Introduction

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The Asia-Pacific region encompasses one of the largest populations worldwide in which there is an endemic presence of chronic hepatitis B. This viral infection, if left untreated, leads to progressive liver damage, culminating in cirrhosis or hepatocellular carcinoma in a substantial proportion of patients. In the Asia-Pacific countries, most persons with chronic hepatitis B virus (HBV) infection acquire it at birth or in early childhood and thus face a lifetime of risk for these serious sequelae. The fact that these complications may manifest at an earlier age than in individuals who acquire the infection as adults heightens the urgency of identifying these carriers and ensuring that they are appropriately followed up and treated. Extremes of variability in health care accessibility and policy in these far-flung regions complicate this important mission.

The articles in this supplement bring useful information to clinicians at a time when many advances are being made in the understanding of chronic hepatitis B. Clinicians who avail themselves of the information in this publication, authored by international experts in the field, will become conversant with the new research that is rapidly filling the gaps in our knowledge of this widespread illness.

Drs. Bowden and Thompson begin the supplement with a discussion of HBV molecular diagnostics and quantitative serology. Interpretation of specific serologic assays is crucial to many aspects of hepatitis B management in the era of antiviral therapy. The authors discuss specific features of signal and target amplification assays, used in HBV DNA quantification. Certain HBV genotypes appear to be

associated with more severe liver disease and better response to specific therapies, although, as of yet, genotype testing has not been incorporated into current treatment guidelines. Genotypes B and C predominate in Asia and Oceania. Recent studies into the mechanisms underlying drug resistance have focused on the role of intrahepatic HBV replicative forms, in particular, covalently closed circular DNA (cccDNA). Persistence of the HBV cccDNA after antiviral therapy can re-establish pretreatment replication levels and may be one reason for treatment relapse. Nucleoside or nucleotide analogs only indirectly affect the pre-existing cccDNA template. There is also some evidence for a correlation between circulating levels of hepatitis B surface antigen (HBsAg) and intrahepatic levels of HBV cccDNA. In line with this, sensitive quantitative assays for HBsAg and also hepatitis B e antigen (HBeAg) are now under development.

The second article in the supplement is a discussion of the role of the innate immune response in the immunopathogenesis of chronic hepatitis B, authored by Drs. Visvanathan and Ratnam. The innate immune system is involved in pathogen surveillance, and it interacts with adaptive immune responses. The authors describe the functions of the key cells and cytokines involved in the innate immune response. Release of intrahepatic interferons is one of the first immune events in the host response to HBV. Indirect antiviral effects of the type 1 interferons include recruitment and activation of antigen-presenting cells, such as Kupffer cells and dendritic cells. Natural killer cells, which are directly cytotoxic, and natural killer T cells, which produce inflammatory cytokines, also appear to play a role in the innate immune response to acute HBV infection. The most characteristic adaptive immunologic feature of chronic HBV infection is a diminished HBV-specific T-cell response, but there is increasing evidence

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that the innate immune system is involved in this response as well. In HBeAg-positive chronic hepatitis B, expression and function of toll-like receptor-2 (TLR-2) is significantly decreased compared with HBeAg-negative patients and healthy controls, while in HBeAg-negative disease, TLR-2 expression and related TNF- α secretion is significantly increased. Moreover, *in vitro* studies have demonstrated that the presence of HBeAg is associated with the down-regulation of TLR-2, suggesting that specific HBV antigens may target particular TLRs to escape immune recognition. Dendritic cells may induce T-cell tolerance, and natural killer cells may be involved in hepatocyte damage. As this article explains, clearing HBV involves both the adaptive and innate arms of the host immune response, acting in a coordinated line of attack.

In their article on the treatment of chronic hepatitis B, Drs. Chang and Suh review current guidelines for initiating treatment and discuss the efficacy and resistance data pertaining to approved and investigational therapies. The context for this discussion is the recent emphasis on suppression of viral replication to the greatest extent possible, preferably to undetectable levels, as the fundamental goal of treatment. The authors review the clinical experience with peginterferon, adefovir, entecavir, and telbivudine, also presenting phase III data for tenofovir. Neither standard interferon nor lamivudine is considered first-line therapy. Despite the existence of various treatment guidelines, many clinicians are uncertain about how to monitor patients during therapy. A monitoring schedule recently recommended by a panel of international experts provides clinicians with a roadmap to follow during and after therapy with oral medications. HBV DNA levels are measured at 12 weeks to determine the presence, if any, of primary treatment failure, and at 24 weeks for assessment of the

level of response. On the basis of the response, the therapy can be modified. This article also outlines strategies to overcome resistance. Combination therapy is an active area of research. Preliminary studies with some combinations have not been encouraging, but addition of adefovir to lamivudine in lamivudine-resistant patients (rather than switching to adefovir) has shown benefit.

The final article, by Dr. Mei-Hwei Chang, is a detailed account of the nature of hepatitis B in children, accompanied by a discussion of the limitations of current therapy for this age group. In endemic areas such as Asia and Africa, most people with chronic HBV infection acquire their infection before early childhood. This article discusses the characteristic serologic and histologic changes seen in the different phases of infection in children. Despite high rates of viral replication, most children will eventually clear HBV DNA and undergo seroconversion. If chronic infection develops, liver injury may accumulate over time. The only two antiviral agents approved for the treatment of chronic hepatitis B in children are conventional interferon alfa and lamivudine, both of which present problems in their use. There is clearly a need for better antiviral therapies that are more tolerable than interferon and present a lower risk of resistance than does long-term monotherapy with lamivudine.

The articles in this supplement provide a useful overview of important developments in understanding hepatitis B, providing new perspectives on the natural history and pathogenesis of chronic hepatitis B, molecular diagnostics, and strategies to diminish the impact of HBV infections on human health. Application of this knowledge to everyday practice may help break the cycle of hepatitis B in geographic areas where it is so disproportionately prevalent.