Human Herpesviruses

This comprehensive account of the human herpesviruses provides an encyclopedic overview of their basic virology and clinical manifestations. This group of viruses includes human simplex type 1 and 2, Epstein–Barr virus, Kaposi’s Sarcoma-associated herpesvirus, cytomegalovirus, HHV6A, 6B, and 7, and varicella-zoster virus. The viral diseases and cancers they cause are significant and often recurrent. Their prevalence in the developed world accounts for a major burden of disease, and as a result there is a great deal of research into the pathophysiology of infection and immunobiology. Another important area covered within this volume concerns antiviral therapy and the development of vaccines. All these aspects are covered in depth, both scientifically and in terms of clinical guidelines for patient care. The text is illustrated generously throughout and is fully referenced to the latest research and developments.

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Human Herpesviruses
Biology, Therapy, and Immunoprophylaxis

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Diseases caused by the human herpesviruses were recognized by the earliest practitioners of medicine. Hippocrates, Celsus, Herodotus, Galen, Avicenna and others described cutaneous lesions typical of infections caused by herpes simplex viruses (HSV) 1 and 2, and varicella-zoster virus (VZV). ‘Herpes,’ the family name of these viruses, is traced to the Greek term for lesions that appeared to creep or crawl over the skin. Among the duties of John Astruc, physician to King Louis XIV, was to understand the diseases of French prostitutes, in Latin, the ‘Puellae publicae,’ which led to his description of herpes genitalis. Distinguishing between genital herpes and syphilis was an obvious concern in this social context as it is now. The modern scientific investigation of HSV can be dated to the work of Gruter, who first isolated the virus and demonstrated its serial transmission in rabbits. During the 19th century, experiments in human subjects showed that HSV and VZV could be transmitted from fluid recovered from HSV and VZV lesions. Demonstrating that Koch’s postulates were fulfilled was important but arguably the truly revolutionary discovery about the herpesviruses was made by Andrews and Carmichael in the 1930s who showed that recurrent herpes labialis occurred only in adults who already had neutralizing antibodies against HSV. Since our modern understanding of all of the human herpesviruses revolves around latency and reactivation as established facts of their biology, it is important to remember that these concepts are far from obvious and to appreciate the creative insights of Doerr who proposed that recurrent HSV was not an exogenous infection but resulted from stimuli to the cell that caused the endogenous production of a virus-like agent and of Burnet and Williams who perfected the notion that HSV persists for life and “remains for the most part latent; but under the stimulus of trauma, fever, and so forth it may at any time be called into activity and provoke a visible herpetic lesion.”
Although their relationships to HSV and VZV were by no means appreciated, the more subtle members of the herpesvirus family began to be discovered after an interval of many hundreds of years. The first of these was human cytomegalovirus (HCMV), which was initially associated with human disease through the detection of enlarged cells containing unusual cytoplasmic inclusions in the urine and organs of infants who were born with signs of intrauterine damage that had been attributed to syphilis. In the early 1950s, HCMV as well as VZV were the first human herpesviruses to be isolated in cultured cells. Within a decade, Epstein-Barr virus (EBV) particles were found in Burkitt’s lymphoma cells and EBV was shown to be associated with mononucleosis. By the mid-1990s, three more human herpesviruses, HHV-6A, HHV-6B and HHV-7, which share a tropism for T lymphocytes, were discovered and the etiologic agent of the unusual vascular skin tumor called ‘Kaposi’s sarcoma, first described in 1872, was identified as “Kaposi’s sarcoma-associated herpesvirus (KSHV, HHV8). These four new human herpesviruses were identified during the early years of the human immunodeficiency virus (HIV) epidemic because these viruses cause aggressive disease in HIV-infected patients or were discovered during intensive research on human T cell biology. In each instance, discovery of the human herpesviruses paralleled technologic progress, illustrated by animal models for HSV, cell culture methods for VZV and CMV, the cultivation of B lymphocytes for the detection of EBV and of T lymphocytes for identification of HHV-6 and 7, and differential nucleic acid detection for revealing the existence of HHV8.

Molecular genetics methods demonstrate that the human herpesviruses share a common ancestor. However, each virus has evolved to occupy a particular niche during millions of years of co-evolution with their primate, and eventually human, host. Understanding the nuances of the adaptive strategies that have allowed all of these viruses to be transmitted efficiently and to persist so successfully in the human population, and often in the same individual, constitutes a fascinating enterprise. At the same time, infections caused by these ubiquitous viruses create a substantial global burden of disease affecting healthy and immunocompromised patients and among people living in developed and developing countries. Because of their serious and potentially life-threatening consequences, the human herpesviruses are medically important targets for basic and clinical research.

The goal of this book is to describe the remarkable recent progress towards elucidating the basic and clinical virology of these new pathogens, in conjunction with a summary of the many new insights about their epidemiology, mechanisms of pathogenesis and immune control, approaches to clinical diagnosis and the recognition of the clinical illnesses that result from primary and recurrent herpesvirus infections across the age spectrum. All of the herpesviruses have common genes, structures, replication strategies and mechanisms of defense against the host response but each virus also has unique properties that allow it to find its particular ecological refuge. An unexpected outcome of research over the past decade is the finding that the human herpesviruses have devised many different ways to achieve the same biologic effect, as illustrated by their unique strategies for down-regulation of major histocompatibility complex proteins. Functional similarities exist among these viruses even when they do not share similar genes or infect similar tissues. Each chapter of the book explores these viral themes and variations from the virologic and clinical perspectives. The contributions of the many distinguished authors highlight the basic science aspects of the field, emphasizing the comparative virology of the human herpesviruses and virus-host cell interactions, and the significant clinical developments, including antiviral drugs and vaccines, that are essential for the best practice of medicine in the 21st century. The concluding chapter illustrates how therapies for cancer may emerge from these advances in basic and clinical research, to create a fundamentally new era in the complex history of the relationship between the human herpesviruses and their hosts.

The editors are deeply grateful for the generosity of the authors who have shared their comprehensive knowledge of the human herpesviruses. We hope that this book will serve as a resource for investigators and physicians, and most importantly, that it will motivate a new generation of students and trainees to address the many unresolved questions about these herpesviruses as agents of human disease. Since the genomes of all of these viruses have been sequenced, it is obvious that many genes exist for which functions have not been identified and we now understand that most herpesviral proteins can be expected to have multiple functions. Basic research on the human herpesviruses also reveals fundamental facts about human cellular biology, including surface receptors, metabolic pathways, cell survival mechanisms, malignant transformation as well as innate antiviral defenses. In the clinical realm, every improvement in diagnostic methods expands the spectrum of clinical disorders that are recognized as being caused by these viruses. Clinical interventions exist that could not have been imagined fifty years ago but the need for better therapeutic and preventive measures has become even more apparent as the burden of herpesvirus disease is defined with precision. Given that four human herpesviruses have been discovered in the past 15 years, are there others?