about 2 quarts of warm water. Evidently the perspiration and osmotic pressure removes the causative toxins. I find it quite helpful” (117). Hey, sounds ok to us.

Section 12: Major Considerations in the Treatment of Lyme Disease

Several areas of debate concerning Lyme disease treatment exist and include issues on 1) the efficacy of treating EM with traditional oral antibiotic programs, 2) the benefit of prophylactic antibiotics after a tick bite, 3) the use and choice of long term intravenous antibiotics in those patients with neuroborreliosis, 4) the evaluation and treatment of co-infections caused by Ehrlichiosis, Babesiosis, and Bartonella species, and 5) the purported role of the now FDA withdrawn Lyme vaccine, LYMErix (see An Ounce of Prevention). The first four areas will be discussed in this section.

The traditional recommended treatment, upon finding an engorged tick and making the clinical diagnosis, is a seven to ten day regimen of doxycycline (100mg po BID) for ages > eight, excluding pregnant women (118). This regimen has the advantage of curing the disease Ehrlichiosis, caused by a gram-negative bacterium carried by Ixodes ticks and a frequent coinfection in endemic areas. Second line therapy includes medications such as amoxacillin and cefuroxime. However, Lyme treating physicians are all cognizant of failures with this traditional approach and, in fact, most quoted published series report less than perfect response rates with doxycycline, amoxacillin, and other oral antibiotic programs. Many quote success rates as low as 80%, with 90% being the highest success rate recorded (119). The reasons for this are poorly understood but almost certainly reflect features such as delay in treatment, inoculum and strain effect of Bb…i.e. the quantity of organism introduced to the patient, as well as various subtleties of various strains and the immune response, areas poorly understood in LD (see previous discussion). As stated earlier in this text, we concur with the recommendations of many Lyme treating physicians who provide a course of doxycycline at 200mg twice daily for up to 30 days as the optimal approach to successful treatment of EM/Lyme, specifically with the goal of aborting cases which otherwise might develop late sequelae.

With regard to prophylactic antibiotic use after a tick bite, recent research suggests that a single dose of 200mg doxycycline given within 72 hours after the I. scapularis bite can decrease the chances of developing LD by 87% in a setting where overall transmission rates were around 3.2% (120). It is interesting to note that LD occurred only after the bite of the nymph form of tick, consistent with what our text has proposed (see discussion above). By the author's reports, infection occurred only if the tick was at least partially engorged and had been estimated to be present > 72 hours. We have previously discussed and disagreed with these timelines for infection (see previous discussion).

Critics of this study point out that a panel of experts of the Infectious Diseases Society of America does not endorse routine antimicrobial use in this setting. They also state that, even in an endemic setting such as upper NY state, approximately 40 people would have to be treated to prevent one case of Lyme disease and that the ratio will be much higher in areas of low endemicity. Moreover, since most cases of LD result from unrecognized tick bites, any benefit from antimicrobial antibiotic use is likely to be reduced significantly. Despite these negative comments, the JEMSEK Clinic is pleased to disagree with the ID Society (to which Dr. Jemsek belongs) and recommends doxycycline prophylaxis for a situation in which an Ixodes scapularis tick has been attached for > 72 hours. Parenthetically, the same ID Society has put forth a formal position on LD treatment which states that the long term use of antibiotics for LD is unnecessary and that persistent LD is rare and overdiagnosed. The panel of nine who claimed this postion for the ID Society included few highly experienced LD treating physician, and included Dr. Allen Steere. The irony here is practically palpable. Steere is a rheumatologist!

For almost two decades, intravenous (IV) therapy, usually with the once daily cephalosporin antibiotic, ceftriaxone (Rocephin), has been an option for various stages of LD. Parenteral or IV therapy is, however, by nature more difficult, sometimes less accessible, potentially more hazardous, and clearly more expensive. The current

consensus for the role of IV antibiotics is that it should be reserved for the treatment of patients with prolonged and life altering neurological findings, whether CNS or peripheral. By definition, these conditions reflect late manifestations of neuroborreliosis. In many centers in recent years, a more controversial indication for the use of IV therapy has been employed, namely for treatment of the chronic or persistent LD or "post-LD syndrome", which involves much more subjective ailments such as fatigue, musculoskeletal pain and cognitive difficulties (see earlier discussion). As reported in a summer 2001 article in the New England Journal of Medicine, approximately 125 individuals with "chronic LD" were randomized into two groups, one receiving placebo and the other 30 days of IV Rocephin followed by 60 days of oral doxycycline. In essence, the trial showed no difference in benefit as gauged by Quality of Life (QOL) questionnaires (121). Certain reviewers saw this as an affirmation of their belief that IV therapy was overused and wasteful, whereas others criticize various aspects of the trial, e.g. arbitrary length of IV antibiotics, the inherent faults in QOL reporting, etc. It's safe to say that the trial has changed few minds and that opposing parties simply reaffirmed their pretrial bias. We regret that this trial did not include, for reasons unexplained, LD patients with documented neurological deficits. On the other hand, the trial was so badly and fatally flawed that this point almost does not matter. Hopefully, better science will follow soon. We deserve it and we need it…….maybe we'll have to do it.

The JEMSEK Clinic has attempted to integrate various elements of what is known about persistent LD and the biology of the infection. On reflection, it seems reasonable to assume that a chronic CNS infection with a slowly replicative organism like Bb will require prolonged therapy, preferably with an antibiotic with a delivery that allows for the highest drug levels possible in the CNS. For this reason, we treat severe and chronic CNS manifestations of neuroborreliosis with IV antibiotics for as long as 16-32 weeks and have noted repeatedly that clinical improvement may not become apparent until several months into therapy, although we generally see some effect by the third month and certainly the fourth month of therapy (more on concepts of therapy below).

The emerging research on a chronic, cystic form of Bb has changed the long-term treatment picture. In theory, biologic and environmental stress promotes conversion or "morphing" of the spirochetal form to a cystic form, apparently within hours, and this form exhibits different surface antigens and therefore a different presentation to the immune system. The converse is documented, i.e. the cystic form can readily convert back to the spirochetal form (122). It is known that antibiotic pressure, utilizing medications effective against the spirochetal form, accelerates cyst formation (123). In vitro, incubation of Bb with ceftriaxone, for example, leads to Bb cyst formation after just four hours, much faster and more completely than doxycycline exposure (123). As expected, neither of these compounds (or any other commonly used antibiotics in LD) have any effect of the cyst. On the other hand, many studies indicate that metronidazole is effective in killing the cystic form, but not the spirochetal form, of the Bb bacteria (124). For that reason, many Lyme aware physicians have begun to see the value of using combination antibiotic therapy with the addition of the agent metronidazole. In our experience, patients with Bb infection routinely develop a Herxheimer reaction (see below) in response to treatment with metronidazole and occasionally these reactions may

be severe and limiting. Long term suffering neuroborreliosis patients seem to have the most difficult time with this therapy, suggesting that the cyst load may be higher in this patient group. If this is the case, one might suggest that conversion to a cyst form is a natural evolution of the illness for at least some Bb strains.

Section 13: Jemsek Clinic Treatment Protocol

In the process of integrating the available information on Bb biology and what is known about the effect, or lack of effect, of various antimicrobial programs, the JEMSEK Clinic developed a treatment protocol for LD in late 1999. Since then, over 250 individuals have been placed on therapy with antibiotics and a host of supportive measures. When advanced CNS involvement or neurological disease is present, both intravenous and oral antimicrobial agents are used to treat Bb in combination; otherwise, cyclic oral therapeutic programs are employed. Our cycles on oral antibiotic are designed to run for four months. Our experience suggests that, if a patient is ultimately going to improve on oral therapy, positive results with clear symptom relief are evident by the third or fourth cycle. If a patient fails to progress, i.e. no clinical improvement in any parameter, absence of Herxheimer effect, and so forth, we are not hesitant to change the antimicrobial program, especially in view of what is known about strain variability and antibiotic response.

Our treatment approach is designed for a Bb organism that is recognized as polymorphic and microaerophilic. Other important features of Bb biological traits are the capacity to exist in either an intracellular or extracellular state. Finally, Bb has a tendency for latency and for slow replication (125), a fact that has profound implications of the length of antibiotic therapy required for eradication. The replication rate for Bb has been reported to be between 7 to 33 hours (126), depending on the environment used for culture and so forth. In contrast, Group A Streptococcus, for example, replicates every 20 to 30 minutes. Current standards of treatment for streptococcal infections is 10 days, or around 500 reproductive cycles. Given these reproductive dynamics, and realizing this is indeed a crude but interesting analogy, treatment of Bb for 500 cycles could entail more than two years of therapy. In summarizing all of these considerations, we have concluded that a treatment protocol employing long-term cyclic, pulse therapy with drugs effective against all forms of the organism might be effective, particularly if given in sequence with agents active against the cyst active form administered late in the cycle.

When oral therapy is employed, the idea of a “drug holiday” after pulsing seems attractive for several reasons. First, it gives the patient some relief from daily antimicrobial therapy. Second, even though a typical holiday is scheduled for four weeks, most patients will relapse, or experience the recurrence of symptoms, within one or two weeks of therapeutic interruption. This is particularly true in the early months of therapy, i.e. after only a couple of cycles. This pattern of relapsing provides useful clinical information for future treatment (see below). Third, in theory, our treatment and the subsequent Bb “die-off”, and then relapse off therapy is an approach that might stimulate immune recognition and activation, thereby improving immune surveillance/eradication of Bb. This idea bears similarities to the auto-immunization theory that has received

attention in HIV therapeutic strategies. That is, if one suppresses HIV with drug treatment, the CD8 cytotoxic/suppressor cell level wanes (127) (these are lymphocytes responsible for activity against cellular pathogens, including HIV). As treatment is withdrawn, the reappearance of the virus causes an augmented or boosted CD8 response that, if repeated cyclically, might build the response to the point that the pathogen could be controlled or eliminated by the immune system. Unfortunately, this analogy is imperfect since HIV specific immunity is lost in most HIV/AIDS cases because of depletion of CD4 cells caused by HIV attack on CD4 cells. Therefore, there is no boosting effect because CD4 cells are critical to the performance of CD8 and there are no cells left with which to create a boost. However, where HIV specific immune responses are preserved, such as in therapy early after the infection, therapeutic interruptions work quite nicely. Our hope is that Bb specific immunity is retained in our patients regardless of severity or chronicity of the infection, and that interrupted therapy will be of some benefit. Realistically though, this is a grossly oversimplified theory and a considerable amount of scientific work will be required to answer these questions. Regrettably, given the current medical and political circumstances for LD, meaningful clinical, epidemiological, and immunologic research are but a faint hope. In the figurative sense, if there were a race to cure HIV and Bb (no judgmental view intended here), the HIV researchers would have a 20-year and a several billion-dollar head start, with the Bb folks falling further and further behind each year for the foreseeable future. Perhaps the silver lining in all this is that all of the wonderful scientific information that has come from the HIV pandemic will benefit our understanding of many other diseases, including neuroborreliosis.

Obviously, our ultimate goal is Bb eradication, if possible, or at least a state of competent immune surveillance resulting in lasting relief from disease. As treatment progresses, return of symptoms off therapy becomes more delayed and symptoms tend to be milder. On the occurrence of relapse in our cycle, the patient is given the option of resuming therapy at the first sign of relapse or they may simply wait until the four-week period is over. Interestingly, during that first week or two on holiday, our patients invariably remark that they feel the best they have since becoming ill. Obviously, when a patient ceases to relapse on holiday, it is taken as a positive indication. It is even more encouraging at that point if the patient fails to exhibit any sign of Herxheimer's reaction (see below) during the ensuing treatment cycle, suggesting that Bb die-off is clinically non-detectable. In general, we have informed patients that therapy may extend for two or three years before they may reach an asymptomatic state. At this point in therapy, we would consider performing a "test of suppression", probably by utilizing newly available urinary antigen detection testing procedures such as the urinary Dot-Blot test through IgeneX laboratory (128), in a protocol that employs an antibiotic challenge to enhance Bb shedding in the genitourinary tract. Like many other practices in the treatment of this complex infection(s), this concept is flawed since the JEMSEK Clinic does not routinely do this testing prior to therapy for financial reasons (unless a laboratory diagnosis is not forthcoming through other methods). We expect the test would be inherently insensitive at this point in our patient's treatment program, but of course a positive test would be highly specific and have important clinical implications for further clinical monitoring and/or treatment.

Two major changes regarding therapy are underway at the JEMSEK Clinic. As we have begun to treat more seriously ill and complex patients with IV therapy, we have decided to add oral antibiotics early in the course of the IV therapeutic program and cycle them through the entire treatment process. This contrasts with most treatment protocols that administer either IV or oral therapy, but not both. We do not interrupt intravenous therapy as we do with our exclusively oral program, but then the intravenous treatment period is also much shorter, generally 16-24 weeks. While the IV drugs we commonly employ, ceftriaxone (Rocephin) and imipenem (Primaxin), meet our needs by achieving excellent serum and CNS levels as well as having excellent in vitro Bb susceptibility data (60), neither drug is capable of penetrating the interior of the cells where Bb may proliferate. We reasoned that Bb suppression would ultimately require three different types of antibiotics, and so we decided not to delay adding an intracellular active drug(s), e.g. an oral drug such as clarithromycin (Biaxin). In addition to Biaxin, which is quite potent against Bb (129), we also employ and cycle doxycycline (Vibratabs) and ciprofloxacin (Cipro), often in combination. By combining two intracellular active drugs, we hoped we might achieve a superior result and our responses to date have confirmed this premise. Where either clarithromycin or doxycycline is in use, we generally add hydroxychloroquine to the antibiotic program. This compound is purported to benefit the activity of these drugs by alkalinizing the interior of the cell (130), which is where Bb is dispatched via killing with lysosomal enzymes. An additional benefit of this important medication is that it downregulates immune response and therefore reduces some of the harmful cytokine effects (131). For this very reason, this medication has established a role as a step one agent for the treatment of other disorders, such as lupus and rheumatoid arthritis. Clinical dogma requires that patients on this compound have routine eye examinations because of some older reports that indicated retinal damage on therapy, albeit at much higher doses. We encourage this practice but have never seen any complications, despite treating hundreds of patients.

In our current protocol with IV therapy, administration of an oral drug begins by the fifth week, which gives us enough time to thoroughly evaluate any problems with intravenous administration. In a similar concept for the Bb patient on orals alone, we cycle orals in our patients on IV therapy, generally rotating or alternating antibiotic programs in order to limit tolerance or toxicity.

The second important change in our program is the use of IV clindamycin, which has now become a routine inclusion in our treatment protocol. This change came about after we began using oral clindamycin (with mepron) empirically for suspected cases of babesiosis coinfection in our most recalcitrant, unresponsive patients . We immediately noted some new and positive developments, e.g. absence of fever and night sweats for the first time in months/years, increased mental acuity, and so forth. Other patients had Herxheimer reactions that they had not experienced for weeks on prior therapy, even though we were treating aggressively with both intravenous and oral antibiotics. Since our most debilitated patients were already on IV therapy, we decided to try short courses of IV clindamycin and the effect has been consistently impressive, even more so than with the oral formulation. We have now gone back and retreated those patients who have

had an incomplete response to prolonged IV therapy, and in 11/12 of these cases, improvement on IV Clindamycin has been dramatic. We are currently in the process of evaluating the optimal use of clindamycin, as we continually do with all of the therapies we employ. Our hope is that these more intensive therapeutic programs, still provided in such a way that they are tolerated, will allow us to shorten the IV program by hastening the time to clinical improvement.

Lastly, in our protocol, we routinely cycle metronidazole during the treatment period, thereby achieving three separate active modes of treatment. Since it is very difficult to maintain a patient on such intensive therapy for a prolonged period, the rotation of oral antimicrobials through the IV treatment period has been quite helpful in term of program tolerance (see below). In fact, out of tolerance concerns, metronidazole is typically given intermittently and on a short term basis because of its propensity to cause severe Herxheimer reactions, especially in patients with advanced illness. Because of the complex drug issues in patients who invariably risk great morbidity, we accommodate each individual with a treatment plan that is best suited for them. While we have developed a protocol for general guidance, we understand that it is the exception to the rule that creates new insights about the treatment of Bb. Quite honestly, this is how our protocol evolved (and continues to evolve) in the first place. Prior to any treatment, IV or oral (or both), our patients are educated in the use of probiotics and schooled to observe for potential side effects. Safety labs are performed weekly or biweekly. Specific considerations in IV therapy include the addition of Actigall (ursediol), which seems to reduce the incidence of ceftriaxone-induced cholelithiasis (personal reference) and is well tolerated. When using imipenem, we add probenecid in order to boost drug levels during twice daily dosing.

In administering these treatment programs, the JEMSEK Clinic is cognizant of criticism concerning outside perceptions and opinions of excessive or unguided antibiotic use by our clinic. Certainly, we do not now and never will condone indiscriminate use of these important and valuable drugs. In view of our training and experience, we are completely confident in our use of these medications. In response to any real or potential criticism, we would reply by pointing out that we are treating seriously ill and/or impaired individuals who have not responded to conventional medical therapies. As mentioned previously, we are encouraged that a significant percentage of our patients are responding to our care, including several individuals who had been totally incapacitated for appreciable periods of time. We acknowledge that the understanding of neuroborreliosis is incomplete and so we continue to study the entire process of diagnosis and treatment for Bb infections. We look forward to the day when funding and scientific support for Bb research is available.

During our discussions, we have routinely mentioned the risk and possibility of co-infection with Babesia, Ehrlichlia, and Bartonella. Regrettably, at present, a thorough discussion of these important tick borne infections is beyond the scope of this presentation. However, the importance of these other pathogens cannot be underestimated. In future times, we hope to expand our scope and include these very important discussions to our presentation.

Section 14: An Ounce of Prevention

Certainly it is better to prevent infection than to be forced to treat. Taking simple precautions during the months of highest risk can easily prevent Lyme disease. When safe proofing the back, it is important to separate the yard from wooded areas that may surround it. Wood chips are useful for this by offering a dry and hostile environment for ticks as well as serving as a safety boundary for young children. Acaricides can be added to the wood chips, however the clips must be treated yearly and the time of treatment is regionally dependant. Simple tick checks after spending time outdoors are useful in preventing attachment. Bathing with a washcloth can easily dislodge a tick before is attaches. It is important to dress protectively during summer months, especially with prolonged outdoor activities. Wearing light clothing will aid in noticing ticks. Also dressing in long pants and long sleeves as well as tucking in pant legs offers additional protection. Bug repellants also offer some protection against ticks. Applying repellant that contains DEET (diethyltoluamide) to clothing prior to out door exposure is recommend for those in highly endemic areas or for those who plan prolonged out door activities.

LYMErix was a vaccination for Lyme disease, developed by Glaxo Smith Kline, which had been approved for patients ages 15-70 years old in the late 1990s. The vaccine was not 100% effective and required multiple dosing and frequent boosters. From the beginning, the vaccine was controversial and highly criticized by LD activists as incompletely studied and scientifically flawed. Several problem areas have been identified. First, the vaccine was developed using a single Bb strain to develop its antigenic profile. This was an obvious error in judgment given the Bb strain heterogeneity previously discussed above. Second, a specific genetic subset with HLA-DR4+ expression, present in up to 30% of individuals, has been recognized as having an increased incidence of adverse reactions to Bb products. Use of the vaccine in this subgroup led to the autoimmune development of polyarthritis. Furthermore, the vaccine developers chose OspA, rather than OspC, as the major immunogen. OspA, as we have discussed, is the major antigenic protein while Bb is in the tick gut, but OspC predominates in human infection. For some reason, this was not fully taken into account by the vaccine development team and it appears the use of OspA may have been the real trigger for the autoimmune reactions in the HLA-DR4+ subgroup. LYMErix was voluntarily removed from the market by its manufacturer after only a couple of years in production. The official policy statement that “disappointing sales and costs of production” were to blame. However, critics state that the vaccine did more harm than good and cite numerous clinical problems as sequalae to its use, including several cases with the appearance of serious neurological symptoms (132,133). Numerous court cases for damages are pending. Nonetheless, vaccine development for LD continues by other researchers. It is our opinion that a successful vaccine for LD will follow only once we understand the full pathologic and immunologic consequences of natural infection, both treated and untreated.

Remember that ticks take their time in both finding a suitable site and becoming engorged (as applies to our knowledge of deer ticks specifically). The more often tick checks are done and the more precautions taken, the less likely one is to contract Bb. If an attached tick is discovered, it is important to remove it properly. Using Vaseline, kerosene, or heat may aggravate the tick and cause it to release bacteria more quickly. We recommend that one simply use a set of tweezers to gently pull the tick from the skin, while being careful not to twist or jerk the tick. Doing otherwise may annoy the tick and promote leaving mouthparts in the skin. If possible, keep the tick; professional medical attention may be helpful in some instances - pray you find a Lyme literate doc. The more engorged the tick has become, the greater likelihood for infection. It is also prudent to record the date that the tick was discovered and any adverse symptoms experienced after the tick is removed. All of these will aid a practitioner in choosing what treatment plan is best.

Section 15: Jemsek Clinic Editorial

I. Controversies In Definition And Diagnosis

The vigorous and sometimes vicious debate drones on among medical professionals and their patients over whether or not persistent or chronic LD exists, and if so, to what extent it is accurately diagnosed and how it should be treated. The debate lies with whether a number of chronic symptoms can be ascribed to LD. The argument is confounded significantly by the fact that we can not easily identify Bb in tissue or blood and that serologic studies are poorly standardized and considered generally insensitive, particularly if one has received antimicrobial therapy over a length of time (134). The traditionalists, Drs. Steere, Sigal and the like, have the proverbial ear of today's medical publishers and, at least in some of the literature we have reviewed, consistently downplay the possible role of persistent LD, often in a condescending, haughty manner, as if one were trying to discipline a willful child who had opinions of their own (135,136). Through self-fulfilling, repetitive, and boorish arguments they consistently attempt to point out the lack of proof for persistent infection and the lack of evidence for prolonged use of antimicrobials in this setting. On the other hand, their explanations used to dismiss persistent or relapsing Bb disease as the etiology for many patients with ongoing unexplained, disabling symptoms, is hardly scientific or convincing. Generally, they simply refer to this group as having "some sort of prolonged immune abnormality" or "depression"(136), as if these explanations provided a satisfying resolution to our understanding of these issues, much less a template for further study and change. This is hardly a gratifying explanation, particularly if you happen to be a neuroborreliosis patient with major cognitive loss, in association with racking pain, polyneuropathy and fatigue so severe you don't consider life worth living. In essence, the Steeres and Sigals of the world are calling for evidence-based medicine and, by definition this assumes we know everything that is important to know about neuroborreliosis. We all agree that evidence-based platforms are preferable when possible. The problem, of course, is that we have only scratched the surface where scientific and clinical information on LD is concerned. We therefore believe that it is unconscionable and wrong to "close the door" on new

ideas when it is obvious that our patients' conditions remain unresolved and many continue to suffer. The New England Journal Medicine is acknowledged as a bastion of science, but they are failing both physicians and patients concerned with Lyme Disease. When they rush to print articles on LD on the premise that great science has been gifted to us, we are offended (137). We hold their editors accountable for their permissive propagation of one dimensional and highly restrictive views on Bb infection, and, furthermore, indict them for not publishing letters of dissent sent to the editor in reference to the articles written by the offending authors, i.e. Sigal, Klempner et.al.

II. Making Our Case - A Brief Summary

In making the case for persistent infection with Bb, we start by drawing on our clinical experience with over 300 patients. The validation provided by the Herxheimer effect (see below) and the clinical gains made by our patients on therapy are irrefutable and well documented in JEMSEK Clinic records. As discussed above, through careful recording of patient history, we believe we have made a strong clinical case for Bb persistence, whether it is in the form of ongoing symptoms or a reactivation event. Through all of this, our learning experience has been intense and quite enlightening. The clinical improvement in many of our patients with previously disabling conditions has been at the same time remarkable and gratifying. For this, we are truly humble and thankful.

We believe that the clinical and immunologic considerations discussed heretofore are as compelling and valid as anything published by those with opposing views. Valid immunologic information in persistent LD is scarce, but at least now we have some data on an immunologic marker, CD57, whose levels correlate with up to 10 years. In truth, however, where diagnostic and treatment considerations are concerned, we must emphasize the fact that the the state of the LD infection for complex interaction between Bb and the human host is just now beginning to be appreciated.

What is known about the biology of Bb leads one to certain conclusions. As discussed earlier, some confounding elements of Bb infection include the existence of Bb as multiply poorly characterized strains with variable and inconsistent antimicrobial sensitivity patterns. Bb replicate very slowly in comparison to other bacterial species (138) and this has significant implications for treatment guidelines. These same organisms demonstrate requirements for a microaerophilic environment (68,69), and manifest a documented polymorphism, possessing the ability to transform from one state to another under various conditions (86). Bb may exist in the host in various antigentically diverse states (spirochete, cell wall free or L form, or a cystic form) (87). In our opinion, these characteristics have a profound effect on the choice and length of antimicrobial therapy (see treatment section). Bb has already been recognized to persist in human cerebrospinal fluid for weeks to months (139) and in human tissue for years (140). Failure of antibiotic therapy, particularly monotherapy such as doxycycline or ceftriaxone (Rocephin) when administered for short periods, should then come as no surprise. Furthermore, all seem in agreement that laboratory detection and monitoring of Bb is grossly inadequate as it exists today. Logically, it follows that some patients with

Bb infection will remain undetected for extended or indefinite periods of time if we insist on current methods of laboratory confirmation of Bb infection to make a diagnosis.

III. Implications Of Current Testing Methods

Lyme literate MDs who base their treatment on history and physical findings, rather than relying on laboratory testing as it exists today, can easily overlook the inadequacies of our current serologic screening methods. Nonetheless, it is a major psychological hurdle for most of us to overcome when we have a situation in which we don't have that laboratory confirmation for Borrelia infection tucked away somewhere in the record. This is a curse of modern medicine- a paradox that says that a man-made and therefore inherently imperfect evidenced-based entity such as laboratory medicine may prevail over the opinion of the experienced physician.

A major problem caused by the current laboratory criteria for LD confirmation is that physicians and other providers unaware of testing shortcomings will unintentionally mislead their patients. This practice is so common in the southeast US that patients presenting to our clinic have generally already been to a large number of physicians, including many who consult specialists at academic centers. These patients typically undergo extensive and oftentimes unnecessary testing and/or procedures without reaching a consensus diagnosis and, of course, without adequate therapy. On the other hand, we find that these patients frequently get the proverbial "cold shoulder", usually from the academic consultant who "tunes out" once the possibility of Lyme disease is broached. We have interviewed countless LD patients who have gone through the academic referral process and who were humiliated at their interview on campus. Certainly in the Carolinas, at this particular time, this is most definitely the case.

Finally, the testing conundrum seems to play directly into the hands of unsympathetic (the kindest word I could conjure) insurers and disability managers who cling to the archaic diagnostic laboratory criteria listed in their respective cookbook manuals that, by design, suit their purpose. When laboratory criteria for Bb infection are not fulfilled, we have sometimes experienced that the insurer finds it an easy matter to deny benefits for our patients. On these occasions, we believe we are witnessing a situation in which businessmen and physician administrators practice medicine from afar and without valid license. Furthermore, they dictate conditions of medical care and outcome without fear of any immediate and personal consequences for their actions. They forget, as many have, that medicine cannot be scripted or practiced through algorithms. As clinicians, we are constantly humbled by our shortcomings in knowledge and understanding of the practice of medicine. We are constantly learning. It is said " half of what we revere as the truth in medicine will be proven wrong in the next 30 years"(141). We physicians are constantly reminded that the wonderful practice of medicine has always been about both science and art. Both are of critical importance, no doubt, as no one wants a fool for a physician. However, in my lifetime, I believe that the "art" will always outweigh the science. It means one has a gift for insight and knowledge of human behavior and the wisdom to know how to integrate the discoveries of modern science with the care of your patient. Above all, this implies caring and a will to grow from your experiences. The practice of

medicine doesn't have to be impossibly complicated. "Just listen to the patient and they will tell you what is wrong with them", as Osler so aptly stated years ago (142).

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