

Myths, legends and realities of relapsing fever borreliosis

S. J. Cutler

School of Health & Bioscience, University of East London, London, UK

E-mail: s.cutler@uel.ac.uk

Abstract

Relapsing fever borreliosis is often shrouded in mystery. From its discovery, it has evaded fulfilment of Koch's postulates. It has resulted in epidemic waves of infection, although it is now mostly localized to particular endemic pockets of infection. Structurally, this spirochaete breaks many paradigms for conventional microorganisms, e.g. through its segmented genomic structure. Disclosure of host-microbial interactions is revealing a plethora of mechanisms, from antigenic variation to binding of various host-derived proteins. We dispel some of the myths and explore current understanding of this much neglected area through a series of reviews within this theme section.

Our understanding of the epidemiology of relapsing fever borreliosis has been complicated, in part, by our lack of understanding of these spirochaetes, compounded by the lack of appropriate research tools with which to investigate their prevalence. Since the discovery of this spirochaete by Otto Obermeier (Fig. 1) [1], diagnostic methods have not changed significantly, with demonstration of the spirochaetes in the blood of febrile patients still providing the primary diagnostic method (Fig. 1). Historically, a plethora of animal models were explored for their ability to differentiate among borreliosis species, using differing susceptibility. The European hedgehog showed some promise; however, these studies were plagued by problems of unclear demarcation among species and lack of experimental reproducibility, through imprecise enumeration and differing routes of infection, not to mention the potential for differential virulence associated with different antigenic variants of these spirochaetes. Instead, the 'one vector-one species' concept became popular for grouping of aetiological agents of relapsing fever [2].

The advent of improved molecular tools with which to study these borreliosis species has helped to clarify our knowledge of which species are present in which environmental niches, but has also raised several questions regarding our earlier beliefs [3-6]. The dogma that *Borrelia duttonii* is truly anthropophilic has recently been questioned [7]. These studies, in keeping with numerous preceding investigations, did not establish the competence of possible extended reservoir species in being able to transmit infection to subsequent recipient hosts.

Phylogenetic investigations, reinforced by genomic sequencing, have raised the possibility that the tick-borne

spirochaete *B. duttonii* and louse-borne *Borrelia recurrentis* are indeed the same spirochaete [8,9]. What is true is that ticks conserve, and lice propagate, borreliosis; this is underscored by the epidemic waves of infection. It remains a realistic possibility that the associated reductionism accompanying louse-borne transmission represents an evolutionary bottleneck from which *B. recurrentis* cannot escape. Researchers have been able to infect lice with traditionally tick-borne species, but their role in subsequent transmission remains undefined.

Our understanding of the pathological mechanisms deployed by these elusive pathogens is only just beginning to emerge. We have now progressed from the days when new dwellings were deliberately infested with ticks to boost immunity against relapsing fever borreliosis [10]. It was thought that high levels of bacteraemia and blood-borne persistence were mediated through antigenic variation alone; however, it is now apparent that multiple immune evasion strategies are at the disposal of these spirochaetes, possibly accounting for their ability to persist in the hostile environment of the mammalian host's bloodstream. Neurotropism and invasion of other tissues provide additional sites where these spirochaetes can sequester. Interestingly, the ability to invade these sites appears to correlate with expression of variable membrane proteins. Furthermore, the complexity of host-microbial interactions and the potential for developmental pathological consequences are slowly being unravelled, e.g. the pivotal role of host chemokines, in particular interleukin-10, in the development of subsequent pathology and the mechanisms that underpin these effects.

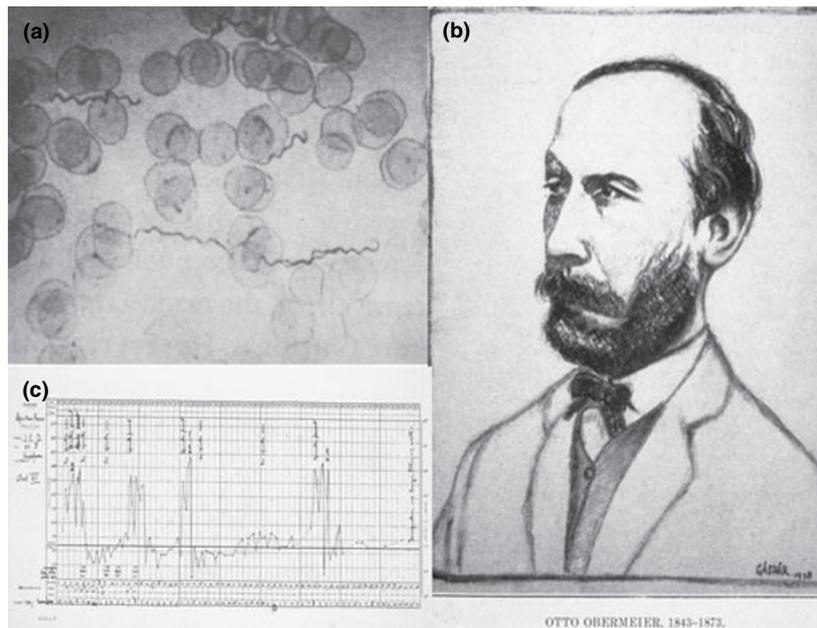


FIG. 1. (a) Line drawing depicting the spirochaetes seen in clinical samples by Otto Obermeier. (b) Otto Obermeier, who first observed relapsing fever spirochaetes in the blood of patients in Berlin [1]. (c) The temperature chart of Dutton while infected with relapsing fever spirochaetes (copyright approval granted by Liverpool School of Tropical Medicine).

References

1. Birkhaug K, Obermeier OHF. In: Moulton FR, ed. *A symposium on relapsing fever in the Americas*. Washington: American Association for the Advancement of Science. Section on Medical Sciences 1942; 7-9.
2. Felsenfeld O. Borreliae, human relapsing fever, and parasite-vector-host relationships. *Bacteriol Rev* 1965; 29: 46-74.
3. Fukunaga M, Okada K, Nakao M, Konishi T, Sato Y. Phylogenetic analysis of *Borrelia* species based on flagellin gene sequences and its application for molecular typing of Lyme disease borreliae. *Int J Syst Bacteriol* 1996; 46: 898-905.
4. Ras NM, Lascola B, Postic D *et al*. Phylogenesis of relapsing fever *Borrelia* spp. *Int J Syst Bacteriol* 1996; 46: 859-865.
5. Bunikis J, Tsao J, Garpmo U, Berglund J, Fish D, Barbour AG. Typing of *Borrelia* relapsing fever group strains. *Emerg Infect Dis* 2004; 10: 1661-1664.
6. Scott JC, Wright DJM, Cutler SJ. Typing African relapsing fever spirochetes. *Emerg Infect Dis* 2005; 11: 1722-1729.
7. McCall PJ, Hume JC, Motshegwa K, Pignatelli P, Talbert A, Kisinza W. Does tick-borne relapsing fever have an animal reservoir in east Africa? *Vector Borne Zoonotic Dis* 2007; 7: 659-666.
8. Cutler SJ, Scott JC, Wright DJM. Phylogenetic relationship between *Borrelia recurrentis* and *Borrelia duttonii*. *Int Med Microbiol* 2008; 298: 193-202.
9. Lescot M, Audic S, Robert C *et al*. The genome of *Borrelia recurrentis*, the agent of deadly louse-borne relapsing fever, is a degraded subset of tick-borne *Borrelia duttonii*. *PLoS Genet* 2008; 4: e1000185.
10. Burgdorfer W. The epidemiology of the relapsing fevers. In: Johnson RC, ed. *The biology of parasitic spirochetes*. New York: Academic Press, 1976; 191-200.