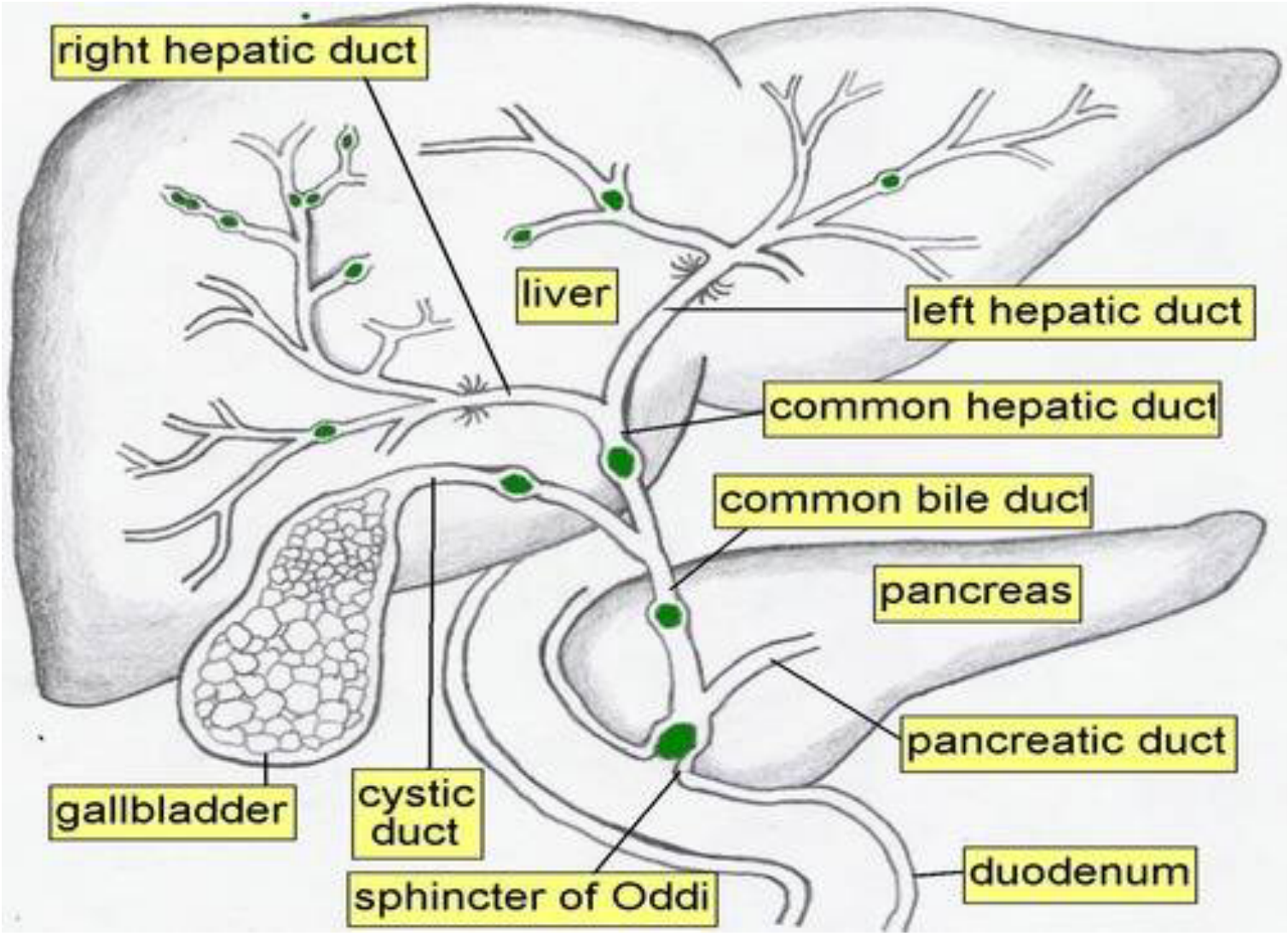
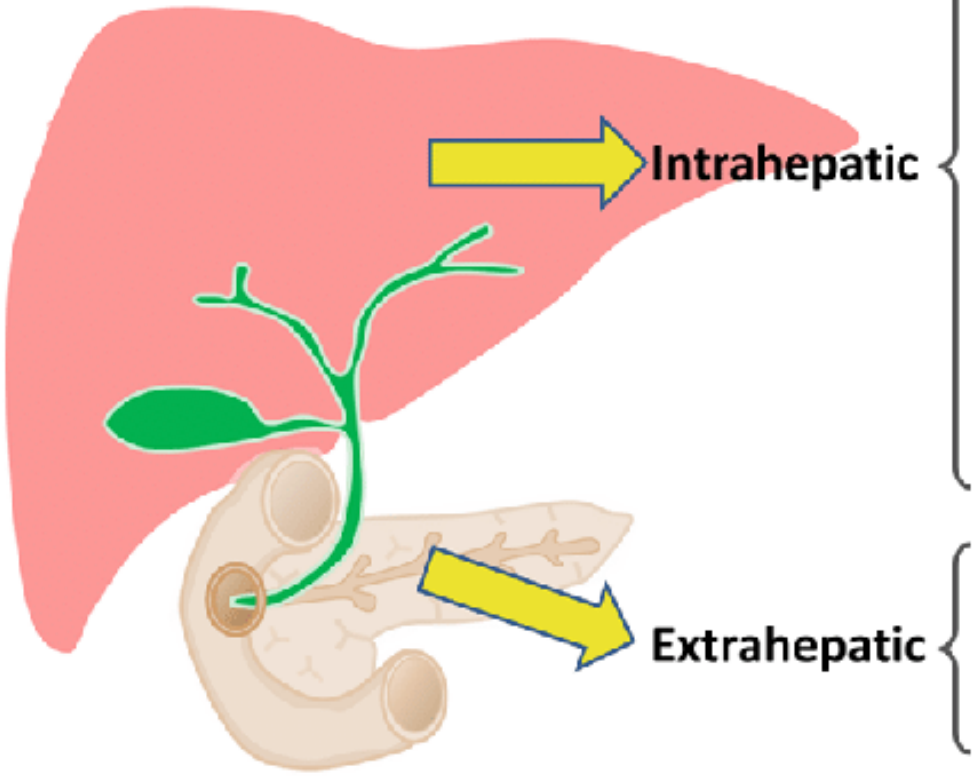




Intrahepatic

- Hepatobiliary infections
- Inherited/metabolic dis
- Ductal anomaly
- Endocrine dis
- Prematurity
- Drugs
- Ischemia
- Parenteral nutrition
- Sepsis

Extrahepatic

- Biliary atresia
- Choledochal cyst
- Tumor
- Cholelithiasis

Liver failure → acute
→ chronic
→ acute on chronic

Acute liver failure

- liver disease that produces hepatic encephalopathy within 6 months
- fulminant liver failure
  → encephalopathy develops in 2 weeks of onset of jaundice
- subfulminant liver failure
  → encephalopathy develops in 3 months.

morphology - massive hepatic necrosis → small and shrunken liver due to loss in parenchyma
- microscopically → large zones of destruction surrounding islands of regenerating hepatocytes

Clinical features
- Nausea, vomiting
- Jaundice and icterus
  → due to retention of bilirubin
  → cholestasis - retention of bilirubin and other solutes eliminated in the bile
- Hepatic encephalopathy
  - disturbance in consciousness ranging from subtle behavioral changes to confusion, stupor, coma, death
  - encephalopathy develop over weeks, months after acute injury → rigidity, hyperreflexia, and asterixis may develop
  - elevated ammonia in blood CNS
    → neurologic problems
    → brain edema
- Coagulopathy → liver is source of many coagulation factors that decline due to liver injury
  → easy bruising, bleeding, DIC
- Portal HTN → due to diminished flow of blood in portal venous system
  → obstruction in prehepatic, intrahepatic or post hepatic levels
  → can be seen in acute liver injury but mostly seen in chronic liver failure
  → in acute → usually intrahepatic and major consequence is ascitis and hepatic encephalopathy

- Hepatorenal syndrome - renal failure due to liver failure
→ sodium retention
→ impaired free water excretion
→ ↓ renal perfusion + ↓ GFR
→ ↓ renal perfusion → systemic vasodilation
→ sympathethic Nervous System activated
→ vasoconstriction of afferent arterioles
→ ↑ activation of RAAS
→ vasoconstriction farther
→ ↓ GFR
→ ↓ urine output and increased creatinine level

Chronic Liver Failure and Cirrhosis

Cirrhosis → morphological changes associated with chronic liver failure
→ diffuse transformation of liver into regenerative parenchymal nodules surrounded by fibrosis band
- caused by: chronic hepatitis B and C, non-alcoholic fatty liver disease and alcoholic liver disease
- cirrhosis wont develop in all cases with chronic liver failure and end stage liver disease

Pathogenesis → 2 primary ingredients: Hepatic fibrosis; regeneration of liver cells

- Injury + loss of cells
→ growth regulators induce - hepatocellular hyperplasia
⇒ produces regenerating nodules
- arterial growth
⇒ angiogenesis

- growth regulators
→ cytokines &
→ hepatic growth factors (epithelial growth factor, hepatocyte growth factor, transforming growth factor alpha, tumor necrosis factor)

- Insulin, glucagon and blood flow determine how and where the nodules form

→ Angiogenesis produces new vessels within fibrosis sheath that surrounds nodules
→ vessels connects hepatic artery and portal vein to hepatic venules
→ restoring intrahepatic circulatory pathway

→ these interconnecting vessels
→ provide low volume but high pressure venous drainage

→ portal vein pressure ↑
→ distorted blood flow contribute to portal HTN, which increase due to regenerating nodules compress hepatic venules

Clinical features

- 40% with cirrhosis are asymptomatic
  - anorexia, weight loss, weakness, jaundice, encephalopathy and coagulation problem

① Chronic Severe Jaundice
→ pruritis
→ can cause infection
→ can be related to cholestasis (might be related to bile salt build up)

② Portal HTN
→ more common in chronic
→ Portosystemic shunts develop due to reversed blood flow from portal to systemic circulation
→ shunts are produced by dilation of collateral vessels

→ Venous bypass develops when portal circulation and systemic circulation share common capillary bed
→ causes esophagogastric varices (40% in chronic)
→ can cause fatal hematemesis

→ Portal HTN leads to congestive splenomegaly
→ lower platelet count

④ Hyperestrogenemia
- impaired estrogen metabolism in males with chronic liver failure
→ leads to - palmar erythema (reflection of local vasodilation)
- spider angioma of skin
- hypogonadism
- gynecomastia

⑤ Hepatocellular carcinoma (HCC)

- Cirrhosis varies in development and can regress on disease remission or cure.
- Portal HTN can persist due to irreversible shunts - biopsy → thin fibrous septa
→ large islands of regenerated parenchyma

biopsy - broad band fibrosis → Portal HTN & HCC
- no parenchyma

Acute on chronic liver failure

- patient with well maintained chronic diseases, suddenly develops acute liver failure
  - → usually established cirrhosis + extensive vascular shunting
  - → large volumes of functioning parenchyma with borderline vascular supply
    - → liver is vulnerable to insult.

Sudden liver insult can cause sudden decompensation.
- → chronic liver disease like Hep D superinfection in chronic hep B
- → sepsis
- → acute cardiac failure
- → toxic injury

SUMMARY

LIVER FAILURE

- Liver failure may follow acute injury or chronic injury, or it may occur as an acute insult superimposed on otherwise well-compensated chronic liver disease.
- The mnemonic for causes of acute liver failure are as follows:
  - A: acetaminophen, hepatitis A, autoimmune hepatitis
  - B: hepatitis B
  - C: cryptogenic, hepatitis C
  - D: drugs/toxins, hepatitis D
  - E: hepatitis E, esoteric causes (Wilson disease, Budd-Chiari syndrome)
  - F: fatty change of the microvesicular type (fatty liver of pregnancy, valproate, tetracycline, Reye syndrome)
- Potentially fatal sequelae of liver failure include coagulopathy, encephalopathy, portal hypertension and ascites, hepatorenal syndrome, and portopulmonary hypertension.

Infectious disorders

Viral Hepatitis
- acute or chronic
- A, B, C, D, E

Hepatitis A virus (HAV)
- benign & self limiting usually
  → cant cause chronic hepatitis.
  → 0.1% chance to cause fulminant hepatitis
- 3-6 weeks incubation
- causes febrile illness associated with jaundice
  → fatigue
  → loss of appetite
- 25% of hepatitis cases worldwide

Hep B virus (HBV)
- can cause ① acute hepatitis with recovery and clearance
  ② Non progressive chronic hepatitis
  ③ Progressive chronic disease ending in cirhosis
  ④ fulminant hepatitis with massive liver necrosis
  ⑤ Asymptomatic → healthy carrier state

Hep C virus (HCV)
- caused by - Intravenous drug abuse
  - multiple sex partner
  - surgery
  - needle stick injury
  - medical employment

Hep D virus
- relies on HBV coinfection to cause infection
  → associated with HBV lifecycle

Hep E virus
- enterically transmited water borne infection
  → usually self limiting

SUMMARY

VIRAL HEPATITIS

- In the alphabet of hepatotropic viruses, some easy mnemonic devices may be useful:
  - The vowels (hepatitis A and E) never cause chronic hepatitis, only AcutE hepatitis.
  - Only the consonants (hepatitis B, C, D) have the potential to cause chronic disease (C for consonant and for chronic).
  - Hepatitis B can be transmitted by blood, birthing, and "bonking" (as they say in the United Kingdom).
  - Hepatitis C is the single virus that is more often chronic than not (almost never detected acutely; 85% or more of patients develop chronic hepatitis, 20% of whom will develop cirrhosis).
  - Hepatitis D, the delta agent, is a defective virus, requiring hepatitis B coinfection for its own capacity to infect and replicate.
  - Hepatitis E is endemic in equatorial regions and frequently epidemic.
- The inflammatory cells in both acute and chronic viral hepatitis are mainly T cells; it is the pattern of injury that is different, not the nature of the infiltrate.
- Patients with long-standing HBV or HCV infections are at increased risk for development of HCC.

Table 16.2 The Hepatitis Viruses

Virus	Hepatitis A (HAV)	Hepatitis B (HBV)	Hepatitis C (HCV)	Hepatitis D (HDV)	Hepatitis E (HEV)
Viral genome	ssRNA	partially dsDNA	ssRNA	Circular defective ssRNA	ssRNA
Viral family	Hepatovirus; related to picornavirus	Hepadnavirus	*Flaviviridae*	Subviral particle in *Deltaviridae* family	Calicivirus
Route of transmission	Fecal-oral (contaminated food or water)	Parenteral, sexual contact, perinatal	Parenteral; intranasal cocaine use is a risk factor	Parenteral	Fecal-oral
Incubation period	2–6 weeks	2–26 weeks (mean 8 weeks)	4–26 weeks (mean 9 weeks)	Same as HBV	4–5 weeks
Frequency of chronic liver disease	Never	5%–10%	>80%	10% (coinfection); 90%–100% for superinfection	In immunocompromised hosts only
Diagnosis	Detection of serum IgM antibodies	Detection of HBsAg or antibody to HBcAg; PCR for HBV DNA	ELISA for antibody detection; PCR for HCV RNA	Detection of IgM and IgG antibodies, HDV RNA in serum, or HDAg in liver biopsy	Detection of serum IgM and IgG antibodies; PCR for HEV RNA

ssRNA, Single-stranded RNA; *dsDNA*, double-stranded DNA; *HBcAg*, hepatitis B core antigen; *HBsAg*, hepatitis B surface antigen; *HDAg*, hepatitis D antigen; *ELISA*, enzyme-linked immunosorbent assay.
From Washington K: Inflammatory and infectious diseases of the liver. In Iacobuzio-Donahue CA, Montgomery EA, editors: *Gastrointestinal and liver pathology*, Philadelphia, 2005, Churchill Livingstone.

Bacterial, Parasite, and Helminthic Infections

Pathways
- ① Ascending infection - gut and billiary tree
② Vascular seeding - through portal system via GI system
③ Direct invasion - adjacent source → bacterial cholecystitis
④ Penetrating injury.

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic, progressive hepatitis with all the features of autoimmune diseases in general: genetic predisposition, association with other autoimmune diseases, the presence of autoantibodies, and therapeutic response to immunosuppression. Risk for autoimmune hepatitis is associated with certain HLA alleles, such as the DRB1* allele in Caucasians, but as in other autoimmune disorders the mechanistic basis for this relationship is unclear. Triggers for the immune reaction may include viral infections or drug or toxin exposures.

SUMMARY

- There are two primary types of autoimmune hepatitis:
  - Type 1 autoimmune hepatitis is most often seen in middle-age women and is characteristically associated with antinuclear and anti–smooth muscle antibodies.
  - Type 2 autoimmune hepatitis is most often seen in children or teenagers and is associated with anti–liver kidney microsomal autoantibodies.
- Autoimmune hepatitis may either develop with a rapidly progressive acute disease or follow a more indolent path; if untreated, both are likely to lead to liver failure.
- Plasma cells are a prominent and characteristic component of the inflammatory infiltrate in biopsy specimens showing autoimmune hepatitis.

Drug and Alcohol Induced Liver Injury

- liver is subject to injury → major drug metabolism
  → detoxification organ

- injury occurs through - direct toxicity
  - hepatic conversion of a xenobiotic compound to an active compound
  - immune mechanism

- acetaminophen - most common cause of acute liver failure

Table 16.3 Patterns of Injury in Drug- and Toxin-Induced Hepatic Injury

Pattern of Injury	Morphologic Findings	Examples of Associated Agents
Cholestatic	Bland hepatocellular cholestasis, without inflammation	Contraceptive and anabolic steroids, antibiotics, HAART
Cholestatic hepatitis	Cholestasis with lobular necrosis and inflammation; may show bile duct destruction	Antibiotics, phenothiazines, statins
Hepatocellular necrosis	Spotty hepatocyte necrosis	Methyldopa, phenytoin
	Massive necrosis	Acetaminophen, halothane
	Chronic hepatitis	Isoniazid
Fatty liver disease	Large and small droplet fat	Ethanol, corticosteroids, methotrexate, total parenteral nutrition
	"Microvesicular steatosis" (diffuse small droplet fat)	Valproate, tetracycline, aspirin (Reye syndrome), HAART
	Steatohepatitis with Mallory-Denk bodies	Ethanol, amiodarone
Fibrosis and cirrhosis	Periportal and pericellular fibrosis	Alcohol, methotrexate, enalapril, vitamin A and other retinoids
Granulomas	Noncaseating epithelioid granulomas	Sulfonamides, amiodarone, isoniazid
	Fibrin ring granulomas	Allopurinol
Vascular lesions	Sinusoidal obstruction syndrome (veno-occlusive disease): obliteration of central veins	High-dose chemotherapy, bush teas
	Budd-Chiari syndrome	Oral contraceptives
	Peliosis hepatis: blood-filled cavities, not lined by endothelial cells	Anabolic steroids, tamoxifen

HAART, Highly active anti-retroviral therapy

Adapted from Washington K: Metabolic and toxic conditions of the liver. In Iacobuzio-Donahue CA, Montgomery EA, editors: *Gastrointestinal and liver pathology*, Philadelphia, 2005, Churchill Livingstone.

Alcoholic and Non-alcoholic fatty liver disease

- alcohol is well known to cause fatty liver disease
  → histologically manifest as → ① steatosis
  ② steato hepatitis
  ③ cirrhosis

- morphological changes between alcohol induced and nonalcohol induced is indistinguishable

MORPHOLOGY

Three types of liver alterations are observed in fatty liver disease: steatosis (fatty change), hepatitis (alcoholic or steatohepatitis), and fibrosis.

Hepatocellular steatosis. Hepatocellular fat accumulation typically begins in centrilobular hepatocytes. The lipid droplets range from small (microvesicular) to large (macrovesicular), the largest filling and expanding the cell and displacing the nucleus. As steatosis becomes more extensive, the lipid accumulation spreads outward from the central vein to hepatocytes in the midlobule and then the periportal regions (Fig. 16.16).

Macroscopically, fatty livers with widespread steatosis are large (weighing 4–6 kg or more), soft, yellow, and greasy.

Steatohepatitis. These changes typically are more pronounced with alcohol use than in NAFLD, but can be seen in either:

- **Hepatocyte ballooning.** Single or scattered foci of cells undergo swelling and necrosis; as with steatosis, these features are most prominent in the centrilobular regions (Fig. 16.17A).
- **Mallory-Denk bodies.** These consist of tangled skeins of intermediate filaments (including ubiquitinylated keratins 8 and 18) and are visible as eosinophilic cytoplasmic inclusions in degenerating hepatocytes (see Fig. 16.17B).
- **Neutrophil infiltration.** Predominantly neutrophilic infiltration may permeate the lobule and accumulate around degenerating hepatocytes, particularly those containing Mallory-Denk bodies. Lymphocytes and macrophages also may be seen in portal tracts or parenchyma.

Steatofibrosis. Fatty liver disease of all kinds has a distinctive pattern of scarring. Like other changes, fibrosis appears first in the centrilobular region as **central vein sclerosis.** Perisinusoidal scarring appears next in the space of Disse of the centrilobular region and then spreads outward, encircling individual or small clusters of hepatocytes in a **chicken wire fence pattern** (see Fig. 16.16). Tendrils of fibrosis eventually link to portal tracts and then condense to create **central portal fibrous septa.** As these become more prominent, the liver takes on a nodular, cirrhotic appearance. Because in most cases the underlying cause persists, the continual subdivision of established nodules by new, perisinusoidal scarring leads to a classic **micronodular** or **Laennec cirrhosis.** Early in the course, the liver is yellow-tan, fatty, and enlarged, but with persistent damage over the course of years the liver is transformed into a brown, shrunken, nonfatty organ composed of cirrhotic nodules that are usually less than 0.3 cm in diameter—smaller than is typical for most chronic viral hepatitis. The end-stage cirrhotic liver may enter into a "burned-out" phase devoid of fatty change and other typical features. A majority of cases of **cryptogenic cirrhosis,** without clear etiology, are now recognized as "burned-out" NAFLD.

Alcoholic liver disease

- caused by excessive alcohol consumption
- causes → ① hepatic steatosis
② Alcoholic hepatitis
③ fibrosis cirrhosis

← same features of alcohol fatty liver

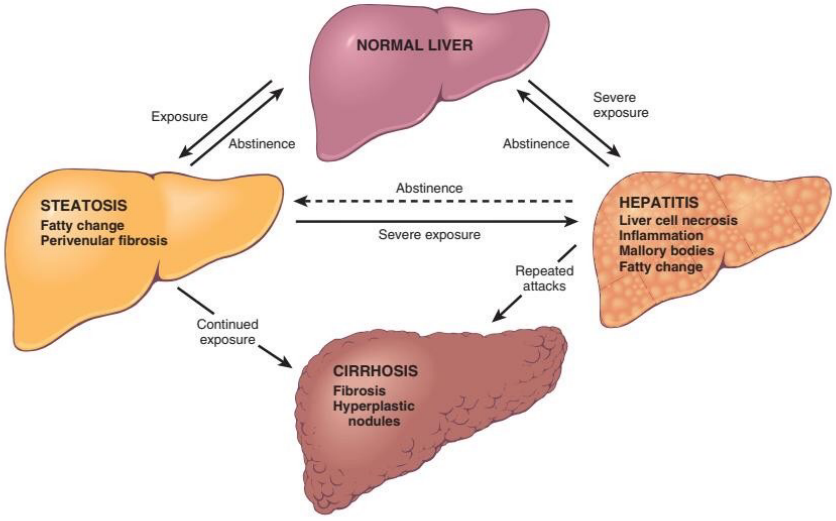


Fig. 16.18 Alcoholic liver disease. The interrelationships among hepatic steatosis, alcoholic hepatitis, and alcoholic cirrhosis are shown and key morphologic features are listed. As discussed in the text, steatosis, alcoholic hepatitis, and steatofibrosis may all develop independently and not along a continuum.

Pathogenesis

- Short term ingestion of 60g per day → reversible fatty liver changes

- Chronic intake - ↓ gastric metabolism of ethanol
- women are more susceptable
- binge drinking causes more damage compared to steady intake

→ hepatocellular steatosis
→ caused by alcohol
→ metabolism of ethanol by alcohol dehydrogenase and acetaldehyde dehydrogenase
→ generates large amounts of nicotinamide-adenine dinucleotide (NADH)
→ increased shunting of substates away from catabolism and toward lipid biosynthesis

→ ethanol impairs the assembly and secretion of lipoproteins
→ causes accumulation of intracellular lipids

→ cause of alcoholic hepatitis is uncertain but it may stem from toxic byproducts of ethanol and its metabolites
→ acetaldehyde - disrupt cytoskeletal and membrane function
→ alcohol - directly effects mitochondrial function and membrane fluidity

→ reactive oxygen species → damage membranes and proteins

- Acetaldehyde and free radicals are mostly produced in centrilobular region
  → this region is more susceptable to toxic injury
  → pericellular and sinusoidal fibrosis develop first in the lobe
  → concurrent hep C infection accelerate liver disease in alcoholics (30%)

- Cirrhosis develops in small fraction of chronic alcoholics
  → unknown reason

Clinical features

- Alcoholic steatosis
  → hepatomegaly
  → mild bilirubin and alkaline phosphatase (ALP) increase
- Alcoholic cirrosis → 15-20 years of drinking
- Alcoholic hepatitis
  → weeks – months needed to develop

- malaise, anorexia, weightloss, upper abdominal discomfort, tenderhepatomegaly and fever
- Typical findings → hyperbilirubinemia
  → elevated ALP
  → neutrophilic leukocytosis
  → ALT and AST elevated but below 500 u/ml

- In chronic alcoholics → ethanol is major source of calories in diet
  → displaces other nutrients
  → malnutrition
  → vitamin deficiency (thiamine, B12)
  ⟹ chronic gastric and intestinal
  - mucosal damage
  pancreatitis

- Treatment is stoping alcohol
- Death caused by hepatic failure
  massive GI hemorrhage
  Intercurrent infection
  Hepatorenal Syndrome
  Hepatocellular carcinoma

SUMMARY

ALCOHOLIC LIVER DISEASE

- Alcoholic liver disease has three main manifestations, hepatic steatosis, alcoholic hepatitis, and cirrhosis, which may occur alone or in combination.
- Cirrhosis typically develops after more than 10 years of heavy drinking, but only occurs in a small proportion of chronic alcoholics; alcoholic cirrhosis has similar clinical signs and symptoms as cirrhosis caused by viral hepatitis.
- The multiple pathologic effects of alcohol include changes in lipid metabolism, decreased export of lipoproteins, and cell injury caused by reactive oxygen species and metabolites of alcohol.

Non-Alcoholic fatty liver disease (NAFLD)

- Condition where fatty liver disease occurs without drinking alcohol
- Steatosis, steatohepatitis and cirrhosis can all occur
- inflammation is less prominent compared to alcoholic liver disease
- Nonalcoholic steatohepatitis (NASH)
  - elevated transaminase
  - histologic features
- NAFLD is associated with insulin resistance and the metabolic syndrome
  → other associated abnormalities are:
    - Type 2 DM (or family hx)
    - Obesity
    - Dyslipidemia (hypertriglyceridemia, low HDL, high LDL)
    - HTN

Pathogenesis

- key initiating events → obesity & insulin resistance (adipose & liver)
  → increased movement of free fatty acids from adipose tissue
  → taken up by hepatocytes
  → stimulate synthesis of free fatty acid within hepatocytes
  → In NAFLD half the lipids found in hepatocytes come from adipose tissue, most of the remainder coming from de Novo synthesis in liver cells.

→ accumulation of lipids in hepatocytes predispose NASH development

→ excess intrahepatic lipids and their metabolites
→ enhance insulin resistance in liver and sensitize hepatocyte to toxic effects of inflammatory cytokines
→ increased production due to metabolic syndrome

→ Hepatocytes in pt with NASH show evidence of inflammasome activation
→ due to direct or indirect effect of some lipids
→ leads to release of pro-inflammatory cytokines IL-1

→ other products of lipid metabolism appear to be directly toxic to hepatocytes → increased production of reactive oxygen species
→ induction of ER stress
→ disruption of mitochondrial function

⟹ liver injury due to those insults causes stellate cell activation, collagen deposition and hepatic fibrosis
→ all this + ongoing hepatocyte damage

⟹ Full blown NASH

Clinical features

- most common cause of ↑ transaminase (ALT & AST)
- most pt with steatosis are asymptomatic
- pt with active steatohepatitis or fibrosis can be asymptomatic
  → may have - fatigue
  - malaise
  - RUQ discomfort
  - can have severe symptoms of chronic liver disease

- liver biopsy need to dx NASH from NAFLD
- NAFLD → can cause cryptogenic cirrhosis
  → increased chance of coronary artery disease

- need lifestyle modifications - diet, weight loss

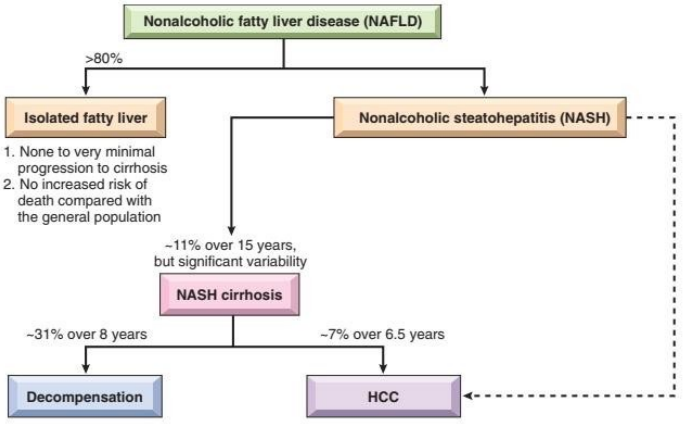


Fig. 16.19 Natural history of nonalcoholic fatty liver disease. Isolated fatty liver disease shows minimal risk for progression to cirrhosis or increased mortality, while nonalcoholic steatohepatitis shows increased overall mortality as well as increased risk for cirrhosis and hepatocellular carcinoma. *DM*, Diabetes mellitus.

SUMMARY

NONALCOHOLIC FATTY LIVER DISEASE

- Nonalcoholic fatty liver disease (NAFLD) is associated with the metabolic syndrome, obesity, type 2 diabetes, and dyslipidemia and/or hypertension.
- NAFLD may show all the changes associated with alcoholic liver disease: steatosis, nonalcoholic steatohepatitis (NASH), and cirrhosis, although the features of steatohepatitis (such as hepatocyte ballooning, Mallory-Denk bodies, and neutrophilic infiltration) often are less prominent than they are in alcohol-related injury.
- Pediatric NAFLD is increasingly being recognized as the obesity epidemic spreads to pediatric age groups, although its histologic pattern differs somewhat from that seen in adults.

INHERITED METABOLIC LIVER DISEASES

SUMMARY

INHERITED METABOLIC LIVER DISEASE

- Hemochromatosis is most commonly caused by mutations in the *HFE* gene and less commonly by mutations in other genes, all of which result in decreased hepcidin levels or function and increased intestinal iron uptake. It is characterized by accumulation of iron in the liver, pancreas, and other tissues.
- Wilson disease is caused by loss-of-function mutations in the metal ion transporter ATP7B, which results in accumulation of copper in the liver, brain (particularly basal ganglia), and eyes (Kayser-Fleischer rings).
- Wilson disease effects on the liver are protean, showing changes ranging from acute massive hepatic necrosis, to fatty liver disease, to chronic hepatitis and cirrhosis.
- α_1AT deficiency is a disease in which mutations in α_1AT lead to its misfolding, causing liver toxicity and a functional deficit of α_1AT in the plasma. This deficiency places affected individuals at high risk for emphysema, particularly smokers, due to the unopposed effects of proteases released from neutrophils.

Cholestatic Syndrome

-impaired bile formation or flow

- Hepatic bile serves two major functions:
  ① emulsification of dietary fat in lumen of gut through bile salts
  ② elimination of bilirubin, excess cholesterol, xenobiotics and other waste products that are insufficiently water soluble and can't be excreted into urine

- Process that interferes with excretion of bile lead to jaundice and icterus due to retention of bilirubin
- Jaundice can occur: - increased bilirubin production (hemolysis)
  - hepatocyte dysfunction (hepatitis)
  - bile flow obstruction (gallstones)

⟹ they all affect either bilirubin production or clearance.

Bilirubin and Bile formation

- Bilirubin is end product of heme degeneration
- Approximately 85% of daily production (0.2-0.3 gm) is from breakdown of old RBC by macrophages in spleen, liver and bone marrow
  The remainder are from turnover of hepatic heme and hemoproteins (eg. P450 cytochromes) and from destruction of red cell precursors in bone marrow

→ intracellular heme oxygenase oxidizes heme to biliverdin
  → reduced to bilirubin by biliverdin reductase

→ Bilirubin binds to albumin
  → this is important because bilirubin is virtually insoluble in aqueous solutions → highly toxic to tissue as well

→ Albumin carries bilirubin to liver
  → bilirubin is taken into hepatocytes
    → becomes conjugated by glucuronic acid by bilirubin uridine diphosphate (UDP) glucuronyl transferase (UGT1A1)

→ water soluble, non toxic bilirubin glucuronides are then excreted into the bile
  → most bilirubin glucuronides are deconjugated in gut lumen by bacterial β-glucuronidase and degraded to colorless urobilinogens
    → urobilinogens and residue of intact pigment are largely excreted in feces
    → 20% of urobilinogens are reabsorbed in ileum and colon, returned to liver and re-excreted into bile.

→ a small amount of reabsorbed urobilinogen is excreted in urine

→ 2/3 of bile is made of bile salts
→ formed by conjugation of bile acids with taurine and glycine
→ primary bile acids are cholic acid and chenodeoxycholic acid.
⟹ Primary physiologic role is to solubline water insoluble lipids secreted by hepatocytes into bile
→ also to solubaline dietary lipids in gut lumen

⟹ 95% of bile salts, conjugated and unconjugated are reabsorbed from gut lumen and recirculate in the liver (enterohepatic circulation)
⟹ maintains a large endogenous pool of bile acids for digestive and excretory purpose

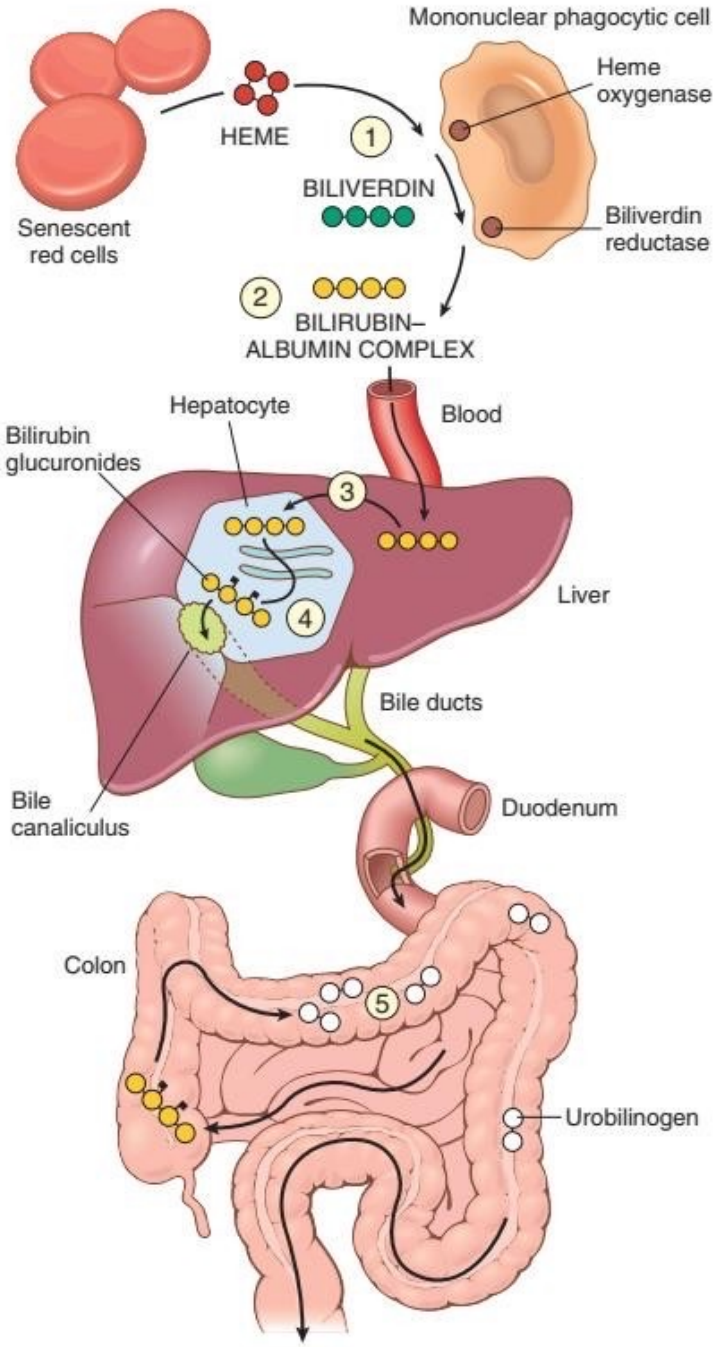


Fig. 16.22 Bilirubin metabolism and elimination.

Pathophysiology of Jaundice

- both conjugated and unconjugated bilirubin can accumulate systemically.
- unconjugated bilirubin is insoluble and tightly bound to albumin
  → even though its high in blood, it cannot be excreted by urine

- if unconjugated bilirubin rises, unbound fraction may diffuse into tissue
  → brain of infant → toxicity
- unbound fraction increases in severe hemolysis or when protein binding drugs displace bilirubin from albumin
  → erythroblastosis fetalis
  → may lead to accumulation of unconjugated bilirubin in brain
  → neurologic damage
  ⟹ Kernicterus

- conjugated bilirubin is water soluble, non toxic and loosely bound to albumin
  → can be excreted in urine

- Normal bilirubin in adult → 0.3 - 1.2 mg/dl
- Jaundice occurs at 2 - 2.5 mg/dl

Defects in hepatocellular bilirubin metabolism

① Neonatal Jaundice
- hepatic machinery for conjugating and excreting bilirubin does not fully mature until 2 weeks age
  → almost all newborns can develop transient and mild unconjugated hyper-bilirubinemia
  - can be excacerbated by breastmilk due to enzymes
    ⟹ physiologic

② Hereditary Hyperbilirubinemia
- Jaundice caused by inborn errors of metabolism

(i) Gilberts syndrome
- inherited
- fluctuating unconjugated hyperbilirubinemia
  → caused by decreased hepatic level of glucuronosyl transferase associated with UGT1A1 mutation
  → not severe normally
  → if severe glucuronosyl transferase deficiency
  → Crigler-Najjar Syndrome type I
  → fatal

(ii) Dubin Johnson Syndrome
- autosomal recessive defect in the transport protein responsible for hepatocellular excretion of bilirubin glucuronides across the canalicular membrane
→ conjugated hyperbilirubinemia

Cholestasis

- caused by extrahepatic or intrahepatic obstruction of bile channels or by defects in hepatocyte bile secretion
→ Jaundice
→ Pruritis
→ skin xanthomas (focal accumulation of cholesterol)
→ intestinal malabsorption - vit A, D, K,

→ elevated ALP and GGT
→ enzymes present in hepatocytes and cholangiocytes

MORPHOLOGY

The morphologic features of cholestasis depend on its severity, duration, and underlying cause. Common to both obstructive and nonobstructive cholestasis is the accumulation of bile pigment within the hepatic parenchyma (Fig. 16.23). Elongated green-brown plugs of bile are visible in dilated bile canaliculi. Rupture of canaliculi leads to extravasation of bile, which is quickly phagocytosed by Kupffer cells. Droplets of bile pigment also accumulate within hepatocytes, which can take on a fine, foamy appearance referred to as ***feathery degeneration***. Occasional apoptotic hepatocytes also may be seen.

(i) Bile duct obstruction and Ascending Cholangitis → inflammation of bile duct system → infection of biliary tract

- most common cause of bile duct obstruction in adults
→ extrahepatic cholelithiasis (gallstones)
- second causes malignent obstruction
- obstruction can also be caused by post surgical strictures

- obstructive conditions in children → biliary artresia
→ Cystic fibrosis
→ Choledochal cysts
→ insufficient intrahepatic duct syndromes

- Ascending cholangitis secondary to bacterial infection of biliary tree
→ fever, chills, Jaundice, abdominal pain
→ complicate bile duct obstruction
→ more severe form of cholangitis
→ suppurative cholangitis
→ purulent bile fills and distends bile duct

MORPHOLOGY

Acute biliary obstruction, either intrahepatic or extrahepatic, causes distention of upstream bile ducts, which often become dilated. In addition, **ductular reactions** appear at the portal-parenchymal interface along with stromal edema and neutrophils. The hallmark of superimposed infection **(ascending cholangitis)** is the influx of periductular neutrophils into the bile duct epithelium and lumen (Fig. 16.24).

Left uncorrected, the inflammation and ductular reactions resulting **from chronic biliary obstruction** initiate periportal fibrosis, eventually generating **secondary or obstructive biliary cirrhosis** (Fig. 16.25). Cholestatic features in the parenchyma may be prominent. These take the form of extensive **feathery degeneration of periportal hepatocytes**, a type of cytoplasmic swelling often associated with **Mallory-Denk bodies** and **bile infarcts** caused by the detergent effects of extravasated bile.

Neonatal Cholestasis

- Prolonged conjugated hyperbilirubinemia in neonate
- causes ① cholangiopathies – biliary atresia
  ② neonatal hepatitis

Biliary Atresia

- complete or partial obstruction of extrahepatic biliary tree that occurs in first 6 months of life

Pathogenesis

Two major forms of biliary atresia are recognized; these are based on the presumed timing of luminal obliteration.

- The *fetal form* accounts for as many as 20% of cases and is commonly associated with other developmental anomalies involving the thoracic and abdominal organs, including malrotation of abdominal viscera, interrupted inferior vena cava, polysplenia, and congenital heart disease.
- Much more common is the *perinatal form* of biliary atresia, in which an apparently normally developed biliary tree is injured and obstructed following birth. The etiology of perinatal biliary atresia is unknown; viral infection and toxic exposures are considered prime suspects.

- Clinical features
  - normal weight gain
  - female predominance
  - acholic stools as disease progresses
  - ascending cholangitis impedes surgical resection
  - transplant liver needed
    → death at 2 years if no surgery.

light coloured

Autoimmune cholangiopathies

- 2 types – Primary biliary cholangitis
  - Primary sclerosing cholangitis.

Cholangitis & → biliary tract infection → inflammation.

(i) Primary biliary cholangitis (PBC)
→ autoimmune disease
→ non suppurative, inflammatory destruction of small and medium sized intrahepatic duct

Pathogenesis
- unclear but we find →
- antimitochondrial antibodies are the characteristic finding
- presence of MHC II on bile duct epithelial cells
- accumulated T cells around bile duct

Clinical features
- assymptomatic mostly
- increased serum ALP
- severe itching

→ confirm by liver biopsy

(ii) Primary Sclerosing Cholangitis (PSC)

- inflamation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts → dilation of preserved segments

Pathogenesis
- immune mediated - linked to ulcerative colitis → T cell migration to liver.
- unclear pathogenesis

Clinical features
- ↑ ALP
- fatigue, pruritis and jaundice

SUMMARY

CHOLESTATIC DISEASES

- **Cholestasis** occurs with impaired excretion of bile, leading to jaundice and accumulation of bile pigment in the hepatic parenchyma. Causes include mechanical or inflammatory obstruction or destruction of the bile ducts or metabolic defects in hepatocyte bile secretion.
- **Large bile duct obstruction** is most commonly associated with gallstones and malignancies involving the head of the pancreas. Chronic obstruction can lead to cirrhosis.
- **Neonatal cholestasis** is not a specific entity; it is variously associated with cholangiopathies such as *biliary atresia* and a variety of disorders causing conjugated hyperbilirubinemia in the neonate, collectively referred to as *neonatal hepatitis*.
- **Primary biliary cholangitis** is an autoimmune disease with progressive, inflammatory, often granulomatous, destruction of small to medium intrahepatic bile ducts. It most often occurs in middle-age women and is associated with anti-mitochondrial antibodies and often with other autoimmune diseases, such as Sjögren syndrome and Hashimoto thyroiditis.
- **Primary sclerosing cholangitis** is an autoimmune disease with progressive inflammatory and sclerosing destruction of intrahepatic and extrahepatic bile ducts of all sizes. Diagnosis is made by radiologic imaging of the biliary tree. It most often occurs in younger men and has a strong association with inflammatory bowel disease, particularly ulcerative colitis.

Circulatory Disorders

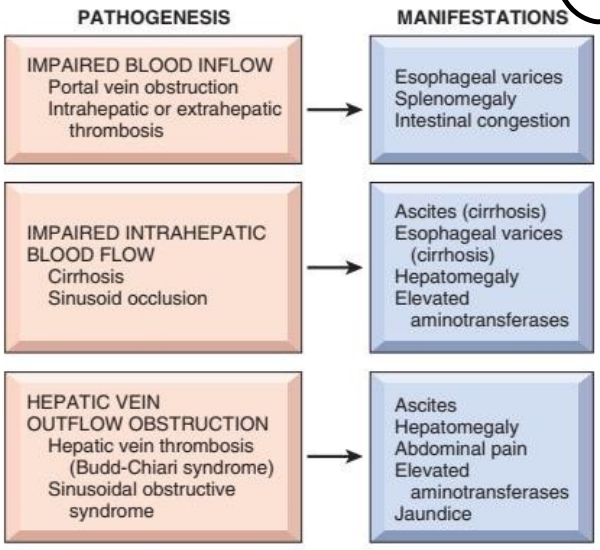


Fig. 16.30 Hepatic circulatory disorders. Forms and clinical manifestations of compromised hepatic blood flow.

Impaired blood flow to liver

① Hepatic Artery Compromise
- rare
- thrombosis or obstruction of an intrahepatic branch of hepatic artery by embolism, neoplasia, polyarteritis nodosa
- may not produce ischemic necrosis
  - retrograde arterial flow from accessory vessels & portal venous is usually sufficient

② Portal vein obstruction and Thrombosis

- abdominal pain
- Portal HTN
  - esophageal varices that are prone to rupture
  - ascites is not common (blockage is presinusoidal)
    → if present
      → massive & intractable

- extrahepatic portal vein obstruction causes →
  → idiopathic
  → Cirrhosis ~25%
  → Hypercoagulable state
  → Inflammatory process involving splenic or portal vein (pancreatitis & intraabdominal sepsis)
  → Trauma or surgical

- obstruction of intrahepatic portal vein radicles
  → acute thrombosis
  → doesn't cause infarction → sharply demarcated area of red blue discoloration → infarct of Zahn

→ no necrosis
→ only severe hepatocellular atrophy
→ congestion and distended sinusoids

- Most common cause of small portal vein branch obstruction
→ schistosomiasis
→ eggs of parasite lodge and obstruct the smallest portal vein branches

Impaired Blood Flow Through the Liver

The most common intrahepatic cause of blood flow obstruction is cirrhosis, as discussed earlier. In addition, physical occlusion of the sinusoids occurs in *sickle cell disease, disseminated intravascular coagulation, eclampsia,* and *intrasinusoidal metastasis* of solid tumors. If severe and unabated, all of these disorders may produce sufficient obstruction of blood flow to cause massive necrosis of hepatocytes and fulminant hepatic failure.

Hepatic venous out flow obstruction

- occlusion can occur in any hepatic vein branches
→ if it occurs in the smallest intrahepatic branch
→ sinusoidal obstruction syndrome

- obstruction of 2 or more major hepatic vein
→ liver enlargement
→ Pain
→ Ascites
→ condition called Budd-Chiari Syndrome

- obstruction of single vein maybe silent
- hepatic damage caused by increased intrahepatic blood pressure

→ death if untreated
→ anticoagulation
→ Angioplasty
→ thrombolysis
→ Portovenous shunts
⟹ decompress liver

MORPHOLOGY

In Budd-Chiari syndrome, the liver is swollen and red-purple and has a tense capsule (Fig. 16.32). There may be areas of hemorrhagic collapse alternating with areas of preserved or regenerating parenchyma, depending on which small and large hepatic veins are obstructed. Microscopically, the affected hepatic parenchyma reveals severe centrilobular congestion and necrosis. Centrilobular fibrosis develops in instances in which the thrombosis is more slowly developing. The major veins may contain fresh occlusive thrombi or, in chronic cases, organized adherent thrombi.

Passive Congestion and Centrilobular Necrosis

These hepatic manifestations of systemic circulatory compromise—passive congestion and centrilobular necrosis—are considered together because they represent a morphologic continuum. Both changes are commonly seen at autopsy, as there is an element of preterminal circulatory failure in virtually every nontraumatic death.

MORPHOLOGY

Right-sided cardiac decompensation leads to passive congestion of the liver. The liver is slightly enlarged, tense, and cyanotic, with rounded edges. Microscopically there is congestion of **centrilobular sinusoids.** With time, centrilobular hepatocytes become atrophic, resulting in markedly attenuated liver cell plates. Left-sided cardiac failure or shock may lead to hepatic hypoperfusion and hypoxia, causing ischemic coagulative necrosis of hepatocytes in the central region of the lobule (**centrilobular necrosis**).

The combination of hypoperfusion and retrograde congestion acts synergistically to cause **centrilobular hemorrhagic necrosis.** The liver takes on a variegated mottled appearance, reflecting hemorrhage and necrosis in the centrilobular regions (Fig. 16.33A). This finding is known as **nutmeg liver** due to its resemblance to the cut surface of a nutmeg. There typically is a sharp demarcation between viable periportal and necrotic or atrophic pericentral regions that are suffused with blood (see Fig. 16.33B). Uncommonly, with sustained chronic severe congestive heart failure, centrilobular fibrosis (**cardiac sclerosis**) or even cirrhosis develops.

Heart failure
→ ↓ cardiac output
⇒ ↓ hepatic blood flow
→ hepatic congestion from venous outflow obstruction
⇒
→ hypertension.
→ ↓ O2 to liver.

RHF – backflow of blood
→ tricuspid regurgitation.

SUMMARY

CIRCULATORY DISORDERS

- Circulatory disorders of the liver can be caused by impaired blood inflow, defects in intrahepatic blood flow, and obstruction of blood outflow.
- Portal vein obstruction by intrahepatic or extrahepatic thrombosis may cause portal hypertension, esophageal varices, and ascites.
- The most common cause of impaired intrahepatic blood flow is cirrhosis.
- Obstructions of blood outflow include hepatic vein thrombosis (Budd-Chiari syndrome) and sinusoidal obstruction syndrome, previously known as *veno-occlusive disease*.

SUMMARY

LIVER TUMORS

- The liver is the most common site of metastatic cancers from primary tumors of the colon, lung, and breast.
- **Hepatocellular adenomas** are benign tumors of hepatocytes. Most can be subclassified on the basis of molecular changes with varying degrees of malignant potential. They are associated with use of oral contraceptives and androgens.
- The two main types of malignant tumors are **hepatocellular carcinomas and cholangiocarcinomas**; HCCs are much more common.
  - HCC is a common tumor in regions of Asia and Africa, and its incidence is increasing in the United States.
  - The main etiologic agents for HCC are hepatitis B and C, alcoholic cirrhosis, hemochromatosis, and exposure to aflatoxins. In the Western population, about 90% of HCCs develop in cirrhotic livers; in Asia, almost 50% of cases develop in noncirrhotic livers.
  - The chronic inflammation and cellular regeneration associated with viral hepatitis are predisposing factors for the development of carcinomas.
  - HCC may be unifocal or multifocal, tends to invade blood vessels, and recapitulates normal liver architecture to varying degrees.
  - Cholangiocarcinoma is a tumor of intrahepatic or extrahepatic bile ducts that is relatively common in areas where liver flukes, such as *Opisthorchis* and *Clonorchis* species, are endemic.

Gall Stones

There are 2 main types of gallstones → cholesterol stones (contain crystalline cholesterol monohydrate)
→ pigment stones (made of bilirubin calcium salts)

Pathogenesis

- bile formation is the only significant pathway for elimination of excess cholesterol
  → either as free cholesterol or bile salts
- Cholesterol becomes water soluble by aggregation of bile salt and lecithins.
- When cholesterol concentration exceeds the solubilizing capacity of bile (supersaturation)
  → they crystallize

- cholesterol gallstones formation is enchanced by hypomobility of gallbladder (stasis)
  → promotes nucleation
  → mucus hypersecretion
  → crystals trapped
  → aggregation into stones

- Pigment stones form when bile contains high conc. of unconjugated bilirubin in biliary tree
  → hemolysis
  → infections of biliary tract - liver flukes

Table 16.6 Risk Factors for Gallstones

Cholesterol Stones
Demography: Northern Europeans, North and South Americans, Native Americans, Mexican Americans
Advancing age
Female sex hormones
Female gender
Oral contraceptives
Pregnancy
Obesity and insulin resistance
Rapid weight reduction
Gallbladder stasis
Inborn disorders of bile acid metabolism
Dyslipidemia syndromes
Pigment Stones
Demography: Asian more than Western, rural more than urban
Chronic hemolysis (e.g., sickle cell anemia, hereditary spherocytosis)
Biliary infection
Gastrointestinal disorders: ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency

MORPHOLOGY

Cholesterol stones arise exclusively in the gallbladder and consist of 50% to 100% cholesterol. Pure cholesterol stones are pale yellow; increasing proportions of calcium carbonate, phosphates, and bilirubin impart gray-white to black discoloration (Fig. 16.39). They are ovoid and firm; they can occur singly, but most often there are several, with faceted surfaces resulting from their apposition. Most cholesterol stones are radiolucent, although as many as 20% may contain sufficient calcium carbonate to be radiopaque.

Pigment stones may arise anywhere in the biliary tree and are classified into black and brown stones. In general, black pigment stones are found in sterile gallbladder bile, while brown stones are found in infected intrahepatic or extrahepatic ducts.

The stones contain calcium salts of unconjugated bilirubin and lesser amounts of other calcium salts, mucin glycoproteins, and cholesterol. Black stones are usually small, numerous, and fragile to the touch (Fig. 16.40). Brown stones tend to be single or few in number and to have a soft, greasy, soaplike consistency owing to the presence of fatty acid salts released from biliary lecithins by bacterial phospholipases. Because of calcium carbonates and phosphates, 50% to 75% of black stones are radiopaque. Brown stones, which contain calcium soaps, are radiolucent.

Clinical features
- asymptomatic 70-80%
- RUQ or epigastric pain
  → caused by gallbladder or biliary tree obstruction or inflammation of gallbladder
- empyema
- perforation
- fistulas
- inflammation of biliary tree
- obstructive cholestasis
- pancreatitis

- small stones can enter cystic and common ducts to produce obstruction

Cholecystitis

- inflammation of the gallbladder
  → acute
  → chronic
  → acute on chronic

① Acute Calculous Cholecystitis

- acute inflammation + stones → obstruction of gallbladder neck or ↓ cystic duct
→ common complication of gallstones
  → emergency cholectomy

→ results from chemical irritation and inflammation wall due to obstruction of bile outflow

② Acute Acalculous Cholecystitis

- no gallstones
- caused by - major surgery
  - trauma
  - severe burn
  - sepsis

other contributing factors → dehydration
gall bladder stasis and sludging
vascular compromise
bacterial contamination

Clinical Features

-Acute calculous cholecystitis
→ biliary pain > 6hrs
→ upper abdominal pain
→ pain radiates to shoulder
→ fever, nausea,
→ conjugated hyperbilirubinemia (obstructed common bile duct)
→ right subcostal markedly tender and rigid
→ tender gall bladder palpated

The diagnosis of acute cholecystitis usually is based on the detection of gallstones by ultrasonography, typically accompanied by evidence of a thickened gallbladder wall. Attention to this disorder is important because of the potential for the following serious complications:

- Bacterial superinfection leading to cholangitis or sepsis
- Gallbladder perforation and local abscess formation
- Gallbladder rupture leading to diffuse peritonitis
- Biliary enteric (cholecystenteric) fistula, with drainage of bile into adjacent organs, entry of air and bacteria into the biliary tree, and potentially gallstone-induced intestinal obstruction (ileus)
- Aggravation of preexisting medical illness, with cardiac, pulmonary, renal, or liver decompensation

Symptoms arising from *acute acalculous cholecystitis* usually are obscured by another serious medical or surgical condition, which sets the stage for the development of cholecystitis. The diagnosis therefore rests on a high index of suspicion. *Chronic cholecystitis* lacks the striking manifestations of the acute forms and is usually characterized by recurrent attacks of steady epigastric or right upper-quadrant pain. Nausea, vomiting, and intolerance for fatty foods are frequent accompaniments. Chronic cholecystitis is a pathologic diagnosis based on the examination of the resected gallbladder. Beyond signs and symptoms mentioned above, its principal importance may lie in the association of gallstones and chronic inflammation with carcinoma of the gallbladder (discussed next).

CARCINOMA OF THE GALLBLADDER

Carcinoma of the gallbladder is the most common malignancy of the extrahepatic biliary tract. It is slightly more common in women and occurs most frequently in the seventh decade of life. The incidence in the United States is 1 in 50,000. Only rarely is it discovered at a resectable stage, and the mean 5-year survival rate has remained unchanged at about 5% to 12% over the past many years. The most important risk factor associated with gallbladder carcinoma is gallstones (cholelithiasis), which are present in 95% of cases. Presumably, gallbladders containing stones or infectious agents develop cancer as a result of chronic inflammation, a known enabler of malignancy in several organs (Chapter 6). Carcinogenic derivatives of bile acids also are suspected to play a role. Primary sclerosing cholangitis is also a risk factor.

MORPHOLOGY

Carcinomas of the gallbladder show two patterns of growth: **infiltrating** and **exophytic.** The infiltrating pattern is more common and usually appears as a poorly defined area of diffuse wall thickening and induration. The exophytic pattern grows into the lumen as an irregular, cauliflower mass, but at the same time invades the underlying wall (Fig. 16.42). Most carcinomas of the gallbladder are adenocarcinomas. About 5% are squamous cell carcinomas or have adenosquamous differentiation.

Clinical Features

Preoperative diagnosis of carcinoma of the gallbladder is the exception rather than the rule, occurring in fewer than 20% of patients. Presenting symptoms are insidious and typically indistinguishable from those associated with cholelithiasis: abdominal pain, jaundice, anorexia, nausea and vomiting. There is no satisfactory treatment of gall bladder cancer due to the advanced stage at the time of diagnosis. Only 10% are diagnosed at a stage that is early enough to attempt curative surgery.

SUMMARY

GALLBLADDER DISEASES

- Gallbladder diseases include cholelithiasis and acute and chronic cholecystitis, and gall bladder cancer.

- Gallstone formation is a common condition in Western countries. The great majority of the gallstones are cholesterol stones. Pigmented stones containing bilirubin and calcium are most common in Asian countries, due to the higher incidence of chronic hemolytic disorders and liver fluke infestations in these locales.
- Risk factors for the development of cholesterol stones are advancing age, female gender, estrogen use, obesity, and heredity.
- Cholecystitis almost always occurs in association with cholelithiasis, although in about 10% of cases it occurs in the absence of gallstones.
- Acute calculous cholecystitis is the most common reason for emergency cholecystectomy.
- Gall bladder cancer is almost always associated with gall stones. Because of the advanced stage at diagnosis, it has a very poor prognosis.