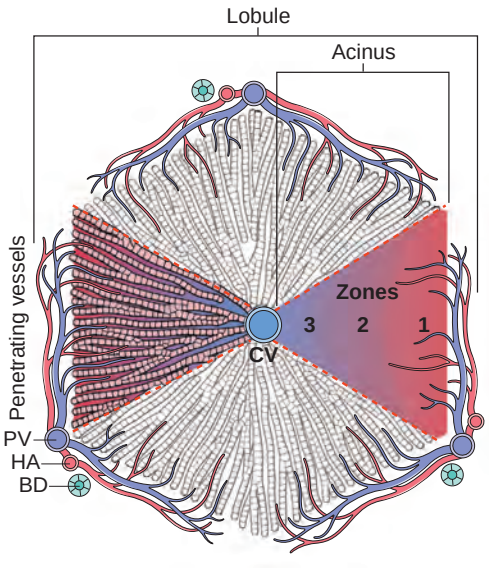

Figure 18-1 Models of liver anatomy. In the lobular model, the terminal hepatic vein (CV) is at the center of a "lobule," while the portal tracts (PV) are at the periphery. Pathologists often refer to the regions of the parenchyma as "periportal" and "centrilobular." In the acinar model, on the basis of blood flow, three zones can be defined, zone 1 being the closest to the blood supply and zone 3 being the farthest. BD, Bile duct; HA, hepatic artery.

called "centrilobular"; those near the portal tract are "periportal." *Division of the parenchyma into zones is a useful concept since certain types of hepatic injury tend to preferentially affect particular zones.* This results in part from the zonal gradient of oxygenation and metabolic activities.

Within the lobule, hepatocytes are organized into anastomosing sheets or "plates" extending from portal tracts to the terminal hepatic veins. Between the trabecular plates of hepatocytes are vascular *sinusoids*. Blood traverses the sinusoids and exits into the terminal hepatic veins through numerous orifices in the vein wall. Hepatocytes are thus bathed on two sides by well-mixed, portal venous and hepatic arterial blood. The sinusoids are lined by fenestrated endothelial cells. Beneath the endothelial cells lies the *space of Disse*, into which protrude abundant hepatocyte microvilli. Scattered *Kupffer cells* of the mononuclear phagocyte system are attached to the luminal face of endothelial cells, and fat-containing myofibroblastic *hepatic stellate cells* are found in the space of Disse. Between abutting hepatocytes are *bile canaliculi*, which are channels 1 to 2 µm in diameter, formed by grooves in the plasma membranes of facing hepatocytes and separated from the vascular space by tight junctions. These channels drain into the *canals of Hering* that, in turn, connect to *bile ductules* in the periportal region. The ductules empty into the *terminal bile ducts* within the portal tracts. Large numbers of lymphocytes are also present in normal liver, comprising as much as 22% of cells other than hepatocytes.

General Features of Liver Disease

The liver is vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults. The major primary diseases of the liver are viral hepatitis, nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, and hepatocellular carcinoma (HCC). Hepatic damage also occurs secondary to some of the most common diseases in humans, such as heart failure, disseminated cancer, and extrahepatic infections. The enormous functional reserve of the liver masks the clinical impact of mild liver damage, but with progression of diffuse disease or disruption of bile flow, the consequences of deranged liver function may become life-threatening.

With the exception of acute liver failure failure, liver disease is an insidious process in which clinical detection and symptoms of hepatic decompensation may occur weeks, months, or many years after the onset of injury. The ebb and flow of hepatic injury may be imperceptible to the patient and detectable only by abnormal laboratory tests (Table 18-1); liver injury and healing may also occur without clinical detection. Hence, individuals with hepatic abnormalities who are referred to hepatologists most frequently have chronic liver disease.

Mechanisms of Injury and Repair

Hepatocyte and Parenchymal Responses

Hepatocytes can undergo a number of degenerative, but potentially reversible changes, such as accumulation of fat (steatosis) and bilirubin (cholestasis). When injury is not reversible, hepatocytes die principally by two mechanisms: necrosis or apoptosis.

In *hepatocyte necrosis*, the cell swells due to defective osmotic regulation at the cell membrane: fluid flows into the cell, which swells and ruptures. Even before rupture, membrane blebs form, carrying off cytoplasmic contents (without organelles) into the extracellular compartment. Macrophages cluster at such sites of injury and mark the sites of hepatocyte necrosis since the dying cells essentially burst and disappear (Fig. 18-2). This form of injury is the

Table 18-1 Laboratory Evaluation of Liver Disease

Test Category	Serum Measurement
Hepatocyte integrity	Cytosolic hepatocellular enzymes†
	Serum aspartate aminotransferase (AST)
	Serum alanine aminotransferase (ALT)
	Serum lactate dehydrogenase (LDH)
Biliary excretory function	Substances normally secreted in bile†
	Serum bilirubin
	Total: unconjugated plus conjugated
	Direct: conjugated only
	Urine bilirubin
	Serum bile acids
	Plasma membrane enzymes (from damage to bile canaliculus)†
	Serum alkaline phosphatase
	Serum γ-glutamyl transpeptidase (GGT)
Hepatocyte synthetic function	Proteins secreted into the blood
	Serum albumin‡
	Coagulation factors:
	Prothrombin (PT) and partial thromboplastin (PTT) times (fibrinogen, prothrombin,factors V, VII, IX,and X)
	Hepatocyte metabolism
	Serum ammonia†
	Aminopyrine breath test (hepatic demethylation)‡

†Increased in liver disease.
‡Decreased in liver disease.