From Hepatitis to Hepatoma: Lessons from Type B Viral Hepatitis

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Though viral hepatitis is an important public health problem worldwide, it is of particular concern in the Asian-Pacific countries, where the disease is unusually prevalent. To date, five distinct viruses (designated A through E) have been identified as etiologic factors causing distinct forms of the disease. Two of these viruses, hepatitis B and C viruses (HBV and HCV), cause important chronic infections. Carriers of HBV and HCV not only become long-term reservoirs of virus but also eventually develop chronic liver disease (*1*). There is overwhelming evidence that HBV and HCV carriers also have a greatly increased risk of developing hepatomas (liver cancer), and this is indeed one of the most common human cancers in Asia and Africa. HBV, the more prevalent of the two viruses, will be emphasized here.

The predominant mode of HBV transmission, particularly among Chinese people, is perinatal. Transfer of the virus by this route is highly efficient: About 90% of the infants born to HBV carrier mothers become carriers themselves (*2*). Intervention at this point is critical because once a chronic infection is established, it persists for life.

The natural history of chronic HBV infection became amenable to investigation after the discovery of hepatitis B surface antigen (HBsAg) (*3*), a component of the virus envelope that could be used as a marker of virus activity. The progress of subsequent research has been dramatic. We now know that chronic infection with HBV proceeds through two distinct phases (*4*) (see figure). The first is a phase of active virus replication, in which abundant amounts of replicative HBV DNA intermediates and the viral core antigen (HBcAg) accumulate in the liver of infected individuals. This phase is also marked by high serum concentrations of HBV DNA and hepatitis B e antigen (HBeAg), a soluble viral protein similar to HBcAg. During this period, the host immune reaction to the virus is minimal.

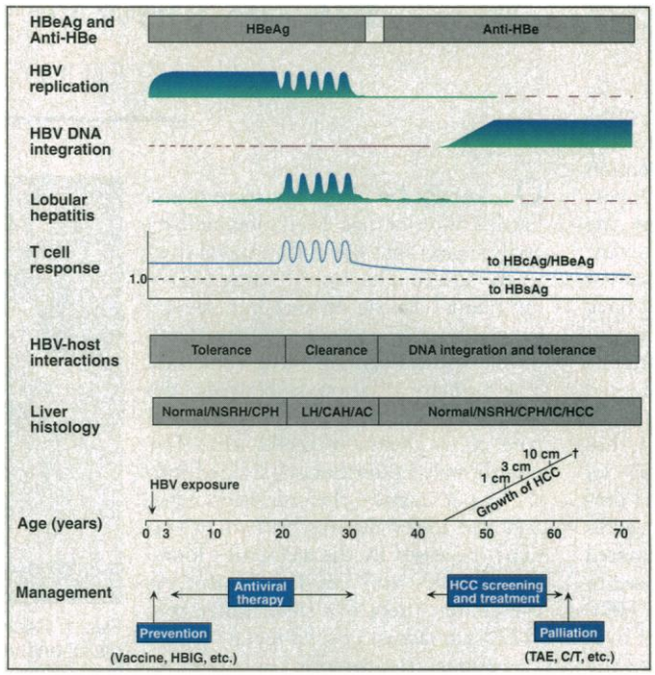
After an average period of 20 to 30 years, a transition occurs and the HBV infection enters its second phase. Perhaps because of less efficient viral replication, the serum concentration of HBeAg decreases and the infected individual begins to produce T cells that recognize HBV-specific antigens. Eventually this leads to a full-fledged, cell-mediated immune response in which the HBV-infected liver cells are killed and the host is cleared of the virus. The most likely viral antigens targeted in the immune response are HBcAg or HBeAg, since cellular response to these antigens increases remarkably in the peripheral blood just before or early in the acute exacerbation of the hepatitis (*5*). Once the HBV-infected liver cells are destroyed by the immune system, active replication of the virus ceases and the HBcAg and HBeAg proteins disappear. Serum HBV DNA also becomes barely detectable, even by polymerase chain reaction assays.

Although HBV does not replicate during this phase, expression of HBsAg persists. This is because the HBV genome can integrate into the host chromosome, and liver cells containing copies of the HBsAg gene continue to express the viral antigen. In the absence of active HBV replication, the liver cells are spared from immune attack, and the host once again becomes "tolerant" to the virus.

At this stage, the liver displays residual lesions resulting from previous insults suffered during the replicative phase of the virus (see figure). About 40% of HBV carriers with severe hepatic lesions will develop cirrhosis at a rate of ~2% per year (*1*, *6*). The cirrhosis progresses insidiously, usually manifesting itself after several decades as a marked decline in liver function. A significant proportion of HBsAg carriers eventually develop liver cancer (*7*).

Like most cancers, liver cancers are thought to arise as the result of a series of genetic and environmental insults. The role of HBV DNA integration in liver carcinogenesis remains uncertain. Although integrated viral DNA can be detected in tumor tissue from most HBsAg-positive patients with liver cancer, integration appears to occur at random sites in the host genome and thus does not seem to be oncogenic. A more consistent genetic alteration, perhaps more likely to play a causative role in carcinogenesis, is mutation in the *p53* tumor suppressor gene, which occurs in about 30% of human hepatomas [reviewed in (*8*)]. Interestingly, somatic mutations at codon 249 of the *p53* gene are observed more often in countries where there is dietary contamination by aflatoxin, a mycotoxin capable of inducing liver cancer in animals (*9*). Aflatoxin B_1 is a mutagen that induces G to T base substitutions and shows a preference for *p53* codon 249 in assays in vitro. Despite the high frequency of *p53* mutations, however, there is evidence that this genetic change is not an early event in liver carcinogenesis (*10*).

Recent progress in imaging diagnosis has facilitated detection of small liver tumors, which in turn has revealed some details about the natural history of this cancer at the subclinical stage. We now know, for example, that liver cancer can emerge at any age in individuals chronically infected with HBV, particularly those infected peri-



The natural history of chronic HBV infection. Parameters that exist in minimal amounts or that contribute minimally to infection at a given time are indicated by dashed lines. [Modified from (*4*) and reprinted with permission from Blackwell Scientific Publications] Abbreviations are as follows: NSRH, nonspecific reactive hepatitis; LH, lobular hepatitis; AC, active cirrhosis; CAH, chronic active hepatitis; CPH, chronic persistent hepatitis; HBIG, hepatitis B immune globulin; HCC, hepatocellular carcinoma; TAE, transcatheter arterial embolization for the treatment of HCC; C/T, chemotherapy for the treatment of HCC; and †, death of the patient.

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natally (*1*). We also know that, contrary to previous belief, liver cancers are slow-growing malignancies. The earlier perception that liver cancers are aggressive tumors was simply a result of our limited ability to diagnose them early. In fact, it may take an average of 3 years (range 0.8 to 11 years) for a liver tumor that is 1 centimeter in diameter to grow to a size large enough to cause symptoms (*11*). When symptoms appear, the HBsAg carrier is already at the terminal stage and will usually die within months. In other HBsAg carriers, liver function may be severely compromised by the refractory hepatitis and the patient may die of hepatic failure or other complications of cirrhosis. A study in Taiwan has estimated that as many as 50% of all HBsAg-positive men will die of cirrhosis or hepatoma (*7*).

Our improved understanding of the natural history of chronic type B hepatitis has led to more effective approaches toward the control of this important viral infection and its sequelae (see figure). Most important, immunization against HBV in the perinatal setting has been shown to prevent chronic infections with an efficacy of about 85%. Forty-seven countries currently have national immunization policies that include hepatitis B vaccination of infants (*12*). One of the earliest programs, adopted in Taiwan in 1984 and involving universal vaccination of infants and children, has proved very effective. The percentage of children carrying HBsAg has dropped dramatically from >10 to <2% (*13*). In addition, the data from mothers and vaccinated infants have been stored and will be used to assess whether prevention of chronic HBV infection also reduces the incidence of liver cancer. If it does, then this would be the first time in history that a human cancer has been prevented by mass vaccination.

Although much has been learned from hepatitis B, many important issues remain unresolved. For existing HBsAg carriers, interferons offer some therapeutic benefits but other effective and inexpensive treatments are also needed. The immunologic mechanisms underlying persistent HBV infection, the immunopathogenesis of chronic hepatitis B, and the progression of chronic HBV infections to hepatomas are other issues that remain to be explored in further detail. Molecular biology will continue to play a key role in solving these fundamental questions. In the meantime, efforts to prevent HBV infection—especially by immunization—should continue, with the goal of controlling hepatoma and cirrhosis by the turn of the century.

References and Notes

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High-Pressure Mineral Physics: An Inside View of the Earth

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Our knowledge of the structure of the Earth's interior has been obtained by analyzing seismic waves that travel deep in the Earth. The "solid" Earth (6370-km radius) can be divided into several concentric layers according to the depth profiles of the seismic wave velocities. The primary division is between the mantle of rock and the metallic molten core at a depth of 2890 km. The mantle may be further subdivided into the upper mantle, the transition zone, and the lower mantle by two prominent increases in the velocities found around 400- and 660-km depths. At the center, there is a small inner core (1220-km radius) of solid metal.

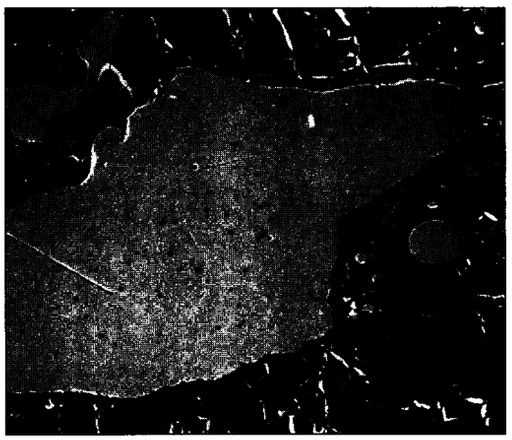

Fig. 1. Secondary electron image of part of a sample quenched at 24 GPa and 2550°C (*19*). The starting material was a mixture of pure iron and $(Mg_{0.9}Fe_{0.1})_2SiO_4$ olivine.

Seismic tomography (*1*) has revealed three-dimensional variations in velocities over most of the mantle and shows descending slabs and the existence of large-scale rising plumes. The goal of high-pressure mineral physics includes interpretation of this seismic information in terms of material science and clarification of the state of the Earth's interior. In the following, I briefly review recent advances by Japanese researchers, but a wide range of high-pressure research is also being carried out at several institutes of the Chinese Academy of Sciences, China, employing both multianvil press and diamond anvil cells (DAC) (*2*). At the Institute of Earth Sciences, Taiwan, DAC experiments are in progress for a variety of topics (*3*). Collaborations under consideration between these and other Asian countries will stimulate new development of high-pressure mineral physics.

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Kimberlite xenoliths, the deepest rocks accessible from the Earth's surface, indicate that the uppermost part of the mantle (down to 150-km depth) is peridotite, composed of mainly olivine associated with Ca-poor and Ca-rich pyroxenes and garnet. Accurate data on the phase equilibria of these mantle minerals at high pressures and temperatures are indispensable to modeling of the mineralogy and chemistry of the deep mantle. Following Akimoto's pioneering work on the olivine-spinel transformation (*4*), Japanese scientists have developed a double-staged, large-volume, multianvil apparatus (*5*). Consequently, phase diagrams relevant to the depth of 800 km in the mantle were constructed in sufficient detail. The phase boundaries have been cross-checked by thermodynamic calculations based on recent measurements of heat of formation and heat capacity for the high-pressure phases (*6*).

Important mineralogical aspects of the