Preface: Hepatitis B Virus: The Past, The Present, and The Future  ix
Tarek I. Hassanein

Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease 607
Noele P. Nelson, Philippa J. Easterbrook, and Brian J. McMahon
Integration of hepatitis B vaccination into national immunization programs has resulted in substantial reductions of hepatitis B virus (HBV) transmission in previously high endemic countries. The key strategy for control of the HBV epidemic is birth dose and infant vaccination. Additional measures include use of hepatitis B immunoglobulin (HBIG) and diagnosis of mothers at high risk of transmitting HBV and use of antiviral agents during pregnancy to decrease maternal DNA concentrations to undetectable concentrations. Despite the substantial decrease in HBV cases since vaccination introduction, implementation of birth dose vaccination in low-income and middle-income countries and vaccination of high-risk adults remain challenging.

Evolution in Our Understanding of Hepatitis B Virus Virology and Immunology 629
Bertram Bengsch and Kyong-Mi Chang
Hepatitis B virus (HBV) infection is a major global health challenge. HBV can cause significant morbidity and mortality by establishing acute and chronic hepatitis. Approximately 250 million people worldwide are chronically infected, and more than 2 billion people have been exposed to HBV. Since the discovery of HBV, the advances in our understanding of HBV virology and immunology have translated into effective vaccines and therapies for HBV infection. Although current therapies successfully suppress viral replication but rarely succeed in viral eradication, recent discoveries in HBV virology and immunology provide exciting rationales for novel treatment strategies aiming at HBV cure.

Interferon Treatment for Hepatitis B 645
Monica A. Konerman and Anna S. Lok
Chronic hepatitis B virus (HBV) infection has a significant public health impact. There are currently 7 approved therapies for chronic HBV, including standard and pegylated interferon (IFN)-α, and 5 nucleos(t)ide analogs (NUCs). IFN offers benefits over NUCs, including a finite duration of therapy and a higher rate of clearance of hepatitis B e antigen and surface antigen. These benefits need to be weighed against the potential adverse effects of IFN therapy. Some patients should not receive IFN because of advanced liver disease or comorbidities. This article reviews the mechanisms of action, efficacy, and clinical use of IFN therapy for HBV infection.
Liver Fibrosis Reversion After Suppression of Hepatitis B Virus

Don C. Rockey

Great strides have been made in hepatitis B virus (HBV)-related fibrosis and cirrhosis. Available evidence indicates that HBV viral suppression causes regression of advanced fibrosis and even cirrhosis, and therefore should be attempted in all patients with advanced fibrosis and cirrhosis. The preferred agents in patients with cirrhosis are entecavir and tenofovir, primarily because the risk of breakthrough is low. HBV viral suppression leads to improved clinical outcomes even in patients with cirrhosis and complications. The risk of hepatocellular carcinoma is reduced, but not eliminated. Thus, patients with HBV cirrhosis should continue to have routine screening for hepatocellular carcinoma, even after viral suppression.

Hepatitis B Virus Infection and Liver Decompensation

Brendon K. Luvisa and Tarek I. Hassanein

The goal in patients with immune active hepatitis B virus (HBV) infection is to significantly suppress viral replication and prevent progression of fibrosis to cirrhosis and liver decompensation and decrease the incidence of hepatocellular carcinoma. This is achievable by the highly active antivirals, entecavir and tenofovir, which are considered first-line therapy in most patients with immune active hepatitis C virus and after liver transplantation to prevent HBV recurrence. Patients with decompensated cirrhosis should be referred for liver transplantation and treated with first-line antivirals as early as possible, with the goal of achieving complete viral suppression in the shortest time possible.

Hepatitis B and Risk of Non–Hepatocellular Carcinoma Malignancy

Ryan M. Kwok and Tram T. Tran

Chronic hepatitis B infection (CHB) is a known risk factor for malignancy. Unlike hepatocellular carcinoma (HCC), less is known about the risk of non-HCC malignancy. However, epidemiology and pathologic evidence suggests a strong association between non-Hodgkin lymphoma and CHB. Data regarding the risk of other malignancies, such as pancreatic adenocarcinoma and intrahepatic cholangiocarcinoma, are mixed. Surveillance and appropriate treatment of infection and malignancy in these patients is essential. Further study of these associations is needed and may bring new insights in the pathogenesis and treatment of these diseases.

Hepatitis B and Hepatocellular Carcinoma

Alan W. Hemming, Jennifer Berumen, and Kristin Mekeel

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer death worldwide, and its incidence has been increasing in the last decade largely in parallel to the incidence and duration of exposure to hepatitis B and C. The widespread implementation of hepatitis B vaccine, hepatitis B antivirals, and the introduction of direct antiviral therapies for hepatitis C virus may have a substantial impact in reducing the incidence of HCC. This report reviews the risk factors and underlying mechanisms associated
with the development of HCC in hepatitis B, along with advances in the diagnosis, imaging, and management of HCC.

**The Management of Hepatitis B in Liver Transplant Recipients**

Sammy Saab, Ping-yu Chen, Clara E. Saab, and Myron J. Tong

Liver transplant (LT) is now an established indication for patients with chronic hepatitis B, mainly because of the development and use of hepatitis B immunoglobulin (HBIG) and oral antivirals for prophylaxis. The combination of low-dose HBIG and antivirals has been considered the standard prophylaxis regimen to prevent post-LT recurrence of hepatitis B. The important remaining issues are related to the long-term cost of HBIG and the risk of escape hepatitis B virus (HBV) mutants. Strategies for prevention of HBV after LT are constantly improving. With the availability of new nucleoside/nucleotide analogues, new post-LT strategies should also emerge.

**Toward Elimination of Hepatitis B Virus Using Novel Drugs, Approaches, and Combined Modalities**

Sebastien Boucle, Leda Bassit, Maryam Ehteshami, and Raymond F. Schinazi

Hepatitis B virus (HBV) causes significant morbidity and mortality worldwide. The majority of chronically infected individuals do not achieve a functional and complete cure. Treated persons who achieve a long-term sustained virologic response (undetectable HBV DNA), are still at high risk of developing morbidity and mortality from liver complications. This review focuses on novel, mechanistically diverse anti-HBV therapeutic strategies currently in development or in clinical evaluation, and highlights new combination strategies that may contribute to full elimination of HBV DNA and covalently closed circular DNA from the infected liver, leading to a complete cure of chronic hepatitis B.