for its replication and expression. Slightly smaller than HBV, HDV is a formalin-sensitive, 35- to 37-nm virus with a hybrid structure. Its nucleocapsid expresses HDV antigen (HDAg), which bears no antigenic homology with any of the HBV antigens, and contains the virus genome. The HDV core is "encapsidated" by an outer envelope of HBsAg, indistinguishable from that of HBV except in its relative compositions of major, middle, and large HBsAg component proteins. The genome is a small, 1700-nucleotide, circular, single-strand RNA of negative polarity that is nonhomologous with HBV DNA (except for a small area of the polymerase gene) but that has features and the rolling circle model of replication common to genomes of plant satellite viruses or viroids. HDV RNA contains many areas of internal complementarity; therefore, it can fold on itself by internal base pairing to form an unusual, very stable, rodlike structure that contains a very stable, self-cleaving and self-ligating ribozyme. HDV RNA requires host RNA polymerase II for its replication in the hepatocyte nucleus via RNA-directed RNA synthesis by transcription of genomic RNA to a complementary antigenomic (plus strand) RNA; the antigenomic RNA, in turn, serves as a template for subsequent genomic RNA synthesis effected by host RNA polymerase I. HDV RNA has only one open reading frame, and HDAg, a product of the antigenomic strand, is the only known HDV protein; HDAg exists in two forms: a small, 195-amino-acid species, which plays a role in facilitating HDV RNA replication, and a large, 214-amino-acid species, which appears to suppress replication but is required for assembly of the antigen into virions. HDV antigens have been shown to bind directly to RNA polymerase II, resulting in stimulation of transcription. Although complete hepatitis D virions and liver injury require the cooperative helper function of HBV, intracellular replication of HDV RNA can occur without HBV. Genomic heterogeneity among HDV isolates has been described; however, pathophysiologic and clinical consequences of this genetic diversity have not been recognized. The clinical spectrum of hepatitis D is common to all eight genotypes identified, the predominant of which is genotype 1.

HDV can either infect a person simultaneously with HBV (*coinfection*) or superinfect a person already infected with HBV (*superinfection*); when HDV infection is transmitted from a donor with one HBsAg subtype to an HBsAg-positive recipient with a different subtype, HDV assumes the HBsAg subtype of the recipient, rather than the donor. Because HDV relies absolutely on HBV, the duration of HDV infection is determined by the duration of (and cannot outlast) HBV infection. HDV replication tends to suppress HBV replication; therefore, patients with hepatitis D tend to have lower levels of HBV replication. HDV antigen is expressed primarily in hepatocyte nuclei and is occasionally detectable in serum. During acute HDV infection, anti-HDV of the IgM class predominates, and 30–40 days may elapse after symptoms appear before anti-HDV can be detected. In self-limited infection, anti-HDV is low-titer and transient, rarely remaining detectable beyond the clearance of HBsAg and HDV antigen. In chronic HDV infection, anti-HDV circulates in high titer, and both IgM and IgG anti-HDV can be detected. HDV antigen in the liver and HDV RNA in serum and liver can be detected during HDV replication.

Hepatitis C Hepatitis C virus, which, before its identification was labeled "non-A, non-B hepatitis," is a linear, single-strand, positive-sense, 9600-nucleotide RNA virus, the genome of which is similar in organization to that of flaviviruses and pestiviruses; HCV is the only member of the genus *Hepacivirus* in the family Flaviviridae. The HCV genome contains a single, large open reading frame (gene) that codes for a virus polyprotein of ~3000 amino acids, which is cleaved after translation to yield 10 viral proteins. The 5′ end of the genome consists of an untranslated region (containing an internal ribosomal entry site, IRES) adjacent to the genes for three structural proteins, the nucleocapsid core protein, C, and two structural envelope glycoproteins, E1 and E2. The 5′ untranslated region and core gene are highly conserved among genotypes, but the envelope proteins are coded for by the hypervariable region, which varies from isolate to isolate and may allow the virus to evade host immunologic containment directed at accessible virus-envelope proteins. The 3′ end of the genome also includes an untranslated region and contains the genes for seven nonstructural (NS) proteins, p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. p7 is a membrane ion channel protein necessary for efficient assembly and release of HCV. The NS2 cysteine protease cleaves NS3 from NS2, and the NS3-4A serine protease cleaves all the downstream proteins from the polyprotein. Important NS proteins involved in virus replication include the NS3 helicase; NS3-4A serine protease; the multifunctional membrane-associated phosphoprotein NS5A, an essential component of the viral replication membranous web (along with NS4B); and the NS5B RNA-dependent RNA polymerase **(Fig. 360-6)**. Because HCV does not replicate via a DNA intermediate, it does not integrate into the host genome. Because HCV tends to circulate in relatively low titer, 10^3–10^7 virions/mL, visualization of the 50- to 80-nm virus particles remains difficult. Still, the replication rate of HCV is very high, 10^{12} virions per day; its half-life is 2.7 h. The chimpanzee is a helpful but cumbersome animal model. Although a robust, reproducible, small animal model is lacking, HCV replication has been documented in an immunodeficient mouse model containing explants of human liver and in transgenic mouse and rat models. Although in vitro replication is difficult, replicons in hepatocellular carcinoma–derived cell lines support replication of genetically manipulated, truncated, or full-length HCV RNA (but not intact virions); infectious pseudotyped retroviral HCV particles have been shown to yield functioning envelope proteins. In 2005, complete replication of HCV and intact 55-nm virions were described in cell culture systems. HCV entry into the hepatocyte occurs via the nonliver-specific CD81 receptor and the liver-specific tight junction protein claudin-1. A growing list of additional host receptors to which HCV binds on cell entry includes occludin, low-density lipoprotein receptors, glycosaminoglycans, scavenger receptor B1, and epidermal growth factor receptor, among others. Relying on the same assembly and secretion pathway as low-density and very-low-density lipoproteins, HCV is a lipoviroparticle and masquerades as a lipoprotein, which may limit its visibility to the adaptive immune system and which may explain its ability to evade immune containment and clearance. After viral entry and uncoating, translation is initiated by the IRES on the endoplasmic reticulum

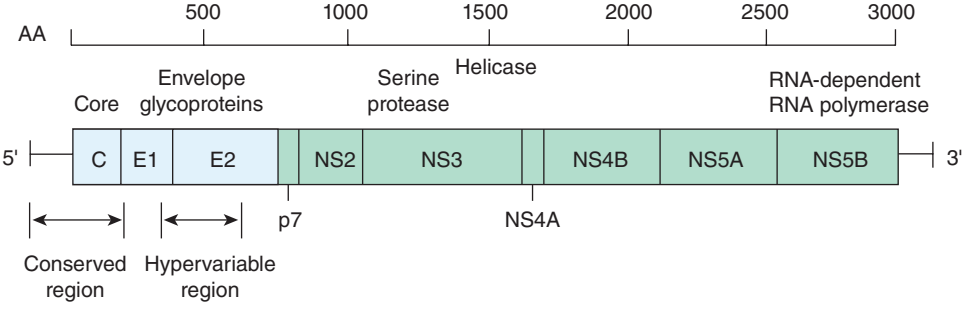

FIGURE 360-6 Organization of the hepatitis C virus genome and its associated, 3000-amino-acid (AA) proteins. The three structural genes at the 5′ end are the core region, C, which codes for the nucleocapsid, and the envelope regions, E1 and E2, which code for envelope glycoproteins. The 5′ untranslated region and the C region are highly conserved among isolates, whereas the envelope domain E2 contains the hypervariable region. At the 3′ end are seven nonstructural (NS) regions—p7, a membrane protein adjacent to the structural proteins that appears to function as an ion channel; NS2, which codes for a cysteine protease; NS3, which codes for a serine protease and an RNA helicase; NS4 and NS4B; NS5A, a multifunctional membrane-associated phosphoprotein, an essential component of the viral replication membranous web; and NS5B, which codes for an RNA-dependent RNA polymerase. After translation of the entire polyprotein, individual proteins are cleaved by both host and viral proteases.