

# And the Empire Strikes back...

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- *From:* "the 3rd Man" <[sir\\_der05@xxxxxxxxx](mailto:sir_der05@xxxxxxxxx)>
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## CORRESPONDENCE

Reply to Pollock, Donta, Wilson, and Arne

Gary P. Wormser,<sup>1</sup> Raymond J. Dattwyler,<sup>2</sup> Eugene D. Shapiro,<sup>5,6</sup> John J. Halperin,<sup>3,4</sup> Allen C. Steere,<sup>9</sup> Mark S. Klempner,<sup>10</sup> Peter J. Krause,<sup>8</sup> Johan S. Bakken,<sup>11</sup> Franc Strle,<sup>13</sup> Gerold Stanek,<sup>14</sup> Linda K. Bockenstedt,<sup>7</sup> Durland Fish,<sup>6</sup> J. Stephen Dumler,<sup>12</sup> and Robert B. Nadelman<sup>1</sup>

Divisions of <sup>1</sup>Infectious Diseases and <sup>2</sup>Allergy, Immunology, and Rheumatology, Department of Medicine, New York Medical College, Valhalla, and <sup>3</sup>New York University School of Medicine, New York, New York; <sup>4</sup>Atlantic Neuroscience Institute, Summit, New Jersey; the Departments of <sup>5</sup>Pediatrics and <sup>6</sup>Epidemiology and Public Health and <sup>7</sup>Section of Rheumatology, Department of Internal Medicine, Yale University School of Medicine, New Haven, and <sup>8</sup>Department of Pediatrics, University of Connecticut School of Medicine and Connecticut Children's Medical Center, Hartford, Connecticut; <sup>9</sup>Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, and <sup>10</sup>Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; <sup>11</sup>Section of Infectious Diseases, St. Luke's Hospital, Duluth, Minnesota; <sup>12</sup>Division of Medical Microbiology, Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland; <sup>13</sup>Department of Infectious Diseases, University Medical Center Ljubljana, Ljubljana, Slovenia; and <sup>14</sup>Medical University of Vienna, Vienna, Austria

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

Reprints or correspondence: Dr. Gary P. Wormser, Rm. 245, Munger Pavilion, New York Medical College, Valhalla, NY 10595 (Gary\_Wormser@xxxxxxxx).

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TO THE EDITOR—Dr. Pollock [1] is correct that the report by Phillips et al. [2] is the key citation in support of the concept that viable *Borrelia burgdorferi* may persist in the bloodstream, despite prior courses of antibiotic treatment. However, 3 follow-up studies have been unable to reproduce the findings (without even a single positive blood culture result) [3–6]. In fact, the novel culture medium employed by Phillips et al. [2] was unable to support the growth of *B. burgdorferi* when the spirochete was directly introduced into it.

There is no convincing evidence of persistence of *B. burgdorferi* in the skin of North American patients who are treated for Lyme disease [7, 8]. The European study that Pollock [1] cites, in which *Borrelia* species were recovered from normal-appearing skin at the site of a resolved erythema migrans skin lesion in 19 (1.7%) of 1148 asymptomatic patients for whom samples were cultured [9], would have been more compelling had the positive culture results been confirmed by an independent detection method performed on the skin samples, such as PCR. Notably, in the 5 cases in which *Borrelia* species isolates could be compared both before and after antibiotic treatment, the *Borrelia* strains were not identical in 4 of the pairs of isolates and were not even from the same species for the fifth [9]. The efficacy of benzathine penicillin G (35%) is too low to justify recommending the drug now that other, much more effective antibiotic regimens are available [10].

In response to the assertion of Dr. Donta [11], it has not been established that the long-term persistence (6 months) of subjective symptoms after treatment occurs more frequently in patients with Lyme disease than in patients with other types of infection or in patients without any infection. Although the frequency of symptoms in patients after treatment of Lyme disease exceeded that of symptoms in control subjects in several retrospective studies, the validity of this observation is uncertain, because these studies included patients whose diagnosis and treatment of Lyme disease would often not satisfy current standards [12, 13]. Moreover, the range of subjective

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complaints by patients with Lyme disease is also observed among patients with numerous other diagnoses and is definitely not "unique" to this infection [14]. A well-designed prospective study that includes a cohort of control subjects who do not have Lyme disease would help to address this issue.

Dr. Donta's clinical experience with "several thousand patients" [11, p. 1134] with post-Lyme disease syndrome is somewhat surprising, in light of the difficulty experienced in finding eligible subjects for the 3 published controlled-treatment trials of post-Lyme disease syndrome conducted by other investigators. To enroll just 184 subjects in total, intensive efforts were required that included increasing the time period for recruitment [3, 15] and adding additional study sites [3].

Clinically directive conclusions cannot be drawn from uncontrolled treatment trials in subjects who have only subjective symptoms. Furthermore, the lack of specificity of the criteria used by Dr. Donta [11] for diagnosing Lyme disease on the basis of results of serologic tests [16, 17] raises the question of whether most of his study subjects ever actually had Lyme disease [18]. Approximately 40% of the general population would be considered to be seropositive on the basis of the criteria Dr. Donta used [11; R. Porwancher, A. Levin, and Immunetics, unpublished data].

The assertion that long-term infection with *B. burgdorferi* suppresses humoral immune responses is not supported by available data, which demonstrate that the profile of antibodies generated to *B. burgdorferi* expands over time [19, 20]. Evidence also indicates that *B. burgdorferi* is principally found in an extracellular location, rather than an intracellular one, as Dr. Donta hypothesizes [11, 21]. We do agree that more research is needed to understand post-Lyme disease syndrome; for that reason, we have proposed a standardized case definition in the guidelines that could be used in future studies [4].

Mr. Wilson's concerns [22] relate to his premise that the majority of patients with Lyme disease do not have the well-recognized objective features of this infection, such as erythema migrans or joint swelling, and instead only manifest 1 subjective complaint from an extensive list. Furthermore, patients with such nonspecific symptoms are assumed to have persistent *B. burgdorferi* infection, irrespective of prior antibiotic therapy for Lyme disease or negative laboratory test results. Following this line of reasoning, diagnosis would need to be made on the basis of the ability to differentiate these complaints from similar ones that occur commonly in the general population or in patients who have a variety of other conditions, including chronic fatigue syndrome and fibromyalgia, among many others [23-26]. Overdiagnosis of Lyme disease would be inevitable.

Mr. Wilson's theory [22] is not supported by convincing

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scientific studies. In contrast to the assertions made, studies show that the majority of patients with *B. burgdorferi* infection present with erythema migrans [27], that there is no convincing evidence for the persistence of *B. burgdorferi* after antibiotic treatment in patients whose only complaints are subjective at the completion of antibiotic therapy (see above discussion) [3–6], and that seroreactivity is both expected and routinely observed in acute–phase and/or convalescent–phase serum specimens obtained from patients who have objective extracutaneous manifestations of Lyme disease [4, 28, 29].

Unfortunately, overdiagnosis of Lyme disease resulting in unnecessary, costly, and potentially dangerous antibiotic treatment is well known in the United States and has also been documented in Canada [30–35]. In 1 study from British Columbia, which is a low–risk area, only 2 (3%) of 65 patients were judged to have Lyme disease when evaluated at a *Borrelia* referral clinic at the University Hospital in Vancouver; moreover, definite alternative diagnoses could be established for 77% of the patients [33].

Because of differences both among the species of *Borrelia* that cause infection and among the clinical manifestations of Lyme disease in Europe, compared with the United States, we developed the guidelines [4] for use in the United States. Consequently, we did not cite many worthwhile European studies. We agree with Dr. Arne [36] that fewer controlled trials of treatment of children with erythema migrans have been conducted in the United States than in Europe [37].

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Potential conflicts of interest. G.P.W. has received consulting fees from Baxter and research support from Immunetics and is a founder of Diaspex, a company that does not offer products or services. R.J.D. is a speaker for Pfizer and a part owner of Biopeptides Corporation, a biotechnology company developing vaccines and laboratory diagnostics, including for *Borrelia burgdorferi*. J.J.H. is an expert witness on behalf of Lymerix (GlaxoSmithKline). A.C.S. has received consulting fees from Baxter. P.J.K. has a patent pending, with a university, on a babesiosis diagnostic procedure that is not yet on the market. All other authors: no conflicts.

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