Lecture 2 liver
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.
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.
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
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.
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
- 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.
Hepatocytes necrosis
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

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.
PYOGENIC LIVER ABSCESSSES

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.

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.
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.

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.
Microscopic features
Initially small lipid droplets accumulate in hepatocytes (microvesicular steatosis) Persistent chronic intake of alcohol is associated with lipid accumulates in a large single vacuole 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
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
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
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)
Gross features

- There are three gross forms of HCC
  1. Unifocal, usually a massive tumor
  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
Hepatocellular carcinoma in cirrhotic liver

Histological section
Microscopic features

- 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 pseudocanaliculari 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
[HEPATOCELLULAR CARCINOMA]. This example of a moderately differentiated HCC shows nuclear atypia in the form of enlarged convoluted nuclei (arrowhead).
Metastatic tumors
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.
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 majority of individuals with gallstones (80%) have no identifying risk factors.

Contributory risk factors include:

1. 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. Ethnic and geographic: gallstones are more prevalent in Western industrialized societies and uncommon in developing ones.

3. 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. Environment: estrogenic influences, including oral contraceptives and pregnancy, increase hepatic cholesterol uptake and synthesis, leading to excess biliary secretion of cholesterol.

5. Obesity, rapid weight loss, and treatment with the hypocholesterolemic agent clofibrate are strongly associated with increased biliary cholesterol secretion.
Pathologic features

Pure cholesterol stones always formed within the gall bladder as pale to tan yellow, and are ovoid and firm. They may be single but most are often multiple. In the latter instance, they assume a faceted surface from apposition to one another. Most cholesterol stones are radiolucent, but 20% of them may have sufficient calcium carbonate to render them radiopaque.
Pigment stones may arise anywhere in the biliary tree (gall bladder, intra- or extra-hepatic bile ducts) and are either 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, 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. Brown stones, which contain calcium soaps, are radiolucent.
Complications of gall stones include
1. Empyema
2. Perforation
3. Fistulae
4. Cholangitis
5. Obstructive cholestasis
6. 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").
Empyema
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
- 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.
Acute cholecystitis
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.
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 enterococcci, can be cultured from the bile in only about one-third of cases.
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.