Preface

Early Scientific Progress

Scientific research on dengue has a long and rich history. The literature has been touched by famous names in medicine – Benjamin Rush, Walter Reed and Albert Sabin, to name a very few – and has been fertile ground for medical historians (Kuno 2009; Rigau-Perez 1998; Kuno 2007; Ashburn and Craig 2004; Pinheiro and Corber 1997; Papaevangelou and Halstead 1977; Halstead 1974; Ehrenkranz et al. 1971). The advances made in those early investigations are all the more remarkable for the limited tools available at the time. The demonstration of a viral etiology for dengue fever (DF), the recognition of mosquitoes as the vector for transmission to humans and the existence of multiple viral variants (serotypes) with only partial cross-protection were all accomplished prior to the ability to culture and characterize the etiologic agent.

Research on dengue in this period was typically driven by circumstances. Epidemics of dengue created public health crises, although these were relatively short-lived in any one location, as the population of susceptible individuals quickly shrunk. Military considerations became a major driving force for research. With the introduction of large numbers of nonimmune individuals into endemic areas, dengue could cripple military readiness, taking more soldiers out of action than hostile fire.

Progress on several fronts was significant and engendered optimism that the disease could be controlled. The campaign against Aedes aegypti accomplished the elimination of this mosquito from much of the Western hemisphere by 1970. Transmission of DENV and the number of cases were sharply reduced. Working in the Pacific, Dr. Sabin and others isolated dengue viruses (DENV) by serial intracerebral passage in suckling mice and in 1945 reported that the adapted virus was attenuated in humans and could induce protective immunity against the virulent parent virus (Sabin and Schlesinger 1945). Development of an effective vaccine was anticipated to follow.

Unfortunately, by the late 1950s, the picture was beginning to become cloudier. A new disease, dengue hemorrhagic fever (DHF), was recognized in Thailand and
the Philippines. The isolation of new DENV serotypes was a focus of early speculation about the pathogenetic basis for this disease but the ability of all DENV serotypes to cause DHF was soon established. Gains in mosquito control in the Western hemisphere were fleeting, as *Aedes aegypti* returned once mosquito control programs were abandoned.

Over the course of the last half of the twentieth century, the global epidemiologic situation worsened, leading some to apply the term “pandemic.” Comprehensive data obtained from active surveillance systems were lacking but a steady increase in reported cases of DF and DHF, as well as the number of countries affected, was documented. This steady increase was further punctuated by spikes associated with large epidemics, often involving multiple countries. Although an increase in attention to the disease and a corresponding increased sensitivity for reporting through passive surveillance systems may have contributed to these trends, there is little doubt that the geographic range and intensity of DENV transmission increased. The first occurrences of epidemic DHF in new regions were particularly striking, as in the case of the 1981 epidemic of DHF in Cuba, the first recorded in the Western hemisphere.

Armed with tools for serologic diagnosis and in vitro culture of DENV, scientific progress in understanding and managing dengue disease continued, led by Halstead, Nimannitya, Rosen, Gubler and Bhamarapravati, among others. The importance of plasma leakage as a key feature of DHF facilitated the development of clinical management guidelines that successfully reduced dengue-related morbidity and mortality. Recognition of the predominant infection of monocytic cells, the increased risk for DHF associated with circulation of multiple DENV serotypes and secondary DENV infections and the association of DHF with enhanced cytokine production in vivo guided development of disease models, diagnostic tests and candidate therapeutics. Isolation and in vitro propagation of DENV strains generated an array of viral strains that have been tested as candidate live, attenuated, vaccines.

Despite the overall increase in knowledge during this period, controversies at times overshadowed progress. The early dichotomy between the “viral virulence” and “immune sensitization” models was particularly acute. Accumulated data supported both models. Although some debate continues, a more complex and nuanced picture has evolved incorporating both models and suggesting that human and vector population dynamics, viral evolution and individual and herd immunity all influence the risk for mild versus severe disease.

**Dengue at the Start of the Twenty first Century**

**The Epidemiologic Situation**

As the first decade of the twenty first century reaches its end, the epidemiologic trends in dengue disease have given little reason for optimism. Countries that have been endemic for dengue for decades in Southeast Asia, Oceania and the Americas
have experienced an increased number of cases (WHO 2007). The number of countries with established endemic DENV transmission has also expanded, with outbreaks of dengue recorded for the first time in Bhutan, Timor-Leste and Nepal (Pandey et al. 2008), the return of dengue to Hawaii after several decades (Effler et al. 2005) and the first outbreaks of DHF recorded in countries that had previously observed only (or predominantly) DF, such as Peru and Brazil (Siqueira et al. 2005). Hyperendemic transmission of all four serotypes has become even further widespread, for example, with the reintroduction of DENV-3 into South America.

With a greater public sensitivity toward emerging infectious diseases, the recent epidemics of dengue have attracted a great deal of attention in the media. Images of tent hospitals being set up in major urban centers, such as in Rio de Janeiro in Brazil in 2008, have been aired on international news programs. The possibility that the global climate will further expand the range of DENV transmission has heightened interest in dengue outbreaks. This increased visibility of dengue as a global health problem has had both positive and negative effects, however. On the positive side, funding for scientific research on dengue from both governmental and nongovernmental sources has surged in the past decade and research papers have been accepted into high-impact, broad-based medical journals. Unfortunately, attention (and resources) has frequently been misdirected at highly visible but ineffective or unproven control strategies (Castle et al. 1999).

**Recent Scientific Progress**

In contrast to the epidemiologic situation, scientific knowledge on DENV and dengue disease has expanded considerably. Many new investigators have initiated research on DENV and dengue disease during the last decade and new centers for research on tropical or emerging virus diseases have been established by universities and private foundations. These investigators have brought with them new areas of expertise and recently-developed technologies in medicine, virology, molecular biology and immunology. Through their efforts, new insights have been gained into the virion structure, the DENV life cycle, the natural history of infection in humans (and mosquitoes) and the pathogenesis of different manifestations of dengue disease. The remaining chapters of this volume highlight some of these recent advances.

**Over the Horizon**

In reviewing recent advances, it is fair to ask how these have or will translate into improved global health. Practical applications of recent observations are still theoretical and uncertain. Progress still faces major obstacles, including the lack of a faithful and tractable animal model (although recent developments leave reason for optimism here, as well). The greater depth of understanding of DENV protein
structure and function and the complex interactions between the virus and its invertebrate and vertebrate hosts (discussed in the chapters by Paranjape and Harris, Munoz-Jordan, Rico-Hesse and Scott and Morrison) suggest that rational design of effective antiviral drugs may be possible for DENV, as it has been for HIV and HCV (Modis et al. 2003). Combination antiviral and immunomodulatory therapies have generated particular interest (Diamond et al. 2002), given current understanding of dengue disease pathogenesis (discussed in the chapters by Rothman and Stephens). Clinical trials of these drugs will require detailed investigation of viral and host immune response kinetics, based on observations in the natural history of dengue disease (reviewed by Endy and colleagues, Trung and Wills and Srikiatkhachorn and Green).

Most public health professionals would agree that vaccines are likely to be the ultimate solution to control dengue-related morbidity and mortality. As reviewed by Durbin and Whitehead, several of the leading vaccine candidates are the result of advances in molecular biology, using viral strains generated through recombinant DNA technology. Several of the vaccine candidates involve construction of “chimeric” flaviviruses using gene segments from different DENV strains and/or the yellow fever virus 17D vaccine strain. Additional mutations are also being inserted into the DENV genomes in an effort to generate further attenuated strains, as described by Blaney et al.

Summary

Dengue and dengue hemorrhagic fever, which assumed pandemic proportions during the latter half of the last century, have shown no indication of slowing their growth during this first decade of the twenty first century. Challenges remain in understanding the basic mechanisms of viral replication and disease pathogenesis, in clinical management of patients and in control of dengue viral transmission. Nevertheless, new tools and insights have led to major recent scientific advances. As the first candidate vaccines enter large-scale efficacy trials, there is reason to hope that we may soon “turn the corner” on this disease.

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References

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