CHAPTER SIX
PATHOLOGY OF THE HEPATO-BILIARY SYSTEM & EXOCRINE PANCREAS

THE LIVER

The dominant primary diseases of the liver are
1. Viral hepatitis
2. Alcoholic liver disease (in the Western world; rare in Iraq)
3. Hepatocellular carcinoma

HEPATIC FAILURE

This is the gravest consequence of liver disease. It should be noted that 80% of hepatic functional capacity must be damaged before failure ensues. In many cases decompensation arises as a result of intercurrent diseases that place further burden on an already sick liver; these include
1. Gastrointestinal bleeding
2. Systemic infection
3. Electrolyte disturbances
4. Severe stress such as major surgery or heart failure.

The morphologic alterations that cause liver failure fall into three categories:
1. Massive hepatic necrosis: most often drug-induced, as from paracetamol overdose, halothane & antituberculous drugs (rifampin, isoniazid). Hepatitis A & hepatitis B infection, and other causes (including unknown) account for about one-third of the cases. Hepatitis C infection does not cause massive hepatic necrosis.
2. Chronic liver disease, which is the most common road to hepatic failure and is the endpoint of persistent chronic hepatitis ending in cirrhosis.
3. Hepatic dysfunction without overt necrosis: hepatocytes may be viable but unable to perform normal metabolic function, as with Reye syndrome, tetracycline toxicity, and acute fatty liver of pregnancy.

Regardless of cause, the clinical signs of hepatic failure are much the same. Jaundice is an almost always present. Hypoalbuminemia, which predisposes to peripheral edema, and hyperammonemia, which may play a role in cerebral dysfunction, are extremely worrying developments. Fetor hepaticus (a characteristic musty body odor) occurs occasionally. Impaired estrogen metabolism and consequent hyperestrogenemia are thought to be the causes of
a. palmar erythema and spider angiomas of the skin
b. hypogonadism and gynecomastia in males

Hepatic failure is life-threatening because with severely impaired liver function, patients are highly susceptible to failure of multiple organ systems. Thus, respiratory failure with pneumonia and sepsis combine with renal failure to claim the lives of many patients. A coagulopathy develops due to impaired hepatic synthesis of blood clotting factors. The resultant bleeding tendency can lead to massive gastrointestinal bleeding as well as petechiae elsewhere (see also esophageal varices). Intestinal absorption of blood places a metabolic load on the liver, which worsens the extent of hepatic failure. The outlook of full-blown hepatic failure is grave: A rapid downhill course is usual, & without liver transplantation, death occurs within weeks to a few months in about 80% of cases.
**Two particular complications signal the gravest stages of hepatic failure**

1. **Hepatic encephalopathy**, which is manifested disturbances of consciousness with rigidity, hyperreflexia, and tremor. It is regarded as a disorder of neurotransmission in the central nervous system and neuromuscular system and appears to be associated with elevated blood ammonia levels, which impair neuronal function and promote generalized brain edema.

2. **Hepatorenal syndrome** refers to the appearance of renal failure in patients with severe chronic liver disease, in whom there are no intrinsic morphologic or functional causes for the renal failure. Sodium retention, impaired water excretion, and decreased renal perfusion and glomerular filtration rate are the main renal functional abnormalities. There is oliguria associated with rising blood urea nitrogen and creatinine. The prognosis is poor, with a median survival of only 2 weeks in the rapid-onset form and 6 months with the insidious-onset form.

**CIRRHOSIS**

Cirrhosis is the end-stage of chronic liver disease & is defined by three characteristics:

1. **Bridging fibrous septae** in the form of delicate or broad bands of fibrosis that link portal tracts with one another and portal tracts with centrilobular veins.

2. **Parenchymal nodules** containing regenerating hepatocytes encircled by fibrosis, with diameters varying from very small micronodules to large macronodules.

3. **Disruption of the architecture of the entire liver**

**Classification of cirrhosis**

The only satisfactory classification of cirrhosis is based on the underlying etiology. The descriptive terms "micronodular" and "macronodular" should not be used as primary classifications. Many forms of cirrhosis are initially micronodular (nodules < 3 mm), but there is a tendency for nodules to increase in size; thus converting it to mixed (micro- & macronodular) & eventually to macronodular form (nodules > 3 mm).

The etiology of cirrhosis varies both geographically and socially. The following are established causes of cirrhosis:

1. Alcoholic liver disease (70% in Western countries)
2. Viral hepatitis (a very common cause in our country)
3. Biliary diseases
4. Primary hemochromatosis
5. Wilson disease
6. α1-Antitrypsin deficiency
7. Cryptogenic cirrhosis

Infrequent types of cirrhosis also include those complicating galactosemia and tyrosinosis in infants and children, and drug-induced cirrhosis, as with α-methyldopa (aldomet). After all the categories of cirrhosis of known causation have been excluded, a substantial number of cases remain (15%) & is referred to as *cryptogenic cirrhosis*. It is possible that many of these cases are due to undiagnosed *nonalcoholic fatty liver disease*. Once cirrhosis is established, it is usually impossible to establish an etiologic diagnosis on morphologic grounds alone.

**Pathogenesis of cirrhosis**

The central pathogenetic processes in cirrhosis are progressive fibrosis and reorganization of the vascular microarchitecture of the liver. In cirrhosis, types I and III collagen are deposited in the lobule, creating delicate or broad septal tracts. New vascular channels in the septae connect the vascular structures in the portal region (hepatic arteries and portal veins) and terminal hepatic veins (centrilobulat & larger veins), shunting blood around the parenchyma. Continued deposition of collagen in the space of Disse is accompanied by the loss of
fenestrations in the sinusoidal endothelial cells. As a result hepatocellular secretion of proteins (e.g., albumin, clotting factors, and lipoproteins) is greatly impaired. The major source of excess collagen in cirrhosis is the perisinusoidal stellate cells, which lie in the space of Disse. Although normally functioning as vitamin A fat-storing cells, during the development of cirrhosis they become activated. It is predominantly the cytokines secreted by activated Kupffer cells and other inflammatory cells that stimulate perisinusoidal stellate cells to divide and to produce large amounts of extracellular matrix. Throughout the process of liver cell damage and fibrosis, remaining hepatocytes are stimulated to regenerate and proliferate as spherical regenerative nodules within the confines of the fibrous septa. The net outcome is a fibrotic, nodular liver in which delivery of blood to hepatocytes is severely impaired, as is the ability of hepatocytes to secrete substances into plasma. Disruption of the interface between the parenchyma and portal tracts obliterates biliary channels as well. Thus, the cirrhotic patient may develop jaundice and even hepatic failure, despite having a liver of normal mass.

**In cirrhosis death is usually due to one or more of the following**

1. Progressive liver failure
2. Portal hypertension related complications
3. The development of hepatocellular carcinoma.

**PORTAL HYPERTENSION**

Increased resistance to portal blood flow may develop in a variety of circumstances, which can be divided into prehepatic, intrahepatic, and posthepatic causes.

*Prehepatic conditions* include

1. Portal vein thrombosis & narrowing
2. Massive splenomegaly through shunting excessive blood into the splenic vein.

*Posthepatic causes* are

1. Severe right-sided heart failure
2. Constrictive pericarditis
3. Hepatic vein outflow obstruction.

*Intrahepatic causes*:

1. Cirrhosis is the dominant cause accounting for most cases of portal hypertension.
2. Schistosomiasis
3. Massive fatty change
4. Diffuse fibrosing granulomatous disease such as sarcoidosis and miliary tuberculosis
5. Diseases affecting the portal microcirculation, exemplified by nodular regenerative hyperplasia

Portal hypertension in cirrhosis results from increased resistance to portal flow at the level of the sinusoids, and compression of terminal hepatic veins by perivenular scarring and expansile parenchymal nodules. Anastomoses between the arterial and portal systems in the fibrous septa also contribute to portal hypertension by imposing arterial pressure on the low-pressure hepatic venous system.

**The four major consequences of portal hypertension in the setting of cirrhosis are**

1. Ascites
2. The formation of portosystemic venous shunts leading to esophageal varices & hemorrhoids
3. Congestive splenomegaly
4. Hepatic encephalopathy
Ascites refers to the collection of excess fluid in the peritoneal cavity. It usually becomes clinically detectable when at least 500 mL has accumulated, but many liters may collect and cause massive abdominal distention. It is generally a serous fluid having less than 3 g/dL of protein (largely albumin) as well as the same concentrations of solutes such as glucose, sodium, and potassium as in the blood. Influx of neutrophils suggests secondary infection, whereas red cells point to possible disseminated intra-abdominal cancer. With long-standing ascites, seepage of peritoneal fluid through transdiaphragmatic lymphatics may produce hydrothorax, more often on the right side.

The pathogenesis of ascites
This is complex, involving the following mechanisms:

1. **Sinusoidal hypertension**, altering Starling's forces and driving fluid into the space of Disse, which is then removed by hepatic lymphatics; this movement of fluid is also promoted by hypoalbuminemia.

2. **Percolation of hepatic lymph into the peritoneal cavity**: normal thoracic duct lymph flow approximates 800 to 1000 mL/day. With cirrhosis, hepatic lymphatic flow may approach 20 L/day, exceeding thoracic duct capacity.

3. **Intestinal fluid leakage**: portal hypertension also causes increased perfusion pressure in intestinal capillaries. This promotes movement of additional fluid out of intestinal capillaries into the abdomen.

4. **Renal retention of sodium and water** due to secondary hyperaldosteronism

INFLAMMATORY & INFECTIOUS DISORDERS
The liver is almost always involved in blood-borne infections such as bacterial (pyogenic abscesses, miliary tuberculosis, salmonelloses), parasitic (malaria, amebiasis), fungal (candidiasis), & viral (infectious mononucleosis, cytomegalovirus & herpes virus). **Never the less Viral hepatitis is the leading primary liver infection.**

**VIRAL HEPATITIS**

Unless otherwise specified, the term viral hepatitis is reserved for “infection of the liver caused by a group of hepatotropic viruses” i.e. having a particular affinity for the liver. This group comprises

1. **Hepatitis A virus** (HAV)
2. **Hepatitis B virus** (HBV)
3. **Hepatitis C virus** (HCV)
4. **Hepatitis D virus** (HDV)
5. **Hepatitis E virus** (HEV)

**Hepatitis A Virus (HAV)**

**Acute viral hepatitis A** (*infectious hepatitis*) is a benign, self-limited disease with an average incubation period of 4 weeks. **HAV does not cause chronic hepatitis or a carrier state and only rarely causes fulminant hepatitis.** Nevertheless, most viral hepatitis epidemics are attributed to HAV. In children, where most cases occur, the disease tends to be mild or asymptomatic. **HAV spreads by ingestion of contaminated water and foods. The viremia is short-lived, thus, blood-borne transmission of occurs rarely; therefore, donated blood is not screened for this virus.**

HAV is a small, RNA virus. It reaches the liver from the intestinal tract after ingestion, replicates in hepatocytes, and is shed in the bile and feces. It appears that the liver cell injury is not directly related to the virus but results from T cell-mediated damage of infected
hepatocytes. Detection of anti-HAV IgM antibody is the best diagnostic marker for the disease.

**Hepatitis B Virus (HBV)** this can produce

1. Acute viral hepatitis B with recovery and clearance of the virus
2. Chronic viral hepatitis B, which is either
   a. Non-progressive or
   b. Progressive ending in cirrhosis
3. Fulminant hepatitis with massive liver necrosis
4. An asymptomatic carrier state.

**Chronic viral hepatitis B** is an important precursor of hepatocellular carcinoma. Liver disease caused by HBV is a real worldwide problem, with an estimated carrier rate of 400 million. HBV remains in blood during the last stages of a long incubation period (4-26 weeks) and during active episodes of both acute and chronic hepatitis. It is also present in all physiologic and pathologic body fluids, with the exception of stool. 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. In endemic regions, vertical transmission from mother to child during birth constitutes the main mode of transmission. HBV infection in adults is mostly cleared, but vertical transmission produces a high rate of chronic infection.

HBV is a DNA virus & its replication does not require integration of the virus in the host DNA, however, integrated HBV is frequently found in cells. After exposure to the virus, there is a long incubation period (average 16 weeks), which may be followed by acute disease lasting weeks to months. The natural course of acute disease can be followed by serum markers. **HBsAg** appears before the onset of symptoms, peaks during overt disease, and then declines to undetectable levels in 3 to 6 months. **Anti-HBs** persists for life, conferring protection; this is the basis for current vaccination policy using noninfectious HBsAg. **HBeAg appears in serum shortly after HBsAg to signify active viral replication.**

**Persistence of HBeAg is an important indicator of**

1. Continued viral replication
2. Infectivity
3. Probable progression to chronic hepatitis

**IgM anti-HBc** (c for core Ag) is detectable with the onset of elevated serum aminotransferase levels and thus indicative of hepatocyte destruction. Later this IgM is replaced by IgG anti-HBc.

*The host immune response to the virus is the main determinant of the outcome of the infection.* A strong response by virus-specific CD4+ and CD8+ interferon γ-producing cells are associated with the resolution of acute infection. HBV, (like HAV) does not seem to cause direct hepatocyte injury as many chronic carriers have virions in their hepatocytes without any evidence of cell injury. Hepatocyte injury and damage seem to be mediated by CD8+ cytotoxic T cells of the virus-infected hepatocytes.

**Hepatitis C Virus (HCV)** is another major cause of liver disease. The worldwide carrier rate is estimated at 175 million persons. A decrease in the incidence has resulted from the marked reduction in transfusion-associated hepatitis C (as a result of screening procedures). *The major route of transmission is through blood inoculation,* with low rates of sexual and vertical transmissions. **HCV infection has a much higher rate (than HBV) of progression to chronic liver disease and eventual cirrhosis.** It is a single-stranded RNA virus. Based on the
genetic sequence, HCV is subclassified into six genotypes. An infected person may carry many HCV variants. This variability seriously hinders efforts to develop an HCV vaccine. The incubation period for hepatitis C has a mean of 6 to 12 weeks. The clinical course of acute viral hepatitis C is usually asymptomatic and is easily missed. Strong immune responses involving CD4+ and CD8+ cells are associated with self-limited HCV infections, but it is not known why only a minority of individuals is capable of clearing HCV infection. Persistent infection is the hallmark of HCV; in 80% of such cases it complicates subclinical acute infection. Cirrhosis develops in 20% of such patients. Fulminant hepatitis is rare.

**Hepatitis D Virus (HDV)** (Hepatitis delta virus) is a unique RNA virus in that it is replication defective, causing infection only when it is encapsulated by HBsAg i.e. HDV is absolutely dependent on HBV co-infection for multiplication. Delta hepatitis arises in two settings:

1. **Acute coinfection** after exposure to serum containing both HDV and HBV and
2. **Superinfection** of a chronic carrier of HBV with a new inoculum of HDV. In the first case, most coinfected individuals can clear the viruses and recover completely. The course is different in superinfected individuals in that most cases show acceleration of hepatitis, progressing to more severe chronic hepatitis. Infection by HDV is worldwide, with the highest prevalence rates (40%) in Africa & the Middle East. *IgM anti-HDV antibody is the most reliable indicator of recent HDV exposure*, but its appearance is transient.

**Hepatitis E Virus (HEV)**

HEV hepatitis is a single-stranded RNA virus that is fecally transmitted. HEV is endemic in India (where it was first documented). Epidemics have been reported from Asia and Africa. HEV is not associated with chronic liver disease or persistent viremia. A characteristic feature of the infection is the high mortality rate among pregnant women, approaching 20%. A specific antigen (HEV Ag) can be identified in the cytoplasm of hepatocytes during active infection. Virus can be detected in stools, and anti-HEV IgG and IgM antibodies are detectable in serum.

**Clinical Features and Outcomes of Viral Hepatitis**

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

1. Asymptomatic infection (serologic evidence only)
2. Acute hepatitis (anicteric or icteric)
3. Chronic hepatitis (with or without progression to cirrhosis)
4. Chronic carrier state (asymptomatic)
5. Fulminant hepatitis (submassive to massive hepatic necrosis with acute liver failure)

With rare exceptions, HAV, HCV, and HEV do not generate a carrier state, and HAV and HEV infections do not progress to chronic hepatitis. Viral persistence and development of chronic disease is much more common after HCV infection than HBV infection. *Because other infectious or noninfectious causes (such as drugs and toxins), can lead to essentially identical syndromes, serologic studies are decisive for the diagnosis of viral hepatitis and identification of virus types.*

**Asymptomatic Infection:**

The patients are identified only on the basis of minimally elevated serum aminotransferases or the presence of antiviral antibodies.

**Acute viral hepatitis**

Any one of the hepatotropic viruses can cause acute viral hepatitis. Acute infections are easily detected for HBV infections but only rarely diagnosed for HCV. A hepatitis virus
etiology is suggested by elevated serum aminotransferase levels. As jaundice appears (icteric phase), symptoms begin to fade away. To begin with there is predominantly conjugated hyperbilirubinemia but later hepatocellular injury interferes with bilirubin conjugation, thus, unconjugated hyperbilirubinemia can also occur. An icteric phase is usual especially in adults infected with HAV, but is absent in about 50% of the cases infected with HBV and in most cases of HCV infection. Within weeks, the jaundice and most systemic symptoms clear as convalescence begins.

**Chronic Hepatitis** is defined as “the presence of clinical, biochemical, or serologic evidence of continuing hepatic disease for more than 6 months, with histological documentation of inflammation and necrosis.”

Although chronic hepatitis is mostly caused by hepatitis viruses, there are other causes of this condition, these include:

- Drugs (isoniazide, α-methyldopa, methotrexate),
- Auto-immune damage (autoimmune hepatitis)
- Wilson disease, α₁-antitrypsin deficiency, chronic alcoholism.

**Causes of death in chronic hepatitis** are related to the complicating cirrhosis e.g. liver failure, hepatic encephalopathy, massive hematemesis from esophageal varices, and hepatocellular carcinoma.

**The Carrier State**

With hepatotropic viruses, carriers are those who harbor one of the viruses & may have nonprogressive liver damage, but are essentially free of symptoms. They constitute reservoirs of infection. HBV infection early in life, particularly through vertical transmission during childbirth, produces a carrier state in 90% to 95% of the cases. In contrast, less than 10% of HBV infections acquired in adulthood yield a carrier state. Individuals with impaired immunity are particularly likely to become carriers. HCV can induce a carrier state, which is estimated to affect 0.2% to 0.6% of the general population.

**Fulminant Hepatitis**

A very small proportion of patients with acute viral hepatitis A, B, or E may develop acute liver failure, resulting from massive hepatic necrosis. Cases with a more prolonged course of several weeks or months are usually referred to as subacute hepatic necrosis; livers of these individuals show both massive necrosis and regenerative hyperplasia. It should be remembered that drugs and chemicals can also cause massive hepatic necrosis.

**Pathological features of viral hepatitis**

The morphologic changes in acute and chronic viral hepatitis are shared among the hepatotropic viruses and can be mimicked by drug reactions.

**Acute viral hepatitis** (Fig. 6-1)

- The normal radial array of the lobules is lost.
- There is diffuse ballooning degeneration of hepatocytes; the cells are swollen with clear, wispy cytoplasm.
- **Hepatocytes necrosis** assume one of 3 morphologic types
  1. **Cytolysis** i.e. dissolution of the hepatocytes. The necrotic cells vanish (cell dropped out). This is detected indirectly as macrophage aggregation
  2. **Apoptosis** i.e. hepatocytes shrink, become intensely eosinophilic, and have fragmented nuclei. Apoptotic cells are phagocytosed within hours by macrophages and hence may be difficult to find despite extensive apoptosis.
3. Confluent necrosis of hepatocytes, seen in severe cases & may lead to bridging necrosis that extends through portal-portal, central-central, or portal-central areas. (Fig. 6-2)

- **Hepatocyte regeneration** as evidenced by irregularly thickened plates with occasional rosettes & and multinucleation.
- **Inflammation** is usually a prominent feature of acute hepatitis. The portal tracts are infiltrated predominantly by lymphocytes. The inflammatory infiltrate may spill over into the parenchyma to cause necrosis of periportal hepatocytes (*interface hepatitis*) and may also infiltrate the sinusoids.
- **Hypertrophy & hyperplasia of Kupffer cells**
- **Cholestasis** may be present, both intracellular (brown pigmentation of hepatocytes) & canalicular (bile plugs in canaliculi).
- **HBV** infection, acute or chronic, may produce two distinctive features of the infected hepatocytes.
  a. *Ground-glass* hepatocytes: a finely granular, eosinophilic cytoplasm due to massive quantities of HBsAg (as seen by electron microscopy).
  b. *Sanded nuclei*, resulting from abundant intranuclear HBcAg.

**Chronic hepatitis** (Fig. 6-3)

The changes are of **variable severity**, ranging from very mild to severe.

- **Hepatocyte necrosis** may occur in all forms of chronic hepatitis.
- The **inflammatory component** consists mainly of lymphocytes, macrophages, and occasional plasma cells. In the mildest forms, significant inflammation is limited to portal tracts. *Lymphoid aggregates* in the portal tract are often seen in HCV infection.
- The liver **architecture is usually well preserved**
- Continued **periportal necrosis (interface hepatitis) and bridging necrosis** are forerunners of progressive liver damage.
- The **hallmark of serious liver damage is the deposition of fibrous tissue**. At first, at the portal tracts, but with time *periportal fibrosis* occurs. This is followed by *bridging fibrosis* that links fibrous septa between lobules.
- Continued loss of hepatocytes with fibrosis results in *cirrhosis, with fibrous septa and hepatocyte regenerative nodules*. This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable but mostly broad bands of fibrosis. The nodules are typically greater than 0.3 cm in diameter; accordingly, the *cirrhosis is by definition macronodular*.

**Autoimmune Hepatitis** is microscopically indistinguishable from chronic viral hepatitis but is associated with a set of immunologic abnormalities. This disease may run an indolent or severe course. Salient features include:

- Female predominance
- Absence of viral infection serologic markers
- **Immunological abnormalities**
  a. Elevated serum IgG (>2.5 g/dl)
  b. High titers of autoantibodies (80% of cases)
  c. Presence of other autoimmune diseases (in 2/3 of the patients), including rheumatoid arthritis, thyroiditis, Sjögren syndrome, and ulcerative colitis.
Pathogenesis
Most patients have a variety of auto-antibodies such as antinuclear, anti-smooth muscle, liver kidney microsomal antibody, etc. The best characterized among these antibodies are smooth muscle antibodies directed against cytoskeletal proteins that include actin, and troponin, and liver kidney microsomal antibodies. The main effectors of cell damage are believed to be CD4+ helper cells. Response to immunosuppressive therapy is usually dramatic. The overall risk of cirrhosis, the main cause of death, is 5%.

PYOGENIC LIVER ABSCESSES
In developing countries most liver abscesses result from parasitic infections, such as amebic, echinococcal, etc. In the Western world, bacterial abscesses are more common, representing a complication of an infection elsewhere. Gram-negative bacteria such as E. coli and Klebsiella sp. are the usual offenders. The organisms reach the liver through one of the following pathways:
1. Ascending cholangitis
2. Vascular seeding, predominantly portal i.e. from the GIT
3. Direct invasion from a nearby focus
Debilitating disease with immune deficiency is a common background e.g. extreme old age, immunosuppression, or chemotherapy.

Gross features
- Pyogenic abscesses may be solitary or multiple, ranging from very small to massive lesions.
- Bacteremic spread through the arterial or portal system tends to produce multiple small abscesses, whereas direct extension and trauma usually cause solitary large abscesses. (Fig. 6-4 A)

Microscopic features
- These are identical to pyogenic abscesses elsewhere.
Liver abscesses are associated with fever and right upper quadrant pain and tender hepatomegaly. Jaundice is often the result of extrahepatic biliary obstruction. Surgical drainage is often necessary.

AMEBIC LIVER ABSCESS is usually single, mostly right sided, & close to liver dome, but tends to be multicentric in immunocompromised patients. Adults are mostly affected but can develop in infants & children.

Gross features (Fig. 6-4 B)
- The necrotic center contains odorless, pasty, chocolate brown fluid.

Microscopic
- Most of the lesion consists of necrotic debris. There few if any neutrophils.
- This centre is surrounded by fibrin, macrophages, lymphocytes & a few fibroblasts with clusters of amebic trophozoites (up to 60 microns with small eccentric nucleus and cytoplasmic vacuoles that may contain red blood cells; resemble histiocytes).

Complications
1. Bacterial superinfection
2. Extension or perforation into the following
   1. Pleuro-pulmonary structures
2. Subphrenic space
3. Peritoneal cavity, and pericardial sac, bile ducts

**Diagnosis:** serology is 90% sensitive

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**HYDATID DISEASE OF THE LIVER**

Three quarters of infected individuals develop one or more hepatic cysts, which grow slowly. The typical hydatid cyst is spherical and may measure up to more than 30 cm in diameter. The majority occur in the right lobe, but they may be multiple, involving all lobes. A characteristic gross feature is the presence of the soft, whitish laminate membrane. (Fig. 6-4 C) Histologic examination of the cyst wall shows an outer fibrous layer; a middle onionskin like laminated membrane, and an inner germinal layer. Calcification in the latter layer signifies that the cyst is dead. The adjacent liver parenchyma often shows pressure atrophy and a portal infiltrate in which eosinophils may be prominent. The viable cyst is filled with colorless fluid, which contains daughter cysts and brood capsules with scolices. Communication with the biliary tract and superimposed infection are frequent. Rupture of the cysts into the peritoneal cavity may result in a fatal anaphylactic reaction or in the formation of innumerable small granulomas grossly resembling peritoneal tuberculosis. Identification of fragments of germinal membrane or scolices in their center points to the diagnosis. Hepatic echinococcus cysts can also rupture inside the gallbladder or through the diaphragm into the pleural space and lung. The laboratory diagnosis can usually be made by hydatid serology and confirmed or established by ultrasound or computed tomography.

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**ALCOHOLIC LIVER DISEASE**

Excessive ethanol consumption is a common cause of chronic liver disease in Western countries and accounts for up to 50% of deaths due to cirrhosis. *Chronic heavy drinkers are predisposed to 3 distinctive forms of alcoholic liver disease; these may overlap.* (Fig. 6-5)

1. **Hepatic steatosis (almost all heavy drinkers)**
2. **Alcoholic hepatitis (30%)**
3. **Cirrhosis (15%)**

**Pathological features**

**Hepatic Steatosis (Fatty Liver):**

**Gross features**

- The liver is large (up to 4 or even 6 kg), soft, yellow, and greasy. (Fig. 6-6 A)

**Microscopic features** (Fig. 6-6 B)

- Initially small lipid droplets accumulate in hepatocytes (*microvesicular steatosis*)
- Persistent chronic intake of alcohol is associated with lipid accumulates in a large single vacuole that compresses and displaces the nucleus to the periphery of the hepatocyte (*macrovesicular steatosis*).
- The affected hepatocytes are centrilobular, but in severe cases the entire lobule is affected.
- With continued alcohol intake fibrous tissue develops around the central veins and extends into the adjacent sinusoids. Until fibrosis appears, the fatty change is completely reversible if there is abstention from further intake of alcohol.

**Alcoholic Hepatitis**

**Gross features**
- The liver is mottled red & yellow-green (bile stained).
- It may increase in size.
- Visible nodules and fibrosis signify progression to cirrhosis.

**Microscopic features (Fig. 6-7)**

Alcoholic hepatitis is characterized by

1. **Ballooning degeneration and necrosis of hepatocytes**
2. **Mallory Bodies**: these appear as pinkish, tangled filaments within the cytoplasm of degenerating hepatocytes
3. **Neutrophil Infiltrations** that permeate the lobule and accumulate around degenerating hepatocytes.
4. **Fibrosis** is characteristically sinusoidal and perivenular
5. **Cholestasis and hemosiderin deposition** in hepatocytes and Kupffer cells

**Alcoholic Cirrhosis**: is the final, irreversible form of alcoholic liver disease.

**Gross features (Fig. 6-8)**

- Initially, the liver is yellow, fatty, enlarged, (usually over 2 kg), & finely (micro-) nodular externally and on section.
- Over several years it becomes brown, shrunken (weighing less than 1 kg) with variably sized small and large nodules that create a "hobnail" appearance externally.

**Microscopic features**

- Initially there are delicate fibrous septa that extend from central veins through the sinusoids to the portal tracts and from portal tracts to portal tracts.
- Regenerative activity of entrapped hepatocytes generates in the early stages uniform small nodules (< 0.3 cm in diameter). This is by definition a micronodular cirrhosis. The nodules eventually become larger & more prominent and are engulfed by ever wider bands of fibrous tissue, and the liver is converted into a mixed micronodular and macronodular cirrhosis.
- Bile stasis often develops.

The induction of cytochrome P-450 by alcohol leads to enhanced transformation of other drugs to toxic metabolites e.g. accelerated metabolism of paracetamol into highly toxic metabolites that increase the risk of liver injury even with therapeutic doses of this commonly used analgesic. Concurrent viral hepatitis, particularly hepatitis C is a major accelerator of liver disease in alcoholics. In chronic alcoholics, alcohol may become a major caloric source in the diet, displacing other nutrients and leading to malnutrition and vitamin deficiencies (e.g., thiamine and vitamin B₁₂). This is accentuated by impaired digestive function, primarily related to chronic gastric and intestinal mucosal damage, and pancreatitis.

With alcoholic cirrhosis, the immediate causes of death are

1. Hepatic failure
2. Massive gastrointestinal hemorrhage
3. Intercurrent infection
4. Hepatorenal syndrome and
5. Hepatocellular carcinoma (5% of cases).
DRUG-INDUCED LIVER DISEASE
The liver is a major drug metabolizing and detoxifying organ in the body, thus, it is subjected to injury from a wide range of therapeutic and environmental chemicals. Injury may result from
1. Direct toxicity
2. Hepatic conversion of a foreign chemical to an active toxin
3. Immune damage, usually initiated by the drug or its metabolites acting as a hapten to convert a cellular protein into an immunogen.

Exposure to a toxin or therapeutic agent should always be included in the differential diagnosis of any form of liver disease. Drug reactions may be classified as predictable (intrinsic) reactions or unpredictable (idiosyncratic) ones. Predictable drug reactions are dose dependent & thus may occur in anyone who accumulates a sufficient dose. Unpredictable reactions are idiosyncratic & depend on the host's ability to mount an immune response to the antigenic stimulus.

Drug-induced chronic hepatitis is clinically and histologically indistinguishable from chronic viral hepatitis or autoimmune hepatitis, and hence serologic markers of viral infection are critical for making the distinction. Examples of predictable drug reactions are associated with paracetamol, tetracycline, antineoplastic drugs, carbon tetrachloride, and alcohol. Examples of drugs that can cause idiosyncratic reactions include chlorpromazine, halothane anesthetic, sulfonamides, α-methyldopa, and allopurinol.

Drugs that may cause acute liver failure due to massive hepatic necrosis include
1. Paracetamol (the most common cause)
2. Halothane,
3. AntiTB drugs (rifampin, isoniazide),
4. Industrial chemicals such as carbon tetrachloride
5. Mushroom poisoning.

Gross features of massive hepatic necrosis (Fig. 6-9 A)
- The entire liver may be involved, (or only random areas are affected).
- With such extensive loss of hepatic substance, the liver shrinks to 500 gm and becomes a floppy, red or bile-stained, soft organ covered by a wrinkled, redundant capsule.

Microscopic features (Fig. 6-9 B)
- Complete necrosis of hepatocytes in contiguous lobules leaves only a collapsed reticulin framework and preserved portal tracts.
- If the patient survives for more than a week, regeneration of surviving hepatocytes occurs. With massive destruction of confluent lobules, regeneration is disorderly, yielding nodular masses of liver cells surrounded by bands of scarring (macronodular cirrhosis).

METABOLIC LIVER DISEASE
Under this heading come the following entities
1. Nonalcoholic fatty liver disease
2. Hemochromatosis,
3. Wilson disease, and
4. α1-antitrypsin deficiency.
Nonalcoholic Fatty Liver Disease (NAFLD) may present as steatosis (fatty liver), nonalcoholic steatohepatitis (NASH) or cirrhosis. The latter is similar to alcoholic hepatitis. NAFLD is associated with
1. Insulin resistance including Type 2 diabetes, is the most common associated condition
2. Obesity
3. Dyslipidemia (hypertriglyceridemia, low HDLP cholesterol, high LDLP cholesterol).
The presence of type 2 diabetes and obesity are the best predictors of severe fibrosis and disease progression. Insulin resistance results in the accumulation of triglycerides in hepatocytes. Fat-laden hepatocytes are highly sensitive to lipid peroxidation products generated by oxidative stress, which can damage mitochondrial and plasma membranes, causing apoptosis. Most persons with steatosis are asymptomatic; patients with NASH or may also be asymptomatic, or present with symptoms of chronic liver disease. Liver biopsy is required for diagnosis. Fortunately, the frequency of progression from steatosis to NASH, and from NASH to cirrhosis seems to be low.

Hereditary hemochromatosis
The most common form of this genetic disease is an autosomal recessive variant of adult onset caused by mutations in the HFE gene. Iron accumulates over the lifetime of the affected individual from excessive intestinal absorption. Total iron accumulation may exceed 50 gm (N: 2-6g), over one-third of which accumulates in the liver (N: 0.5 g).

Fully developed cases of hereditary hemochromatosis show
1. Cirrhosis (all patients)
2. Diabetes mellitus (75%)
3. Skin pigmentation (75%).
Iron accumulations from known sources of excess iron are called secondary iron overload or (secondary hemochromatosis), the most important of these are
1. Multiple transfusions
2. Ineffective erythropoiesis (as in β-thalassemia and sideroblastic anemia)
3. Increased iron intake (Bantu siderosis).
Chronic liver diseases can also cause iron accumulation in the liver e.g. alcoholic liver disease.
Pathogenesis
In hereditary hemochromatosis there is a dysregulation of intestinal absorption of dietary iron. This leads to net iron accumulation of up to 1.0 gm/year. It appears that HFE gene regulates the levels of hepcidin, the iron hormone produced by the liver. Hepcidin normally interferes with the flowing out of iron from the intestines and macrophages into the plasma and inhibits iron absorption. As might be expected, hepcidin levels are reduced in all currently known genetic forms of hemochromatosis.

Gross features (Fig. 6-10 A)
- Hemosiderin deposition occurs in several organs & tissues e.g. the myocardium, pituitary, adrenal, thyroid, parathyroid gland, joints, skin
- The liver is typically chocolate brown in color.
- Fibrous septa develop slowly, leading ultimately to micronodular cirrhosis in an intensely pigmented liver.

Microscopic features
- The golden-yellow hemosiderin granules accumulate in the cytoplasm of periportal hepatocytes; these stain blue with the Prussian blue stain (Fig. 6-10 B).
• With increasing iron load, there is progressive deposition in the rest of the lobule, along with bile duct epithelium and Kupffer cells. (In secondary iron overload, the iron is mainly in Kupffer cells, not hepatocytes, at least initially)

• Iron is a direct hepatotoxin, and inflammation is characteristically absent.

In normal individuals the iron content of unfixed liver tissue is less than 1000 μg/gm dry weight. Adult patients with hereditary hemochromatosis exhibit over 10,000 μg/gm dry weight of iron; hepatic iron concentrations in excess of 22,000 μg/gm dry weight are associated with the development of fibrosis and cirrhosis.

Males predominate (ratio of 5 to 7:1), partly because physiologic iron loss (menstruation, pregnancy) retards iron accumulation in women. In the most common forms, caused by HFE mutations, symptoms usually first appear in the age range of 40 to 60 years. The classic clinical triad of cirrhosis (with hepatomegaly), skin pigmentation, and diabetes mellitus may not develop until late in the course of the disease. Death may result from cirrhosis, hepatocellular carcinoma, or cardiac involvement. Treatment of iron overload does not remove the risk of hepatocellular carcinoma (200 times higher than in normal populations).

Wilson Disease (Hepatolenticular degeneration)

This autosomal recessive disorder of copper metabolism is characterized by the accumulation of toxic levels of copper in many tissues and organs, principally the liver, brain, and eyes. The genetic defect responsible for Wilson disease is a mutation in ATP7B, the defective function of which leads to failure on the part of hepatocytes to excrete copper into bile, which is the primary route for copper elimination from the body. The defect also inhibits secretion of ceruloplasmin from hepatocytes into the plasma. Copper thus accumulates progressively in the liver, apparently causing toxic liver injury. Usually by the age of 5 years, copper that is not ceruloplasmin bound spills over into the circulation, causing hemolysis and pathologic changes at other sites, such as brain, cornea, and kidneys. Concomitantly, urinary excretion of copper increases markedly. The biochemical diagnosis of Wilson disease is based on a decrease in serum ceruloplasmin, increase in hepatic copper content, and increase in urinary excretion of copper.

Pathological features

• Fatty change of the liver may be mild to moderate, the hepatocytes also show vacuolated nuclei (glycogen or water) and focal necrosis.

• An acute hepatitis can mimic acute viral hepatitis, except for the fatty change.

• A chronic hepatitis resembles chronic hepatitis due to other causes but may show such distinguishing features as fatty change, vacuolated nuclei, and Mallory bodies.

• With progression of chronic hepatitis, cirrhosis develops.

The demonstration of increased copper content of the hepatocytes by using special stains is not an exclusive feature of Wilson disease. However, the demonstration of hepatic copper content in excess of 250 μg/gm dry weight is most helpful for making the diagnosis. In the brain, toxic injury affects the basal ganglia, particularly the putamen, which shows atrophy & cavitation (hepatolenticular degeneration). Nearly all patients with neurologic involvement develop eye lesions called Kayser-Fleischer rings (green to brown deposits of copper in the Descemet’s membrane of the cornea). (Fig. 6-11) Wilson disease rarely manifests before 6 years of age. The most common presentation is acute or chronic liver disease. Neuropsychiatric manifestations, including frank psychosis, or a Parkinson disease-like syndrome, are the initial features in most of the remaining cases. Demonstration of Kayser-
Fleischer rings or markedly elevated hepatic copper levels in a person with a low serum ceruloplasmin value strongly favor the diagnosis.

α1-Antitrypsin (AAT) Deficiency
AAT deficiency is an autosomal recessive disorder characterized by abnormally low serum levels of this protease inhibitor. The major function of AAT is the inhibition of proteases, particularly neutrophil elastase released at sites of inflammation. AAT deficiency leads to pulmonary emphysema because a relative lack of this protein permits the unrestrained activity of destructive proteases. AAT is a plasma glycoprotein synthesized predominantly by hepatocytes. The AAT gene is very polymorphic, and at least 75 forms have been identified. However, homozygotes for the Z allele (PiZZ genotype) have circulating AAT levels that are only 10% of normal levels. Because the mutant protein cannot be secreted by the hepatocyte, it accumulates in the endoplasmic reticulum. Curiously, all individuals with the PiZZ genotype accumulate AAT in the liver, but only 8% to 20% develop significant liver damage.

Pathological features
- Hepatocytes in AAT deficiency contain round to oval cytoplasmic globular inclusions of retained AAT, which are strongly positive with PAS stain (Fig. 6-12).
- Hepatic injury associated with PiZZ may range from marked cholestasis with hepatocyte necrosis in newborns, to childhood cirrhosis, or to a chronic hepatitis or cirrhosis that becomes apparent only late in life.

In older children, adolescents, and adults, presenting symptoms may be related to chronic hepatitis, cirrhosis, or pulmonary disease. Hepatocellular carcinoma develops in 3% of PiZZ adults.

Neonatal Cholestasis
Mild transient elevations in serum unconjugated bilirubin are common in normal newborns. Prolonged conjugated hyperbilirubinemia in the newborn, termed neonatal cholestasis, affects approximately 1 in 2500 live births. The major causes are
1. Extrahepatic biliary atresia
2. Neonatal hepatitis; 50% of the cases are idiopathic
The finding of "neonatal cholestasis" should evoke a diligent search for recognizable toxic, metabolic, and infectious liver diseases. 50% of cases of neonatal hepatitis are idiopathic. Infants with any form of neonatal cholestasis present with jaundice, dark urine, light or acholic stools, and hepatomegaly. Differentiation between the two most common causes of neonatal cholestasis (extrahepatic atresia and idiopathic hepatitis) assumes great importance, because definitive treatment of biliary atresia requires surgical intervention, whereas surgery may adversely affect the clinical course of a child with idiopathic neonatal hepatitis. Fortunately, discrimination between these diseases can be made in about 90% of cases using clinical data and liver biopsy.

Reye Syndrome is a rare disease characterized by fatty change in the liver and encephalopathy. It primarily affects children younger than 4 years of age, typically developing few days after a viral illness. The majority recover, but 25% of the cases progress to coma, accompanied by elevations in the serum levels of bilirubin, aminotransferases, and particularly ammonia. Death occurs from progressive neurologic deterioration or liver
failure. Reye syndrome is now recognized as the prototype of a wide variety of conditions known as "mitochondrial hepatopathies." Reye syndrome has been associated with aspirin administration during viral illnesses, but there is no evidence that salicylates play a causal role in this disorder. The key pathologic finding in the liver is microvesicular steatosis. In the brain, cerebral edema is usually present.

DISEASES OF THE INTRAHEPATIC BILIARY TRACT (Fig. 6-13)

Primary Biliary Cirrhosis (PBC) is a chronic, progressive cholestatic liver disease with eventual development of micronodular cirrhosis and liver failure over years to decades. The primary feature of this disease is an inflammatory destruction of small and medium-sized intrahepatic bile ducts. In the early lesions there is a dense lymphocyte/plasma cell infiltrate around small bile ducts in portal tracts, and granulomatous lesions may also appear. Primary biliary cirrhosis is primarily a disease of middle-aged women. More than 90% of persons with PBC have high titers of antimitochondrial antibodies. However, it is still unclear why intrahepatic bile ducts are the targets for these antibodies. Recent evidence suggests that exposure to certain xenobiotics may modify mitochondrial proteins leading to a decrease of immunologic tolerance to some of these proteins. Pruritus is the initial presenting feature; jaundice develops late. Serum alkaline phosphatase and cholesterol levels are almost always elevated; hyperbilirubinemia is a late development and usually signifies incipient hepatic decompensation. Associated extrahepatic conditions include Sjögren syndrome, scleroderma, thyroiditis, rheumatoid arthritis, Raynaud phenomenon, etc.

Primary Sclerosing Cholangitis (PSC) is a chronic cholestatic disorder, characterized by progressive fibrosis and destruction of extrahepatic and large intrahepatic bile ducts. Because the changes in the ducts are patchy, retrograde cholangiography shows a characteristic "beading" of the contrast medium in the affected segments of the biliary tree. The large bile ducts show periductal fibrosis that obliterates the lumen, leaving a solid cord scar with few inflammatory cells. Affected portal tracts show concentric periductal onion-skin fibrosis and a modest lymphocytic infiltrate (Fig. 6-14). Primary sclerosing cholangitis is commonly seen in association with inflammatory bowel disease, particularly chronic ulcerative colitis, which coexists in approximately 70% of the PSC cases. The disorder tends to occur in the age range of 20 to 50 years. Evidences suggest that PSC is an immunologically mediated disease. Cholangiocarcinoma complicates PSC in 10% of individuals.

CIRCULATORY DISORDERS

Hepatic Artery Obstruction: liver infarcts are rare due to the double blood supply to the liver. Interruption of the main hepatic artery does not always produce ischemic necrosis of the organ, because of the accessory vessels and the portal venous supply that may sustain the liver parenchyma. The one exception is hepatic artery thrombosis in the transplanted liver, which generally leads to loss of the organ. Thrombosis or compression of an intrahepatic branch of the hepatic artery by polyarteritis nodosa, embolism, neoplasia, or sepsis may result in a localized parenchymal infarct.

Portal Vein Obstruction and Thrombosis

Oclusion of the portal vein or its major branches typically produces abdominal pain, ascites and other manifestations of portal hypertension, principally esophageal varices that are prone to rupture. The ascites, when present, is often massive and intractable.
Extrahepatic portal vein obstruction may arise from the following:

a. Peritoneal sepsis (e.g., acute appendicitis leading to pylephlebitis)
b. Pancreatitis: this initiates splenic vein thrombosis, which propagates into the portal vein
c. Thrombogenic diseases and postsurgical thromboses
d. Vascular invasion by primary or secondary cancer in the liver that progressively occludes portal inflow to the liver; extensions of hepatocellular carcinoma can even occlude the main portal vein
e. Banti syndrome, in which subclinical thrombosis of the portal vein (as from neonatal omphalitis or umbilical vein catheterization) produces a fibrotic, partially recanalized vascular channel presenting as splenomegaly or esophageal varices years after the occlusive event.

**Intrahepatic thrombosis of a portal vein radicle.** When acute, does not cause ischemic infarction but instead results in a sharply demarcated area of red-blue discoloration (infarct of Zahn). There is no necrosis, only hepatocellular atrophy and markedly congested & distended sinusoids.

**Impaired Blood Flow through the Liver**
The most common intrahepatic cause of portal blood flow obstruction is cirrhosis. In addition, physical occlusion of the sinusoids occurs in sickle cell disease, this leads to panlobular necrosis. Disseminated intravascular coagulation may cause occlusion of sinusoids. This is usually inconsequential except for the periportal sinusoidal occlusion and parenchymal necrosis that may occur in the eclampsia of pregnancy. Subsequent suffusion of blood under the capsule may precipitate a fatal intra-abdominal hemorrhage. (Fig. 6-15)

**Passive Congestion and Centrilobular Necrosis**
Right-sided cardiac failure leads to passive congestion of the liver, and if persistent, can cause centrilobular necrosis, and perivenular fibrosis in the areas of necrosis. In most instances, there is only a small elevation of serum aminotransferase levels & sometimes mild to moderate jaundice.

**Gross features**
- In right-sided heart failure, the liver is slightly enlarged, tense, and cyanotic, with rounded edges.

**Microscopic features**
- There is congestion of centrilobular sinusoids associated with atrophy of centrilobular hepatocytes resulting in markedly attenuated liver cell cords.
- An uncommon complication of sustained chronic severe congestive heart failure is cardiac sclerosis (not cirrhosis). The pattern of liver fibrosis is distinctive, inasmuch as it is mostly centrilobular.
- Left-sided cardiac failure or shock may lead to hepatic hypoperfusion and hypoxia. In this instance, centrilobular hepatocytes undergo ischemic necrosis.
- The combination of left-sided hypoperfusion and right-sided retrograde congestion acts synergistically to generate a distinctive lesion, centrilobular hemorrhagic necrosis. The liver takes on a variegated mottled appearance, reflecting hemorrhage and necrosis in the centrilobular regions, alternating with pale midzonal areas, known traditionally as the "nutmeg" liver. (Fig. 6-16).
Hepatic Vein Outflow Obstruction

1. Hepatic Vein Thrombosis (Budd-Chiari Syndrome) results from the thrombosis of two or more major hepatic veins and is characterized by hepatomegaly, ascites, and abdominal pain. Causes of hepatic vein thrombosis are (in order of frequency)
   1. Myeloproliferative disorders including polycythemia vera
   2. Pregnancy, the postpartum state, or the use of oral contraceptives
   3. Paroxysmal nocturnal hemoglobinuria (PNH)
   4. Intra-abdominal cancers, particularly hepatocellular carcinoma.
   All of the above produce thrombotic tendencies or, in the case of liver cancers, sluggish blood flow.
   5. Mechanical obstruction to blood outflow, as by a massive intrahepatic abscess or parasitic cyst, or by obstruction of the inferior vena cava at the level of the hepatic veins by thrombus or tumor.
   6. Idiopathic (10% of cases)

Gross features
- With acutely developing thrombosis of the major hepatic veins or inferior vena cava, the liver is swollen, red-purple, and has a tense capsule (Fig. 6-17).

Microscopic features
- There is severe centrilobular congestion and necrosis.
- Centrilobular fibrosis develops in instances in which the thrombosis is more slowly developing.
- The major veins may contain occlusive fresh thrombi or, in chronic cases, organized adherent thrombi.

2. Sinusoidal Obstruction Syndrome (veno-occlusive disease) was originally described in Jamaican drinkers of bush-tea containing pyrrolizidine alkaloid. It is caused by toxic injury to sinusoidal endothelium. Damaged endothelial cells slough off and create emboli that block blood flow. Endothelial damage is accompanied by passage of red blood cell into the space of Disse, proliferation of stellate cells, and fibrosis of terminal branches of the hepatic vein. This syndrome now occurs primarily in the first 20-30 days after bone marrow transplantation (up to 20% of cases). The sinusoidal injury is believed to be caused by drugs such as cyclophosphamide, and by total body radiation, used in pre- or post-transplantation regimens. The presentation of the disease varies from mild to severe. Severe sinusoidal obstruction syndrome that does not resolve after 3 months of treatment can cause death.

TUMORS AND HEPATIC NODULES

The most common hepatic neoplasms are metastatic carcinomas, with colon, lung, and breast heading the list as sites of the primary tumor.

Solitary or multiple benign hepatocellular nodules may develop in the liver. These include
1. Focal nodular hyperplasia
2. Macrogeneative nodules
3. Dysplastic nodules

Focal nodular hyperplasia is localized, well-demarcated but poorly encapsulated nodular regeneration. It consists of hyperplastic hepatocyte with a central fibrous scar. (Fig. 6-18)
The nodules appear in noncirrhotic livers in response to local vascular injury and may reach up to many centimeters in diameter. It is usually an incidental finding, most commonly in women of reproductive age. In about 20% of cases, focal nodular hyperplasia coexists with hepatic cavernous hemangiomas.
Macrogenregenerative nodules appear in cirrhotic livers (Fig. 6-19). They are larger than surrounding cirrhotic nodules but do not display atypical features. They do not seem to be precursors of malignant lesions.

Dysplastic nodules are lesions larger than 1 mm in diameter that appear in cirrhotic livers. Hepatocytes in dysplastic nodules and in smaller lesions called dysplastic foci are highly proliferative and show atypical features such as crowding and pleomorphism. The dysplastic features can be of low or high grade. High-grade dysplastic lesions are considered to be precursors of hepatocellular cancers.

Benign Tumors

Cavernous hemangiomas (Fig. 6-20) are most common benign lesions of the liver are. These well-circumscribed lesions consist of vascular channels and intervening stroma. They appear as discrete red-blue, soft nodules, usually less than 2 cm in diameter, often directly beneath the capsule. Their chief clinical significance is the importance of not mistaking them for metastatic tumors; blind percutaneous needle biopsy may cause severe intra-abdominal bleeding.

Hepatic (liver cell) Adenoma usually occurs in women of childbearing age who have used oral contraceptive steroids, and it may regress on discontinuance of hormone use. The tumor is yellow-tan, well-demarcated nodules, up to 30 cm in diameter and is often located beneath the capsule (Fig. 6-21).

It is composed of sheets and cords of cells that may resemble normal hepatocytes with prominent arteries and veins. Liver cell adenomas are significant for three reasons:
1. May be mistaken for HCC
2. May rupture, particularly during pregnancy causing life-threatening intra-abdominal hemorrhage
3. With β-catenin mutations they carry a risk of cancerous transformation.

Hepatocellular Carcinomas (HCC)
The incidence (generally 5% of all cancers) varies widely in different areas of the world. More than 85% of cases occur in countries with high rates of chronic HBV infection e.g. Asian and African countries in which HBV is transmitted vertically, and thus the carrier state starts in infancy. Moreover, many of these populations are exposed to aflatoxin, which, combined with HBV infection, increases the risk of HCC development by more than 200-fold over noninfected, nonexposed populations. The peak incidence of HCC in these areas is between 20 and 40 years of age, and in almost 50% of cases, HCC may appear in the absence of cirrhosis. In Western populations HCC is rare and seldom present before age 60, and in 90% of cases tumors develop in cirrhotic livers. There is a pronounced male preponderance of HCC throughout the world.

Pathogenesis

- Three major etiologic associations have been established:
  1. Infection with HBV or HCV
  2. Alcoholic cirrhosis
  3. Aflatoxin exposure
- Other associations include
  4. Hemochromatosis
  5. Hereditary tyrosinemia (40% of patients develop HCC)
- Cirrhosis seems to be an important, but not essential contributor to the occurrence of HCC. In most cases, HCC develops from high-grade dysplastic nodules.
Carcinogenesis is greatly enhanced in the presence of cell injury and replication, as occurs in chronic viral hepatitis. *HCV infection is the greatest risk factor,* HCC in such patients occurs almost exclusively in the setting of cirrhosis. In certain regions of the world, such as China and South Africa, where HBV is endemic, there is also high exposure to dietary aflatoxins derived from the fungus *Aspergillus flavus.* Aflatoxin can bind covalently with cellular DNA and cause a mutation in p53. Neither HBV nor HCV contains oncogenes. The carcinogenic capacity of these viruses probably relates to their capacity to cause continuing cell death, chronic inflammation, and regeneration; these are believed to be main contributors to DNA damage.

Autonomous hepatocyte replication can occur by over-expression of specific cellular genes (such as β-catenin), mutation of the tumor suppressor gene *p53,* methylation changes, and expression of growth factors.

**Gross features**

- There are three gross forms of HCC
  1. **Unifocal,** usually a massive tumor ([Fig. 6-22 A](#))
  2. **Multifocal** i.e. made of variably sized nodules
  3. **Diffusely infiltrative** i.e. permeating widely and sometimes involving the entire liver
- Particularly in the latter two patterns, it may be difficult to distinguish regenerative nodules of cirrhotic liver from nodules of neoplasm of similar size. The cancerous masses are usually yellow-white, punctuated sometimes by bile staining and areas of hemorrhage or necrosis.
- **All patterns of HCC have a strong propensity for invasion of vascular channels.** Extensive intrahepatic metastases ensue, and occasionally snakelike masses of tumor invade the portal vein (with occlusion of the portal circulation) or inferior vena cava, extending even into the right side of the heart.

**Microscopic features** ([Fig. 6-22 B](#))

- HCCs range from well-differentiated to poorly differentiated lesions. In well differentiated HCC the neoplastic hepatocytes are arranged in broad trabeculae, which are separated by sinusoids.
- Central necrosis in the broad trabeculae may produce a pseudoglandular pattern.
- Poorly differentiated tumors are composed of large multinucleate anaplastic tumor giant cells.
- In the better differentiated variants, globules of bile may be found within the cytoplasm of cells and in pseudocanaliculi between cells.
- Mallory bodies may be found within the cytoplasm of the neoplastic cells.
- HCC displays scant connective tissue stroma (that is why it is soft in consistency)

**Fibrolamellar carcinoma** is a distinctive clinicopathologic variant of HCC, in that
- It occurs in young male and female adults (20-40 years of age) with equal incidence
- It has no association with cirrhosis or other risk factors
- It usually appears grossly as a single large, hard "scirrhous" tumor
- Histologically it is composed of well-differentiated neoplastic hepatocytes growing in nests or cords and separated by thick fibrous lamellae around groups of tumor cells. ([Fig. 6-23](#))

In patients with cirrhosis a rapid increase in liver size, sudden worsening of ascites, or the appearance of bloody ascites, fever, and pain call attention to the development of HCC. Laboratory studies are helpful but not diagnostic. Half of the patients have elevated levels of *serum α-fetoprotein.* However, this tumor "marker" lacks specificity, because moderate
Elevations are also encountered in other conditions, such as cirrhosis, chronic hepatitis, normal pregnancy, fetal death, fetal neural tube defects and gonadal germ cell tumors. Very high levels (>1000 ng/mL), however, are rarely encountered except in HCC. This marker is only rarely elevated to the levels considered diagnostic for HCC. The overall prognosis of HCC is poor, but it is significantly better for individuals who have a single tumor less than 2 cm in diameter and good liver function. The median survival is 7 months.

Metastatic tumors (Fig. 6-24)
The following malignant tumors frequently involve the liver by direct extension
1. Gallbladder
2. Extrahepatic bile ducts
3. Pancreas
4. Stomach

The following carcinomas metastasize to the liver with regularly
1. Large bowel
2. Lung
3. Breast
4. Pancreas
5. Kidney
6. Stomach

Sarcomas of soft tissues or internal organs and malignant melanomas also frequently metastasize to this organ.

Gross features
- Most metastatic tumors in the liver form discrete masses that may locally elevate the capsule.
- Central necrosis with umbilication occurs in the larger lesions
- Metastases are very rare in cirrhotic livers; whatever the reason for this may be (nonreceptive soil for the metastatic growth or simply the fact that most cirrhotic patients do not live long enough to develop them), the conclusion can be drawn that the large majority of malignant tumors occurring in cirrhotic livers are primary.
The microscopic picture reflects the features of the primary cancer.

DISORDERS OF GALLBLADDER AND EXTRAHEPATIC BILIARY TRACT

GALLBLADDER DISEASES
Cholelithiasis (Gallstones)
Gallstones trouble up to 20% of adult populations and are mainly of two types
1. Cholesterol stones composed of crystalline cholesterol monohydrate (80%)
2. Pigment stones composed predominantly of bilirubin calcium salts (20%)

Pathogenesis and Risk Factors
- Bile is a major pathway for elimination of excess cholesterol from the body. Cholesterol is rendered water soluble through mixing with bile salts and lecithins that are secreted into bile. When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol deposited as solid cholesterol crystals.
- Cholesterol gallstone formation involves four concurrently occurring steps:
  1. Supersaturation of the bile with cholesterol
  2. Establishment of a nidus by microprecipitates of calcium salts
  3. Hypomobility of the gallbladder (stasis), which promotes nidus formation
  4. Mucus hypersecretion to trap the crystals and thus enhancing their aggregation
The presence of \textit{unconjugated bilirubin} in the biliary tree increases the likelihood of pigment stone formation. This occurs in hemolytic anemias and biliary tract infections. The precipitates are insoluble calcium bilirubinate salts.

The majority of individuals with gallstones (80\%) have no identifying risk factors.

Contribution risk factors include:

1. \textit{Age and gender}: the incidence of gall stones increases with age in that only 5\% of the population younger than age 40 but 25\% of those older than 80 years develop stones. The prevalence in women is about twice as high as in men.

2. \textit{Ethnic and geographic}: gallstones are more prevalent in Western industrialized societies and uncommon in developing ones.

3. \textit{Heredity}: family history imparts increased risk, as do a variety of inborn errors of metabolism such as those associated with impaired bile salt synthesis and secretion.

4. \textit{Environment}: estrogenic influences, including oral contraceptives and pregnancy, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol.

5. \textit{Obesity, rapid weight loss}, and \textit{treatment with the hypocholesterolemic agent clofibrate} are strongly associated with increased biliary cholesterol secretion.

6. \textit{Gallbladder hypomotility} predisposes to gallstones. It is associated with pregnancy, rapid weight loss, and spinal cord injury. In most cases, however, the hypomotility is present without obvious cause.

\textbf{Pathologic features}

\textbf{Pure cholesterol stones} always formed within the gall bladder as pale to tan yellow, and are ovoid and firm (Fig. 6-25). They may be single but most are often multiple. In the latter instance, they assume a faceted surface from apposition to one another. \textit{Most cholesterol stones are radiolucent, but 20\% of them may have sufficient calcium carbonate to render them radiopaque.}

\textbf{Pigment stones} may arise anywhere in the biliary tree (gall bladder, intra- or extra-hepatic bile ducts) and are either \textit{black or brown}. In general, black pigment stones are found in sterile bile, while brown stones are found in infected bile. Black stones are usually small, present in large numbers (Fig. 6-26), and crumble easily. Brown stones tend to be single or few in number. Because of the incorporation of calcium carbonates and phosphates, 50\% to 75\% of black stones are radiopaque. \textit{Brown stones, which contain calcium soaps, are radiolucent.}

Gallstones are asymptomatic in 75\% of the cases. Pain is the principal symptom and it tends to be severe, either constant or "colicky" from an obstructed gallbladder or when small gallstones move down-stream and lodge in the biliary tree. Inflammation of the gallbladder, in association with stones, also generates pain.

\textbf{Complications of gall stones include}

1. \textit{Empyema}
2. \textit{Perforation}
3. \textit{Fistulae}
4. \textit{Cholangitis}
5. \textit{Obstructive cholestasis}
6. \textit{Pancreatitis}

It is the very small stones that are dangerous; the larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction. Occasionally a large stone may
erode directly into an adjacent loop of small bowel, generating intestinal obstruction ("gallstone ileus").

**Cholecystitis**
This may be acute, chronic, or acute superimposed on chronic, and almost always occurs in association with gallstones. Its epidemiologic distribution closely parallels that of gallstones.

**Gross features**

**Acute cholecystitis (Fig. 6-27)**
- The gallbladder is usually enlarged, tense, and bright red or blotchy, violaceous to green-black discoloration. The latter is due to subserosal hemorrhages.
- The serosal covering is frequently covered by fibrin or suppurative exudate.
- In 90% of cases stones are present, often obstructing the cystic duct.
- The gallbladder lumen is filled with cloudy or turbid bile (contain fibrin, blood, and frank pus). When the exudate is pure pus, the condition is referred to as *empyema of the gallbladder*.
- In mild cases the gallbladder wall is thickened, edematous, and hyperemic.
- In more severe cases the gallbladder is transformed into a green-black necrotic organ, termed *gangrenous cholecystitis*.

**Microscopical features**
- The inflammatory reactions consist of the usual patterns of acute inflammation (i.e., edema, neutrophilic infiltration, vascular congestion. It may be suppurative with frank abscess formation, or eventuates in gangrenous necrosis.

**Acute Calculous Cholecystitis** refers to acute inflammation of a gallbladder that contains stones and is precipitated by obstruction of the gallbladder neck or cystic duct. *It is the most common major complication of gallstones and the most common reason for emergency cholecystectomy.*

Initially it is the result of chemical irritation and inflammation of the gallbladder wall in the setting of obstruction to bile outflow.

**Acute Non-Calculous Cholecystitis**
Up to 10% of gallbladders removed for acute cholecystitis contain no gallstones. Most of these cases occur in seriously ill patients e.g. after severe trauma such as a major surgery, motor vehicle accidents, severe burns as well as sepsis. In such cases many events are thought to contribute to this condition such dehydration, gallbladder stasis and sludging, vascular compromise, and, ultimately, bacterial contamination.

**Chronic Cholecystitis** may be the sequel to repeated bouts of acute cholecystitis, but in most instances it develops de novo. *Like acute cholecystitis it is almost always associated with gallstones* but these do not seem to have a direct role in the initiation of inflammation. Rather, supersaturation of bile predisposes to both chronic inflammation and, in most instances, stone formation. Microorganisms, usually *E. coli* and enterococci, can be cultured from the bile in only about one-third of cases.

**Pathological features (Fig. 6-28)**
- The changes are extremely variable and sometimes minimal.
- The mere presence of stones within the gallbladder, even in the absence of acute inflammation, is often taken as sufficient justification for the diagnosis.
- The gallbladder may be contracted, of normal size, or enlarged.
• The submucosa and subserosa are often thickened from fibrosis.
• In the absence of superimposed acute cholecystitis, mural lymphocytes are the only feature of inflammation.

DISORDERS OF EXTRAHEPATIC BILE DUCTS
Choledocholithiasis and Cholangitis are frequently seen together. Choledocholithiasis is the presence of stones within the biliary tree. Almost all these stones are derived from the gallbladder. Symptoms are absent in 10% of the cases, but when occur they are due to biliary obstruction or its sequele such as pancreatitis, cholangitis, hepatic abscess, secondary biliary cirrhosis, or acute calculous cholecystitis.

Cholangitis refers to acute mostly bacterial inflammation of the wall of bile ducts. Most cases are due to obstruction bile flow, mostly by choledocholithiasis. However, surgical reconstruction of the biliary tree is also a recognized cause. Uncommon causes include tumors, indwelling stents or catheters, acute pancreatitis, and benign strictures. Bacteria most likely enter the biliary tract through the sphincter of Oddi, rather than by the hematogenous route. Ascending cholangitis refers to the tendency of bacteria, once within the biliary tree, to infect intrahepatic biliary ducts. The usual pathogens are E. coli, Klebsiella, Clostridium, Bacteroides, etc. Charcot’s triad (pain, jaundice and fever) is the most common mode of presentation.

The most severe form of cholangitis is suppurative cholangitis, in which purulent bile fills and distends bile ducts, with an attendant risk of liver abscess formation.

Secondary Biliary Cirrhosis
Prolonged obstruction of the extrahepatic biliary tree results in secondary biliary cirrhosis.

Causes include
1. Extrahepatic cholelithiasis (the most common cause)
2. Malignancies of the biliary tree and head of the pancreas
3. Strictures resulting from previous surgical procedures
4. Biliary atresia

The initial morphologic features of cholestasis are entirely reversible with correction of the obstruction. However, secondary inflammation resulting from biliary obstruction initiates periportal fibrogenesis, which eventually leads to scarring and nodule formation, generating secondary biliary cirrhosis. Subtotal obstruction may promote ascending cholangitis, which further contributes to the damage. Enteric organisms such as coliforms and enterococci are common offenders.

Biliary Atresia is a major cause of neonatal cholestasis (30%). Biliary atresia is defined as a complete obstruction of bile flow caused by destruction or absence of all or part of the extrahepatic bile ducts. It is the most frequent cause of death from liver disease in early childhood. The salient features of biliary atresia include
1. Inflammatory fibrosing stricture of extrahepatic biliary tree (hepatic or common bile ducts)
2. Inflammatory destruction of the major intrahepatic bile ducts
3. Features of biliary obstruction on liver biopsy
4. Periportal fibrosis and cirrhosis within 3 to 6 months of birth

Laboratory findings do not distinguish between biliary atresia and intrahepatic cholestasis, but a liver biopsy provides evidence of bile duct obstruction in 90% of cases of biliary atresia. Without surgical intervention, death usually occurs within 2 years of birth.
**TUMORS**

*Carcinoma of the Gallbladder* is the most frequent malignant tumor of the biliary tract. It occurs most frequently in the age group 60-70 years. The mean 5-year survival is 5% because it is rarely discovered at a resectable stage. Gallstones are present in about 75% of the cases. Presumably, gallbladders containing stones or infectious agents develop cancer as a result of recurrent trauma and chronic inflammation. The presence of abnormal choledocho-pancreatic duct junction is considered to be a risk factor.

**Gross features**
- The cancer is either *exophytic (fungating)* or *infiltrative* growth.
- The infiltrative pattern, which is the more common, usually appears as a poorly-defined area of thickening and induration of part or whole of gall bladder wall.
- The exophytic pattern grows into the lumen as cauliflower mass, but at the same time it invades the underlying wall (Fig. 6-29).

**Microscopic features**
- Well- to poorly-differentiated infiltrative adenocarcinomas that is sometimes *papillary*. By the time gallbladder cancers are discovered, **most have invaded the liver directly** and many have extended to the cystic duct and adjacent bile ducts and lymph nodes at the portahepatis.

Preoperative diagnosis of gall bladder carcinoma is seen in only a 20% of the cases. The fortunate person develops early obstruction and acute cholecystitis before extension of the tumor into adjacent structures or undergoes cholecystectomy for coexistent symptomatic gallstones. Preoperative diagnosis rests largely on detection of gallstones along with abnormalities in the gallbladder wall documented by imaging studies.

*Cholangiocarcinomas* are adenocarcinomas arising from cholangiocytes (epithelial cells lining) in bile ducts within and outside of the liver. *Extrahepatic cholangiocarcinomas* (2/3 of the cases) may develop at the hilum (*Klatskin tumors*) or more distally in the biliary tree, down to the peripancreatic portion of the distal common bile duct. They occur mostly in individuals 50 to 70 years of age. The prognosis of cholangiocarcinomas is poor because they are generally asymptomatic until late, and most patients have unresectable tumors.

**Risk factors include**
1. *Primary sclerosing cholangitis*
2. *Fibrocystic diseases of the biliary tree*
3. *Exposure to Thorotrast* (which is no longer used in radiography of the biliary tree).

**Pathological features** (Fig. 6-30).
- Due to early development of obstructive jaundice, these tumors are detected as small firm, gray nodules within the bile duct wall. Alternatively, they are diffusely infiltrative lesions that create thickening of the wall.
- These adenocarcinomas are generally well-differentiated with an abundant fibrous stroma
- Cholangiocarcinomas may spread to extrahepatic sites such as regional lymph nodes, lungs, & bones.

Mean survival time is around 12 months.
THE EXOCRINE PANCREAS
CONGENITAL ANOMALIES

Pancreas divisum is the most common clinically significant congenital anomaly resulting from failure of fusion of pancreatic ducts. This leads to the main pancreatic duct draining only a small portion of the head, while the bulk of the pancreas drains through a minor duct. This creates a state of inadequate drainage for the bulky pancreatic secretions thus predisposes to chronic pancreatitis.

Annular pancreas results from abnormal pancreatic fusion due to failure of ventral bud to rotate properly; head of pancreas encircles duodenum as a collar and may constrict lumen completely. It can lead to duodenal obstruction.

Ectopic Pancreas is uncommon; favored sites are the stomach and duodenum. The ectopic tissue is small and submucosal in location. It can cause localized inflammation, or mucosal bleeding.

Congenital cysts: the kidney, liver, and pancreas can all contain cysts (polycystic disease).

PANCREATITIS

Acute Pancreatitis is relatively common in developed countries. Causes implicated include
1. Gallstones and excessive alcohol intake; these are the main offenders.
2. Non-gallstone obstruction of the pancreatic ducts e.g. by periamplullary tumors
3. Medications as with thiazide & frusemide diuretics
4. Trauma, both blunt and iatrogenic during surgery or endoscopy
5. Others such as metabolic disorders, ischemia and infections as with mumps

In up to 20% of patients there is no identifiable cause (idiopathic pancreatitis).

Gross features (Fig. 6-31)
- In milder forms there is edema & congestion of the organ with foci of fat necrosis. Fat necrosis results from enzymatic destruction of fat cells; the released fatty acids combine with calcium to form insoluble salts that precipitate locally and appear as yellow-white chalky deposits within & outside the pancreas e.g. in the omentum and mesentery.
- The peritoneal cavity contains a brown-tinged fluid with fat globules.
- In the most severe forms there is extensive parenchymal necrosis accompanied by diffuse hemorrhage.

Microscopical features
- These parallel the gross changes of edema, acute inflammation, and focal fat necrosis.
- In more severe forms, necrosis involves all tissue constituents including islets of Langerhans
- Vascular damage causes hemorrhage into the parenchyma of the pancreas.

Pathogenesis
- The microscopic changes favor autodigestion of the pancreatic substance by activated pancreatic enzymes. Trypsin seems to have a central role because it can activate other enzymes (e.g. phospholipases and elastases) that can participate in the process of autodigestion. Trypsin can also leads to activation of the kinin system & factor XII and thus the clotting and complement systems.
- Pancreatic duct obstruction causes an increase in intraductal pressure, thus allowing accumulation of an enzyme-rich interstitial fluid that causes tissue injury. Edema further compromises local blood flow, causing vascular insufficiency and ischemic injury to acinar cells.
- The role of alcohol as a cause of pancreatitis is still unknown, proposed mechanisms include contraction of the sphincter of Oddi and direct toxic effects on acinar cells.
Inherited mutations in genes important for normal pancreatic exocrine function are investigated.

Laboratory findings include markedly elevated serum amylase during the first 24 hours, followed (within 3-4 days) by rising serum lipase levels. Hypocalcemia can result from precipitation of calcium in the extensive areas of fat necrosis. The enlarged inflamed pancreas can be visualized by CT or MRI. Although most individuals with acute pancreatitis eventually recover, some die from shock; ARDS and acute renal failure. In those who survive complications include pancreatic abscesses or pancreatic pseudocysts.

Pancreatic Pseudocyst is the most common cystic lesion of the pancreas and a common complication of acute pancreatitis. Liquefied necrotic pancreatic tissues become surrounded by fibrous tissue wall to form a cystic space, lacking an epithelial lining ("pseudo"). Drainage of pancreatic secretions into this space over months to years (from damaged pancreatic ducts) can cause massive enlargement of the cyst (up to 30 cm in diameter). They can become secondarily infected, and larger pseudocysts can compress or even perforate into adjacent structures. It is commonly attached to the surface of the gland and may involve peripancreatic tissues. (Fig. 6-32)

Chronic Pancreatitis is characterized by longstanding inflammation and fibrosis with destruction of the exocrine pancreas; in the late stages, the islets are also lost. Causes of chronic pancreatitis include:

1. Chronic alcoholism (the most common cause).
2. Long-standing pancreatic duct obstruction (e.g., by pseudocysts, calculi, neoplasms)
3. Tropical pancreatitis: seen in Africa and Asia, and attributed to malnutrition
4. Hereditary pancreatitis due to mutations of genes, some encoding trypsin inhibitor.
5. Cystic fibrosis

In some cases there is no obvious cause (idiopathic); as with acute pancreatitis, a growing number of these cases are associated with inherited mutations in genes concerned with normal pancreatic exocrine function.

Gross features: the gland is hard, sometimes with extremely dilated ducts and visible calcifications

Microscopic features (Fig. 6-33)

- Parenchymal fibrosis, reduced number and size of acini, and variable dilation of the ducts.
- A chronic inflammatory infiltrate around remaining lobules and ducts.
- Islets of Langerhans are relatively spared but eventually they disappear.

Pathogenesis

This is still not established with certainty. However, several hypotheses are proposed:

1. Ductal obstruction by concretions: alcohol increases the protein concentration of pancreatic secretions; these can form ductal plugs.
2. Toxic: alcohol can exert a direct toxic effect on acinar cells leading to their destruction
3. Oxidative stress induced by alcohol generates free radicals in acinar cells, which lead to fusion of lysosomes and zymogen granules with resulting acinar cell necrosis, inflammation, and fibrosis.
4. Necrosis-fibrosis due to recurrent episodes of acute pancreatitis

Chronic pancreatitis can present with repeated bouts of jaundice, persistent or recurrent abdominal and back pain. It may be entirely silent until pancreatic insufficiency and diabetes develop.

Chronic pancreatitis may present as attacks of abdominal pain with some elevation of serum amylase. Gallstone-induced obstruction may cause jaundice &/or elevation in serum alkaline
phosphatase. A helpful finding is visualization of calcifications within the pancreas by CT or ultrasonography. Weight loss and hypoalbuminemia with edema from malabsorption can also occur.

**PANCREATIC NEOPLASMS**

**Cystic Neoplasms**

Some of these are entirely benign (e.g., serous cystadenoma); others, such as mucinous cystic neoplasms, can be benign but frequently have malignant potential.

**Pancreatic Carcinoma** has a very poor prognosis in that the 5-year survival rate is less than 5%.

**Pathogenesis:** like all cancers, it arises as a consequence of inherited and acquired mutations in cancer-associated genes. There is a progressive accumulation of genetic changes in pancreatic epithelium as it proceeds from non-neoplastic, to noninvasive lesions in small ducts and ductules, to invasive carcinoma. Antecedent lesions are called "pancreatic intraepithelial neoplasias" (PanINs). They are often found adjacent to infiltrating carcinomas and share with the latter a number of the same genetic mutations. The more common molecular alterations in pancreatic carcinogenesis affect *K-RAS* (oncogene), and the tumor suppressor genes *p16*, *SMAD4*, and *p53*.

Carcinoma is primarily a disease of the elderly (60 and 80 years). *Smoking* has the strongest environmental influence. *Chronic pancreatitis and diabetes mellitus* are also associated with an increased risk. *Familial clustering* of pancreatic cancer has been reported, and *familial pancreatitis* (related to mutations in a trypsinogen gene) is associated with up to 80-fold increased risk.

**Gross features** (Fig. 6-34)

- The head is most commonly involved (60%), whereas the tail is the least common site (5%)
- The cancer is usually hard, gray-white, poorly defined mass.
- Most carcinomas of the head obstruct the distal common bile duct leading to distention of the biliary tree, and obstructive jaundice.
- In marked contrast, carcinomas of the body and tail do not interrupt the biliary tract and hence remain silent for some time. They may be quite large and widely disseminated by the time of the diagnosis.
- The regional lymph nodes & the liver are often involved by metastases as are the lungs & bones.

**Microscopical features**

- Most carcinomas are ductal adenocarcinomas.
- Two features are characteristic of pancreatic cancer:
  1. *It is highly invasive*; even in the early stages, thus infiltrates peripancreatic tissues extensively
  2. *It elicits an intense fibroblastic (desmoplastic) response.*
- Perineural and lymphatic invasions are commonly seen.

*Migratory thrombophlebitis (Trousseau syndrome)* occurs in about 10% of patients. Endoscopic ultrasonography and CT, are helpful in diagnosis and in performing guided percutaneous needle biopsy.