The development of methods to successfully immunize the human host against acute viral infections is rightly recognized as one of science's great gifts to medicine. More recently, efforts to prevent chronic viral disease by vaccination have also met with some success—notably, in the cases of hepatitis B and varicella/zoster—and these successes motivate continuing efforts to achieve protection against the more challenging problems of hepatitis C and AIDS. But it is important to remember that the availability of successful immunoprophylaxis is of no benefit to those already chronically infected. In the case of hepatitis B virus (HBV), this represents a population of over 300 million people worldwide, all of whom are persistently viremic, usually at levels 100 to 1,000 times higher than typical carriers of HIV and HCV. Although these carriers are not globally immunosuppressed, they display striking hyporesponsiveness to HBV at the T cell level (for review see reference 1). By contrast, patients with acute hepatitis B who clear the infection have vigorous T cell responses (both $CD4^+$ and $CD8^+$) to multiple epitopes on each of the viral gene products. These T cell responses and the secondary antigen nonspecific inflammatory responses they engender are thought to be decisive for viral clearance. Failure to mount such responses—or their active suppression—is thought to predispose to chronic infection.

Because HBV cannot be transmitted to experimentally tractable inbred animals, it has been difficult to determine whether the T cell hyporesponsiveness is the cause or the consequence of chronic HBV infection. And if it is the latter, does it result from deletion of the responsible T cell lineages or might there be a component of reversibility to the process? In the present issue of the *Journal*, Boni et al. (2) provide an important first insight into these questions by taking advantage of recent progress in HBV virology and therapeutics. The discovery that HBV replicates by reverse transcription has led to the identification of nucleoside analogues that can block viral replication. The first clinically useful nucleoside is lamivudine (3TC), which can reduce serum viremia by about 2 logs without toxicity. (Although this activity is substantial, it is nowhere near a knockout punch—hepatitis B early antigen (HBeAg)-positive carriers often have circulating viral titers of 10^8/ml or more). Nonetheless, the ability to at least partially inhibit HBV replication allowed Boni et al. to ask whether such inhibition has an impact on host T cell responsiveness. They examined the T cells of 12 chronically infected individuals for their proliferative responses to HBV e and c antigens, an assay that measures primarily $CD4^+$ cell responses. As expected, before treatment 10 of the 12 had undetectable responses to HBeAg; hepatitis B core antigen (HBcAg) responses were more variable. However, responses to both antigens were significantly upregulated by treatment, with kinetics that closely paralleled the drug-induced decline in serum virus titer. Limiting dilution analysis showed that circulating e antigen–specific T cell frequencies rose to levels often seen during acute hepatitis B, a situation in which 90% of subjects ultimately clear viremia. (However, it is important to note that none of the present patients cleared HBsAg during the study.)

These results have important implications for our understanding of HBV immunology, and perhaps for the design of treatment strategies. They demonstrate clearly that helper T cell hyporesponsiveness is not due to irreversible deletion of virus-specific cells; the broad range of epitopes recognized by T cells of treated subjects suggests that most of the helper repertoire is still viable. Interestingly, more global defects in mitogen responsiveness were also noted in the chronically infected subjects, and these deficits were also ameliorated by therapy. How HBV engenders these virus-specific and nonspecific impairments remains a deep mystery, the resolution of which will likely tell us much about virus–host interactions. And while it is tempting to imagine that these defects are important in influencing the natural history of infection, this notion still rests principally on correlative observations alone. Clearly there is much left to discover here. A significant limitation of the present work is that it is focused primarily on $CD4^+$ responses. It will be important to note if therapy has similar effects on cytotoxic T-lymphocyte responses, as current views of HBV immunopathogenesis have assigned key roles to such effectors in triggering viral clearance.

What, if any, implications might these observations have for the therapy of chronic hepatitis B? A nuanced answer to this question requires consideration of several facts of HBV biology. First, HBV replication is not itself injurious to hepatocytes: liver injury results primarily from cellular immune responses to infected hepatocytes (1). Second, a very large population of infected hepatocytes exists in chronic hepatitis B, and since hepatocytes survive for up to a year in vivo, this large reservoir can be expected to take a long time to drain, even with highly active antiviral drugs. In principle, if putative hepatic stem cells are uninfected, it is possible to imagine that prolonged arrest of viral replication could allow the natural turnover of infected cells (for example, by apoptosis) to lead to their replacement by uninfected cells. But more likely, active killing of infected cells by immune effector mechanisms will be necessary if we are to contemplate radical cure of HBV in infected individuals. If the present observations hold true for virus-specific CTLs, then such immune responses may emerge during prolonged antiviral therapy, or they may be potentiated by deliberate therapeutic immunization. Given the potential of such responses to provoke liver injury, it will be important to reduce the number of infected hepatocytes before such immune stimulation. Thus, a rational paradigm emerges for how the treatment of chronic HBV infection may be approached: prolonged antiviral therapy to reduce the burden of infectious centers in the liver and foster the expansion of uninfected cells that support hepatic function, followed by deliberately pro-

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voked immunological attack on the small number of remaining infected cells. (The current use of α-interferon represents a crude form of immunotherapy whose safety and efficacy might be significantly enhanced by using it in such a sequence.) For this to become a reality, we will likely need several safe and orally bioavailable antivirals (to forestall the emergence of drug resistance) as well as more regulatable and reproducible ways to stimulate HBV-specific T cell responses. But by showing that at least some T cell responses can recover after being sheltered from the storm of viral replication, Boni et al. have provided an early clue that such an approach may, in fact, be possible.

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