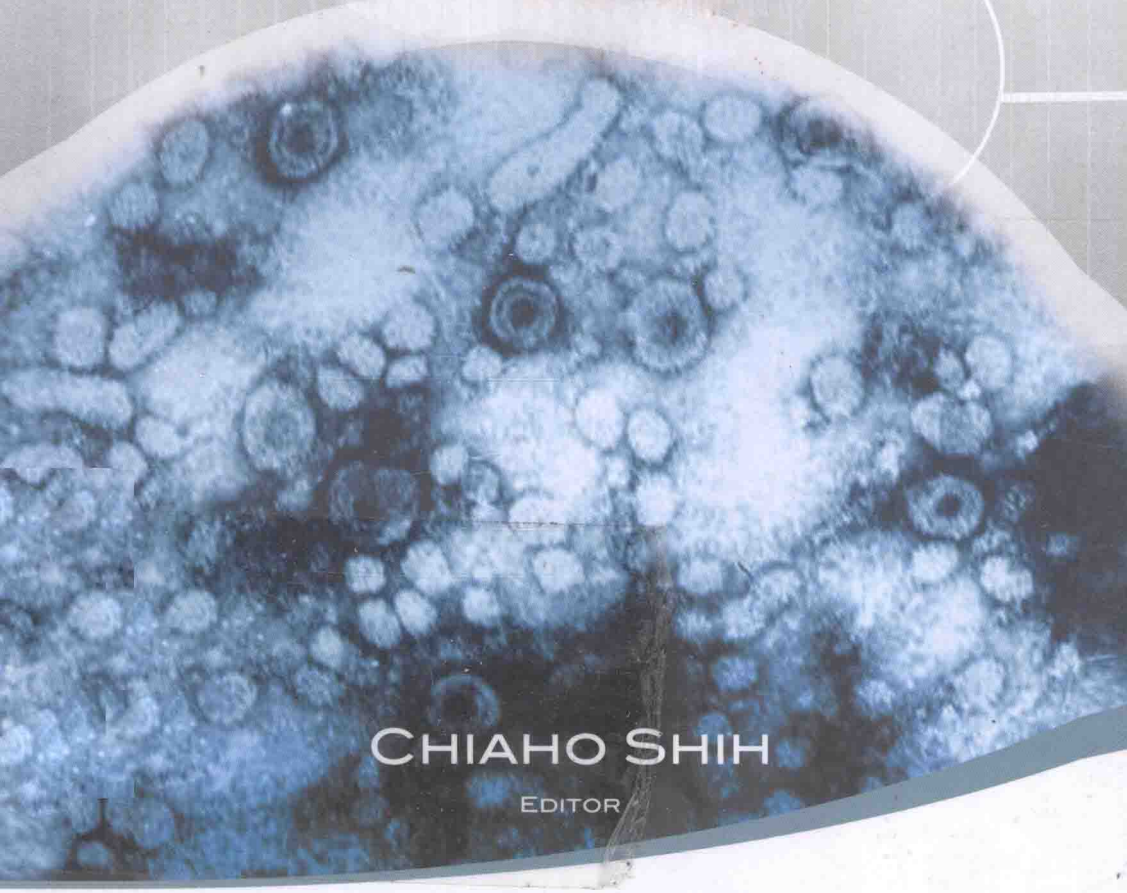
Chronic Hepatitis B and C

Basic Science to Clinical Applications



Chiaho Shih
Editor

World Scientific

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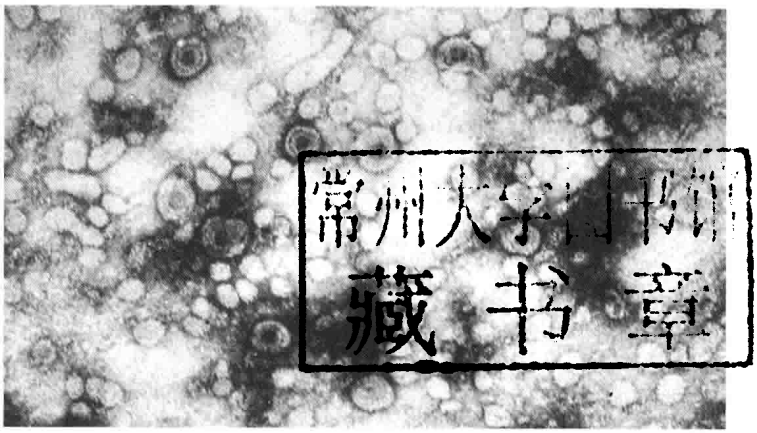
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CHRONIC HEPATITIS B AND C

Basic Science to Clinical Applications

Foreword

This is an excellent book for use in teaching about chronic hepatitis to graduate students, medical and other health sciences students and as a reference for the professional research community.

Nobel laureate Baruch S. Blumberg, M.D., D.Phil., who discovered HBV, was originally going to write the foreword to this book. Sadly, Dr Blumberg passed away in 2011 before the book was ready for release. (I think it is terrific that the Editor has chosen to dedicate the book to him)

Since I worked with Dr Blumberg, during his time at The University of Oxford, and he then worked with us here, at the Hepatitis B Foundation (HBF) labs, until his death, the book's editor, Dr Shih, asked me for comments. Although I am no substitute for Dr. Blumberg, I can say with confidence that this is a book he would really have enjoyed. For one thing, it combines the practical with the basic science, putting discovery science into a clinically relevant context. That was of course, his life's work, having discovered the cause of chronic hepatitis B and then helped produce an effective assay for the virus and preventive vaccine. On the other hand, the book covers a wide range of topics regarding viral hepatitis B, C and D, from detection, prevention, pathobiology to therapeutic management. Dr. Blumberg's interests were broad, and he always felt clinical hepatitis and liver disease should be understood in the context of fundamental science. Finally, and of course, many of his close friends and colleagues are contributors, making the book all the more meaningful.

The discovery of hepatitis and development and use of an effective vaccine is one of the great accomplishments in medical and public health of the last century. The complicated natural history of hepatitis B disease

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Dr. Baruch Blumberg (right) reunites with Dr. Harvey Alter (left), friend and colleague from the National Institutes of Health, at the Hepatitis B Foundation's Princeton Workshop in 2002 (photo provided by Joan and Tim Block).

in people made the discovery of its etiology, all the more remarkable. The disease pathobiology is thoughtfully covered by two leading clinician scientists, Drs. Chu and Liaw. The immunology of hepatitis B is central to prevention, pathogenesis and resolution, and the chapter on immune responses is by one of the field's thought leaders, Prof. David Milich. He systematically addresses the major known facts about the host B and T cell response to chronic HBV, as well as drills down to explaining the complex interplay between cytokines and chronic infection.

HBV is ubiquitous, and its epidemiology is stunning, with more than 350 million people chronically infected worldwide, and as many as 2 billion with exposure and resolved infections. One of the most serious outcomes of chronic HBV is primary cancer of the liver, and the chapter by Drs. McGlynn, London and Evans, shows the relationship between HBV and HCC, and provide excellent illustrative graphs of disease incidences that will be useful to anyone researching or teaching this subject.

The molecular biology of HBV and of HBV- induced disease has been among the most surprising in virology. HBV replicates via an

obligate RNA genomic intermediate, despite being a DNA virus. HBV clearly causes cancer in people, despite having no clear oncogene. These fascinating paradoxes are summarized nicely in the chapter by Drs. Hodgson and Slagle.

There is a growing body of evidence that mutations in the virus play important, perhaps even in some cases, decisive roles in the course of infection in people. Mutants of HBV emerge that may frustrate treatment, vaccination, or contribute to pathobiology. The chapter by Dr. Shih takes a mechanistic and functional approach to this fundamental issue, particularly from the perspective of naturally occurring core and surface antigen variants. A virion secretion defect, or a compensatory effect on such a defect, appears to be a common feature in these naturally occurring variants.

Chronic HBV is treatable, but not curable, and long term therapy is needed. The molecular basis for the two categories of medications, the direct acting antiviral (DAA) polymerase inhibitors (small molecules) and the immuno-modulatory interferons (biologicals), and the emergence of clinically relevant and observed resistance, is well described in the chapter by a group that has been among the leading authorities of the subject (Drs. Nguyen, Desmond & Locarnini).

Hepatitis D, the extraordinary sub-virus that requires co-infection with HBV to complete its replication cycle and is associated with worsened outcomes, continues to be a major, although often overlooked health threat. It is not overlooked in this book! The chapter by Dr. Sureau shows how the molecular biology and natural history of liver disease associated with HDV are as fascinating as it is complicated and goes a long way to making it all understandable.

But, let's face it, these are times that are no less than revolutionary in chronic viral hepatitis C. Hepatitis C is curable. That is an extraordinary thing to write, and even seeing it in print, with my own hand, causes me to step back in awe.

The management of HCV clearly involves a combination of immunological and direct acting antiviral strategies, and this is covered in the chapters by Drs. Liu and Chen and Drs. Yu and Chuang. Development of tissue culture infectivity systems has revolutionized the study of HCV and development of antiviral. These discoveries and the interplay between the immune system, the

therapeutic interferon's and HCV are also nicely addressed by the groups that help make breakthroughs in this area (Drs. Kato and Wakita and Drs. Horner and Gale).

The molecular biology of HCV is discussed in a chapter that focuses on the recently discovered HCV F protein (which appears to be the results of an internal start site), written by one of the groups making this discovery (Drs. Yuksek and Ou).

There are clear extra hepatitis affects of HCV, from influences upon the immune systems, to neurological and vascular diseases, and perhaps even non-hepatic malignancies. The chapter by Drs. Machida and Lai take a candid look on these possibilities, evaluating the relevant epidemiological and molecular evidence.

The book looks at an individual's host and genetic factors that affect outcome of natural HCV infection and treatment. HCV genotype plays a strong role in determining outcome of treatment with interferon and ribavirin. However, the infected individuals' genetics and other clinical factors also play important roles in natural infection and treatment related outcomes. Drs. Tanaka and Mizokami review both viral and host genetics of HCV. Again, how these factors influence, and can be used, in the use of the current and upcoming antiviral treatments is reviewed by Drs. Yu and Chuang, where the use of the kinetics of virological response to intervention is also explained.

So, I do think that Dr. Blumberg would have been one of this book's fans. It is a shame he is unable to write these words himself, and I feel frankly presumptuous, in the role of a substitute hitter. However, for teaching and for research, I think he would have enjoyed the contents.

Timothy M. Block, Ph.D.
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Preface

Viral hepatitis is a very ancient disease. Hepatitis B virus (HBV) and hepatitis C virus (HCV) can cause acute and chronic liver inflammation. Chronic infection with HBV or HCV can lead to cirrhosis, liver failure, and highly malignant hepatocellular carcinoma. Furthermore, coinfection with HBV and hepatitis delta virus (HDV) often causes more severe liver disease.

Diagnosis of HBV by ELISA or PCR is available, and vaccination of HBV surface antigen is successful in reducing the incidence of HBV infection and liver cancer in Taiwan and other parts of the world. However, the treatment of HBV chronic infection remains a challenge. Long term treatment with nucleoside or nucleotide analogs often leads to drug resistance. Interferon alpha (IFN-alpha) is more expensive and associated with side effects. The efficacy of pegylated IFN-alpha is low for most perinatally infected chronic HBV carriers. Similarly, at present, there is no effective treatment for hepatocellular carcinoma. Worldwide, there are approximately 350 million chronic HBV carriers. Therefore, there remains an urgent need to research more on both basic and clinical science of HBV.

Diagnosis of HCV by ELISA or PCR is also available. Treatment of HCV infection with pegylated interferon and ribavarin is successful for most HCV genotypes. Several new oral drugs targeting HCV NS3, NS5A and NS5B are being actively developed. However, to date, there is no HCV vaccine available. Despite the establishment of an *in vitro* cell culture system for HCV, the study of HCV innate immunity and liver pathogenesis remains a problem due to the lack of a small animal model for *in vivo* HCV infection. The recent finding

of the correlation between certain types of interferon lambda (IL28B) polymorphism and the clearance of HCV, provides another opportunity for individualized therapy of chronic HCV carriers.

This book consists of 14 chapters, including 7 special topics on HBV and HCV, respectively. The scope of the book is very broad, and the selected topics range from epidemiology, immunology, molecular virology and oncology, to clinical therapy. I hope this book will serve as a friendly introduction for students, and as a resource of information for investigators in both basic and clinical science.

HBV was first discovered by Dr. Baruch Blumberg, who kindly agreed to write the Foreword for this book. Unfortunately, Dr. Blumberg passed away suddenly last year. Dr. Timothy Block, who is a close friend and a long term collaborator of Dr. Blumberg, graciously agreed to prepare the Foreword for this book. We also thank Joan and Tim Block for providing a photo of Dr. Blumberg. It was taken at a workshop held by the Hepatitis B Foundation, in Princeton. It appropriately includes Dr. Harvey Alter, who was Dr. Blumberg's long time friend, and helped in the discovery of HBV and is credited as being a co-discoverer of hepatitis C. This was a photo that Dr. Blumberg treasured, since it reflected the friendship and collaboration. For me, it shows two giants, representing a golden age of hepatitis research.

Last, but not the least, I would like to thank Szu-Yao Wu, Chih-Yin Lee, and Shu-Fan Chou in my lab for careful proofreading of book chapters, and Ms. Sook Cheng Lim at World Scientific for her outstanding dedication in editing this book. Finally, I thank all the contributing authors for their generosity in sharing with us their insight and knowledge in chronic hepatitis B and C.

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