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Preface

In January 1962, the International Union against Tuberculosis declared its victory over tuberculosis (TB), "*If I had tuberculosis. . . this idea formerly terrifying, no longer makes anyone tremble. . . antibiotics have appeared, sanatoria have disappeared; as far as the public is concerned, the problem is solved, the disease has been conquered*" (Waksman 1964, p. 1). In the 1960s and 1970s, we, with our bias on the industrialized world, thought that the problem could and would be solved soon in the rest of the world.

Accordingly, research and development (R&D) on new diagnostics, drugs, and vaccines for TB dwindled from the 1970s on. This decline in interest in TB is reflected in the low number of publication hits in PubMed on TB, with numbers in the low thousands of hits annually in the years before 1990; this was followed by an increase leading to a doubling of publications on TB in 1995, 2 years after the WHO global emergency call for TB in 1993 (WHO 1993). The latest figures for 2013 are much more than 10,000 publications. The output of publications on TB follows the funding situation. In the 1980s, there was <US$10 million annually spent on TB (Kaufmann and Parida 2007). The beginning of this century has witnessed a clear increase, with ~US$500 million in funding since 2010 (Moran et al. 2013; WHO 2013). This increased financial investment in R&D activities for TB intervention measures is now starting to show signs of success. In recent years, we have witnessed introduction of a new rapid TB diagnostic test, the GeneXpert MTB-RIF Assay, the clinical evaluation of a dozen new TB drugs, and a portfolio of new TB vaccines in different stages of clinical trials.

However, this is only one side of the coin. TB remains a leading cause of illness and death worldwide and there is a worrying rise in the number of cases of multidrug-resistant (MDR)-TB and extensively drug-resistant (XDR)-TB in Asia, Eastern Europe, and Southern Africa. We are currently experiencing the emergence of drug-resistant strains of *Mycobacterium tuberculosis* that are totally resistant to all known first- and second-line TB drugs. Clearly, the misconception in the last quarter of the last century about TB, and the complacency that followed, has led to our failure to control this disease.

TB has been with humankind for tens of thousands of years. Originally, it was feared as phthisis, describing the wasting form of this disease, or scrofulosis, characterized by severe lymph node swellings. For centuries, these diseases were viewed as totally independent until the pathologist and anatomist Franciscus Deleboe Sylvius (1614–1672) became intrigued by the similarities of the "hidden" tubercles in the lungs of phthisis patients and the distracting swollen lymph nodes of scrofulosis patients (Deleboe 1679). In 1834, Johann Lukas Schönlein (1793–1864) used the term "tuberculosis" (tuberkulose) for the first time (Schönlein 1841) to describe diseases characterized by the formation of tubercles, as the characteristic granulomatous lesions were referred to, under a single heading. Even though he recognized the differences between scrofulosis and phthisis, the two polar forms of TB, he considered similarities more important and grouped them together in his scheme, analogous to the botanical system of Carl von Linné (1707–1778).

At the time when Schönlein introduced the term "tuberculosis," the anatomist Jakob Henle (1809–1885) was lecturing on anatomy at the University of Göttingen, Germany. He thought intensively about contagious diseases and postulated, without any experimental evidence, three crucial features of such an elusive type of illness: (1) the presence of a living organism (*contagium animatum*) in all affected tissues; (2) the isolation of the *contagium animatum* from these tissues; and

(3) experimental analysis of the *contagium animatum* outside of the body. Thus, the soil was prepared for his student Robert Koch (1843–1910), who ultimately proved the etiology of TB by elegant experiments published in 1882 (Koch 1882). True, Koch was not the first to transmit TB in experimental animal models, but his experiments were the first to provide formal proof of Henle's principles by the identification of *M. tuberculosis* in affected tissues in patient material, isolation and culture of *M. tuberculosis* in pure form as single colonies on solid plates, and elicitation of a similar disease in a large variety of experimental animals.

Although we now know the genome sequence of *M. tuberculosis* today, we remain puzzled by the tricks this pathogen plays. We hope that this book brings the reader closer to the most recent insights into at least some of the tricks and to new ways of harnessing these for novel intervention measures. There have been a number of textbooks on different aspects in the field of TB published in the past decade, notably, the *Handbook of Tuberculosis* (Kaufmann and Britton 2008; Kaufmann and Rubin 2008; Kaufmann and van Helden 2008), comprising three volumes that appeared in 2008, the treatise *Tuberculosis—A Comprehensive Clinical Reference* (Schaaf and Zumla 2009), and *Tuberculosis* (Zumla and Schaaf 2011). The book you have in hand is distinguished by being up to date and more concise, allowing researchers, clinicians, field-workers, students, patients, advocates, and the public ready access to state-of-the-art information about specific topics of interest, as well as more distant areas, across the entire field of TB.

We have divided the book into three sections of more than 10 chapters each: Section 1. Vaccines, Immunology, Host Cells, and Biomarkers, edited by Stefan H.E. Kaufmann; Section 2. Drugs and Biology of Tuberculosis, edited by Eric Rubin; and Section 3. Clinical Tuberculosis, edited by Alimuddin Zumla.

Section 1 covers all aspects of the host response to *M. tuberculosis*, ranging from basic research to medical application. The chapters by Srinivasan et al. and by Deretic describe the important role of cellular processes in host immunity—notably, in cell death caused by apoptosis and autophagy. Similarly, cell-autonomous effector mechanisms contribute to host defense against *M. tuberculosis*, as described by MacMicking. These mechanisms are probably the outcome of the intimate cross talk between pathogen and myeloid cells and participate in host immunity, as discussed by Lugo-Villarino and Neyrolles. Mayer-Barber and Barber provide an introduction to the highly intertwined cross talk between the innate and acquired immune responses in TB. Immunity against TB is mediated by T lymphocytes and effected by mononuclear phagocytes. In addition to conventional $CD4^+$ and $CD8^+$ T cells, nonclassical T cells participate in acquired immunity against TB, as discussed in chapters by Lindestam Arlehamn et al. and by De Libero et al. T cells stimulate various effector functions in macrophages, as described by MacMicking. These interactions are complex and in the in vivo setting, they are focused on the granuloma as the tissue site of both protection and pathology in TB (Pagán and Ramakrishnan). A concept that has long been championed by Casedevall and colleagues suggests that B lymphocytes and their products, antibodies, play a greater role in acquired immunity than thus far appreciated (Achkar et al.). TB is a highly complex disease; hence, in vitro studies need to be complemented by appropriate experimental animal models and human studies. The spectrum of the major animal models for TB with all their advantages and disadvantages is discussed in four chapters, which focus on mice (Cooper), guinea pigs (Clark et al.), zebrafish (van Leeuwen et al.), and nonhuman primates (Scanga and Flynn). The immune response in TB patients is covered by Walzl et al., with an emphasis on biomarkers indicative for disease and latent infection. This chapter is complemented by a description of state-of-the-art biomics approaches toward a better understanding of molecular mechanisms underlying TB (Maertzdorf et al.). Finally, the chapter by Andersen and Kaufmann describes how to best harness our increasing understanding of the immune response to *M. tuberculosis* for the development of novel vaccines against TB with an emphasis on those that have already entered the clinical pipeline.

Section 1 therefore spans the whole spectrum from basic cell biology and immunology to applied areas of biomarkers as a basis for novel diagnostic measures and vaccine candidates for prevention of this major health threat.

Section 2 describes the broad spectrum of the many unique biological characteristics of *M. tuberculosis* in a series of chapters. The cell wall of mycobacteria is made up of structures found in few other pathogens (Jackson and Alderwick et al.). Both this unusual structure and specific metabolic requirements (Warner) have led to cell division processes and regulation that, again, differ from those found in many other bacteria (Uhía et al.). Many of these critical processes are targeted by existing drugs, several of which, because of their molecular mechanisms of action, narrowly target *M. tuberculosis* (Chakraborty and Rhee). However, there is a substantial need for new antibiotics that are more rapidly effective and able to act against drug-resistant bacteria. These are being developed using newer approaches (Schnappinger and Mdluli et al.) with important pharmacologic considerations kept in mind (Davies). Given what we know about the mechanisms of host resistance described in other sections, therapies that influence the host–pathogen relationship can also potentially be manipulated (Tobin). But the genome is not just useful for drug discovery—it is also an important tool for tracking disease (Niemann and Supply) and understanding the evolution of the organism (Behr). All of these aspects of pathogen biology remain rich areas of inquiry with potential impact on disease in the very near future.

Section 3 contains 11 elegantly written chapters by a global authorship, providing the latest up-to-date information that will be useful to physicians and allied health-care workers dealing with TB worldwide. The epidemiology chapter (Glaziou et al.) shows that although there has been a steady, slow decline in total numbers of drug-sensitive TB, the emerging and alarming problems of MDR-TB and XDR-TB globally are worrying. The growing pipeline of new TB diagnostics and several evaluations of the GeneXpert MTB/RIF and urine LAM assays (Lawn) now enable missed TB cases to be detected at points of care. The highly illustrated chapter on imaging in TB (Bomanji et al.) includes PET scanning for localizing extrapulmonary TB and its potential use as a biomarker of disease activity. The chapter on TB treatment and drug regimens (Sotgiu et al.) details the current TB drug pipeline and recommended drug regimens for drug-sensitive and drug-resistant TB. With an estimated 2 billion people living with latent TB infection, the importance of screening for latent TB in migrants and in those who are immunosuppressed is highlighted in the chapter on latent TB (Muñoz et al.). Five chapters provide state-of-the-art coverage of clinical aspects of TB in adults (Loddenkemper et al.); children (Marais and Schaaf); management of drug-resistant TB (Seung et al.); TB–HIV coinfection (Bruchfeld et al.); and TB and comorbid conditions (Bates et al.). The final chapter (Nardell) covers the importance of infection control and measures to reduce transmission in the community and in health-care facilities.

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