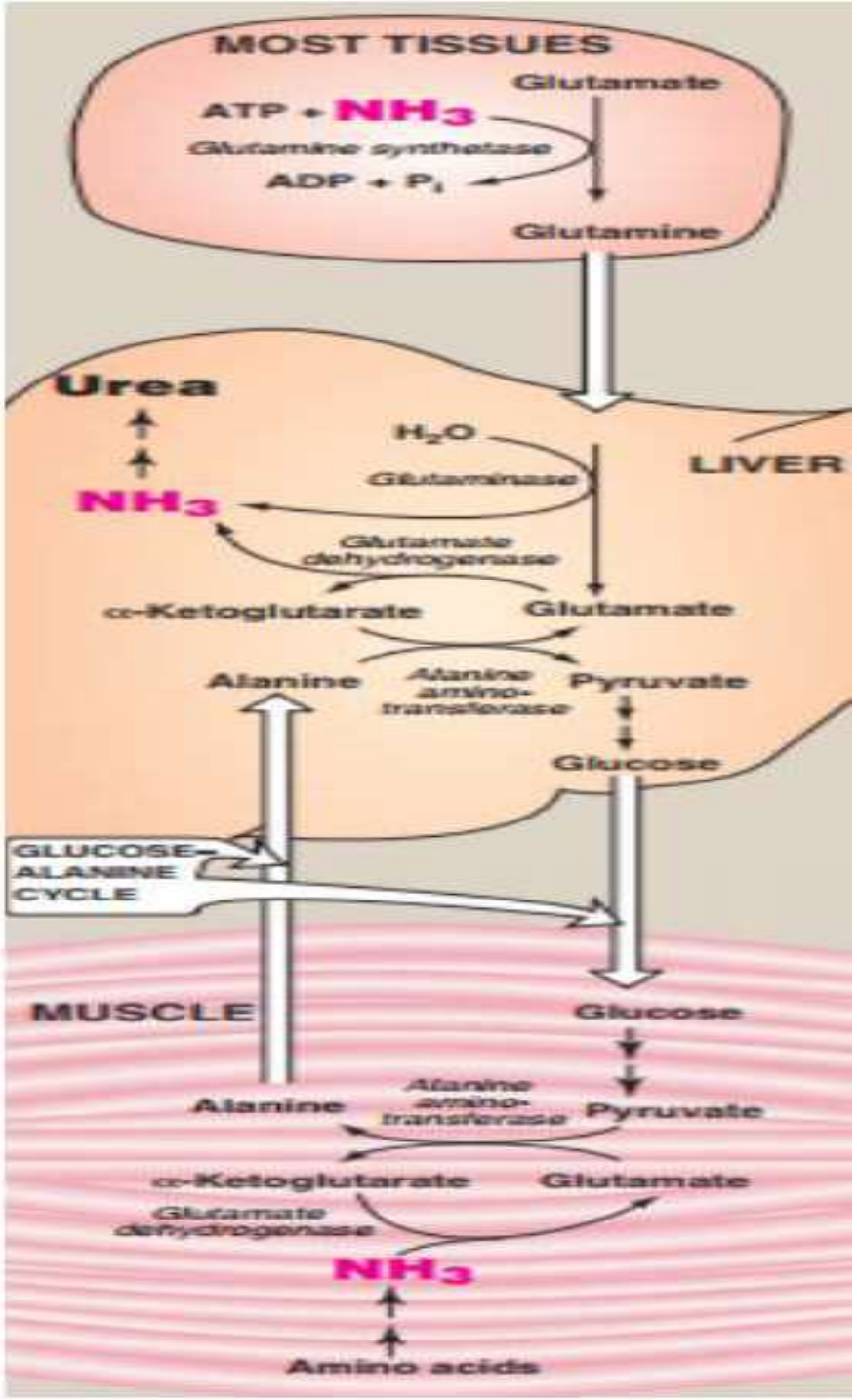
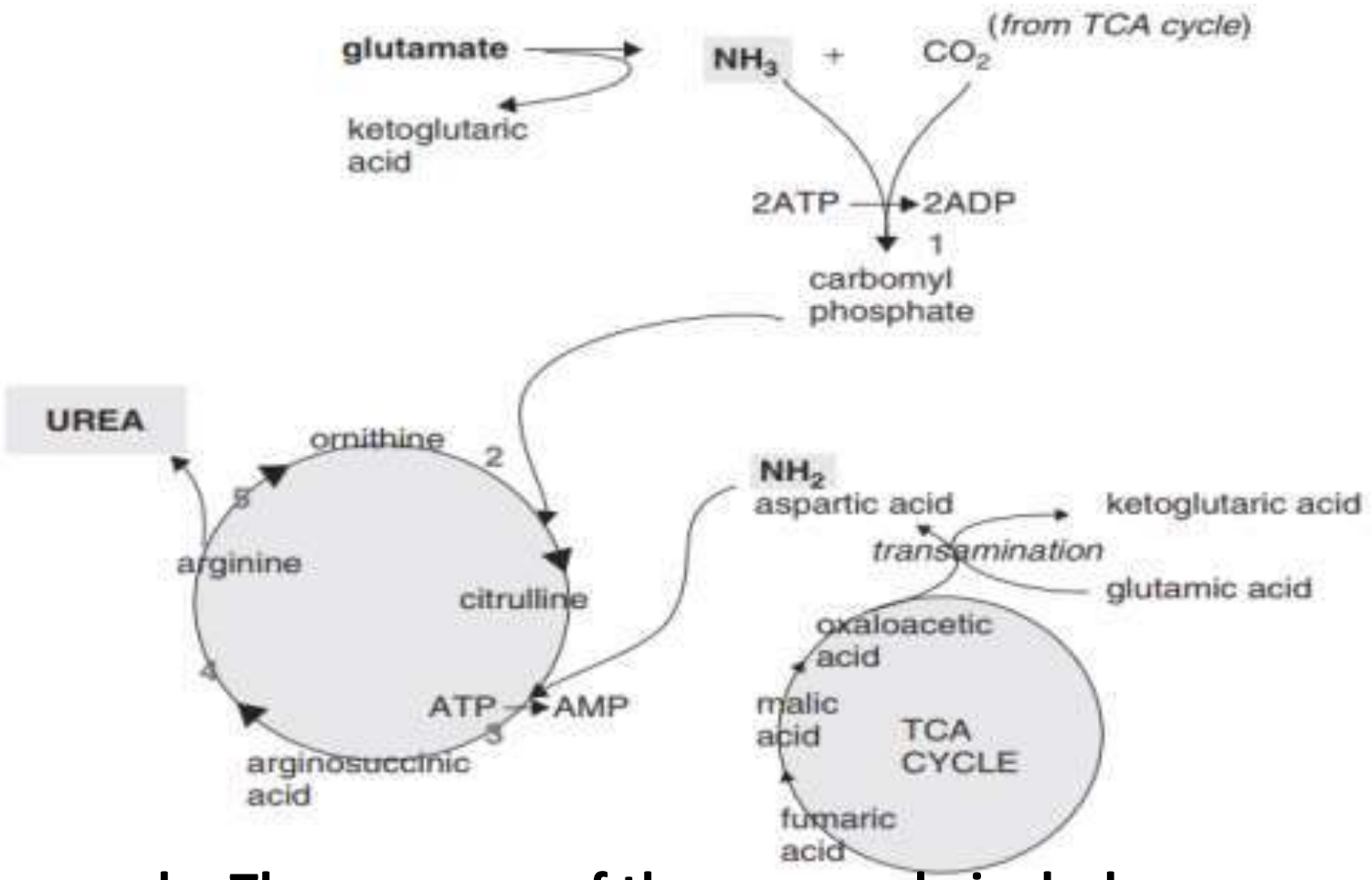
محاضرات التقنية الوسطى
محاضرات 9,10,11
The Liver - 3

The urea cycle:

The urea cycle is responsible for the excretion of some 80% of the body's excreted nitrogen in the form of urea; this is generated in the liver. Regulation of the urea cycle: The urea cycle operates only to eliminate excess nitrogen. On high- protein diets the carbon skeletons of the amino acids (keto acids) are oxidised for energy or stored as fat and glycogen, but the amino nitrogen must be excreted. To facilitate this process, urea-cycle enzymes are closely controlled at the gene level. With long-term changes in the quantity of dietary protein, changes of 20-fold or greater in the concentration of cycle enzymes are observed. Under conditions of starvation, enzyme levels rise as proteins are degraded and amino acid carbon skeletons are used to provide energy, thus increasing the quantity of nitrogen that must be excreted.


MOST TISSUES
Glutamate
ATP + NH3
Glutamine synthetase
ADP + Pi
Glutamine
Urea
H2O
LIVER
Glutaminase
NH3
Glutamate dehydrogenase
α-Ketoglutarate
Glutamate
Alanine
Alanine amino-transferase
Pyruvate
Glucose
GLUCOSE-ALANINE CYCLE
MUSCLE
Glucose
Alanine
Alanine amino-transferase
Pyruvate
α-Ketoglutarate
Glutamate
Glutamate dehydrogenase
NH3
Amino acids



Urea cycle: The enzymes of the urea cycle include,

1: carbamoyl phosphate synthetase-I,

2: ornithine transcarbamoylase,

3: argininosuccinate synthetase,

4: argininosuccinase,

5: arginase.

Alcohol metabolism and cirrhosis

 There are three enzyme systems involved in the metabolism of alcohol:

- ADH system (alcohol dehydrogenase)
- Microsomal cytochrome P450 isoenzyme CYP2E1
- Peroxisome catalase system.

ADH system : Ethanol, CH3–CH2–OH, is a low-molecular-weight hydrocarbon that is rapidly absorbed across both the gastric mucosa and the small intestines, reaching a blood peak concentration 20–60 minutes after ingestion. Ethanol is a toxin; too high a dose triggers a primary defense mechanism, namely vomiting. Women absorb and metabolise alcohol differently from men; their lower body water content and a lower activity of alcohol dehydrogenase (ADH) in the stomach result in a more rapid and significant absorption . **Methanol** is oxidised **to formaldehyde** in the liver by ADH, which can lead to blindness or death. An effective treatment to prevent formaldehyde toxicity after methanol ingestion is to administer ethanol. ADH has a higher affinity for ethanol, preventing methanol from binding and acting as a substrate; any remaining methanol will thus have time to be excreted through the kidneys. Remaining formaldehyde will be converted to formic acid and be excreted.

Microsomal cytochrome P450 system

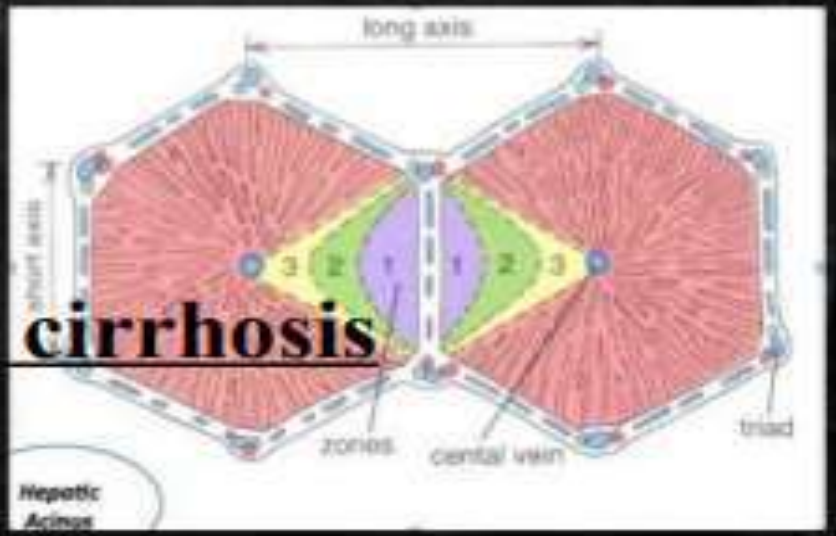
The microsomal cytochrome P450 system consists of a superfamily of hemoproteins that catalyse the oxidative metabolism of a wide variety of exogenous chemicals, including drugs, carcinogens, toxins and endogenous compounds such as steroids, fatty acids and prostaglandins. The principal microsomal enzyme involved in alcohol metabolism is the isoenzyme CYP2E1. This isoenzyme is responsible for about 10–20% ethanol metabolism in a moderate drinker, but represents a major adaptive response to chronic alcohol consumption because of the increased expression of CYP2E1.

Peroxisome catalase system

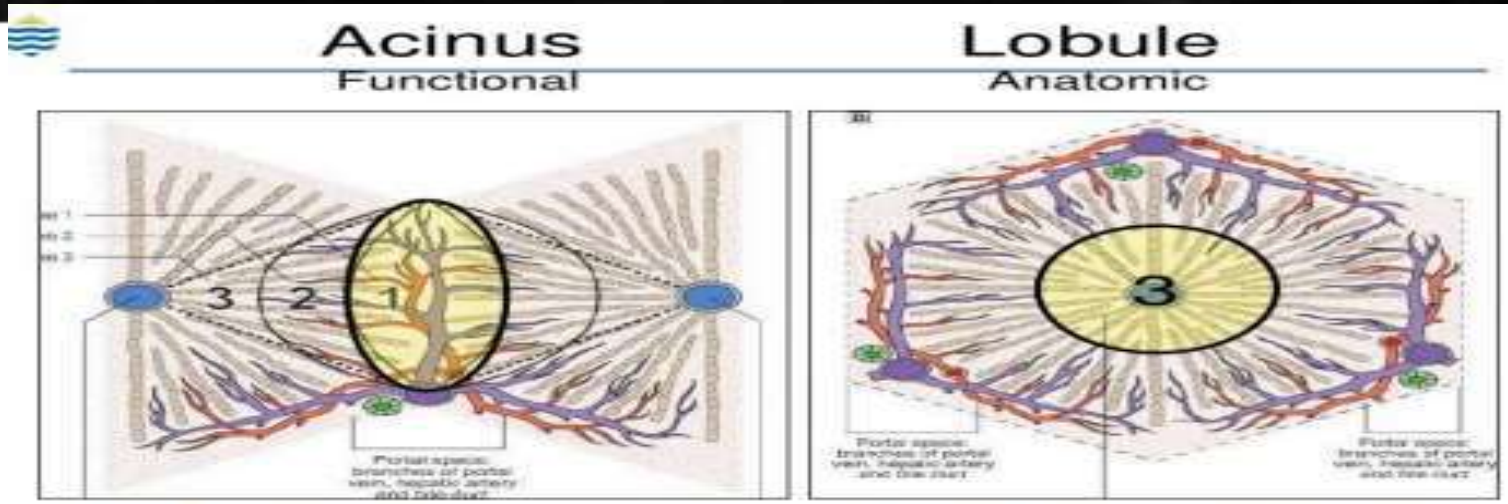
The peroxisome catalase system catalysis the hydrogen peroxide (H_2O_2)-dependent oxidation of ethanol to acetaldehyde and water. Normally it contributes little to the oxidation of alcohol because of the limited availability of hydrogen peroxide. However, activation of peroxisomal catalase, by the increased generation of hydrogen peroxide via peroxisomal β-oxidation, leads to an increased metabolism of alcohol. This state may contribute to an alcohol-related inflammation and necrosis in alcoholic liver disease.

Liver Acinus

- Functional Microvascular
- Three Zones
  - Z I -> Periportal -> High Po2
  - Z II -> Midzone
  - Z III -> Pericentral -> Low Po2
- Zone I – Highest Mitochondria
  - Synthetic, glycogen
- Zone III – High SER, Cyt P450
  - Xenobiotics



Some of liver **cirrhosis**



Zone 1 – Toxin damage.

Zone 3 – Ischemic damage

Alcoholic liver disease	Develops in 15% of individuals who drink heavily for more than a decade. Patients may also have concurrent alcoholic hepatitis with fever, hepatomegaly, jaundice and anorexia. AST and ALT are both elevated but less than 300 IU/l, with a AST : ALT ratio >2.0, a value rarely seen in other liver diseases.
Chronic hepatitis C	Viral infection causes inflammation and low-grade damage that can lead to cirrhosis. Can be diagnosed with serologic assays for hepatitis C antibody or viral RNA.
Chronic hepatitis B	Most common worldwide, but less common in the Western world. Inflammation and low-grade damage can lead to cirrhosis.
Non-alcohol steatohepatitis	Fat build-up in the liver eventually causes scar tissue; associated with diabetes, protein malnutrition, obesity and coronary artery disease. Treatment with corticosteroid medications. Biopsy is needed for full diagnosis.
Primary biliary cirrhosis	May be asymptomatic. Prominent rise in alkaline phosphatase, cholesterol and bilirubin. More common in women. Diagnosis through detection of antimitochondrial antibodies, with biopsy.
Primary sclerosing cholangitis	A progressive cholestatic disorder. Strong association with inflammatory bowel disease.
Autoimmune hepatitis	Immunologic damage to the liver causing inflammation, scarring and eventually cirrhosis. Elevations in serum globulins, especially gamma globulins.
Hereditary haemochromatosis	Usually with family history of cirrhosis, skin hyperpigmentation, diabetes mellitus, pseudo-gout and/or cardiomyopathy, all due to iron overload.
Wilson's disease	Autosommal recessive, low serum ceruloplasmin and increased hepatic copper content.

LIVER FUNCTION TESTS

Liver function tests: They are tests done to assess the functional capacity of liver (Table 1,3).

Functions of liver:

1. Metabolism: Carbohydrates, lipids and proteins
2. Excretion: Bilirubin, bile acids and bile salts
3. Synthesis: Albumin, α- and β-globulins, clotting factors, cholesterol, lipoprotein
4. Storage: Glycogen, vitamins (A, D, B12), etc.
5. Detoxification and drug metabolism.

Liver function tests are used to:

1. Detect and diagnose liver disease
2. Evaluate the severity of liver disease
3. Monitor response to therapy
4. Assess prognosis of liver disease

Table 1:(liver function tests).

Class	Tests
Tests based on **excretory** function	Estimation of serum/urine bilirubin, bromsulfthalein
Tests based on **serum enzymes (indicator of liver damage/cholestasis)**	Estimation of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT)
Tests based on **synthetic** functions	Total proteins, serum albumin, globulin, albumin globulin ratio, prothrombin time
Tests based on **detoxification**	Hippuric acid test, blood ammonia

Table 2:(important liver function tests).

Tests	Normal range	Methods	Clinical utility
Total bilirubin	0.2–0.8 mg/dL	van den Bergh reaction	Helps in diagnosis of jaundice
Direct bilirubin	0.1–0.2 mg/dL	van den Bergh reaction	↑ in hepatic and obstructive jaundice
Indirect bilirubin	0.2–0.6 mg/dL	Total bilirubin – direct bilirubin	↑ in hemolytic jaundice
ALT	5–40 U/L	Enzymatic method	↑ in liver damage (e.g. hepatitis)
AST	5–40 U/L	Enzymatic method	↑ in liver damage (e.g. hepatitis)
ALP	40–140 U/L	Enzymatic method	↑ in obstructive jaundice
Total protein	6–8 g/dL	Biuret	↓ in cirrhosis of liver
Albumin	3.5–5 g/dL	Biuret	↓ in cirrhosis of liver
Globulin	2–3.5 mg/dL	Total protein – albumin	↑ in multiple myeloma, ↓ in HIV infection

HIV, human immunodeficiency virus; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; ↑ = increased; ↓ = decreased.

Table 3:(other tests with uses).

Tests	Normal range	Clinical utility
γ-glutamyl transferase (GGT)	10–50 U/L	↑ in alcoholic hepatitis and obstructive jaundice
Prothrombin time	< 14 second	↑ in hepatocellular disease
Plasma ammonia	25–94 µg/dL	↑ in severe hepatocellular disease
Alfa-fetoprotein (AFP)	< 15 ng/mL	↑ in germ cell tumor, ↑ in maternal serum in neural tube defect in fetus

↑ = increased; ↓ = decreased

2. The biochemical findings in blood, urine and feces in different types of jaundice. Definition: Jaundice is defined as yellowish discoloration of skin, nail beds and sclera. It is caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood. When bilirubin concentration is more than 1 mg/dL, the condition is called hyperbilirubinemia. At a concentration of more than 2 mg/dL, bilirubin diffuses into tissues, which then becomes yellow, leading to jaundice or icterus**. Classification**: Jaundice is classified into three major types: i. **Prehepatic (hemolytic):** Due to excessive hemolysis, bilirubin production exceeds the capacity of liver to conjugate it. ii. **Hepatic**: Impaired uptake, conjugation or excretion of bilirubin. iii. **Postherpetic (obstructive):** Caused by an obstruction in the biliary tract (Table 4).

Table 4: (Classification and findings in jaundice)

Type of jaundice	Causes	Serum bilirubin	Urine and feces	Serum ALT and AST	Serum ALP
Prehepatic [MN: MARS]	**M**alaria **A**utoimmune hemolytic anemia **R**h incompatibility **S**ickle cell anemia	↑ unconjugated bilirubin	• ↑ urobilinogen • Bilirubin negative • ↑ stercobilinogen	Normal or slight ↑	Normal or slight ↑
Hepatic	Hepatitis	↑ conjugated and ↑ unconjugated bilirubin	• Bilirubin present (if microobstruction) • ↓ urobilinogen (if microobstruction)	Markedly elevated	Normal or slight ↑
Post-hepatic	Gallstones Pancreatic tumor	↑ conjugated bilirubin	• Urobilinogen absent	Normal or slight ↑	Markedly elevated
	Cholangiocarcinoma		• Bilirubin present • Clay-colored stool		

↑ = increased; ↓ = decreased

3. Congenital hyperbilirubinemia. Definition: A group of hereditary disorders of bilirubin metabolism due to defect in uptake, conjugation or secretion of bilirubin (Table 5)

Table5: (Congenital hyperbilirubinemia)

Condition	Defects	Clinical features
Crigler-Najjar syndrome Type I	Severe deficiency of UDP-glucuronyl transferase	↑↑↑ serum unconjugated bilirubin Profound jaundice–does not respond to phenobarbital; often fatal
Crigler-Najjar syndrome Type II	Mild deficiency of UDP-glucuronyl transferase	↑ serum unconjugated bilirubin; mild jaundice; responsive to phenobarbital therapy
Gilbert syndrome	Reduced activity of glucuronyl transferase	↑ serum unconjugated bilirubin; mild jaundice
Dubin-Johnson syndrome	Abnormality in secretion of conjugated bilirubin into biliary system	↑ serum conjugated bilirubin; moderate jaundice
Rotor syndrome	Cause not known	↑ serum conjugated bilirubin; mild jaundice

↑ = increased; ↑↑↑ = markedly increased

Question s time :-

1- Urea cycle is responsible for the elimination of:-

a. Nitrogen from RNA .

b. Nitrogen from DNA .

c. Nitrogen from amino acids directly .

d. Ammonia generated from glutamate .

e. Amid group from glutamine.

2- Treatment of Methanol poisoning is treated with drinking ethanol because Ethanol :-

a. Can solubilize methanol.

b. Is more soluble than methanol .

c. Decreases absorption of methanol .

d. Has high affinity for Alcohol dehydrogenase than methanol .

e. None of the above .

3- Alcoholic liver disease is mainly duo to oxidation of ethanol by :-

a. Alcohol dehydrogenase system .
b. Microsomal cytochrome p450 system .
c. Peroxizome catalase system .
d. NAD- dependant oxidoreductase.
e. FAD-dehydrogenase.

4- For the assessment of synthetic function of the liver , we measure :-

a. Total bilirubin .
b. Total protein .
c. Prothrombin time .
d. Total cholesterol .
e. Triacylglycerol .

5- One of the following test is not important for liver function :-

a. Direct bilirubin .
b. Total protein .
c. Fating blood sugar .
d. Albumin .
e. Alkaline phosphatase .

6- Marked elevation of both ALT and AST is most likely due to :-

a. Hemolysis .
b. Gallstone .
c. Hepatitis .
d. Grigler – Najjar syndrome .
e. Obstructive jaundice .

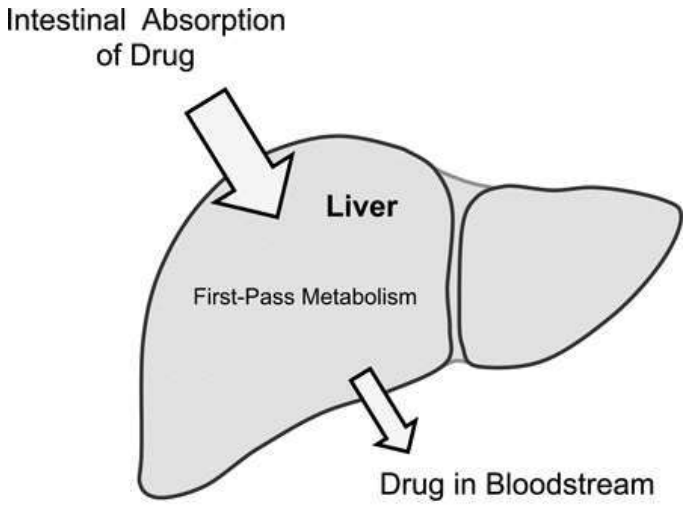
7- Chalky stoole (pale color of feces)is most likely caused by :-

a. Hemolytic anemia .
b. Obstructive jaundice .
c. Dubin-Jonson syndrome .
d. Hepatitis .
e. Autoimmunodisease

محاضرات التقنية الوسطى
محاضرات 9,10,11
The Liver - 2

Drug metabolism and detoxification

Most drugs, and particularly oral drugs, are modified or degraded in the liver. In the liver, drugs may undergo first-pass metabolism, a process in which they are modified, activated or inactivated, before they enter the systemic circulation; alternatively, they may be left unchanged. An oral drug that is absorbed and metabolised in the liver is said to show the ‘first-pass effect’. Medications that are metabolised by the liver must be used with caution in patients with hepatic disease; such patients may need lower doses of the drug.



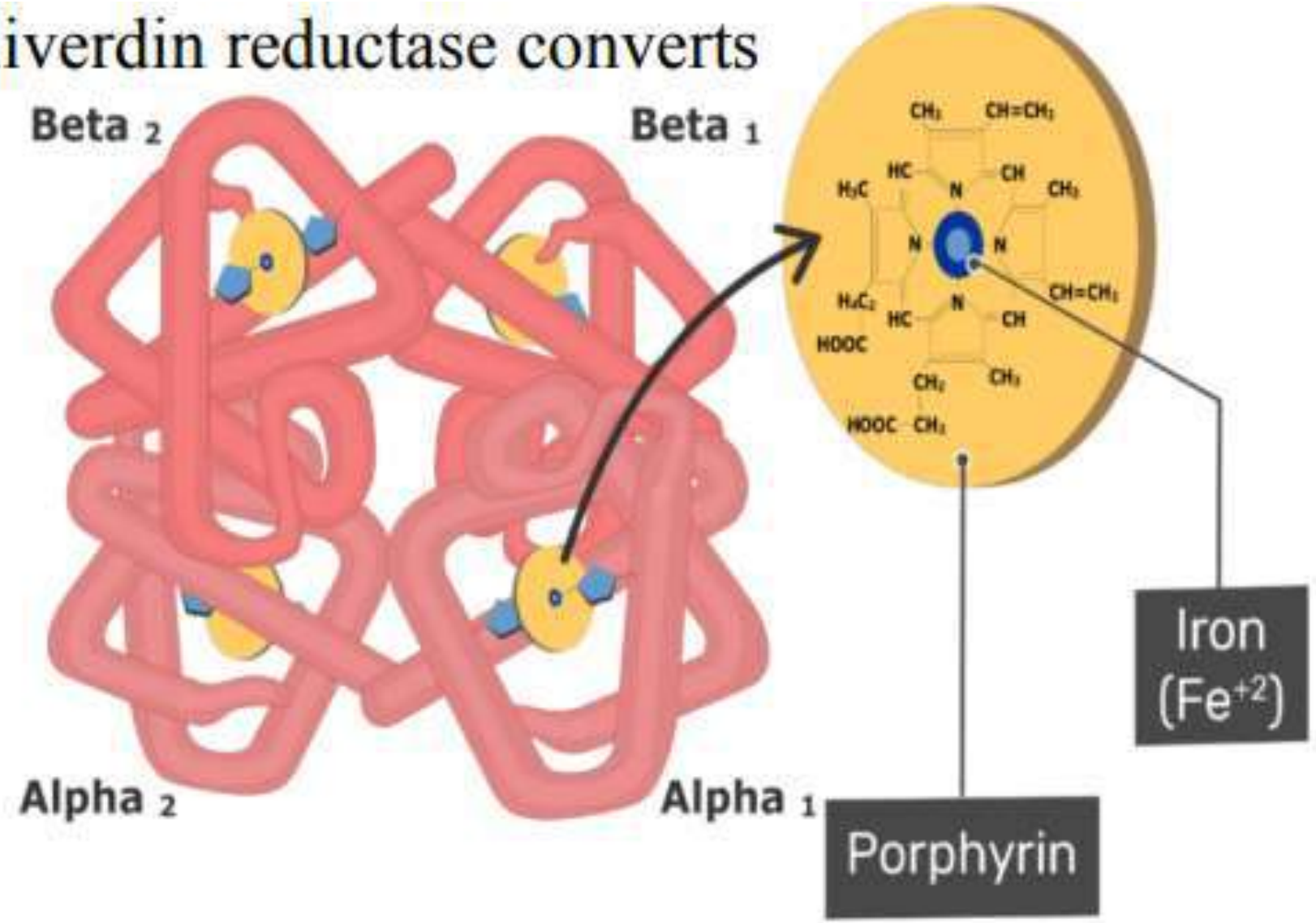
Phase I and phase II drug detoxification reactions

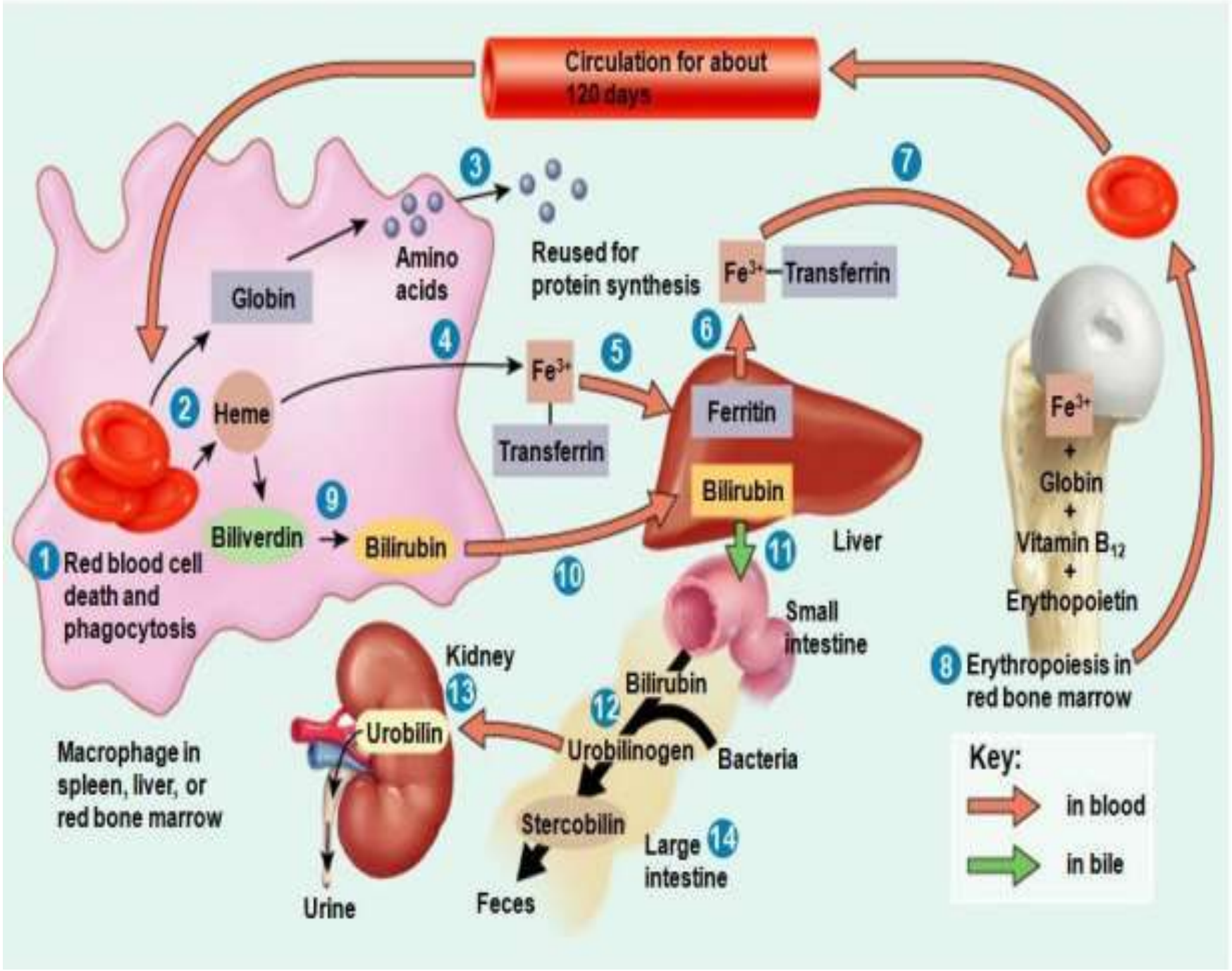
Phase I reactions	Phase II reactions
Oxidations	Glutathione S-transferases
Cytochrome P450 monooxygenase system	Mercapturic acid biosynthesis
Flavin-containing monooxygenase system	UDP-glucuronosyltransferases
Alcohol dehydrogenase and aldehyde dehydrogenase	N-acetyltransferases
Monoamine oxidase	Amino acid N-acyl transferases
Co-oxidation by peroxidases	Sulphotransferases
Reduction	
NADPH-cytochrome P450 reductase	
Reduced (ferrous) cytochrome P450	
Hydrolysis	
Esterases and amidases	
Epoxide hydrolase	

Haemoglobin degradation

Red blood cells, the largest repository of haem in the human body, have a life span of about 120 days, representing a turnover of about 6 g/day of haemoglobin. This presents two potential problems: first, the porphyrin haem ring is hydrophobic and must be solubilised to be excreted, and second, iron must be conserved for new haem synthesis. Normally, senescent red blood cells are engulfed (phagocytosed) by cells of the reticuloendothelial system; globin is converted into amino acids, which in turn are recycled or catabolised as required, while haem is oxidised by the haem oxygenase system. Oxidation (introduction of oxygen) splits the porphyrin ring to give the linear tetrapyrrole biliverdin, releasing ferric iron (Fe^{3+}) and carbon monoxide (CO). Released iron is recycled. In a reduction reaction, biliverdin reductase converts biliverdin to bilirubin. 'Native' bilirubin, as produced, is an unconjugated bilirubin; it is a hydrophobic molecule that must be transported to the liver in the plasma bound to albumin. At the sinusoidal surface of the liver, unconjugated bilirubin detaches from albumin and is transported through the hepatocyte membrane by facilitated diffusion. Within the hepatocyte, bilirubin is bound to two major intracellular proteins, cytosolic Y protein (ligandin or glutathione Stransferase B) and cytosolic Z protein (also known as fatty acid-binding protein). The binding of bilirubin to these proteins decreases the efflux of bilirubin back into the plasma, and therefore increases net bilirubin uptake.

biliverdin reductase converts

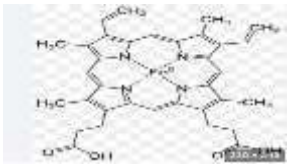



Circulation for about 120 days
1 Red blood cell death and phagocytosis
2 Heme
Globin
3 Amino acids
Reused for protein synthesis
4
Fe3+
Transferrin
5
6
Fe3+—Transferrin
Ferritin
Bilirubin
Liver
7
8 Erythropoiesis in red bone marrow
Fe3+ + Globin + Vitamin B12 + Erythopoietin
9 Biliverdin → Bilirubin
10
11
Small intestine
Bilirubin
12
Urobilinogen
Bacteria
Kidney
13
Urobilin
Urine
Stercobilin
Feces
Large intestine 14
Macrophage in spleen, liver, or red bone marrow
Key:
in blood
in bile

The Bilirubin

In adults some 250–400 mg of bilirubin is produced daily; 70–80% is derived from degradation of the haem moiety of haemoglobin, 20–25% is derived from the hepatic turnover of haem proteins, such as myoglobin, cytochromes and catalase. Bilirubin is a potentially toxic catabolic product of haem metabolism. It is poorly soluble in water at physiologic pH, and conversion to a water-soluble form is essential for elimination by the liver and kidney. Within the hepatocyte, the enzyme glucuronyl transferase UGT-1 covalently attaches one or two molecules of glucuronic acid to bilirubin, generating either bilirubin mono- or di-glucuronide. These glucuronic acid-attached species of bilirubin are termed "Conjugated Bilirubin" and are now water soluble. Conjugated Bilirubin cannot be transported past the GI mucosa and so travels down the GI Tract. However, the normal GI bacterial flora convert the vast majority of conjugated bilirubin to colorless "Urobilinogen" and a small amount to brown-colored "Urobilin". About 90% of urobilinogen is excreted along with the feces; however, about 10% is resorbed by the GI Mucosa and enters the blood stream where it is once again recaptured by hepatocytes and re-excreted in the bile. The majority of urobilin is also excreted in the feces, giving it the characteristic brown color after converted to stercobilin; however, a small minority is resorbed by the GI mucosa and is ultimately excreted by the kidneys, giving urine its yellowish hue (color).

Haemoglobin



Haem + globin → aa pool

(hydrophobic)

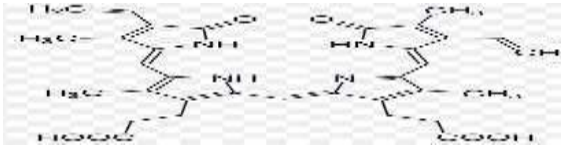
Oxygenase system

O_2

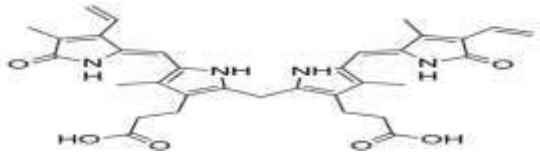
Tetrapyrrole ring + CO + Fe^{+3} → Store

Biliviridin (hydrophobic)

(Green)



Biliviridin reductase



Free Bilirubin (yellow)

(Uncojugated , hydrophobic)

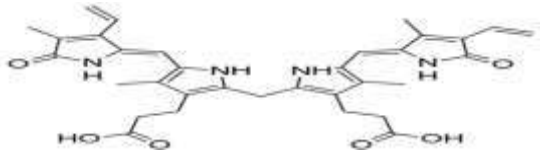
(Binds to albumin to become soluble)

Albumin

Bilirubin in hepatocytes

(conjugated with glucuronide)

Biliviridin reductase



Free Bilirubin (yellow)

(Uncojugated , hydrophobic)

(Binds to albumin to become soluble)

Albumin

Bilirubin in hepatocytes

(conjugated with glucuronide)

(binds with cytosolic Z or Y protein)

Decrease plasma level

In Bile

Urobilin ← Kidney — Urobilinogen (by intestinal bacteria) → Stercobilin

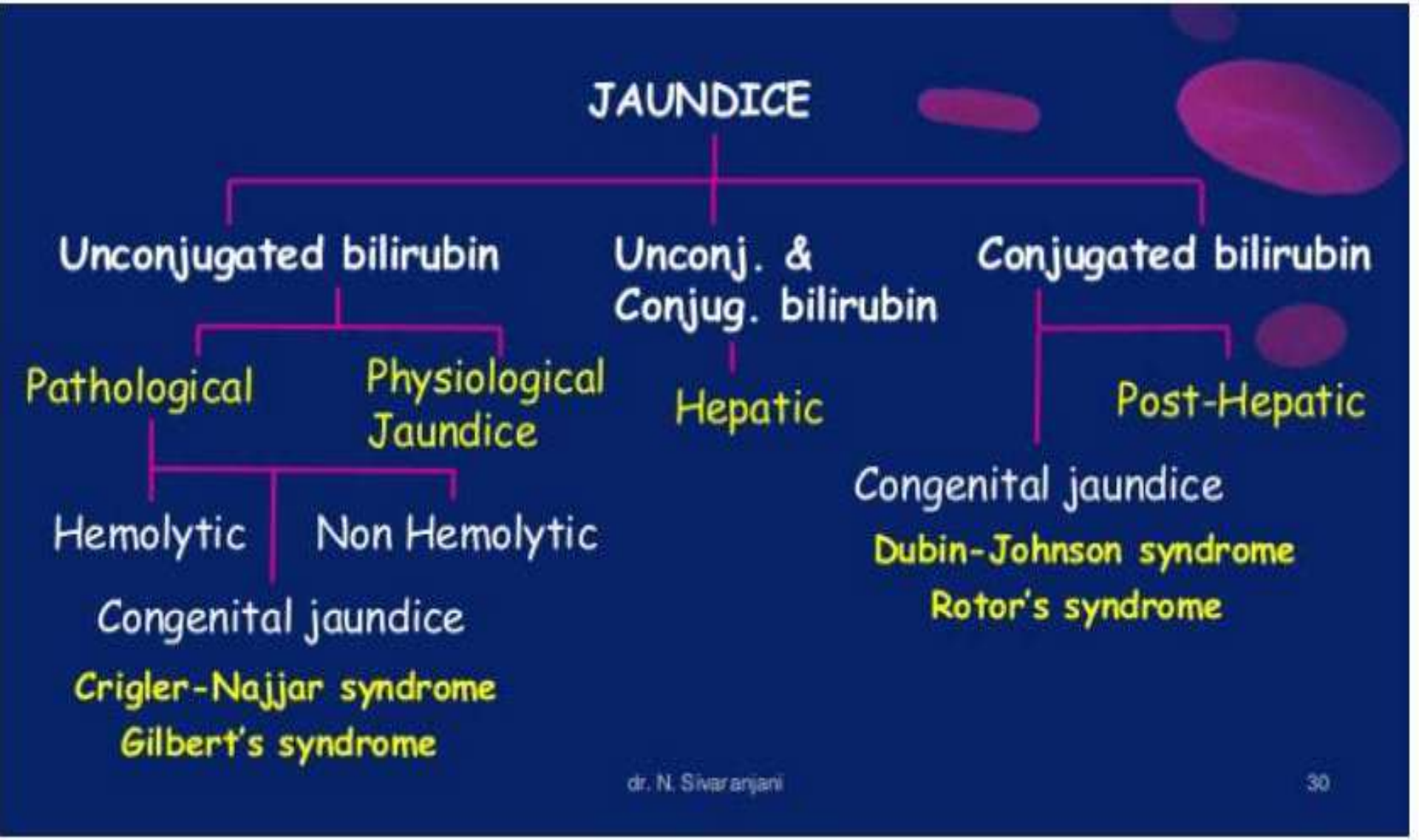
(Urine) (Feces)

Jaundice

It is a clinical term referring to yellowing of body tissues due to deposition of bilirubin. Because bilirubin has a high affinity for the sclera of the eye, the most sensitive indicator of Jaundice is yellowing of the sclera, termed scleral icterus, which occurs when plasma bilirubin levels are greater than 3.0mg/dl. At higher concentrations of bilirubin, the skin and tissue underneath the tongue will also gain a yellowish hue. Jaundice is classified, depending upon whether the bilirubin is 'free' or conjugated to glucuronic acid, into: • conjugated jaundice (direct) • unconjugated jaundice (indirect). Total bilirubin measures both direct and indirect; indirect bilirubin is calculated from the total minus the direct bilirubin. Bilirubin levels reflect the balance between production and excretion; there is no 'normal' level of bilirubin and levels may be affected by a number of factors. Table is describing a

Bilirubin type	Bilirubin level
Total bilirubin	0.3–1.0 mg/dl or 5.1–17.0 mmol/l
Direct bilirubin	0.1–0.3 mg/dl or 1.7–5.1 mmol/l
Indirect bilirubin (total bilirubin level minus direct bilirubin level)	0.2–0.8 mg/dl or 3.4–12.0 mmol/l

Bilirubin levels reflect the balance between production and excretion; there is no ‘normal’ level of bilirubin and levels may be affected by a number of factors . The following Table is describe a number of disorders associated with bilirubin metabolism


JAUNDICE
Unconjugated bilirubin
Unconj. & Conjug. bilirubin
Conjugated bilirubin
Pathological
Physiological Jaundice
Hepatic
Post-Hepatic
Hemolytic
Non Hemolytic
Congenital jaundice
Crigler-Najjar syndrome
Gilbert's syndrome
Congenital jaundice
Dubin-Johnson syndrome
Rotor's syndrome

Factors that can affect bilirubin levels in the blood

Mild rises in bilirubin may be caused by	Moderate rise in bilirubin may be caused by	Very high levels of bilirubin may be caused by
Haemolysis or increased breakdown of red blood cells.	Drugs (especially anti-psychotic and some sex hormones)	Neonatal hyperbilirubinaemia, where the newborn's liver is not able to properly conjugate the bilirubin
Gilbert's syndrome – a genetic disorder of bilirubin metabolism which can result in mild jaundice, found in about 5% of the population.	Hepatitis (levels may be moderate or high)	Unusually large bile duct obstruction, for example gallstone in common bile duct, tumour obstructing common bile duct. Choledocholithiasis (chronic or acute) is the presence of gallstones in the common bile duct
	Chemotherapy	Severe liver failure with cirrhosis
	Biliary stricture (benign or malignant)	Severe hepatitis. Crigler–Najjar syndrome Dubin–Johnson syndrome

protein metabolism; production of albumin

The liver orchestrates the metabolism of proteins and amino acids. Most blood proteins (except for antibodies) are synthesised and secreted by the liver. One of the most abundant serum proteins is albumin. Impaired liver function that results in decreased amounts of serum albumin may lead to oedema, swelling due to fluid accumulation in the tissues. Albumin is manufactured by the liver at a rate of 9–12 g/day, and catabolised at about the same rate; there is no storage or reserve, and it is not catabolised during starvation. It is highly soluble, with a strong overall negative charge. Its rate of production is controlled by changes in the colloid osmotic pressure and the osmolarity of the extravascular liver space. Synthesis is also increased by insulin, thyroxine and cortisol. It is both an intravascular protein and an extravascular (interstitial) protein.

Protein metabolism – nitrogen metabolism and the urea cycle:

The interconversion of amino acids, mainly through transamination reactions catalysed by aminotransferases, is essential to balancing the requirements for protein synthesis, while in protein catabolism the amino nitrogen must be removed in the form of ammonia (ammonium) and converted to urea for excretion by the kidneys. Most amino acids are glucogenic, meaning that their carbon skeletons (ketoacid) can be converted to glucose through gluconeogenesis. There are specific aminotransferases for all amino acids, except threonine and lysine, and they are particularly abundant in the liver. Alanine transaminase (ALT) and aspartate transaminase (AST) are used as clinical markers of tissue damage. ALT has an important function in the delivery of skeletal muscle carbon and nitrogen (in the form of alanine) to the liver. In skeletal muscle, pyruvate is transaminated to alanine, thus affording an additional route of nitrogen transport from muscle to liver. In the liver, ALT transfers the ammonia to α-ketoglutarate and regenerates pyruvate. The pyruvate can then be diverted into gluconeogenesis. This process is referred to as the glucose–alanine cycle. In peripheral tissues, two enzymes, namely glutamate dehydrogenase and glutamine synthetase, are important in the removal of reduced nitrogen, and particularly so in the brain, which is highly susceptible to free ammonia.

The glutamine synthase reaction is important in several respects. First, it produces glutamine, one of the 20 major amino acids. Second, glutamine is the major amino acid found in the circulatory system. Its role is to carry ammonia to and from various tissues, but principally from peripheral tissues to the kidney, where the amide nitrogen is hydrolyzed by the enzyme glutaminase (reaction below); this process regenerates glutamate and free ammonium ion, which is excreted in the urine. glutamine + H20 → glutamate + NH3 In this way, ammonia arising in peripheral tissue is carried in a nonionisable form, with none of the neurotoxic or alkalosis-generating properties of free ammonia. In the liver, glutamate dehydrogenase converts glutamate to α-ketoglutarate and ammonia (the reverse to the reaction occurring in the peripheral tissues), and the ammonia generated enters the urea cycle.

1) Reactions in the liver for detoxification involves the following EXCEPT :-

a. Oxidation .

b. Reduction .

c. Transamination .

d. Hydrolysis .

e. Non of the above .

2) The product of heam breakdown include the following EXCEPT :

a. Ferric ion .

b. CO .

c. Bilirubin .>

d. Albumin .

e. Biliviridine

3)The end product of heam metabolism found in feces is :-

a. Bilirubin .
b. Biliviridin .
c. Urobilinogen .
d. Stercobilin .
e. Urobilin .

4) In hepatocytes , bilirubin is converted into :-

a. Stercobilin .
b. Urobilin .
c. mono or di glucuronides .
d. Biliviridine .
e. Urobilinogen .

5) Hepatic jaundice is characterized by :

a. Low level of unconjugated bilirubin.
b. Low level of conjugated bilirubin .
c. Both conjugated and unconjugated are elevated .
d. Both conjugated and unconjugated are lowered .
e. Non of the above .

محاضرات التقنية الوسطى

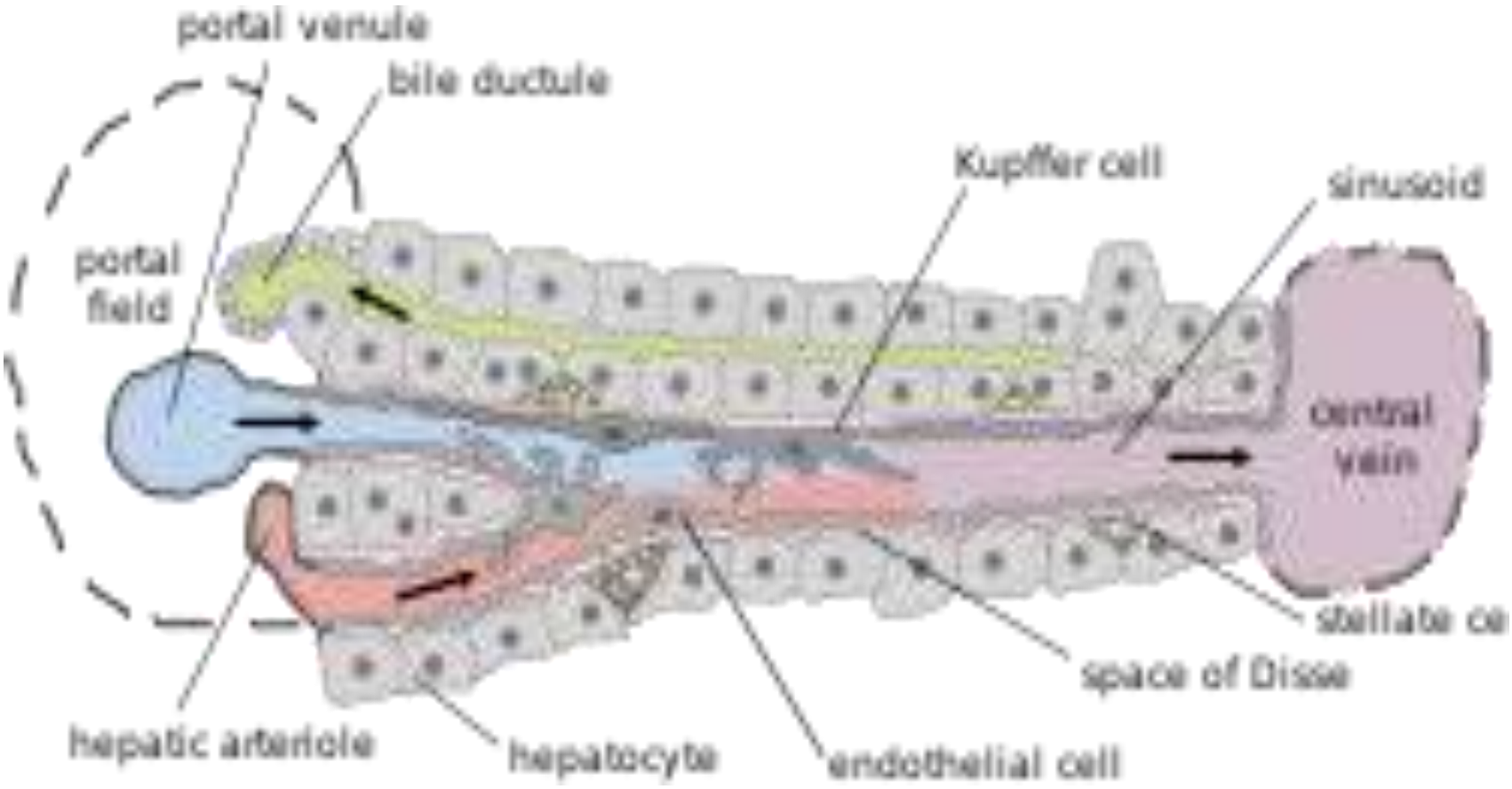
محاضرات 9,10,11

The Liver

The liver regulates, synthesizes, stores and secretes many important proteins and nutrients, and purifies, transforms and clears toxic or unnecessary compounds from the blood. Hepatocytes are optimized for function through their contact with sinusoids (leading to and from blood vessels) and bile ducts. A special feature of the liver is its ability to regenerate, maintaining function even in the face of moderate damage.

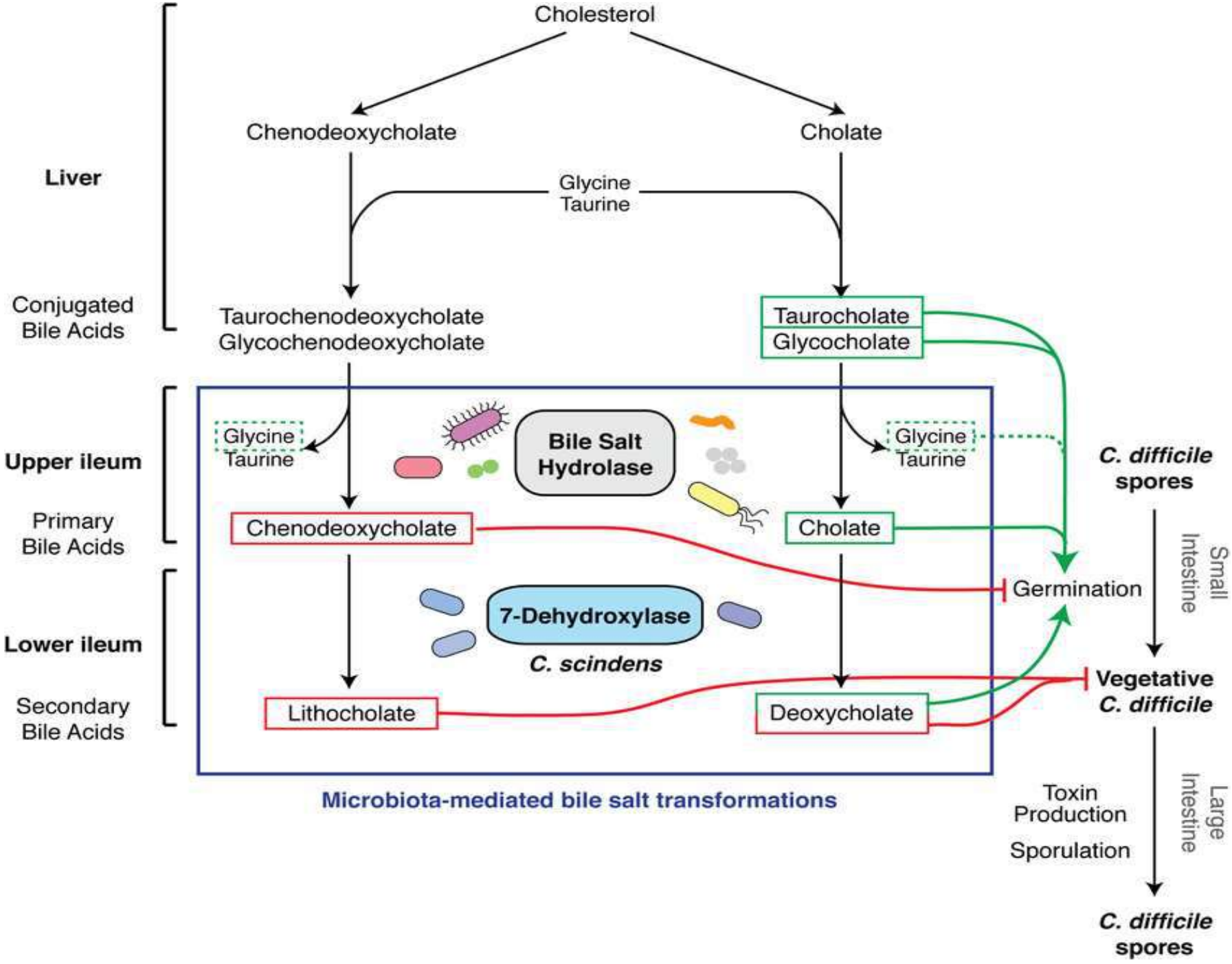
General liver metabolism :- More than 500 vital functions are associated with the liver; some of the better characterized are listed below:

- production and excretion of bile
- cholesterol metabolism
- drug metabolism and detoxification
- hemoglobin degradation
- protein metabolism; production of albumin
- nitrogen metabolism, ammonia detoxification
- synthesis of coagulation factors
- storage, including glucose (in the form of glycogen), vitamin B12, iron and copper
- carbohydrate metabolism • lipid metabolism • red blood cell production (first trimester fetus; by the 32nd week of gestation, the bone marrow has almost completely taken over this task)
- Further, the reticuloendothelial system of the liver contains many immunologically active cells, acting as a ‘sieve’


portal venule
bile ductule
Kupffer cell
sinusoid
portal field
central vein
stellate ce
space of Disse
hepatic arteriole
hepatocyte
endothelial cell

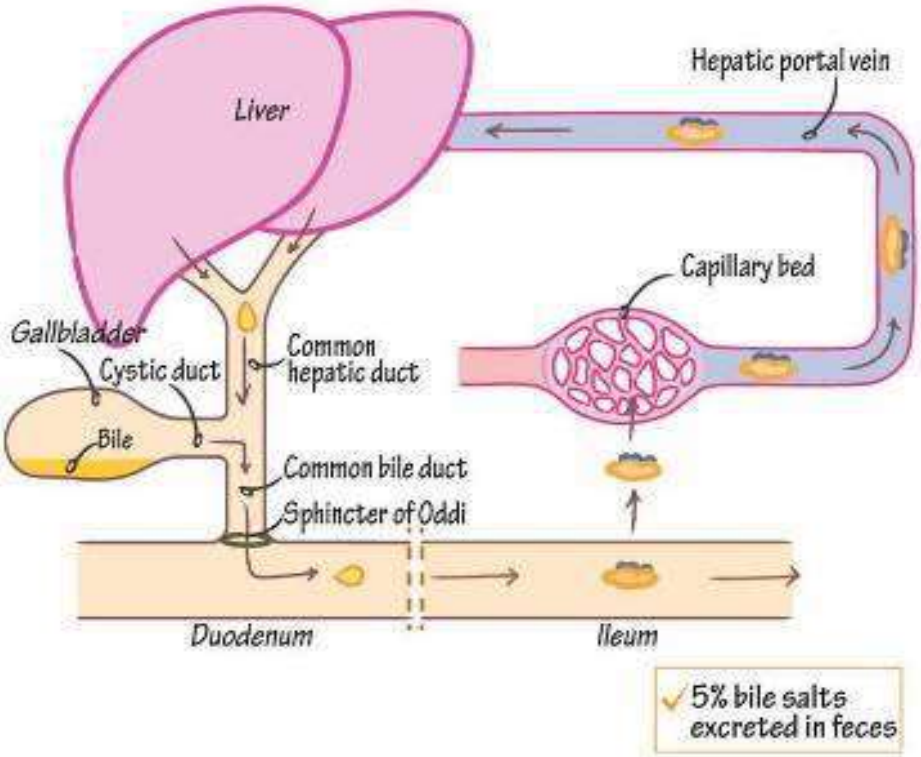
Production and excretion of bile

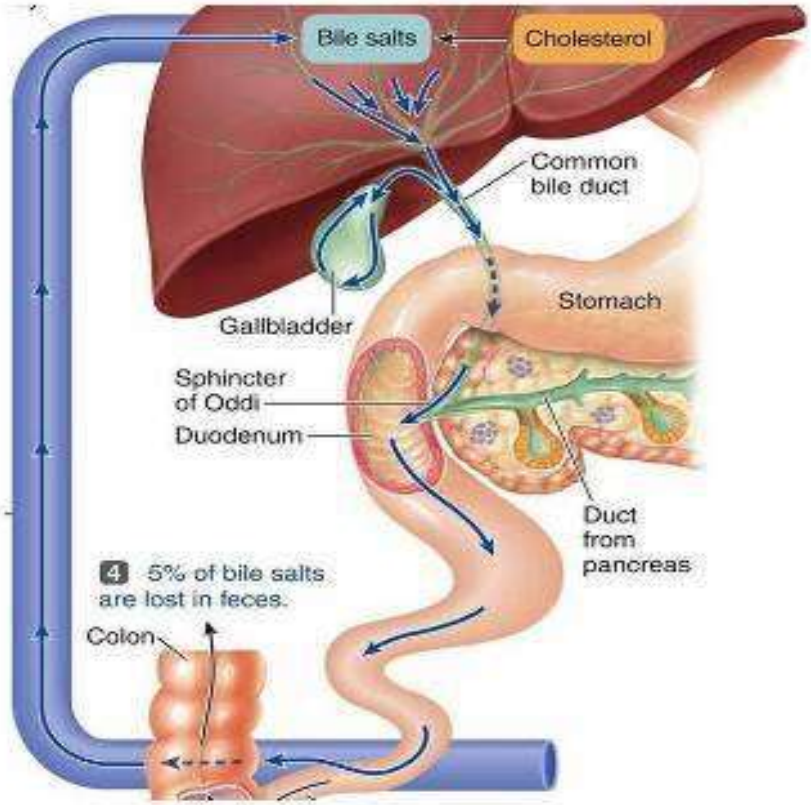
Bile is a mixture of electrolytes, bile acids, cholesterol, phospholipids and bilirubin. Adults produce between 400 and 800 ml of bile daily. Hepatocytes secrete bile into canaliculi, then into bile ducts, where it is modified by addition of a bicarbonate-rich secretion from ductal epithelial cells. Further modification occurs in the gall bladder, where it is concentrated up to fivefold, through absorption of water and electrolytes. Bile acids are steroids, primary bile acids are: **cholic acid** and **chenodeoxycholic acid**. Within the intestines, bacteria convert primary bile acids to secondary bile acids, for example **deoxycholate** (from **cholate**) and **lithocholate** (from **chenodeoxycholate**). Both primary and secondary bile acids are re-absorbed by the intestines and delivered back to the liver via the portal circulation. In the duodenum's alkaline environment, **bile acids become bile salts** (e.g., sodium glycolcholate). Bile acids are conjugated (joined together) with glycine or taurine, via formation of an amide bond, to yield glycocholic acid and taurocholic acid respectively, in this form they are stored in the gall bladder.


Cholesterol
Chenodeoxycholate
Cholate
Liver
Glycine
Taurine
Conjugated
Bile Acids
Taurochenodeoxycholate
Glycochenodeoxycholate
Taurocholate
Glycocholate
Upper ileum
Primary
Bile Acids
Glycine
Taurine
Bile Salt
Hydrolase
Glycine
Taurine
C. difficile
spores
Chenodeoxycholate
Cholate
Small
Intestine
Germination
Lower ileum
Secondary
Bile Acids
7-Dehydroxylase
C. scindens
Vegetative
C. difficile
Lithocholate
Deoxycholate
Toxin
Production
Sporulation
Large
Intestine
C. difficile
spores
Microbiota-mediated bile salt transformations

Only relatively small quantities of bile acids are lost from the body; approximately 95% of bile acids delivered to the duodenum are absorbed back into blood within the ileum. Venous blood from the ileum goes straight into the portal vein, and hence through the sinusoids of the liver (enterohepatic circulation). Hepatocytes extract bile acids very efficiently from sinusoidal blood; they are re- secreted into canaliculi. The net result of enterohepatic recirculation is that each bile salt molecule may be reused up to 20 times, and often 2 or 3 times during a single digestive phase.

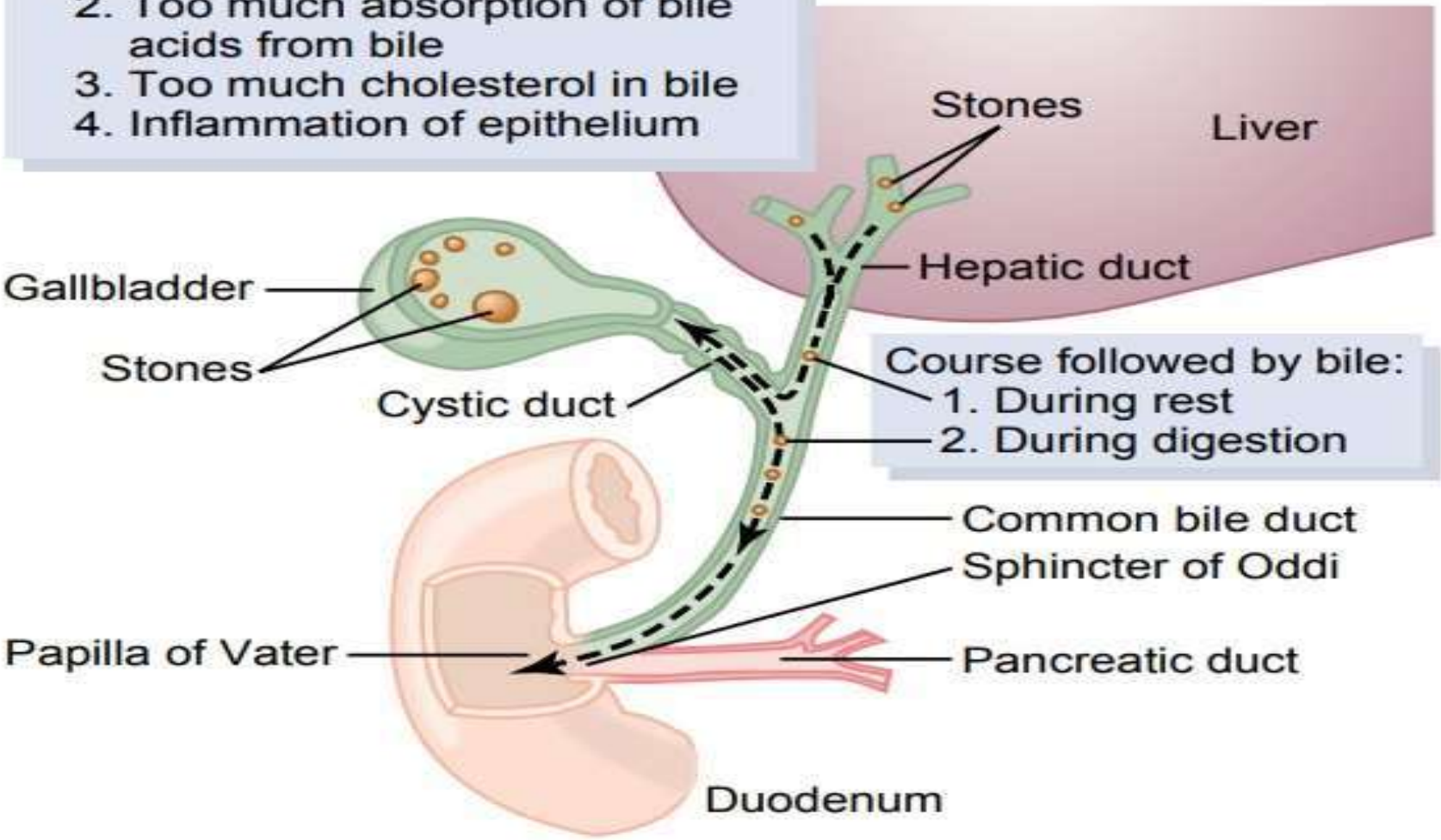
Bile Salts, Formations, Entero-hepatic Circulation And Functions Of Bile Salts





Causes of gallstones:

1. Too much absorption of water from bile
2. Too much absorption of bile acids from bile
3. Too much cholesterol in bile
4. Inflammation of epithelium



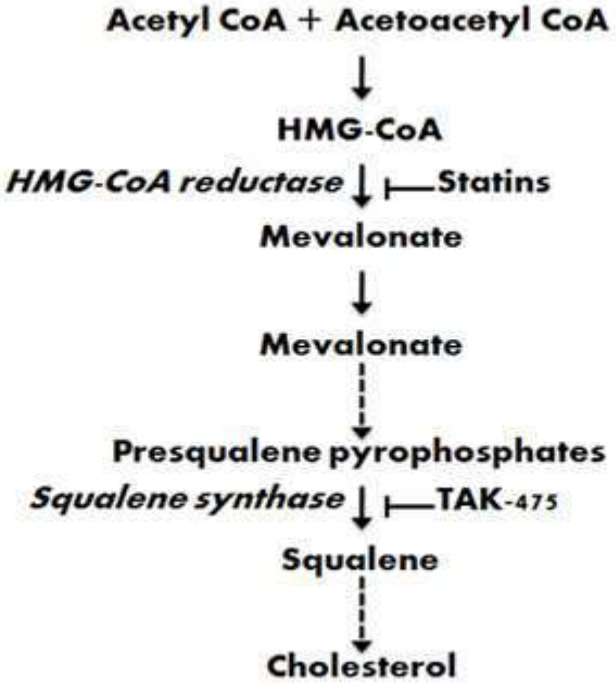
Formation of gallstones.

Bile acids perform four physiologically significant functions:
1. They facilitate the digestion of dietary triacylglycerols by acting as emulsifying agents; emulsification increases the surface area of fat, making it available for digestion by lipases.
2. They facilitate the intestinal absorption of fat-soluble vitamins (vitamin A, vitamin D, vitamin E, and vitamin K).
3. Their synthesis and subsequent excretion in the feces represents the only significant mechanism for the elimination of excess cholesterol. In humans, roughly 500 mg of cholesterol is converted to bile acids and eliminated in bile every day.
4. Bile acids and phospholipids solubilize cholesterol in the bile, thereby preventing the precipitation of cholesterol in the gall bladder.

- **Cholesterol metabolism** :

Slightly less than half of the cholesterol in the body derives from biosynthesis de novo; biosynthesis in the liver accounts for approximately 10% and in the intestines approximately 15% each day. Cholesterol synthesis occurs in the cytoplasm and microsomes (smooth endoplasmic reticulum). The process has five major steps:

1. Acetyl-CoA is converted to 3-hydroxy-3-methylglutarylCoA (HMG-CoA).
2. HMG-CoA is converted to mevalonate (rate limiting step).
3. Mevalonate is converted to the isoprene (IPP).
4. IPP is converted to squalene.
5. Squalene is converted to cholesterol.



Clinical significance of bile secretion, since bile acids are made from endogenous cholesterol, the enterohepatic circulation of bile acids may be disrupted as a way to lower cholesterol. Bile acid sequestrates bind bile acids in the gut, preventing their reabsorption. In so doing, more endogenous cholesterol is directed to the production of bile acids, thereby lowering cholesterol levels. The sequestered bile acids are excreted in the faeces. Gallstones, most of which are composed predominantly of cholesterol, result when cholesterol precipitates from solution. Liver damage or obstruction of a bile duct (e.g., by gallstones) can lead to cholestasis, the blockage of bile flow, resulting in the malabsorption of dietary fats with steatorrhea (foul-smelling diarrhea caused by non-absorbed fats) and jaundice. Liver disease, and damage to the canalicular system, can result in escape of bile acids into the systemic circulation. Assay of systemic levels of bile acids is used clinically as a sensitive indicator of hepatic disease.

1- One of the following is not a function of the liver :-

a. Cholesterol metabolism.

b .Drug metabolism and detoxification .

c. Hemoglobin degradation .

d. Protein metabolism; production of albumin.

e. Synthesis of vitamin D .

2- **The following compound are classified as bile acids except** :-

a. Cholic acid .

b. Chenodeoxycholic acid .

c. Sodium glycolcholate .

d. Deoxycholate .

e. Lithocholate .

3- Which one of the following food components is mostly affected by the bile :-

a. Carbohydrates .

b. Lipids .

c. Proteins .

d. Nucleic acids .

e. Amino acids .

4) Which step in the biosynthesis of cholesterol is rate limiting :-

a. Acetyl-CoA is converted to 3-hydroxy-3-methylglutarylCoA (HMG-CoA).
b. HMG-CoA is converted to mevalonate.
c. Mevalonate is converted to the isoprene.
d. IPP is converted to squalene.
e. Squalene is converted to cholesterol.

5) The following are components of bile except :-

a. Electrolytes .
b. Bile acids .
c. Cholesterol.
d. Lipases.
e. Phospholipids .

Lectures 1&2

Water homeostasis

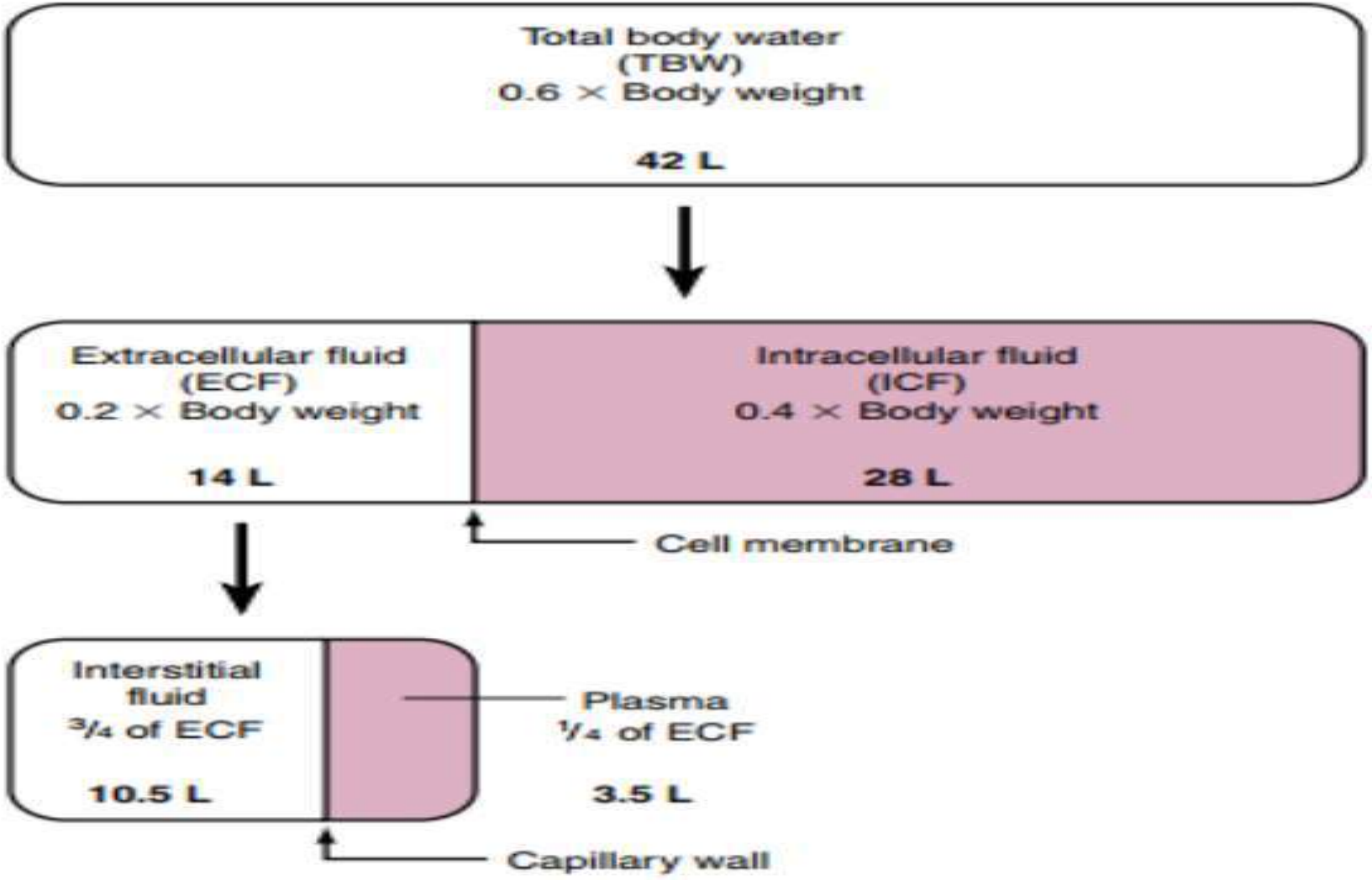
Water is an essential body constituent, and homeostatic processes are important to ensure that the total water balance is maintained within narrow limits, and the distribution of water among the vascular, interstitial and intracellular compartments is maintained. The body maintains a balance of water intake and output by a series of negative feedback loops involving the endocrine system and autonomic nervous system.

Distribution of Water:

In a 70-kg man, the Total Body Water (TBW) is about 42 L and contributes about 60 per cent of the total body weight.

Two thirds of the water are in the Intra Cellular Fluid (ICF), and one third is in the Extra Cellular Fluid (ECF). Because the plasma membrane of most cells is highly permeable to water, ICF and ECF are in osmotic equilibrium.

The ECF is divided into a vascular compartment (plasma) and an interstitial fluid compartment. Expressed as percentages of body weight, the volumes of total body water, ICF, and ECF are: Total body water = 0.6 × (body weight) , ICF = 0.4 × (body weight) , ECF = 0.2 × (body weight



Water Intake—Water is supplied to the body by the following processes:

a. Dietary liquids

b. Solid foods

c. Oxidation of foodstuffs: It is obtained from the combustion of fats, proteins and carbohydrates. The oxidation of fats yields 107 ml/100 gm, proteins 41 ml/100 gm and carbohydrates 56 ml/100 gm.

Water output: Water is lost from the body by the following routs:

a. Urine

b. Respiration

c. Lactation

d. Faeces

e. Evaporation from skin and lungs

f. Eyes (tears)

FUNCTIONS OF WATER

1. **Solvent**: One of the most important properties of water is its capacity to dissolve different kinds of substances. It is therefore the most suitable solvent for cellular components. Water brings together various substances in contact when chemical reactions take place.
2. **Catalytic action**: Water accelerates a large number of chemical reactions in the body due to its ionizing power.
3. **Lubricating actions**: Water acts as a lubricant in the body and prevents friction in joints, pleura, conjunctiva, and peritoneum.
4**. Heat regulation**: By virtue of its high specific heat, water prevents any significant rise in the body temperature due to heat liberated from body reactions. The loss of heat from the body is also regulated by the evaporation of water from skin and lungs and its removal in urine.

Water intake			*Water loss*		
Drinks	48 %	1350 ml	Lungs	12%	500 ml
Solid	40 %	900 ml	Skin	24%	700 ml
Oxidation of food	12%	450 ml	Urine	56%	1400 ml
			Faeces	08%	100 ml
	100%	2700 ml		100%	2700 ml

Disturbances of Water Homeostasis

• Gain or loss of extracellular fluid volume.
• Gain or loss of solute.

In many instances disturbances of water homeostasis involve imbalances of both volume and solutes.

Four specific examples of water homeostasis:

• **Hypervolemia** . • **Overhydration** , • **Hypovolemia** , • **Dehydration**

Hypervolemia: • occurs when too much water and solute at the same time. Although extracellular fluid volume increases, plasma osmolarity may remain normal.

Overhydration: • occurs when too much water is taken by drinking without solute, volume increases, but because solute is not present, plasma osmolarity decreases.

Hypovolemia: • occurs when water and solutes are lost at the same time. This condition primarily involves a loss of plasma volume. Plasma osmolarity usually remains normal even though volume is low. Too much IV fluids can increase plasma volume dramatically, but with an isotonic solution the plasma osmolarity would remain normal and result in hypervolemia.

Dehydration: • When water, but not solute, is lost, dehydration occurs. Dehydration involves a loss of volume but, because solutes are not lost in the same proportion, plasma osmolarity increases. Although sweating causes the loss of some solute through the skin, much more water is lost, and the person becomes dehydrated.

Mechanisms of Fluid Balance

• The body have mechanisms that regulate fluid levels within a narrow range, the body fluids remain within certain physiological limits, an important aspect of homeostasis, four primary mechanisms regulate fluid homeostasis

-Antidiuretic hormone or ADH

-Thirst mechanism

-Aldosterone

-Sympathetic nervous system

• Three of these mechanisms involve the kidneys.

Effect of ADH

- When loses water by sweating, plasma becomes more concentrated in solutes.
- Osmoreceptors in the hypothalamus detect the increased osmolarity or concentration of solutes in the plasma.
- In response to this increased concentration, antidiuretic hormone is released into the blood at the posterior pituitary.
- The target tissue for ADH is the late distal convoluted tubule and collecting duct cells in the kidney .

ADH in the Nephron

- These cells become permeable to water only in the presence of ADH.
- ADH promotes the addition of water channels into the cells of the late distal convoluted tubule and collecting duct, allowing water to move from the filtrate to the plasma by way of osmosis.
- ADH therefore increases the reabsorption of water.

Thirst Mechanism

• The thirst mechanism is the primary regulator of water intake and involves hormonal and neural input as well as voluntary behaviors.

• There are three major reasons why dehydration leads to thirst:

1. When saliva production decreases, the mouth and throat become dry. Impulses go from the dry mouth and throat to the thirst center in the hypothalamus, stimulating that area.

2. When you are dehydrated, blood osmotic pressure increases, stimulating osmoreceptors in the hypothalamus and the thirst center in the hypothalamus is now further activated.

3. Decreased blood volume causes a decrease in blood pressure that stimulates the release of renin from the kidney. This causes the production of angiotensin II which stimulates the thirst center in the hypothalamus.

• Stimulation of the thirst center in the hypothalamus gives the desire to drink.

Results of Fluid Ingestion • This fluid ingestion:

1. Relieves the dryness in the mouth and throat.
2. Fluid ingestion also stimulates stretch receptors in the stomach and intestine to send inhibitory signals to the thirst center.
3. When normal fluid volume is restored, dehydration is relieved. Renin secretion from the kidney and angiotensin II now decreases to baseline levels.

Effect of Aldosterone

• When a person donates large amounts of blood, they lose salts as well as water. When electrolytes and water are lost at the same time, blood volume decreases, threatening hypovolemia.

• When a person experiences blood loss, blood pressure decreases.

• Because a hypovolemic person experiences a decrease in blood pressure, juxtaglomerular cells in the arterioles of the kidney release renin

Renin to Aldosterone

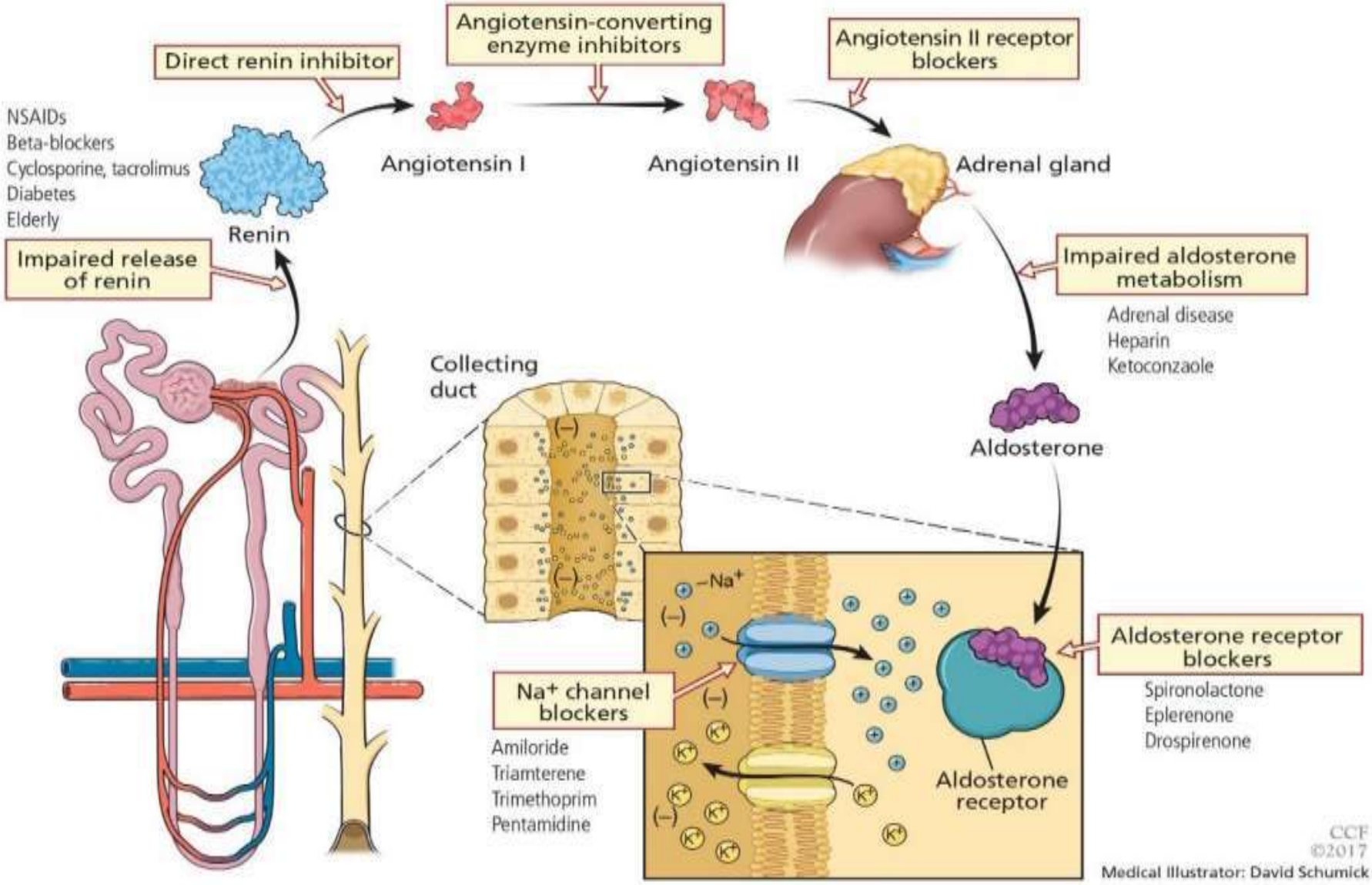
- As renin travels through the bloodstream, it binds to an inactive plasma protein, angiotensinogen, activating it into angiotensin I.
- As angiotensin I passes through the lung and other capillaries, an enzyme called Angiotensin Converting Enzyme, or ACE, converts angiotensin I to angiotensin II.
- Angiotensin II continues through the blood stream until it reaches the adrenal gland. Here it stimulates the cells of the adrenal cortex to release the hormone aldosterone.
- Angiotensin II also has a vasoconstriction effect that helps to increase the blood pressure.
- Aldosterone can also be released when potassium concentrations in the blood are high.

Aldosterone in the Nephron

- In the absence of aldosterone, the cells in the late distal convoluted tubule and collecting ducts allow little sodium and potassium ions to pass because there are few sodium and potassium channels in the cell membrane facing the kidney tubule. There are also few sodium/potassium ATPase pumps on the basal side of these cells.
- Aldosterone exerts its effect by inserting additional channels in the late distal convoluted tubule and collecting duct of the kidney. This allows more sodium to move from the filtrate into the blood and potassium to move from the blood into the filtrate.

Results of Aldosterone Action

- The net result of aldosterone action is the reabsorption of sodium and the secretion of potassium.
- If ADH is also present, water is reabsorbed into the blood at the kidney, preventing further water loss from the body. As a result, blood volume and blood pressure are stabilized until water is consumed.



Based on information in Palmer BF. A physiologic-based approach to the evaluation of a patient with hyperkalemia. Am J Kidney Dis 2010; 56:387–393.

Sympathetic Stimulation

• A decrease in blood volume and therefore blood pressure will further stimulate the sympathetic nervous system.

• When blood pressure is low, baroreceptors in the heart, aortic arch, and carotid arteries send sensory information to the medulla.

• The information sent from the baroreceptors to the medulla will cause an increase in the sympathetic impulses to the kidney.

Sympathetic Stimulation in the Nephron

• Release of neurotransmitters from the sympathetic nerves in the kidney stimulates smooth muscle cells in the afferent arteriole to constrict.

• This process causes a decrease in blood flow into the glomerulus and a drop in glomerular filtration rate and results in less urine formation. Less water leaves the body.

• Sympathetic stimulation also causes the release of renin which, by stimulating aldosterone secretion, will increase the reabsorption of sodium.

• As a result, blood volume will stop decreasing and blood pressure may stabilize. However, because the blood pressure and blood volume have not yet returned to normal, the baroreceptors will continue to be stimulated to prevent further loss of blood volume.

• In order to bring this person back into to homeostasis, we need to increase the blood volume by drinking fluids. In fact, after an individual has given blood, they are encouraged to drink juice to increase their plasma volume level.

Questions :

7 , 24 , 27 , 45 , 61 , 73 , 74 ,83 , 84 , 91 ,92

Al-Noor University College
Department of Medical Laboratory Techniques
Stage :Third year
Subject :Clinical Biochemistry
Semester: Second
Lecture number : 20 , 21 , 22
Topic : Tumor markers (modified 2023)

Tumor Markers These are biochemical indicators of the presence of a tumor. In clinical practice, it refers to molecules that can be detected in plasma and body fluids.

Tumor markers are measurable biochemical that are associated with malignancy. These markers are either produced by tumor cells (tumor-derived) or by the body in response to tumor cells (tumor-associated). They are typically substances that are released into the circulation and thus measured in the blood. Tumor markers are not the primary modalities for cancer diagnosis rather they can be used as a laboratory test to support the diagnosis.

Why use tumor markers?

Screening and Early Detection of Cancer. Screening refers to looking for cancer in people who have no symptoms of the disease. Some newer tumor markers help to assess how aggressive a cancer is likely to be or even how well it might respond to certain drugs. Cancer Markers are also be used to detect cancers that recur after initial treatment. Some tumor markers can be useful once treatment has been completed and with no evidence of residual cancer left.

Determination direction

Tumor markers can be measured qualitatively or quantitatively by:

1. Chemical methods.
2. Immunological methods.
3. Molecular biological methods to determine the presence of cancer.

Characteristics of Ideal Tumor Markers

1. Specificity for cancer: the substance should be produced only by the tumor.
2. Sensitivity for cancer: a very small tumor growth will produce measurable amounts of the marker.
3. The amount of marker produced: will correlate well with the tumor load.
4. The assay for the marker: must be inexpensive, easy to perform, and sensitive.
5. The half-life of the marker: must be short enough, so
6. That when production drops, the level falls off rapidly.

Classification of Tumor Markers

1. Enzymes and isoenzymes.
2. Hormones, neurotransmitters, and their metabolites.
3. Receptors (estrogen, progesterone, androgen, and corticosteroid).
4. Serum proteins examples of (immunoglobulins, glycoproteins, carcinoembryonic proteins, or oncofetal antigens).

MARKER	ASSOCIATED CANCER(S)	USUAL SAMPLE	USE(S)	COMMENTS
ha-feto protein)	Certain liver, ovarian, testicular	Blood	Helps diagnose, monitors treatment and for recurrence	Also elevated during pregnancy and hepatitis
munoglobulin gene ement	B-cell lymphoma	Bone marrow, tissue, body fluid, blood	Helps diagnose, monitor treatment and for recurrence	Detects characteristic changes in specific genes in B-cells
icroglobulin	Multiple myeloma, some leukemias, and lymphomas	Blood, urine, CSF	Determines prognosis, monitors treatment & for recurrence	Elevated in other conditions, such as kidney disease
Cancer antigen 15-3 27.29 are two tests for same	Breast	Blood	Monitors treatment and for recurrence	Also elevated in other cancers (lung, ovarian), benign breast conditions,endometriosis, hepat
Cancer antigen 19-	Pancreatic, sometimes bile ducts, gallbladder, stomach, colon	Blood	Monitors treatment and for recurrence	Also elevated in other forms of digestive tract cancer and non-cancer, thyroid disease, pancreat bile duct obstruction, inflammat bowel disease

Tumor markers :-

1-Tumor markers are best described as :-

a) Chemical compounds secreted by tumor cells.

b) Antigens produced by humans in response to tumor .

c) Indicators of presence of a tumor can be detected in plasma and body fluid .

d) Molecules that can only be detected by histochemical means .

e) Biological substances released by a tumor .

2-Tumor markers are used for the following except :-

a) Primary modalities for cancer diagnosis .

b) Screening and early diagnosis of cancer.

c) Diagnosing cancer in most cases .

d) Used to detect cancer after initial treatment.

e) As laboratory test to support the diagnosis .

3-Ideal tumor markers are characterized by the following except :-

a) Specific for cancer .

b) Sensitive for cancer .

c) Must be inexpensive .

d) Must have short half-life to .

e) Its plasma level stay high even after production drops.

.

4-Tumor markers may be categorized into the following except :-

a) Enzymes and Isoenzymes .

b) Hormones.

c) Lipoprotein .

d) Receptors .

e) Serum proteins .

5 - **Tumor markers can be measured by :-**

a) Spectrophotometric method .

b) Chromatographic method .

c) Electrophoretic method .

d) Immunological methods .

e) None of the others

1. c , 2. a , 3. e , 4. c , 5. d

The kidneys- 2 + The pancreas
التقنية الوسطى بعد التعديل

Acute kidney injury

In adults, **oliguria** is defined as a urine output of less than 400 mL/day, or less than 15 mL/h; it usually indicates a low GFR and a rapid decline in renal function over hours to weeks, with retention of creatinine and urea (nitrogenous waste products). Oliguria may be caused by the factors discussed below.

1-Acute oliguria with reduced GFR (pre-renal)

This is caused by factors that reduce the hydrostatic pressure gradient between the renal capillaries and the tubular lumen. A low intracapillary pressure is the most common cause. It is known as renal circulatory insufficiency ('pre-renal uraemia') and may be due to:

- intravascular depletion of whole blood (haemorrhage) or plasma volume (usually due to gastrointestinal loss), **or reduced intake???**.
- reduced pressure as a result of the vascular dilatation caused by 'shock', causes of which include myocardial infarction, cardiac failure and intravascular haemolysis, including that due to mismatched blood transfusion.

2- Acute oliguria due to intrinsic renal damage

This may be due to:

- prolonged renal circulatory insufficiency.
- acute glomerulonephritis, usually in children.
- the history of a sore throat and the finding of red cells in the urine usually make the diagnosis obvious,
- septicaemia,(**Disease caused by the spread of bacteria and their toxins in the bloodstream)** which should be considered when the cause of oliguria is obscure.
- ingestion of a variety of poisons or drugs.
- myoglobulinuria.
- Bence Jones proteinuria.(Bence Jones protein is a monoclonal globulin protein or immunoglobulin light chain found in the urine, with a molecular weight of 22–24 kDa)

3- Acute oliguria due to renal outflow obstruction (postrenal)

Oliguria or anuria (absence of urine) may occur in post-renal failure. The cause is usually, but not always , clinically obvious and may be due to the following:

- **Intrarenal obstruction**, with blockage of the tubular lumina by haemoglobin, myoglobin and, very rarely, urate or calcium.
- **Extrarenal obstruction**, due to calculi, neoplasms, for example prostate or cervix, urethral strictures or prostatic hypertrophy, any of which may cause sudden obstruction.

Chronic kidney disease

Chronic renal dysfunction [defined as being reduced eGFR (estimated GFR), proteinuria, haematuria and/or renal structural abnormalities of more than 90 days' duration] is usually the end result of conditions such as diabetes mellitus, hypertension, primary glomerulonephritis, autoimmune disease, obstructive uropathy, polycystic disease, renal artery stenosis, infections and tubular dysfunction and the use of nephrotoxic drugs. It is common, perhaps affecting about 13% of the population.

Acute or chronic renal dysfunction can occur when angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are given to patients with renal artery stenosis; a clue to this is an increase in plasma creatinine of about 20 % and/or a decrease in eGFR of about 15 % soon after initiation of the drug.

NEPHROTIC SYNDROME

The nephrotic syndrome is caused by increased glomerular basement membrane permeability, resulting in protein loss, usually more than 3 g a day (or a urine protein to creatinine ratio of > 300 mg/mmol), with consequent hypoproteinaemia, hypoalbuminaemia and peripheral oedema. All but the highest molecular weight plasma proteins can pass through the glomerular basement membrane. The main effects are on plasma proteins and are associated with hyperlipidaemia and hyperfibrinoginaemia. Uraemia occurs only in late stages of the disorder, when many glomeruli have ceased to function. This comprises reduced eGFR, oedema, hypertension and proteinuria with significant haematuria. It is usually associated with systemic disease such as postinfectious glomerulonephritis, e.g., post-streptococcal or immunoglobulin A (IgA) nephropathy, ANCA associated vasculitis, e.g., Wegener's granulomatosis or microscopic polyarteritis, or antiglomerular basement membrane disease (Goodpasture's disease).

Pancreatic Functions and Pancreatic Functions Tests (Lectures 18 Pancreas):

Pancreas is only second in size to the liver, weighing about 70–105 g. It is located behind the peritoneal cavity across the upper abdomen at about the level of the first and second lumbar vertebrae, about 1–2 inches above the umbilicus. It is located in the curve made by theduodenum. **The pancreas is composed of two morphologically and functionally different tissues: endocrine tissue and exocrine tissue** The endocrine (hormone-releasing) component is by far the smaller of the two and consists of the islets of Langerhans, which are well-delineated, spherical or ovoid clusters composed of at least four different cell types. The islet cells secrete at least four hormones into the blood: **insulin, glucagon, gastrin, and somatostatin.**

The larger, exocrine pancreatic component (enzyme-secreting) secretes about 1.5–2 L/day of fluid, which is rich in digestive enzymes, into ducts that ultimately empty into the duodenum. The digestive enzymes:

(1) the proteolytic enzymes as trypsin and chymotrypsin.

(2) lipid-digesting enzymes as lipase.

(3) pancreatic amylase.

Tests of pancreatic function • pancreatic function may be suspected when there is evidence of increased amylase and lipase.

Fecal Fat Analysis : Fecal lipids are derived from four sources: unabsorbed ingested lipids, lipids excreted into the intestine (predominantly in the bile), cells shed into the intestine, and metabolism of intestinal bacteria.

• Quantitative Fecal Fat Analysis • The definitive test for steatorrhea is the quantitative fecal fat determination, usually on a 72-hour stool collection, although the collection period may be increased to up to 5 days.

• Sweat Electrolyte Determinations. Measurement of the sodium and chloride concentration in sweat is the most useful test for the diagnosis of cystic fibrosis (a genetic condition. It's **caused by a faulty gene that affects the movement of salt and water in and out of cells**.)

1- In the renal tubule , transport of charged ions produces electrochemical gradient which is minimized by :

a- Isoosmotic transport .

b- Ion exchanged .

c - Active excretion of H .

d- Both a and b .

e- None of the above **.**

2-The following compounds are reabsorbed by the nephrons except :-

a- Glucose .

b-Na .

c- K .

d-Creatinine .

e-Water .

3-Which of the following finding indicates Nephrotic syndrome :-

a- High blood urea .

b-High serum creatinine .

c-High urinary protein .

d-Hypokalemia .

e-Hyperglycemia

4-**Abnormal finding in chronic renal disease include the following except :-**

a- Uremia .

b-Hyperkalemia .

c-Metabolic acidosis .

d- Reduced serum Ca level .

e-Glycosuria .

5-The exocrine pancreatic juice contains :-

a-Proteolytic enzymes .

b-Lipases .

c-Amylase .

d-Nucleases .

e-All of the other choices .

6-**Pancreatic malfunction is indicated when** :-

a- Increased amylase level .

b- Increased lipase level .

c- Increased sweat electrolytes level .

d- both a and b .

e- None of the above .

7-**Quantitative fecal fat is used to diagnose :-**

a- Liver functions .

b- Intestinal absorption dysfunction .

c- Pancreatic function .

d- Gastric indigestion .

e- None of the above.

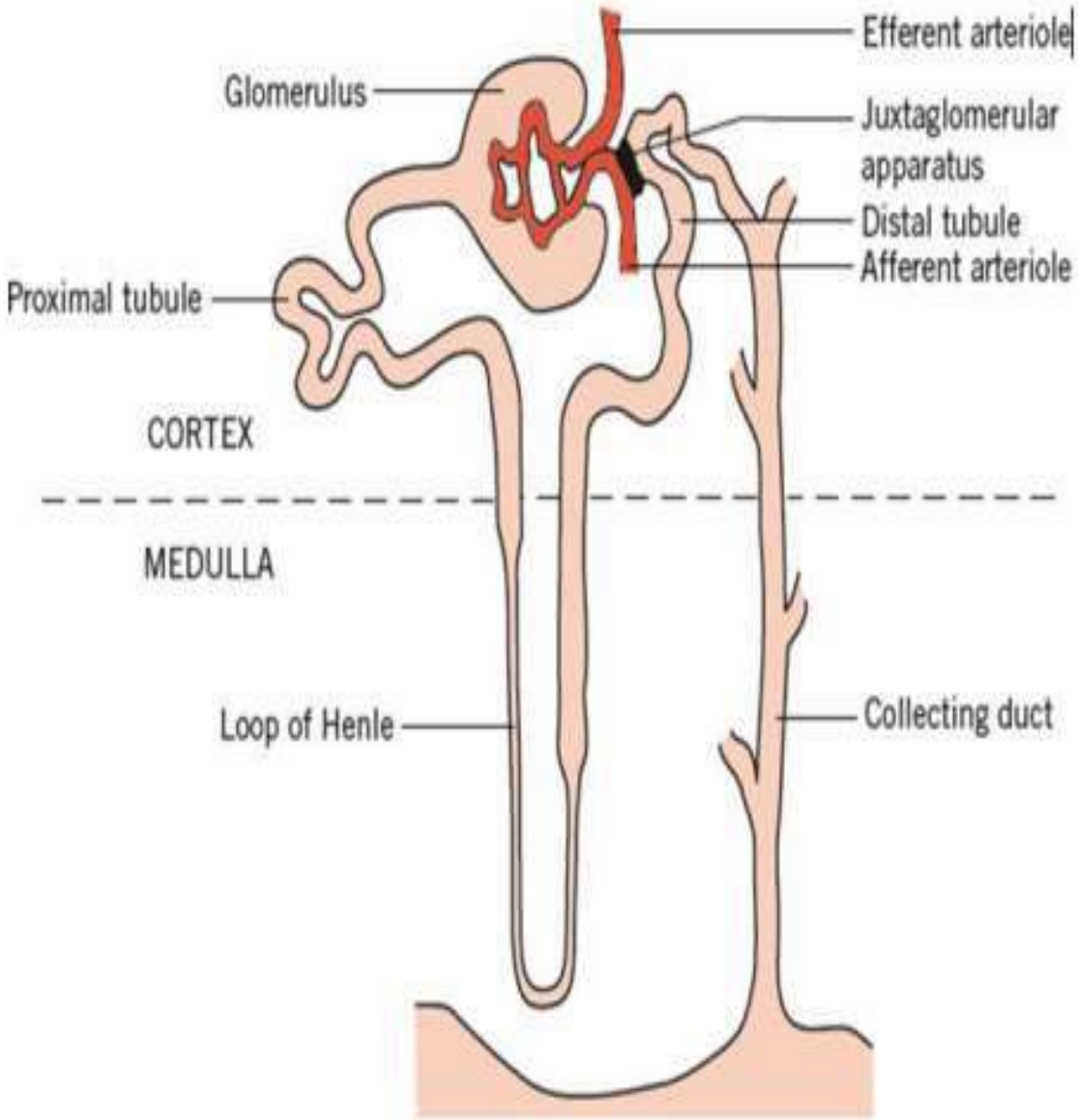
1- d , 2- d , 3- c , 4- e , 5- e , 6- d , 7-c

محاضرات التقنية الوسطى
محاضرات 12و 13
The Kidneys

-The kidneys excrete metabolic waste products, and have an essential homeostatic function in that they control the body solute and water status and the acid–base balance.

-There are about one million nephrons per kidney, each of which is made up of five main functional segments.

1-The glomeruli, in the cortex of the kidney, surround by a capillary network of blood vessels derived from the afferent, and draining into the efferent, arterioles. Small molecules and water are passively filtered during the passage of blood through these capillaries, the ultrafiltration passing through the vessel walls and the glomerular membranes into the glomerular spaces (Bowman's capsules).


Efferent arteriole
Glomerulus
Juxtaglomerular apparatus
Distal tubule
Afferent arteriole
Proximal tubule
CORTEX
MEDULLA
Loop of Henle
Collecting duct

2-The proximal convoluted tubules : also in the cortex, receive filtrate from the glomerular spaces. Convolution increases the tubular length and therefore contact between the luminal fluid and the proximal tubular cells.

3-The loops of Henle extend down into the renal medulla and ascend again after forming the loop.

4-The distal convoluted tubules, situated in the cortex, are important for fine adjustment of luminal fluid. They lie near the afferent arterioles, with the juxtaglomerular apparatus between them. The enzyme renin is produced by the latter and its release is controlled by local blood flow.

5-The collecting ducts start as the distal tubules lead down into the medulla and end by opening into the renal pelvis. The modified fluid from the original filtrate flows from the collecting ducts into the renal tract.

RENAL TUBULAR FUNCTION

Changes in filtration rate alter the total amount of water and solute filtered, but not the composition of the filtrate. From the 200 L of plasma filtered daily, only about 2 L of urine are formed. The composition of urine differs markedly from that of plasma, and therefore of the filtrate. The tubular cells use adenosine triphosphate dependent(ATP) active transport, sometimes selectively, against physicochemical gradients. Transport of charged ions tends to produce an electrochemical gradient that inhibits further transport. This is minimized by two processes.

Isosmotic transport : This occurs mainly in the proximal tubules and reclaims the bulk of filtered essential constituents. Active transport of one ion leads to passive movement of anion of the opposite charge in the same direction, along the electrochemical gradient. The movement of sodium (Na^+) depends on the availability of diffusible negatively charged ions, such as chloride (Cl^-). The process is 'isosmotic' because the active transport of solute causes equivalent movement of water reabsorption in the same direction. Isosmotic transport also occurs to a lesser extent in the distal part of the nephron.

Ion exchange :This occurs mainly in the more distal parts of the nephrons and is important for fine adjustment after bulk reabsorption has taken place. Ions of the same charge, usually cations , are exchanged and neither electrochemical nor osmotic gradients are created.

Clinical and biochemical features of renal disease

Different parts of the nephrons are in close anatomical association and are dependent on a common blood supply. Renal dysfunction of any kind affects all parts of the nephrons to some extent, although sometimes either glomerular or tubular dysfunction is predominant. The net effect of renal disease on plasma and urine depends on the proportion of glomeruli to tubules affected and on the number of nephrons involved, first with a low glomerular filtration rate (GFR) and normal tubular function, and then with tubular damage but a normal GFR.

Uraemia is the term used to describe a raised plasma urea concentration and is almost always accompanied by an elevated creatinine concentration: usually referred to as azotemia (a raised nitrogen concentration).

Reduced glomerular filtration rate with normal tubular function

The findings in venous plasma and urine from the affected nephrons will be as follows :

Plasma

- High urea (uraemia) and creatinine concentrations.
- Low bicarbonate concentration, with low pH (acidosis).
- Hyperkalaemia.
- Hyperuricaemia and hyperphosphataemia.

Urine

- Reduced volume (oliguria).
- Low (appropriate) sodium concentration – only if renal blood flow is low, stimulating aldosterone secretion.
- High (appropriate) urea concentration and therefore a high osmolality – only if ADH secretion is stimulated.

Normal glomerular filtration rate with reduced tubular function :

Thus, the findings in venous plasma and urine from the affected nephrons will be as follows.

Plasma

- Normal urea and creatinine concentrations (normal glomerular function).

Due to proximal or distal tubular failure:

- low bicarbonate concentration and low pH.
- hypokalaemia.

Due to proximal tubular failure:

- hypophosphataemia, hypomagnesaemia and hypouricaemia.

Urine

Due to proximal and/or distal tubular failure:

- increased volume,
- pH inappropriately high compared with that in plasma.

Due to proximal tubular failure:

- generalized amino aciduria, - phosphaturia, - glycosuria.

Questions time :

1- The following s are functions of the kidneys except :-

a) Excretion of metabolic waste products .
b) Homeostatic function .
c) Control of body solute and water status .
d) Control of acid-base balance .
e) Perform many metabolic pathways .

2- The glomeruli function is to :-

a) Reabsorb water .
b) Reabsorb Sodium .
c) Excrete Hydrogen ions .
d) Allow small molecules and water to be filtered .
e) Excrete Urea .

3- The luminal fluid (filtered in the glomeruli) is finely adjusted in the :-

a) Proximal tubule .
b) Loop of Henle .
c) Distal convoluted tubule .
d) The collecting duct .
e) Glomerulus .

4- The followings are found in plasma in case of reduced GFR with normal tubular functions except :-

a) Uremia .
b) Acidosis .
c) Hyperuricemia .
d) Hyperkalemia .
e) Glycosuria .

5- A common finding in serum of both reduced GFR with normal tubule function and normal GFR with reduced tubular function :-

a) Hyperka;emia .
b) Uremia .
c) Low bicarbonate and Ph level .
d) Low Na concentration .
e) Hyperuricemia .

6- A common feature of acute kidney injury is :-

a) Low blood pressure .
b) Low GFR and a decline in renal function .
c) Normal GFR and reduced tubular function .
d) Polyuria .
e) None of the above .

1- e , 2- d , 3- c , 4- e , 5- c , 6 – b .

محاضرات التقنية الوسطى بعد التعديل
المحضرات 14 و 15
Lipids and their disorders

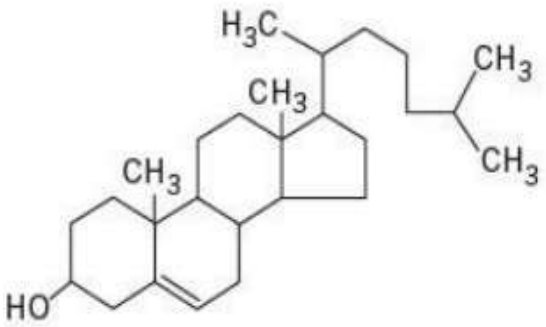
Lipids are defined as organic compounds that are poorly soluble in water but miscible (soluble) in organic solvents. Lipids play a critical role in almost all aspects of biological life – they are :-

1-Structural components in cells . and

2- They are involved in metabolic and hormonal pathways.

The importance of having a knowledge of lipid disorders is due to its association with atherosclerosis such as coronary heart disease .

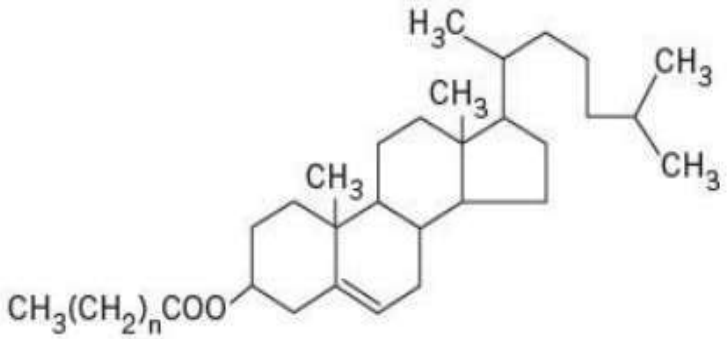
PLASMA LIPIDS The chemical structures of the four main forms of lipid present :



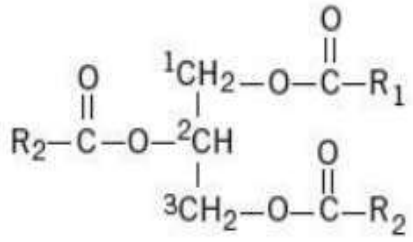
CHOLESTEROL

$CH_3(CH_2)_nCOO^-$

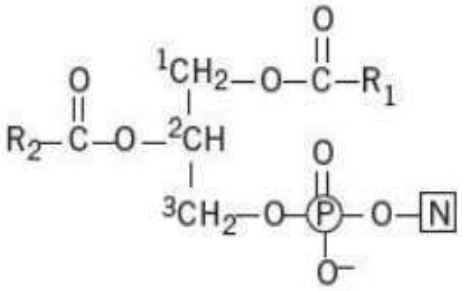
FATTY ACID



CHOLESTEROL ESTER



TRIGLYCERIDE



PHOSPHOLIPID

FATTY ACIDS These are straight-chain carbon compounds of varying lengths. They may be saturated, containing no double bonds, monounsaturated, with one double bond, or polyunsaturated, with more than one double bond. Fatty acids can esterify with glycerol to form triglycerides or be non-esterified (NEFAs) or free.

TRIGLYSERID Triglycerides are transported from the intestine to various tissues, including the liver and adipose tissue, as lipoproteins. Following hydrolysis, fatty acids are taken up, re-esterified and stored as triglycerides. Plasma triglyceride concentrations rise after a meal, unlike that of plasma cholesterol.

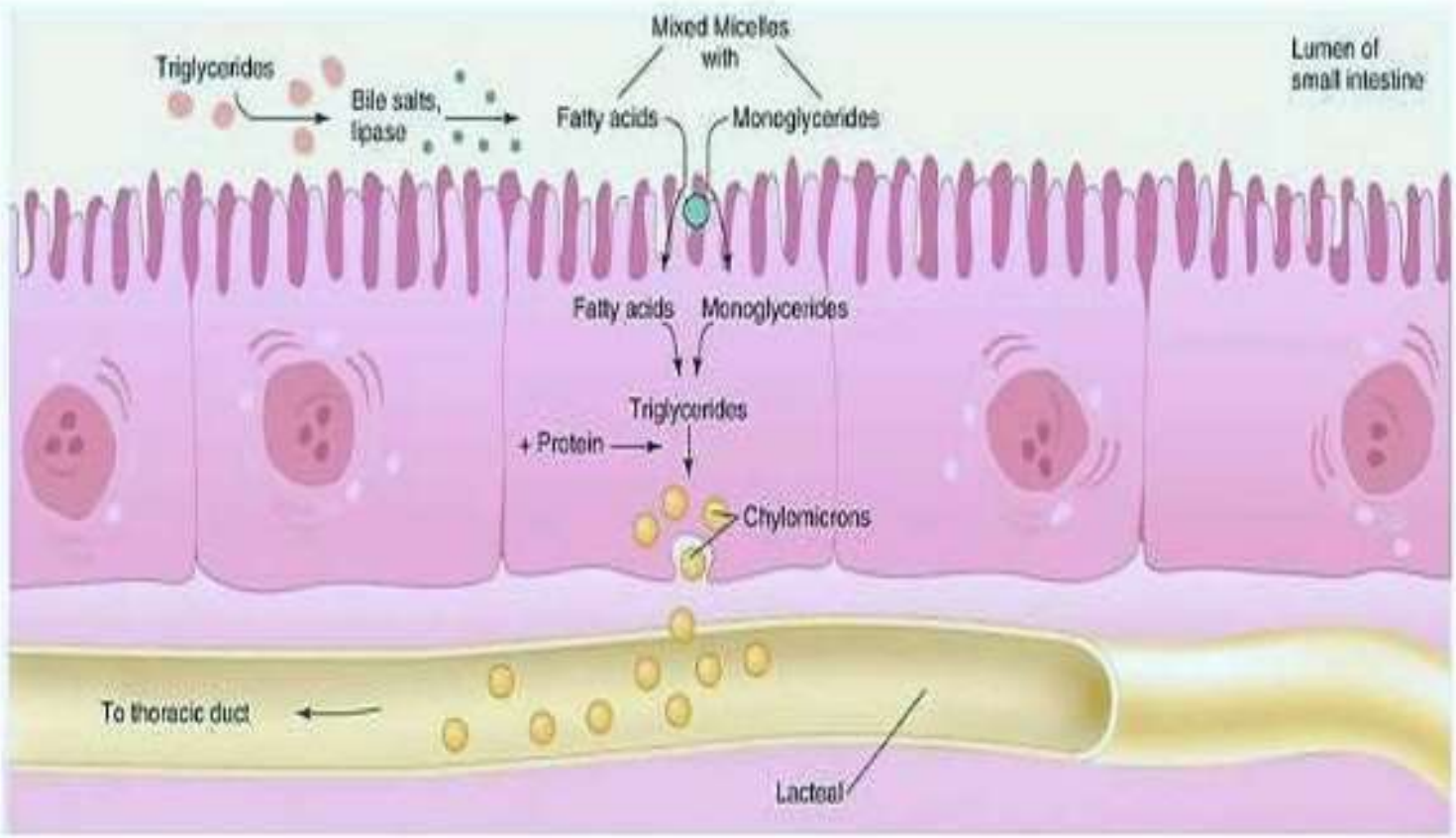
PHOSPHOLIPIDS Phospholipids are complex lipids, similar in structure to triglycerides but containing phosphate and a nitrogenous base in place of one of the fatty acids.

CHOLESTEROL Cholesterol is a steroid alcohol found exclusively in animals and present in virtually all cells and body fluids. It is a precursor of numerous physiologically important steroids, including bile acids and steroid hormones.

LIPOPROTEINS

Because lipids are relatively insoluble in aqueous media, they are transported in body fluids as, often spherical soluble protein complexes called lipoproteins. Lipoproteins can be classified into five main groups. The first three are triglyceride rich and, because of their large size, they scatter light, which can give plasma a turbid appearance (lipidemic) if present in high concentrations:

Formation and Transportation of Chylomicrons



1- **Chylomicrons** are the largest and least dense lipoproteins and **transport exogenous lipid** from the intestine to all cells.

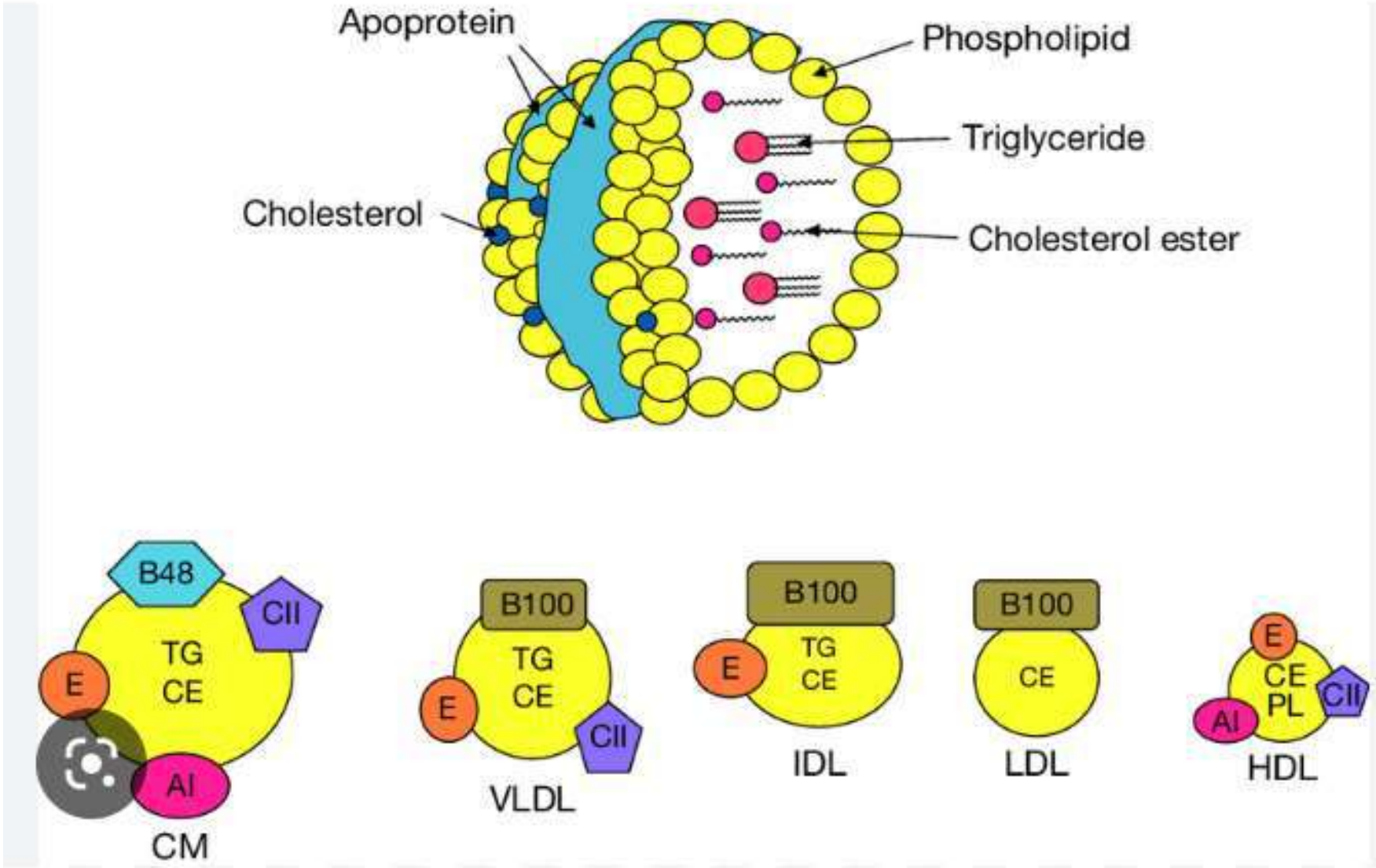
2- **Very low-density lipoproteins (VLDLs) transport endogenous lipid** from the liver to cells.

3- **Intermediate-density lipoproteins (IDLs),** which are transient and formed during the conversion of LDL to low - density lipoprotein (LDL), are not normally present in plasma.

The other two lipoprotein classes contain mainly cholesterol and are smaller in size:

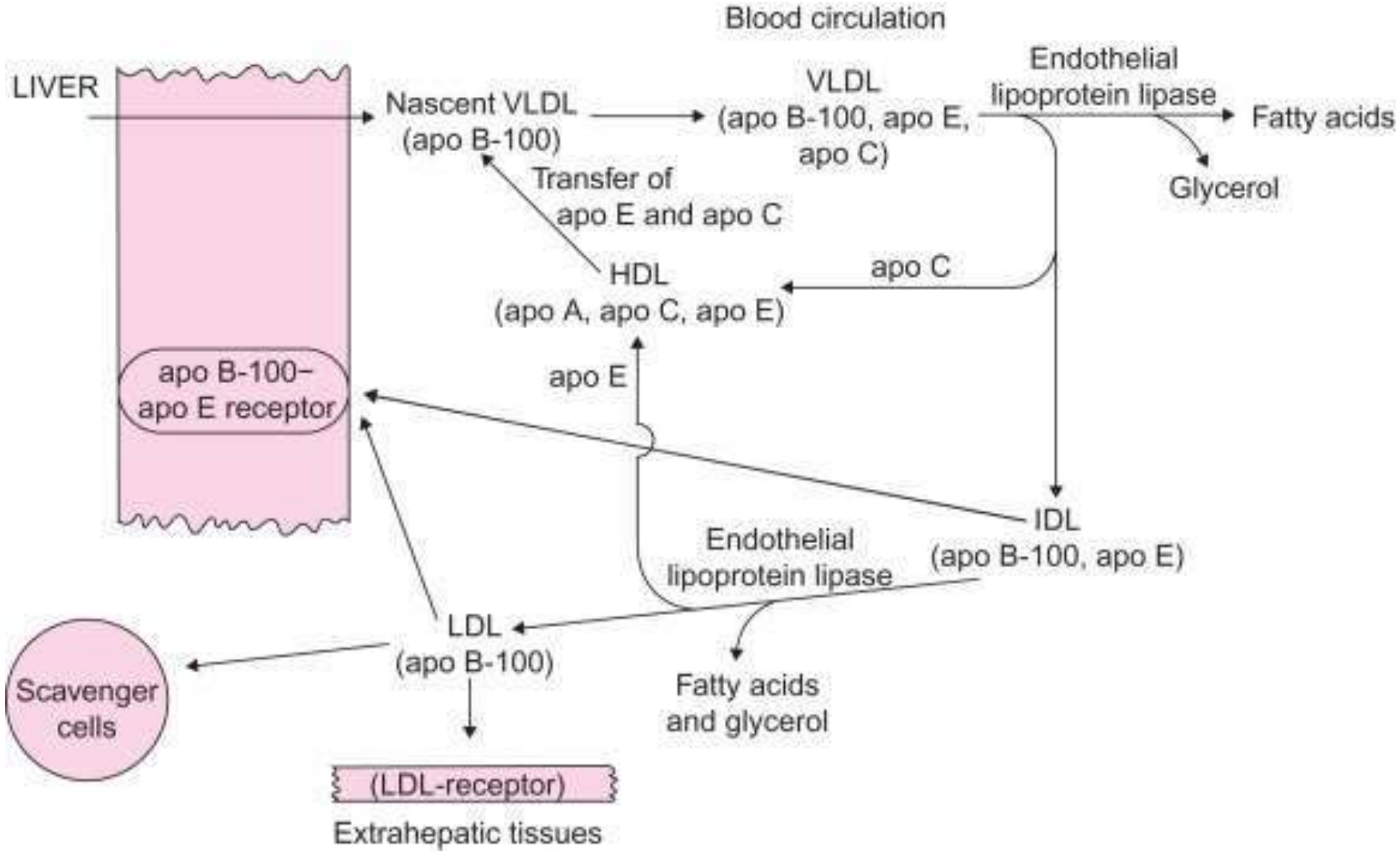
4- **Low-density lipoproteins** are formed from VLDLs and carry cholesterol to cells.

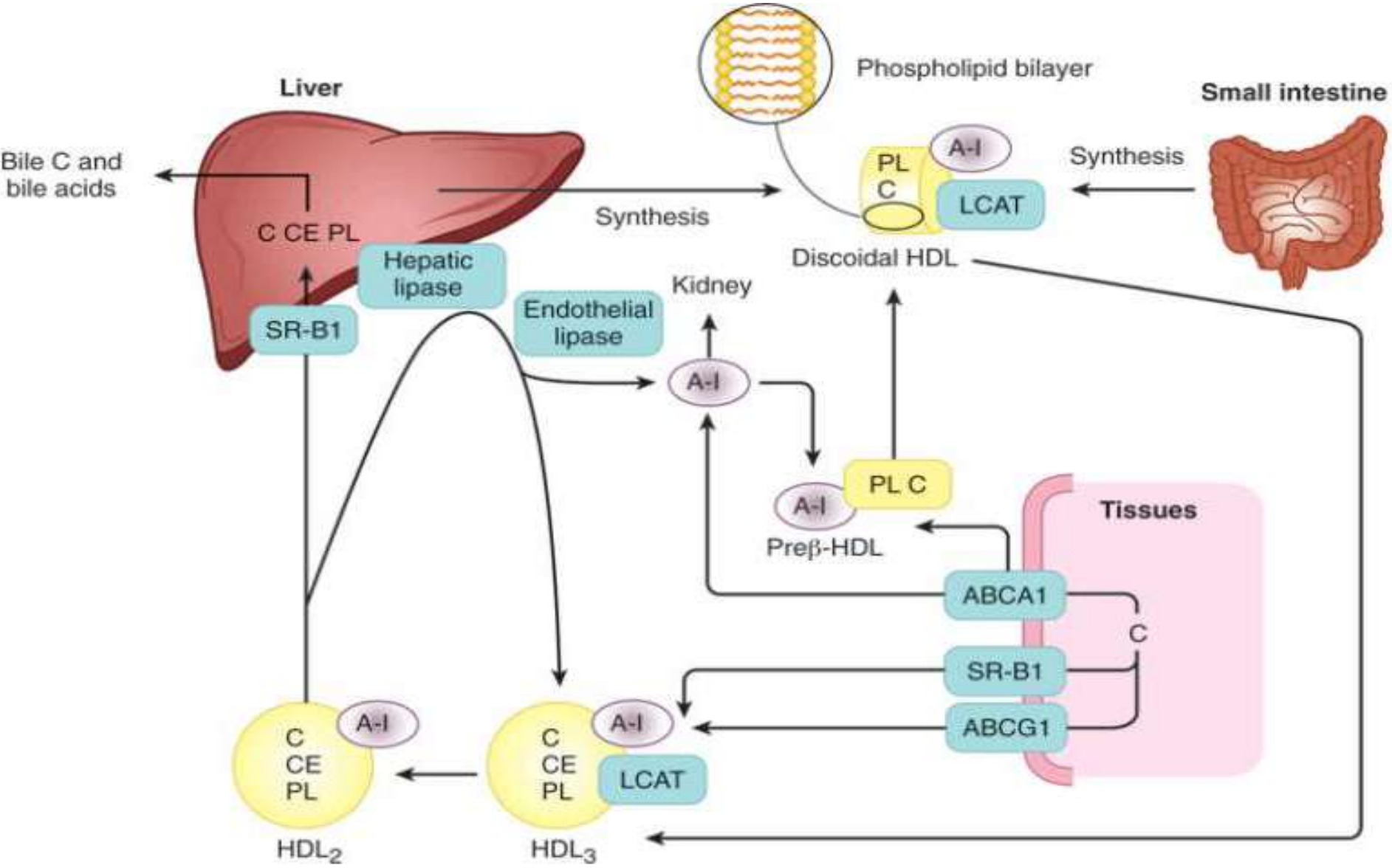
5- **High-density lipoproteins (HDLs)** are the densest lipoproteins and are involved in the transport of cholesterol from cells back to the liver (reverse cholesterol transport).



Lipoprotein structures. Lipoproteins

Visit


Blood circulation
LIVER
Nascent VLDL
(apo B-100)
VLDL
(apo B-100, apo E,
apo C)
Endothelial
lipoprotein lipase
Fatty acids
Glycerol
Transfer of
apo E and apo C
HDL
(apo A, apo C, apo E)
apo C
apo B-100–
apo E receptor
apo E
IDL
(apo B-100, apo E)
Endothelial
lipoprotein lipase
LDL
(apo B-100)
Scavenger
cells
Fatty acids
and glycerol
(LDL-receptor)
Extrahepatic tissues


Liver
Bile C and bile acids
C CE PL
Hepatic lipase
SR-B1
Synthesis
Phospholipid bilayer
Small intestine
Synthesis
A-I
PL C
LCAT
Discoidal HDL
Kidney
Endothelial lipase
A-I
PL C
A-I
Preβ-HDL
Tissues
ABCA1
C
SR-B1
ABCG1
A-I
C CE PL
HDL2
A-I
C CE PL
LCAT
HDL3

Clinical significance of lipid fractionation

Disorder of plasma lipoprotein is called dyslipoprotenemia. Dyslipoprotenemia include hyperlipoproteinemia and hypolipoprotenemia. **I) Hyperlipoproteinemia** (also called hyper lipidemia): The condition of elevation of one or more lipoprotein fraction in the plasma is known as hyperlipoprotenemia. According to Frederickson 's classification there are6 types of hyperlipoproteinemia **a)Type-1 hyperlipoproteinemia**: Metabolic defect**: Lipoprotein lipase enzyme deficiency**. Plasma chylomicron and VLDL (Plasma TG level) level are increased) increases. **b)Type-II a hyperlipoproteinemia** (or Familial hypercholesterolemia): Metabolic defect: **LDL receptor deficiency**. Plasma LDL cholesterol is increased. **c)Type II b hyperlipoproteinemia**: Defect: **Overproduction of apo B**. Both LDL and VLDL increases . Both plasma TG and cholesterol level increases

d)Type III hyperlipoproteinemia: Increase in IDL
e)Type IV hyperlipoproteinemia: Increase in VLDL
f)Type V hyperlipoproteinemia: Increase in VLDL & chylomicron.

II) Hypolipoproteinemia: a condition of decreased lipoprotein fraction .

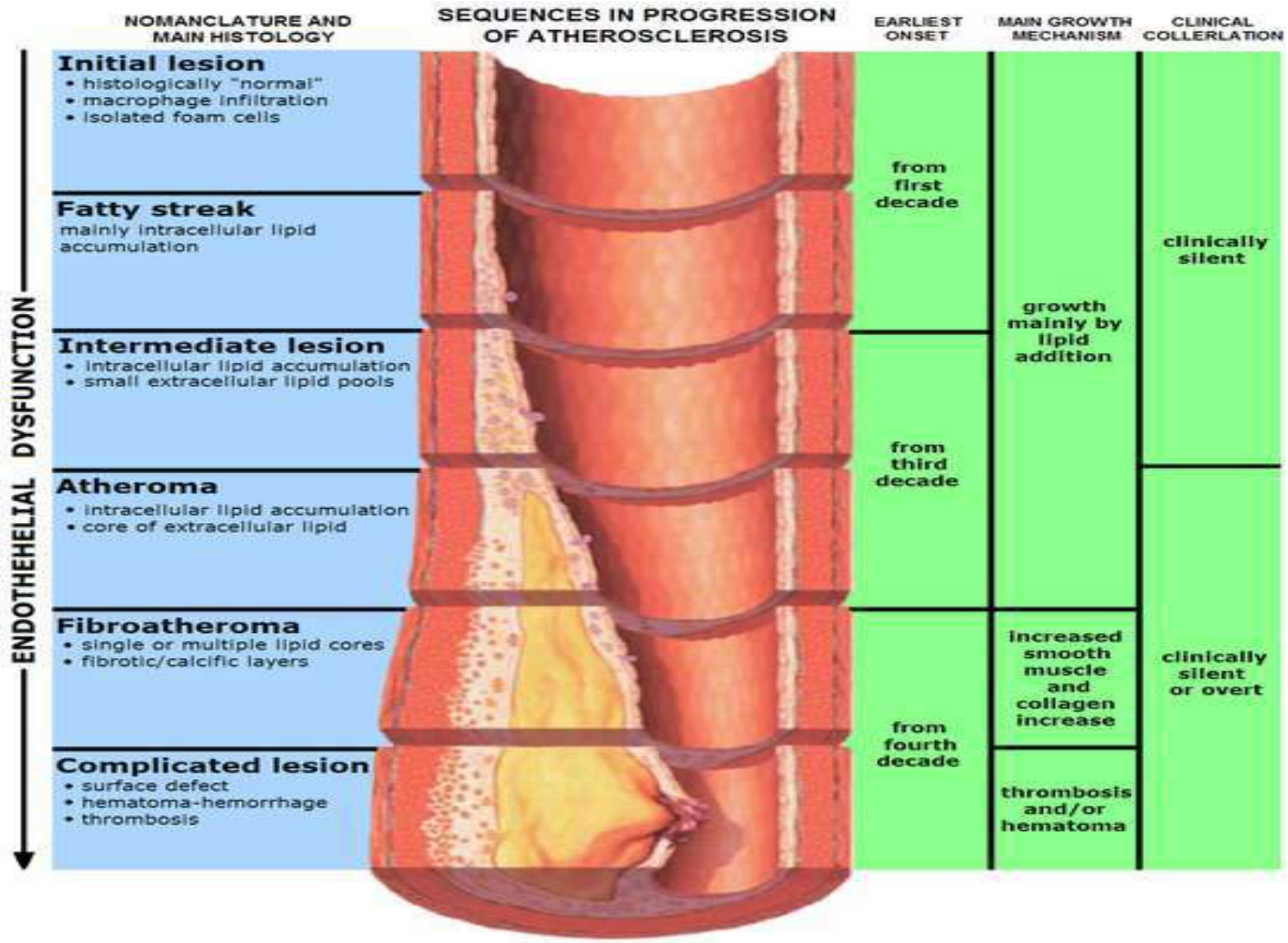
a)Familial hypolipoprotenemia: Defect: Failure in the synthesis of apo B lipoproteins. LDL level increases in the blood.

b)Abeta lipoprotenemia: Defect: Absence of Apo B100. LDL fraction is completely absent.

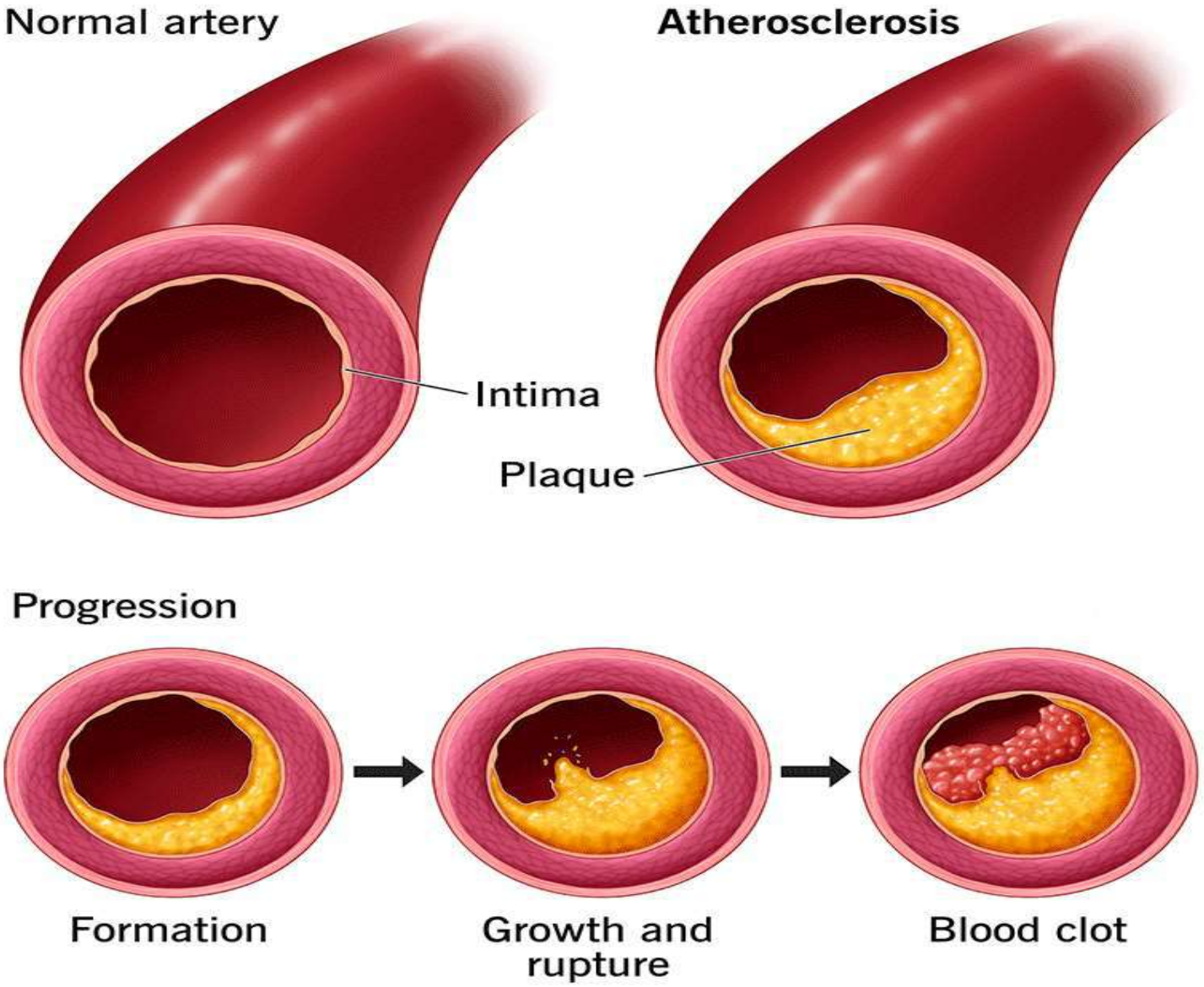
c)Familial α-lipoprotein deficiency (Tangier disease): Defect: HDL deficiency, due to reduction in Apo A synthesis.

Cholesterol :Normal level of cholesterol in serum is 150-220 mg/ di. Elevated serum cholesterol level is the major risk factor in promoting atherosclerosis.

Hypercholesterolemia and development of atherosclerosis and CHD: Hypercholesterolemia is mostly associated with increased LDL cholesterol levels. Increased cholesterol level (mainly LDL fraction) leads to the deposition of cholesterol in the intimal side (inner side) of the arteries, resulting in the formation of fibrous plaques and consequent thickening and hardening of arterial wall causing the condition**. Atherosclerosis**. Coronary arteries, aorta and cerebral vessels are predominantly affected. The atherosclerotic plaques lead to narrowing of blood vessels. So, the blood flow through them becomes turbulent and there is increased tendency for clot formation.


NOMANCLATURE AND MAIN HISTOLOGY
SEQUENCES IN PROGRESSION OF ATHEROSCLEROSIS
EARLIEST ONSET
MAIN GROWTH MECHANISM
CLINICAL COLLERLATION
ENDOTHEHELIAL DYSFUNCTION
Initial lesion
• histologically "normal"
• macrophage infiltration
• isolated foam cells
Fatty streak
mainly intracellular lipid accumulation
Intermediate lesion
• intracellular lipid accumulation
• small extracellular lipid pools
Atheroma
• intracellular lipid accumulation
• core of extracellular lipid
Fibroatheroma
• single or multiple lipid cores
• fibrotic/calcific layers
Complicated lesion
• surface defect
• hematoma-hemorrhage
• thrombosis
from first decade
from third decade
from fourth decade
growth mainly by lipid addition
increased smooth muscle and collagen increase
thrombosis and/or hematoma
clinically silent
clinically silent or overt

Atherosclerosis



Causes of Hypercholesterolemia (and atherosclerosis and CHD):

- **Diabetes mellitus**: Due to increased cholesterol synthesis since the availability of acetyl CoA is increased.
- **Obstructive jaundice**: Cholesterol is mainly excreted through bile. obstructive jaundice, there is an obstruction in the cholesterol excretion through bile, causing hypercholesterolemia.
- **Hypothyroidism**: Thyroid hormones play a role in reducing serum cholesterol level. So, cholesterol levelincreases in hypothyroidism.
- **Nephrotic syndrome**: in nephrotic syndrome, lipoprotein lipase (which is required to clear lipids from blood) may be lost in the urine.
- **Familial Hypercholesterolemia** (Familial type II a hyperlipoproteinemia): due to the defect in LDL receptors (required for hepatic cholesterol uptake), cholesterol level increases in blood.
- **Other risk factors** that alter the serum cholesterol level are heredity, high BP, smoking, obesity, lack of exercise, emotional stress, excess coffee drinking, sucrose consumption.

1- Lipoproteins rich in triglycerides :-

a-Chylomicrones .

b-Very low density lipoprotein .

c- Both a and b .

d-Intermediate density lipoprotein .

e-Low density lipoprotein .

2-A lipoprotein contain the highest cholesterol proportion is :-

a-Low density lipoprotein .

b-Intermediate density lipoprotein .

c-Very low density lipoprotein .

d-High density lipoprotein .

e-Chylomicrons .

3-**The following may cause hypercholesterolemia except :-**

a-Diabetes mellitus .

b-Obstructive jaundice .

c-Hypothyroidism .

d-Metabolic acidosis .

e-Nephrotic syndrome .

4-**Fatty liver may be caused by diabetes mellitus because :-**

a-Increased mobilization of fat from adipose tissues .

b-Decreased production of insulin .

c-Hyperglycemia .

d-Decreased formation of VLDL .

e-Increased fatty acids synthesis .

(1- C , 2- a , 3- d < 4 – a)

Al-Noor University College
Department of Medical Laboratory Techniques
Stage :Third year
Subject :Clinical Biochemistry
Semester: Second
Lecture number : 26 - 30
Topic : Hormones (modified 2023)

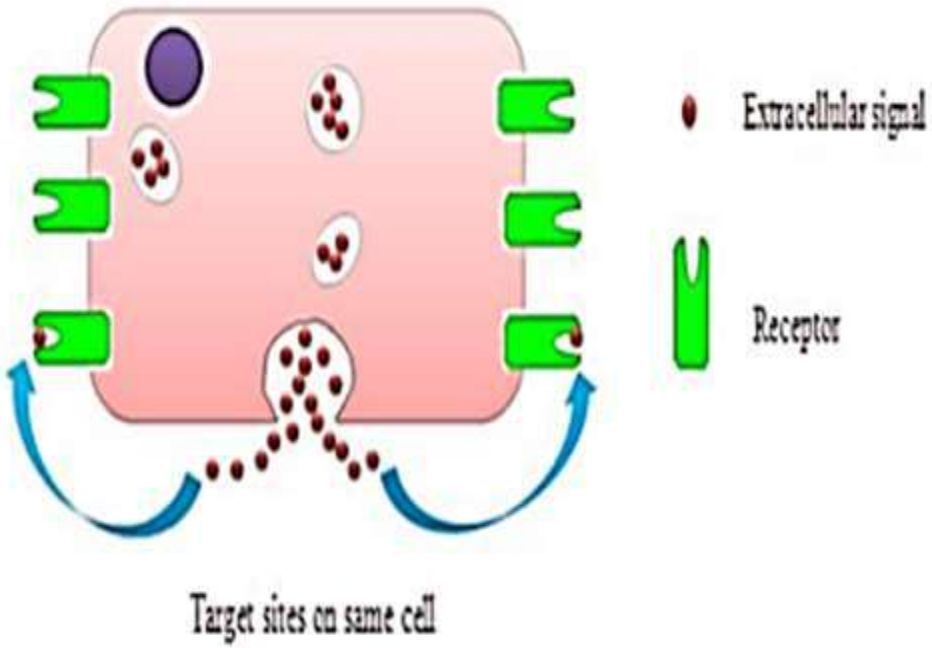
Concept of hormones

Hormones are chemicals that are responsible for controlling and regulating the activities of certain cells and organs. These hormones are secreted by ductless glands known as endocrine glands.

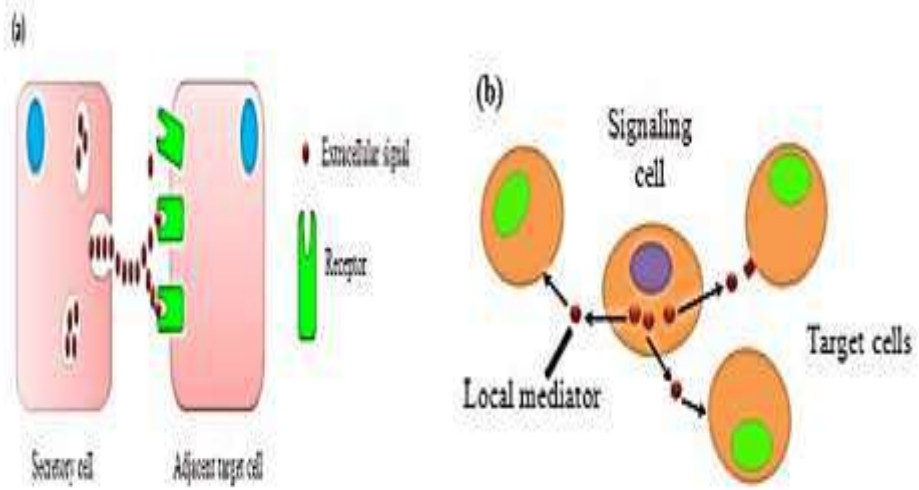
The nervous system and endocrine system are the major control mechanisms that integrate the functions of the tissues in the body. The nervous system transmits electrochemical signals between the brain and peripheral tissues for coordinating diverse body functions.
The endocrine system releases chemical mediators or hormones into circulation. However, both these systems converge, so that neural regulation of endocrine glands are affected.

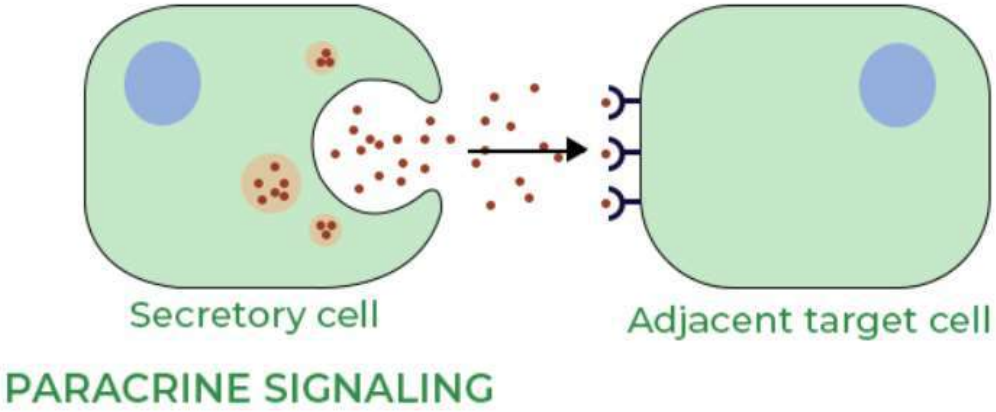
Signal molecules are of different types and the process of transferring the signal into the cell is called signal transduction. There are two types of cells in signal transduction the sender cell where the signal originates and the target cell that receives the signal. The signal alters or modulates the activity/function of the cell. The types of these signals are:

1- **Autocrine signaling** occurs when the same cell acts as sender and recipient, e.g., growth.

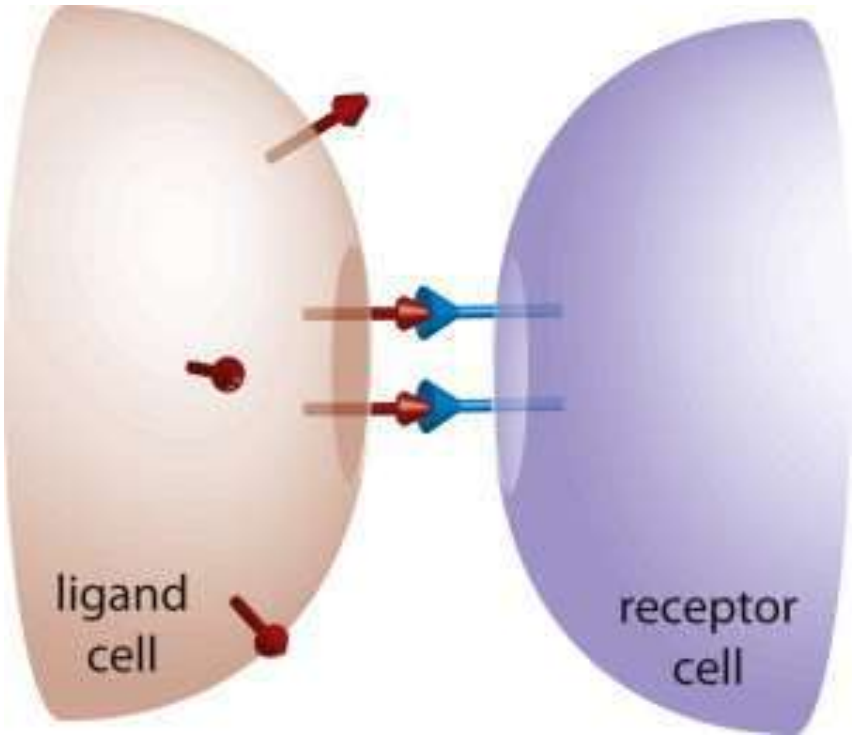


2- **Paracrine signaling** is affected by local mediators which have their effect near the site of secretion without entering the circulation.

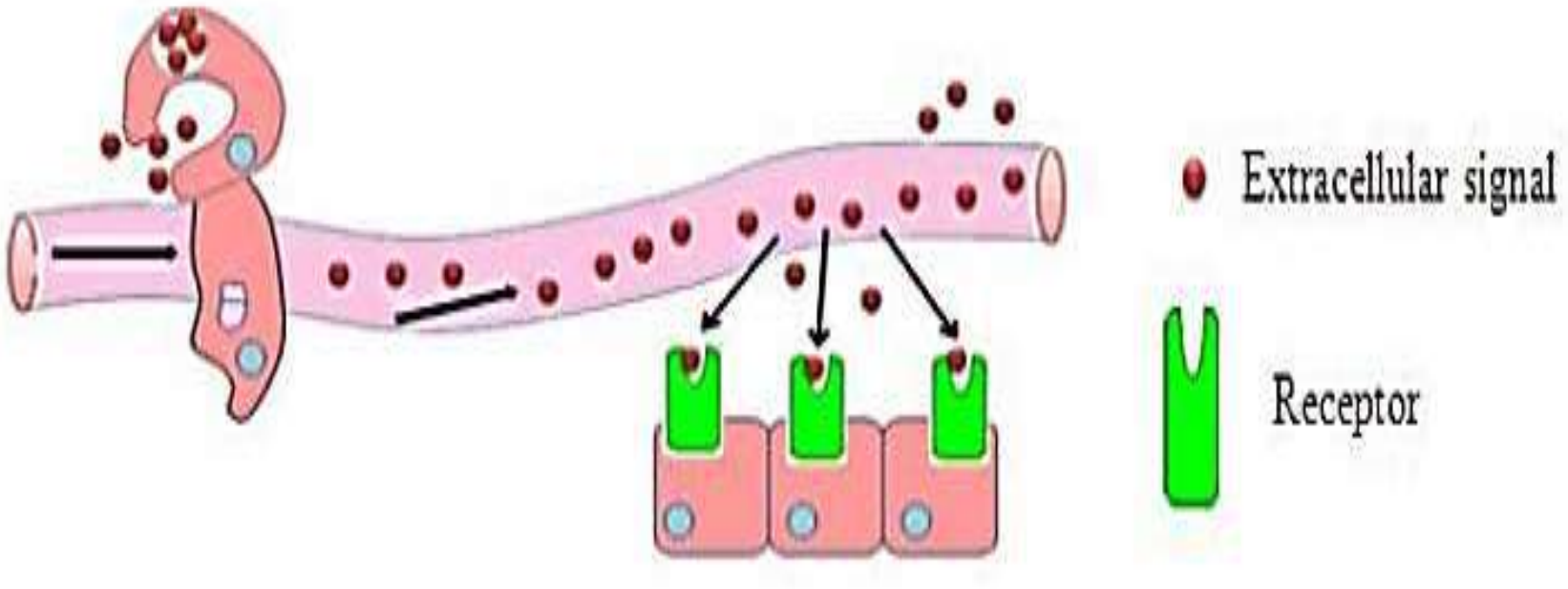




3- Juxtracrine signaling occurs when the two types of cells are adjacent to each other



4- Endocrine signaling is between cells that are located at a distance from each other and the signal may be hormones or chemical messengers **secreted into circulation**. Once they reach the target cell, **they bind to specific target cell receptors** with high affinity.

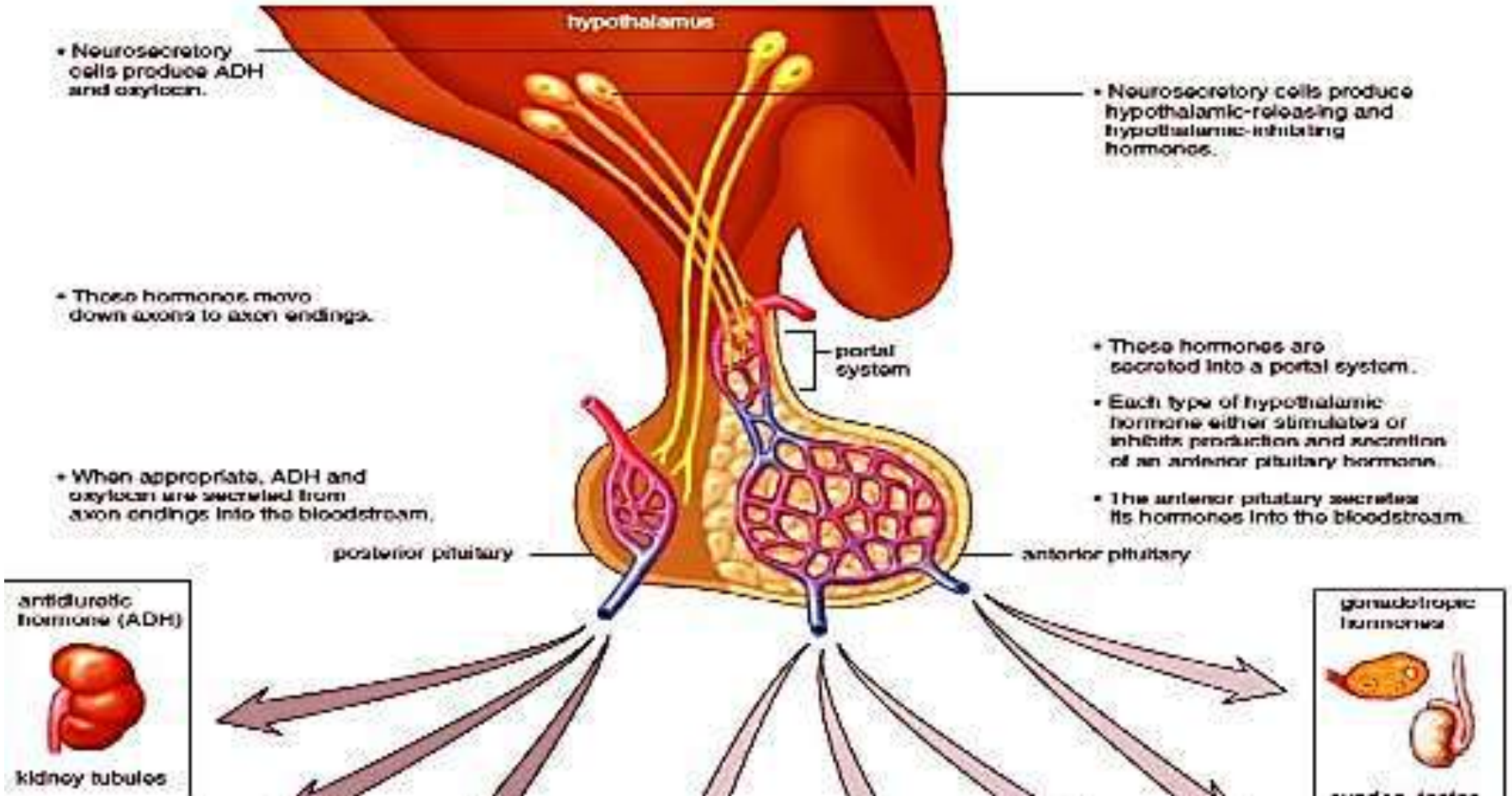


The hypothalamus produces two types of endocrine factors:

a- Hypothalamic neuropeptides. These neurohormones are **antidiuretic hormone (ADH)** and **oxytocin**.

b- Hypothalamic releasing factors : The **releasing factors are neurosecretions synthesized in the hypothalamus and released through the hypothalamic-pituitary portal circulation**. They have an effect on the secretion of **pituitary tropic hormones.**

(Tropic hormones :- are a class of hormones from the anterior pituitary gland that affect secretion of other endocrine glands **)**


hypothalamus
• Neurosecretory cells produce ADH and oxytocin.
• Neurosecretory cells produce hypothalamic-releasing and hypothalamic-inhibiting hormones.
• These hormones move down axons to axon endings.
portal system
• These hormones are secreted into a portal system.
• Each type of hypothalamic hormone either stimulates or inhibits production and secretion of an anterior pituitary hormone.
• The anterior pituitary secretes its hormones into the bloodstream.
• When appropriate, ADH and oxytocin are secreted from axon endings into the bloodstream.
posterior pituitary
anterior pituitary
antidiuretic hormone (ADH)
kidney tubules
gonadotropic hormones

Name	Chemical nature	Biological actions
TRH; thyrotropin releasing hormone	Tripeptide; (pyro-Glu-His-Pro-NH_2)	Induces secretion of TSH and PRL; neuromodulator
GnRH; gonadotropin releasing hormone	Biologically active portion is a decapeptide	Releases LH and FSH; induces spermatogenesis, ovulation and testosterone
GHRH; growth hormone releasing hormone	37–44 amino acid; amino terminal end is tyrosine	Stimulates growth hormone secretion
CRF; corticotropin releasing factor	Amidated peptide with 41 amino acids	Release of ACTH. Inhibited by cortisol
Somatostatin; growth hormone inhibitory factor	Cyclic peptide with 14 amino acids	Inhibits secretion of GH and TSH. Inhibits gut hormones, pancreatic and gastric secretion
PIF; prolactin inhibitory factor	Dopamine	Inhibits PRL release

A Direct connection between hypothalamus & adrenal medulla: it controls epinephrine & norepinephrine secretion.

The pituitary gland is the master gland: The pituitary is a small, pea-sized gland situated at the base of the brain, anterior : The pituitary controls **3 endocrine glands**: the thyroid, adrenal glands, and gonads. 3 endocrine glands not controlled by the pituitary;

Acronym	*Full name*	*Chemical nature*	*Mol.wt. in kD*	*Amino acids*
GH	Growth hormone	Polypeptide	22	191
ACTH	Adrenocortico-tropic hormone	Polypeptide	4.5	39
LH	Luteinizing hormone	Glycoprotein; α,β chains	29	α = 89 β = 115
FSH	Follicle stimulating	Glycoprotein; α,β chains hormone	29	α = 89 β = 115
TSH	Thyroid stimulating hormone	Glycoprotein; α,β chains	28	α = 96 β = 115
MSH	Melanocyte stimulating hormone	Polypeptide	13	α = 13 β = 18 γ = 12
PRL	Prolactin b Endorphins	Polypeptide Polypeptides	22 4	198 31
LPH	Lipotropic hormone	Polypeptide	11	β = 91 γ = 60

Several other glandular tissues are considered to secrete hormones:
Heart: atrial natriuretic peptide (ANP).
kidney: produce the hormone erythropoietin, renin &1,25(OH)2cholecalciferol.
Thymus: This produces a hormone that circulates from this organ to stem cells in the lymphoid organ inducing them to become immunologically competent lymphocytes.
GI tract: are called GI Hormones.

The characteristics of endocrine hormone:

1- They are secreted directly in blood in small amounts (very active).

2- Some hormones have generalizer action e.g., growth hormone & thyroxine. Others affect specific target organs e.g., sex hormones & ACTH.

3- Hormones are removed either by target cell uptake, metabolism inactivation by the liver, or excretion by the kidney.

4- Hormones play a key role in the regulation of almost all body functions including metabolism, growth, development, H2O and electrolyte balance, reproduction, and behavior.

Biochemical structure & synthesis hormones: they are classified as:

1. **Steroid hormones**: such as adrenocorticosteroid hormones, and progesterone.
2. **Amino acid derivatives**: such as epinephrine, norepinephrine and thyroid hormones.
3. **Peptide/Protein hormones**: such as Insulin, glucagon, parathormone, calcitonin, pituitary hormones,

Chemical structure & synthesis of hormones		
	Water soluble	Lipid soluble
Chemical nature	Protein & polypeptide (most hormones)	Steroid (sex hormones)
Gland	Pituitary, pancreas & parathyroid	Gonads & adrenal cortex
Action	Activation of enzymes	Synthesis of enzymes
Onset	Rapid action (minutes)	Slow action (hours or days)
Site of formation	In rER	In SER from cholesterol
Storge	more	Little
Release	By exocytosis	Carried plasma proteins

The Plasma carrier proteins exist for all classes of endocrine hormones. Carrier proteins for peptide hormones prevent hormone destruction by plasma proteases. Carriers for steroid and thyroid hormones allow these hydrophobic hormones to be present in the plasma. Carriers for small, hydrophilic amino acid-derived hormones prevent their filtration through the renal glomerulus, greatly prolonging their circulating half-life.

1 -------- are responsible for synthesis and secretion of hormones :- (M)

a) Adipose tissues ;

b) The pancrease .

c) The kidneys .

d) The endocrine glands .

e) The intestine .

2-The following are types of signals except :-

a) Juxtracrine signalling .

b) Autocrine signaling .

c) Paracrine signaling .

d) Tumor markers .

e) Endocrine signaling .

3**-Hormones may have the following chemical structure except :-**

a) Steroid .

b) Peptides .

c) Polysaccharides .

d) Protein .

e) Amino acid derivative .

4- Endocrine signaling is characterized by :-

a) Occurs between two adjacent cells .

b) Do not enter into the general circulation .

c) Occurs between cells located at a distance form each other .

d) They have low affinity to their receptors .

e) They are neurotransmitters .

5) Paracrine signaling is characterized by :-

a) Occurs in the same cell .

b) Affects cells which are near the site of secretion .

c) Occurs between two adjacent cells .

d) Occurs between cells far away from each others .

e) None of the others .

6) The hypothalamic neuropeptides are :-

a) Glucagon .

b) Insulin .

c) Antidiuretic hormone .

d) Oxytocin .

e) Both c & d .

7-**The hypothalamus produce s the following tropic hormones except :-**

a) Thyrotropin releasing .
b) Antidiuretic
c) Gonadotropin releasing .
d) Growth hormone releasing hormone .
e) Corticotropin releasing .

8- The following endocrine glands are controlled by the pituitary gland :-

a) Atrial naturetic poly peptide .
b) The thyroid .
c) The adrenal .
d) The gonads .
e) All b , c & d .

9- One of the following hormones is not controlled by the hypothalamus :-

a) Insulin .
b) Growth hormones .
c) Luteinizing hormone .
d) Thyroid stimulating hormone .
e) Prolactin .

10- The functions of plasma carrier proteins :-

a) All of b,c and e .

b) To prevent destruction by proteases .

c) To allow hydrophobic hormones to be present in plasma .

d) To facilitate their diffusion into the cells .

e) To prevent their filtration by the glomerulus .

1.d , 2. d , 3. c , 4.c, 5. b , 6. e, 7. b , 8 . e , 9. e , 10 , a

كلية النور الجامعة
قسم تقنيات المختبرات الطبية
أمتحانات منتصف الفصل الثاني النظرية / 2022 - 2023

Day	Date	المرحلة الاولى (وجبة اولى)	المرحلة الثانية (وجبة ثانية)	المرحلة الثالثة (وجبة أولى)	المرحلة الرابعة (وجبة ثانية)
Saturday	29/4/2023	Human Biology II	Parasitology	Clinical Chemistry	Diagnostic Microbiology
Sunday	30/4/2023			English Language	English Language
Tuesday	2/5/2023	Anatomy	Histology	Hematology	Medical Parasitology
Wednesday	3/5/2023	Arabic Language			
Thursday	4/5/2023		Microbiology	Mycology	Clinical Immunology
Saturday	6/5/2023	General chemistry II	Molecular Biology	Histopathology	Advanced Clinical Chemistry
Sunday	7/5/2023			Human Genetics	Laboratory Management
Monday	8/5/2023	Computer applications II	Biochemistry		
Tuesday	9/5/2023			Advanced Laboratory Tech.	Pathology
Wednesday	10/5/2023				
Thursday	11/5/2023	Laboratory instrument II	Physiology	Immunology	Blood Transfusion

ملاحظات مهمة:

- الامتحانات النظرية : (الوجبة الاولى) تبدأ الساعة التاسعة والنصف صباحا ولمدة ساعة ونصف, (الوجبة الثانية) تبدأ الساعة الثانية عشرة ظهرا ولمدة ساعة ونصف.
- المواد التي باللون الاصفر ستتم امتحاناتها بطريقة ال Bubble Sheet.
- على الطالب إحضار هوية الكلية وتعتبر أساسا لدخول القاعة الامتحانية, ويمنع منعا باتا إدخال الهواتف النقالة والساعات الذكية والوسائط اللاسلكية إلى قاعة الامتحان.
- في حالة حصول عطلة رسمية في أحد أيام الامتحانات فيتم تأجيل الامتحان بتلك المادة إلى يوم سيتم الاعلام عنه لاحقا.
- جميع أمتحانات مواد التحميل (العبور) تتم في قاعة (الطلبة المحملين) في الطابق الخامس بناية العمادة.
- لا يسمح بتأجيل الامتحانات الا في حالة المرض وجميع أمتحانات الطلبة المؤجلين ستجري خلال يوم واحد فقط هو يوم السبت المصادف 2023/5/13.

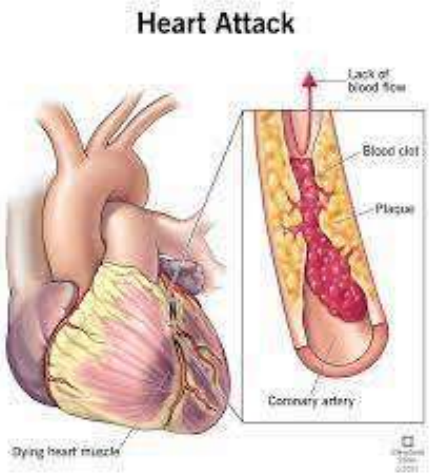
محاضرات التقنية الوسطى المحدثة

HEART FUNCTIONS AND ITS TESTS

L : 16 -17

Heart Diseases include:

- **Myocardial infarction (MI):** also known as “heart attack,” is caused by decreased or complete cessation of blood flow to a portion of the myocardium. Myocardial infarction may be “silent” and go undetected, or it could be a catastrophic event leading to hemodynamic deterioration and sudden death. Most myocardial infarctions are due to underlying coronary artery disease.



- **Cardiac arrest**: is the sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation. If corrective measures are not taken rapidly, this condition progresses to sudden death.

Atherosclerosis: is a chronic inflammatory disease in which there is a buildup of plaques inside arteries. Atherosclerosis mainly develops through the continuous process of arterial wall lesions due to lipid retention by trapping in the intima by a matrix such as proteoglycans resulting in a modification which, in turn, aggravates chronic inflammation at vulnerable sites in the arteries and plays an important role at all phases of the atherogenic progression.

- **Angina**: is chest pain or discomfort caused when heart muscle doesn't get enough oxygen-rich blood. It may feel like pressure or squeezing in chest.

Cardiac biomarkers

These are substances that are released into the blood when the heart is damaged or stressed. Measurements of these biomarkers are used to help diagnose acute coronary syndrome (ACS) and cardiac ischemia, conditions associated with insufficient blood flow to the heart.

• Tests for cardiac biomarkers can also be used to help determine a person's risk of having these conditions or to help monitor and manage someone with suspected ACS and cardiac ischemia .The root causes of both acute coronary syndrome (ACS) and cardiac ischemia are usually the buildup of plaque in artery walls and hardening of the arteries (atherosclerosis). This can result in severe narrowing of the arteries leading to the heart for a sudden blockage of blood flow through these coronary arteries . Cardiac ischemia is caused when the supply of blood reaching heart tissue is not enough to meet the heart's needs. • When blood flow to the heart is blocked or significantly reduced for a longer period of time (usually for more than 30-60 minutes), it can cause heart cells to die and is called an acute myocardial infarction (AMI or heart attack).

Cardiac biomarkers

Biomarkers of myocardial injury: This test measures the levels of cardiac biomarkers in the blood. These markers include enzymes, hormones, and proteins (LDH, GOT, CK, cardiac troponin, myoglobin, other markers) .

1**. Lactate dehydrogenase isoenzymes**: were used widely in the past for diagnosis of myocardial infarction, but more recently, due to availability of troponin immunoassays, lactate dehydrogenase isoenzyme assay has been mostly discontinued in the clinical setting for diagnosis of myocardial infarction. Briefly, LDH exists in five isoenzymes forms (LDH1 , LDH2, LDH3, LDH4, and LDH5) Usually LDH isoenzymes levels increase after 24–72 hours following myocardial infarction and reach a peak concentration in 3–4 days. The levels remain elevated for 8 to 14 days, making it a late marker for myocardial infarction. Concentration can be elevated in hemolytic anemia, stroke, pancreatitis, ischemic cardiomyopathy, and a variety of other diseases.

2. GOT (glutamate oxaloacetate transaminase) : The first biomarker used to aid in the diagnosis of acute MI was GOT, also called aspartate aminotransferase (AST). The GOT released from cardiomyocytes undergoing necrosis would be useful in diagnosing acute MI

3-Creatine kinase: is an enzyme found primarily in heart muscle cells. There are three isoforms are called isoenzymes:

a-CK-MM (found in skeletal muscles and the heart)

b-CK-MB (found mostly in the heart, but small amounts found in skeletal muscles).

c-CK-BB (found mostly in the brain and smooth muscle

4- Myoglobin: The small heme protein that assists in oxygen transport in all muscle tissues, is released within 1 -4 hour and rises more rapidly than Troponin or CKMB. peaks in nearly 8 to 10 hours, and returns to normal within 24 hours.

5-Troponins:

Troponins are a complex of 3 protein subunits , namely troponin C, troponin T and troponin I, located on the thin filaments of the skeletal and cardiac muscle fibers. Troponin C is the calcium-binding component, troponin T is the tropomyosin-binding component and troponin I is the inhibitory component. As the isoforms of troponin C is identical in the skeletal and cardiac muscle, troponin C is not extremely specific for myocardialinjury. Troponin I is extremely specific for the cardiac muscle and has not been isolated from the skeletal muscle. This absolute specificity makes it an ideal marker of myocardial injury.

Cardiac markers : questions

1- The most important factor in all heart diseases is :-
a- Reduced heart rate .
b- Reduced blood pressure .
c- decreased blood flow to the myocardium .
d- Reduced oxygen availability .
e- Ischemia .

2-, what is the best single test for cardiac function :-
a- LDH isoenzymes .
b- GOT .
c- Myoglobin .
d- Troponin I .
e- CK-MM .

3- Troponin I is used to qualitatively assess heart function because : -
a- It is a quick test .
b- it is most specific .
c- It is the cheapest .
d- It does not require special equipment .
e- All of the above .

1- c , 2- d , 3 - e

محاضرات التقنية الوسطى المحدثة

ENZYMES AND ISOENZYMES
(L : 23 , 24 , 25)

Enzymes are catalysts that increase the rate or velocity of physiological reactions.

Each and every reaction in our body takes place with the help of an enzyme.

- **Enzymes present in plasma can be classified into 2 types, they are:**
  - **Functional Plasma enzymes and**
  - **Non-functional plasma enzymes**

- **Functional plasma enzymes**: They are Present in plasma at a higher concentration than in tissues.

  1- Mostly synthesized by the liver

  2- Usually decreased in disease conditions (E. g. Clotting enzymes)

Non-functional plasma enzymes:

1-Present in plasma at a lower concentration than tissues

2-Does not have any function in the plasma

3-Mostly synthesized by the liver, skeletal muscle, heart, brain

Usually increased in disease conditions

(E. g. Creatine kinase, Alanine transaminase)

Assessment of Cell Damage and Proliferation

Plasma enzyme activities can be used in the diagnosis of disease and the prognosis of treatment. Plasma enzyme levels depend on the balance between the rate of influx of active enzyme into the circulation and its eventual clearance from the blood.

Estimation of more than one enzyme

Many enzymes are widely distributed, but their relative concentrations may vary in different tissues. For Ex., Alanine and aspartate transaminases (GOT&GPT) are abundant in the liver, but the concentration of aspartate transaminase (GOT) is much greater than that of alanine transaminase (GPT) in heart muscle .

Isoenzyme's determination

Some enzymes exist in more than one form: these isoenzymes may be separated by their different physical or chemical properties (electrophoresis).

Pancreatic enzymes :-

α-Amylase: Marked increase (five to 10 times the upper reference limit): Acute pancreatitis, Severe glomerular impairment .

Moderate increase (up to five times the upper reference limit): Perforated peptic ulcer, Acute cholecystitis, Intestinal obstruction, Salivary gland disorders like mumps, salivary calculi

Lipase

Plasma lipase levels are elevated in acute pancreatitis and carcinoma of the pancreas.

Clinical Significance

Serum **amylase** is increased in mumps, pancreatic disease, or due to some other cause, whereas **lipase** is increased only in pancreatitis. Therefore, the determination of both amylase and lipase together helps in the diagnosis of acute pancreatitis

Trypsin

• Trypsin: (TRY): is a serine proteinase that hydrolyzes the peptide bonds formed by the carboxyl groups of lysine arginine with other amino acids. Increased in pancreatic disease

Liver enzymes:

There are three types of enzymes:

1. Enzymes that are normally present inside the hepatocytes and released into the blood when there is hepatocellular damage = markers of **hepatocellular damage**.
2. Enzymes that are primary membrane-bound (plasma membrane or side of hepatocytes) = **markers of cholestasis**
3. Enzymes that are synthesized in the hepatocyte = indicate disturbances in the **hepatocellular synthesis**

Markers of hepatocellular damage:

Aminotransferases/Transaminases (GPT): Elevated plasma GPT is considered to be relatively specific for liver disease . GOT may be elevated in other forms of tissue damage, such as myocardial infarction, muscle necrosis, and renal disorders.

Markers of cholestasis

1. Alkaline phosphatase (ALP). Half-life= 10 days.
2. Gamma-glutamyl-transferase (glutamyl transferase; GGT): catalyzes the transfer of the–glutamyl group from peptides, GGT occurs mainly in the cells of the liver

Isoenzymes of creatine kinase

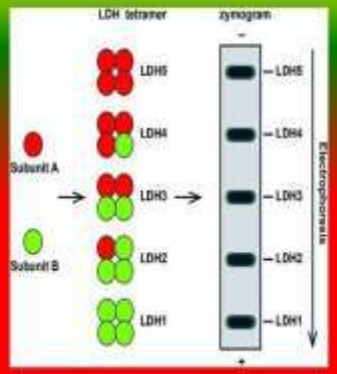
• CK consists of two protein subunits, M (for muscle) and B (for the brain), which combine to form three isoenzymes. BB (CK-1), MB (CK-2) and MM (CK-3).
• **CK-MM** is the predominant iso-enzyme in skeletal and cardiac muscle and is detectable in the plasma of normal subjects.
• **CK-MB** accounts for about 35 percent of the total CK activity in cardiac muscle and less than five percent in skeletal muscle
• **CK-BB** is present in high concentrations in the brain and in the smooth muscle of the gastrointestinal and genital tracts.

Lactate Dehydrogenase

• Lactate Dehydrogenase catalysis the reversible inter-conversion of lactate and pyruvate. The enzyme has high concentrations in cells of cardiac and skeletal muscle, liver, kidney, brain, and erythrocytes.

Lactate Dehydrogenase (LDH) Isoenzymes Test

Medical Lab Tests



Types of LDH Isoenzymes

- LDH-1: heart and red blood cells
- LDH-2: white blood cells
- LDH-3: lungs
- LDH-4: kidneys, placenta, and pancreas
- LDH-5: liver and skeletal muscle

Enzymes and Isoenzymes :-

1-Non – functional plasma enzymes :-

a) Are present at higher concentration than tissues .
b) They have specific functions in plasma .
c) They have no diagnostic benefit .
d) They are the clotting enzymes .
e) Are mostly synthesized by the liver , muscles , heart , and brain .

2- ---------- are biological catalyst present in more than one form :-

a) Enzymes rarely found in plasma.
b) Enzymes of the pancreatic origin .
c) Isoenzymes .
d) Enzymes of the gastrointestinal origin .
e) None of the above .

3- A hydrolase enzyme catalyzes the hydrolysis of 1,4 glycosidic linkage :-

a) Renin .
b) Pancreatic amylase .
c) Hydrolyses peptides .
d) Increase serum activity in hepatitis .
e) Are normally present at high concentration in the urine .

4- In the heart muscle , an enzyme is present at higher concentration than the liver is :-

a) Lactate dehydrogenase (LDH) .
b) Creatine kinase (CK) /
c) Aspartate transaminase (GOT) .
d) Alanine transaminase (GPT) .
e) Gamma glutamyle transferase (GGT) .

5- A marker for cholestsis :-

a) Alkaline phosphatase (ALP) .
b) Alanine transaminase (GPT) .
c) Aspartate transaminase (GOT) .
d) Amylase .
e) CK-MB .

6- The most specific enzyme for liver disease is :-

a) Lactate dehdrogenase (LDH) .
b) Gmma glutamyle transferase (GGT) .
c) Alkaline phosphatase (ALP) .
d) Pancreatic lipase .
e) Alanine transaminase (GPT) .

7- Lactate dehydrogenase (LDH) is present in the following tissue except :-

a) Skeletal muscle .

b) The liver .

c) Heart muscle .

d) Kidneys .

e) The pancreas .

1. e , 2. c , 3. b , 4. c , 5. a , 6. e , 7. e

Lectures 3 & 4
Electrolytes and Elements
(new and revised)

Electrolytes and Minerals (Trace Elements) Metabolism

Minerals are inorganic substances mined from the earth. They are not of plant or animal origin. They exist naturally on and in the earth and many are critical parts of human tissue and are termed “essential” nutrients. Of the 92 naturally occurring elements, the 14 minerals that have been shown by research to be essential to human health are: calcium, chromium, copper, fluorine, iodine, iron, magnesium, manganese, molybdenum, phosphorus, potassium, selenium, sodium and zinc. Essential macro minerals are those needed in significant quantities (such as calcium) – usually measured in milligrams, and essential trace minerals are those needed in minute quantities (such as selenium) – usually measured in micrograms (one microgram [µcg] equals 1/1,000th of a milligram [mg]). We have less than 100 years of knowledge on role of elements in the human body. It is estimated that 98% of the body mass of man is made up of nine nonmetallic elements. The four main electrolytes namely sodium, magnesium, potassium, and calcium constitute about 1.98 %, while the rest 0.02% or 8.6 g of an average human adults is made up of 10 typical trace elements. However, this tiny fraction exerts a tremendous influence on all body functions.

Minerals are required for a variety of physiological functions, their functions are:

1. Maintenance of osmotic pressure of cell
2. Transport of oxygen
3. Growth and maintenance of tissues and bones
4. Working of nervous system
5. Muscle contraction
6. Maintenance of electrolytic balance
7. Acid-base balance

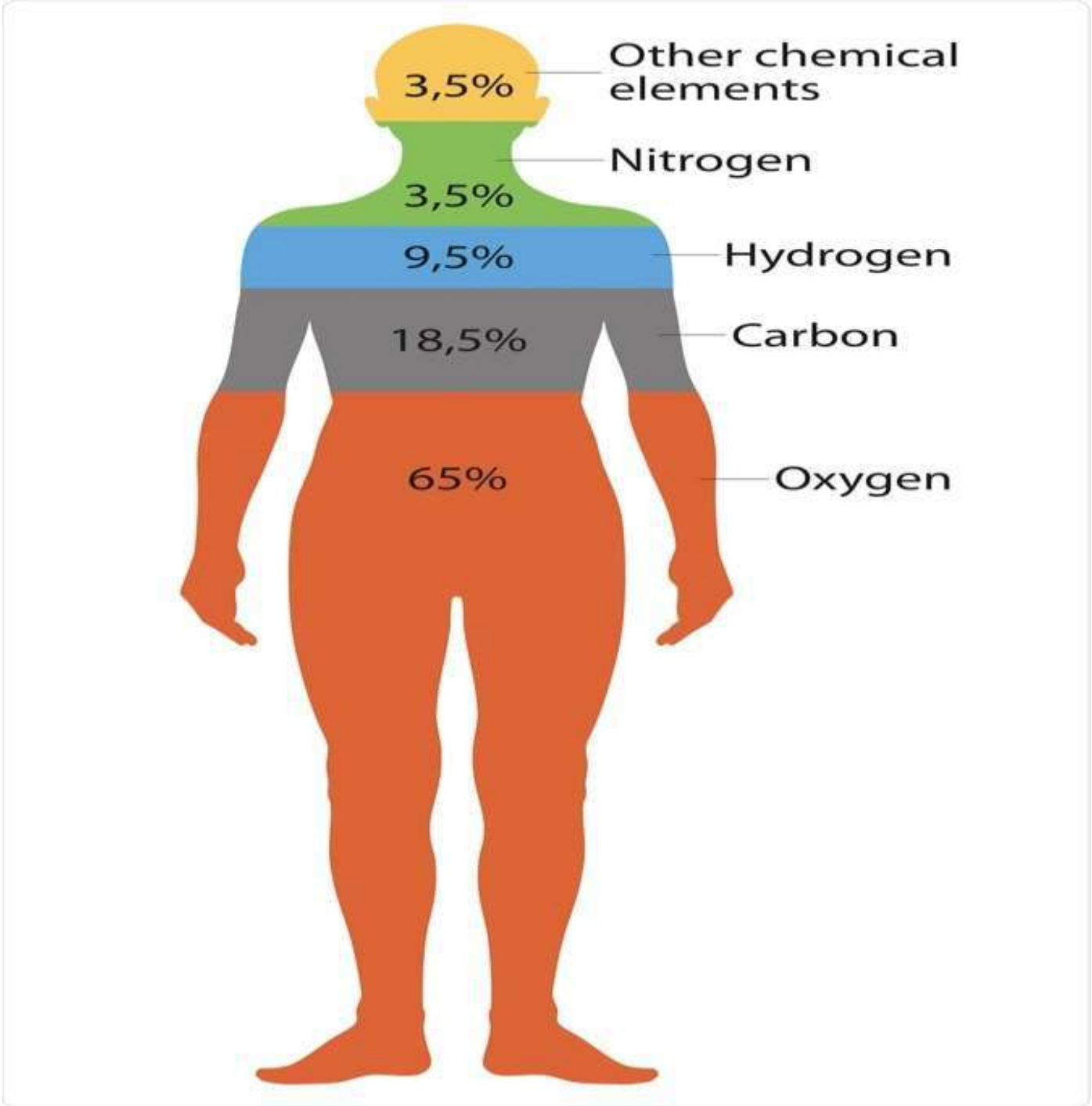
Mineral content of human :-

Approximate amount of Elements in body (in gm) in 70 Kg adult. usually measured in micrograms (one microgram [µcg] equals 1/1,000th of a milligram [mg]).

Ca++ : 1.50 % , 1050 (g)
P : 1.00 % , 700 (g)
K + : 0.35 % , 245 (g)
Na+: 0.15 % , 105 (g)
Cl–: 0.15 % , 105(g)
Mg++: 0.05 % . 35 (g)
Fe++ : 0.004% , 3 (g)
Zn++ : 0.0033 % , 2(g)

O2 : 65 % (45 Kg)
C : 18 % (12.6 kg)
H2 : 10 % (7 kg)
N2 : 3 % (2.1 kg)

Electrolytes — **Na** (Sodium), **Mg** (Magnesium), **K** (Potassium), **Ca** (Calcium), **P** (Phosphorus), **S** (Sulfur), **Cl** (Chlorine).
Essential trace elements (less than 0.01%)— **Mn** (Manganese), **Fe** (Iron), **Co** (Cobalt), **Ni** (Nickel), **Cu** (Copper), **Zn** (Zinc), **Mo** (Molybdenum), **Se** (Selenium), **I** (Iodine).
Function suggested from active handling humans, but no specific identified biochemical functions — **Li** (Lithium), **V** (Vanadium), **Cr** (Chromium), **B** (Boron), **F** (Fluorine), **S**i (Silicon), **As** (Arsenic).


3,5%
Other chemical elements
Nitrogen
3,5%
9,5%
Hydrogen
18,5%
Carbon
65%
Oxygen

Electrolytes (Na, K, Mg, Ca, Cl)

Sodium (Na++): Sodium is a major cation and contributor to the osmolality of the extracellular fluid of the body, which is one-third of the body water in adults. The sodium content of natural food varies between 0.1 and 3.3 mmol/100 g. In contrast, processed foods have a sodium content of 11–48 mmol/100 g, partly sodium nitrate is used as a preservative. Sodium is concentrated in the extracellular fluid, giving osmolarity and charge. moves from the extracellular fluid into cells cause a change in charge and concentration.

Absorption and availability of sodium : Intestinal sodium absorption is very efficient in both the small intestine and colon. Sodium is absorbed by a variety of processes. In the proximal intestine sodium is absorbed, in part by a solute dependent cotransport system, and is involved in nutrient absorption. In the more distal intestine and colon, sodium absorption is by a sodium/hydrogen interchange; in the colon this process is coupled to chloride/bicarbonate exchange. In the distal intestine and colon, the process is electroneutral and involves protein carriers. In the distal colon active sodium transport occurs against an electrochemical gradient. Water absorption is a passive process that requires active transport of sodium and chloride. The optimum absorption of water occurs when the concentration of glucose in the intestinal lumen is around 110 mmol/l. This finding has been of great importance in the development of oral replacement solutions (ORS).

Sodium content of the body

A male adult weighing 65–70 kg has a total body sodium content of 4 mol (100 g):

- 500 mmol (11.5 g) in intercellular fluid (concentration 2 mmol/l)
- 1500 mmol (34.5 g) in bone
- 2000 mmol (46 g) in extracellular fluid (concentration 130–145 mmol/l)
- daily dietary intake is 50–200 mmol (1.15–4.6 g).

Sodium regulation : Sodium is found in significant amounts in bone, but this pool is not readily available at times of rapid loss of sodium. The extracellular fluid sodium content is regulated in parallel with the extracellular fluid volume control. When the extracellular fluid or blood volume falls, neural sympathetic activity increases, and the response comprises vasoconstriction, a redistribution of renal blood flow, reduced glomerular filtration, and increased sodium and water retention. In addition, there are increases in renin production, circulating angiotensin II, noradrenaline, adrenaline, ACTH and ADH.

Sodium excretion Sodium is filtered from the plasma in the kidneys, the reabsorption of sodium occurring as an osmotic phenomenon in the proximal tubule, loop of Henle and distal tubule. Distal tubular absorption is very important, and is under the control of atrial natriuretic factor(**ANF**). Renal sodium excretion is also controlled by angiotensin II, prostaglandins and the kallikrein–kinin system.

Sodium depletion Sodium is lost largely via the urine, with only minimal loss occurring via the faeces or skin, unless there are abnormal situations such as diarrhea or excessive sweating. A reduced body sodium pool results in reduced extracellular fluid volume. Increased sodium loss in urine can occur in diseases, e.g., diabetes mellitus and Addison's disease (adrenal cortical insufficiency), following excessive doses of diuretic drugs, and in cases of renal tubular damage, as in chronic renal failure. Healthy kidneys maintain a consistent level of sodium in the body by adjusting the amount excreted in the urine. When sodium consumption and loss are not in balance, the total amount of sodium in the body is affected. The concentration of sodium in the blood may be -Too high (hypernatremia) -Too low (hyponatremia)

Hypernatremia, the body contains too little water for the amount of sodium. The sodium level in the blood becomes abnormally high when water loss exceeds sodium loss. Usually, hypernatremia results from dehydration. For example, people may lose body fluids and become dehydrated due to: **1-Drinking too little. 2-Vomiting. 3-Having diarrhea. 4-Using diuretics. 5-Sweating excessively. 6-Insufficient water intake usually plays an important role**. People with diabetes mellitus and high blood sugar levels may urinate excessive amounts, causing dehydration. Dehydration can also be caused by kidney disorders and by diabetes insipidus, which also causes people to urinate excessive amounts although without high blood sugar levels, and is due to inadequate or ineffective vasopressin secretion or action

Potassium(k+): in natural and processed foods the potassium content varies from 2.8 to 10 mmol/kg. Dietary potassium tends to be derived from fresh vegetables and meat. An adult male weight approximately 70 kg contains 2800–3500 mmol (110– 137 g), of which 95% is intracellular (150 mmol/l). Cellular potassium concentrations are affected by pH, aldosterone, insulin and the adrenergic nervous system. The plasma concentration of 3.5–4.5 mmol/l is dependent on intake, excretion, and the balance between extracellular and intracellular compartments. There is a direct, reciprocal relationship between plasma potassium and aldosterone production. Control is mainly through urinary loss, with some additional colonic loss. Insulin excretion is increased when the plasma potassium increases, possibly provoking cellular uptake of potassium.

Transport and absorption of potassium: The transport of potassium into cells is under the control of the Na/KATPase enzyme, and allows transport of potassium against a concentration gradient. The ratio of extracellular to intracellular potassium concentration is important in the membrane potential difference in neuron and muscle cells (Na+ /K+ -ATPase exchange pump system). Over 90% of dietary potassium is absorbed in the proximal small intestine. In the small intestine potassium absorption is passive, but in the colon, it is an active process. In the sigmoid colon absorption is mediated by a K+ /H+ mechanism. Body stores of potassium most of the potassium is intracellular, i.e., in the cell fluid compartment.

Potassium homoeostasis: the homoeostasis of potassium in the body is controlled by renal glomerular filtration and tubular secretion. Chronic increased dietary potassium intake increases potassium secretion via the kidneys. There is an associated degree of hyperaldosteronism. Increased sodium entering the distal nephron results in an increased, simultaneous urinary loss of potassium. Excretion Potassium is largely lost in the urine, although 10% of the daily loss occurs through the distal ileum and colon. Small amounts are lost in sweat and vomit. Potassium is necessary for the normal functioning of cells, nerves, and muscles. The body must maintain the potassium level in blood within a narrow range. A blood potassium level that is -Too high (hyperkalemia) -Too low (hypokalemia) The body can use the large reservoir of potassium stored within cells to help maintain a constant level of potassium in blood. Some potassium is also lost through the digestive tract and in sweat. Healthy kidneys can adjust the excretion of potassium to match changes in consumption. Some drugs and certain conditions affect the movement of potassium into and out of cells, which greatly influences the potassium level in blood.

Hyperkalemia, the level of potassium in blood is too high. A high potassium level has many causes, including kidney disorders, drugs that affect kidney function, and consumption of too much supplemental potassium. Usually, hyperkalemia must be severe before it causes symptoms, mainly abnormal heart rhythms. Doctors usually detect hyperkalemia when blood tests or electrocardiography is done for other reasons.

Causes: Usually, hyperkalemia results from several simultaneous problems, including the following:

1-Kidney disorders that prevent the kidneys from excreting enough potassium
2-Drugs that prevent the kidneys from excreting normal amounts of potassium (a common cause of mild hyperkalemia)
3-A diet high in potassium
4-Treatments that contain potassium
5-Addison disease can also cause hyperkalemia.

Hypokalemia, the level of potassium in blood is too low. A low potassium level can make muscles feel weak, cramp, twitch, or even become paralyzed, and abnormal heart rhythms may develop.

Causes Typically, the potassium level becomes low because too much is lost from the digestive tract due to vomiting, diarrhea, or excessive laxative use. Sometimes too much potassium is excreted in urine, usually because of drugs that cause the kidneys to excrete excess sodium, water, and potassium (diuretics). In many adrenal disorders such as **Cushing syndrome**, the adrenal glands produce **too much aldosterone**, a hormone that causes the kidneys to excrete large amounts of potassium.

Calcium (Ca++): is one of the body's electrolytes, which are minerals that carry an electric charge when dissolved in body fluids such as blood (but most of the body's calcium is uncharged). About 99% of the body's calcium is stored in the bones, but cells (particularly muscle cells) and blood also contain calcium. About 40% of the calcium in blood is attached (bound) to proteins in blood, mainly albumin. Protein-bound calcium acts as a reserve source of calcium for the cells but has no active function in the body. Only unbound calcium affects the body's functions. Calcium is essential for the following:

-Formation of bone and teeth

-Muscle contraction

-Normal functioning of many enzymes

-Blood clotting

-Normal heart rhythm

Calcium absorption and balance Calcium absorption is largely from the jejunum, but may also occur in the ileum and colon. The predominant absorptive process is by active transport and there is also some simple passive diffusion in the ileum. Phytate (Phytic acid) binds calcium to form insoluble salts within the intestinal lumen, and reduces calcium absorption. Approximately 60% of the total plasma calcium is filtered in the kidney glomeruli, and in health 97% of this calcium is reabsorbed. Several hormones are involved, including PTH, with increased absorption of calcium and decreased tubular absorption of phosphate.
The level of calcium in blood is regulated primarily by two hormones:
-Parathyroid hormone
-Calcitonin
Too much calcium in the blood is called hypercalcemia. Too little calcium in the blood is called hypocalcemia.

Hypercalcemia: At first, people have digestive problems, feel thirsty, and may urinate a lot, but if severe, hypercalcemia leads to confusion and eventually coma. If not recognized and treated, the disorder can be life threatening.

Causes: Causes of hypercalcemia include the following: -**Hyperparathyroidism**: One or more of the four parathyroid glands secrete too much parathyroid hormone, which helps control the amount of calcium in blood. -**Too much calcium intake**: Occasionally, hypercalcemia develops in people **with peptic ulcers if they drink a lot of milk and take calcium-containing antacids** for relief. The resulting disorder is called the **milk-alkali syndrome**. -**Too much vitamin D intake**: If people take very high daily doses of vitamin D over several months, the amount of calcium absorbed from the digestive tract increases substantially. -**Cancer**: cells in kidney, lung, and ovary cancers may secrete large amounts of a protein that, like parathyroid hormone, increases the calcium level in blood. Calcium released into the blood when cancer spreads (metastasizes) to bone and destroys bone cells. Such bone destruction occurs most commonly with prostate, breast, and lung cancers. **Multiple myeloma** (a cancer involving bone marrow) can also lead to the destruction of bone and result in hypercalcemia. Other cancers can increase the calcium level in blood by means not yet fully understood. -B**one disorders**: If bone is broken down (resorbed) or destroyed, calcium is released into the blood, sometimes causing hypercalcemia. **In Paget disease**, bone is broken down, but the calcium level in blood is usually normal. Severe **hyperthyroidism** can also cause hypercalcemia by increasing resorption of bone tissue.

Hypocalcemia, the calcium level in blood is too low. A low calcium level may result from a problem with **the parathyroid glands**, as well as **from diet**, **kidney disorders,** or **certain drugs.** As hypocalcemia progresses, muscle cramps are common, and people may become confused, depressed, and forgetful and have tingling in their lips, fingers, and feet as well as stiff, achy muscles. Usually, the disorder is detected by routine blood tests. Calcium and vitamin D supplements may be used to treat hypocalcemia. Thus, hypocalcemia causes problems only when the level of **unbound calcium is low**. Unbound calcium has an electrical (ionic) charge, so it is also called **ionized calcium**.

Magnesium (Mg++): is one of the body's electrolytes, which are minerals that carry an electric charge when dissolved in body fluids such as blood, but the majority of magnesium in the body is uncharged and bound to proteins or stored in bone. Bone contains about half of the body's magnesium. Blood contains very little. Magnesium is necessary for the formation of bone and teeth and for normal nerve and muscle function.

Many enzymes in the body depend on magnesium to function normally. Magnesium is also related to the metabolism of calcium and the metabolism of potassium. The level of magnesium in the blood depends largely on how the body obtains magnesium from foods and excretes it in urine and stool and less so on the total body stores of magnesium. The level of magnesium in the blood can become -Too high **(hypermagnesemia**) -Too low (**hypomagnesemia)** Hypermagnesemia, the level of magnesium in blood is too high.

Hypermagnesemia is uncommon. It usually develops only when people with kidney failure are given magnesium salts or take drugs that contain magnesium (such as some antiacids or laxatives). Hypermagnesemia may cause

-Muscle weakness

-Low blood pressure

-Impaired breathing When hypermagnesemia is severe, the heart can stop beating.

Hypomagnesemia, the level of magnesium in blood is too low. **Causes** Usually, the magnesium level becomes low because people consume less (most often, because of starvation) or because the intestine cannot absorb nutrients normally (called malabsorption). But sometimes hypomagnesemia develops because the kidneys or intestine excrete too much magnesium. Hypomagnesemia may also result from the following: -**Consuming large amounts of alcohol** (common), which **reduces consumption of food** (and thus magnesium) and increases excretion of magnesium -**Protracted diarrhea** (common), which increases magnesium excretion -**High levels of aldosterone**, **vasopressin** (antidiuretic hormone), or **thyroid hormones**, which increase magnesium excretion -Drugs that increase magnesium excretion, **including diuretics**, the antifungal drug **amphotericin B**, and the chemotherapy drug **cisplatin -Breastfeeding**, which increases requirements for magnesium

CHLORIDE (Cl–) Chloride concentration in plasma is 96-106 mEq/L and in Cerebrospinal fluid (CSF), it is about 125 mEq/L. Chloride concentration in CSF is higher than any other body fluids. Since CSF protein content is low. Renal threshold for Cl – is about 110 mEq/L. Daily excretion of Cl– is about 5-8 gm/day. Intake, output and metabolism of sodium and chloride run in parallel. The homeostasis of Na+ , K+ and Cl– are interrelated. Chloride is important in the formation of hydrochloric acid in gastric juice.

Hyperchloremia is seen in:

1. Dehydration
2. Cushing's syndrome. Mineralocorticoids cause increased reabsorption from kidney tubules.
3. Severe diarrhea leads to loss of bicarbonate and compensatory retention of chloride.
4. Renal tubular acidosis.

Hypochloremia: Causes

1. Excessive vomiting. HCl is lost, so plasma Cl– is lowered. There will be compensatory increase in plasma bicarbonate. This is called hypochloremia alkalosis.
2. Excessive sweating.
3. In Addison's disease, aldosterone is diminished, renal tubular reabsorption of Cl– is decreased, and more Cl– is excreted.

Chloride channels The CFTR (Cystic Fibrosis Transmembrane Conductance Receptor) chloride conducting channel is involved in Cystic fibrosis. In Cystic Fibrosis, a point mutation in the CFTR gene results in defective chloride transport. So, water moves out from lungs and pancreas. This is responsible for the production of abnormally thick mucus. This will lead to infection and progressive damage and death at a young age.

Manganese (Mn): Manganese content of foods varies greatly. found the highest concentrations in nuts, grains, and cereals; the lowest in dairy products, meat, poultry, fish, and seafood. Relatively high concentrations of manganese were found in soluble ("instant") coffee and tea and account for 10% of the total daily intake. The total body content average human adult has about 15 mg of manganese, typically seen in nucleic acid. Daily requirement is about 2-5 mg/day. Manganese acts as an activator of enzyme and as a component of metalloenzymes. They have a role to play in oxidative phosphorylation, fatty acids and cholesterol metabolism, mucopolysaccharide metabolism, and urea cycle. Manganese is found in all mammalian tissues with concentrations ranging from 0.3 to 2.9 µg manganese/g. Tissues rich in mitochondria and pigments (e.g., retina, dark skin) tend to have high manganese concentrations. Bone, liver, pancreas, and kidney typically have higher manganese concentrations than other tissues. The largest tissue store of manganese is **in the bone**. Some of the enzymes which are present along with magnesium are arginase, diamine oxidase, pyruvate carboxylate, glutamine synthetase. The deficiency cause bleeding disorders due to increased prothrombin time while **accumulation** over a long period causes anorexia, apathy, headache impotence, leg cramps, speech disturbance, encephalitis like syndrome and parkinsonian like syndrome.

Zinc (Zn): The metal zinc is an omnipotent metal that has amphoteric nature. Hence, it is ionized either in acidic or alkaline forms. Content of zinc is is 2-3 g in an average adult. About 99% is intracellular while the rest is in plasma. The average daily requirement is 15-20 mg/day. Phytase decreases fibers, phosphates, calcium, and copper competes with zinc for absorption from small intestine. About **2-5 mg/day is excreted via pancreas and intestine**. The other mode of **excretion is via proximal tubule and sweat glands**. **Plasma zinc levels are decreased in pregnancy, fluid loss, oral contraceptive usage, blood loss, acute myocardial infarction, infections, and malignancies.** The function of zinc in cells and tissues is dependent **on metalloproteinase** and these enzymes are associated **with reproductive, neurological, immune, dermatological systems, and GIT**. **It is essential for normal spermatogenesis and maturation**, the genetic disorder related with zinc metabolism is acrodermatitis enteropathica which is an autosomal recessive defect where there is an inability in Zn absorption. Zinc also supports normal growth and development during pregnancy, childhood, and adolescence.

Fluorine (F): Fluorine is a lightest element; **fluorine plays an important role in the hard tissues of the body such as bone and teeth.** It helps in producing **denser bones** and fluoride has been suggested as a therapeutic agent **in the treatment of osteoporosis**. It is thought that fluoride, in conjunction with calcium, stimulates osteoblastic activity. Fluorine has profound antienzyme properties and prevents dental caries. The **increased fluoride** utilization **could be responsible for the anticariogenic action**. **Fluoride or fluorine deficiency** is a hypothetical disorder, which may **cause increased dental caries and possibly osteoporosis due to a lack of fluoride in the diet.** High levels of dietary fluoride cause fluorosis (bone disease) and mottling of teeth. High levels of fluoride cause dental lesions. Acute toxicity of fluoride is very rare and can occur due to a single ingestion of a large amount of fluoride and can be fatal. The amount of fluoride considered lethal when taken orally is 35-70 mg F/kg body weight. Symptoms of acute toxicity occur rapidly. There is a diffuse abdominal pain, diarrhea, vomiting, excess salivation, and thirst. Chronic toxicity is caused due to long-term ingestion of smaller amounts of fluoride in drinking-water. **Excessive fluoride** more than 8 ppm in drinking water daily for many years can lead to **skeletal and dental fluorosis**. Severe cases are normally found only in warm climates where drinkingwater contains very high levels of fluoride. Due to chronic toxicity, bone density slowly increases; the joints stiffen and become painful.

Copper (Cu++): Copper plays a very important role in our metabolism largely because it allows many critical enzymes to function properly. Acidic conditions promote the solubility which incorporates copper ions either **in cupric form or cuprous form into the food chain.** Mainly copper is available in **the liver, shellfish, dried fruit, milk and milk products, sunflower seeds, sesame seeds, tahini, and sun-dried tomatoes**. The average adult human of 70 kg weight contains about 100 mg. The daily requirement is about 2-5 mg of which 50% is absorbed from the gastrointestinal tract (GIT). Rest is excreted via bile and kidney. **Copper accumulates in the liver, brain and kidney more than rest of body. Over 90% of plasma copper is associated with ceruloplasmin** and 60% of red blood cell (RBC) is bound to superoxide dismutase. In human blood, copper is principally distributed between the erythrocytes and in the plasma. **In erythrocytes, 60% of copper occurs as the copper-zinc metalloenzyme superoxide dismutase**, the remaining 40% is loosely bound to other proteins and amino acids. Total erythrocytes copper in normal human is around 0.9-1.0 pg/ml of packed red cells. **Copper has a selected biochemical function in hemoglobin (Hb) synthesis, connective tissue metabolism, and bone development**. Excessive Cu either from diet or through any other sources acquired rapidly produces nausea, vomiting, diarrhea, profuse sweating, and renal dysfunction. The symptoms of copper deficiency are hypochromic anemia, neutropenia, hypopigmentation of hair and skin, abnormal bone formation with skeletal fragility and osteoporosis, joint pain, lowered immunity, vascular abnormalities.

Iron (Fe): Iron is an essential constituent **of haemoglobin** and certain enzymes such as **cytochrome oxidase, catalase and peroxidase**. It performs two important functions in the body—to **transport oxygen** to tissues (through Hb) and to take part in **oxidation-reduction reactions (cytochrome system)**.

Sources: meat, liver, eggs, spinach and fruits.

Absorption: Dietary intake of iron is **mainly in ferric (Fe+++)** form as hydroxides or in organic compounds. The action of gastric HCl and of some organic acids liberates free ferric ions, which in turn are **reduced to ferrous ions (Fe++) by reducing substances such as cysteine or ascorbic acid.** The **ferrous form of iron is more soluble and thus easily absorbed**. The absorption of iron occurs in duodenum and stomach.

Transport and storage: Iron is transported in plasma **in ferric form**, which remains firmly bound to a **specific βglobulin, transferrin**. The normal concentration of protein bound iron in plasma is 50 - 180µ gm/ 100ml. **Iron is stored chiefly in mucosal cells of intestine, liver, spleen and bone marrow as ferritin**.

Daily requirement: Infants – 6–15 mg, Children- 10–18 mg, Adult (male) 10 mg, female- 18 mg.

أسئلة المتحان التقويمي (الدور الاول)2023

- 5 , 12 , 22 , 45 , 88 , 90 (repeated 22)

Diabetes Extra
(changes according to College of health and medical techniques – Baghdad

Signs of Diabetes Mellitus :

- Excessive urine production (polyuria)
- Thirst and increased fluid intake (polydipsia)
- Blurred vision
- weight loss (in type 1)
- Lethargy
- Changes in energy metabolism.

Types of diabetes mellitus:

1- **Genetic defects of b-cell function**

- Maturity-onset diabetes of the young (MODY):

– MODY 1: mutation of the hepatocyte nuclear factor (HNF4A) gene,

– MODY 2: mutation of the glucokinase gene,

– MODY 3: mutation of the HNF1A gene.

Some cases are thought to be point mutations in mitochondrial deoxyribonucleic acid (DNA) associated with diabetes mellitus and deafness and are usually autosomal dominant.

- Type A insulin resistance (insulin receptor defect).

2- defects of insulin action receptor (insulin resistance (type 2)

3-Insulin deficiency due to pancreatic disease

- Chronic pancreatitis.
- Pancreatectomy.

4-Drugs

- Interferon-a.
- Glucocorticoids.

5-Infections

- Septicemia.
- Congenital rubella.
- Cytomegalovirus. Rare forms of autoimmune-mediated diabetes
- Anti-insulin receptor antibodies.

6-Genetic syndromes associated with diabetes

- Down’s syndrome.
- Turner’s syndrome.
- Klinefelter’s syndrome

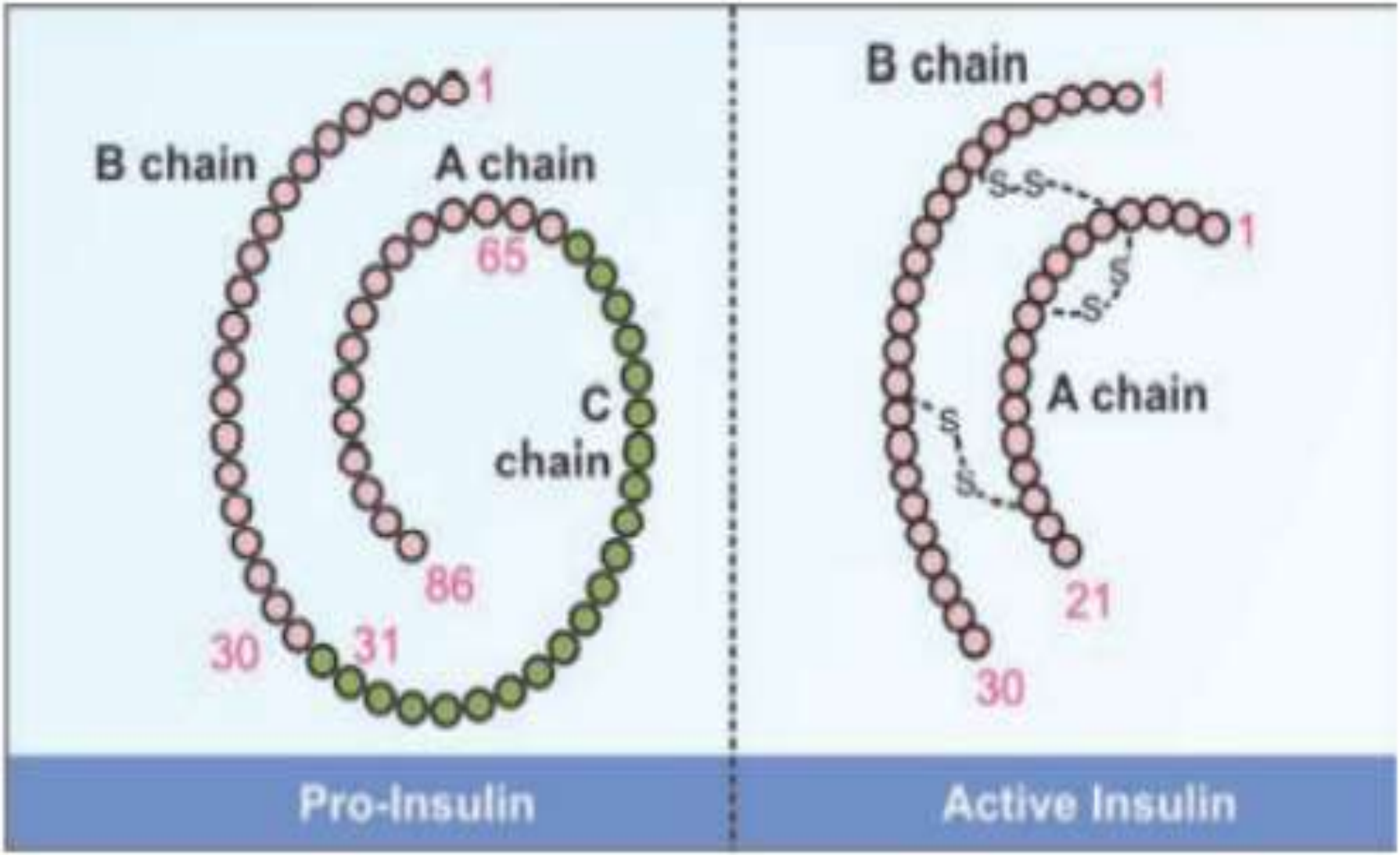
Structure of insulin

Insulin is a protein hormone with 2 polypeptide chains. The A chain has 21 amino acids and B chain has 30 amino acids. These two chains are joined together by two interchain disulphide bonds, between A7 to B7 and A20 to B19. There is also an intrachain disulphide link in A chain between 6th and 11th amino acids. **Species variation is restricted to amino acids 8,9 and 10 of A chain and C terminal of B chain**. **Biosynthesis of insulin**

i. Insulin is a protein synthesized and secreted by the beta cells of the islets of Langerhans of the pancreas.

ii. The insulin is synthesized as a larger precursor polypeptide chain, the pre-pro-insulin. It has 109 amino acids. It is rapidly converted to pro-insulin in the endoplasmic reticulum by removal of leader sequence of 23 amino acid residues.

iii. The proinsulin with 86 amino acids is transported to Golgi apparatus where it is cleaved by a protease. Thus C peptide or connecting peptide with 33 amino acids is removed. (The number of amino acids in C peptide may vary according to species). Insulin (active) with 51 amino acids is thus formed.


B chain
1
A chain
65
C
chain
86
30
31
Pro-Insulin
B chain
1
S-S
1
S
S
A chain
S
S
21
30
Active Insulin

The mechanism of insulin release

The secretion of insulin from pancreatic β-cells is a complex process involving the integration and interaction of multiple external and internal stimuli. The primary stimulus for insulin secretion is the β-cell response to changes in glucose level. First-phase insulin release occurs within the first few minutes after exposure to an elevated glucose level; this is followed by a more enduring second phase of insulin release. **Of particular importance is that first-phase insulin secretion is lost in patients with type 2 diabetes**. The generally sequence of events involved in glucose-induced insulin secretion is as follows:

1. Glucose is transported into β-cells through facilitated diffusion by Glucose transporter 2 (GLUT2).
2. The glucose is oxidized to pyruvate via glycolysis.
3. The pyruvate is oxidized by the pyruvate dehydrogenase complex . (PDHc) and the resulting acetyl CoA which in the (Tricarboxylic acid) TCA cycle is oxidized.
4. The resulting Nicotinamide adenine dinucleotide (NADH) and Flavin adenine dinucleotide, FADH2 are oxidized via the oxidative phosphorylation machinery resulting in increased ATP levels.

5. The increased ATP inhibits the K+ -ATP channel resulting in membrane depolarization leading to an influx of Ca2+ ions triggering migration of insulin-containing vesicle to the plasma membrane releasing the insulin to the blood

1, 2 , 3 , 10 , 13 , 15 , 21 , 38 ,52 , 54 , 55 , 70 , 82 ,

Glycation

Many of the pathological effects of diabetes arise from the process of glycation. Glycation is the non-enzymatic and haphazard condensation of the aldehyde and ketone groups in sugars with amino groups in proteins, leading to their functional impairment (the enzyme-controlled addition of sugars to protein or lipid molecules is termed glycosylation). These may undergo further chemical reactions to produce 'advanced glycation end products', or (AGEs). Glycation damages collagen in blood vessel walls, leading to inflammation and atherosclerosis. This process is now considered to be a major contributor to diabetic pathology and has resulted in greater clinical emphasis on good glycaemic control. Clinical measurement of glycated haemoglobin (HbA1c) and serum albumin is used to assess the adequacy of blood sugar regulation in diabetic patients (see in table). Normal (non-diabetic) values of glycated haemoglobin are 4.0–6.5%; that is, approximately 6 red cells out of every 100 will have glucose attached.

Clinical HbA1c level

HbA1c (%)	Normal/abnormal	Average blood glucose (mM)
4–6.5	Normal (without diabetes)	3–8
6.5–7.5	Target range (with diabetes)	8–10
8–9.5	High	11–14
>9.5	Very high	>15

Blood protein components and diseases

L: 19 , 20

Blood proteins:

Proteins are the main and most abundant constituents of the blood serum or plasma, having many essential physiological functions. The most of proteins present in the blood are biochemically not pure; usually, they are a mixture of simple proteins combined with other substances: glycoproteins, lipoproteins, and other conjugated proteins . Proteins have a specific intra-molecular structure and amphoteric nature, containing the balanced portions of hydrophilic and hydrophobic groups.

plasma and serum

Plasma is fluid portion of whole blood, and it is obtained when whole blood containing anti-coagulant is centrifuged, Plasma contains clotting factors.

Serum is fluid portion of clotted blood, and it is obtained after centrifuging clotted blood. Serum does not contain clotting factors that are normally present in plasma.

Total Protein

Total Protein in plasma is made up of Albumin and Globulins. Clinical Biochemistry labs routinely measures Total Protein and Albumin usually in serum.

Globulin fraction = Total protein – Albumin

Other plasma proteins (e.g., Immunoglobulin's) are measured as Classes. Immunochemical methods are used to measuring specific plasma proteins, hormones or enzymes. Electrophoresis can be used to separate protein components

Principal plasma proteins

Class	Protein	Approximate mean serum concentration (g/L)
	prealbumin	0.25
	albumin	40
α_1-globulin	α_1-antitrypsin	2.9
	α_1-acid glycoprotein	1.0
α_2-globulin	haptoglobins	2.0
	α_2-macroglobulin	2.6
	caeruloplasmin	0.35
β-globulin	transferrin	3.0
	low density lipoprotein	1.0
	complement components (C3)	1.0
γ-globulins	IgG	14.0
	IgA	3.5
	IgM	1.5
	IgD	0.03
	IgE	trace

What are the functions of proteins:

- Blood clotting factors: proteins in coagulation cascade.
- Immune defense: Immunoglobulin's, Complement proteins involved in inflammatory responses .
- Acute phase response proteins: C-reactive protein, alpha-acid glycoprotein.
- Transport /binding proteins: Albumin, Caeruloplasmin, Haptoglobin, Retinolbinding protein, Sex hormone-binding globulin, Thyroid hormone-binding protein, Transferrin.

What are some of the functions of Albumin

- Albumin is one of the major plasma proteins; it is synthesized and secreted by the Liver, the biological half-life of Albumin in plasma: 20 days.

What are some of the possible causes of Hypoalbuminemia?

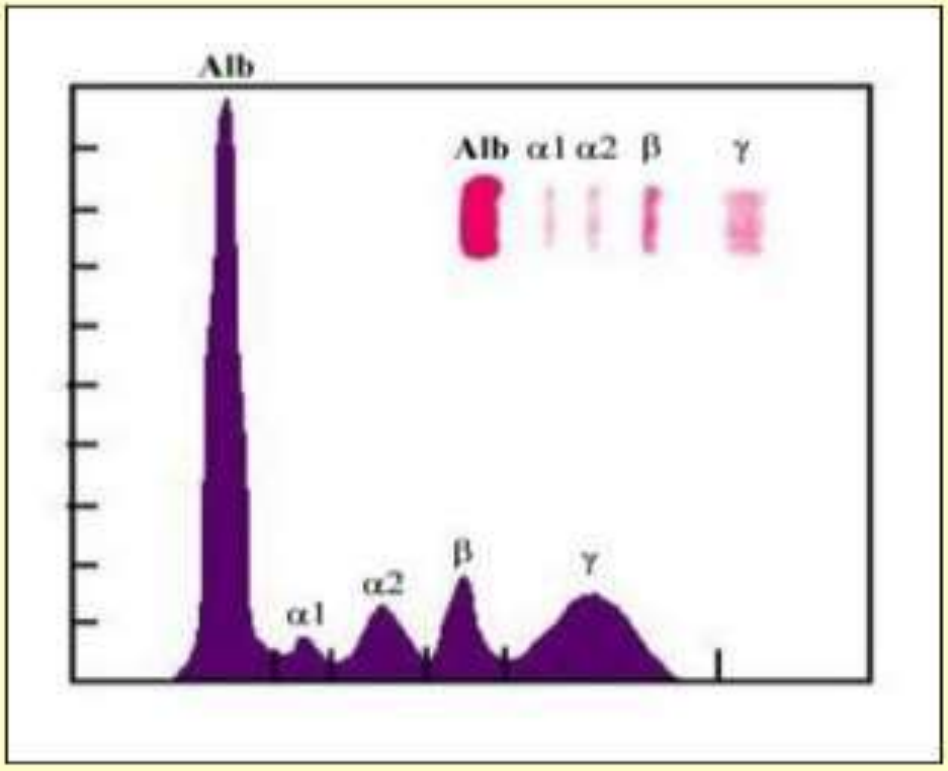
- Albumin, the most abundant plasma protein, makes the major contribution (about 80%) to the oncotic pressure of plasma.
- **hypoalbuminaemic** states, the decreased plasma oncotic pressure disturbs the equilibrium between plasma and interstitial fluid is seen clinically as edema
- **Hyperalbuminemia:** can be either an artifact, for instance as a result of venous stasis during blood collection or over-infusion of albumin, or be a result of dehydration.

Globulin

- Globulin fraction includes hundreds of serum proteins including carrier proteins, enzymes, complement, and immunoglobulins.
- Globulins are divided into four groups by electrophoresis. The four fractions are **α1, α2, β and γ**, depending on their migratory pattern between the anode and the cathode.
- Increases in the globulin fraction usually result from an increase in immunoglobulins , but there can be an increase in other proteins in pathologic states that have characteristic electrophoretic patterns.
- decrease in total globulins due to decreased synthesis, and nephrotic syndrome can cause a decrease due to protein loss through the kidney.

Serum proteins electrophoresis in diagnostics of diseases

Normal pattern



Reference ranges:

Total protein	6.0 - 8.0 g/dL
Albumin	3.5 - 5.0 g/dL
α1-globulins	0.1 - 0.4 g/dL
α2-globulins	0.4 - 1.3 g/dL
β-globulins	0.6 - 1.3 g/dL
γ-globulins	0.6 - 1.5 g/dL

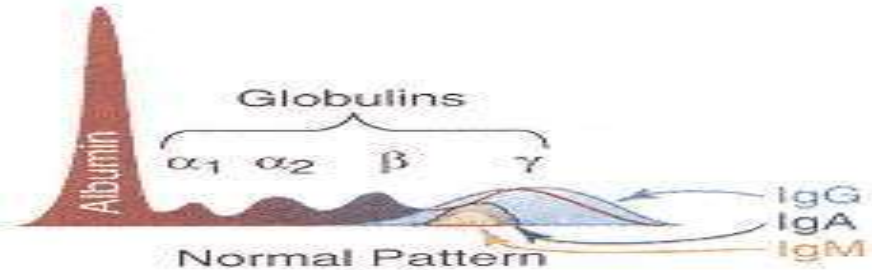
α- globulin

1. α1 fraction: consists mainly of α1 antitrypsin. Significant decreases of this fraction are seen in patients with congenital α1 antitrypsin deficiency; an increase is seen in acute inflammatory disorders because α1 antitrypsin is an acute phase reactant.
2. α2 region: include α2 macroglobulin and haptoglobin. There is an increase in α2 macroglobulin in the nephrotic syndrome when lower molecular weight proteins are lost in the urine. Haptoglobin rises in response to stress, infection, acute inflammation, or tissue necrosis, probably by stimulation of synthesis

β- globulin • Increased β- globulin proteins may indicate: A disorder in which the body has problems breaking down fats (for example, hyperlipoproteinemia, familial hypercholesterolemia) Estrogen therapy

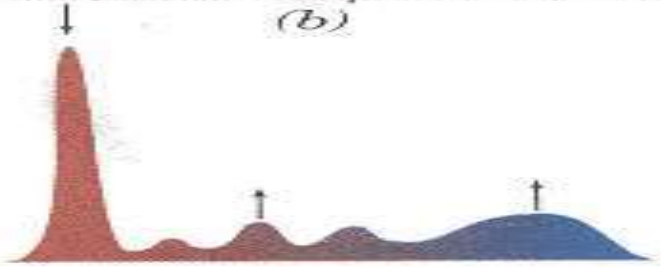
- Decreased β- globulin proteins may indicate abnormally low level of LDL cholesterol · Malnutrition

γ –region Globulin The most frequent abnormalities in the γ region are a broad-based polyclonal increase or a narrow monoclonal spike. Polyclonal increases are seen in chronic infections. Monoclonal spikes suggest multiple myeloma, lymphoma. hypogammaglobulinemia which is characterized by a decrease in the γ component. It is seen in congenital immune deficiency syndromes.



Normal Pattern
(a)

"Immediate Response Pattern"
(b)

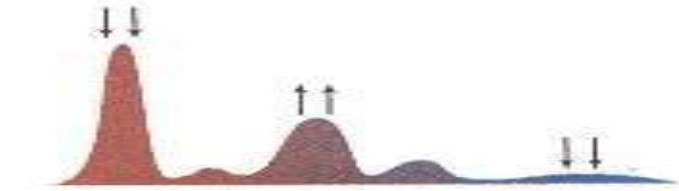


"Delayed Response Pattern"
(c)

Hypogammaglobulinemia
(d)

Hepatic Cirrhosis
("Polyclonal Gammopathy")
(e)

Paraprotein
("Monoclonal Gammopathy")
(f)



Nephrotic Syndrome
(g)

Protein-losing Enteropathy
(h)

1-Electrophoresis of serum proteins shows the following bands :-

a) Albumin + globulin .
b) Albumin + alpha and beta globulin .
c) Albumin + alpha , beta and gamma globulin .
d) Albumin + alpha-1 , alpha-2 , beta and gamma globulin .
e) None of the others .

2-Albumin has the following properties except :-

a) Synthesized by the liver .
b) Has a biological half-life of 20 days .
c) Responsible for 80% of plasma oncotic pressure .
d) Contribute to the formation of lipoproteins .
e) Represent more than 50% of total serum proteins .

3-A decrease in oncotic pressure is caused by :-

a) Hypoalbuminemia .
b) Hyperalbuminemia .
c) Anemia .
d) Uricemia .
e) Uremia .

4 -In serum electrophoresis , immunoglobulins would appear in ---------band :-

a) Albumin .
b) Alpha 1 globulin .
c) Alpha 2 globulin .
d) Beta globulin .
e) Gamma globulin .

5- The difference between serum and plasma is :-

a) Serum contains all portions of protein .
b) Plasma contains all portions of protein .
c) Serum contains the clotting factors .
d) Plasma does not require anti-coagulant .
e) Both serum and plasma contain all portions of protein .

6- The following serum proteins are transporters except : -

a) Transferrin .
b) Caeruloplasmin .
c) Immunoglobulins .
d) Retinolbinding protein,
e) Thyroid hormone binding protein .

7- Increased B-globulin fraction may indicate :-

a) Acute inflammation .
b) Increased macroglobulin .
c) Hyperlipoproteimemia .
d) Nephrotic syndrome .
e) Tissue necrosis .

8- The following diseases may cause increase γ-globulin except :-

a) Polyclonal increase .
b) Multiple myeloma .
c) Lymphoma .
d) Liver cirrhosis .
e) Angina.

1. d , 2. d , 3. a , 4. e , 5. b , 6. c , 7. c , 8. e

Lectures 5&6

Blood gases

Blood pH and Buffer

Normal cell metabolism depends on the maintenance of **blood pH within very narrow limits (7.35-7.45).** Even relatively mild excursions outside this normal pH range can have deleterious effects, including reduced oxygen delivery to tissues, electrolyte disturbances and changes in heart muscle contractility; **survival is rare if blood pH falls below 6.8 or rises above 7.8**. The problem for the body is that normal metabolism is associated with continuous production of hydrogen ions (H^+) and carbon dioxide (CO_2), both of which tend to reduce pH. The mechanism which overcomes this problem and serves **to maintain normal blood pH (i.e., preserve acid-base homeostasis) is a complex synergy of action involving chemical buffers in blood, the red cells (erythrocytes), which circulate in blood, and the function of three organs: lungs; kidneys and brain .**

Before explaining how these five elements contribute to the overall maintenance of blood pH, it would be helpful to quickly review some basic concepts.

What is an acid, **what is a base** and **what is pH**?

An acid is a substance which releases hydrogen ions (H+) on dissociation in solution. For example: Hydrochloric acid (HCl) dissociates to hydrogen ions and chloride ions - $HCl \rightarrow H^+ + Cl^-$, Carbonic acid ($H_2CO_3$) dissociates to hydrogen ions and bicarbonate ions - $H_2CO_3 \rightarrow H^+ + HCO_3^-$.

A base is a substance which in solution accepts hydrogen ions. For example, bicarbonate (HCO_3^-) accepts hydrogen ions to form carbonic acid: $HCO_3^- + H^+ \rightarrow H_2CO_3$

pH is a measure of hydrogen ion concentration [H+]. pH is a scale of 0-14 of acidity and alkalinity. Pure **water has a pH of 7** and is neutral (neither acidic nor alkaline). pH above 7 is alkaline and below 7 acidic. Thus, the pH of blood (7.35-7.45) is slightly alkaline although in clinical medicine the term **alkalosis is, perhaps confusingly, reserved for blood pH greater than 7.45** and the term **acidosis is reserved for blood pH less than 7.35**.

The two are related according to the following equation:

[H+] = 0.00000004 Eq/L

Log [H+] = log (0.00000004)

Log [H+] = - (7.4) - log[H+] = 7.4 , **{**power [H+] = 7.4 , p [H+] = 7.4**}**

pH 7.4 = H+ concentration of 40 nEq/L

pH 7.0 = H+ concentration of 100 nEq/L

pH 6.0 = H+ concentration of 1000 nEq/L

What is a buffer?

A buffer is a solution of a weak acid and its conjugate base.

– The bicarbonate (HCO_3^-) buffer system

Buffers are chemicals in solution which minimize the change in pH which occurs when acids are added by hydrogen ions. In blood, the principal buffer system is the weak acid, carbonic acid (H_2CO_3) and its conjugate base, bicarbonate (HCO_3^-). To explain how this system minimizes changes in pH, suppose we add a strong acid, e.g., HCl, to the bicarbonate buffer: The acid will dissociate, releasing hydrogen ions: $HCl \rightarrow H^+ + Cl^-$ The bicarbonate buffer then 'absorbs' the hydrogen ions, forming carbonic acid in the process: $HCO_3^- + H^+ \rightarrow H_2CO_3$ (carbonic acid). This relationship, known as the **Henderson-Hasselbalch equation**, shows that **pH is governed by the ratio of base [HCO_3^-] concentration to acid [H_2CO_3]** concentration.

$$\mathbf{pH = 6.1 + \log([HCO_3^-] / [H_2CO_3])}$$

Acid -base balance

physiology of acid-base balance: In fact, the **lungs ensure removal of carbonic acid (as carbon dioxide)** and the **kidneys ensure continuous regeneration of bicarbonate**.

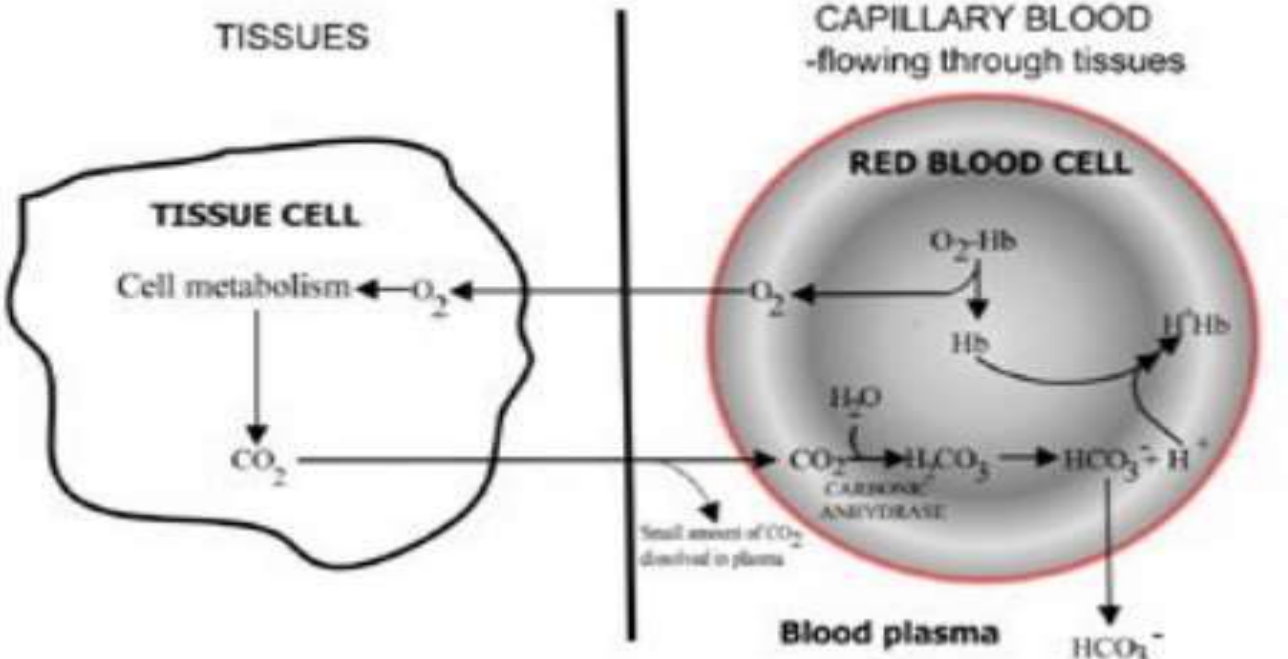
This role of the lungs is dependent on characteristic of the bicarbonate buffering system and that is the ability of carbonic acid to be converted to carbon dioxide and water, the following equation outlines the relationship of all elements of the bicarbonate buffering system as it operates in the body

$H + + HCO_3 - \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$

It is important to note that the reactions are reversible. Direction is dependent on the relative concentration of each element. So that, for example, **a rise in carbon dioxide concentration forces reaction to the left with increased formation of carbonic acid and ultimately hydrogen ions.**

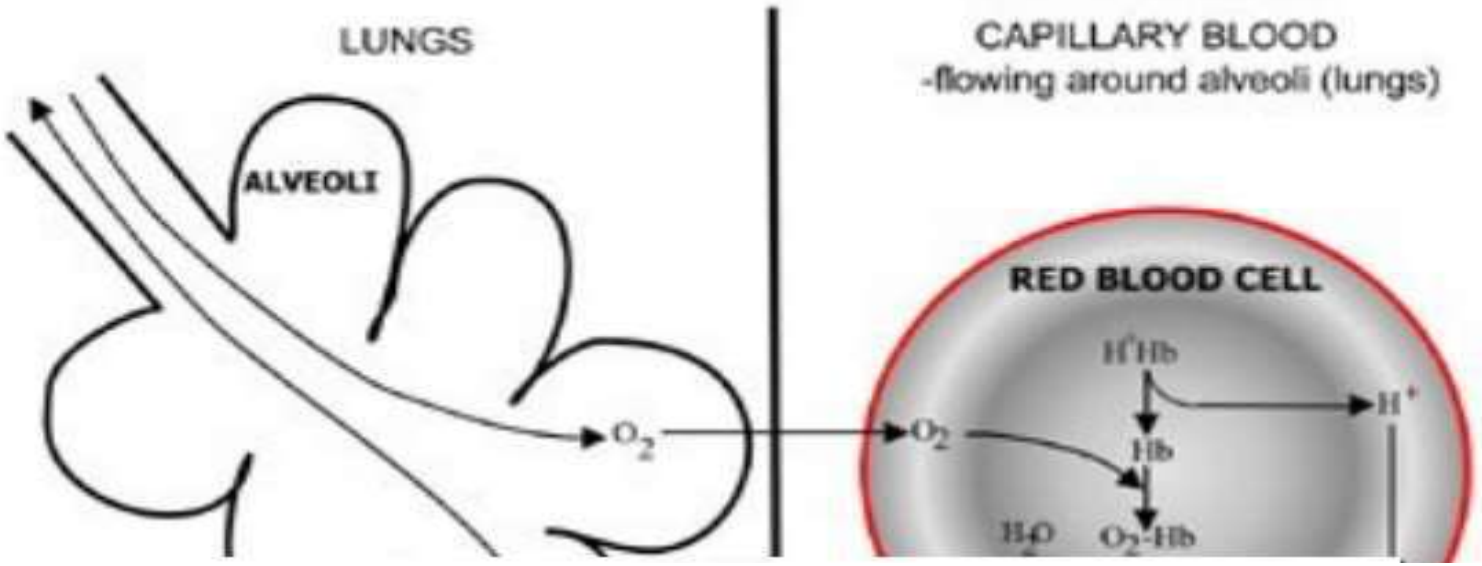
Lung function, transport of CO2 and acid-base balance

A constant amount of CO2 in blood, essential for normal acid-base balance, reflects a balance between that produced as a result of tissue cell metabolism and that excreted by the lungs in expired air. **By varying the rate at which carbon dioxide is excreted, the lungs regulate the carbon dioxide content of blood**. Carbon dioxide diffuses out of tissue cells to surrounding capillary blood (Fig. 1a), a small proportion dissolves in blood plasma and is transported to the lungs unchanged, **but most diffuses into red cells where it combines with water to form carbonic acid**. **The acid dissociates with production of hydrogen ions and bicarbonate.** Hydrogen ions combine with deoxygenated hemoglobin (hemoglobin is acting as a buffer here), preventing a dangerous fall in cellular pH, and **bicarbonate diffuses along a concentration gradient from red cell to plasma**. Thus, most of the carbon dioxide produced in the tissues is transported to the lungs as bicarbonate in blood plasma .



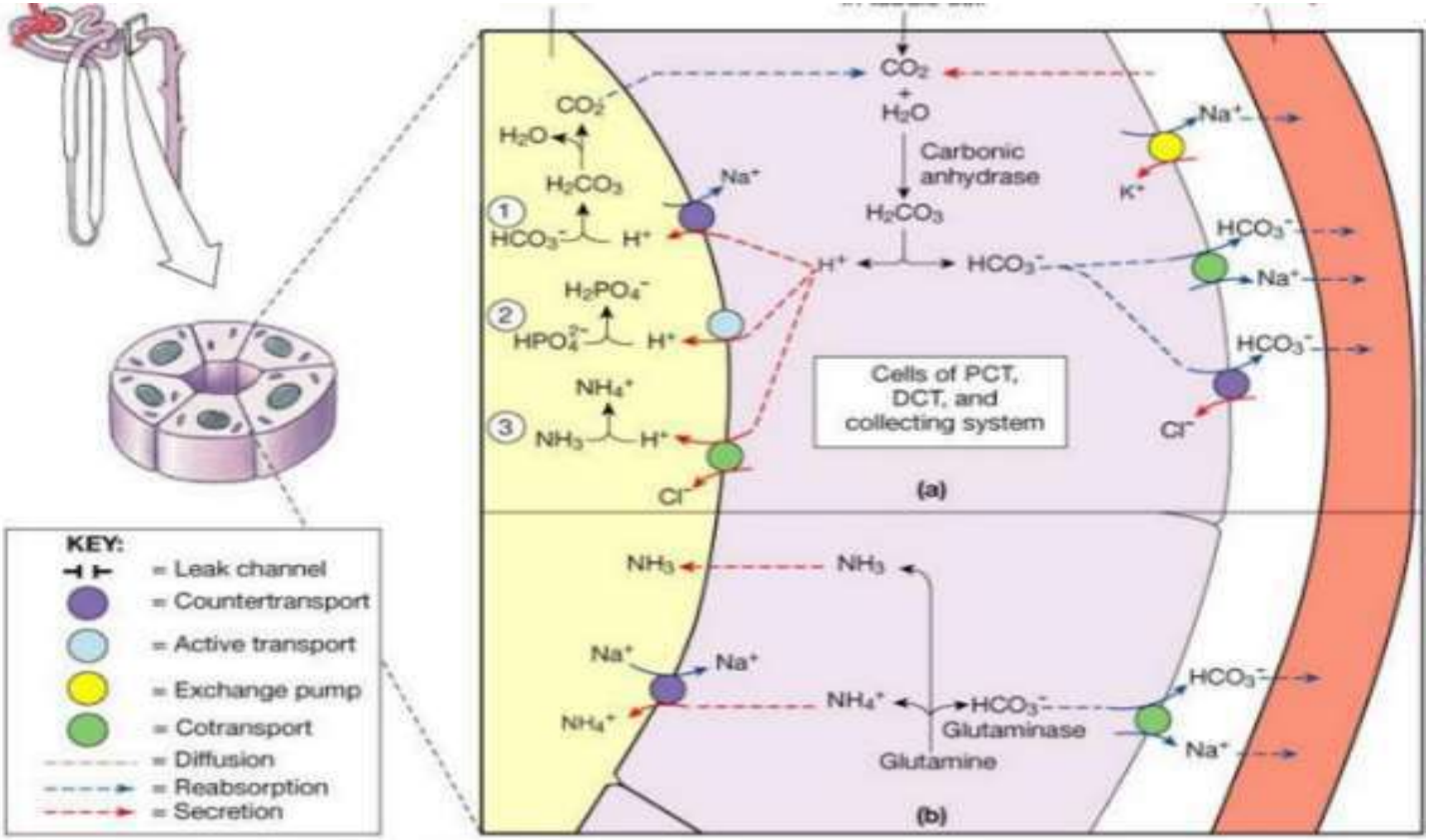
$$CO_2 + H_2O + \xleftrightarrow{slow} H_2CO_3 \xleftrightarrow{fast} H^+ + HCO_3^-$$

At the alveoli in the lungs the process is reversed (Fig. 1b). Hydrogen ions are displaced from hemoglobin as it takes up oxygen from inspired air. The hydrogen ions are now buffered by bicarbonate which diffuses from plasma back into red cell, and carbonic acid is formed. As the concentration of this rises, it is converted to water and carbon dioxide. Finally, carbon dioxide diffuses down a concentration gradient from red cell to alveoli for excretion in expired air. **Respiratory chemoreceptors** in the brain stem respond to changes in the concentration of carbon dioxide in blood, causing increased ventilation (breathing) if carbon dioxide concentration rises and decreased ventilation if carbon dioxide falls. At the lungs bicarbonate converted back to CO2 and eliminated by the lungs.



Kidneys and acid-base balance

These two tasks**, elimination of hydrogen ions** and **regeneration of bicarbonate**, are accomplished by the kidneys. Renal tubule cells are rich in the enzyme **carbonic unhydrase**, which facilitates formation of carbonic acid from carbon dioxide and water. Carbonic acid dissociates to bicarbonate and hydrogen ions. The bicarbonate is reabsorbed into blood and the hydrogen ions pass into the lumen of the tubule and are eliminated from the body in urine.



Disturbances of acid-base balance

Most acid-base disturbances result from

• disease or damage to organs (kidney, lungs, brain) whose normal function is necessary for acid-base homeostasis,

• disease which causes abnormally increased production of metabolic acids such that homeostatic mechanisms are overwhelmed

• medical intervention (e.g. mechanical ventilation, some drugs). Arterial blood gases (ABG) are the blood test used to identify and monitor acid-base disturbances. Three parameters measured during blood gas analysis, arterial blood pH, partial pressure of carbon dioxide in arterial blood (pCO2), concentration of bicarbonate (HCO_3^-) are of crucial importance.

Arterial blood gases (ABG)

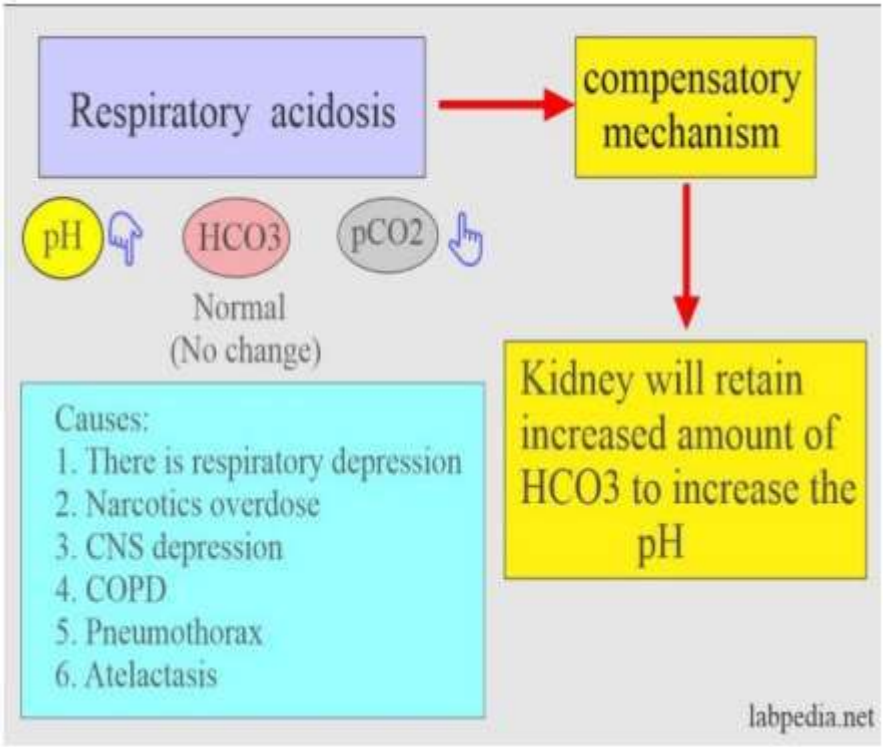
measured during blood gas analysis

pH	$PaCO_2$	HCO_3
7.35 to 7.45	35 to 45	22 to 26
↑ Acidosis ↓	↓ CO_2 = pH ↑	↓ HCO_3 = pH ↓
↓ Alkalosis ↑	↑ CO_2 = pH ↓	↑ HCO_3 = pH ↑

Results of these three allow classification of acid-base disturbance to one of four etiological categories:

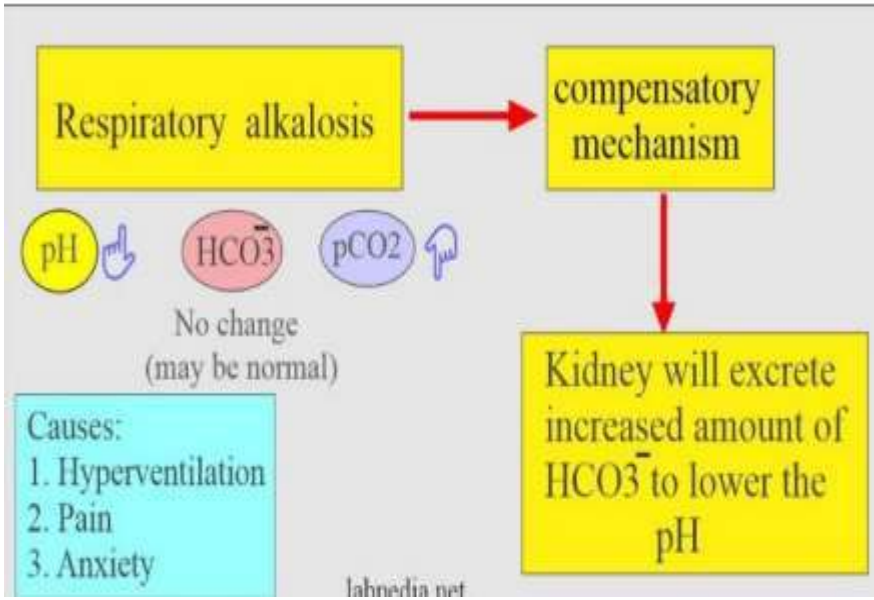
Respiratory acidosis – (raised pCO2, reduced pH)

Respiratory acidosis is characterized by increased pCO2 due to inadequate alveolar ventilation (hypoventilation) and consequent reduced elimination of CO2 from the blood. Respiratory disease, such as bronchopneumonia, emphysema, asthma and Chronic Obstructive Pulmonary Disease (COPD), may all be associated with hypoventilation sufficient to cause respiratory acidosis. Some drugs (e.g., morphine and barbiturates) can cause respiratory acidosis by depressing the respiratory center in the brain. Damage or trauma to the chest wall and the musculature involved in the mechanics of respiration may reduce ventilation rate. This explains the respiratory acidosis that can complicate the course of diseases such as poliomyelitis, and recovery from severe chest trauma.



Respiratory alkalosis – (reduced pCO_2, increased pH)

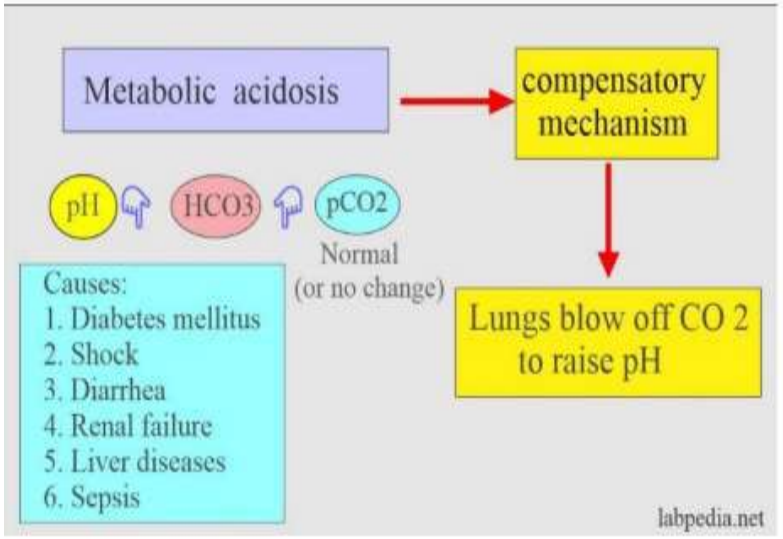
By contrast, respiratory alkalosis is characterized by decreased pCO2 **due to excessive alveolar ventilation and resulting excessive elimination of CO_2 from blood**. Disease in which, due to reduced oxygen in blood (hypoxemia), the respiratory center is stimulated can result in respiratory alkalosis. Examples here include **severe anemia**, **pulmonary embolism** and **adult respiratory syndrome**. Hyperventilation sufficient to cause respiratory alkalosis can be a feature of anxiety attacks and response to severe pain. One of the less welcome properties of salicylate (aspirin) is its stimulatory effect on the respiratory center. This effect accounts for the respiratory alkalosis that occurs following **salicylate overdose**.



Primary disturbances of pCO_2 (respiratory acidosis and alkalosis) are compensated for by **renal adjustments of hydrogen ion excretion which result in changes in [HCO_3 –]** that compensate appropriately for primary change in pCO_2. Thus, the **renal compensation for respiratory acidosis (raised pCO_2) involves increased reabsorption of bicarbonate**, and **renal compensation for respiratory alkalosis (reduced pCO_2) involves reduced bicarbonate reabsorption**.

Respiratory compensation for a primary metabolic disturbance occurs much more quickly than metabolic (renal) compensation for a primary respiratory disturbance. In the second case, compensation occurs over days rather than hours. If compensation results in return of pH to normal then the patient is said to be fully compensated. But in many cases the compensation returns pH towards normal without actually achieving normality; in such cases the patient is said to be partially compensated. For reasons described above, metabolic alkalosis is very rarely fully compensated.

- Metabolic acidosis – (decreased HCO_3^-, decreased pH) Reduced bicarbonate is always a feature of metabolic acidosis. Consider the patient with metabolic acidosis whose pH is low because bicarbonate [HCO_3^-] is low. To compensate for the low [HCO_3^-] and restore the all-important ratio towards normal the patient must lower his pCO_2. Chemoreceptors in the respiratory center of the brain respond to a rising hydrogen ion concentration (low pH), causing increased ventilation (hyperventilation) and thereby increased elimination of carbon dioxide; the pCO_2 falls and the ratio [HCO_3^-]: pCO_2 returns towards normal.

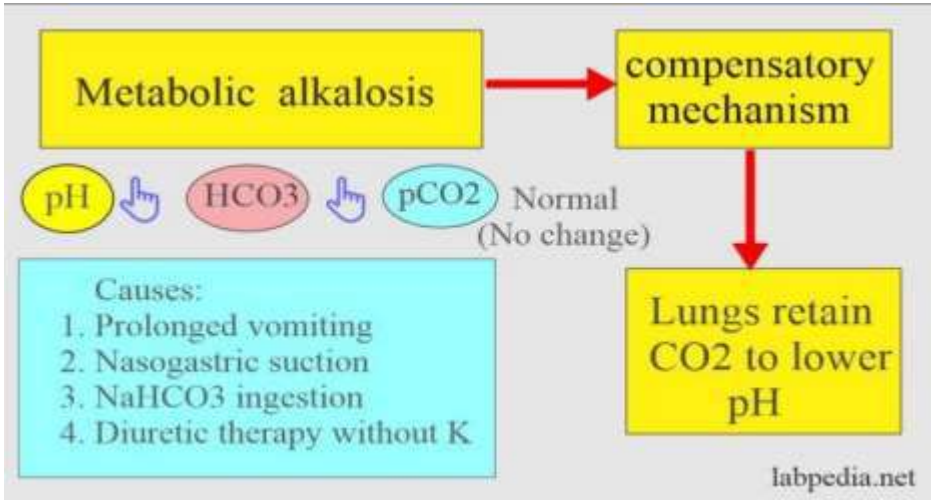


This occurs for one of two reasons: **increased use of bicarbonate in buffering an abnormal acid load** or **increased losses of bicarbonate from the body**. **Diabetic ketoacidosis** and **lactic acidosis** are two conditions characterized by overproduction of metabolic acids and consequent exhaustion of bicarbonate. In the first case, abnormally high blood concentrations of keto-acids (b-hydroxybutyric acid and acetoacetic acid) reflect the severe metabolic derangements which result from insulin deficiency. All cells produce lactic acid if they are deficient of oxygen, so increased lactic acid production and resulting metabolic acidosis occur in any condition in which oxygen delivery to the tissues is severely compromised. Examples include cardiac arrest and any condition associated with hypovolemic shock (e.g., massive fluid loss). Failure to regenerate bicarbonate and excrete hydrogen ions explains the metabolic acidosis that occurs in renal failure.

Metabolic alkalosis – (increased HCO_3^-, increased pH)

Bicarbonate is always raised in metabolic alkalosis. Compensation for metabolic alkalosis in which [HCO_3^-] is high, by contrast, **involves depression of respiration and thereby retention of carbon dioxide so that the pCO_2 rises to match the increase in [HCO_3^-]**. However, depression of respiration has the unwelcome side effect of **threatening adequate oxygenation of tissues**. For this reason, respiratory compensation of metabolic alkalosis is limited. Rarely, excessive administration of bicarbonate **or ingestion of bicarbonate in antacid preparation can cause metabolic alkalosis,** but this is usually transient. **Abnormal loss of hydrogen ions from the body can be the primary problem**. Bicarbonate which would otherwise be consumed in buffering these lost hydrogen ions consequently accumulates in blood. **Gastric juice is acidic and gastric aspiration or any disease process in which gastric contents are lost from the body represents a loss of hydrogen ions.**

The projectile vomiting of gastric juice, for example, explains the metabolic alkalosis that can occur in patients with **pyloric stenosis**. **Severe potassium depletion can cause metabolic alkalosis** due to the reciprocal relationship between hydrogen and potassium ions.



Acid-base disturbance	pH (N 7.35-7.45)	$PaCO_2$ (N 33-45 mm Hg)	$[HCO_3^-]$ (N 22-28 mmol/L)	Primary	Compensatory
Respiratory acidosis	↓	↑	↑	↑ $PaCO_2$	↑ $[HCO_3^-]$
Respiratory alkalosis	↑	↓	↓	↓ $PaCO_2$	↓ $[HCO_3^-]$
Metabolic alkalosis	↑	↑	↑	↑ $[HCO_3^-]$	↑ $PaCO_2$
Metabolic acidosis	↓	↓	↓	↓ $[HCO_3^-]$	↓ $PaCO_2$

Questions of June 2023

18 , 23 , 47 , 57 , 71 , 99