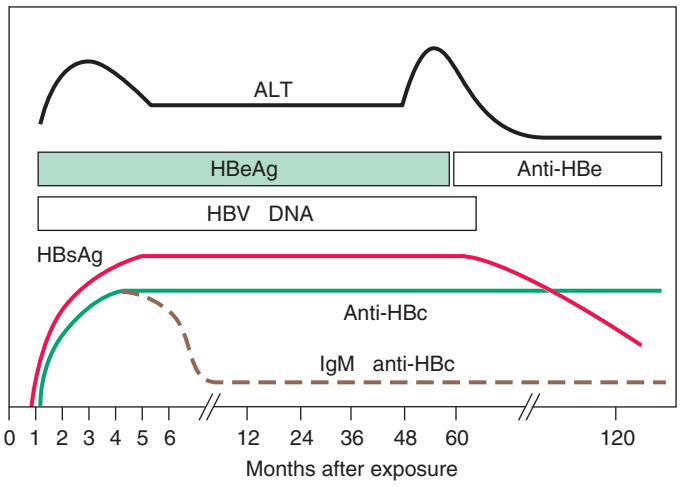

FIGURE 360-5 Scheme of typical laboratory features of wild-type chronic hepatitis B. HBeAg and hepatitis B virus (HBV) DNA can be detected in serum during the relatively *replicative phase* of chronic infection, which is associated with infectivity and liver injury. Seroconversion from the replicative phase to the relatively *nonreplicative phase* occurs at a rate of ~10% per year and is heralded by an acute hepatitis–like elevation of alanine aminotransferase (ALT) activity; during the nonreplicative phase, infectivity and liver injury are limited. In HBeAg-negative chronic hepatitis B associated with mutations in the precore region of the HBV genome, replicative chronic hepatitis B occurs in the absence of HBeAg.

the time of maximal infectivity and liver injury; HBeAg is a qualitative marker and HBV DNA a quantitative marker of this replicative phase, during which all three forms of HBV circulate, including intact virions. Over time, the relatively replicative phase of chronic HBV infection gives way to a relatively *nonreplicative phase*. This occurs at a rate of ~10% per year and is accompanied by seroconversion from HBeAg to anti-HBe. In many cases, this seroconversion coincides with a transient, usually mild, acute hepatitis-like elevation in aminotransferase activity, believed to reflect cell-mediated immune clearance of virus-infected hepatocytes. In the nonreplicative phase of chronic infection, when HBV DNA is demonstrable in hepatocyte nuclei, it tends to be integrated into the host genome. In this phase, only spherical and tubular forms of HBV, *not intact virions*, circulate, and liver injury tends to subside. Most such patients would be characterized as *inactive HBV carriers*. In reality, the designations *replicative* and *nonreplicative* are only relative; even in the so-called nonreplicative phase, HBV replication can be detected at levels of approximately $\leq 10^3$ virions with highly sensitive amplification probes such as the polymerase chain reaction (PCR); below this replication threshold, liver injury and infectivity of HBV are limited to negligible. Still, the distinctions are pathophysiologically and clinically meaningful. Occasionally, nonreplicative HBV infection converts back to replicative infection. Such spontaneous reactivations are accompanied by reexpression of HBeAg and HBV DNA, and sometimes of IgM anti-HBc, as well as by exacerbations of liver injury. Because high-titer IgM anti-HBc can reappear during acute exacerbations of chronic hepatitis B, relying on IgM anti-HBc versus IgG anti-HBc to distinguish between acute and chronic hepatitis B infection, respectively, may not always be reliable; in such cases, patient history is invaluable in helping to distinguish de novo acute hepatitis B infection from acute exacerbation of chronic hepatitis B infection.

MOLECULAR VARIANTS Variation occurs throughout the HBV genome, and clinical isolates of HBV that do not express typical viral proteins have been attributed to mutations in individual or even multiple gene locations. For example, variants have been described that lack nucleocapsid proteins (commonly), envelope proteins (very rarely), or both. Two categories of naturally occurring HBV variants have attracted the most attention. One of these was identified initially in Mediterranean countries among patients with severe chronic HBV infection and detectable HBV DNA but with anti-HBe instead of HBeAg. These patients were found to be infected with an HBV mutant that contained an alteration in the precore region rendering the virus incapable of encoding HBeAg. Although several potential mutation sites exist in the pre-C region, the region of the C gene necessary for the expression of HBeAg (see "Virology and Etiology"), the most commonly encountered in such patients is a single base substitution, from G to A in the second to last codon of the pre-C gene at nucleotide 1896. This substitution results in the replacement of the TGG tryptophan codon by a stop codon (T*A*G), which prevents the translation of HBeAg. Another mutation, in the core-promoter region, prevents transcription of the coding region for HBeAg and yields an HBeAg-negative phenotype. Patients with such mutations in the precore region and who are unable to secrete HBeAg may have severe liver disease that progresses more rapidly to cirrhosis, or alternatively, they are identified clinically later in the course of the natural history of chronic hepatitis B, when the disease is more advanced. Both "wild-type" HBV and precore-mutant HBV can coexist in the same patient, or mutant HBV may arise late during wild-type HBV infection. In addition, clusters of fulminant hepatitis B in Israel and Japan were attributed to common-source infection with a precore mutant. Fulminant hepatitis B in North America and western Europe, however, occurs in patients infected with wild-type HBV, in the absence of precore mutants, and both precore mutants and other mutations throughout the HBV genome occur commonly, even in patients with typical, self-limited, milder forms of HBV infection. HBeAg-negative chronic hepatitis with mutations in the precore region is now the most frequently encountered form of hepatitis B in Mediterranean countries and in Europe. In the United States, where HBV genotype A (less prone to G1896A mutation) is prevalent, precore-mutant HBV is much less common; however, as a result of immigration from Asia and Europe, the proportion of HBeAg-negative hepatitis B–infected individuals has increased in the United States, and they now represent approximately 30–40% of patients with chronic hepatitis B. Characteristic of such HBeAg-negative chronic hepatitis B are lower levels of HBV DNA (usually $\leq 10^5$ IU/mL) and one of several patterns of aminotransferase activity—persistent elevations, periodic fluctuations above the normal range, and periodic fluctuations between the normal and elevated range.

The second important category of HBV mutants consists of *escape mutants*, in which a single amino acid substitution, from glycine to arginine, occurs at position 145 of the immunodominant *a* determinant common to all HBsAg subtypes. This HBsAg alteration leads to a critical conformational change that results in a loss of neutralizing activity by anti-HBs. This specific HBV/*a* mutant has been observed in two situations, active and passive immunization, in which humoral immunologic pressure may favor evolutionary change ("escape") in the virus—in a small number of hepatitis B vaccine recipients who acquired HBV infection despite the prior appearance of neutralizing anti-HBs and in HBV-infected liver transplant recipients treated with a high-potency human monoclonal anti-HBs preparation. Although such mutants have not been recognized frequently, their existence raises a concern that may complicate vaccination strategies and serologic diagnosis.

Different types of mutations emerge during antiviral therapy of chronic hepatitis B with nucleoside analogues; such "YMDD" and similar mutations in the polymerase motif of HBV are described in Chap. 362.

EXTRAHEPATIC SITES Hepatitis B antigens and HBV DNA have been identified in extrahepatic sites, including lymph nodes, bone marrow, circulating lymphocytes, spleen, and pancreas. Although the virus does not appear to be associated with tissue injury in any of these extrahepatic sites, its presence in these "remote" reservoirs has been invoked (but is not necessary) to explain the recurrence of HBV infection after orthotopic liver transplantation. The clinical relevance of such extrahepatic HBV is limited.

Hepatitis D The delta hepatitis agent, or HDV, the only member of the genus *Deltavirus*, is a defective RNA virus that co-infects with and requires the helper function of HBV (or other hepadnaviruses)