

Preface

Remarkably, ten years have elapsed since the publication of ***Borrelia: Molecular Biology, Host Interaction and Pathogenesis***. By 2010, Lyme disease (Lyme borreliosis) had become the prototype of an ‘emerging infectious disease’. Once an obscure cause of arthritis in Southeastern Connecticut, in the span of three decades, Lyme disease was by then well recognized as the most prevalent vector-borne illness in the United States and Europe and a growing threat to global health. The first edition reflected two currents impacting the *Borrelia* field. One was the evolution of the study of pathogenic *Borrelia* from an arcane branch of microbiology to the mainstream of bacterial pathogenesis and clinical/translational research. The other was the advent of an unprecedented sociologic phenomenon – a coalition of self-proclaimed authorities accusing the biomedical community of conspiring to conceal the ‘real truths’ about the diagnosis and treatment of Lyme disease and the insidious nature of its etiologic agent. The book was the product of experts who pooled their energies and intellects to create the first state-of-the-art reference work covering the myriad, interlaced facets of the enzootic disorders caused by pathogenic *Borrelia*. The editors and authors had other intentions as well. We sought to showcase the extraordinary progress on a multitude of scientific and clinical fronts stemming from well-controlled, carefully executed, peer-reviewed research. And we conceived of the book as a vehicle for pushing back against the sophistry and shibboleths proffered to the public and legislators by our ‘Lyme literate’ detractors.

So, what, other than the title of the second edition, has changed during the last decade? Plenty. In reviewing the 24 chapters that comprise the volume, the editors have been impressed not just by the amount of new information generated by our colleagues but also its scope, technical virtuosity, and ingenuity. In fact, it should be evident to readers familiar with the first edition that the second edition is much more than an update; it is a reboot, and, in many instances, a re-evaluation of ideas and concepts prevalent at the time of the first edition. We now have much greater insight into the intricate

ecologic factors that sustain *Borrelia* species in the wild and the environmental forces driving their alarming expansion throughout the Northern Hemisphere. With the availability of next-generation sequencing, genomic sequences for numerous *Borrelia* strains and species, sophisticated methods for genetic manipulation, transcriptomics, and structural data for many virulence-related proteins, our understanding of borrelial evolutionary biology, physiology, pathogenicity, and immune evasion has increased exponentially. Genomics and genetics have brought us to the cusp of unraveling the great mystery of how different species and strains of Lyme disease spirochetes elicit such varied clinical outcomes; indeed, it has become increasingly clear that the answer lies to a large extent in the evolutionary and immunologic mismatch between the spirochete and its incidental, reservoir-incompetent human host. In 2010, experimentation with ticks was limited to a few laboratories. Now, many investigators study the tick phases of the enzootic cycle and our coverage of vector biology and *Borrelia*-tick interactions has expanded to provide more guidance for this experimental approach. In addition, live imaging of spirochetes was just coming online a decade ago: the second edition contains an expansive treatment of the options available to investigators who need to track live spirochetes and evaluate gene expression *in situ* in ticks and mice. The importance of motility and chemotaxis for borrelial invasiveness has long been appreciated; however, cryoelectron microscopy, in combination with genetics and structural biology, has provided stunning visual insights into the workings of the flagellar motor that enables these serpentine organisms to migrate from the bite site to distal tissues where they inflict damage. At the time of the first edition, the signaling molecule c-di-GMP and the transcription factor BosR had only just been discovered in *B. burgdorferi* and there was essentially no mention of the stringent response. In the ensuing ten years, genetic and biochemical dissection of the molecular mechanisms modulating gene expression as the spirochete traverses its enzootic cycle has revealed hitherto unrecognized complexities and, considering the small size of the

borreliar genome, a surprisingly sophisticated network of regulatory pathways. The composition of the field has changed as well. The author list contains the names of many gifted, enthusiastic early career investigators willing to take on the challenge of *Borrelia* for their life's work. Unfortunately, one thing has not changed – the Lyme Wars continue, led by individuals who espouse flawed studies purporting to show that Lyme disease spirochetes in humans adopt a persistent state impervious to antimicrobial therapy that causes chronic symptomatology. In this edition, three authorities offer their analysis of these and other data as well as their perspectives on the chronic Lyme disease controversy that continues to ensnare our field.

This book was completed in the shadow of COVID-19. It seems ironic that one newly emergent infectious disease would nearly derail our efforts to bring to fruition ten years of progress studying another. Everyone's research and personal lives were upended by the pandemic; some of the authors served on the front lines. We, the editors, wish to express our deepest gratitude to our colleagues for their perseverance and commitment.

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