LIVER & BILIARY PHYSIOLOGY

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Summarized Functions Of Liver

- Filtration and storage of blood
- Metabolism of carbohydrates, proteins, fats, hormones, and foreign chemicals
- Formation of bile
- Storage of vitamins and iron
- Formation of coagulation factors.

Physiologic Anatomy of Liver

- Largest organ in the body (1.5 kg= 3.3 pounds)
- It contributes 2% of total body weight in average adult human
- Functional unit = liver lobule
- The human liver contains 100,000 to 1 million lobules.
- A 3-pound liver has 200 billion hepatocytes!

Structure of liver lobule

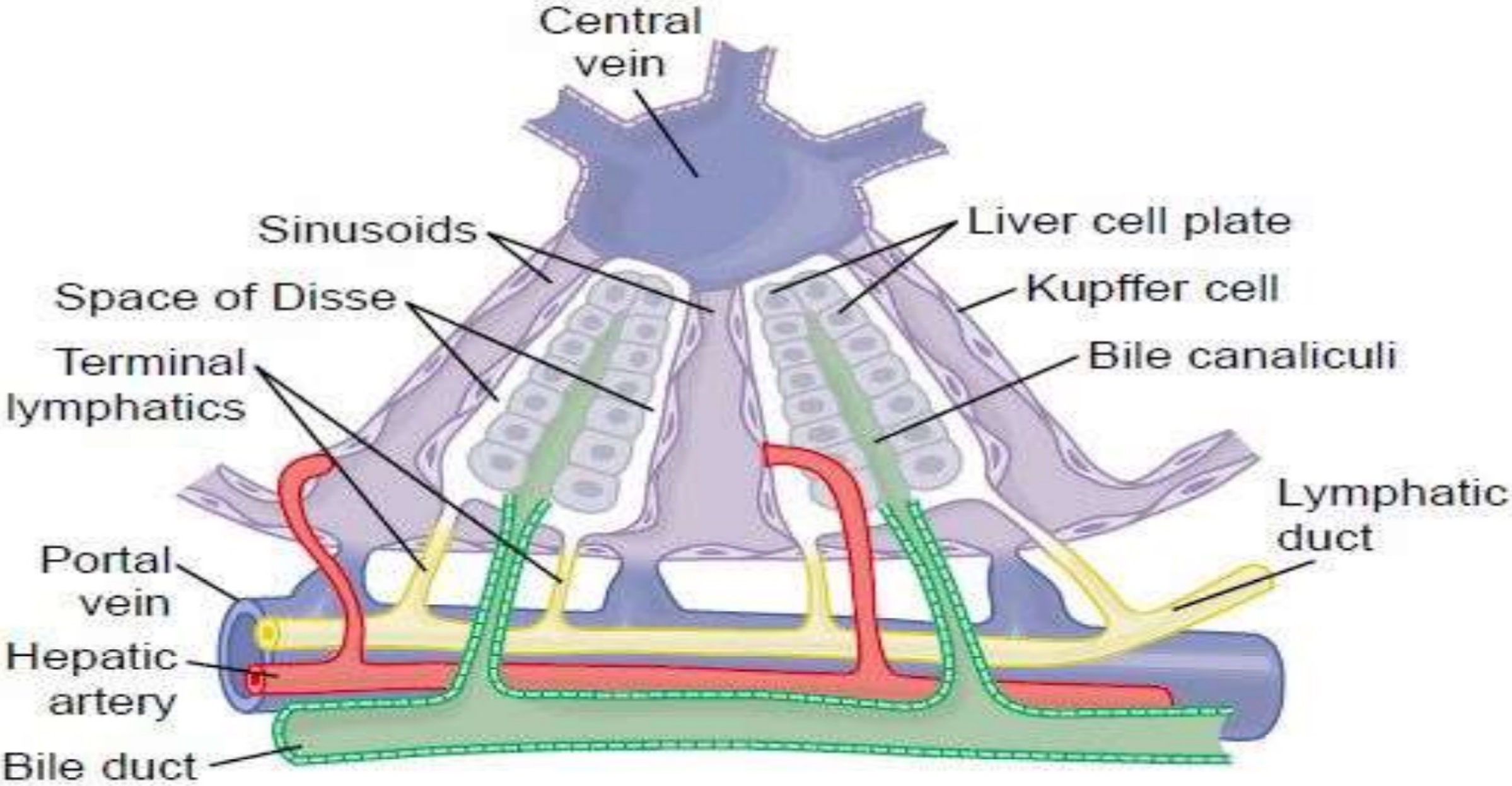
- It is a cylindrical structure with
- Length= 2-3millimeters
- Diameter= 0.8-2 millimeters
- It is constructed around a central vein

Main components of a lobule

- Central vein
- Cellular plates
- Portal venules
- Hepatic sinusoids
- Hepatic arterioles

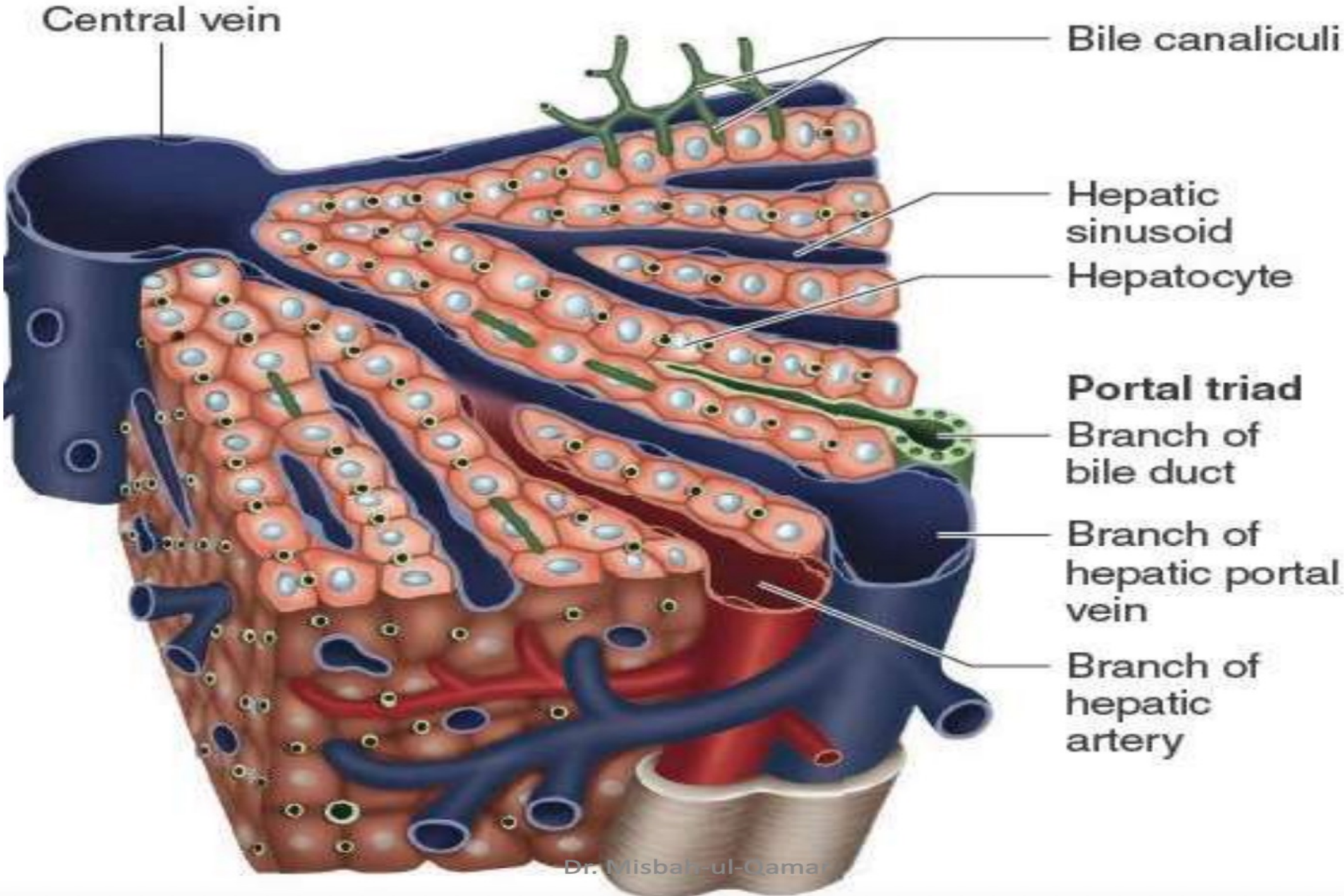
Structure of Liver Lobule

- Central Vein
  - In the center (central vein > hepatic veins >vena cava
- Lobule is composed of Cellular Plates
  - Radiate from the central vein like spokes in a wheel
  - Each plate is usually two cells thick
  - Between adjacent cells lie bile canaliculi that empty into bile ducts
- There are fibrous septa which separate adjacent liver lobules
  - In the septa lie bile ducts, portal venules, hepatic arterioles & lymphatic vessels
- Portal Venules
  - Receive their blood from portal vein (venous outflow of GIT)
  - From venules, blood flow into hepatic sinusoids


Central vein
Sinusoids
Liver cell plate
Space of Disse
Kupffer cell
Terminal lymphatics
Bile canaliculi
Lymphatic duct
Portal vein
Hepatic artery
Bile duct

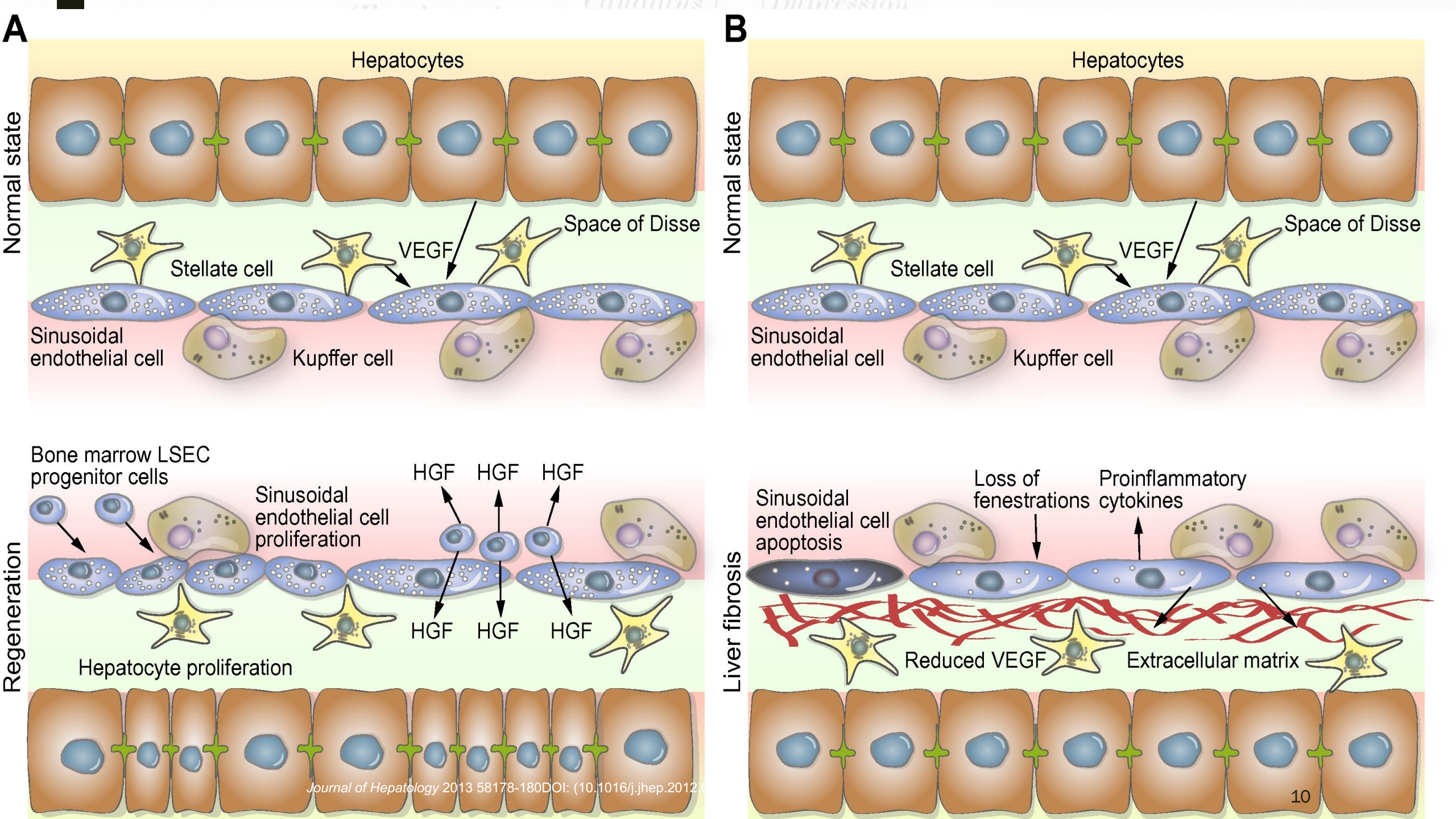
Structure of Liver Lobule

- Hepatic Sinusoids
  - Lie between the hepatic plates
  - Blood flows from portal venules and arterioles to sinusoids then into the central vein
  - That's how hepatic cells are exposed continuously to portal venous blood
- Hepatic arterioles
  - Supply arterial blood to the septal tissues between the adjacent lobules
  - Many of arterioles drain directly into sinusoids



Venous sinusoids are lined by

- Endothelial cells
- Kupffer cells (liver macrophages)
  - Significance of Kupffer cells
    - They line the sinusoids and break down old RBCs
    - They are capable of phagocytizing bacteria & other foreign matter in hepatic sinus blood



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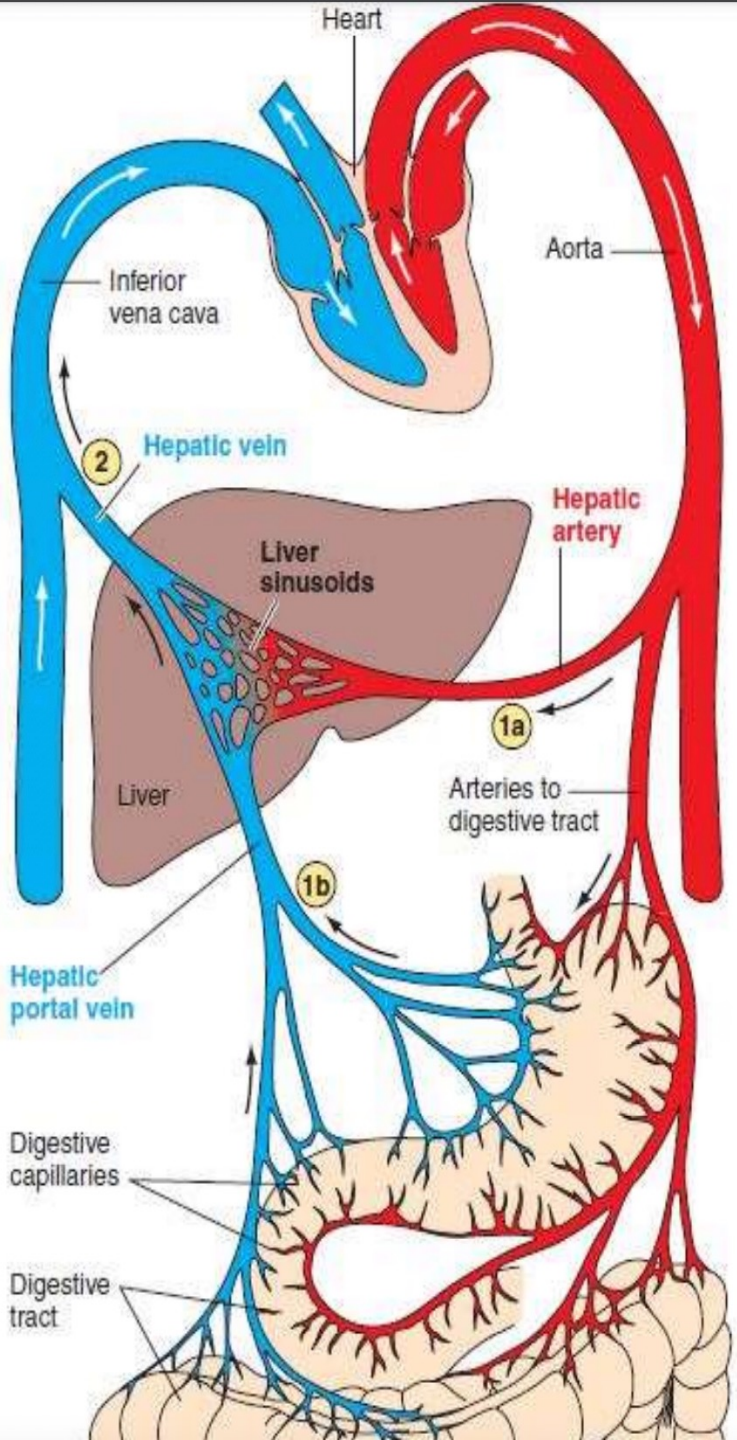
Spaces of Disse

- Also called peri-sinusoidal spaces
  - Narrow tissue spaces between endothelial cells and the hepatic cells
  - Endothelial lining has extremely large pores
  - These spaces connect with lymph vessels in septum
- Significance
  - Excess fluid in spaces is removed through lymphatics
  - Large substances (portions of plasma proteins) can move freely into spaces through large pores of endothelium



1. The liver receives blood from two sources:
   - a. Arterial blood, which provides the liver's O_2 supply and carries blood-borne metabolites for hepatic processing, is delivered by the **hepatic artery**.
   - b. Venous blood draining the digestive tract is carried by the **hepatic portal vein** to the liver for processing and storage of newly absorbed nutrients.
2. Blood leaves the liver via the **hepatic vein**.

Blood Flow Design in Liver

There are unique features of circulation through liver

Hepatic Vascular and Lymph Systems

- Blood flows through liver from portal vein and hepatic artery
  - High blood flow
  - Sinusoids receive 1350 ml/min (27% of CO)
  - From portal vein @ 1050ml/min
  - From hepatic artery @ 300ml/min
- The liver has high blood flow and low vascular resistance
  - Low vascular resistance
  - Pressure in portal vein @ 9 mmHg
  - Pressure in hepatic vein @ 5 mmHg
  - This small pressure difference shows very low resistance to blood flow through sinusoids

Cirrhosis of the liver greatly increases resistance to blood flow

- Cirrhosis
  - Destruction of parenchyma of liver and its replacement with fibrous tissue
  - Fibrous tissue contracts around the blood vessels, and impedes blood flow thus increasing resistance
- Cause
  - Alcoholism Ingestion of poisons like carbon tetrachloride
  - Viral diseases like hepatitis

The liver has a very high lymph flow

- Half of the lymph formed in the body arises in the liver.
- Hepatic sinusoids are very permeable.
- Passage of fluid and proteins into the spaces of Disse
- Protein concentration of lymph from liver = 6g/dl (slightly less than that of plasma)
- Extreme permeability of the liver sinusoid epithelium allows large quantities of lymph to form.

In case of high hepatic vascular pressure

- When pressure in hepatic vein rises (3-7mmHg above normal)
  - Excessive amount of fluid begin to transude into lymph
  - Fluid also leak into abdominal cavity through outer surface of liver capsule
- Similarly, blockage of portal flow causes portal hypertension

Portal hypertension

- Prolonged elevation of portal venous pressure above normal
- Increased capillary pressure in intestinal wall
- Loss of fluid from capillaries into wall and lumen of the intestines

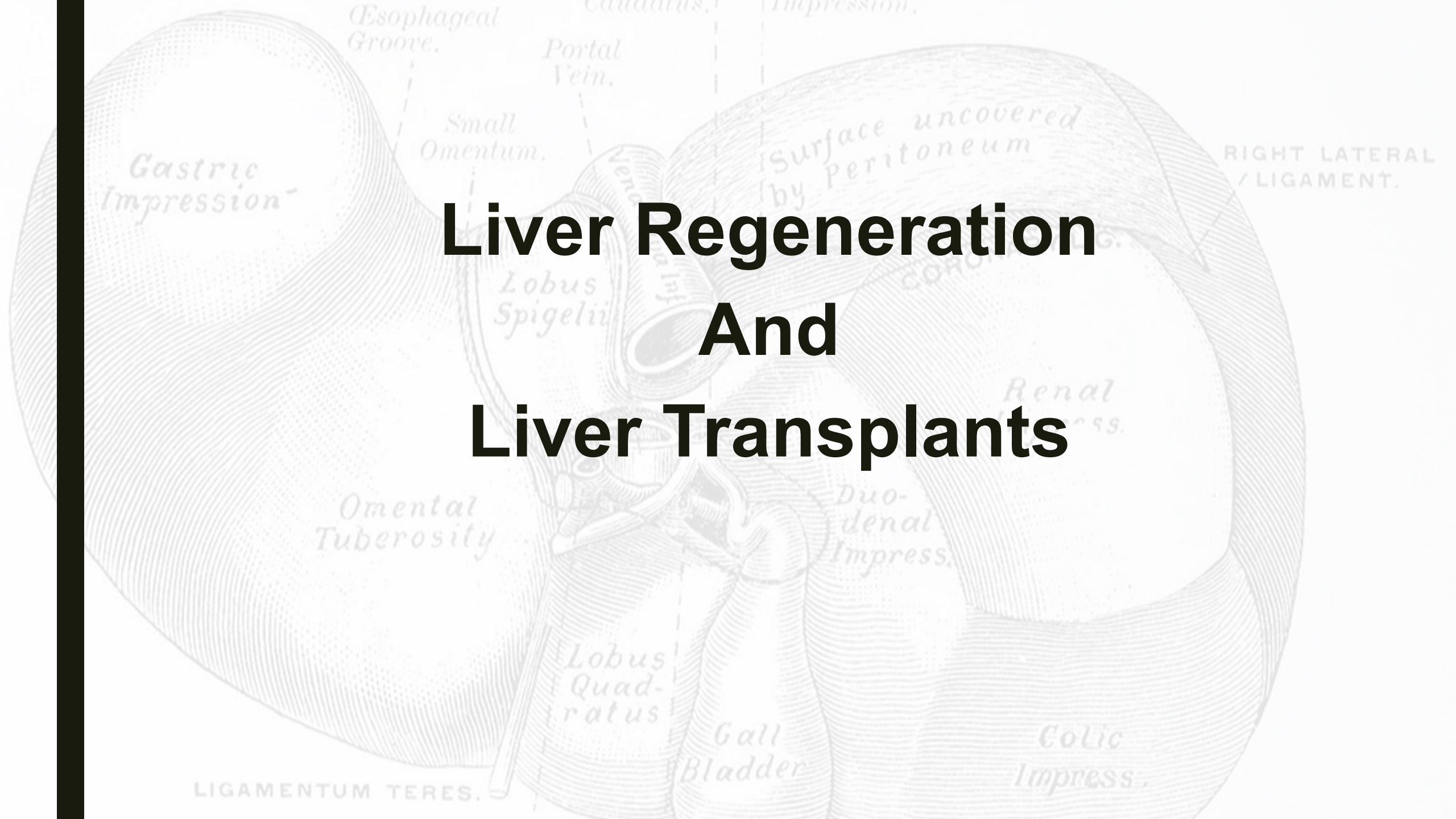
Causes of portal hypertension

- Formation of clot (portal vein thrombosis)
- Cirrhosis of liver
- Veno-occulusive disease
- Cystic liver disease
- Sarcoidosis
- Drugs

Ascites

- Collection of free fluid in the peritoneal cavity
- Transudation of fluid into lymph and leakage from surface of liver into abdominal cavity due to high pressure in hepatic veins

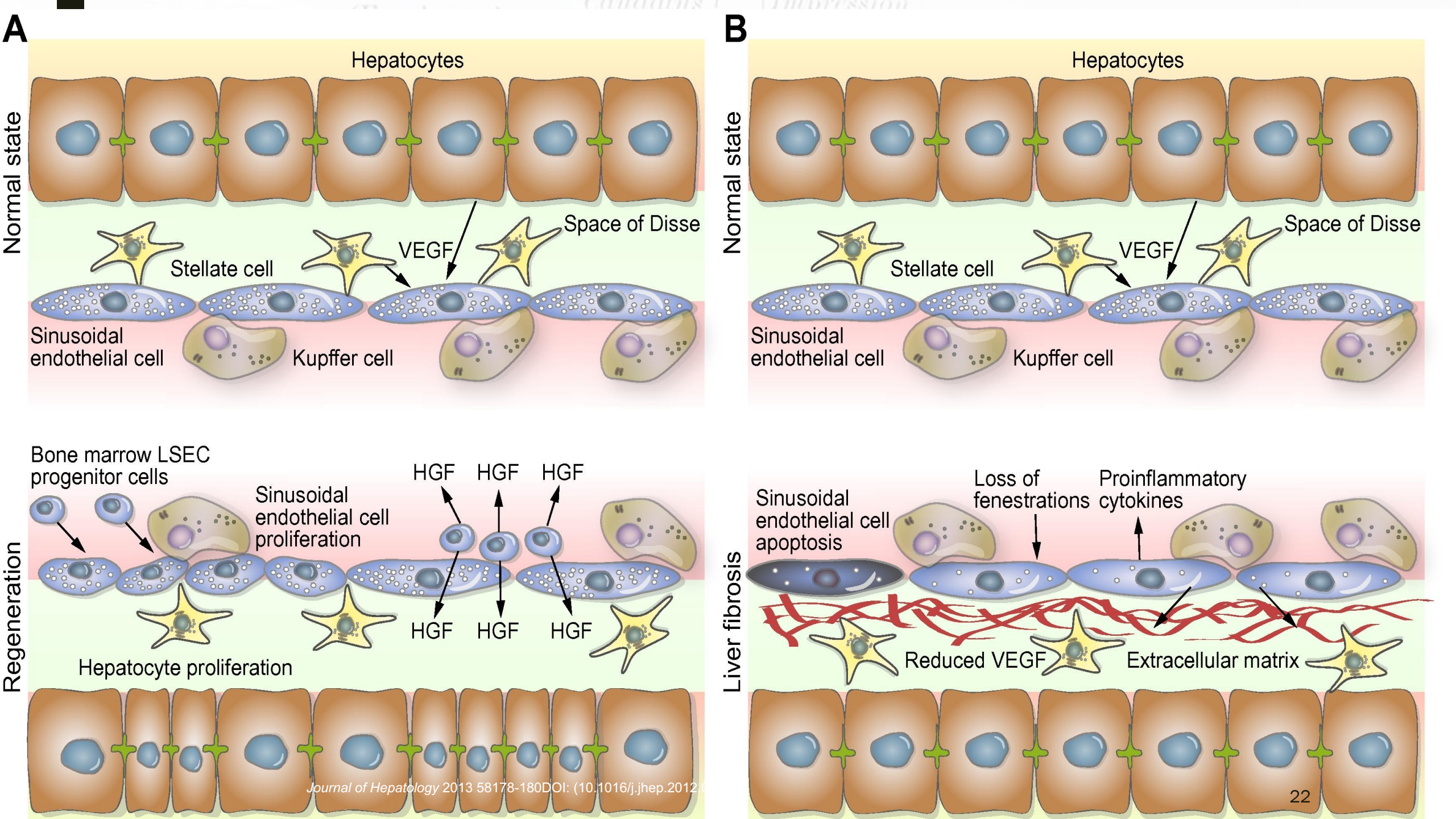
Liver Regeneration
And
Liver Transplants



Regulation of liver mass

- Regeneration liver possesses a remarkable ability to restore itself after significant hepatic tissue loss from either partial hepatectomy or acute liver injury as long as injury is uncomplicated by infection or inflammation.
  - During this process, hepatocytes replicate until original size and volume has been restored
  - Hepatocyte growth factor, produced by mesenchymal cells, cause liver cell division
  - Blood levels increase 20 times after partial hepatectomy

- Other growth factors are also involved like
  - Epidermal growth factor
  - Tumor necrosis factor
  - Interleukin-6
- Termination of regeneration
  - Transforming growth factor
  - β, a cytokine released by hepatocytes is a potent inhibitor of liver cell proliferation.
- Role of Hepatic stellate cells in liver regeneration
  - These are liver specific resident mesenchymal stem cells
  - They secrete growth factors promoting the regeneration of hepatic epithelial cells



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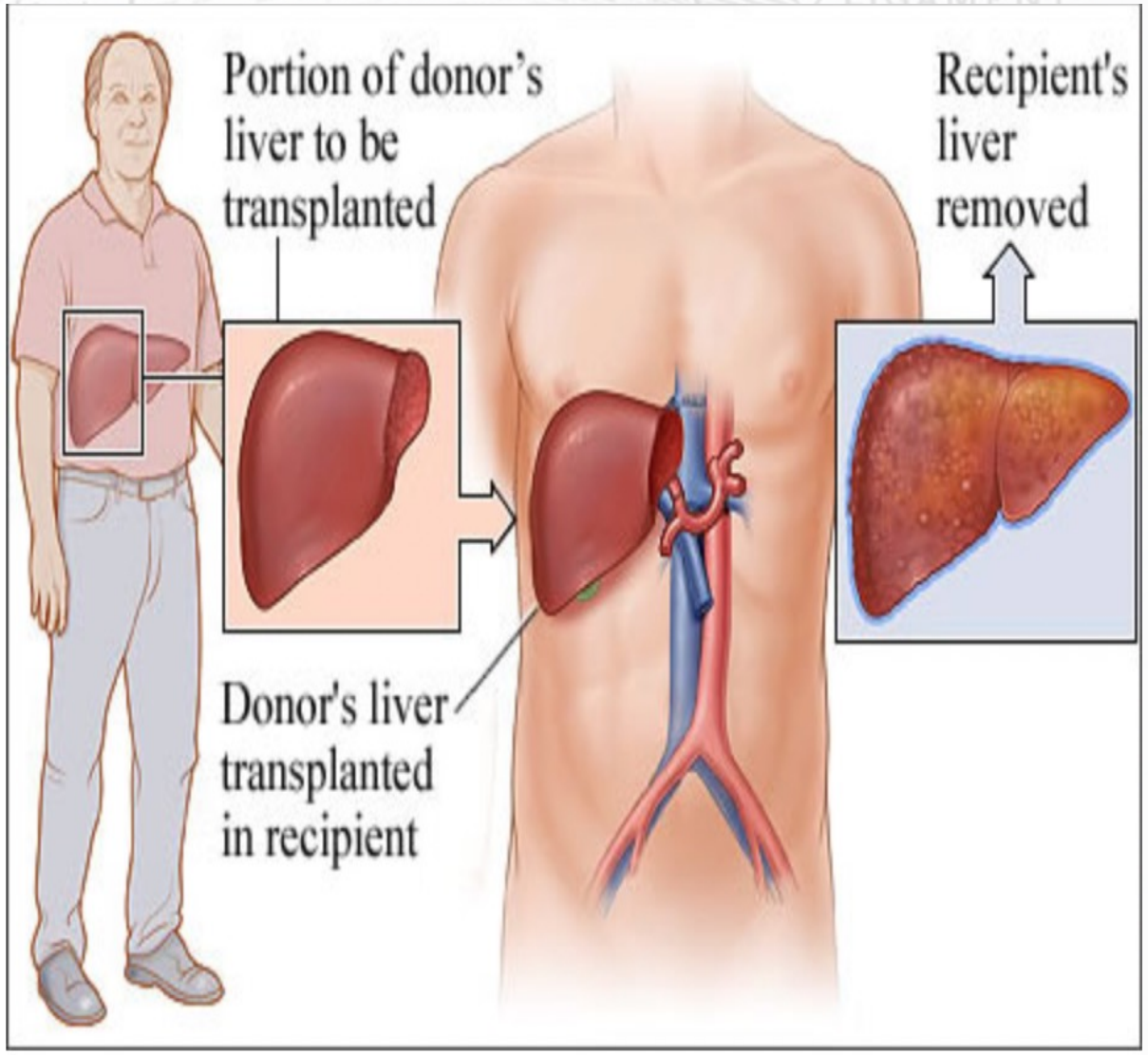
Liver Transplant

Only a small portion of donor's liver is transplanted which attains normal mass through regeneration

Pediatric Liver Transplant



Functions of Liver

Major 4 functions of liver

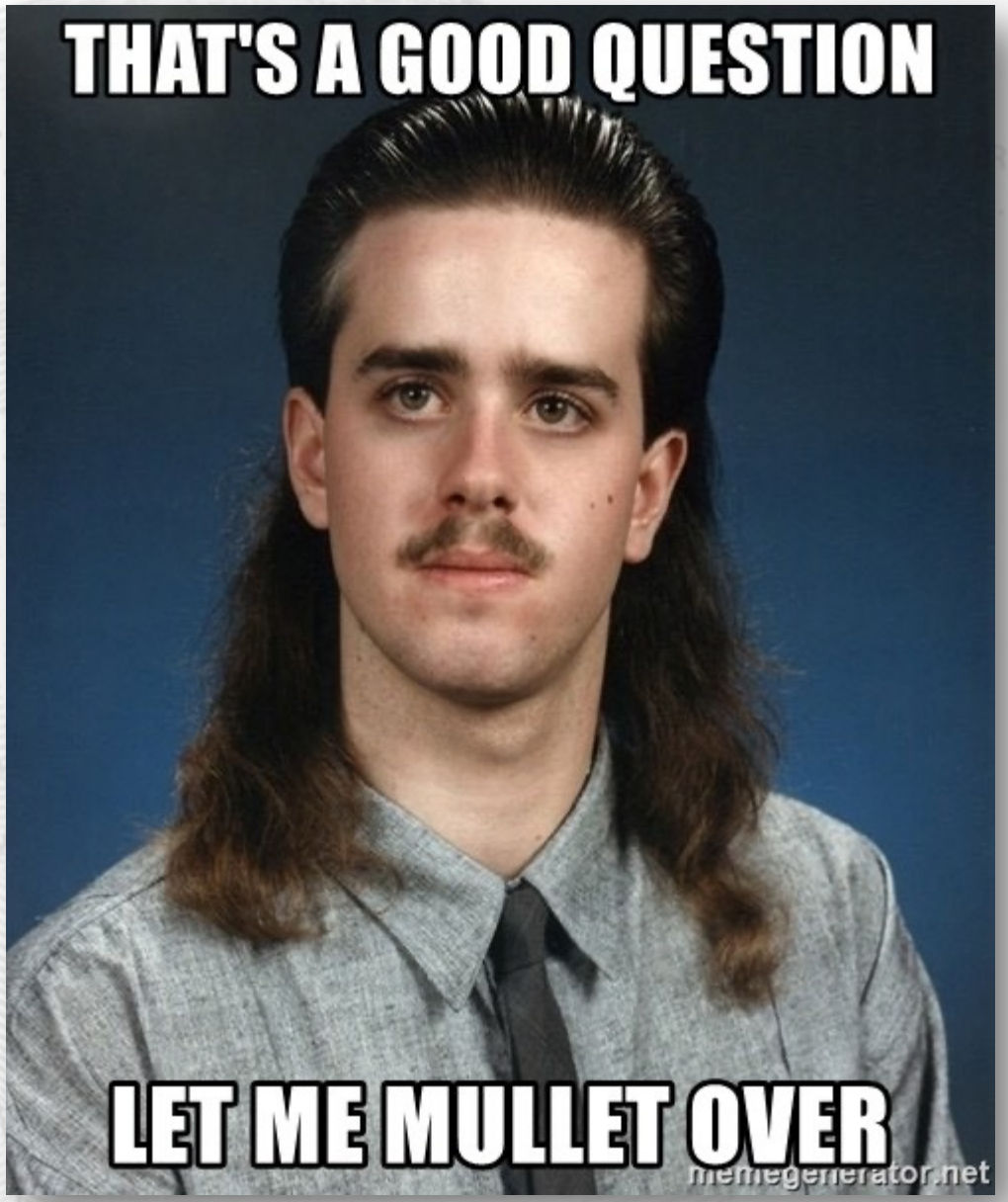
- Reservoir function
- Blood cleansing function
- Metabolic functions
- Bile formation & excretion

The Liver Functions as a Blood Reservoir

- Liver is a large expandable, venous organ capable of acting as a blood reservoir.
- Blood is stored in its blood vessels.
- Supplies extra blood in times of diminished blood volume.
- Normal blood volume in liver = 15-16 ounces
  - (including that in both hepatic veins & hepatic sinuses)
- Maximum blood volume which can be stored in liver = 0.5 to 1liter

What conditions cause increased blood storage in liver?

- Congestive cardiac failure - right sided
- When high pressure in right atrium causes back pressure in liver
- In times of excess blood/plasma volume



Blood Cleansing Function

Why portal blood needs cleansing

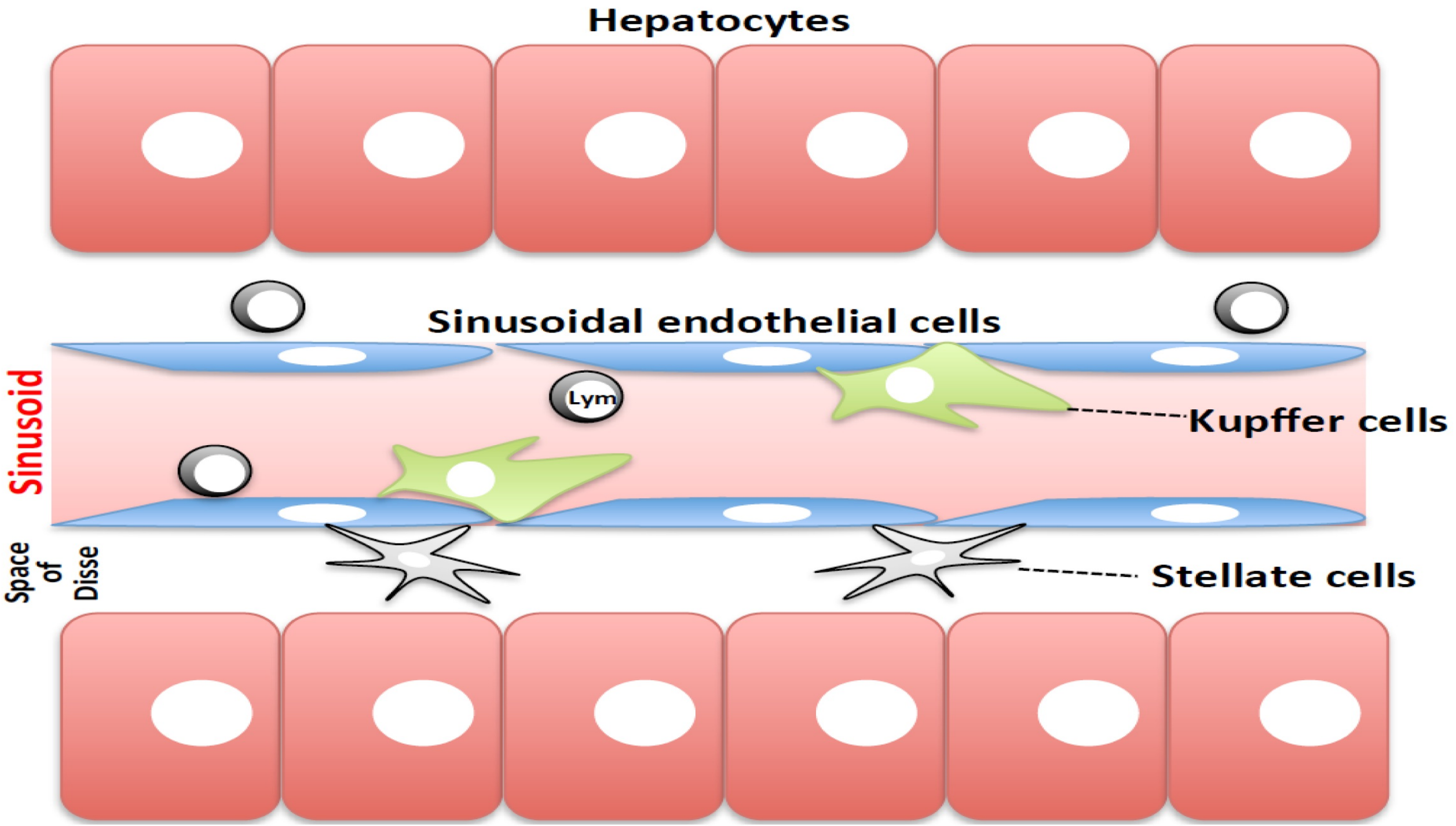
- Blood flowing through intestinal capillaries picks up many bacteria from intestines
- As indicated by the growth of colon bacilli in:
  - Blood sample from portal vein before it enters liver s always has bacteria when cultured
  - Blood sample from systemic circulation rarely has bacteria

Hepatic Macrophage System consisting of Kupffer cells

- What are Kupffer cells
  - Large phagocytic macrophages that line the hepatic venous sinuses
- Main Function
  - Cleanse blood of bacteria & endotoxins from portal circulation as it passes through the sinuses
  - Cellular debris, viruses, proteins & particulate matter in blood are also phagocytized
- Other functions performed by Kupffer cells
  - Processing of antigens
  - Release of various proteins, enzymes, cytokines and other chemical mediators D

Cleansing effectiveness of liver

- Kupffer cells perform their action at a high speed
- Only a momentary contact of 0.01 second with a bacterium transports it inward through the wall of Kupffer cell
- Bacterium is permanently lodged inside macrophage until digested
- Less than 1% of the bacteria entering the portal blood succeeds in passing through the liver

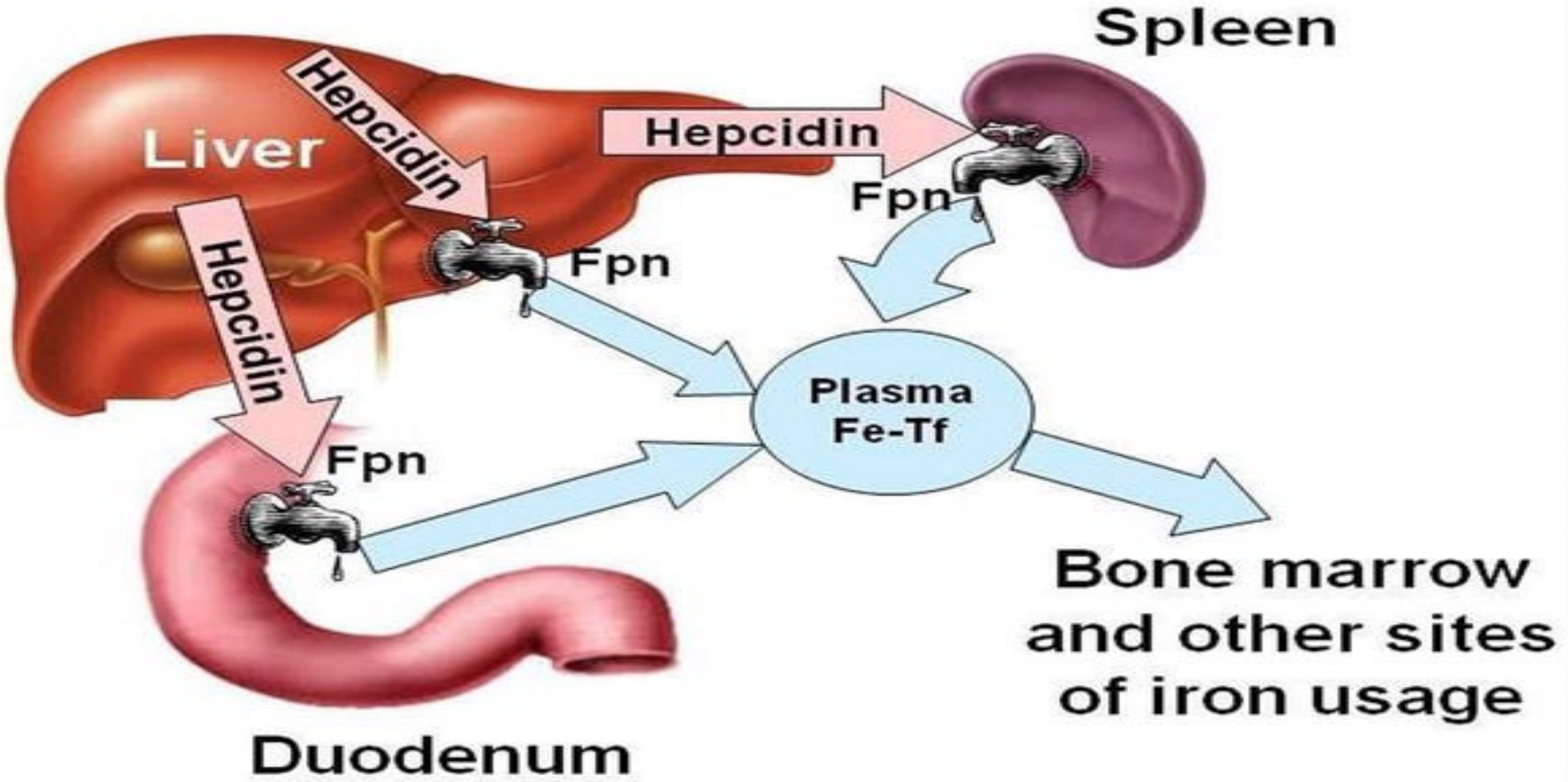

Hepatocytes
Sinusoidal endothelial cells
Sinusoid
Lym
Kupffer cells
Space of Disse
Stellate cells

Endocrine Function

Secretion of Hormones

- Erythropoietin
  - stimulates RBC production
  - 10% is secreted from liver / 90% from kidney
- Thrombopoietin
  - stimulates platelet production
- Insulin like growth factor
  - Stimulates growth
- Hepcidin
  - Inhibits iron uptake from the intestines
- Activating vitamin D in conjunction with kidneys

How hepcidin regulates iron



- Formation of blood cells
  - During intrauterine life
  - This function is lost at birth, but liver retain the potentiality of forming red blood cells
- Removal of worn-out red blood cells by reticuloendothelial cells in conjunction with spleen and bone marrow - Lifespan of RBC is 100-120 days

Metabolic functions of liver

- Liver is a large, chemically reactant pool of cells that have a high rate of metabolism
- Involved in metabolism of
  - Protein
  - Carbohydrate
  - Fats

Protein Metabolism

- The liver also plays an important role in the metabolism of proteins
- Liver cells change amino acids in foods so that they can be used to produce energy, or make carbohydrates or fats.
- Ammonia is a by-product of this process.
  - This ammonia is toxic to the body. So, it is detoxified in the liver of the animals.

Protein Metabolism

- Extremely important function of liver
- When protein metabolism ceases, as in liver failure, death occurs within 1-2 days.
- Deamination of amino acids
- Formation of urea for removal of ammonia
- Formation of all plasma proteins
- Inter-conversions of the various amino acids and synthesis of other compounds from amino acids

De-amination

- It is required before protein is used for energy or converted into carb or fat
- Enzymatic processes convert amino acids to their respective keto acids.
  - Some deamination can occur in other tissues of body (kidney) but mainly in liver
- Large amount of ammonia is also formed in deamination

Formation of Urea

- Ammonia formed from deamination is highly toxic to tissues
  - ↑ ammonia due to liver disease = hepatic coma
  - Decreased blood flow through liver (shunting of portal vein into vena cava) ⟶ excessive ammonia (extremely toxic)
- 2 molecules of ammonia + CO_2 = Urea
- Urea thus formed readily diffuses out of liver & can be excreted by kidneys

Formation of plasma proteins

- 90% of plasma proteins formed by liver
  - Albumin
  - Alpha1-antitrypsin
  - Proteases/elastases
  - All coagulation factors (not Von Willebrand factor)
- Maximum rate of plasma protein production by liver: 15-50g/day
  - Even if half plasma proteins lost somehow, liver can replenish in 1-2 weeks
- Plasma protein depletion causes liver enlargement by rapid mitosis of hepatic cells ⟶ rapid output of PPs.
- Chronic liver disease like cirrhosis ⟶ edema & ascites due to very low albumin

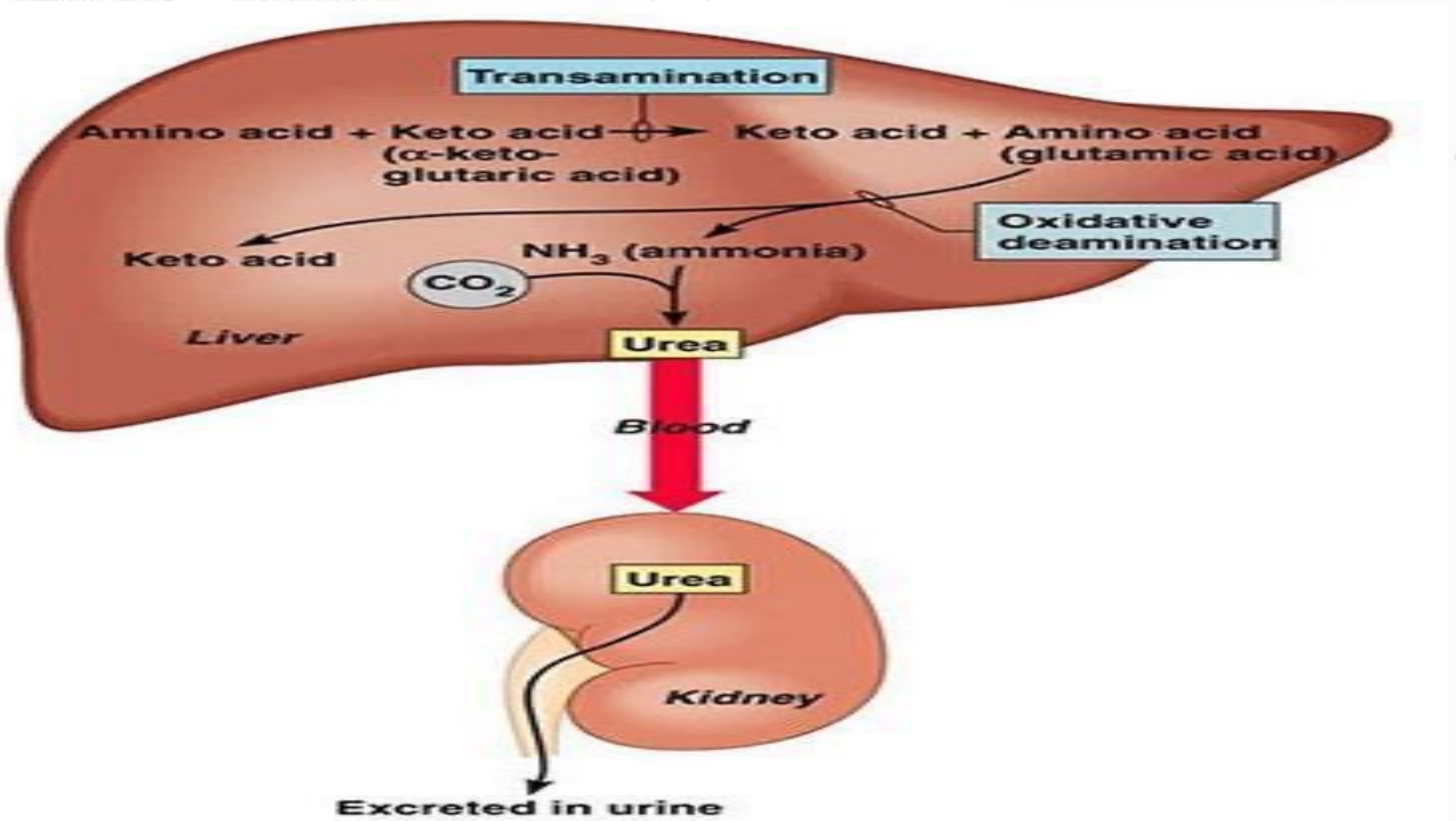


Figure 2: Protein catabolism

Role of liver in Carbohydrate metabolism

- Glycogen storage
- Inter-conversion of carbs
- Gluconeogenesis
- Formation of chemical compounds

Glycogen storage

- Storage of large amounts of glycogen
- Only liver (100 g) & muscle (500 g) can store significant amount of glycogen
- Most of glucose absorbed from meal is stored as glycogen in liver
- When glycogen storage is exceeded, glucose is stored as fat in liver or adipose tissue

Glucose buffer action

- Glycogen storage function allows liver to perform its glucose buffer action
- Remove excess glucose from blood & thus maintain normal blood glucose concentration
- Returns it when blood levels fall
- Importance of liver's buffer action:
  - In a person with poor liver function, the glucose level after carb rich meal may rise 2-3 times

Inter-conversion of carbs

- Conversion of galactose and fructose to glucose
- Final products of carbohydrate metabolism are glucose, fructose & galactose
- All cells utilize glucose to produce energy in form of ATP via glycolysis or citric acid cycle

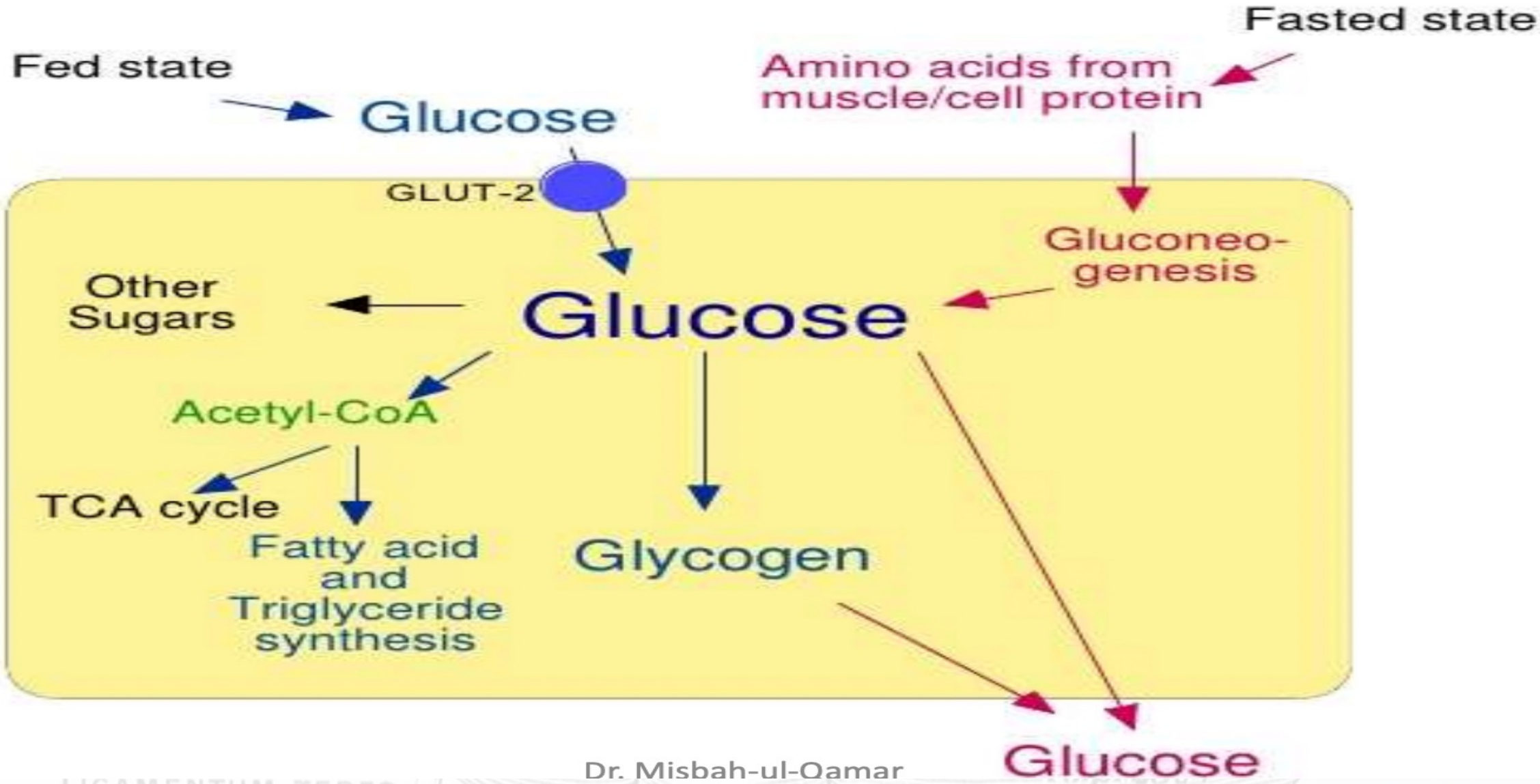
Gluconeogenesis

- Gluconeogenesis refers to **synthesis of new glucose from noncarbohydrate precursors**
- Provides glucose when dietary intake is insufficient or absent
- To maintain blood glucose concentration when glucose level falls below normal
- Glucocorticoids, catecholamines, glucagon & thyroid hormone greatly enhance gluconeogenesis by liver, but insulin inhibits it

Carbohydrate metabolism

- Formation of many chemical compounds from intermediate products of carbohydrate metabolism
- Liver & kidney are unique in their capacity to form lactate, pyruvate, amino acids & glycerol.
- Liver can also utilize the phosphoglycerate pathway which not only provides energy but also produces an important cofactor in synthesis of fatty acids.

Liver and Glucose Metabolism



Fat Metabolism

- Although most cells of the body metabolize fat, certain aspects of fat metabolism occur mainly in liver
  1. Oxidation of fatty acids to supply energy for body functions
  2. Synthesis of large quantities of cholesterol, phospholipids, and most lipoproteins
  3. Synthesis of fat from proteins and carbohydrates

How energy is extracted from fats

- Neutral fat is first split into glycerol & fatty acids
- Then fatty acids are split by beta oxidation into two-carbon acetyl radicals that form acetyl coenzyme A
- acetyl-CoA can enter the citric acid cycle & be oxidized to liberate energy

Liver's role in energy provision to other tissues

- Liver itself cannot use all all the acetyl-CoA that is formed
- It is transported throughout body in a highly soluble form (acetoacetic acid)
- In tissues it is reconverted to acetyl CoA & is oxidized for energy

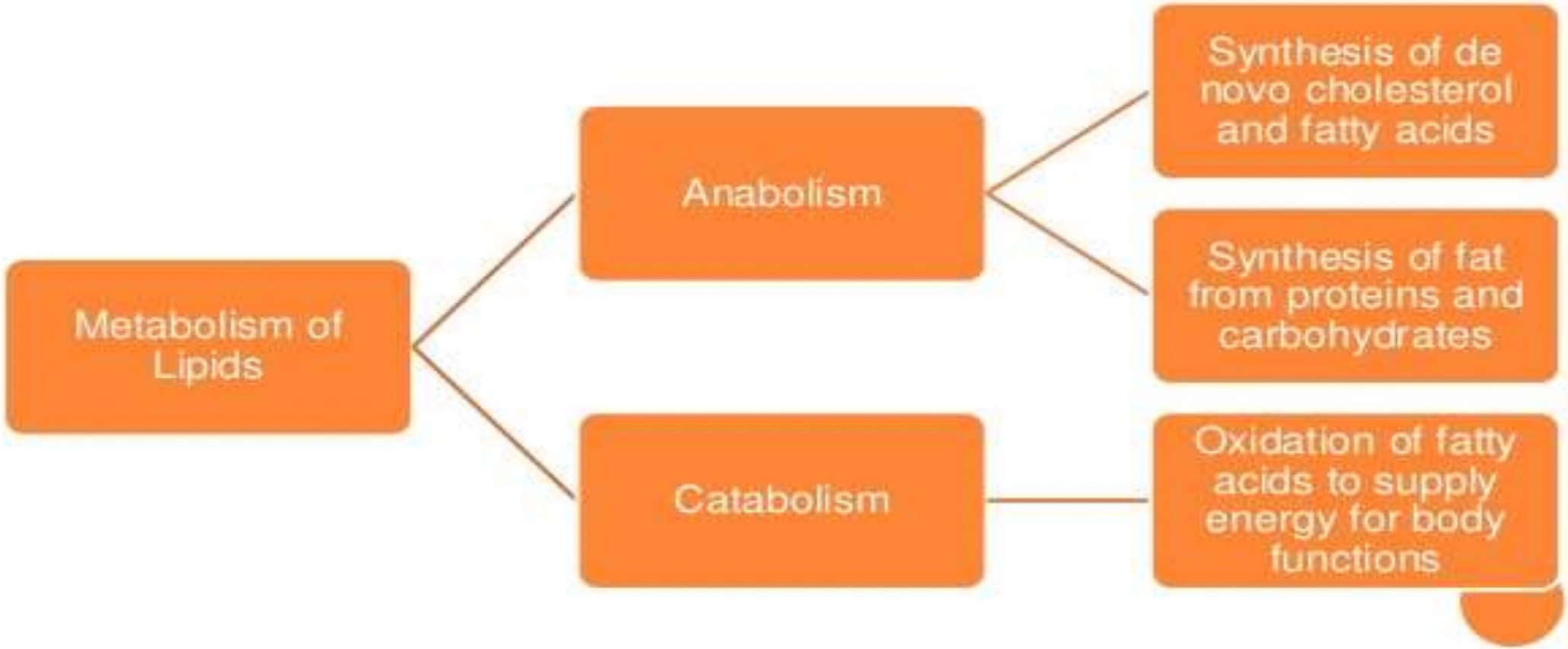
Anabolic role of liver in fat metabolism

- 80% of cholesterol synthesized in liver is converted into bile salts
- Remainder of cholesterol & phospholipids are transported in lipoproteins to tissue cells where they form:
  - Cell membranes
  - Intracellular structures
  - Multiple chemical substances for cellular function

Anabolic role of liver in fat metabolism

- When carb stores are saturated, liver converts excess ingested carb into fat
- Almost all the fat synthesis in body from carb & proteins occur in liver
- Fatty acids thus formed can be used immediately or are transported in lipoprotein to adipose tissue

Overview of role of Liver in lipid metabolism



Other Metabolic Functions of the Liver

- The liver is a storage site for vitamins.
- The liver stores iron as ferritin.
- The liver forms a large proportion of the blood substances used in coagulation.
  - fibrinogen, prothrombin, Factor VII,
  - Vit K dependent : prothrombin , Factors VII, IX, and X
- The liver removes or excretes drugs, hormones, and other substances.

Storage of vitamins

- Vitamins stored in greatest quantity in liver is Vitamin A
- Large quantities of Vitamin D & B12 also stored in liver
- It can store enough vitamin A and vitamin B12 for **four years**, and enough vitamin D for four months.
- Approximately 50-90% of the body's total stores of vitamin A are located within the liver.
- In the liver, 90% of the vitamin is rapidly transferred to and stored within the stellate cells

Storage of iron as ferritin

- Greatest proportion of body's extra iron is stored in hepatic cells
- Apoferritin protein in hepatocytes can combine reversibly with iron
- Liver is also important blood iron buffer as ferritin releases the iron when body fluids' iron levels are low

Formation of blood substances used in coagulation

- Makes most of the pro-coagulants
  - Fibrinogen, Prothrombin, Accelerator globulin, Factor VII
  - For these coagulants to work, liver requires vitamin K
- In its absence coagulation may be prevented by decreased concentration of these substances
- Liver also makes protein regulators of coagulation & fibrinolytic pathways.
  - Such regulators include Protein C, Plasminogen activator inhibitor, Antithrombin III.

Coagulopathy in liver disease

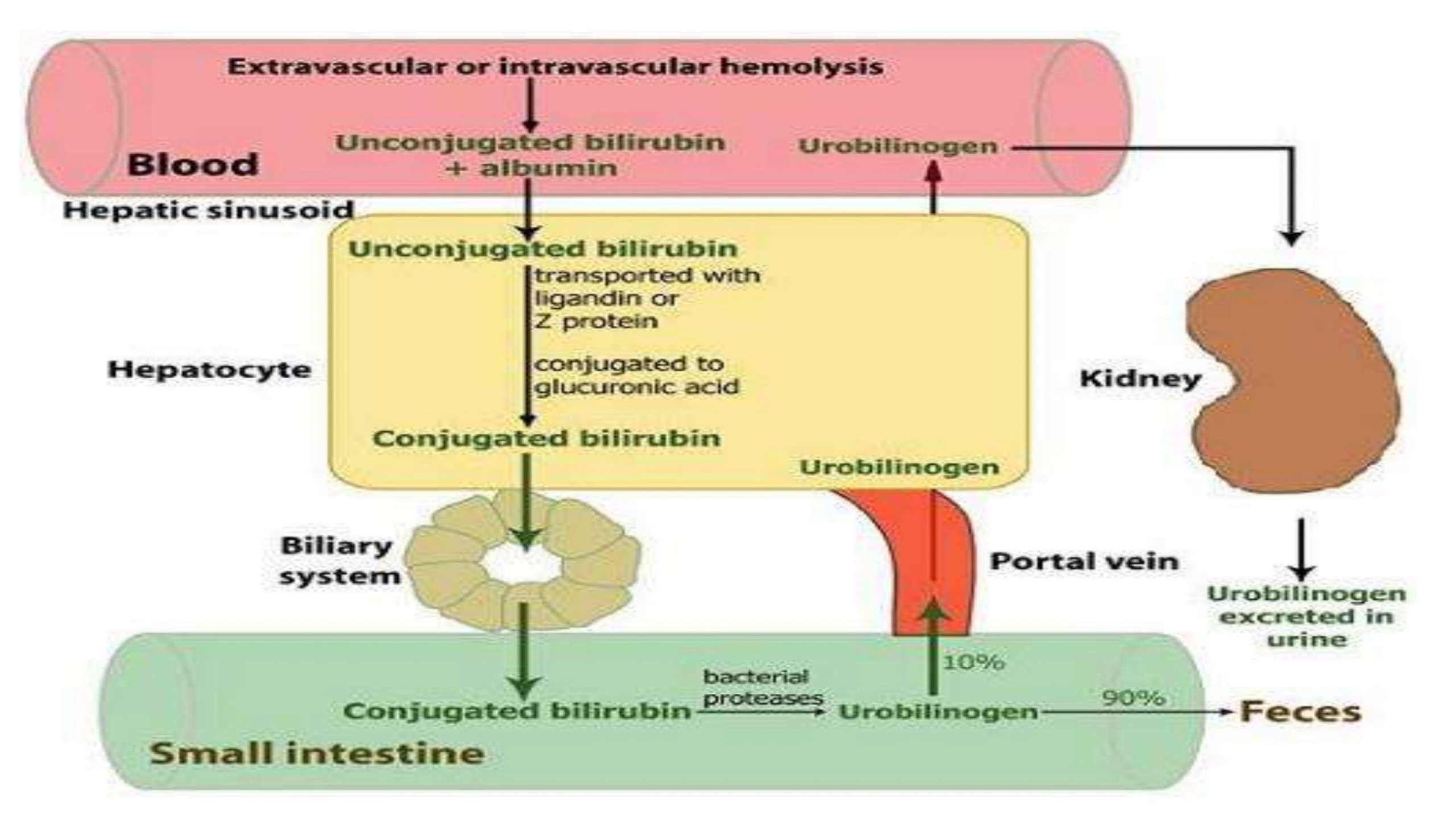
- Most common coagulation disturbances occurring in liver disease include thrombocytopenia & impaired humoral coagulation.
- A liver function test called the INR is used to measure blood clotting time.
  - An INR (**international normalized ratio**) is a type of calculation based on ProThrombin test results.
- A high INR usually means that liver is not working optimally.

Removal and excretion of drugs, hormones and minerals

- Liver provides an active chemical medium to detoxify drugs into bile such as
  - Sulfonamides
  - Penicillin
  - Ampicillin
  - Erythromycin
- Thyroxine & steroid hormones (estrogen, cortisol, aldosterone) are either altered or excreted by liver
- A major site of degradation for insulin, glucagon & ADH
- Excretion of body calcium also depend on liver through bile

Excretion of bilirubin

- It is a greenish yellow pigment which is an end product of Hb degradation
- Measurement of bilirubin provides valuable tool for diagnosing blood & liver diseases


Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

600-1000ml/day Bile

Composition Of Bile

- Water
- Inorganic salts : Na^+ , K^+ , Ca^{++} , Cl^- , HCO_3
- Bile salts: Sodium tauro-cholate , Sodium glycocholate
- Pigments: Bilirubin and Biliverdin
- Lipids: Cholesterol, Lecithin and traces of fatty acid

4 major functions of bile

- Fatty acid metabolism
- Excretion of waste products
- Kill off bad microbes
- Blood sugar metabolism
  - Bile acids stimulates insulin secretion, and therefore, are involved in carbohydrate and fat metabolism

Basic functions of bile

- Plays main role in fat digestion & absorption because of bile salts
- It serves as a mean for excretion of waste products (bilirubin & excess cholesterol) from blood
- Alkalinity of bile help in neutralizing acidity of chyme
- Excretion of bile pigments, heavy metals, toxins, cholesterol, and lecithin

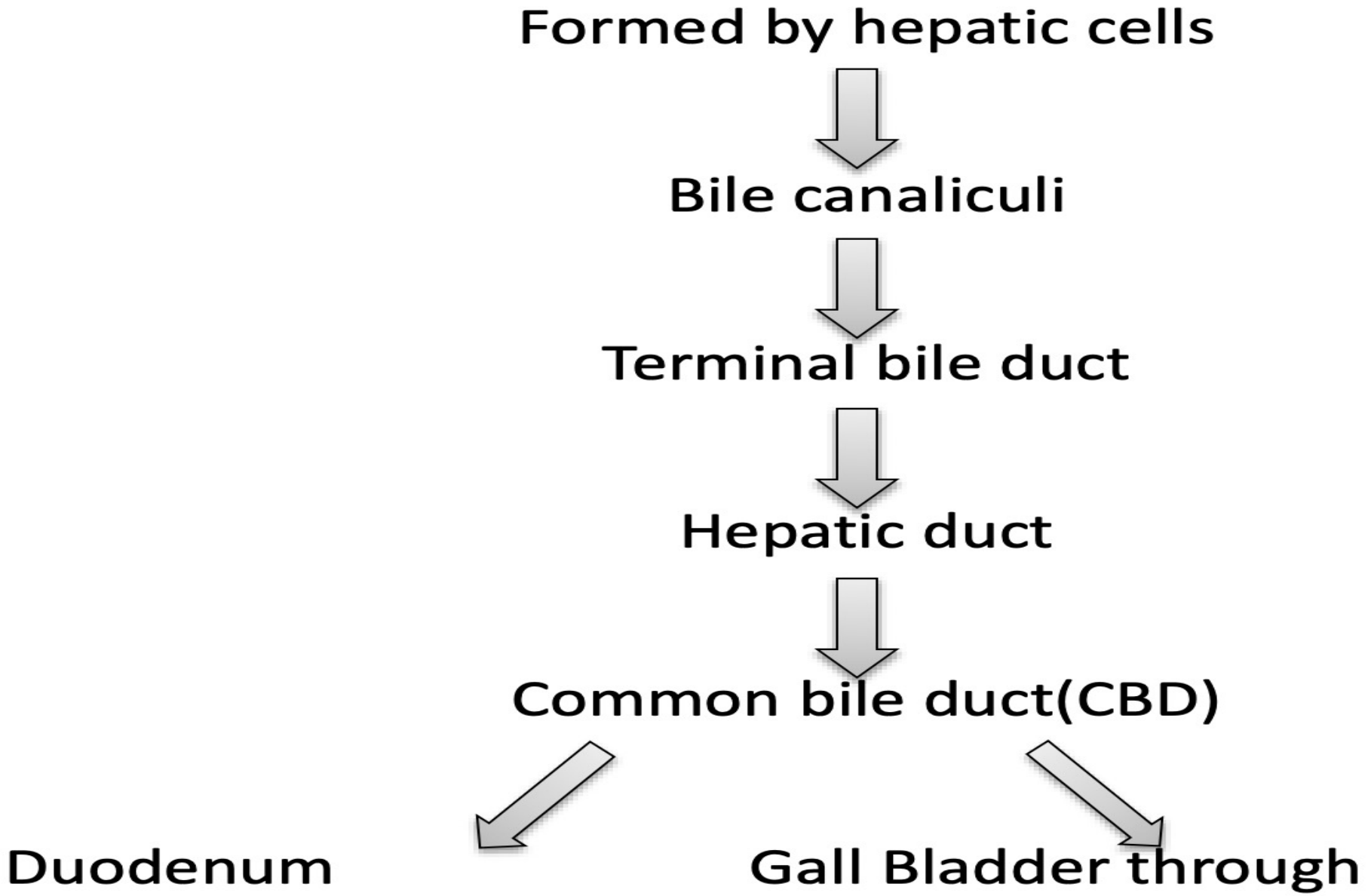
Functions of bile due to bile salts

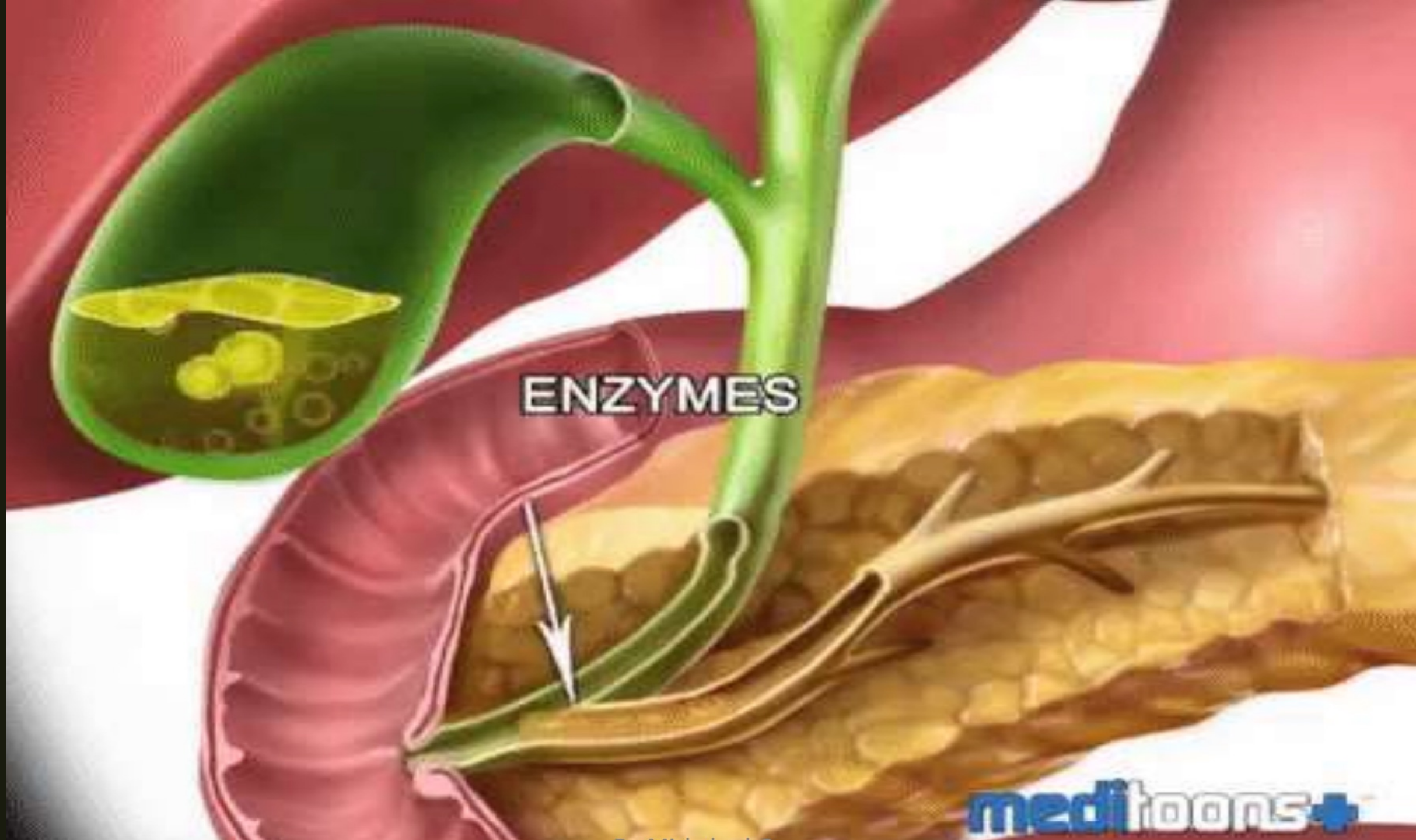
- Bile salts emulsify fat globules-help in digestion
- Absorption of fats
- Bile salts stimulate secretion of bile from liver choleretic action
- Cholagogue action-increase release of bile from gall bladder by stimulating the secretion of cholecystokinin
- Bile salts act as laxatives by causing CCK release (enhancing motility)

Overview of biliary transport

- Secretion of bile
  - Secreted by hepatocytes
  - Contains large quantities of bile acids, bile pigments, cholesterol, lecithin and fatty acids
  - Bile from the hepatocytes is secreted into biliary canaliculi

Formation And Conduction Of Bile




ENZYMES
meditoons

Stages of bile secretion

- Initial bile contains large amounts of bile acids, cholesterol & other organic constituents
- Additional secretion:
  - This additional secretion is watery solution of sodium & bicarbonate, stimulated by secretin
  - It can increase total quantity of bile as much as 100%

Role of secretin in controlling bile secretion

- Secretin may increase bile secretion, sometimes doubling it after a meal
- This increase consists of rich watery solution of sodium bicarbonate by epithelial cells of bile ductules
- This bicarbonate helps in neutralizing the HCl from stomach

Storage of bile

- Bile is secreted continually by hepatocyte liver cells
- It is stored in gallbladder until needed in duodenum
- Gallbladder can hold 1-2 ounces(30-60ml)
- Bile is concentrated 5-fold (up to 20-fold)
- Gall bladder is not a passive reservoir of bile
  - It absorbs, secretes & alters constituents of bile

How the bile is concentrated in the gall bladder

Concentration of bile in gallbladder

- Water, sodium, chloride & other electrolytes (HCO_3^-) are absorbed from gallbladder mucosa
- Absorption is caused by active transport of sodium through epithelium
- This transport is followed by secondary absorption of chloride, water & others
- Bile is concentrated which contains bile salts, cholesterol, lecithin & bilirubin

Composition of the Bile

	Liver Bile	Gallbladder Bile
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145.04 mEq/L	130 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^{++}	5 mEq/L	23 mEq/L
Cl^-	100 mEq/L	25 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L

Liver secretion of cholesterol

- Bile salts are formed in hepatic cells from cholesterol in blood plasma
- In the process of secreting bile salts
  - 1-2 grams of cholesterol are removed from blood plasma
  - It is secreted into the bile each day
- Amount of cholesterol in bile is determined by quantity of fat that the person eats

Formation of Gallstones

- Cholesterol is insoluble in pure water
- Bile salts & lecithin in bile combine with cholesterol & form a colloidal solution in gallbladder
- Cholesterol gallstones develop when bile contains too much cholesterol and not enough bile salts.
- Besides a high concentration of cholesterol, two other factors are important in causing gallstones.

Formation of Gallstones

- The first is how often and how well the gallbladder contracts; incomplete and infrequent emptying of the gallbladder may cause the bile to become overconcentrated and contribute to gallstone formation.
- The second factor is the presence of proteins in the liver and bile that either promote or inhibit cholesterol crystallization into gallstones.
- In addition, increased levels of estrogen, or the use of estrogen-containing birth control pills, may increase cholesterol levels in bile and also decrease gallbladder motility, resulting in gallstone formation

Functions of Gallbladder

- Storage of bile
- Mucosal absorption
- Concentration of bile constituents
- Maintenance of pressure in biliary system
- Secretion of mucin
- Alteration of bile pH

Functions of Gallbladder

- Storage of bile because bile is continuously formed & released by hepatocytes but not continuously utilized
  - Released from gallbladder intermittently when required
- Mucosal absorption absorbs H_2O, Na+, Cl- and other electrolytes from bile
- Bile concentration - Concentrates bile salts, cholesterol, lecithin and bilirubin in bile

Functions of Gallbladder

- Maintenance of pressure in biliary system
  - Due to the concentrating capacity, gallbladder maintains pressure in biliary system
  - This pressure is essential for release of bile into intestine
- Secretion of mucin
  - Mucin is added to bile when bile is released into intestine
  - Mucin acts as lubricant for movement of chyme in intestine
- Alteration of bile pH
  - pH of bile is decreased from 8-8.6 to 7-7.6
  - It becomes less alkaline when it is stored in gallbladder

Bile salts

- Liver cells synthesize about 6 gm of bile salts daily
- Precursor of bile salts: cholesterol
  - Sources of cholesterol is from diet and is synthesized in liver cells during course of fat metabolism
- Functions of Bile Salts
  - Emulsification of fats
  - Micelles formation

Emulsification of fats

- Bile salts and agitation by GI tract breaks fat globules to smaller size
- This emulsification is also called detergent function of bile salts
  - Detergent action decreases the surface tension of particles
  - It allows agitation in intestinal tract to break fat globules into minute sizes

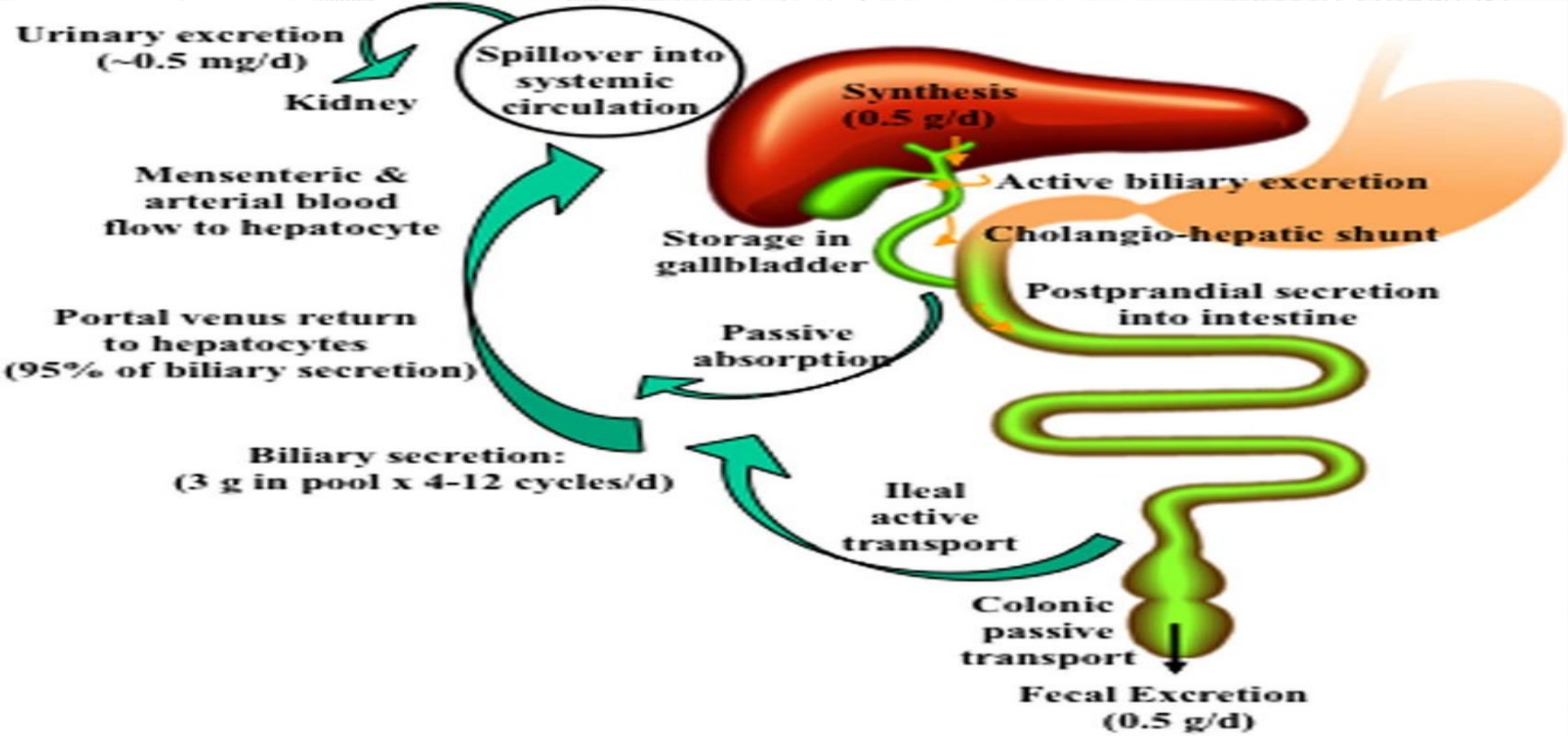
Micelles formation

- Micelles are small physical complexes of lipid molecules that arrange themselves in a spherical form in aqueous solutions.
- Micelles help the body absorb lipid and fat-soluble vitamins.
- They help the small intestine to absorb essential lipids and vitamins from the liver and gall bladder.
- They also carry complex lipids such as lecithin and lipid soluble vitamins (A, D, E and K) to the small intestine.

Micelle formation

- It is even more important function of bile salts than emulsification.
- The micelles are semi-soluble in chyme due to electrical charges of bile salts.
- This is how bile salts carry micelles to intestinal mucosa for absorption.
- Without bile salts, 40% of ingested fats are lost in feces.

Recycling of bile salts occurs in the enterohepatic circulation



- Bile salts are synthesized and conjugated in the liver
- Bile salts are secreted into bile stored temporarily in the gallbladder
- Bile salts are passed from the gallbladder into the duodenum
- They are then absorbed throughout the small intestine, especially in the ileum; and returned to the liver via the portal vein.
- The bile salts will make this circuit 17 times before being excreted in the feces.

ENTEROHEPATIC CIRCULATION

94% of bile salts are absorbed from gut into portal blood

↓

Passed to liver, absorbed by hepatocytes through sinusoids

↓

Again excreted into bile

↓

Again reabsorbed

Reabsorption Of Bile Salts From Gut

- On average bile salts make an entire circuit 17 times before being excreted in feces
- Sites for reabsorption:
  - The bile salts which are reabsorbed from gut, one half are absorbed by diffusion through mucosa in early portion of small intestine
  - Remainder is absorbed by active transport process through mucosa of distal ileum

Importance of enterohepatic circulation

- Quantity of bile secreted each day is highly dependent on availability of bile salts
- Greater the quantity of bile salts in enterohepatic circulation ⟶ greater the rate of bile secretion

Amount of bile salts

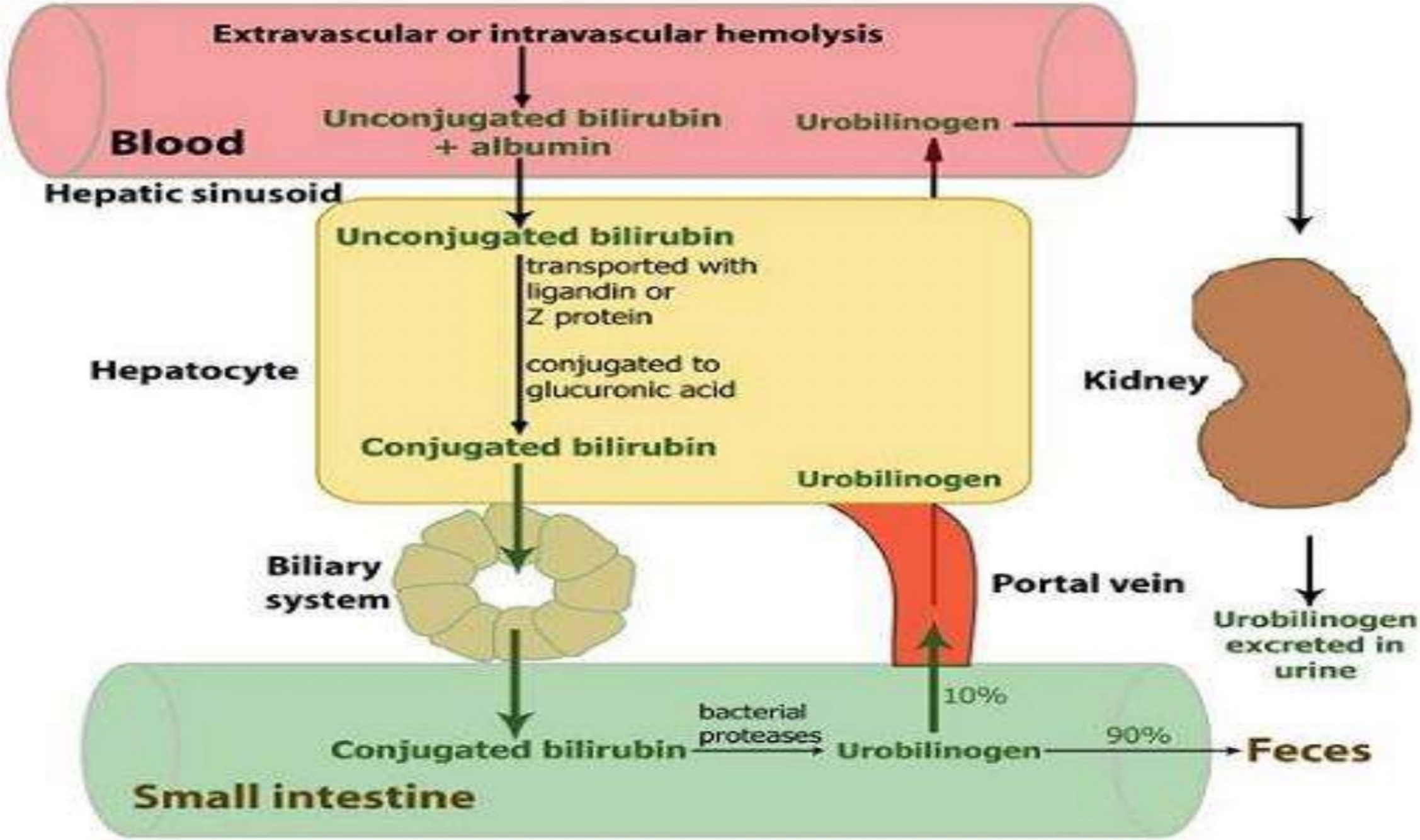
- Total amount of bile salts in circulation is 2.5 grams
- 1.1g/dl bile salts secretion from liver

Bilirubin

- Many waste substances are excreted in the bile and eliminated in the feces
- One of these is the greenish yellow pigment Bilirubin
- Bilirubin
  - Major end product of hemoglobin degradation
  - Helps in diagnosing hemolytic blood diseases and various types of liver diseases

Origin & fate of bilirubin

- RBCs rupture after 120 days
- Released hemoglobin is phagocytized by tissue macrophages
- Split into globin and heme
- Heme ring is opened to give
  - Free iron (Stored as ferritin)
  - Protoporphyrin IX (Converted to bilirubin)


Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

Jaundice

- Excess Bilirubin in the extracellular fluid
- Large quantities of bilirubin in the extracellular fluids
- Normal plasma concentration = 0.5 mg/dl
- Detectable clinically when plasma bilirubin exceeds 1.5mg/dl
- Can rise to = 40 mg/dl
- The clinical presentation of jaundice with peripheral yellowing of the eye sclera, also called scleral icterus, is best appreciated when serum bilirubin levels exceed 3 mg/dl.