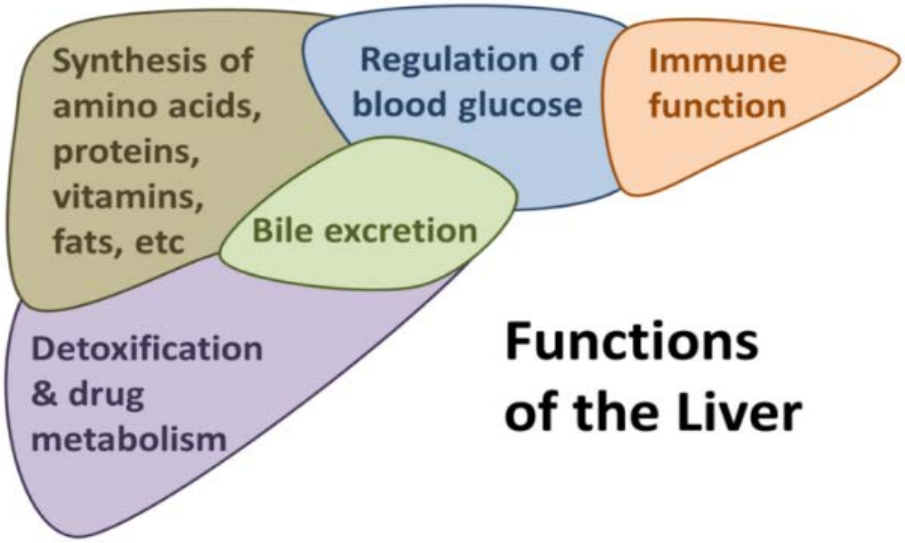
Chapter 1. Basic Science

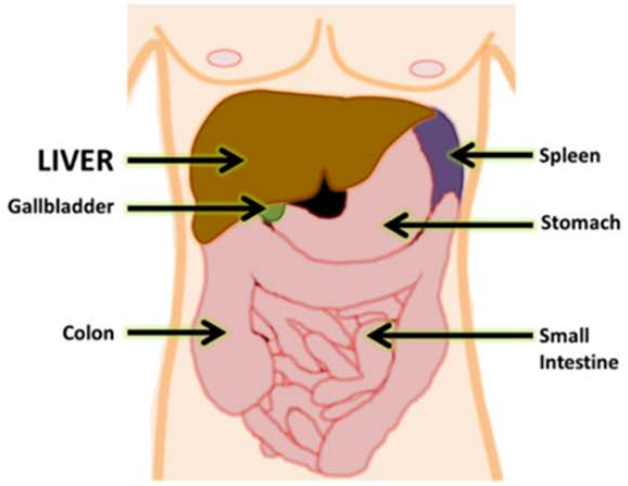
1.1 Functions of the Liver

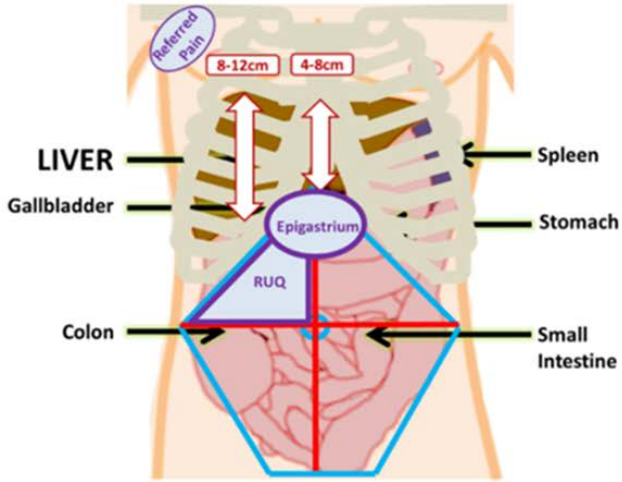
- The liver is the most amazing organ in the body!
- It is the main factory responsible for the synthesis and storage of amino acids, proteins (enzymes, clotting factors, etc.), vitamins, and fats (including lipids and cholesterol)
- It is responsible for detoxification of materials in our diet, including drugs and alcohol
- It produces bile, which not only helps us digest fat in our diet, but is also a way of eliminating waste materials (e.g. bilirubin and drugs)
- It is essential in blood glucose homeostasis, including the storage of glycogen
- It is also a very important part of our innate immune system



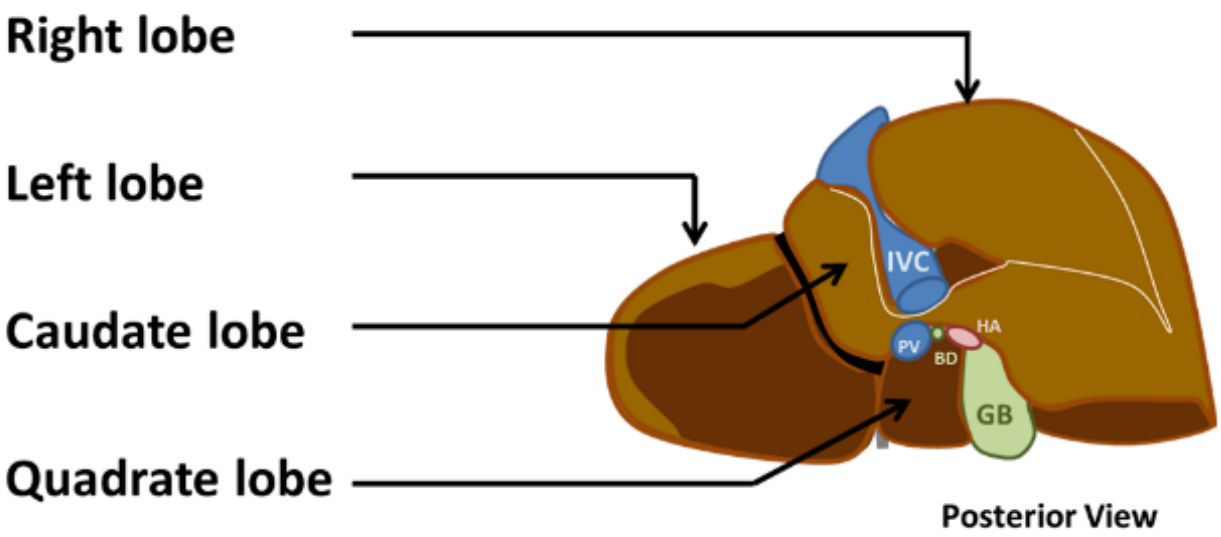
1.2 Anatomy

- The liver lies on the right side of the abdominal cavity, separated from the chest cavity (lungs) by the diaphragm
- The gallbladder is located under the liver and the liver lies in close proximity to the stomach, duodenum, colon and spleen
- In adults, a normal liver measures 8-12 cm in the mid clavicular line and 4-8 cm in the mid sternal line
- The liver is almost completely protected by the ribs and therefore only the bottom edge of the liver can normally be palpated (with a deep breath or inspiration) and the size of the liver needs to be estimated on clinical exam using percussion
- Frequently, we describe the abdomen as having four quadrants, with two lines dissecting the abdomen horizontally and vertically through the umbilicus (belly button)
- Inflammation in the liver or gallbladder is most frequently felt in the right upper quadrant (RUQ) or epigastrium (area below the sternum or breast bone)
- Pain from the liver can also sometimes be referred to the right shoulder
- It may enlarge downward into the epigastrium or RUQ due to hepatomegaly or liver masses

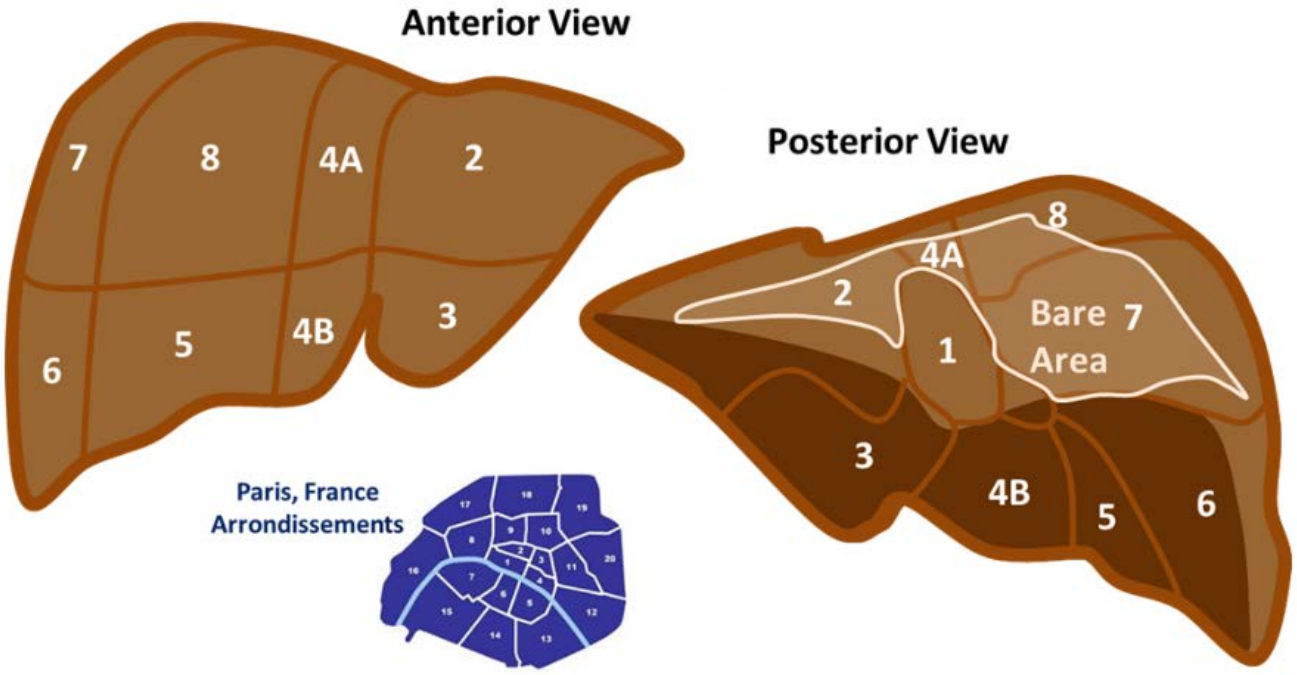




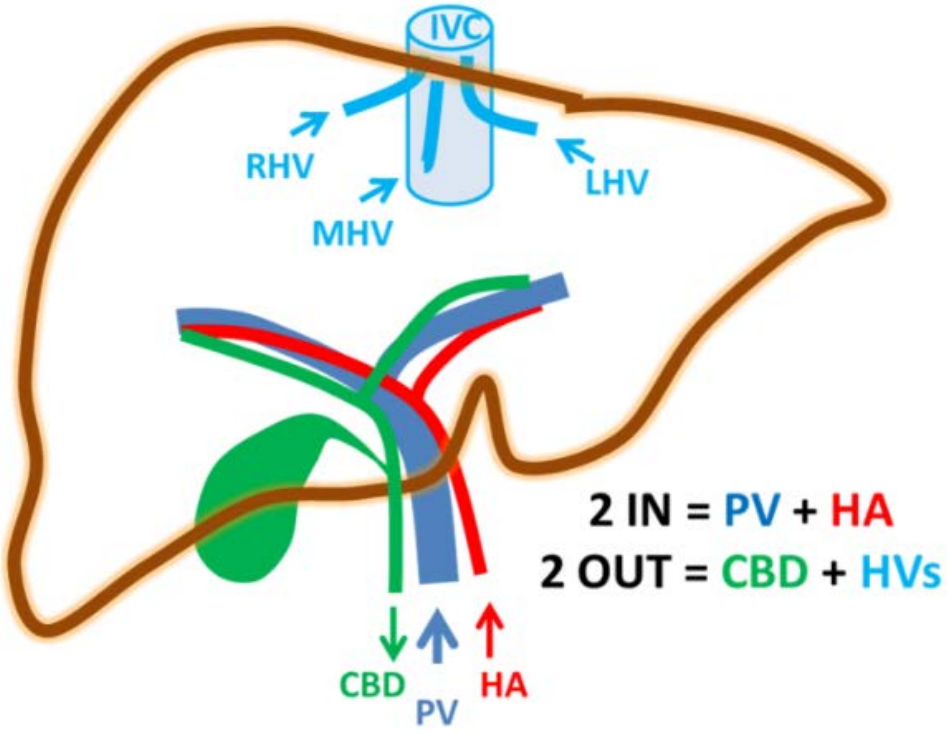
- Viewed from the back, the liver wraps around the inferior vena cava (IVC)
- Inferiorly, you will find the gallbladder (GB) and the portal hepatis, which contain the main portal vein (PV), common hepatic artery (HA), and common bile duct (BD)
- The liver is divided into the right lobe, left lobe, and the caudate lobe
- The quadrate lobe is an area on the under surface of the right lobe between the fossa of the umbilical vein, the porta hepatis and the gallbladder



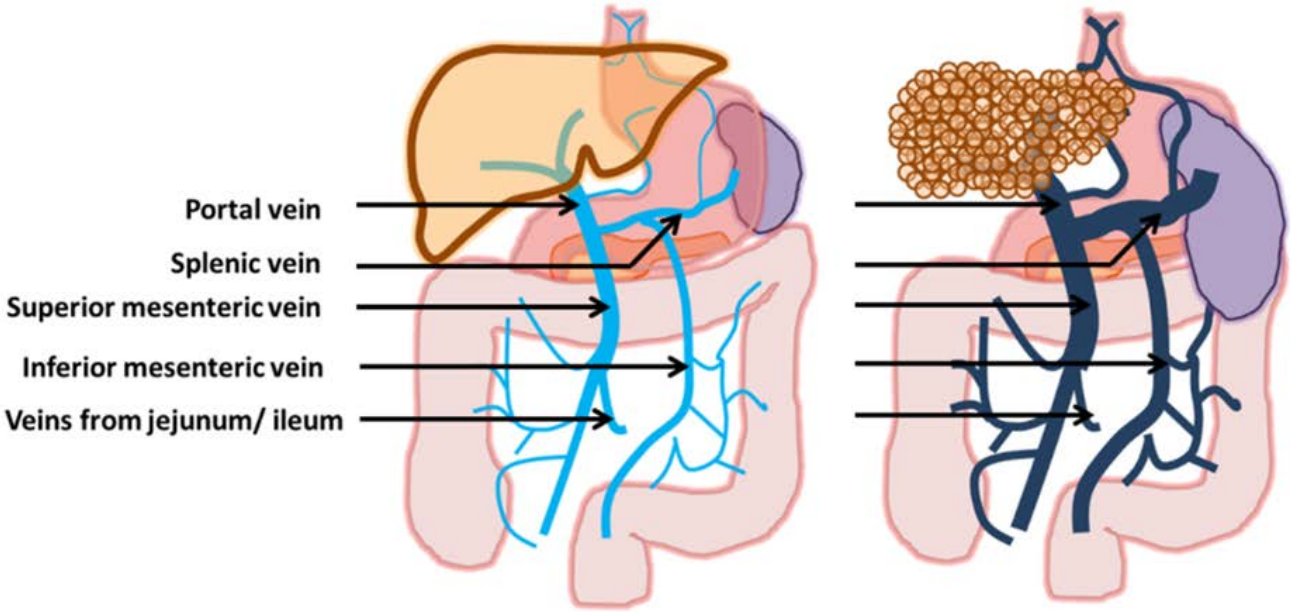
- Couinaud, a French surgeon, described the segments of the liver, and at first the numbering may not make sense, but it is apparently based on the layout of the districts in Paris, France
- The caudate lobe is segment 1, the left lobe is comprised of segments 2, 3 and 4 (which is broken down to 4A and 4B), and the right lobe contains segments 5, 6, 7 and 8
- The reflection of the peritoneum to form the coronary ligament (which holds the liver in place) means that posteriorly there is part of the liver which does not have a peritoneal lining
- This so called “Bare Area” can be important in that tumours or abscesses in this area are more likely to directly invade the diaphragm



- The basic anatomy of the liver is structured around its plumbing
- There are two inflows of blood (it is the only organ with a dual blood supply) and two outflows (one blood and one bile)
- Like all other organs, the liver has an arterial blood supply through the hepatic artery (HA), which supplies about 20% of the blood flow
- The liver also has a unique blood supply. The portal vein (PV) supplies 80% of blood flow, and takes nutrient rich blood from the gut (and blood from the spleen) to liver for processing
- Blood leaves the liver through the hepatic veins (HV), including the right hepatic vein (RHV), middle hepatic vein (MHV) and left hepatic vein (LHV), which flow into the inferior vena cava (IVC) and back to the heart
- The caudate lobe drains directly in to the IVC

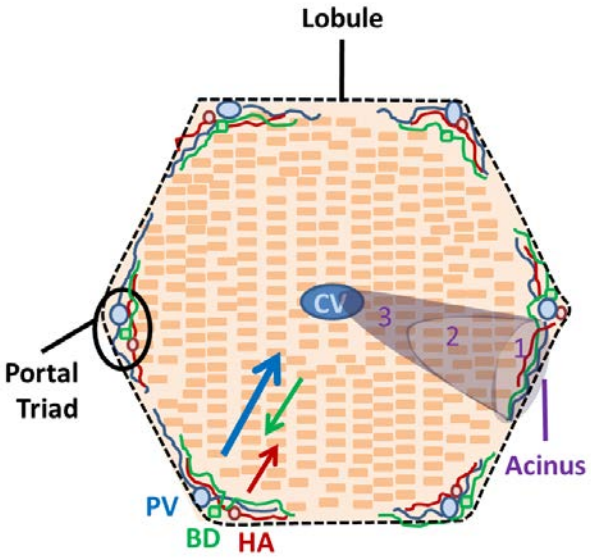


- The portal circulation is unique to the liver
- The splenic vein (drains the spleen), inferior mesenteric vein (drains the left colon) and the superior mesenteric vein (drains the small bowel, right and transverse colon) come together to form the main portal vein
- The portal vein divides into the right and left portal veins to supply each side of the liver
- When the liver becomes scarred (cirrhosis), blood has trouble flowing through the liver and the pressure within the portal vein increases
- This **portal hypertension** is responsible for many of the clinical manifestations and complications of cirrhosis
- With portal hypertension patients may develop splenomegaly, leading to sequestration of platelets, which is an important cause of thrombocytopenia (low platelets)

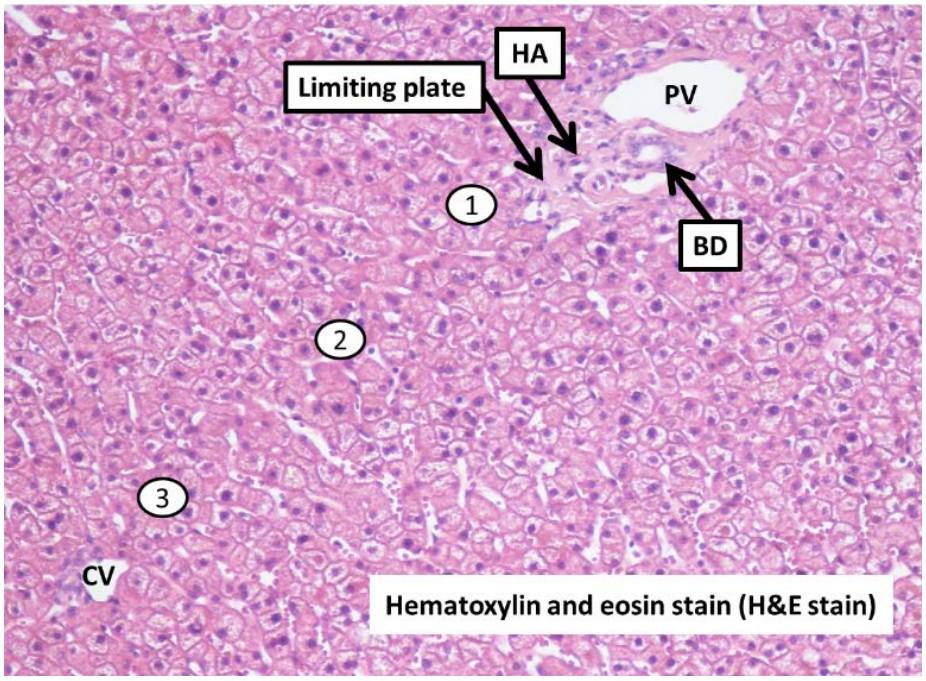


1.3 Histology

- The hepatic artery (HA) and portal vein (PV) travel with the bile duct (BD) to form the portal triad within the liver
- Blood (from the PV and HA) flows past the liver cells (hepatocytes) as it travels towards the central vein (CV), which then drains into the larger hepatic veins
- Bile produced by the hepatocytes travels in the opposite direction toward the bile ducts, and these drain into the common bile duct (CBD), which subsequently enters into the second part of the duodenum
- The functional unit of the liver is the **acinus** which starts at the terminal afferent vasculature and bile ductule branches (zone 1) and ends at the terminal hepatic venules or central veins (zone 3)
- However, histology & pathology of the liver is typically described by the hepatic **lobule**, with a central vein surrounded by several portal spaces, which is similarly broken down into Zone 1 (oxygen rich area around portal triad), Zone 2 (in the middle), and Zone 3 (oxygen depleted area around the central vein)

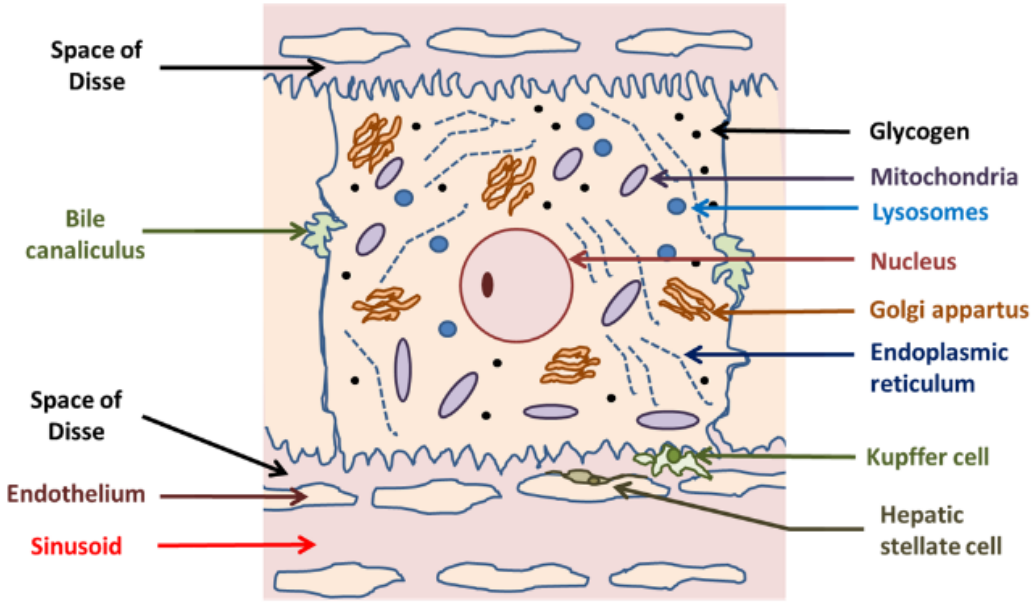


- A **liver biopsy** can be obtained to evaluation the histology of the liver and to look for pathology often with a hematoxylin and eosin (H&E) stain
- The portal triad is composed of the thin walled portal vein (PV), the thicker walled hepatic artery (HA) and the bile duct (BD), which is lined by cuboidal epithelial cells (cholangiocytes)
- The portal triad is supported by connective tissue and is delineated from the pink liver cells (hepatocytes) by the "limiting plate"
- The hepatocytes are arranged in sheets of cells which are normally one cell thick
- Blood from the PV and HA flow by the hepatocytes in the sinusoids toward the central vein (CV)
- Bile produced by the hepatocytes flows in the opposite direction through canaliculi toward the bile duct (BD)



1.4 Cell Biology

- The major cell of the liver is the **hepatocyte**
- The **cholangiocyte** is the epithelial cell which lines the bile ducts
- **Kupffer cells** are the macrophage of the liver and are a very important part of the innate immune system
- The **hepatic stellate cell** (HSC), in the inactivated form is also known as the **Ito cell,** and is responsible for fat storage, but when activated the HSC is responsible for the production of fibrosis which leads to scarring in the liver
- The liver is also populated by **stem cells**, which have a role in liver regeneration, as well as a potential role in the development of hepatic malignancies
- The **hepatocyte** is the most important cell within the liver and is responsible for manufacturing, metabolism, detoxification and the production of bile
- It contains glycogen and the organelles found in any nucleated cell
- Blood travelling within the **sinusoids** can easily come in contact with the hepatocytes as the endothelium is fenestrated (has holes)
- Between the sinusoids and the hepatocytes lies the perisinusoidal space, also known as the **Space of Disse**, containing the **Kupffer cells** (liver macrophage) and **hepatic stellate cells** (HSC)
- On the basolateral surface of the hepatocyte is the **bile canaliculus**, where bile and its components are exported and travel toward the bile ducts



1.5 Bilirubin metabolism

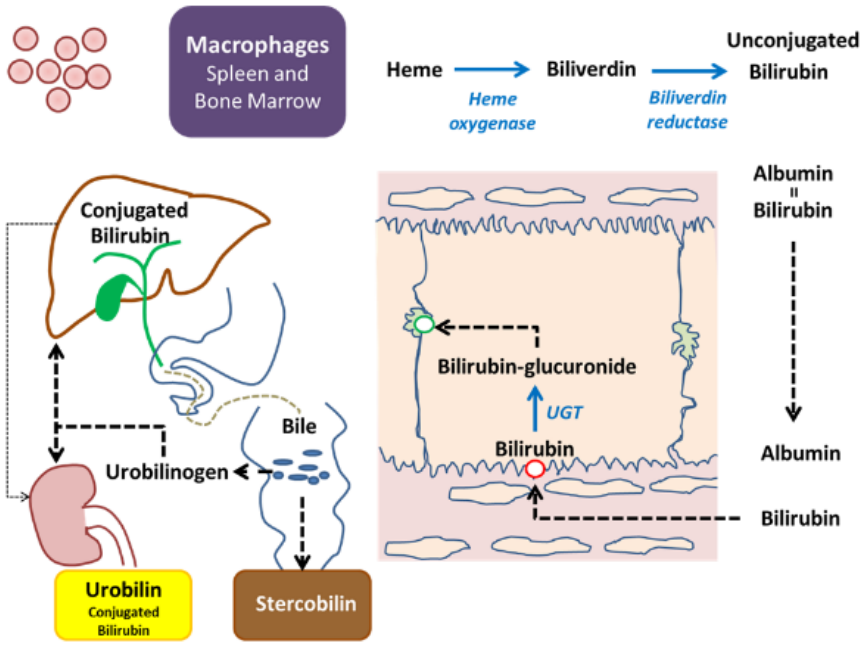
- Bilirubin comes from the breakdown of hemoglobin and is measured by the lab as **direct (conjugated) bilirubin** or **total bilirubin**, which is a combination of direct and indirect (unconjugated) bilirubin
- Senescent red blood cells, after approximately 120 days in circulation, are removed by the macrophages of the spleen and bone marrow
- Hemoglobin is broken down to globin and heme, which is then metabolized into biliverdin and subsequently then to **unconjugated bilirubin**
- This unconjugated bilirubin is transported to the liver bound to albumin
- In the hepatic sinusoids, bilirubin is released from albumin and is taken up by the hepatocyte through transporters
- Within the hepatocyte, bilirubin is conjugated by the UGT enzymes to make bilirubin more water soluble

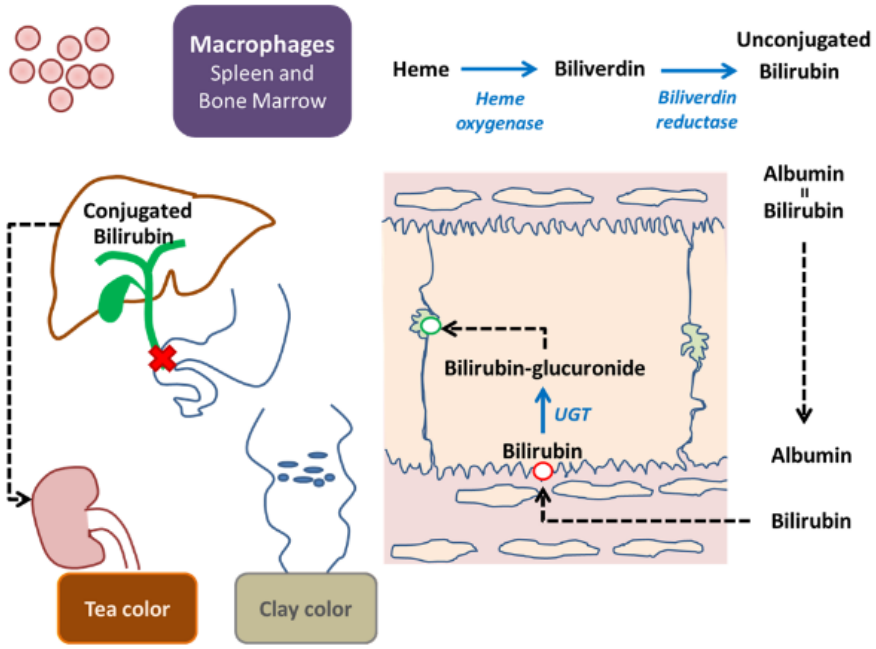
- **Conjugated bilirubin** is then ready for excretion into the bile through special transporters on the bile canaliculus
- Conjugated bilirubin flows down the bile duct and enters the duodenum
- Bacteria in the colon, act upon bilirubin to form stercobilin (makes stool brown in colour) and urobilinogen which is absorbed and taken to the kidneys, where it is converted to urobilin (makes urine yellow in colour)
- Some conjugated bilirubin, which is water soluble, can be excreted by the kidneys
- When there is a blockage to bile flow (e.g. common bile duct stone or cancer in the head of the pancreas) the bile duct will become dilated (best seen on ultrasound)

o Bilirubin no longer makes it to the colon and the stool will turn clay-coloured

o Conjugated bilirubin, which is now very high, will result in jaundice and dark tea-coloured urine

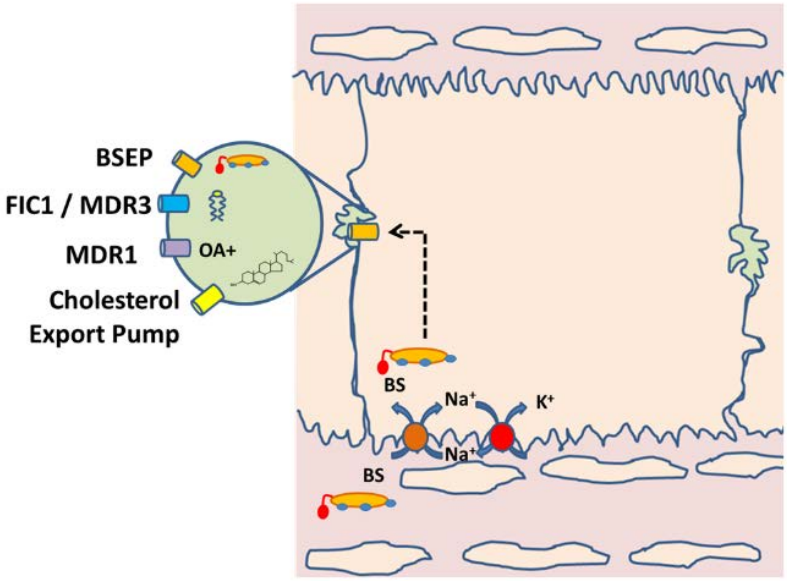
o The patient may also experience pruritus (itching) and the alkaline phosphatase (produced by the bile canaliculus) will increase in the blood (extra-hepatic cholestasis)





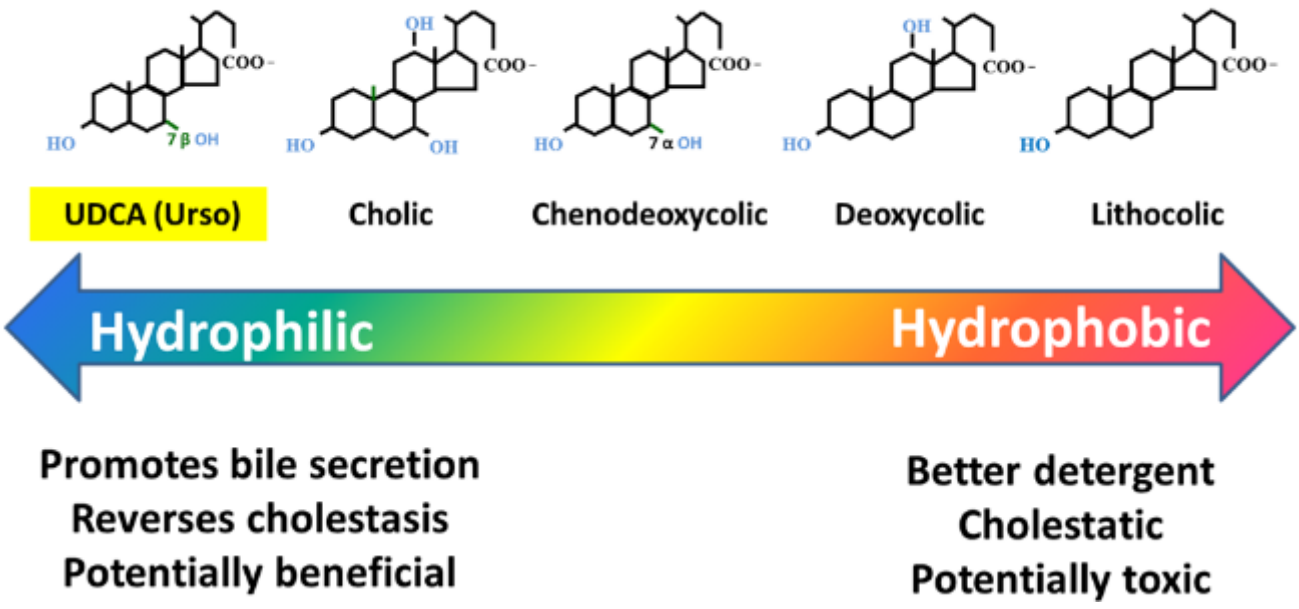
1.6 Bile Physiology

- Bile composition
  - 90% of bile is made of bile salts, lecithin and cholesterol
  - 10% is bilirubin, proteins, and various ions (Na, K, Ca, Mg, HCO3, Cl)
- Bile excretion
  - Bile salts (BS) and other components of bile are transported into the canaliculus by specific transporters (see below)
    - **BSEP** = bile salt export pump
    - **FIC-1** = protein responsible for phospholipid translocation
    - **MDR3** (multi-drug resistance protein 3) = phosphatidylcholine translocation
    - **MDR1** (multi-drug resistance protein 1) = organic anion transporter
    - Cholesterol export pump

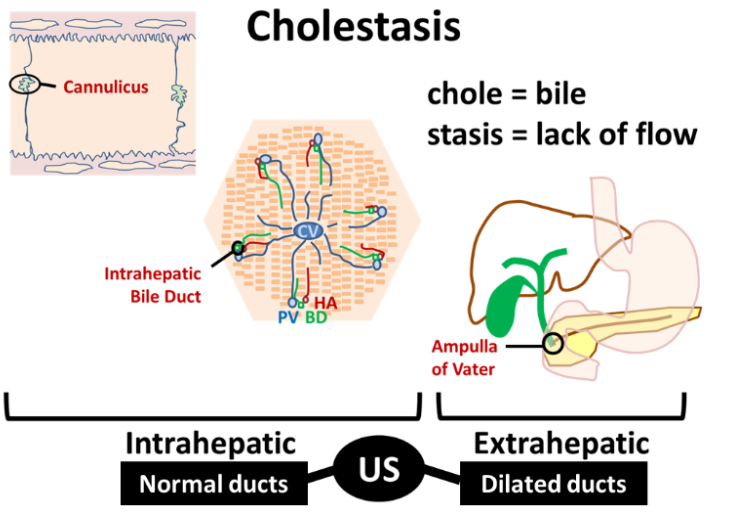


- Bile acids
  - Hydroxylation makes them more water soluble, so they can act as detergents to dissolve fat
  - Conjugation, with glycine or taurine, helps keep bile acids in the gut and in enterohepatic circulation
- Bile acid functions
  - Transporters in liver = promote bile formation and flow (choloretic) and help in excretion of wastes (bilirubin, copper, drugs, etc.)
  - Prevents gallstone formation = too little means supersaturated bile (risk for stones)
  - Cholesterol homeostasis = 1/3 of cholesterol is excreted as bile acids
  - Detergent molecules = for absorption of dietary fat
  - Body defenses = anti-microbial and anti-cancer properties in the colon
  - Intestinal motility = stimulates mucin and influences water / electrolyte absorption in colon

- Enterohepatic circulation
  - 95% of bile acids taken up in terminal ileum (active transporter)
  - More likely if bile acids are conjugated
  - They travel to liver via the portal vein
  - Bile salts (BS) taken up by hepatocytes using specific active transporters (see figure above)
    - Sodium / potassium (Na/K) ATPase (in red in figure above)
    - Sodium taurocholate co-transporting polypeptide (in orange in figure above)
- Bacteria in the colon deconjugate and dehydroxylate primary bile acids (cholic acid and chenodeoxycholic acid) to form secondary bile acids (deoxycholic acid and lithocolic acid), which are better detergents but are potentially toxic if bile is not flowing
- **Ursodeoxycholic acid (UDCA)** is more hydrophilic and promotes bile secretion, reverses cholestasis and is used as a treatment for some cholestatic liver diseases



- **Cholestasis** is a lack of bile flow
  - It can occur at the level of the canaliculus or intrahepatic bile ducts (intrahepatic cholestasis, where the ultrasound shows no dilated ducts) or in the extrahepatic bile ducts (where the ultrasound shows dilated bile ducts)



Abbreviations:

BD – bile duct

BS – bile salts

BSEP – bile salt export pump

CBD – common bile duct

CV – central vein

GB – gallbladder

H & E – hematoxylin and eosin

HA – hepatic artery

HSC – hepatic stellate cell

HV – hepatic veins

IVC – inferior vena cava

LHV – left hepatic vein

MDR1 – multi-drug resistance protein 1

MDR3 – multi-drug resistance protein 3

MHV – middle hepatic vein

OA+ – organic acid

PV – main portal vein

RHV – right hepatic vein

RUQ – right upper quadrant

UDCA – ursodeoxycholic acid

UGT – uridine 5'-diphospho-glucuronosyltransferase

US – ultrasound

