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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Contributors

Åse Bengård Andersen
Mycobacteria Department, Sector for Biotechnology, Statens Seruminstitut, DK-2300 Copenhagen, Denmark

W. Emmett Barkley
Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815

Peter F. Barnes
HMR 904, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033

Joseph H. Bates
Department of Medicine, University of Arkansas School for Medical Sciences, John L. McClellan Memorial Veterans' Hospital, 4300 West 7th Street, Little Rock, AR 72205

Gurdyal S. Besra
Department of Microbiology, Colorado State University, Fort Collins, CO 80523

Barry R. Bloom
Howard Hughes Medical Institute and Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461

Patrick J. Brennan
Department of Microbiology, Colorado State University, Fort Collins, CO 80523

Jeanne E. Burlein
MedImmune Inc., 35 West Watkins Mill Road, Gaithersburg, MD 20878

John Chan
Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467

Delphi Chatterjee
Department of Microbiology, Colorado State University, Fort Collins, CO 80523

Stewart T. Cole
Unité de Génétique Moléculaire Bactérienne, Institut Pasteur, 28, rue du Docteur Roux, 75724 Paris Cedex 15, France

Frank M. Collins
The Trudeau Institute, Saranac Lake, NY 12983

M. Joseph Colston
National Institute for Medical Research, Mill Hill, London NW7 1AA, England

Nancy D. Connell
Department of Microbiology and Molecular Genetics, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103

Jack T. Crawford
Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333
x Contributors

**Thomas M. Daniel**
Center for International Health, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106

**Arthur M. Dannenberg, Jr.**
Department of Environmental Health Sciences, School of Hygiene and Public Health, The Johns Hopkins University, 615 North Wolfe Street, Baltimore, MD 21205-2179

**Elaine O. Davis**
National Institute for Medical Research, Mill Hill, London NW7 1AA, England

**Katharine A. Downes**
Center for International Health, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106

**Philip Draper**
National Institute for Medical Research, Mill Hill, London NW7 1AA, England

**Jerrold J. Eliner**
Division of Infectious Diseases, University Hospitals of Cleveland, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106-4984

**Joseph A. Falkingham III**
Department of Biology, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061

**Paul E. M. Fine**
London School of Tropical Medicine and Hygiene, Keppel Street, London WC1E 7HT, United Kingdom

**Brigitte Gicquel**
Unité de Génétique Mycobactérienne, Département de Bactériologie et Mycologie, Institut Pasteur, 25, rue du Dr. Roux, 75724 Paris Cedex 15, France

**Robert C. Good**
National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C-09, 1600 Clifton Road, N.E., Atlanta, GA 30333

**Christophe Guilhot**
Unité de Génétique Mycobactérienne, Département de Bactériologie et Mycologie, Institut Pasteur, 25, rue du Dr. Roux, 75724 Paris Cedex 15, France

**Mark S. Hanson**
MedImmune Inc., 35 West Watkins Mill Road, Gaithersburg, MD 20878

**Graham F. Hatfull**
Department of Biological Sciences, University of Pittsburgh, Pittsburgh, PA 15230

**Leonid B. Heifets**
National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206

**Philip C. Hopewell**
University of California, San Francisco, and Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, CA 94110

**Juraj Ivanyi**
MRC Tuberculosis and Related Infections Unit, Clinical Sciences Centre, London W12 ONN, United Kingdom
Contributors

William R. Jacobs, Jr.
Howard Hughes Medical Institute, Albert Einstein College of Medicine, Bronx, NY 10461

Vivian Jonas
Gen-Probe Incorporated, 9880 Campus Point Drive, San Diego, CA 92121

Stefan H. E. Kaufmann
Department of Immunology, University of Ulm, Albert-Einstein-Allee 11, D-89070 Ulm, Germany

Arata Kochi
Tuberculosis Programme, World Health Organization, CH-1211, Geneva 27, Switzerland

George P. Kubica
2323 Walton Place, Atlanta, GA 30338

Sebastian Lucas
Department of Histopathology, University College London Medical School, London WC1, United Kingdom

Ruth A. McAdam
Department of Microbiology and Immunology, Albert Einstein College of Medicine of Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10461

David N. McMurray
Department of Medical Microbiology and Immunology, Texas A&M University Health Science Center, College Station, TX 77843-1114

Robert L. Modlin
Division of Dermatology, 52-121 CHS, University of California Los Angeles School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90024

Andrew R. Moss
Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, CA 94110

Christopher J. L. Murray
Harvard Center for Population and Development Studies, Harvard School of Public Health, 9 Bow Street, Cambridge, MA 02138

Ann Marie Nelson
Division of AIDS Pathology M003B, Armed Forces Institute of Pathology, Washington, DC 20306-6000

Hiroshi Nikaido
Department of Molecular and Cell Biology, c/o Stanley/Donner Administrative Services Unit, 229 Stanley Hall, Berkeley, CA 94720

Shawn Offutt
MedImmune Inc., 35 West Watkins Mill Road, Gaithersburg, MD 20878

Ian M. Orme
Mycobacteria Research Laboratories, Department of Microbiology, Colorado State University, Fort Collins, CO 80523

Colin Ratledge
Department of Applied Biology, University of Hull, Hull HU6 7RX, United Kingdom

Mario Raviglione
Tuberculosis Programme, World Health Organization, CH-1211, Geneva 27, Switzerland
Contributors

Graham A. W. Rook
Department of Medical Microbiology, School of Pathology, University College London Medical School, 67-73 Riding House Street, London W1P 7LD, United Kingdom

Thomas M. Shinnick
Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333

Peter M. Small
Division of Infectious Diseases and Geographic Medicine, Beckman Center, Room 251, Stanford University, Stanford, CA 94305-5425

Douglas R. Smith
Collaborative Research Inc., 1365 Main Street, Waltham, MA 02154

Peter G. Smith
Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Dixie E. Snider, Jr.
Office of the Director, Centers for Disease Control and Prevention, Atlanta, GA 30333

C. Kendall Stover
Department of Tuberculosis and Infectious Diseases, PathoGenesis Corp., 201 Elliott Avenue, West, Seattle, WA 98119

Charles O. Thoen
Department of Microbiology, Immunology, and Preventive Medicine, Iowa State University, Ames, IA 50011

Jelle Thole
Department of Immunohaematology and Blood Bank, University Hospital, 2300 RC Leiden, The Netherlands

Jan D. A. van Embden
Unit Molecular Microbiology, National Institute of Public Health and Environmental Protection, P.O. Box 1, 3720 BA, Bilthoven, The Netherlands

Lawrence G. Wayne
Tuberculosis Research Laboratory (151), Department of Veterans Affairs Medical Center, 5901 East Seventh Street, Long Beach, CA 90822

Paul R. Wheeler
Department of Clinical Sciences, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom

Douglas B. Young
Department of Medical Microbiology, St. Mary’s Hospital Medical School, Norfolk Place, London W2 1PG, United Kingdom
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-
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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