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UZHHOROD NATIONAL UNIVERSITY
FACULTY OF MEDICINE
DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY

Functional biochemistry of blood, liver and kidneys

Manual for medical students

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FOREWORD

This manual provides information about functional biochemistry of blood, liver and kidneys in normal and some pathology conditions. The following topics are described: physical and chemical properties and composition of blood, respiratory function of erythrocytes, iron metabolism, function of blood plasma proteins, acid-base balance and its disorders, porphyrin metabolism, some questions enzyme diagnostics, integral role of liver in metabolism, bilirubin metabolism and biochemistry of jaundices, biotransformation of xenobiotics and endogenous metabolites, kidney functions, properties and composition of urine, water-mineral metabolism and its disorders, etc.

In order to improve the preparation of students of higher medical educational institutions for practical classes in biochemistry and better understanding of theoretical material, in last chapter test bank of these topics have been arranged. The tests include tasks of different types of difficulty: multiple choice questions, theoretical questions, situational tasks related to clinical medicine.

Biological chemistry is a fundamental medical discipline. A perfect understanding of the theoretical material is the basis for the study of clinical disciplines, interpretation of laboratory parameters and future medical practice.

CHAPTER 1. BIOCHEMISTRY AND PATHOBIOCHEMISTRY OF BLOOD

Blood as a specialized tissue of the body, its composition. Functions of blood.

Blood is fluid tissue composed of cells (formed elements of the blood) and an extracellular liquid medium. The overlying liquid (supernatant) of blood sample obtained on precipitation of the blood cells in the presence of an anticoagulant is called **blood plasma.** The plasma is an opalescent liquid containing all extracellular components of the blood. The blood cells account for about 45%, and the plasma, for about 55% of the blood volume. The clear liquid that separates from the blood when it is allowed to clot completely is called **blood serum.** Actually, the blood serum is the plasma from which fibrinogen has been removed in the process of clotting.

Suspended in the watery plasma are seven types of cells and cell fragments:

1) Red blood cells (RBCs) or erythrocytes;
2) Platelets or thrombocytes;
3) Five kinds of white blood cells (WBCs) or leukocytes: three kinds of granulocytes (neutrophils, eosinophils, basophils); two kinds of leukocytes without granules in their cytoplasm (lymphocytes, monocytes).

If one takes a sample of blood, treats it with an agent to prevent clotting, and spins it in a centrifuge, the red cells settle to the bottom the white cells settle on top of them forming the "buffy coat". The fraction occupied by the red cells is called the **hematocrit.** Normally it is approximately 45%. Values much lower than this are a sign of anemia.

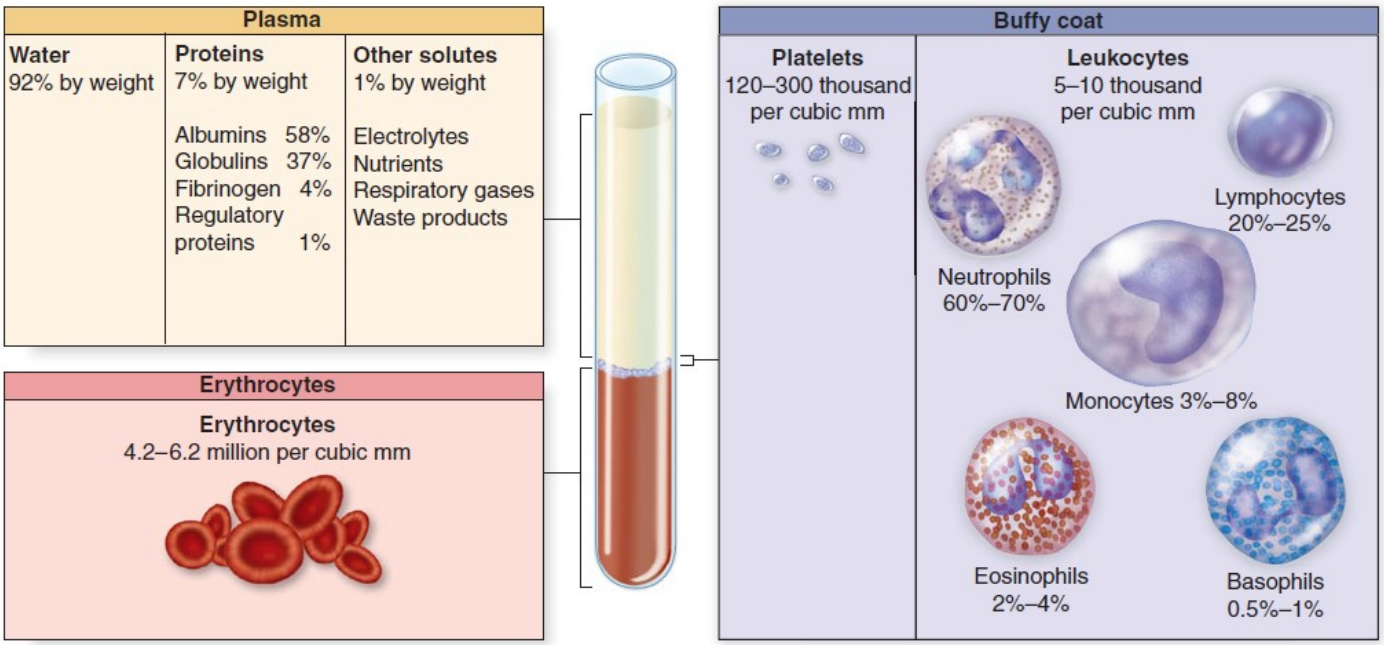


Figure 1. Separation of blood into its basic components (Janson, 2012)

Major functions of blood:

1) Respiration (transport of O_2 from the lungs to the tissues and CO_2 from tissues to lungs).
2) Transport function (transport of different substances).
3) Excretion (transport of metabolic products to the kidneys, lungs, skin and intestine for removal).
4) Maintenance of the normal acid-base balance in the body.

5) Regulation of water balance through the effects of blood on the exchange of water between the circulating fluid and the tissue fluid.
6) Regulation of body temperature by means of distribution of body heat.
7) Defense against infection by the white blood cells and circulating antibodies.
8) Transport of hormones and regulation of metabolism.

Blood as source for medicinal preparations. The blood is used as a raw material for producing a variety of medicinal preparations which, by their therapeutic applications, are divided into four groups:
1) systemic effect agents (albumin, protein, native blood plasma);
2) immunologically active preparations (gamma-globulin, antistaphylococcic, interferon)
3) hemostatic preaparations (antihemophilic plasma, thrombin, fibrin sponge, fibrin film, fibrinogen);
4) antianemic and stimulating preparations (polyobolin – dry powdered protein components of blood plasma, eryheme-dehydrated hemolyzate of erythrocytes, etc.).

Physical and chemical properties of blood. Inorganic components of blood.

Normally the average blood volume is 5200 ml in men and 3900 ml in women. The blood plasma accounts for about 55% of the total volume. The erythrocytes constitute a major fraction of blood cells and account for 44% of the total blood volume. Other blood cells account only 1%. The relative **density** of whole blood is 1,05-1,064, of blood plasma – 1,024-1,030, of blood cells – 1,08-1,097. **Viscosity** of blood is 4-5 fold that of water. It is provided by means of high content of proteins and erythrocytes.

An essential physico-chemical characteristic of the blood is the **osmotic pressure** of blood plasma. It is provided by osmotic concentration that is by the sum total of all the blood particles per unit of volume. At a body temperature of 37°C, the blood plasma osmotic pressure is about 7,6 atm. (768-818 kPa). The major contributors to this value are NaCl and other low-molecular weight substances, contained in the blood. Osmotic pressure constancy provides the normal transport of substances from blood to tissues and back, promotes the stability of erythrocytes. The part of osmotic pressure, which is provided by proteins, is called **oncotic (or colloid osmotic) pressure.** Oncotic pressure accounts for about 0,03 atm. (0,5% of osmotic pressure). But oncotic pressure is very important, as proteins cannot penetrate through semipermiable membrane and therefore oncotic pressure facilitates the reverse stream of fluid to venous part of capillaries.

Mineral substances of blood:

Sodium is a major osmotically active ion in the extracellular space. In **hypernatriemia,** a syndrome associated with the organism's hyperhydration is commonly observed to develop. The accumulation of excessive sodium in the blood plasma occurs in a specific renal disease known as parenchymatous nephritis, in patients with congenital cardiac insufficiency, also in primary (or true) and secondary hyperaldosteronism. **Hyponatremia** is accompanied by dehydration of the organism.

Potassium. The potassium level in the cells is much higher as compared to the extracellular space. **Hyperkalemia** is observed in acute renal insufficiency or in hypofunction of adrenal cortex. By contrast, an increased production of aldosterone by adrenal cortex leads to **hypokalemia.** The progressive hypokalemia leads to grave disturbances of cardiac performance. Occasionally, a decreased level of potassium in the blood serum was observed as a side effect on administration of large therapeutic doses of adrenal cortex hormones to patients.

Calcium. In tumoral lesions of bone tissue, hyperplasia, or parathyroid adenoma, a marked **increase of calcium** level in the blood plasma is observed. The state of **hypocalcemia** is observed in hypoparathyrosis. The hypofunction of parathyroid gland results in a drastic drop of calcium concentration in the blood, with the eventual development into a convulsive state (tetany). Hypocalcemia is also observed in rickets, sprue, obstructive jaundice, nephroses, glomerulonephritis.

<table>
<tr><th colspan="2">Chemical composition of blood plasma</th></tr>
<tr><td>I. Proteins
1. Total protein 65-85 g/L
2. Albumins 35-50 g/L
3. Globulins 25-35 g/L
4. Fibrinogen 2.0-7.0 g/L
5. Haptoglobin 0.28-1.90 g/L
6. Prothrombin 10-15 mg/dL
7. Plasminogen 1.4-2.8 μmol/L (20-40 mg/dL)
8. Transferrin 19.3-45.4 μmol/L (170-400 mg/dL)
9. Ceruloplasmin 1.52-3.31 μmol/L (23-50 mg/dL)
10. β-Lipoproteins 3.0-6.0 g/L (300-600 mg/dL)
HDL – high density lipoprotein (α-LP) 1.063-1.210 mmol/L (80-400 mg/dL)
LDL – low density lipoprotein (β-LP) 1.006-1.063 mmol/L (360-640 mg/dL)</td><td>II. Enzymes
1. Alanyl aminotransferase (ALT) 0.16-0.68 mmol/h·L or (15-75 IU/L)
(glutamate pyruvate transferase, GPT)
2. Aspartate aminotransferase (AST) 0.10-0.45 mmol/h·L or (10-50 IU/L)
(glutamate oxaloacetate transferase, GOT)
3. Lactate dehydrogenase 0.8-4.0 mmol/h·L
4. Creatine kinase < 1.2 mmol/h·L or (< 90 IU/L)
5. Fructose-biphosphate aldolase (F-1,6-PA) 3.6-21.8 mmol/h·L
6. Acetylcholine esterase 160-340 mmol/ h·L
7. α-Amylase 15-30 g/h·L or (< 300 IU/L)
8. Alkaline phosphatase 30-150 IU/L
9. Acidic phosphatase < 62 nkat/L
10. γ-Glutamyl transferase (γGT or GGT) < 60 IU/L</td></tr>
<tr><td>III. Nonproteinic nitrogenous compounds
1. Nitrogen residual (nonproteinic) 19.5-30.0 mmol/L
2. Nitrogen of amino acids 3.5-5.5 mmol/L
3. Creatine 15-70 mmol/L
4. Creatinine 60-150 μmol/L
5. Urea 3.3-6.7 mmol/L
6. Uric acid 0.1-0.4 mmol/L
7. Bilirubin total 8-20 μmol/L
8. N-Acetylneiraminic acid 1.8-2.2 mmol/L
9. Histamine 17.99-71.94 nmol/L (0.2-0.8 ng/dL)
10. Adrenalin 1.91-2.46 nmol/L (0.35-0.45 ng/L)
11. Serotonine 0.3-1.7 μmol/L (5.0-30.0 μg/dL)
12. Thyroxine 64.36-141.59 nmol/L (5-11ng/dL)</td><td>IV. Carbohydrates and metabolites
1. Glucose 2.8-6.0 mmol/L
2. Lactate 0.5-2.0 mmol/L
3. Pyruvate < 0.1 mmol/l
4. Citric acid 88.5-156.1 μmol/L (1.7-3.0 mg/dL)

V. Lipids and metabolites
1. Total lipids 4.0-8.0 g/L
2. Triacylglycerides 0.5-2.1 mmol/L
3. Total phospholipids 2.0-3.5 mmol/L
4. Total cholesterol 4.0-8.6 mmol/L
5. Free fatty acids 0.3-0.8 mmol/L
6. Ketone bodies 100-600 μmol/L</td></tr>
<tr><td>VI. Mineral components
1. Sodium (Na^+) 135-155 mmol/L
2. Potassium (K^+) 3.6-5.0 mmol/L
3. Chlorides (Cl^-) 97-108 mmol/L
4. Calcium (Ca^{2+}) 2.25-2.75 mmol/L
5. Phosphate inorganic 0.8-1.4 mmol/L
6. Magnezium (Mg^{2+}) 0.7-1.0 mmol/l
7. Sulphates 0.4-0.6 mmol/L
8. Iron (Fe) 14-32 μmol/L (65-175 μg/dL)
9. Copper (Cu) 12-19 μmol/L
10. Zinc (Zn) 12-20 μmol/L
11. Ammonia 10-47 μmol/L</td><td>Indices of blood
1. Hemoglobin: males 130-180 g/L (13-18 g/dL), females 120-160 g/L (12-16 g/dL)
2. Hydrogen ion: arterial blood 35-46 nmol/L (pH=7.36-7.44) (38°C)
3. Oxygen (pO_2) in arterial blood: 11-15 kPa (85-105 mm Hg)
4. Bicarbonate total (CO_2) 22-30 mmol/L
5. Carbon dioxide (pCO_2) in arterial blood: 4.5-6.0 kPa (35-46 mm Hg)</td></tr>
</table>

Buffer blood systems. Acid-base balance, its regulation. Acidosis and alkalosis.

Acid-base balance is the relation between concentrations of hydrogen and hydroxyl ions in liquids of organism. This balance is characterized by the hydrogen ion concentration (in nmoles per liter), or by the pH value which is the negative logarithm (to base 10) of hydrogen ion concentration. Blood hydrogen ion concentration [H^+] is maintained with tight limits in health. Normal levels lie between 35-45 nmol/L (pH 7,35-7,45). Values greater than 120 nmol/l (pH 6,92) or less than 20 nmol/L (pH 7,7) are usually incompatible with life. The total amount of hydrogen ion produced each day in this way is of the order of 60 mmoles. If all of this was be diluted in the extracellular fluid (~14 liters), [H^+] would be 4 mmol/L or 100 000 times more acid than normal. This just does not happen, as all the hydrogen ions produced are efficiently excreted in urine.

The „first line" of defense from changing pH is buffer systems. The buffer system is a conjugated acid-base pair composed of a donor and an acceptor of hydrogen ions (protons). The acid-base balance of a buffer solution is described by the Henderson-Hasselbach equation: $pH = pK_a + \log$ [proton acceptor]/[proton donor]. The major buffer systems of blood are bicarbonate, phosphate, protein, and especially hemoglobin systems.

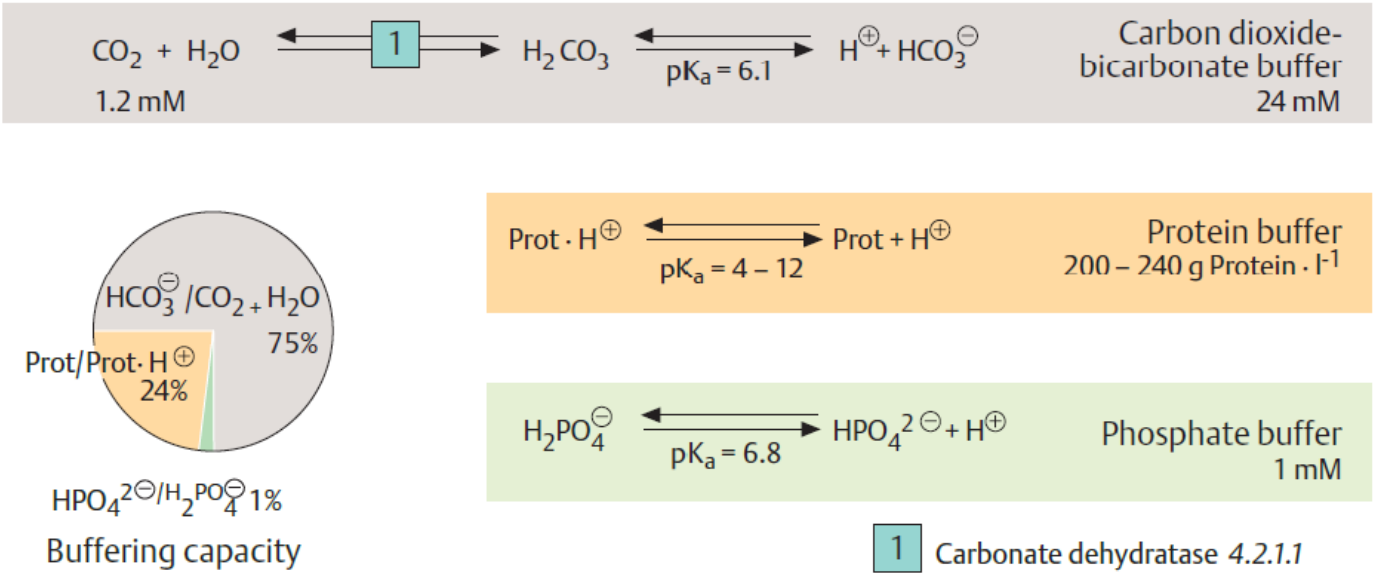


Figure 2. Buffer systems in the plasma (Koolman, 2005)

The bicarbonate buffer system is powerful and perhaps the most controlable system of both the extracellular fluid and blood. Bicarbonate buffer system accounts for about 10% of the total buffering capacity of blood.

H_2CO_3 (proton donor) ↔ $H^+ + HCO_3^-$ (proton acceptor)

$[HCO_3^-] = 27$ mmol/L

$[H_2CO_3] = 1{,}35$ mmol/L

$[HCO_3^-] / [H_2CO_3] = 20/1$

Bicarbonate buffer system functions as an effective medium regulator within a close range of pH 7,4. The limit to the effectiveness of the bicarbonate system is the initial concentration of bicarbonate. Only when all the bicarbonate is used up the system has no further buffering capacity. The acid-base status of patients is assessed by consideration of the bicarbonate system of plasma. The extracellular fluid contains a large amount of bicarbonate about 24 mmol/L.

Phosphate buffer systems is a conjugated acid-base pair composed of ion $H_2PO_4^-$ (proton donor) and ion HPO_4^{2-}(proton acceptor).

$[HPO_4^{2-}] / [H_2PO_4^-] = 4/1$

Phosphate buffer system accounts about 1% of the blood buffering capacity. Nonetheless, in the tissues, especially in kidneys, this system is a major one. This buffer is operative within a range of pH variation from 6,1 to 7,7.

Protein buffer system is of minor importance for maintaining the acid-base balance in the blood plasma as compared to other buffer systems. Proteins form a buffer system owing to the occurrence of acid and basic groups in their molecules:

$$\text{Protein H} \leftrightarrow \text{Protein} + H^+$$

The protein buffer system of blood plasma is effective within a pH range 7,2-7,4.

Hemoglobin buffer system is the most powerful buffer system of blood. This buffer system accounts for about 75% of the total buffering capacity of blood. The involvement of hemoglobin in the control of blood pH is primarily associated with the function of hemoglobin in the transport of oxygen and carbon dioxide. The dissociation constancy of acidic hemoglobin groups is liable to variation depending on the degree of hemoglobin saturation with oxygen. Hemoglobin, on its uptake of oxygen, becomes a stronger acid ($H^+ + HbO_2$). By contrast hemoglobin without oxygen is a very weak organic acid (HHb).

Disturbances of acid-base balance.

Acidosis: the hydrogen ion concentration in the blood is above the normal; level of pH below 6,92 (↑$[H^+]$ 120 nmol/l) causes death.

Alkalosis: the hydrogen ion concentration in the blood is lower the normal; level of pH above 7,7 (↓$[H^+]$ 20 nmol/l) is incompatible with life.

Blood gas results			
Metabolic acid-base disorders		Respiratory acid-base disorders	
$[H^+]$ elevated	**$[H^+]$ decreased**	**H^+ elevated**	**H^+ decreased**
↓	↓	↓	↓
Acidosis	**Alkalosis**	**Acidosis**	**Alkalosis**
↓	↓	↓	↓
HCO_3^-↓	**HCO_3^-↑**	**pCO_2↑**	**pCO_2↓**
↓	↓	↓	↓
metabolic acidosis	**metabolic alkalosis**	**respiratory acidosis**	**respiratory alkalosis**

Metabolic acidosis is the most common form of disturbed acid-base balance. It is associated with the accumulation of organic acids in the tissues and the blood. Causes of metabolic acidosis:

1) Renal disease (acute and chronic glomerulonephritis; acute and chronic pyelonephritis). The decrease of excretion of protons by kidney.

2) Ketoacidosis (imperfect oxidation of lipids: in diabetes mellitus, starvation, fever; ketogenic diet).

3) Lactate acidosis (imperfect oxidation of carbohydrates, lung diseases, cardiovascular diseases, different types of hypoxia).

4) Certain causes of over dosage of poisoning (salicylate → lactate; methanol → formate; ethylene glycol → oxalate).

5) Chronic diarrhea or intestinal fistula.

Clinical effects of metabolic acidosis. The compensatory response to metabolic acidosis is hyperventilation since the increased [H^+] acts as a powerful stimulant of the respiratory centre. The deep, rapid and gasping respiratory pattern is known as Kussmaul breathing. Hyperventilation is the appropriate physiological response to acidosis and it occurs rapidly. A raised [H^+] leads to increased neuromuscular irritability. There is a hazard of arrhythmias progressing to cardiac arrest, and this is made more likely by the presence of hyperkaliemia which will accompany the acidosis.

Metabolic alkalosis is due to loss of a large amount of acid equivalents (for example, in noncontrolable vomiting), the accumulation of base equivalents in tissues (for example in tetany), a wrong correction for metabolic acidosis, high doses of glucocorticoids. The condition may be due to:

1) Loss of hydrogen ion in gastric fluid during vomiting.
2) Ingestion of an absorbable alkali such as sodium bicarbonate.
3) Potassium deficiency.

In severe potassium depletion, often a consequence of diuretic therapy, hydrogen ions are retained inside cells to replace the missing potassium ions. In the renal tubule more hydrogen ions, rather than potassium, are exchanged for reabsorbed sodium. So, despite there being an alkalosis, the patient passes an acid urine. This is often referred to as a "paradoxical" acid urine, because in other causes of metabolic alkalosis urinary [H^+] usually falls.

Clinical effects of metabolic alkalosis. The clinical effects of alkalosis include hypoventilation, confusion and eventually coma. Muscle cramps, tetany and parasthesia may be consequence of a decrease in the unbound plasma calcium concentration which is a consequence of the alkalosis.

Recognizing primary **metabolic acid-base disorders** by inspecting the HCO_3^- concentration.

Respiratory acidosis develops because of a reduced minute respiratory volume (for example, in bronchiole asthma, edema of lungs, emphysema, atelectasis and traumatic asphyxia). Respiratory acidosis may be acute or chronic. Examples of acute, and uncompensated, respiratory acidosis are:

1) choking;
2) bronchopneumonia;
3) acute exacerbation of asthma.

Chronic respiratory acidosis is usually a long-standing condition and is accompanied by maximal renal compensation. Examples of chronic respiratory disorders are:

1) chronic bronchitis;
2) emphysema.

Respiratory alkalosis arises from a sharply intensified pulmonary ventilation (in inhalation of pure oxygen, in compensatory dyspnea). Respiratory alkalosis is much less common than acidosis. Examples are:

1) hysterical over breathing;
2) mechanical over ventilation;
3) raised intracranial pressure or hypoxia, both of which may stimulate the respiratory centre.

Blood plasma proteins. Pathoproteinemia. Acute phase proteins. Lipoproteins. Non-protein organic compounds of blood. Azotemia.

Proteins account for 6,5-8,5% out of the total 9-10% of dry blood plasma residue.

Total proteins – 65-85 g/L

Albumins – 40-50 g/L Globulins – 20-40 g/L Fibrinogen – 1,5-3,5 g/L

The most of blood serum proteins are synthesized in liver, but some of them are formed in other tissues. For example, γ-globulins are synthesized by lymphocytes; peptide hormones are mainly secreted by endocrine glands; peptide hormone erythropoietin is formed by kidney cells. Almost all the blood plasma proteins, with the exception of albumin, are glycoproteins.

Group	Protein	M_r in kDa	Function
Albumins:	Transthyretin	50-66	Transport of thyroxin and triiodothyronin
	Albumin: 45 g · l^{-1}	67	Maintenance of osmotic pressure; transport of fatty acids, bilirubin, bile acids, steroid hormones, pharmaceuticals and inorganic ions.
α_1-Globulins:	Antitrypsin	51	Inhibition of trypsin and other proteases
	Antichymotrypsin	58-68	Inhibition of chymotrypsin
	Lipoprotein (HDL)	200-400	Transport of lipids
	Prothrombin	72	Coagulation factor II, thrombin precursor (*3.4.21.5*)
	Transcortin	51	Transport of cortisol, corticosterone and progesterone
	Acid glycoprotein	44	Transport of progesterone
	Thyroxin-binding globulin	54	Transport of iodothyronins
α_2-Globulins:	Ceruloplasmin	135	Transport of copper ions
	Antithrombin III	58	Inhibition of blood clotting
	Haptoglobin	100	Binding of hemoglobin
	Cholinesterase (3.1.1.8)	ca. 350	Cleavage of choline esters
	Plasminogen	90	Precursor of plasmin (*3.4.21.7*), breakdown of blood clots
	Macroglobulin	725	Binding of proteases, transport of zinc ions
	Retinol-binding protein	21	Transport of vitamin A
	Vitamin D-binding protein	52	Transport of calciols
β-Globulins:	Lipoprotein (LDL)	2.000-4.500	Transport of lipids
	Transferrin	80	Transport of iron ions
	Fibrinogen	340	Coagulation factor I
	Sex hormone-binding globulin	65	Transport of testosterone and estradiol
	Transcobalamin	38	Transport of vitamin B_{12}
	C-reactive protein	110	Complement activation
γ-Globulins:	IgG	150	Late antibodies
	IgA	162	Mucosa-protecting antibodies
	IgM	900	Early antibodies
	IgD	172	B-lymphocyte receptors
	IgE	196	Reagins

Figure 3. Plasma proteins (Koolman, 2005)

Functions of blood proteins: they take part in blood clotting; they provide viscous properties of blood; maintaining acid base balance; transport function; protective function; reserve of amino acids; regulation function; they maintain the oncotic pressure; maintaining a needed level of cations in blood.

Albumin level in blood plasma protein is 35-50 g/L. Albumins make up approximately 60% of the total plasma protein. Functions of albumins:

1) Albumins are responsible for 75 – 80% of oncotic pressure of human's plasma. The decreasing albumin concentration below 30 g/L leads to edema.
2) Transport function. It transports free fatty acids, calcium, certain steroids hormones, bilirubin, copper, different drugs etc.

Globulins: are divided into α_1-globulins (3-6 g/L), α_2-globulins (4-9 g/L), β-globulins (6-11 g/l) and γ-globulins (7-15 g/L). They perform transport and protective functions.

α-Globulins:

Haptoglobin (Hp) (is component of α_2-globulin fraction). This glycoprotein binds extracorpuscular hemoglobin. The haptoglobin-hemoglobin complex can be absorbed by the macrophage system and cannot pass the glomerulus of the kidney. Thus Hp prevents a loss of free hemoglobin by kidney and provides the conservation and reutilization of iron.

Ceruloplasmin (α_2–globulin) is a blue, copper-containing (0,32%) glycoprotein found in mammalian blood plasma. It contains about 3% of total amount of copper in organism and more 90% Cu of blood plasma. Cerruloplasmin exhibits a weakly pronounced catalytic activity in the oxidation of ascorbic acid, adrenaline, dihydrophenylalanine and a number of other compounds, and ferrooxidase activity ($Fe^{2+} \rightarrow Fe^{3+}$). It is antioxidant. In Wilson's diseases the concentration of ceruloplasmin in the blood plasma is significantly lowered which a major diagnostic test for this pathology.

α_1-Antitrypsin can inhibit trypsin and other proteolytic enzymes. The level of trypsin inhibitors is increased in inflammatory processes, in pregnancy and in a number of other states of organism. In inflammatory process the level of α_1-antitrypsin increases in result of stimulation of its synthesis in hepatocytes. In acute pancreatitis the enchanced level of α1-antitrypsin arises from delivery of active pancreatic proteinases. Deficiency of α1-antitrypsin is associated with emphysema and one type of liver diseases (α_1-antitrypsin deficiency liver disease).

α_2- Macroglobulin is a large plasma glycoprotein (720 kDa). It is inhibitor of serine-, thiol-, carboxy- and metal proteinases. Therefore it is involved in regulation of blood clotting, immunologic processes, inflammatory processes. In addition, it binds many cytokines (eg. platelet-derived growth factor, transforming growth factor-β, etc.) and is involved in targeting them toward tissues.

β-Globulins:

C-reactive protein is able to form a precipitate with the somatic C polysaccharide of pneumococcus C-reactive protein does not occur in the blood serum of healthy organisms. It is detected in many pathologic states attendant to inflammation and necrosis of the tissues. This protein is „acute phase" protein.

Hemopexin binds free heme.

Transferrin is glycoprotein with a molecular mass of approximately 80 kDa. Transferrin plays a central role in the body's metabolism of iron, because it transports iron (2 moles of Fe^{3+} per moll of transferrin) in the circulation to sites where iron is required, e.g. from the gut to the bone marrow and other organs.

γ-Globulins:

Cryoglobulin is absent in the blood serum of healthy individuals. It is found only in pathologic states. A specific feature of this protein is its solubility at a temperature 37°C and ability to form a precipitate or a gel in decreasing temperature to 4°C. It is detected in blood serum in myeloma, nephrosis, cirrhosis of the liver, rheumatism, lymphosarcoma, leukosis and other diseases.

Interferons are specific proteins synthesized on the organism's cells invaded by virus. Interferon can inhibit viral multiplication in the cells however it has no effect on the viral particles that have been formed in the cell. Interferon is easy to leave the cell and to enter the blood stream in which it is carried over to tissues and organs. There are 3 types of interferons: IFN-α, IFN-β, and IFN-γ. IFN-α are mainly synthesized by leukocytes; IFN-β by fibroblasts; IFN-γ by T- and B-lymphocytes.

Immunoglobulins (humoral antibodies) are synthesized mainly in plasmocytes, specialized cells of B-cell lineage that synthesize and secrete immunoglobulins into plasma. All immunoglobulin molecules consist of 4 polypeptide chains, which are linked by disulfide bonds: two identical light (L) chains and two identical heavy (H) chains. L-chains have molecular mass 23000 Da. They are common to all the classes of immunoglobulins. They are two types: kappa (κ) and lambda (λ). A given immunoglobin molecule contains or two identical κ, or two λ chains. Heavy chains have molecular mass 50000-75000 Da. Five types of heavy chains exist: α (alpha), γ (gamma), μ (mu), δ (delta), ε (epsilon). The type of H chain determines the class of immunoglobulin and thus its effector function. There are five immunoglobulin classes: IgG (γ-chains), IgA (α-chains), IgM (μ-chains), IgD (δ-chains), IgE (ε- chains). Every light and heavy chain consist of 2 segments: variable (V) and constant (C). The constant regions of immunoglobulin molecules are responsible for the class specific effectors functions of the different immunoglobulin molecules, e.g. complement fixation or placental transfer.

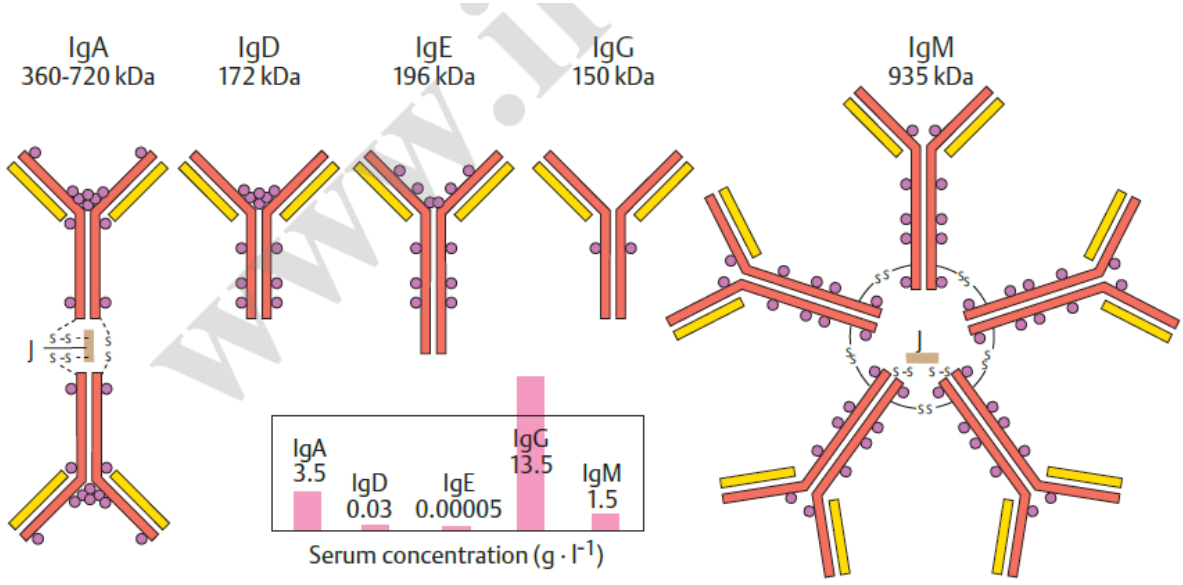


Figure 4. Classes of immunoglobulins (Koolman, 2005)

IgGs (7-20 g/L) and IgMs (0,5-2 g/L) are basic classes of immunoglobins. They realize humoral immune response on the incorporation of foreing antigens. IgMs participate in the primary immune response, they activate complement system. IgGs participate in the secondary immune response, activate a complement system. IgG is the only immunoglobin which is able to pass placenta. IgA (0,7-1,5 g/L) is antibody of other biological liquids and secretions (secretions of mucous, lungs). IgD (0,000001-0,0003 g/L) and IgE (0,02-0,02g/L) are minor components of blood serum. IgE participate in allergic reactions.

In clinical practice, there have been reported states characterized by alteration in both the total content of blood plasma proteins and the percentage of individual protein fractions.

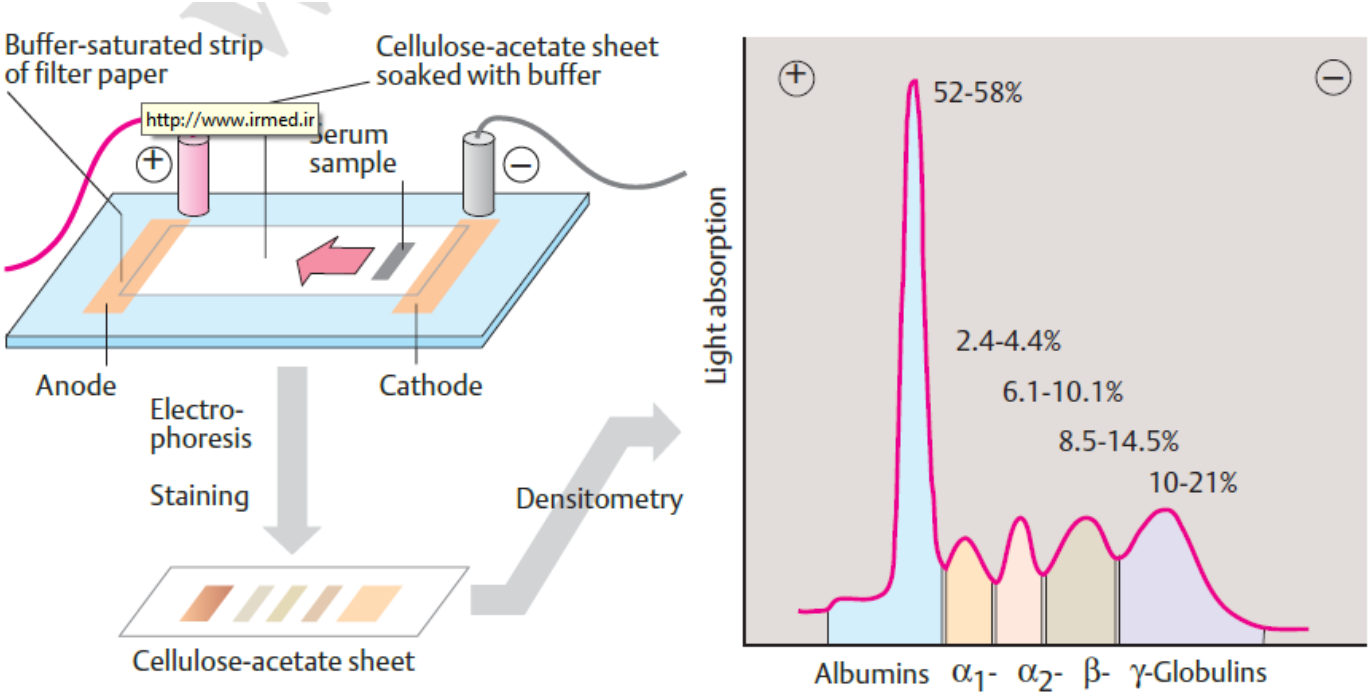


Figure 5. Electrophoresis (Koolman, 2005)

Hypoproteinemia (a decrease in the total concentration of blood plasma proteins) is usually linked with the decreasing albumins. Hypoproteinemia occurs:
1) in nephrotic syndrome;
2) in liver disease (acute atrophy of the liver, toxic hepatitis, and other states);
3) in a drastically increased permeability of the capillary wall,
4) in protein deficiency (affected gastrointestinal tract, carcinoma, etc).

Paraproteinemia is the occurrence in the blood plasma of proteins, normally untypical to the healthy organism (for example, in myeloma). In the blood serum of patients with myeloma specific „myelomatous" proteins are detected.

Hyperproteinemia is a pathologic condition manifested by an increased content of blood plasma proteins. Hyperproteinemia:
1) relative (it is caused by loss of liquid by organism (diarrhea in children; vomiting, due to an obstruction of the upper small intestine, or by extensive burns);
2) absolute (it is caused by an elevated level of γ-globulins.

Dysproteinemia is the changing ratio of individual protein fractions, while the total protein content in the blood serum is normal. γ-Globulin fraction is increased in chronic inflammation, chronic polyartritis etc. α_2-Globulin fraction is increased in acute infections, acute rheumatism. The level of some proteins may be sharply raised in acute inflammatory processes and some other pathologic states (trauma, burns, myocardial infarction). Those proteins are called «**acute phase**» proteins, because they take part in development of inflammatory reaction of organism. Main inducer of the synthesis of the most acute phase proteins in hepatocytes is interleukin-1 liberated by mononuclear phagocytes. Haptoglobin, C-reactive protein, α_1-antitrypsin, acid α_1- glycoprotein, fibrinogen belong to proteins of acute phase.

Blood plasma lipoproteins.

To transport through the blood water-insoluble lipids from one tissue to another special transport forms exist – lipoproteins. There are 5 classes of blood lipoproteins:
1. Chylomicrons;

2. VLDL (Very Low Density Lipoproteins);
3. IDL (Intermediate Density Lipoproteins);
4. LDL (Low Density Lipoproteins);
5. HDL (High Density Lipoproteins).

Despite their differences in lipid and protein composition, all lipoproteins share common structural features, notably they have a spherical shape, and consist of a core of triacylglycerols or/ and cholesterol esters surrounded by a single layer of phospholipids, into which a mixture of cholesterol and proteins (apoproteins) is inserted.

Note that the phospholipids and cholesterol are oriented with their polar head groups facing outward to interact with solvent water and thus shield the hydrophobic lipids inside from the water outside. The proteins also contribute to the formation of lipoprotein polar surface, but additionally act as cofactors for enzymes, which take part in lipoprotein metabolism, and function as recognition sites for the various lipoprotein receptors throughout the body.

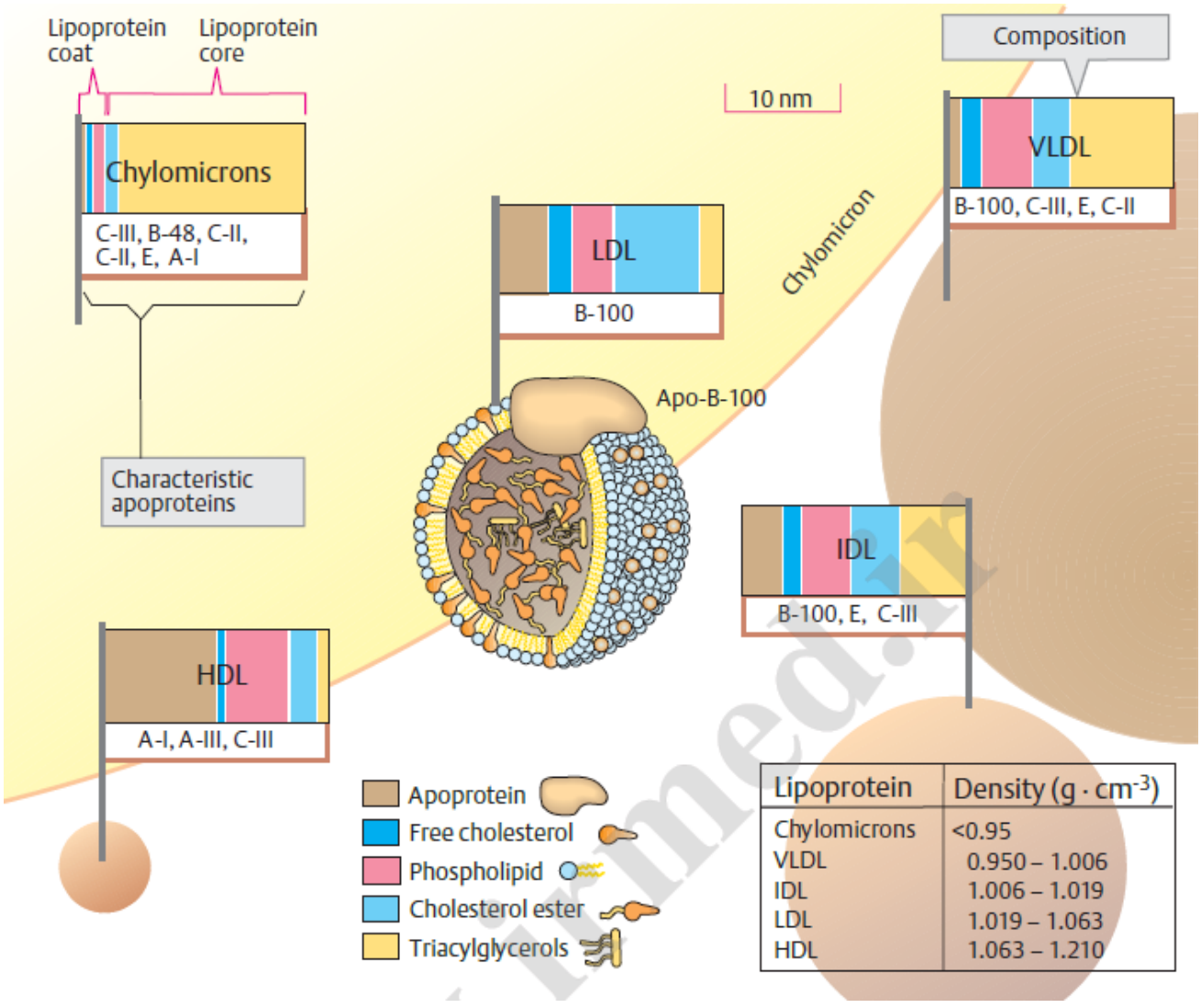


Figure 6. Composition of lipoprotein complexes (Koolman, 2005)

Chylomicrons serve to transport triacylglycerols and cholesterol esters from the intestines to other tissues and eventually to the liver. Chylomicrons are synthesized in intestinal epithelial cells. They are the largest and least dense of the blood lipoproteins because they have the most triacylglycerol (about 90%) and rather low content of protein.

Their triacylglycerols and cholesterol are derived from the dietary lipids, and their major protein is apo B-48. Chylomicrons enter the lymphatic system and travel through the lymph into the blood. Additional apoproteins (apo CII and apo E) are transferred to nascent chylomicrons from HDL, and mature chylomicrons are formed. In capillaries of peripheral tissues, particularly adipose and muscle, chylomicrons become the target for lipoprotein lipase. Lipoprotein lipase is activated by apo CII and hydrolyzes triacylglycerols to fatty acids and glycerol. Fatty acids are taken up and used by peripheral cells. As chylomicrons are degraded, chylomicron remnants are formed. Remnants interact with apo E receptors of hepatocytes, undergo endocytosis and lysosomal degradation.

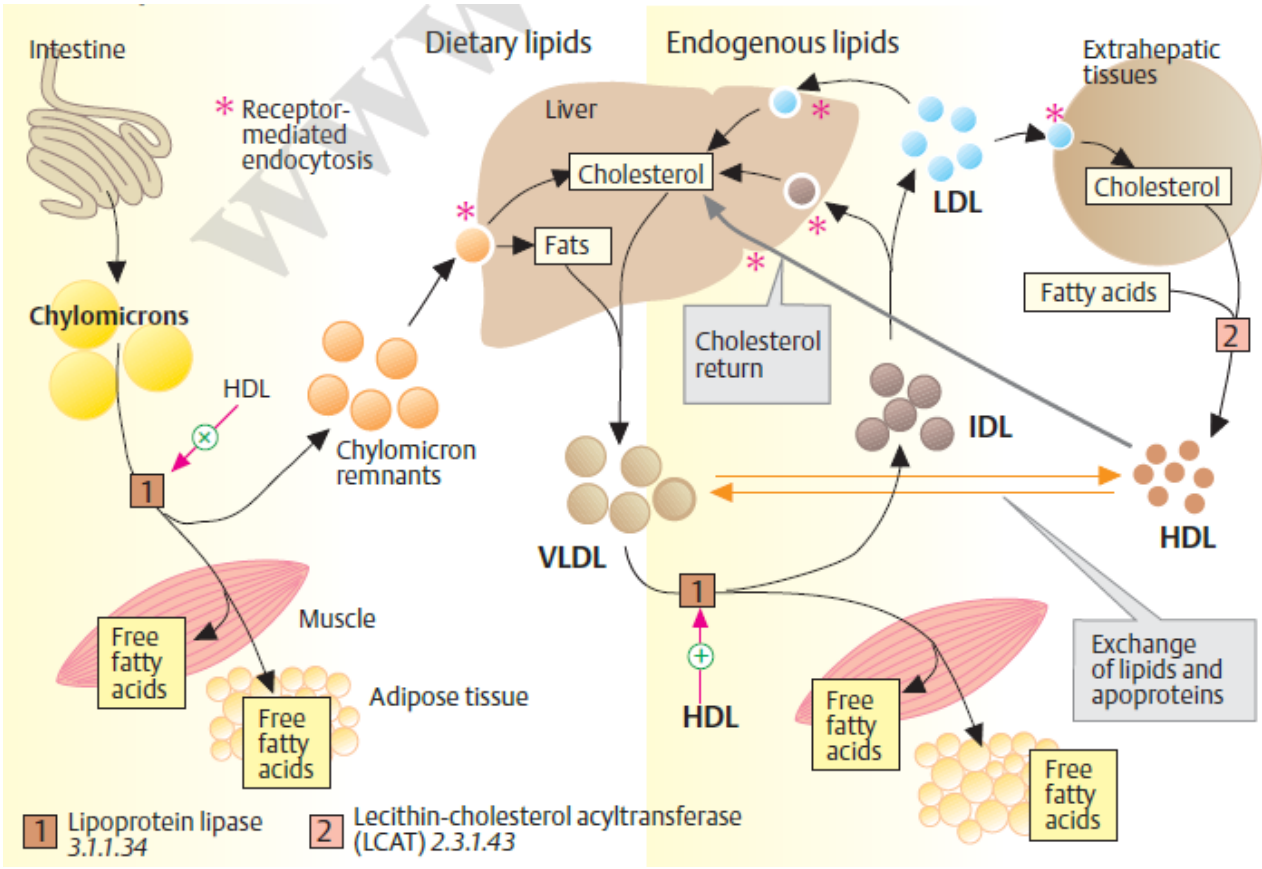


Figure 7. Transport of lipoproteins (Koolman, 2005)

VLDL, **IDL** and **LDL** form a group of related particles that deliver endogenous triacylglycerols and cholesterol from the liver to the peripheral tissues. VLDL is synthesized in the liver. Its' core is formed from triacylglycerols (about 55%) and cholesterol esters. The phospholipids, cholesterol and apoprotein apo B-100 form the coat. VLDL particles are released into the blood and get additional apoproteins (apo CII and apo E) from HDL. In peripheral tissues, VLDL triacylglycerols are hydrolyzed by lipoprotein lipase, and VLDL is converted to IDL. Most of IDL return to the liver, bind to apo E receptors, undergo endocytosis and lysosomal degradation. About 25% of IDL in liver sinusoids are acted on by hepatic lipase. Further hydrolysis of triacylglycerols and removal of additional apoproteins results in LDL formation. LDLs react with apo B-100 receptors (LDLreceptors) on the cells of various tissues, are taken up by endocytosis and decomposed in lysosomes. LDL is regarded as the vehicle delivering cholesterol to the peripheral tissues. Three regulatory mechanisms are used by cells to prevent excessive accumulation of cholesterol:

1) Cholesterol inhibits HMG-CoA reductase, the key enzyme of de novo cholesterol biosynthesis.
2) Cholesterol activates acyl-CoA:cholesterol acyltransferase (ACAT), which converts free cholesterol to cholesterol ester (cholesterol storage form).
3) Cholesterol inhibits synthesis of LDL-receptors thus reduces the amount of cholesterol taken up by the cell from the blood.

The removal of modified LDLs from the bloodstream occurs due to macrophages through their scavenger receptors. Scavenger receptors are not down-regulated by cholesterol, and unlimited uptake of LDL particles transforms macrophages to the "foam cells". The accumulation and death of such foam cells in the intima of arteries cause atherosclerotic plaque formation, with cholesterol being its chief chemical constituent. Therefore, LDLs are referred to as "bad cholesterol", and prolonged elevation of LDL levels followed by their oxidative and other modifications lead to atherosclerosis.

HDL is synthesized by the liver and released into the blood as disc-shaped particles. The major constituents of nascent HDL are phospholipids and proteins (apo A, C, D, E). HDLs participate in metabolism of chylomicrons and VLDLs providing apoproteins required for their metabolism. Besides, HDL takes cholesterol from the peripheral tissues and transports it back to the liver. Excessive cholesterol from the cells may be passed to HDL, converted to cholesterol ester by lecithin:cholesterol acyltransferase (LCAT) and shifted to the interior of the particle. LCAT is activated by apo A1. As cholesterol esters accumulate in the core of the lipoprotein, the particle becomes spherical (mature HDL). With the aid of apo D cholesterol esters partly may be transferred to the chylomicron remnants, IDL or other lipoproteins. Finally, HDLs get unloaded of cholesterol in the liver, where it may be converted to the bile acids and secreted into the bile. Therefore, HDLs are often referred to as "good cholesterol" because they function to deliver cholesterol from peripheral tissues to the liver and help to lower total serum cholesterol.

Familial hypercholesterolemia (FH) is a hereditary disease caused by mutations affecting LDL receptor. Cells from FH individuals have an impaired ability to take up cholesterol via receptor mediated endocytosis. The result of these mutations is a higher than normal level of serum LDL and cholesterol. High LDL levels favor oxidation of their components and ultimately formation of atherosclerotic plaques. Individuals who are homozygous for the disease have very high levels of cholesterol in the blood and usually die of heart disease before age 20. People heterozygous for the disease have higher than normal cholesterol levels and are at high risk for heart attacks and cerebral infarcts.

Atherosclerosis contributing factors and treatment strategies. The incidence of atherosclerosis and coronary heart disease correlates with the serum total cholesterol and LDL cholesterol, and is in inverse relationship with HDL concentrations. The major factors affecting the blood lipoprotein levels are heredity, age, gender, nutritional and life style. Regular exercise and the diet rich in fibers, essential fatty acids and other lipotropic factors are effective in lowering plasma LDL and raising HDL. Widely used cholesterol-lowering drugs inhibit HMG-CoA reductase and decrease endogenous cholesterol biosynthesis (statins), or inhibit the absorption of cholesterol and bile acids in intestines (resins, ezetimibe). Other drugs used (fibrates) mainly decrease plasma triacylglycerols and VLDL.

Non-protein organic compounds of blood.

Total nitrogen of the blood includes a protein nitrogen and nonprotein nitrogen (or residual nitrogen):

N total = N prot. + N res. N res. = 14,3-25 mmol/L.

Residual nitrogen of the blood includes: urea nitrogen (50%), amino acid nitrogen (25%), creatine nitrogen (5%), creatinine nitrogen, ammonia nitrogen, indican nitrogen, bilirubin nitrogen, uric acid nitrogen etc. **Ammonia** level (25-40 μmol/L) increases in liver diseases, inherited disturbances of ornithine cycle. **Urea** level (3,3-8,3 mmol/L) increases in chronic diseases of kidney, cancer of ureteral ducts, tuberculosis of kidney, some infectious diseases, sepsis and other. Its level decreases in liver diseases (hepatitis, cirrhosis), pregnancy, inherited disturbances of urea cycle. **Creatinine** (53-105 μmol/L) increases in retential azotemia, indicates the degree of chronic renal insufficiency. **Uric acid** level (149-405 μmol/L) increases in gout.

Azotemia is the increased level of residual nitrogen in blood.

Productive azotemia is observed in an excessive delivery of nitrogenous products to the blood as result of accelerated degradation of tissues proteins in different states: inflammation, wounds, extensive burns, cachexia and other states.

Retention azotemia is caused by incomplete urinary discharge of nitrogen containing products on their normal delivery to the blood stream.

1) Renal retention azotemia is caused by reduced excretory function of kidney (reduced renal clearance). Urea is mainly responsible for the increased residual nitrogen level in renal retention azotemia. Urea constitutes 90% of residual nitrogen of blood instead of 50% in normal conditions.

2) Extrarenal retention azotemia may arise from an acute circulatory insufficiency, low arterial pressure, or reduced renal blood flow. Also, the frequent cause of extrarenal retention azotemia is an obstruction to the urine outflow from the kidney.

Blood plasma enzymes. Enzyme diagnostics.

Enzyme diagnostics is one of the branches of enzymology. It has two main directions:
1) use of enzymes as reagents for determination of normal and pathological components in serum, urine, gastric juice etc.
2) determination of enzyme activity in biological material with a diagnostic purpose.

Serum enzymes are divided into 3 groups:
1) Cellular enzymes enter the blood from different organs. Their activity in serum depends on enzyme content in organs, molecular weight, intracellular localization, rate of elimination. Cellular enzymes are divided into non-specific and organ specific.
2) Secretory enzymes are synthesized by cells, enter the bloodstream and fulfill their specific functions in the circulatory system. These are enzymes of coagulation system and fibrinolysis, choline esterase etc.
3) Excretory enzymes are synthesized by glands of GIT and enter the blood (amylase, lipase).

Enzymes synthesis, functioning and breakdown take place continuously and simultaneously; providing their given concentration and activity. Enzymes are localized in different cellular compartments (cytoplasm, lysosomes, cellular membrane, mitochondrions). That is why increased activity of certain enzymes can indicate the degree of severity of cellular damage. Here, we have provided information about enzymes which are most frequently used in clinical practice for diagnosis, prognosis and therapy monitoring of different pathologies. Their determination in blood serum has high clinical significance.

α-amylase. High activity of this enzyme is observed in the liver, skeletal muscles, microvillus of enterocytes, tears, secretion of mammary glands. Pancreas and salivary glands are richest in amylase. Plasma contains two isoenzymes of α-amylase: pancreatic (P-type) -

secreted by pancreas and salivary (S-type) - produced by salivary glands. In norm pancreatic amylase constitutes 40 % of total serum amylase activity, and salivary – 60%. Determination of α-amylase activity is very important for diagnosis of pancreatic pathology. Two times and more increased activity of α-amylase strongly indicates pancreatic damage.

In acute pancreatitis, α-amylase activity in the blood and urine increases 10-30 times. Initial increase of α-amylase activity is observed within 4-6 hours after the beginning of the disease, reaches peak within 12-24 h; then decreases and returns to norm within 2-6 days. Serum amylase level does not correlate with the degree of severity of pancreatitis. Pathogenetically hyperamylasaemia appears when edema of interstitial tissue blokes the pancreatic ducts. It characterizes fatty pancreatic necrosis. In haemorrhagical pancreatic necrosis, rise in α-amylase activity is observed in blood with subsequent rapid decrease. This reflects progressing pancreatic necrosis.

Aminotransferases (ALT and AST). Aminotransferases catalyze the process of transamination, they are present in every organ and tissue. Isoenzymes of AST are localized both in cytoplasm and in mitochondrions. ALT predominates in cytoplasm. High concentration of AST is noted in heart and skeletal muscles, liver, kidneys, pancreas and erythrocytes. Damage of any of them leads to significant increase of AST in the blood serum. The most significant increase of AST is observed in myocardial damage. In myocardial infarction, AST activity in blood serum can increase 4-5 times. In acute myocardial infarction, 93-98% of patients have high AST activity; the latter has the same dynamic as Creatine Kinase MB (CK-MB). However, CK-MB increase is more significant. Increase in AST activity reveals hepatic pathology. The most significant increase is observed in acute viral and toxic hepatitis. From mild to moderate increase in AST occurs in liver cirrhosis (2-3 times), obstructive jaundice and liver metastasis. It can be also so in skeletal muscular pathology, for example progressive muscular dystrophy; in pancreatitis; intravascular hemolysis.

Low AST activity usually reveals vitamin B6 deficiency, renal failure, pregnancy.

Highest concentration of ALT is noted in the liver cells. Skeletal muscles, kidneys and heart also contain ALT, but much less. Increased ALT activity is most frequently revealed in acute liver and biliary ducts diseases. ALT activity rises significantly in the early stages of acute viral hepatitis: in 50% of patients ALT increases 5 days before jaundice and hepatomegaly appear, in 90% of patients – 2 days before these symptoms. AST/ALT ratio is called **de Ritis ratio**. Its normal value 1-1,3. It decreases in liver diseases and increases in heart diseases. In toxic (alcoholic) liver damage AST activity rises predominantly, where de Ritis ratio exceeds 2. In viral hepatitis de Ritis ratio decreases. This ratio increases in obstructive jaundice, cholecystitis, liver cirrhosis, while ALT and AST activity increase slightly.

Alkaline phosphatase (ALP). The isoenzymes of alkaline phosphatase (ALP) are produced by various tissues: intestinal mucous membrane, osteoblasts, biliary ducts, placenta, mammary gland during lactation. This enzyme is situated on the cellular membrane and takes part in transport of phosphorus.

Several isoenzymes of ALP are present in blood serum. Bone, liver and placental ones are the most significant for clinical and diagnostic purposes.

1) Bone ALP. In bones ALP is secreted by osteoblasts. It is possible, that ALP takes part in maturation of a bone matrix and its mineralization. ALP increases with bone formation. Its significant increase in blood serum results from high osteoblastic activity: growth of bones (children show higher ALP activity then adults; it also increases in the last

trimester of pregnancy), reactivation after prolonged immobilization, fractures, deforming ostitis, rickets. It is also a characteristic for osteomalacia (malignant bone tumors, multiple myeloma), tuberculosis of bones, leukemia.

2) Liver ALP. There are two isoenzymes. The first one increases in blood serum in biliary obstruction, due to decreased elimination of enzyme with bile. It also increases in pregnancy (the second half). It is the main indicator of biliary tract pathology. The second isoenzyme increases in hepatocellular pathology: viral hepatitis, liver cirrhosis. But this increase is less significant in comparison to aminotransferases. 1/3 patients with jaundice and liver cirrhosis show increase in ALP activity. Rise in ALP activity is also revealed in 20% of patients with primary liver cancer or liver metastasis.

3) Intestinal ALP. It originates from enterocytes, enters the intestinal lumen and is partially absorbed in the blood. It accounts for a small part of total ALP activity. Its activity can be increased in people with I or III blood groups; especially after meals; in intestinal diseases accompanied by diarrhoea.

4) Placental ALP. It normally appears in pregnancy. The highest activity is revealed during the third trimester. It is the most thermostable isoenzyme of ALP. The most significant increase develops in women with eclampsia as a result of placenta damage. Low ALP activity in pregnancy indicates placental insufficiency.

Gamma-Glutamyl Transpeptidase (GGT). The determination of GGT is of great significance in diagnosis of hepatic and hepatobiliary pathology. This test is much more sensitive than either ALP or the transaminase test in detecting obstructive jaundice, cholangitis, cholecystitis.

The highest GGT activity is noted in kidneys – 7000 times higher than in blood serum. In healthy individuals serum GGT activity is low. The liver is considered as the main source of normal serum activity, despite the fact that the kidney has the highest level of the enzyme. Pancreas also contains GGT. Small enzyme concentration is detected in intestine, brain, heart, spleen, prostate gland, skeletal muscles. GGT is located in cellular membrane, lysosomes, cytoplasm. Membrane localization of GGT is characteristic for cells with high secretory, excretory or reabsorption activity. Serum GGT activity increases in any pathology of liver and bile ducts. If GGT activity is normal, liver disease probability is very low. Thus, GGT is good marker for differential diagnosis of liver pathology. The most significant increase is observed in cholestasis and slight increase - in parenchymal liver disease (necrosis of hepatocytes). GGT activity rises on the early stage of the disease and remains high for a long time. Beside this, GGT is a specific indicator of liver disease, because in comparison to ALP its activity is normal in healthy children, pregnant women and patients with bone diseases.

Determination of GGT activity is also used for diagnosis of alcoholic liver disease and its therapy monitoring. Alcohol induces GGT synthesis in the liver and release from cell membranes. It leads to increase of enzyme activity in the blood serum without hepatic cell damage.

GGT test is also used for diagnosis of pancreatic pathology. Nowadays in Europe, this parameter is used even more often than α-amylase – traditional indicator of pancreatic pathology. 100% of patients with acute pancreatitis show GGT activity 10-20 times higher than normal.

This test can also be useful for laboratory diagnosis of renal pathology. It is proven that GGT activity in urine rises significantly in pyelonephritis, glomerulonephritis and renal

calculi. Determination of GGT in urine allows to diagnose the early stages of kidney disease, which is accompanied by proximal renal tubular damage.

Creatine Kinase (CK). CK is a dimer and consists of 2 protein subunits: B (brain) and M (muscle), which combine to form 3 isoenzymes:

1) CK-BB (CK-1) – brain
2) CK-MB (CK-2) – cardiac
3) CK-MM (CK-3) – muscle

CK-BB is present in large amount in brain tissue, prostate, stomach, lungs, urinary bladder, urethra, placenta, thyroid gland. CK-MB accounts for 25-46 % of total CK activity in cardiac muscle and less than 5% in skeletal muscle. CK-MM is present mainly in skeletal and cardiac muscle. CK-MM accounts for 94-96 % of total creatine kinase serum activity, CK-MB – 4-6 %, CK-BB – trace amount or is not detectable in serum. Total CK activity increases in different pathologies: traumas, surgical operations, myocardial infarction, reduced perfusion of muscles, myopathy, dermatomyositis, muscular dystrophy, myocarditis, intoxication, hypothyroidism, infectious diseases (typhoid fever). In some cases, slight increase occurs in arthritis, congestive heart failure, tachycardia, pulmonary embolism. In myocardial infarction increase in CK activity occurs within 3-6 hours after an onset of pain. However, determination of its activity within 8 hours gives positive results in 31% of cases. CK is a reliable test for myocardial infarction diagnosis within 8-10 hours after onset of pain. It reaches maximal level within 24 hours and returns to norm within the next 48 hours even in extensive myocardial infarction. Relative increase of CK in myocardial infarction is higher than other enzymes. The determination of CK every 4-6 hours during 24 hours is most informative.

CK-MM increases in blood serum in the same cases, as total CK. CK-BB in blood serum slightly or moderately increases in cancer of certain localizations (lungs, intestine, urinary bladder, prostate gland), trauma of cardiac muscle, connecting tissue diseases. During parturition serum CK-BB may be 6 times higher than normal (the source of its activity are uterus and placenta). In neonates and infants, the activity is considerably elevated, especially during the first 24 hr post-partum.

Lactate Dehydrogenase (LDH) catalyzes reversible reduction of pyruvate to lactate. LDH consists of two subunits – M (muscle) and H (heart). There are 5 isoenzymes in serum, which are distinguished by their subunit composition. They are identified as follows according to decreasing electrophoretic mobility (movement to anode): LDH-1 (H4), LDH-2 (H3M1), LDH-3 (H2M2), LDH-4 (H1M3), LDH-5 (M4).

LDH is present in cytoplasm of every tissue. In the liver, heart, kidneys, skeletal muscles and erythrocytes LDH activity is 500 times higher than in serum. That is why damage of these organs is accompanied by elevation of serum LDH. Increase in this enzyme occurs in tissue necrosis, especially in acute myocardial injury, hemolysis (erythrocyte damage), injury of kidneys, skeletal muscles, liver, lungs and skin. Significant increase is observed in hemolytic anemias or B_{12}-folate deficiency.

Normal proportion of LDH isoenzymes in serum is: LDH-1 – 15-30%; LDH-2 – 22-50%; LDH-3 – 15-30%; LDH-4 – 0=15%; LDH-5 – 0=15%. In myocardial infarction increase in LDH occurs within 12-32 hours after an onset of pain and remains elevated during 8-14 days. LDH-1 is the most specific test for diagnosis of myocardial infarction. If within 8-24 hr after the onset of pain LDH (and also CK-MB and AST) level does not increase, we can exclude myocardial infarction. Some patients show correlation between LDH level and extensiveness of myocardial injury. In some cases, LDH1/LDH2 ratio can

give an additional diagnostic information. Its normal range is 0,6-0,7. In acute myocardial infarction it exceeds 1,0 and returns to norm after 2-3 weeks. LDH-1 also increases in tumors of reproductive organs: teratoma, testicle seminoma, ovarian dysgerminoma.

LDH-2, LDH-3 and LDH-4 have intermediate properties. Activity of these enzymes grows in massive platelet destruction (pulmonary embolism, massive blood transfusions) and lymphatic system involvement. In non-lymphocytic leukemia, LDH-3 and LDH-4 levels increase. LDH-3 also increases in pancreatitis. LDH-4 level rises in viral, toxic and traumatic liver damage, exacerbation of chronic hepatitis, in active phase of rheumatism, in cardiosclerosis, severe diabetes mellitus, acute nephritis, tumors of the liver, prostate, uterine cervix, mammary gland, intestine.

Skeletal muscles, liver, skin, mucous membranes, some kinds of malignant cells contain small amount of LDH-5. Significant increase in LDH-5 occurs in traumas, inflammatory and degenerative muscular diseases and different liver diseases (hepatitis, cirrhosis and others). Oncologic diseases (i.e. lymphocytic leukemia) also can lead to increase in LDH-5. Its activity also grows in active phase of rheumatism, kidney tumors, rejection of kidney transplant, severe diabetes mellitus.

Respiratory function of erythrocytes. Transport of O_2 and CO_2. Hemoglobin, its synthesis. Metabolism of porphyrins. Metabolism of iron. Disorders of hemoglobin metabolism: hemoglobinopathy, thalassemia, porphyria.

Erythrocytes constitute about 44% of the total blood volume (4,5-5x1012/L). The life of erythrocytes is 120 days. New synthesized erythrocytes contain ribosomes and elements of endoplasmic reticulum. Mature erythrocytes don't contain ribosomes, mitochondria, lysosomes, Golgi apparatus. Synthesis of erythrocytes is regulated by erythropoietin. Erythropoietin is synthesized in kidney. It is liberated to blood in hypoxia and is transported to bone marrow.

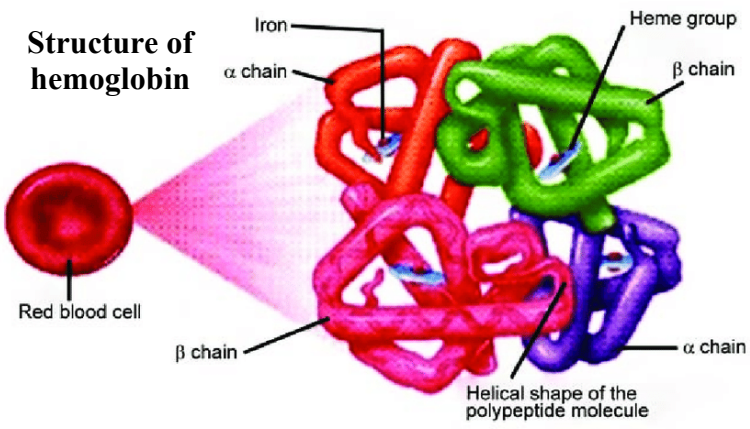
Erythrocytes have unique and relatively simple metabolism:

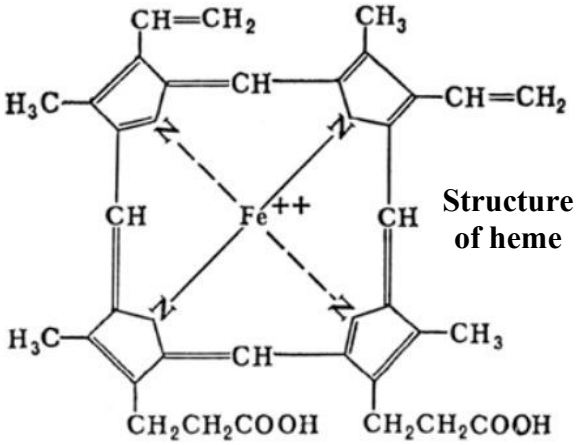
1) Main source of energy is glucose.
2) Source of ATP is anaerobic glycolysis.
3) The formation of 2,3-bisphosphoglycerate from 1,3-bisphosphoglycerate by Rappoport-Leubering shunt is very important for regulation of affinity of Hb to O_2.
4) 5-10% of glucose are metabolized by means of pentose phosphate pathway. NADPH is necessary for reduction of glutathione. Deficiency of glucose-6-phosphate dehydrogenase is the cause of drug-induced hemolytic anemia
5) Glutathione may be synthesized in erythrocytes. It is necessary for elimination of peroxides.
6) Autooxidation of Hb results in formation of metHb (1,7% under normal conditions). This is accompanied by formation of $O_2^{\bullet}$ (superoxide radical). NADH-dependent methemoglobin reductase converts metHb to Hb.
7) The synthesis of glycogen, fatty acids, proteins, nucleic acids do not occur in erythrocytes. Some lipids, for example cholesterol, may be exchanged with corresponding lipids of plasma.
8) Erythrocytes have some enzymes of nucleotide metabolism.

The main function of erythrocytes is the **transport of gases.** Hemoglobin constitutes 95% intracellular proteins of erythrocytes. Hemoglobin is the principal for transport in the blood of both oxygen and CO_2.

Functions of hemoglobin: respiratory, maintaining acid-base balance (buffer system).

Structure of hemoglobin: prosthetic group (4 hemes), protein part (globin, 4 subunits).





Heme is cyclic tetrapyrrole. Tetrapyrroles consist of four molecules of pyrrole linked in a planar ring by four α- methenyl bridges. Tetrapyrrole has 8 substitutions: 4 methyl groups, 2 – vinyl and 2 – propionate ones. One atom of ferrous iron (Fe^{2+}) is at the center of this planar ring.

Globin part of HbA_1 is $\alpha_2\beta_2$ (α – 141 amino acid residues, β – 146 amino acid residues). Secondary structure: 75% of every polypeptide chain is α-helix. Tertiary structure is globule. Hydrophobic amino acid radicals are directed inside of protein molecule; hydrophilic amino acid radicals are directed outside. This facilitates the formation of hydrophobic heme pocket. This pocket defenses heme iron from oxidation. Quaternary structure: polypeptide chains of Hb are linked by means of hydrophobic interactions and salt bridges. Quaternary structure provides positive cooperative effect between subunits in binding O_2. Binding last molecule of O_2 occurs 300 times more readily, than the first one. Binding O_2 is accompanied by the rupture of salt bonds between four subunits. Subsequent O_2 binding is facilitated, since it involves a rupture of fewer salt bonds. Iron atoms of deoxyhemoglobin lie about 0,06 nm beyond the plane of the heme ring. On oxygenation the iron atoms move into the plane of the heme ring. This is accompanied by conformational changes and leads to rupture of salt bonds.

Heterogeneity of Hb		
Ontogenetic	Heterogeneity of adults	Heterogeneity, which is provided by mutations (abnormal Hb)
1. Embryonal HbP is found in first three months of intrauterine life of the baby. Gower I (ξ_4) Gower II ($\alpha_2\xi_2$) 2. HbF ($\alpha_2\gamma_2$) 3. HbA ($\alpha_2\beta_2$) Newborns contain 80% HbF and 20% HbA	1. HbA ($\alpha_2\beta_2$) – 90-95%. 2. HbA2 ($\alpha_2\delta_2$) – 2,5%. 3. HbF – 0,5% 4. HbA_{1c} (glycosylated): in normal individuals 3-5%, in diabetes mellitus – 6-15%	Examples: HbS (glutamic acid of 6-th position of β-chain is replaced by valine). HbM (amino acid sequence is altered either in α- or β- chains: or α_{58}His → α_{58}Tyr, or β_{63}His → β_{63}Tyr)

Quaternary structure of Hb provides its **allosteric properties.** The affinity of Hb to O2 is regulated by low molecular mass ligands, for example by CO_2, 2,3-bisphosphoglycerate

(2,3-BPG). 2,3-BPG is formed from the glycolytic intermediate 1,3-bisphosphoglycerate. 2,3-BPG decreases the affinity of Hb to O_2 by forming additional salt bridges.

This plays the important role in adaptive processes in hypoxia, in supplying of embryo by oxygen. 2,3-BPG regulates fetal hemoglobin in less extent, than adult one. Therefore, fetal Hb has a higher affinity to oxygen than does HbA. This provides the transfer of oxygen from Hb of mother to Hb of embryo.

Derivatives of Hb:

1) **Oxyhemoglobin** (HbO_2). Oxygen adds to the hemoglobin heme via iron coordination bonds, the iron is in reduced state (Fe^{2+}). Factors, influencing the formation of HbO_2:
a) partial pressure of O_2 (P O_2) favours oxygenation;
b) partial pressure of CO_2 (P CO_2) favours dissociation;
c) temperature decreases the affinity of Hb to O_2;
d) pH of the medium (acidosis favours liberation of O_2);
e) 2,3-bisphosphoglycerate diminishes the affinity of Hb to O_2.
2) **Carboxy-Hb** (HbCO). Oxygen adds to the hemoglobin heme via iron coordination bonds, the iron is in reduced state (Fe 2+). The affinity of Hb to CO is 210 times more than to O_2. Dissociation of HbCO is 30 times less than HbO_2. However, as the partial pressure of oxygen in the inspired air increases, CO is in part eliminated from its binding with hemoglobin.
3) **Carb-Hb** ($HbCO_2$). CO_2 combines with NH_2-group of globin. This is a normal and constant physiologic reaction and accounts for 2 to 10% of CO_2 transported by the blood.
4) **Methemoglobin** (HbOH). It is a derivative in which Fe is in the ferric state (Fe^{3+}). In normal healthy adult small amount of methemoglobin may be present (about 1,7% of total Hb). This is converted to normal Hb by methemoglobin reductase.

In vivo HbOH is produced by certain drugs or exposure to certain poisons which are oxidants. Injection of intravenous glucose or methylene blue helps to reduce methemoglobin (Fe^{3+}) to Hb (Fe^{2+}). Other causes:
a) Familial methemoglobinemia is inherited disorder due to lack or absence of the enzyme methemoglobin reductase.
b) Methemoglobinemia may also be found in individuals with abnormal hemoglobin as HbM.

The increased formation of HbOH is used for the treatment of cyanide poisoning. The letal and toxic action of cyanides is provided by inhibition of cytochrome oxidase. Cyanides and HCN do not react directly with hemoglobin but they react with methemoglobin to form cyanmethemoglobin, which is not toxic.

In medical practice of common use is the analysis for blood pigment which is based on a study of spectral properties of hemoglobin heme or of its oxidized products – hemin or hematin, produced by treating hemoglobin with a dilute alkaline solution or with acetic acid in the presence of sodium chloride. Hematin reduced by ammonium sulphite in the presence of globin, produces a hemoglobin derivative hemochromogen. It exhibits a characteristic absorption spectrum. This method is widely used in forensic medical practice for examination of blood spots.

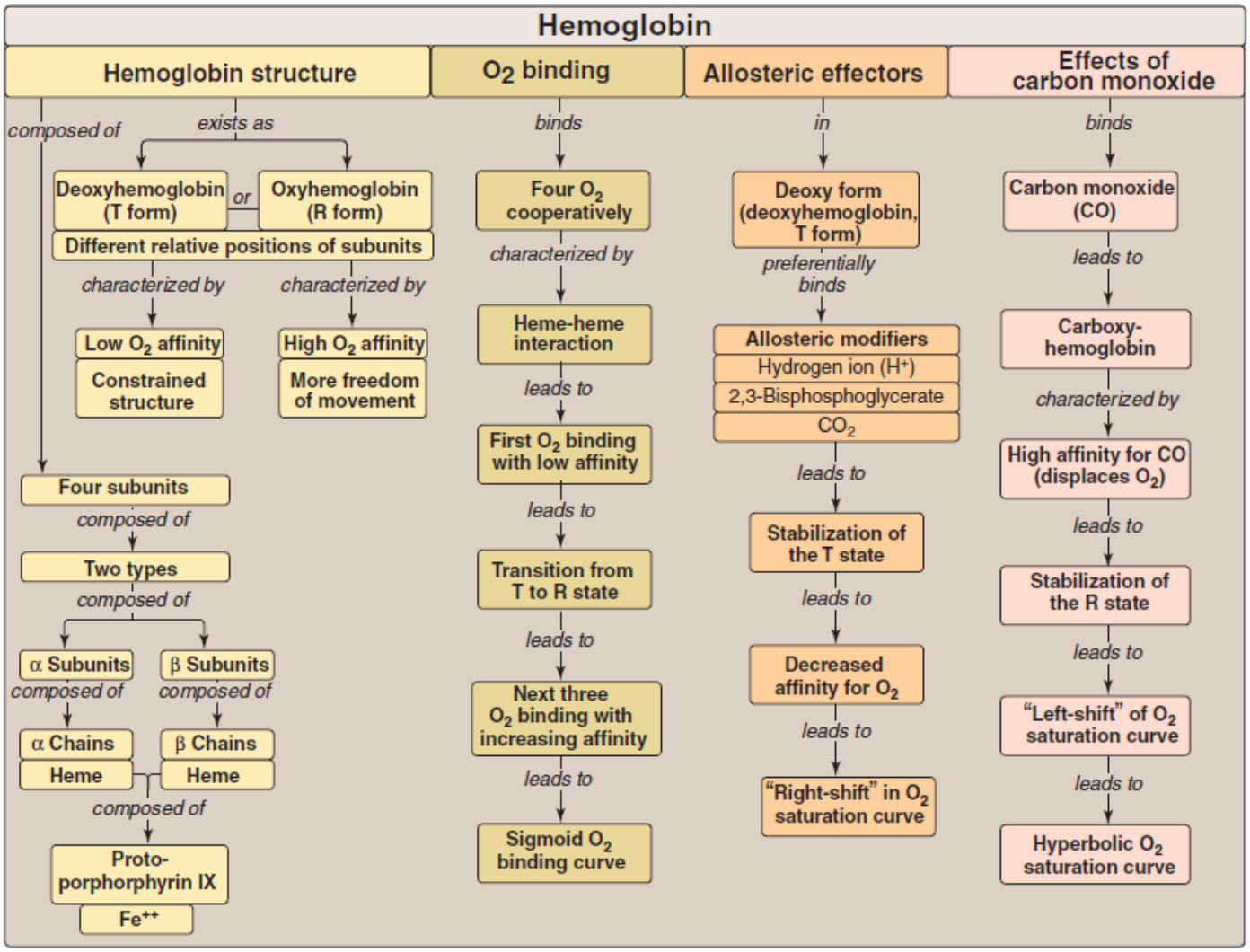


Figure 8. Key concept map for hemoglobin structure and function (Harvey, 2011)

Transport of oxygen.

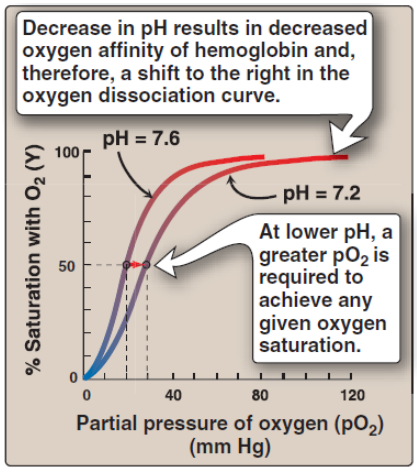
Oxygen is continuously supplied to the tissue cells. The total requirement of O_2 is around 250 mL/minute in the resting state and more than ten times during vigorous exercise. The requirement of O_2 to the tissue is fulfilled in two ways: oxygen in physical solution; by oxyhemoglobin. A small amount of O_2 can be dissolved to form a solution (0,3 mL of O_2 per 100 mL of blood).

Most of O_2 is supplied to the tissues as HbO_2. One gram of Hb can carry 1,34 ml of O_2 at complete saturation. The hemoglobin concentration in the blood in healthy individual is 130-160 g/L. At the arterial blood the oxygen saturation of hemoglobin is 96%. Under these conditions the amount of O_2 which is linked with Hb is 19,3 ml of O_2 per 100 ml of blood.

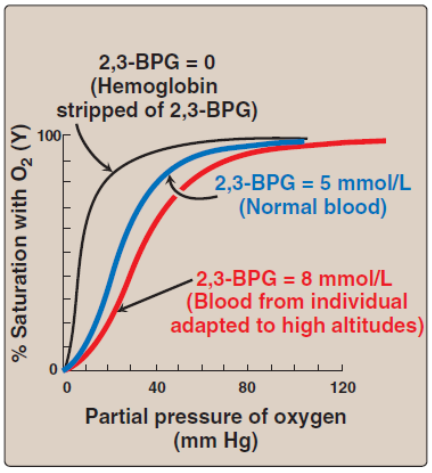
Blood, which contains 150 g/L of Hb:	
Arterial blood	Venous blood
pO_2 95 mm of Hg pCO_2 40 mm of Hg Hb: 97% of saturation by O_2	pO_2 40 mm of Hg pCO_2 46 mm of Hg Hb: 75% of saturation by O_2

Oxygen supply to tissue cells is facilitated by high pO_2 levels in lungs. It is enhanced by the relatively high pCO_2 (Bohr effect), high acidity (low pH), high temperature in metabolically active tissues.

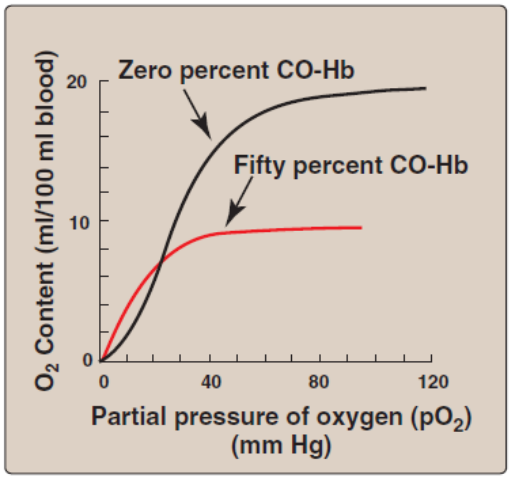
Allosteric effects (Harvey, 2011)



Effect of pH on the oxygen affinity of hemoglobin. Protons are allosteric effectors of hemoglobin.



Allosteric effect of 2,3-BPG on the oxygen affinity of hemoglobin.



Effect of carbon monoxide on the oxygen affinity of hemoglobin.

Transport of carbon dioxide.

Carbon dioxide is transported from the tissues to lungs at the rate of about 180 ml/min: 6-7% of CO_2 is transported in a physically dissolved state, 3-10% in Hb CO_2; most CO_2 is transported in the bicarbonate form.

Carbon dioxide is supplied to erythrocytes. It is converted into H_2CO_3 under the influence of capboanhydrase. Deoxyhemoglobin is weak acid, it binds H^+. Accumulated bicarbonate anions (HCO_3^-) are transported from erythrocyte cell to plasma. They are exchanged for chloride ions (the chloride shift).

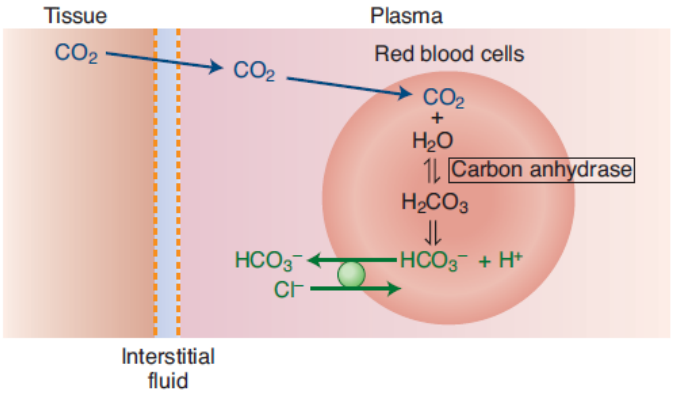


Figure 9. Fate of CO_2 in the red blood cell (Janson, 2012)

Synthesis of hemoproteins.

A specific feature of hemoproteins is the metabolic involvement of the nonprotein moiety of these conjugated proteins. The hemoglobin of blood erythrocytes and of marrow cells accounts for a major portion (about 83%) of hemoproteins in the human organism. The remainder is myoglobin of skeletal muscles and heart (about 17%) and cellular hemoproteins – cytochromes, catalase, and peroxidase (1%).

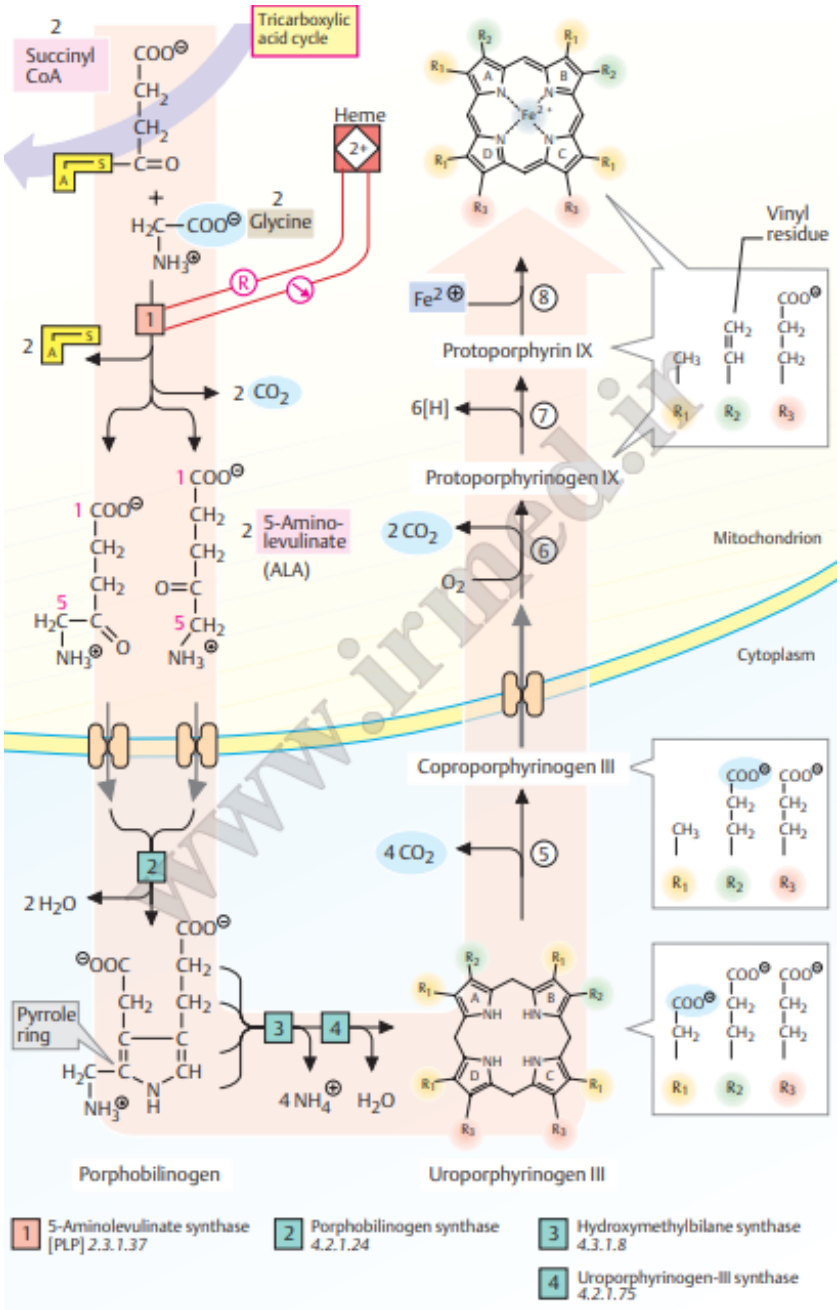


Figure 10. Heme biosynthesis (Koolman, 2005)

Glycine and succinyl~SCoA are the starting compounds in heme synthesis. The reaction involving the pyridoxal-assisted enzyme δ-aminolevulinate synthetase yields δ-aminolevulinic acid. Two molecules of δ-aminolevulenic acid are combined with the participation of porphobilinogen synthetase, to form porphobilinogen, a direct precursor of porphyrins. One of these is coproporphyrin III which is directly converted to protoporphyrin IX. The insertion of iron ions (Fe^{2+}) into the protoporphyrin IX ring is effected with the assistance of ferrochelatase. At the ultimate step, heme becomes complexed with globin to form hemoglobin or myoglobin. In the synthesis of other hemoproteins, heme adds to the specific protein moiety of cytochromes or other hemo-containing enzymes. It these is not a sufficient quantity of protein to bind the reaction step of porphyrin synthesis.

The enzymes involved in heme biosynthesis are found in the marrow, nucleated erythrocytes, liver, kidneys, and intestinal mucosa. The reactions leading to δ-aminolevulinic acid proceed in the mitochondria; the production of porphobilinogen and the subsequent synthesis of coproporphyrinogen III occur in the cytoplasm, and the synthesis of heme from coproporphyrinogen III, in mitochondria.

Disturbances of Hb synthesis.

Hemoglobinopathies are due to a hereditary change in the primary structure of peptide chains, for example, in sickle cell anemia HbS (β-chain: 6 Glu → 6 Val).

Thalassemias are due to a disturbed synthesis of one of the normal hemoglobin chains. For example, in β-chain thalassemia an excess of α-chains occurs which can combine with δ-chains producing an increase in HbA_2 or with γ-chains producing an increase in HbF (15-60%).

Hereditary Porphyrias:

1) **Congenital erythropoietic porphyria** (Hunter's disease) is due to a deficiency of uroporphyrinogen III cosynthase. Patients with congenital erythropoietic porphyria excrete large quantities of the type I isomers of both uroporphyrinogen and coproporphyrinogen, which in the urine are spontaneously oxidized to uroporphyrin I and coproporphyrin I, both fluorescent red pigments. Urine is usually red colored. Teeth and bones may be brownish or pink due to porphyrin deposition. Affected individuals exhibit abnormal sensitivity to light (photosensitivity) and development of skin lesions.

2) **Intermittent acute porphyria** (IAP) is due to a deficiency of porhobilinogen deaminase (uroporphyrinogen I synthase). Patients with IAP excrete massive quantities of porphobilinogen and aminolevulinate in the urine. Both of these compounds are colorless, but porphobilinogen upon exposure to light and air polymerizes spontaneously but slowly to form 2 colored compounds: porphobilin and porphyrin. The concentration of δ-aminolevulinate and porphobilinogen are increased. They are neurotoxins. Clinical symptoms are abdominal pain, neurophychiatric symptoms.

3) **Protoporphyria** is due to a deficiency of ferrochelatase. Photosensitivity is observed.

Acquired porphyrias are observed in iron deficiency anemia, in liver diseases, in exposure to toxic compounds.

Metabolism of iron.

Blood uses carrier proteins to transfer essential nutrients as part of each person's metabolism. One important example is iron that is involved in a vast array of important biologic reactions:

1. Binds O_2 as part of Hb molecule. An adult human has approximately 4 g of iron, of which about two-thirds is employed in the O_2-carrying role of Hb.

2. Mediates a wide variety of oxidative-reductive reactions by serving as an essential cofactor for many proteins via oxidation between ferric (Fe^{3+}) and reduced Fe^{2+} states.

3. Iron is important for many microorganisms. Keeping iron sequestered from these invaders is an important part of the immune system.

In most well-rounded Western diets, meats and green, leafy vegetables provide adequate iron to prevent iron deficiency. Certain iron-poor diets, such as vegan diets, however, can result in iron deficiency if not supplemented. Once iron is ingested, it is converted from the Fe^{3+} state to the Fe^{2+} state by intestinal ferric reductase. Fe^{2+}, not Fe^{3+}, is transported into the intestinal epithelial cell through the divalent metal transporter (DMT1) protein. Fe^{2+} is transported out of the intestinal epithelial cells into blood through a second transporter, ferroportin.

Intestinal lumen ferric (Fe^{3+}) reductase reduces Fe^{3+} to Fe^{2+}. Fe^{2+} is transported from the lumen into the intestinal epithelial cell through heme transporter (HT), endosomes, and/or divalent metal transporter 1 (DMT1). Fe^{2+} can be converted back to Fe^{3+} and bound to transferrin within the intestinal cell or can be transported into the blood by ferroportin (FP) and hephaestin (HP). The Fe^{2+} oxidized to Fe^{3+}, which binds to plasma transferrin, is carried through the circulation to the tissues.

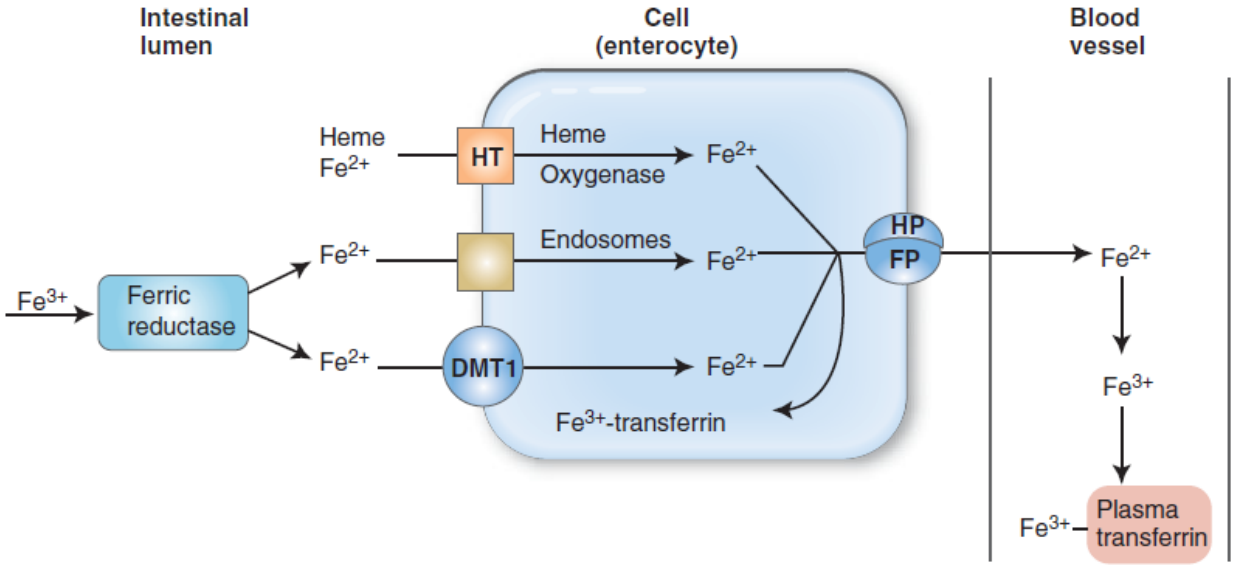
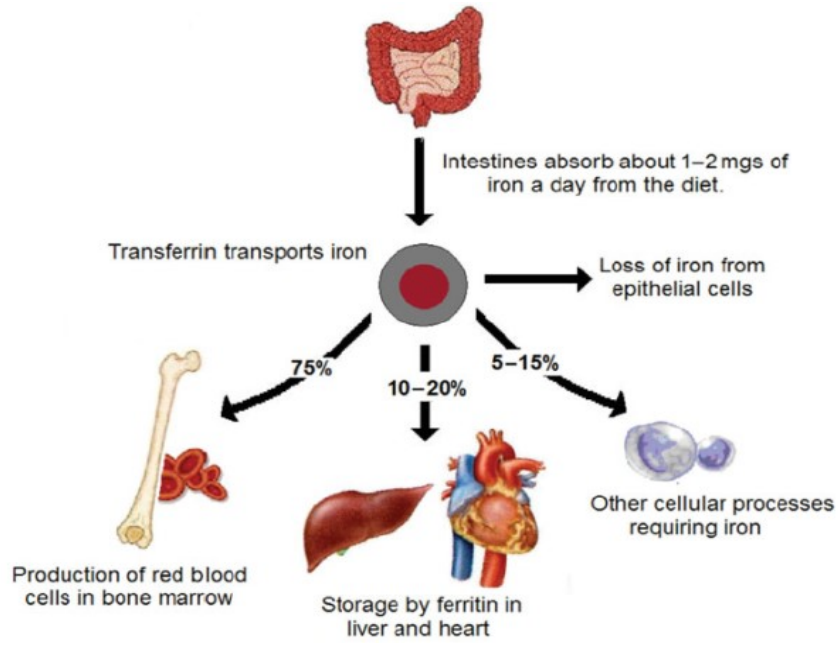


Figure 11. Overview of iron transport (Janson, 2012)



Transferrin. Once in the blood, the Fe^{2+} is quickly oxidized back to Fe^{3+} and bound by the iron carrier protein, transferrin. The affinity of transferrin for Fe^{3+} at pH 7.4 is 10-23, which means that transferrin will bind Fe^{3+} even when its concentration is 10-23 (10 yoctomolar or 0.01 zeptomolar). This affinity suggests that in the entire 5 l blood volume of an adult, there would be only approximately five free molecules of Fe^{3+} at a time.

Figure 12. Iron transportation by transferrin (Janson, 2012)

This exceedingly high affinity is the biochemical mechanism that the human body has adapted to prevent any free iron from existing in the blood stream. The iron bound transferrin circulates through the blood stream until it binds to a transferrin receptor on the surface of a cell. Cells that express transferrin receptors have high iron demands. These include developing RBCs, dividing cells, and microorganisms. The transferrin-iron-transferrin-receptor complex is endocytosed through the classic clathrin-coated pit pathway. Following endocytosis, pH of the endocytic vesicle is reduced to 5, liberating iron from its carrier protein and making iron available for biologic reactions.

Transferrin transports iron in the blood to the bone marrow to make hemoglobin and red blood cells (erythropoiesis). Transferrin also carries iron to the liver and heart for storage in ferritin molecules, as well as to other parts of the body for various enzymatic and other functions.

Ferritin. Although Hb is the most abundant protein that uses iron, ferritin is the most important protein for iron storage. Ferritin consists of a 24-unit multimer of heavy (H) and light (L) chains that create a hollow shell. Iron is imported into the shell as Fe^{2+} but is converted to Fe^{3+} within the ferritin core by the H chain. A fully loaded molecule of ferritin contains 4500 atoms of iron. It is for this reason that the ferritin molecule is metaphorically referred to as a "bag of rust." A pathologic form of iron deposition is called **hemosiderin**. This is a nonstructural conglomerate of intracellular iron and is often a pathologic consequence of prolonged inflammation. Prolonged deposition of hemosiderin can cause fibrosis (scarring) of tissues. The importance of iron is highlighted by the fact that the human body has no natural way to excrete it. Unlike other ions, such as sodium, potassium, and calcium, kidneys do not excrete excess iron in the urine. Indeed, the physiological default is to conserve iron. Iron deficiency is much easier to treat than iron overload. Accumulated iron is toxic to a variety of tissues, especially the heart and liver. Infusion of an iron chelator, such as **deferoxamine** or **deferasirox**, provides the only means of reducing some of the iron accumulation. Chelation works by the drug-binding free iron in the blood followed by excretion of the iron-drug complex. The body does lose a small amount of iron each day by the sloughing of skin and epithelial cells and in women through their menstrual flow. However, the same reactivity that makes it a valuable cofactor for proteins also means that free iron can be dangerous because it can easily generate damaging O_2 free radicals. Thus, the body has a powerful system to control the metabolism of this precious and perilous metal.

Regulation of iron availability by hepcidin. Although the human body has no natural way of excreting excess iron, it is able to regulate the uptake and availability of iron through the protein hepcidin. Hepcidin is synthesized as an 84-amino acid precursor, which is then processed to the 25-amino acid active form. Hepcidin acts as a negative regulator of ferroportin, blocking the ability of cells to export iron from the cytoplasm into the blood. In the intestinal cell, this inhibition results in decreased iron absorption from the diet. In reticuloendothelial cells, the primary storage depot for iron, this results in a decreased ability of iron to be mobilized from storage pools to cells that need it. Hepcidin is made in the liver, and the levels of hepcidin in the blood are controlled by a variety of different stimuli, including the total iron stores in the body, the erythropoietic demands of making RBCs, hypoxia, and inflammation. When iron stores are high, the level of hepcidin is increased and the amount of iron absorbed is decreased. When the demand for making RBCs is increased, for example, in response to acute blood loss, the level of hepcidin decreases and the amount of bioavailable iron is increased. Similarly, when tissues do not receive sufficient O_2 (hypoxia), it signals that more RBCs are needed, and hepcidin production is decreased. Finally, infl ammation, such as signaled through the inflammatory cytokine interleukin-6 (IL-6), causes an increase in hepcidin production. This inflammatory regulation is thought to reflect a host defense mechanism because it sequesters iron away from infectious organisms, limiting their growth. If the inflammatory state persists, however, hepcidin sequesters iron away from both the microorganism and the human cells. There is insufficient iron to support the demands for RBC production, and a state of anemia of inflammation or anemia of chronic disease develops.

Iron deficiency anemia is the most common nutritional disorder in the world, believed to affect 1 billion people. In children, in the developed world, the most common cause of iron deficiency anemia is the excess consumption of cow's milk. Excess cow's milk can cause inflammation damaging the intestinal lining, resulting in blood loss as well as a

diminished capacity to absorb iron. The first manifestation of iron deficiency is an anemia that stems from an inadequate iron supply to sustain erythropoiesis. The symptoms of iron deficiency anemia include pallor, weakness, and lethargy. Severe and prolonged iron deficiency can result in neuropsychological problems. The diagnosis of iron deficiency is usually made by laboratory studies that demonstrate a microcytic anemia (smaller, pale RBCs), reflective of poor Hb production. Blood studies also show low ferritin level and low transferrin saturation (only 10% contain iron as compared with the normal 30-40%). Because ferritin is an acute phase reactant that increases in times of stress and illness, sometimes it can be paradoxically high even in iron-deficient states.

The treatment for iron deficiency is to give iron. The most bioavailable dietary iron is in red meat, but often the patient is unable or unwilling to pursue this method. In this situation, oral elemental iron is given. Because iron is transported by DMT1 as Fe^{2+}, not Fe^{3+}, some physicians will advise their patients to simultaneously drink orange juice or take ascorbic acid (vitamin C). Ascorbic acid reduces Fe^{3+} iron to the Fe^{2+} state, facilitating the absorption of elemental iron. In treating iron deficiency anemia in children, caused by excessive milk consumption, it is important to both administer elemental iron and dramatically decrease milk consumption. In rare cases of adult and child anemia, such as poor compliance or anatomic or genetic defects in iron absorption, iron is administered intravenously. Supplemental iron is given until the microcytic anemia is resolved and normal levels of ferritin and transferrin saturation are achieved.

Summary of the causes of some important disorders affecting RBCs (Murray, 2003)	
Disorder	Sole or major cause
Iron deficiency anemia	Inadequate intake or excessive loss of iron
Methemoglobinemia	Intake of excess oxidants (various chemicals and drugs) Genetic deficiency in the NADH-dependent methemoglobin reductase system Inheritance of HbM
Sickle cell anemia	Sequence of codon 6 of the β chain changed from GAG in the normal gene to GTG in the sickle cell gene, resulting in substitution of valine for glutamic acid
α-Thalassemias	Mutations in the α-globin genes, mainly unequal crossing-over and large deletions and less commonly nonsense and frameshift mutations
β-Thalassemia	A very wide variety of mutations in the β-globin gene, including deletions, nonsense and frameshift mutations, and others affecting every aspect of its structure (eg, splice sites, promoter mutants)
Megaloblastic anemias Deficiency of vitamin B_{12} Deficiency of folic acid	 Decreased absorption of B_{12}, often due to a deficiency of intrinsic factor, normally secreted by gastric parietal cells Decreased intake, defective absorption, or increased demand (eg, in pregnancy) for folate
Hereditary spherocytosis	Deficiencies in the amount or in the structure of α or β spectrin, ankyrin, band 3 or band 4.1
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	A variety of mutations in the gene (X-linked) for G6PD, mostly single point mutations
Pyruvate kinase (PK) deficiency	Presumably a variety of mutations in the gene for the R (red cell) isozyme of PK
Paroxysmal nocturnal hemoglobinemia	Mutations in the PIG-A gene, affecting synthesis of GPI-anchored proteins

CHAPTER 2. BIOCHEMISTRY OF LIVER. XENOBIOTICS AND DETOXIFICATION PROCESSES.

The role of the liver in protein, carbohydrate and lipid metabolism. Biosynthesis of specialized proteins. Digestion, storage and excretion of different metabolites.

Weighing 1,5 kg, the liver is one of the largest organs in the human body. Although it only represents 2-3% of the body mass, it accounts for 25-30% of oxygen consumption. Liver plays the central role in regulation and integration of metabolism. Hepatocytes make up 90% of the cell mass of liver. They are in close contact with the blood, which enters the liver from the portal vein (more than 70%) and the hepatic arteries (30%), flows through capillary vessels known as sinusoids, and is collected again in the central vein of the hepatic lobes. Hepatocytes are particularly rich in endoplasmic reticulum as they carry out intensive protein and lipid synthesis. The cytoplasm contains granules of glycogen. Between hepatocytes there are bile capillaries through which bile components are excreted.

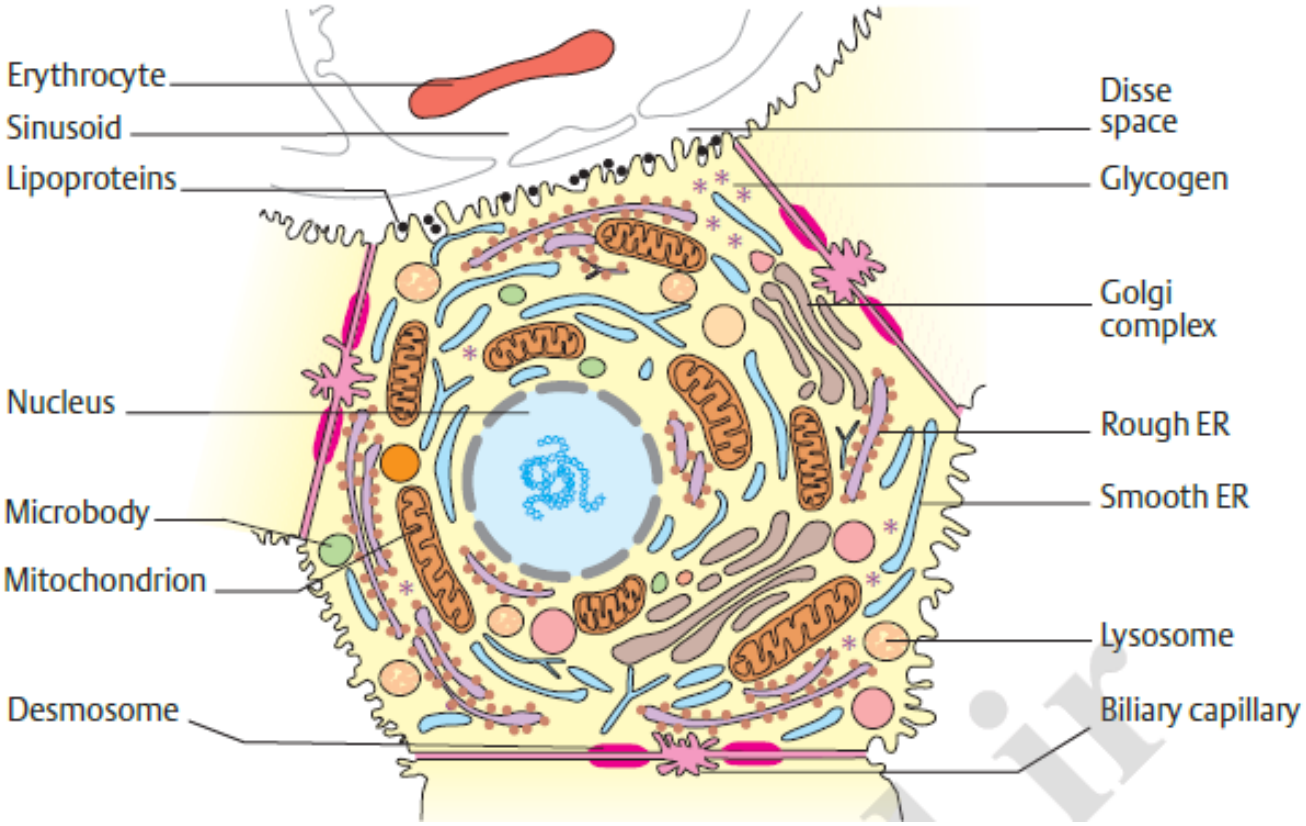


Figure 13. Diagram of a hepatocyte (Koolman, 2005)

Functions of liver.

1) Uptake of nutrients supplied by intestine via the portal vein.
2) Biosynthesis of endogenous compounds and storage, conversion and degradation of them into excretable molecules (metabolism). In particular, the liver is responsible for the biosynthesis and degradation of almost all plasma proteins.
3) Supply of the body with metabolites and nutrients.
4) Detoxification of toxic compounds by biotransformation.
5) Excretion of substances with the bile.

Role of the liver in carbohydrate metabolism.

The liver plays the important role in supporting glucose concentration constancy in blood. This is provided by the following mechanisms:

1) The liver takes up glucose and other monosaccharides from the plasma.

2) Transporters in the plasma membrane of hepatocytes allow insulin-independent transport of glucose and other sugars in both directions. The liver has the enzyme glucokinase, which has higher Km (10mM) as compared with hexokinase (0,01-0,1 mM). This enzyme can react by increasing activity in response of the enhance of glucose content in portal vein after food intake.

3) Glucose is then either stored in the form of polysaccharide glycogen or converted into fatty acids. When there is a drop of the blood glucose level, the liver releases glucose again by breaking down glycogen. In contrast to muscle, the liver possesses the enzyme glucose-6-phosphatase, which can release glucose from glucose-6-phosphate. Therefore glycogen of liver is used by not only this organ but also by other tissues and organs.

4) If the glycogen store is exhausted, glucose also can be synthesized by gluconeogenesis from lactate, glycerol or the carbon skeletons of amino acids. Regeneration of glucose (up to 250 g per day) mainly takes place in the liver. The tubule cells of the kidney are also capable of carrying out gluconeogenesis, but due to their much smaller mass, their contribution only represents around 10% of total glucose formation.

5) Fructose and galactose are mainly metabolized by the liver, which channels them into glycolysis.

6) The process of glucose utilization is also intensive in liver:

- metabolites of glycolysis and acetyl-CoA are used for biosynthesis of TAGs;
- NADPH, which is formed in pentose phosphate pathway, is used for the synthesis of fatty acids and cholesterol;
- ribose-5-phosphate is used for synthesis of nucleic acids.

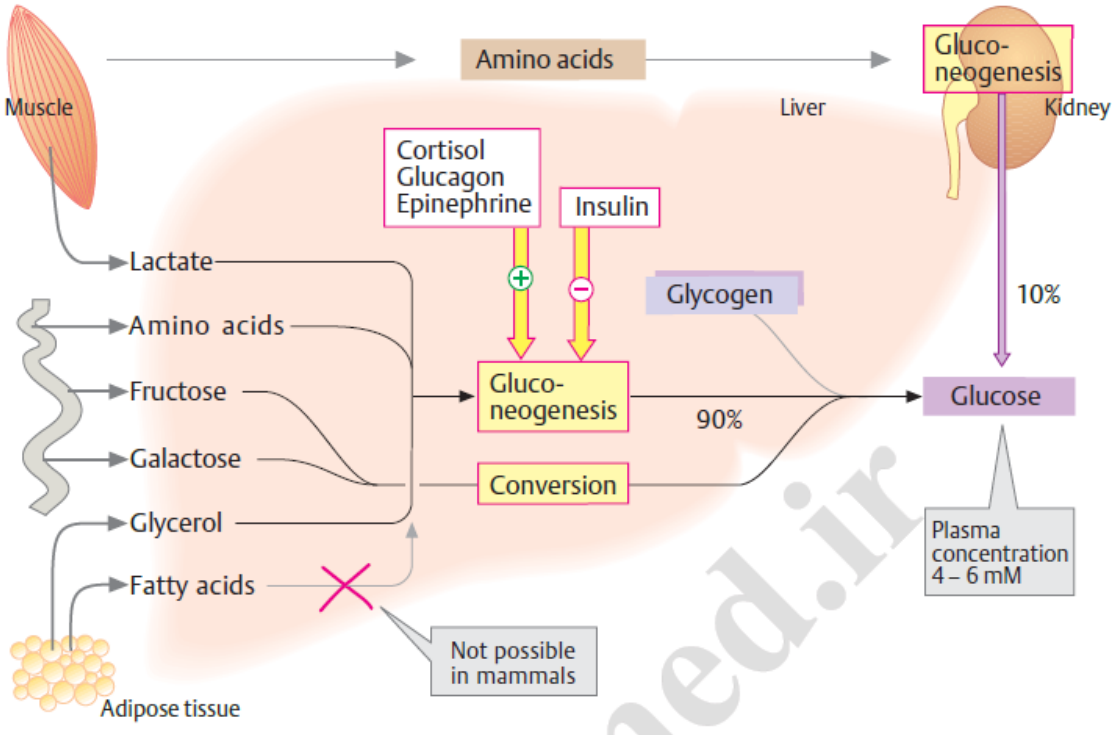


Figure 14. Gluconeogenesis in liver (Koolman, 2005)

Role of liver in lipid metabolism.

The liver is the most important site for the formation of fatty acids, fats (triacylglycerols), cholesterol and the only site for the synthesis of ketone bodies. Most of these products are released into the blood. In contrast, the triacylglycerols synthesized in adipose tissue are stored there.

1) Lipid metabolism in the liver is closely linked with carbohydrates and amino acids metabolism. When it is a good supply of nutrients in the resorptive state, the liver converts glucose via acetyl-CoA into fatty acids. Fatty acids are converted into fats and phospholipids. Together with apoproteins they are packed into VLDLs and then released into the blood by exocytosis.

2) The most of cholesterol (250-500 mg/day, 50-80%) is synthesized in the liver. It is transported to tissues by means of LDLs. LDLs are mainly formed in blood stream from VLDLs. Small amount of LDLs is synthesized immediately in liver. Some cholesterol is required for the synthesis of bile acids. The liver also contributes to the cholesterol metabolism by taking up from the blood and breaking down lipoproteins that contain cholesterol and cholesterol esters (HDLs, IDLs, LDLs).

3) The synthesis of ketone bodies is located in liver. Acetoacetate and β-hydroxybutyrate are alternative fuel for extrahepatic tissues (skeletal muscles, heart, kidneys). Brain also uses ketone bodies in long starvation. Acetone cannot be metabolized and is exhaled via the lungs or excreted with urine.

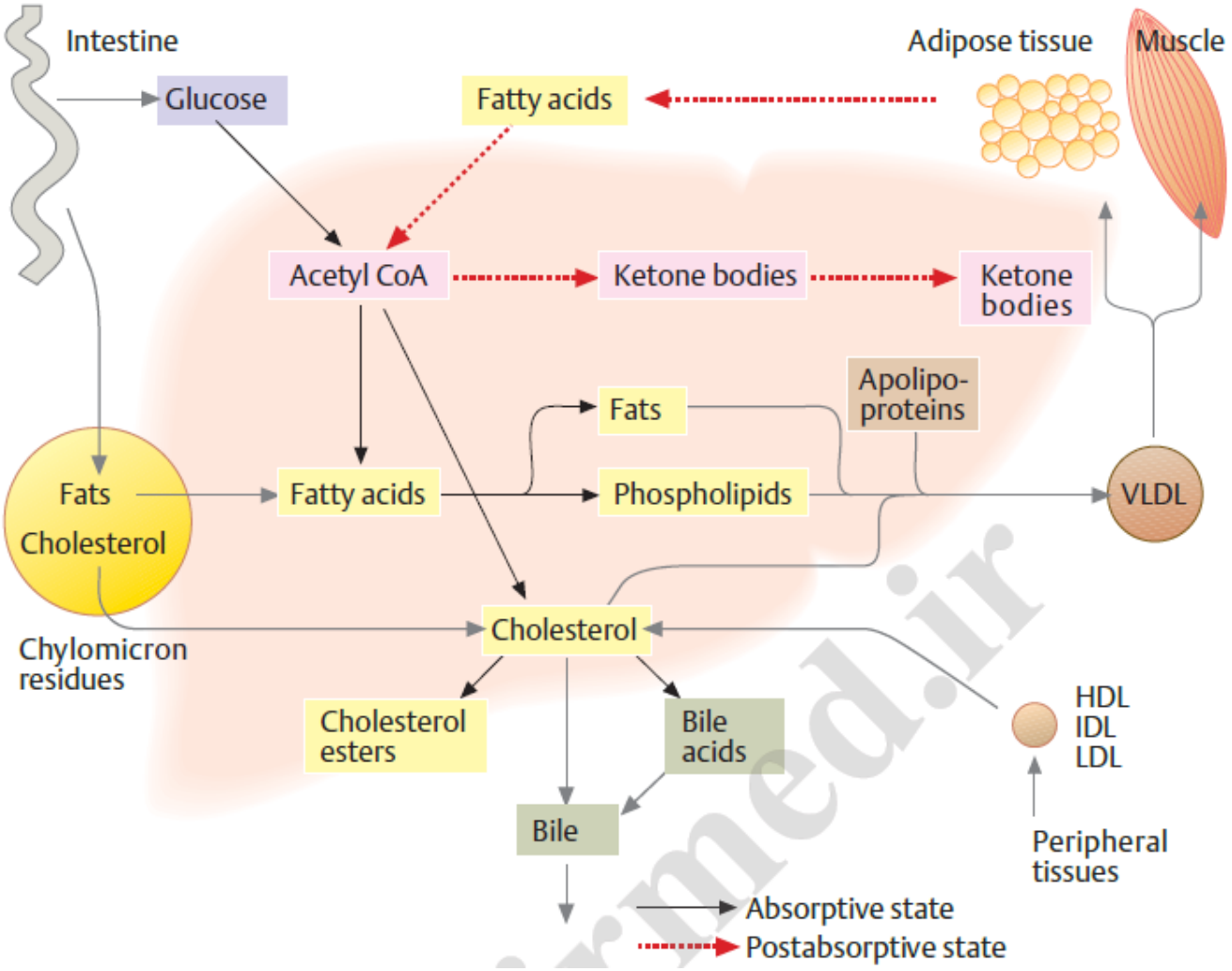


Figure 15. Lipid metabolism in liver (Koolman, 2005)

Role of liver in protein metabolism.

1) The liver controls the plasma level of amino acids. Excess amino acids are broken down. In patients with severe liver insufficiency level of amino acids in blood is 21mmol/L instead 2,9-4,3 mmol/L.
2) The carbon skeleton of amino acids enters intermediary metabolism and serves for glucose synthesis or energy production.
3) The liver is the only organ with complete complex of enzymes for urea synthesis. Disturbances of functioning urea cycle lead to accumulation of ammonia in blood and tissues. Brain neurons are the most sensitive to such pathological situation. This is manifested by development of liver encephalopathy and coma.
4) Synthesis of choline, creatine, hydroxylation of phenylalanine occurs in the liver.
5) Most of the plasma proteins (albumins, 13-18 g/day; 80% of globulins, factors of blood clotting, fibrinolytic systems of blood: II, V, IX, X, XI, XII, XIII fibrinogen, antithormbin, antiplasmin) are synthesized in the liver.

Storage function.

The liver not only stores energy reserves and nutrients for the body, but also certain mineral substances (including iron) and vitamins (A, D, K, folic acid, B_{12}).

Summary of Liver Functions (Janson. 2012)

Function	Molecule(s)	Description
Amino acid/ protein metabolism	Amino acid synthesis	Liver enzymes are responsible for most of amino acid synthesis
	Protein degradation	Liver enzymes are responsible for most of protein degradation
Carbohydrate metabolism	Gluconeogenesis	Liver enzymes account for a significant amount of gluconeogenesis
	Glycogenesis	Liver enzymes account for a significant amount of glycogen synthesis
	Glycogenolysis	Liver enzymes account for a significant amount of glycogen breakdown
Lipid metabolism	Lipogenesis	Liver enzymes are responsible for much of lipid (triglyceride) synthesis
	Cholesterol/ lipoproteins	Liver enzymes are responsible for endogenous cholesterol/lipoprotein metabolism. These reactions and pathways are discussed in detail in the text below.
	Apolipoproteins	Major site of **apolipoprotein** synthesis, proteins responsible for increasing the solubility and transporting dietary fats in the blood, lipoproteins components involved in cholesterol metabolism. Apolipoproteins can also serve as cofactors and can bind to receptors as part of their function.
Coagulation factor synthesis/ clot formation and breakdown	Coagulation factors	Synthesis of coagulation factors I (fibrinogen), II (Prothrombin), V, VII, IX, X, and XI
	Fibronectin (soluble)	Soluble **fibronectin**, which differs from the insoluble, extracellular matrix form, is a glycoprotein, which, along with **fibrin**, helps to form the initial blood clot following injury. The soluble fibrin/fibronectin clot is replaced by other matrix proteins, including the insoluble form of fibronectin, as part of the process of wound healing.
	α_2-macroglobulin	Functions as an inhibitor of **thrombin** coagulation and **plasmin**/**kallikrein** fi brinolysis
	α_1-antitrypsin	Serine protease inhibitor, which covalently binds to **trypsin** and inactivates its function, including cleavage of lung elastase. Deficient α1-antitrypsin leads to a variety of diseases in the lungs, including **cystic fibrosis**, and **congenital, panacinar emphysema/ chronic obstructive pulmonary disease (COPD)**.
	Antithrombin III	Glycoprotein serine protease in blood, which inactivates **thrombin** (coagulation factor IIa) as well as **kallikrein** and **plasmin** molecules, thereby inhibiting clot formation. Antithrombin III activity is increased by the binding of heparin. Antithrombin III also inactivates trypsin and other serine protease enzymes of the classical complement pathway

	Plasminogen/ plasmin	Serine protease, produced as **plasminogen** in the liver and subsequently converted to **plasmin** in the blood by **coagulation factor XII (Hageman)**, **tissue plasminogen activator**, and/ or **urokinase plasminogen activator**. Activated plasmin breaks down fi brin/fibronectin clots (**fibrinolysis**). Plasmin activates parts of the complement system and collagen-cleaving enzymes known as **collagenases**. Self-cleavage of plasminogen produces the molecule **angiostatin**, a potent inhibitor of the formation of new blood vessels. Plasmin also breaks down the wall of Graafi an follicles to allow **ovulation**.
	α_2-antiplasmin	Serine protease inhibitor, which inactivates **plasmin** and, thereby, inhibits fibrinolysis, the breakdown of the initial fibrin clot formed upon injury.
Bile synthesis	Bile	Utilized in small intestine for digestion and absorption of lipids. Includes water, bile acids (normally conjugated to taurine or glycine), bile pigments, including bilirubin, from breakdown of hemoglobin porphyrin molecules, cholesterol, phospholipids, and bicarbonate.
Breakdown of hemoglobin	Bilirubin	Breakdown of heme from degenerating red blood cells starts in the spleen with reduction of the heme by reduced nicotinamide adenine dinucleotide phosphate (NADPH) to biliverdin/free Fe^{3+} ion and then a further reduction with NADPH to bilirubin. This form is known as **unconjugated bilirubin.** Bilirubin is transported by albumin (see below) to the liver where it is conjugated to glucuronic acid by the enzyme **UDP-glucuronosyltransferase**, a process that makes the molecule more soluble. This form is known as **conjugated bilirubin** and is excreted in bile into the intestine where it is converted by bacteria into **urobilinogen**. Urobilinogens are partly absorbed in the intestine and fi nally excreted in urine as **urobilin** or are converted to **stercobilin** for excretion in feces. Urobilinogens are responsible for the yellow color of urine; stercobilin is responsible for the brown color of feces.
Urea cycle	Urea	Main site of conversion of amino acid nitrogen to urea via the urea cycle. Urea synthesis also occurs, although to a lesser extent, in the kidney.
Detoxification	Various toxins, drugs, and alcohol	Breakdown and elimination of a variety of toxic substances, including **toxins**, **medications**, and **alcohol**. Many toxic molecules are normally metabolized in two overall steps (phases I and II). Drug detoxification also occurs to a lesser extent in the digestive system, lungs, kidneys, and skin. **Phase I** normally occurs prior to phase II reactions and usually involves reactions that increase the polar nature of the molecule (e.g., reduction/oxidation, hydrolysis, and cyclization/decyclization). Many drugs are designed to be activated, inactivated, or modified for elimination in urine or feces (via bile conjugation) by phase I reactions. Phase I enzymes in the liver include the **cytochrome p450 system** (oxidation and reduction reactions) and alcohol dehydrogenase (converts alcohol to acetaldehyde) and acetaldehyde dehydrogenase (converts acetaldehyde to acetic acid). Alcohol metabolism can also occur in other tissues, including stomach epithelium (men only) and the brain. **Phase II** reactions normally involve the addition of biochemical groups (e.g., glucuronic acid, sulfonates, glutathione, methylation, acetylation, and/or amino acid residues) to polar groups added in phase I, including carboxyl (COOH), hydroxyl (OH), amino (NH_2), and sulfhydryl (SH) groups. Phase II reactions normally permanently inactivate the toxin or drug.
Storage	Albumin	Important carrier protein of multiple molecules in the blood, including thyroid hormones and other fat-soluble hormones (see additional hormone transport proteins below). Also, transports fatty acids on their way to the liver for storage, or oxidation for energy generation, unconjugated bilirubin (see above), and several medications. Other globulins produced by the liver serve the same role(s), although to a lesser extent than albumin.
	Glycogen	The liver stores glucose in the form of **glycogen**
	Vitamin A (retinol)	Stores vitamin A transported from the intestine esterifi ed with palmitate via chylomicrons. The liver can store up to a 2-year supply of vitamin A. See below for release, transport, and use.
	Vitamin B_{12} (cobalamin)	Storage of vitamin B_{12} (approximately 50% of body's total). Because of the efficient recirculation and restorage by the liver, years worth of vitamin B_{12} can be stored.

	Vitamin D (as calcidiol)	Vitamin D in the liver is converted by carbon 25-hydroxylation of vitamin D_3 (**cholecalciferol**) by cholecalciferol 25-hydroxylase into a prohormone form called "**calcidiol**" (25-hydroxy vitamin D_3). When released for use, calcidiol is then converted to its active form by a second hydroxylation at the 1 position to form "**calcitriol**" (1, 25-dihydroxy vitamin D_3) by the kidney. The liver can store up to a 4-month supply.
	Vitamin E	Ingested vitamin E is taken up by the liver but only the α-tocopherol form is stored. Other forms (β-, γ-, and δ-tocopherols and α-, β-, γ-, and δ-tocotrienols) are metabolized and excreted.
Transport/ "carrier" proteins	α-fetoprotein	Binds to calcium ions affecting the total, available calcium concentration. Serves as a pH buffer and as an osmotic molecule to maintain colloid osmotic pressure (oncotic pressure) that influences the movement of water from and to the blood. Serves a similar role in the developing fetus and, as such, is used as part of a prenatal screen for Down syndrome, neural tube defects, and abdominal wall defects (omphalocoele). Serves as a tumor marker for cancer of liver cells and some germ cell and testicular cancers.
	Ceruloplasmin	Enzyme that contains six copper atoms and is responsible for carrying approximately 90% of the body's total copper (additional 10% is contained in albumin).
	Haptoglobulin	Transports free hemoglobin molecules released from degenerating red blood cells. Also produced by several other tissues, including kidney, skin, and lung.
	Hemopexin	Transports free heme porphyrin molecule released from degrading hemoglobin. In doing so, it preserves iron and protects the body from the damaging oxidative effects of the free heme group.
	Insulin-like growth factor 1 (IGF-1)-binding protein	Transports IGF-1
	Retinol-binding protein	Binds to de-esterified, alcohol form of retinol (vitamin A) released from storage in the liver and transports to tissues in the body.
	Sex hormonebinding protein	Transports testosterone and estradiol. Also produced in the placenta, testes, uterus, and brain.
	Thyroxin-binding globulin	Transports thyroxine (T_4) and 3,5,3′-triiodothyronine (T_3).
	Transcortin	Transports cortisol, aldosterone, and progesterone.
	Transferrin	Important carrier protein of iron (Fe^{3+}) as well as the primary store of iron in the body. Transferrin is composed of two, identical monomers, linked by disulfide bonds, each of which can bind and carry one or two Fe^{3+} ions. Primarily produced in liver but also made in other tissues (e.g., brain).
	Transthyretin	Transports thyroxine (T_4). Also produced in the choroid plexus and retinal pigment epithelium.
	Vitamin D-binding protein	Transports vitamin D to tissues in the body. Also, has actin binding activity that may serve as a scavenger role for actin monomers released from injured cells or tissues.
Miscellaneous	Angiotensinogen	Peptide hormone that, when converted to angiotensin I by the enzyme renin (and subsequently to angiotensin II by angiotensin-converting enzyme), raises blood pressure via a number of mechanisms
	C-reactive protein (CRP)	Protein whose liver production is increased because of inflammation, specifically the release of interleukin 6 (IL-6) by macrophages and adipocytes. CRP binds to phosphocholine molecules on degenerating cells to activate the complement system, leading to their phagocytosis by macrophages; CRP may play other roles in the immune system. CRP is used as a marker for inflammation. Its use for risk assessment for heart attack, high blood pressure, high cholesterol/lipids, and diabetes is still being investigated but has been shown not to be as useful as once thought. Investigations of CRP measurement for cancer screening are also ongoing.
	Complement proteins	Synthesis of complement proteins C 1–9, including the complement component 3 utilized in both the classical and alternative complement pathways

	Insulin	The majority of insulin is degraded in liver cells. Other cells are also able to breakdown insulin as well as other hormones.
	IGF-1	Polypeptide hormone mainly responsible for growth in early childhood. Also produced as an autocrine hormone in several target tissues
	Fetal red blood cell (erythrocyte) production	Site of production of fetal red blood cells (erythrocytes), containing hemoglobin F. The liver is the sole site of production during the first trimester and is gradually replaced by the developing bone marrow.
	Kupffer cells (reticulendothelial system)	Monocyte/macrophage-type cells of the reticuloendothelial system, which serve as antigen monitors sampling circulating antigens to determine whether an immune response should be mounted.
	Thrombopoietin	Glycoprotein hormone that promotes the production of platelets by bone marrow from precursor megakaryocyte cells. Also produced in the kidney.

Hemoglobin metabolism, its breakdown. Bile formation.

The life of red cells is 120 days. After this period of time, the erythrocytes suffer degradation to release hemoglobin. About 6g Hb are renovated every day in adult human. This leads to releasing about 25 mg of iron. Free iron is toxic, but association with transferrin diminishes its potential toxicity and also directs iron to where it is required in the body. The major organs responsible for the erythrocytolysis and hemoglobin breakdown are: liver, spleen, bone marrow.

The **catabolism of heme** from all the heme proteins is carried out in the microsomal fraction of reticuloendothelial cells by a complex enzyme system called heme oxygenase. This process starts with a cleavage of the α-methylene bridge between the rings I and II of the porphyrin ring system to produce verdoglobin and carbon monoxide. Verdoglobin is spontaneously cleft into iron (ferric ion), globin and biliverdin. Biliverdin reductase reduces the methenyl bridge between pyrrole III and pyrrole IV to a methylene group to produce bilirubin. The chemical conversion of heme to bilirubin by the reticuloendothelial cells can be observed in vivo as the purple color of the heme in a hematoma is slowly converted to the yellow pigment of bilirubin. The further metabolism of bilirubin occurs primarily in the liver. It can be divided into 3 processes: 1) Uptake of bilirubin by liver parenchymal cells. 2) Conjugation of bilirubin in the smooth endoplasmic reticulum. 3) Secretion of conjugated bilirubin into the bile.

Bilirubin is hydrophobic molecule. Therefore, bilirubin formed in cells of reticulo-endothelial system of spleen and bone marrow is transported to the liver by plasma albumin. Each molecule of albumin appears to have one high affinity site and one low affinity site for bilirubin. In 100 ml of plasma approximately 25 mg of bilirubin can be tightly bound to albumin. 1g of Hb degradation yields 35 mg of bilirubin. The daily bilirubin formation in human adults is approximately 250-350 mg, deriving mainly from Hb, but also from various other hemoproteins such as cytochrome P_{450}. Bilirubin which is not bound with albumin, is toxic, because it is hydrophobic. It can pass through blood-brain barrier and can form complexes with collagen of intercellular matrix and with lipids of membranes. The diminishing pH of blood decreases the affinity of albumin to bilirubin. Some drugs compete with bilirubin to bind with high affinity site of albumin. In the liver, the bilirubin is removed from albumin and taken up by hepatocytes with a carrier-mediated saturable system. In smooth endoplasmic reticulum of hepatocytes bilirubin is converted to a polar form by adding glucuronic acid molecules to it. This process is called conjugation and is catalyzed by **UDP-glucuronyl transferase.** Secretion of conjugated bilirubin into the bile occurs by an active transport mechanism. Secretion of bilirubin is the rate limiting stage of metabolism of bilirubin in liver. Conjugation and secretion of bilirubin are induced by phenobarbital.

Cells of reticulo-endothelial system of liver, spleen, bone marrow	Hemoglobin ↓ Verdoglobin ↓ biliverdin (green pigment) ↓ bilirubin	+ $2NADPH_2+O_2$ **heme oxygenase** – Fe^{3+}+globin **bilirubin reductase**
Blood	↓ bilirubin + albumin	indirect, free, unconjugated
Liver	↓ bilirubin ↓ bilirubin monoglucuronide (30%) + bilirubin diglucuronide (70%)	+ UDP-glucuronic acid **UDP-glucuronyl transferase** direct, conjugated
Bile	↓ bilirubin glucuronides	
Intestine: terminal ileum and the large intestine	↓ bilirubin glucuronide ↓ bilirubin ↓ stercobilinogen (urobilinogen)	**β-glucuronidase** (bacterial enzyme)
	↓ stercobilin (feces) 40-280 mg/day urobilin (urine) 4 mg/day	

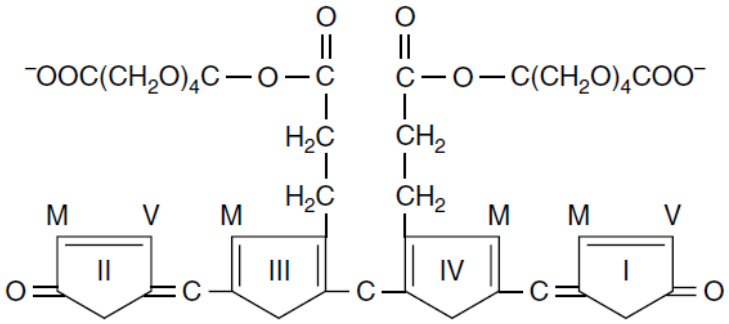


Figure 16. Structure of bilirubin diglucuronide (Murray, 2003)

Small amount of conjugated bilirubin enters to blood. This bilirubin is called direct, conjugated. Direct bilirubin is hydrophilic; therefore, only direct bilirubin may be excreted in the urine. As the conjugated bilirubin reaches the terminal ileum and the large intestine, the glucuronides are removed by specific bacterial enzymes (β-glucuronidases). Then bilirubin is finally reduced to stercobilinogen (urobilinogen) by influence of microflora enzymes. Part of it is absorbed, supplies to liver and then or is excreted with bile (large amount) or enters to blood and is excreted in the urine (small amount). Stercobilinogen, which is excreted with feces, is oxidized to stercobilin.

Total bilirubin of blood – 8,5-20 μmol/L (75% indirect 25% direct). Determination of bile pigments is very important for differential diagnosis of different forms of jaundice.

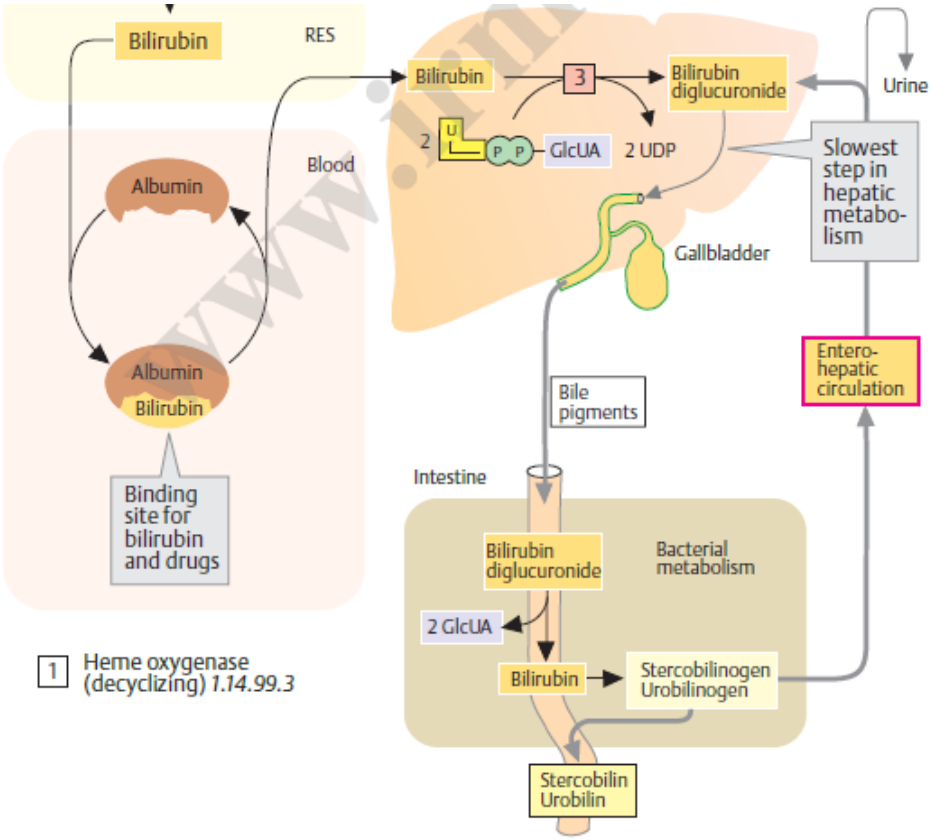


Figure 17. Bilirubin metabolism (Koolman, 2005)

Bile formation function of liver.

Bile is an important product released by hepatocytes. It promotes the digestion of fats from food by emulsifying them in small intestine. The emulsifying components of bile, apart from phospholipids, mainly consist of bile acids and bile salts. The bile also contains bile pigments, free cholesterol, which are excreted by this way. The cholesterol excreted with the bile is poorly water-soluble. Together with phospholipids and bile acids it forms micelles, which keep it in solution. If the proportions of phospholipids, bile acids and cholesterol shift, gallstones can arise. These mainly consist of precipitated cholesterol (cholesterol stones), but can also contain Ca^{2+} salts of bile acids and bile pigments.

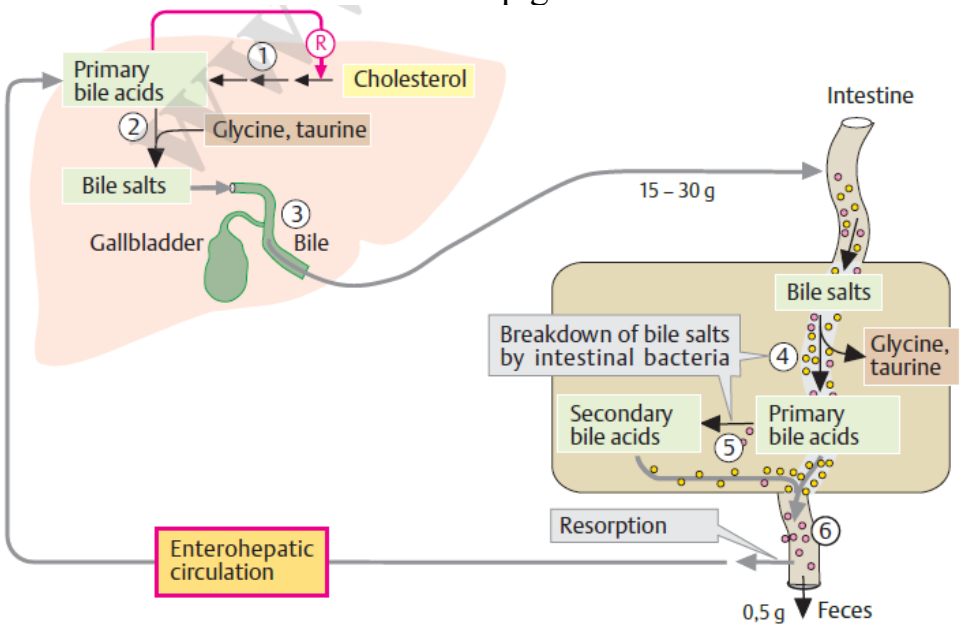


Figure 18. Metabolism of bile salts (Koolman, 2005)

Biochemistry of jaundice (hemolytic, hepatic, obstructive): causes, clinical symptoms, differential diagnostics.

Hyperbilirubinemia causes jaundice

When bilirubin in the blood exceeds 1 mg/dL (17.1 μmol/L), hyperbilirubinemia exists. Hyperbilirubinemia may be due to the production of more bilirubin than the normal liver can excrete, or it may result from the failure of a damaged liver to excrete bilirubin produced in normal amounts. In the absence of hepatic damage, obstruction of the excretory ducts of the liver – by preventing the excretion of bilirubin – will also cause hyperbilirubinemia. In all these situations, bilirubin accumulates in the blood, and when it reaches a certain concentration (approximately 2-2.5 mg/dL), it diffuses into the tissues, which then become yellow. That condition is called **jaundice** or **icterus.**

In clinical studies of jaundice, measurement of bilirubin in the serum is of great value. A method for quantitatively assaying the bilirubin content of the serum was first devised by van den Bergh by application of Ehrlich's test for bilirubin in urine. The Ehrlich reaction is based on the coupling of diazotized sulfanilic acid (Ehrlich's diazo reagent) and bilirubin to produce a reddish-purple azo compound. In the original procedure as described by Ehrlich, methanol was used to provide a solution in which both bilirubin and the diazo regent were soluble. Van den Bergh inadvertently omitted the methanol on an occasion when assay of bile pigment in human bile was being attempted. To his surprise, normal development of the color occurred "directly." This form of bilirubin that would react without the addition of methanol was thus termed **"directreacting."**

It was then found that this same direct reaction would also occur in serum from cases of jaundice due to biliary obstruction. However, it was still necessary to add methanol to detect bilirubin in normal serum or that which was present in excess in serum from cases of hemolytic jaundice where no evidence of obstruction was to be found. To that form of bilirubin which could be measured only after the addition of methanol, the term **"indirect-reacting"** was applied. It was subsequently discovered that the indirect bilirubin is "free" (unconjugated) bilirubin en route to the liver from the reticuloendothelial tissues, where the bilirubin was originally produced by the breakdown of heme porphyrins. Since this bilirubin is not water-soluble, it requires methanol to initiate coupling with the diazo reagent. In the liver, the free bilirubin becomes conjugated with glucuronic acid, and the conjugate, bilirubin glucuronide, can then be excreted into the bile. Furthermore, conjugated bilirubin, being water-soluble, can react directly with the diazo reagent, so that the "direct bilirubin" of van den Bergh is actually a bilirubin conjugate (bilirubin glucuronide).

Depending on the type of bilirubin present in plasma – ie, unconjugated or conjugated – hyperbilirubinemia may be classified as **retention hyperbilirubinemia,** due to overproduction, or **regurgitation hyperbilirubinemia,** due to reflux into the bloodstream because of biliary obstruction.

Because of its hydrophobicity, only unconjugated bilirubin can cross the blood-brain barrier into the central nervous system; thus, encephalopathy due to hyperbilirubinemia **(kernicterus)** can occur only in connection with unconjugated bilirubin, as found in retention hyperbilirubinemia. On the other hand, because of its water-solubility, only conjugated bilirubin can appear in urine. Accordingly, **choluric jaundice** (choluria is the presence of bile pigments in the urine) occurs only in regurgitation hyperbilirubinemia, and **acholuric jaundice** occurs only in the presence of an excess of unconjugated bilirubin.

Elevated amounts of unconjugated bilirubin in blood occur in a number of conditions

Hemolytic anemias. Hemolytic anemias are important causes of unconjugated hyperbilirubinemia, though unconjugated hyperbilirubinemia is usually only slight (<4 mg/dL; <68.4 μmol/L) even in the event of extensive hemolysis because of the healthy liver's large capacity for handling bilirubin.

Neonatal "physiologic jaundice". This transient condition is the most common cause of unconjugated hyperbilirubinemia. It results from an accelerated hemolysis around the time of birth and an immature hepatic system for the uptake, conjugation, and secretion of bilirubin. Not only is the bilirubin-UGT activity reduced, but there probably is reduced synthesis of the substrate for that enzyme, UDP-glucuronic acid. Since the increased amount of bilirubin is unconjugated, it is capable of penetrating the blood-brain barrier when its concentration in plasma exceeds that which can be tightly bound by albumin (20-25 mg/dL). This can result in a hyperbilirubinemic toxic encephalopathy, or **kernicterus,** which can cause mental retardation. Because of the recognized inducibility of this bilirubin-metabolizing system, phenobarbital has been administered to jaundiced neonates and is effective in this disorder. In addition, exposure to blue light (phototherapy) promotes the hepatic excretion of unconjugated bilirubin by converting some of the bilirubin to other derivatives such as maleimide fragments and geometric isomers that are excreted in the bile.

Crigler-Najjar syndrome, type I; congenital nonhemolytic jaundice. Type I Crigler-Najjar syndrome is a rare autosomal recessive disorder. It is characterized by severe congenital jaundice (serum bilirubin usually exceeds 20 mg/dL) due to mutations in the gene encoding bilirubin-UGT activity in hepatic tissues. The disease is often fatal within the first 15 months of life. Children with this condition have been treated with phototherapy, resulting in some reduction in plasma bilirubin levels. Phenobarbital has no effect on the formation of bilirubin glucuronides in patients with type I Crigler-Najjar syndrome. A liver transplant may be curative.

Crigler-Najjar syndrome, type II. This rare inherited disorder also results from mutations in the gene encoding bilirubin-UGT, but some activity of the enzyme is retained and the condition has a more benign course than type I. Serum bilirubin concentrations usually do not exceed 20 mg/dL. Patients with this condition can respond to treatment with large doses of phenobarbital.

Gilbert syndrome. Again, this is caused by mutations in the gene encoding bilirubin-UGT, but approximately 30% of the enzyme's activity is preserved and the condition is entirely harmless.

Toxic hyperbilirubinemia. Unconjugated hyperbilirubinemia can result from toxin-induced liver dysfunction such as that caused by chloroform, arsphenamines, carbon tetrachloride, acetaminophen, hepatitis virus, cirrhosis, and Amanita mushroom poisoning. These acquired disorders are due to hepatic parenchymal cell damage, which impairs conjugation.

Obstruction in biliary tree is the commonest cause of conjugated hyperbilirubinemia

Obstruction of the biliary tree. Conjugated hyperbilirubinemia commonly results from blockage of the hepatic or common bile ducts, most often due to a gallstone or to cancer of the head of the pancreas. Because of the obstruction, bilirubin diglucuronide cannot be excreted. It thus regurgitates into the hepatic veins and lymphatics, and conjugated bilirubin appears in the blood and urine (choluric jaundice).

The term **cholestatic jaundice** is used to include all cases of extrahepatic obstructive jaundice. It also covers those cases of jaundice that exhibit conjugated hyperbilirubinemia

due to micro-obstruction of intrahepatic biliary ductules by swollen, damaged hepatocytes (eg, as may occur in infectious hepatitis).

Dubin-Johnson syndrome. This benign autosomal recessive disorder consists of conjugated hyperbilirubinemia in childhood or during adult life. The hyperbilirubinemia is caused by mutations in the gene encoding MRP-2, the protein involved in the secretion of conjugated bilirubin into bile. The centrilobular hepatocytes contain an abnormal black pigment that may be derived from epinephrine.

Rotor syndrome. This is a rare benign condition characterized by chronic conjugated hyperbilirubinemia and normal liver histology. Its precise cause has not been identified, but it is thought to be due to an abnormality in hepatic storage.

Some conjugated bilirubin can bind covalently to albumin.

When levels of conjugated bilirubin remain high in plasma, a fraction can bind covalently to albumin (delta bilirubin). Because it is bound covalently to albumin, this fraction has a longer half-life in plasma than does conventional conjugated bilirubin. Thus, it remains elevated during the recovery phase of obstructive jaundice after the remainder of the conjugated bilirubin has declined to normal levels; this explains why some patients continue to appear jaundiced after conjugated bilirubin levels have returned to normal.

Urobilinogen and bilirubin in urine are clinical indicators.

Normally, there are mere traces of urobilinogen in the urine. In **complete obstruction of the bile duct,** no urobilinogen is found in the urine, since bilirubin has no access to the intestine, where it can be converted to urobilinogen. In this case, the presence of bilirubin (conjugated) in the urine without urobilinogen suggests obstructive jaundice, either intrahepatic or posthepatic.

In **jaundice secondary to hemolysis,** the increased production of bilirubin leads to increased production of urobilinogen, which appears in the urine in large amounts. Bilirubin is not usually found in the urine in hemolytic jaundice (because unconjugated bilirubin does not pass into the urine), so that the combination of increased urobilinogen and absence of bilirubin is suggestive of hemolytic jaundice. Increased blood destruction from any cause brings about an increase in urine urobilinogen.

Condition	Serum Bilirubin	Urine Urobilinogen	Urine Bilirubin	Fecal Urobilinogen
Normal	Direct: 0.1–0.4 mg/dL Indirect: 0.2–0.7 mg/dL	0–4 mg/24 h	Absent	40–280 mg/24 h
Hemolytic anemia	↑ Indirect	Increased	Absent	Increased
Hepatitis	↑ Direct and indirect	Decreased if micro-obstruction is present	Present if micro-obstruction occurs	Decreased
Obstructive jaundice[1]	↑ Direct	Absent	Present	Trace to absent

Figure 19. Laboratory results in normal and patients with three different causes of jaundice (Murray, 2003)

The commonest causes of obstructive (posthepatic) jaundice are cancer of the head of the pancreas and a gallstone lodged in the common bile duct. The presence of bilirubin in the urine is sometimes referred to as choluria – therefore, hepatitis and obstruction of the common bile duct cause choluric jaundice, whereas the jaundice of hemolytic anemia is referred to as acholuric. The laboratory results in patients with hepatitis are variable, depending on the extent of damage to parenchymal cells and the extent of micro-obstruction

to bile ductules. Serum levels of ALT and AST are usually markedly elevated in hepatitis, whereas serum levels of alkaline phosphatase are elevated in obstructive liver disease.

Figure 19 summarizes laboratory results obtained on patients with three different causes of jaundice – hemolytic anemia (a prehepatic cause), hepatitis (a hepatic cause), and obstruction of the common bile duct (a posthepatic cause). Laboratory tests on blood (evaluation of the possibility of a hemolytic anemia and measurement of prothrombin time) and on serum (eg, electrophoresis of proteins; activities of the enzymes ALT, AST, and alkaline phosphatase) are also important in helping to distinguish between prehepatic, hepatic, and posthepatic causes of jaundice.

Biotransformation of xenobiotics and endogenous toxins. Microsomal oxidation.

All the substances supplied to the organism in a variety of ways pass through several basically similar stages such as absorption, distribution (mechanical transport), and excretion. The transit rate of substance at these stages may either be increased, or lowered, depending on the structural features and physico-chemical properties of a substance as well as on its affinity to biological molecules. The discipline, dealing with rate characteristics at the stages in which any substance entering the organism is involved, is referred to as chemobiokinetics which treats, in a broader sense, movements of substances in the living organism. Conceptually, chemobiokinetics is divided into three subdisciplines: pharmacokinetics, toxicokinetics, and biokinetics. Pharmacokinetics confines itself to the study of drugs; toxicokinetics, to the study of toxic substances; and biokinetics, to the study of substances not alien to the organism. In many respects, this classification is rather arbitrary, since the distinction between a drug and a poison in many instances may be evasive. Moreover, even autobiogenous compounds taken in improper doses may exhibit toxic properties. The subsequent history of a substance after its uptake by the organism is dependent to a significant degree on the rates at which it is converted by various enzymes, i.e. on its metabolic transformations. In point of fact, the metabolism of biogenous substances and xenobiotics used as drugs is governed by the laws of enzymic kinetics. Biogenous substances, being natural substrates for enzymes, are converted at the rates characteristic of catalytic properties of the enzymes involved. The metabolic evolution of xenobiotics is dependent on the occurrence of enzymes capable of catalyzing the conversion of these xenobiotics. If no enzymes that are potentially capable of catalytic intervention of the xenobiotics are available, the xenobiotics behave as metabolically inert. Apparently, in the course of evolution, highly substrate-specific enzymes have laid a basis for the intrinsic metabolism in living organisms, while the enzymes with low specificity towards substrates have taken up defense functions aimed at the inactivation of extraneous invaders.

Biochemistry studies enzyme-assisted conversions of drugs in the organism by making use of appropriate methods and techniques. The drug metabolism in the organism may be represented within the framework of a general scheme:

Drug → Enzymes → Metabolites → End Metabolites

absorption → intrinsic metabolism → excretion or storage

The drug metabolism is studied by determining the drugs and their metabolites in biological fluids, tissues, and excretions as well as by estimating the activity and kinetics of enzymes involved in the drug metabolism.

Experimentally, the two approaches are used in the studies on metabolism of xenobiotics. In the clinic, the drug metabolism is assessed, as a rule, by measuring the concentration of administered drug and its metabolites in blood, urine, and other excretions.

Stages in the metabolism of xenobiotics.

Biogenous substances, as distinct from xenobiotics, are involved in the conventional metabolic process. Xenobiotics, in the course of their conversion, are subject to two major stages: modification (nonsynthetic stage) and conjugation (synthetic stage).

The **modification stage** is an enzyme-assisted modification of the initial structure of a xenobiotic resulting either in a cleavage of bonds within the xenobiotic molecule, or in the insertion of additional functional groups (e.g. hydroxyl or amino groups) into its molecule, or in a release of its functional groups blocked in the initial structure (for example, by hydrolysis of ester or peptide bonds). The modification leads to an increased solubility of the xenobiotic (xenobiotic becomes more hydrophilic). Additional functional groups are needed to enable the xenobiotic to enter the conjugation stage.

Conjugation stage is viewed as an enzyme-assisted process for building covalent bonds between the xenobiotic and biomolecules occurring in the organism's media (e.g. glucuronic acid, sulphates, and others). The conjugation stage terminates in the synthesis of a novel compound whose constituents are, on the one hand, the xenobiotic moiety and, on the other hand, a conjugate (biomolecule).

Relationship between metabolism of xenobiotics and their structure. Xenobiotics invaded into the organism are liable to a chain of modifications, or nonsynthetic conversions (oxidation-reduction, isomerization, cyclization, ring opening, and hydrolysis) carried out by the respective enzymes (oxidoreductases, isomerases, lyases, and hydrolases):

$$RH + O_2 + 2H^+ + 2e^- \rightarrow ROH + H_2O$$

Depending on the number of functional groups in the molecule of modified xenobiotic, its conjugation can proceed by a variety of routes in which each of the xenobiotic functional groups becomes bound with a conjugating agent. If the xenobiotic is not functionalized (e.g. benzene), it cannot enter the conjugation stage. In contrast, if the introduced xenobiotic is in possession of an appropriate functional group (e.g., 4-aminobiphenyl); it may become immediately engaged in the conjugation stage with UDP-glucuronic acid.

The knowledge of principles that govern the enzyme-assisted conversions of xenobiotics provides an opportunity to prognosticate metabolic behaviour of any xenobiotic taking into account its structural specificities.

Xenobiotic routes in the organism.

Xenobiotics are either eliminated from the organism, or become accumulated in tissues. Xenobio-tics are excreted as:

1) supplied (unmodified by enzymes);
2) metabolites (modified by enzymes);
3) conjugates (by action of conjugating enzymes);
4) complexed with biomolecules (for example, metal-containing xenobiotics become bound to cysteine by glutathione and excreted as complexes).

The xenobiotics that accumulate in the organism are those capable of interacting with macromole-cules (proteins, nucleic acids, and lipid entities). For example, organochloric compounds, which are readily soluble in lipids, are quite resistant to catabolic conversion and are difficult to eliminate from the organism. They tend to accumulate in lipid-rich tissues. Heavy metals (mercury, cadmium, silver, arsenic, and lead) and preparations containing organometallic compounds become bound with proteins and likewise accumulate in the organism.

Metabolism and physiological action of drugs.

Substances introduced into organism may exhibit either medicinal or toxic properties. Commonly, any drug can exert both medicating and side (toxic) effects. Therefore, generally speaking, the mo-re active the drug, the faster its toxic properties become manifest. During metabolism, the specific activity and toxicity of xenobiotics are susceptible to alterations. Biological activity alterations show up in:

1) deactivation, i.e. a loss of medicinal or biological activity of drugs;
2) activation, i.e. induced activity of an inactive preparation;
3) modification of the major effect, i.e. when the administered drug, on having metabolized, exhi-bits properties different from those of the initial preparation.

The alterations of toxicity are manifested in:

1) deintoxication, i.e. a loss or reduced toxicity of drug;
2) toxification, i.e. enhanced toxicity of drug.

The above instances may be exemplified as follows:

Deactivation is observed as the functional groups responsible for the biological activity of a drug are either eliminated from, or blocked in the drug molecule. For example, the active sulphanilamide, after its conjugation with acetyl-ScoA, is converted to an inactive acetylsulphanilamide.

Activation is observed when the biologically active groups that have been blocked in the initial preparation become deblocked during metabolism:

Phthalsulphathiazole (inactive drug) → hydrolysis → Sulphathiazole (active drug) + Phthalic acid

or acquire functional groups that are necessary for eliciting the drug activity:

Benzopyrene (inactive procarcinogen) → hydrolysis → Hydroxybenzopyrene (carcinogen)

Modification of the major drug effect manifests itself as a variant of activation. For example, codeine (morphine 3-methyl ether) exhibits mainly antitussive and mildly analgesic action. When codeine undergoes demethylation in the organism, it converts to morphine, which is a strong analgetic.

Deintoxication resembles deactivation and is a defense reaction to the toxic effect of a drug. For example, phenol is a toxic compound, while phenol sulphate, which is a product of phenol conjugation in the organism, is nontoxic.

Toxication shows up as an enhanced side effect due to a drug administered into the organism. By mechanism, toxification resembles activation. Occasionally, toxification is produced by “lethal” molecules synthesized from the introduced compounds during their metabolism in the organism. The lethal synthesis with the involvement of a xenobiotic leads to a metabolic block and to the death of organism. For example, the administered fluoroacetate enters the Krebs cycle in tissues to produce a toxic product, fluorocitrate, which blocks aconitate hydratase and interrupts conversion steps in the Krebs cycle. Toxification effects are taken into account in the development of chemicals against rodents and other vermin.

Localization of drug metabolism in the organism.

Depending on the site of conversion of biogenous preparations and xenobiotics in the organism, the drug metabolism is classified into cavitary (enteral), extracellular (humoral), and cellular, or tissue, types of metabolism.

The cavity, or enteral, drug metabolism is effected by hydrolytic enzymes supplied to the cavity of gastrointestinal tract. Hydrolysis of biogenous preparations occurs with the involvement of pancreatic and intestinal digestive enzymes. Xenobiotics whose molecules contain peptide, carboxyester, glycoside, amide and phosphamide bonds are also liable to

hydrolysis. This process involves proteolytic and lipolytic enzymes as well as enzymes capable of hydrolyzing glycoside bonds. In addition, a large group of esterases (e.g. carboxyesterases and phosphatases) and phosphamidases (involved in hydrolysis of phosphamide bonds in drugs) are found in the intestine. Trypsin, while being a proteolytic, exhibits also an esterase activity and is capable of hydrolyzing the ester bonds in xenobiotics.

Extracellular, or humoral, drug metabolism takes place in the extracellular fluids (after uptake and subsequent circulation of a drug in the organism), i.e. in the blood, lymph, cerebrospinal, and extracellular proper, fluids. Possibly, metabolic conversions therein are chiefly confined to hydrolysis of the preparations delivered (both biogenous and xenogenous). In the blood and other fluids, this function is performed by proteinases and esterases (e.g. pseudocholine esterase, phosphatases). In the extracellular fluids, other enzymes, for example, alcohol dehydrogenase, aminooxidases, etc., are available in small amounts, but the activity of these enzymes is rather low. The contribution of the humoral metabolic link to the overall drug metabolism is insignificant. At the humoral level, drug hydrolysis plays a role in drug inactivation; this metabolic link should be taken into account.

Cellular (tissue) drug metabolism. In the cells, the whole varieties of metabolic transformations, including those of xenobiotics, are being accomplished. However, the substances, before being subjected to the action of enzymic systems, should be transported from the site of their introduction to the cells and allowed to penetrate the intracellular space through the cell membrane. Xenobiotics are transported by the same mechanisms as biogenous substances. In the blood plasma, they either become dissolved in the liquid medium, or adsorbed, mostly on albumin. In a dissolved or in a protein-bound state, xenobiotics are delivered to the cells (tissues). They gain access to the cells mostly by simple and facilitated diffusion; large molecules enter the cells by endocytosis. Xenobiotics synthetically derived from biogenous substances can be actively transported across the cell membranes using natural substance transport systems.

Not all the tissues and organs are equally active when they convert xenobiotics. The most actively engaged organ is liver which is in possession of enzymes that perform modification and conjugation of drugs. The other organs and tissues are less active in the metabolism of xenobiotics.

The metabolic conversion of xenobiotics occurs in various organelles of the liver cells. The most powerful metabolic system is found in endoplasmic reticulum (in microsomes). The microsomes are fragments of endoplasmic reticulum that are formed, for example, on trituration of a tissue sample and spontaneously close into small bladder-like structures (vesicles). Thus, with reference on its localization, the metabolism of xenobiotics is differentiated into microsomal and extramicrosomal. The extramicrosomal metabolism occurs in hyaloplasm, lysosomes, peroxisomes, and mitochondria.

The enzymic reactions conducive to conversion of xenobiotics may be divided into the following major groups: 1) oxidation-reduction reactions; 2) hydrolytic reactions 3) synthetic reactions, or conjugation reactions; 4) other reactions (isomerization, ring opening, etc., which are effected by isomerases and lyases).

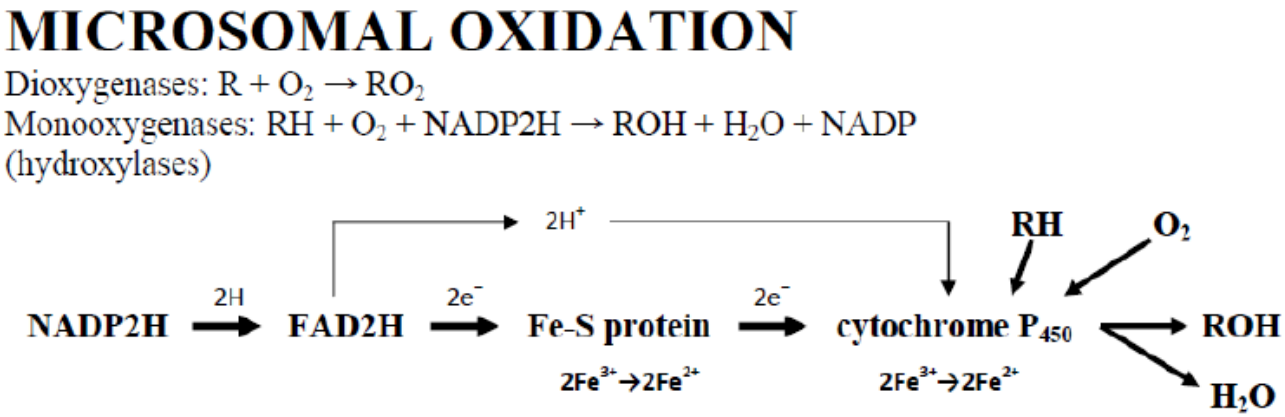
Microsomal oxidation of substances.

In the microsomes, there are found enzymic chains for oxidation of substances. These chains are represented by two short electron-proton transfer chains built into the membranes of endoplasmic reticulum or into microsomal membranes. Microsomal oxidation is connected with these chains. One of these chains is a monooxigenase oxidation chain (in which the source of electrons and protons is reduced NADP), and the other is a reductase

oxidation chain, with reduced NAD as a supplier of electrons and protons. The source of $NADPH^+$ in the monooxigenase chain is the pentose phosphate cycle, and the source of $NADH^+$ is glycolysis.

The microsomal $NADPH^+$-dependent monooxigenase chain is composed of flavoprotein (FP2), with FAD for a coenzyme, and cytochrome P_{450}. Flavoprotein exhibits a $NADPH^+$-dehydrogenase activity, FAD acting as an acceptor for two protons and two electrons. From flavoproteins, electrons are transported onto cytochrome P_{450}, and protons are lost into the environment (cytosol). Cytochrome P_{450} is the terminal self-oxidizable link of this chain. Like all the cytochromes, it belongs to hemoproteins. Its protein moiety is represented by a single polypeptide chain. The molecular mass of cytochrome P_{450} is about 50,000. The P_{450} is capable of complexing with carbon monoxide, CO. The light absorption maximum for these complexes is at 450 nm; hence the name for the given cytochrome.

Cytochrome P_{450} performs a dual function: it activates molecular oxygen by transferring electrons onto it, and uses the activated oxygen to oxidize substances R, with the concomitant formation of water. Consequently, one oxygen atom adds to the oxidizable substance (RO), and the other, by accepting two H^+ ions from the medium, makes up water.
The $NADH^+$-dependent reductase oxidation chain occurs not only in the microsomal membranes; it is also available in the outer mitochondrial membrane, in the nuclear membrane, and in the erythrocytic cell membranes. The reductase chain is thus included among the most rapid reactions of biological oxidation, but its function in the cell remains still unclear. The self-oxidizable component of this chain capable of activating the oxygen has never been identified either; quite probable that this function is exercised by cytochrome P_{450} itself. The $NADPH^+$- and $NADH^+$-dependent chains can exchange electrons. For example, the electrons from FP2 and cytochrome b5 may be transferred onto cytochrome P_{450} to be used in the oxidation of substrates.



Cojugation of xenobiotics, its mechanism and role.

The conjugation stage, or synthetic stage, is essential for the formation of nontoxic and easily excretable drug metabolites. By their mechanism, the conjugation reactions are divided into two groups:

Reactions of I type. Initially, conjugating agents, i.e. biomolecules, are activated and then transferred onto xenobiotics to form conjugates. This type of conjugation reactions occurs in all tissues of the organism.

Reactions of II type. Initially, a xenobiotic is activated to be transferred onto a conjugating biomolecule to form a conjugate. This conjugation type is of rare occurrence and is only observed in liver and kidney.

Various groups for conjugation reactions of I and II types are distinguished, depending on the nature of a conjugating species involved. In the I type reactions, glucuronide, sulphate, acetyl, methyl, thiosulphate conjugations are to be noted, and in the II type, glycine and glutamine conjugations.

Glucuronide conjugation. UDP-glucuronic acid is the source for glucuronic acid residues in this process. Endogenous substances and xenobiotics are subject to glucuronide conjugation (known are glucuronides of bilirubin, steroid hormones, vitamin D, etc.). Xenobiotics can enter glucuronide conjugation if they possess or have acquired, during modification, a hydroxyl, carboxyl, and amino group (commonly, in the aromatic ring), or, at least, a SH-group. The conjugation reaction proceeds with the participation of UDP-glucuronosyltransferase by the scheme:

$$RXH + UDP{\sim}C_6O_9O_6 \rightarrow UDP + RX\text{-}C_6H_9O_6$$

Among xenobiotics (drugs and poisons), susceptible to glucuronide conjugation are phenols, polyphenols, phenolic steroids, aromatic amino acids, and others.

Sulphate conjugation. Active form of a conjugating agent is 3'-phosphoadenosine-5'-phospho-sulphate (PAPS for short). PAPS, which may also be designated as $PAP{\sim}SO_3H$, is a source of labile sulphate groups used in the conjugation of natural compounds and xenobiotics. The natural substances as subject to sulphate conjuation include endogenous toxic products, e.g. indole, scatol, phenol as well as steroids, iodothyronines, tocopherols, and others. The sulphate conjugation reaction proceeds with the involvement of a special enzyme, sulpho-transferase, according to the scheme:

$$RXH + PAP{\sim}SO_3H \rightarrow RX\text{-}SO_3H + PAP$$

Acetyl conjugation. The source of labile acetyl groups in this variety of conjugation reactions is acetyl~ScoA, which is produced by degradation of carbohydrates, triacylglycerides, and amino acids. Endogenous substances and xenobiotics containing a free NH_2 group may be acetylated.

N-acetylation is an essential biochemical reaction in the synthesis of monosaccharide derivatives (N-acetylglucosamine, N-acetylgalactosamine, and neuramic acid) that are further used in the synthesis of heteropolysaccharides. N-acetylation is also a route to neutralization of biogenous amines: serotonine, histamine, GABA, and others. N-acetylation of histones and nonhistonic chromatin proteins is an important regulatory mechanism of DNA transcription. For endogenous substances, the only case of O-acetylation has been reported, which is a reaction of acetylcholine formation.

Xenobiotics possessing a free NH_2 group (commonly, on the aromatic ring) are subject to acetylation. This reaction is effected by means of a special acetyltransferase called arylamine-N-acetyltransferase. This enzyme exhibits a low specificity to xenobiotics to be acetylated. The reaction proceeds by the scheme:

$$RNH_2 + CH_3\text{-}CO{\sim}SCoA \rightarrow R\text{-}NH\text{-}CO\text{-}CH_3 + CoASH$$

Among the xenobiotics susceptible to acetylation, sulphanylamides, isonicotinic acid hydrazides, and aniline derivatives can be mentioned; these preparations are widely used in medical practice.

Methyl conjugation. In this reaction methyl groups derived from the active form of methionine, S-adenosylmethionine, serve as a conjugating agent. S-adenosylmethionine is a participant in numerous reactions of methylation of endogenous compounds. It is also a methyl group donor for conjugation reactions of xenobiotics (RXH), which proceed with the involvement of methyltransferases, ac-cording to the scheme:

$$RXH + S{\sim}Adenosylmethyonine \rightarrow RX\text{-}CH_3 + S{\sim}Adenosylhomocysteine$$

Xenobiotics containing an NH_2 group or heterocyclic nitrogen, as well as OH and SH groups, are subject to methylation by addition of methyl groups to N, O, and S atoms. Among the preparations used in therapy, liable to methylation are mono- and polyphenols, and heterocyclic compounds of pyridine, quinoline, isoquinoline, and thiouracil type.

Thiosulphate conjugation. This kind of conjugation is used in the enzymic detoxication of cyanides. The transfer of sulphur from thiosulphate onto a cyanide ion is catalyzes by a specific enzyme, thiosulphatesulphide transferase:

$$CN^- + S_2O_3^{2-} \rightarrow SCN^- + SO_3^{2-}$$

Glycine conjugation. This reaction belongs to type II conjugations, which require a prior activation of the substrate rather than of the conjugating agent. In principle, any carboxylic acid can serve as a conjugation substrate. The mechanism of glycine conjugation may be exemplified by the formation of hippuric acid. According to the mechanistic concept of type II conjugation reactions, the initial step is activation of benzoic acid with the involvement of arylacyl~ScoA synthetase. Then benzoyl (or, in a wider sense, any activated substrate in the reactions of this type) is transferred onto the glycine amino group. This process is catalyzed by acyl-N-glycine transferase, which is specific to acylation of only glycine, barring other amino acids.

Similarly, glycine conjugates of other compounds are formed: aromatic acids (nicotinic), phenyl-substituted acetic acids (phenylacetic and hydratropic), steroid acids (cholic and deoxycholic).

Glutamine conjugation is a rare variety of conjugation, distinctly observable in patients with phenylketonuria. In normal humans, the glutamine conjugation of xenobiotics has never been reported.

To detoxify heavy metals, the liver contains **metallothioneins**, a group of cysteine-rich proteins with a high affinity for divalent metal ions such as Cd^{2+}, Cu^{2+}, Hg^{2+},and Zn^{2+}. These metal ions also induce the formation of metallothioneines via a special metal-regulating element (MRE) in the gene's promoter.

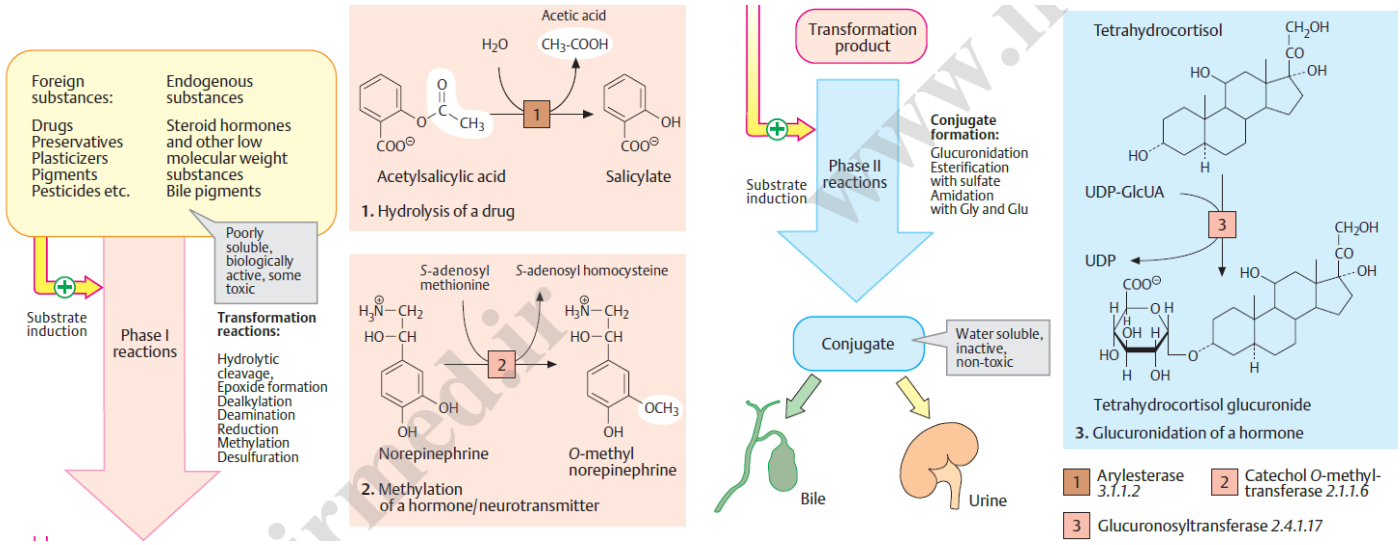


Figure 20. Biotransformations (Koolman, 2005)

Factors affecting drug metabolism.

Drug metabolism is affected by a variety of factors. These include genetic, age- and organ-specific, neuroendocrine, environmental factors, and the manner a drug has been administered. The rate at which a drug supplied to the organism is metabolized is dependent

on the number of enzymes involved in modification and conjugation of the drug. In enzymophathies associated with defective enzymes that are involved in drug metabolism, a decrease in the drug metabolism rate is observed. Molecular diseases due to a defective UDP-glucuronosyltransferase are known. These molecular diseases are characterized by the disturbed glucuronide conjugation not only of bilirubin, but of other endogenous substrates and drugs too. For this reason, the prescription of sulphanilamides, salicylates, and phenol-derived preparations, which are metabolized by glucuronide conjugation, leads to aggravated symp-toms of the disease; even normal doses of these drugs produce a negative effect.

The age is an important factor in drug metabolism. In neonates and infants, the enzymic apparatus of xenobiotic metabolism is poorly developed. As the young organism develops, the physiological enzymic deficiency disappears, while hereditary enzymopathies in adult humans persist.

Liver is the major organ responsible for drug metabolism. Environmental factors such as light, ambient temperature, radiation have been noted to influence the drug metabolism. The action of these factors is accomplished indirectly, via the neuroendocrine system. Over 200 preparations are known to be drug metabolism enzymes, primarily microsomal ones. They include butadion (antiinflammatory), amidopyrine (analgesic), novocain (local anesthetic), ethanol, and others. Phenobarbital (soporific) acts as the most powerful inducer. It drastically enhances the synthesis of microsomal oxidation enzymes in the liver by affecting the genetic apparatus of the liver cells. Phenobarbital elicits the synthesis of UDP-glucuronosyltransferase and facilitates the conjugation stage in the metabolism of various materials.

Inducers for drug metabolism enzymes are biogenic preparations such as thiamine, riboflavin and their coenzymes, carnitine, pantothenic acid, androgens, and anabolic steroids; preparations of progesterone and estrogens inhibit these enzymes.

Ethanol toxicity and its metabolism

The major site of ethanol degradation is the liver, although the stomach is also able to metabolize ethanol. Most of ethanol is initially oxidized by alcohol dehydrogenase to form acetaldehyde. A further oxidation, catalyzed by aldehyde dehydrogenase, leads to acetate. Acetate is then converted with the help of acetate-CoA ligase to form acetyl-CoA. In addition to cytoplasmic alcohol dehydrogenase, catalase and inducible “microsomal ethanol-oxidizing system” also contribute to a lesser extent to ethanol degradation. The rate of ethanol degradation in the liver is limited by alcohol dehydrogenase activity. The calorific value of ethanol is 29,4 kJ/g. Alcoholic drinks – particularly in alcoholics – can therefore represent a substantial proportion of dietary energy intake.

Toxicity of ethanol.

Ethanol is rapidly distributed throughout the body. A large amount is taken up by muscles and brain. In the brain, ethanol is deposited in membranes and influences receptors for neurotransmitters. The effect of GABA is enhanced, while that of glutamate declines. High ratio of NADH/NAD^+ facilitates the conversion of pyruvate into lactate, acetoacetate into β-hydroxybutyrate, biogenic amines into alcohols, the shifting acid-base balance to acidosis. Accumulation of lactate increases renal threshold for uric acid. The increase [lactate]/[pyruvate] ratio leads to gluconeogenes isinhibition and to hypoglycemia development. Ethanol inhibits the metabolism of some drugs in liver (for example, barbiturates), because it competes with them for P_{450}.

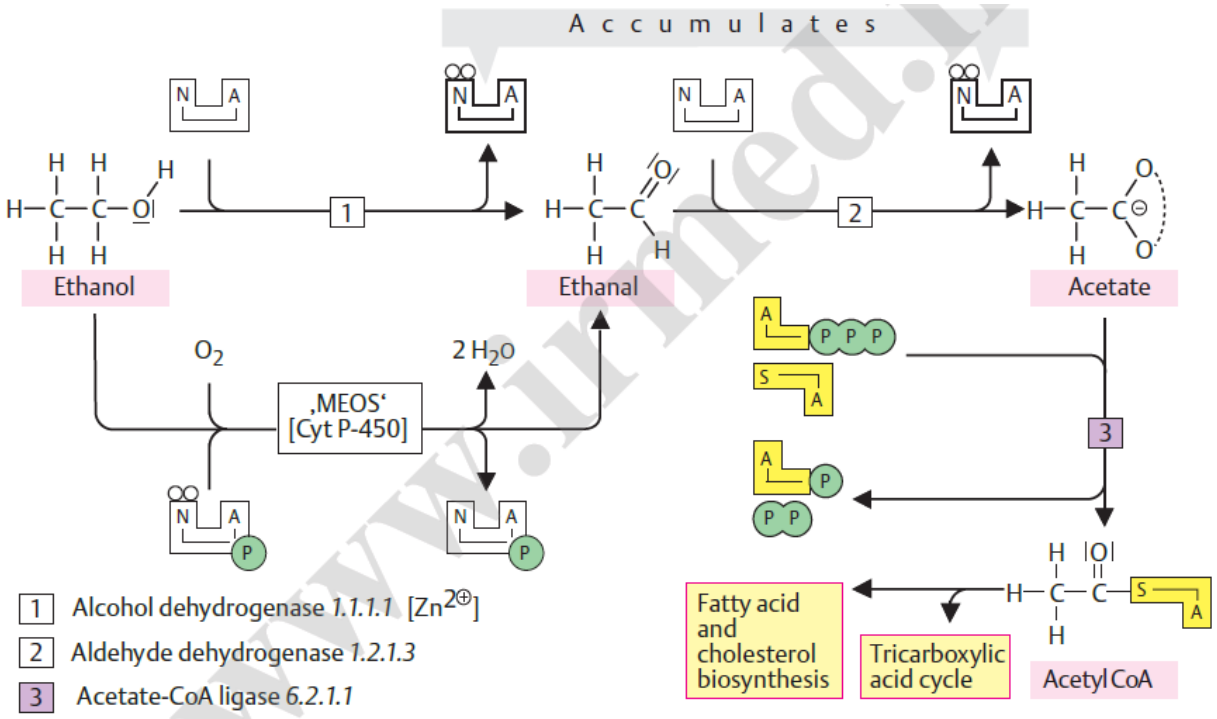


Figure 21. Ethanol metabolism (Koolman, 2005)

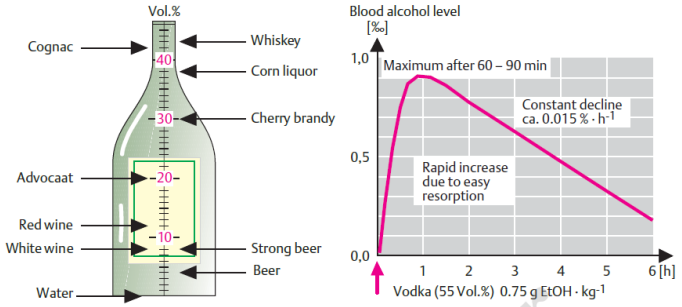


Figure 22. Blood ethanol level (Koolman, 2005)

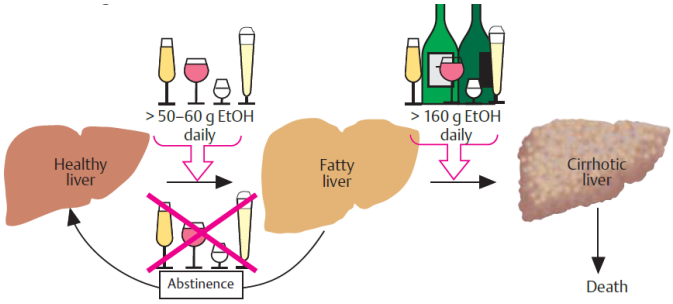


Figure 23. Liver damage due to alcohol (Koolman, 2005)

High ethanol consumption over many years leads to liver damage. Ethanolrelated high levels of NADH+H$^+$ and acetyl-CoA in the liver lead to increased synthesis of neutral fats and cholesterol. However, since the export of the form VLDLs is reduced due to alcohol, storage of lipids occurs (fatty liver). The increase in the fat content of the liver (from less than 5% to more than 50% of the dry weight) is initially reversible. But in chronic alcoholism hepatocytes are increasingly replaced by connective tissue. When liver cirrhosis occurs the damage of the liver finally reaches an irreversible stage, characterized by progressive loss of liver functions. Acetaldehyde, which is about 15 times more toxic than alcohol, enters into condensation reactions with biogenic amines to form endogenous alkaloids. Acetaldehyde together with dopamine leads to the formation of salsolinol as well as tetrahydropapaveroline and β-carbolines. They bind with opiate receptors, causing hallucinations, stimulation of "enjoyment" centre. This explains the development of pathologic attraction to alcohol. Competitive inhibition of acentaldehyde dehydrogenase (for example, disulfiram) blocks the breakdown of acetaldehyde. The simultaneous intake of alcohol and disulfiram leads to increased acetaldehyde levels in the blood. This results in perspiration, tachycardia, nausea, vomiting and even severe circulatiry failure.

CHAPTER 3. BIOCHEMISTRY OF KIDNEYS AND URINE. WATER-MINERAL METABOLISM.

Functions of the kidneys. Filtration, secretion, reabsorption, excretion. The mechanism of urine formation. Renal clearance.

In the adult human organism the mass of the two kidneys is about 300g. The primary function of the kidney is to provide for a constancy of the internal medium of the organism. Two zones are distinguished in the renal tissue:

1) the outer, or cortical, zone colored brown-red;
2) the inner, or medullary, zone colored lilac-red.

The basic functional unit of renal parenchyma is the nephron. In humans, the two kidneys number about 2 million nephrons.

In the nephron three major processes occur:

1) filtration at the glomerulus;
2) tubular reabsorption;
3) tubular secretion.

Glomerular filtration.

Glomerular filtration is a passive process. The total renal blood flow is about 1300 ml/min in adult human males. In health, the mean filtration rate is 125 ml/min. The filtration rate is determined by the filtration pressure:

$$FP = CP – (OP + Caps\ P),$$

where FP – filtration pressure, CP – capillary pressure, OP – oncotic pressure,

Caps P – intracapsular pressure.

In health FP ~ 30 mm Hg.

Capillary pressure within the kidney is dependent not so much on the arterial pressure as on the lumen ratio of the ″afferent″ and ″efferent″ glomerular arterioles. The efferent arteriole is narrower (by about 30% in diameter) than the afferent arteriole. The lumen ratio regulation for these arterioles is effected primarily by the kinin system.

The primary urine, practically devoid of proteins, is produced by ultrafiltration of the blood plasma into the lumen of Bowman's capsule. In health, proteins as colloid particles are incapable of penetrating the capsular cavity of the glomerulus through the capillary wall. Approximately 180 L of primary urine is produced. The pores in the glomerular basal membrane, which are made up of type IV collagen, have an effective mean diameter of 2,9 nm. This allows all plasma components with a molecular mass of up to about 15kDa to pass through membrane. At increasing masses, molecules are progressively held back; at masses greater than 65 kDa, they are completely enable to enter the primary urine. This applies to almost all plasma proteins – which in addition, being anions, are repelled by the negative charge in the basal membrane.

Reabsorption and Secretion.

Only 1% of the total fluid, filtrated in the glomerulus, is converted into urine. 99% of water, sodium chloride, hydrocarbonate ions, amino acids, 93% of potassium ions and 45% of urea are reabsorbed in the renal tubules. The cells of the proximal segment of the nephron reabsorb glucose, amino acids, vitamins and electrolytes, 6/7 of the fluid constitutive of the primary urine is also subject to reabsorption in the proximal tubules. In the tubule, organic substances (e.g., glucose, amino acids, lactate and ketone bodies) are recovered by secondary active transport. There are several group-specific transport systems for resorbing amino

acids, with which hereditary diseases can be associated (eg, cystinuria, glycinuria and Hartnup's disease).

Additional regulated reabsorption of water, Na^+ and Cl^- occurs in the distal tubules. These processes are controlled by hormones (aldosterone, vasopressin). In the distal tubules potassium, ammonium, hydrogen ions may be secreted into the lumen of the nephron.

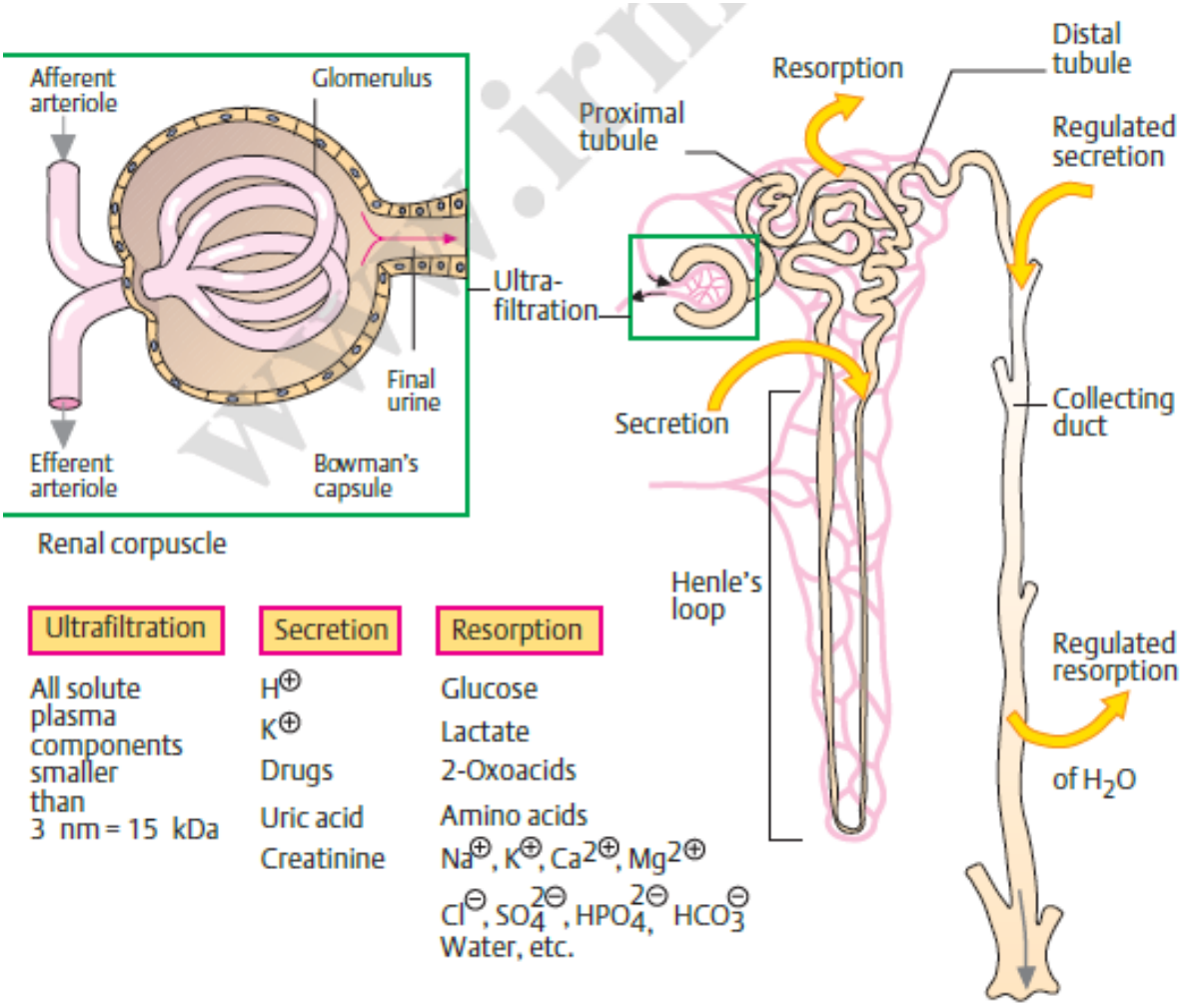


Figure 24. Urine formation (Koolman, 2005)

Renal clearance is used as a quantitative measure of renal function. It is defined as the plasma volume cleared of a given substance per unit of time. Inulin, a fructose polysaccharide with a mass of 6 kDa that is neither actively excreted nor reabsorbed but it freely filtered, has a clearanse of 120 mL/min in healthy individuals.

Sodium ions penetrate from the tubular lumen into the cell by passive transport and they are transported from cells to the extracellular fluid by means of Na^+-pump. About 80% of the ATP energy in channel's cells is spend on the Na^+- pump.

The water uptake in the proximal segments is effected passively, assisted by the active absorption of sodium ions.

Functions of kidney.

They include: the regulation of water and salt balance; the maintenance of acid-base balance; the maintenance of osmotic pressure; the removal of final products of metabolism; metabolic function; hormonal function.

Metabolic function. Specific features of renal tissue metabolism. Kidney uses at least 8-10% of the total oxygen consumed by the human organism. Concentrating urine and

transporting it through membranes are processes that require large amounts of energy. The kidneys therefore have very high energy demands.

In the proximal tubule, the ATP needed is obtained from oxidative metabolism of fatty acids, ketone bodies, and several amino acids. To a lesser extent, lactate and glycerol are also used. In the distal tubule and Henle's loop, glucose is the main substrate for the energy metabolism. The endothelial cells in the proximal tubule are also capable of gluconeogenesis. The substrates for this are mainly carbon skeletons of amino acids. Their amino group is used as ammonia for buffering urine. Enzymes for peptide degradation and the amino acid metabolism occur in the kidneys at high levels of activity (e.g., amino acid oxidases, amine oxidases, glutaminase).

The first stage of creatine synthesis is performed in the renal and pancreatic tissues. Glycine amidinotransferase (or arginine-glycine transamidinase) catalyzes this reaction. The observation of this enzyme in the blood may be linked either to a renal disease or to pancreonecrosis. Hydroxylation of 25-hydroxycholecalciferol occurs in kidney.

Hormonal function. The kidney plays an important role as an incretory (endocrine) organ. The juxtaglomerular cells, located in the region of the vascular pole of the glomerulus, produce rennin. Rennin, through the agency (see water-salt metabolism) of angiotensin, exerts influence on the blood pressure of the whole organism, and on the production of aldosterone and ADH. The kidney also elaborates erythropoietin which stimulates the red blood cell production (erythropoiesis). Erythropoietin is a glycoprotein hormone. Its biosynthesis in the kidney is activated in a number of stress states – hypoxia, loss of blood, shock etc. The kidney produces prostaglandins, which are capable of influencing the responsiveness of the renal cells to the action of certain hormones.

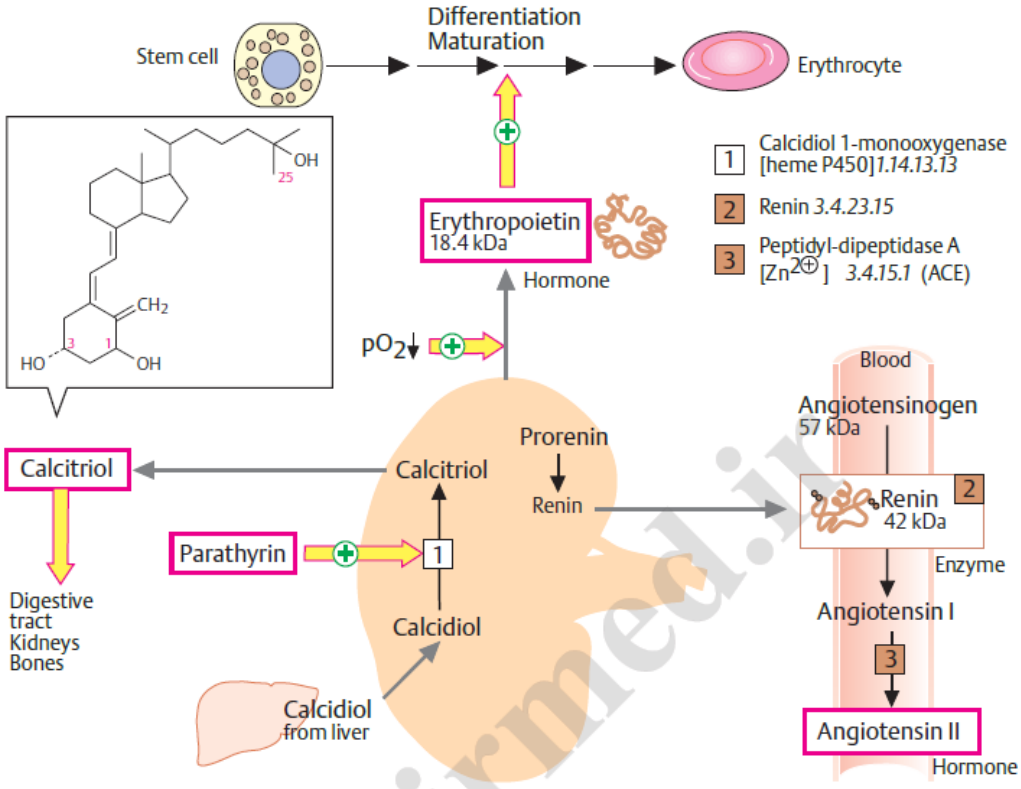


Figure 25. Renal hormones (Koolman, 2005)

Role of kidney in maintenance of osmotic pressure is provided by means of rennin-angiotensin system. In addition to this, kidney is the target of aldosterone and ADH action. 3 main mechanisms:

1) Secretion of hydrogen ions; and formation and conversion of carbonic acid.

2) Sodium ions reabsorption and conversion of disubstituted phosphates to monosubstituted phosphates. In blood monosubstituted-to-disubstituted phosphate ratio is 1:4; in glomerular filtrate 9:1; in urine of the distal segment of the nephron 50:1.

NaH_2PO_4/Na_2HPO_4 = 1/4 (blood) = 9/1 (glomerular filtrate) = 50/1 (urine)

3) Renal production of ammonia and its use instead of other cation for neutralization of acid equivalents and their urinary discharge.

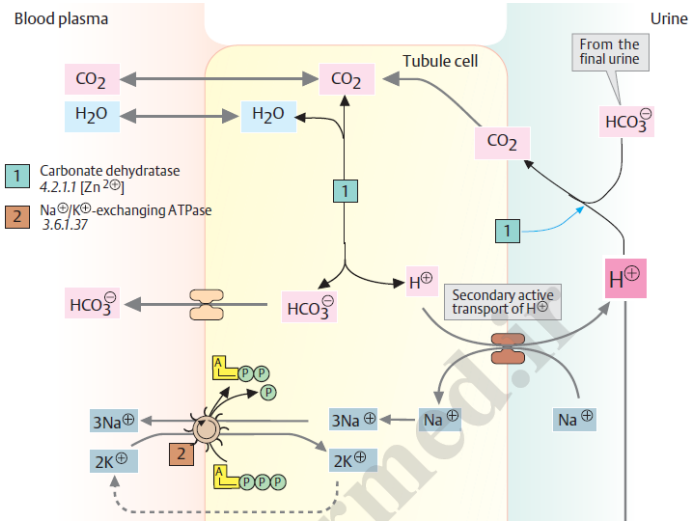


Figure 26. Proton secretion (Koolman, 2005)

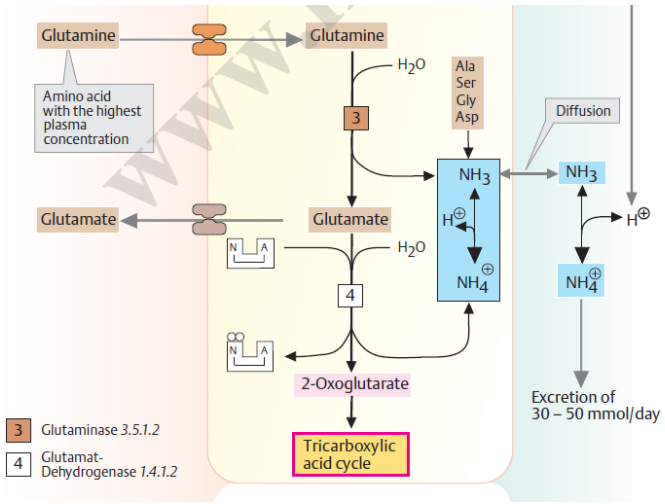


Figure 27. Ammonia excretion (Koolman, 2005)

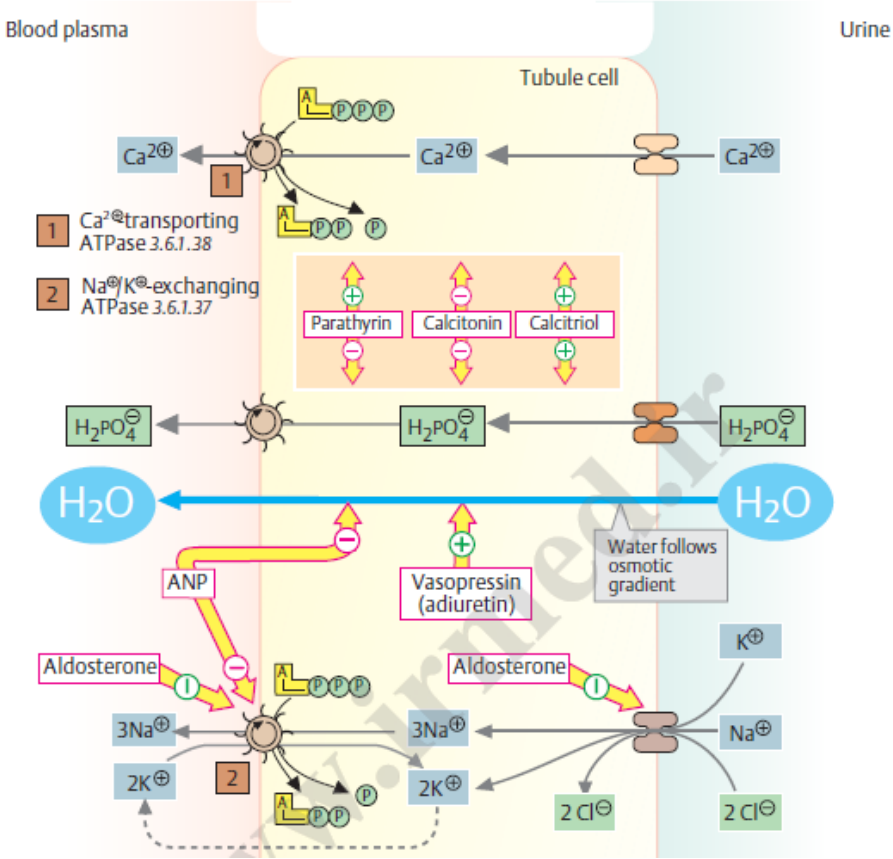


Figure 28. Electrolyte and water recycling (Koolman, 2005)

Inulin/creatinine clearance.

The measurement of the glomerular filtration rate (GFR) (volume of fluid filtered from the afferent arteriole into the renal corpuscle per unit time) allows clinicians to determine the health of the kidneys and to quantify any degree of kidney or renal failure. GFR is most accurately measured by injection of inulin into the bloodstream, a polysaccharide molecule from plants, which is neither reabsorbed nor secreted by the kidney. A more practical method of estimating GFR, though, is to measure blood creatinine, a molecule derived in muscle from the breakdown of creatine phosphate, a rapidly available source of adenosine triphosphate (ATP) energy for muscle and brain. Creatinine is exclusively excreted by the kidneys, completely filtered at the renal corpuscle, and only small amounts are secreted into the peritubular capillaries. The natural occurrence of steady levels of creatinine in the blood and urine offers an easy way to establish GFR and, therefore, kidney function. Varying mathematical formulas allow for correction of known variations depending on the patient's muscle mass, age, gender, race, and/or size. The normal range of GFR is (100-130) ml/min/1.73 m2 but this varies in children and older adults. A GFR of over 60 ml/min/1.73 m2 is usually sufficient for normal health, although high blood pressure, diabetes, and other chronic diseases can decrease kidney function and result in chronic kidney disease (CKD). CKD is enumerated in six stages, depending on the patient's GFR.

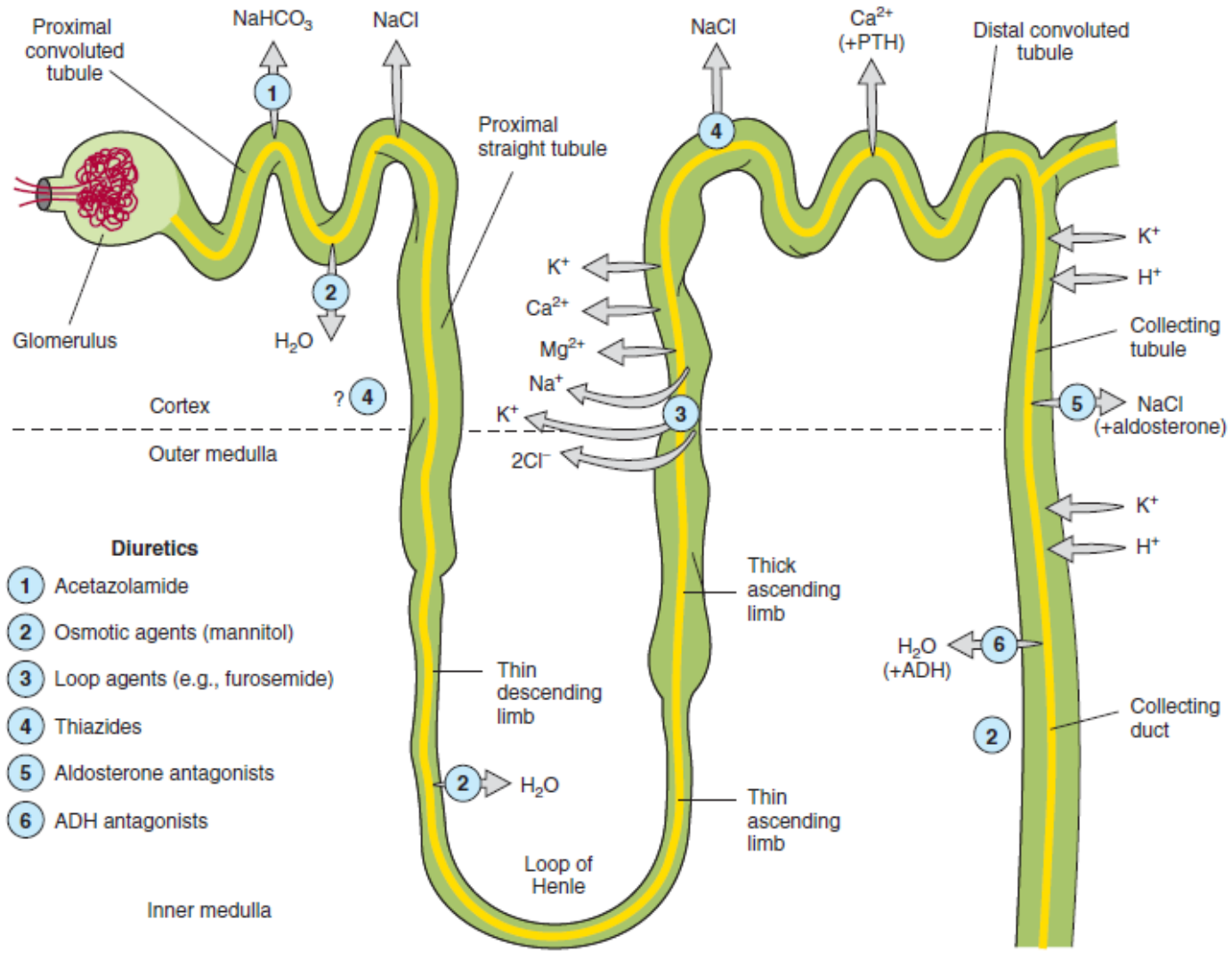


Figure 29. Overview of nephron and urine production (Janson. 2012)

Physical and chemical properties of urine.
Composition of urine under normal and pathological conditions.

Physico-chemical properties of urine.

Daily urine (diurnal diuresis): 1000-2000 ml (1500 ml). Pathologic state: <500 ml and >2000 ml. **Polyuria** (increased excretion of daily urine): after large fluid intake; after dietary intake of nutrients stimulating diuresis (eg. water melon and pumpkin).

Pathologic polyuria: in renal diseases (chronic nephritides and pyelonephritides), diabetes mellitus, diabetes insipidus (up to 15 liters).

Oligouria (diminished excretion of daily urine): in insufficient fluid intake, in febrile state, vomiting, toxicosis, acute nephritis. **Anuria** is complete or nearly complete suppression of urinary excretion: in severely affected renal parenchyma, ureteral obstruction.

In health, the urinary excretion is larger in the day time than at night. The diuretic day-to-night ratio varies from 4:1 to 3:1. In certain pathologic states (early stages of cardiac decompensation, cystopielitis) the passage of urine is larger at night than during the day. This state is known as **nycturia.**

Color. Normal urine is yellow. Colorless urine is under diabetes insipidus, excessive drinking, taking diuretics. **Red ("meat slops") color** is caused by **hematuria.** Hematuria can be renal (as symptom of glomerulonephritis, trauma, nephrolytiasis) and extrarenal (under cystitis and uretritis). Red color of urine is also observed at porphyria and hemoglobinuria. **Orange color** is observed after taking several vitamins. **Red-violet** color occurs after beet eating. **Green color** is the sign of increasing putrefaction processes in intestine, after ingestion of rhubarb. **Color of dark beer** is examined under hepatitis. Blue color is observed after ingestion of methylene blue or as a sign of Hartnup disease. **Black urine** is present in patients with alkaptonuria.

Odour. Normal urine shows the characteristic smell or smell of "meat broth". Ammonia odour occurs under hyperammoniemia. Aceton smell is observed in diseases which are accompanied by accumulation of ketone bodies. "Mouse or mould" smell shows phenylketonuria. "Maple syrup" or "beer yeasts" smell is the sign of leucinosis (maple syrup urine disease). "Cabbage" or "cat's urine" smell occurs under tyrosinemia. The smell of rotted fish is present under trimethylglycinuria or dymethylaminuria. "Dirty socks" odour occurs under isovaleric aciduria.

Transparency. Normal urine is transparent. Muddy urine is observed at pyuria, hematuria, proteinuria, crystalluria, bacteriuria.

Density. The relative urine density in the adult human is liable to diurnal variation within a fairly wide range (from 1,002 to 1,035). Most commonly the urine density ranges from 1,017 to 1,020. Low density: in diabetes insipidus. High density: in acute nephritis, in diabetes mellitus.

Isostenuria – urine density is equal to that of the primary urine, or ultrafiltrate (~1,010). It is observed only in a severe renal insufficiency. The isostenuria indicates a disturbed concentration function of the kidney. This state has been recorded in chronic nephrites, "contracted kidney".

pH. The urine usually has a slightly acidic pH value (pH 5,3-6,5). However, the pH value is strongly affected by metabolic status. After ingestion of large amount of plant food, it can increase to over 7. In meat rich diet it is acidic. The decrease of pH is observed in febrile states; diabetes mellitus; in starvation The increase of pH is observed in cystitis, pyelitis, curative intake of alkaline mineral water.

Characterization of urine components in norm and in pathology.

The urinary excretion of various materials reflects alterations in the processes that occur in the kidney and other tissues and organs of the organism. The daily volume of final urine amounts to 1.0-2.0 liters and the dry weight of final urine is about 60 g. Since the urine is a filtrate of blood plasma, it appears expedient to consider the urinary concentrations of various groups of biological materials from the standpoint of their occurrence in the blood plasma.

Proteins. In norm, the daily urinary excretion of proteins amounts to about 30 mg, which is not detectable by common laboratory techniques and routinely specified as "traces, or absence of urinary proteins". Among the urinary proteins, enzymes are also present. The origin of normal urinary proteins is different.

In pathology, the urinary protein concentration may be increased; depending on the location of the damage, prevalent in the urine may be either plasmic proteins, or cellular proteins of the urinary tract. In inflammatory renal diseases (glomerulonephritides), the permeability of the basal membrane of nephron glomerulus increases; proteins are filtered in an amount above normal and fail to be reab-sorbed completely. Disturbances in the tubular protein reabsorption (nephroses) are conducive to a similar pathology. For this reason, in patients with glomerulonephritides and nephroses the urinary excretion of proteins may vary from 1 to 15-40 g per day. Nonetheless, even in such a contingency, the urinary proteins concentrations are small and can be detected only using special techniques. For example, in pancreatites, an enhanced activity of α-amylase and trypsin is observed both in blood and urine.

Nonproteinic nitrogenous urinary components.

Urea is a major nitrogenous component of the urine. The normal excretion of urea is 333 to 583 mmol per day, which accounts for 60% to 80% of the overall urinary nitrogen. An increased urinary concentration of urea is observed in the states with pronounced catabolism of proteins and other nitrogenous components (starvation, burns, traumatism, atrophy of tissues, etc.). A decreased excretion of urea is observed in affected liver (urea-producing organ) and in impaired in the blood (this state is called azotemia).

Uric acid. Normally, the urinary excretion of uric acid is 2.35 to 5.90 mmol per day. Its increased urinary concentration is observed in a diet rich in nucleic acids or as produced by breakdown of cells and tissues, for example, leucocytes in patients with leucosis.

Creatinine. In norm, the urinary excretion of creatinine is 4.4 to 17.6 mmol per day; variations in creatinine concentration are dependent on muscular development. Physiological excretion of creatinine is normal only in children. In adult humans, creatinuria is a sign of pathology (e.g. muscular dystrophy).

Amino acids. In norm, the urinary excretion of amino acids is 0.29 to 5.35 mmol per day (as based on nitrogen). The urinary concentrations of glycine, histidine, and alanine are higher than those of other amino acids. In pathology (e.g. burns, diabetes mellitus, affected liver, and muscular dystrophy) hyperaminoaciduria may occur. Heriditary hyperaminoaciduria is associated with defective proteins-carriers for amino acids in the proximal renal tubules. In a disordered amino acid tissue metabolism, the urinary excretion of normally nonexcretable amino acid metabolites occurs (e.g. homogentisine acid, in alcaptonuria; phenylpyruvic acid in phenylketonuria).

Ammonium salts. In norm, the urinary excretion of ammonia as a component of ammonium salts (ammonium chloride) is 30-60 mmol per day. In pathology, an increased urinary elimination of ammonium salts may be observed (in diseases accompanied by

acidosis). A diminished excretion of ammonium salts occurs in diseases associated with alkalosis, in renal diseases due to affected distal tubules in which ammoniogenesis takes place.

Hippuric acid. The urinary excretion of hippuric acid is dependent solely on the amount of ingested vegetable food, since in the organism this acid endogenically is not produced. Commonly, the daily urine contains to 5.5 mmol of hippuric acid.

Indican (indoxyl sulphuric acid). Normal urine contains indican (in the form of potassium indoxyl sulphate) in trace amounts. In detectable quantities, indican appears in the urine on excessive alimentary intake of meat products; it also occurs as a byproduct of putrefactive processes in the intestine.

Nitrogenous pigments. Representative of these is stercobilinogen, a product of hemoprotein breakdown. Stercobilinogen is convertible to stercobilin and normally is excreted in the urine. In pathology, urinary excretions contain bile acids and a variety of bile pigments, for example, in affected liver and in toxicoses conducive to hemolysis.

Nitrogen-free components of urine.

Glucose and other monosaccharides. In norm, the daily urine contains a more 0.3-1.1 mmol of glucose. Such amounts escape detection by conventional analytical techniques; for this reason, glucose is not reckoned as a component of normal urine. However, in excessive dietary intake of carbohydrates, when the glucose concentration in blood attains a threshold value, i.e. of the order of 8.3-8.8 mmol/liter, alimentary glucosuria may develop in the organism. In pathology, glucosuria occurs due either to an increased blood glucose concentration, or to a defective carrier protein involved in glucose reabsorption in the renal proximal tubules. The former case is the most commonly encountered in the clinic, for example, in diabetes mellitus or in steroid diabetes. The latter case is the so-called renal diabetes. For example, the occurrence of fructose or pentose in the urine (renal fructosuria or renal pentosuria) is indicative of affected transport systems of the renal tubules.

Lactic and pyruvic acids. In norm, the daily urinary excretions of lactic and pyruvic acids amount to 1.1 and 0.11 mmol, respectively. An increased concentration of lactic acid in the urine is observed under intensive muscular work and in hypoxia. An increased urinary excretion of pyruvic acid occurs in diabetes mellitus and in B_1 hypovitaminosis.

Ketone bodies. In norm, the daily urine contains 20 to 50 mg of ketone bodies. At this level, they are not detectable by the analytical methods currently employed in the clinic. In pathology, increased concentrations of ketone bodies, i.e. a state called ketonuria, occur in diabetes mellitus, steroid diabetes, and starvation.

Mineral salts. In norm, the daily urine contains (in mmol): sodium, 174-222; potassium, 61-79; calcium, 4.02-4.99; inorganic phosphorus, 33. In pathology, an increase in urinary excretion of sodium and a decrease in excretion of potassium are observed in the adrenal hypofunction; the reverse situation occurs in hyperaldosteronemia and when mineralocorticoids and glucocorticoids are prescribed as drugs. A decreased urinary concentration of calcium and a distinct phosphaturia are observed when large doses of vitamin D and parathyrin are administered; a high urinary loss of calcium is characteristic of rickets and hypoparathyroidism.

The biological role of water. Osmotic pressure. Disorders of water metabolism (dehydration, hyperhydration).

Water Metabolism. Structure features: Water molecule is dipole. Hydrogen bonds are formed between water molecules. This explains high boiling temperature and high thermal capacity of water.

Biological role of water:

1) Water is universal dissolvent. Water polarity provides good solubility of different substances and electrolyte ionization in water. Water is chemically inert, therefore substances dissolved in it keep their chemical and biological properties.
2) Water plays an important role in supporting unique structure and functions of cell organelles.
3) Water is obligatory component of biochemical processes. All the reactions in the organism are performed either in presence, or with participation of water.
4) Water performs transport function.
5) It participates in supporting osmotic pressure.
6)Water is an important thermoregulation factor.

Water content in organism. The total amount of body water is about 60-65% in adults, and 72% in newborns. The proportion of weight as water declines with age and with increased body fat content. By the age of 60 men have 51,5% of water and women 45,5% of it.

Body water distribution. Body water is distributed between 2 main compartments: **intracellular** and **extracellular**. Intracellular water comprises 70-72% of total body water of normal healthy adults. Extracellular water includes that of interstitial fluid and that of plasma, lymph, cartilage, etc. Major differences in composition between intracellular and extracellular fluids are the following:

1) Potassium is the principal cation within cells, whereas sodium predominates in extracellular fluid.
2) Because of many phosphorylated organic compounds are present within cells, phosphate is the primary intracellular anion, chloride replaces it in extracellular fluids.
3) Finally, the intracellular protein concentration is higher than that of blood plasma.

Water balance. Water is essential nutrient factor. A loss of 12-25% of water leads to death. In a normal healthy person, total body water volume remains remarkably constant, fluctuating less than 1% of body weight per day, and this constancy is maintained in spite of large variations in water intake. Daily water intake is 2,5-3 l. It depends on age, occupation, climate, diet, etc. Water need is higher in children, than in adults, namely: in children it is 100-150 g per kg of weight; in adults it is 30-50 g per kg.

Water sources:

1) Exogenic water is 85%. This is food and drinking water.
2) Endogenic water (15%). This is metabolic water.

The oxidation of 100 g of each carbohydrate, protein and fat yields 55.6; 41.3 and 107.1 g of water, respectively, but the total amount of metabolic water is quite small (200-400 ml per day) relative to that ingested in food or drink.

Water losses:

Water is required to replace fluid lost through the skin, lungs and gastrointestinal tract and to accompany renal excretion of urea, salts and other osmotically active substances. The amounts of these obligatory losses vary significantly with climate, activity level, state of health, and diet. Hot temperature, dry climate, vigorous physical activity and fever increase water losses from the skin and lungs. Great amount of water is secreted into gastrointestinal

tract with juices. Water secreted into the gastrointestinal tract is usually reabsorbed, but diarrhea and other intestinal diseases can result in very large water losses and organism dehydration. Total urine volume generally depends on water intake, but a minimum amount of water – an obligatory volume – is required to accompany the excretion of osmotically active substances especially urea, sodium chloride.

Regulation of water-salt metabolism.

Regulation of water-salts metabolism come to supporting: constant osmotic pressure; constancy of total water volume in organism and its distribution between different fluid spaces; constancy of ionic composition; acid-base balance.

Constancy of ionic composition is provided by means of systems of active transport.

Distribution of water between fluid spaces of the organism is generally determined by physico-chemical mechanisms. This process is influenced by the following factors:

1) Osmotic pressure. Gradient of molar concentrations between fluid spaces of organism is motive force of water current between them. Water will be transferred to water space with greater molar concentration.
2) Oncotic pressure. Decreasing protein content in blood plasma leads to edema.
3) Hydrodynamic pressure in vessels (is created by heart work).
4) Permeability of cell membranes.
5) Active biological transport of ions.

Regulation of total water volume constancy and osmotic pressure of blood is performed by neurohumoral way. Osmotic pressure of extracellular fluid in greater extent depends on [NaCl], therefore base mechanism of osmotic pressure regulation is linked with the change of excretion rate or water, or sodium chloride. Regulation of extracellular fluid volume is performed by simultaneous change of excretion rate both water and sodium chloride. Supply of water to the organism depends on the thirst sense. Center of thirst is located in dorsal and central nucleus of hypothalamus. The water excretion by kidneys is regulated by neurohumoral way with participation of antidiuretic hormone.

Antidiuretic hormone (vasopressin) is synthesized in special neurons of the hypothalamus from which it is transported to the posterior pituitary and is secreted directly in blood. This is nonapeptide. Vasopressin stimulates the contraction of the muscular tissue of blood vessels (the vasopressory action). However, its major function is water balance control. It stimulates the reabsorption of water in the renal tubules through the adenylyl cyclase system and increasing hyaluronidase activity. Vasopressin secretion is stimulated by increasing osmotic pressure and by considerable decreasing volume of extracellular fluid. It should be noted, that the system of osmotic regulation functions in very limited range: a change of osmolality by 1% only leads to vasopressin secretion, which corrects this change. With the blood volumstem get opposite signals (for examples, the loss of blood under hyponatremia conditions, it must be decreased about 7-15 % before similar response reaction is arisen. If both system get opposite signals (for examples, the loss of blood under hyponatremia conditions), a "volume" regulation prevails over osmotic regulation.

In pathology, for example, in atrophy of posterior pituitary, **diabetes insipidus** develops, a diseased state manifested by an excessive urinary water discharge. Vasopressin has important value for restoration of total volume of fluid in the organism. But increased reabsorption of water without sodium by vasopressin is little effective in restoration of extracellular fluid because 2/3 of reabsorbed water enters into intracellular space.

The regulation of sodium concentration is necessary to support the constancy of extracellular fluid volume. This regulation is performed by **aldosterone** and **sodium uretic**

factor. In kidney aldosterone increases the sodium ions reabsorption (together with chloride) in distal tubules. This leads to a delay of sodium chloride in organism. **In hyperaldosteronism** the surplus delay of sodium chloride leads to increasing osmotic pressure. This is a signal to vasopressin secretion. Vasopressin enhances water reabsorption in the kidneys. Accumulation of sodium chloride and water is observed. Extracellular fluid volume is increased. Under supporting normal osmotic pressure, blood pressure is increased.

The primary regulators of aldosterone production by the glomerulosa cells are the **renin-angiotensin system** and potassium. Sodium, neural regulation, ACTH, adrenoglomerulotropin (isolated from pineal gland) are also involved.

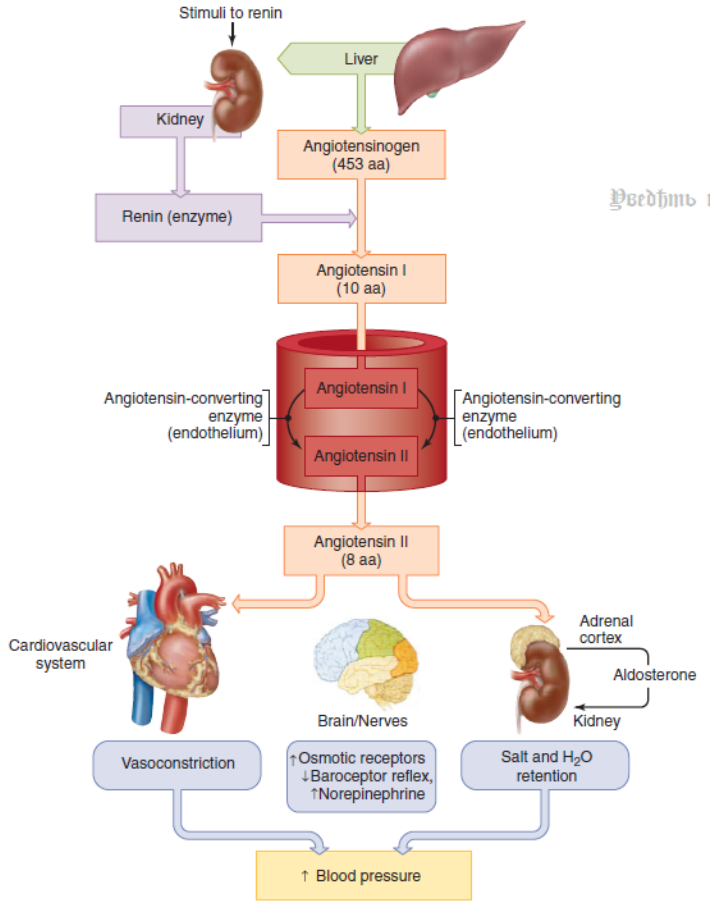


Figure 30. RAAS (Janson. 2012)

Main mechanism of the regulation of the aldosterone secretion is reninangiotensin system. **Renin** is proteolytic enzyme, which is synthesized in juxtaglomerular cells of the renal afferent arteriol. They are sensitive to blood pressure change, to change of Na^+ and Cl^- concentration in the renal tubular fluid. Any combination of factors, that decreases fluid volume or decreases NaCl concentration, stimulates rennin release. Renal sympathetic nerves that terminate in the juxtaglomerulas cells mediate the central nervous system effects on rennin release (through the β-adrenoreceptors). Renin is able to convert angiotensinogen (a_2-globulin, produced by liver) into decapeptide angiotensin I. Angiotensin-converting enzyme, a glycoprotein, removes two carboxyl terminal amino acids from the decapeptide angiotensin I to form angiotensin II.

Various nonapeptide analogs of angiotensin I and other compounds act as competitive inhibitors of converting enzyme and are used for treating renin-dependent hypertension. These are reffered to as angiotensin converting enzyme inhibitors. Converting enzyme also degrades bradikinin, a potent vasodilator; thus, this enzyme increases blood pressure in two distinct ways.

Angiotensin II increases blood pressure by causing vasoconstriction of the arteriole and is a very potent vasoactive substance. It is the potent stimulator of aldosterone production. It causes thirst. Angiotensin II inhibits renin release from the juxtaglomerular cells by feed-back mechanism.

Sodium uretic factor is synthesized by cells of auricle of the heart: 1) It stimulates excretion of sodium ions; 2) It shows vasodilatory effect; 3) It inhibits aldosterone synthesis; 4) It inhibits renin release.

Supporting of pH constancy. Acid-base balance is the relation between concentrations of hydrogen and hydroxyl ions in liquids of organism. Under normal conditions pH of blood is 7.35-7.45; pH of intracellular liquid is lower, than extracellular one, and pH value inside cells of different types may be different, but constant for the given type of cells. pH in different compartments of one type cell may be different. Difference of pH inside cells of various types and in various compartments of the given type of cells is explained by the features of metabolism, by mechanisms of active transport, by election permeability of membranes. Regulation of acid-base balance is achived by physico-chemical (buffer systems) and physiological mechanisms (lungs, kidney).

Water and mineral metabolism disorders.

Disturbances of water and mineral metabolism are distinguished into water and electrolyte imbalance (dishydrations) and disturbances of metabolism of separate minerals. Water imbalance is distinguished into:

1. Dehydration:
- primary (hyperosmolar, pure water depletion);
- secondary (hypoosmolar, pure salt depletion);
- mixed (isoosmotic, water and salt depletion).

2. Water intoxication (hyperhydration):
- total hyperhydration;
- intracellular hyperhydration;
- extracellular hyperhydration.

Primary dehydration (pure water depletion). Causes:
- inadequate water intake (coma, dysphagia etc.);
- in infants great amount of water practically without electrolytes may be lost through lungs in hyperventilation, fever, acidosis;
- excessive loss of water by kidney in diabetes insipidus.

Osmotic pressure in extracellular space is increased. Water flows from intracellular space to extracellular space. Intracellular dehydration develops. Symptoms: thirst, oligouria, hyperosmia, azotemia due to oligouria, hypernatremia.

Secondary dehydration (hypoosmolar). Causes: excessive sweating (mainly NaCl depletion); vomiting, diarrhea, duodenal fistules, cholera, etc.; Addison's disease; vigorous use of diuretics. From hypoosmolar extracellular space water flows to cells. This leads to intracellular edema. Symptoms: thirst is absent; dryness of skin; decreasing turgor of skin; headache; collapse.

Mixed dehydration (isoosmolar) occurs: in bleeding; peritonitis; exudates; in burns. The volume of both extracellular and intracellular fluids is decreased.

Water intoxication (hyperhydration).

Total hyperhydration occurs due to excessive water intake or insufficient water excretion. Water is accumulated in all water spaces. Causes: severe stagnant cardiovascular insufficiency; hypersecretion of ADH following administration of anesthetics for surgery, administration of narcotic drugs or in stress (including any surgery); excess of aldosterone (Conn's syndrome); excessive parenteral administration of fluids. Symptoms: headache, nausea, depression.

Intracellular hyperhydration. Causes: infusion of hypotonic solutions; excessive drinking; insuficient excretion of fluid in nephropathies.

Extracellular hyperhydration (edema syndrome) due to the accumulation of water in interstitial fluid. Causes: reduction in colloid-osmotic pressure; increase of hydrostatic pressure; disturbances of functioning the heart; allergic and inflammatory processes.

Disturbances of metabolism of separate minerals can be **primary** and **secondary** ones. **Primary** disturbances are caused by deficiency or excess of any minerals in diet. Examples: endemic goiter (deficiency of I), fluorosis (excess of F).

Secondary disturbances of mineral metabolism may be caused:
- by insufficient amount of protein-carrier (for example, Addison-Biermer disease);
- by lack of apoenzyme (for example, insufficiency of sulfite oxidase – Mo containing enzyme – leads to mental retardation);
- by hormonal disbalance (for example, hypofunction of adrenal cortex – Addison's disease, hyperaldosteronism – Conn's syndrome).

The biological role of Na, K, Cl, Ca, Mg and P, disorders of their metabolism. The biological role of microelements. Dyselementoses.

Most of minerals (sodium and potassium are notable exception) form salts and other compounds that are relatively insoluble, they are not readily absorbed, and most ingested minerals are excreted in feces. Mineral absorption often requires specific carrier proteins; the synthesis of these proteins serves as an important mechanism for control of mineral levels in the body. Transport and storage also require specific binding to carrier proteins. Excretion of most minerals is accomplished by kidneys, but many minerals are also secreted into the digestive juice and bile and are excreted with feces.

Calcium. The human body contains more calcium than any of other essential minerals – about 1-1.5kg g in 70-kg adults. Functions:

1) Plastic function. About 99% of the total amount of Ca is in bones and teeth. Most skeletal calcium is deposited as a form of hydroxyapatite, $Ca_{10}(PO_4)_6(OH)_2$, but bone also contains considerable amounts of noncrysralline calcium phosphates and carbonates as well as a small amount of other salts. Because bone is constantly being remodeled, its mineral levels reflect the equilibrium between daily deposits and withdrawals. As much as 700 mg calcium may enter and leave the bones every day.
2) It is necessary for blood clotting.
3) Ca^{2+} takes part in coupling of excitation and contraction in muscle.
4) It provokes initial mediator secretion during synaptic excitation.
5) It is necessary for adequate functioning of membrane channels.
6) It is the "second messenger" that mediates cellular responses to a wide range of stimuli similar to the regulatory actions of cyclic nucleotides. The action of calcium appears to be mediated by intracellular receptor protein, calmodulin that binds calcium ions when their concentration increases in response to a stimulus. Calmodulin has been found to be present in every nucleated cell type examined. When Ca^{2+} is bound to calmodulin it modulates the activities of a great variety of enzymes, including those involved in cyclic nucleotide metabolism, protein phosphorylation, secretory function, muscle contraction, glycogen metabolism.

Phosphorus.

1) This participates in bone formation (50% all the phosphorus in organism).
2) Phosphorus takes place in maintaining acid-base balance.
3) It is also an integral compound of nucleic acids, nucleotides, nucleotide coenzymes, phospholipids, some proteins, 2.3-bisphosphoglycerate.

4) It participates in formation of macroergic phosphate bonds (ATP, creatine phosphate etc.).

Ca and P metabolism regulation. Many hormones influence the calcium and phosphorus metabolism. Parathyroid hormone, calcitonin and hydroxylated forms of cholecalciferol are main of them. Normal plasma contains the equivalent of 9-11 mg of calcium per deciliter (2,25-2,75 mmol/L). The symptoms of calcium deficiency include tetany and related muscle and neurologic disorders. Low serum Ca^{2+} levels occur in vitamin D deficiency, hypoparathyroidism or renal insufficiency. The net negative Ca^{2+} balance leads to rickets in children or osteomalacia in adults. High serum Ca^{2+} levels accompany clinical disorders such as hyperparathyroidism, vitamin D intoxication, sarcoidosis, and cancer. Osteoporosis, which mainly occurs in women following the menopause, is based (at least in part) on a reduction in estrogen levels. Estrogens normally inhibit the stimulation of osteoblast differentiation by osteoblasts. If the effects of estrogen decline, osteoclasts predominate and excess bone removal occurs.

Sodium. Sodium is the cation (Na^+) of the extracellular fluid. The concentration of Na^+ in blood plasma is 126-152 mM, in erythrocytes 13,4-21,7mM. 1-3.5 g of Na is required daily for adults. Infants need 0.1-0.5 g and children 0.3-2.5 g daily. Functions of sodium:

1) Maintaining and supporting normal water balance and distribution of water in the organism.
2) Na^+ is also important in the maintenance of osmotic pressure of body fluids and thus in protection against excessive fluid loss.
3) It is largely associated with chloride and bicarbonate in the regulation of acid-base equilibrium.
4) It participates in formation of resting membrane potential and regeneration of excitation potential.
5) It participates in supporting normal neuromuscular excitability.
6) It facilitates formation of conformation of enzyme molecule which is needed to precise orientation of catalytic groups.
7) It intensifies proteins swelling and increases the amount of water bound with them.

Every 24 hours approximately 2500 mmol of sodium are filtered by the kidneys. However, due to tubular reabsorption less than 1% of this sodium appears in the urine (100-200 mM/day). Approximately 80% of the filtered sodium are reabsorbed in the proximal tubules with equivalent amount of water. The reabsorption of sodium in the distal tubules is 5 times less than in the proximal ones. The reabsorption in the distal tubules takes place contrary to a concentration gradient and is regulated by aldosterone.

Hyponatremia may be relative and absolute. Relative hyponatremia is caused by excessive drinking or excessive parenteral infusion of hypotonic solutions. Absolute hyponatremia is caused by diuretic medication, intensive sweating, prolonged vomiting, intestinal fistula, in hypoaldosteronism.

Hypernatremia may also be relative and absolute. Relative hypernatremia is observed in hyperosmolar dehydration, in limited liquid intake. Absolute hypernatremia is developed in excessive Na intake, in primary hyperaldosteronism (Conn's syndrome), in secondary hyperaldosteronism, in chronic nephritis. The secondary hyperaldosteronism is caused by hyperproduction of renin. This mechanism is observed in hypertonic disease, in cardiovascular insufficiency, etc.

Potassium. Potassium is the major intracellular cation. The concentration of potassium is 3.8-5.4 mM in blood serum and 79.8-99.3 mM in erythrocytes. Functions:

1) It participates in formation of resting membrane potential.

2) It favors the activation of some enzymes. It is needed for the synthesis of proteins, ATP, glycogen.
3) Potassium potentiates the function of parasympathetic nervous system and the action of acetylcholine on the nerve terminals in muscles.
4) It is involved in supporting acid-base balance.
5) It plays an important role in cardiac function.

Hypokalemia is observed in insufficient potassium intake, in changing redistribution of potassium between intracellular and extracellular fluids and in increased loss. Insulin facilitates the supply of potassium in cells, therefore hypokalemia is observed after infusion of insulin to patients with Diabetes mellitus. Loss of K^+ in gastro-intestinal diseases, renal and exstrarenal polyuria, diuretic therapy, primary and secondary hyperaldosteronism, metabolic and respiratory alkalosis causes hypokalemia. Hypokalemia is accompanied by muscle hypotonia, weakness, paresthesia, change of contractive function of miocardium, tachycardia. Potassium deficiency results in changes of electrochemical gradient of cell membranes of myocardium, a decrease of potential difference and depolarization of membrane.This leads to increasing muscular excitability. Low resting membrane potential causes slow enhancing and low amplitude of action potential. Therefore excitation irradiation is reduced. Myocardium insufficiency develops.

Hyperkalemia. The mechanism for excretion of potassium in normal persons is so effective that it is difficult to produce hyperkalemia simply increasing the oral intake. Hyperkalemia however may occur after rapid intravenous infusion of potassium salts. Hyperkalemia is also caused by excretion disturbance and by sudden release of potassium from the intracellular space. Decreased excretion of potassium is observed in renal failure, in hypofunction of adrenal cortex (Addison's disease). Damage of body cells from any cause results in release of cell contents including K^+ into extracellular fluid. Crush injuries with damages to large volumes of muscle tissue, massive hemolysis are examples. In ketoacidosis there is substantial loss of intracellular K^+ to the extracellular fluid. If ketoacidosis presents for a long time, there will be major depletion of total body K^+. In hyperkalemia the changes in myocardium are observed. Bradicardia, arrhythmia, blockade, asystole occur.

Classifications of chemical elements, which are found in the organism:

Macroelements: Na, K, Ca, Mg, P, S, Cl.
Microelements (trace elements): Fe, Cu, Zn, F, I, Se, Cr, Mn, Co, Mo.
Ultramicroelements: Br, Si, Sr, Li, Hg, Au, Ni, Ti, Ra, Cd, As, Ti, Sn etc.

Each element has to be supplied in organism in optimal concentration. Decreased supply results in diminishing biochemical process intensivity. Increased supply leads to toxicosis.

Summary of Important Minerals (Janson 2012)

Mineral	Function	Disease(s)
Na	Involved in maintenance of fluid volume and osmotic pressure per the kidneys and associated hormones (e.g., renin, aldosterone, antidiuretic hormone, atrial natriuretic peptide). Essential for generation and maintenance of electric or transport potential across membranes (e.g., nerve conduction, muscle contraction, and membrane pumps)	Hyponatremia. Neurological symptoms secondary to cell swelling and electrolyte imbalance; potentially fatal. Hypernatremia. Deficit in free water in the body. Variable symptoms, including neurological, potentially fatal.

K	Usually the partner to sodium, essential for generation and maintenance of electric and transport potential across membranes (e.g., nerve conduction, muscle contraction, and membrane pumps), as well as potassium-specific pumps.	Hypokalemia and hyperkalemia. Muscle and neurological symptoms; both may lead to fatal abnormal heart rhythm, especially hyperkalemia.
Cl	Involved in conjunction with sodium in maintenance of fluid volume and osmotic pressure per the kidney. Essential role in neurological functions (e.g., glycine and GABA neurotransmitters) and acid-base balance via transport of bicarbonate.	Hypochloremia and hyperchloremia. Often secondary to vomiting and/or diarrhea; usually asymptomatic but may have respiratory symptoms.
Ca	Required for bone formation and remodeling; important cofactor for several enzymes and signal for signaling pathways (i.e., diacylglycerol/ IP_3), including blood clotting and muscle contraction; neurotransmitter for some neuron signals and plays a prominent role in maintaining a potential difference across membranes	Hypocalcemia. Neurological symptoms; may be followed by potentially fatal spasms of larynx and abnormal heart rhythm. Hypercalcemia. Constipation (groans), psychotic episodes (moans), pain in bones, kidney stones, and depression, etc. (psychiatric overtones); abnormal heart rhythm can also develop.
Mg	Magnesium stabilizes phosphate groups, including those in ATP; cofactor in several enzymatic processes	Hypomagnesemia. Muscle weakness, nerve problems/ tremors, psychiatric episodes/ epileptic fits; may lead to heart failure. Hypermagnesemia. Weakness, breathing problems, and potentially fatal heart rhythms.
P	Essential structural and functional element for nucleic acids, bone/ teeth, and phospholipid component of membranes; addition or removal of phosphate to/ from a protein/enzyme serves as a key regulator of enzymes	Hypophosphatemia. Nerve, bone, red and white blood cells, membrane, and muscle functional problems. Hyperphosphatemia. (Interference with other minerals, promotes calcification of soft tissue organs).
Fe	Essential cofactor in numerous enzymes and proteins (e.g., heme); essential for oxidation processes or oxygen transport	Iron deficiency (anemia). Iron excess (hemachromatosis).
I	Essential element for thyroid hormones; can act as antioxidant outside of thyroid, may play a role in the development of breast and/or stomach cancer, and affects immune system and salivary gland health	Iodine deficiency (goiter; cretinism).
Zn	Cofactor in almost 100 enzymes, serving a multitude of roles in metabolism, transcription and translation, acid-base balance, immune function, and protein synthesis; part of unique, tertiary protein structures (e.g., zinc fingers); part of nerve response of glutamate and essential for learning	Zinc deficiency. Directly impacts the enzymatic processes that rely on it; initial signs may be seen in skin, hair, and nails. Zinc excess. Can impair the absorption of other ions (e.g., iron and copper); corrosive damage to soft tissues.
Mn	Essential cofactor for several types of enzymes involved in numerous biological functions as well as several specific types of peptides	Manganese deficiency. Possible association with inflammatory diseases, diabetes, and some neurological and psychiatric problems. Manganese excess (manganism). Progressive neurological/ psychiatric symptoms.

Cu	Cofactor in several enzymes involved in electron transport or oxidation-reduction reactions (e.g., cytochrome c oxidase). Also, used for electron transport	Copper deficiency (anemia symptoms, decreased metabolism, and psychiatric manifestations). Copper excess. Wilson's disease (neurological and psychological effects).
S	As part of cysteine and methionine amino acids, plays an essential role in component of primary and tertiary protein structure via disulfi de bond as well as role in sulphur-containing enzymes (e.g., cytochrome c oxidase, coenzyme A (CoA); reduction of reactive species via glutathione	NA
Co	Component of cobalt-containing cofactors/ enzymes, the most prominent of which is vitamin B_{12}	Cobalt excess. Potentially fatal. Cobalt deficit (pernicious anemia).
Ni	Important cofactor in some enzymes (e.g., urease), especially those involved in reduction reactions	Nickel deficiency. Potential impact on involved enzymes, although not manifested as symptoms. Nickel excess. Skin irritant and potential cancercausing agent.
Cr	Possible role in carbohydrate and/ or lipid metabolism	Chromium deficiency (extremely rare; effects controversial). Chromium excess (Cr^{3+}. damage to DNA; Cr^{6+}. can act as a cancer-causing agent and damages internal organs).
F	Role in strengthening of teeth and bone and, as such, used for prevention of cavities and treatment of osteoporosis	Fluoride deficiency. Possible connection to weakened teeth and bones. Fluoride excess. Neuromuscular and other symptoms that can result in death.
Se	Essential cofactor for certain antioxidant enzymes (e.g., glutathione peroxidase), which remove reactive oxygen species; believed to be cofactor in thyroid hormone conversion of T_4 to T_3	Selenium deficiency. Rarely seen but may contribute to destruction of heart or connective tissue; also affects thyroid hormone synthesis Selenium excess (selenosis). Affects liver and lungs; potentially fatal.
Mo	Cofactor in several enzymes, including oxidizing enzymes (e.g., xanthine oxidase)	Affects enzymes requiring cofactor; neurological symptoms may result; possible association with development of esophageal cancer.

CHAPTER 4. FUNCTIONAL BIOCHEMISTRY TEST BANK

List of the theoretical questions:

1. Blood as a specialized tissue of the body, its composition. Functions of blood. Blood preparations.
2. Physical and chemical properties of blood. Inorganic components of blood. Imbalance of blood electrolytes (Na, K, Ca).
3. Acid-base balance, its regulation. Buffer blood systems. Acidosis and alkalosis: types, causes, mechanisms of compensation.
4. Blood plasma proteins. Albumins and globulins, their biological role. Hyper-, hypo- and dysproteinemia: causes, clinical symptoms. Paraproteinemia. Acute phase proteins.
5. Blood plasma lipoproteins. Atherosclerosis.
6. Non-protein organic compounds of blood. Residual nitrogen. Azotemia.
7. Blood plasma enzymes. Enzymodiagnostics.
8. Respiratory function of erythrocytes. Hemoglobin (structure, properties). Transport of oxygen and carbon dioxide. Factors affecting the binding of hemoglobin to oxygen. Hemoglobin derivatives.
9. Hemoglobin metabolism, its synthesis. Metabolism of porphyrins.
10. Disorders of hemoglobin metabolism: hemoglobinopathy, thalassemia, porphyria. Metabolism of iron. Iron deficiency anemia.
11. System of hemostasis. Blood coagulation system, factors of blood plasma. Role of vitamin K in blood clotting. Inherited coagulopathies.
12. Anticoagulant and fibrinolytic systems of blood.
13. Functions of the liver. The biological role of the liver in nitrogen metabolism and biosynthesis of specialized proteins.
14. The biological role of the liver in carbohydrate and lipid metabolism.
15. The biological role of the liver in metabolism of vitamins. Digestion, storage and excretion of different metabolites.
16. Hemoglobin metabolism, its breakdown. Bile formation.
17. Biochemistry of jaundice (hemolytic, hepatic and obstructive): causes, clinical symptoms, differential diagnostics. Hereditary jaundice: Crigler-Nayar, Gilbert, Dabin-Johnson syndromes. Neonatal physiological jaundice.
18. Biotransformation of xenobiotics and endogenous toxins. Microsomal oxidation. Ethanol toxicity and its metabolism.
19. Functions of the kidneys. Filtration, secretion, reabsorption, excretion. The mechanism of urine formation. Renal clearance.
20. The role of the kidneys in the regulation of osmotic pressure and acid-base balance. Endocrine renal function.
21. Physical and chemical properties of urine. Composition of urine under normal and pathological conditions.
22. The biological role of water. The distribution of water and electrolytes in the body, its regulation. Osmotic pressure. Disorders of water metabolism (dehydration, hyperhydration): types, causes, clinical symptoms.
23. The biological role of sodium, potassium and chlorine, regulation and disorders of their metabolism. The biological role of calcium, magnesium and phosphorus, regulation and disorders of their metabolism.
24. The biological role of microelements (Fe, Cu, Zn, F, I, S, Se, Cr, Mn, Co, Mo). Dyselementoses: causes, clinical symptoms.

Multiple Choice Questions:

1 12 hours after an acute attack of retrosternal pain a patient presented a jump of aspartate aminotransferase activity in blood serum. What pathology is this deviation typical for?
A) Viral hepatitis
B) Diabetes insipidus
C) Collagenosis
D) Diabetes mellitus
E) Myocardial infarction

2 62 y.o. woman complains of frequent pains in the area of her chest and backbone, rib fractures. A doctor assumed myelomatosis (plasmocytoma). What of the following laboratory characteristics will be of the greatest diagnostic importance?
A) Proteinuria
B) Hypoproteinemia
C) Hypoglobulinemia
D) Hyperalbuminemia
E) Paraproteinemia

3 A 2-year-old boy began to suffer from respiratory diseases, stomatitis, pustular skin lesions. Even small damages of gums and mucous membranes were complicated by long-lasting inflammation. It was found out that immunoglobulins of all classes were practically absent in his blood. The decrease in the functional activity of a cell population that underlies the described syndrome is observed. Which cell population is affected?
A) Neutrophils
B) NK-lymphocytes
C) T-lymphocytes
D) B-lymphocytes
E) Macrophages

4 A 28-year-old patient undergoing treatment in a pulmonological department has been diagnosed with pulmonary emphysema caused by splitting of alveolar septum by elastase and trypsin. The disease is caused by the congenital deficiency of the following protein:
A) Alpha-1-proteinase inhibitor
B) Haptoglobin
C) Cryoglobulin
D) Alpha-2-macroglobulin
E) Transferrin

5 A 34-year-old patient was diagnosed with chronic glomerulonephritis 3 years ago. Edema has developed within the last 6 months. What caused the edema?
A) Liver dysfunction of protein formation
B) Hyperosmolarity of plasma
C) Proteinuria
D) Hyperproduction of vasopressin
E) Hyperaldosteronism

6 A 4 y.o. child with signs of durative proteinic starvation was admitted to the hospital. The signs were as follows: Growth inhibition, anemia, oedema, mental deficiency. Choose the cause of oedema development:
A) Reduced synthesis of lipoproteins
B) Reduced synthesis of glycoproteins
C) Reduced synthesis of hemoglobin
D) Reduced synthesis of globulins
E) Reduced synthesis of albumins

7 A 47-year-old patient was brought to an emergency department with the diagnosis of myocardial infarction. What enzyme activity would prevail in the patient's blood serum during the first 3-4 hours after the beginning of this pathological state?
A) LDH1
B) Aspartate amino transferase
C) LDH3
D) Creatine phosphate kinase MM isozyme
E) LDH5

8 A 49-year-old male patient with acute pancreatitis was likely to develop pancreatic necrosis, while active pancreatic proteases were absorbed into the blood stream and tissue proteins broke up. What protective factors of the body can inhibit these processes?
A) Immunoglobulin
B) Ceruloplasmin, transferrin
C) a2-macroglobulin, a1-antitrypsin
D) Cryoglobulin, interferon
E) Hemopexin, haptoglobin

9 A 55 y.o. women consulted a doctor about having continuous cyclic uterine hemorrhages for a year, weakness, dizziness. Examination revealed skin pallor. Hemogram: Hb – 70 g/L, erythrocytes- 3.2 x 1012/L, color index – 0.6; leukocytes – 6.0 x 109/L, reticulocytes – 1%, erythrocyte hypochromia. What anemia is it?
A) Iron-deficiency anemia
B) B12-folate-deficiency anemia
C) Hemolytic anemia

D) Aplastic anemia
E) Chronic posthemorrhagic anemia

10 A 63-year-old woman developed symptoms of rheumatoid arthritis. Their increase of which blood values indicators could be most significant in proving the diagnosis?
A) R-glycosidase
B) Acid phosphatase
C) Lipoproteins
D) General cholesterol
E) Additive glycosaminoglycans

11 A 67-year-old male patient consumes eggs, pork fat, butter, milk and meat. Blood test results: cholesterol – 12.3 mmol/l, total lipids – 8.2 g/l, increased low-density lipoprotein fraction (LDL). What type of hyperlipoproteinemia is observed in the patient?
A) Hyporlipoproteinemia type I.
B) Hyperlipoproteinemia type IV
C) Cholesterol, hyperlipoproteinemia
D) Hyperlipoproteinemia type IIa
E) Hyperlipoproteinemia type IIb

12 A breastfed child suffers from diarrhea due to improper feeding. One of its main consequences is the excretion of large amounts of sodium bicarbonat~Which form of acid-base disorder is observed in this case?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) No changes in acid-base balance

13 A child with signs of prolonged protein starvation was hospitalized: growth retardation, anemia, edema, and mental retardation. The reason for the development of edema in this child is a decrease in the synthesis of:
A) Hemoglobin
B) Globulins
C) Albumins
D) Lipoproteins
E) Glycoproteins

14 A decrease in blood residual (rest) nitrogen level was revealed in a patient with liver insufficiency. The diminished blood non-protein nitrogen was due to:
A) Urea
B) Ammonium
C) Amino acids
D) Bilirubin
E) Uric acid

15 A female complains of frequent chest and spine pain, fractures of ribs. A doctor suspected myeloma (plasmacytoma). Which of the laboratory parameters mentioned below will be of the greatest diagnostic significance?
A) Hypoproteinemia
B) Hyperalbuminemia
C) Hypoalbuminemia
D) Proteinuria
E) Paraproteinemia

16 A female patient, a worker of a paint and varnish factory, complains of general weakness, weight loss, apathy, drowsiness. Chronic lead intoxication was confirmed by laboratory methods: hypochromic anemia was reveale~Blood protoporphyrin level is increased and δ-aminolevulinic acid level is lowered, which indicates the abnormal synthesis of:
A) DNA
B) RNA
C) Protein
D) Mevalonic acid
E) Heme

17 A group of children ate watermelon. One of the children had weakness, dizziness, vomiting, shortness of breath, tachycardia, acrocyanosis. Laboratory analysis of watermelon showed the high content of nitrates. What is the leading mechanism in the pathogenesis of poisoning in this child?
A) Superoxide dismutase insufficiency
B) Cytochrome oxidase inhibition
C) Methaemoglobin reductase insufficiency
D) Glutathione peroxidase deficiency
E) Catalase insufficiency

18 A male patient with type 1 diabetes mellitus is hospitalized due to coma. Laboratory tests revealed hyperglycemia, ketonemia. Which of the metabolic disorders mentioned below can be found in this patient?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) No changes in acid-base balance

19 A patient complains of general weakness, dizziness, and rapid fatigue. The content of hemoglobin is 80 g/L. Microscopically, erythrocytes

have abnormal shape. The cause of this condition is:
A) Parenchymal jaundice
B) Addison's disease
C) Acute intermittent porphyria
D) Obturative jaundice
E) Sickle-cell anemia

20 A patient complains of vomiting, general weakness. Residual (rest) nitrogen in blood is 35 mmol/L, renal function is not affected. Which type of azotemia is developed?
A) Relative azotemia
B) Renal azotemia
C) Retention azotemia
D) Productive azotemia

21 A patient had a hemoglobin gene mutation. This led to the development of sickle cell anemia. How is the pathological hemoglobin, formed in this disease, called?
A) Bart-Hb
B) HbF
C) HbS
D) HbA
E) HbA1

22 A patient had airway obstruction at the level of small and middle-sized bronchi. Which changes in the acid-base balance can develop in a patient?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) No changes in acid-base balance

21 A patient had pathological changes in the liver and brain. A sharp increase of copper in the urine and its decrease in the blood are observed. Wilson disease was diagnosed. Which enzyme activity in the blood serum should be investigated to confirm the diagnosis?
A) Carbonic anhydrase
B) Xanthine oxidases
C) Leucine aminopeptidases
D) Ceruloplasmin
E) Alcohol dehydrogenase

22 A patient had visually seen blisters and enhanced pigmentation after exposure to UV rays. Urine turns red after exposing to the air. Which parameter of the urine makes it possible to verify Gunther's disease?
A) Hemoglobin
B) Uroporphyrinogen I
C) Bilirubin
D) Creatinine
E) Acetone

23 A patient has an increased skin sensitivity to sunlight. When exposing to the air, urine turns dark red. What is the most likely cause of this condition?
A) Hemolitic jaundice
B) Porphyria
C) Albinism
D) Pellagra
E) Alkaponuria

24 A patient has been ill for 10 years. Periodically he complaints of acute pain in the abdomen, convulsions, impaired vision. His relatives have similar symptoms. Urine is red. The patient was hospitalized with acute intermittent porphyria. The cause of the disease may be the abnormal synthesis of:
A) Insulin
B) Bile acids
C) Heme
D) Prostaglandin
E) Collagen

25 A patient has experienced thirst, frequent urination, weight loss, and fatigue. Analysis of his blood reveals below normal pH, above normal glucose level. What is the primary cause for the decrease of normal pH in this patient?
A) Hyperventilation
B) Water loss due to frequent urination
C) Diabetes insipidus
D) Renal failure
E) Ketoacidosis

26 A patient has hemorrhagic stroke. An increased concentration of kinins was found in the blood. The doctor prescribed contrical, which is an inhibitor of one of the foloowing proteinases:
A) Pepsin
B) Trypsin
C) Chymotrypsin
D) Collagenase
E) Kallikrein

27 A patient has high levels of hydroxyproline, sialic acids, and C-reactive protein in the blood. Which pathology is exacerbated?
A) Rheumatic fever
B) Enterocolitis
C) Hepatitis
D) Bronchitis

E) Pancreatitis

28 A patient has low blood pH values and hydrocarbonate ions (decreased alkaline reserve of blood), increased levels of lactic and pyruvic acids in blood and urine. Which type of acid-base balance disorder is observed?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis

29 A patient has rheumatic fever in the active phase. Which blood serum parameter is of diagnostic significance in this pathology?
A) C-reactive protein
B) Uric acid
C) Urea
D) Creatinine
E) Transferrin

30 A patient has sickle-cell anemia. Which amino acid is replaced in the polypeptide chain of hemoglobin for valine?
A) Glutamic acid
B) Aspartic acid
C) Leucine
D) Arginine
E) Threonine

31 A patient is diagnosed with hereditary coagulopathy that is characterized by factor VIII deficiency. Specify the phase of blood clotting during which coagulation will be disrupted in the given case:
A) Clot retraction
B) Thromboplastin formation
C) Fibrin formation
D) Plasmin formation
E) Thrombin formation

32 A patient shows signs of mountain sickness: dizziness, dyspnea, tachycardi~Blood pH is 7.5, pCO2 is 30 mm Hg, the buffer base shift is +4 mmol/L. Which acidbase disorder developed?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) Excretory acidosis

33 A patient suffering from chronic renal failure has an increase in the level of residual (rest) nitrogen to 35 mmol/L. More than half of its is urea. This type of azotemia is called:
A) Hepatic
B) Productive
C) Retentional
D) Residual
E) Mixed

34 A patient underwent an examination and was diagnosed with hyperglycemia, ketonuria, polyuria, and glucosuria. Which form of acid-base balance disorders is observed?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) No changes in acid-base balance

35 A patient was diagnosed with erythropoietic porphyria (Gunther's disease): urine is red, a noticeable red coloration of teeth is observed under the ultraviolet radiation. Which substance metabolism is affected?
A) Heme
B) Globin
C) Adenine
D) Creatine
E) Cholesterol

36 A patient was diagnosed with iron-deficiency sideroachristic anemia, which was accompanied by skin hyperpigmentation, development of pigment liver cirrhosis, damage to the pancreas and heart. The content of iron in the blood serum is increased. What is the reason for the abnormal iron metabolism?
A) Excessive intake of iron from food
B) Abnormal iron absorption in the intestine
C) Iron is not used and is deposited in tissues
D) Increased consumption of iron by the body

37 A patient was diagnosed with myeloma. The total blood protein level is 180 g/L. Such protein level was due to:
A) Transferrin
B) Albumins
C) Paraproteins
D) Haptoglobin
E) Immunoglobulin

38 A patient was examined in a hospital. Since childhood, his hemoglobin has been varying from 90 to 95 g/L. Treatment with iron supplements was ineffective. There are the following blood indices: RBCs-3.2, Hb-85 g/L, color index – 0.78,

anisocytosis, poikilocytosis, target cells, reticulocytes - 16%. The diagnosis is thalassemia. To which kind of hemolytic anemia belongs this disease?
A) Hereditary membranopathy
B) Acquired enzymopathy
C) Hereditary hemoglobinopathy
D) Hereditary enzymopathy
E) Acquired membranopathy

39 A patient who had been working hard under condition of elevated temperature of the environment has now a changed quantity of blood plasma proteins. What phenomenon is the case?
A) Absolute hyperproteinemia
B) Relative hyperproteinemia
C) Absolute hypoproteinemia
D) Disproteinemia
E) Paraproteinemia

40 A patient who is being treated for hepatitis B shows signs of liver failure. Which blood changes that indicate abnormal protein metabolism are most likely observed in this case?
A) Absolute hyperglobulinemia
B) Blood protein spectrum is not affected
C) Absolute hyperproteinemia
D) Absolute hypoproteinemia
E) Absolute hyperfibrinogenemia

41 A patient with acute pancreatitis had a threat of pancreatic necrosis, which was accompanied by the release of active pancreatic proteinases into the bloodstream and tissues and breakdown of tissue proteins. Which protective factors can inhibit such processes?
A) Ceruloplasmin, transferrin
B) Hemopexin, haptoglobin
C) Cryoglobulin, interferon
D) Immunoglobulin
E) α2-Macroglobulin, α1-antitrypsin

42 A patient with diabetes mellitus has a diabetic coma due to an acid-base balance disorder. Which kind of acid-base balance disorders occurs in this case?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) No changes in acid-base balance

43 A patient with diabetes mellitus has hyperglycemia, ketonuria, glucosuria, hypersthenuria, and polyuria. Which form of acid-base balance disorders occurs in this situation?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis
E) Excretory alkalosis

44 A patient with diabetes mellitus was hospitalized in a severe precomatous state. Metabolic acidosis was found. What is the primary mechanism for the identified acid-base balance disorder?
A) Impaired use of O2 in cells
B) Formation of underoxidized products
C) Abnormal blood buffer systems
D) Excretion of alkaline components in the urine
E) A decrease in CO2 excretion

45 A patient with hypochromic anemia has splitting hair and loss of hair, increased nail bottling and taste alteration. What is the mechanism of the development of these symptoms?
A) Deficiency of vitamin B12
B) Decreased production of thyroid hormones
C) Deficiency of vitamin A
D) Decreased production of parathyrin
E) Deficiency of iron-containing enzymes

46 A patient, hospitalized to the pulmonological department, was diagnosed with pulmonary emphysema, which resulted from the destruction of interalveolar septa by tissue trypsin. Which protein congenital insufficiency can cause the development of this disease?
A) Transferrin
B) α2-Macroglobulin
C) Cryoglobulin
D) α1-Proteinase inhibitor
E) Haptoglobin

47 A person suffers from diabetes mellitus, which is accompanied by fasting hyperglycemia (more than 7.2 mmol/L). Which plasma protein level allows assessing the level of glycemia retrospectively (for 4-8 weeks before the examination)?
A) Glycosylated hemoglobin
B) C-Reactive protein
C) Fibrinogen
D) Ceruloplasmin
E) Albumin

48 A significant increase in the activity of

creatine phosphokinase MB and LDH1 was revealed in the patient's blood. What is the possible pathology?
A) Myocardial infarction
B) Hepatitis
C) Rheumatism
D) Pancreatitis
E) Cholecystitis

49 A worker has decreased buffer capacity of blood due to exhausting muscular work. What acidic substance that came to blood caused this phenomenon?
A) 3-phosphoglycerate
B) 1,3-bisphosphoglycerate
C) Lactate
D) α-ketoglutarate
E) Pyruvate

50 According to clinical data, a patient was diagnosed with acute pancreatitis. Which biochemical test can confirm this diagnosis?
A) Acidic phosphatase activity in the blood
B) Activity of alkaline phosphatase in the blood
C) Blood amylase activity
D) Aminotransferase activity in the blood
E) Blood creatinine level

51 After a surgery a 36-year-old woman was given an intravenous injection of concentrated albumin solution. This has induced intensified water movement in the following direction:
A) From the intercellular fluid to the capillaries
B) No changes of water movement will be observed
C) From the intercellular to the cells
D) From the cells to the intercellular fluid
E) From the capillaries to the intercellular fluid

52 After repairing the car in the garage, the driver was hospitalized with symptoms of poisoning with exhaust fumes. Which blood hemoglobin type will be increased in the blood?
A) Carboxyhemoglobin
B) Methemoglobin
C) Carbhemoglobin
D) Oxyhemoglobin
E) Glycosylated hemoglobin

53 After the accident in the chemical plant, the environment was polluted with nitro compounds. People living in that area experienced weakness, headache, shortness of breath, dizziness. What was the cause of hypoxia?
A) Inhibition of dehydrogenases
B) Formation of carboxyhemoglobin
C) Reduced function of flavin-dependent enzymes
D) Formation of methemoglobin
E) Inactivation of cytochrome oxidase

54 All of blood plasma proteins are transporters EXCEPT one in this list. Choose it:
A) Transferrin
B) Albumin
C) Ceruloplasmin
D) Fibrinogen
E) VLDL

55 All of the following are required for normal clot formation except:
A) Vitamin K
B) Calcium
C) Plasmin
D) Thrombin
E) Proteolysis

56 Along with the normal types of hemoglobin in adults, there are also pathological ones. Select one of them.
A) HbA1
B) HbS
C) HbA2
D) HbF
E) HbO2

57 An increase in the concentration of carbon monoxide in the air can lead to poisoning. It affects the oxygen transport by hemoglobin from lungs to tissues. Which hemoglobin derivative is formed in this case?
A) Oxyhemoglobin
B) Methemoglobin
C) Carboxyhemoglobin
D) Carbhemoglobin
E) Hemochromogen

58 Analysis of blood serum of a patient revealed the increase of alanine aminotransferase and aspartate aminotransferase levels. What cytological changes can cause such a situation?
A) Disturbance of genetic apparatus of cells
B) Cellular breakdown
C) Disorder of enzyme systems of cells
D) Disturbance of cellular interrelations
E) Disturbed energy supply of cells

59 Apparatus of artificial ventilation of lungs has been attached to a patient with severe trauma. Determination of acid-base balance indices show a

decrease in the content of blood carbon dioxide and an increase in its removal. These changes are typical for:
A) Respiratory alkalosis
B) Respiratory acidosis
C) Metabolic alkalosis
D) Metabolic acidosis

60 Approximately 20% of the world population have a decrease in the activity of glucose-6-phosphate dehydrogenase in erythrocytes. Such people have a higher risk of hemolysis due to the impairment of:
A) Hemoglobin synthesis
B) Glycolysis in erythrocytes
C) Activities of calcium-magnesium-ATPase
D) Activity of sodium-potassium-ATPase
E) Antioxidant system of erythrocytes

61 At rest a man makes himself to breathe frequently and deeply within 3-4 minutes. How it affects the acid-base balance of an organism?
A) There is metabolic alkalosis.
B) There is respiratory acidosis
C) There is respiratory alkalosis
D) There is metabolic acidosis
E) Acid-base balance is not affected

62 Biochemical analysis of an infant`s erythrocytes revealed evident glutathione peroxidase deficiency and low concentration of reduced glutathione. What pathological condition can develop in this infant?
A) Hemolytic anemia
B) Megaloblastic anemia
C) Siclemia
D) Iron-deficiency anemia
E) Pernicous anemia

63 Biochemical analysis of the baby's erythrocytes reaveled a marked glutathione peroxidase deficiency and low levels of reduced glutathione. Which pathological condition can develop?
A) Pernicious anemia
B) Megaloblastic anemia
C) Sickle cell anemia
D) Hemolytic anemia
E) Iron deficiency anemia

64 Blood analysis revealed a decrease in hemoglobin. Which blood function was affected?
A) Provision of immunity
B) Transport of hormones
C) Transport of nutrients
D) Transport of medicines
E) Transport of gases

65 Blood analysis revealed azotemia. The percentage of urea nitrogen in the (rest) residual blood nitrogen is significantly reduced. Which organ is affected?
A) Stomach
B) Liver
C) Kidney
D) Intestine
E) Heart

66 Blood is the tissue needed for the transport of all absorbed products in the gut after digestion processes. Name the function of the blood described above:
A) Body temperature regulatory function
B) Transport of hormones
C) Nutrition function
D) The maintenance of acid-base balance in the organism
E) Protection against microbial agents

67 Blood pH is 7,3 in a patient with diabetes mellitus. Which buffer system components are used for diagnostics of acid-base balance disturbances?
A) Phosphate
B) Bicarbonate
C) Oxyhemoglobin
D) Hemoglobin
E) Protein

68 Blood sampling for bulk analysis is recommended to be performed on an empty stomach and in the morning. What changes in blood composition can occur if to perform blood sampling after food intake?
A) Reduced contents of erythrocytes
B) Increased contents of erythrocytes
C) Increased contents of leukocytes
D) Increased plasma proteins
E) Reduced contents of thrombocytes

69 C-reactive protein is revealed in blood serum:
A) After physical loading
B) In remission phase of disease
C) In lipid metabolism disturbances
D) In acute phase of inflammatory diseases
E) In diabetes mellitus

70 Choose the anticoagulant normally present in the blood plasma:

A) Vitamin K
B) Heparin
C) Hyaluronidase
D) Dicumarol
E) None of the above

71 Choose the blood plasma index that is used in screening of newborn for phenylketonuria estimation:
A) Phenylalanine
B) Dihydroxyphenylalanine
C) Acetone
D) Acetoacetate
E) Pyruvate

72 Choose the location of most plasma protein synthesis:
A) Liver
B) Lungs
C) Small intestine
D) Kidney
E) Skin

73 Complement can combine:
A) IgM and IgG
B) IgA
C) IgD
D) IgE
E) Nothing from above mentioned

74 Considerable disturbances of blood circulation in response to shock provide the development of:
A) Metabolic acidosis
B) Respiratory acidosis
C) Respiratory alkalosis
D) Metabolic alkalosis

75 Considerable losses of gastric juice in prolonged vomiting provide the development:
A) Respiratory acidosis
B) Metabolic alkalosis
C) Respiratory alkalosis
D) Metabolic acidosis

76 Considerable losses of gastric juice in prolonged vomiting provide the development of:
A) Respiratory acidosis
B) Metabolic alkalosis
C) Respiratory alkalosis
D) Metabolic acidosis

77 Continue the statement: "Estimation of glycosylated hemoglobin in the blood helps to know the ____".
A) Time duration of untreated diabetes mellitus
B) Rate of ketoacidosis
C) Rate of glucose utilization in tissues
D) The rate of oxygen saturation by hemoglobin
E) Reason of diabetes mellitus development

78 Conversion of prothrombin to thrombin requires one or more factors from the following list: Choose them:
A) Factor X and Ca2+only
B) Factor V and Ca2+only
C) Factors X, V, Ca2+, acidic phospholipids
D) Factors XI, VI, Ca2+, acidic phospholipids
E) Factors X, V and Mn2+

79 Creatine level is much higher then normal, creatinine level is lower then normal in the blood plasma of patient. Choose the probable diagnosis for this patient:
A) Myocardium infarction
B) Cholestasis
C) Viral hepatitis
D) Phenylketonuria
E) Muscular dystrophy

80 Diabetes mellitus causes ketosis as a result of activated oxidation of fatty acids. What disorders of acid-base equilibrium may be caused by excessive accumulation of ketone bodies in blood?
A) Metabolic alkalosis
B) Metabolic acidosis
C) Respiratory alkalosis
D) Respiratory acidosis
E) Any changes won't happen

81 Edema rapidly develops in a patient. Which protein is reduced in blood serum in edema?
A) α1-Globulins
B) α2-Globulins
C) Albumins
D) β-Globulins
E) Fibrinogen

82 Electrophoretic study of a blood serum sample, taken from the patient with pneumonia, revealed an increase in one of the protein fractions. Specify this fraction:
A) γ-globulins
B) Albumins
C) α1-globulins
D) β-globulins
E) α2-globulins

83 Embolism of respiratory tract by phlegm is observed in a patient. Which disorder of acid-base balance may be found in blood?
A) Respiratory acidosis
B) Metabolic acidosis
C) Acid-base balance is normal
D) Respiratory alkalosis
E) Metabolic alkalosis

84 Erythema and vesicular rash on the skin appeared in a child under the action of sunlight. The child complains of itching. Blood tests revealed a decrease in blood serum iron content, as well as an increase in urinary excretion of uroporphyrinogen I. The most likely hereditary pathology is:
A) Methemoglobinemia
B) Hepatic porphyria
C) Erythropoietic porphyria
D) Coproporphyria
E) Intermittent porphyria

85 Erythrocytes are sickle-shaped in a patient with severe forms of hemolytic anemia. What is the molecular cause of this disease?
A) Replacement of glutamate with valine
B) Abnormal porphyrin synthesis
C) Disorders of hemoglobin alpha chain synthesis
D) Abnoral synthesis of hemoglobin beta-chain
E) Impaired heme synthesis

86 Examination of 27-year-old patient revealed pathological changes in liver and brain. Blood plasma analysis revealed an abrupt decrease in the copper concentration, urine analysis revealed an increased copper, concentration. The patient was diagnosed with Wilson's degeneration. To confirm the diagnosis it is necessary to study the activity of the following enzyme in blood serum:
A) Leucine aminopeptidase
B) Xanthine oxidase
C) Alcohol dehydrogenase
D) Ceruloplasmin
E) Carbonic anhydrase

87 Examination of a 56-year-old female patient with a history of type 1 diabetes revealed a disorder of protein metabolism that is manifested by aminoacidemia in the laboratory blood test values, and clinically by the delayed wound healing and decreased synthesis of antibodies. Which of the following mechanisms causes the development of aminoacidemia?
A) Increased proteolysis
B) Decrease in the concentration of amino acids in blood
C) Albuminosis
D) Increase in the oncotic pressure in the blood plasma
E) Increase in low-density lipoprotein level

88 Examination of a patient revealed hyperglycemia, glycosuria, hyperketonemia and ketonuria, polyuria. Which type of acid-base balance disorder is observed in this case?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Metabolic alkalosis
D) Respiratory acidosis
E) Acid-base balance is not affected

89 Factors of nonspecific immunity are:
A) Complement system
B) Interferon
C) Lysozyme
D) All above mentioned
E) Nothing from above mentioned

90 Heme synthesis is regulated by feedback mechanism at the stage of:
A) Incorporation of iron ion into protoporphyrin
B) Formation of δ-aminolevulinic acid
C) Condensation of porphobilinogen molecules
D) Formation of protoporphyrin III
E) Synthesis of porphobilinogen

91 Hemoglobin of adultsis a protein-tetramer consisting of two α- and two β-peptide chains. What is the structure of this protein?
A) Tertiary
B) Secondary
C) Quartenary
D) Primary
E) -

92 Hereditary defects in heme synthesis enzymes are associated with the increased sensitivity of patients' skin to sunlight. Urine is red. Which hemoglobin metabolites are accumulated causing such symptoms?
A) Mesobilinogens
B) Stercobilinogens
C) Urobilinogens
D) Porphyrinogens
E) Bilirubin

93 Human red blood cells do not contain mitochondria. What is the main pathway for ATP production in these cells?

A) Creatine kinase reaction
B) Anaerobic glycolysis
C) Cyclase reaction
D) Aerobic glycolysis
E) Oxidative phosphorylation

94 IgA takes part in the following reactions:
A) Local immunity
B) Bacteria neutralizing
C) Comlement binding
D) Local immunity and bacteria neutralizing
E) All the above mentioned

95 IgE takes part in following reactions:
A) Local immunity
B) Allergy reactions
C) Comlement binding
D) Primary immune responce
E) All the above mentioned

96 Immune reactions of organism are provided by high-specific interaction "antigen-antibody". Such specificity of immunoglobulins depends on their molecular structure. Immunoglobulins are:
A) Lipoproteins
B) Metalloproteins
C) Chromoproteins
D) Glycoproteins
E) Nucleoproteins

97 Immune system by means of cellular and humoral mechanisms provides the distinguishing, binding and destroying of antigens. The main classes of blood immunoglobulines, which realize humoral immune response, are:
A) Ig A and Ig E
B) Ig G and Ig M
C) Ig D and Ig A
D) Ig A and Ig M
E) Ig E and Ig D

98 Immunoglobulins are synthesized by:
A) T-lymphocytes
B) Neutrophyls
C) Plasmacytes
D) Macrophages
E) All the above mentioned

99 In a number of hemoglobinopathies, amino acid substitutions occur in the α- and β- chains of hemoglobin. Which of them is typical for HbS (sickle cell anemia)?
A) Aspartate-lysine
B) Alanine-serine
C) Methionine-histidine
D) Glycine-serine
E) Glutamate valine

100 In diabetes mellitus the activation of fatty acid oxidation leads to ketosis. Which disorders of acid-base balance can lead to excessive accumulation of ketone bodies in the blood?
A) Metabolic alkalosis
B) There will be no changes
C) Metabolic acidosis
D) Respiratory acidosis
E) Respiratory alkalosis

101 In erythrocytes, an additional intermediate metabolite of glycolysis is formed in a significant amount, which plays the role in allosteric regulation of hemoglobin function. Choose this metabolite.
A) 3-Phosphoglycerate
B) 1,3-Bisphosphoglycerate
C) C.2.3-Bisphosphoglycerate
D) 2-Phosphoglycerate
E) Phosphoenolpyruvate

102 In fever development the increase of "acute phase" proteins (ceruloplasmin, fibrinogen, C-reactive protein) is characteristic. Which mechanism of this is possible?
A) Proliferate action of IL-2 to T-lymphocytes
B) Damage action of temperature to organism cells
C) Degranulation of tissue basophils
D) Stimulating influence of IL-1 to hepatocytes

103 In patients with erythropoietic porphyria (Gunther's disease), teeth are fluoresced in the ultraviolet with a bright red color, the skin is sensitive to light, urine is red. Which enzyme insufficiency is observed?
A) Delta-aminolevulinate synthase
B) Uroporphyrinogen decarboxylase
C) Uroporphyrinogen I synthase
D) Ferrochelatase
E) Uroporphyrinogen III cosyntase

104 Inflammatory processes in the body are associated with the synthesis of acute phase proteins. Their synthesis is stimulated by:
A) Interleukin-1
B) Immunoglobulins
C) Interferons
D) Biogenic amines
E) Angiotensins

105 Inhibition of respiratory center in the brain by

narcotic drugs results in:
A) Respiratory acidosis
B) Metabolic acidosis
C) Hyperglycemia
D) Respiratory alkalosis
E) Metabolic alkalosis

106 It has been known that the pentose phosphate pathway actively functions in erythrocytes. What is the main function of this metabolic pathway in erythrocytes?
A) Prevention of lipid peroxidation
B) Detoxication of xenobiotics
C) Oxidation of glucose into lactate
D) Activation of microsomal oxidation
E) Enhancement of lipid peroxidation

107 Laboratory investigation of the blood respiratory function showed the worsened CO2 transport. Which enzyme is deficient in the red blood cells?
A) 2,3-Diphosphoglycerate
B) Adenylate cyclases
C) Carbonic anhydrase
D) Protein kinases
E) Phosphorylases

108 Marked increase of activity of MB-forms of CPK (creatine phosphokinase) and LDH-1 was revealed by examination of the patient's blood. What is the most probable pathology?
A) Myocardial infarction
B) Hepatitis
C) Pancreatitis
D) Rheumatism
E) Cholecystitis

109 Mature RBC contains all except one from the following list. Point out it:
A) Enzymes of HMP shunt pathway
B) Enzymes of TCA cycle
C) Glycolytic enzymes
D) Pyridine nucleotides
E) Hemoglobin

110 Metabolic acidosis is observed in patient` organism due to the accumulation of:
A) Sodium ions
B) Glucose
C) Pyruvate
D) Fructose
E) Glycerol

111 Molecular analysis of the hemoglobin in a patient with anemia revealed a 6Glu substitution for 6Val in β-chain. What is the molecular mechanism of the pathology?
A) Chromosomal mutation
B) Genomic mutation
C) Gene mutation
D) Gene amplification
E) Gene transduction

112 Most affinity of blood plasma iron ion is seen with one compound listed below. Choose it:
A) Transferrin
B) Ferritin
C) Hemoglobin
D) Ceruloplasmin
E) Albumin

113 Name the blood plasma protein used as inhibitor of some proteolytic enzymes:
A) Albumin
B) Immunoglobulin G
C) C-reactive protein
D) Alpha1-antitrypsin
E) Ceruloplasmin

114 Name the enzyme which is the indicator of myocardium damage if its activity will be increased in the blood plasma in 10 times or more:
A) Alkaline phosphatase
B) Malate dehydrogenase
C) Glutamate dehydrogenase
D) Guanine transaminase
E) Aspartate transaminase

115 Name the excretory enzyme of the blood plasma:
A) Alkaline phosphatase
B) Malate dehydrogenase
C) Glutamate dehydrogenase
D) Alanine transaminase
E) Aspartate transaminase

116 Name the factor of blood coagulation system needed for fibrin formation from fibrinogen:
A) Plasmin
B) Heparin
C) Thrombin
D) Prothrombin
E) Lysine

117 Name the index of blood plasma which helps to recognize the change in biliary system function at cholestasis state:
A) Fibrinogen

B) Conjugated bilirubin
C) Uric acid
D) Urea
E) Creatine

118 Name the indexes of blood plasma whose content may be higher at insulin-dependent diabetes mellitus:
A) Glucose
B) Cholesterol
C) Pyruvate
D) Ketone bodies
E) All the indexes named above

119 Name the method used now as modern technique for the separation and determination of the content of some proteins in the blood plasma at the same time:
A) Dialysis
B) Immunoelectrophoresis
C) Spectrophotometry method
D) X-ray radiation method
E) Densitometry method

120 Name the process that can be considered in the blood, only:
A) Synthesis of proteins
B) Destruction of hormones
C) Thrombosis
D) β-Oxidation of fatty acids
E) High fatty acid synthesis

121 Neurological abnormalities, skin jaundice, the increase of blood serum unconjugated bilirubin level were revealed in sick 10-years-old child. Which enzyme disturbed synthesis leads to development of Gilbert's disease?
A) UDP-dehydrogenase
B) UDP-glucuronyltransferase
C) Glycerol kinase
D) Galactose-1-phosphate uridyltransferase

122 One of the major complications of diabetes mellitus is the development of ketoacidosis due to the accumulation of ketone bodies in the blood serum. Which form of acid-base balance disorders occurs in this case?
A) Respiratory alkalosis
B) Metabolic acidosis
C) Respiratory acidosis
D) Metabolic alkalosis

123 Osmolality of blood plasma is:
A) Osmolarity per kg of solvent
B) Osmolarity per liter of solvent
C) Osmoles of solute per kg of solvent
D) Number of osmoles of solute per liter of solution
E) A liter of solvent per 1 mole

124 Paraproteins are proteins of the γ-globulin fraction that appear in the blood plasma of people with leukemia, myeloma, lymphosarcoma. Which of the following proteins is a paraprotein capable of forming a gelatinous precipitate when the temperature decreases?
A) C-Reactive protein
B) α1-Glycoprotein
C) Fibronectin
D) Cryoglobulin
E) Ceruloplasmin

125 Patient has high photosensitivity, lesions of skin, abdominal pain, neuropsychiatric disturbances. Urine becomes of red color when leaving for some period of time. Which diagnosis is the most probable?
A) Hemolytic jaundice
B) Pellagra
C) Alkaptonuria
D) Porphyria
E) Albinism

126 Plasmacytes are formed from:
A) B-lymphocytes
B) T-lymphocytes
C) Macrophages
D) Fibroblasts
E) Nothing from above mentioned

127 Point out a blood buffer system, which is the most important in the regulation of acid-base balance:
A) Phosphate
B) Hemoglobin
C) System of blood plasma proteins
D) Bicarbonate

128 Point out normal region of blood pH:
A) 6.85-7.0
B) 7.05-7.2
C) 7.77-8.0
D) 7.38-7.4
E) 7.45-7.6

129 Point out the blood microelement:
A) Sodium
B) Copper
C) Calcium

D) Potassium
E) Magnesium

130 Point out the component of blood, which belongs to nitrogen-free compounds:
A) ATP
B) Thiamin
C) Ascorbic acid
D) Creatine
E) Glutamine

131 Point out the main blood plasma protein, participating in the blood oncotic pressure maintaining:
A) Globulin
B) Lipoprotein
C) Ceruloplasmin
D) Hemoglobin
E) Albumin

132 Point out the major transport form of triacylglycerols from the intestine to the liver and other tissues:
A) Chylomicrons
B) LDL
C) VLDL
D) IDL
E) HDL

133 Point out the most important compensatory mechanism in metabolic acidosis:
A) Hyperventilation
B) Increased NH3 excretion by kidneys
C) Increased filtration of phosphates
D) Increased HCO3- production
E) Urea production in the liver

134 Point out the most mobile and important buffer in extracellular fluid:
A) Hemoglobin
B) Phosphate
C) Protein
D) H2CO3/HCO3-
E) Na+/K+

135 Point out the most powerful buffer system of the blood:
A) The bicarbonate buffer system
B) The phosphate buffer system
C) The protein buffer system
D) Haemoglobin buffer system
E) The acetate buffer system

136 Point out the most probable location of the plasma proteins synthesis:
A) Kidneys
B) Muscle tissue
C) Nervous tissue
D) Liver
E) Lungs

137 Point out the non-protein nitrogenous component of the blood plasma that is in a level about 50% of total non-protein nitrogen:
A) Uric acid
B) Creatine
C) Creatinine
D) Amino acids
E) Urea

138 Point out the permissible range of the pH fluctuation in the blood:
A) 8.0-8.61
B) 7.36-7.44
C) 7.81-7.94
D) 6.2-6.84
E) 6.85-7.0

139 Point out the protease of blood that helps to solvate the fibrin clot:
A) Plasminogen
B) Plasmin
C) Thromboplastin
D) Antifibrinolysinogen
E) Lysokinase

140 Point out the protease of blood that helps to solvate the fibrin clot:
A) Plasminogen
B) Lysolipase
C) Plasmin
D) Antifibrinogen
E) Tromboplastin

141 Point out the protein of blood plasma which provides the processes of coagulation hemostasis?
A) Albumin
B) Haptoglobin
C) LDL
D) Ceruloplasmin
E) Fibrinogen

142 Point out the protein, which is not observed in the blood serum of healthy people:
A) Cryoglobulin
B) Albumin
C) Transferin
D) Haptoglobin

E) Alpha2-macroglobulin

143 RBCs don't contain mitochondria. What is the major pathway of ATP synthesis in them?
A) Creatine kinase reaction
B) Adenylate kinase reaction
C) Oxidative phosphorylation
D) Aerobic glycolysis
E) Anaerobic glycolysis

144 RBCs require energy in the form of ATP. Which process provides these cells with the necessary amount of ATP?
A) Pentose phosphate pathway
B) Beta-oxidation of fatty acids
C) Anaerobic glycolysis
D) Aerobic glucose oxidation
E) Tricarboxylic acid cycle

145 Renal insufficiency was proposed to look at patient due to the change of the ratio [Urea]/Residual nitrogen (80%). Name the index of the blood plasma whose content will prove this diagnosis:
A) High levels of sodium ion
B) Low levels of copper ion
C) High levels of glucose
D) High levels of creatinine
E) High levels of creatine

146 Rest (residual) nitrogen and urea were determined in the patient's blood. The proportion of urea in the residual nitrogen is significantly reduced. Which organ is affected?
A) Stomach
B) Liver
C) Kidney
D) Intestine
E) Heart

147 Rest (residual) nitrogen in the patient's blood was 48 mmol/L, urea - 15.3 mmol/L. Which organ is affected?
A) Stomach
B) Liver
C) Kidney
D) Intestine
E) Spleen

148 Severe form of hypoxia (shortness of breath, cyanosis) developed in a 3-month-old child. Which process of hemoglobin formation is affected?
A) Replacement of hemoglobin F to hemoglobin M
B) Replacement of hemoglobin F to hemoglobin S
C) Replacement of hemoglobin F to glycosylated hemoglobin
D) Replacement of hemoglobin F to methemoglobin
E) E. Replacement of hemoglobin F to hemoglobin A

149 Sickle cell anemia is common in some areas of South Africa. In this case, erythrocytes have the shape of a sickle due to the replacement of the amino acid glutamate with valine in the molecule of hemoglobin. What causes this disease?
A) Genomic mutation
B) Crossingover
C) Gene mutation
D) Impaired mechanisms for the implementation of genetic information
E) Transduction

150 Skin, scleras and mucosa are of yellow color in patient. Urine has the color of dark beer, feces are acholic. The increased level of both direct and indirect bilirubin, the enhanced AlAT, LDH4 and LDH5 activities are revealed in bloo~Bilirubin is found in the urine. Which is the type of jaundice?
A) Inherited
B) Hemolytic
C) Obstructive
D) Hepatic
E) Neonatal physiologic jaundice

151 Substrates for the synthesis of pyrrol rings of porphyrin are:
A) Acetyl-CoA and glycine
B) Acetoacetyl-CoA and serine
C) Succinyl-CoA and serine
D) Succinyl-CoA and glycine
E) Malonyl-CoA and serine

152 Substrates for the synthesis of pyrrol rings of porphyrin are:
A) Acetyl-CoA and glycine
B) Acetoacetyl-CoA and serine
C) Succinyl-CoA and serine
D) Succinyl-CoA and glycine
E) Malonyl-CoA and serine

153 Symptoms of liver cirrhosis with ascites and edema of lower extremities appeared in a patient who had hepatitis C and constantly consumed alcohol. Which changes in blood composition underlied edema development?
A) Hypoglobulinemia
B) Hypoalbulinemia
C) Hypokaliemia
D) Hypoglycemia

E) Hypocholesterolemia

154 The activation of the inflammatory process, some autoimmune and infectious diseases lead to a sharp increase in the level of acute phase proteins in the blood plasma. Which of the following proteins can form a gel when the serum is cooled?
A) Haptoglobin
B) Cryoglobulin
C) C-reactive protein
D) α2-Macroglobulin
E) Ceruloplasmin

155 The activities of lactate dehydrogenase (LDH1, LDH2), aspartate aminotransferase, creatine kinase in the blood plasma of patient are increased. In which of the following organs (tissues) is the pathological process probably developing?
A) In the myocardium
B) In the skeletal muscles
C) In adrenal glands
D) In the connective tissue of cartilages
E) In the liver

156 The activities of lactate dehydrogenase (LDH4, LDH5), alanine aminotransferase, carbamoyl phosphate ornithine transferase are increased in the blood plasma of patient. What organ (tissue) is the pathological process developing in?
A) Skeletal muscles
B) Myocardium
C) Liver
D) Kidneys
E) Bones

157 The amount of plasma proteins changed in a person after physical exercise under high temperature. What is the cause of such changes?
A) Absolute hyperproteinemia
B) Dysproteinemia
C) Absolute hypoproteinemia
D) Relative hyperproteinemia
E) Paraproteinemia

158 The content of residual (rest) nitrogen in patient's blood is 48 mmol/L; urea level reaches 15.3 mmol/L. Which organ disease may be the cause of such changes:
A) Spleen
B) Liver
C) Stomach
D) Kidney
E) Pancreas

159 The content of total protein in blood plasma is normal. Which of the below - mentioned parameters corresponds to physiological norms?
A) 33-45 g/L
B) 50-60 g/L
C) 55-70 g/L
D) 65-85 g/L
E) 85-95 g/L

160 The content of total protein in blood plasma is normal. Which of the below mentioned parameters (g/L) corresponds to physiological norm?
A) 33-45
B) 50-60
C) 55-70
D) 65-85
E) 85-95

161 The examination of several classes of immunoglobulins in newborns can be used as diagnostic test to verify the fetal infection. Which class of immunoglobulins can pass through placenta?
A) Ig M
B) Ig A
C) Ig G
D) Ig E
E) Ig D

162 The excessive accumulation of iron in tissues is observed in a 42-year-old woman. The accumulation occurs due to transferrin deficiency. Each of the following statements about transferrin is correct except:
A) Transferrin is a protein that binds iron and is secreted by neutrophiles
B) Transferrin is a glycoprotein secreted by parenchymatous cells of liver
C) Iron binding by transferrin is the mechanism of protection from iron toxicity
D) Iron and transferrin amounts are proportional in blood
E) Transferrin directs a flow of iron to cells which actively synthesize hemoglobin

163 The high level of lactate dehydrogenase (LDH) isozymes concentration showed the increase of LDH-1 and LDH-2 in a patient's blood plasma. Point out the most probable diagnosis.
A) Diabetes mellitus
B) Skeletal muscle dystrophy
C) Myocardial infarction
D) Acute pancreatitis
E) Viral hepatitis

164 The hypoproteinemia (30-40 g/l) is indicated at nephritis syndrome, and it causes an edema. Point out the protein of the blood plasma, whose content is decreased in this case:
A) Fibrinogen
B) Albumin
C) LDL
D) Interferon
E) Transferrin

165 The prolonged action of a number of antibiotics and sulfonamides is caused by the fact that they circulate in the blood for a long time in a complex with:
A) Hemoglobin
B) Albumin
C) Haptoglobin
D) Transferrin
E) Hemopexin

166 The synthesis of heme is regulated by feed-back mechanism on the stage:
A) Incorporation of iron ion into protoporphyrin
B) Formation of δ-aminolevulinic acid
C) Condensation of porphobilinogen molecules
D) Formation of protoporphyrin III
E) Synthesis of porphobilinogen

167 The toxic damage to the liver cells with their impaired functions led to the development of edema. Which changes in the blood plasma composition are the main causes of edema in this case?
A) An increase in the content of globulins
B) Reduction of fibrinogen content
C) An increase in albumin content
D) Reduction of the content of globulins
E) Reduction of albumin content

168 The toxic damage to the liver leads to the impairment of its protein-synthesizing function. Which kind of dysproteinemia is observed in this case?
A) Absolute hyperproteinemia
B) Relative hypoproteinemia
C) Absolute hypoproteinemia
D) Relative hyperproteinemia
E) Paraproteinemia

169 There are several dozens of proteins in blood plasma of healthy individuals. New proteins may appear in blood during various diseases, in particular "acute phase proteins." One of the following proteins belongs to this group:
A) Immunoglobulin A
B) C-Reactive protein
C) Prothrombin
D) Immunoglobulin G
E) Transcobalamin

170 There is an abnomal formation of a metalloprotein, which is the source of iron for heme synthesis, in the liver of a patient with iron deficiency anemi~How is this protein called?
A) Ceruloplasmin
B) Ferritin
C) Hemosiderin
D) Myoglobin
E) Cytochrome c

171 To prevent the long-term consequences of four-day malaria, a patient was prescribed with primaquin. Abdominal and heart pain, dyspepsia, general cyanosis, hemoglobinuria appeared on the third day after the beginning of treatment with therapeutic doses of the drug. What was the reason for the development of the side effects?
A) Potentiation of action by other drugs
B) A decrease in activity of microsomal liver enzymes
C) Genetic insufficiency of glucose-6-phosphate dehydrogenase
D) Low urinary excretion of the drug
E) Cumulation of the drug

172 To study blood serum proteins, it is possible to use different physical and physicochemical methods. In particular, blood serum albumins and globulins can be separated using the method of:
A) Polarography
B) Dialysis
C) Spectrography
D) Electrophoresis
E) Refractometry

173 Under the action of oxidizing agents (hydrogen peroxide, nitric oxide, etc.), hemoglobin that contains Fe^{2+} is converted to a compound containing Fe^{3+} that is unable to carry oxygen. What is the name of this compound?
A) Methemoglobin
B) Carboxyhemoglobin
C) Carbhemoglobin
D) Oxyhemoglobin
E) Glycosylated hemoglobin

174 What is the action of bradykinin on vessels?
A) Vasodilation
B) Vasoconstriction

C) An increase in blood pressure
D) An increase in blood clotting
E) A decrease in vascular permeability

175 What is the cause of metabolic acidosis development?
A) Increased production and decreased oxidation of ketone bodies
B) Increased production and decreased oxidation of lactate
C) Loss of basic equivalents
D) Ineffective hydrogen ions secretion, retention of acids
E) All options mentioned above are correct

176 What is the cause of metabolic alkalosis development?
A) Uncompensated loss of hydrogen ions
B) Loss of potassium
C) Retention of alkalis
D) Intake of alkalis
E) All options mentioned above are correct

177 What of the following enzymatic actions is in need for vitamin K use?
A) Activation of factor X of blood coagulation system
B) Regulation of blood calcium levels
C) Conversion of fibrinogen to fibrin
D) Synthesis of prothrombin
E) Transcriptional control of fibrinogen synthesis

178 Which blood plasma protein binds and transports copper?
A) Transferrin
B) Bradykinin
C) C–reactive protein
D) Kallikrein
E) Ceruloplasmin

179 Which buffer system plays an important role in supporting pH of urine?
A) Phosphate
B) Hemoglobin
C) Bicarbonate
D) Protein

180 Which components of blood residual (rest) nitrogen fraction prevail in productive azotemia?
A) Ketone bodies
B) Lipids, carbohydrates
C) Amino acids, urea
D) Porphyrins, bilirubin

181 Which fraction of blood globulins provides humoral immunity performing a function of antibodies?
A) α1-Globulins
B) β-Globulins
C) γ-Globulins
D) Cryoglobulins
E) α1-Macroglobulins

182 Which is the action of bradykinin on vessels?
A) Vasodilation
B) Vasoconstriction
C) The increase of blood pressure
D) Increasing blood clotting
E) The decrease of vessel wall permeability

183 Which level of residual (rest) nitrogen is normal for adults?
A) 14.3-25 mmol/L
B) 25-38 mmol/L
C) 42.8-71.4 mmol/L
D) 70-90 mmol/L

184 Which level of residual nitrogen is normal for adults?
A) 14,3-25 mmol/L
B) 25-38 mmol/lL
C) 42,8-71,4 mmol/lL
D) 70-90 mmol/L

185 Which mechanisms provide blood pH stability?
A) CO2 removal by lungs
B) Buffer systems
C) Hydrogen ion secretion by kidney
D) Metabolism of substances
E) All options mentioned above are correct

186 Which mechanisms provide the pH stability of blood?
A) CO2 removal by lungs
B) Buffer systems
C) Hydrogen ion secretion by kidney
D) Sodium reabsorption by kidney
E) All the above mentioned

187 Which of the below mentioned pH values corresponds to normal pH in blood?
A) 7.25 - 7.31
B) 7.40 - 7.55
C) 7.35 - 7.45
D) 6.59 - 7.0
E) 4.8 - 5.7

188 Which of the following statements about porphyrias is not correct?
A) Genetic disturbance of heme synthesis
B) They are divided into erythropoietic and hepatic
C) They are accompanied by the increased excretion of bile pigments in urine and feces
D) They manifest by dermatitis and neuropsychiatric disorders E. Some symptoms are similar to those caused by lead poisoning

189 Which of the following statements about porphyrias is uncorrect?
A) Genetic disturbance of heme synthesis
B) They are divided into erythropoietic and hepatic
C) They are accompanied by the increased excretion of bile pigments with urine and feces
D) They are manifested by dermatitis and neuropsychiatric disturbances
E) Some symptoms are similar to produce by light

190 Which of the pH values mentioned below corresponds to normal blood pH?
A) 7.25-7.31
B) 7.40-7.55
C) 7.35-7.45
D) 6.59-7.0
E) 4.8-5.7

191 Which physical and chemical properties of blood are provided by electrolytes?
A) Oncotic pressure
B) Erythrocyte sedimentation rate
C) Osmotic pressure
D) Viscosity

192 Which physical and chemical property of protein is the base of the method of electrochemical determination of blood protein spectrum?
A) Viscosity
B) Presence of charge
C) Ability to be denaturated
D) Hydrophility and ability to swell
E) Optical activity

193 Which physico-chemical property of protein is the base of the method of electrochemical determination of blood protein spectrum?
A) Viscosity
B) Presence of charge
C) Ability to denaturation
D) Hydrophility and ability to swelling
E) Optical activity

194 Which protein binds to hemoglobin in order to transport it to the reticuloendothelial system of the liver?
A) Haptoglobin
B) Albumin
C) Ferritin
D) Transferrin
E) Ceruloplasmin

195 Wilson disease (hepatocerebral dystrophy) is accompanied by low ceruloplasmin levels. What is the consequence of this transport protein insufficiency?
A) Breakdown of tissue proteins
B) Complex formation of amino acids with copper
C) Decarboxylation of amino acids
D) Urea synthesis
E) Transamination of amino acids

196 Wilson disease is associated with a decrease in the plasma content of the protein that transports copper ions. Select this protein.
A) Ceruloplasmin
B) Transferrin
C) Haptoglobin
D) Fibronectin
E) C-Reactive protein

197 A biochemical urine analysis has been performed for a patient with progressive muscular dystrophy. In the given case muscle disease can be confirmed by the high content of the following substance in urine:
A) Urea
B) Porphyrin
C) Hippuric acid
D) Creatine
E) Creatinine

198 A boy (of 10 years) complains of general weakness, dizziness, and tiredness. A mental retardation is observed. A concentration of valine, leucine, isoleucine is high in blood and urine. Urine has a specific odour. Name the probable diagnosis:
A) Maple syrup urine disease
B) Phenylketonuria
C) Histidinemia
D) Tyrosinemia
E) Hartnup disease

199 A female patient with an acute attack of hepatic colic was hospitalized to the gastroenterological department. Body temperature is 38ºC, sclera, mucous membranes and skin are icteric, urine is dark, feces are lightly colored. The

patient complains of itching. What is the cause of jaundice in this patient?
A) Hepatocyte destruction
B) Enhanced destruction of erythrocytes
C) Obstruction of the bile duct
D) Impaired lipid metabolism
E) Prolonged use of carotene - containing products

200 A female was hospitalized with complaints of weakness, irritability, sleep disturbance. The skin and sclera are yellow. An elevated level of direct bilirubin is found. Feces are acholic. Dark color (bile pigments) of urine is observed. Which type of jaundice should be diagnosed?
A) Hemolytic
B) Mechanical
C) Parenchymal
D) Gilbert syndrome
E) Crigler-Najjar syndrome

201 A male complains of nausea, vomiting, pain in the right hypochondrium. The patient has skin and sclera jaundice, increased body temperature, enlarged liver, dark urine, hypocholic feces, hyperbilirubinemia (due to direct and indirect bilirubin), bilirubinuria, urobilinuria, hypoproteinemia, decreased blood clotting. Which of the conditions mentioned below are characterized by such changes?
A) Hemolytic jaundice
B) Cellular parenchymal jaundice
C) Acute pancreatitis
D) Pedicular jaundice
E) Acute cholecystitis

202 A male with yellow skin has anemia, splenomegaly, hyperbilirubinemia (indirect bilirubin), urobilinuria, dark-yellow feces. These changes are the most typical for:
A) Hemolytic jaundice
B) Obstructive jaundice
C) Hepatocellular jaundice
D) Gilbert's syndrome
E) Liver insufficiency

203 A newborn has physiological jaundice. The level of free bilirubin in the blood significantly exceeds the normal values. Which enzyme deficiency is observed?
A) Transaminases
B) Xanthine oxidases
C) Adenosine deaminases
D) Hemoxygenase
E) UDP-glucuronyl transferase

204 A newborn has signs of jaundice. The administration of small doses of phenobarbital, which induces the synthesis of UDP-glucuronyl transferase, has contributed to the improvement of the child's health. Which of the following processes is activated in this case?
A) Conjugation
B) Microsomal oxidation
C) Tissue respiration
D) Gluconeogenesis
E) Glycogen synthesis

205 A patient complains about dyspnea provoked by the physical activity. Clinical examination revealed anaemia and presence of the para-protein in the zone of gamma-globulins. To confirm the myeloma diagnosis it is necessary to determine the following index in the patient's urine:
A) Ceruplasmin
B) Bilirubin
C) Antitrypsin
D) Bence Jones protein
E) Haemoglobin

206 A patient has been admitted to the contagious isolation ward with signs of jaundice caused by hepatitis virus. Which of the symptoms given below is strictly specific for hepatocellular jaundice?
A) Bilirubinuria
B) Cholemia
C) Hyperbilirubinemia
D) Increase of ALT, AST level
E) Urobilinuria

207 A patient has been suffering from pain in the right hypochondrium for several days after eating fatty food. The jaundice of the sclera and skin is visually noted. Acholic feces are observed. Urine has a "color of beer." Which substance is present in the urine and causes a dark color of urine?
A) Ketone bodies
B) Indirect bilirubin
C) Stercobilin
D) Bilirubin glucuronides
E) Direct bilirubin

208 A patient has immune hemolytic anemia. Which parameter is increased in the serum at most?
A) Indirect bilirubin
B) Direct bilirubin
C) Protoporphyrin
D) Mesobilinogen
E) Stercobilinogen

209 A patient suffers from hepatic cirrhosis. Examination of which of the following substances excreted by urine can characterize the state of antitoxic function of liver?
A) Uric acid
B) Creatinine
C) Ammonium salts
D) Hippuric acid
E) Amino acids

210 A patient was hospitalized with complaints of general weakness, abdominal pain, and bad appetite. Symptoms of jaundice were observed. Blood serum total bilirubin content was 77.3 μmol/L; conjugated bilirubin level was 70.76 μmol/L. Which diagnosis is the most possible?
A) Obstructive jaundice
B) Acute hepatitis
C) Cirrhosis of liver
D) Hepatic jaundice
E) Hemolytic jaundice

211 A patient with encephalopathy was admitted to the neurological in patient department. There was revealed a correlation between increasing of encephalopathy and substances absorbed by the bloodstream from the intestines. What substances that are formed in the intestines can cause endotoxemia?
A) Indole
B) Ornithine
C) Acetacetate
D) Butyrate
E) Biotin

212 A patient with jaundice has the increased content of direct bilirubin and bile acids in blood. There is no sterocilinogen in the urine. Which type of jaundice can be diagnosed?
A) Parenchymal
B) Hepatic
C) Hemolytic
D) Posthepatic
E) Mechanical

213 A patient with signs of jaundice due to viral hepatitis was hospitalized to the infectious department. Which of the following parameters is strictly specific, distinguishing parenchymal jaundice from the other types?
A) Cholechemia
B) Hyperbilirubinemia
C) Bilirubinuria
D) Increased activity of ALT, ASAT
E) Urobilinuria

214 A patient with symptoms of acute alcohol poisoning was brought to the hospital. What carbohydrates metabolism changes are typical for this condition?
A) The anaerobic glucose metabolism predominates in muscles
B) The gluconeogenesis is increased in the liver
C) The breakage of glycogen is increased in the liver
D) The gluconeogenesis velocity in the liver is decreased
E) The anaerobic breakage of glucose is increased in muscles

215 A premature newborn on the second day of life has yellow coloration of the skin and mucous membranes. Which enzyme temporary deficiency is the cause of this condition?
A) UDP-glucuronyltransferase
B) Aminolevulinate synthase
C) Hemoxygenases
D) Heme synthase
E) Biliverdin reductase

216 A young male has a hereditary UDP-glucuronyl transferase deficiency. Laboratory tests allowed determining hyperbilirubinemia, mainly due to the increase in blood concentrations of:
A) Direct bilirubin
B) Urolilinogen
C) Indirect bilirubin
D) Sterkobilinogen
E) Biliverdin

217 All of the following may have a physiological antioxidant role except
A) Beta-carotene
B) Vitamin C
C) Selenium
D) Iron
E) Vitamin E

218 Ammonia content in urine is important index of acid-base balance of organism. Ammonia amount increases both under respiratory and metabolic acidoses. It is connected with following enzymes stimulation in the renal epithelial cells under acidosis:
A) Glutaminase
B) Krebs cycle
C) Carboanhydrase
D) ATP-ase

E) Hyaluronidase

219 Appearance of albumins in the urine of diseased person may be at:
A) Acute nephritis
B) Chronical nephritis
C) Severe form of diabetes mellitus
D) Pyelonephritis
E) All that is placed above

220 Arthritis occur in
A) Alkaptonuria
B) Cystinosis
C) Maple syrup diseases
D) Homocystinuria
E) Addison's disease

221 As a result of the transfusion of Rh antigen incompatible blood, hemolytic jaundice developed in a patient. Which laboratory blood parameter can confirm this type of jaundice?
A) Accumulation of urobilinogen
B) A decrease in the content of unconjugated bilirubin
C) Accumulation of unconjugated bilirubin
D) Reduction of the content of sterbilin
E) Reduction of the content of conjugated bilirubin

222 Barbiturates activate UDP-glucuronyl transferase synthesis in the liver, which causes the formation of:
A) Direct bilirubin
B) Indirect bilirubin
C) Biliverdin
D) Protoprophyrine
E) Heme

223 Benzoic acid causes the toxic effect at its accumulation in the liver. Choose the main conjugative agent to detoxify it:
A) Glycine
B) PAPS
C) S-adenosyl methionine
D) Glutathione
E) Acetyl-CoA

224 Benzoic acid has the formula C6H5-COOH and causes the toxic effect at its accumulation in the liver. Choose the main conjugative agent for this substance:
A) Glycine
B) PAPS
C) S-adenosyl methionine
D) Glutathione
E) Urea

225 Bilirubin content (indirect bilirubin) in a newborn is increased; feces are intensively colored (the enhanced level of stercobilin). Bilirubin is not found in urine. Which type of jaundice may be diagnosed?
A) Hepatocellular
B) Hemolytic
C) Obstructive
D) Inherited
E) Neonatal physiologic jaundice

226 Choose metabolites of methanol which may be produced in the liver:
A) Acetaldehyde + Acetic acid
B) Formaldehyde + Formic acid
C) Pyruvate + Pyruvic acid
D) Fumarate + Fumeric acid
E) Glyceroaldehyde + Glycerol

227 Choose normal amount of proteins excreted in urine/24 hours.
A) Less than 150 mg
B) 200 mg - 225 mg
C) 450 mg – 500 mg
D) More than 800 mg
E) 150 mg – 250 mg

228 Choose one wrong continuation of a phrase: Oxidation of ethanol…:
A) Occurs, basically, in a liver
B) Is catalyzed by alcohol dehydrogenase
C) Is slowed down at increase NADH/NAD+ in a cell
D) Can proceed under microsomal system action
E) Results in the formation of an intermediate product of Pentose phosphate cycle

229 Choose one wrong continuation of a phrase: Phase I of xenobiotics transformation:
A) Is carried out by enzymes of endoplasmic reticulum
B) Demands presence of NADPH
C) Results in increase of polarity of a substance
D) Occurs in anaerobic conditions
E) Proceeds at participation of cytochrome P450

230 Choose the correct statement about hepatic monooxygenases linked with cytochrome P450 enzyme.
A) Located mainly in smooth EPR
B) Catalyzes oxidation, reduction and hydrolysis reactions at the same time

C) Certain drug inactivate and certain drug enhance their reactions
D) Positions A, C are correct
E) Their action always causes the detoxification of xenobiotics

231 Choose the exogenous factor (the drug) that can induce the UDP-glucuronosyltransferase gene expression in the liver:
A) Calcitriol
B) Thyroxine
C) Riboxin
D) Phenobarbital
E) Thiamine diphosphate

232 Choose the form of the bile pigment, which is the normal urine component:
A) Uroporphyrin
B) Unconjugated bilirubin
C) Conjugated bilirubin
D) Mesobilinogen
E) Stercobilinogen

233 Choose the main biochemical tests for diagnostics of kidney diseases:
A) Urea content in the blood plasma and in the urine
B) Creatinine content in the blood and urine
C) Sodium ions content in the blood and urine
D) N-acetyl-beta-D-glucosaminidase activity (blood serum, urine)
E) All that is placed above

234 Choose the process that is not placed in the liver:
A) Urea synthesis
B) Bile acid synthesis
C) Detoxification of xenobiotics
D) Cortisol synthesis
E) Deposition of fat soluble vitamins

235 Choose the right continuation of the statement: "In mammalian bile, the bile acids are normally present____".
A) In their free form
B) As cholesterol esters
C) As conjugated with glycine or taurine
D) As conjugated with beta-glucuronic acid
E) As conjugated with bilirubin

236 Choose the specific gravity region (g/ml) for urine of healthy person:
A) 1.005-1.015
B) 1.030-1.040
C) 1.015-1.020
D) 1.030-1.040
E) Less then 1.010

237 Choose the urine component, whose concentration increases at consuming a lot of meat food:
A) Glucose
B) Protein
C) Uric acid
D) Ketone bodies
E) Fructose

238 Choose the urine index that is used to estimate detoxification function of the liver:
A) Citric acid
B) Acetyl-CoA
C) Pyruvate
D) Hippuric acid
E) Uric acid

239 Confirmation of elevation of alkaline phosphatase of hepatic origin is by
A) SGOT (Serum glutamic oxaloacetic transaminase)
B) SGPT (Serum glutamic pyruvic transaminase)
C) GGT (Gamma-glutamyl transferase)
D) LDH (Lactate dehydrogenase)
E) Acid phosphatase

240 Creatinine levels in the urine and blood are used to test kidney function. Creatinine is useful for this test because it is not significantly reabsorbed nor secreted by kidney, and metabolically it is:
A) Produced at a constant rate
B) Produced only in kidney
C) A storage form of energy
D) An acceptor of protons in renal tubules
E) A precursor for phosphocreatine

241 Daily water requirement for adults is:
A) 30-50 ml/kg
B) 75-100 ml/kg
C) 75-80 ml/kg
D) 100-120 ml/kg

242 Desulfiram is widely used in medical practice to prevent alcoholism, it inhibits aldehyde dehydrogenas~Increased level of what metabolite causes aversion to alcohol?
A) Acetaldehyde
B) Ethanol
C) Malonyl aldehyde
D) Propionic aldehyde
E) Methanol

243 Examination of a 43 y.o. anephric patient revealed anemia symptoms. What is the cause of these symptoms?
A) Folic acid deficit
B) Vitamin B12 deficit
C) Reduced synthesis of erythropoietins
D) Enhanced destruction of erythrocytes
E) Iron deficit

244 Fat dystrophy of liver is examined in the patient. The disturbance of which substance synthesis can lead to such pathology?
A) Cholic acid
B) Urea
C) Phosphatidic acid
D) Tristearylglycerin
E) Phosphatidylcholine

245 Find out the enzyme name which is specific for liver tissue, only:
A) Succinate dehydrogenase
B) Arginase
C) Alanine amino transferase
D) Aspartate amino transferase
E) Isocitrate dehydrogenase

246 Find out the enzyme of liver tissue participating in the detoxification of cyanides:
A) NADH - dehydrogenase
B) Cytochrome b
C) Thiosulfate transferase
D) Cytochrome c
E) Cytochrome P450

247 Find the correct definition of the term "xenobiotic":
A) A substance that is an obligatory component of food products
B) A substance that is unnatural for humans
C) A substance that is synthesized in small quantities in humans
D) A substance that regulates metabolism in organism
E) A substance that is a terminal product of metabolism

248 Find the enzyme participating in the function of the microsomal monooxygenase chain:
A) NADP - dehydrogenase
B) Cytochrome b
C) Cytochrome c1
D) Cytochrome c
E) Cytochrome P450

249 Find the protein name that is synthesized in the liver, only:
A) Albumin of blood plasma
B) Alpha2-macroglobulin
C) Alpha1-antitrypsin
D) Ceruloplasmin
E) All the names above are right answers

250 Glucose-6-Phosphate is the key metabolite of carbohydrate metabolism. Point out the pathway of its utilization which is present in liver:
A) Glycogenesis
B) Gluconeogenesis
C) Glycolysis
D) Hexose Monophosphate Shunt
E) All of the above

251 Goiter is a disease which is widely spread in some biogeochemical areas of the earth. Which element deficiency causes this disease?
A) Iron
B) Iodine
C) Zinc
D) Copper
E) Cobalt

252 In a patient the development of acute pancreatitis is accompanied by the obstruction of common bile duct. What can develop as a result?
A) Hepatic coma
B) Portal hypertension
C) Mechanical jaundice
D) Haemolytic jaundice
E) Parenchymal jaundice

253 In a patient with a pronounced yellowness of the skin, sclera, mucous membranes, urine became of color of dark beer, feces were lightly colored. The content of direct bilirubin is elevated, bilirubin is found in urine. Which type of jaundice is observed?
A) Obstructive
B) Parenchymal
C) Hemolytic
D) Conjugative
E) Excretory

254 In course of metabolic process active forms of oxygen including superoxide anion radical are formed in the human body. By means of what enzyme is this anion inactivated?
A) Catalase
B) Glutathione reductase
C) Peroxidase

D) Superoxide dismutase
E) Glutathione peroxidase

255 In patients with a genetic enzymatic disease (Gilbert's disease), conjugation of bilirubin in the liver is impaired. Which enzyme is blocked in this case?
A) UDP-glucosopyrophosphorylase
B) UDP-glycogentransferase
C) Ornithine carbamoyltransferase
D) UDP-glucuronyl transferase
E) Phosphoribosyl pyrophosphate amidotransferase

256 In the patient the average daily output of water is lower than its intake. Which disease can lead to that state?
A) Renal disease
B) Hepatitis
C) Pancreatitis
D) Infectious diseases
E) Myocardial infarction

257 It was found in 1970s that the cause of severe neonatal jaundice was abnormal bilirubin conjugation in hepatocytes. Which substance is used to form the conjugate?
A) Uric acid
B) Sulfuric acid
C) Lactic acid
D) Glucuronic acid
E) Pyruvic acid

258 Jaundice of the skin and mucous membranes developed in a patient after the blood transfusion. Blood levels of total and indirect bilirubin are high. Urobilin is found in the urine. Stercobilin is found in the urine. Which kind of jaundice can be suspected?
A) Hereditary
B) Obturative
C) Parenchymal
D) Jaundice of newborns
E) Hemolytic

259 Kidney insufficiency development will cause the infringements in those processes:
A) Erythropoietin synthesis and secretion
B) Calcitriol synthesis
C) Mineralization of bone tissue
D) Creatine synthesis
E) All that is placed above

260 Kidney insufficiency in patient is accompanied with:
A) Excess levels of urea in the blood plasma
B) Excess levels of potassium ions in the blood plasma
C) Disturbed clearance
D) Disturbed filtration and reabsorption processes
E) All that is placed above

261 Kidneys make all functions excepting:
A) Excretion of final products of metabolism
B) Regulation of water-salt metabolism
C) Keeping osmotic pressure
D) Regulation of blood pressure
E) Breakdown of urea to CO2 and H2O

262 Liver cirrhosis in patient is accompanied with:
A) Disturbed production of urea
B) Accumulation of bililrubin total in the blood
C) Hypoproteinemia
D) Disturbed function of coagulation system of the blood
E) All that is placed above

263 Liver does not produce one compound from the following list. Point out it:
A) Albumin
B) Gamma-globulin
C) Fibrinogen
D) Prothrombin
E) Haptoglobin

264 Liver synthesizes all the compounds from the following list EXCEPT:
A) Clotting factor II
B) Clotting factor XII
C) Urea
D) Stercobilin
E) Cholesterol

265 Monooxygenase and reductase chains of EPR (smooth part) are necessary for:
A) Saturated HFA synthesis
B) Structure modification of endogenous substrates only
C) Structure modification of xenobiotics and endogenous substrates
D) Structure modification of xenobiotics only
E) Energy reception at the oxidation of xenobiotics

266 Name organic compound which is terminal for humans and not reabsorbed in renal tubules:
A) Globulins
B) Glucose
C) Albumin
D) Creatinine

E) Bilirubin

267 Name the compound metabolized in the liver across conjugation reaction like xenobiotics:
A) Bilirubin
B) Cholesterol
C) Urea
D) Acetylcholine
E) Uric acid

268 Neurologic abnormalities, yellow skin, an increase in blood serum unconjugated bilirubin levels were found in an ill 10-year-old child. Which enzyme abnormal synthesis leads to the development of Gilbert's syndrome?
A) UDP dehydrogenase
B) UDP-glucuronyl transferase
C) Glycerol kinase
D) Galactose-1-phosphate uridyltransferase

269 One of liver functions is maintenance of glucose concentration in the blood. Point out the carbohydrate metabolic pathway in the liver that provides realization of this function at exception of diet carbohydrates:
A) Aerobic oxidation of glucose
B) Anaerobic oxidation of glucose
C) Gluconeogenesis
D) Pentose phosphate cycle
E) Glycogenesis

270 One way of acid-base balance maintenance in organism by means of kidney is ammonia salts formation. Point out the enzyme in kidney that takes part in this process:
A) Monooxygenase
B) Arginase
C) Carbamoyl phosphate synthetase
D) Glutaminase
E) Alanine amino transferase

271 Organ specific enzyme for kidneys is:
A) Lactate dehydrogenase
B) Succinate dehydrogenase
C) Aspartate aminotransferase
D) Transamidinase
E) Creatinephosphokinase

272 Point out the chemical nature of prosthetic group of cytochrome P450:
A) Nucleotide
B) Fe3+
C) Fe2+
D) Phosphate
E) Heme

273 Point out a major source of ammonia in kidney tissue:
A) Urea
B) Aspartate
C) Glutamine
D) Glutamate
E) Uric acid

274 Point out the amino acid that is conjugative agent at Quick`s test:
A) Lactic acid
B) Glycine
C) Valine
D) Leucine
E) Histidine

275 Point out the blood serum enzyme elevated in alcoholic cirrhosis of liver:
A) Alcohol dehydrogenase
B) Creatine kinase
C) Acidic phosphatase
D) Gamma-glutamyl transpeptidase
E) Aspartate transaminase

276 Point out the conjugation agent that is conjugative agent at the detoxification of heterocyclic alcohols in the liver:
A) Glutathione
B) Glycine
C) Valine
D) PAPS
E) Histidine

277 Point out the conjugation agent that is in need to detoxify heterocyclic alcohols in the liver:
A) Glutathione
B) Glycine
C) Valine
D) PAPS
E) Histidine

278 Point out the conjugation agent used for conjugated bilirubin formation in the liver cell:
A) Glycine
B) Cysteine
C) UDP-glucuronic acid
D) PAPS
E) Acetyl-CoA

279 Point out the donor of sulfate group in the conjugation phase of xenobiotics transformation:
A) Glutathione

B) UDP-glucuronic acid
C) Adenosine 3́-phosphate-5́-phosphosulfate
D) Acetyl-CoA
E) S-adenosylmethionine

280 Point out the enzyme located in the cytoplasm of hepatocytes and participating in the modification of a xenobiotic:
A) Glutamine synthetase
B) Alcohol dehydrogenase
C) Alanine amino transferase
D) Carbomoyl phosphate transferase
E) Glutamate dehydrogenase

281 Point out the enzyme of monooxygenase chain as a final electron acceptor from NADPH:
A) Cytochrome b5
B) Cytochrome b
C) Cytochrome P450
D) Cytochrome c1
E) Cytochrome aa3

282 Point out the enzyme whose activity is decreased in the blood plasma at liver cirrhosis in patient:
A) Glutamine synthetase
B) Glutamate dehydrogenase
C) Alanine amino transferase
D) Choline esterase
E) UDP - glucoronyl transferase

283 Point out the enzyme whose activity is determined in the blood plasma of patients to estimate the liver parenchyma damage:
A) Lactate dehydrogenase
B) Palmitate synthase complex
C) Alanine amino transferase
D) Cytochrome c1
E) Adenylate cyclase

284 Point out the lipid mainly synthesized in the liver:
A) Ganglyoside
B) Phospatidyl ethanol amine
C) Cholesterol
D) Phosphatidyl choline
E) Phosphatidyl inositol

285 Point out the liver enzyme participating in the neutralization of xenobiotics, their metabolites and harmful endogenous products:
A) Glutamine synthetase
B) Glutamate dehydrogenase
C) Alanine amino transferase
D) Carbomoyl phosphate synthetase
E) UDP - glucoronyl transferase

286 Point out the liver enzyme participating in the neutralization of xenobiotics, their metabolites and harmful endogenous products:
A) Glutamine synthetase
B) Glutamate dehydrogenase
C) Alanine amino transferase
D) Carbomoyl phosphate synthetase
E) UDP-glucuronyl transferase

287 Point out the liver enzyme participating in the neutralization of ammonia:
A) Glutamine synthetase
B) Glutamate dehydrogenase
C) Carbomoyl phosphate synthetase
D) Alanine amino transferase
E) All the enzymes in A, B, C positions

288 Point out the main enzyme in monooxygenase system of EPR responsible for modification of xenobiotics:
A) Glucuronyl transferase
B) Glutathione S-transferase
C) NADPH reductase
D) Cytochrome P450
E) Cytochrome C oxidase

289 Point out the main place for the location of microsomal oxidation in a cell:
A) Nucleus
B) Cytoplasm
C) EPR, smooth part
D) EPR, rough part
E) Lysosomes

290 Point out the normal component of urine:
A) Coniugated bilirubin
B) Glucose
C) Ketone bodies
D) Uric acid
E) Albumins

291 Point out the pathological component of urine:
A) Haemoglobin
B) Urea
C) Uric acid
D) Creatinine
E) Amino acids

292 Point out the pathological urine component that appears in the urine during nephritis, some

cardiac diseases, some forms of idiopathic hypertension and pregnancy pathology. Test with sulphosalicylic acid for that component is the most sensitive reaction:
A) Amino acids
B) Urea
C) Uric acid
D) Hippuric acid
E) Protein

293 Point out the pathways placed mainly in the liver:
A) 25-hydroxycholecalciferol synthesis
B) Taurine synthesis
C) Cholic acid synthesis
D) Sex hormone binding protein synthesis
E) All of the above

294 Point out the peptide participating in the conjugation of some harmful products in the liver:
A) Glutathione
B) Methionine
C) Trialanine
D) Oxytocin
E) Prolylproline

295 Point out the peptide participating in the conjugation of some harmful sulfur containing products in the liver:
A) Glutathione
B) Methionine
C) Trialanine
D) Oxytocin
E) Prolylproline

296 Point out the process of carbohydrate metabolism which is occurred only in liver:
A) Glycogenolysis
B) Glycogenesis
C) Heparin synthesis
D) Pentose phosphate pathway
E) Aerobic glycolysis

297 Point out the qualitative reaction to prove the presence of blood pigments in urine:
A) Heller's test
B) Benzidine test
C) Lugol's test
D) Trommer's reaction
E) Rozine's reaction

298 Point out the qualitative reaction to prove the presence of proteins in urine:
A) Heller's test
B) Benzidine test
C) Lugol's test
D) Trommer's reaction
E) Rozine's reaction

299 Point out the substance that appears in the urine in a case of alkaptonuria:
A) Fructose
B) Protein
C) Homogentisic acid
D) Glucose
E) Tryptophan

300 Pyruvate concentration in the patient’s urine is increased 10 times than the normal level. Choose the vitamin, the deficiency of which in the organism can be the reason of this change:
A) Vitamin B1
B) Vitamin K
C) Vitamin A
D) Vitamin C
E) Vitamin B2

301 Study of conversion of a food colouring agent revealed that utilization of this xenobiotic takes place only in one phase – microsomal oxidation (modification phase). Name an enzyme of this phase:
A) Cytochrome aa3
B) Cytochrome C oxidase
C) Cytochrome P-450
D) Cytochrome C1
E) Cytochrome b

302 Tabun, zarin, fluorodiisopropyl phosphate (phosphororganic substances) are poisons of neuro-paralytic action. Which of the mentioned enzymes is inhibited by phosphororganic substances?
A) Cytochrome P450
B) Phospholipase A2
C) Angiotensin converting enzyme
D) Tyrosine aminotransferase
E) Acetylcholine esterase

303 The activity of UDP-glucuronyl transferase is reduced at Gilbert Syndrome. What metabolite concentration will raise in the blood at these patients?
A) Direct bilirubin
B) Indirect bilirubin
C) Mesobilirubinogen
D) Stercobilinogen
E) Mesobilinogen

304 The concentration of what urine component will decrease in a case of viral hepatitis:
A) Glucose
B) Protein
C) Urea
D) Lipids
E) Carbohydrates

305 The decrease of blood residual nitrogen level was revealed in the patient with liver insufficiency. The diminishing blood nonprotein nitrogen is due to:
A) Urea
B) Ammonium
C) Amino acids
D) Bilirubin
E) Uric acid

306 The detoxification of natural metabolites and xenobiotics is disturbed in the patient's liver. The decrease of which chromoprotein activity can be reason of this?
A) Cytochrome b
B) Hemoglobin
C) Cytochrome oxidase
D) Cytochrome P450
E) Cytochrome c1

307 The development of Addison-Biermer's disease (pernicious hyperchromic anemia) is due to a deficiency of vitamin B12. Choose metal which is included to composition of this vitamin:
A) Zink
B) Cobalt
C) Molybdenum
D) Magnesium
E) Iron

308 The diuresis in healthy adults is about:
A) 400-700 ml
B) 1000-2000 ml
C) 2000-3000 ml
D) 700-900 ml
E) 3000-4000 ml

309 The patient complains of thirst and polyuria. The urine analysis revealed: daily diuresis - 10 L; urine density - 1.001 (normal – 1.012-1.024). Which disease causes the indexes?
A) Diabetes mellitus
B) Steroid diabetes
C) Thyrotoxicosis
D) Acromegaly
E) Diabetes insipidus

310 The patient has an acute attack of cholelithiasis. What will be changed in laboratory tests?
A) Positive reaction for stercobilin in feces
B) The presence of connective tissue in feces
C) Fibers in feces
D) Negative reaction for stercobilin in feces
E) The presence of starch granules in feces

311 The rate of high fatty acids synthesis in the liver is high. Point out the precursor for this process and its intracellular location:
A) Acetyl CoA, Matrix
B) Acetyl CoA, Cytoplasm
C) Glucose, Matrix
D) Amino acids, Cytoplasm
E) Amino acids, Matrix

312 The violation of the hormone secretion is followed by polyuria. Choose this hormone:
A) Adrenalin
B) Insulin
C) Testosterone
D) Vasopressin
E) Oxytocin

313 There is yellowness of the skin at newborn. The content of bilirubin in the blood is moderately increased due to indirect bilirubin. The fecal level of stercobilinogen is raised, bilirubin is not present in the urine. What type of a jaundice take place:
A) Prehepatic jaundice
B) Hepatic jaundice
C) Posthepatic jaundice
D) Crigler-Najjar syndrome
E) Gilbert syndrome

314 This lipoprotein class is synthesized in the liver, and is in need for the transport of triacylglycerols and cholesterol from the liver to tissues. Name it:
A) IDL
B) HDL
C) LDL
D) VLDL
E) Chylomicrons

315 What is the urine color when intestinal rotting processes are intensified:
A) Brown
B) Straw-yellow
C) Red
D) Green or blue
E) Beer like color

316 What organic compounds accumulate in final urine at severe form of diabetes mellitus?
A) Albumins
B) Glucose
C) Ketone bodies
D) Bilirubin conjugated
E) All that is placed in positions A, B, C

317 What process is stimulated in the liver at starvation:
A) Glycogenolysis
B) Gluconeogenesis
C) Non-oxidative phase of HMP
D) Ketogenesis
E) All of the above

318 Which following cytochrome participates in drug metabolism?
A) Cytochrome aa3
B) Cytochrome C1
C) Cytochrome C
D) Cytochrome P450
E) Cytochrome b

319 Which hormone influences the blood sodium and potassium levels?
A) Calcitonin
B) Histamine
C) Aldosterone
D) Thyroxine
E) Parathyroid hormone

320 Which is a physiological constituent of urine
A) Globulins
B) Glucose
C) Albumin
D) Creatinine
E) Bilirubin

321 Which is the normal blood calcium level (in mmol/L)?
A) 1.50-1.75
B) 1.75-2.00
C) 2.25-2.75
D) 3.0-4.5
E) 0.65-1.60

322 Which of the following substances is not excreted in the urine?
A) Conjugated bilirubin
B) Unconjugated bilirubin
C) Urobilinogen
D) Stercobilinogen

323 Wilson's disease (hepatolenticular degeneration) is accompanied by the decrease of:
A) Fibrinogen
B) Transferrin
C) Albumin
D) C-reactive protein
E) Ceruloplasmin

Situational Tasks:

1. A diabetic patient has hyperglycemia, ketonuria, glucosuria, hyperstenuria and polyuria.
a) What form of acid-base disturbance occurs in this situation?
b) How does the pH, pCO2 and blood bicarbonate content change under these conditions?
c) What compensatory mechanisms arise under these conditions?

2. The patient has an increase in serum activity of tartrate-resistant acid phosphatase activity.
a) The lesion of which organ is most likely in the patient.
b) Which group of blood enzymes does it belong to?
c) The activity of which other enzymes increases in the serum when this organ is damaged?

3. In the analysis of blood for patient the rest nitrogen was – 48 mmol/l, urea – 15.3 mmol/l.
a) What its mean "rest nitrogen"? Name its components.
b) Describe the results of analysis. What is the pathological condition? The impression of which organ is most likely.

c) What other component of residual nitrogen will be increased under these conditions?

4. In the analysis of blood in a patient with burn disease, rest nitrogen was 40 mmol/l, urea – 9.5 mmol/l.
a) Describe the results of analysis. What is the pathological condition?
b) Specify the cause of its occurrence. How will the level of amino acids in the serum change under these conditions?
c) How will the oncotic blood pressure change under these conditions? What are the consequences of this for the body?

5. In the patient of 27 years revealed the pathological changes of a liver and a brain. Diagnosed with Wilson's disease.
a) What protein deficiency is observed in the patient? Which class of globulins does it belong to?
b) Specify the biological role of this protein.
c) Which trace element is disturbed under these conditions and how will its content in blood and urine plasma change?

6. In the laboratory examination of blood serum it is established that the activity of ALT is 0.45 mmol/(h*l), AST – 0.95 mmol/(h*l).
a) Describe the results of analysis.
b) The pathology of which organ is most likely.
c) Which group of blood enzymes do they belong to?

7. The content of C-reactive protein is increased in the patient's blood.
a) Name the pathological process in the patient.
b) To which group does this protein belong? Specify the biological role of this protein group.
c) What other proteins will grow under these conditions?

8. The patient has impaired airway patency at the level of small and medium bronchi.
a) What form of acid-base disturbance occurs in this situation?
b) How does the pH, pCO2 and blood bicarbonate content change under these conditions?
c) What compensatory mechanisms arise under these conditions?

9. The patient undergoes an operation using artificial ventilation. He obtained the following parameters of laboratory studies: pH – 7.49, pCO2 – 25 mmHg, bicarbonate content – 24 mmol/l.
a) Describe the results of analysis.
b) What is the form of acid-base disturbance that occurs in this situation?
c) What compensatory mechanisms arise under these conditions?

10. A patient with severe vomiting in the laboratory study obtained the following parameters: pH – 7.50, pCO2 – 36 mmHg, bicarbonate content – 30 mmol/l.
a) Describe the results of analysis.
b) What is the form of acid-base disturbance that occurs in this situation?
c) What compensatory mechanisms arise under these conditions?

11. The patient has a concussion, accompanied by vomiting and shortness of breath. In the laboratory, the following parameters were obtained: pH – 7.50, pCO2 – 29 mmHg, bicarbonate content – 32 mmol/l.
a) Describe the results of analysis.
b) What is the form of acid-base disturbance that occurs in this situation?
c) What compensatory mechanisms arise under these conditions?

12. A patient of 20 years complains of general weakness of dizziness, rapid fatigue. The examination revealed: hemoglobin of blood 80 g/l, microscopically – erythrocytes sickle-shaped.
a) What disease can be suspected?
b) What is the molecular basis of its development?
c) What types of hemoglobin can be detected in this patient?

13. Environmental pollution caused by nitrogen compounds after a chemical industry accident. People living in the area experience severe weakness, headache, shortness of breath, dizziness.
a) What is the cause of hypoxia? What substance accumulates in red blood cells under these conditions?
b) Name the erythrocyte enzyme that counteracts the accumulation of this substance.
c) What treatment measures should be carried out under these conditions?

14. The patient has increased sensitivity to light, anemia, red color of urine. Defective uroporphyrinogen III cosyntase was found in additional studies.
a) What is the name of this pathology?
b) What is the molecular basis of its development?
c) Specify the cause of photodermatitis in these conditions.

15. A patient with kidney disease in the laboratory examination of serum found: total protein content – 50 g/l, albumin – 30 g/l.
a) Describe the results of analysis. What is the pathological condition? Specify the reason for its occurrence.
b) What is the main clinical symptom of this condition? Specify the reason for its occurrence.
c) How does the duration and toxicity of aspirin under these conditions change if it binds to albumin in the blood?

16. A 7-year-old girl has obvious signs of hemolytic anemia. Laboratory deficiency of pyruvate kinase in erythrocytes.
a) Violation of which metabolic process in erythrocytes is observed in this case?
b) What reaction is catalyzed by pyruvate kinase in erythrocytes, indicate its value?
c) What are the reasons for the development of hemolysis of erythrocytes under these conditions?

17. In order to prevent malaria, an anthropologist who was going on an expedition to South Africa was prescribed an antimalarial drug, acridine. Against the background of his admission, the patient developed hemolytic jaundice.

a) What is the cause of hemolysis of erythrocytes when taking an antimalarial drug?
b) Violation of which biochemical process and synthesis of which reducing agent is observed under these conditions?
c) What is the mechanism of anemia?

18. In a 45-year-old patient, the content of total cholesterol in the blood plasma is 4.5 mmol/l, the level of LDL is 4.0 mmol/l, HDL is 1.2 mmol/l.
a) Comment on the results of the analysis.
b) High risk of which pathology in the patient?
c) How will the risk of developing this pathology change if the serum HDL content is 0.7 mmol/l?

19. The patient has an enlarged liver and spleen (hepatosplenomegaly), xanthoma on the skin (fat deposition in the skin). The blood has a high content of triglycerides, blood serum has the form of milk, with its prolonged standing a creamy layer is formed.
a) An increase in which lipoproteins is most likely in a patient?
b) Indicate the features of the structure, properties and biological role of these lipoproteins.
c) Deficiency of which enzyme is the cause of this condition?

20. A dispensary examination of a 40-year-old patient revealed a thickening of the carotid artery wall, serum total cholesterol was 7.2 mmol/l, and HDL cholesterol was 0.8 mmol/l.
a) Comment on the results of biochemical analysis.
b) What pathology is characterized by such changes?
c) Name the lipoproteins that transport cholesterol and indicate their biological role.

21. In order to diagnose liver damage (hepatitis, cirrhosis) in the serum determine the activity of LDH and ALT.
a) Give the full names of these enzymes.
b) To which classes (according to the International Classification of Enzymes) do they belong?
c) Which of them has isoenzyme forms? Which isoform activity increases in hepatitis?

22. In order to diagnose myocardial infarction in the serum determine the activity of CPK and AST.
a) Give the full names of these enzymes.
b) To which classes do they belong according to the International Classification of Enzymes.
c) Which of them has isoenzyme forms? Which isoform activity increases during a heart attack?

23. In order to diagnose myocardial infarction in the serum determine the activity of LDH.
a) Give the full name of the enzyme and the class (according to International Classification of Enzymes to which it belongs?).
b) Explain the structure of LDH isoenzymes
c) Name the localization of LDH isoenzymes.

24. Indirect anticoagulants (dicoumarins) disrupt the synthesis of prothrombin and other blood clotting proteins in the liver.
a) Structural analogues of which vitamin are they?
b) The activity of which enzyme is inhibited by dicoumarins?
c) What type of inhibition occurs?

25. Increase in activity of alanine aminotransferase enzyme is noted in the patient in serum.
a) What reaction catalyzes this enzyme? Specify the coenzyme.
b) Which organ pathology is most likely? Describe the answer.
c) What is the coefficient de Ritis? How it changes with this pathology?

26. Jaundice has developed after the bite of a poisonous snake in humans. Total plasma bilirubin is 80 μmol / l, indirect bilirubin is 72 μmol / l, urine and feces are intensely colored.
a) Describe the results of analysis.
b) Name the type of jaundice.
c) What is the cause of intense stool and urine staining?

27. In the laboratory analysis of the serum of a patient with hepatitis established: the content of total protein - 55 g / l, albumin - 30 g / l.
a) Describe the results of analysis.
b) Destroy of which liver function is registered in the patient?
c) What are the consequences for the body of this disorder?

28. In the laboratory analysis of the serum of a patient with hepatitis established: urea content - 2.0 mmol / l, ammonia - 75 mmol / l.
a) Describe the results of analysis.
b) Destroy of which liver function is registered in the patient?
c) What are the consequences for the body of this disorder?

29. A patient with a sleep disorder is assigned a drug from the group of barbiturates that did not cause a hypnotic effect at the usual therapeutic dose. From the anamnesis it is established that the patient misuses alcohol.
a) What phenomenon is observed under these conditions?
b) Specify the cause of its occurrence.
c) What is the clinical significance of this phenomenon for doctors?

30. In the process of dealkylation of codeine, a much stronger narcotic analgesic of morphine is formed.
a) What phase of biotransformation takes place under these conditions?
b) Name the enzymes and coenzymes that provide this conversion. In which organelle cells it passes.
c) What is the significance of the dealkylation process?

31. The anti-tuberculosis drug isoniazid in the human body is subject to acetylation processes.

a) What phase of biotransformation takes place under these conditions?
b) How are people divided by the rate of acetylation? What is the clinical significance?
c) How is isoniazid toxicity altered in people with different acetylation rates?

32. Long-term alcohol intake causes toxic damage to the liver.
a) Which ethanol metabolite is the most toxic to cells?
b) In what reactions is it formed and with which enzymes?
c) Specify the mechanism of its toxic action?

33. A woman suffering from gallstone disease has a yellowing of the skin, sclera. Urine of color of "dark beer", cal - gray-white. Total plasma bilirubin - 180 μmol / l, Florence sample (urinary uroline) – negative.
a) Describe the results of analysis. Name the type of jaundice.
b) What are the causes of discoloration of urine and feces?
c) Name the blood plasma enzymes - indicators of cholestasis (bile flow outflow).

34. The patient is diagnosed with viral hepatitis A (Botkin's disease). The content of indirect bilirubin in blood plasma is 48 μmol / l, direct bilirubin is 95 μmol / l, urine is dark beer.
a) Describe the results of analysis.
b) Name the type of jaundice.
c) Name the enzymes of blood plasma - indicators of cytolysis of hepatocytes.

35. Jaundice has emerged in a 16-year-old boy after the use of the antimalarial drug primachin. The content of indirect bilirubin in the blood plasma is 76 μmol / l, direct bilirubin - 4.5 μmol / l, urine and cal - dark color, hemoglobin (hemoglobinuria) is detected in the urine.
a) Describe the results of analysis.
b) Name the type of jaundice.
c) Specify the cause of jaundice.

36. A young man with Gilbert's disease is marked with yellowness of the sclera, the content of total bilirubin in the blood plasma - 48 μmol / l, indirect bilirubin - 37 μmol / l, feces and urine - normal color.
a) Describe the results of analysis.
b) Specify the cause of jaundice.
c) Specify a drug that can reduce these disorders.

37. A newborn baby has a progressive increase in jaundice, CNS lesions. The content of indirect bilirubin in blood plasma is 340 μmol / l, direct bilirubin is 0 (absent), hemolysis of erythrocytes is not detected. The introduction of phenobarbital did not reduce the signs of jaundice.
a) Describe the results of analysis.
b) Name the type of jaundice.
c) Specify the mechanism of neurotoxic effect of indirect bilirubin.

38. After the donor blood transfusion, the patient's body temperature increased, lumbar

pain occurred, and yellowing of the skin developed. The content of indirect bilirubin is 100 μmol / l, direct - 4.0 μmol / l, urine and feces are intensely colored.
a) Describe the results of analysis.
b) Name the type of jaundice and its cause.
c) Compare the properties of direct and indirect bilirubin.

39. In the laboratory analysis of blood serum it is established that the activity of ALT is 1.05 mmol / (h ^ l), AST - 0.40 mmol / (h ^ l).
a) Describe the results of analysis.
b) The pathology of which organ is most likely.
c) Research on the activity of which enzymes will confirm the diagnosis?

40. The patient has pain in the right hypochondrium. Laboratory analysis revealed an increase in the activity of alkaline phosphatase and GGTP in serum.
a) What is the pathological condition of the patient?
b) How can total serum bilirubin and its fractions be changed under these conditions?
c) Hypovitaminosis what vitamins should expect?

41. The patient was admitted to the infectious hospital with complaints of rampant vomiting.
a) What the defection of water-mineral metabolism is observed under these conditions?
b) What clinical symptoms are characteristic of this disorder?
c) What are the other causes for the development of such defection of water-mineral metabolism?

42. The patient with renal pathology found: in the serum, urea content - 5.5 mmol / l, creatinine - 75 μmol / l, glucose - 4.8 mmol / l; in urine glucose - 2.5%.
a) Describe the results of analysis.
b) Which kidney function is destroyed?
c) In which nephron part do the abnormalities occur?

43. The patient has a tumor of the medulla oblongata, accompanied by pronounced hypersalivation (6-7l per day).
a) What the defection of water-mineral metabolism is observed under these conditions?
b) What clinical symptoms are characteristic of this disorder?
c) What are the other causes for the development of such defection of water-mineral metabolism?

44. During the analysis of the electrolyte composition of the serum, it was found that the sodium content was 175 mmol / l, potassium - 4.0 mmol / l, calcium - 2.5 mmol / l.
a) Describe the results of analysis.
b) Under these conditions, how does the osmotic blood pressure change? Specify its regulatory metrics.
c) What clinical symptoms are characteristic of this disorder?

45. After prolonged administration of diuretic, the patient has tachycardia and cardiac arrhythmias.

a) What disturbance of electrolyte metabolism is observed under these conditions?
b) What is the reason for the development of these defection?
c) Name the hormone that regulates the level of this electrolyte in the blood.

46. A patient with a syndrome of prolonged muscle contraction developed bradycardia and after some time cardiac arrest in diastole was registered.
a) What disturbance of electrolyte metabolism is observed under these conditions?
b) What is the reason for the development of these defection?
c) What is the biological role of this electrolyte?

47. In women with chronic kidney disease, there is an increase in blood pressure, with a high renin content in the blood.
a) Specify the reason for the increase in renin content under these conditions.
b) Which regulatory system activation causes blood pressure to rise? Which metabolite of this system is a potent vasoconstrictor?
c) How does serum potassium and sodium content change under these conditions?

48. A patient with kidney disease complains of bone fragility. The serum content of calcium is 1.75 mmol / l.
a) Describe the results of analysis.
b) Specify the cause of the pathological condition.
c) What hormone is involved in the regulation of calcium metabolism in the kidneys? What is its biological role?

49. In a patient with renal pathology diuresis - 400 ml, in serum: urea content - 10.3 mmol / l, creatinine - 200 μmol / l.
a) Describe the results of analysis.
b) Which kidney function is destroyed?
c) What other indicator is used to evaluate this kidney function?

50. During the analysis of the specific gravity in different portions of daily urine it was found that this indicator ranges from 1,004-1,007 g / ml.
a) Describe the results of analysis.
b) Which kidney function is destroyed?
c) At what pathological condition do such changes occur?

51. A 40-year-old woman diagnosed with gallstone disease was prescribed chenodeoxycholic acid.
a) What are the main causes of cholesterol crystallization?
b) For what purpose the patient is prescribed chenodeoxycholic acid.
c) Why does gallstone disease occur more often in women?

52. Child weak, apathetic. Convulsions often occur in the backpack on an empty stomach. Liver biopsy revealed a significant deficiency of glycogen.
a) Name the pathological condition of the child.
b) Deficiency of which enzyme occurs?
c) What is the cause of the convulsions?

53. A dry cleaner who has worked with organic solvents for a long time has been diagnosed with fatty liver disease. Lipotropic substances were used for treatment.
a) Indicate the mechanism of development of fatty degeneration of the liver under these conditions.
b) Explain the term "lipotropic substances".
c) Explain the mechanism of lipotropic action of carnitine and choline.

54. Captopril is an antihypertensive drug that is a competitive inhibitor of angiotensin-converting enzyme (ACE). ACE is a carboxydipeptidyl peptidase that converts the angiotensin I proenzyme to the angiotensin II enzyme.
a) Name the mechanism of activation of angiotensin I in angiotensin II.
b) What type of chemical bonds are hydrolyzed by peptidases? What kind of specificity of their action?
c) To which class of enzymes do peptidases belong?

55. A patient with suspected acute pancreatitis was brought to the emergency clinic.
a) Increased activity of which enzymes in the blood and urine will confirm the diagnosis?
b) The activity of which of the enzymes of the pancreas in the urine is determined by the method of Wolgemut?
c) Indicate the normal values of the activity of this enzyme in the urine.

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