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To our wives, April T.G. Hamatake and Jane W.S. Fang-Lau, for their unfailing support, and our children, Kyle Hamatake, David Hamatake, Grace (Ling-Ling) Lau, Gillian (Gi-Gi) Lau, and Gabrielle (Ching-Ching) Lau, for keeping us rejuvenated.
Despite the availability of an effective vaccine, there are still 400 million people, worldwide who are chronically infected with hepatitis B virus (HBV). For them, the vaccine, as currently applied, has no value. Given the possible consequences of HBV infection, the number of those chronically infected with HBV presents an enormous public health challenge. For example, the major etiology of hepatocellular carcinoma (HCC) is chronic infection with HBV. Although fifth in cancer incidence, worldwide, HCC/liver cancer is the third leading cause of cancer death. The high mortality associated with HCC arises because the disease is often detected late and is unresponsive to treatment. The number of deaths caused by HCC is expected to rise over the next 20 years. Those chronically infected with HBV have a life risk of death to HCC of between 10 and 25%. Even the limited efficacy of drugs for the treatment of chronic HBV helps underscore the point that this disease is responsive to therapy. Drugs that target the polymerase (e.g., hepsera and lamivudine) and interferon alpha represent two distinct strategies and show that both conventional antiviral and immunotherapeutic approaches can be used in management. However, the current inventory of therapeutics is inadequate. Interferon alpha is of limited value, only parenterally available, and fraught with adverse reactions. The polymerase inhibitors are undermined by either a high frequency of resistance or, in the case of hepsera, additional concerns about toxicity. Other areas of concern also remain. There is still no reliable means of predicting disease outcome for chronic carriers, making early detection of liver disease and decisions about drug efficacy, as well as who should be treated and for how long, difficult. Moreover, tests for HBV DNA levels (and other markers) are often of dubious quantitative value. Because HBV patients are becoming more sophisticated and more demanding about these markers and many follow their viremia (DNA) levels like investors follow the Dow Jones Industrial values, it is essential that meaningful lab values be provided. The current vaccines are effective, but they are expensive, and escape mutants may be a problem waiting to happen.

Thus, without a doubt, more work needs to be done in all of the key areas of the management of HBV.

The good news is that there have been important advances. A clearer picture about the kinds of drugs that can be effective, their pathogenesis, and the development of research tools should facilitate the discovery process.

It is the matter of research tools that these volumes address. In an almost encyclopedic fashion, Hamatake and Lau have assembled a comprehensive, “how to” guide for the study of HBV. It is worth noting that many of the methods described will have value in the study of other viruses and liver diseases in general, despite being highly focused upon HBV.

This is a very practical resource, in every respect. In more than 40 chapters, leaders in the field who have “been there” have contributed step-by-step “programmed” approaches,
telling the readers how to reproduce their findings. It is something of a users guide for do-it-yourselfers.

It is not an overstatement to write that nearly every aspect of HBV research is covered, section by section, virus detection through vaccine and drug development. Thus, *Hepatitis B and D Protocols* is likely to become as essential a resource to those studying HBV as was the fabled Maniatis series (published by Cold Spring Harbor Press) for Molecular Biology. It is certainly going to get a great deal of attention in the Hepatitis B Foundation labs, and, because of its value, we hope it is used in labs throughout the world. The more it is used, the more likely HBV research will be advanced.

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*Baruch S. Blumberg, MD, PhD*
Nobel Laureate, 1976
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The identification of the “Australian antigen” by Dr. Blumberg, which was subsequently recognized to be the hepatitis B virus surface antigen, marks the discovery of an important pathogen for liver diseases. The virus was the first hepatitis virus discovered almost four decades ago. Despite the magnitude of the infection and the significant efforts by the scientific community, hepatitis B continues to be a global health problem affecting more than 350 million people worldwide. Many scientific milestones in basic and clinical research on hepatitis B had profound impact on this viral infection in the history of medicine: hepatitis B virus vaccine was introduced two decades ago; interferon alpha was approved for the treatment of chronic hepatitis B and two other antiviral drugs have also been approved; liver transplantation under high dose hepatitis B immunoglobulin coverage can now be offered to patients with end-stage hepatitis B related liver disease. These advances have also introduced new paradigms in our understanding of the fundamental concepts of viral infection in general. Certainly, more work looms ahead of us in order to ultimately conquer this viral infection. To equip the basic and clinical investigators with all the available tools is of utmost importance in this quest. As illustrated in this book, the marriage between basic science and clinical medicine is critical.

In the last few decades, we have witnessed the groundbreaking progress and the introduction of new clinical paradigms in hepatitis B virus infection. The next decade must underscore further application of our knowledge to translational research, bridging basic science and clinical medicine, and to capitalize on our understandings to conquer this viral infection. Undoubtedly, with all the scientific efforts contributed by many dedicated scientists and with our willingness to share knowledge, the common goal of improving human health by eradicating this virus can be achieved in this millennium.

T. Jake Liang, MD
Chief, Liver Diseases Section
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Preface

The 36 years since the identification of hepatitis B virus (HBV) in 1967 has seen the establishment of HBV virology as a rich and extensive field of science and the recognition of HBV as one of the top 10 leading causes of death in the world. There are an estimated 400 million people chronically infected with HBV worldwide with 20–30% of these projected to die from complications of chronic liver disease, including cirrhosis and liver cancer. Hepatitis delta virus (HDV) was first identified in 1980 as a novel transmissible agent distinct from HBV that requires the HBV envelope protein for its infectivity. HDV co-infection in chronic HBV patients is associated with a more severe disease outcome than those not co-infected. HBV and HDV infections represent a significant health burden to the worldwide community.

Despite the lack of an inflectable cell culture system, an enormous amount of information has been obtained on the virology and immunology of HBV and HDV infections. Modern molecular biological techniques and research with related viruses have enabled much of the HBV and HDV life cycle to be elucidated, leading to a number of therapeutic approaches for treating chronically infected patients. Innovative detection methods based on these findings and techniques have led to diagnostic and clinical monitoring assays of increasing sensitivity. However, our understanding of the viral life cycle and virus–host interactions is incomplete and will require much more research for a complete comprehension of the pathogenesis of disease caused by viral infection. Hepatitis B and D Protocols contains a collection of research techniques, divided into two volumes, used in the study of HBV and HDV. The authors represent a number of scientific disciplines, but share in common their interest in hepatitis research and their expertise in their respective areas. Although most of these techniques have been described in peer-reviewed journals, these chapters provide far more detail and are written so that investigators can use them as manuals. A few reviews are included in some specialized areas such as antiviral testing and the design of clinical trials. We hope that this compilation of techniques used in the different areas of HBV and HDV research will prove useful to scientists and encourage multidisciplinary approaches to their research, so that clinical investigators will find it beneficial for their understanding of the current HBV and HDV research.

We would like to take this opportunity to extend our gratitude to our teachers and friends: Dr. Zhi Hong, Dr. Maria Seifer, Dr. David Standring, Professor P. C. Wu, Professor C. L. Lai, Dr. H. J. Lin, Professor Roger Williams, and Dr. Graeme J. M. Alexander. Without their guidance and support, we would not have the opportunity of presenting this highly practical manual to you today.

Robert K. Hamatake, PhD
Johnson Yiu-Nam Lau, MD
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