Liver

Gross Anatomy
- Located in right upper quadrant of abdominal cavity.
- Weighs 1400-1600 grams.
- Blood Supply
  - 60-70% comes from portal vein.
  - Remainder from hepatic artery.
- Lobes (4) vs. Segments (8)

Microscopic Anatomy
- Cords of hepatocytes
- Blood flows through sinusoids lined by discontinuous endothelium.
- Space of Disse where microvilli from hepatocytes extend.
- Kupffer cells attached to blood flow surface of endothelium.
- Ito cells contain fat and in Space of Disse.
- Canaliculi between connecting surfaces of hepatocytes. Part of biliary tree.

Inflammatory Progression
- Inflammation → Hepatitis
  - Viral Hepatitis
  - Toxic Hepatitis
  - Autoimmune

Patterns of Hepatic Injury
- Degeneration and intracellular accumulation
  - Ballooning degeneration (hepatitis)
  - Iron deposits (hemochromatosis)
  - Copper deposits (Wilson disease)
  - Microvesicular steatosis (Reyes Syndrome)
  - Macrovesicular steatosis (alcoholic liver disease)

Necrosis & Apoptosis
- Apoptosis (cell death hepatitis)
- Centrilobular necrosis (ischemia and toxic drugs)
- Bridging necrosis between lobules (chronic hepatitis)
- Massive, submassive, necrosis (fulminant hepatitis)

Hepatic Diseases
- Primary liver diseases
  - Hepatitis – Acute liver failure
  - Cirrhosis – Chronic liver failure
  - Hepatocellular carcinoma
- Secondary liver diseases
  - Hyperemia
  - Metastatic tumors
  - Liver involvement in systemic diseases
- Biliary tract diseases - Jaundice

Morphology
- HBV hepatocytes have ground glass appearance due to spheres and tubules of HBsAg.
- Cholestasis is an inconsistent finding. (Bile blockage)
- Fatty change unusual except with HepC
- “Dropout” necrosis due to cell rupture with macrophages
- Apoptosis with macrophages and ± effector T-cells
- Inflammation:
  - Kupffer cells hypertrophy and hyperplasia
  - Portal tracts infiltrated with mix of inflammatory cells
- Bile duct proliferation
- HBV hepatocytes sometimes will have a “sanded” appearance due to HBCAg and indicating active viral replication. – (No slide)
- Ballooning degeneration - indicative of active hepatitis.
- **Picornaviridae – Heparnavirus**
  - ssRNA virus (icosahedral capsid)
  - **Mild**, Self limiting
  - Incubation 2-6 weeks
  - Fecal-oral transmission
  - No chronic disease
  - **Diagnosis:**
    - IgM antibody acute phase
    - IgG antibody later indicating immunity

- **Hepadnaviridae**
  - dsDNA virus (enveloped)
  - Incubation period 4-26 weeks
  - Parenteral transmission
  - Acute hepatitis with resolution
  - Chronic hepatitis:
    - Cirrhosis, Carrier
    - Fulminant hepatitis
  - Predisposes to hepatocellular carcinoma
  - **Diagnosis:** (From Robbins)
    - HBsAg ↑ early and then ↓ in 3 - 6 mo.
    - Anti-HBs: ↑ after acute. May persist for life. **Vaccine**
    - HBeAg, HBV DNA/polymerase → viral replication
    - IgM anti-HBc, ALT: before sx, then replaced by IgG

- **Flaviviridae – Hepacivirus**
  - ssRNA (enveloped)
  - Incubation period 2-26 weeks
  - Transmission parenteral and close contact
  - **Course**
    - Resolution (15%)
    - Chronic hepatitis (majority)
    - Fulminant very rare
  - **Diagnosis:**
    - HCV RNA in acute phase for 1-3 weeks
    - HCV antibodies after 3-6 weeks

---

**Hepatitis B Outcomes**

- **Acute Hepatitis**
  - Recovery*
  - Fulminant hepatitis
  - Icteric disease
  - Chronic hepatitis
  - Recovery**
  - Healthy*** carrier state
  - Cirrhosis
  - Hepatocellular carcinoma

**Hepatitis C**

- **Incubation Period**
  - Acute Disease
  - Convalescence and Recovery
  - Chronic Disease
Chronic Hepatitis

- Symptomatic, biochemical or serologic evidence of continuing or relapsing hepatic disease > 6 months with histologic documentation
- Etiology > Histology

Clinical Course (Variable + Unpredictable)
- Clinical signs:
  o May only be ↑ transaminases
  o May be fatigue
  o Less common jaundice and malaise
- Physical findings:
  ▪ Spider angiomas
  ▪ Palmar erythema
  ▪ Mild hepatosplenomegaly
  ▪ Hepatic tenderness.
- Can be spontaneous recovery, indolent or rapidly progressive to cirrhosis.
- Major causes of death:
  o Liver failure with hepatic encephalopathy
  o Massive hematemesis from varices
  o Hepatocellular CA with HBV (particularly neonatal) or HCV.

Viruses: (most common)
- HepB, HepC, HepB + HepD Coinfection
- Other causes:
  o Wilson disease (↓ copper excretion into bile)
  o α₁-antitrypsin deficiency
  o Chronic alcoholism
  o Drugs
    ▪ Ex. isoniazid and methyldopa
  o Autoimmunity

Labs
- ↑ prothrombin time (PT)
  o Intrinsic path. (VII, X, II, V, and fibrinogen)
- Sometimes ↑ globulins, ↑ bilirubin, ↑ AP (mild)
- With HBV and HBC
  o ~ immune complex vasculitis (PAN!!!)

Grading Chronic Hepatitis
1. Bridging: delicate bands of fibrous CT replace adjacent lobules
2. Parenchymal nodules
   a. Due to regeneration of encircling hepatocytes; small (micronodules) < 3 cm - large (macronodules) several cm.
3. Disruption of architecture
4. Diffuse injury: has to be throughout liver
5. Nodularity
   a. Balance between regeneration / scarring
6. Fibrosis - irreversible
7. Vascular architecture reorganized
   a. Due to parenchymal injury and scarring, abnormal interconnections between vascular inflow and hepatic vein outflow channels

When progressive get bridging necrosis and fibrosis that extends beyond limiting plate and links portal to portal or portal to terminal hepatic venule leading to cirrhosis
# Fulminant Hepatitis

- When hepatic insufficiency progresses from onset of symptoms to hepatic encephalopathy within 2-3 weeks.
- Viral hepatitis is responsible for 50-65% of fulminant hepatitis.
- Any of the viruses A-E can cause it.
- Drug and chemical toxicity are responsible for the rest e.g. acetaminophen, isoniazid, monoamine oxidase inhibitors, halothane, methylidopa and mycotoxins.

## Toxins
- **Acetaminophen**
  - Antidepressants
  - Methylidopa
- **Morphology massive necrosis**
- **Clinical presentation**
  - Hepatic encephalopathy

## Histology
- Massive to submassive necrosis (diffuse to patchy necrosis)
- Shrunken liver with collapse of architecture with little to no inflammation.
- 2. Some regeneration if patient survives for a while.

## Signs & Symptoms

<table>
<thead>
<tr>
<th>Other</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteria, parasites and helminths can cause hepatitis</strong></td>
<td><strong>Liver abscesses e.g. Entameba histolyticum, Echinococcal infection and other parasites.</strong></td>
<td></td>
</tr>
<tr>
<td>- Generally more focal to multifocal lesions</td>
<td>- Usually in developing countries</td>
<td></td>
</tr>
<tr>
<td>- Can impact parenchyma and/or biliary tree</td>
<td>- 2° bacterial infections lead to abscesses, pyogenic, organisms reach liver thru portal system, arterial supply, ascending infect of biliary tract, direct invasion and penetrating injuries. May get bacteremia</td>
<td></td>
</tr>
</tbody>
</table>

## Jaundice
- **Hypoalbuminemia**
- **Hyperammonemia**
- **Coagulopathies**
- **Hepatic encephalopathy (↑blood ammonia)**
- **Impairment of neuronal functions**

## Hyperestrogenemia
- **Palmar erythema (local vasodilatation)**
- **Spider angiomas**
- **Hypogonadism in males**
- **Gynecomastia in males**

## Hepatorenal syndrome

## Indistinguishable from viral hepatitis clinically
- Responds well to anti-inflammatory drugs
- 60% of patients: other autoimmune disease, e.g. rheumatoid arthritis, thyroiditis, Sjögren syndrome and ulcerative colitis
- Diagnose by exclusion
- Women (70%)
- HLA-B8 or HLA Drw3

## Serology: (No virus!)
- **↑ immunoglobulins (IgG)**
- **+ve ANA (80%)**
- **+antismooth muscle antibody SMA**
- **Anti LKM₁ (liver, kidney, microsomes)**
- **Course can lead to cirrhosis (40%)**

## Autoimmune

<table>
<thead>
<tr>
<th>Causative Agents:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetaminophen</strong></td>
<td><strong>Treatment:</strong></td>
<td><strong>Histology</strong></td>
</tr>
<tr>
<td>- Diffuse or massive necrosis</td>
<td>- Remove causative agent</td>
<td>- Immediate or delayed injury</td>
</tr>
<tr>
<td><strong>Tetracycline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Microvesicular fatty change</td>
<td></td>
<td></td>
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<tr>
<td>- Salicylates e.g. Reyes syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Methotrexate</strong> (Antifolate: cancer/autoimmune dis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fibrosis-cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CCl₄</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Centrilobular necrosis</td>
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<td></td>
</tr>
</tbody>
</table>

## Drug/Toxin Hepatitis

<table>
<thead>
<tr>
<th>Drug/Toxin Hepatitis</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetaminophen</strong></td>
<td><strong>Histology</strong></td>
<td></td>
</tr>
<tr>
<td>- Centrilobular necrosis</td>
<td>- Necrosis of hepatocytes</td>
<td></td>
</tr>
<tr>
<td><strong>Tetracycline</strong></td>
<td>- Obstruction of biliary tree (Cholestasis)</td>
<td></td>
</tr>
<tr>
<td>- Microvesicular fatty change</td>
<td>- Insidious onset of liver dysfunction</td>
<td></td>
</tr>
<tr>
<td>- Salicylates e.g. Reyes syndrome</td>
<td>- Chronic forms indistinguishable from chronic viral hepatitis</td>
<td></td>
</tr>
<tr>
<td>Clinical Course</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatic steatosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o no signs or symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o mild swelling with elevation of bilirubin and alkaline phosphatase</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alcoholic hepatitis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Variable with 10-20% chance of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Cirrhosis with repeated bouts</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cirrhosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Portal hypertension, jaundice, ascites and abnormal labs. Maybe clinically silent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 year outlook:
- 90% survival in abstainers free of clinical symptoms
- 50-60% survival if continue to drink
- Causes of death:
  o Hepatic coma
  o Massive GI bleed
  o Intercurrent infection
  o Hepatorenal syndrome
  o Hepatocellular carcinoma in 3-6%

- Daily intake of 80 gm or more (8 beers): severe risk of hepatic injury
- Daily ingestion of 160 gm or more for 10-20 years is consistently associated with severe hepatic injury
- Only 10-15% of alcoholics develop cirrhosis

Pathogenesis:
- Steatosis due to shunting normal substrates away from catabolism and to lipid biosynthesis:
  o ↑ generation of NADH by alcohol dehydrogenase and acetaldehyde dehydrogenase
  o Impaired assembly and secretion of lipoproteins
  o ↑ peripheral catabolism of fat.
- Induction of cytochrome p-450 that makes other drugs toxic
- Free radical from microsomal ethanol-oxidizing system oxidizes alcohol and they react with cell membranes
- Alcohol directly affects microtubular and mitochondrial function and membrane fluidity
- Acetaldehyde induces lipid peroxidation and acetaldehyde:
  o Protein adduct formation disrupts cytoskeleton and membrane
  o Alcohol induces immunologic attack on hepatic neoantigens (antigens formed from metabolism)

<table>
<thead>
<tr>
<th>Non-alcoholic Fatty Liver (NAFL) and Steatohepatitis – Steatonecrosis (NASH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Obesity, insulin resistance/hyperinsulinemia, Dyslipidemia, Type 2 diabetes</td>
</tr>
<tr>
<td>- Principal cause of cryptogenic cirrhosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcoholic Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hepatocyte swelling and necrosis; swelling is from fat, fluid and non-exported proteins</td>
</tr>
<tr>
<td>- Neutrophils - around degenerating hepatocytes especially those with Mallory bodies; lymphocytes and macrophages seen also</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Collagen</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Stimulated by inflammatory cytokines or those from Kupffer cells</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-alcoholic Fatty Liver (NAFL) and Steatohepatitis – Steatonecrosis (NASH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Hepatic steatosis (Fatty Liver) ↓↑</td>
</tr>
<tr>
<td>o small intake → microvesicular fat</td>
</tr>
<tr>
<td>o chronic intake → macrovesicular globules</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gross</th>
</tr>
</thead>
<tbody>
<tr>
<td>- liver yellow and greasy</td>
</tr>
<tr>
<td>- Until Fibrosis occurs, steatosis is reversible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alcoholic Hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mallory bodies -cytokeratin intermediate filaments and other proteins;</td>
</tr>
<tr>
<td>o not specific for alcohol e.g. primary biliary cirrhosis, Wilson disease and hepatocellular tumors to name a few</td>
</tr>
</tbody>
</table>
### Inborn Errors of Metabolism and Pediatric Liver Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogenesis</th>
<th>Diagnosis</th>
</tr>
</thead>
</table>
| **Hemochromatosis** | - Excess iron in in parenchymal cells  
- Primary (inherited) or Secondary (acquired)  
- Primary defect is excess absorption of iron | - Cirrhosis + Fe in hepatocytes  
- ↑ serum Fe  
- ↑ serum ferritin |
| **Wilson Disease**  | - Kayser-Fleischer Rings  
  - Green-yellow copper pigment in Descemet’s membrane encircles cornea  
  - Neurologic manifestations | - ↑ urine copper  
- ↓ ceruloplasmin  
- ↑ hepatic copper |
| **α₁-AT Deficiency** | - Neonatal hepatitis  
- Cirrhosis  
- Late onset hepatitis  
- Emphysema | - PiZZ people have very low activity  
- PAS positive intrahepatic inclusions (cytoplasmic) |

### Cirrhosis

- May be clinical silent  
- Non-specific - wt. Loss, anorexia, weakness osteoporosis and frank debilitation.  
- Mechanisms of death  
  - Progressive liver failure  
  - Complications of portal hypertension  
  - Hepatocellular carcinoma  
- Progression  
  - Redistribution of vasculature within the newly formed fibrous septa  
  - Inhibition of hepatocellular secretion of proteins and other solutes  
  - Loss of fenestration in the sinusoidal endothelium

### Fibrosis

- Normal liver  
  - Type I and III collagen in portal areas  
  - Type IV in sinusoids

### Cirrhosis

- Type I and III in lobule as delicate or broad fibrous bands  
- Vascular channels in bands connect hepatic arteries and portal veins in portal regions with terminal hepatic venules shunting blood around the parenchyma  
- Deposition of collagen in preserved lobules  
  - ↓ fenestrations in endothelial cells of sinusoids  
  - ↓ exchange of solutes from hepatocytes  
  - e.g. albumen, lipoproteins and clotting factors  
- Activation of the perisinusoidalstellate cells of Ito  
  - Normally for Vitamin A storage  
  - Become myofibroblasts  
  - Stimuli from inflammatory cytokines TNFα, endogenous cell cytokines (Kupffer cells), disrupted matrix, direct stimulation of cells by toxins  
  - ↑ Mitosis, ↑ synthesis/secretion of ECM  
- Liver mass may be normal  
- Problem is blood supply to hepatocytes and hepatocyte secretory abilities
### Signs & Symptoms

<table>
<thead>
<tr>
<th><strong>Ascites</strong></th>
<th><strong>Pathogenesis</strong></th>
<th><strong>Histology</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>excess fluid in peritoneal cavity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 500 ml can be detected but many liters can collect</td>
<td>- <strong>Pre-hepatic</strong> - Obstructive thrombosis, narrowing of portal vein and massive splenomegaly shunting blood into splenic vein</td>
<td>- <strong>Portosystemic Shunts</strong> - 1. Esophageal varices</td>
</tr>
<tr>
<td>- usually serious unless infected</td>
<td>- <strong>Intra-hepatic</strong> - Cirrhosis, (also: schistosomiasis + fatty liver)</td>
<td>- 2. Hemorrhoidal veins</td>
</tr>
<tr>
<td>- red blood cells suggest intra-abdominal cancer</td>
<td>- <strong>Post-hepatic</strong> - Severe right sided heart failure, constrictive pericarditis and obstructions to hepatic vein outflow</td>
<td>- 3. Falciform ligament collaterals in periumbilical region</td>
</tr>
<tr>
<td>- <strong>Pathogenesis</strong></td>
<td>In cirrhosis:</td>
<td></td>
</tr>
<tr>
<td>o sinusoidal hypertension</td>
<td>- ↑ resistance to portal flow at sinusoid level</td>
<td></td>
</tr>
<tr>
<td>o percolation of hepatic lymph into peritoneum due to increase hepatic lymphatic flow</td>
<td>- Compression of central veins by fibrosis</td>
<td></td>
</tr>
<tr>
<td>o intestinal fluid leakage from increased perfusion pressure in intestinal capillaries</td>
<td>- Compression by expansile regenerating nodules</td>
<td></td>
</tr>
<tr>
<td>o renal retention of sodium and water due to hyperaldosteronism</td>
<td>- <strong>Anastomoses</strong> between low pressure portal venous system and high pressure arterial system in fibrous bands</td>
<td></td>
</tr>
</tbody>
</table>

**Portosystemic Shunts**
- 1. Esophageal varices
- 2. Hemorrhoidal veins
- 3. Falciform ligament collaterals in periumbilical region

### Etiology

- **Pre-hepatic** - Obstructive thrombosis, narrowing of portal vein and massive splenomegaly shunting blood into splenic vein
- **Intra-hepatic** - Cirrhosis, (also: schistosomiasis + fatty liver)
- **Post-hepatic** - Severe right sided heart failure, constrictive pericarditis and obstructions to hepatic vein outflow

**In cirrhosis:**
- ↑ resistance to portal flow at sinusoid level
- Compression of central veins by fibrosis
- Compression by expansile regenerating nodules
- **Anastomoses** between low pressure portal venous system and high pressure arterial system in fibrous bands

### Pathogenesis

- **Splenomegaly** (congestive) - spleens up to 1000 grams
  - hypersplenism (XS destruction of RBC)
- **Hepatic encephalopathy** - abnormal neurotransmission in CNS and periphery probably due to ↑ ammonia

**Hepatic encephalopathy**
- abnormal neurotransmission in CNS and periphery probably due to ↑ ammonia

### Histology

- **Portosystemic Shunts**
  - 1. Esophageal varices
  - 2. Hemorrhoidal veins
  - 3. Falciform ligament collaterals in periumbilical region

### Impaired Blood Flow into the Liver

- Hepatic artery compromise
  - Usually no changes because of double blood supply
- Portal vein obstruction
  - Signs and symptoms of portal hypertension
  - Causes: Sepsis, Trauma, Surgery
- Passive congestion and centrilobular necrosis
  - If severe → cardiac cirrhosis
- **Peliosis hepatits** (blood-filled cavities in liver)
  - 1yr dilatation of sinusoids (steroids)
  - Usually asymptomatic
  - If severe, intraabdominal hemorrhage

### Hepatic Disease in Pregnancy

- **Preclampsia** (hypertension) and **Eclampsia** (seizures)
- **HELLP Syndrome**
  - Hemolysis
  - Elevated liver enzymes
  - Low platelets
  - DIC
- **Acute fatty liver of pregnancy**
- **Intrahepatic cholestasis**
  - Pruritus in 3rd trimester
  - Jaundice, dark urine
  - Light stools
  - Caused by hormonal changes during pregnancy

### Hepatic Venous Outflow Obstruction

- Veno-occlusive disease (Sinusoidal obstruction syndrome)
- **Hepatic vein thrombosis** (Budd-Chiari Syndrome)
  - Acute, subacute and chronic occlusive:
    - hepatomegaly
    - weight gain
    - ascites
    - abdominal pain
- **Passive congestion** (Cardiac sclerosis)
<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign Neoplasms</strong></td>
<td>- Well circumscribed, encapsulated and yellow-tan, but may be bile-stained.</td>
</tr>
<tr>
<td>- Focal nodular hyperplasia</td>
<td>- Well differentiated microscopically, but no portal areas</td>
</tr>
<tr>
<td>- Benign neoplasms</td>
<td></td>
</tr>
<tr>
<td>- Cavernous hemangiomas</td>
<td></td>
</tr>
<tr>
<td>- Adenomas</td>
<td></td>
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<tr>
<td>- Women on oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>- Could be mistaken for carcinoma</td>
<td></td>
</tr>
<tr>
<td>- Not premalignant</td>
<td></td>
</tr>
</tbody>
</table>

**Focal Nodular Hyperplasia**
- Well circumscribed, encapsulated and yellow-tan, but may be bile-stained.
- Not premalignant

**Primary Carcinoma**
- Clinical signs ill-defined
- Some can be palpated as nodular liver
- ↑ serum α-fetoprotein (AFP) in 60-75% of patients with hepatocellular tumors
- CT, MRI, ultrasound, hepatic angiography best for small tumor diagnosis

**Epidemiology**
- Marked variation between regions:
  - North and South America: 2-4 cases/100,000
  - Korea, Taiwan and S.E. China: 150 cases/100,000
- Strongly linked to HBV prevalence
- Vertical transmission: 200x risk

**Natural Course**
1. Hepatocellular tumors progress until encroaches on hepatic function or metastasizes to lungs.
2. Death within 10 months of dx e.g. cachexia, GI bleed, liver failure, rupture of tumor leading fatal hemorrhage
3. Cholangiocellular CA not detected until late and death occurs within 6 months

**Pathogenesis**
- Repeated cell death and regeneration with HBV and HCV infections
  - Viral DNA integrated into cell genome and accompanies transformation
  - HBV DNA integration induces broad genomic instability
  - Aflatoxins from spoiled foods are carcinogenic
  - Cirrhosis

**Metastasis**
- More common than primaries
- Common primaries are:
  - Breast
  - Lung
  - Colon
- Usually multiple lesions leading to striking hepatomegaly with marked increase in weight.
- Lesions outgrow blood supply leading to necrosis
- Often absence of clinical and laboratory evidence

**Rare Malignant Cancers**
- Children:
  - Hepatoblastoma
    - Epithelial
    - Mixed epithelial and mesenchymal
    - Chromosomal deletions
- Adult:
  - Angiosarcoma
    - Exposure to arsenic, vinyl chloride
    - Long latent period from exposure
    - Very aggressive