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Chronic Lyme disease: in defense of the scientific enterprise

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ABSTRACT **There is no better example of a relentless attack on evidence-based biomedical research and the integrity of outstanding scientists than that associated with the treatment of a poorly defined condition called "chronic Lyme disease." Here, a scientifically naive general population, the lay press, and legislators, who in most instances are unable to evaluate and judge scientific evidence properly, have been misled by patient advocate groups to believe that extended antibiotic therapy is the best and only solution to this condition. This has resulted in the unprecedented intrusion of government and the legal systems into the practice of medicine and scientific research. Because there is no clinical evidence that this condition is due to a persistent infection, advocating extended antibiotic therapy is not justified and has been shown to be harmful and of no benefit.—Baker, P. J. Chronic Lyme disease: in defense of the scientific enterprise. *FASEB J.* 24, 000–000 (2010). www.fasebj.org**

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THE PEER REVIEW SYSTEM OF GRANTS sponsored by the National Institutes of Health (NIH), which supports >90% of all biomedical research in the United States, is emulated throughout the world. It is responsible for most of the many advances made in medicine and biomedical research. Obtaining an NIH grant is an extremely competitive process in which <20% of applications submitted are funded. Publishing the results of NIH-sponsored research is likewise a demanding process; manuscripts considered for publication must pass the test of rigorous peer review. Investigators whose work survives such scrutiny are rightly considered to be among the very best the scientific community has to offer. Many are not only members, but also officers in prestigious organizations such as The American Academy of Sciences, The Institute of Medicine, The American Society for Microbiology, The Federation of American Societies for Experimental Biology, The American Association for the Advancement of Science, and the Infectious Diseases Society of America (IDSA), to name but a few. Since many of these outstanding and internationally known investigators have documented achievements in basic and/or clinical research on Lyme disease, they often are invited to serve on NIH Study Sections, as well as Lyme disease advisory panels; indeed, they represent a national resource of reliable information for community physicians, research investigators, and the public at large on Lyme disease.

Despite the numerous achievements of this extremely rigorous and demanding enterprise, controversy and misinformation abound concerning a poorly defined condition called "chronic Lyme disease" (1). This has caused some to question wrongfully the integrity of many outstanding research scientists, as well as the institutions to which they belong. During a past session of the Maryland House of Delegates, legislation was proposed that would have compelled health insurance companies to pay for extended antibiotic therapy for the treatment of chronic Lyme disease, and prohibited local medical boards and/or societies from disciplining physicians who administer such therapy. Similar legislation has been proposed in other states (Pennsylvania, Connecticut, Massachusetts, Minnesota, New Hampshire, Vermont, Maine, and New York) where Lyme disease is endemic. These unwarranted legislative interventions into the practice of medicine are unprecedented and part of a well-organized campaign by Lyme disease activists who, contrary to all published scientific evidence, propagate the unproven view that chronic Lyme disease is the result of a persistent infection that requires long-term antibiotic therapy to cure. Such legislation was proposed despite the facts that there is no clinical evidence to support either of these claims; the published results of 4 NIH-supported placebo-controlled clinical trials indicate that extended antibiotic therapy is neither beneficial nor safe (2–4); and several peer-reviewed publications from Lyme disease referral centers indicate that "most patients unresponsive to conventional antibiotic therapy never had Lyme disease, do not have it, or were cured of their *Borrelia burgdorferi* infection" (5). Some practitioners accept undocumented testimonials from patients, whose condition is claimed to have been improved after extended antibiotic therapy. However, one should be skeptical of such isolated reports, since the results of a rather large placebo-controlled clinical trial on the efficacy of

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extended antibiotic therapy for the treatment of chronic Lyme disease showed a placebo effect as high as 39% (2). Also, it has been shown that several β-lactam antibiotics used to treat Lyme disease, including ceftriaxone, which is often used to treat chronic Lyme disease, have profound neuroprotective properties that can ameliorate neurological symptoms (6, 7); such a pharmacological effect, rather than the elimination of a presumed persisting infection, might account for the short-lived beneficial effects sometimes seen. If that is the case, it would be more appropriate and safer to use other drugs with such properties instead of antibiotics.

At the behest of Lyme disease activists, an antitrust investigation was launched against the IDSA for its failure to cite, in its guidelines on the treatment of Lyme disease (8), nonexistent evidence that chronic Lyme disease is due to a persistent infection that requires extended antibiotic therapy to cure. This unprecedented action, which was resoundly condemned by distinguished attorneys and members of the medical profession (9), prompted an extensive review of the published IDSA guidelines by an independent review panel. That panel issued a final report in which it unanimously approved all of the recommendations made in the IDSA's current guidelines (10). The review panel, which relied on >1000 published scientific papers in making its deliberations, also affirmed that there is no published evidence to indicate that extended antibiotic therapy is beneficial for the treatment of chronic Lyme disease; there is "no well-accepted definition of post-Lyme disease syndrome"; and there is "no convincing biological evidence for the existence of symptomatic chronic *Borrelia burgdorferi* infection among patients given recommended treatment regimens for Lyme disease" (10).

It should be noted that the IDSA's recommendations for the treatment of Lyme disease are in agreement with those of the European Federation of Neurological Societies (11), the European Union of Concerted Action on Lyme Borreliosis (12), the American Academy of Neurology (13), the Canadian Public Health Network (14), and the German Society for Hygiene and Microbiology (15). They also are in agreement with recommendations made by expert panels from 10 European countries, *i.e.*, The Czech Republic, Denmark, Finland, France, The Netherlands, Norway, Poland, Slovenia, Sweden, and Switzerland. [An excellent summary of these expert panel recommendations may be found in the presentation by O'Connell in the guidelines section posted on the American Lyme Disease Foundation (ALDF) website at http://www.aldf.com.] None of these organizations or expert panels—as well as the Centers for Disease Control (CDC) and the NIH—recommends extended antibiotic therapy for the treatment of chronic Lyme disease. In contrast to the false and misleading information being propagated on the Internet *via* Lyme disease patient support websites, the IDSA guidelines (8), as well as websites sponsored by the NIH (http://www.nih.gov), the CDC (http://www.cdc.gov), and the ALDF (http://www.aldf.com), are the best source of factual information extant on Lyme disease for community physicians, medical practitioners, and the general public.

Some Lyme disease activists continue to make the astounding claim that this overwhelming consensus of independent expert opinion is the result of conflicts of interest and/or a vast conspiracy by a cabal to suppress the truth. This is absurd, especially when such claims are made by "Lyme-literate physicians" who profit immensely from the prolonged treatment of chronic Lyme disease. It should be noted that the composition of the IDSA guideline review panel was approved by an independent ethicist, who found no evidence of conflict of interest with respect to any member of the review panel (10). Instead of casting doubts on the reputation of distinguished scientists and the organizations to which they belong, those who disagree would be well advised to do the following if they wish to gain acceptance from the scientific and medical community for their unproven views:

1) Develop a precise definition of what is meant by "chronic Lyme disease" so that it can be distinguished unequivocally from other medical conditions with similar symptoms.

2) Provide direct and unequivocal evidence that a patient suspected of having chronic Lyme disease really has a persistent *B. burgdorferi* infection that justifies antibiotic therapy.

3) Demonstrate, from the results of published, peer-reviewed, randomized, placebo-controlled trials, that extended antibiotic therapy is beneficial and safe for the treatment of chronic Lyme disease.

The results of NIH-supported studies frankly acknowledge that some patients with chronic Lyme disease experience significant pain and indeed have deficits with respect to their physical health status (2). Obviously, these patients require appropriate medical attention and care. However, because there is no evidence to indicate that their symptoms are caused by a persistent *Borrelia burgdorferi* infection, antibiotic therapy is neither a prudent nor a beneficial option. It is time to discard this unproven approach and begin to consider alternative causes and symptomatic treatment options, if we truly wish to achieve common ground and provide relief for these patients (16). In this context, the results of a small pilot study indicated that treatment with gabapentin alleviates the neurotropic pain associated with chronic Lyme disease (17); since the Food and Drug Administration has approved the use of pregabalin (similar to gabapentin) for the treatment of fibromyalgia, a condition with symptoms similar to those ascribed to chronic Lyme disease, this approach requires further investigation. Other studies indicate that psychiatric comorbidity and other psychological factors (*e.g.*, the tendency to catastrophize pain) distinguish chronic Lyme disease patients from those with fibromyalgia and chronic fatigue syndrome and were associated with poor functional outcomes (18). It has been reported that antineural antibody activity is significantly higher in patients with chronic Lyme dis-

ease than in post-Lyme disease healthy and normal subjects; this exciting recent finding suggests the existence of a differential immune system response in patients with chronic Lyme disease and offers new clues about its etiopathogenesis that may be useful in devising novel and effective treatment strategies (19). FJ

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