BOOK REVIEWS

The Unveiling of Pathogenesis

Molecular Genetics of Bacterial Pathogenesis. A Tribute to Stanley Falkow. VIRGINIA L. MILLER, JAMES B. KAPER, DANIEL A. PORTNOY, and RALPH R. ISBERG, Eds. ASM Press, Washington, DC, 1994. xl, 529 pp., illus. $79; to American Society for Microbiology members, $65.

Humans have led a precarious life of coexistence with pathogenic microbes through much of our evolutionary history. But it is only in the last few decades that we have begun to get insight into the complex interactions between these microbes and their host. Stanley Falkow has probably contributed more than anyone else to the development in this field by bringing into it rigorous, molecular genetic methods. Thus it was a fitting tribute that his former disciples produced this compilation of succinct reviews on the occasion of his 60th birthday.

The book begins with a wonderful autobiographical chapter by Falkow. He comes from an orthodox Jewish family of limited resources. His father never finished grammar school, and his mother had only an elementary-school education. At age 11, Falkow was fascinated by Paul de Kruif's book *Microbe Hunters* and decided to become a bacteriologist. He went to the University of Maine and received almost personal tutoring as one of the only two bacteriology majors in his class. He entered graduate school at the University of Michigan, but had to withdraw owing to illness and ended up doing much of his Ph.D. work at Walter Reed Army Institute of Research. Walter Reed was an exciting place at that time, and such scientists as Lou Baron, Sam Formal, and Richard Finkelstein were trying to apply the newly developed methods of bacterial genetics to pathogenic bacteria, and more specifically to the study of mechanisms of pathogenesis. Falkow demonstrated that a bacterial plasmid was indeed a DNA molecule separate from the chromosomal DNA by taking advantage of the differences in buoyant density of chromosomal DNA among various bacterial species. This work led to Falkow's well-known characterization, at the molecular level, of R plasmids, the extrachromosomal pieces of DNA that confer antibiotic resistance on the host bacterium and are often transmitted efficiently among bacterial species. It is remarkable that he chose this path rather than staying in the "pure science" area of molecular biology. Falkow's interest in what is happening in the real world, from transmissible antibiotic resistance to microbial pathogenesis, perhaps is characteristic of scientists trained in the best traditions of microbiology, whose founders, Pasteur, Koch, Winogradsky, and Beijerinck, never strayed far away from real-life problems. Falkow's main area of interest remained the R plasmids while he was a faculty member at Georgetown University (1966–1972) and to a large extent after he moved to the University of Washington (1972–1981).

His emphasis, however, began to shift to the study of microbial pathogenesis during his tenure at the University of Washington, and this has been almost the sole focus of his flourishing laboratory at Stanford University since 1981. The ability of certain bacteria to cause severe diseases has always fascinated microbiologists, especially because of its apparent specificity. It requires only a few cells of *Shigella* sp., for example, to produce severe diarrheal disease in humans, but the presence of billions or even more of some of its relatives can do no harm. For that matter, *Shigella* cells present in billions cause no infections in most other animals. What could be the basis of this pattern? I remember that the Ph.D. thesis topic that was given to me in 1956 in Japan was the biochemical analysis of bacterial pathogenesis. But very little had been known in this area (and I eventually chose a topic only remotely connected to pathogenesis), mainly because of the complexity of the problem. Falkow had the brilliant idea of simplifying the study of this area by utilizing the then-emerging methods of molecular genetics. His co-workers have thus introduced many mutations into bacterial genomes, and analysis of sometimes thousands of these mutants has very often led to a clear-cut analysis of the pathogenic process, through the identification of the genes involved.

One of Falkow's many admirable traits is his ability as a teacher. He has won awards for outstanding teaching many times from students both at the University of Washington and at Stanford. But even more important, he has been remarkably successful in training graduate students and postdoctoral fellows who continue to make significant contributions to the understanding of bacterial pathogenesis. This is reflected in the fact that practically all of the reviews contributed to this volume by his former disciples are of excellent quality, a rare feat for a compilation of this sort. Most of the reviews are also concise and up-to-date and will be pleasurable and profitable reading for any microbiologist.

Part 1 of the book contains several "retrospective" reviews that summarize Falkow's earlier studies of R plasmids and bacterial toxins. The remaining parts deal with the current status of research on bacterial pathogenesis. The discussion begins with the first step in host-bacteria interaction, that is, macromolecules that cause the adhesion of bacteria to specific host cells. Several pathogenic bacteria have the unusual ability to grow inside host cells, and the molecular requirement for this mode of existence is discussed in the next part of the book. Other pathogens live outside host cells but must produce various macromolecules to avoid the attack of phagocytes or antibodies or to cause injury to the phagocytic cells; these processes are described in the next part of the book. Finally, the discussion turns to the intricate regulation of the virulence genes in various bacteria, as well as the other practical uses of DNA methods, such as the identification of pathogens that are difficult to cultivate in the laboratory.

Considering that real progress in this field has occurred only in the last two decades, the amount of knowledge accumulated is impressive. For example, we now know how the pathogenic bacteria subvert, to their advantage, the normal regulatory signals and processes of host cells. *Listeria*, a pathogen that multiplies inside host cells, spreads from cell to cell by literally injecting itself into a new host cell by activating the polymerization of actin bundles. Entry of other pathogens into the host cell utilizes changes in the host's cytoskeleton structure induced by the binding of the bacteria to surface receptors that presumably sense the state of the extracellular environment. The study of the molecular mechanisms of bacterial pathogenesis thus can contribute to our understanding of the working of our own cells. Not only that, such study is now producing data that clarify the way bacterial cells, even nonpathogenic ones, work, for example by elucidating the pathway through which macromolecular virulence factors, polysaccharides and proteins, are exported across the cell membrane and the cell wall. The breadth of the coverage of this book and the excellent quality of most of the chapters make the book "must" reading for those interested in medical microbiology; it can even be used profitably as a textbook at a graduate level.

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