**Chronic Lyme Disease and Co-infections: Clinical Overview**
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*This paper summarizes the major clinical issues surrounding chronic Lyme disease and the underlying pathophysiology of the disease. This information will serve as a foundation for the herbal practitioner's clinical approach to chronic Lyme disease. The corresponding presentation at the AHG conference will focus on specific case studies and the nuts and bolts of seeing clients with Lyme disease.*

**Introduction to Lyme Disease**
Lyme disease or Lyme borreliosis, is a multi-system infectious disease caused by a tick-transmitted spirochete, *Borrelia burgdorferi*. Although the disease was named for Lyme, Connecticut, where an outbreak of rheumatoid arthritis was initially misdiagnosed in the late 1970's and later discovered to be caused by an infectious agent, the first reported case was in Germany in 1883. *Borrelia burgdorferi* is the most common species in the United States; there are 100 strains in the US alone and 300 strains worldwide. There are actually several other infectious species of *Borrelia* in the US and abroad. There are 15 species that are infectious to man, including *B. garinii*, *B. afzelii*, *B. japonica*, *B miyamoto*, *B lonestari*, and *B andersonii*. From this point forward I will use the abbreviation (Bb) to refer to *Borrelia burgdorferi* and related species.

Generally acute and early-disseminated Lyme disease is marked by fever and bulls-eye rash and yet in many cases transmission may be asymptomatic or atypical. If the infection goes untreated or even if the infection is treated it may become chronic. The organism can lay dormant for many years and be reactivated (Rubel, 2006). Symptoms are diverse and elusive. "Initially thought to be a disorder beginning in the skin and progressing to involve the joints, Lyme disease is now ranked as one of the great mimickers of other diseases, in a manner similar to that once ascribed to syphilis," (Duray, 1989). The complex nature of the disease is elucidated later in this paper.

Bb is the most genetically complex bacteria identified to date. Bb contains 132 functional genes, compared to the syphilis spirochete *Treponema pallidum*'s mere twenty-two. Ninety percent of these genes are novel to all bacteria. Bb's genome is 2/3 the size of the human genome. Bb contains 21 plasmids, more than any other bacteria. This characteristic allows the organism to be highly adaptive to its environment, with the ability to survive in a number of different hosts (Stricker, 2006; Wikel, 2006; Porcella & Schwan, 2001).

Lyme disease is the fastest growing vector-borne disease; found on 5 continents (Sigler, Kershaw et al., 1997; Stricker, 2006). Reported cases are estimated to represent 10% of the actual number of cases in the United States. The Centers for Disease Control and Prevention (CDC) reported 24,000 cases in 2002. With vast underreporting, the actual number of cases was likely to be 240,000 that year (Stricker, 2006).

The reason for the growth and spread of Lyme disease is multifaceted. Plausible reasons include degradation of natural habitats, climactic changes, suburban sprawl, increase in vector populations, human, animal and bird migration, and genetic and evolutionary changes of pathogenic organisms, which may be triggered by the misuse of antimicrobial agent (Ranga, Trivedi, et al. 1997; Stricker, 2006). Infected ticks have been found on migratory birds that travel between states, countries and continents (Gardner, 2001). Since 1900 the US deer population has multiplied 70-80 times from 500,000 to 35-40 million. (Ranga et al., 1997; Stricker, 2006). Using Baltimore County, Maryland as a microcosm of geographic correlations with disease incidence, Glass et al. found a higher incidence of Lyme disease with proximity to forest edge, moderate altitudes, and soil type, in particular soil suited for conifers but not herbaceous vegetation (Glass, Schwartz, et al., 1995).

***Box 1*** **Six Key Issues of Treatment**

1. There is no definitive test for the presence of *Borrelia*, chronic Lyme disease is a clinical diagnosis
2. Response to antibiotics and treatment is variable
3. The *Borrelia* organism is pleiomorphic and evasive
4. Rate of co-infections is high
5. There are other, less known, modes of transmission of *Borrelia* and co-infections
6. There are two standards of care in the conventional medical community.

**Issues of Diagnosis and Treatment**
Numerous issues complicate the treatment and diagnosis of chronic and pervasive Lyme disease (see *Box 1* for a summarized list). Understanding these issues will help the herbalist and health care practitioner to more effectively support their clients with Lyme disease.

**<u>Issue #1:</u> There is no definitive test for the presence of Bb; chronic Lyme disease is a clinical diagnosis.**
Direct detection of Bb through laboratory tests is not commonly available. Bb is a slow growing organism and is difficult to culture from tissue samples. According to the CDC, Lyme disease is a clinical diagnosis. Aside from acute or early-disseminated infection, the existence of chronic and/or persistent Lyme disease (active infection with or without 14-21 days of antibiotics) is not commonly recognized by medical professionals, largely due to lack of reliable testing.

The Lyme-literate clinician reviews symptoms, available laboratory tests, history of rash and tick bite(s), exposure, place of residence and response to treatment. Unfortunately the gold star diagnostic, an Erythema Migrans (EM) rash occurs in less than 50% (possibly as low as 30%) of positively diagnosed patients. It often presents in an atypical fashion, not the typical bulls-eye rash (Stricker, Lautin, et al., 2005). The tests commonly used in Lyme-literate practices are the **Polymerase Chain Reaction (PCR)** and antibody detection methods.

A PCR detects small strands of Bb DNA in tissue and blood samples. This form of testing has a high rate of false negatives and low diagnostic value, largely due to Bb's affinity for body tissue rather than fluids. But with close to 100% specificity, false positives are rare (Aguero-Rosenfeld, Wang et al., 2005). PCR is the preferred method of testing for acute infection (Schmidt, Muelleger et al., 1996). Antibody detection methods include both the **Enzyme-Linked Immuno-Sorbant Assay (ELISA)** and the **Western Immunoblot**. ELISA has a lower specificity and sensitivity than the Western blot. The latter is the preferred antibody detection method and the most commonly used lab test in Lyme-literate medical practices. The Western blot measures both IgG and IgM antibodies to several Bb specific antigens.

Diagnosing chronic and persistant infection is more challenging. The implications of a positive Western blot with persistent IgG and/or IgM antibodies after antibiotic treatment is unclear. Is it chronic infection, indicative of past infection or cross-reactive antibodies? Asymptomatic individuals can test positive and clinically diagnosed patients can test negative. It is estimated that 30% of clinically positive patients test negative on the Western blot (Harris, 2006; Jones, 2004). In one study, of 55 patients with EM, 20% were seronegative with Western Blot (Aguero-Rosenfeld et al., 2005). There are several possible explanations for negative tests in clinically positive individuals aside from potential misdiagnosis: Antibodies could be bound in circulating immune complexes, there is a diversity of antigenic profiles due to multiple strains, evasion of immune recognition by the organism, intracellular location of organisms, and/or the hosts immune system may be suppressed (Harris, 2006; Taylor, 2004). It is interesting to note, that clinically positive yet seronegative patients will often test positive on the Western blot after a course of antibiotic treatment (Burrascano, 2006). A negative test does not rule out chronic Lyme disease, and a positive test does not diagnose Lyme disease. Ultimately it is a clinical diagnosis; the presence of antibodies is weighted against clinical picture and response to treatment.

**Other Clinical Tests**
Two less conventional laboratory tests used to measure progress and treatment are levels of CD57+ NK cells and Vitamin D 1,25 (active form of D in the body) and Vitamin D ,25 (inactive form). CD57 is a particular glycoprotein marker found on the cell surface of certain aggressive Natural Killer cells. Labcorps is the only lab currently running this test. Normal levels are > 200, but there is a standard deviation of +/- 30. Preliminary research and empirical data suggest that low levels are correlated with clinical diagnosis of chronic Lyme & elevated pro-inflammatory cytokines. It is a potential marker for differential diagnosis, as low levels are not commonly seen in Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE), Lou Gehrig's Disease (ALS) (Savely, 2006). It is unclear if low levels of this NK cell contribute to the disease state or simply serve as a marker of unresolved infection.

Researcher Trevor Marshall, author of the Marshall protocol for Lyme disease, demonstrated that Vitamin D 1,25 and Angiotensin II (A-II) are key players in a self-perpetuating cycle of inflammation and Th1 cytokine production in chronic Lyme disease. A standard blood test, the ratio of 1,25-D and ,25-D can be useful clinical marker for inflammation and Th1 activation (Mozayeni, 2007; Marshall, Lee et al., 2006).

**Issue #2: Treatment response to long-term and short-term antibiotics is variable.**
The Infectious Diseases Society of American (IDSA) recommends a treatment course of 10 - 21 days in acute infection (Wormsler, Dattwyler et al., 2006). According to ILADS this approach is insufficient. Failure rates are significant and acute infection often goes undetected due to atypical presentation. As an example, one study demonstrated 74.2% of patients with previous EM rash, treated with 3 weeks to 2 months of oral or intravenous antibiotics had positive urine PCR (Bayer, Zhang et al. 1996). Treatment failure occurred in 32/165 of patients with three months of antibiotics and of those who relapsed 40% were seropositive for Lyme (Oksi, Marjamaki, et al., 1999). A review of antibiotic treatment for Lyme disease is available at www.lymeinfo.net/medical/LDPersist.pdf.

Mixed reviews of antibiotics' benefits have several implications: clients are confused by treatment choices; length of treatment is ambiguous; it's unclear if symptomology post-treatment is reflective of persistent infection or post-infectious immune dysregulation; and lastly, there is a need for a more holistic and broader treatment approach. No clinical trials, to date, have studied the use of antibiotics in conjunction with herbs and nutritional supplements to support immune function and body terrain.

**Issue #3: The *Borrelia* organism is pleiomorphic and evasive.**
Many of the issues of testing, diagnosing, and treating Lyme disease stem back to the very nature of Bb. Under stress, in the presence of antibiotics or cerebro-spinal fluid, the organism changes morphology. Currently identified morphological variations include: Spirochetal form (coiled & uncoiled), cystic form or spheroplasts, blebs and granules, and the cell wall deficient or L form (MacDonald, 2006; Rubel, 2003b). These forms have been identified in vitro and in symptomatic patients (Mursic et al,

1996); they enable the organism to become latent for long periods of time, resist treatment, evade immune recognition, and trigger an immune response (MacDonald, 2006; Brorson, 2006; Brorson & Brorson, 2006; Rubel, 2003b).

The cystic form, a non-replicating form of the organism, can evade immune recognition by turning the cellular membrane inside-out and presenting a different antigenic profile (Brorson, 2006; Rubel, 2003b; Brorson & Brorson, 1997), helping to explain negative spinal fluid PCR seen in patients with neuroborreliosis (Brorson & Brorson, 1998). The cystic form has demonstrated the ability to convert back to a spirochetal form *in vivo* (Gruntar & Malovrh, 2001); and even after 6 years of dormancy the cystic forms are able to convert back to spirochetal form *in vitro* (Brorson & Brorson, 2006).

Skin biopsies of symptomatic yet seronegative patients with dermatological manifestations of Lyme have demonstrated small granular structures of *Borrelia* among collagen fibers (Aberer, 2006; Aberer & Kerston, 1996). These granules are likely to be infective. They can penetrate cell membranes and possibly transfer DNA (Rubel, 2003b; Beermann, Wunderli-Allenspach, et al., 2000). Kersten, Poitschek et al. "identified intact spirochetal parts," with transmission electron microscopy, "mostly situated in cysts … seen up to 96 h after exposure with … three antibiotics (penicillin, doxycycline, and ceftriaxone)," (1995). For a pictorial review of diverse Bb morphology see http://www.molecularalzheimer.org/files/Spirochetal_diversity_3_pages.pdf.

**Issue #4: Presence of co-infections**

Borreliosis may be co-transmitted with other tick-borne infections. The most common co-infectious organisms are *Babesia microti* (Babesiosis), *Ehrlichia spp* & *Anaplasma phagocytophila* (Ehrlichiosis), and *Bartonella spp* Rates of co-infections vary. DeMartino, Carlyon et al. found that one out of every five individuals who were seropositive for Bb also showed immunological evidence of exposure to Ehrlichiosis (2001). Prevalance of Babesiosis can range from 10% to 60% in individuals who are seropositive for *Borrelia* (Rubel, 2003c; Kraus, McKay et al, 2002). In a random selection of *Ixodes scapularis* ticks in New Jersey, 33.6% were positive for *Borrelia burgdorferi*, 8.4% for *Babesia*, 1.9% *Anaplasma*, and 34.5% *Bartonella* (Adelson, Rao et al., 2004).

Distinguishing individual infections in the clinic is challenging as the clinical manifestations overlap. For instance, acute Babesiosis and Ehrlichiosis can manifest in a nondescript flu-like illness. Testing for co-infections is limited. For instance, of the 13 strains of *Babesia* found in ticks, clinical tests are only available for *B. microti*, WA1, and *B. duncani*. Testing should not rule out co-infections. Patients with Bb and one or more co-infections often have more complex, severe, and persistent symptoms along with longer recovery periods. Further research is needed to clarify how co-infections affect disease dissemination (Kraus et al, 2002).

*Babesia* is a protozoa not a bacteria. It is a distant cousin to the infectious agent of malaria, *Plasmodium spp.* Clinical signs and symptoms include a high fever at the time of acute infection, chronic low grade fever, chills, night and day sweats, low RBC, hematocrit, and hemoglobin counts, thrombocytopenia, air hunger and migraine-like headaches (Burrascano, 2006; Horowitz, 2006; Kraus et al 2002). Two random screenings of residents in Sonoma County, California found that 16-19% of residents were positive for *B. microti* WA1 (Jerant & Arline 1999; Persing & Herwaldt, 1995).

Co-infection with *Bartonella* may present as CNS symptoms that are out of proportion to the physical, including anxiety, insomnia, agitation, and confusion, with eye manifestations, sore soles and/or fevers upon waking (Burrascano, 2006; Horowitz, 2006). Clinically, Ehrlichiosis can be mild or severe, and commonly is associated with acute onset of symptoms, leucopenia and thrombocytopenia, elevated liver enzymes, knife-like headaches, muscle aches predominant over joints (Burrascano, 2006; Horowitz, 2006).

**Issue #5: Other modes of transmission**

The deer tick (*Ixodes dammini*) and the black-legged tick (*Ixodes scapularis*) are not the only ticks able to transmit Bb. Others include Lone Star ticks (*Ammblyoma americanum*), western black-legged ticks (*Ixodes pacificus*) and dog ticks (*Dermacentor variabilis*) (*Taylor*, 2004). The prevalence of these vectors is largely underreported. In addition to ticks, both mosquitos and flies have been found to be carriers of Bb (Magnarelli, Anderson et al., 1986). Empirical data suggests that transmission from biting flies may occur (Fishman, 2007; Luger, 1990).

New evidence continues to emerge which demonstrates that Lyme and co-infections are not solely tick-borne diseases. Animal and human models demonstrate that Bb is present in semen, vaginal fluid, breast milk, and the placenta of pregnant women (Rubel , 2006; Bach, 2001). Peer reviewed literature offers evidence of gestational transmission in humans and animals (Silver, Yang et al. 1995, Duray & Steere, 1988). "It is clear that B. burgdorferi can be transmitted in the blood of infected pregnant women across the placenta into the fetus. This has now been documented with resultant congenital infections… Spirochetes can be recovered or seen in the infant's tissues including the brain, spleen and kidney," (Duray & Steere, 1988).

Several well know Lyme-literate doctors have devoted their practice to children born with gestational Lyme disease. In an unpublished clinical review of 102 children born of mothers who were either seropositive or infected at the time of pregnancy, Dr. Jones found that over 60% of the mothers had difficult pregnancies. In the same study, of the 102 children born with

gestational Lyme, 80% of the children had cognitive problems, 72% fatigue, 69% chronic pain, 59% low grade chronic fever. Over 50% of the children tested positive with the Western blot (Jones & Gibb, 2006).

Empirical data and one pilot study demonstrate that *Borrelia* organisms may be transmitted sexually. At Optimal Health Physicians and other clinics around the country, it is common for both sexual partners to test positive with PCR and/or Western Blot. In a presentation at the *14th Annual International Scientific Conference on Lyme Disease*, Bach presented that 14 out of 32 Lyme patients tested (44%) had *Borrelia* DNA nucleotide sequences in semen samples identified with PCR tests. 100% of those individuals with sexual partners, had partners test positive as well (Bach, 2001).

More than 40 cases of Babesiosis from blood transfusion have also been reported (Lux, Weiss et al., 2003), and a screening of blood donors reported a 3–8% prevalence of Babesiosis in the general population (Homer, Aguilar-Delfin et al., 2000). *Borrelia* spirochetes are viable after 6 weeks of cold storage in blood banks; transfusion of Borreliosis is a theoretical possibility (Nadelman, Sherer et al., 1990).

***Box 2*** **International Lyme and Associated Diseases Society (ILADS) Guidelines for Treatment from www.ilads.com**

- Since there is currently no definitive test for Lyme disease, laboratory results should not be used to exclude an individual from treatment.
- Lyme disease is a clinical diagnosis and tests should be used to support rather than supersede the physician's judgment
- The early use of antibiotics can prevent persistent, recurrent, and refractory Lyme disease
- The duration of therapy should be guided by clinical response, rather than by an arbitrary (i.e., 30 day) treatment course
- In (persistent Lyme disease), it is reasonable to continue treatment for several months after clinical and laboratory abnormalities have begun to resolve and symptoms have disappeared.

**Issue #6: Conflicting Medical Opinions**

The existence of chronic and persistent Lyme disease is debated in medical communities. The recently published guidelines of the IDSA (www.idsociety.org) deny a need for long-term treatment, recommending no more than 21-28 days of antibiotic treatment. The lead author states, "There is no convincing biological evidence for the existence of symptomatic chronic *B. burgdorferi* infection among patients after receipt of recommended treatment regimens for Lyme disease," (Wormsler, Dattwyler et al., 2006). Many health professionals and researchers in this camp claim that chronic Lyme disease is over-diagnosed.

On the other hand, the International Lyme and Associated Diseases Society (ILADS www.ilads.com) takes a progressive approach to treatment and diagnosis (see the recently published recommendations in *Box 2*), claiming under-diagnosis is prevalent among medical professionals and that long-term antibiotic treatment may be necessary. For the patient, these conflicting medical opinions often drive them to the Internet for medical answers, some find themselves without medical coverage for ongoing treatment.

**Part II: Overview of Pathophysiology and Clinical Presentation**

The pathophysiology of chronic Lyme disease is complex and difficult to convey in a short paper. It can be roughly divided into cytopathic (direct cytotoxic effects of the organism) and immunopathic (physiological changes that are immunologically mediated) aspects of disease progression (see *Diagram 1*). This diagram is a mind map of physiological processes that will be discussed in this section. These pathways are not clearly delineated, for instance vasculitis may be promoted by intracellular invasion of epithelial cells as well as immune-mediated inflammation in the blood vessels.

**CYTOPATHIC EFFECTS**

Bb is both an intracellular and extracellular organism. Bb is not commonly found in body fluids but rather has an affinity for collagenous tissue, such as the bladder wall, synovium, myelin sheath of nerve fibers, and the meninges (Stricker, 2006). Bb uses various techniques to bind to proteins and proteoglycans of the ECM to travel to distant sites of the body often far from the original site of injury. In this process, the organism causes tissue damage and ECM remodeling (Sricker, 2007; Lagal, Portnoi et al., 2006; Wikel, 2006, Buhner, 2005; Coleman, Roemer et al., 1999). Bb has been found in practically every tissue and organ in the body (Rubel, 2006). A tissue culture in mice, found the bladder to be the most frequent site of appearance: Bladder 94%, Kidney 75%, Spleen 61%, Blood 13%, Urine 0% (Oksi, Marjamaki et al., 1999). Bb can coat itself with plasmin and fibrin helping it evade immune recognition (Horowitz, 2006; Colemen et al., 1999; Coyle, Deng et al., 1993).

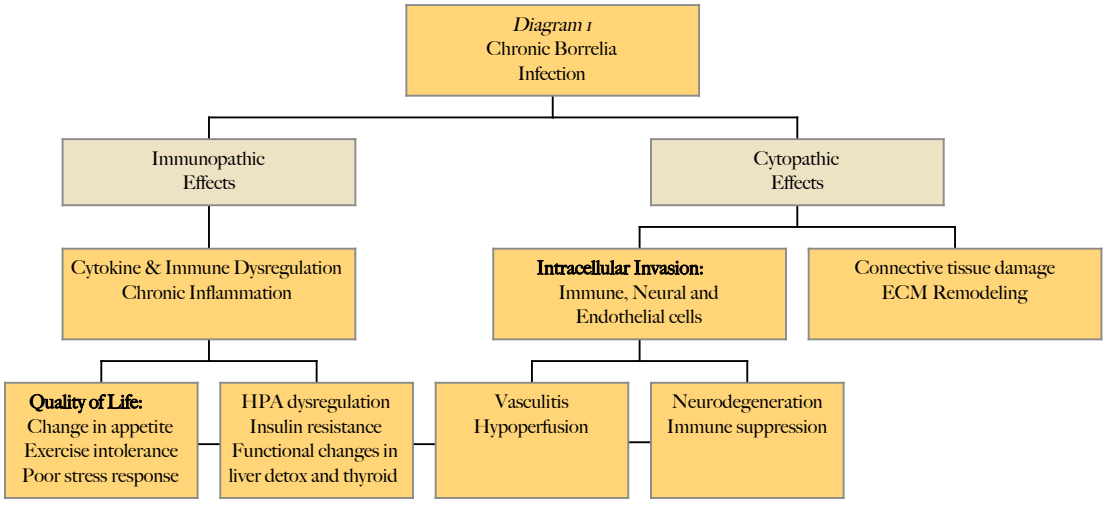
Patients with neuroborreliosis commonly have signs of cortical atrophy and demyelination (Oksi et al., 1996). MRI scans can present lesions and/or cerebral atrophy (Rubel, 2006). Bb DNA can be found at the site of tissue inflammation, suggesting direct tissue invasion of the organism. It has been shown that Bb can cross the blood-brain barrier and hide from the immune system in this "immunoprivileged" site (Stricker 2007, Oksi et al., 1996).

Along the same lines, *Borrelia burgdorferi* cysts and DNA segments have been discovered in brain tissue and cerebrospinal fluid (CSF) samples from patients diagnosed with AD and MS. The DNA discovered in AD patients was often at the site of tissue

injury and beta amyloid plaque formation (MacDonald, 2006a; MacDonald, 1988). Cystic forms of *Borrelia* discovered in the cerebral spinal fluid of 10 randomly selected MS patients in Norway were still viable and reemerged as spirochetal forms when placed in culture (Brorson & Brorson, 2001). The implication of this research is unclear. Is this misdiagnosis or is Bb a causative factor these neurodegenerative conditions? Neuroborreliosis can mimic AD, MS, ALS, and many other conditions. Borrelia-induced neurological changes are comparable to the chronic inflammation, dementia, amyloid deposition and corticol atrophy in late stage syphilis (MacDonald, 2006a; Miklossy et al., 2004; MacDonald, 1988).

As an intracellular organism, *Bb* demonstrates the ability to induce cell death via multiple mechanisms (MacDonald, 2006b; Dorward, Fischer et al., 1997). The organism has the ability to invade many types of cells in the body, including endothelial cells, lymphocytes, macrophages including kupffer cells, fibroblasts, neuroglial and cortical neuronal cells (Stricker 2006; Livengood & Gilmore, 2006).

Lyme disease is a risk factor for cardiovascular disease and events. In 35 of 39 Bb infected non-human primates, carditis and spirochetal infiltration in cardiac tissue was evident. It is estimated that carditis occurs in 25% of humans with Bb infection (Cavidad, Bai et al, 2004). In addition, multiple factors of the disease process promote vasculitis, including infection and invasion of the endothelial cells, influx of inflammatory mediators, and circulating immune complexes (Horowitz, 2006; *Taylor* 2004; Coleman et al., 1999; Oksi et al., 1996; Coyle et al., 1993). Vasculitis may be one of the primary mechanisms of Lyme pathology (Oksi et al., 1996), contributing to impaired peripheral and cerebral blood flow and compounding neurodegenerative effects of the disease process (Fallon, Keilp et al., 2003; Oksi et al., 1996).




**IMMUNOPATHIC EFFECTS**

*Borrelia burgdorferi* dynamically interacts with the host's immune system. At the time of initial infection in humans, the organism demonstrates several mechanisms for immune suppression including inhibition of the complement cascade (Stricker, 2007, Wikel, 2006). An initial strong Th1 cytokine response helps reduce severity of tick-transmitted infection acutely (Wikel, 2006) and helps to reduce chronicity (Zhang, 2007).

Bb lipoproteins are potent activators of pro-inflammatory cytokines, including IFNγ, IL-12, TNFα, and IL-6. These cytokines can remain elevated, tending to a predominance of Th1 type cytokines in chronic infection (Kumradt, 2002; Ghosh, Seward et al., 2006). Interleukin-4 and Il-10 (Th2 cytokines) tend to be decreased in the chronic state. IL-10 is recognized as a potent anti-inflammatory cytokine, and Mice deficient in IL10 developed more severe arthritis after acute infection with Bb (Brown, Zachary et al., 2006). In animal models, Bb infection is also characterized by elevated expression of COX2, associated up-regulation of inflammatory eicosanoids and subsequent arthritis (Ghosh et al., 2006; Anguita, Samanta et al., 2002).

Another explanation for persistent symptoms is autoimmunity. Individuals with persistent Lyme arthritis more commonly carry the genetic marker HLA-DR4 that is associated with rheumatoid arthritis. Molecular mimicry is a proposed mechanism of autoimmunity in Lyme arthritis, in particular where Bb DNA is not evident in the synovial fluid or tissue. Bb surface proteins OspA and OspC are potential triggers for cross-reactive T cells and several auto-antigens have been proposed (Ghosh et al., 2006; Kamradt, 2002). Molecular mimicry is also proposed in neuroborreliosis; autoreactive B cells have been found in the CSF of patients with persistent neuroborreliosis (Oksi et al., 1996).

One of the most confusing aspects of Lyme disease for the new clinician is addressing neurocognitive symptoms such as insomnia, mental agitation and anxiety. Patients are often unresponsive to a standard approach, whether it is SSRIs prescribed by their physician or skullcap (*Scutellaria lateriflora*) recommended by their herbalist. The client's symptom presentation is often due to an underlying immune dysregulation from chronic infection. Needless to say, skullcap may have undiscovered immunomodulating properties, considering the pharmacology of its relative Baikal skullcap (*S. baicalensis*), but the key point here is that altered immune function and cytokine dysregulation has multisystem effects and may be a key underlying factor in symptomology.

**Potential secondary effects**

Secondary effects due to immunological and tissue changes of chronic Lyme include increased insulin resistance, HPA axis dysfunction, weight gain, thyroid dysfunction, and altered liver detoxification (Fishman, 2007; Burrascano, 2006). Patients with disseminated Lyme are more likely than the general population to have elevated liver function tests (Rubel, 2006)

**Symptoms and Clinical Presentation**

Lyme disease offers a complex symptom picture for the clinician. Infection with Bb may be overlooked due to common misperceptions about disease presentation and pervasiveness (Stricker et al., 2005). Lyme disease can be misdiagnosed as fibromyalgia, CFIDS, Multiple Sclerosis, Lupus, Parkinson's, Alzheimer's, Rheumatoid Arthritis, ALS, and a number of neuropsychiatric disorders (Taylor, 2004).

Disease onset and progression is varied with multi-system involvement and diverse clinical presentation. "Symptoms can be surprisingly variable, so that days of near normality can alternate with days of profound debility," (Pachner, Dail et al., 1995). Bb's reputation is surpassing that of the syphilis spirochete, *Treponema pallidum* as the "Great Imitator," able to mimic many common conditions. It is becoming more imperative to rule out Lyme in a variety of presenting cases. Unlike syphilis, stages of disease development do not follow a clear or chronological pattern. In particular, neurocognitive symptoms can show up in early or late phases of the disease process. The Canadian Lyme Disease Foundation provides a great symptom checklist compiled from peer-reviewed literature (See *Box 3*).

It is important to be familiar with the *Jarisch-Herxheimer Reaction* (herx) when working with clients with Lyme disease. Commonly, individuals experience a temporary flare of symptoms with treatment geared to eliminating the pathogen. This reaction can be attributed to a phenomenon first identified by Jarisch and Karl Herxheimer in 1895. The phenomenon is common to other complex organisms, such as those causing leprosy and tuberculosis. One explanation of the phenomenon is that inflammatory endotoxins are released from the dying organism (The Roger Wyburn-Mason and Jack M. Blount Foundation for the Eradication of Rheumatoid Disease, 1991). During the reaction, eosinophils are not elevated suggesting it is unlikely to be an allergic reaction to antibiotics (RWM & JMB Foundation, 1991).

***Box 3*** **Symptoms of Lyme Disease,** www.canlyme.com

Tick Bite • Rash at site of bite • Rashes on other parts of the body • Rash basically circular and spreading out (or generalized) • Raished rash disappearing and recurring • Unexplained hair loss • Headache, mild or severe • Seizures • Pressure in head, white matter lesions in head (MRI) • Twitching of facial or other muscles • Facial paralysis, Bell's Palsy • Tingling of nose, (tip of) tongue, cheek or facial flushing • Stiff or painful neck • Jaw pain or stiffness • Dental problems (unexplained) • Sore throat, clearing throat a lot, phlegm, hoarseness, runny nose • Double or blurry vision • Increased floating spots • Pain in eyes, or swelling around eyes • Oversensitivity to light • Flashing lights/Peripheral waves/phantom images in corner of eyes • Decreased hearing in one or both ears, plugged ears • Buzzing in ears • Pain in ears, oversensitivity to sounds • Ringing in one or both ears • Diarrhea • Constipation • Irritable bladder (trouble starting, stopping) or Interstitial cystitis • Upset stomach (nausea or pain) or GERD (gastroesophageal reflux disease) • Bone pain, joint pain or swelling, carpal tunnel syndrome • Stiffness of joints, back, neck, tennis elbow • Muscle pain or cramps, Fibromyalgia • Shortness of breath, can't get full/satisfying breath, cough • Chest pain or rib soreness • Night sweats or unexplained chills • Heart palpitations or extra beats • Endocarditis, Heart blockage • Tremors or unexplained shaking • Burning or stabbing sensations in the body • Fatigue, CFIDS,weakness, peripheral neuropathy or partial paralysis • Pressure in the head • Numbness in body, tingling, pinpricks • Poor balance, dizziness, difficulty walking • Increased motion sickness • Lightheadedness, wooziness • Mood swings, irritability, bi-polar disorder • Unusual depression • Disorientation (getting or feeling lost) • Feeling as if you are losing your mind • Over-emotional reactions, crying easily • Too much sleep, or insomnia • Difficulty falling or staying asleep • Narcolepsy, sleep apnea • Panic attacks, anxiety • Memory loss (short or long term) • Confusion, difficulty in thinking • Difficulty with concentration or reading • Going to the wrong place • Speech difficulty (slurred or slow) • Stammering speech • Forgetting how to perform simple tasks •Loss of sex drive • Sexual dysfunction • Unexplained menstral pain, irregularity • Unexplained breast pain, discharge •Testicular or pelvic pain • Unexplained weight gain, loss • Extreme fatigue • Swollen glands/lymph nodes • Unexplained fevers (high or low grade) • Continual infections (sinus, kidney, eye, etc.) • Symptoms seem to change, come and go • Pain migrates (moves) to different body parts • Early on, experienced a "flu-like" illness, after which you have not since felt well • Low body temperature • Allergies • Chemical sensitivities • Increased effect from alcohol and possible worse hangover

The author was skeptical of such reactions at first, associating them with harsh therapies. However, the author has found herxheimer reactions to be less severe with herbs and concurrent herbal antiinflammatories but unavoidable in many cases. It is noted by other herbal practitioners, strength of reaction often correlates with clinical improvement and organism load (Zhang, 2007).

It is common for clients to report cyclical fluctuations of symptoms in 4-week cycles. This may be correlated with their menstrual cycle. Harris noted that urine PCR on days 2, 3, 4 of menses (in female Lyme patients) were more active for Bb (2006). The author has made it a practice to compare clients self reported symptom shifts or flares with phases of the moon, and has noted a correlation. The majority of clients interviewed flared at or around the full moon. In a review of lunar effects on physiology, Zimecki pointed to two independent studies demonstrating antibody production peaking at full moons in response to presented antigens in vitro and in vivo. He also noted that endogenous steroids tended to be lowest at the full moon (2006).

Colleague and Mind-Body worker Kathleen Rogers has worked with many clients with Lyme diagnosis, and has found some commonalities in their beliefs about self and healing. In a review of 25 patients diagnosed with Lyme, seeking mind-body-energy therapy at an integrative clinic, 92% expressed routine negative expectations about life and the world, and 68% expressed strong issues about being alive. Common statements expressing these beliefs included: "I am not important," "I can't exist," "The world is not a safe place," (Rogers, 2006).

**The Herbalist's Multifaceted Approach**

Conventional medical practitioners may be stymied by lack of clear testing or diagnostics, but the herbalist can move forward and work to support an individual's immune and body function. Diverse *Borrelia burgdorferi* morphology and presence of co-infections require broad-spectrum antimicrobial therapies. The herbalist's Materia Medica is a great source of therapies, providing herbs with combined antibacterial, antispirochetal, antiprotozoal and antifungal properties. Persistence of infection after short and long-term antibiotic treatment suggests antibiotic-resistance and/or immune dysregulation not being addressed by antibiotics alone.

Despite the complexity and persistence of the pathogen, the herbalist's philosophy, rooted in supporting *the innate vitality of the human body*, is an excellent approach to aiding the individual with Lyme. As debated by Claude Bernard and Louis Pasteur, is it the body terrain or infectious organism that causes disease? It is important to address both. Lyme disease is caused by the organism and the immune system. Reframing this for the client is empowering. It takes some focus away from an adversarial relationship with the infectious organism, expanding the client's purview to include the co-evolution of humans and microorganisms. There are asymptomatic and symptomatic carriers of Lyme disease. Completely eliminating the body of Bb may not be possible, but getting the body to its healthiest potential is a useful goal for the client.

The herbalist's approach to chronic infection with Lyme is three-fold: 1) help eliminate the pathogen(s) and/or reduce side effects of antibiotic treatment 2) reduce or mitigate pathogen's effect on immune and tissue function and 3) support and manage body's vital force.

**Help eliminate the pathogen(s) and/or reduce side effects of antibiotic treatment**

The long-term use of antibiotics requires additional support for the gut and the liver. Liver support is particularly important with the use of pharmaceutical anti-protozoals. A broad spectrum live probiotic is essential, as well as hepatotrophorestoratives . Candida and other secondary infections from antibiotic use are common, despite the use of probiotics.

At Optimal Health Physicians, the integrated practice where the author works, some of the main reasons clients work with herbs instead of antibiotics are a) preference b) sensitivity to antibiotics c) persistent symptoms despite the use of long-term antibiotic and antiprotozoal treatment. In some cases, the medical team at OHP will have clients work with antibiotics and herbs to eliminate the pathogen(s) simultaneously. There are many possibilities here, treatment protocols largely depends on the individual client and the philosophy of the practitioner.

The main antispirochetal herbs I use are garlic (*Allium sativum)*, *Houttyunia cordata*, Oregon grape root (*Berberis aquifolium*), *Scutellaria b*, *Coptis chinensis*, and sarsparilla (*Smilax glabra*). Herbal approaches for *Babesia* co-infection can model treatment for malaria, with the use of antiprotozoals. The predominant herb here is sweet annie (*Artemisia annua*); Clinically, it may be appropriate to use herbal antiprotozoals in combination with pharmaceuticals for particularly resistant infections.

**Reduce or mitigate pathogen's effect on immune and tissue function**

The herbalist needs to think about supporting connective tissue systemically and at organ-specific sites. Echinacea (*Echinacea angustifolia*) and gotu kola (*Centella asiatica*) both have potential benefits here for reparation and protection of collagen tissue. Herbs that inhibit Matrix metalloproteinases (MMP's) will also have benefit here, in particular Dan shen (*Salvia miltiorrhiza*). Vitamin C and glucosamine sulfate are two nutritional supplements that can act as building blocks of connective tissue.

Since the organism uses a fibrin and plasmin coating to evade immune recognition and elimination (Horowitz, 2006; Coleman et al., 1999; Coyle et al., 1993), adding fibrinolytics to an antimicrobial protocol can enhance their effectiveness. Walk gently with proteolytic enzymes between meals, as sensitive clients can "herx" to even small amounts.

Chronic inflammation and immune dysregulation is key to ongoing symptoms. The herbalist has a vast array of immune modulators (see below). Dietarily, this means increasing consumption of Omega 3 fatty acids, which are modifying to Th1 dominance (Hughes, Darlington et al., 2004). Modifying Angiotensin II may be a useful immune modulator in chronic Lyme

disease. Joyce Waterhouse and Trevor Marshall noted, anecdotally, that clients with autoimmune disorders prescribed Angiotensin Receptor Blockers (ARB) for hypertension reported symptom improvement related to immune function. Later, through molecular modeling, Marshall demonstrated that ARB's may have potent anti-inflammatory effects in Th1 dominant conditions (Marshall, Lee et al., 2006). A recent review of the anti-inflammatory effects of ARB's and ACE inhibitors in humans, suggests these interventions have effects independent of their ability to lower blood pressure, specifically lowering matrix metalloproteinase 9 (MMP-9), IL-6, TNF-α, Reactive Oxygen Species, and increasing IL-10 (Dandona, Dhindsa et al., 2007).

Marshall elucidates the potential role of angiotensin in a self-perpetuating cycle of inflammation in his "Angiotensin Hypothesis," summarized as follows (2006):

> As the circulating concentration of 1,25-D increases within the inflamed tissue, a much larger quantity of hematopoetic stem cells differentiate to produce monocytes. Monocyte differentiation into macrophages and epithelioid giant cells is enhanced. The differentiating macrophages and giant cells release Angiotensin Converting Enzyme. This ACE catalyzes Angiotensin I to form Angiotensin II (A-II). The A-II then binds at A-II Type 1 receptors on the macrophages and activated T-lymphocytes, stimulating Nuclear Factor-kappaB (NF-κB) to signal the release for a cascade of Th1 cytokines. At least one of these cytokines, Gamma Interferon, increases the amount of 25-D (inactive form of Vitamin D) being converted to 1,25-D in the macrophages, which in turn catalyses the differentiation of monocytes into even more macrophages and giant cells.

Modifying angiotensin receptors and inhibiting ACE, although largely theoretical, has demonstrated better and faster treatment outcomes in the clinic with both pharmaceutical and herbal approaches. The two main herbs I use for their "ACE inhibiting effects" are *Salvia m* and *Scutellaria b*, again largely theoretical. Yet both of these herbs have many other benefits for the individual with chronic Lyme disease.

In addition to herbs that modify cytokines, the herbalist can look at specific inhibition of Cox-2 and eicosanoid production, which has been associated with better outcomes in animal models (Anguita et al., 2002). Inflammation in the blood vessels may be one of the main mechanisms of the disease process. Herbs to consider here are protective to the endothelial tissue, decreasing vasculitis. Also, consider herbs to improve tissue perfusion first by stimulating circulation, decreasing viscosity and improving flow dynamics (Baskurt, 2003).

Fever therapy was used traditionally in syphilis and has usefulness today in chronic Lyme disease as an adjunct to herbs and pharmaceuticals. It may assist with killing the organisms and improving blood perfusion. Spirochetal forms of Bb have low tolerance for high temperatures whereas cystic forms can survive 30 minutes at 176˚F. Spirochetes replicate quickly at 98.6˚F, a temperature increase to 102.2 ˚F decreases growth significantly, and twenty-four hour exposure to 104˚F kills all Bb in culture (Porcella, 2001; Brorson, 2006).

**Support and manage body's vital force.**
Many individuals suffering with chronic Lyme disease have a significant decrease in quality of life. The body's adaptive mechanisms are engaged, allostatic load is high, and there is little room for added stressors. Before making dramatic diet or lifestyle changes, it is important to assess an individual's adaptive capabilities and support systems. It is important to keep bowels moving and the body hydrated and rested. Gentle supportive changes are recommended, including plenty of sleep, and minimal alcohol use. Vigorous exercise can often exacerbate symptoms and cause a setback in treatment. Gentle exercise is recommended. It is noted that vigorous exercise can increase IL-6 (Hughes, Darlington et al., 2004), a pro-inflammatory cytokine elevated in chronic Lyme. Exercise tolerance can be a marker for recovery. The easiest dietary changes are ones that incorporate more healthy foods, in particular anti-inflammatory phytonutrients, water, and soluble fiber, and secondarily good quality fish and grass fed meats.

Adaptogens can play a useful role here to support stress adaptation, in particular those with secondary benefits, i.e. the immune modulating properties of Ashwagandha (*Withania somnifera*), Siberian ginseng (*Eleutherococcus senticosus*), *Cordyceps sinensis* and Korean ginseng (*Panax ginseng*) and the antimicrobial benefits of Neem (*Azadirachta indica*).

**Primary Herbal (and Nutritional) Therapies by Action:** This list incorporates the herbs the author most commonly uses in formulation and is by no means exhaustive.

| | |
|---|---|
| ACE Inhibitors: | *Allium s.*, Hawthorne (*Crataegus spp*), *Salvia m.*, *Scutellaria b.* |
| Adaptogens: | *Azadirachta*, *Cordyceps*, *Eleutherococcus*, *Panax g.*, *Withania* |
| Alteratives: | *Berberis a.*, *Smilax* |
| Antiprotozoal: | *Artemesia a.* (artemisinin) |
| Antibacterials: | *Allium s.*, *Azadirachta*, *Coptis*, *Berberis a*, *Houttyunia*, *Scutellaria b.* |

| | |
|---|---|
| Antispirochetal: | *Coptis*, *Houttyunia*, *Smilax*, Grapefruit Seed Extract (Brorson, 2006) |
| Collagen support: | *Centella*, *Crataegus*, *Echinacea purpurea*, *E. angustifolia*, Vitamin C |
| Enhance phagocytosis: | *Berberis a*, *Echinacea*, *Houttyunia*, Cat's claw (*Uncaria tomentosa*) |
| Fibrinolytics: | *Allium s*, Proteolytic enzymes |
| Hepatotrophorestorative: | *Azadrichta*, Milk Thistle (*Silybum marianum*) |
| Immunomodulators: | *Allium s*, *Berberis a.*, *Cordyceps*, *Echinacea*, *Panax g.*, *Scutellaria b.*, *Silybum*, *Uncaria t.*, *Withania* |
| Improve Blood Rheology: | *Salvia m* |
| Improve microcirculation: | Cayenne (*Capsicum frutescens)*, *Ginkgo biloba*, Periwinkle (*Vinca minor*), *Zingiber* |
| Inflammation modulators: | Turmeric (*Curcuma longa*), *Scutellaria b.*, *Uncaria t.*, Ginger (*Zingiber officinalis*) |
| Lymphatics: | *Calendula officinalis*, Red root (*Ceanothus spp*), *Echinacea*, Cleavers (*Galium aparine*), Poke (*Phytolacca decandra)* |
| Stimulate NK activity: | *Cordyceps*, *Echinacea*, *Panax g.*, *Uncaria t.* |
| Nerve restoration: | *Withania*, Omega 3, Phosphatidyl choline |
| Vascular tonics: | *Crataegus*, Bilberry (*Vaccinium myrtillus*) |

**Herbs and Cytokine Modulation,** based on *in vitro*, *in vivo* and *ex vivo* research (Spelman, Burns et al., 2006)
↓ IL-2 – *Allium s.*, *Silybum*
↓↑ IL-2 - *Cordyceps*
↑ IL-2 – *Smilax*, *Withania*
↓IFNγ - *Allium s.*, *Uncaria t.*
↓↑IFNγ - *Cordyceps*
↓TNFα - *Allium s.*, *Curcuma*, *Scutellaria b*., *Smilax*, *Uncaria t.*
↓↑ TNFα - *Withania*
↓IL-6 – *Allium* s., *Astragalus*, *Coptis*, *Scutellaria b.*
↑IL-6 – *Echinacea*, *Silybum*, *Uncaria t.*, *Zingiber*
↓IL-12 – *Allium s.*
↑↓IL-4 – *Panax g.*, *Silybum*
↑IL-10 – *Allium s.*, *Echinacea*, *Silybum*

**Significant Herbs in Lyme Disease**
***Allium sativum*, Garlic**
While difficult to achieve patient compliance, garlic is arguably the most potent herbal antibacterial in an herbalist's materia medica. Garlic's broad-spectrum applicability make it useful where secondary infections are taking hold, it has demonstrated antiprotozoal and antifungal effects (Buhner, 1999, Zhang & Zhang, 2006). The metabolites demonstrate ability to cross the blood-brain barrier. Dr. Zhang recommends 1-2 mg allicin per kg of body weight. For a 60 kg individual, that is 120 mg Allicin daily (Zhang, 2006 & 2007). Eating raw garlic, as Dr. Duke suggests, is certainly the least expensive way to consume this herb and food, although consuming large amounts of raw garlic can cause gastric upset. Garlic has many benefits for the individual with chronic Lyme disease: It can increase body temperature, blood perfusion and cardiovascular functioning, and is a fibrinolytic (Blumenthal, 2003; Mills & Bone, 2000). It lowers several pro-inflammatory cytokines that tend to be elevated in chronic Lyme, while nudging IL-10 and potentially down-regulating inflammation (Spelman et al., 2006; Bergner, 2005). Dr. Harris, a Lyme-literate physician, had a case of Lyme-induced blindness in a young boy reversed with the use of garlic (Zhang, 2007). Results of the first clinical trial using an herb, and in this case garlic, in Lyme disease will be released later this year. Conducted by Allimax Nutraceuticals, it is reported that the initial results look promising.

***Artemesia annua*, Sweet Annie, Qing Hao,**
Pharmaceutical treatments for *Babesia* co-infection are modeled after treatment for malaria. Artemisinin and its water-soluble derivative artesunate are both active constituents of Sweet Annie and are metabolized to dihydroartemisinin (DHA). Chen states that DHA is the most powerful schizonticidal agent for malaria. It is the World Health Organization's first line treatment for malaria (Zhang, 2007; Schaller, 2006; Chen, 2004), with lower microbial resistance than chloroquine (Chen, 2004). Dosing is challenging, as studies in pharmacokinetics demonstrate that artemisinin upregulates its own metabolic elimination, causing a "five- to sevenfold decrease(s) in its concentrations over 5 to 7 days of administration in both malaria patients and healthy subjects," (Gordi, Huong et al., 2002, p. 1026). Metabolic derivatives of artemisinin have been shown to have a direct lethal effect on the organism (Zhang & Zhang, 2006; Chen, 2004), as well as cause damage to the organism by free radicalizing iron in red blood cells (Schaller, 2006). Low hematocrit, hemoglobin and RBC levels are not uncommon in clients with Babesia co-infection, co-supplementing with a food-based iron may enhance the effect of artemisinin (Schaller, 2006). Energetically in TCM, the whole plant is used for yin deficient heat conditions. It cools blood in late stage febrile disorders (Chen, 2004).

***Astragalus membranaceous*, Astragalus**
There are 3220 pubmed hits for Astragalus. As pointed out by Buhner, several studies support its use to promote a Th1 response in the first few days of acute Lyme infection (Mao, Cheng et al., 2004; Liu, Zhang et al. 2003; Wei, Sun et al., 2003). Tick saliva modulates human immune response upon initial infection, more specifically increasing IL4 and driving Th2 polarization of CD4

T cells. It is suggested that a Th1 cytokine response initially may help to prevent the intensity of tick transmitted infection (Wikel, 2006). In addition, Astragalus has been shown to enhance body vitality, NK activity, potentiate monocytes, increase phagocytosis and immunoglobulin production, and balance CD4:CD8 ratios (Bone, 2006; Buhner, 2005). Astragalus is therefore a good preventative, as the initial immune response to acute Lyme disease affects chronicity (Zhang, 2007).

***Berberis aquifolium*, Oregon Grape Root**

"*Berberis aquifolium* has won its reputation chiefly as a remedy for the syphilitic taint. The more chronic the conditions or results of the disease, the more it has been praised," (Felter, 1922, p. 244). Felter recommends substantial dosing and cites its specificity for emaciation and weakness and improving appetite (1922). In vivo models suggest a protective effect of Berberine on endotoxin-induced immune dysregulation, in particular augmenting IL10 while lowering TNFα and IFNγ. This anti-inflammatory cytokine pattern is almost identical to the inflammatory cascade stimulated by bacterial surface lipoproteins (Li, Wang, et al. 2006).

In addition to its traditional and pharmacological use as an alterative, current pharmacological models of herbal medicine note berberine (one of the main active alkaloids in *Berberis*) to be a specific for 25 strains of bacteria, as well as fungal, protozoal and spirochetal infections (Zhang, 2007; Chen, 2004; Mills & Bone, 2000). Berberine was comparable to quinine in vitro against two clones of human malaria (Mills & Bone, 2000). Another berberine containing plant, Huang Lian **(***Coptis chinensis*) has been used as an antispirochetal, where it is thought to be most commonly used herbal antimicrobial agent in China (Zhang, 2007; Chen, 2004).

***Echinacea angustifolia* and *E. purpurea***

Of eleven Eclectics interviewed in 1908, the 3 most popular remedies used in Syphilis were *Iris versicolor*, *Phytolacca*, and *Echinacea a.* (Ellingwood, 1908). *Echinacea* is an immunomodulator and lymphatic (Mills & Bone, 2000), enhancing immune function by activating macrophage activity, NK cell activity, enhancing bacteriolysis, improving antibody binding, and activating the alternative complement pathway (Spelman, 2003). *Echinacea* demonstrates ability to decrease inflammation and increase IL-10 production (Spelman et al, 2006). Also, *Echinacea* demonstrates ability to protect collagen integrity and improve tissue regeneration, inhibiting hyaluronidase, stimulating fibroblasts and the manufacture of glycosaminoglycans (Spelman, 2003).

***Houttuynia cordata*, Yu Xing Cao**

Traditionally used to clear damp heat and poisons, with doses ranging 9 – 60 grams (Bensky & Gamble, 1986). Recent studies demonstrate that 15 - 30 grams daily was effective in prevention and treatment of leptospirosis (another spirochetal disease) in humans. It has also demonstrated antimicrobial effects *in vitro* against leptospirosis (cystic and spirochetal forms). It increases phagocytosis in animal models, as well as reduces mortality rate in mice with tuberculosis (Zhang & Zhang, 2006; Chen, 2004). The active constituent is decanoyl acetaldehyde, and the most potent form I have found on the market (with an LD50 of .8 – 2.4 g/kg) is Hepapro's "HH Capsules" with 90 mg decanoyl acetaldehyde per capsule (Zhang, 2007).

***Salvia miltiorrhiza*, Dan Shen**

Dan shen is the herb premier for improving blood rheology and cardiovascular health as it relates to chronic Lyme disease. Traditionally, *Salvia* is used to decrease blood stasis, improve peripheral and cerebrovascular circulation, and nourish the blood (Bensky & Gamble, 1986). Clinical trials support its use in recovery from stroke, heart disease, hepatitis and to reduce hyperviscosity of the blood (Bone, 2006). *Salvia* demonstrates ability to down-regulate matrix metalloproteinases (MMP-2 & MMP-9 specifically) that tend to be elevated in atherosclerosis and chronic Lyme disease (Jin, Kang et al., 2006; Zhang &Wang, 2006).

*Salvia* has ACE-inhibiting effects (Kang, Oh et al., 2003; Kang, Yun et al., 2002; Ouyang, Takahashi et al., 2001). Although not as potent in the brain, *Salvia* does affect the level of Angiotensin II in both the brain and plasma (Wang, Chen et al., 1991). The water-soluble extracts were found to have the most activity (Gao, Xu et al., 2004).

In a clinical review, Adams et al. discussed *Salvia*'s ability to prevent clot formation and increase clot dissolution with unique mechanisms of anticoagulation. *Salvia* increased arterial dilation in the brain improving blood perfusion, with benefits to stroke victims for repair of neurological functioning. In the last 10 years, Dan shen has become the most commonly used herbal medicine for stroke victims in China, improving quality of life 74% on average (17 reports). Dan shen also demonstrated anti-inflammatory effects, inhibiting arachidonic acid metabolism and decreasing production of eicosanoids (2006).

***Scutellaria baicalensis*, Baikal Skullcap, Huang Qin**

A potent anti-inflammatory and antioxidant, the herb is commonly used for inflammatory disorders, asthma, allergies, sinusitis, rhinitis, hepatitis, and compromised liver function (Bone, 2006). Baikal skullcap was traditionally used in formula with *Smilax* and *Coptis* for late stage syphilis in China, and has been utilized there for centuries as an antibacterial (Chen, 2004; Zhang, 2007). Constituents of the root demonstrate blood pressure lowering and endothelial protective effects (Huang, Tsang et al., 2005). Traditionally the herb was used to clear heat, cool the blood, sedate fire, and eliminate toxins (Chen, 2004).

***Smilax glabra*, Sarsparilla, Tu Fu Ling**
*Smilax* is a traditional remedy for spirochetal diseases in the East and the West. Clinical studies in China demonstrate the herb's effectiveness in syphilis and leptospirosis at doses ranging from 60 g to 150 g, commonly used in combination with *Glycyrrhiza*, *Scutellaria b*., *Stephania t*., and *Artemisia* (Chen, 2004). At this dosage range, cure rates in syphilis are estimated to be 90%, and in late stage disease 50% (Zhang, 2006). Although used by the Eclectics, somewhere along the way several authors seemed to become disenchanted with Smilax's usefulness in syphilis, however they were using much smaller doses than the Chinese, i.e. 2-8 grams daily (Felter, 1922, Felter & Lloyd, 1898).

***Uncaria tomentosa*, Cat's Claw, Una de Gato**
Cat's claw is an anti-inflammatory specific to rheumatic conditions. It has been shown to stimulate NK cell and macrophage activity, as well as protective effects on the endothelium and memory. Cat's claw has also demonstrated the ability to modify a Th1 immune response (Spelman et al., 2006; Buhner, 2005; Winkler, Wirleitner et al, 2004; Kemper, 1999).

Cat's claw contains sixty unique oxindole alkaloids that vary 10-40 fold depending on season, cultivation, location, and soil. The pentacyclic oxindole alkaloids (POA's) and tetracyclic oxindole alkaloids (TOA's) can account for up to 80% of total alkaloid content (Kemper, 1999; Keplinger, Laus et al., 1999). Several products advertise TOA-free, based on a study which demonstrated that isolated POA's significantly inhibited proliferation of lymphoblastoid cell lines *in vitro* and stimulated the differentiation of B and T lymphocytes. Isolated TOA's reduce the effects of these POA's in a dose dependent manner (Kemplinger et al., 1999). This study has been criticized for its methodology. Winkler, Wirleitner, et al. (2004) demonstrated that both POA's and TOA's had similar if not synergistic effects on PBMC (peripheral blood mononuclear cells) and cytokine activity, specifically lowering IFNγ and reactive oxygen species (ROS) in macrophages.

Mediherb, an Australian manufacturer, has not seen a raw sample without TOA's, varying 1% to 10% in raw samples (Ryan, 2006). Several of the TOA-free cat's claw products are dosed at very low levels (i.e. 1-20 drops daily) with drastically different clinical effects than the whole-plant Galenical extracts that the author uses in clinic. Optimal Health Physicians hired an independent lab to test one such TOA-free product with High Performance Thin Layer Chromatography. This test demonstrated no appreciable quantities of the herb in the product.

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