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'Lyme disease': ancient engine of an unrecognized borreliosis pandemic?☆

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Summary Unexpectedly we have found large numbers of chronically ill *Borrelia burgdorferi* PCR- and seropositive patients in Houston, Texas, a zoonotically 'non-endemic' area. In order to understand this finding prior to sufficient data availability, we chose to examine critically currently accepted but troublesome 'Lyme disease' concepts. Our method was to analyze each foundation 'Lyme disease' premise within the context of available medical and veterinary literature, then to reconstruct the disease model consistent with the preponderance of that data. We find the present conceptualization of the illness seriously truncated, with a high likelihood of two distinct but connected forms of human *B. burgdorferi* infection. The yet-unrecognized form appears to have a broader clinical presentation, wider geographic distribution, and vastly greater prevalence. We conclude that 'Lyme disease' currently acknowledges only its zoonosis arm and is a limited conceptualization of a far more pervasive and unrecognized infection state that must be considered a global epidemic.

INTRODUCTION

'No part of the aim of normal science is to call forth new sorts of phenomena; indeed those that will not fit the box are not seen at all'. Thomas Kuhn: *The Structure of Scientific Revolutions* (1).

In 2000, Paul Ewald advanced the hypothesis that evolutionary biology principles, if followed faithfully, predict that infection likely underpins many current illnesses without known etiology, perhaps via a single agent (2). Here we present evidence that may identify one such agent.

Twenty-six months ago, our practice began to test chronically ill patients with multi-system presentation for *Borrelia burgdorferi* (*Bb*) infection. Our criteria further included suspicion of protracted infection and inability to otherwise find a diagnosis. About a third of initial tests were positive via CDC Western blot criteria or serum/urine PCR; however, repeat testing eventually revealed that most are positive. We had not expected these results, as we are in Southeastern Texas, a 'non-endemic' region. (The prevalence of *Borrelia*-infected ticks in Texas is about 1–2%.) (3–5).

Concurrently, we recognized a striking similarity in symptoms and signs of test-positive individuals to other untested patients of ours. Most fit within the presentation criteria of 'late, disseminated Lyme disease' but with some prominent differences. We began antibiotic treatment of all test-positive patients, and most, regardless of presentation, began noticeable improvement within 3 to 6 months.

Since no history of erythema migrans (EM) rash or illness following tick bite was reported by these patients, and most had been ill for many years with similarly ill family members, we set out to understand what we were confronting. Our experience did not match the CDC case definition or the epidemiological evidence for late 'Lyme

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disease'. To resolve this conundrum, we concluded that our best initial strategy was to derive our own conclusions by careful assessment of all available relevant data.

METHOD

We began by examining the present conceptualization of 'Lyme disease' for comprehensiveness and accuracy. We chose the US Centers for Disease Control and Prevention (CDC) 'surveillance case definition' of 'Lyme disease' as the current standard model of human *Bb* infection. We next isolated what we believed to be the linchpin premises supporting that model, examining each against available pertinent National Library of Medicine (NLM) medical and veterinary *Bb* data. Each premise was addressed independently with relevant data categorized and summed. We then derived a modified illness model of human *Bb* infection by combining the reassessed premises. Finally, we examined this newly-derived illness model within the context of current medical nosology and the realities of contemporary clinical medicine for plausible fit and superior predictability potential.

FINDINGS

Semantics: 'Lyme disease' examined

The origin and conceptualization of 'Lyme disease'

'Lyme disease' is the label given to a human illness first recognized in Old Lyme, CN in 1975 (*6*). The initial cases resulted from a zoonosis present in local vertebrate reservoirs/hosts and transferred incidentally to humans via an arthropod vector, *Ixodes scapularis* (*6*–10). The responsible agent was later identified as *B. burgdorferi*, a spirochetal bacterium, with human disease considered to result exclusively from the genospecies cluster *B. burgdorferi sensu lato* (*Bbsl*). (7,11). Globally, the species presently within this cluster include *B. burgdorferi sensu stricto* (*Bbss*), *B. afzelii*, *B. garinii*, *B. lonestari*, and possibly *B. valaisiana* (12,13).

As the knowledge base expanded internationally in the subsequent 26 years, the zoonosis-only conceptualization of 'Lyme disease' persisted with emphasis on acute and early stages. The exclusive focus on zoonosis resulted in a major portion of resources being concentrated on reservoir and vector prevalence (14). The 1975 conceptual model reached 'standard-of-care' status little changed with publication of the CDC 'case classification' in 1997 (15).

'Lyme disease' as defined by the CDC: the prevailing view

The CDC initially published case definitions for Public Health Surveillance in October, 1990. For the first time, uniform criteria were available to be used in case reporting that included 'Lyme disease' (16). The full CDC criteria for 'Lyme disease' were published in the May, 1997 MMWR (CDC Morbidity and Mortality Weekly Report) for surveillance purposes and included clinical description, laboratory diagnostic criteria, confirmed case classification, and relevant definition of terms (15). We refer the reader to the referenced MMWR for the complete surveillance criteria, all contained under the title: 'Lyme Disease (Revised *9/96*) clinical description'. More extensive descriptions of the illness presentation, course, epidemiology, and diagnosis may be found in subsequent CDC sources (17,18). We included these in our synthesis of the most comprehensive current conceptualization of 'Lyme disease', but considered the 1997 'surveillance case definition' as authoritative.

The foundation premises of the 'Lyme disease' model

Following are what we consider to be the foundation premises used to create and support the present internationally endorsed conceptualization (model) of 'Lyme disease' believed to represent all human *Bb*-induced illness. (All illness models incorporate a set of premises derived from numerous observations, assumptions and definitions by inductive reasoning. Collectively, the premises deductively create a conceptual framework that constitutes the model. The model is then used deductively to derive diagnosis and treatment.) We state each premise separately, then compare to the available published data. (We reviewed 951 peer-reviewed papers and 13 books to cover what we deemed the relevant literature.) A re-summarization completes the process. Assessment of these 13 premises constitutes the body of our argument.

Before examining the premises which we believe support the concept of '*Lyme disease*', we stress that our use of this label will be limited to its presently defined conceptual boundaries. The CDC defines '*Lyme disease*', exclusively as a zoonotic illness. Congenital and gestational transfer cases have been disregarded for reasons not evident to us. This limited perspective is the first important illness-model error that will further compound as we examine its premises.

The 13 premises are grouped into five general areas: Initial Clinical Presentation (1–3), Testing/Confirmation (4–5), Pathogen Transfer, (*6–9*), Course and Outcome (10–11), and Distribution and History (12–13).

Premise 1: The erythema migrans rash consistently heralds initial *B. burgdorferi* infection

In most early and many recent studies, the presence of an EM rash is presumed to consistently verify *initial*

human inoculation of *Bbsl* via tick (17). This assumption is, in fact, the foundation of many important conclusions reached about 'Lyme disease' despite numerous papers that acknowledge secondary EM lesions occur (15,17).

Available data do not support the EM rash to be dependable for diagnosis. The EM rash may follow initial tick inoculation (primary), or it may occur months to years later (secondary) (19–28). The rash also frequently fails to appear following tick inoculation (26). It is not known to be a marker in gestational or congenital *Bbsl* transfer (13). Baranton's recent data show that some Lyme-derived *Bbsl* variants do not cause EM lesions (29).

Premise 2: *Borrelia burgdorferi* infection is sub-clinical in some infected humans with assumed benign outcome

Copious data support that *B. burgdorferi* infection can be 'sub-clinical' and thus unnoticed in infected individuals (20,30–54) and animals (55,56). The average symptomatic/asymptomatic ratio (S/A) in these studies from endemic areas, primarily using serology for diagnosis, is close to 1:1, much as Steere first noted in 1986 (57). The S/A ratio in 'non-endemic' areas may be similar or higher (58). Notably, no recent 'Lyme disease' study referenced by the CDC considers the asymptomatic state to be significant (17,18).

The question of whether sub-clinical cases activate or fail to activate at some future date is intriguing. Lack of sufficiently prolonged longitudinal follow-up in available studies fails to provide an answer. Baranton's recent data, however, show differing pathogenicity among *Bbsl* species, lending support to the reality of some prolonged innocuous sub-clinical infections although study design limits insight into ultimate outcome (59). When prolonged longitudinal outcome has been considered, several studies do support reactivation among patients (31,33,36,37,41,43,49,53,57,60).

Premise 3: Arthritis is a primary late musculoskeletal 'Lyme' infection sequela, where 'late' in CDC parlance is vague

Objective joint swelling is a 'late Lyme disease' symptom criterion (15). This frequently-documented standard, however, was derived primarily from data limited to patients meeting strict 'Lyme disease' requirements, necessitating vector inoculation for inclusion and recent enough for high antibody levels (6,61–69). False-seronegative individuals would have necessarily been rejected, possibly including those with low antibody levels and those infected by sexual, congenital or gestational routes. Further, we find no concise or consistent definition of 'late' in published 'Lyme disease' definition criteria, obfuscating the time when arthritis might be expected to appear (17,18).

In our 'non-endemic' region, we have rarely seen rheumatic joint presentation in our 455 seropositive or PCR positive patients. Many have migratory and intermittent *arthralgias*, however, and most have been ill far longer than one year. We find no data to support our clinical experience, however, likely because our patients fall outside the 'Lyme disease' inclusion criteria.

Premise 4: Humans with late stage 'Lyme disease' show high antibody levels and high numbers of Western blot test bands

The data support this position when applied strictly to presently defined 'Lyme disease' (17,70). These data do not address non-zoonotic transfer cases. An exhaustive review addressing 'Lyme disease' antibody data may be found in a recent work by Gardner (13). IgG and IgM response curves are reproducible within reasonably consistent ranges (8,71–74). Of note, however, referenced patients were studied only a limited number of months following initial vector inoculation, most less than a year (25,72,75–78).

We found no study characterizing immune reactivity to *Bbsl* in untreated patients from non-endemic regions and where symptoms have been present for one year to decades. Consistently, most serious studies have examined and tested only patients from limited geographic areas where high tick infection rate and acute human disease coincide. The immune reaction of infected patients not meeting 'Lyme disease' criteria have fallen outside rigorous scrutiny.

Gardner and others have shown conclusively that a group of *Bbsl*-infected humans was not inoculated transdermally but rather acquired their disease congenitally or gestationally (13,79–81). How might their antibody picture appear? Gardner's exhaustive review of antibody production following gestational *Bbsl* transfer is instructive. In her Table 11-8, 72% of neonates with tissue-verified borreliosis did not produce antibodies in sufficient quantity to be seropositive (13). Review of normal human fetal and neonatal antibody production in general reveals as well lagging IgG and IgM antibody levels to age one year (graph data, P46) (82). Beyond one to three years, we find no clarifying data.

Premise 5: Serologic testing to verify spirochete viability in late 'Lyme disease' cases is reliable

Numerous potential problems confound conclusions from the available in-vivo serology data (37,83–86). Terms such as 'symptomatic' are typically defined within the case definition of *early* (We assume much less than one year after inoculation) 'Lyme disease'. The presumed presence of *B. burgdorferi* in the human host

is dependent on a strong history of vector inoculation and the subsequent (early) pattern of antibody response. Other requirements imposed for 'proof of infection' include endemic area residence, length of tick attachment, or recent memory of EM-like rash. High background seropositivity in 'non-endemic' areas is dismissed as 'false' without adequate proof. Studies are also insufficiently longitudinal. The extensive data linking serologic outcome with spirochete presence in the host limit this connection to relatively early 'Lyme disease' and thus exclude late and all non-zoonotic patients.

Once *Bbsl* disseminates in the host, other immune-related factors apply that have not been sufficiently addressed in the 'Dearborn criteria' defining seropositivity (87). Pleomorphism, variable antigen presentation, immune avoidance, individual immune variance, host-derived enzyme cloaking, immune complex sequestration, and antibody inaccessibility to spirochete-privileged sites argue against sustained or consistent immune response (88–92). Recent findings by Wang and Hilton suggest the presence or absence of *Bb* antibody production is associated with unique individual HLA specificities of the Class II (93). Eighteen of 44 (41%) variously symptomatic patients were found seronegative where infection was verified by PCR to Osp A in cerebrospinal fluid or mononuclear cells.

Other data support serology test uncertainty: (1) Seronegativity does not prove absence of a viable *Bb* infection (45,90,93), which is consistent with the principle that negative findings cannot be used to prove lack of positivity. (2) Antibodies may exist minimally or rarely in very late *Bbsl*-infected humans (90). (3) Culture and histological methods have been used extensively by veterinarians, and provide substantial data supporting the inaccuracy and insensitivity of serology in identifying living *B. burgdorferi* in non-human subjects (51,52,60,94–98). (4) By ''similarity'', the presence of antibodies to *T. pallidum* generally means the presence of spirochetes (99). An evolutionary biology perspective is further to the point. Any persistent pathogen (relevant if *Bbsl* survives into late illness) must effectively escape the immune system. An example is *Chlamydia pneumoniae* infection where antibodies appear only when the agent is causing active pneumonia, yet the organism persists primarily unnoticed and undetected (2).

Bbsl prevalence data are rife with a mixture of asymptomatic seropositive as well as symptomatic seronegative findings (43–45,49,53,65,90,100–107). Many presumptions have been used to rationalize this data. Curiously, none have considered the possibility that the subject pools may include a high number of intra-human transfer cases.

In summary, the preponderance of available data cast serious doubt on the validity of current serology criteria for diagnosing viable human *Bb* infection.

Premise 6: The presumed US human 'Lyme disease' agent is limited to one species of Bbsl: *B. burgdorferi sensu stricto* (*Bbss*)

Until very recently, the presumed sole United States (US) human 'Lyme disease' agent is the species *Bbss*. The preponderance of available data, based on the assumption that all *B. burgdorferi* human infection is zoonotic, supports this assumption (29,59). James has now published evidence, however, that *Borrelia lonestari* infects humans in the US via the vector *Amblyomma americanum* (12). *Borrelia valaisiana* has also been found to infect humans in two US cases (13).

Bbss was the first species to be identified shortly after discovery of the disease in the Northeastern US. Because the illness was immediately assumed solely a zoonosis, this assumption resulted in the tendency to look for other possible species and strains less among ill humans than in vectors and animal reservoirs. Such a 'self-fulfilling' assumption built into the 'Lyme disease' model may have helped assure that the only species identified until recently would be the prevailing regional endemic zoonotic species. Our Houston clinical experience of numerous patients with *Acrodermatits chronicum atrophicans* (ACA), typically found in *Borrelia afzelii*, support the likelihood that other *Borrelia* genospecies cause human disease within the US.

Premise 7: 'Lyme disease' is exclusively a vector-borne (primarily arthropod) illness

To date, the vector considered primary for transmission of *Bbsl* to humans is the arthropod (17) likely related to its role in the initial 1975 recognition of 'Lyme disease' in humans (6). Many arthropod species have been found infected with *Bbsl* and causal transfer established (13). The tick has been studied in North America exhaustively, having the characteristics of a highly effective vector: long life, vertebrate blood meal feeding, and bacterial transovarial passage (13). Its role in 'Lyme disease' is assured, because it is the vector in what is considered exclusively a zoonosis.

Data are available, however, that expand the possible diversity of *Borrelia* vectors worldwide beyond the arthropod. Other possible carriers include the flea (108,109), mosquito (110–112), fly (111), and mite (113). Related enzootic cycles have been only rarely examined, although some data link non-arthropod vectors with animal hosts (110,112–114). We suggest that early,

sustained myopic focus on the arthropod as sole vector in the spread of 'Lyme disease' within the zoonosis context likely delayed early consideration of other enzootic cycles as well as non-zoonotic *Bbsl* transfer directly between humans.

We propose the human may well be the most likely 'vector' for *Bbsl* transfer to other humans. The label 'Lyme disease' has become, by convention, a semantic boundary that excludes consideration that an infectious agent responsible for a zoonosis may also exist independently as a *non-zoonosis*. CDC-defining criteria do not address human congenital transfer and in at least one reference deny without proof that sexual transfer occurs (17). This mindset assures that *Bbsl* cases falling outside 'Lyme disease' criteria have not been considered in most research, nor reported to local health agencies.

Premise 8: Congenital (vertical) transmission between humans does not occur

The CDC position on intra-human *Bbsl* transmission is that 'Lyme disease bacteria are not transmitted from person-to-person' (17). Current human and veterinary data make this position indefensible (79,80).

Schlesinger and MacDonald reported the first human congenital transfer cases of *Bbsl*. Gardner provided the initial and now most recent exhaustive review of available human gestational transfer cases (13,81). Her credible supporting studies utilized histological, PCR, or culture identification of *Bb* in both mother and newborn or aborted fetus. She reviewed 263 *Bbsl*-infected cases and summarized the birth outcomes. If mothers are untreated, Gardner notes the high percentage of negative pregnancy outcomes along with symptomatic, as well as seemingly asymptomatic, neonates. Indirect data supports the possibility of human congenital *B. burgdorferi* transfer (95,96,115), including similarity to other spirochetal diseases such as *Treponema pallidum* (116–118).

Contrary data suggest that congenital human (24,119–122) and congenital animal (123–126) transfer does not occur. Use of the 'Lyme disease' model for these studies (with inclusion criteria of EM rash, tick attachment history, or endemic region residence) necessarily excludes congenital transfer, which obviates their conclusions (15). Most of the human data were based on simple surveys of birth outcome, without satisfactory proof of spirochetal absence (likely a current impossibility). The contrary veterinary data appear credible and employ a search for spirochetes by culture or histological methods. These data support animal species that exhibit congenital transference and those that may not, which suggested species-specific transfer differences.

Not unexpectedly, we find no serious or credible epidemiological studies that have attempted to identify the true *rate* of human congenital *Bbsl* transfer. The only method we have of estimating congenital human *Bb* transfer is by other intra-human illnesses. Transfer rates of Cytomegalovirus and Toxoplasmosis range from 14% to 59% (127). The congenital transfer rate of *Treponema pallidum* has been reported as high as 68% in one cohort of *treated* infected mothers (116).

There is evidence to support the possibility that *Bb* may present clinically differently in congenitally infected versus vector-inoculated humans, and a review of similar chronic trans-placental diseases in humans is instructive (82,127). Common in congenital infection are 'silent' transfer, differential neonate illness presentation, and a negative effect on later immune competence. The general principles of neonate immune function, adult immune function, and transplacental transfer of pathogens provide further insight into the relationship between trans-placental agents and a new and developing immune system (13). This information collectively suggests that silent or atypical birth presentation may be common, possibly resulting in delayed or complete lack of recognition of the transfer.

Premise 9: Sexual (horizontal) transfer between humans does not occur

The CDC position on sexual intra-human *Bbsl* transmission is that it does not occur (17).

We find no study that addresses sexual transmission of *Bb* among humans; conversely, we find no study supporting that it does *not* occur. Inferential data, however, suggest the possibility of human sexual transfer. The data come from sound veterinary studies (96,98,115), the finding of *Bb* in human semen and breast milk (128,129), and by similarity to *Treponema pallidum* where sexual transfer is abundantly documented (117,130,131).

Our clinical experience strongly suggests that predictable, possibly inevitable *Bbsl* transfer between sexually active couples occurs. The preponderance of infected spouses we have tested to date also exhibit positive serology or PCR for *Bbsl* presence.

Premise 10: 'Lyme disease' is not considered a persistent infection, implying self-limited outcome

Most CDC-referenced studies support this assumption. There is insufficient or no follow up after initial diagnosis or treatment in these studies, however, to support this position. Extensive use of unsupported presumptions is troubling as well. The latter include labeling patients with persisting or recurring disease characteristics as 'reinfected' without serology or tissue evidence, or pre-

suming lack of infection because subsequent positive antibody tests do not meet 'Lyme disease' inclusion criteria (patients were not from 'endemic' areas, etc.) (17,18).

Substantial data support the probability that human *Bbsl* infection can persist indefinitely. This state may obtain even when treatment is provided according to 'standard guidelines' (52,90,132–135). The supporting rationale for persistence is summarized as follows: (1) Latency and relapse are widely observed *Bb* phenomena (43,89,94,100,136,137). (2) Symptoms frequently re-emerge following therapy (89,94,100,137). (3) Many mechanisms of potential survivability have been found in the highly complex and adaptable *Bb* organism (138–141). (4) An inert survival state is implied by the lengthy time to grow viable spirochetes from EM incubated cultures (43,142). (5) Animal models support extensive survival of *Bb* in tissue despite lack of detectable presence in body fluids (51,52). (6) Cyst forms have been found in-vivo to transfer infection directly without reversion to spirochete form, suggesting a possible alternative mechanism for silent transfer (143). (7) Recent *T. pallidum* data unexpectedly support prolonged human spirochetal infection despite use of standard treatment protocols (144).

Premise 11: Long-term 'Lyme disease' sequelae are autoimmune-induced or the result of past infection damage

This premise is a corollary of premise 10, where long-term infection sequelae are used to rationalize lack of infection persistence. Very few 'Lyme disease' CDC-referenced studies conclude that long-term sequelae are a result of chronic infection (17,18). Several hypotheses, nevertheless, have been advanced to address the nature of 'late' sequelae. Autoimmune effect is one proposed mechanism derived from indirect evidence (145–147). Another is anatomic damage assumed induced by *Bbsl* in earlier infection (148). Both positions are hypothetical and use unsupported assumptions.

On the other hand, substantial data suggest that late sequelae are the result of persistent infection (see Premise 3). We believe this large number of published studies supporting that a high probability of persistent *Bbsl* infection casts doubt on the above two mechanisms as primary determinants of pathology. They may, we believe, be included *within the context of persistence* as potential contributory mechanisms of ongoing pathology.

A search for other clinical outcomes of prolonged *Bb* infection in published data yields no clear answer. The CDC position in 2001 is limited to a few sentences: 'Infrequently, Lyme disease morbidity may be severe, chronic, and disabling. An ill-defined post-Lyme disease syndrome occurs in some persons following treatment for Lyme disease. Lyme disease is rarely, if ever, fatal.' (17). Most published research avoids comment on long-term sequelae (149).

Because of the present dearth of relevant data, we propose use of another perspective to address the question of sequelae from late active *Borrelia* infection. Late effects differing from early effects is used as a rationale that, because of this difference, support that active infection no longer exists. Examination of other persistent infections contradicts this argument. Many infections often present with dissimilar acute and late effects. Examples are Chicken Pox later appearing as 'Shingles', and 'strep throat' manifesting eventually as Rheumatic Fever. Some chronic infections have no acute phase. An example is the virus HHV-8 later manifesting as Kaposi's Sarcoma. Thus, there exists the possibility in late *Bbsl* infection of not recognizing the presentation.

Asymptomatic patients with late infection may also be easily overlooked, and assumed non-infected (20,30–54). Further, ill patients presenting with disseminated symptoms without meeting defined 'Lyme disease' endemicity criteria are also at serious risk of not being considered *Bbsl* infected.

Premise 12: Lyme disease is geographically constrained to areas of high zoonosis prevalence, mostly in North America and Eurasia

Gardner has comprehensively summarized international 'Lyme disease' distribution data (13). The resulting map concentrates illness primarily into a Northern Hemisphere temperate zone belt covering most of Europe and the United States. Expectedly, maps of zoonotic endemicity overlie the illness maps faithfully. We conclude a high likelihood that 'Lyme disease' is constrained to areas of high zoonotic endemicity simply because endemic area occurrence is an inclusion criterion. This illustrates the circularity of creating a predicted disease outcome by limiting its definition.

An extensive search of published literature reveals that distribution of human borreliosis may be much broader than described, practically is essentially globally disseminated. *Bbsl* presence in humans, other vertebrate reservoirs or both, have been reported from over thirty countries on six continents and several islands (5,22,54,55,58,110–112,114,150–179). Failure to document the full geographic extent of the organism may stem from simple lack of public health resources in most countries or lack of recognition of the disease in humans. We find no credible studies of human *Bbsl* infection prevalence conducted outside 'endemic' zoonotic regions.

Premise 13: 'Lyme disease' is a contemporary human illness

Bbsl was first acknowledged as a human pathogen in the US medical literature from 1982 to 1983 (7–9,11). The limited historical data that address earlier human infection do so indirectly by examining reservoir (*Peromyscus*, Massachusetts, 1894) or vector (*Ixodes ricinus*, Germany, 1884) infection using museum DNA evidence(163,180), or disease categorizations based on skin manifestations of unknown etiology (26,30,172,181–185).

Data from outside the 'Lyme disease' zoonosis model vaguely suggest the possibility that *Bbsl* is not a recent pathogen in nature, including human infection. Isolated papers examining *Bb* dissemination address such possibilities as: (1) The birth of the pathogen as a trans-kingdom mutation from African Swine Fever virus (186). (2) European 'Lyme disease' gradient rising from West to East (22). (3) Extensive presence of *Borrelia garinii* and *afzelii* in Eurasia (13). (4) Extensive presence of the spirochete (Garinii and Afzelii only) in Northeast Asia (Vladivostok) in a common Ixodid vector providing opportunity for Siberian-Alaska land bridge transfer 10,000–30,000 BC (187). (5) A recent hypothesis that *Bbsl* may be the protective agent of juvenile and adult arthritis in Louisiana Tchefuncte Indians between 500 BC and 300 AD (187,188). (6) Documented human presence in central and southern South America. (7) *Bb sensu stricto* main genospecies in North America (18). (8) Evidence for spread of *Bb sensu stricto* from the Western hemisphere to Europe after 1492 (189). Together, we suggest these data hint at a possible but unexamined circum-global dissemination of the pathogen over many human generations.

We believe the global occurrence of *B. burgdorferi* and its many strains provides the strongest evidence to support the likelihood that *Bbsl* has been present in nature and in humans for centuries to millennia. Protracted existence of the spirochete, if validated, would provide strong support for broad intra-human spread that began some indefinite time following early vector-to-human transfer.

Re-synthesis of premises by 'preponderance of data' weighting

'Lyme disease' was the label initially given to the illness conceptualization (disease model) of human *Bb* infection. The model congealed about 20 years ago as a zoonosis principally from locally available information. Subsequent worldwide data appear to have been gathered within the contextual boundaries of this initially conceived model. We find that the preponderance of this data support the conclusion that the zoonotic model was, and remains, incomplete, and includes only a portion of all *B. burgdorferi* infected humans. The data suggest there may exist a much larger unrecognized pool of *Bbsl*-infected individuals sustained by persistent intra-human transfer that we provisionally call 'Epidemic Borreliosis'. A summary comparing these two populations is shown in Table 1.

Clinical diagnosis of long-infected patients has been inconsistent and puzzling, specifically regarding the signs of EM rash and arthritis. The erythema migrans rash, initially considered the herald lesion for infection, actually occurs both sporadically in initial inoculation and later as secondary lesions. Its absence alone is thus of no value in rejecting a diagnosis, although its presence alerts to the probability of infection. A symptomatic state may be present or absent in the initial presentation, where absence of symptoms can mask the presence of a non-pathogenic strain. Arthritic joints are considered common in disseminated zoonotic *Bbsl*, but paradoxically, only intermittent and migratory joint pain is described in very late borreliosis.

Laboratory tests are presently reliable for supporting a diagnosis of recent vector-transferred 'Lyme disease' but seem highly unreliable if the transfer was zoonotic more than a year earlier, or was congenital. In these cases where antibodies are likely sparse, serology is valid only when positive. Negative results are necessarily inconclusive and may be seriously misleading, regardless of symptoms. The argument supporting 'false positive' serology, when based on zoonosis criteria, is invalid if *Bbsl* infection is widespread from prolonged intra-human transfer.

The pathogen responsible for 'Lyme disease' is a limited subset of the genospecies *B. burgdorferi*. Until recently, only one human pathogen had been identified in the continental United States: *B. burgdorferi sensu stricto (Bbss)*. The exclusive position of this species likely arose from limiting the early search for vectors to the geographic region where 'Lyme disease' was initially discovered. Given the global diversity of species such as *Borrelia afzelii* and *garinii*, the reality of intra-human transfer, and the probability of prolonged infection, we expect extensive regional diversity of *Bbsl* species in humans both in endemic and non-endemic regions of the earth. We propose that anticipating other species will improve identification by broadening the carriers tested to humans as well as zoonotic vectors and reservoirs.

Transfer of *Bbsl* to humans occurs via both zoonotic vectors ('Lyme disease') and other humans. Congenital transfer is fact. Animal data support that sexual transfer can occur, and other data suggest its possibility. 'Lyme disease' reservoirs and vectors may be even more globally widespread than currently modeled, increasing the probability of broader and historically longer inoculation of *Bbsl* into the human population. The finding of *Bbsl* in

Table 1 Comparison of proposed illness characteristics

	'Lyme disease'[a]	Epidemic Borreliosis[b]
What is the initial disease presentation?		
Erythema Migrans (EM) rash	Frequent but inconsistent	Secondary; occasional
Symptoms present if 'early'	None to flu-like	In neonates: none to fatal
Symptoms present if 'late'	None to multi-organ	None to multi-organ
Joint symptoms if 'late'	Arthritis	Arthralgias[c]
Cardiac signs if 'late'	High-degree block	Arrhythmias, T-waves unstable[c]
Typical illness length at initial presentation	<1 year	<2 years
How is the infection diagnosed?		
Number of Bb species	One (region-specific)	Many (non region-specific)
Serum antibody levels	High and constant	Low or occasional
Accuracy of serology	Accurate	High number of false negatives
Relationship of serology to region of diagnosis	Direct	None
Usefulness of EM rash	Alerts to recent inoculation	Announces infection presence
Usefulness of arthritis	Suggests 'late' infection stage	Suggests zoonosis transfer
How is the disease conferred to humans?		
By Zoonotic Vector?	Yes	No
Congenitally?	No	Yes (proven)
Sexually	No	Yes (not studied)
Regional?	Yes: endemic areas	No: anywhere
What is the disease course & outcome?		
Self-limited?	Defined as likely	No; likely lifelong infection
Latent?	Yes	Yes
Activate or reactivate?	No by assumption	Yes
Considered long-term sequelae	Autoimmunity/residual damage	Infection persistence/(mechanisms not elucidated)
Asymptomatic seropositive patient infection status	Considered infected only if from endemic region	Infected regardless of region of residence
What other epidemiological factors pertain?		
Primary worldwide vector	Arthropod	Human
Bbsl presence in human population (time)	Not addressed	Millennia
Distribution in humans	Confined to endemic areas	Worldwide, diffuse

[a] '*Lyme disease*' – All human cases of human *Borrelia burgdorferi* infection **within** the defined limits of the CDC case definition (15).
[b] Epidemic borreliosis – all human *Borrelia burgdorferi* infection cases **outside** the CDC case definition of 'Lyme disease'. Includes Zoonosis vector-transferred infections more than one year old and all congenital, gestational and sexual intra-human transferred infections whether symptomatic or asymptomatic.
[c] Author's clinical experience.

virtually all countries where it is sought also implies more uniform global distribution of the infection in humans. We expect regionally endemic 'Lyme disease' cases now to be far fewer than intra-human disease cases (Epidemic Borreliosis), and that many of the latter are unrecognized principally due to mislabeling.

Regardless of initial transfer route, human infection with pathogenic *Bbsl* may persist for life. Symptoms and signs may vary from sub-clinical to extensive and severe, including cycling between these states (33,77,190,191). Clinical sequelae from prolonged infection appear likely and may be cumulative with various mechanisms operant. An unknown number of sub-clinical cases may remain undetected for life, regardless of whether latency persists or unrecognized activation occurs. If lifetime persistence is the rule, then all living, untreated patients infected at any time during their lives remain infected.

The preponderance of all reviewed data suggest that *B. burgdorferi* may have been present in both natural reservoirs as well as in humans via intra-human transfer for centuries or millennia. We propose that this concept, if verified, predicts a much larger current population of congenitally and possibly sexually infected individuals worldwide than infected via zoonotic vectors.

In summary, we propose a significantly modified human *Bbsl* infection illness model that incorporates 'Lyme disease' only as one engine feeding a larger reservoir of chronic, *Borrelia*-infected humans (Fig. 1). We believe zoonosis was the likely source of initial human disease, and continues to contribute newly infected cases. We further propose that vertical and horizontal intra-human transmission over generations has likely had a non-linear amplifying effect on human prevalence. If true, this transmission mechanism now significantly exceeds the contribution of new cases from zoonotic vectors, and has reached pandemic proportion on all continents where humans reside. These conclusions strongly support our clinical experience.

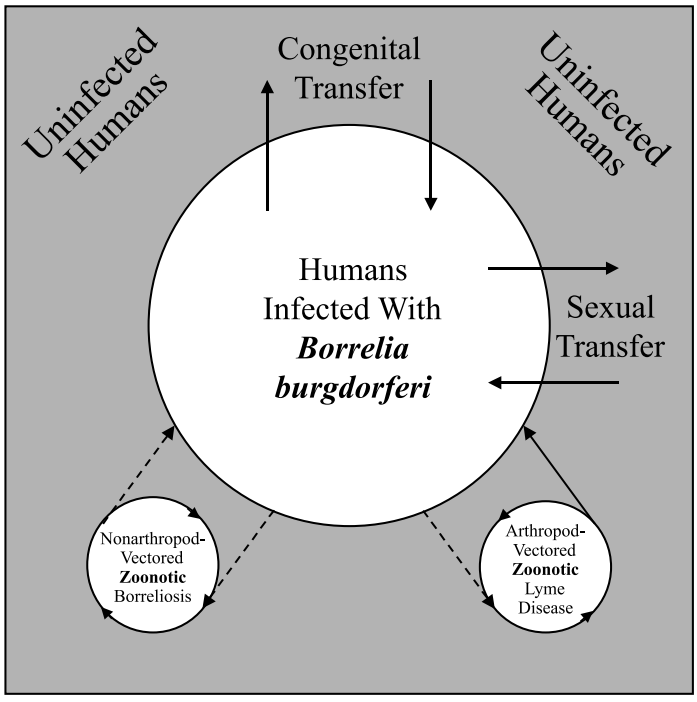

Fig. 1 Revised model of Human Epidemic Borreliosis.

CONCLUSIONS

We propose there are at least two similar and unified, but distinct forms of human *B. burgdorferi* infection: 'Lyme disease', and 'Epidemic Borreliosis' (disease spread directly between humans). Late (more than one year old) zoonotic disease may overlap both forms.

'Lyme disease' is the only presently acknowledged *Bb* illness form, conceptualized as a zoonotic disease where intra-human transfer is considered rare. As defined, 'Lyme disease' is primarily located in limited geographic areas, is clinically recognized relatively early after inoculation, and the reported case numbers are small. Human infection in this model is considered accidental and 'self-limited'.

We propose the existence of a much larger 'non-Lyme' pool of *B. burgdorferi*-infected humans with a clinical presentation of extraordinary variability, global geographic distribution, and far greater prevalence. Transfer is intra-human (congenital and almost certainly sexual) and is initially silent or unrecognized. If not successfully treated, infection is life-long, and latency, late activation, and reactivation are common. Zoonotic cases more than one year old may present similarly. We label this larger pool 'Epidemic Borreliosis'.

Combining both the 'Lyme' and 'non-Lyme' concepts results in a significantly altered model of human *B. burgdorferi* infection. Zoonotic borreliosis is fact and is the milieu within which the complete human disease has existed, perhaps for millennia. Zoonotic transfer was likely the initial route of human inoculation and continues with regularity into the larger pool of infected humans in zoonotically endemic regions. We believe that human endemicity is virtually ubiquitous wherever humans live worldwide and has now reached pandemic proportion. Overlap of these two groups occurs where competent infected vectors exist, but we believe the numbers of 'non-Lyme' cases predominate significantly even here. Infection prevalence has not likely reached numerical stability, since the amplifying effect of congenital transfer, coupled with the current global population expansion, suggests the probability of continuing prevalence rise.

We propose that 'Lyme disease' is a limited conceptualization of a far more pervasive *Borrelia* infection state that is now an unrecognized global epidemic.

DISCUSSION

Our proposed model further challenges many aspects of medical science now believed to be true. Not only does it consign 'Lyme disease' to a minor role in *B. burgdorferi* infection prevalence but supports the idea that a zoonosis can initiate what can later become a vastly more extensive intra-human infectious disease. As a medical model, we find this revised concept works with exceptional success. Until now, the current model has seriously limited our capacity to diagnose and treat many

patients. In our patient population, the revised model provides a rational mechanism that far better explains our experience. It effectively resolves the conflicting viewpoints held by clinicians and academicians about what has been labeled 'chronic Lyme disease' and is now allowing us to resolve or minimize illness in most of these patients.

Unexpectedly, the revised model has provided us much more. Most of our patients arrive with a diagnosis from diverse specialty areas but unsuccessfully treated. Use of this reframed model provides rational insight into many of these cases. It provides a successful diagnosis and treatment strategy that, when applied, resolved many patients' symptoms, thus suggesting to us that *B. burgdorferi* may underpin these illnesses as cofactor or origin.

We wondered if all of these 'atypical' *Borrelia*-infected patients might give us a clue to the true magnitude of the infection prevalence. A large number of clinically-similar (to late *Bbsl* infection) medical conditions with unknown etiology exist within the inclusive medical framework. Aaron, reviewing evidence from unexplained medical conditions (chronic fatigue syndrome, fibromyalgia, the irritable bowel syndrome, multiple chemical sensitivities, temporomandibular disorder, tension headache, interstitial cystitis, and the post-concussion syndrome), found substantial clinical overlap (192). Clauw likewise found similar clinical overlap among several of these illness categories, as have others, that include Gulf War Syndrome variants, overtraining syndromes, and numerous 'functional somatic syndromes' (193–197). A single paper by Pachner and Steere written in 1985 provides a credible rationale for most of the neurological symptoms and signs described in these illnesses as well as in human *Bbsl* infection (198). Later papers describe a persistent, infection-based inflammation that may provide the fundamental pathology mechanism (106,145,199–215).

These 'orphan' illnesses that constitute most of our (now) *Borrelia*-positive Houston patients sum to at least a double-digit prevalence in the United States even if we consider only four of these 'chronic syndromes'. Estimates of case-definition fibromyalgia include 2–4% (193,216,217), chronic fatigue syndrome, 0.42% (218), Gulf War syndrome, 4% (219) and multiple chemical sensitivities, 2–5% (220). Vague model boundary limits in these similar 'syndromes' coupled to illness labels where no prevalence data is available make this information unquestionably imprecise. However, when combined with the unknown but finite prevalences of the many other illness categories mentioned above including unknown overlap, however they hint that the combined number is not small.

We wondered whether our proposed model could generate such numbers as the infection rates reported by the CDC support a much lower prevalence (18). When the CDC data are examined using our derived assumptions, however, and a 'zoonosis-only' prevalence is generated, the outcome is 0.6% (Appendix A).

We next generated a crude estimate of the expected background prevalence of 'Lyme disease' in non-endemic regions using the assumptions of Masters (221). The resulting point prevalence is 2% once system stability has been reached. If congenital transfer is added and assumed ongoing for 1000 years, which we think not unreasonable, the point prevalence in 2000 AD becomes 6.5%. If sexual transfer is further added with the same assumptions at a 50% transfer rate, the combined point prevalence becomes 15.5%. Details of this exercise are found in Appendix B.

Another combined prevalence estimate based only on symptoms was generated by one of us in 1993 from an annual medical history form. 2683 employees of a Department of Energy plant were queried regarding 30 common symptoms and signs of late *Bb* infection. Endemicity and EM or tick bite criteria were excluded. 12.8% of the employees met similar symptom criteria. (Appendix C: unpublished data).

These unexpected numbers of possible *Bbsl*-infected patients hidden for decades by mislabeling, fit comfortably within our proposed model and are then not difficult to explain. We propose that where data were not initially available, temporary hypothetical bridges, although dissimilar, were necessarily created by early investigators to fill their model framework gaps. Our proposed model now fills in most such gaps for all these illnesses. It also revises framework elements of other illnesses we had considered unassailable parts of the standard medical paradigm.

We believe failure to recognize the breadth of this infection is readily explainable by inadvertent research errors: (1) most data have been derived only from zoonotically endemic areas, (2) 'validation' rested on inadequate serologic diagnostic methodology, and (3) controls, when used, were useless since half those infected are 'sub-clinical'. Clearly, discovery of the illness in an area of high zoonotic endemicity contributed to early and continuing clinical myopia but was the necessary first step in its recognition.

Other factors contribute to clinical recognition failure. Silent transfer, latency, late activation, and recurrent activation likely combine to create a setting resistant to standard epidemiological detection methods. The pathogen's extreme complexity is another probable contributor. Its adaptability, pleomorphism, genetic diversity, and differential tissue tropism create extraordinary symptom variability. Likewise, activation of numerous latent viruses and opportunistic bacteria from immune depression in late disease may further expand illness

complexity. Such varied presentation is not likely to have previously been considered to have a single infectious etiology, thus which excludes *Bbsl* from most differential diagnoses.

We propose that zoonotic transfer combined with human transfer on a global scale for centuries can indeed result in double-digit prevalence.These numbers applied to our model hint at the highly improbable: that the prevalence of all humans infected with *Bbsl* could constitute an even larger percentage of the population by including the sub-clinical cases mostly excluded from epidemiological surveys to date.

The technological solution that can validate our proposed model is a more sensitive and specific laboratory test likely not based on serum antibody presence. We do not offer a specific solution but propose that detection of the organism itself or unique biochemical markers altered by the infection are required. Because of unpredictable latency and inability to use controls, use of Koch's postulate or sophisticated epidemiological methods are no longer adequate in cases such as this and have likely reached the historical limits of their usefulness here (2).

Despite the need for dramatically improved detection methods, there exists even now an instrument capable of recognizing the scope of this illness: the astute clinician willing to carry what Carl Sagan called the 'burden of skepticism' (222). This perspective is an essential medical tool, as the 'system' within which the clinician works requires reframing prevailing cognitive paradigms before unfamiliar ideas can be 'seen' at all (222,223). (The history of medicine, in fact, is built on examples of mindset that delayed recognition or evolution of most illness concepts (224).)

We believe that reliance on familiar models is ultimately the principal reason that what we here term 'Epidemic Borreliosis' remains hidden from the view of science. Our purpose in publishing this newly proposed model is to encourage skepticism by investigators as well as clinicians: to consider the possibility that 'Lyme disease' is an inadequate conceptualization of all human *Bb* infection. We are confident that once considered, others will 'see' what we are finding in clinical practice (223).

We thus propose that 'Lyme disease' is only the herald encounter with a human infectious disease of currently inconceivable proportion. We anticipate that if our model is validated and the proposed high prevalence of *B. burgdorferi* in humans is verified, the conceptual framework of this and many other human diseases will be radically altered.

RECOMMENDATIONS

Our recommendations are based on verifying or disproving the disease model we present here and are derived from the gaps remaining in the data we have reviewed.

The initial task must be to identify all humans infected with *B. burgdorferi*. This likely requires first understanding antibody status in late (beyond 18 months) infections and the pathophysiological mechanisms linking *Bbsl* presence and human disease. Commercial tests to reliably detect living *Bbsl* in humans as well as reservoirs and vectors must then follow to reveal the agent's true worldwide prevalence. Extensive effort will be required to prove or disprove persistence, and to determine all disease entities associated with *Bbsl* infection: whether cause-and-effect, co-factor, or unrelated. Finally, the full extent of epidemiological science must be applied to determine the scope and efficiency of human congenital transfer and to investigate sexual *Bbsl* transfer. Answers will guide development of preventive strategies.

Concurrently, treatment modalities and schedules to eradicate *B. burgdorferi* from all patients regardless of infection route or duration, must be created. If our experience holds, this will be a difficult task, and will require serious and rapid commitment from all nations.

APPENDIX A. DERIVED 'LYME DISEASE' PREVALENCE USING CDC INFECTION RATES

The number of 'Lyme disease' cases reported by the CDC appears unreasonably small compared to our estimates. Within the defined parameters of the current 'Lyme disease' model employed by state and federal public health agencies, 16,273 cases were reported (more likely underreported) in the US in 1999 (0.06% of the population) (17). However, *assuming lifetime prevalence and no treatment*, the 1992–1997 crude mean annual incidence of 5.1 reported cases/100,000 persons/year roughly corresponds to a prevalence of 1,070,000 infections over the 75-year period, 1925–2000 AD (18). This number, likely an underestimate of true prevalence, is nevertheless 0.6% of the period population mean (1963). This suggests that *a 2% true zoonotic-only* stable *Bb* human prevalence may not be unreasonable in the US and, we propose, globally.

APPENDIX B. ESTIMATING THE FULL PREVALENCE OF HUMAN *Bbsl* INFECTION

We used a simple exercise to estimate the possible human *Bbsl* prevalence. Employing complex statistical methods was of no value because insufficient data exists to use precision. We sought only a 'ballpark' number to make the point that the *possibility* of unexpectedly high prevalence exists.

(1) *Assumption 1: Transfer is via Zoonotic vector only.*

- Assume: zoonotic transfer only, one tick bite per decade per human (221), 1% of ticks infected (5), 50% chance of tick-to-human transfer, and prevalence stability.
- Point prevalence = 8 tick bites/lifetime × 1% of ticks infected × 50% chance of infection if bitten × 1/2 (average human at midlife) = PP = 8 (TIR) (CI)/2 = 2%.
- This exercise predicts that 2% of humans are infected with *Bb* in Texas. We propose this number approximates the worldwide background prevalence of humans infected via zoonosis vector transfer regardless of region endemicity.

(2) *Assumption 2: If congenital transfer is combined with vector transfer for at least one millennium.*

- Assume: 2% of the population in 1000 AD was infected via zoonosis only, the prevalence and infection rate are stable, congenital transfer rate is 50%, full population turnover per 100 years, male/female ratio is 1:1, and no congenital transfer occurs before 1000 AD.
- Then 2% of all mothers after 1000 AD are already infected at conception.
- At a 50% transfer rate, 1% of all female newborns will be infected congenitally by 1100 AD.
- These 1% newborn females (1/2% of population) mature and join the 2% infected via zoonotic vectors = 2.5% Infected mothers at 50% transfer rate by 3–4 generations (assume 100 years).
- In the subsequent 100 years after 1000 AD, 2% of population already infected by tick + 1/2% infected congenitally by 1100 AD.
- Every succeeding 100 years, 1/2% more humans will be infected (ignore compounding for simplicity and conservatism): Point Prevalence = 2% + 1/2% $(y - 100)/(100) = 2\% + 1/2\%(900/100)$.
- Human point prevalence now = 2% + 4.5% = 6.5% (from 1000 to 2000 AD).

(3) *Assumption 3: If Vector, congenital and sexual transfer are combined for at least one millennium.*

- Assume: Use above assumptions. Add: fathers infect new mothers at a 50% rate, begin in 1000 AD. 2% infected fathers infect 1% more mothers = 3%.
- In 1100 AD all humans born to 2.5% + 1% infected mothers (2% infected fathers infect 98% uninfected mothers at 50% sexual transfer rate).
- Assume 50% rate in congenital transfer continues.
- Using the information in (2), infected humans = 2% + 1.5% $(y - 100)/(100)$.
- Point prevalence now = 2% + 13.5% = 15.5% (from 1000 to 2000 AD).

This exercise has been invoked to demonstrate the possibility that if intra-human transfer is established as common, the numbers of humans presently infected with *Bbsl* may significantly exceed the number of humans infected via zoonotic transfer. The difference is in the stability of the transfer system. Zoonotic systems reach some stability if populations are relatively stable over the short term and exposure remains close to constant. In recent years, the human population has risen rapidly, but so has urbanization with diminished outdoor work and leisure activity. Overall, in the 20th century, we estimate human-vector contact has remained relatively constant. Prior to the 20th century, human-vector contact was more extensive, making our estimates conservative.

Although made possible initially by vector infection, intra-human infection prevalence rises with the passage of time. The latter will rise in absolute numbers as the population size increases. This exercise assumes that human zoonosis infections remain relatively stable. When intra-human transfer occurs extensively, however, prevalence rise can approach geometric progression. Thus, the importance of time in estimating differences in the two types of transmission.

APPENDIX C. OCCUPATIONAL MEDICAL HISTORY SURVEY

In 1993, one of us, while Medical Director of a US Department of Energy facility in a non-endemic state, attempted to estimate the prevalence of chronically ill employees with symptoms similar to late, disseminated Lyme disease. A computerized medical history form was crafted for the required annual medical examination, in which 2683 actively working employees participated. Randomly interwoven in the Review of Systems portion of the questionnaire were 30 questions characteristic of the illness. 'Inclusion' criteria were: 50% of the questions had to be answered in the affirmative, with five questions determined most important: frequent headaches, persistent muscle pain, persistent activity limitation, intermittent and/or migratory joint pain, and any recurrent unexplained neurological symptom such as seizure, vertigo, or focal special-sense phenomenon (e.g., tinnitus or photophobia). There was no follow-on testing for borreliosis.

Active employees (343 (12.8%)) were found to meet our criteria for diagnosis. A random review of 35 (10%) charts selected from this group revealed symptoms had been present from less than a year to nearly 30 years (the full length of employment). A much broader degree of morbidity than in the inclusion criteria was found, with six employees near termination for number of lost workdays due to illness. None of the 35 records revealed a prior diagnosis that might account for the full symptom complex, although the fiscal resources expended on

imaging, electronic tests (e.g., EMG, EEG, and EKG), and repeated outpatient visits was considerable. None had been tested for *B. burgdorferi* by any test method.

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