Liver diseases I
• The major **primary** diseases of the liver are:
  - Viral hepatitis,
  - Nonalcoholic fatty liver disease (NAFLD),
  - Alcoholic liver disease,
  - 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.
Liver Failure

- The most severe clinical consequence of liver disease is liver failure:
  - **acute liver failure**: the result of sudden and massive hepatic destruction.
  - **chronic liver failure**: which follows upon years or decades of insidious, progressive liver injury.
  - **Acute on- chronic liver failure**, in which an unrelated acute injury supervenes on a well-compensated late-stage chronic disease or the chronic disease itself has a flare of activity that leads directly to liver failure.
• **80% to 90%** of hepatic functional capacity must be lost before hepatic failure ensues.

• When the liver can no longer maintain homeostasis, *transplantation* offers the best hope for survival; the mortality rate in persons with hepatic failure without liver transplantation is about 80%.
Acute Liver Failure

- has been referred to as “fulminant liver failure” until recently.
- Acute liver failure is defined as an acute liver illness associated with encephalopathy and coagulopathy that occurs within **26 weeks** of the initial liver injury in the absence of pre-existing liver disease.
• Pathogenesis:
- Acute liver failure is caused by **massive hepatic necrosis**, most often induced by drugs or toxins.
  *Accidental or deliberate ingestion of acetaminophen --- 50%
*autoimmune hepatitis,
*other drugs/toxins,
*acute hepatitis A and B infections
In Asia, acute hepatitis B and E predominate.

- The mechanism of hepatocellular necrosis may be:
  *direct toxic damage (as with acetaminophen),
  *but more often is a variable combination of toxicity and immune-mediated hepatocyte destruction (e.g., hepatitis virus infection).
• Rarely, there may be diffuse poisoning of liver cells without obvious cell death and parenchymal collapse,

• usually related to primary mitochondrial dysfunction, hepatocytes are unable to perform their usual metabolic functions.

• diffuse microvesicular steatosis: fatty liver of pregnancy

idiosyncratic reactions to toxins (tetracycline)
Clinical Course:
- Nausea, vomiting, and jaundice—encephalopathy, and coagulation defects.
- Serum liver transaminases are markedly elevated. And liver is initially enlarged due to hepatocyte swelling and edema.
- As parenchyma is destroyed, however, the liver shrinks dramatically with decline of serum transaminases.
- With unabated progression, multiorgan system failure occurs and, if transplantation is not possible, death ensues.
- **jaundice** and icterus
- **cholestasis**
- **Hepatic encephalopathy**--- subtle behavioral abnormalities, confusion and stupor, deep coma and death.

*Asterixis*, a particularly characteristic sign, is manifested as nonrhythmic, rapid extension-flexion movements of the head and extremities.

**Elevated ammonia levels** in blood and the central nervous system correlate with impaired neuronal function and cerebral edema.

- **Coagulopathy**--- Easy bruisability, fatal intracranial bleeding.

Due to impaired hepatic synthetic function of vitamin K-dependent and -independent clotting factors.

**disseminated intravascular coagulation**---- due to decreased hepatic function to remove activated coagulation factors from the circulation.

- **Portal hypertension** (more in chronic liver failure)
- **Hepatorenal syndrome**----- is a form of **renal failure** occurring in individuals with liver failure in whom there are no intrinsic morphologic or functional causes for kidney dysfunction.
Chronic Liver Failure and Cirrhosis

• The leading causes of chronic liver failure worldwide include:
  - Chronic hepatitis B, chronic hepatitis C,
  - Nonalcoholic fatty liver disease,
  - Alcoholic liver disease.

Cirrhosis, a condition marked by the diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular (often portosystemic) shunting.
• Liver failure in chronic liver disease is most often associated with cirrhosis
• But not all cirrhosis leads to chronic liver failure and not all end-stage chronic liver disease is cirrhotic.

• classification of cirrhosis:
  class A (well compensated),
  Class B (partially decompensated),
  Class C (decompensated)
• the term cirrhosis implies the presence of severe chronic disease, it is not a specific diagnosis and it lacks clear prognostic implications.

• The term **cryptogenic cirrhosis** is sometimes used to describe cirrhosis when there is no clear cause.
• Although uncommon, regression of fibrosis, albeit rarely, in fully established cirrhosis, does occur; this is another reason why cirrhosis should not be automatically equated with end stage disease.
• With increasing numbers of effective treatments for cirrhosis-causing conditions, however, we now understand that regression of scars can take place. Scars can become thinner, more densely compacted, and eventually fragment.
• All cirrhotic livers show elements of both progression and regression, the balance determined by the severity and persistence of the underlying disease.
Figure 18-7  Cirrhosis resulting from chronic viral hepatitis. Note the depressed areas of dense scar separating bulging regenerative nodules over the liver surface.
Figure 18-8 Alcoholic cirrhosis in an active drinker (A) and following long-term abstinence (B). A, Thick bands of collagen separate rounded cirrhotic nodules. B, After a year of abstinence, most scars are gone. (Masson trichrome stain) (Courtesy Drs. Hongta Zhu and Isabel Fiel, Mount Sinai School of Medicine, New York.)
Clinical Features:
About 40% of individuals with cirrhosis are asymptomatic until the most advanced stages of the disease.

When symptomatic:
- they present with nonspecific manifestations: anorexia, weight loss, weakness,
- in advanced disease, symptoms and signs of liver failure discussed earlier.
- hepatocellular carcinoma
- bacterial infections (resulting from damage to mucosal barrier in the gut and Kupffer cell dysfunction)
• Impaired estrogen metabolism and consequent hyperestrogenemia in male patients with chronic liver failure can give rise to palmar erythema (a reflection of local vasodilatation) and spider angiomas/telangiecta of the skin.

• In men, hyperestrogenemia also leads to hypogonadism and gynecomastia.

• Hypogonadism can also occur in women from disruption of hypothalamic-pituitary axis function, either through nutritional deficiencies associated with the chronic liver disease or primary hormonal alterations.
Portal Hypertension:
increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into prehepatic, intrahepatic, and posthepatic. The dominant intrahepatic cause is cirrhosis, accounting for most cases of portal hypertension.

The pathophysiology of portal hypertension is complex and involves resistance to portal flow at the level of sinusoids and an increase in portal flow caused by hyperdynamic circulation.

The four major clinical consequences of portal hypertension are:
(1) ascites,
(2) the formation of portosystemic venous shunts,
(3) congestive splenomegaly,
(4) hepatic encephalopathy
<table>
<thead>
<tr>
<th>Location and Causes of Portal Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prehepatic causes</strong></td>
</tr>
<tr>
<td>Obstructive thrombosis of portal vein</td>
</tr>
<tr>
<td>Structural abnormalities such as narrowing of the portal vein before it ramifies in the liver</td>
</tr>
<tr>
<td><strong>Intrahepatic causes</strong></td>
</tr>
<tr>
<td>Cirrhosis from any cause</td>
</tr>
<tr>
<td>Nodular regenerative hyperplasia</td>
</tr>
<tr>
<td>Primary biliary cirrhosis (even in the absence of cirrhosis)</td>
</tr>
<tr>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Massive fatty change</td>
</tr>
<tr>
<td>Diffuse, fibrosing granulomatous disease (e.g., sarcoid)</td>
</tr>
<tr>
<td>Infiltrative malignancy, primary or metastatic</td>
</tr>
<tr>
<td>Focal malignancy with invasion into portal vein (particularly hepatocellular carcinoma)</td>
</tr>
<tr>
<td>Amyloidosis</td>
</tr>
<tr>
<td><strong>Posthepatic causes</strong></td>
</tr>
<tr>
<td>Severe right-sided heart failure</td>
</tr>
<tr>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td>Hepatic vein outflow obstruction</td>
</tr>
</tbody>
</table>
Figure 18-9 Major clinical consequences of portal hypertension in the setting of cirrhosis, shown for the male. In women, oligomenorrhea, amenorrhea, and sterility as a result of hypogonadism are frequent. Clinically significant findings are bold faced.
• **Ascites.**

- The accumulation of excess fluid in the peritoneal cavity.
- The fluid is generally serous
- The pathogenesis of ascites is complex, involving the following mechanisms:
• Portosystemic Shunts:
With the rise in portal system pressure, the flow is reversed from portal to systemic circulation by dilation of collateral vessels and development of new vessels.
Venous bypasses develop wherever the systemic and portal circulation share common capillary beds. Principal sites are: veins around and within the rectum (manifest as hemorrhoids), the esophagogastric junction (producing varices), the retroperitoneum, and the falciform ligament of the liver (involving periumbilical and abdominal wall collaterals).

Abdominal wall collaterals appear as dilated subcutaneous veins extending from the umbilicus toward the rib margins (caput medusae).
• **Splenomegaly:**

The massive splenomegaly may secondarily induce hematologic abnormalities attributable to hypersplenism, such as thrombocytopenia or even pancytopenia.
two additional syndromes that occur in chronic liver failure:

**Hepatopulmonary syndrome:**
- intrapulmonary vascular dilations —— inadequate time for oxygen diffusion —— ventilation-perfusion mismatch —— hypoxia.
- Hypoxia and resultant dyspnea occur preferentially in an **upright position** rather than in the recumbent position, as gravity exacerbates the ventilation-perfusion mismatch.

**Portopulmonary hypertension:**
- pulmonary arterial hypertension arising in liver disease and portal hypertension.
- The most common clinical manifestations are **dyspnea** on exertion and **clubbing of the fingers**.