Unless otherwise specified, the term "viral hepatitis" is reserved for infection of the liver caused by a group of viruses having a particular affinity for the liver (Table 18-6). Systemic viral infections that can involve the liver include (1) infectious mononucleosis (Epstein-Barr virus), which may cause a mild hepatitis during the acute phase; (2) cytomegalovirus, particularly in the newborn or immunosuppressed patient; and (3) yellow fever, which has been a major and serious cause of hepatitis in tropical countries. Infrequently, in children and immunosuppressed patients, the liver is affected in the course of rubella, adenovirus, herpesvirus, or enterovirus infections. Hepatotropic viruses cause overlapping patterns of disease. Each hepatotropic virus and the disease conditions it causes will be introduced before a general discussion of hepatitis.

Table 18-6 -- The Hepatitis Viruses

<table>
<thead>
<tr>
<th>Agent</th>
<th>Hepatitis A Virus</th>
<th>Hepatitis B Virus</th>
<th>Hepatitis C Virus</th>
<th>Hepatitis D Virus</th>
<th>Hepatitis E Virus</th>
<th>Hepatitis G Virus *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Parenteral; close contact</td>
<td>Waterborne</td>
<td>Parenteral</td>
</tr>
<tr>
<td>Incubation period</td>
<td>2–6 wk</td>
<td>4–26 wk</td>
<td>2–26 wk</td>
<td>4–7 wk</td>
<td>2–8 wk</td>
<td>Unknown</td>
</tr>
<tr>
<td>Carrier state</td>
<td>None</td>
<td>0.1–1.0% of blood donors in U.S. and Western world</td>
<td>0.2–1.0% of blood donors in U.S. and Western world</td>
<td>1–10% in drug addicts and hemophiliacs</td>
<td>Unknown</td>
<td>1–2% of blood donors in U.S.</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>None</td>
<td>5–10% of acute infections</td>
<td>&gt;50%</td>
<td>&lt;50% coinfection, 80% upon superinfection</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Unknown, but unlikely</td>
<td>None</td>
</tr>
</tbody>
</table>

* At present, hepatitis G virus is not considered pathogenic.

Hepatitis A Virus
Hepatitis A virus (HAV), the scourge of military campaigns since antiquity, is a benign, self-limited disease with an incubation period of 2 to 6 weeks.\textsuperscript{16} HAV does not cause chronic hepatitis or a carrier state and only rarely causes fulminant hepatitis, so the fatality rate associated with HAV is about 0.1%. The outcome of HAV infection may be more severe if it is superimposed on chronic hepatitis due to Hepatitis B virus (HBV), Hepatitis C virus (HCV), or alcohol. HAV occurs throughout the world and is endemic in countries with substandard hygiene and sanitation, so populations there may have detectable anti-HAV by the age of 10 years. Clinical disease tends to be mild or asymptomatic and rare after childhood. In developed countries, the prevalence of seropositivity increases gradually with age, reaching 50% by age 50 years in the United States. In this population, acute HAV tends to be a sporadic febrile illness. Overall, HAV accounts for about 25% of clinically evident acute hepatitis worldwide and an estimated 270,000 new cases per year in the United States.\textsuperscript{4}

HAV is a small, nonenveloped, single-stranded RNA picornavirus that occupies its own genus, \textit{Hepatovirus}. Ultrastructurally, HAV is an icosahedral capsid 27 nm in diameter. HAV is spread by ingestion of contaminated water and foods and is shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice. Thus, close personal contact with an infected individual or fecal-oral contamination during this period accounts for most cases and explains the outbreaks in institutional settings such as schools and nurseries and the waterborne epidemics in places where people live in overcrowded, unsanitary conditions. HAV is not shed in any significant quantities in saliva, urine, or semen. In developed countries, sporadic infections may be contracted by the consumption of raw or steamed shellfish (oysters, mussels, clams), which concentrate the virus from seawater contaminated with human sewage. Infected workers in the food industry may also be the source of outbreaks. Outbreaks of the disease in September and November, 2003, in the United States involved more than 600 infected persons and caused at least three deaths. Consumption of raw green onions contaminated with HAV was the most likely cause of these outbreaks. Because HAV viremia is transient, blood-borne transmission of HAV occurs only rarely; therefore, donated blood is not specifically screened for this virus.

Serologic Diagnosis.

Specific antibody against HAV of the immunoglobulin (Ig) M type appears in blood at the onset of symptoms, constituting a reliable marker of acute infection (\textbf{Fig. 18-8}). Fecal shedding of the virus ends as the IgM titer rises. The IgM response usually begins to decline in a few months and is followed by the appearance of IgG anti-HAV. The latter persists for years, perhaps for life, providing protective immunity against reinfection by all strains of HAV. Hence, the HAV vaccine is effective.
Hepatitis B Virus

Hepatitis B virus (HBV) can produce (1) acute hepatitis with resolution, (2) chronic hepatitis, which may evolve to cirrhosis, (3) fulminant hepatitis with massive liver necrosis, and (4) the backdrop for hepatitis D virus infection. Patients with chronic hepatitis represent carriers of actively replicating virus and hence are a source of infection to other individuals. HBV also plays an important role in the development of hepatocellular carcinoma. The approximate frequencies of clinical outcomes of HBV infection are depicted in Figure 18-9.
Liver disease due to HBV is an enormous problem globally, with an estimated worldwide carrier rate of 350 million. It is estimated that HBV has infected over 2 billion of the individuals alive today at some point in their lives. Seventy-five percent of all chronic carriers live in Asia and the Western Pacific rim. The global prevalence of chronic hepatitis B infection varies widely, from high (>8%) in Africa, Asia, and the Western Pacific to intermediate (2% to 7%) in Southern and Eastern Europe to low (<2%) in Western Europe, North America, and Australia. In the United States alone, there are an estimated 185,000 new infections per year. Because circulating host IgG antibodies effectively neutralize HBV, the HBV vaccine has been highly effective in reducing the prevalence of HBV in endemic areas, particularly in a mass vaccination program in Taiwan. As a public health measure, vaccination against HBV thus offers the hope that a viral vaccine may reduce the risk of malignancy, hepatocellular carcinoma, in high-risk geographic areas (see below under "Hepatocellular Carcinoma").

HBV has a prolonged incubation period (4 to 26 weeks). Unlike HAV, HBV remains in the blood up to and during active episodes of acute and chronic hepatitis. It is also present in all physiologic and pathologic body fluids, with the exception of stool. HBV is a hardy virus and can withstand extremes of temperature and humidity. Thus, whereas blood and body fluids are the primary
vehicles of transmission, virus may also be spread by contact with body secretions such as semen, saliva, sweat, tears, breast milk, and pathologic effusions. Transfusion, blood products, dialysis, needle-stick accidents among health care workers, intravenous drug abuse, and homosexual activity constitute the primary risk categories for HBV infection. In one third of patients, the source of infection is unknown. In endemic regions such as Africa and Southeast Asia, spread from an infected mother to a neonate during birth (vertical transmission) is common. These neonatal infections often lead to the carrier state for life.

HBV is a member of the Hepadnaviridae, a family of DNA-containing viruses that cause hepatitis in multiple animal species. The mature HBV virion is a 42-nm, spherical double-layered "Dane particle" that has an outer surface envelope of protein, lipid, and carbohydrate enclosing an electron-dense, 28-nm, slightly hexagonal core. The genome of HBV is a partially double-stranded circular DNA molecule having 3200 nucleotides (Fig. 18-10). All regions of the HBV genome encode protein sequences. [18]

1. A nucleocapsid "core" protein (HBcAg, hepatitis B core antigen) and a longer polypeptide transcript with a precore and core region, designated HBeAg (hepatitis B "e" antigen). The precore region directs the HBeAg polypeptide toward secretion into blood, whereas HBcAg remains in hepatocytes for the assembly of complete virions.

2. Envelope glycoprotein (HBsAg, hepatitis B surface antigen). Infected hepatocytes are capable of synthesizing and secreting massive quantities of noninfective surface protein (HBsAg), over and above HBcAg synthesis. HBsAg appears in cells and the serum as spheres and tubules approximately 22 nm in diameter.

3. A DNA polymerase that exhibits reverse transcriptase activity; genomic replication occurs via an intermediate RNA template.

4. A protein from the X region, HBx, which is necessary for virus replication and acts as a transcriptional transactivator of the viral genes and a wide variety of host genes. HBx modulation of gene transcription affects viral replication and the function of hepatocyte cell cycle checkpoints. HBx may play a role in deregulation of hepatocyte replication and development of hepatocellular carcinoma in HBV-infected patients.
HBV infection of a hepatocyte passes through two phases. During the **proliferative phase**, HBV-DNA is present in episomal form, with formation of complete virions and all associated antigens. Cell surface expression of viral HBsAg and HBeAg in association with MHC class I molecules leads to activation of CD8+ cytotoxic T lymphocytes. Hepatocyte destruction occurs if a cytotoxic T lymphocyte interacts with the infected hepatocyte. For the infected hepatocytes that are not destroyed by the immune system, an **integrative phase** may occur in which viral DNA is incorporated into the host genome.
With cessation of viral replication within hepatocytes and the appearance of antiviral antibodies, infectivity ends and liver damage subsides. However, because of the HBV DNA integrated into the host genome, the risk of hepatocellular carcinoma persists.

There is little doubt that HBV is not directly toxic to liver cells; instead it is the immune response to viral antigens, expressed on infected hepatocytes, that cause liver cell injury. In keeping with this, patients with immune defects suffer relatively mild liver injury (but are more prone to develop a carrier state, discussed later). HBV evokes both a humoral and cellular immune response, the latter involving both CD4+ helper T cells and CD8+ cytotoxic T cells. Whereas on one hand, cytotoxic T cells mediate hepatocellular injury (by lysis of infected liver cells), on the other hand, they also help clear the infection by destroying the intracellular reservoirs of HBV. Recent studies suggest that some of the anti-viral effects of T cells may also be mediated by the secretion of γ-interferon. The antibody response can confer long-term protection against HBV, as is discussed next.

Serologic Diagnosis.

After exposure to HBV, the long asymptomatic 4- to 26-week incubation period (mean: 6 to 8 weeks) is followed by acute disease lasting many weeks to months (Fig. 18-11). Most patients experience a self-limited illness:

- HBsAg appears before the onset of symptoms, peaks during overt disease, and then declines to undetectable levels in 3 to 6 months.
- HBeAg, HBV-DNA, and DNA polymerase appear in the serum soon after HBsAg, and all signify active viral replication.
- IgM anti-HBc becomes detectable in serum shortly before the onset of symptoms, concurrent with the onset of elevation of serum aminotransferases. Over months, the IgM antibody is replaced by IgG anti-HBc.
- Anti-HBe is detectable shortly after the disappearance of HBeAg, implying that the acute infection has peaked and the disease is on the wane.
- IgG anti-HBs does not rise until the acute disease is over and is usually not detectable for a few weeks to several months after the disappearance of HBsAg. Anti-HBs may persist for life, conferring protection; this is the basis for current vaccination strategies using noninfectious HBsAg.
The carrier state is defined by the presence of HBsAg in serum for 6 months or longer after initial detection. The presence of HBsAg alone does not necessarily indicate replication of complete virions, and patients may be asymptomatic and without liver damage. In contrast, chronic replication of HBV virions is characterized by persistence of circulating HBsAg, HBeAg, and HBV DNA, usually with anti-HBc and occasionally with anti-HBs (Fig. 18-11B). In these patients, progressive liver damage may occur.

**Hepatitis C Virus**

Hepatitis C virus (HCV) is a major cause of liver disease worldwide. Forty thousand new infections of HCV are estimated to occur annually in the United States. Approximately 3.9 million Americans, or 1.8% of the population, have antibodies against HCV. Fully 70% of these individuals, or 2.7 million, have evidence of chronic infection as determined by the presence of viral DNA in the serum. This makes HCV the most common chronic blood-borne infection and accounts for almost half of all patients in the United States with chronic liver disease. There has been a slight decrease in seropositivity since the peak of slightly over 2.0% in the mid-1990s. Notably, there also has been a decrease in the annual incidence of infection from its mid-1980s peak of over 150,000 new infections per year to a current 40,000 new infections per year. Nevertheless, the number of patients with long-standing infection is projected to increase fourfold over the 25 years from 1990 to 2015. Hence, the prevalence of life-limiting chronic liver disease and the risk of hepatocellular carcinoma are only expected to increase.

The major routes of transmission are inoculations and blood transfusions. Intravenous drug use accounts for 60% of cases, transfusions prior to 1991 account for 10%, and hemodialysis patients
and health care workers make up less than 5%. Sexual transmission is the only presumed risk factor in 15% of cases, although the case risk for transmission is low (12 events per 1000 person-years in the sexual partners of HCV-infected patients). The risk of perinatal transmission is much lower with hepatitis C (6% of births to infected mothers) than with hepatitis B (20% to 60% of births to infected mothers). Against the background anti-HCV seroprevalence of 1.8% in the United States, the prevalence is higher in house contacts, homosexuals, hemodialysis patients, hemophiliacs, and intravenous drug abusers (the last approaching 50% to 90%). Patients with unexplained cirrhosis and hepatocellular carcinoma have anti-HCV prevalence rates exceeding 50%. Acute HCV infection is generally undetected clinically. In contrast to HBV, progression to chronic disease occurs in the majority of infected individuals, and cirrhosis eventually occurs in approximately 20% of patients with chronic HCV infection. Thus, over the next decade, HCV could become the leading cause of chronic liver disease in the Western world, as there is a substantial reservoir of individuals at risk for progression to cirrhosis.

![Figure 18-12 Schematic of the potential outcomes of hepatitis C infection in adults, with their approximate frequencies in the United States.](image)

HCV, and the closely related hepatitis G virus, is a hepacivirus and occupies a genus in the Flaviviridae family. HCV is a small, enveloped, single-stranded RNA virus, with a 9-kb genome that codes for single polyprotein of approximately 3010 amino acids in one single open reading frame. This protein is subsequently processed into functional proteins. The 5' end of the genome encodes a highly conserved nucleocapsid core protein, followed by envelope proteins E1 and E2. Two hypervariable regions (HVR 1 and 2) are present in the E2 sequence. A protein of uncertain function, p7, is coded next. Toward the 3' end are six less conserved nonstructural proteins: NS2, NS3, NS4A, NS4B, NS5A, and NS5B. NS5B is the viral RNA-dependent RNA polymerase. The 3' sequences of both the positive- and negative-strand RNAs contribute cis-acting functions that are essential for viral replication. The secondary structure and protein-binding properties of these highly conserved nontranslated regions are thought to promote HCV RNA synthesis and genome stability through the binding of various host and viral proteins.
Figure 18-13  Diagrammatic representation of the genomic structure and transcribed components of the hepatitis C virion. The hepatitis C virion is transcribed in one single transcript, as depicted in the top line; 340 nucleotides at the 5’ end and 128 nucleotides at the 3’ end are not translated into protein. The protein products cleaved from the single translated peptide are shown in the bottom bar.

Owing to the poor fidelity of the HCV RNA polymerase (NS5B), the virus is inherently unstable, giving rise to multiple genotypes and subtypes. Indeed, within any given patient, HCV circulates as a population of divergent genomes exhibiting a quasispecies distribution.[20] Specifically, over time, several dozen mutant strains can be detected within one individual and mapped as derivative strains of the original HCV strain infecting that individual. The E2 protein of the envelope is the target of many anti-HCV antibodies but is also the most variable region of the entire viral genome, enabling emergent virus strains to escape from neutralizing antibodies. This genomic instability and antigenic variability have seriously hampered efforts to develop an HCV vaccine. In particular, elevated titers of anti-HCV IgG occurring after an active infection do not confer effective immunity. Moreover, HCV is able to actively evade the interferon (IFN)-mediated cellular antiviral response, because E2 and NS5A inhibit the interferon-induced double-stranded RNA-activated protein kinase, which is involved in the antiviral response to IFN.[21] A characteristic feature of HCV infection, therefore, is repeated bouts of hepatic damage, the result of reactivation of a preexisting infection or emergence of an endogenous, newly mutated strain. Persistent infection and chronic hepatitis are the hallmarks of HCV infection, despite the generally asymptomatic nature of the acute illness. Cirrhosis may develop over 5 to 20 years after acute infection.

Serologic Diagnosis.

The incubation period for HCV hepatitis ranges from 2 to 26 weeks, with a mean between 6 and 12 weeks. HCV RNA is detectable in blood for 1 to 3 weeks, coincident with elevations in serum transaminases (Fig. 18-14A). In symptomatic acute HCV infection, anti-HCV antibodies are detected in only 50% to 70% of patients; in the remaining patients, the anti-HCV antibodies emerge after 3 to 6 weeks. The clinical course of acute HCV hepatitis is milder than that of HBV; rare cases may be severe and indistinguishable from HAV or HBV hepatitis.
In chronic HCV infection, circulating HCV RNA persists in many patients despite the presence of neutralizing antibodies, including more than 90% of patients with chronic disease (Fig. 18-14B). Hence, in patients with symptoms of chronic hepatitis, HCV RNA testing must be performed to assess viral replication and to confirm the diagnosis of HCV infection. A clinical feature that is quite characteristic of chronic HCV infection is episodic elevations in serum aminotransferases, with intervening normal or near-normal periods.

**Hepatitis D Virus**

Also called “hepatitis delta virus,” hepatitis D virus (HDV) is a unique RNA virus that is replication defective, causing infection only when it is encapsulated by HBsAg. Thus, although taxonomically distinct from HBV, HDV is absolutely dependent on the genetic information provided by HBV for multiplication and causes hepatitis only in the presence of HBV. Delta hepatitis thus arises in two settings (Fig. 18-15).

- **Acute coinfection** occurs following exposure to serum containing both HDV and HBV. The HBV must become established first to provide the HBsAg necessary for development of complete HDV virions.

- **Superinfection** of a chronic carrier of HBV with a new inoculum of HDV (and HBV) results in disease about 30 to 50 days later. The carrier may have been previously “healthy” or may have had underlying chronic hepatitis.
Simultaneous coinfection with HBV and HDV results in hepatitis ranging from mild to fulminant, fulminant disease being more likely (about 3% to 4%) than with HBV alone. Chronicity rarely develops. When HDV is superimposed on chronic HBV infection, there are three possible outcomes: (1) acute, severe hepatitis may erupt in a previously healthy HBV carrier; (2) mild HBV hepatitis may be converted into fulminant disease; and/or (3) chronic, progressive disease may develop (in 80% of patients), often culminating in cirrhosis.

Infection by the delta agent is worldwide, but the prevalence varies greatly. In Africa, the Middle East, and southern Italy, 20% to 40% of HBsAg carriers have anti-HDV antibody. In the United States, delta infection is uncommon and is largely restricted to drug addicts and hemophiliacs, who exhibit prevalence rates of 1% to 10%. Other groups at high risk for HBV, such as homosexual men and health care workers, are at low risk for HDV infection, for unclear reasons. Surprisingly, delta infection is uncommon in the large population of HBsAg carriers in Southeast Asia and China.

HDV is a 35-nm, double-shelled particle that by electron microscopy resembles the “Dane particle” of HBV. The external coat antigen of HBsAg surrounds an internal polypeptide assembly, designated delta antigen (HDAg). Associated with HDAg is a small (1689 base pairs), circular molecule of single-stranded RNA, whose length is smaller than the genome of any known animal virus. This RNA is considered “genomic,” but HDAg is the only HDV-encoded protein product that has been detected to date.
Serologic Diagnosis.

HDV RNA is detectable in the blood and liver just prior to and in the early days of acute symptomatic disease (Fig. 18-16). IgM anti-HDV is the most reliable indicator of recent HDV exposure, although its appearance is late and frequently short-lived. Nevertheless, acute coinfection by HDV and HBV is best indicated by detection of IgM against both HDAg and HBcAg (denoting new infection with hepatitis B). With chronic delta hepatitis arising from HDV superinfection, HBsAg is present in serum, and IgM anti-HDV persists for months or longer.

![Figure 18-16](image)

**Figure 18-16**  Sequence of serologic markers for hepatitis D viral hepatitis depicting (A) coinfection with hepatitis B virus (HBV) and (B) superinfection of an HBV carrier.

Hepatitis E Virus

Hepatitis E virus (HEV) hepatitis is an enterically transmitted, water-borne infection that occurs primarily in young to middle-aged adults; sporadic infection and overt illness in children are rare. Epidemics have been reported from Asia and the Indian subcontinent, sub-Saharan Africa, and Mexico. Sporadic infection seems to be uncommon and is seen mainly in travelers. Indeed, HEV accounts for over 50% of cases of sporadic acute hepatitis in India, exceeding the frequency of HAV. A characteristic feature of HEV infection is the high mortality rate among pregnant women, approaching 20%. In most cases, the disease is self-limiting; HEV is not associated with chronic liver disease or persistent viremia. The average incubation period following exposure is 6 weeks.

HEV is an unenveloped, single-stranded RNA virus that is structurally similar to the Caliciviridae. Viral particles are 32 to 34 nm in diameter, and the RNA genome is approximately 7.6 kb in size. A specific antigen (HEV Ag) can be identified in the cytoplasm of hepatocytes during active infection, and virions are shed in stool during the acute illness.
Serologic Diagnosis.

Before the onset of clinical illness, HEV RNA and HEV virions can be detected in stool and liver. The onset of rising serum aminotransferases, clinical illness, and elevated IgM anti-HEV titers are virtually simultaneous. Symptoms resolve in 2 to 4 weeks, during which time the IgM is replaced with a persistent IgG anti-HEV titer.

Other Hepatitis Viruses

Epidemiologic studies have established that some cases of hepatitis are caused by infectious agents other than those listed earlier. The epidemiologic event that was ascribed to a putative "F" has not been repeated, and no F agent has been identified. However, a flavivirus bearing similarities to HCV was cloned in 1995 and designated hepatitis G virus. Later, an identical virus called GB virus type C (GBC) was isolated. HGV is transmitted by contaminated blood or blood products and possibly via sexual contact. The prevalence of HGV RNA in blood donors ranges from 1% to 4%; and in a report from Taiwan, the incidence of new HGV infections among hemodialysis patients exceeds 2% per year. In up to 75% of infections, HGV is cleared from plasma; in the remainder of cases, HGV infection becomes chronic. The site of HGV replication is most likely in mononuclear cells; hence, HGV is inappropriately named, as it is not hepatotropic and does not cause elevations in serum aminotransferases. Extensive data do not indicate any pathologic effects of HGV, and the blood supply does not appear to need screening for HGV RNA. This virus commonly co-infects patients with HIV, and curiously this dual infection is somewhat protective against HIV disease.

Clinicopathologic Syndromes

A number of clinical syndromes may develop following exposure to hepatitis viruses:

- Acute asymptomatic infection with recovery: serologic evidence only
- Acute symptomatic hepatitis with recovery: anicteric or icteric
- Chronic hepatitis: without or with progression to cirrhosis
- Fulminant hepatitis: with massive to submassive hepatic necrosis

Each of the hepatotropic viruses can cause acute asymptomatic or symptomatic infection. A small number of HBV-infected patients develop chronic hepatitis; HCV is notorious for chronic infection. With rare exceptions, HAV and HEV do not cause chronic hepatitis. Fulminant hepatitis is unusual, and almost unheard of with HCV. Other infectious or noninfectious causes, particularly drugs and toxins, can lead to essentially identical clinical syndromes. Therefore, serologic and molecular studies are essential for the diagnosis of viral hepatitis and the distinction between the various types.

Acute Asymptomatic Infection with Recovery
Patients in this group are identified only incidentally on the basis of minimally elevated serum transaminases or, after the fact, by the presence of antiviral antibodies. Worldwide, HAV and HBV infection are frequently subclinical events in childhood, verified only in adulthood by the presence of anti-HAV or anti-HBV antibodies. Although asymptomatic acute infection is most often the case for HCV-infected patients for whom the exposure event is not known, recovery and eradication of the virus are not common.

Acute Symptomatic Infection with Recovery

Any one of the hepatotropic viruses can cause symptomatic acute viral hepatitis, although this is uncommon for acute HCV infection. Whatever the agent, the disease is more or less the same and can be divided into four phases: (1) an incubation period, (2) a symptomatic preicteric phase, (3) a symptomatic icteric phase, and (4) convalescence. The incubation period for the different viruses is given in Table 18-6. Peak infectivity occurs during the last asymptomatic days of the incubation period and the early days of acute symptoms.

The preicteric phase is marked by nonspecific, constitutional symptoms. Malaise is followed in a few days by general fatigability, nausea, and loss of appetite. Weight loss, low-grade fever, headaches, muscle and joint aches, and pains and diarrhea are inconstant symptoms. About 10% of patients with acute hepatitis, most often those with hepatitis B, develop a serum sickness-like syndrome. This consists of fever, rash, and arthralgias, attributable to circulating immune complexes. The true origin of all these symptoms is suggested by elevated serum aminotransferase levels. Physical examination reveals a mildly enlarged, tender liver. In some patients, the nonspecific symptoms are more severe, with higher fever, shaking chills, and headache, sometimes accompanied by right upper quadrant pain and tender liver enlargement.

The icteric phase, if it appears, is caused mainly by conjugated hyperbilirubinemia. Icteric hepatitis is usual in adults (but not children) with acute HAV infection, but it is absent in about half the cases of HBV and in the majority of cases of HCV. Curiously, as jaundice appears and these patients enter the icteric phase, other symptoms begin to abate and the patient feels better. Although not the result of biliary obstruction, the jaundice is nevertheless caused predominantly by conjugated hyperbilirubinemia and hence is accompanied by dark-colored urine related to the presence of conjugated bilirubin. The stools may become lighter owing to cholestasis. Retention of bile acids can cause distressing pruritus. The liver may be mildly enlarged and moderately tender to percussion. Laboratory findings include prolonged prothrombin time and hyperglobulinemia; the serum alkaline phosphatase is usually only mildly elevated. In a few weeks to perhaps several months, the jaundice and most of the other systemic symptoms clear as convalescence begins. Recovery is heralded by the generation of strong T cell responses against viral antigens expressed on infected liver cells.

Chronic Hepatitis

Chronic hepatitis is defined as symptomatic, biochemical, or serologic evidence of continuing or relapsing hepatic disease for more than 6 months, with histologically documented inflammation and necrosis. Although the hepatitis viruses (HBV, HCV, and HBV + HDV) are responsible for most
cases of chronic hepatitis, there are many other causes of chronic hepatitis (described later). They include chronic alcoholism, Wilson disease, α₁-antitrypsin deficiency, drugs (e.g., isoniazid, α-methyldopa, methotrexate), and autoimmunity. *In all instances of chronic hepatitis, etiology is the single most important indicator of likelihood to progress to cirrhosis.*

Chronic viral hepatitis constitutes a "carrier" state, in that these individuals harbor replicating virus and therefore can transmit an organism. With "carriers" of hepatotropic viruses, there are (1) those who harbor one or more of the viruses but are suffering little or no adverse clinical or histologic effects, (2) those who have chronic disease by laboratory or histologic findings but are essentially free of symptoms or disability, and (3) those who have clinically symptomatic chronic disease. All constitute reservoirs of infection. In the case of HBV, infection early in life, particularly via vertical transmission during childbirth, produces a carrier state 90% to 95% of the time. In contrast, only 1% to 10% of adult HBV infections yield a carrier state. *Individuals with impaired immunity are particularly likely to become HBV carriers,* because the protective T cell response does not develop. The situation is less clear with HDV, although there is a well-defined low risk of posttransfusion hepatitis D, indicative of a carrier state in conjunction with HBV. HCV can clearly induce a carrier state given its high rate of chronicity.

The clinical features of chronic hepatitis are extremely variable and are not predictive of outcome. In some patients, the only signs of chronic disease are persistent elevations of serum transaminases. The most common symptom is fatigue; less common symptoms are malaise, loss of appetite, and occasional bouts of mild jaundice. Physical findings are few, the most common being spider angiomas, palmar erythema, mild hepatomegaly, hepatic tenderness, and mild splenomegaly. Laboratory studies may reveal prolongation of the prothrombin time and, in some instances, hyperglobulinemia, hyperbilirubinemia, and mild elevations in alkaline phosphatase levels. Occasionally, in cases of HBV and HCV, immune complex disease may develop secondary to the presence of circulating antibody-antigen complexes, in the form of vasculitis (subcutaneous or visceral, Chapter 11) and glomerulonephritis (Chapter 20). Cryoglobulinemia is found in about 35% of patients with chronic HCV hepatitis.

The clinical course of viral hepatitis is unpredictable. Patients may experience spontaneous remission or may have indolent disease without progression for many years. Conversely, some patients have rapidly progressive disease and develop cirrhosis within a few years. The major causes of death are cirrhosis, with liver failure and hepatic encephalopathy or massive hematemesis from esophageal varices, and hepatocellular carcinoma in those with long-standing HBV (particularly neonatal) or HCV infection.

**Morphology of Acute and Chronic Hepatitis.**

The general morphologic features of viral hepatitis are given in Table 18-7 and are depicted schematically in Figure 18-17. The morphologic changes in acute and chronic viral hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions. Tissue alterations caused by acute infection with HAV, HBV, HCV, and HEV are similar, as is the chronic hepatitis caused by HBV, HCV, and HBV + HDV. A few histologic changes may be indicative of a particular type of virus. HBV-infected hepatocytes may exhibit a cytoplasm
packed with spheres and tubules of HBsAg, producing a finely granular eosinophilic cytoplasm ("ground glass hepatocytes," Fig. 18.18). HCV-infected livers frequently show lymphoid aggregates within portal tracts and focal sublobular regions of hepatocyte macrovesicular steatosis, which are to be distinguished from the extensive panlobular microvesicular and macrovesicular steatosis seen in many forms of toxic hepatitis (e.g., alcohol-induced).

Table 18-7  -- Key Morphologic Features of Viral Hepatitis

<table>
<thead>
<tr>
<th>Acute Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enlarged, reddened liver; greenish if cholestatic</td>
</tr>
<tr>
<td>Parenchymal changes:</td>
</tr>
<tr>
<td>Hepatocyte injury: swelling (ballooning degeneration)</td>
</tr>
<tr>
<td>Cholestasis: canalicular bile plugs</td>
</tr>
<tr>
<td>HCV: mild focal fatty change of hepatocytes</td>
</tr>
<tr>
<td>Hepatocyte necrosis: isolated cells or clusters</td>
</tr>
<tr>
<td>Cytolysis (rupture) or apoptosis (shrinkage)</td>
</tr>
<tr>
<td>If severe: bridging necrosis (portal-portal, central-central, portal-central)</td>
</tr>
<tr>
<td>Lobular disarray: loss of normal architecture</td>
</tr>
<tr>
<td>Regenerative changes: hepatocyte proliferation</td>
</tr>
<tr>
<td>Sinusoidal cell reactive changes:</td>
</tr>
<tr>
<td>Accumulation of phagocytosed cellular debris in Kupffer cells</td>
</tr>
<tr>
<td>Influx of mononuclear cells into sinusoids</td>
</tr>
<tr>
<td>Portal tracts:</td>
</tr>
<tr>
<td>Inflammation: predominantly mononuclear</td>
</tr>
<tr>
<td>Inflammatory spillover into adjacent parenchyma, with hepatocyte necrosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chronic Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes shared with acute hepatitis:</td>
</tr>
<tr>
<td>Hepatocyte injury, necrosis, and regeneration</td>
</tr>
<tr>
<td>Sinusoidal cell reactive changes</td>
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<tr>
<td>Portal tracts:</td>
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<tr>
<td>Inflammation:</td>
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<tr>
<td>Confined to portal tracts, or</td>
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<tr>
<td>Spillover into adjacent parenchyma, with necrosis of hepatocytes (&quot;interface hepatitis&quot;), or</td>
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Bridging inflammation and necrosis

Fibrosis:
- Portal deposition, or
- Portal and periportal deposition, or
- Formation of bridging fibrous septa

HBV: “ground-glass” hepatocytes, “sanded” nuclei
HCV: bile duct epithelial cell proliferation, lymphoid aggregate formation

Cirrhosis: The end-stage outcome

Figure 18-17  Diagrammatic representations of the morphologic features of acute and chronic hepatitis. Bridging necrosis (and fibrosis) is shown only for chronic hepatitis; bridging necrosis may also occur in acute hepatitis (not shown).
**Figure 18-18** Hepatitis B viral infection. A, Liver parenchyma showing hepatocytes with diffuse granular cytoplasm, so-called ground glass hepatocytes. (H&E) B, Immunoperoxidase stain for HBsAg from the same case, showing cytoplasmic inclusions of viral particles.

**Acute Hepatitis.**

With acute hepatitis (Fig. 18-17A and Fig. 18-19), hepatocyte injury takes the form of diffuse swelling ("ballooning degeneration"), so the cytoplasm looks empty and contains only scattered eosinophilic remnants of cytoplasmic organelles. An inconstant finding is *cholestasis*, with bile plugs in canaliculi and brown pigmentation of hepatocytes. The canalicular bile plugs result from cessation of the contractile activity of the hepatocyte pericanalicular actin microfilament web. Two patterns of hepatocyte cell death are seen. In the first, rupture of cell membranes leads to cytolysis and focal loss of hepatocytes. The sinusoidal collagen reticulin framework collapses where the cells have disappeared, and scavenger *macrophage aggregates* mark sites of hepatocyte loss. The second pattern of cell death, *apoptosis*, is more conspicuous. It is caused by anti-viral cytotoxic T cells. Apoptotic hepatocytes shrink, become intensely eosinophilic, and have fragmented nuclei; effector T cells may still be present in the immediate vicinity. Apoptotic cells also are phagocytosed within hours by macrophages and hence might be difficult to find despite a brisk rate of hepatocyte injury. In severe cases of acute hepatitis (not depicted in Fig. 18-17A), confluent necrosis of hepatocytes may lead to *bridging necrosis* connecting portal-to-portal, central-to-central, or portal-to-central regions of adjacent lobules. Hepatocyte swelling and regeneration compress sinusoids, and the more or less radial array of the parenchyma is lost.
Inflammation is a characteristic and usually prominent feature of acute hepatitis. Kupffer cells undergo hypertrophy and hyperplasia and are often laden with lipofuscin pigment due to phagocytosis of hepatocellular debris. The portal tracts are usually infiltrated with a mixture of inflammatory cells. The inflammatory infiltrate may spill over into the adjacent parenchyma to cause necrosis of periportal hepatocytes; this “interface hepatitis” can occur in both acute and chronic hepatitis. Finally, bile duct epithelia may become reactive and even proliferate to form poorly defined ductular structures (ductular reaction), particularly in cases of HCV hepatitis.

Chronic Hepatitis.

The histologic features of chronic hepatitis (Fig. 18-17B and Fig. 18-20 ) range from exceedingly mild to severe. In the mildest forms, significant inflammation is limited to portal tracts and consists of lymphocytes, macrophages, occasional plasma cells, and rare neutrophils or eosinophils. Liver architecture is usually well preserved, but smoldering hepatocyte necrosis throughout the lobule may occur in all forms of chronic hepatitis. Even in mild chronic hepatitis due to HCV infection, common findings are lymphoid aggregates and bile duct damage in the portal tracts and focally mild to moderate macrovesicular steatosis. In all forms of chronic hepatitis, continued interface hepatitis and bridging necrosis are harbingers of progressive liver damage. The hallmark of irreversible liver damage is the deposition of fibrous tissue. At first, only portal tracts exhibit increased fibrosis, but with time, periporal septal fibrosis occurs, followed by linking of fibrous septa between lobules (bridging fibrosis).
Chronic viral hepatitis due to hepatitis C virus, showing portal tract expansion with inflammatory cells and fibrous tissue and interface hepatitis with spillover of inflammation into the adjacent parenchyma. A lymphoid aggregate is present.

**Continued loss of hepatocytes and fibrosis results in cirrhosis, with fibrous septae and hepatocyte regenerative nodules.** This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable but mostly broad scars (Fig. 18-21). Historically, this pattern of cirrhosis has been termed **postnecrotic cirrhosis**, but it should be noted that the term "postnecrotic cirrhosis" has been applied to all forms of cirrhosis in which the liver shows large, irregular-sized nodules with broad scars, regardless of etiology. Autoimmune hepatitis, hepatotoxins (carbon tetrachloride, mushroom poisoning), pharmaceutical drugs (acetaminophen, α-methyldopa), and even alcohol (discussed later) may give rise to a cirrhotic liver with irregular-sized large nodules. In some cases that come to autopsy, the inciting cause of the so-called postnecrotic cirrhosis cannot be determined at all ("cryptogenic cirrhosis"). In essence, the morphology of the end-stage cirrhotic liver is neither helpful in determining the basis of the liver injury, nor can it be easily related to any specific set of clinical circumstances.

**Figure 18-20** Chronic viral hepatitis due to hepatitis C virus, showing portal tract expansion with inflammatory cells and fibrous tissue and interface hepatitis with spillover of inflammation into the adjacent parenchyma. A lymphoid aggregate is present.

**Figure 18-21** Cirrhosis resulting from chronic viral hepatitis. Note the broad scar and coarse nodular surface.
Fulminant Hepatitis

When hepatic insufficiency progresses from onset of symptoms to hepatic encephalopathy within 2 to 3 weeks, it is termed fulminant hepatic failure. A less rapid course, extending up to 3 months, is called subfulminant failure. Causes of fulminant hepatitis include:

- In the United States, fulminant viral hepatitis is responsible for about 12% of cases of fulminant hepatic failure; almost all due to HAV or HBV. Sometimes, reactivation of chronic hepatitis B or acute herpesvirus infection is the cause.
- Drug and chemical toxicity account for a substantial remainder (52%), acting either as direct hepatotoxins or via idiosyncratic inflammatory reactions. Principally implicated are acetaminophen (in suicidal doses), other drugs such as isoniazid, antidepressants (particularly monoamine oxidase inhibitors), halothane, and methyldopa.
- Miscellaneous other causes such as exposure to the mycotoxins of the mushroom Amanita phalloides account for the remainder. In about 18% of cases, the cause of fulminant hepatic failure is unknown.

Much rarer causes, but just as life-threatening, are ischemic hepatic necrosis, obstruction of the hepatic veins, massive malignant infiltration of the liver, Wilson disease, hyperthermia (heat stroke), and microvesicular steatosis syndromes, particularly acute fatty liver of pregnancy. The evolution of hepatic failure is extremely variable and is significantly influenced by the previous status of the liver and patient age (younger patients fare better).

Fulminant hepatic failure may present as jaundice, encephalopathy, and fetor hepaticus, as described previously. Notably absent on physical examination are stigmata of chronic liver disease (e.g., gynecomastia, spider angiomas). Life-threatening extrahepatic complications include coagulopathy and bleeding, cardiovascular instability, renal failure, adult respiratory distress syndrome, electrolyte and acid-base disturbances, and sepsis. The overall mortality rate ranges from 25% to 90% in the absence of liver transplantation.

Morphology.

All causative agents produce essentially identical morphologic changes that vary with the severity of the necrotizing process. With all, the distribution of liver destruction is extremely capricious: The entire liver may be involved or only random areas. With massive loss of substance, the liver may shrink to as little as 500 to 700 gm. In so doing, it is transformed into a limp, red organ covered by a wrinkled, too-large capsule. On transection (Fig. 18-22A), necrotic areas have a muddy red, mushy appearance with blotchy bile staining. Microscopically, complete destruction of hepatocytes in contiguous lobules leaves only a collapsed reticulin framework and preserved portal tracts. There may be surprisingly little inflammatory reaction. Alternatively, with survival for several days,
there is a massive influx of inflammatory cells to begin the phagocytic cleanup process (Fig. 18-22).

Figure 18-22  Massive necrosis. A, Cut section of liver. The liver is small (700 gm), bile-stained, and soft. The capsule is wrinkled. B, Microscopic section. Portal tracts and terminal hepatic veins are closer together than normal, owing to necrosis and collapse of the intervening parenchyma. The rudimentary ductal structures are the result of early ductular regeneration. An infiltrate of mononuclear inflammatory cells is present.

Patient survival for more than a week also permits secondary regenerative activity of surviving hepatocytes and bile ducts. The bipotential proliferative compartment linking hepatocytes with the biliary tree—the canal of Hering—also is a major site of the regenerative response, giving rise to poorly formed ductular structures. A dormant stem cell population lying alongside the bile ductules and canals of Hering also proliferates, generating a population of small cells with a high nuclear:cytoplasmic ratio (so-called oval cells) interspersed with surviving hepatocytes (see Chapter 3). Given sufficient time (i.e., survival of the patient beyond the first several weeks), the liver can recover completely with maturation of all proliferating cell populations into morphologically normal hepatocytes and bile duct epithelial cells.

With centrilobular zonal necrosis caused by direct hepatotoxins (acetaminophen, carbon tetrachloride) or ischemia, the parenchymal framework is preserved. Regeneration is directly from hepatocytes, and native liver architecture is restored in time. With more massive destruction of confluent lobules, regeneration is disorderly, yielding nodular masses of liver cells that produce a more irregular liver on healing.

Fibrous scarring may occur in patients with a protracted course of submassive or patchy necrosis, representing a route for developing so-called postnecrotic cirrhosis, as noted earlier.
(From: http://www.mdconsult.com/das/book/body/110253190-6/0/1249/207.html?tocnode=51156750&fromURL=207.html#4-u1.0-B0-7216-0187-1..50022-5--cesec35_2475)