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Spirochaetes: past lessons to future directions

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Spirochaetes today are often sidelined as an interesting exception within the microbial world, yet spirochaetes have played a major role in our understanding of microbial pathogenesis. As a group, they have challenged our established understanding of microbial infections, and still have a plethora of other secrets to disclose. Within this themed issue, we examine a range of spirochaetal examples, ranging from relapsing fever, the expanding group of *Borrelia burgdorferi* sensu lato, through to *Leptospira* and the complex polymicrobial role of oral treponemes in causing periodontitis. Each of these examples provides challenges to our accepted views and thus serves to stimulate new concepts, adding to our understanding of the mechanisms of pathogenesis.

The impact of spirochaetal infections on human health became well established in Europe following the return of the conquistadores from America. Starting in 1493 in Barcelona, syphilis, which was originally called 'Spanish disease', rapidly spread throughout Europe. As such, this spirochaete was the focus of many early therapeutic efforts with mercury (with or without various local remedies), thus laying the foundations for the fight against infectious diseases. The aetiological agent '*Spirochaeta pallida*' (now *Treponema pallidum*) was discovered by the German zoologist Fritz Schaudinn in 1905. This opened the floodgates for development of diagnostics and improved arsenical therapeutics [1]. This discovery was part of 'the golden age' of German microbiological discovery of the 19th century and early 20th century. Our first review, by Wright and Boyce [2], describes some of these early milestone discoveries related to *Borrelia* that have paved the way for microbiologists of the current era. Following Ehrenberg's original recognition of the *Spirochaetae* as a new phylum (cited by Wright and Boyce) [2], the pathogenic potential of its members was first revealed by Obermeier in 1866 (cited in Wright and Boyce) [2]. To further clarify this pathogenic potential, animal inoculation was attempted, but this, unlike for many infectious agents under study at this time, proved unsuccessful, because of the host specificity of these spirochaetes. Several microbiologists subsequently engaged in self-inoculation, eventually establishing a pathogenic role for *Borrelia recurentis*, the cause of louse-borne relapsing fever.

More recently, emphasis has shifted towards another borrelial infection, that of Lyme borreliosis. Wright and Boyce [2] continue through to the current German spirochaetologists, who remain at the forefront of significant research efforts, particularly the delineation of new genospecies and the deciphering of host–spirochaete immune interactions. This theme is further expanded in relation to the many new species now recognized within the *B. burgdorferi* sensu lato complex. The review by Stanek and Reiter [3] updates our recognition of the increasing genospecies within the Lyme *Borrelia* complex. Of these, those with established pathogenicity for humans include *Borrelia afzelii*, *B. burgdorferi* sensu stricto and *Borrelia garinii* [4]; however, some of the more recently recognized genospecies, such as *Borrelia bissettii*, *Borrelia lusitaniae*, *Borrelia spielmanii* and *Borrelia valaisiana*, have been implicated as potential pathogens. As discussed by Stanek and Reiter, [3] the contribution of these new members to the clinical manifestations of Lyme borreliosis remains to be fully elucidated. Conversely, their role might be merely that of complicating the diagnosis of genuine cases through stimulation of cross-reactive serology.

The application of molecular typing to the Lyme *Borrelia* complex has not only revealed the heterogeneity between genospecies, but has, significantly, also been used to subtype within genospecies. Stanek and Reiter [3] describe how this has disclosed correlations of particular genotypes with invasive disease, and this might, in the future, yield greater insights into the pathogenici mechanisms employed by these spirochaetes.

The differential host susceptibility seen among both relapsing fever and Lyme borreliae has stimulated significant research interest. Over recent years, the interaction of these spirochaetes with various immune mediators, such as factor H and factor H-like proteins, binding of host plasminogen and subsequent hypothesized mechanisms of complement evasion have been of considerable interest [5–9]. These mechanisms are in addition to the antigenic variation (either through whole gene replacement or modulation of gene cas-

settes) for which borreliae have provided an exemplary example for many years [10,11].

Spirochaetal diversity is a theme continued by our other reviewed examples. Hartskeerl *et al.* [12] highlight the enormity of the global threat of leptospirosis. These authors describe this truly global zoonosis, which appears to be re-emerging, with notable outbreaks over recent years in Nicaragua, Sri Lanka and the Philippines. However, possible leptospirosis is often only considered as an afterthought, if indeed it is considered at all. In part, this is encouraged through its ability to clinically mimic other conditions that are generally deemed to be of greater importance for the healthcare agenda. Lack of surveillance in either human or livestock populations make it difficult to map the true extent of the problem, with the data available being a gross underestimation of the true burden of infection. Hartskeerl *et al.* [12] describe how the pathogenic serovars of *Leptospira* have now expanded to nearly 300, often showing distinct host adaptations. In their natural host, they persist with little clinical consequence (including, often, a failure to produce a serological response), and are excreted through the urine into the environment, whereby they can be acquired by 'accidental' hosts such as humans. It is here that the impact of infection becomes apparent. Despite our knowledge of acute clinical manifestations, we know almost nothing about the late consequences of infection. In the review of Hartskeerl *et al.* [12], it is proposed that 27% of human cases have long-term complaints, of which 11% were serious, and 1.3% caused the patients to remain permanently unfit to work.

Hartskeerl *et al.* describe infection control that has been targeted to specific hosts, such as cattle and companion animals; however, our simplistic view of control of zoonoses by reducing infection in the reservoir host may be somewhat short-sighted. The dynamics that influence which leptospires reside in which host species are both complex and currently poorly understood. Alarmingly, reduction of a targeted serovar in a particular host species through vaccination might encourage selective pressure and adaptation of other serovars to these hosts. Similarly, populating new areas with non-indigenous species, as is common practice in farming, could result in changes in both the distribution and disease patterns of leptospirosis.

Hartskeerl *et al.* [12] go on to discuss the complexity of detecting cases, arising from lack of suspicion, resulting in delays (and thus failure to collect optimal samples), the considerable complexity of many of the diagnostic methods for leptospirosis, and the lack of any reporting system through which data can be collated and shared. To further complicate diagnostics, the questions that need answers for human and livestock cases are not necessarily concordant. For the first, a genus diagnosis will suffice, but for the latter, it is essential to determine serovar, as this impacts on the likely success of vaccinational control measures, which are usually serovar-specific. The failure of current vaccines to cross-protect and produce long-term immunity is an area that needs to be urgently addressed. Although potential improvements through the introduction of subunit vaccines are likely to be significant for human and companion animals, they are too expensive for control of infection among livestock.

This review reminds us of the threats resulting from increasing globalization, and, indeed, the popularity of many highly endemic areas as tourist attractions where visitors frequently partake in high-risk exposure activities, such as watersports, jungle treks and caving, must be remembered when a returning traveller presents with fever [12–14].

Our last spirochaetal example, reviewed by Visser and Ellen, [15] is one that sounds far less 'exotic', but remains hugely significant, namely the oral treponemes. Their clinical significance is suggested through their prominent role in the aetiology of the polymicrobial infection of periodontitis. Research efforts have largely focused on the cultivable members of the oral treponemes, with *Treponema denticola* having a pivotal role in our initial insights into potential virulence mechanisms and host evasion strategies. Virulence mechanisms that have been elucidated for *T. denticola* and some of the less well-known oral treponemes are reviewed [15]. These spirochaetes constitute approximately 1% of the normal subgingival flora, but, remarkably, this shifts to 50% in the plaque of periodontitis cases. More than 70% of oral *Treponema* phylotypes remain uncultivatable, with only ten species having been cultivated. Of these, *T. denticola* has been best studied, revealing a wealth of factors that enable penetration of host tissues and host evasion [15]. Our understanding of the role of these spirochaetes in periodontal disease has benefited hugely from genomic sequencing efforts coupled with the ability to use directed genetic manipulation to study the contributions of various gene products to pathogenesis. Spirochaetes in general have been particularly resilient to genetic manipulation, which is considered commonplace for many other microorganisms.

Oral treponemes need to rapidly outgrow competing microorganisms within the diseased periodontal pocket. To facilitate this, they need a comprehensive means of detecting shifts in the dynamics of their local environment. Through genomic sequencing efforts, a range of two-component regulatory systems have been disclosed that are likely to bring about this sensory ability. These spirochaetes dedicate approximately 2% of their whole genomes to chemotaxis genes, including those encoding chemoreceptors that enable rapid responses to environmental changes, particularly attr-

actants such as serum and glucose, which are increased in diseased periodontal pockets [15]. Within this polymicrobial environment, there is ample opportunity for genetic exchange, both between *Treponema* species and between genera. This capacity for lateral gene flow is further supported by the detection of transposases and bacteriophages in oral treponemes.

Visser and Ellen [15] go on to describe the significant research efforts that have focused on the mechanism of adhesion of these spirochaetes to the extracellular matrix, which is essential for the initiation of pathogenesis. Here, binding to collagen, fibronectin and laminin is important, but the ability to bind to these appears to be heterogeneous among oral treponemes. Host damage appears to be mediated through a variety of proteases, such as dentilisin, which is able to degrade extracellular matrix proteins, and a range of host immune mediators, which thus provide the dual functions of host damage and immune evasion. Despite treponemal activation of toll-like receptors (TLR2 and TLR4), it is thought that they may also induce immune tolerance. Interference with the typical host response to lipopolysaccharide of other periodontal bacteria has been demonstrated in the presence of glycolipids and/or phospholipids of oral treponemes [15].

Thus, from the insights given within these reviews, we can see that, far from spirochaetes being a rather neglected microbial 'special case', they actually still carry the torch forwards in our expanding appreciation of the microbial world and in deciphering host–microorganism interactions.

Transparency Declaration

The author has no conflicts of interest to declare.

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