

# Preface

Dengue is an enormous problem. It is both local and global. In its behavior, dengue most nearly resembles the intimate and ubiquitous respiratory diseases that make life miserable for human beings on an equal opportunity basis and whose treatments fill the pages of standard medical textbooks. In hundreds of millions of households on earth there lives a stealthy insect. It is happy in its domesticity, rearing its generations on human blood. Dengue, the commensal virus that this insect harbors, is perfectly adapted to a generational cycle — man to mosquito to man. It evolved from a common ancestor virus, no doubt one harbored by subhuman primates and transmitted by jungle mosquitoes. A period of isolation and the accumulation of a succession of small mistakes in RNA transcription resulted in the evolution of four distinct serotypes. Serial infection with one or more types is now the fate of perhaps 2.5 billion people who live in tropical and subtropical countries. This book describes aspects of the dengue story in a format designed for students at various levels. It is not a comprehensive presentation of contemporary dengue research, but rather a compact, accessible and authoritative description of major biological features in the complex story of dengue as a human disease.

*Dengue: Overview and History.* This chapter, written by the Editor, reviews the history of the term dengue, the viruses associated with the dengue syndrome and the history of dengue hemorrhagic fever. Statistics are provided showing the impact of dengue in terms of morbidity, mortality and cost during the past 40 years.

*The Infections Agent.* This chapter, written by highly productive arbovirologists Drs. David Beasley and Alan Barrett, University of Texas Medical Branch, Galveston, describes the genetic and amino acid sequences of the four dengue virus types and their genotypes, the structure of the entire virus and of key surface proteins. Descriptions are provided of the structure of gene products along with a summary of the current understanding of mechanisms of entry of dengue into cells, uncoating, transcription of RNA, translation of RNA, the composition and function of specified proteins, and the respective contribution of viral and host enzymes and replicative machinery to viral replication.

*Epidemiology.* In this authoritative chapter, the Editor describes the bioeconomics of dengue mosquito vectors together with many of the elements that contribute to influencing the transmission of dengue viruses, including the mosquito, factors in the environment and the complex controls contributed by the host.

*Resistance to Infection.* US Army physicians, led by Dr. David Vaughn, who spent more than two decades conducting research on dengue vaccines, have written this chapter. They summarize knowledge of the antibody responses to dengue infection and the role of antibodies in protection against dengue infections. The current status of dengue vaccine development is reviewed.

*Clinical Features of Dengue.* Written by Dr. Jeremy Farrar, Director, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam, this chapter describes the signs and symptoms of mild and severe dengue diseases, including unusual manifestations.

*Treatment.* Principles and details of treating children and adults with mild and severe dengue syndromes are given by Dr. Bridget Wills, an acknowledged world authority who conducts clinical research on dengue illnesses at the Oxford Clinical Research Unit, Ho Chi Minh City, Vietnam.

*Pathogenesis.* This is the beginning of the story of severe dengue disease. The Editor describes the role that dengue antibodies play in governing the

outcome of infection by neutralizing or enhancing dengue virus infections, providing controls for the major afferent mechanism that governs the intensity of dengue infections and the severity of dengue diseases.

*Elimination of Infection.* This chapter, by Dr. Alan Rothman, Professor of Medicine, University of Massachusetts Medical Center, a world authority on immune responses to dengue infection, summarizes the rich contemporary research experience on the cellular immune response to dengue virus infection. Emphasis is on the kinetics and specificity of the cell-mediated responses to dengue infection and the role these play in elimination of dengue-virus-infected cells and in producing the pathophysiological changes of dengue diseases.

*Pathophysiology.* The Editor describes how and when immunological responses to dengue infections generate chemokine and cytokine responses. Evidence concerning the role that cytokines play in the pathophysiological responses to dengue infection is presented and discussed. New findings that provide amazing insights into the compelling story of antibody-dependent enhancement of dengue infection are presented.

*Diagnosis.* Diagnosis of recent primary or secondary dengue and other flavivirus infections is presented. Included are serological methods, virus isolation, detection of viral antigen by various methods, and the use of PCR and molecular probes to detect and quantitate viral nucleic acid in blood or infected tissues. This chapter has been written by Prof. Timothy Endy along with dengue virologists who served as virologists at the Armed Forces Research Institute of the Medical Sciences in Bangkok, Thailand, and at the Walter Reed Army Institute of Research, Washington, D.C.

*Mosquito Control.* Control of mosquito vectors is covered in three chapters. Chapter 11 provides a seminar on classical methods of the control of dengue vector mosquitoes. It has been written by an authority with a specialist experience or perspective — the late Dr. Normal Gratz, Chief of Vector Control, World Health Organization. This chapter assesses the strengths and weaknesses of contemporary vector control, including the

proper and improper use of insecticides and other mechanical or chemical antilarval methods. In Chap. 12, Dr. Brian Kay, Director, Entomology, Queensland Institute of Medical Research, Brisbane, Australia, a world authority, discusses biological control of mosquito larvae. And in Chap. 13, Drs. Peter Winch and Elie Leontsini, Associate Professors, Department of International Health, Johns Hopkins School of Hygiene and Public Health, review methods for community-based programs to effect the control of dengue mosquito vectors.

*Controversies.* Unique to this series are discussions on major controversies in dengue pathogenesis and diagnosis. Dr. Jose Rigau-Perez, formerly with the CDC Dengue Laboratory in Puerto Rico, critiques the usefulness of the current WHO case definition of dengue hemorrhagic fever as an epidemiological and clinical management tool, with rebuttal by the Editor. David Morens, Assistant to the Director, NIAID, NIH, and the Editor present and discuss the pros and cons, respectively, of four major controversies relating to the causation of severe dengue disease.

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