Misconceptions about Lyme Disease: Confusions Hiding behind Ill-Chosen Terminology

"The beginning of wisdom is to call things by their right names."

—Ancient Chinese proverb

Nomenclature influences perceptions of reality and frames ensuing discussions. Imprecision contributes to misinterpretation of observations and studies, altering clinicians' approaches. The impact of imprecision and novel reinterpretation of terminology can be seen in the Lyme disease debate. A quarter century after its initial description, a review of the terminology contributing to confusion about Lyme disease is needed.

Lyme disease is treatable and curable with antibiotics (1–4), especially if treated promptly, usually with an excellent long-term prognosis. The term "promptly" taken out of context suggests one *must* treat without any delay. In fact, even untreated patients have a good prognosis. A 10- to 20-year follow-up of patients at Yale's Lyme Disease Clinic from 1976 to 1983, many of whom were not treated for early Lyme disease, shows that the patients with erythema migrans did not differ from normal controls in current symptoms, physical findings, results of neuropsychological testing, or responses to the Short-Form 36 Health Assessment Questionnaire (5). However, significant long-term sequelae occurred in patients with untreated facial palsy who probably had disseminated Lyme disease at initial evaluation and probably required intravenous therapy (5).

"Chronic Lyme Disease"—A Term in Search of Definition

Despite this generally optimistic picture, claims of persisting infection and antibiotic unresponsiveness have contributed to anxiety. "Chronic Lyme disease" (6, 7) is a common clinical diagnosis in some geographic areas (8, 9) and is based on thinking that is at odds with scientifically validated findings. No objective physical findings or unique historical features define "chronic Lyme disease," a term used by support groups and their few physician allies, not the academic medical community. Although the subject of much debate, "chronic Lyme disease" is not well defined. The term is usually applied to patients with symptoms, such as fatigue, achiness, malaise, and difficulty with concentration and memory, after treatment of documented Lyme disease or illnesses thought to be Lyme disease, or in patients without preceding illness (9). Once the term Lyme disease is applied, it *is* Lyme disease, forever and irrefutably, a diagnosis often "reaffirmed" by cross-referral between "Lyme literate" physicians.

Many patients receive repeated courses of antibiotics, with transient or waning responses, leading to more or a combination of antibiotics. Occasionally, this course of treatment can go on for years, with little relief. Originally, "chronic" was used in the context of Lyme arthritis, which, in the era before it was determined that Lyme disease was responsive to antibiotics, persisted for years, finally resolving spontaneously (10). Antibiotics are of proven value for Lyme arthritis (11); treatment of early Lyme disease usually prevents arthritis.

A Nexis-Lexis review reveals that "chronic" was first applied to Lyme disease in 1985: Lyme disease was "a potentially chronic and debilitating illness transmitted by tick bites" (12). In 1986, "chronic" referred to outcomes if antibiotics were not administered (13). A letter to the editor by Drs. Falvo and Nadelman urged more support for research: Lyme disease could cause "birth defects, fetal death, unilateral blindness, and chronic debilitating arthritis" (14) (the first and second occurrences still unproven, the third rare, and the last well reported). An adjective appropriate for Lyme arthritis before the identification of antibiotic responsiveness (1, 2, 10, 11) was used to describe patients not responding to antibiotics, suggesting that antibiotics do not kill *Borellia burgdorferi*.

Some Internet sites, support and advocacy groups, and some clinicians claim that the truth is deliberately being obscured: that "chronic Lyme disease" is far more common than the authorities allow us to know; antibiotics are often not curative; infection can be controlled only by long-term antibiotic therapy, often more than insurance companies allow; serologic tests are inaccurate and often yield falsely negative results, thereby incorrectly discouraging diagnosis; the prognosis is not nearly so rosy as "they" (the nefarious academic experts) claim;

Table 1. **What Is Accepted about Lyme Disease**

Lyme disease is also known as Lyme borreliosis and occasionally as erythema migrans disease.

Lyme disease is a multisystem inflammatory condition of the temperate Northern hemisphere caused by spirochetes collectively known as *Borrelia burgdorferi* sensu lato.

Borrelia burgdorferi sensu lato consists of three pathogenic genospecies: in the United States, Lyme disease is caused by *B. burgdorferi* sensu stricto; in Europe and Asia, Lyme borreliosis is due to infection with *B. garinii*, *B. afzelii*, and *B. burgdorferi* sensu stricto.

Lyme disease is spread by *Ixodes* ticks: *I. scapularis* in the northeastern, north midwestern, and Middle Atlantic states of the United States and *I. pacificus* along the northern Pacific coast; *I. ricinus* in Europe; and *I. persulcatus* in Asia. (*I. scapularis* is also found in the southeastern United States, but little if any Lyme disease is reported from that region.)

Most reported cases of Lyme disease in the United States are from southern New England, the Middle Atlantic states, Wisconsin, Minnesota, and northern California. Scattered cases have been reported from the upper South and the Midwest. Erythema migrans–like lesions have been reported from other regions, such as North Carolina (15) and Missouri (16), without serologic confirmation of exposure to *B. burgdorferi*.

Lyme arthritis was described in studies of an outbreak of presumed juvenile rheumatoid arthritis in Connecticut; the association with preceding erythema migrans (then known as erythema chronicum migrans) and tick bites became apparent soon thereafter.

As nonarticular features were identified, the spectrum of Lyme disease became clear and the similarities of Lyme disease with clinical findings from erythema migrans in Europe emerged.

After identification and cultivation of pathogenic borrelial genospecies from tick and human specimens, serologic tests measuring anti–*B. burgdorferi* antibodies were developed and criteria for their interpretation were established.

The clinical spectrum of Lyme disease includes effects on the skin, heart, peripheral and central nervous systems, and the musculoarticular system; these effects have been reviewed elsewhere (1, 2, 5, 7, 10, 17).

Lyme disease has been described using three phases of infection:
1. Early localized disease: erythema migrans and associated symptoms
2. Early disseminated disease: multiple erythema migrans and associated symptoms; Lyme carditis; neurologic features, including facial (and other cranial nerve) palsies, lymphocytic meningitis, and radiculoneuropathies
3. Late disease: neurologic features, including peripheral neuropathies and chronic mild encephalopathy; arthritis, including migratory polyarthritis and/or monoarthritis

The pathogenesis of Lyme disease is not entirely understood, but some of the features of Lyme disease depend on the presence of the organism at the site of damage. Immunologic mechanisms, summarized elsewhere (18), may underlie other features of the disease.

many lives have been ruined; and many people have died (8–10). None of these claims is supported by scientific medical literature, yet they disseminate regularly, acquiring verity by their repetition.

By focusing on terminology, we may understand how some confusion has been promulgated and exacerbated. Insight may aid in clarification and be useful in addressing non–Lyme disease areas of contention. The contents of **Table 1** are probably acceptable to most researchers and clinicians who think about Lyme disease. Beyond these "absolute" facts lie concepts involving terms such as "very unlikely," "has been reported," "usually," or "in most patients"—modifiers describing "shades of gray." Physician-scientists are good at communicating facts, but "shades of gray" are often difficult to convey; the more precise one tries to be about the limits of our knowledge, the more doubts are planted, and the more misinterpretations occur. This is the root of endless debate, the home of a Cartesian dualism of sorts.

RATIONALISTS VERSUS EMPIRICISTS

The opposing sides in this debate about the true nature of Lyme disease can be described as "rationalists" and "empiricists." Rationalists use scientific studies, both clinical and molecular, to develop models of disease and appropriate diagnostic and therapeutic responses. Empiricists base models on community events, developing diagnostic and management schemas that are compatible with observations, but often at odds with scientific conclusions. In conveying their message, empiricists often adopt terminology that contradicts the terminology's intended meaning. Most published clinical and basic research on Lyme disease is from rationalists, physicians searching for objective evidence of infection. The empiricists' ranks include support groups and physicians in practices devoted to the care of patients with "chronic Lyme disease," who are given a diagnosis and are treated on the basis of nonspecific symptoms, such as fatigue, cognitive dysfunction, and pain, rather than objective evidence of infection. Empiricists "listen to the patient" rather than follow the advice of scientific studies, as if these were mutually exclusive. Rationalists fear that physicians, with the help of misinterpreted test results, occasionally misdiagnose serious illnesses as "chronic Lyme disease." Empiricists often diagnose without formulating a differential diagnosis—this *is* Lyme disease. Some call these two opposing views "two schools of thought," but I prefer to call them proponents of "reality" and "alternative reality." The sage of Baltimore, H.L. Mencken, could have been referring to this divide when he penned his introduction to the first American edition of *The Antichrist* by Nietzsche: "The majority of men prefer delusion to truth. It is easier to

grasp. Above all, it fits more snugly into a universe of false appearances . . . ."

"Delusions" may satisfy needs; facts offer cold comfort to the sufferer. When false appearances assume the cloak of "reality," "alternative reality" is established.

The debate between these two groups includes diagnosing the illness, use of testing in diagnosis and management, duration and forms of therapy, prognosis, and defining a cure. Inattention to details and facts, their manipulation, and incorrect citation have fed this occasionally rancorous disputation (12), further confusing most clinicians and patients on the sidelines and causing the suffering of innocent patients and families.

Lyme Disease as "The Great Imitator"

The term "The Great Imitator" as applied to Lyme disease (an attempt to form an analogy with another spirochetal disease, syphilis [19]) contributed to confusion. The comparison was meant not to denote clinical similarities between these diseases but to suggest that, as with syphilis in a previous era, Lyme disease included a broad range of findings and mimicked other diseases. However, it soon became clear that most cases of Lyme disease are recognizable in a well-described spectrum (20–25), the rare exceptions being, by definition, outliers (26). Most patients have objective abnormalities (2). Used correctly, testing is helpful: Immunologic (antibodies in serum and cerebrospinal and synovial fluids) (27), molecular biological (polymerase chain reaction identification of specific DNA), electrophysiologic (heart and neurologic), and neuropsychological (28) tests can support the diagnosis (8). Instead, "The Great Imitator" was misinterpreted as suggesting that Lyme disease routinely mimics and is mimicked by many other diseases. Some empiricists believed Lyme disease was difficult to explicitly diagnose and had to be part of the differential diagnosis of *all* problems of *all* diseases it *might* imitate (11). Lyme disease is often considered in many patients whose symptoms do not explicitly suggest Lyme disease and who receive that diagnosis merely because no other diseases can be explicitly diagnosed.

Centers for Disease Control and Prevention Criteria: Use and Misuse

The belief that Lyme disease is often overlooked is expressed as dissatisfaction with (even anger at) the Centers for Disease Control and Prevention (CDC) surveillance criteria as dangerous stricture, inexplicably designed to minimize reports of "accepted" cases (29). The criteria were designed for surveillance (and are useful as entry criteria for studies) but were not meant for diagnostic purposes. Tabulation of cases that satisfy criteria allows comparison from year to year, assessing numeric and geographic expansion. Not all cases meet the criteria (30).

"Lyme Disease Is a Clinical Diagnosis"

The original meaning of "Lyme disease is a clinical diagnosis" was that one should not diagnose solely on the basis of test results but also on historical and physical evidence that explicitly suggests Lyme disease. Such findings should suggest *the possibility* of Lyme disease—no finding, even in endemic areas, is diagnostic. The phrase has been manipulated into something far from its original intent. History and physical examination may not suggest Lyme disease, serologic testing may yield negative results, but one makes a "clinical diagnosis" simply because one decides the nonspecific symptoms (for example, fatigue and achiness) are due to Lyme disease: The "patient had symptoms compatible with Lyme disease" and lived in an endemic area. Lyme disease becomes a "diagnosis of exclusion" (9), often without any effort to exclude other diagnoses. "Virus-like" symptoms, such as fever, myalgia, and arthralgia, are common in early Lyme disease, although respiratory and gastrointestinal symptoms are uncommon. Nonetheless, "flu-like" symptoms are diagnosed as Lyme disease and are another example of imprecision; patients with acute viral syndromes years into the course of long-standing clinical problems are said to have the "flu-like" symptoms of Lyme disease.

"Symptoms Compatible with Lyme Disease" and the Misuse of Serologic Testing

A patient with "symptoms compatible with Lyme disease," absent physical findings, may receive a diagnosis of Lyme disease because of positive results on "Lyme disease tests" or "Lyme serologies." These tests measure antibodies binding *B. burgdorferi* in vitro, nothing more. The antibodies *may* be a marker of exposure, but they do not document current infection and may indicate a false-positive result. The intrinsic degeneracy of the humoral immune response assures that antibodies against other organisms may bind in such tests. Thus, a positive

result on serology does not prove *B. burgdorferi* exposure. Bayesian theory predicts the clinical utility of testing—minimal positive predictive value if a priori likelihood was low (9). Serologic tests were developed as an adjunct to clinical diagnosis (31), and a positive test result increases a priori likelihood. However, a weakly positive test result is often the sole "evidence" favoring Lyme disease. "Lyme disease test" and "Lyme serologies" are misleading terms, suggesting the incorrect but seemingly logical conclusion that a positive result diagnoses Lyme disease. There is no such thing as a "Lyme disease test" (8, 9, 31).

The second test in the two-tiered serologic approach is immunoblot. Antibodies to individual proteins ("bands") are assigned an approximate molecular mass in kilodaltons. The CDC recommendation is that positive or equivocal results on enzyme-linked immunosorbent assays be supplemented by immunoblot (31) because the latter is more specific and the former, a first-level test, is intended to be more sensitive. Criteria were established for interpretation of results on immunoblot—IgM assays for early disease and IgG for later disease (31).

The "clinical diagnosis" of Lyme disease is often incorrectly secured by positive serologic results with negative findings on immunoblot (a "biologic false-positive" test result, borrowing again from syphilis). If a priori belief in the diagnosis is sufficient, a negative test result is dismissed—after all, "we all know how inaccurate the tests are." Regardless of results, the "clinical diagnosis" stands. Serologies are useful; their major limitation is the knowledge of the clinician who orders them and interprets the results.

Misinterpretation of immunoblot was common with earlier assays, often because of the assignment of "positive" or "negative" results to each "band," with the "positive" band being misread as a positive immunoblot finding. New reportage suggests referring to small print at the bottom of the report and understanding that IgM and IgG criteria should be used for early and later infection, respectively. Isolated IgM reactivity does not indicate chronic Lyme disease—IgG reactivity should have emerged. IgM reactivity occurs in *early* infection but has been misinterpreted as indicating *active* infection. Seroreactivity, even with IgM, can persist long after cure—persisting seroreactivity is not evidence of ongoing infection (27, 32–34). Nonetheless, a single reactive band has been misinterpreted as indicating infection, and "chronic Lyme disease" has been misdiagnosed because of seroreactivity persisting after therapy.

The Permanence of a Lyme Disease Diagnosis

Even if proof of diagnosis at inception is tenuous, subsequent physicians may accept the previous Lyme disease diagnosis, often without independent scrutiny, as if it were proven beyond doubt. The diagnosis becomes permanent (35), all future findings perforce Lyme disease-related, making post hoc ergo propter hoc ("after this, therefore, because of this") logic all the more fallacious since the initial diagnosis was incorrect. The neologism "chronic Lyme disease" is the most damaging term in this developing imprecise lexicon. The diagnosis becomes life-long, a misdiagnosis causing missed diagnoses; the explanation for the patient's problems is never identified, and the accepted misdiagnosis prevents further search. Musculoskeletal pain is "Lyme arthritis,"and cognitive dysfunction is "central nervous system disease."

Many patients cleave to "chronic Lyme disease" despite lack of response, expense, and significant toxicities (36). It is human nature to seek explanations. The fear of the unknown can be greater than the fear of even incurable chronic disease. Anxiety and fear drive the pursuit of diagnosis, testing, and treatment (37). Achieving a diagnosis, even one of incurable "chronic Lyme disease," may offer patients with chronic symptoms comfort and assurance.

The Effects of Antibiotics on "Chronic Lyme Disease"

Symptoms that develop or worsen during antibiotic therapy are "Herxheimer-like" reactions. A Jarisch–Herxheimer reaction occurs in about 10% of patients within days of initial antibiotic administration and not after subsequent courses. Worsening of symptoms without objective findings with a periodicity of about 28 days (the organism's "natural rhythm") is neither a Jarisch–Herxheimer nor a Herxheimer-like reaction; neither Jarisch nor Herxheimer would recognize these as what they described (36).

If symptoms persist despite antibiotic use, there may be ongoing infection (36) requiring further treatment. This could include months or years of oral or intrave-

Table 2. **Lyme Disease Terminology: Present and Proposed**

Current Term	Proposed Substitution	Why the Change Is Needed
Clinical diagnosis	No change	It is and always will be a clinical diagnosis, but the diagnosis must be based on explicit evidence of the disease and never made as a "diagnosis of exclusion."
Diagnostic tests	Sero-confirmatory tests	Testing should never be used as the sole basis for the diagnosis of Lyme disease. A positive test result is not diagnostic; it merely increases the likelihood of the diagnosis previously based on explicit clinical evidence. "Vide supra"–Bayes theorem: if the clinical suspicion of Lyme disease is low, a positive test result does not make the diagnosis. In a case with a high a priori likelihood of Lyme disease, a positive test result can do no more than confirm the clinician's conclusion of a reasonably high likelihood of disease. Some argue persuasively that even "sero-confirmatory" is too strong a term—perhaps more accurate (but less euphonious) would be "sero-suggestive."
Lyme disease test	Anti–*Borrelia burgdorferi* antibody test	The test does not diagnose Lyme disease. The test merely identifies antibodies binding to *Borrelia burgdorferi* in vitro, antibodies possibly not made in an immune response to *B. burgdorferi* in the first place. So, why not call it what it really is?
Flu-like symptoms	Viral syndrome	Influenza often includes prominent pulmonary symptoms that are relatively rare in Lyme disease. Likewise, gastrointestinal symptoms are not prominent in early Lyme disease.
Chronic Lyme disease	–*	This term is of no proven value in the management of patients with established Lyme disease. Until scientific studies prove that chronic *B. burgdorferi* infection exists, especially following what would otherwise seem to be adequate antibiotic therapy, this term should not be used. This is in contrast to the term "post–Lyme disease syndrome," which appears to describe a real clinical entity not associated with ongoing *B. burgdorferi* infection.
Lyme disease	Lyme borreliosis	The term "Lyme disease" means so many different things to different people at this point that a new name emphasizing the underlying infection with *B. burgdorferi* might help shift the focus back where it belongs—to a multisystem inflammatory disease due to an infection with *B. burgdorferi*.
Symptoms of Lyme disease	–*	The symptoms seen in patients with Lyme disease are not unique for any of the clinical manifestations of the diseases, but most emphatically for early disease. Patients with early Lyme disease may have fever, myalgias, and arthralgias, suggesting a "viral syndrome," but such symptoms are not unique to or specific for this infection; such symptoms in the summer or early fall are probably related to a viral infection. Thus this term is rendered meaningless by its lack of specificity.
Symptoms compatible with Lyme disease	–*	This term is also rendered useless by its imprecision and bias. So many of the symptoms of Lyme disease are found in other diseases that there is no way to directly ascribe them to Lyme disease—nearly all nonspecific symptoms thereby are "compatible" with Lyme disease. "Symptoms compatible with Lyme disease" takes in the entire spectrum of medicine and is a needlessly biased and suggestive term that should be abandoned.
"Lyme literate"	–*	A neologism, coined by lay support groups, that seems to identify clinicians subscribing to the empiricists' approach. "Listening to the patient" is not an attribute unique to clinicians in this group, just as all "Lyme literate" practitioners do not eschew the development of an appropriate and thorough differential diagnosis in order to make Lyme disease a "diagnosis of exclusion."

* The absence of a proposed replacement suggests that this term should be deleted from use for the reasons noted.

nous antibiotics, or combination antibiotics, occasionally including agents that are inactive against *B. burgdorferi* (for example, atovaquone). With few exceptions, such as *Tropheryma whippelii* and mycobacteria, no bacteria necessitate long-term antibiotic therapy as is used for "chronic Lyme disease."

Long-term antibiotic therapy, however, is needed because *B. burgdorferi* becomes dormant or hides within cells (38–41); these interactions protect the organism from antibiotics (42) (in vitro phenomena not documented in vivo) so that organisms are not responsive. Empiricists call proven regimens "conservative therapy" (1–3, 20, 22), a pejorative term suggesting incompetence of rationalist approaches. Transient response indicates a need for more treatment; many antibiotics have nonantimicrobial effects (43). Inadequacy of treatment is the only explanation for lack of response; the nonexistence of infection is not considered. A recent National Institutes of Health–funded trial showed that 3 months of antibiotics for "chronic Lyme disease" was ineffective (44); unfortunately, empiricist criticism will probably dismiss the results.

Peer-reviewed experience from academic referral centers indicates that most patients unresponsive to antibiotics do not have Lyme disease (35, 45–48). Some never had it; others were cured of *B. burgdorferi* infection. Symptoms following Lyme disease should not necessarily be ascribed to preceding *B. burgdorferi* infection. Such patients should be evaluated for objective evidence of inflammation and organ damage and evidence of cur-

rent infection; the post hoc ergo propter hoc approach has often proven hazardous. There are "post-Lyme disease syndromes," such as fibromyalgia and depression, that do not respond to antibiotics (35, 44–47); fibromyalgia following Lyme disease is not due to ongoing infection. Objective neurologic deficits may be due to irreversible brain damage from Lyme disease, but if previous therapy was adequate, antibiotics are unlikely to be useful. Anxiety elicited by fears of incurable "chronic Lyme disease" does not respond to antibiotics. Above all, one must individualize the approach to the patient.

The Effects of "Chronic Lyme Disease" on the Patient

Long-term antibiotic therapy is not without financial and physical costs, such as bone marrow toxicity, central line sepsis (49, 50), or even death (51). Hidden in this epidemic of chronic disease and debility is the psychological cost of accepting a disease as a permanent part of yourself, that you will never be cured, that the disease will be with you forever, no matter how powerful the drugs or how aggressively they are given. Assumption of the "sick role" leaves an invisible scar that may be the most devastating effect of "chronic Lyme disease" (8).

Proposals for Changes in Terminology—Reducing Bias in the Language

Twenty-five years after the description of Lyme disease we have come far: clinical features are well described, accurate tests support the diagnosis, effective therapy is available, and there is an effective vaccine. It is time to reflect on the jargon that contributes to misdiagnosis and mistreatment. **Table 2** highlights some of the more troublesome terms and proposed substitutions. Use of less suggestive, accurate, unbiased terminology will help us focus on Lyme disease and take proper care of our patients, many of whom have been ill-served by cant and rhetoric. Those convinced that "chronic Lyme disease" is real, that long-term antibiotics are needed, will not be easily deterred by this analysis. However, the unbiased may use this analysis to carefully inspect the rationalist and empiricist approaches and decide which fulfills our sacred responsibility to "do no harm." Issues considered in this review may help physicians deal rationally with future clinical controversies.

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