# "The New Lyme" — A Look at Babesia/Borrelia Co-infection

**by Jean Hubbard**

"I humbly propose we redefine what we have been calling Lyme," suggests Dr. Joseph Burrascano, talking about what he calls "the new Lyme disease" – prolonged disease caused by co-infections with multiple tickborne agents. "Co-infection is not surprising, for ticks ... literally live in the dirt and drink the blood of wild animals. To think that a significant tick bite transmits only one infection is narrow minded indeed." The price of such narrow-mindedness? – "creation of chronic, persistent forms of each of these infections" [1].

This must sound alarming to people who aren't already so familiar with chronic, persistent illness. But for chronic Lyme patients the new understanding of co-infections offers a ray of hope – the possibility of more effective treatment. It also underscores the need for prompt recognition, diagnosis and treatment of tickborne diseases. Three articles in this issue of the Lyme Times review some of what has been learned so far about the most systematically studied of these co-infections – *Babesia microti* plus *Borrelia burgdorferi*. In this article we look at how Babesia co-infection affects Lyme disease. A second article discusses the people and regions most at risk for this co-infection [page 39, this issue], The third glances at a promising new treatment for it [page 44, this issue]. A final article, slated for our next issue, will explore some information related to diagnosis. [*Ed note: References for all articles are on pages 45-47*]

**Debilitating fatigue, prolonged spirochetemia and persisting symptoms characterize Babesia/ Lyme disease co-infections**

How does Babesia co-infection affect Lyme disease? The persistent illness Dr. Burrascano mentions has been decisively demonstrated in early *Babesia microti/Borrelia burgdorferi* co-infections [2]. And the initial illness is not only longer lasting, but also substantially more severe than Lyme disease alone .

By itself, babesiosis – the disease resulting from infections of red blood cells by Babesia parasites – varies in severity. Early babesial infections in fact are usually silent, i.e. without clinical symptoms [2,3,4]. When symptoms do occur, they vary from low-grade and brief to a "fulminant malaria-like disease" that is persistent and severe and occasionally ends in death [5]. Symptoms may first occur after long periods of silent infection. They may recur even after treatment, particularly following suppression of the immune system by splenectomy, AIDS, cancer, chemotherapy, corticosteroid use, or simply aging [3,5,6,7]. Lyme disease by itself likewise varies from silent to severe, and patients often note their early symptoms disappear quickly only to recur later.

But if the tick that carries Lyme disease also carries babesiosis, the person bitten by that tick is very likely – as much as 95% of the time – to become sick immediately, often very sick and for a very long period of time, according to an important study led by infectious disease pediatrician Peter Krause, MD of the University of Connecticut School of Medicine [2]. Debilitating and prolonged fatigue, accompanied by apparently increased and prolonged spirochetemia, dominated the clinical picture seen in co-infected patients.

Block Island, the site of the study, is a small Rhode Island community of about 1200 residents. Beginning in 1990, Dr. Krause, working with Dave Persing of the Mayo Clinic and colleagues from the National Institute of Allergy and Infectious Diseases, tried to estimate how many Block Islanders had been exposed to tickborne diseases. They mounted an impressive campaign to educate island residents about Lyme disease and babesiosis, using local newspapers and cable TV channels and posting information at the island's only medical center. Their educational effort was so successful that an amazing 1156 of the 1200 residents had their blood tested for both diseases, providing an unusual opportunity to compare the effects of each kind of infection in a population relatively free of selection bias.

Over the first five summers of the study, when members of this alerted and well-informed citizenry presented to the island's medical center with clinical symptoms suggestive of either disease, more than 200 were diagnosed, by strict CDC criteria, with either Lyme disease, babesiosis, or both. Most of them – 206 people – were diagnosed with early Lyme disease; 23 of the 206 Lyme disease patients – 11% – also had babesiosis, i.e., were co-infected. A total of 33 patients were diagnosed with babesiosis; 23 of them –70% – also had Lyme disease. This is more than twice as many as had babesiosis without Borrelia co-infection – only 10 of 23, or 30.3.%.

Co-infected people were not only more likely to become sick, but became impressively sicker, with a wider array of symptoms, and remained ill significantly longer – even after antibiotic treatment – than patients with either disease alone. They also had PCR-detectable borrelial DNA in their blood more often and for longer durations than those with Lyme disease alone. In one case spirochetemia persisted for nearly nine months despite early antibiotic treatment.

Co-infection without illness was rare indeed: only one of 19 Block Islanders with a four-fold rise in antibody titer to both infections remained free of symptoms – i.e. the silent co-infection rate by this standard was only 5%. The silent infection rate in those infected only by *B. burgdorferi* was three times higher – 16%. In other words, 28 of 175 people infected with *B. burgdorferi*, using the same criterion of a four-fold rise in titer, remained symptom-free and therefore were not diagnosed with Lyme disease. In this study it appears that an impressive 79% (30 of 38) of those infected only by *Babesia microti* had silent infections without symptoms [2], although in a later study Dr. Krause estimates silent infections as closer to one-third [5], in agreement with an early study by Ruebush [4].

**Persistent, debilitating fatigue:**

The most dramatically increased symptom of early co-infection was fatigue, leading Dr. Krause to conclude that "persistent and debilitating fatigue characterized co-infection." Even after very early antibiotic treatment, begun an average of five days after illness onset, more than one-third of the co-infected patients (35%) had fatigue that lasted for longer than six months, compared to only 3% of patients with Lyme disease alone. Their fatigue was serious and debilitating, bad enough to limit daily activities by at least 25%. Many additional co-infected patients experienced this degree of fatigue for shorter durations – four-fifths (81%) of them, compared to 48% of patients with only Lyme disease. Prior health seems not to have been a factor: no patient had experienced persistent fatigue prior to the onset of the tickborne illnesses.

Other Lyme symptoms were also increased in the patients with both infections: co-infected patients complained of headaches more often than those with only Lyme disease (77% compared to 40%), as well as nausea (23% compared to 5%), sweats (46% compared to 10%), chills (42% compared to 22%), anorexia (31% compared to 13%), emotional lability (23% compared to 7%), and conjunctivitis (12% compared to 2%). Enlarged spleens were found in 8% of patients with both diagnoses and in one of the 10 patients diagnosed with *Babesia microti* alone, but no patient in this cohort with only Lyme disease had detectable splenomegaly. All these differences were statistically significant.

Neck stiffness and musculoskeletal complaints like arthralgia and myalgia, on the other hand, were reported about as often by patients with Lyme disease alone as by co-infected patients. Progression to joint swelling was relatively rare (3 to 4%) in these quickly diagnosed patients, presumably due to their early treatment, and co-infection did not increase its occurrence. Patients did not display signs indicative of neurologic or cardiac Lyme disease, again most likely because of early antibiotic treatment.

***Debilitating fatigue, prolonged spirochetemia and persisting symptoms characterize Babesia/ Lyme disease co-infections.***

**Increased spirochetemia:**

Co-infection with *Babesia microti* also intensified and prolonged the presence of spirochetes in the blood of Lyme disease patients. PCR was able to detect blood-borne *B. burgdorferi* spirochetal DNA more than four times as often in patients with both diagnoses as in Lyme disease-only patients (27% compared to 6%), and for a dramatically longer time: Although they had received early antibiotic treatment, Borrelial DNA was detectable for an average of three months (91 days) in the co-infected patients, but for only 12 days in those with Lyme disease alone. One co-infected patient still had PCR-detectable Borrelial DNA when tested nearly nine months (265 days) after illness began, again despite antibiotic treatment. The final PCR test on this patient's blood was done a month prior to the next tick season, and it was thought unlikely this persisting spirochetemia resulted from re-infection.

Dr. Krause believes detection of spirochetal DNA in blood by PCR implies the presence of living spirochetes in the body's circulation. At a minimum the more frequent detection of blood-borne *B. burgdorferi* DNA in the Block Island co-infected patients than in patients with only Lyme disease strongly suggests they had larger numbers of spirochetes in their blood. Their relatively prolonged PCR positivity is strong evidence for relative prolongation of the spirochetemia that disseminates *B. burgdorferi* to tissues remote from the site of tick bite. In Lyme disease by itself spirochetes typically are rapidly cleared from – or become undetectable in – the bloodstream (by about 12 days in this Block Island study). This study examined only the first year of Borrelial/Babesial co-infections in patients given early antibiotic treatment, but its findings seem likely to have important consequences for later and chronic Lyme disease in co-infected patients as well. Larger numbers of spirochetes circulating in the bloodstream over longer durations would allow the spirochetes to more intensely invade tissues in more parts of the body, thus causing not only the more varied and longer lasting symptoms seen during the first year of disease, but probably also increasing spirochetal loads in "immunologically privileged sites" like tendons, eye, brain and within cells, where they would be relatively protected from

control by antibodies or eradication by antibiotics, thus setting the stage for chronic illness, especially in patients not receiving early treatment.

Babesia seems to suppress the immune system in mice, cattle and dogs [8]. Whether this happens in humans has yet to be examined, but Krause et al suggest that Babesia-induced immunosuppression could underlie the increased symptoms and more persistent spirochetemia seen in Lyme disease when babesiosis is present [2].

**Persistent Parasitemia:**

The effect of Lyme disease on babesial infections is less clear. While fatigue, sweats, anorexia and nausea were experienced somewhat more often by Borrelia/Babesia co-infected patients than by those infected only with Babesia, the differences were not significant. A later Block Island study [5] found no evidence that antibiotically treated Lyme disease co-infection increased the persistence of blood-borne babesial parasites in patients with babesiosis [but see 9]. However, in one patient with three tickborne diseases – Lyme disease, babesiosis and human granulocytic ehrlichiosis – PCR was able to detect *Babesia microti* DNA in blood for 208 days (nearly seven months), more than twice as long as the average for those with babesiosis alone [5].

Babesial infection by itself, however, "may persist for months or even years." Even when it is asymptomatic or silent, it "may recrudesce spontaneously, or after splenectomy or immunosuppression" [5]. Prior beliefs about the persistence of *Babesia microti* were based on actually seeing babesial parasites within red blood cells under the microscope, but this is not a sensitive test because parasites are sparse in people [10]. In the most recent study of Block Island and Connecticut patients with newly diagnosed babesiosis, published just this summer [5], parasites were seen within red blood cells only briefly, for less than a week, even though 100 fields of thin blood smears were examined microscopically. PCR, however, detected blood-borne babesial DNA for much longer in the same patients – an average of 82 days, or nearly three months. Persistent PCR-detected parasitemia was often accompanied by persistent symptoms.

Again Krause et al. argue that the presence of detectable DNA in the blood implies persistence of infection. They note that in one initially asymptomatic patient, PCR was able to detect blood-borne babesial DNA initially and again five months later. At 17 months (in April, when re-infection was thought unlikely) the same patient had what was apparently his first episode of babesial illness, with fever, chills, sweats, anorexia, nausea and stupor. On examination of blood smears, 3% of his erythrocytes (red blood cells) were found to contain parasites. He was hospitalized, found to have an intracapsular renal tumor, was treated with clindamycin and quinine and became symptom-free and apparently parasite-free one week later. When he returned to hospital for removal of the kidney six weeks after that – 27 months after the initial parasitemia – again 1% of his erythrocytes showed parasites [5].

***"Human babesiosis may be more persistent and less benign than previously thought"***

Such findings heighten the concern – echoed by other researchers – that "human babesiosis may be more persistent and less benign than previously thought" [5]. In both naturally and experimentally infected animals, "chronic infection is the rule rather than the exception" [10]. Some animals remain parasitemic for life and may develop worsening chronic disease before death [3]. Dogs infected with *Babesia gibsoni*, for example, have developed liver lesions and chronic membranoproliferative glomerulonephritis even after anti-babesial treatment with clindamycin and quinine [11,12]. And of course malaria, a similar infection of red blood cells often indistinguishable from Babesia on blood smears, is well known for its chronicity.

Like most good research, the Block Island studies raise as many questions as they answer about how these two infections affect one another. A few important ones, because they're likely to affect many people: What happens when one infection follows another rather than both occurring simultaneously? Many Lyme patients report multiple tick bites. What happens if antibody responses to one or both infections don't meet strict CDC criteria? Does the Babesia-induced immunosuppression suspected in other animals [8] affect humans as well, and in ways that might, as Burrascano [1] and Magnarelli [13] have suggested, complicate diagnostic testing? Antibody titers to *Borrelia burgdorferi* were higher rather than lower in the acutely ill Block Island Borrelia/Babesia co-infected patients, according to Persing [14], who thought this probably due to the increased spirochetemia. But animal studies show *Babesia microti* reduces antibody response to some toxic antigens, especially "memory" antibody responses, and may heighten susceptibility to other infections [3,15,16].

Already there are four species of babesia known to be pathogenic to humans (*Babesia microti*, *Babesia divergens*, WA1 and MO1) [3], and Persing reports there are also regional strains of *Babesia microti*, showing different sequences of outer surface proteins [16]. Will co-

infections of Lyme disease and these other species of Babesia produce the same severe illness that *B. burgdorferi/Babesia microti* did in the Block Islanders? Will co-infections of Lyme disease and the other species even be common, given that MO1 and WA1 may have other tick vectors [3,18]? What additional complications arise when other Ixodes tickborne agents such as human granulocytic ehrlichiosis, flaviviruses, or infections not yet identified are involved? Are people at risk for Ixodes tick bites also more at risk for bites from other human-biting ticks that carry yet more infections?

And, most urgently, what happens when co-infections are untreated and perhaps persist for years? Untreated acute *Borrelia burgdorferi/Babesia microti* co-infection has resulted in at least three deaths [19,20]. In fact one of the few reported Lyme disease fatalities was in a patient co-infected with Babesia; in spite of his having reported no cardiac symptoms, he died of spirochetal invasion of heart muscle with all layers of his heart inflamed, i.e., with severe myocarditis, endocarditis and pericarditis [19]. The Block Island researchers state that babesial infection enhances Lyme disease myocarditis in mice, and are concerned that this co-infection may "synergize spirochete-induced lesions in human joints, hearts, and nerves" [2]. Burrascano observes that "severe headaches, dizziness and encephalopathy out of proportion to the other Borrelial symptoms" is a common sign of co-infection [1]. Is this co-infection, probably undetected, in fact resulting in more severe, persistent cardiovascular and central nervous system Lyme disease?

Bosler and Schulze found *Babesia microti* co-infection of *B. burgdorferi*-infected wild white-footed mice to correlate both with hematuria and the presence of spirochetes in their urines and bladders [21]. Might *Babesia microti* also promote spirochetal infections and damage within the human urinary tract, as is seen in some dogs with Lyme disease [22,23]?

Clearly, late interactions between spirochetes and babesial parasites, each with tendencies to persist, subside and reappear, are likely to be complex. Research into even this one known co-infection has just begun, and there are unknown other tickborne co-infections to consider, now that we all – researchers, physicians and patients alike – are beginning to look at what Burrascano calls "the New Lyme" and Magnarelli calls "the broader picture" [13]. The tick, as Willy Burgdorfer says, is a Pandora's box [24].

# Who is at risk for Borrelia/ Babesia co-infection?

Borrelia/Babesia co-infections – at least those that are already known – cluster along the New England seaboard and around the Great Lakes region in the upper Midwest [3]. Coastal islands of New England are infamous hot spots for babesiosis, and these islands –Nantucket Island, Martha's Vineyard, Naushon Island and Cape Cod in Massachusetts; Block Island and elsewhere in Rhode Island; Shelter Island and Long Island in New York [20] – have attracted most of the babesiosis and Borrelia/Babesia co-infection research attention.

However, babesiosis is not easily recognized clinically. Symptoms are usually either absent or low-grade. When more intense illness develops, it is easily mistaken for a number of other illnesses, including flu, malaria and other tickborne diseases [12,18]. Until recently it was thought to be very rare and a disease only of the elderly or immunocompromised [5,12]. Unless physicians know to look for both, a diagnosis of Lyme disease would mask it, and review of epidemiologic studies suggests that this happens often [see below]. A recurring theme in the history of babesiosis research in any given region is how often the first cases were diagnosed "incidentally" or accidentally [e.g.12,25].

Researchers warn that wherever both pathogens are endemic, people are at risk for Borrelia/Babesia co-infection [2,3,5,26] because in the Northeast and Midwest the two pathogens share the same reservoir hosts (small rodents, especially the white-footed mouse) and vector (*Ixodes scapularis*), both of which are often co-infected [13,14,17,27].

Given all this, it seems likely that published cases and the epidemiologic studies mentioned below may represent only – as we hear so often about tickborne diseases – "the tip of the iceberg." A case in point is New Jersey: A Medline search disclosed only one article about human babesiosis in the New Jersey, published in 1990 [28], but babesiosis is probably highly endemic there. Varda et al.'s recent PCR study of infections in 100 adult *Ixodes scapularis* ticks in New Jersey's Hunterdon County found 5% of the ticks infected with *Babesia microti*. The five Babesia-infected ticks were widely distributed in the county – one each was found at half of the 10 sites sampled. Four of these five Babesia-infected ticks carried another tickborne disease as well: two were co-infected with *B. burgdorferi*, and two were co-infected with the agent for HGE [29].

Stony Brook researcher Ed Bosler found, on highly endemic Long Island, rates of *Babesia microti* infection in adult ticks that ranged from 7% to 20% [30], and Telford, in a study of Nantucket (where babesiosis is so endemic it used to be called

"Nantucket fever"), found a 9% infection rate in adult ticks. The 5% rate in Hunterdon ticks is lower, but not all that much lower. Hunterdon is hyperendemic for *B. burgdorferi*: in 1996 it had the third-highest case rate of Lyme disease of all counties in the United States (524/100,000) [29], and the state of New Jersey reported 2,190 cases to the CDC the same year [31]. The risk of Borrelia/Babesia co-infection in tick-infested areas of New Jersey thus seems likely to be substantial in spite of its nearly complete omission from the medical literature.

Published studies also report Borrelia/Babesia co-infections in Connecticut [32], Wisconsin and Minnesota [33,34]. One study found *Babesia microti* in North Carolina [35], and new species of human Babesia have been discovered very recently – WA1 on the West Coast in 1991 [3,12], and MO1 in Missouri in 1992 [36]. On the West Coast, in California and Washington, research into babesiosis is still very new, and there seem to be no studies of Oregon. There are anecdotal reports of *Babesia microti* cases in California [12], and some Lyme patients say they've been diagnosed with co-infections, but published case studies and serosurveys so far have found only Babesia WA1 [3,12,37,38]. Insights into Borrelia/Babesia co-infection gained from the Northeastern experience [see the first article in this series, page 36] may or may not apply on the West Coast since the two infections may well turn out to be vectored by different ticks [3,17,37]. To date there has been only one Missouri case, and again the vector and host are not yet known [36].

Data from some of these studies are described in more detail below. But first, in the interest of correcting a dangerous myth about babesiosis, some more information from Block Island:

**Children and babesiosis:**

Children do get babesiosis. They are at least as susceptible as adults to babesial infections, whether silent or clinical, and to the more severe and persistent illness caused by co-infection with Lyme disease and babesiosis, despite the latter's reputation as being a disease mainly of older adults and people without spleens. As late as 1992, when pediatrician Peter Krause addressed the problem, there were only five published case reports of severe babesiosis in children [26]. One was infected by blood transfusion, one was a splenectomized teenager, and three were infants – raising the specter of congenitally acquired infection but not proving it [39]. Although four of these five cases were considered moderate to severe, and three required treatment by replacement transfusion, the medical community has generally believed that otherwise healthy children either do not become infected with Babesia or fail to develop symptoms from it [26]:

***Physicians are taught that babesiosis is a geriatric rather than a pediatric disease and don't even consider the diagnosis in children.***

Since 1992, three serosurveys have reported data about Babesia infections in children. During the first five months of the Block Island tickborne disease serosurvey by Dr. Krause et al, in the fall of 1990, nearly three-fourths of the island's 800 permanent (i.e. winter) residents were tested for antibodies to *Babesia microti* by an immunofluorescence assay (IFA); 12% of children and 9% of adults were seropositive, and people who had experienced typical symptoms of babesiosis during the prior season were as likely to be children as adults. Dr. Krause concluded that children are infected at least as often as adults with *Babesia microti* and that the infection also leads to actual illness at least as often [26].

Krause believes babesiosis has been underdiagnosed in children – even more so than in adults – because physicians are taught that babesiosis is a geriatric rather than a pediatric disease and don't even consider the diagnosis in children. (Severity of babesiosis does seem to be greatly increased in people over 55, so their rate of diagnosed babesiosis is much higher.) He notes that there are a variety of more common childhood illnesses that present with the persistent fever and flu-like symptoms typical of babesiosis, and that these symptoms, particularly persistent fever, are usually more aggressively evaluated in adults than in children [26].

Hu et al, in a serosurvey of other areas of Rhode Island [40], also found children to be frequently infected with *Babesia microti*. Looking at sera obtained from three hospitals, they found 4.1% of blood samples tested (24/589) to be Babesia-positive by IgG IFA. Children had a comparatively high rate of seropositivity (5% to 6% for children to age 19), second only to people 70 years of age or older (6.7%). Young adults had a comparatively low rate (1.3% to 1.5% for people age 30 to 39). The age differences in Babesia seropositivity, like those in the Krause study, are suggestive but failed to reach statistical significance.

A third serosurvey, of a semi-rural community near Sonoma, California, also found a higher proportion of children to be IFA seropositive for Babesia – in this case the West Coast Babesia WA1 – and in this study the difference between children and adults was statistically significant [38]. The actual numbers per age group weren't published, but of a total of 219 community residents tested, including 18 children, 39 (17.8%) were seropositive for WA1 at high titers that ranged from 1:320 to 1:2560 (nearly 10 times the titers found in East Coast studies, which

usually range from 1:32 to 1:256). Half the children up to age 16 were positive for at least one tickborne disease, and the majority were positive for WA1. No one in this community had been diagnosed with babesiosis, and no one was seroreactive to *Babesia microti*.

**Human Borrelia/Babesia co-infections in the Northeast:**

The following review samples some of the published studies on babesiosis, focusing first – to the extent it is possible to separate these questions – on how often people with babesiosis have been found to have a Lyme disease co-infection, and then on how often people with Lyme disease have been found to have Babesia co-infection. There are also some clues about how often both infections go unrecognized and undiagnosed, and even some findings suggesting that babesiosis has been spreading into new areas. Note that the studies aren't exactly comparable since they use different criteria – some look at antibodies in blood as evidence of infections (serologic studies or serosurveys), while some require actual diagnoses of the diseases, usually by the rigid CDC criteria that may well miss many cases of *B. burgdorferi* infection.

**How often do people with babesiosis have Lyme disease?**

In the Northeast, the single most important risk factor for babesial infection is a diagnosis of Lyme disease [40]. Babesiosis certainly occurs in people without Lyme disease, but co-infections seem to be more common. In the seminal Block Island co-infection study by Krause et al [2], for example, 33 people were diagnosed with babesiosis; 23 of them, or 69%, also had a diagnosed co-infection with Lyme disease. Borrelia/Babesia co-infections were thus twice as frequent as babesiosis without co-infection (23 with both diseases compared to 10 with only babesiosis).

Babesiosis patients in other endemic regions also frequently have Lyme disease. In Connecticut, more than half (5/8) of babesiosis patients who were tested for Lyme disease had high Lyme ELISA titers of 1:640 to 1:5,120. Babesia parasites were isolated from 27 of 59 mice captured in or near the yards of patients, and 25 of the mice were co-infected with *B. burgdorferi* [41].

This co-infection is amply documented on Long Island: In 1981, Benach and Habicht et al reported that 21% (4/9) of babesiosis patients had erythema migrans [42]. In 1985, Benach et al reported that 56% (23/41) of Long Island babesiosis patients had Lyme disease [43]. In 1992, Sean Meldrun of the New York State Department of Health and colleagues reported that 23% of babesiosis patients (31/136) from the same area had concurrent Lyme disease [20].

***Babesial antibodies were much more common in patients who were also seropositive for B. burgdorferi infections.***

Stony Brook researcher William Golde, in a study begun just last year, is using PCR to study co-infections in Long Islanders. As of June he had been able to test only four patients with a primary diagnosis of babesiosis, but three of them were co-infected: two had PCR-documented co-infections with *B. burgdorferi* as well as HGE, i.e. were triply infected, and another was co-infected with just HGE [44].

These percentages of Long Island babesiosis patients who have a *B. burgdorferi* co-infection – 21%, 56%, 23%, 50% –are impressive, but to fully appreciate what an impact this co-infection is having on people in the Long Island vicinity, it helps to know how often people are being diagnosed with babesiosis there. Six of 102 Shelter Island residents seroconverted to *Babesia microti* (a fourfold rise in antibody titer) over just one summer in the late 1970s [45]. Between 1982 and 1991, Shelter Island and northeastern Long Island (East Hampton and Southampton) had official annual incidence rates of diagnosed babesiosis averaging 154.5, 22.1 and 7.5 per 100,000 respectively. Travel to these areas was thought to account for even more cases reported during that period, and Meldrun cautioned, "As with Lyme disease, babesiosis may pose a threat to vacationers who return to areas where local physicians may be unfamiliar with the disease" [20].

**How often do people with Lyme disease have babesiosis?**

Krause's initial Block Island co-infection study diagnosed 206 patients with Lyme disease; 23 of them, or 11%, had Babesia co-infection [2]. According to Mayo Clinic microbiologist Dave Persing, another investigator in that study, the percentage of Block Island Lyme patients with babesial co-infection ranged from 9% to 20% over the years from 1990 to 1994, with the average being about 15% [14].

The Rhode Island serosurvey by Hu et al [40] examined blood samples from 505 people seeking medical care, using antibodies as evidence for infections. Babesial antibodies were much more common in patients who were also seropositive for *B. burgdorferi* infections (9.7%) than in patients who were *B. burgdorferi*-seronegative (3.2%) or in those who weren't even tested for *B. burgdorferi* (1.8%). There were 24 people seropositive for *Babesia microti* in this study, but none of them, whether co-infected with Borrelia or not, had been diagnosed with babesiosis.

In the Connecticut serosurvey by Krause et al [32], *Babesia microti* seropositivity was 9.5% in people diagnosed with Lyme disease,

compared to 1.0%, 2.5% and 2.6% in college students, people with no known exposure to ticks, and random outpatients respectively. These percentages are strikingly similar to those found in Hu's Rhode Island study as well as to Krause's earlier study of Block Island [above].

Another important finding from this study suggests that *Babesia microti* may have come rather recently to Connecticut: there was no evidence of babesial infection in college students who had resided in Connecticut from 1959 to 1985, while 2.9% of college students were seropositive in the years after 1985. Krause also notes that most of the people seropositive for Babesia came from the same Connecticut region most endemic for Lyme disease – near Mystic, on the southeastern shore of the state, a resort area visited by many summer vacationers (including college students) during the summer season when transmission of both diseases is at its height.

Another Connecticut serosurvey, reported in 1995 by Lou Magnarelli of the Connecticut Agriculture Station [46], found 7.5% of 40 patients with Lyme disease diagnosed by strict CDC criteria and with histories including erythema migrans [EM] to be seropositive to *Babesia microti*. Again this figure – 7.5% – is very close to the figures found by Krause and Hu.

On the other hand, in this same study no co-infections of any sort were found in 15 Lyme disease patients diagnosed with arthritis but without history of EM, or in 25 Lyme disease patients from Yale University Lyme Disease Clinic. The differences in co-infection between patients with and without EM are curious, but likely to be accidental or artifactual [47]. *Babesia microti* antibodies were also absent from 112 healthy people from Connecticut, 25 healthy people from Minnesota, and 30 Minnesota Lyme disease patients with EM in this study. (Two of the Minnesota Lyme disease patients had antibodies to HME, however. Evidence for other tickborne diseases was also found in the Connecticut Lyme patients with babesial co-infection; their sera revealed that 10% were seropositive for HME and 7.5% seropositive for HGE.).

Minnesota (and Wisconsin) Lyme disease patients were found to have babesiosis co-infections the following year, however. A study by Mitchell et al of 96 Wisconsin and Minnesota Lyme disease patients found four of them, or 4.1%, to also have *Babesia microti* infections. Again other co-infections were found: five Lyme disease patients (5.2%) were co-infected with HGE (human granulocytic ehrlichiosis) infections. When these researchers examined the sera of 19 patients who had been diagnosed with HGE, one was seropositive for *B. burgdorferi*, one for *Babesia microti* and one for both pathogens [33].

***The human co-infection data are consistent with co-infection rates found in field studies of host animals and ticks from the same regions.***

Golde's new study [44] is also using PCR to look for other tickborne infections in sera from Long Island patients with a primary diagnosis of Lyme disease. Although his first PCR failed to detect babesial parasitemia in 18 patients who presented with EM, eight of the 18 (44%) were seropositive for *Babesia microti* using a new serology kit from Immunetics for testing three tickborne diseases. Golde is unsure whether the serologic results were false positives, or whether, as he suspects, the PCR he was using was insufficiently sensitive and/or at least some of these patients had been infected but had fought off the parasites. He has developed a new PCR that is more sensitive for early babesial parasitemia and is now looking at sera from patients who presented with erythema migrans this summer. It is noteworthy that 14 of the 18 Lyme disease patients had fairly strong documentation of co-infection with HGE. A number of common threads connect these studies: HGE is sometimes involved in double and even triple co-infections with *Babesia microti*. Diagnosed babesiosis patients very often, in fact more often than not, have Lyme disease co-infection even by restrictive CDC diagnostic criteria. In areas where both pathogens are found, diagnosed Lyme disease patients are co-infected with *Babesia microti* from 4.1% to 20% of the time, with one outlying and perhaps suspect figure of 44%.

*Babesia microti* may have expanded into at least two new regions –Wisconsin and Connecticut – as recently as 1983 to 1985 [27,32]. An apparently new focus was also reported in 1986 on a North Carolina Indian reservation, where six of 185 serum samples from children were found to be positive at titers of 1:256 or higher when the *Babesia microti* IFA test was being evaluated for cross-reactivity [35]. Babesiosis is often particularly prevalent in resort areas, and patients with diagnosed babesiosis had traveled to these resort areas, some immediately prior to their illness [20,32]. Finally, seropositivity for *B. microti* is much more common than actual diagnoses of babesiosis, even when there is co-infection with *B. burgdorferi* [26,37,38,40].

The human co-infection data are consistent with co-infection rates found in field studies of host animals and ticks from the same regions [30] and with what is known about the endemicity of the two pathogens. *B. burgdorferi* still dominates the world of tickborne infections. Even when it is looked for, *Babesia microti* is less often found; it is so dependent on the

same ecology that supports *B. burgdorferi* that, when found, it is more often than not accompanied by its more prevalent companion – whether one looks at ticks, animals or people.

**More endemic areas to come?**

Although nearly all systematic Borrelia/Babesia research has been done in just a few sites in the highly endemic, tickborne disease-aware Northeastern and Midwestern sections of the country, it is important to remember that both Lyme disease and babesiosis exist in other parts of the United States, as well as in the rest of the world.

Babesiosis almost surely exists in regions where it has never been diagnosed. Recognition of babesiosis takes a high degree of suspicion on the part of patient and physician like. For example, in spite of babesiosis having become a reportable disease in Rhode Island in 1989, and in spite of its now very clear importance there – thanks to the impressive body of work by Krause and colleagues – no case of babesiosis had been reported in that state prior to July, 1991 [26]. Patients in areas where babesiosis is not already known to be endemic usually have to be very sick or even die, with high numbers of their erythrocytes invaded by parasites, before their cases are diagnosed and published [25,36]. As Pat Conrad of the University of California at Davis puts it, "Fatalities are when they really get noticed" [12].

Conrad also tells a story [12] about one of the first known California cases of WA1 that emphasizes just how accidental discovery of regional endemicity can be: a man was diagnosed only after a week of hospitalization at UCLA with worsening symptoms. The diagnosis was made then only because a physician visiting from the Northeast recognized the syndrome – flu symptoms plus chills, headache and dark urine in a splenectomized young man – and suggested looking at a smear for Babesia. It showed many parasites. When they looked back over 32 blood samples that had already been taken from this patient, parasites were found in all of them; on one smear there were parasites in 28% of his red blood cells. He was negative on an IFA for *Babesia microti* but had a titer of 1:5120 for Babesia WA1 [37].

**Will WA1 be another Borrelia/ Babesial co-infection?**

Are West Coast Lyme disease patients at risk for WA1 Babesia co-infections? Relevant research into the relationship between these two infections has barely begun and is likely to be complicated. The strongest evidence so far for Borrelia/ WA1 co-infection comes from Denmark, where 14 of 132 "definite Lyme neuroborreliosis patients" were found to be reactive to WA1 at titers of 1:512 and above [48]. Still, as noted above, it is not even known yet whether the two infections share the same vector tick.

The serologic study in the Sonoma, California area that found so many WA1 seropositive people (17.8% of those tested) was undertaken in part to address this question. Many members of the small community studied had been diagnosed with Lyme disease, many with EM rashes, and had been treated with antibiotics; a fourth of sick dogs in the neighborhood had tested positive for *B. burgdorferi*. But at the time of the study, about three years later, none of the WA1-positive residents was also *B. burgdorferi* seropositive by the strict two-tier CDC criteria using either B31 or CA92-0953 as antigen [38]. There are a number of reasons to doubt the appropriateness of the *B. burgdorferi* serology used in this study [49], but certainly no evidence of Borrelia/Babesia co-infection was found. In a separate study of 11 WA1-seropositive Californians (soldiers stationed at Fort Ord and residents of a community in Ukiah hyperendemic for Lyme disease), only one was also seropositive for *B. burgdorferi* [37].

Interestingly, however, 124 blood donors from the Sacramento blood bank were used as a comparison control for the WA1 serology in the Sonoma study. To the surprise of almost everyone – since it was then thought that *Ixodes pacificus* ticks (one of the suspects for the tick vector) were relatively rare in this inland area – 20% were seropositive to WA1, with high titers ranging from 1:320 to 1:1280. However, all but one of the WA1 seropositive donors lived in foothills of the Sierra mountains (as determined by county of residence and zip codes), in Butte, El Dorado, Nevada and Placer counties. Last year Butte became the county with the highest number of CDC-confirmed Lyme disease cases in California. Many patients there are very ill, and several hundred of them and some 150 of their health care providers attended the October 1998 Lyme Disease Resource Center Tickborne Disease Conference in Chico [50].

Jerant and Arline [51] suggest Southern California as another possibility for an endemic WA1 focus. Their patient – the first known California case of WA1, had a titer of 1:64,000 to *Babesia gibsoni*, a pathogen found, at that time, only in Asian and California dogs. A few years earlier Conrad et al had reported on 11 dogs with *Babesia gibsoni* infections apparently acquired in Los Angeles, Kern and San Bernardino counties [52]. Since then her students have found woodrats in the Sonoma area to be seropositive for WA1, as well as 6.3% and 55% of two mouse species in the Malibu Canyon area of Los Angeles County [12], where a number of patients have been diagnosed with Lyme disease in recent years.

It will be interesting to see if future studies discover any of the Chico and Malibu patients to have *B. burgdorferi*/Babesia WA1 co-infections.

# Mepron — new drug brings hope to Lyme disease patients co-infected with Babesia

Earlier this year one of the Internet Lyme disease discussion groups was abuzz with talk of Mepron. Longtime chronic Lyme disease patients said that after being diagnosed with babesial co-infection and taking this "new drug" they felt better than they had in years. Reports were so glowing and enthusiastic that someone asked if it was okay to take it even if you didn't have babesiosis [53]. *The Lyme Times* also received a letter describing its use in treating a young boy [see p 4, this issue].

There are other medications for treating babesiosis, but most seem to "reduce parasitemia ... but not eradicate the infection" [54]. The recommended treatment since 1983, based on its superior effectiveness, has been clindamycin plus quinine. However, some treatment failures are reported, relapses occur, and significant numbers of patients find quinine impossible to tolerate. When Krause and colleagues, for example, treated 22 patients with recent-onset babesiosis with this regimen [5], it significantly reduced persistence of parasites in the blood as detected by PCR, but PCR-detectable parasitemia persisted for longer than a month in 36% of the treated patients. One patient who wasn't treated until later in the course of infection (because at first he was symptom-free), displayed parasites on his blood smears that first disappeared after treatment, then reappeared six weeks later.

Reactions to treatment in this study also prompted Krause et al. to observe that "the quinine-containing regimen generally used to treat human babesiosis appeared to produce illness in nearly half the patients" (actually 41%). Drug reactions included gastrointestinal symptoms like anorexia, vomiting, diarrhea and stomach pain; auditory problems like hearing loss and tinnitus; and acute hypotension during IV infusion. Six patients had toxic reactions so severe the drugs were either discontinued or the dosage reduced [5].

Case-report reviews and animal studies reveal that a handful of people with severe parasitemia [25,55] have died even after clindamycin/quinine treatment for their babesiosis. Such severe drug reactions and treatment failures, combined with reports that babesiosis is commonly benign and patients recover without treatment [4], have caused physicians to be very cautious about treating babesiosis unless the patient is very ill. It is almost as if this treatment is worse than the milder forms of this disease (although no one actually says that).

***...Physicians caring for Lyme disease patients... should consider the additional diagnosis of babesiosis.***

But is it safe not to treat even apparently mild babesiosis? As evidence accumulates that babesiosis is likely to be more persistent than previously thought, Krause et al. as well as other researchers are calling for better treatments [3,5].

Given the evidence that, at least in some regions, human babesiosis occurs more often as a co-infection with Lyme disease than as a simple single infection [56], and given the increased severity and persistence of Lyme disease in this co-infection [57], it may be dangerous not to treat it. Increased numbers of Borrelia spirochetes circulating in the blood for prolonged periods [58] may become, over time, something much more than a mild flu-like illness.

Mepron (atovaquone) is new enough that a Medline search reveals no published clinical trials of its use as a treatment for human babesiosis. However it has been used successfully for several years as an antimalarial preventive and treatment and as a treatment for opportunistic parasitic infections like toxoplasmosis and *Pneumocystis carinii* pneumonia in HIV patients, for which it has FDA approval [59]. Clinical studies have been published describing its success in treating those infections, including trials specifically assessing safety and efficacy in children [e.g. 60,61], and these researchers comment on atovaquone's "remarkable safety record."

There are also several published studies of its efficacy in treating babesiosis in animals, and again atovaquone (especially when combined with azithromycin) was found to be more effective than other treatment regimens and apparently safe. Promising preliminary data from a study that used Mepron and azithromycin to treat chronic Lyme disease patients was presented as a poster exhibit at this year's Lyme Disease Foundation conference, and this combination is also recommended by Dr. Burrascano in his new Treatment Guidelines [see p 24, this issue.]

A few specifics from the babesiosis studies: Pediatric infectious disease researchers Walter Hughes and Helieh Oz, in a study published in 1995 [54], compared the effects of atovaquone, clindamycin plus quinine, and no treatment at all on 30 hamsters experimentally infected with *Babesia microti*. All 30 hamsters received vancomycin to prevent

colitis. All of the 10 untreated hamsters had died by day 12 post-infection. Two of 10 hamsters treated with clindamycin plus quinine also died by day 12, and another two died after receiving a month of corticosteroids to suppress their immune systems. Although six hamsters treated with clindamycin/quinine remained alive on day 54 after treatment, blood smears showed an average of 19% of their red blood cells remained infected.

All but one of the 10 hamsters treated with atovaquone survived with nearly undetectable parasitemia (no parasites at all were detected in any of them on day 54) despite 42 days of immunosuppression with corticosteroids. The only death in the atovaquone-treated group was due to anesthesia used to collect a blood sample [54].

In 1996, Wittmer and colleagues from the Departments of Parasitology and Pathology at Albert Einstein College of Medicine in the Bronx reported another study of hamsters infected with *Babesia microti* [62]. Their study compared atovaquone alone to atovaquone plus azithromycin. While both treatments were initially effective, hamsters treated with atovaquone alone occasionally had later recurrence of parasites. When babesial organisms taken from the hamsters with recurrent infections were injected into uninfected hamsters, the infections produced in the recipient hamsters were no longer responsive to atovaquone, suggesting the development of atovaquone-resistant Babesia. Resistant organisms did not emerge in hamsters treated with the atovaquone plus azithromycin regimen. The investigators suggest that this combined treatment should be considered for babesiosis patients who "have either failed standard therapy or have become intolerant to such therapy."

Krause et al. also advise, based on their studies of persistent parasitemia [5], babesiosis in children [26], and Lyme disease/babesiosis co-infections [2], that physicians caring for Lyme disease patients, especially patients "experiencing episodes of 'atypical Lyme disease' or whose response to antibiotic treatment is delayed or absent," should consider the additional diagnosis of babesiosis [2]. They stop short of actually recommending treatment with atovaquone and azithromycin, but note that "recent observations ... suggest this therapy "may cure human babesiosis" [5].

Internist Richard Horowitz, like Dr. Burrascano, clearly has been "considering this additional diagnosis." Dr. Horowitz described some interesting preliminary observations from his Hyde Park, NY practice in a poster presented at the Lyme Disease Foundation Conference this year [63]. He found 120 of his 800-plus chronic Lyme patients to have positive antibody titers to *Babesia microti* as well as inadequate responses to antibiotics for Lyme disease – they had experienced either little improvement or repeated relapses. He tried treating the Babesial infection in these patients with two different medication regimens, using pre- and posttreatment symptom questionnaires plus a health self-evaluation scale to evaluate treatment responses.

More than half the patients treated with the currently recommended clindamycin plus quinine regimen stopped taking their medications because of severe side effects. His patients tolerated Mepron plus Zithromax (atovaquone plus azithromycin) better than clindamycin plus quinine, although some did stop treatment after developing severe rashes. Other side effects included poor taste, nausea, vomiting, diarrhea, fatigue, and dizziness. Herxheimer-like symptom flares were also noted (Burrascano also observes this in his patients [1].). None had serious changes on CBC and liver function panels. Of the 45 patients who completed 21 days of Mepron plus Zithromax, 87% experienced perceived improvement that averaged about 40%.

Vomiting also seems to be a prominent side effect of atovaquone plus proguanil treatment of children with malaria, as observed by Lell et al. [60], who report no other obvious side effects. According to Korraa and Saadeh [59], rash, headache, diarrhea and gastrointestinal disturbances are also common side effects when atovaquone is used to treat *Pneumocystis* in AIDS patients. They also state that atovaquone is excreted through the gastrointestinal tract and is therefore contraindicated in patients with persistent diarrhea, as it might not be absorbed well enough to achieve high serum concentrations. The United States Pharmacopoeial Convention, Inc. [64], adds cough and trouble sleeping to the side-effect list for AIDS patients taking Mepron, and advises them to report fevers and rashes to their doctors.

Dr. Horowitz's patients with babesiosis also had chronic, treatment-resistant Lyme disease. Their significant clinical improvement on Mepron plus Zithromax offers some hope that this treatment may be effective even for chronic babesiosis and chronic co-infection (as reported by the Internet patients), a possibility that has yet to be explored by published studies. Dr. Horowitz believes, along with Dr. Burrascano, that it also implies that chronic babesial infection plays an important role in the ongoing symptomatology of chronic Lyme disease. We look forward to more information addressing these important issues.

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# Conference

The recent Lyme Disease Resource Center tick-borne disease conference in the small college town of Chico, California, (pop. 53,000) attracted approximately 150 medical professionals for a 3-hour program.

For several years there has been an active fibromyalgia support group in the Chico area, attracting up to 400 patients from surrounding towns in the Sierra Nevada foothills. Recently many of these fibromyalgia patients discovered that they tested positive on both direct and indirect tests to *Borrelia burgdorferi*, the organism that causes Lyme disease. They are currently being treated and many have recovered.

Then, a number of children have been seriously ill with what is presumed to be Lyme disease. Antibiotic treatments had limited success, so when William Fife of Texas A & M announced his experimental study of the use of hyperbaric oxygen (HBO) in the treatment of Lyme disease, several Chico parents enrolled their children and made the trip to Texas. One boy who before HBO had been wheelchair bound and unable to attend school because of severe neurologic problems, is now riding his skateboard, roping steer, and carrying a full load as a sophomore at the local high school. Initially seronegative, after two years of treatment he seroconverted.

Then, four months ago, a young man died after suffering from severe Lyme disease for several years. An avid deer hunter, he also was seronegative and it took four years for doctors to diagnose him, although he had had tick bites and bull's-eye rashes. During his final illness he was hospitalized and his spinal fluid tested. It was positive for Lyme. At autopsy, his brain, heart and liver were positive for spirochetes by PCR.

People in the small community were touched by this tragedy. Members of an enthusiastic Lyme disease patient support group lobbied for a conference and laid the groundwork for success by months of promotional activities. They turned out in droves for the public forum.

*continued on back page*

findings may have merit is neither rational nor scientific. People trying to report discoveries that threaten the status quo are rejected by publishers and subjected to personal attacks by professional colleagues. This is not science, rather a nasty picture of incumbents protecting their turf.

Given the current state of our knowledge about tick-borne diseases – knowledge that is still very rudimentary – it is premature to form hard-line positions. Our advice to physicians is to keep an open mind, listen to your patients, and try to make them well. Stay current with the basic research. Respect others' opinions. They have a different experience set. There may be yet-to-be-discovered factors at play and your own ignorance may be the cause of your lack of understanding.

Both science and professional ethics certainly demand a higher standard than we have been witnessing. Politics may make money and reputations, but it does not cure disease. As patient advocates, we call for an end to the posturing which has made a political football out of Lyme disease, but does not help the patients. We beg for a return to science.

# Letters

*We do not recommend any of the doctors or treatments which may be mentioned here by writers. You should discuss any treatment options with your physician. Signed letters of general interest may be printed.*

## Child with seronegative babesiosis responds dramatically to Mepron

I'm writing to inform you of my son's apparent cure from clinically diagnosed Lyme disease, a disabling illness he suffered from for 3 1/2 years, beginning on his 8th birthday. I'm not writing simply to share my joy at this development (though we can all stand to hear some news like this once in a while!) but because his sudden, dramatic return to health raises some very important, fundamental questions about how "Lyme disease" is defined.

Some background: My son first became acutely ill with fever, severe head, abdominal, back and leg pain, fatigue, irritability and insomnia. He also had frequent ulcerated, red sore throats. These were preceded by several weeks of occasional vomiting/retching, episodes of extreme paleness, "lightning" leg pains, and a red, roughened area over the knuckles of each hand, with white circles or disc shaped spots on his face surrounded/connected by a pale, lacy, red rash.

Based upon his acute symptoms, negative Lyme tests and a palpably swollen liver and tender, distended spleen, he was initially diagnosed with mononeucleosis, which serology failed to confirm. For the following 3 1/2 years, his most frequent and disabling symptoms were head and abdominal pain, fatigue, hyperacusis and insomnia.

He was diagnosed with Lyme disease after a year of illness, and took a variety of oral antibiotics, some in combination, and he always improved, but remained less than well on them, always incapable of physical exertion or athletics. His greatest improvement was this past year with doxycycline. He always relapsed, nearly 6 weeks to the day, each time we took him off of antibiotics. Last June, I asked his Lyme doctor about attempting a trial of Mepron; I had always suspected babesiosis (even though my son had NEVER tested positive for it), based upon my reading of the literature on it (and the fact that incidents of coinfection appear to be highest in our area), but neither his doc nor I was ever willing to do an empiric trial of the harsh combination of Clindamycin/quinine on a young child. Because Mepron seemed to be so "well tolerated" by his young patients, the doctor agreed, and prescribed half the adult dose for my son, in combination with Zithromax.

Within a week and a half to two weeks, my son was in agony; everything hurt, including his bones and joints (a symptom he had never really suffered much from), his fatigue, head pain and hyperacusis were extraordinarily bad. His doctor suggested taking him off of Mepron a few days shy of the three-week mark, and resuming it again in a week if he were better; if the Mepron were making him sick, we would know once we resumed it.

My son became well within 24 - 48 hours of stopping that first round of Mepron, then easily tolerated subsequent courses with no difficulty and has had NO RESIDUAL SYMPTOMS since!

He is doing about 3-4 hours of strenuous karate per week, gym class three times per week, walking to school, and had lots of stamina for hiking, biking and swimming this past Summer. He is no longer taking any medications. Some questions, made particularly salient by the recent Krause publication [Krause et al, "Concurrent Lyme Disease and babesiosis. Evidence for increased severity and duration of illness," JAMA 275(21):1657-1660 (1996)]:

1) Was Lyme disease in Connecticut or anywhere else EVER a simple borrelial infection, or did they just stop looking for pathogens once Burgdorfer found Bb?

2) In a case like my son's, are we dealing with seronegative babesiosis, as suggested by his response to Mepron, or are there even MORE pathogens/parasites etc. implicated in "Lyme disease" than we know?

3) As the prevalence of HGE,

HME and babesia, along with RMSF, encephalitis-inducing deer tick virus and who-knows-what-else become better known, are we completely blowing our Lyme disease research budget at NIAID by doing an antibiotic treatment study before we know what the totality of the disease IS and why some folks get better and some can't seem to throw it off with any amount of antibiotics?

Additionally, I want to make the obvious observation: often we just don't know for sure what we actually have with tick borne diseases or with suspected TBDs. Most academic researchers make the case (and, in fact, some denied that my son was even ill, despite his pediatrician's report and grave concerns) that if they don't get the magic lab result or eyeball and measure the rash themselves, no treatment is in order. The problem is, they are routinely casting vulnerable lives aside, making no effort to relieve suffering. When children are involved, this is particularly shameful and must not be tolerated.

At the same time, I am acutely aware of the risks of pouring powerful drugs into anyone's body, much less my child's, and for years at a time! My husband and I agonized over our choices often, as did my son's Lyme doc, but it always came down to our trying to buy our child some quality of life each time it slipped away again. With competent, compassionate and educated care from a clinically astute doctor not afraid to try to help despite the prevailing orthodoxy, we just kept pushing buttons for two and a half years until we hit the right ones.

I know we got very, very lucky.

I'm hoping the news of our experience brings the same kind of "luck" to some other Lyme disease patients. I guess I'm describing educated guesswork here, and these may not have been acceptable odds to play for some orthodox academic medical folks or clinicians who weigh risk/benefit by another standard. But he's not their kid.

I wonder -- what if he had been?

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*Please read our articles on co-infection and Mepron in this issue: pages 36-47.*

## Lab experts criticize ACP diagnostic guidelines

*Introduction by Dr. Harris: Richard Tilton, Ph.D, ABMM, Mary Sand, Ph.D. and I responded to the position statement on Lyme Disease Diagnosis which was published in the Annals of Internal Medicine (127:1106-23,1997). After nine months the editors have decided not to publish our response. The three of us are all board certified in our respective fields of laboratory science and have over sixty years of experience running the most technologically advanced immunology, microbiology and molecular diagnostic laboratories in the nation. We have serious reservations about the article in question and felt the "Letter to the Editor" was the most appropriate forum for discourse between us and the authors. Apparently the Editors did not see it that way. Our concerns are still valid and need to be aired. That is the reason for presenting it in the current format.*

We have several concerns with the report entitled "Guidelines for Laboratory Evaluation in the Diagnosis of Lyme Disease" (Annals Int. Med 127, 1106-1123, 1997)

• The Centers for Disease Control have developed a set of clinical and diagnostic criteria for surveillance purposes. The authors of these "Guidelines" state that these criteria, with no substitution, are also applicable to the clinical diagnosis of Lyme disease. To our knowledge, no such evidence exists. It would appear that the published "Guidelines" have as a basis a clinical criterion for Lyme disease diagnosis which has never been tested except for clinical studies published by the authors themselves. There is no external validation to support the claim of equivalence between clinical diagnostic criteria and the CDC surveillance definition.

• The authors state that "testing with ELISA is the cornerstone of laboratory diagnosis for Lyme disease". In fact, it is not. The commercially available ELISA assays for Lyme disease do not meet acceptable criteria according to the group that is responsible for much of the United States Laboratory proficiency testing program in Lyme disease. The data, from a recent study by Bakken et al.. (J. Clin. Microbiol. 35:537-543,1997), indicated "that the sensitivity and specificity of the currently used tests for Lyme disease are not adequate to meet the two-tier test approach being recommended by the CDC/ ASTPHLD group". Bakken et al. (1997) also stated that a screening test must have >95% sensitivity to adequately screen for Lyme disease and that the currently available ELISA tests do not perform at that level.

• The authors have not followed the CDC/ASTPHLD recommendation for two-tiered testing. That is, all indeterminate and reactive ELISAs should be reflexed to Western blot (WB), not just indeterminate ELISAs as the authors of the "Guidelines" suggest. Certainly the authors realize that reactive Lyme ELISA results may be nonspecific because of a number of cross reacting antibodies (e.g. antibody to the 41 Kda flagellin protein).

• The authors have missed some important studies of Western blotting, especially those that may be critical of the recommendations of Dressler et al. (J. Infect. Dis. 167, 392-400,1993) and the CDC/ ASTPHLD. The report by Engstrom et al (J.Clin.Microbiol. 33:419-427,

1995) found, for example, that 20% of their Lyme patients remained seronegative throughout the study and that fewer bands on the IgG WB could be appropriately used for interpretation. They noted that the WB was more specific and more sensitive than the ELISA. Their study also showed that only 19% of patients treated with antibiotics for 20 days still had a positive ELISA antibody response after one year, yet almost 60% of their patients continued to be WB positive at the end of the first year. The study by Aguero-Rosenfeld et al. (J. Clin. Micro. 34:1-9, 1996) reported that 89% of patients with culture-confirmed erythema migrans (EM), developed specific IgG antibodies by WB, but only 22% of these patients were positive by the interpretive criteria proposed by the CDC/ASTPHLD. They further reported that the duration of the antibody response was related to the duration of the EM. Tilton et al. (1997) stated that a highly sensitive and specific Western blot is desirable for a two tiered test approach or as a primary test. Despite the CDC/ASTPHLD recommendations, many physicians who treat patients for LD do not believe that an ELISA is an appropriate screening test and consequently use the Western blot as a primary test.

• The authors state that patients not be tested for Lyme disease unless the pretest probability of disease is between 0.20 and 0.80. These recommendations will:

a) rule out any laboratory detection of *B. burgdorferi* antibodies, antigens, and/or DNA in non-endemic areas.

b) require physicians to screen patients based on epidemiological data which may not be available to them outside their own local area

c) require physicians to know the performance characteristics of a wide variety of Lyme disease tests.

• The authors in their comment on non-antibody based tests have chosen to overlook a number of publications on the utility of direct detection tests for Lyme disease. A comprehensive review of molecular techniques for diagnosis of Lyme disease has recently been published by Schmidt (Clin. Micro Rev. 10, 185-201, 1997). They state "evidence is growing that a positive PCR test can be associated with active disease; after adequate therapy, PCR results are usually negative." Manak et al. (J. Spirochet. Tick-Borne Dis. 4., 11-20. 1997), in a well controlled study using the CDC criteria for selection of patients, indicated that PCR on serum, plasma, or buffy coat could be effectively used to monitor the efficacy of therapy. Similarly, Harris et al. (J. Spirochet. Tick Borne Dis. 237, 1995) have validated the Lyme urinary antigen test (LUAT) in more than 700 LD patients and controls. The LUAT has a specificity of >95%.

These "Guidelines" only complicate an already complex disease diagnostic process.

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*The Lyme Times is pleased to have the opportunity to publish this important critique of the American College of Physicians "Guidelines for Laboratory Evaluation in the Diagnosis of Lyme Disease." Part of our mission is to ensure that worthy ideas are allowed free expression in the public foruum. We regret that the ACP peer-reviewers and editors have apparently found it expedient to close the door to healthy debate when so many questions about the diagnosis of Lyme disease still remain unanswered.*

## Physicians make a "Modest Proposal" regarding neuroborreliosis

*From American Psychiatric Association's newsletter, "Psychiatry News," Sept. 18th, 1998 issue, Letters to the Editor. Reprinted by permission.*