Tuberculosis
PATHOGENESIS, PROTECTION, AND CONTROL
To the generations of scientists and physicians who kept the spirit of inquiry and research on tuberculosis and leprosy alive—and especially to Karel Styblo, Philip D’Arcy Hart, Dennis Mitchison, T. Ramakrishnan, Annik Rouillon, Dixie Snider, Sriram Tripathi, Jacinto Convit, S. K. Noordeen, and Tore Godal.
"Il bacillo non è ancora tutta la tuberculosis."
("The bacillus is not yet all there is to tuberculosis.")

G. Bacelli, ca. 1882
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Preface

Today, as it has been for centuries, tuberculosis remains the leading cause of death in the world from infectious disease. Approximately a third of the world's population has been infected with *Mycobacterium tuberculosis* and is at risk for developing disease. Globally, tuberculosis accounts for almost 3 million deaths annually and one-fifth of all deaths of adults in developing countries. Tuberculosis is a reemergent problem in many industrialized countries. In the modern world of global interdependency, rapid transportation, expanding trade, and changing social and cultural patterns, tuberculosis in any country is a threat to people in every country. In the context of infectious diseases, there is no place in the world from which we are remote and no one from whom we are disconnected.

Current knowledge of evolutionary biology and genetics makes clear that what is at stake in the battle against infectious diseases is the survival not only of human and animal hosts but of the pathogens themselves, a confrontation that cannot be taken lightly. Human interventions serve as selections for genetic mutations, adaptations, and migrations that enable pathogens to survive. While societies traditionally deal with epidemics and outbreaks of infectious diseases in an episodic or discontinuous fashion, the evolutionary process of the pathogens is a continuous one. That elementary truth demands vigilance rather than complacency in applying the tools we have and a continuing scientific effort both to anticipate new threats from infectious pathogens and to develop new tools with which to protect the public health. In the case of tuberculosis, the demise of the disease in the industrialized world has been taken for granted and its persistence in developing countries largely ignored. Support for research dwindled, and the expertise of a generation of scientists and clinicians knowledgeable about tuberculosis was lost.

The current global reemergence of tuberculosis can be attributed to several factors. The compromise of immune mechanisms in human immunodeficiency virus (HIV)-infected individuals that leads either to reactivation of old tuberculous infections or to increased susceptibility to new infection is a major contributor to the increasing incidence of tuberculosis. Other factors are social dislocations, poverty, overcrowding, and a failure to invest in public health infrastructures. Particularly ominous is the emergence of multidrug-resistant tubercle bacilli. In the preantibiotic era, the case fatality rate of untreated tuberculosis was about 50%. With appropriate treatment, cure rates greater than 85% can now be achieved in both HIV-positive and immunocompetent individuals with conventional tuberculosis, even in developing countries. However, the case fatality rates of multidrug-resistant tuberculosis in the United States are about 40% for immunocompetent individuals and over 80% for HIV-infected individuals. Thus, tuberculosis has emerged as a major and devastating global threat to health, and many of the tools currently available for rapid diagnosis, prevention, and treatment are woefully lacking.

The aim of this book is to provide in one volume an overview of the current state of knowledge about tuberculosis and a critical appraisal of the exciting new molecular, immunological, and epidemiological ap-
Preface

Proaches to understanding and controlling tuberculosis. The emphasis is on research. The authors hope to make existing knowledge and new avenues of research accessible to a new generation of researchers and clinicians. We hope to encourage scientists, clinicians, and students in many disciplines to undertake research on tuberculosis and want to facilitate the rapid generation of new knowledge, insights, and interventions.

Distinguished scientists knowledgeable in major areas of tuberculosis research and control have contributed critical reviews of current understanding and their thoughts on new approaches to each area. For most chapters in this book, I asked world experts to write collaboratively in order to provide balance, multiple perspectives on key issues, and critical delineation of the areas of consensus and contention. The authors were asked to be provocative rather than comprehensive. Our hope is that most chapters will be read with interest by anyone concerned with tuberculosis. Our intention is for the book to serve both as a challenge to scientists knowledgeable about aspects of tuberculosis and as a useful introduction to those with expertise in other disciplines who may wish to apply their knowledge and skills to the problem of tuberculosis. We hope, too, that the book will make accessible to scientists and students in developing countries, where the needs are greatest, the excitement of the new approaches to pathogenesis, resistance, and control.

Acknowledgments

Because of current interest in the problem of tuberculosis, the limited number of experts on the disease are always in great demand. I wish to express my deep appreciation to each of the authors for giving so much of their valuable time and effort to this volume. I am particularly indebted to William R. Jacobs, Jr., and Patrick Brennan for providing continuing advice and wisdom in the planning of this book. Such a project would not have been possible to contemplate without the continuing support of my research from the Howard Hughes Medical Institute. Words cannot repay the dedication and heroic efforts of my secretary, Sandra Glass, for seeing to it that everything got done. I am very grateful for the commitment and care given to this project by the editorial staff of the American Society for Microbiology, particularly Patrick Fitzgerald, Susan Birch, and Marie Smith, whose contributions have been truly outstanding. Finally, I wish to express my deep appreciation for the patient understanding and support of my wife, Irene, and daughter, Inae, for the many hours I was preoccupied with this book.
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