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Persistent infection in chronic Lyme disease: does form matter?

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Abstract

Lyme disease remains a controversial illness. The controversy is based on a profound disagreement over the existence of persistent infection with the Lyme spirochete, *Borrelia burgdorferi*, and the ability of this persistent infection to cause chronic symptoms in patients who are untreated or undertreated for the initial spirochetal disease. In this article, we summarize evidence from animal models, human studies and in vitro experiments that support persistent spirochetal infection as the cause of chronic Lyme disease. Specifically, the role of cysts and biofilms in this process is outlined, and the need for better treatment options for patients with chronic Lyme disease is defined.

Keywords: Lyme disease, *Borrelia burgdorferi*, cysts, biofilms, animal models

Introduction

More than 35 years after its discovery, Lyme disease remains a controversial illness [1-4]. At the heart of this controversy lies a profound disagreement over the existence of persistent infection with the Lyme spirochete, *Borrelia burgdorferi*, and the ability of this persistent infection to cause chronic symptoms in patients who are untreated or undertreated for the initial spirochetal disease. Although the Infectious Diseases Society of America (IDSA) maintains that there is no "credible scientific evidence" for persistent infection with *B. burgdorferi* following 2-4 weeks of antibiotic therapy [3], a growing number of animal and human studies provide evidence for persistent infection as a cause of chronic symptoms in Lyme disease patients, thereby disputing the IDSA point of view [5] (**Tables 1** and **2**).

Review

A recently published monkey study by Embers *et al.,* provides the best animal evidence for persistent infection as a model of chronic Lyme disease [6]. The study was conceived as an animal counterpart to the human trial by Klempner *et al.,* that was published in 2001 [7], and the monkeys were treated with a regimen of intravenous ceftriaxone followed by oral doxycycline that was identical to the protocol used in the human trial. The results of this study showed that three-quarters of the monkeys failed treatment, and these animals had evidence of persistent infection in various tissues at necropsy using culture, immunofluorescence and polymerase chain reaction (PCR) techniques [6]. Equally important, the study showed that 25% of treated monkeys cleared their infection, thereby demonstrating antibiotic efficacy in some animals. This finding contradicts the negative treatment results reported by Klempner *et al.,* that IDSA cites to support its belief that antibiotics are not effective in treating patients with persistent Lyme disease symptoms [8]. Although the monkey study was designed and conducted with the approval and funding of the National Institutes of Health, curiously it took a dozen years for the study to see the light of day while the IDSA continued its campaign to discredit the persistent infection theory of chronic Lyme disease [9].

In another recently published study, Bockenstedt *et al.,* present a mouse model of *B. burgdorferi* infection that on the surface appears to contradict the monkey study [10]. Following infection, the mice were treated with subcutaneous ceftriaxone or doxycycline administered in drinking water. The authors arrive at the conclusion that non-infectious spirochetal "debris" gets deposited around the joints of these mice, and instead of being cleared by the reticuloendothelial system this "debris" is responsible for persistent inflammation in mouse tissues [10]. The "debris", which contained both DNA and protein particles, could not be cultured, transmitted to other mice via ear transplants or to ticks that were allowed to feed on the mice (xenodiagnosis). This novel theory of non-infectious persistence of *B. burgdorferi* "debris" including the presence of DNA is highly speculative and contradicts previous experimental results. For example, Malawista *et al.,* showed that *B. burgdorferi* DNA is rapidly cleared from culture-negative ear and bladder tissues of mice following prompt antibiotic treatment [11], and Lazarus *et al.,* demonstrated that DNA from dead spirochetes is routinely cleared from mouse skin within several hours [12]. Furthermore the study methods of Bockenstedt *et al.,* may have been insufficient to rule out persistent spirochetal forms of *B. burgdorferi* , since ear transplants are often negative following antibiotic treatment, and using an insufficient number of animals for xenodignosis may fail to demonstrate transmissible infection [13,14]. Of greater importance, there appear to be two alternative mechanisms of *B. burgdorferi* persistence that merit consideration in these mice.

In his Commentary on the mouse study, Alan Barbour proposes the alternative hypothesis that cell-wall deficient L-forms, or cysts, may be responsible for *B. burgdorferi* persistence in these animals [15]. He notes that these cystic structures,

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Table 1. Evidence for Persistent Infection in Animal Models of Lyme Disease*.

Study/Year/ Reference	Animal Origin	Persistence of *B. burgdorferi* Shown by	B. burgdorferi Detection**	Sample Source
1. Rodents				
Preac-Mursic *et al.,* 1990 [39]	Gerbils	Culture, Histology	6 months	Joints, Skin, Spleen
Duray & Johnson, 1986 [40]	Hamsters	Culture, Histology	9 months	Spleen, Kidney, Eye
Goodman *et al.,* 1991 [41]	Hamsters	Culture, Histology	3 months	Heart, Bladder
Schmitz *et al.,* 1991 [42]	Hamsters	Culture, Histology	16 months	Synovium, Spleen
Moody *et al.,* 1990 [43]	Rats	Culture,Histology	12 months	Spleen, Kidney, Joints
Sonnesyn et al, 1994 [44]	Guinea Pigs	Culture, Histology	16 weeks	Bladder, Heart, Spleen, Joints, Muscles
Malawista *et al.,* 1994 [45]	Mice	Culture, PCR	60 days†	Ear, Bladder
Moody *et al.,* 1994 [46]	Mice	Histology	90 days†	Joints, Heart
Bockenstedt *et al.,* 2002 [47]	Mice	PCR, Xenodiagnosis	12 weeks†	Joints, Bladder
Hodzic *et al.,* 2008 [48]	Mice	PCR, Histology, Xenodiagnosis	12 weeks†	Joints, Heart
Yrjänäinen *et al.,* 2010 [49]	Mice	PCR	30 weeks†	Joints
Barthold *et al.,* 2010 [50]	Mice	PCR, Histology, Xenodiagnosis	12 weeks†	Joints, Heart, Muscle
Bockenstedt *et al.,* 2012 [10]	Mice	PCR, Histology	12 weeks†	Joints
2. Dogs				
Straubinger *et al.,* 1997 [51]	Dogs	PCR, Histology	3-6 months†	Skin, LN, Joints
Straubinger, 2000 [52]	Dogs	PCR	500 days†	Skin, Muscle, Joints
3. Monkeys				
Roberts *et al.,* 1995 [53]	Monkeys	Culture, PCR, Histology	6 months	Joints, Nerve
Roberts *et al.,* 1998 [54]	Monkeys	Culture, PCR, Histology	46 months	Nerve
Pachner *et al.,* , 2001 [55]	Monkeys	Culture, Histology, PCR	3 months	Brain, Nerve, Heart
Cadavid *et al.,* 2004 [56]	Monkeys	Culture, Histology, PCR	32 months	Heart
Miller *et al.,* 2005 [57]	Monkeys	PCR	3 months	Brain, Nerve, Heart, Muscle, Skin, Bladder
Embers *et al.,* 2012 [6]	Monkeys	Culture, Histology, PCR, Xenodiagnosis	6-12 months†	Skin, Heart, Bladder, Joints, Tendon, Spleen
4. Horses				
Chang *et al.,* 2005 [58]	Ponies	Culture	5 months†	LN, Joints, Muscle
Imai *et al.,* 2011 [59]	Horses	Histology, PCR	1-4 years†	Brain, Nerve

*PCR, polymerase chain reaction; LN, lymph node.
**Time from initial infection to final positive testing point.
†Detectable *B. burgdorferi* following antibiotic treatment.

which Bockenstedt *et al.,* observed in their infected animals (Figure 2 in their study [10]), have been described as a persister mechanism employed by many bacteria, including *B. burgdorferi* [16-24]. The study authors claim that these are not true cysts because they form too fast, appearing in minutes rather than hours or days. However, Brorson and Brorson have demonstrated that cysts of *B. burgdorferi* may develop in minutes under appropriate culture conditions [25]. Thus the observation of Bockenstedt *et al.,* supports *B. burgdorferi* cyst formation in their mouse model, and this cyst formation appears to be a better explanation for spirochetal persistence compared to the "debris" that the authors postulate.

As noted above, the methods employed by Bockenstedt *et al.,* may not have been sufficient to exclude persistent spirochetal forms in their animals. Persistent viable organisms may have been hidden in biofilms, the adherent polysaccharide-based matrices that protect bacteria against the host immune system and antibiotic therapy [1]. Biofilms of *B. burgdorferi* have been demonstrated *in vitro* by Sapi *et al.,* [26]. These biofilms may take the form of "debris" on intravital microscopy, and they may contain organisms that are non-cultivable but still viable and prone to reactivation [26,27]. Biofilms of *B. burgdorferi* would also be consistent with the "amber hypothesis" proposed as a mechanism of persistent Lyme disease symptoms [28]. Persister spirochetes in biofilms could explain the experimental results of Bockenstedt *et al.,* and would offer a more plausible explanation than the "debris" hypothesis for the reasons outlined above.

Conclusions

Like most aspects of Lyme disease, the role of cysts and biofilms in persistent *B. burgdorferi* infection has been controversial [1,27,29]. However, the study by Bockenstedt *et al.,* and the open-minded commentary by Barbour may open up new vistas on this fascinating aspect of bacterial persistence. Whether chronic Lyme disease arises from persisting spirochetal forms hidden in biofilms (as suggested by the monkey study of Embers *et al.,* and the experimental work of Sapi *et al.*) or from cell wall-deficient cysts (L-forms) of *B. burgdorferi* (as suggested by the mouse study observations of Bockenstedt *et al.,* and the interpretation of Barbour), persisting forms of bacteria require treatment. To date the treatment options for these bacterial persisters are extremely limited, but their recognition dictates a more aggressive approach to eradication of Lyme disease using combination antibiotic therapy modelled on treatment regimens for tuberculosis and HIV disease [2]. The fact that *B. burgdorferi* shares resistance genes with pathogenic mycobacteria supports the need for

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Table 2. Evidence for Persistent Human Infection Following Treatment of Lyme Disease*†.

Study/Year/ Reference	Study Origin	Persistence of *B. burgdorferi* Shown by	Sample Source
Weber *et al.*, 1988 [60]	Europe	Histology	Brain, liver (Autopsy)**
Schmidli *et al.*, 1988 [61]	Europe	Culture	Synovial Fluid
Cimmino *et al.*, 1989 [62]	Europe	Histology	Spleen
Preac-Mursic *et al.*, 1989 [63]	Europe	Culture	Skin Bx, CSF
Pfister *et al.*, 1991[64]	Europe	Culture	CSF
Strle *et al.*, 1993 [65]	Europe	Culture	Skin Bx
Preac-Mursic *et al.*, 1993 [66]	Europe	Culture	Iris Bx
Haupl *et al.*, 1993 [67]	Europe	Culture	Ligament Bx
Strle *et al.*, 1996 [68]	Europe	Culture	Skin Bx
Preac-Mursic *et al.*, 1996 [69]	Europe	Culture	Skin Bx, CSF
Oksi *et al.*, 1996 [70]	Europe	Culture	CSF
-	-	PCR	Brain Bx
-	-	PCR	Brain (Autopsy)
Priem *et al.*, 1998 [71]	Europe	PCR	Synovial Bx/Fluid
Oksi *et al.*, 1999 [72]	Europe	Culture, PCR	Blood
Breier*et al.*, 2001 [73]	Europe	Culture	Skin Bx
Hunfeld *et al.*, 2005 [74]	Europe	Culture	Skin Bx
Hudson *et al.*, 1998 [75]	Australia	Culture, PCR	Skin Bx
Steere *et al.*, 1988 [76]	USA	Histology	Synovial Bx
Kirsch *et al.*, 1988 [77]	USA	Histology	LN (Autopsy)
Liegner *et al.*, 1993 [78]	USA	Histology	Skin Bx
-	-	PCR	Blood
Battafarano *et al.*, 1993 [79]	USA	Histology, PCR	Synovial Bx/Fluid
Chancellor *et al.*, 1993 [80]	USA	Histology	Bladder Bx
Nocton *et al.*, 1994 [81]	USA	PCR	Synovial Fluid
Shadick *et al.*, 1994 [82]	USA	Histology	Brain (Autopsy)
Masters *et al.*, 1994 [83]	USA	Culture	Blood
Lawrence *et al.*, 1995 [84]	USA	PCR	CSF
Bayer *et al.*, 1996 [85]	USA	PCR	Urine
Nocton *et al.*, 1996 [86]	USA	PCR	CSF

†Adapted from Reference [1].
*Except for case of Weber *et al.*, (see below), all patients received a minimum of 10 days of antibiotic therapy.
PCR, polymerase chain reaction; Bx, biopsy; CSF, cerebrospinal fluid; LN, lymph node.
**Mother treated with antibiotics for one week during pregnancy; newborn died.

this therapeutic approach [30,31]. It remains to be seen which form of *B. burgdorferi* is the true culprit in chronic Lyme disease and which form of treatment is most efficacious in clearing both forms of bacteria from patients [32-38].

List of abbreviations
PCR: Polymerase chain reaction
LN: Lymph node
Bx: Biopsy
CSF: Cerebrospinal fluid
IDSA: Infectious Diseases Society of America
ILADS: International Lyme and Associated Diseases Society

Competing interests
Raphael B. Stricker serves without compensation on the medical advisory panel of QMedRx Inc. He has no financial ties to the company. Lorraine Johnson has no conflicts to declare.

Authors' contributions
Raphael B. Stricker and Lorraine Johnson meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). Both authors made substantial contributions to the conception and design of the article and were involved in the analysis and interpretation of data. Both authors were involved in all stages of manuscript development and have approved the final version.

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