11. Thomas V, Anguita J, Barthold SW, Fikrig E. Coinfection with *Borrelia burgdorferi* and the agent of human granulocytic ehrlichiosis alters murine immune responses, pathogen burden, and severity of Lyme arthritis. *Infect Immun.* 2001;69:3359–3371.
12. Lautin A, McNeil EL, Liegner KB, Stricker RB, Sigal LH. Lyme disease controversy: Use and misuse of language. *Ann Intern Med.* 2002;137:775–777.

LYME DISEASE PRESENTING AS AN INFLUENZA-LIKE ILLNESS

To the Editor:

I read with interest the article by Steere et al. (1) on seroconversion to *Borrelia burgdorferi* with either immunoglobulin (Ig) G or IgM Western blot in a group of patients presenting with a summer "flu-like" illness without rash. A minority had concurrent ehrlichiosis or babesiosis, often more symptomatic than those with Lyme disease alone. The authors recommend considering Lyme disease in patients with "systemic symptoms during summer, especially when headache or arthralgia but no upper respiratory or gastrointestinal symptoms is reported" (1). A closer look at these specific symptoms demonstrates that only 63% had fever, 54% had headache, and 71% had arthralgias. The authors do not specify whether all or just some of the above symptoms are required to justify serologic testing. Although gastrointestinal or respiratory symptoms were rarely seen in the current series, these observations could be related to methodology. The source of the current report was a Lyme disease vaccine trial wherein study subjects were provided an instructional packet that encouraged reporting of flu-like illnesses "without predominant respiratory or gastrointestinal symptoms" (2,3). Additionally, the original study definition of possible Lyme disease excluded patients with "cough, coryza, diarrhea, or vomiting" (3). Thus, the absence of notable gastrointestinal or respiratory symptoms in this set of patients could be a consequence of both reporting bias and the case definition used.

Presumably a substantial fraction of patients presenting with nonspecific constitutional symptoms have viral illnesses, and clinical criteria that can separate Lyme disease without rash from viral processes are needed. A recent small prospective study by Belongia et al. (4) was not able to distinguish summertime "flu-like" illnesses due to tick-related infection from viral illnesses on the basis of clinical presentation. Although most investigators have noted a high incidence of hematologic and liver enzyme abnormalities in patients with ehrlichiosis or babesiosis (5–7), these laboratory tests were not incorporated into the current authors' diagnostic approach. Because the patients studied by Steere et al. (1) represent a subset of a much larger cohort derived from a prospective Lyme vaccine study, those patients screened for Lyme disease but who were rejected might have formed the basis of a control group against which those with "flu-like" symptoms due to Lyme disease could have been compared. Barring more complete epidemiological studies and appropriate predictive models, caution should be exercised in routinely ordering serology for *B. burgdorferi* based on nonspecific symptoms.

Richard Porwancher
University of Medicine and Dentistry of New Jersey—
Robert Wood Johnson Medical School
New Brunswick, New Jersey

1. Steere AC, Dhar A, Hernandez J, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. *Am J Med.* 2003;114:58–62.
2. Smith RP, Schoen RT, Rahn DW, et al. Clinical characteristics and treatment outcome of early Lyme disease in patients with microbiologically confirmed erythema migrans. *Ann Intern Med.* 2002;136:421–428.
3. Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme disease with recombinant *Borrelia burgdorferi* outer-surface protein A with adjuvant. *N Engl J Med.* 1998; 339:209–215.
4. Belongia EA, Reed KD, Mitchell PD, et al. Tickborne infections as a cause of nonspecific febrile illness in Wisconsin. *Clin Infect Dis.* 2001;32:1434–1439.
5. Krause PJ, McKay K, Thompson CA, et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. *Clin Infect Dis.* 2002;34:1184–1191.
6. Zaidi SA, Singer C. Gastrointestinal and hepatic manifestations of tickborne diseases in the United States. *Clin Infect Dis.* 2002;34: 1206–1212.
7. Wormser GP, Horowitz HW, Nowakowski J, et al. Positive Lyme disease serology in patients with clinical and laboratory evidence of human granulocytic ehrlichiosis. *Am J Clin Pathol.* 1997;107:142–147.

The Reply:

Dr. Porwancher questions whether study methodology was the reason that gastrointestinal or respiratory symptoms were rarely seen in our series of 42 patients who had systemic symptoms without erythema migrans (1). We do not think so. Early symptoms of Lyme disease were originally described in 314 patients with erythema migrans (2). These patients often had malaise and fatigue, headache, fever and chills, myalgias, or arthralgias. A few patients had cough, chest pain, or diarrhea, but these were not the predominant symptoms. In our recent study (1), the same clinical picture was observed in patients without erythema migrans.

The vaccine study was designed to identify all participants who developed *Borrelia burgdorferi* infection (3). Patients were encouraged to report to their study physician if they had any symptoms, alone or in combination, which might be due to Lyme disease, as previously described in the medical literature. During the study, more than 400 participants were evaluated for flu-like illness, but only 28 had immunoglobulin (Ig) G seroconversion to *B. burgdorferi* when these symptoms were present (1). In these patients, headache and arthralgias were common, but gastrointestinal and respiratory symptoms were not. We do not think that Lyme

disease cases were missed, because serum samples were obtained from all of the nearly 11,000 study participants before and after the summer tick transmission season. Of the 30 additional patients who were identified with IgG seroconversion, 9 reported myalgias or arthralgias, sometimes with fever, during the period of seroconversion, but none reported gastrointestinal or respiratory symptoms.

The unexpected finding was that about 16% of the Lyme disease cases presented with systemic symptoms during summer without erythema migrans (1). A challenge for physicians is early recognition and treatment of such cases before the more debilitating and harder to treat later manifestations of the infection develop.

Drs. Stricker and Phillips are concerned about antibiotic treatment for chronic, post–Lyme disease syndrome (sometimes called chronic Lyme disease), the reliability of serologic tests, and the possible role of coinfection. None of these issues was addressed in our study. In our study, 7 patients, including 2 with coinfection, had arthralgias or fatigue that persisted for weeks or months after 3- or 4-week courses of oral doxycycline or amoxicillin. However, none of the 42 patients developed later manifestations of Lyme disease or chronic, post–Lyme disease syndrome. Moreover, long-term persistence of the spirochete has not been substantiated in any large series of patients treated with currently recommended antibiotic regimens (4,5). In a double-blind placebo-controlled trial that sought to determine whether patients with post–Lyme disease syndrome would benefit from additional 3-month courses of therapy (6), none had positive cultures or positive results by polymerase chain reaction before treatment, and no differences were noted in outcome between the antibiotic and placebo groups.

After several weeks of infection, the sensitivity and specificity of the IgG response to *B. burgdorferi* is high, using the two-test approach of enzyme-linked immunosorbent assay (ELISA) and Western blot (7). The new IgG VlsE peptide ELISA has been shown to be promising as an improved serologic test (8). Although these tests do not distinguish between active or past infection, they are reliable in showing exposure to *B. burgdorferi* in patients with systemic infection.

Patients with early Lyme disease who are infected with other tickborne agents, including *Babesia microti* or *Anaplasma phagocytophila*, may have more severe disease (9) or fatigue for months after treatment (10). However, neither babesiosis nor human anaplasmosis has been shown to cause chronic infection. As with patients infected with *B. burgdorferi* alone, there is no evidence that longer courses of antibiotic therapy are beneficial in coinfected patients.

Allen C. Steere, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Vijay K. Sikand, MD
Tufts University School of Medicine
Boston, Massachusetts

1. Steere AC, Dhar A, Hernandez J, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme disease. *Am J Med.* 2003;114:58–62.
2. Steere AC, Bartenhagen NH, Craft JE, et al. The early clinical manifestations of Lyme disease. *Ann Intern Med.* 1983;99:76–82.
3. Steere AC, Sikand VK, Meurice F, et al. Vaccination against Lyme disease with recombinant outer-surface protein A in adjuvant. *N Engl J Med.* 1998;339:209–215.
4. Nocton JJ, Dressler F, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in synovial fluid in Lyme arthritis. *N Engl J Med.* 1994;330:229–234.
5. Nocton JJ, Bloom BJ, Rutledge BJ, et al. Detection of *Borrelia burgdorferi* DNA by polymerase chain reaction in cerebrospinal fluid in patients with Lyme neuroborreliosis. *J Infect Dis.* 1996;174:623–627.
6. Klempner MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med.* 2001;345:85–92.
7. Dressler F, Whalen JA, Reinhardt BN, Steere AC. Western blotting in the serodiagnosis of Lyme disease. *J Infect Dis.* 1993;167:392–400.
8. Liang FT, Steere AC, Marques AR, Johnson BJ, Miller JN, Philipp MT. Sensitive and specific serodiagnosis of Lyme disease by enzyme-linked immunosorbent assay with a peptide based on an immunodominant conserved region of *Borrelia burgdorferi* VlsE. *J Clin Microbiol.* 1999;37:3990–3996.
9. Krause PJ, Telford SR, Spielman A, et al. Concurrent Lyme disease and babesiosis: evidence for increased severity and duration of illness. *JAMA.* 1996;275:1657–1660.
10. Krause PJ, McKay K, Thompson CA, et al. Disease-specific diagnosis of coinfecting tickborne zoonoses: babesiosis, human granulocytic ehrlichiosis, and Lyme disease. *Clin Infect Dis.* 2002;34:1184–1191.

STATINS AND LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS

To the Editor:

It is well known that the types of patients, clinical presentations, and treatment outcomes in everyday medical practice can vary greatly from those in controlled clinical studies. Thus, it is not surprising that Frolkis et al (1) found that statins in clinical practice were associated with low-density lipoprotein (LDL) cholesterol reductions that were 20% less than the reductions projected by package insert guidelines (1). Although I agree with the authors' conclusion that physicians should be aware of this disparity, I am concerned that this will lead physicians to prescribe stronger initial doses of statins. This would be a mistake for several reasons.

It should be noted that 38% of patients in this study had LDL cholesterol reductions that were greater than 100% of the expected reductions. This explains the substantial number of patients who cannot tolerate standard initial statin doses, but who achieve their target LDL cholesterol levels without adverse effects