GI Pathology II- Liver, Gall Bladder, Pancreas

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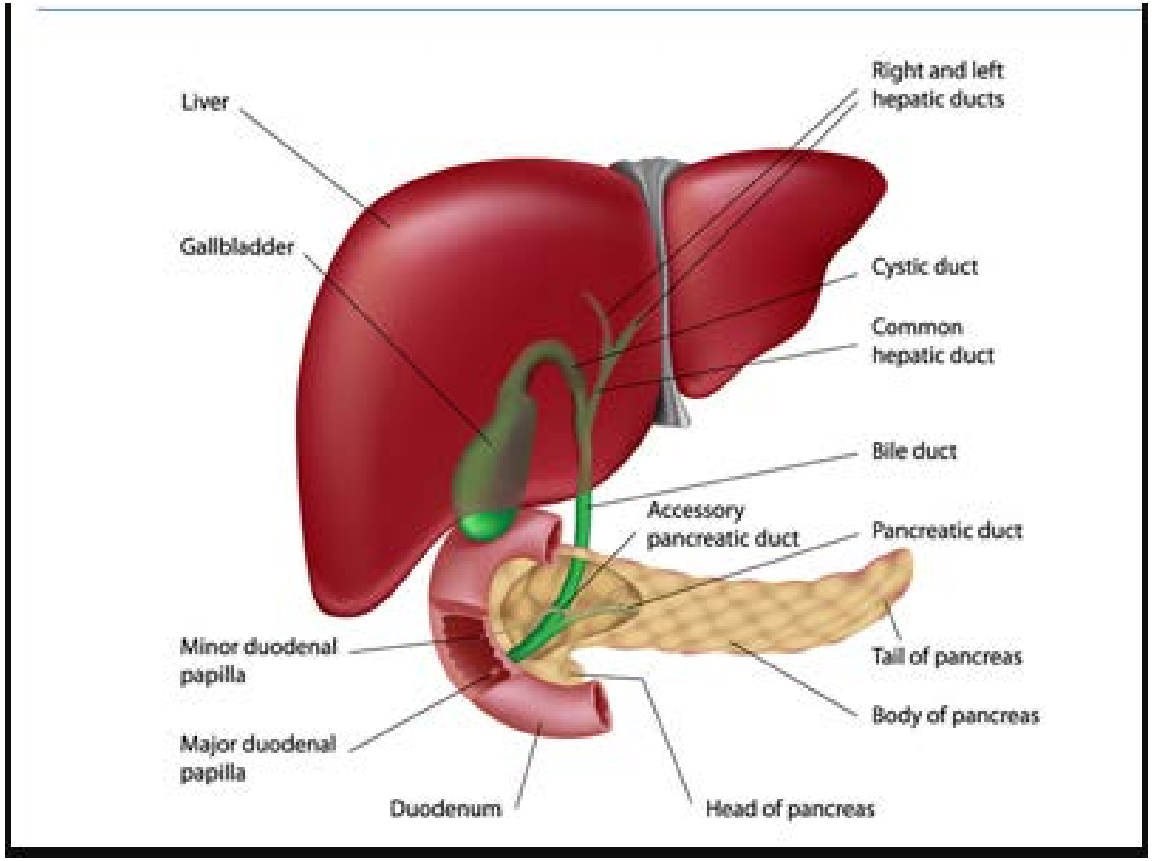
OPTH 727

Pathology of the Liver, Gall Bladder and Pancreas



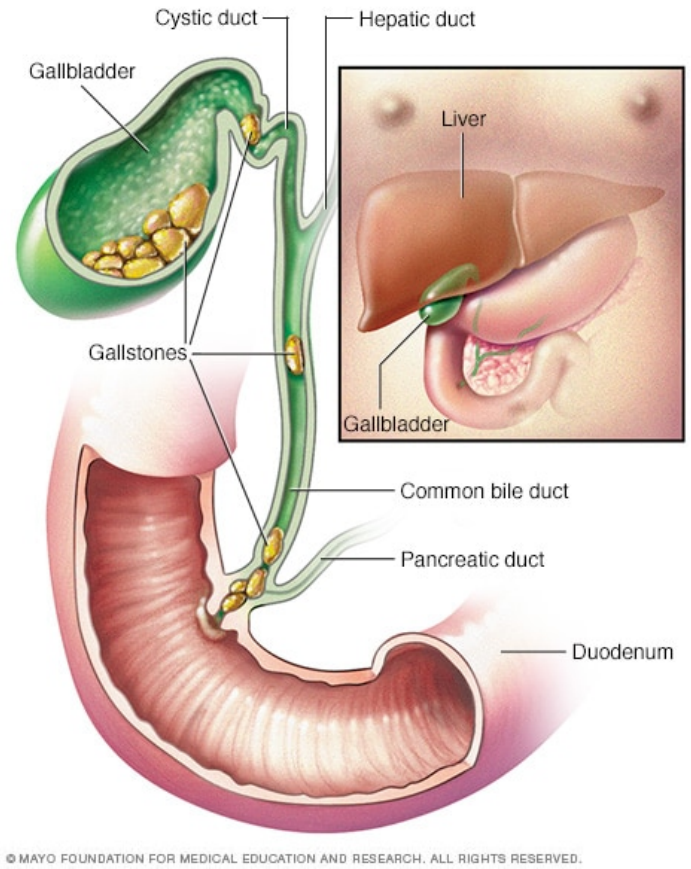
- Cancers (see next slide)
- Gall Bladder
  - Cholelithiasis
  - Cholecystitis
- Pancreas (exocrine)
  - Pancreatitis, acute and chronic
- Liver
  - Jaundice
  - Liver Failure
  - Hepatitis
  - Cirrhosis
  - Others

Cancers (and other tumors) of liver, gall bladder, pancreas

- Gall bladder
  - **Carcinoma of gall bladder** – usually associated with presence of gallstones (**cholelithiasis**)
- Pancreas
  - **Adenocarcinoma of pancreas**
    - Very poor prognosis typically- poorest prognosis of all GI related cancers
- Liver
  - Liver is site of numerous benign tumors (unlike pancreas and gall bladder)
  - Cancers of liver
    - **Metastatic disease**. In the USA, liver cancer is most often a metastatic deposit of another cancer (i.e. colon, breast, lung, pancreas, etc.)
    - **Hepatocellular carcinoma** is the most common primary liver cancer
      - Commonly associated with Hepatitis B or Hepatitis C infection
        - Therefore, vast majority of cases occurs in Asia and sub-Saharan Africa where Hepatitis B infection is endemic
      - Also associated with cirrhosis of the liver

Gall bladder disease usually predicated on gallstones (**cholelithiasis**)

- Stones are usually a mixture of cholesterol, unconjugated bilirubin, and calcium salts.
- Stones can occur:
  - Gall bladder itself
  - Anywhere in ducts
    - Blockage of ducts near Ampulla of Vater can lead to **pancreatitis**
    - Blockage of common bile duct may lead to obstructive jaundice
- Gall stones may be very painful
  - Many are asymptomatic
  - Gall bladder removal (cholecystectomy) is indicated if symptomatic.
- Cholelithiasis is very common
  - ~ 3 million cases per year
  - ~600K cholecystectomy procedures are done per year
  - Gall bladder not “necessary” therefore can be removed



Causes of cholelithiasis are unclear, however, there are numerous risk factors including

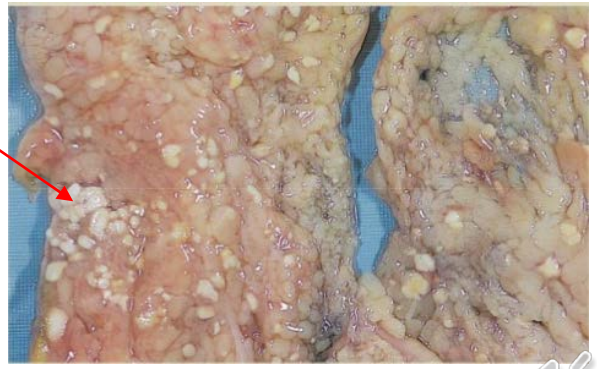
- Being female (3 times more likely than males)
  - Thought to be due to estrogens
    - Excess female hormones thought to decrease bile salt production
    - Females who are pregnant or still fertile are more susceptible
      - Certain types of contraceptives or hormone replacement therapy may play a role
- Being overweight
  - Possibly related to high-fat or high cholesterol diet
    - Too much cholesterol and not enough bile salts produced…. This leads to cholesterol precipitating out and possibly forming gallstones
- Being over 40 years of age
- Other systemic diseases, i.e. liver disease
  - Liver disease may mean more unconjugated bilirubin, less bile salt production

Sequelae of gallstones

- **Cholecystitis** – inflammation of gall bladder
  - Gallstones may irritate gall bladder wall and produce cholecystitis
    - Severe cases could lead to gall bladder rupture and peritonitis.
  - This could lead to symptoms requiring gall bladder removal.
- Predisposition to gall bladder cancer
- May affect liver (biliary obstruction) and/or pancreas depending on location of gallstones

Pancreatitis – inflammation of pancreas

- **Acute pancreatitis**
  - May cause severe (upper) abdominal pain
    - May lead to peritonitis
  - Severe inflammation may lead to necrosis of pancreatic parenchyma
    - Pancreas produces numerous digestive enzymes (e.g. lipase)… these enzymes may be liberated following tissue death and can "digest" the local tissue. The necrosis associated with acute pancreatitis is Fat Necrosis
    - May cause a systemic inflammatory response and lead to shock
  - (Some) Causes of acute pancreatitis
    - Gallstones and other obstructions… blockage of duct leads to back up of digestive enzymes
    - Alcohol, medications
    - Certain infections



Pancreatitis – inflammation of pancreas

- **Chronic pancreatitis**
  - Chronic inflammation leads to:
    - Fibrosis of gland – loss of pancreatic parenchyma
      - Reduction in enzymes – possible malabsorption
    - Fibrosis (and constriction) of ducts
      - Leads to reduced ability of enzymes to leave the pancreas and dump into duodenum
        - This could also lead to malabsorption
        - May result in recurrent bouts of acute pancreatitis (because enzymes are staying in pancreas)
  - Causes of chronic pancreatitis:
    - Chronic alcoholism --- #1 cause
    - Idiopathic – cause uncertain… old age - possibly associated with peripheral vascular disease
    - Duct blockage

Some key functions of the liver

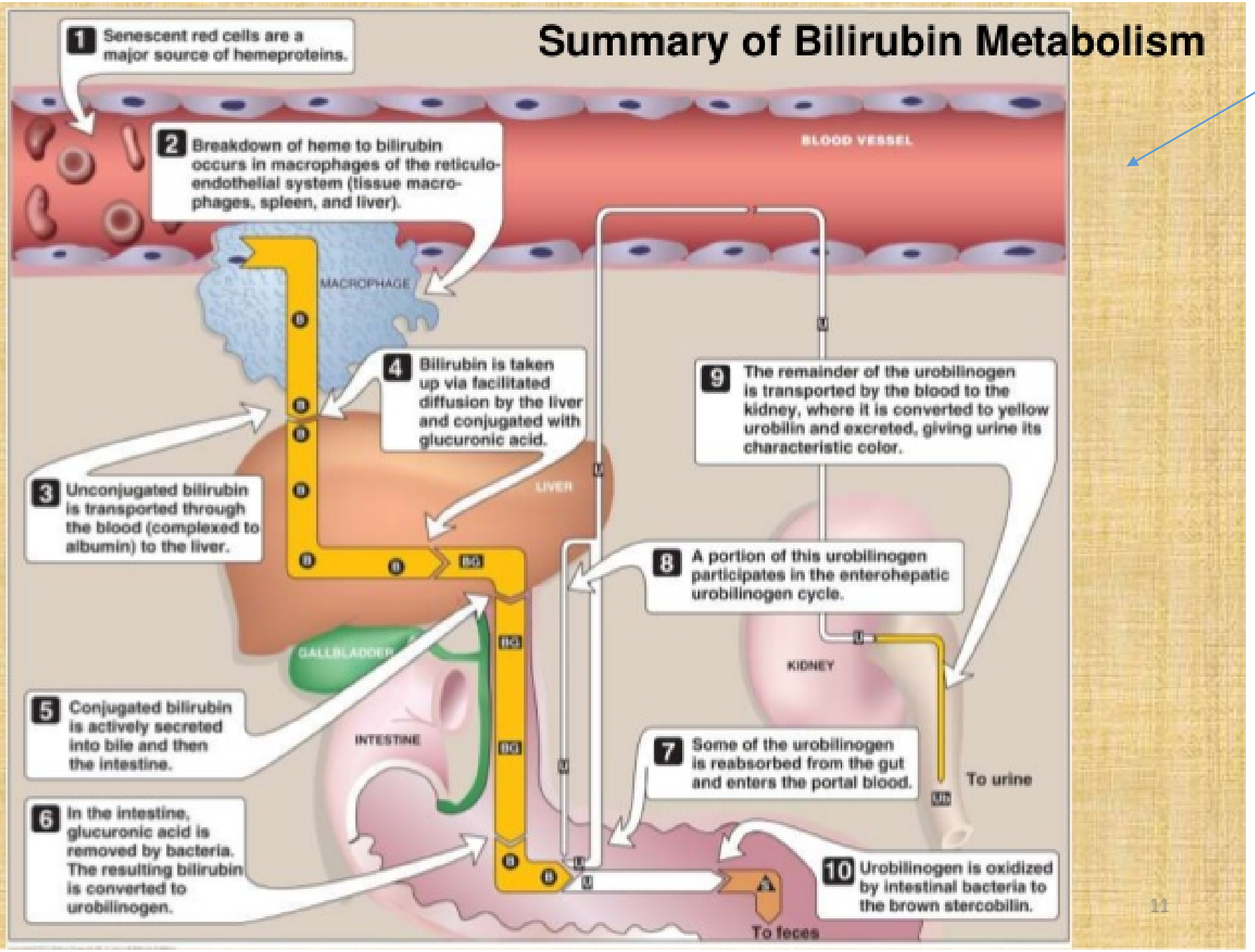
For review, not on exam

- Carbohydrate metabolism
  - Glycogen storage
  - Maintains glucose concentrations within set range
- Fat metabolism
  - Process dietary fats to lipoproteins (used in cellular metabolism)
- Protein metabolism
  - Liver is a major site of protein synthesis
    - Albumin, clotting factors, transport proteins, many cytokines involved with inflammation
      - Sign of liver disease is failure to produce these proteins
  - Amino acid catabolism (urea production)
- Bile synthesis (cholesterol, bile salts) conjugation of bilirubin
- Storage
  - Glycogen, fat-soluble vitamins
- Detoxification
  - Filters bacteria, endotoxin, antigen-antibody complexes
  - Filters other toxic chemicals (drugs, alcohol)

Liver Pathology – Diagnostic methods

- Liver is highly complex and diverse in its function (over 200 distinct functions)
- Numerous diagnostic methods to detect liver diseases
  - Biochemistry
    - Is the liver producing the proteins that it should be producing?
      - If not, may be a sign of liver disease
    - Are there liver enzymes circulating in the blood?
      - Could be a sign of liver necrosis.
    - Bilirubin levels
    - Circulating antibodies
      - Many autoimmune processes affect the liver
  - Imaging- ultrasound
    - Size of liver, dilation of intrahepatic and extrahepatic bile ducts.
  - Liver biopsy
    - Image guided needle biopsy

Summary of Bilirubin Metabolism



For review, not on exam

- <u>Cliff notes version of bilirubin breakdown:</u>
- Bilirubin results from breakdown of red blood cells (mostly from spleen and liver). This bilirubin is “unconjugated” and fat soluble and is complexed to albumin proteins.

- Bilirubin detaches from albumin and enters hepatocytes where it gets conjugated to glucuronic acid in the liver (making it water soluble).

- Conjugated bilirubin gets excreted into the bile and then into the gut; most of the conjugated bilirubin gets excreted in feces.

- Unconjugated bilirubin (is fat soluble) may be highly toxic to brains of neonates.

In general, what does the presence of excess conjugated or unconjugated bilirubin in the blood signify?

- Unconjugated hyperbilirubinemia
  - Often a sign of excess red blood cell breakdown (i.e. hemolytic anemia – discussed later in the course) or other diseases of RBCs
    - Liver is overloaded and cannot conjugate all of the excess bilirubin
  - May be due to genetic diseases resulting in reduced ability to conjugate bilirubin. **Gilbert's Syndrome** is a mild genetic disease affecting 3% of the population.
- Conjugated hyperbilirubinemia
  - Usually due to biliary obstruction inside or outside liver (gallstones)
  - Damage to hepatocytes not suspected because liver has "done its job" and conjugated the bilirubin.
  - Some obstruction of bile secretion into gut causes only conjugated bilirubin to return to blood.
- Mixed hyperbilirubinemia
  - Increases in unconjugated and conjugated bilirubin in the blood.
  - Often a sign of generalized liver damage
    - Liver conjugates some bilirubin but not all of it
      - This leads to some unconjugated bilirubin in the blood
    - Liver disease usually also produces some obstruction of bile drainage.

Jaundice- a yellowish (or greenish) pigmentation of the skin and sclera ("whites of the eyes") due to high bilirubin levels (hyperbilirubinemia).

- Numerous causes of jaundice (hepatic and non-hepatic) see next few slides
- Hyperbilirubinemia can be unconjugated, conjugated or mixed (see previous slide). Any of these can produce jaundice
- In most cases, jaundice is a sign of another disease and not toxic in itself
  - However, severe jaundice in neonates may produce serious brain injury (**kernicterus**). Caused by unconjugated hyperbilirubinemia.

Neonatal jaundice

- Very common – most cases resolve within two weeks after birth with no lingering effects
  - Still, must be careful due to effects on brain of excess bilirubin in neonates
    - Phototherapy – breaks down unconjugated bilirubin
  - Mostly due to low gluconyl transferase levels in liver shortly after birth

- May also be due to more serious causes
  - Various genetic diseases
  - Biliary atresia

Hepatitis

- **Hepatitis** loosely means “inflammation of the liver” and is the basis for liver damage.
- Many causes:
  - Infections… this is mostly what we think of when we say “hepatitis”
    - Most infections are viral (Hep A, B, C, D, E) – these will be covered in microbiology courses
  - Autoimmune diseases
  - Drug reactions
  - Chronic alcohol exposure
- Hepatitis can be acute or chronic
  - Both lead to liver dysfunction
    - Acute – sudden onset and more severe
    - Chronic – gradual onset and less severe

Acute Liver Failure

- Occurs when there has been damage to a majority of hepatocytes

**
  - Acute Liver Failure is a severe, life-threatening condition where 80% of patients die
  - Death may be caused by many things including
    - Hepatic encephalopathy (nitrogenous waste compounds not cleared by liver are toxic to brain)
    - Uncontrolled hemorrhage (reduced clotting factor production)
    - Sepsis (dysfunctional liver cannot clear bacteria)
- Three main causes
  - Acute liver damage due to drug or severe infection (acute hepatitis)
  - Systemic shock
  - Acute decline in someone with chronic liver disease (from chronic hepatitis or cirrhosis)

Chronic liver disease

- Several gross disease patterns may result from insult to liver. Two include:

- **Fatty liver** – aka hepatic steatosis - deposition of excess fat in liver
  - Liver has some fat, steatosis is excess fat – often seen in alcoholics
    - Can be asymptomatic, or produce liver dysfunction (due to inflammatory response)
  - Fatty liver can be reversible with lifestyle modifications
  - Fatty liver sometimes seen in people who consume little to no alcohol
    - Obesity and type 2 diabetes are risk factors

- Hepatocytes have a remarkable ability to regenerate. However, chronic, repeated damage from unresolved causes may produce an altered pattern of regeneration called **cirrhosis of the liver**. (see next slide)
  - Cirrhosis results from repeated injury/ inflammation/ fibrosis
  - Cirrhosis is chronic and irreversible.

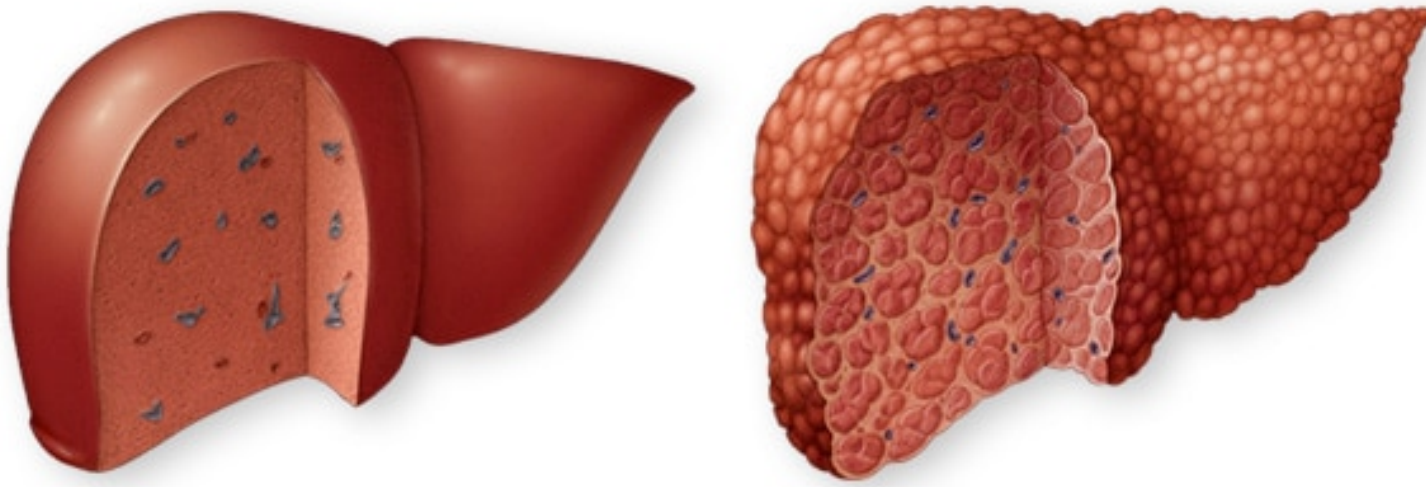
Cirrhosis of the Liver

- Cirrhosis may result in
  - Reduced hepatocyte function
  - Disturbance of blood flow and/or bile flow
    - May result in **portal hypertension**
  - Reduced immune function
    - Increased susceptibility to infections
  - Increased risk of hepatocellular carcinoma

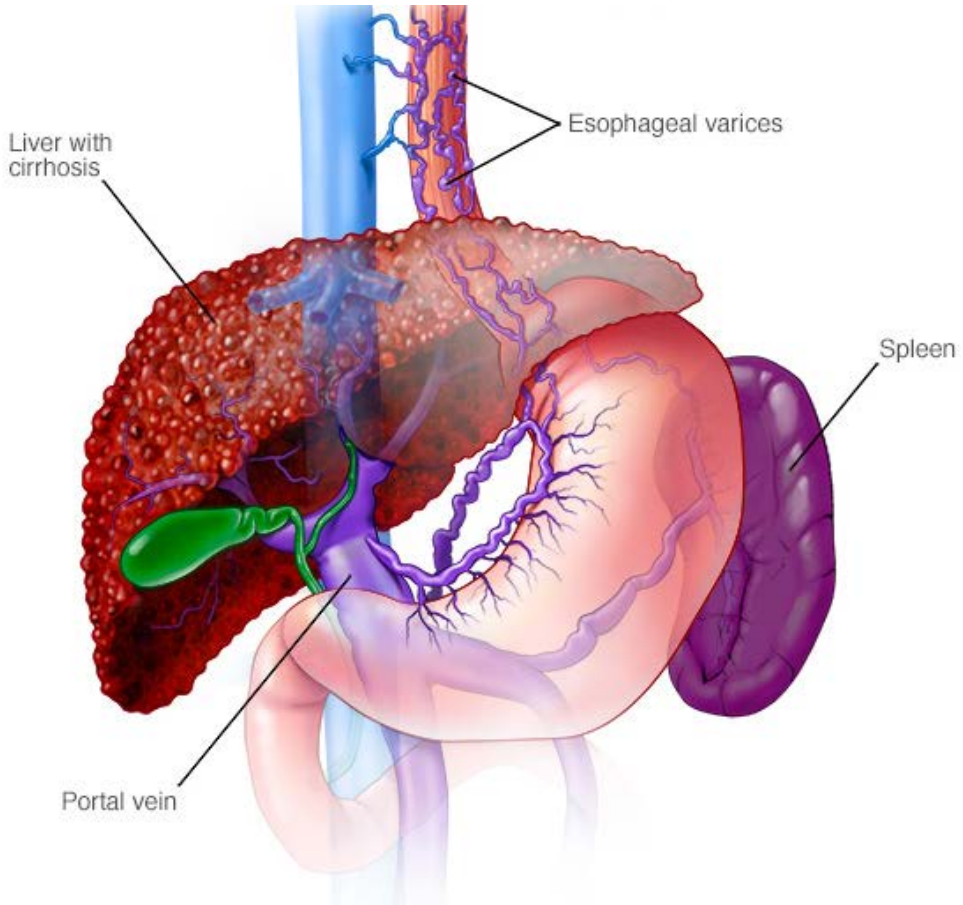
  - Alcoholism is a major cause of cirrhosis

Normal Liver

Cirrhosis of the Liver….Nodules of regenerated liver cells separated by bands of collagen (fibrosis)



Portal hypertension



- The portal vein carries blood to the liver from the spleen and GI tract
- Cirrhosis leads to congested blood flow in liver
  - This backs up blood in portal vein leading to increased pressure, hence… portal hypertension.
- Main complication of portal hypertension is varicosities in GI tract – especially in esophagus
  - **Esophageal varices** may rupture and produce severe hemorrhage