Editorial

Jekyll and Hyde: Bugs with Double Personalities that Muddle the Distinction between Commensal and Pathogen

"Good and evil are so close as to be chained together in the soul."

– Robert Louis Stevenson, *The Strange Case of Dr. Jekyll and Mr. Hyde*.

In 1886, the Scottish author Robert Louis Stevenson published *The Strange Case of Dr. Jekyll and Mr. Hyde*, creating one of the most enduring and widely recognized allegories for the dualistic good-*versus*-evil nature of humankind. The story centers around the highly respected Dr. Henry Jekyll, who creates a serum that unleashes his more selfish and vile attributes with murderous consequences. The embodiment of good and evil within a single individual sparks the human imagination, and no doubt fuels our fascination with real-life villains like Jack the Ripper who began to stalk the alleys of Whitechapel just 2 years after publication of Mr. Stevenson's novel. Jekyll-and-Hyde has also come to shape our views of microbes, which were entering the limelight as germ theory gained broader acceptance in the 1880s on the heels of pioneering work by John Snow, Luis Pasteur, Robert Koch, and many others. The microbe hunters of the nineteenth century made causal links between microbial colonization of the host and disease, giving rise to the concept of pathogens [1]. It was appreciated that these "bad" microbes were distinct from the multitude of seemingly innocuous microorganisms that were replete within the environment [2,3]. However, the definition of a pathogen has always been on shaky ground, as it was realized early on that erstwhile pathogens can also colonize and persist within a host without eliciting overt disease [4].

Over the past 13 decades researchers have come to appreciate that the virulence of microbial pathogens is plastic, being shaped by numerous variables within the microbe, the host, and the environment at large [3]. These include the gain or loss of genes by the microbe, changes in the regulation of virulence and fitness factors, and the genetic background and health status of the host. The composition and metabolic activities of the microbial communities that comprise the host microbiota can also impact host susceptibility, providing resistance to pathogen colonization and growth [5]]. Antibiotic-mediated disruption of the microbiota can reduce intermicrobial competition, allowing for easier colonization of the host by infiltrating pathogens or facilitating the outgrowth of potentially dangerous indigenous members of the microbiota known as pathobionts. Furthermore, there is a growing appreciation that some microbes, including pathobionts, can modify the onset and progression of numerous diseases that were not traditionally associated with infections (e.g., Refs. [6–9]).

This Special Issue of the *Journal of Molecular Biology* explores the tenuous dichotomy of microbes that occupy the gray zone between overtly virulent pathogens and innocuous commensals. Articles within this issue reveal how the interplay between host and microbial factors can lead to disease, while also highlighting potential avenues for therapeutic intervention. In their original research article, Le *et al*. [10] examine the normally innocuous skin-associated gram-positive commensal *Staphylococcus epidermidis* and its ability to colonize medical implants by forming dense surface-attached bacterial aggregates known as biofilms. The authors find that the development and restructuring of biofilms by *S. epidermidis* is regulated by bacterial-derived amphipathic, alpha-helical peptides known as phenol-soluble modulins. The secretion of phenol-soluble modulins allows *S. epidermidis* cells within a biofilm to act in concert to facilitate expansion into new host environments.

This primary research article is complemented by a cadre of six reviews and one perspective that cover a broad spectrum of would-be pathogens. In their detailed review, Armistead *et al*. [11] consider the double life of the gram-positive microbe group B streptococcus. These bacteria are carried asymptomatically within the gastrointestinal or vaginal tracts of many women, but can disseminate and cause life-threatening invasive infections in pregnant women and neonates. Host and bacterial factors that control the ability of group B streptococcus to cause disease are discussed. Kao and Kline [12] examine the pathogenic potential of another gram-positive microbe, *Enterococcus faecalis*. These organisms are normal components of the healthy human gut microbiota. However, *E. faecalis* is highly adaptable and can disseminate from the gut to colonize numerous host niches and cause a number of diseases, including urinary tract and bloodstream infections. The success of *E. faecalis* as an

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opportunistic pathogen is in part attributable to its ability to dampen host immune responses. Immune suppression by *E. faecalis* can also enhance host colonization by other microorganisms, promoting the development of polymicrobial infections. The review by Wiles and Guillemin [13] provides a refreshing look at the use of model systems to delineate the "thin line between pathogenic and mutualistic relationships," highlighting roles for inflammation and changes in the physical architecture of bacterial communities within the gut as moderators of disease. Shifts in the structure of microbial communities can also promote inflammation and disease within the oral cavity, as described in a very enlightening review of the oral microbiome and its impact on periodontal disease by Valm [14]. Shaler *et al*. [15] return us to the gut to consider adherent-invasive *Escherichia coli*. Like uropathogenic strains of *E. coli*, these genetically and phenotypically heterogenous microbes lack any definitive sets of virulence factors, and they resemble in many ways commensal *E. coli* isolates. However, unlike commensal *E. coli* strains, adherent-invasive *E. coli* can bind and invade the intestinal mucosa and can act as a pathobiont, exasperating gut inflammation in individuals who are genetically susceptible to irritable bowel disorders like Crohn's disease. The final review article in this issue, penned by Denham *et al*. [16], takes us into the realm of eukaryotic pathogens, delivering an in-depth primer detailing how ubiquitous environmental fungi can adapt to host niches where they can either persist asymptomatically or cause severe systemic infections.

A common theme among many opportunistic pathogens is that the factors that allow for their asymptomatic carriage also often expedite their dissemination and virulence. The capacity of many of these normally mild-mannered microbes to modulate host inflammation appears to be central to their ability to cause disease. An especially stark example of this is relayed in a *Perspective* by Seifert [17], in which he proposes that sexually transmitted human-restricted pathogenic *Neisseria* species arose from a commensal ancestor, in part, by gaining the ability to induce robust neutrophil recruitment into the genital tract. It is hypothesized that the association of *Neisseria* with infiltrating neutrophils facilitates bacterial transmission between human hosts during sexual contact.

The collection of manuscripts in this special edition highlights the wide degree of interactions that individual microbial species can have with their hosts. Much of the work described in these pages builds on observations made with model reference strains, coupled with cutting-edge research on primary clinical and environmental isolates. The use of model reference strains provides a baseline for comparison of results both within and between laboratories over time, and can greatly simplify the dissection of molecular and genetic factors that can impact virulence. However, the view that model strains can offer has limited scope, as the genetic and phenotypic versatility of a microorganism can easily become lost when studied within the isolation of a petri dish. Furthermore, reference strains that were, in some cases, collected decades earlier may not accurately reflect the spectrum of pathogens that are currently in circulation. Consequently, model reference strains may give us only fleeting snapshots of the diversity and adaptability of pathogen populations that face ever-changing selective pressures within real-world environmental and clinical settings. When coupled with robust infection models and clinical data, the use of low-passage clinical or environmental isolates to validate and extend findings based on model reference strains is a powerful approach that can enhance translational relevance as well as our understanding of intra-species pathogen diversity. We hope that the articles presented in the special issue will inspire you the reader to delve deeper into the heterogeneity and dualistic Jekyll-and-Hyde potential of the microbes that you study.

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