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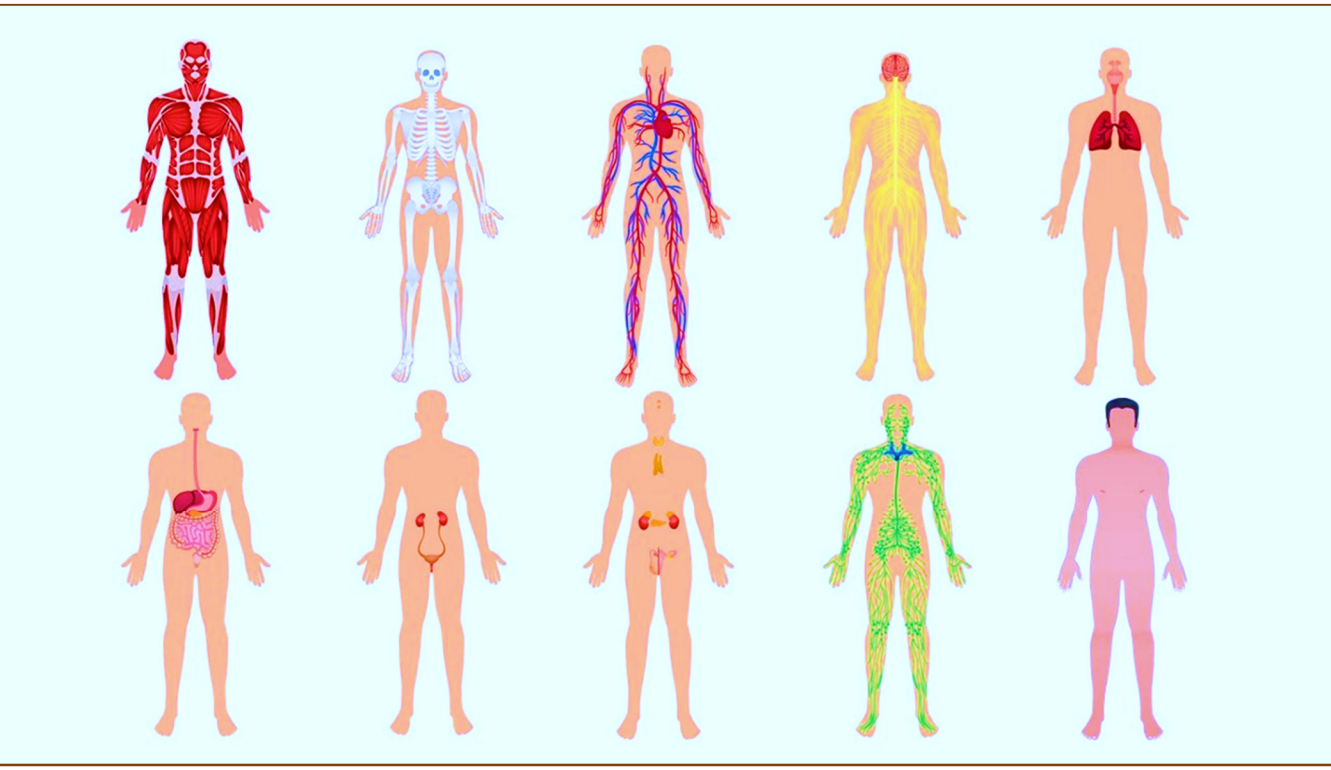
ANATOMY, PHYSIOLOGY AND PATHOPHYSIOLOGY

COURSE NOTES

FOR PHARMACY STUDENTS



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SUMMARY

1. THE CARDIOVASCULAR SYSTEM

The cardiovascular system consists of the heart, blood vessels and lymphatic vessels. It represents a coordinated functional unit permanently adapted to the needs of the body. The heart is the pump that provides the necessary force for the circulation of blood in the body, through the two "circulations":

- pulmonary (small circulation)
- systemic (large circulation)

The arteries represent the blood distribution system up to the tissue level.

Microcirculation (represented by the capillary vessels) provides exchanges between blood and tissues.

The veins serve as reservoirs and collect the blood to bring it back to the heart.

1.1 The heart

The heart is a muscular organ that rhythmically pumps into the arteries the blood it receives through the veins. The heart is in the thorax, behind the sternum, about 4-5 cm from the midline; it has the shape of a flattened cone with the axis obliquely oriented from right to left, from top to bottom and from the posterior to the anterior. It beats (contracts) 60-100 times per minute (about 100,000 beats/day) and pumps over 7200 l of blood/day. Its contractions begin in the embryo phase, about 3 weeks after conception, and continues throughout the life of the individual.

- Capacity: 500-600 cm^3
- Weight: 270-300 g
- Dimensions:
  - longitudinal diameter = 133 mm
  - transverse diameter = 103 mm
- Limits:
  - *upper limit*: right costal cartilage III (to the right) and intercostal space II (to the left)
  - *lower limit*: from the lower extremity of the sternum, the costal cartilage VI and the intercostal V-space towards the tip
  - *to the right* – costal cartilage III - VI
  - *to the left* – space II - V intercostal (medioclavicular line)

It consists of two pumps placed side by side, separated by a thick and resistant wall called a ***longitudinal septum***. The longitudinal septum that separates the 2 atria is called the interatrial septum, and the sept. that

separates the 2 ventricles is called the interventricular septum. Each half is divided in turn by a ***transverse (atrioventricular) septum*** in an atrium towards the base of the heart and a ventricle towards the tip of the heart.

Each of the two cavities of the heart is bicameral:

- the upper chamber, resembling a thick and elastic bag called **the atrium (Left A – LA and Right A – RA)** which has the function of a "waiting room" for blood
- the lower chamber has thicker walls and more muscle fibers called **the ventricle (left V – LV and right V – RV)** and produces the pressure necessary for blood to be expelled into the arteries.

The right side of the heart pumps blood with a low oxygen content to the lungs through the pulmonary artery. In the lungs the blood collects a new reserve of oxygen, then returns to the side

Through the two cave veins, the oxygen-poor blood reaches the RA level and from here, at the RV level, crossing the tricuspid valve. Blood charged with carbonic gas reaches the lungs through the pulmonary artery. From the lungs, oxygenated blood reaches as through the 4 pulmonary veins (2 for each lung). From LA, crossing the mitral valve, oxygenated blood reaches LV; from here it is ejected into the aorta, through the aortic valve, and sent forth, to the tissues and organs.

Between each atrium and each ventricle there is a **valve.** The valves cause the blood to move in the right direction. The cardiac valvular system comprises:

1. Atrioventricular valves – located between the atria and ventricles:
   - Mitral valve– between LA and LV
   - Tricuspid valve – between RA and RV
2. Arterial valves – located between the ventricles and the major arteries:
   - Aortic valve (left crescent)– between the LV and the aorta
   - Pulmonary valve (right crescent) – between RV and pulmonary artery

Each valve has 3 cups, except for the mitral valve, with only 2 cusps. They are anchored to the walls of the ventricles by tendinous cordages with the role of fixing and preventing their opening inwards during ventricular contraction.

The tendinous cordages are anchored to the papillary muscles (they support together the valve and thus do not allow the prolapse of the valve - they prevent blood regurgitation between the cuspoids).

The control of opening and closing the valves is given by the pressure differences generated by the heart.

Vascularization of the heart

The heart is also fed by the 2 coronary arteries, branches of the root of the aorta:

❖ *Right coronary* artery; irrigates the RV

- it detaches from the bulb of the aorta (orifice located immediately above the right crescent valve) → descends between the RA and the emergence of the pulmonary artery trunk → reaches the anterior coronary ditch → to the right → surrounds the right edge of the heart → passes into the posterior coronary ditch → reaches the posterior interventricular groove → the tip of the heart. This last part is also called the posterior interventricular artery = posterior descending artery (PDA).

❖ *A. left coronary artery*:

- irrigates 75% heart
- it detaches from the bulb of the aorta (orifice located immediately above the left crescent valve) it goes obliquely downwards and to the left → reaches the anterior coronary ditch → is bifurcated = >

· anterior interventricular artery = Left anterior descending artery (LAD)
· circumflex artery (atrioventricular) (LCX)

Within the cardiac venous system, the following are described:

❖ *Large coronary vein:*

- collects most of the venous blood of the heart
- it originates at the level of the tip of the heart, surrounds the left edge of the heart → reaches the posterior coronary ditch → continues with a dilated terminal portion, called the coronary sinus → is continued in AD

• *Small coronary vein:*

- starts from the right edge of the heart and flows into the coronary sinus

• *Posterior interventricular vein*

- starts from the tip of the heart and ends in the coronary sinus

• *Right anterior atrioventricular vein*

- it flows into the large coronary vein

• + other accessory cardiac veins, which are drained directly into the RA.

Structure of the heart

• *The endocardium represents the* internal layer that covers all the internal structures of the heart: *endothelial* tissue (non-stratified epithelial

paving tissue), located on a basal membrane + *subendothelial layer* (consisting of collagen fibers, reticulin fibers, elastic fibers, few conjunctive cells, and numerous sensory nerve endings.)

- *The myocardium* is best represented stra; it is made up of striated cardiac muscle fibers. Besides myocardial cells, there are also cells specialized in generating and conducting the contraction impulses that constitute *the nodal excitoconductor tissue*.
- *The pericardium is the* fibrous sac that holds the heart in place and protects it. It consists of:

- fibrous pericardium + serous pericardium (formed in turn duin 2 leaflets: parietal and visceral = EPICARD) that delimits the pericardial cavity

- between foils: 15-40 ml liquid with a lubricating role

The myocardium

The myocardium possesses two types of cells:

- **specialized cells** (atypical cardiomyocytes, **myocardial conducting cells/pacemaker cells**), capable of generating and transmitting an excitatory impulse; they form *the electrical conduction system of the hear/ modal tissue.*
- **muscle cells** (heart fibers, typical/ working cardiomyocytes, **myocardial contractile cells**) that respond to stimulation by contraction; they form *the contractile myocardium.*

1.1.1 The contractile myocardium

The contractile myocardium consists of cardiac striated muscle cells (fibers), elongated, shaped as forked cylinders called cardiomyocytes. Each muscle fiber has on the outside a membrane, the sarcolemma and contains the small cylinders called myofibrils (several hundred to several thousand). Inside the fiber, myofibrils are suspended in a matrix, namely in the sarcoplasm that also contains large amounts of potassium, magnesium, phosphates and proteins-enzymes. Among the myofibrils there are cellular organelles, sarcoplasmic reticulum (SR) and mitochondria, with extremely important functions in cellular metabolism. Myofibrils are formed by other identical cylinders, of smaller size, called sarcomeres. The sarcomere represents the morphological and functional unit of myocardial fiber. It is bordered by two Z-lines and contains two types of proteins, contractile proteins and regulating proteins. The contractile proteins are represented by fine actin filaments and thick filaments of myosin, both playing an important role in muscle contraction.

Muscle contraction occurs through a filament sliding mechanism and in a a calcium-dependent manner. Initiation of contraction of the heart muscle begins with the action potential of the cardiac muscle fiber. Electric currents spread in the vicinity of each myofibril uniformly.

The mechanism of contraction:

1. Electric pulse/action potential (PA) generation
2. Rapid PA propagation from one cell to another by means of connexons (transmembrane/gap junctions that connect the cytoplasm of 2 adjacent cardiomyocytes)
3. PA is driven along the sarcolemma → T tubules
4. In the plateau phase of the PA ⇒ slow influx of Ca^{2+} (through the sarcolemma L channels)
5. The influx of Ca^{2+} acts as a trigger ⇒ ↑ Ca^{2+} released from SR ⇒ "Ca^{2+} induces the release of Ca^{2+} "
6. => ↑ Ca^{2+} intracellular => Ca^{2+} releases the inhibition given by TN-I => the displacement of tropomyosin from the actin binding sites => allows the interaction of actin-myosin => the formation of actomyosin bridges
7. => the myosin head "flexes" towards the center of the sarcomere => approach to the line Z ⇒ sarcomere shortening
8. At the end of the plateau phase ⇒ the influx Ca^{2+} suddenly stops ⇒ ↓ intracellular [Ca^{2+}] = > the contraction is stoped until a new PA is generated.

1.1.2 The electrical conduction system of the heart

The electrical conduction system of the heart is specialized in the generation, conduction and transmission of the contractile stimulus to the working myocardium. The nodal tissue is made up of cells particularly organized in privileged points of cardiac muscle tissue, from where the wave of the action potential (PA), that generates the automatic and rhythmic beats of the heart muscle, starts.

The electrical conduction system of the heart consists of:

- sinoatrial node Keith-Flack (NSA) – in the wall of RA
  - discharge rate 60-100 /min = physiological pacemaker
- atrioventricular node Aschoff-Tawara (NAV) – in the depth of the lower part of the interatrial septum
  - discharge rate 40-50 /min = determines the physiological block

- inactive pacemaker

- The bundle of His (atrioventricular) – passes through the interventricular septum
  - inactive pacemaker
- Purkinje fibers
  - inactive pacemaker
- Internodal pathways

Pacemaker cells, like atrial or ventricular muscle cells, present: single nucleus, mitochondria, endoplasmic reticulum, and sarcomere units. They are distinguished from working myocardial cells by a lesser number of myofibrils that are arranged irregularly. Also, in the electrical conduction system, there are many sympathetic and parasympathetic fibers.

The electrical conduction system of the heart „dictates" the normal, physiologically dominant rhythm of the heart, at a frequency of 60-100 beats /min. This frequency is characteristic to the normal sinus rhythm.

1.1.3 Cardiomyocyte function

Heart fibers have the characteristics of all muscle fibers, namely, the resting potential and the action potential.

The resting potential (PR) is given by the difference in the ionic distribution on both sides of the cell membrane (Na^+, K^+, Cl^-). At rest, the cell is polarized, showing a balance between the positive electrical charges at the level of the external surface and the negative electrical charges inside the cell. The stimulation of a heart fiber through a mechanical or electrical stimulation causes changes in the cellular surface potential → the appearance of an action potential.

The action potential (PA) is determined by the reversal of cellular polarity.

There are two types of heart fibers (depending on the type of response) with different characters in terms of resting potential (PR) and action potential (PA):

- Fast-response fibers:
  - contractile fibers (atrial and ventricular)
  - Purkinje network
- Slow-response fibers:
  - pacemaker cells (NSA and NAV)

Fast-response fibers:
PR = - 80 → -90 mV
PA:

- **phase 0** (rapid depolarization): Stimulation ⇒ ↑↑ influx of Na^+ (by opening the voltage-dependent Na^+ channels) ⇒ ↑ membrane potential at +20 /+30 mV
- **phase 1** (initial rapid repolarization): inactivation of Na^+ influx + activation of the transient K^+ efflux = > the membrane is rapidly and transiently repolarized ≈ 0 mV (a value at which the type-L Ca^{2+} channels are opened)
- **Phase 2** (the plateau): slow Ca^{2+} influx (via L-type channels) + slow K^+ efflux => initiation of contraction
- **phase 3** (final rapid repolarization): K^+ efflux ⇒ ↓ membrane potential from 0 mV → - 90 mV
- **phase 4** (the resting phase): the ionic balance is restored via Na^+/K^+ pump, Ca^{2+} pump and Na^+/Ca^{2+} antiporter

Slow-response fibers:
The cells have only a maximum diastolic potential (**PDM**, -60 mV)
PA:

- **Phase 4** (diastolic slow depolarization - DLD): slow influx of Na^+ (via non-gated channels) + slow Ca^{2+} influx (via Ca^{2+} T-type channels) up until the threshold potential is achieved (- 40 mV)
- **phase 0** (depolarization): begins after reaching threshold membrane potential (≅ - 40 mV) ⇒ ↑Ca^{2+} conductance (Ca^{2+} L-type channels) ⇒ influx of Ca^{2+} ⇒ ↑ membrane potential ≅0 mV
- **phase 3** (repolarization): ↑ conductance for K^+ ⇒ K^+ efflux leading to membrane repolarization (to negative values) ⇒ hypo-excitability

1.1.4 Properties of the heart muscle

- Rhythmicity ***(chronotropic function)*** is the property of the heart to contract successively as a result of impulses generated by the NSA.
- Conductibility ***(dromotropic function)*** is the property of the myocardium, especially of the nodal tissue to conduct waves of contraction from the NSA level throughout the heart.
- Excitability ***(bathmotropic function)*** is the property of the myocardium to respond by a contraction to appropriate stimuli.
    - absolute refractory period = the period during which the myocardium can no longer respond to a second stimulus
    - in the absolute refractory period, contraction takes place

- Contractility ***(inotropic function)*** is the property of the myocardium to contract when properly stimulated.
- Tonicity ***(tonotopic function)*** = the ability of cardiac cells to maintain a basal contractile tone, dependent on metabolic processes.

The contraction of the myocardium is called a systole and the relaxation is called a diastole.

During systoles the ventricles contract strongly, forcing blood to flow into the arteries through the pulmonary and aortic valves.

1.1.5 The cardiac revolution

Cardiac revolution involves:

1. Atrial diastole: aspiration of blood in the atria; lasts 0.7s
2. Ventricular diastole:
   - it begins with *the isovolumetric relaxation* phase and the sudden decrease in ventricular pressure that leads to the closure of the sigmoid valves (the pressure in the vessels is superior to the diastolic pressure in the ventricles);
   - continues with the filling phase: the opening of the atrioventricular valves (the pressure in the ventricles is inferior to that in the atria).
   - takes 0.5s
3. Atrial systole: the ventricular filling ends by expelling the blood still contained by the atria, into the ventricles. At the end of ventricular filling, the pressure is higher in the ventricles than in the atria: the closure of the atrioventricular valves occurs. Lasts 0.1s
4. Ventricular systole:
   - initially, *isovolumetric contraction*, in other words tensioning of the ventricular muscles, when the ventricular orifices are still closed. The pressure increases progressively in the ventricular cavity, and from the moment the ventricular pressure becomes superior to arterial pressure, the sigmoid valves open immediately;
   - finally, *the ejection phase of* ventricular blood into the large arteries.
   - takes 0.3s

*The end-diastolic volume (EDV)*is the volume of blood contained in the ventricle at the end of the filling/diastole; it is about 120 ml at rest.

The stroke volume (SV) is the volume of blood ejected by a ventricle at each systole; at rest it has a value of about 80ml.
Ejection fraction (EF) = ejection volume/telediastolic volume (VE/VTD) = approximately 0,67.
End-systolic volume (ESV) is the volume that persists in the ventricle at the end of the systole and represents approximately 40ml.
Cardiac output (CO) is the amount of blood expelled by the left ventricle into the aorta at each contraction of the heart over a minute. It is defined as the product of *SV* and heart rate (HR= average of 70 beats/ min). Cardiac output at rest: 0,08 l x 70/min = 5,6 l/min. This value can be increased by 5 times, within an intense muscular effort.

1.1.6 Regulating phenomena

Intrinsic regulation of cardiac activity

The Frank-Starling Mechanism states that: "Under physiological conditions the heart pumps a volume of blood equal to the volume it receives (in other words, venous return)."
The higher the preload/afterload ⇒ the cardiac muscle increase its force of contraction ⇒ ↑ end-diastolic volume (EDV) ⇒ ↑ SV ⇒ ↑ CO.

This mechanism prevents the accumulation of blood in the heart and veins.

Extrinsic regulation of cardiac activity

a. Control of heart function through the SNV

The heart is not under the influence of the central nervous system (CNS) containing the brain and spinal cord. It is under the influence of the autonomic nervous system also called the neuro-vegetative system (SNV), also involved in the control of smooth muscles and endocrine glands. The SNV has 2 anatomically distinct, and antagonized systems: the parasympathetic system and the sympathetic system.

The parasympathetic system contains ganglions located near the target organs and releases acetylcholine as a neurotransmitter. The neurotransmitter is the chemical released by one neuron at the level of the synapse, which changes in a specific manner the activity of another cell. When stimulated, the parasympathetic system produces **cardio-moderator effects:**

- decreases cardiac heart rate (causes sinus bradycardia)
- increases atrioventricular conduction time
- decreases the contraction force of the myocardium

The parasympathetic cardio-regulating centers are located as symmetrical pairs in the spinal bulb. Their motor nerve is the vague nerve

(a Xa pair of cranial nerves). The vague nerve permanently imprints a certain slowdown of the spontaneous heart rate – the moderator vagal tone. The chemical mediator is acetylcholine which acts on nodal tissue and on the myocardium by working through cholinergic receptors. Cholinergic receptors are stimulated by acetylcholine and inhibited by atropine.

The sympathetic system **contains** ganglions located at a distance from the target organs and uses norepinephrine as a neuromodulator. When stimulated, the sympathetic system produces **cardio-acceleratory effects:**

- increases the cardiac heart rate (causes sinus tachycardia)
- decreases the atrioventricular conduction time
- increases the contraction force of the myocardium.

The sympathetic cardioacceleratory centers are located in the anterior horns of the spinal cord, at the level of the lower cervical spine and the superior dorsal spine. Their motor nerves are sympathetic nerves that leave the spinal cord at the level of each vertebra and form the sympathetic plexus until it distributes to the heart and branches throughout the tissue. Sympathetic nerves permanently produce a certain acceleration of the heart rate. The chemical mediator is norepinephrine, released at the level of the extremities of the sympathetic cardiac nerves, which acts both on the nodal tissue and on the working myocardium, through adrenergic receptors. Adrenergic receptors are: *β1 myocardial* (they increase the ventricular contraction force and cardiac frequency), *β2 - coronary*, cerebral, hepatic and skeletal striated muscle vessels (vasodilator effect) and *α1 vascular* (vasoconstrictor effect).

b. The medullo-pontine centers

They are localized in the upper portion of the medulla oblongata and in the lower third of the pons. These are not proper centers, but areas. Thus, a pressive area and a depressor area, formed by complex networks of interacting neurons, are discovered:

a) The presive area

- located in the dorso-lateral portion;
- is the cardioacceleratory and vasomotor area
- controls the activity of sympathetic medullary neurons; adrenal medulla

Stimulation of the pressive area causes:

1. ↑ heart rate (HR) and ↑ force of cardiac contraction, with ↑ cardiac output (CO)
2. ↑ vascular tone (vasoconstriction - VC) ⇒ ↑ peripheral vascular resistance (PVR)

b) Depressor area

- located in the ventro-median portion;
- is the cardioinhibitory area

Stimulation of the depressant area causes inhibition of the pressor area and vagal stimulation = >

1. ↓ heart rate (HR) and ↓ force of cardiac contraction, with ↓ cardiac output (Co)
2. ↓ vascular tone (↓ VC) ⇒ ↓ peripheral vascular resistance (PVR)

c. Receptors that regulate cardiac activity

Baroreceptors - carotid sinus and aortic arch. They are mechanoreceptors that are stimulated by the stretching of the vessels, phenomena caused by the pressional variations of the blood; thus, thesee receptors are not directly stimulated by the blood pressure variation.

1. Stimulation
2. The signal is transmitted through the afferent path: represented by the IX nerve (glossopharyngeal) and X (vagus)
3. The nerves arrive at the cardio-vascular centers are located in the medullo-pontine area;
4. The efferent pathway: vague stimulation towards the heart and decrease of sympathetic tone on the vessels

Their stimulation causes the depressor reflex which leads to ↓ HR vand vasodilation = > ↓ blood pressure.

Chemoreceptors = receptors that are stimulated by the concentration variation of some blood compounds (pO2, pCO2, H+, etc.). They are distributed into 2 carotid bodies and 3 aortic bodies.

Their stimulation is given by the modification of various substances in the circulating blood: specifically by PO_2, PCO_2 and H^+ ions (↓PO_2,↑PCO_2 and ↑H^+)).

Result: triggering of a pressor reflex: ↑ HR and ↑ VC => ↑ blood pressure.

1.2 Circulatory system

The heart is connected to a closed system of complex "pipes" called blood vesseels. The role of the blood vessels is to bring the blood into contact with all the tissues within the body. This is possible due to the existence of a large exchange area, consisting of a huge number of extremely fine vessels (similar to hairs) called capillaries. The heart and the blood vessels are therefore serving a single purpose: to allow the passage of blood through the capillaries, which are the place for all the exchanges that occurs in the organsim.

The vascular tree consists of **arteries** (it provides transport of blood from the heart to tissues and organs), **veins** (provides for the transport of blood from the body to the heart) and capillaries (small-caliber vessels that provide the gaseous, nutritious exchanges between blood and tissues).

The structure of arteries and veins

Although arteries and veins differ structurally and functionally, they have several **common features:**

- **Lumen**
- **Intima/tunica intima**: simple squamous epithelium *(endothelium*) placed on a basal membrane + connective tissue (elastic and collagen fibers)
- **Media/tunica media**: the thickest layer; contains smooth circular and longitudinal muscle fibers + circular elastic fibers
- **Adventitia/tunica externa**: formed from conjunctivo-elastic fibers; here is where the nerve endings of the SNV fibers reach
- **Vasa vasorum** = "vessels of the vessel"

Differences:

- Arteries and arterioles have thicker walls than veins and venules
- Arteries and arterioles have a smaller lumen and appear round; the veins have larger lumen and appear flattened
- The intima has an internal elastic membrane only in the larger arteries
- The tunica media of the arteries is formed predominantly from smooth muscle cells and *elastic fibers* (their proportions vary

depending on the distance from the heart), the external elastic membrane is *present* in the larger arteries; The average tunic of the veins *does not have* an external elastic membrane and is predominantly formed by smooth muscle cells and *collagen fibers.*

Arteries are the vessels that carries blood from the heart into the body.

- those closest to the heart have an increased percentage of elastic fibers in all the tunics elastic arteries (→ diameter > 10 mm).
- as it moves away from the heart: the percentage of elastic fibers decreases and the percentage of tissue mdry smooth muscle arteries increases (→ diamter 0.1 - 10 mm).

Arteriolele

- have a diameter of about 30 μm
- their structure is simmilar to that of arteries

The veins are the blood vessel that brings blood to the heart from the tissues/organs.

- large veins (porta, inf./sup. cava) have a diameter between 0.6- 1.2 cm
- are vessels with low pressure (10 mmHg at the origins of the venous system and 0 mmHg in AD)
- they have valves on their trajectory that prevent the venous return and promote unidirectional blood flow.

The venules have a diameter between 8 - 100 μm.

- they are formed from endothelium, a thin middle layer with a few muscle cells and elastic fibers, plus an outer layer of connective tissue fibers that constitute a very thin external tunic.

The structure of the capillaries

The capillaries have an outside a layer formed from connective tissue, with numerous collagen and reticulin fibers, and on the inside a monolayered endothelium placed on a basal membrane with occasional smooth muscle fibers.

- are small vessels, diameter: 5 - 10 μm

- the blood flow through capillaries is often described as microcirculation
- thei are the place where the exchange for nutrients, catabolism products, respiratory gases and water exchange between blood and tissues occurs.

Classification:

- continuous:

- the most common, characterized by a complete endothelial lining with tight junctions between endothelial cells
- allow the passage ofher glucose, water, gases, hormones, various leukocytes and small hydrophobic molecules

- fenestrated:

- have pores (or phenestrations) + tight junctions in the endothelial mucosa
- are permeable to larger molecules
- found in the small intestine, kidneys, the hypothalamus, pituitary and glandof the thyroid

- sinusoid:

- have extensive intercellular voids + incomplete basal membrane + cracks and intercellular phenestrations
- found in liver, spleen, bone marrow, lymphattic ganglions

1.2.1 The artrial system

The arterial system starts from the LV with the artery ascending aorta. At the base of the aorta, 2 coronary arteries (right and left) branch out; after 1-2 cm, the ascending aorta forms the aortic arch. Here 3 other arteries branch out: brachiocephalic trunk (the right subclavicular artery and the right common carotid artery), as well as the left common carotid artery and the left subclavicular artery. The right and left carotid artery irrigates the brain, eye, neck, frontal and occipital region of the head. The subclavicular arteries branch into axillary and brachial arteries that irrigate the walls of the armpit, the lateral wall of the chest and the whole arm.

The aorta artery then continues down and forms the descending thoracic aorta (which then forms the esophageal, bronchial and intercostal arteries) and the abdominal descending aorta (which forms the celiac trunk,

the superior mesenteric artery, the renal arteries - 2, the genital arteries - 2, and the inferior mesenteric artery). At the end, the abdominal descending aorta divides into the external and internal iliac arteries, right and left that irrigate the lower limbs.

Large arteries provide support for the force exerted by blood ejected under pressure from the heart and are therefore considered "high-pressure reservoirs".

Small arteries and smooth muscle arterioles increase blood distribution to the organs by regulating the diameter in response to sympathetic stimulation and local control mechanisms and are therefore considered "resistance vessels".

Arteries contain ≈ 20% of the total blood volume .

1.2.2 Venous system

The venous system begins with the jugular veins that collect unoxygenated blood from the head and neck. The axillary veins take over the unoxygenated blood from the armpits, upper limbs and from the side of the chest. The jugular and axillary veins flow into the subclavicular veins, and then into the upper vena cava. The inferior vena cava collects unoxygenated blood from the lower part of the body, more precisely from: renal veins, common iliac veins, splenic vein and hepatic veins. The pulmonary veins, two for each lung, are the only veins that carry oxygenated blood to the heart (in LA).

The veins contain most of the blood volume (≈75%) at a low pressure and are considered capacitance vessels.

1.2.3 Lymphatic system

The lymphatic system includes all the vessels through which the lymph circulates from the tissues/organs to the heart. The lymphatic system includes: i) collecting lymphatic vessels, ii) lymphatic capillaries (simple lymphoid formations), iii) lymphatic trunks, iv) lymphatic ducts and v) lymph nodes (lymphatic ganglions).

The lymphatic system is different from the blood circulatory system by two characteristics:

- the wall of lymphatic capillaries are thinner than blood capillaries

- unlike blood capillaries that occupy an intermediate position between the arterial and venous systems, the lymphatic vessels formthe terminal networks

Roles:

- drain the water and catabolites that have not been taken over by venous circulation (10%)
- collects the remaining proteins at the tissue level, which they return to the systemic circulation
- potentiates the immune status (lymph nodes)
- ensures the absorption of lipids (chilomicrons) at the level of intestinal villi
- returns the excess of fluid from the interstitial space into circulation

The lymphatic system begins with the lymphatic capillaries, which have the same structure as the blood capillaries. Through the confluence of the lymphatic capillaries, lymphatic vessels are born (provided on the inside with semilunar valves that facilitate lymph circulation). The walls of lymphatic vessels have a vein-like structure. The lymph collected from the various tissues and organs circulates to the large lymphatic trunks, eventually reaching two large lymphatic collectors:

- the thoracic canal: the largest lymphatic collector 25-30 cm
- the right lymphatic vein: 1–2 cm

Lymph is a colorless and weakly opalescent liquid. It has a pH between 7.5-7.9 and contains water, salts, proteins, hormones, lipids and leukocytes (lymphocytes and granulocytes). Its role is to eliminate cellular residues and transport lipids and other nutrients important to the normal conduct of cellular functions throughout the body.

1.2.4 Blood pressure

The blood is transported from the heart to the body's tissues through the arteries, the blood pressure representing the force with which it pushes the blood into the walls of the arteries. At each heartbeat (60-70 beats/minute at rest), blood is pumped into the arteries.

Blood pressure/blood pressure (BP) is the pressure exerted by the blood against the vascular walls, generated by the cardiac pump.

The flow of blood into the arterial system, in other words the average arterial pressure is conditioned by two factors:

1. Operating conditions of the pump – *cardiac output (CO)*
2. Resistance to blood flowing in the vessels – *peripheral vascular resistance (PVR) or total vascular resistance (TVR).*

PVR is the peripheral resistance that opposes the total flow of the vascular bed: peripheral resistance = arterial resistance + arteriolar resistance + capillary resistance + enous revsistance. Arteriolar resistance is predominant (60% of PVR), arterial resistance accounts for 10%, capillary resistance and venous resistance, each accounting for 15% of PVR.

The formula for calculating average blood pressure is as follows:

BP = CO x PVR

If we take into account that the volume of blood is constant, BP is directly influenced by factors that change:

- CO – respectively: the force of contraction of the heart muscles and the heart rate
- PVR - the diameter of the arterioles.

BP is maximum at the time of heart contraction and blood pumping: ***systolic blood pressure - SBP***.

When the heart relaxes, between beats, the blood pressure decreases: ***diastolic blood pressure - DBP***.

Blood pressure depends on several factors:

- Blood volume (BP decreases in case of bleeding)
- The size of arterioles (BP decreases in the case of vasodilation)
- Elasticity of arterial trunks (BP increases in case of loss of this elasticity in the elderly, for example)
- Cardiac output (BP increases in the case of cardio-celeration).

The World Health Organization (WHO) has proposed since 2003, for all age groups, the following normal values:

I. Optimal BP: SBP < 120 mmHg and DBP < 80 mmHg
II. Normal BP: SBP < 130 mmHg and DBP < 85 mmHg
III. Maximal limits of normal: SBP 130 -139 mmHg and DBP 85-89 mmHg

1.3 Pathophysiology – Arterial hypertension

The term arterial hypertension (**AHT**) signifies an increase in blood pressure: SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.

Tabel 1. Arterial Hypertension Classification after the Eurpean Society for Hypertension (2003):

Stage AHT	SBP	DBP
I	140-159	90-99
II (moderate AHT)	160-179	100-109
III (severe AHT)	>180	>110
Systolic isolated AHT	>140	<90

AHT mechanisms

Arterial pressure is the product of CO and total PVR: PA = DC x RPT. So AHT occurs either as a result of increased cardiac output, or resistance, or both. In the first case we can talk about ***hyperdynamic AHT*** where SBP grows more than DBP. In the second case we have ***the resistant AHT*** where tas and DBP increase proportionally, or (most commonly) tad grows more than SBP.

Hyperdynamic AHT

The increase in cardiac output is due to either an increase in heart rate (HR) or an increase in ejection volume (EV).

1. *Increased HR* (tachycardia) secondary to sympathetic stimulation is associated with physical exertion, stress, febrile states.
2. *The increase in the EV* depends on the volemia. The increase in volemia, which represents the blood mass made up of plasma and blood elements, causes an increase in the venous return to the heart, and therefore of the VE. Volemia is dependent on total water, but also on the main osmotic ion, sodium. *The regulation of volemia is carried out by: the renin-angiotensin-aldosterone system (RAAS) and vasopressin/ antidiuretic hormone.*

Activation of RAAS is carried out with the help of renin. Renin is a proteolytic enzyme synthesized in the walls of the renal glomeruli in response to decreased renal perfusion, decreased renal sodium excretion and sympathetic stimulation. The effector of the system is angiotensin II (ATII) which increases BP through several effects, acting at the level of AT1 receptors located in the blood vessels, heart, kidneys, and adrenal

cortical glands. ATII is directly responsible for increasing the PVR and directly stimulates the secretion of aldosterone by the adrenal cortical glands. Aldosterone is a mineralocorticoid hormone that favors the primary reabsorption of sodium and secondary reabsorption of water, which will have the effect of increasing the volemia and thus the venous return to the heart with the increase of CO and cardiovascular remodeling.

Vasopressin or antidiuretic hormone (ADH) is produced by the hypothalamus and stored in the posterior pituitary gland; its release is stimulated by hypovolemia or hyperosmolarity, with consecutively increases volemia by primary water reabsorption.

Resistant AHT

The increase in vascular resistance is determined by the exaggerated vasoconstriction of peripheral arterioles or narrowing of peripheral vessels.

Vasoconstriction is the consequence: an increase in sympathetic activity, an increase in ATII concentration or an inefficient self-regulation mechanism.

The n*arrowing of peripheral vessels* is the consequence of atherosclerosis lesions in the arterial system, which commonly occur in the elderly (the evolution is aggravated by AHT).

Classification

1. Primary AHT

Most people (90-95%) do not present an exact cause for the occurrence of AHT. This kind of AHT is called essential or primary hypertension. Anyone can develop AHT, but some people are more prone to develop it. Studies show that men suffer from AHT more frequently than women; however, after menopause women develop AHT more frequently than men at the same age. Hereditary factors increase the prevalence to develop AHT. If parents and/or grandparents suffer from AHT, the risk for that person to have AHT in life greatly increases. Also, the environmental factors increase the risk of AHT as follows: the increased salt intake (common especially in industrialized countries, > 5 g of NaCl/day); overweight and obesity; chronic, professional, or related mental stress the personality of the subject; the presence of associated disorders: atherosclerosis, diabetes mellitus.

2. Secondary hypertension

Between 5-10% of people suffer from AHT secondary to another disease, such as: chronic kidney disease, adrenal tumors, pheochromocytoma, primary hyperaldosteronism, excess contraceptive pills or pregnancy in women. This type of AHT is generally curable if the determining causes are corrected.

Therapeutic principles

AHT treatment addresses the fundamental mechanisms that led to the onset of the disease, being used a combination of different classes of antihypertensives. The classification of antihypertensive drugs according to their mode of action:

1. Antihypertensives that act by reducing volemia: diuretics.
2. Antihypertensives that act by reducing the effectiveness of the cardiac pump (decrease in contractility and HR):
    - beta-blockers: propranolol, atenolol, bisoprolol (suffix ″olol″)
    - calcium antagonists: verapamil, diltiazem.
3. Antihypertensives that act by decreasing the PVR (vasodilators):
    - direct vasodilators (direct action on vascular smooth muscle):
        - calcium antagonists: nifedipine, nicardipine, amlodipine (suffix″ dipine″)
        - inhibitors of the converting enzyme (IEC): enalapril, lizinopril, fozinopril (suffix ″pril″)
        - ANGIOTENSIN II AT1 receptor blockers (ARA II): losartan, valsartan (suffix ″sartan″)
    - indirect vasodilators:
        - alpha-blockers: prazosin
        - central antihypertensives: clonidine, alpha-methyl-DOPA

1.4 Pathophysiology – Atherosclerosis and coronary artery disease

1.4.1 Atherosclerosis

Atherosclerosis is the disease of the arteries, with slow evolution, during which the arterial intima thickens as a result of lipid storage and fibrosis, resulting in atheroma plaques that lead to the progressive narrowing of the lumen of the blood vessels.

The most common localizations of these plates are:

- abdominal aorta
- coronary arteries
- internal carotids
- cerebral arteries

Plasma cholesterol circulates in two forms:
- *low density lipoproteins* (LDL) being the strongest pro-atherogenic factor; they carry 70% of cholesterol to the vessel wall, where it is stored
- *high density lipoproteins* (HDL) that have an anti-atherogenic protective role; they are capable of mobilizing the cholesterol deposited at the level of the vessel walls –"cleaning" the vascular wall from cholesterol.

Risk factors of atherosclerosis

A cardiovascular risk factor is defined as a factor whose presence increases the risk of coronary heart disease; consecutively, suppression or its improvement diminishes this risk.

I. Non-influential factors:

- Genetic factors – there is a family predisposition for coronary artery disease.
- Age – atherosclerosis begins in childhood, but only after the age of 50 the incidence of atherosclerotic lesions increases.
- Sex – men are the most affected, up to the age of 50 years; after menopause, the incidence is equalized

II. Influencing factors

- Hyperlipidemia: represents the increase in LDL cholesterol >200mg%. The decrease in HDL < 35mg% is also an independent risk factor. In these situations, an appropriate diet should be followed, associated with a lipid-lowering drug treatment (statins and fibrates).
- AHT – the mechanical stress produced by endothelium microlesions and barometric overload increases the oxygen requirement in the myocardium. The normal maintenance of blood pressure values is achieved with the help of drug treatment.
- Sedentary lifestyle and stress are also risk factors. Exercise is one of the simplest and most effective treatments in preventing atherosclerosis.

- Smoking – smoking has a toxic effect by:
  - increasing endothelial permeability and platelet viscosity
  - LDL oxidation
  - favoring coronary spasm
- Diabetes mellitus – produces several unfavorable effects:
  - cellular abnormalities – adhesion of platelets, proliferation of smooth muscle cells at the level of vascular walls
  - metabolic abnormalities – secondary hyperlipidemia, etc.
  - In this case, blood sugar must be controlled all your life

Pathogenesis of atherosclerosis

Endothelial cell lesions are the first events that take place; the reaction to these phenomena ultimately leads to the formation of atheroma plaques. Endothelial lesions are produced by i) the risk factors mentioned above, ii) hemodynamic factors (the turbulent blood flow at the level of arterial bifurcations that alter the mechanisms that protect against the initiation of atherosclerotic lesions) and iii) bacterial toxins and viral infections.

The injured endothelium then allows *the penetration and accumulation of LDL* at the level of the intima, where these molecules are oxidized, thus forming *the lipid streaks* (the earliest signs of the atherosclerosis process). At the level of these lipid streaks can adhere blood cells (monocytes and platelets). The blood monocytes penetrate the intima and turn into *active macrophages*, which cause: i) the capture of oxidized LDL (following their overload with oxidized LDL, they take a characteristic, foamy appearance, hence the name of frothy macrophages), ii) secrete cytokines (which stimulate the proliferation of smooth muscle cells from the vascular walls and their migration from the media to the intima and attraction of other inflammatory cells) and iii) produce oxygen free radicals (which stimulate the proliferation of smooth muscle cells from the vascular walls additionally alters the structure of the endothelium and favors the oxidation of LDL). Blood platelet form microthrombus (thus causing arterial occlusion) and release growth factors for the smooth muscles of arterial vascular walls.

As a result of migration from the media, smooth muscle cells secrete *fibrous proteins* (collagen, proteoglycan). This accumulation of fat

cells and fibers causes the *atheroma plaque* to grow and stiffen, leading to the formation of *fibrous plaques*.

ThHe atheroma plaque may rupture or crack, thus leading to the formation of *complicated lesions*. The crack/rupture of a fragile atheroma plaque releases tissue factors that trigger the coagulation process, causing *the formation of a thrombus*. The consequence of incomplete vascular occlusion (temporary interruption of blood flow) is *myocardial ischemia (angina pectoris),* while complete occlusion of the affected vessel (irreversible obliteration of the affected artery) causes *cell death (myocardial infarction).*

Angina pectoris and myocardial infarction, occurring as a result of atherosclerosis, are thus the two clinical aspects of coronary artery disease.

1.4.2 Coronary heart disease

The myocardium has 2 coronary arteries, originating from the root of the aorta: the right coronary artery and the left coronary artery. Coronary circulation is closely related to the oxygen needs of the myocardium. Following a physical activity, the oxygen requirement of the myocardium increases, because the contractility and heart rate are increased as a result of sympathetic stimulation. Even in the case of this overload, a healthy heart can restore the balance in oxygen concentration, by increasing the blood irrigation to a value that iss 5 times higher than the resting value; this capacity of the heart is called the coronary reserve.

The decrease in coronary reserve is a major feature of coronary artery disease; it will lead to an imbalance between the oxygen supply of the heart (which is low) and the oxygen requirement (which is increased).

Definition: Ischemic heart disease or coronary heart disease (CHD) is a pathological condition characterized by an imbalance between the supply and the necessary of oxygen at the level of the myocardium. Hence, in coronart heart disese either the intake of oxygen decreases or the oxygen requirement increases.

Mechanisms

I. Reduction of blood/oxygen suply

The main cause (99% cases) of CHD is the progressive narrowing of the lumen of the coronary arteries due to the formation of atheroma

plaques; the atheroma plaque is responsible for the decrease in blood supply of a myocardial territory, a process that can produce in certain conditions myocardial ischemia. In 1% of the cases CHD can be caused by prolonged vasospastic angina, a condition in which the vascular smooth muscle cells are hyper-reactive, probably due to endothelial dysfunction.
The two clinical manifestations of myocardial ischemia are:

1. angina pectoris, in the case of partial arterial occlusion
2. myocardial infarction, in case of complete occlusion of an arrtery

II. Increase of O_2 need

Another cause of coronary reserve decrease is the increase of the oxygen requirement at rest, as a result of:

1. Volume overload (aortic or mitral insufficiency)
2. Barometric overload of the heart (AHT, aortic stenosis, vasoconstriction during physical exertion, mental stress, cold)

In these cases, in order for the blood, which has an increased volume, to be ejected, or to defeat the ejection resistance, the tension of the walls and therefore the necessary in oxygen to maintain a normal DC value, it must increase.

The imbalance between the supply and the need for oxygen in the myocardium causes a myocardial deficit in oxygen. If the duration is less than 20 minutes, we are talking about an angina crisis, or angina pectoris. If the oxygen deficiency lasts more than 20 minutes, we are talking about myocardial infarction.

Angina pectoris

Angina pectoris is a transient myocardial ischemia, lasting less than 10-15 minutes, which is defined as a painful paroxysmal thoracic crisis (it appears and disappears suddenly). The character is constrictive, oppressive, suffocating and gives way with the cessation of effort, or after taking nitrates (nitroglycerin sublingually). On average, the angina crisis lasts 3-5 minutes and does not cause irreversible myocardial damage, cellular necrosis does not set in.

The diagnosis is ralised based on ECG, where the ST segment is drepssed; the T wave can be inversed or positive.

The localization of pain is retrostenal with typical irradiation in the left shoulder, the cubital edge of the left arm, up to the level of the little finger, or with atypical irradiation in the mandible (can be confused with toothache), epigastrium (can be confused with gastric pain), interscapular, right arm (can be confused with rheumatic pains).

If the thoracic pain is triggered by known thresholds of effort, we are talking about *stable angina* that disappears with the cessation of effort. If the pains occurs suddenly, if it is stronger and more frequent, we are talking about unstable *angina*, this being often the signal that announces the occurrence of myocardial infarction. It can also occur in the repause, during sleep.

Myocardial infarction

Myocardial infarction (MI) is a serious and prolonged myocardial ischemia, over 20 minutes, which causes the death (necrosis) of myocardial cells. The main cause is the rupture of an atheroma plate with the displacement of a thrombus. The pain characteristics are the same as in the case of angina pectoris, but they do not respond to either nitroglycerin or opioids.

The diagnosis is made on the ECG where the enlarged Q wave appears, which signifies necrosis and persists throughout life. The ST segment is elevated - indicating the lesion while the T wave is negative – showing the ischemia of the cells irrigated by the blocked artery. Serologically, during MI the enzymes creatine kinase (CK), myoglobin and troponins T and I, lactate dehydrogenase (LDH) are increased due to their increased release into the palsma from the necrotic cells.

Complications:

1. Electrical complications (in the first minutes/hours): arrhythmias – ventricular fibrillation has an increased deadly risk.
2. Mechanical complications (in the coming days): rupture of tendinous filaments with acute mitral insufficiency and decrease in CO with heart failure.

Therapeutic principles

The prophylactic therapeutic attitude in coronary patients is the chronic administration in small doses of antiplatelet agents: aspirin, ticagrelor, clopidogrel, cilostazol, etc. These prevent the adhesion of platelets and thrombus formation – the treatment is administred for life. The antiischemic medication in the case of coronary subjects aims to restore as rapidly and completely as possible the oxygen balance and the aerobic heart metabolism. To achieve this goal, the antianginal medication either reduces the oxygen requirement of the myocardium (beta blockers) or increases the blood supply to the myocardium (the rest of the classes).

The main therapeutic classes used are:

1. beta blockers (atenolol, metorprolol, acebutolol)
2. calcium inhibitors (amlodipine, diltiazem, verapamil)
3. nitrate derivatives (nitroglycerin, mono-, isosorbite dinitrate, molsidomin)
4. potassium channel antagonists (nicorandil).

Modern surgical therapy tries to increase the diameter of the stenosed coronary arteries with the help of dilating balloons and by implanting a stent inside the affected vessel (coronary angioplasty). Also, the affected territory can be revascularized with the help of a vascular fragment (taken from the saphenous vein, mammary artery), that supasses the blocked artery, called coronary bypass.

1.5 Pathophysiology – Rhythm disturbances/Arrhythmias

Rhythm disturbances (arrhythmias, dysrhythmias) are changes in the genesis of excitation in the heart tissue.

Causes:

- coronary artery disease (myocardial ischemia)
- electrolyte imbalances (hypo- or hyperkalemia, hypomagnesemia, hypercalcemia)
- drug overdoses (digitalis intoxication or intoxication with anti-arrhythmics: quinidine, procainamide, dizopiramide)
- valvopathies

Sinus rhythm

The sinus rhythm represents the heart rate imposed by the dominant pacemaker of the heart (sinoatrial node).

ECG criteria of the sinus rhythm:

- Positive P waves in all derivatives (except aVR derivation)
- Constant PR interval with a duration of 0.12-0.20 seconds
- Heart rate between 60-100 beats/minute

I. Rhythm disturbances

1. Sinus arrhythmias

Represent either acceleration of the sinus rhythm (sinus tachycardia) or excessive slowing of the sinus rhythm (sinus bradycardia).

Sinus tachycardia: atrial frequency >100 beats/min, 180 (rarely even 200 min). It occurs in states of stress, anemia, anxiety, inflammation, fever, organic diseases (myocardial ischemia, shock, congestive heart failure, hyperthyroidism), after administration of drugs (atropine, catecholamines, thyroid hormones), coffee excess, alcohol, nicotine, or drugs.

Sinus bradycardia: the HR is less than 50 beats/min, and the patient is asymptomatic most of the time. It occurs in healthy adults (athletes, during sleep), as well as in pathological conditions: intracranial hypertension, tumors, meningitis, myocardial infarction, denutrition, pregnancy, secondary to the administration of some drugs (beta blockers, calcium antagonists, amiodarone, and clonidine).

2. Atrial/supraventricular arrhythmias

Atrial extrasystole is a heartbeat that occurs prematurely relative to the underlying rhythm, determined by the spontaneous electrical discharge of an ectopic focus (agglomeration of myocardial cells, located outside the sinus node, which takes over its functions of discharging cardiac electrical impulses responsible for the contraction of the heart).

Atrial fibrillation represents an irregular arrhythmia with HR = 350-600/minute having on the ECG route the form of permanent oscillations from the baseline (f waves). It can occur in the absence of cardiopathy, especially in a context of ethylism. In general, however, it complicates the evolution of a valvopathies, AHT or an MI. In the case of chronic arterial fibrillation, patients are at increased risk of stroke and/or arterial embolism.

Atrial flutter is a regular arrhythmia with HR = 250-350/minute; a rare rhythm disorder that can occur in the absence of cardiopathy, or in the same conditions as atrial fibrillation. The atrial activity is special, the P waves being substituted with the F waves with characteristic morphology, of saw˝teeth˝.

3. Ventricular arrhythmias

Ventricular extrasystole is defined as a premature cardiac contraction in relation to the basic rhythm, determined by an ectopic focus located at the level of the ventricles that does not disturb the atrial activity of the sinus node, but prevents sinus activity at the level of the ventricle. They have an increased risk of sudden death, which is why they are extremely dangerous.

Ventricular fibrillation results from a very rapid and disordered excitation of the ventricles, HR = 130-250/minute. On the first place in terms of causes that can determine the appearance of ventricular fibrillation is ischemic cardiopathy, especially in the case of patients with myocardial infarction in history. Ventricular fibrillation is the main cause of sudden death of cardiac etiology.

II. Conduction disorders

Atrioventricular blocks (AVB) are the delay or blockage in the transmission of the electrical impulse from the atria to the ventricles. There are three classes of atrioventricular blocks: AVB grade I, AVB grade II and AVB grade III. In principle, acute AVB disappears with the disappearance of the determining cause. Among these causes are: the administration of medicines, acute myocardial infarction (the appearance of the block is always transient), chronic diseases. The definitive treatment, proposed in the case of a chronic disorder, consists in implanting a pacemaker.

BAV grade I and BAV grade II occur due to the delay in impulse transmission from the sinus node to the ventricles. BAV grade III incurs debts to complete blockage of the transmission of electrical impulse from the atria to the ventricles. Thus, the atria and ventricles are stimulated independently, at their own pace, phenomena called atrioventricular dissociation.

Therapeutic principles

Antiarrhythmics are drugs that cause the suppression of a heart rhythm disorder and/or the prevention of relapse. Depending on their electrophysiological properties, antiarrhythmic drugs are grouped into 4 classes:

1. class I: predominantly slow down the conduction speed of the nervous influx (quinidine, lidocaine)
2. class II: beta-blockers
3. class III: delays ventricular repolarization (amiodarone, sotalol)
4. class IV: calcium inhibitors (verapamil, diltiazem).

1.6 Pathophysiology – Heart failure

Congestive heart failure (CHF) is defined as the inability of the heart to provide, under normal conditions, the necessary blood flow to the body's needs. Consequently, the cardiac output decreases, initially at effort, then also at rest; in the latest case, we are talking about the inadequacy of the pump function of the heart.

Causes:

- all heart diseasea can sooner or later lead to heart failure.

1. Heart failure due to decreased contractility (insufficiency due to myocardial diseases):

- *Coronary artery disease* (chronic ischemia or after a myocardial infarction).
- *Cardiomyopathy*: primary diseases of the myocardium whose etiopathogenesis is not known. Dilated cardiomyopathy is the dilation of the cavities (especially of the VS) that leads to an important volume overload. It is manifested by the alteration of systolic function with a decrease in EF and the formation of blood clots in the cavities. Hypertrophic (obstructive) cardiomyopathy represents the thickening (hypertrophy) of the VS and of the septum. On the functional level, this asymmetrical hypertrophy leads to the impairment of the diastolic function (the decrease of the VS disensibility) and obstruction in the blood ejection path. Restrictive cardiomyopathy is fibrosis of the subendocardial layers of the myocardium.
- *Myocarditis:* inflammation of the myocardium of diverse etiology (viral, bacterial, auto-immune)

2. Heart failure due to hemodynamic overload

- *CHF due to a barometric overload* (where the pressure in the VS must increase to ensure CO). In the case of chronic barometric overloads, the major compensation is achieved by concentric hypertrophy.

- High blood pressure (AHT) associated with coronary artery disease is the leading cause of heart failure in practice.
- Aortic stenosis occurs where retraction of the aortic orifice occurs.

In these two cases, the resistance in the ejection pathway will be surmounted by a more important contraction of the VS; the pressure in VS during the systole will increase, so that the normal resting flow will be ensured over a longer period of time (a few years).

- Pulmonary hypertension (increased pressure in the pulmonary artery), rarer than AHT, is especially associated with chronic lung diseases (chronic bronchitis, emphysema), but also mitral stenosis.

The consequence of chronic overloading of pressure is concentric hypertrophy of the right heart and finally, insufficiency of the right ventricle.

- *CHF due to a volumetric overload* (increase in the volume of blood ejected by the ventricle).

- In aortic insufficiency, blood regurgitation occurs from the aorta in the LV, with volume overload during ventricular diastole (the LV receives blood from RA, but also blood from the aorta).
- In mitral insufficiency, blood regurgitation occurs from LV to LA, during ventricular systole, due to valvular incompetence (thus, in order to maintain a normal ejection volume, in the direction of the aorta, despite this oscillating volume, during the next diastole, the LR must have a larger volume than normal).

In the two cases, the regurgitation of the blood leads to an increase (of varying degrees) of the ventricular blood volume, responsible for the important dilation of the cavity. In the case of chronic volumetric overloads, the major compensation is achieved by eccentric hypertrophy and progressive dilation of the heart.

3. CHF due to an increase in tissue metabolic needs

Occurs due to pathologyes (or pregnangy) that require increased cardiac output, suc as:

- Hyperthyroidis, the thyroid gland secretes a greater amount of thyroid hormones (thyroxine) responsible for stimulating lipid, carbohydrate and protein metabolism, and also for stimulating growth. Thus, the needs of the tissues in oxygen increase, and the heart must send a greater amount of blood to the tissues.
- In pregnancy, the heart must ensure the supply of oxygen and nutrients to the tissues of the mother and fetus.
- In anemia and hypoxia, compensatory tachycardia that occurs in this situation, will cause fatigue of the heart.

4. CHF due to iatrogenic myocardial lesions induced by:

1. Cytostatics - used in the treatment of cancer; they are cardiotoxic drugs (one such prototype is doxorubicin).
2. Antitumor radiation therapy - used in certain malignancies. Irradiation of the heart can cause a cardiac fibrosis.

Compensatory mechanisms

In order to cope with a hemodynamic overload, the heart has several mechanisms of adaptation: *neuro-hormonal stimulation, peripheral redistribution of flow and ventricular hypertrophy and remodeling.*

Neuro-hormonal stimulation

Reducing cardiac output in CHF will trigger a number of neuro-humoral consequences as systemic compensation mechanisms, which aim to restore cardiac output and arterial pressure. The reduction of cerebral and renal perfusion plays a main role in the activation of these mechanisms implies: the reduction of the cerebral flow represents the stimulus for the sympathico-adrenergic activation, while the decrease of the renal flow participates in the activation of the renin-angiotensin-aldosterone system (RAAS).

a. Sympathetic stimulation is the fundamental adaptive element, responsible for the effects at cardiac and peripheral level. At the cardiac level, as a result of activation of cardiac β1 adrenergic receptors, occurs increased HR (sinus tachycardia) and increased contractility with a new increase in CO. At the peripheral level, as a result of the activation of vascular α adrenergic receptors, venous vasoconstriction occurs with increased venous return to the heart and, therefore, of the central blood volume and inhomogeneous arteriolar vasoconstriction. Selective vasoconstriction in certain territories, leads to the decrease of blood circulation at the level of skeletal muscles (fatiguability), skin (pallor) and kidneys (oliguria) to make possible the blood irrigation of the priviledge territories (heart and brain) – a phenomena called the ″centralization of circulation″. But this rapid adaptation mechanism runs out as the contractile reserve decreases.

b. The activation of RAAS starts from renin, a proteolytic enzyme synthesized in the walls of the renal glomeruli, in response to the decrease of the renal perfusion, the decrease of the renal sodium excretion and the sympathetic stimulation. The activation of RAAS produces, as its main consequence, the hydrosaline retention. This retention occurs as a direct effect of angiotensin II (ATII, responsible for proximal hydrosaline retention), or as an indirect effect of aldosterone secretion by the adrenal gland (responsible for distal hydrosaline retention). The end result is increased reabsorption of water and sodium, with increased circulation blood volume. Increased volemia and increased ventricular load leads to increased telediastolic volume and also increased cardiac output (this effect is called the Frank-Starling effect).

c. Vasopressin release (antidiuretic hormone / ADH), produced by the hypothalamus and stored in the posterior pituitary, stimulates hypovolemia or hyperosmolarity, and causes the increase of volemia by primary reabsorption of water at the level of the distal nephron.

Forms of heart failure

1. Left CHF: shows the following peripheral signs, due to a decrease in left ventricular flow:

- Congestive signs upstream blood accumulates in LV: in LA, in pulmonary veins and capillaries. In the left CHF, congestion (blood stasis) occurs in the pulmonary circulation and the main symptom is consecutively, dyspnea. The following degrees can be described:

- dyspnea triggered by effort
- dyspneea that occurs when resting
- paroxysmal nocturnal dyspnea
- pulmonary edema - the most severe form, a therapeutic emergency. Pulmonary edema occurs as a result of fluid accumulation of plasma origin, initially in the interstitial tissue (interstitial edema) and then in the alveoli (alveolar edema) with the risk of acute respiratory failure.

- Downstream signs (appear due to circulatory deficiency and reduction of perfusion): the appearance of an abnormal fatiguability at effort, pallor of the extremities, oliguria.

2. Right CHF: shows the following peripheral signs, due to the reduction of the right ventricular flow:

- Congestive signs upstream of RV, in the cave veins: at the level of the superior cave vein appears jugular turgidity, at the level of the liver appears hepatalgia and hepatic distention, at the level of the lower limbs - peripheral edema.

3. Overall heart failure: it is the most serious form, constituted as a result of the association of a left ventricular failure (which usually precedes by a few years the right CHF) and a right heart failure.

Therapeutic principles

The adverse effects of adaptation mechanisms must be combated by using:

1. Tonicardiacs (digitalis) that increase the contractile force, causing an increase in CO and a secondary reduction in heart congestion.
2. Diuretics and inhibitors of angiotensin converesion enzyme (ACE) combat congestive signs (edema) due to hydrosodized retention.
3. Excessive hypertrophy should be avoided, as the exaggerated thickening of the ventricular wall induces an increase in the oxygen

requirement for a larger mass of myocardial tissue, thus increasing the risk of myocardial ischemia. Pharmacological compounds that trigger cardiac hypertrophy/remodeling are used: ACE inhibitors, angiotensin II receptor antagonists, beta blockers (to prevent coronary risk).

2. THE BLOOD

Physiological characteristics

The human body contains a volume of blood that represents 7% of the body weight, that is about 4.5 l in a normal adult, (men have 5-6 L of blood, women have 4-5 L of blood). It is 5 times more viscous than water with a pH between 7.35 – 7.45. The color varies between bright red (oxygenated blood) to dark red (deoxygenated blood).

Blood composition

The blood consists of 55% plasma (consisting of 92% water, 7% plasma proteins and 1% other substances) and 45% blood cells (red globules - erythrocytes, white blood cells - leukocytes and blood platelets-thrombocytes).

Functions of the blood

1. Transport of respiratory gases, nutrients, hormones and metabolites
2. Regulation of pH and electrolyte composition of interstitial fluids in the body
3. Defense against toxins and pathogens
4. Stabilization of body temperature

Blood and transport

Red blood cells contain the protein called hemoglobin (Hb) that carries O_2 and CO_2. The nutrients absorbed at the intestinal level are distributed by the blood to the tissues, from where the blood takes over the metabolism products transported to the kidneys to be eliminated. The blood transports also the hormones from the endocrine glands to the target organs. Metabolites produced by tissue cells are passed into the blood and then transported to the kidneys for excretion. The blood absorbs heat from the skeletal muscles and distributes it to other tissues.

Blood and protection

The blood has white blood cells, specialized cells that migrate to peripheral tissues to fight infections and eliminate cellular detritus's. White blood cells produce antibodies, proteins that attack invading organisms and foreign compounds. The blood contains enzymes that act by repairing the discontinuities occurring in the walls of blood vessels, where they form a blood clot that prevents the loss of fluids.

Formation of blood cells (hematopoiesis)

During intrauterine life, fetal cells are formed in the liver, spleen and bone marrow. After birth and in adults, they continue to form in the bone marrow.

Hematogenous red bone marrow is a particular substance located in the central portion of short and /or flat bones: sternum, iliac crest, vertebrae, ribs, head of the femur, skull. Hematopoiesis (greek, ema = blood, poiesis = to manufacture), hence the name hematopoietic organ. The place of formation of the figurative elements explains the way of achieving the bone punctures (sternal puncture, puncture at the level of the iliac ridge). It is used to diagnose blood cell abnormalities, especially in the case of severe anemia, or to determine a medullary infiltration with neoplastic cells or adipose tissue.

All blood cells come from pluripotent stem cells. Two hormones secreted at the renal level participate in this process: erythropoietin, with a role in the maturation and proliferation of erythrocytes, and thrombopoietin, with a role in the formation of platelets. The maturation of lymphocytes, which come from lymphocytic precursors, occurs partly at the level of the bone marrow, partly at the level of the thymus.

2.1 Erythrocytes (red blood cells)

The most numerous blood cells (99.9% of the figured elements). Normal values: in men 4.5-6.3 million erythrocytes/mm^3 and in women: 4.2-5.5 million erythrocytes/mm^3. It contains the red pigment called hemoglobin, which binds and transports O_2 and CO_2, each erythrocyte being a biconcave disc. This shape provides a larger area for capturing/yielding O_2 and allows the shape to change when erythrocytes enter small capillaries.

Erythrocytes have no nucleus and not most organelles. They are simple membranous sacs that contain hemoglobin. Erythrocytes are subject to incredible mechanical stress. After about 120 days, cracks or lesions of the erythrocyte membrane are detected by phagocytic cells, and then the erythrocyte is phagocyted. Ageing erythrocytes are captured and destroyed by fixed macrophages, present in the spleen and liver (whose ensemble forms the so-called reticule-endothelial system - RES), as well as in the hematogenous marrow. If hemolysis of erythrocyte occurs, its content in hemoglobin will be excreted by the kidneys.

Hemoglobin (Hb) is the protein that binds and transports O2 and is found in abundance in erythrocytes. It is charged with O_2 at the pulmonary level (oxyHb) and at the tissue level it gives way (deoxyHb) and takes up CO_2 (carboxyHb) from where it transports it to the lungs followed by elimination.

Hb, consisting of 5% heme and 95% globin, is a tetramer made up of 4 globin chains and 4 heme molecules - also made up by combining iron with porphyrin.

The level of Hb is expressed in g/100mL of whole blood (g/dL).

- 14-18g/dL in men
- 12-16g/dL in women
- 14-20g/dL in children

Hematocrit (Ht) is the percentage of blood occupied by erythrocytes. Normal values: in men approx. 46% (40%-54%) and in women: approx. 42% (37%-47%). It is higher in men because androgens (testosterone) stimulate the synthesis of erythrocytes, while estrogens do not stimulate it. Ht is determined by centrifuging the blood sample so that the figurative elements settle. Low Ht values indicate an anemia, while elevated values indicate a polycythemia with an increase in the number of erythrocytes in the circulation.

Erythropoiesis

Physiological erythropoiesis requires numerous factors:

- for the DNA synthesis associated with the multiplication of the erythrocytic precursors, vitamin B12 (present in meat) and folic acid (present in plants) are absolutely necessary.
- for the synthesis of hemoglobin in the cytoplasm requires mandatory iron (enter into the composition of hem); Vitamin C (favors the absorption of Fe^{2+} at the gastric level) vitamin B6 (intervenes in the synthesis of porphyrin), as well as amino acids (necessary for the synthesis of globin chains).

The lack of these factors determines the alteration of erythropoiesis with a consequent decrease in the production of erythrocytes and the appearance of anemia.

Regulation of erythropoiesis is carried out at the hormonal level. Erythropoietin is synthesized mainly at the renal level and a small part of it is synthesized in other organs, especially in the liver. Renal hypoxia (due to anemia, or any other cause that causes the decrease of the concentration

of O_2 in those living at high altitudes) leads to the synthesis of erythropoietin and the differentiation of erythropoietic sues cells and the synthesis of Hb.

Pathophysiology of the red series

Anemia is the decrease in the number of erythrocytes and the concentration of Hb.

Classification:

1. Anemias by decreasing erythrocyte production due to:
   - Alteration of hemoglobin synthesis: iron deficiency anemia
   - Alteration of DNA synthesis: megaloblastic anemias
   - Bone marrow deficiency of erythropoiesis function: aplastic anemia
2. Anemia by increasing erythrocyte destruction
   - Hemolytic anemias

These changes will have as a consequence the appearance of hypoxia (an inadequate supply of oxygen to the tissues).

Clinical manifestations of hypoxia are:

- Tachycardia
- Asthenia
- Dyspnoea
- Skin pallor

Iron deficiency anemia is an anemia characterized by alteration of hemoglobin synthesis due to the decrease in the total amount of iron in the body. It is the most common anemia in the world. The lack of iron prevents the normal synthesis of Hb and small erythrocytes (microcytes) appear, containing a small amount of Hb (hypo-chrome anemia).

Causes:

- increased losses through chronic small (occult) bleeding: digestive cancers (stomach, colon), menorrhagia (prolonged menstruation) or metrorrhagias (intermenstrual bleeding, e.g. uterine fibroids) in women – the most common cause
- increasing iron requirements in children during the period of rapid growth, pregnancy and lactation
- decreased intestinal absorption: gastritis with achlorhydria, gastric resection, diet with iron chelators (grain phytates, tannings in teas).

The absorption of iron requires its reduction to ferrous iron (ferric iron is not absorbed) by the acidity of gastric juice, being favored by vitamin C (ascorbic acid). The treatment requires the correction of the cause and the administration of iron preparations (orally in combination with vitamin C to increase absorption) until the normal value of hemoglobin is restored.

Anemia by altering DNA synthesis due to vitamin B12 deficiency

Causes of vitamin B12 deficiency:

- The gastric mucosa produces a substance called intrinsic factor, necessary for the absorption of vitamin B12. Lack of intrinsic factor: pernicious anemia
- decreased intestinal absorption: resection, intestinal inflammation
- decreased intake: strictly vegetarian diet

The treatment lasts a lifetime with intramuscular injections of vitamin B12.

Anemia by altering the synthesis of DNA due to folic acid deficiency

Causes:

- decreased intestinal absorption: chronic alcoholism is the most common cause
- cytostatic medication (methotrexate) that inhibits folate metabolism
- decrease in intake - poor nutrition in plants

Aplastic anemia occurs due to a bone marrow deficiency in erythropoiesis; it is produced by the destruction of hematogenous bone marrow by: bacterial toxins, drugs, radiation.

Hemolytic anemia involves premature lysis of red blood cells (reducing the life span of red blood cells).

Causes

- hemoglobin abnormalities
- transfusion incompatibility
- parasitic infection
- autoimmune causes

Diagnostic:

In practice, any type of anemia is diagnosed by:

1. decrease in the number of circulating erythrocytes
2. decrease in hemoglobin (Hb)
3. decrease in hematocrit (Ht) below normal values.

The counting of erythrocytes, namely the determination of the number of erythrocytes and leukocytes per mL of blood, is one of the most common tests and a very effective screening and diagnostic method. It can be performed manually or automatically. Various diseases can have a dramatic effect on the total number of erythrocytes or on the relative proportion of blood cells.

Blood groups

The blood of each person belongs to a certain blood group. At the root of the differences between blood groups are some chemicals found on the erythrocyte membrane. The appearance of blood groups is the consequence of the presence of antigenic proteins (denoted A, B) called agglutinogens on the surface of red blood cells and of the presence in plasma of antibodies (denoted alpha, beta) and called agglutinins. The presence of these is genetically determined. Agglutinin and the corresponding agglutinogen never appear together in the blood.

Several blood group systems have been described, but the AB0 system, discovered in 1900, is the most important. Based on the presence of agglutinogens and agglutinins, four blood groups are defined in the ABO system: 0I (no A, B, and alpha and beta), AII (have A and beta), IBII (have B and alpha), and ABIV (have both) (have A,B and do not have alpha and beta). Knowing your blood groups is critical for transfusions because agglutinogens and agglutinins should not come into direct contact (A with alpha, respectively B with beta). Otherwise, the patient's own blood considers the donor's blood a foreign body because the chemical differences between them will destroy the red blood cells in the other, similar to bacteria, putting the patient's life in danger. Antigens of the Rh system are still present on the surface of red blood cells in approximately 85% of individuals. Rh positive people are those who have rh system antigens; Rh negative people are those who do not have rh system antigens. Knowing the Rh character is important in blood transfusions as well as in the case of Rh-negative pregnant women carrying Rh-positive fetuses.

There are no spontaneous antibodies in the plasma of the Rh system, but when the blood of a Rh negative person comes into contact with Rh-positive blood in the Rh negative organism, anti-Rh antibodies form. If a Rh- person receives a transfusion of Rh+ blood (or a Rh- woman with a Rh+ fetus), a reaction occurs between the anti-Rh antibodies in the

plasma and the Rh antigens on the surface of the red blood cells, resulting in hemolysis and severe anemia.

Fetal erythroblastosis: the form of hemolytic anemia

It is a type of hemolytic anemia that occurs when a Rh- mother has her first Rh+ child. The placenta ruptures during childbirth, and the baby's blood mixes with the mother's blood. This will sensitize the mother to the Rh antigen, resulting in the production of anti-Rh antibodies. Because the first child is already born, he is not in danger. If the mother has another Rh+ child, her anti-Rh antibodies will cross the placenta and attack the fetal erythrocytes. This is known as fetal erythroblastosis (or hemolytic disease of the newborn). Without blood transfusions, the child becomes anemic and hypoxic, resulting in brain damage and death.

2.2 Leukocytes (white blood cells)

They are also produced by the bone marrow and have a normal value between 5,000-10,000/mm^3. They have a globular appearance and serve as the body's defense against infections. Leukocytes are classified into two types: granulocytes/polymorphonuclears (PMN: neutrophils, basophils, and eosinophils) and mononuclear (lymphocytes - LB and LT and monocytes). White blood cells can easily pass through capillary walls and are abundant in various tissues.

Granulocytes function by engulfing foreign particles, which they then digest through the process called *phagocytosis*. Diapedesis is the ability to leave blood vessels, passing between two cells that constitute the wall of capillaries. This passage is possible due to the presence of pseudopods (extensions of the cytoplasm).

Phagocytosis (Greek phagein = to eat) is the essential role of PMN, to destroy foreign particles (microbes, bacteria, etc.), incorporating them into the cytoplasm and then destroying them. Digestion involves the use of enzymes contained in cytoplasmic particles, called lysosomes. Thus, phagocytosis leads extremely quickly to the death of foreign particles (2-15 microbes digested as a result of their toxicity). The increase in the number of PMN in the blood suggests the presence of an infectious place in the body. PMN are attracted to the infectious focus by specific substances produced by it. The potential for attraction by chemicals is called chemotaxis.

1. *PMN* - *neutrophils* are also called microphages because they are the main ones involved in phagocytosis. In the case of an infection, they are attracted to the inflammatory focus by chemotactic agents and leave the blood vessels through diapedesis, being the first to be responsible for phagocytosis.
2. *PMN* - *eosinophils* are less capable of phagocytosis, increase in parasitic infections and in allergies, including medicinal.
3. *PMN* - *basophils* have the least known role. They intervene in inflammation (by releasing histamine) and in coagulation (by releasing heparin) from their granules, at the tissue level mast cells have a role in allergies.

Lymphocytes patrol the body more slowly and react more slowly by producing antibodies.

1. *Monocytes*, the largest leukocytes, also capable of diapedesis, can pass into the tissues 24 -48 hours after the microphages. They are called macrophages because they phage large particles, including the microphages destroyed in infectious foci.
2. *Lymphocytes* are small mononuclear cells responsible for the specific defense or immune response that is directed against a particular Ag (any substance foreign to the body). They are classified as:
   - B lymphocytes: in the presence of an Ag they differentiate into plasma cells (plasmocytes) that secrete antibodies, these being the effectors of humoral immunity.
- T lymphocytes: stimulated by antigen differentiates into subpopulations of specialized lymphocytes, being the effectors of cellular immunity:
    - killer (direct attack of antigen)
    - helper (increase the secretion of antibodies by plasma cells)

Pathophysiology of leukemias

Leukocyte formula: neutrophils (65-70%), monocytes (25-30%), monocytes (6-8%), eosinophils (1-3%), basophils (0-1%). The leucocyte count (WBC) represents a routine laboratory performed peripheral blood in order to identify and count the cellular white blood cell subtypes.

Quantitative changes

Leukopenia occurs when we have a number of leukocytes < 4000/mm^3

1. Granulocytopenia represents the decrease in the number of PMN caused usually by the administration of some drugs: chloramphenicol, anticonvulsants, anti-thyroid medication, exposure to X-rays or following cytostatic treatment.

2. Lymphocytopenia represents the decrease in the number of circulating lymphocytes (rarely). It may occur in the conditions mentioned above, and sometimes after administration of corticosteroids.

Leukocytosis occurs when the number of leukocytes increases above 10,000/mm^3.

Depending on the type of cell involved, the following are distinguished:

- Neutrophilia - increased number of PMN neutrophils, as occurs in:
  - acute bacterial infections
  - acute inflammation
  - myocardial infarction
  - states of stress (release of catecholamines)
- Eosinophilia - increased number of eosinophils, as occurs in:
  - allergic conditions
  - allergic drug reactions
  - parasitosis
- Lymphocytosis - increased number of lymphocytes, as occurs in: acute viral infections, chronic bacterial infections and auto-immune diseases.

Qualitative changes - leukemias

Leukemia is considered a malignancy with a high mortality rate and represent a broad term for cancers of the blood cells. Leukemia is characterized by the uncontrolled proliferation of leukocyte precursors in the hematogenous bone marrow from where cells pass into the blood and infiltrate tissues and organs.

The proliferation of leukemia cells prevents the formation of the other cell lines; as a result, the bone marrow produces less erythrocytes, platelets and normal leucocytes, thus leading to anemia, thrombocytopenia with a risk of bleeding and leukopenia, respectively, with a risk of serious recurrent infections (because leukocytes, even if there are many, are cancer cells incapable of defense). It is associated with increased cell destruction with accelerated cellular metabolism with significant weight loss.

The causes of leukemias are known very little. Genetic factors, environmental factors, ionizing radiation, chemicals (asbestos), cytostatic and immunosuppressive medication, Epstein Barr virus, HIV, HTLV ("Human T Cell Leukemia Virus") seem to be involved.

Classification:

Depending on the cell type that proliferates:

- •myeloid leukemia: in which granulocytes proliferate
- •lymphocytic leukemia: in which lymphocytes proliferate

Depending on the evolution:

- •acute leukemias: in which the young, immature elements (blasphemies) of the respective series proliferate.
- •chronic leukemias: in which mature elements proliferate.

Acute leukemias

Clinical features:

- sudden onset, rapid evolution, severe prognosis (death in a few months in the absence of treatment)
- proliferation of immature, blast cell forms, precursors of myeloid or lymphoid series at the medullary level with the blocking of cell differentiation and maturation
- rapid infiltration of the hematogenous marrow with suppression of normal hematopoiesis and the appearance of medullary insufficiency manifested by: severe anemia, granulocytopenia with infectious syndrome and thrombocytopenia with hemorrhagic syndrome.

Chronic leukemias

Clinical features

- insidious onset, slower evolution, reclined prognosis
- proliferation and accumulation in a first phase of well-differentiated leukemia cells of mature type
- slow infiltration of the hematogenous marrow with progressive onset of anemic, infectious and hemorrhagic syndrome.

Therapeutic principles

The goal of the treatment is to induce remission with the help of various combinations of cytostatic drugs. Remission is characterized by the temporary decrease or absence of clinical symptoms, but is not synonymous with healing; the only curative therapy is bone marrow transplantation.

2.3 Platelets (thrombocytes)

Platelets are blood cells that play a role in hemostasis (stopping a hemorrhage). The hemostasis represents the body's defense mechanism against exaggerated blood loss. If a vessel is injured, the platelets gather around the lesion, stick to each other and to the surface of the vessel – a process called adhesion and aggregation. Platelets and substances released from the damaged tissue initiate the coagulation process.

Platelets are formed in the hematogenous marrow by the fragmentation of large precursor cells called megakaryocytes. The normal number in the circulating blood is 150.000 – 300.000/mm^3, being the smallest figurative elements of the blood, without a nucleus, the cytoplasm having numerous small grains. The life span is 7–12 days and they are destroyed by the macrophages of the reticulo-endothelial system in the spleen.

Hemostasis, is carried out with the participation of 3 groups of factors: vascular, platelet and plasma factors of coagulation.
In the course of the hemostatic process, 3 main times are distinguished:

- Vascular time (primary hemostasis)
- Plasma time (secondary hemostasis)
- Fibrinolysis

2.3.1 Primary hemostasis

Is performed with the participation of vascular and platelet factors.
Vascular factors intervene in hemostasis by: i) reflex vasoconstriction – which decreases blood flow in the injured area and by ii) exposure of subendothelial structures (collagen, basal membrane) – which initiates the adhesion, aggregation and release of platelet mediators with the formation of white thrombus.
Platelet factors, namely platelets, intervene in hemostasis by: i) the formation of white thrombus (formed from platelets aggregates and fibrin) within primary hemostasis and by ii) participation in secondary hemostasis (coagulation).

Stages of white thrombus formation:

- platelet adhesion that occurs at the level of subendothelial structures (collagen, basal membrane)
- activation and reaction of release of the contents of platelet-rich granules: thromboxane A2 (TxA2) which stimulates the adhesion and aggregation of platelets and has a vasoconstrictor effect
- platelet aggregation (induced by ADP and/or thrombin)

2.3.2 Secondary hemostasis-coagulation

It leads to the formation of the fibrin clot (red thrombus – contains fibrin, red blood cells and platelet aggregates). In order to occur, the coagulation needs specific proteins called coagulation factors that are synthesized in the liver, in the inactive form. The coagulation factors are activated by upstream activated coagulation factors, leading to the so-called coagulation cascade. The coagulation cascade begins (is activated) via 2 pathways: the intrinsic and extrinsic pathway. The intrinsic pathway is activated by factors found in the blood (collagen, kallikrein), whereas the extrinsic one by damage to the endothelial wall cells which release tissue factor. The ultimate step in the coagulation cascade is the activation of fibrinogen in fibrin by thrombin. However, fibrin is initially soluble, and then converted into the final fibrin (insoluble, effective in hemostasis) under the influence of a stabilizing factor (activated XIII factor) and Ca^{2+}.

Abnormal activation of hemostasis is prevented by the coagulation inhibitory system, which includes several factors:

•Antithrombin III (AT III) which inhibits thrombin; its activity increases by binding to heparin.

•The C and S protein system that inhibits certain coagulation factors and is activated by thrombin.

2.3.3 Fibrinolysis

It consists in the lysis of the fibrin clot under the action of plasmin with the permeabilization of the vessel obstructed by coagulation. Plasmin results by activating plasminogen.

Fibrinolysis inhibitors are:

- α2 antiplasmin and α2 macroglobulin forming a plasmin complex
- tissue activator inhibitors (PAI).

In summary, the hemostasis occurs in the following sequence:

• Vasoconstriction and white thrombus formation in primary hemostasis

• Activation of coagulation and formation of fibrin clot in secondary hemostasis

• Retraction and lysis of the clot in a process called fibrinolysis.

2.3.4 Coagulopathies

Hemophilia type A or B are the most well-known coagulation disorders, occurring as a result of the genetic deficiency of certain

coagulation factors that have genetic transmission from mother to fetus. The cause of hemophilia is the lack of:

- factor VIII - Hemophilia A (most common)
- factor IX - Hemophilia B.

The main feature of these diseases is the occurrence of a latency period of several hours between trauma and hemorrhage (because the primary hemostasis is normal). Hemorrhages can occur even after a minor trauma or spontaneous; as a consequence, ecchymosis, subcutaneous or intramuscular hematomas, recurrent hemarthrosis can occur. The treatment involves the administration of fresh plasma and products containing the missing factor VIII/IX, extracted from the blood plasma.

2.3.5 Antithrombotic medication

Antithrombotic medication includes: anticoagulants, fibrinolytics and antiplatelet agents.

Anticoagulants prevent blood clotting by acting on the different factors of coagulation via a:

a) a direct mechanism:

- standard heparin (deep venuous thrombosis or pulmonary embolism)
- low molecular weight heparin (fraxiparins, clexane) which inhibits certain coagulation factors and also inhibits certain platelet functions, thus decreasing the viscosity of the blood.

b) an indirect mechanism

- antivitamin K drugs - coumarin anticoagulants (warfarin). They act by inhibiting the enzymes involved in the synthesis of vitamin K–dependent coagulation factors II, VII, IX, and X.

Fibrinolytics produce rapid thrombus lysis and recanalization of the obstructed vessel, activate directly / indirectly plasminogen. Their usefulness is in acute thrombosis, acute pulmonary embolisms, myocardial infarction (streptokinase, urokinase).

Antiplatelet agents of prevent or reduce the formation of platelet thrombi by inhibiting various platelet functions, by inhibiting the synthesis of (thromboxane A2 - aspirin) or by stimulating the synthesis of prostacyclin's (dipyridamole).

3. THE RESPIRATORY SYSTEM

The respiratory system supplies the body with oxygen and removes carbon dioxide through a process called hematosis. Breathing is a vital function of the body, which cannot store oxygen and needs the continuous intake of this gas for a large number of biochemical reactions. Combustion reactions inside the cells ensure the degradation of food and the production of energy, also participating in the defense of the body, also intervening in the homeostasis of the acid-base balance.

3.1 Functional anatomy

The respiratory system includes the following organs: nose, nasal cavity, oral cavity, pharynx, larynx, trachea and lungs (with bronchi, bronchioles and pulmonary alveoli). The respiratory system is divided into respiratory areas and conduction areas. The gaseous exchanges take place in the respiratory areas, not in the conduction areas.

The conduction areas heat the air that enters the body due to a rich blood capillary network and humidifies and purify it through the serous-mucous glands. The waste is agglutinated at the level of the mucous membrane walls, being embedded by the mucus existing at this level. They are either destroyed immediately at the site of deposition, phagocytic by the white blood cells (micro- and macrophages), or eliminated on the outside by means of vibrating cilia on the surface of the ciliated cells, which function by countercurrent mechanism. The elimination on the outside of the foreign bodies accidentally introduced into the airways is done through the reflex of coughing and sneezing.

Nasal cavity

The nose and nasal cavity form the first segment of the respiratory. They possess a double functional role: respiratory and olfactory. The nasal cavity opens outside through the nostrils and to the pharynx through the internal nostrils, or choanae. They have irregular shape due to the existence of 3 nasal conchae (superior, middle, inferior) which divide the innter of the nasal cavity in the inferior nasal meatus, middle nasal meatus and superior nasal meatus. The pink mucosa is rich in blood vessels and has numerous mucous glands that keep moisture constant; it provides heating, moisture and partial filtration of the inhaled air. In the upper portion of the nasal cavity (superior nasal meatus) the mucosa is called the yellow

mucosa. It has a sensitive role (olfactive) and is poor in blood vessels and glands, but contains the nerve endings of the olfactory nerve.

Mouth

It occupies the lower part of the face having 6 walls: two side walls, representing the internal faces of the cheeks, the anterior wall - represented by the lips, the lower face - represented by the tongue, superior – the hard palate and posterior - the soft palate (has a fibromuscular extension oriented downward called the uvula) and pharynx.

The oral cavity also allows air to pass from the outside to the pharynx, and then into the larynx. Phonation occurs due to the position, movements and contraction of the tongue by intervening in the emission of sounds. The tongue is the gustatory organ, the receptors are represented by the lingual papillae.

Pharynx

The pharynx is the place of aerodigestive crossroads, arbitrarily divided into 3 parts: the upper part, in the continuation of the nasal cavity called the nasopharynx / nasopharynx (where air circulates); the middle part, in continuation of the oral cavity called the oropharynx (circulates air and food bowl) and the lower part, in relation to the larynx - the hypopharynx.

Larynx

The larynx is an organ with double function: respiratory and phonatory. It has the shape of a triangular pyramid trunk with the base up. The base communicates with the pharynx through an orifice, delimited anteriorly by the epiglottis and posteriorly by the arytenoid cartilages. The tip of the larynx continues down with the trachea.

The larynx is formed on a cartilaginous framework; its role is to protect the respiratory path while also acting as the organ of phonation. It consists of the union of three unpaired cartilages: thyroid, cricoid and epiglottis and three paired cartilages: arytenoid, corniculates and cuneiforms, articulated with each other and presenting as means of union, ligaments and membranes. The larynx is a cavitary organ, lined by a mucous membrane and presents inside two pairs of vocal folds arranged anteroposterior. The upper vocal folds are called ventricular or false vocal cords, and the lower ones, the real vocal cords.

The laryngeal cavity is submerged, in relation to the vocal folds, in three floors: the space between the vocal folds is called the glottis or the middle floor; above is the supraglottic floor or laryngeal vestibule, and below, the infraglottic floor, which communicates directly with the trachea. In the formation of the voice occurs the rhythmic contraction of a vocal cord that produces then a vibration of the air column.

Trachea

The trachea is a rigid tubular duct that crosses the anterior face of the neck before reaching the upper part of the mediastinum, where it divides into 2 branches. It is 12 cm long and has 2.5 cm in diameter. It consists of 15-20 cartilaginous rings connected to each other by annular ligaments. Posteriorly, joining the two ends of the cartilaginous horseshoe, there is the tracheal membrane, in the thickness of which is located the tracheal muscle. Its contraction decreases the caliber of the trachea. It ends at the level of the chest in the 2 main right or left bronchi.

The trachea is lined by a mucosa rich in mucous cells and vibratory cilia with a role in air purification and foreign bodies elimination.

Topographically, the trachea presents a cervical segment from c6-7 to T1 and a thoracic segment that ends at the T4-5, where the bifurcation of the trachea occurs in the two main or primary bronchi, which also ends at the level of the respective pulmonary hilum.

Bronchi

The right primary bronchus is shorter (2-3 cm) than the left one (5 cm), but has a larger caliber. The primary left bronchus is longer and a trajectory closer to the horizontal. From the pulmonary hilum, the primary bronchi branch into three (or 2 for the left one) secondary or lobar bronchi for each lobe, and from here, in segmental bronchi for each lung segment.

Bronchial tree

Each main bronchus serves a lung. Inside the lungs, the primary bronchi divide into the secondary bronchi. Secondary (lobar) bronchi subdivide into tertiary (segmental) bronchi and so on. Thus, the bronchial tree is formed. Air ducts that are less than 1mm in diameter are called bronchioles; the terminal bronchioles represent the last part of the conduction area.

The respiratory area

Terminal bronchioles turn into respiratory bronchioles, the first part of the respiratory area. The respiratory bronchioles become alveolar ducts completed by terminal bunches of alveoli structured in alveolar sacs. The external surface of the alveoli is lined by numerous capillaries with a thin wall, elastic fibers and smooth muscles. The alveolar wall (alveolar epithelium) and capillary wall (capillary endothelium) form the alveolo-capillary membrane, a fine (0.6–2 μm) blood–air barrier or air–blood barrier with a surface of 60–160 m^2, where the gases (O_2 and CO_2) are exchanged between the 2 sides. The effectiveness of pulmonary exchanges is explained by the narrowness of the two membranes, the richness of the blood capillaries and the large area of exchange.

Mediastinum

It's the space between the two lungs. Anteriorly it reaches the sternum, posteriorly it stretches to the spine, the lower part extends to the diaphragm, and the upper part communicates wide with the base of the neck.

Lungs

The lungs are the main organs of the respiratory system, located in the chest cavity, having an elastic, sponge consistency. The external face of the lungs is convex, and comes in relation to the ribs. On this face there are deep grooves, called fissures, which divide the lungs into lobes. The right lung has two fissures, which divide it into three lobes: upper, middle and lower. The left lung has a fissure, which divides the left lung into two lobes (upper and lower).

The internal face is flat and comes in relation to the organs in the mediastinum. On this face is the pulmonary hilum, where the vessels, nerves and the main bronchi enter or exit the lungs. The base of the lungs is concave and comes in relation to the diaphragm. The tip of the lung exceeds upwards the first rib and comes in relation to the organs at the base of the neck.

At birth, the lungs are red in color, and after the first breaths, pink. In the newborn who has not breathed, the lungs are whitish-gray. In adults, the color of the lungs becomes grayish.

Pulmonary parenchyma

The lung parenchyma is made up of spongy elastic tissue that has the ability to expand and the ability to retract which explains why exhalation is a passive time.

Pleura

The pleura is a serous membrane that airtightly surround both lungs. The outer wall (external or parietal pleural foul) adheres to the inner wall of the chest boxes. The internal wall adheres to the external surface of the lungs (internal or visceral pleural foitis). Between the two walls, there is a pressure lower than atmospheric pressure, so the pressure is negative (zero pressure is considered the pressure naturally occurring at the earth's surface, considered atmospheric pressure). This negative intrapleural pressure allows the lungs to dilate to be able to occupy the entire thoracic volume. A thoracic lesion that allows air to enter the pleural cavity is called pneumothorax and which thus equalizes the intrapleural pressure with the atmospheric pressure, causing a rapid collapse (from Latin, collapsus = fall) of the lung from the injured side.

Chest box

The lungs are located in the chest box, the removal of the trachea, esophagus and heart. The role of the chest box is to protect the lungs and heart and for the insertion of the respiratory muscles.

Vascularization of the lungs

The lungs have a double vascularization: nutritious and functional. *The nutritional vascularization* is provided by the bronchial arteries, from the thoracic aorta, which bring blood with oxygen to the lung. They enter the lung through the hil and accompany the bronchial tree. Venous blood reaches the upper vena cava. The nutritional vascularization of the lung is part of the great circulation. *Functional vascularization* belongs to the small circulation, it begins through the trunk of the pulmonary artery that has its origin in the right ventricle. The trunk of the pulmonary artery brings blood loaded with CO2 to the lung. It divides into the right and left pulmonary artery which, through the terminal branches, reach around the alveoli, succumbing to CO2. Oxygenated blood is taken up by the pulmonary veins and transported into the left atrium.

3.2 Physiology of respiration

"Breathing" involves 4 different processes:

1. Ventilation - represented by the movement of air inside and outside the lung
2. External respiration - involves the gaseous exchanges between the blood and the pulmonary cavities filled with air
3. Gas transport
4. Internal respiration - represented by gaseous exchanges between blood and tissue cells

3.2.1 Ventilation

Ventilation allows air renewal at the level of the alveoli having two inspiratory and expiratory phases.

The Inspiration

It begins with the contraction of the diaphragm and the external intercostal muscles. This causes the increase of the thoracic volume, which leads to the increase of the pulmonary volume. Consequently, the pressure inside the lungs decreases. The alveolar pressure is lower than the atmospheric pressure, so the air will move according to the concentration gradient and enter the lungs. The inspir ends when the alveolar pressure is equal to the atmospheric pressure.

Exhale

Normal exhalation is a passive process, achieved due to the elasticity of the lungs. Forced exhalation is an active process performed with the help of contraction of the abdominal muscles and the internal intercostal muscles.

Forced respiratory movements

In addition to normal respiratory movements, there are also, under voluntary effect, larger respiratory movements, called forced respiratory movements.

Forced inspiration involves accessory respiratory muscles (subclavian, SCM, pectoral) whose contraction ensures the traction of the ribs even closer to the horizontal, in order to obtain a maximum possible increase in the pulmonary volume. The forced exhalation involves the action of the particular abdominal-thoracic muscles (small teeth, obliques and lumbar squares) that determine the return of the ribs to the position of

maximum obliqueness, with the expulsion on the outside of the maximum possible amount of air.

Forced respiratory movements are used during the exploration of pulmonary ventilation. With the help of the spirometer which is a device in which the subject breathes through an oral piece, and the volumes of air inspired and exhaled by the subject are recorded as a function of time.
The investigation is done fasting, the patient not being allowed to smoke at least an hour before. The subject, after a nasal clamp is applied to him (breathing is prevented through the nose), is coupled to the spirometer and allowed to breathe normally for 1 min. It is then prompted to execute a maximum breath, followed by an exhalation as slowly and completely as possible.

Respiratory volumes

During a normal breath, about 500 mL is circulated during each breath and represents the current volume. The volume of air that can be additionally inserted into the lung at the end of a resting breather is the spare inspiratory volume. The spare expiratory volume is the volume of air that can still be expelled from the lung at the end of a resting exhale. The volume of air that cannot be expelled from the lung nor by a forced exhalation is the residual volume of about 1500 ml.

Respiratory capacities

Inspiratory capacity is the total volume of air that can be inspired after a resting exhale: CI = VT + VIR.
Functional residual capacity is the volume of air present in the lung at the end of a resting exhale: CRF = VER + VR.
The vital capacity represented by the total volume of air participating in the gaseous exchanges: CV = VT + VIR + VER.
The total lung capacity is the volume of air contained in the lung at the end of a maximum breath: CPT = CV + VR.

3.2.2. Transport of respiratory gases

The membrane that separates the alveolar air from the blood is called the alveolo-capillary membrane, made up of the cytoplasmic wall of the alveoli, the layer of the interstitial fluid and the layer of the cell that constitutes the capillary wall.

Gaseous pressure differences between blood and alveolar air favor gaseous exchanges. The alveolar air is rich in O_2 (PO_2= 100 mmHg) and

poor in CO_2 (PCO_2= 40 mmHg). This distribution is reversed at the level of the venous blood that reaches the alveoli (PO_2= 40 mmHg, PCO_2= 45 mmHg). For the 2 gases, the passage is made from the high-pressure area to the low-pressure area, through a process called gas diffusion.
Disturbances of gaseous exchanges:
• hypercapnia is the increase in arterial pressure of the carbonic gas: PCO_2>45 mmHg.
• hypoxemia is the decrease in blood pressure of oxygen: PO_2<60 mmHg.

3.2.3. Air gas transport

Respiratory gases are circulated in the body from the capture site (lungs) to the place of use (cells) through the blood. There are 2 forms of conveyance of gases in the blood: the dissociated form and the combined form. The volume of dissociated gas in the blood plasma is directly proportional to the dissociation pressure: the higher the gas pressure, the greater the amount of dissociated gas. Certain substances circulated by the blood have the chemical property of forming a reversible combination with respiratory gases. The partial pressure of a gas sometimes conditions its dissociation into serum, as well as its combination with certain substances in the blood. The partial pressure of a compound in a gaseous mixture (because that gas constitutes a part of the mixture) is the pressure that that gas would exert if it occupied by itself the entire volume occupied by that mixture. It is expressed in mmHg.

O2 transport

Oxygen is transported by the blood in two different forms:
•3% is dissociated into the blood plasma, only this dissociated fraction of oxygen can be used directly by the cells.
•97%: in combination with Hb
Hb contains Fe^{2+} atoms with which oxygen is combined to be able to circulate in the blood, bound to the red blood cells.

The oxygen + hemoglobin association is oxyhemoglobin, a reversible combination, oxyhemoglobin can split into hemoglobin and free oxygen. Oxyhemoglobin is not directly used by cells, being only a form of storage and transport of oxygen in the blood. The amount of oxygen bound to hemoglobin is in equilibrium with the amount dissociated in plasma. Thus, when this last quantity is diminished by the consumption of

cells, hemoglobin releases the oxygen that will dissociate in plasma, thus being able to be used by the cells.

Transport of carbon gas

Carbonic gas is transported by blood in three different forms:

•5% is dissociated into plasma. This part plays an extremely important functional role, as in the case of dissociated oxygen;

•25% is combined with hemoglobin, resulting in carbohemoglobin, a reversible combination;

•70% is fixed in the form of bicarbonates (carbonates + carbonic gas = bicarbonates) in plasma, and also in erythrocytes that ensure the regulation of the acid-base balance.

As with oxygen, there is a balance between these different forms and the environment, the essential factor of this balance being the partial CO_2 pressure.

3.2.4. Gaseous exchanges at the cellular level

Capillary blood is rich in oxygen, whereas the cell is poor in oxygen because it's consumed for the cell metabolism. Given this difference in pressure, the diffusion phenomenon will cause oxygen to pass from the blood to the cell. This decrease in dissociated oxygen will produce the release of oxygen from hemoglobin.

In the case of carbon gas, the passage is carried out in the opposite direction, to the blood, which is much poorer in carbonic gas than the cellular cytoplasm. The blood will thus return to the lungs charged with carbonic gas and low in oxygen.

At rest, Ventilation/minute = 6 l/min and respiratory rate, 14-16 cicles/min.

3.2.5. Regulation of breathing

The rhythm of breathing is programmed by nerve centers; more precisely, there are two in the medulla and one in the pons. Inflows go through the intercostal and phrenic nerves, which stimulate the diaphragm and intercostal muscles. The respiratory centers work automatically, without the help of voluntary activity (this characteristic is demonstrated by breathing during sleep), periodically inflows are sent to the inspiratory muscles, via the nerves of breathing (the vague and phrenic nerve), at an average rate of 14-16 cycles (inhale + exhale)/minute. Voluntary action

occurs only in the case of forced breathing and exhaling movements. Breathing is a spontaneous, complex act, the rhythm and amplitude of which can be altered by various external elements (disease, alcohol, sleeping pills) that inhibit the involved neurons.

Voluntary control, emotions, changes in pH and CO_2 and O_2 concentration, stretching of the lungs, stimuli such as touch, temperature, and pain can cause changes in the respiratory center, thus altering breathing.

3.3 Pathology of the respiratory apparatus

3.3.1 Dyspnea

It represents the difficulty to breath. Unlike normal breathing, which is involuntary, dyspneic breathing is conscious, voluntary. The sick person feels a "thirst for air". In other words, the dyspneic patient feels on the one hand the need to breathe, and on the other hand he perceives the respiratory effort he makes is insufficient.

Classification:

By the circumstances of occurrence are distinguished:

1. permanent dyspnea (advanced heart failure, pneumothorax),
2. exertion dyspnea (pleuro-pulmonary processes that decrease pulmonary ventilation, heart failure),
3. dyspnea of decubitus (the sick person cannot lie down, but in a semisezindic position),
4. paroxysmal dyspnea, encountered in bronchial asthma and insufficiency of the left ventricle (cardiac asthma and acute pulmonary edema).

After the type of breathing that is disturbed:

1. inspiratory dyspnea (edema of the glottis, foreign body in the larynx),
2. expiratory dyspnea (bronchial asthma and pulmonary emphysema)
3. mixed dyspnea, in which difficulty interests both inspiration and exhalation, and which is found both in pleurisies with a lot of fluid and in massive pneumonia.

In current practice, dyspnea is the expression of a disease of the respiratory or cardio-vascular apparatus.

3.3.2 The cough

Coughing is a reflex or voluntary act, which results in the violent expulsion of air, and in some cases of foreign bodies from the airways.
The act of coughing encompasses:
• the inspiratory phase, in which air enters the lungs
• the compression phase, by closing the glottis
• sudden expulsion of air by contraction of the abdominal muscles, violent lifting of the diaphragm and forced opening of the glottis; along with the air column, expectoration, mucus or foreign bodies are also projected outwards.

Cough can be: *i) dry, without expectoration* (pleurisy, the initial phase of acute bronchitis or pulmonary tuberculosis) or *ii) wet, followed by expectoration* (the sign of a bronchial process or lung parenchymal: acute or chronic bronchitis, pneumonia, etc.).

Dry cough is harmful, can spread the infection, deplete the right heart and disturb sleep - that is why it must be combated.
By etiology, cough can be:

- pharyngeal (acute and chronic pharyngitis),
- laryngeal (laryngitis or laryngeal tumors),
- bronchial (bronchitis, bronchial cancer),
- pulmonary (acute or chronic pneumopathies),
- pleural (pleuritis),
- mediastinal (tumors, heart failure, pericarditis).

3.3.3 Hemoptysis

Hemoptysis represents the elimination by mouth of an amount of blood coming from the lower airway. Epistaxis occurs when the blood comes from the level of the nasopharynx.

Hemoptysis can occur unexpectedly, but usually it is preceded by prodromas: feeling of retrosternal heat, slightly metallic-salty taste, state of fear, laryngeal tickling, which immediately precedes coughing. The removal of blood is sudden. The sick person experiences a coughing crisis, during which he removes clean, live-red, aerated, foamy blood, the amount varying from 100 to 300 ml. The general signs consist of pallor, sweating, breathlessness, tachycardia.
The causes of hemoptysis can be multiple, but six dominate by frequent:

1. pulmonary tuberculosis
2. bronchial cancer

3. bronchial dilatation
4. aerial cysts
5. mitral stenosis
6. pulmonary infarction

The other causes, although numerous, are rare:

- hemorrhagic syndromes
- benign tumors
- asthma
- allergic bronchitis
- chest trauma.

3.3.4 Respiratory infections

Upper respiratory tract infections are represented by:

- rhinitis
- pharyngo-tonsillitis
- sinusitis
- otitis

Lower respiratory tract infections

- Bronchitis
- Pneumonia

They are the most common infectious diseases, having a maximum incidence within communities, especially in the winter months.

Upper respiratory tract infections

Rhinitis is characterized by inflammation, hypersecretion and rhinorrhea (leakage of fluid from the nasal cavities or sinuses) affecting the mucous membranes of the nasal cavities and of the upper respiratory tract. Viral rhinitis is produced by viruses with a duration of 3-4 days until spontaneous healing, with the risk of complications such as bacterial superinfection, that usually leads to sinusitis, bronchitis (especially in the case of the children). The treatment is symptomatic with antipyretics, local vasoconstrictors (diminishing the size of blood vessels, and therefore of inflammation), antibiotics being contraindicated if the bacterial superinfection is absent.

Allergic rhinitis is produced by allergenic agents such as pollen, mites (house dust), animal hair (especially cat's), various types of molds.

Allergic rhinitis is a risk factor for asthma, studies have shown that most people suffering from rhinitis also have a nonspecific bronchial hyperreactivity and so, an asthmatic susceptibility.

Pharyngitis or pharyngitis-tonsillitis is the acute inflammation of the pharynx and surrounding lymphoid tissues, of various origins: infectious (bacterial / viral infection) or non-infectious (allergy, irritants, sinusitis). The main bacterium involved is Group A beta hemolytic streptococcus. The infection caused by this streptococcus is the only one that requires therapy with antibiotics. Penicillin is the antibiotic of choice, and in the case of penicillin allergy, the use of a macrolide is indicated. Complications of streptococcal pharyngitis are: infectious (tonsillitis, phlegmon, sinusitis, otitis) or non-infectious (acute joint rheumatism and acute glomerulonephritis).

Acute sinusitis is the inflammation of the perinasal sinuses with infectious (viral, bacterial, fungal) or non-infectious (allergic reactions) origin. The most common is the bacterial sinusitis that most often results from a primary infection of viral origin. Antibiotics are indicated only in case of suspicion of acute bacterial sinusitis: amoxicillin or cefuroxime or cotrimoxazole (10-14 days). The major complication of acute sinusitis is chronic sinusitis, a complication that can occur either under the conditions of incorrect treatment or in the case of patients who do not respond to treatment. The treatment consists in the administration of decongestants, analgesics, corticosteroids and antibiotics.

Acute otitis media is an acute bacterial or viral infection of the mucous membrane of the middle ear cavities, generally secondary to an upper respiratory tract infection. After nasopharyngitis, it is the most common infection in the pediatric urgent care, especially those up to 3 years of age. The bacterial etiology is the most common, the bacteria involved being the same as in the case of sinusitis. In most cases, the natural evolution of otitis media is towards spontaneous healing. Therapy with antibiotic is initiated only in the case of children up to 6 months, the antibiotic of first intention being amoxicillin.

Lower respiratory tract infections

Acute bronchitis is the acute inflammation of the tracheo-bronchial tree, caused by infectious (most frequently viral) or non-infectious /

irritative (caused by mineral and vegetable waste, pollutants, volatile organic solvents, smoking) causes.

In most cases, acute viral bronchitis is the consequence of rhinitis, nasopharyngitis, or a flu.

The pathogenesis of acute viral bronchitis is not fully elucidated. Viruses infect and alter the respiratory epithelium, causing the release of proinflammatory cytokines, which increase the production of secretions and diminish mucociliary clarence. In most cases, with or without symptomatic treatment, the healing of acute bronchitis is spontaneous.

Symptomatic treatment consists in the administration of analgesics and antipyretics, antitussives or expectorants (depending on the type of cough), bed rest, fluids. In the case of adults with acute bronchitis, antibiotic therapy is not justified.

Pneumopathies are inflammatory/infectious diseases of the deep lung structures (acini and alveoli); most of them have bacterial origins produced by pathogens, mainly Streptococcus pneumoniae and Haemophilus influenze.

The infection can be:

- pure alveolar: franc lobar pneumonia (bacterial etiology)
- interstitial: interstitial pneumonia (viral etiology)
- bronchial and alveolar: bronchopneumonia (bacterial etiology).

An empirical antibiotic treatment should be instituted immediately (48-72h). Amoxicillin (+/- clavulanic acid) is the antibiotic of first intention. Anti-pneumococcal and anti-influenza vaccines are prevention measures, the maximum effectiveness of which is in the case of high-risk patients.

3.3.5 Asthma

It is a chronic inflammatory disease of the small and medium-sized bronchi, characterized by a nonspecific hyperreactivity of the airway, due to:

- contraction of bronchiolar smooth muscles
- edema of the bronchiole's mucosa
- hypersecretion of viscous and adherent mucus, with reversible obstruction, transient (in paroxysmal crises).

Extrinsic (allergic) asthma

It is mainly found in children and young people, being triggered by an allergy against respiratory antigens (inhalation allergens). The allergens (pollens, hair, feathers, dust, etc.) induce an allergic hypersensitivity reaction, as follows: during the first contact, the allergens (transported by air) reach the lungs where a synthesis of a specific antibody takes place, namely IgE. IgE is then fixed on the cells of the bronchial mucosa, called mast cells, and on their circulating counterparts, called basophilic granulocytes, which they sensitize. Following a new contact with the same allergen, the antigen/antibody (Ag-Ac) reaction takes place at the level of the mast cell membrane, which causes the rapid degranulation of the mast cells with the release of two types of mediators of acute inflammation. These mediators are responsible for the two types of inflammatory responses:

1. The immediate response (asthma crisis) with acute obstruction, vasodilation and increased permeability of capillaries, with edema of bronchial walls, hypersecretion of viscous and adherent mucus and bronchospasm. The asthma crisis is manifested by the following symptoms:
    - expiratory dyspnea
    - wheezing
    - cough
    - expectoration

2. The late response (between seizures), chronic obstruction of the airway produced by an inflammatory infiltrate composed of inflammatory cells (eosinophils, neutrophils, monocytes) attached to the air walls by means of chemotactic factors (ECF, NCF). In this chronic inflammatory process are also involved nerve endings. The result is a bronchial hyperreactivity, an exaggerated response of bronchiolar smooth muscles, to the action of nonspecific irritant agents. In the conditions in which the process becomes chronic, hypertrophy and fibrosis of the smooth muscles of the bronchiolar walls appears, and the functional transient obstruction becomes a permanent organic obstruction.

Intrinsic asthma (idiosyncratic)

It is mainly found in adults. Idiosyncrasy represents the exaggerated response to the action of non-specific factors, which are in very low concentration, such as:

1. air pollutants (irritating gases such as: SO2, NO2, benzene)
2. infections (especially viral ones)
3. medications (aspirin, beta blockers)
4. physical exertion
5. smoking
6. mental stress
7. cold air

These factors (called nonspecific) do NOT trigger the synthesis of antibodies, in other words they will NOT induce an allergic syndrome, but induce (via numerous and little-known mechanism) a direct degranulation (without IgE intervention) of mast cells and basophils, with the same pathophysiological consequences (immediate and late response).

During the asthma crisis, air accumulates in the lungs, causing the residual volume to increase, which will lead to swelling of the alveoli, a process called pulmonary hyperinflation and consecutive hypoxia. Hypoxia of the hypo-ventilated alveoli will trigger two compensatory mechanisms:

- reflex hyperventilation (the patient breathes quickly and superficially). Carbonic gas is eliminated in larger quantities, which will lead to hypocapnia and respiratory alkalosis
- reflex vasoconstriction with increased pulmonary vascular resistance, the long-term result is barometric overload of the right ventricle and right heart failure.

Therapeutic principles

Combinations of drugs administered by inhalation, to increase the local effects and to prevent the general side effects:

- Bronchodilators:
  - Beta2 sympathomimetics (salbutamol, salmeterol, fenoterol, terbutaline), the strongest bronchodilators.
  - Theophylline, a powerful bronchodilator with anti-inflammatory action.

- Parasimpatolytics (ipratropium bromide, oxytropium, tiotropium) are less powerful and slower bronchodilators than the previous ones.

- Anti-inflammatories
  - Corticoids in inhaled form and in high doses (1000-2000 μg/day) having a major breakthrough in the treatment of asthma, allowing its relatively rapid improvement in 2-3 weeks.

- Inhibitors of mastocytic degranulation (mast cells contain proinflammatory substances that are released when masocytes degranulate): sodium cromoglicate, nedocromil.
- Leukotriene receptor antagonists (suffix "lukast"): montelukast, zafirlukast is the new class of asthma medications that oppose the effects of leukotrienes, which are major bronchoconstrictors.

3.3.6 Chronic obstructive pulmonary disease (COPD)

It is a condition that groups 2 clinical entities, chronic bronchitis and pulmonary emphysema.

The disease presents itself in the form of regular exacerbations that are not followed by a complete recovery of respiratory function.

Chronic bronchitis is defined by productive coughing at least 3 months a year, at least two consecutive years, in the absence of any bronchopulmonary disease.

Classification:

Simple (unobstructive) chronic bronchitis influences the middle bronchi and large trunks (central obstruction), with mucous or purulent expectoration in the absence of other respiratory disorders.

Chronic obstructive bronchitis corresponds to irreversible lesions, especially at the level of peripheral bronchioles (distal obstruction) with obstructive syndrome and disturbances of gaseous exchanges. In 10-15 years it can lead to the onset of respiratory failure.

Etiopathogenesis:

Risk factors:

- cigarette smoke
- urban, professional, domestic pollutants
- repetitive respiratory infections

Pulmonary emphysema represents the abnormal and permanent distention of the distal airspaces of the terminal bronchioles, with the rupture of the alveolar walls.

Classification:

1. Centrolobular (centroacinar) emphysema:
   - the lesions (dilation and destruction) affect the central region of the acini (respiratory bronchioles), while the peripheral regions (alveoli and the perialveolar capillary network) are unaffected.
   - is an evolutionary stage of a chronic obstructive bronchitis in the case of large smokers.
1. Pan-lobular emphysema (pan-acinar):
   - uniform distension and destruction of the respiratory bronchioles, alveolar ducts, alveoli and perialveolar capillaries
   - associated either with aging (with age decreases the force of pulmonary retraction) or with the deficiency of α1-antitrypsin.

Pathogenesis

Pulmonary emphysema occurs due to the imbalance between the increase in proteolytic activity of elastase (enzyme released by neutrophils and macrophages and caused by chronic smoking) and/or the decrease in the activity of α1 antitrypsin (an antienzyme that neutralizes leukocyte elastase), produced by smoking or genetic deficiency of α1-antitrypsin. The decrease in protease inhibition will cause the destruction of connective and elastic lung tissue.

3.4. Acid-base balance

The acid-base balance is determined by the concentration of hydrogen ions. In order to achieve homeostasis, there must be a balance between the internal production of hydrogen ions and their elimination from the body. The concentration of hydrogen ions is expressed using a logarithmic scale, using pH units, the pH being the negative logarithm of the concentration of H^+ ions.

The maintenance of the pH in the internal environment is essential for the cellular metabolic processes, the maintenance of cellular excitability, the functioning of the enzymatic systems and also for chemical reactions.

Ph homeostasis is achieved through fast and short-term mechanisms, such as buffer systems, and through slow and long-lasting

mechanisms, such as pulmonary and renal compensation mechanisms, which have the role of restoring the buffer systems to their original state.

The main buffer system of the blood, the one that predominates quantitatively and determines the pH of the internal environment, is the *bicarbonate/carbonic acid system.*

Bicarbonate is the metabolic factor; its concentration is determined by the reabsorption and renal generation of HCO_3^-. Acid-base disorders caused by the primary modification of bicarbonate are called metabolic acidosis or metabolic alkalosis.

Carbonic acid is the respiratory factor; it dissociates in the lungs into water and CO_2, as follows:

$$H_2CO_3 \leftrightarrow H_2O + CO_2$$

Thus, its concentration is determined by pCO_2 in the alveoli: $\alpha \times PaCO_2 = 0.03 \times 40 = 1.2$ mEq/l (α = constant of carbonic gas solubility). Disorders caused by the primary change in carbonic acid are called respiratory acidosis or respiratory alkalosis.

The equilibrium of this buffer system is expressed by the Henderson-Hasselbach equation: pH = pka + logHCO_3-/H2CO_3

- pka = carbonic acid dissociation constant: 6,1
- HCO_3^- = plasma bicarbonate concentration: 24 mEq/l
- H_2CO_3 = plasma concentration of carbonic acid: 1,2mEq/l.

1. Metabolic acidosis

- primary decrease of $HCO_3^- \rightarrow \downarrow$ HCO ratio$_3^-$ / $H_2CO_3 \rightarrow \downarrow$pH
- causes: diabetic ketoacidosis, from inanition, alcoholic, lactic acidosis, toxic acidosis (with methanol, salicylates), acidosis from acute or chronic renal failure
- compensation: increased respiratory rate in the lungs (alveolar hyperventilation)

2. Metabolic alkalosis

- primary increase of $HCO_3^- \rightarrow \uparrow$ HCO ratio$_3^-$ / $H_2CO_3 \rightarrow \uparrow$pH
- causes: ingestion of alkaline substances (sodium bicarbonate), loss of H^+ during vomiting
- compensation: decrease in the respiratory rate in the lungs (alveolar hypoventilation)

3 Respiratory acidosis

- primary increase in H_2CO_3→ ↓ HCO ratio$_3^-$ / H_2CO_3 → ↓pH
- can be acute and chronic
- causes: emphysema, chronic bronchitis, asthma, suffocation
- compensation: preservation of bicarbonate ions and increase of net acid excretion at the renal level

4. Respiratory alkalosis

- primary decrease in H_2CO_3 → ↑ HCO ratio$_3^-$ / H_2CO_3 → ↑pH
- can be acute and chronic
- causes: physical exertion, pregnancy, anesthetics, febrile states, encephalitis
- compensation: increased excretion of bicarbonate ions at the renal level.

4. THE DIGESTIVE SYSTEM

The digestive system consists of the digestive tract (oral cavity, pharynx, esophagus, stomach, small intestine and large intestine) and the annexed glands (salivary glands, gallbladder, liver and pancreas).

General structure

Along its entire length, from the pharynx to the anal canal, the structure of the wall of the digestive tract is represented by 4 main layers, with the mention that each segment has in addition certain properties characteristic of the function it performs. Thus, from the inside, from the lumen of the tube, to the outside, the following are distinguished:

- mucosa: whose roles are absorption and secretion
- submucosa: which contains blood vessels, nerve plexuses and lymphoid formations
- muscularis: that is responsible for peristalsis, thus ensuring the progression of the food bowl
- serosa

Innervation

The innervation of the digestive system is provided by the vegetative (autonomic) nervous system. This innervation regulates glandular secretion, vasodilation and vasoconstriction, as well as motility of smooth muscle fibers:

- sympathetic fibers (adrenergic) diminish digestive secretions and motility
- parasympathetic fibers (cholinergic) stimulate them

General functions

1. The digestive function

The essential role of the digestive system is the digestive function comprising 4 processes:

- food ingestion
- digestion with (i) mechanical digestion through the process of mastication and (ii) chemical transformation of large molecules into smaller molecules, by means of enzymes present in digestive secretions;

- absorption of food principles in the blood and lymphatic circulation
- waste disposal

2. Body defense: through the lymphoid structures disseminated along the entire length of the digestive tract wall. They are in the form of diffuse lymphocytic infiltrate and lymphoid follicles organized in the tonsils of the oral cavity or in the Peyer plaques of the ileum and appendix.

3. Endocrine function: through the cells that secrete hormones - isolated and disseminated into the wall of the digestive tract or regrouped in islands in the endocrine pancreas.

4.1 General anatomy

Mouth

The process of digestion begins in the oral cavity. The role of the oral cavity is in the ingestion of food through the mouth and the preparation of food for digestion, with the help of two concomitant processes, namely the shredding of food by dental mastication and the mixing of masticated fragments with saliva secreted by the salivary glands. These processes cause food pieces to be converted into a pasty mass called a food bowl. Saliva is secreted by the salivary glands: submaxillary, sublingual and parotid. The appendage glands of the oral cavity ending each through an excretory duct.

Saliva is an aqueous secretion (99% water) that contains mucus, mineral salts (especially calcium salts, which lead to the formation of tartar and dental plaque) and enzymes, the most important being salivary amylase. Saliva has several roles:

- a digestive role consisting in the lubrication of food, which also favors mastication and swallowing and food carbohydrates hydrolysis by salivary amylase (cleaves starch to turn it into maltose)
- nondigestive roles: role of permanent humidification of the oral mucosa, antiseptic role by means of lysozyme, antibacterial enzyme (especially regarding dental caries).

Saliva secretion is abundant (1-1.5 l/ day) and is reabsorbed entirely in the intestines. Its secretion is under the control of SNV through the parasympathetic fibers that stimulate the secretion of an abundant aqueous saliva and through the sympathetic fibers that stimulate the secretion of a less abundant and dense saliva, rich in mucin.

Esophagus

The esophagus connects the pharynx to the stomach and it's located behind the trachea. It crosses the mediastinum and penetrates through the diaphragmatic orifice into the stomach. At the entrance with the stomach the esophagus ends in the cardia orifice. The esophagus has a fundamental role in the swallowing process:

1. a passive role in the passage of liquids (under the effect of gravity)
2. an active role in terms of solid food, by means of peristaltic movements (contraction waves of smooth muscle fibers of the esophageal walls).

Swallowing is a reflex act that allows the passage of the food bowl from the oral cavity into the gastric cavity in one voluntary and one involuntary phase:

Buco-pharyngeal time (voluntary) is initiated by placing the food bowl at the level of the tongue, raising the tongue and propelling the bowl into the pharynx. Simultaneously, breathing is inhibited and the glottis closes to prevent the food bowl from entering the respiratory shaft.

Esophageal time (involuntary) begins with the relaxation of the upper esophageal sphincter. The food bowl is driven from the pharynx to the stomach, passing through the esophagus due to peristaltic waves. When the food bowl reaches at the level of the cardia, it opens to allow the bowl to pass into the stomach.

In the state of rest, between meals, the peristaltic movements of the esophagus cease. It is closed at both extremities, by the contraction of the two esophageal sphincters that prevent the reflux of acidic fluid from the stomach into the esophagus, the mucosa of which would not bear this acidity (the stomach is naturally protected from the acidity of gastric juice).

Stomach

The stomach is a storehouse for food. This is where the chemical decomposition of proteins begins, and the food is converted into a paste called gastric chyme. It is located in the upper left quadrant of the abdominal cavity, almost hidden from the liver and diaphragm. When empty, the stomach is collapsed and has some large creases called folds.

From the anatomical point of view, the stomach has three parts (bottom/fornix, body and pyloric antrum), 2 curvatures and two orifices (upper-cardia sphincter and inferior-pyloric sphincter).

The physiological functions of the stomach are:

- temporary storage (2-3 hours on average) of ingested food
- chemical role, due to the fact that gastric secretion acts on food through a series of physico-chemical transformations
- mechanical role due to gastric motor moves; thus, the stomach transforms the ingested food into a liquid paste, called gastric chyme, in which the food molecules are found in solution or in suspension. Gastric chyme passes theninto the duodenum, crossing the pylorus, and from there into the rest of the small intestine.

The stomach is structured in several layers:

1. Mucous membrane (mucosa): in contact with the gastric lumen. It consists of a single cell layer or gastric epithelium, sealed by connective tissue called the chorion. The gastric epithelium invaginates in the chorion. Epithelial cells are responsible for the secretion of gastric juice.
2. Submucosa: formed by connective tissue
3. Muscular: made up of muscle tissue designed to mix and propel food into the stomach
4. Serosa: composed of connective tissue with a protective role.
   The structure of the gastric mucosa comprises

The gastric mucosa consists of:

1. the epithelial cells that secrete mucus
2. the main cells responsible for the production of pepsinogen that will be activated in pepsin (the main proteolytic enzyme that cleaves proteins into polypeptides).

3. parietal cells secrete: HCl which provides chemical disaggregation of food, preparing them for protein digestion, H+ ions, and Cl- are secreted separately, the intrinsic factor (GP required for absorption of vit. B12 at the level of the ileum). The absence of intrinsic factor, most often noted in atrophic gastritis (lack of main and parietal cells) leads to Biermer anemia, because vitamin B12 is indispensable in the formation of red blood cells.
4. endocrine cells secreting polypeptide hormones, with a primordial role in gastric activity.

The defense mechanisms of the gastric mucosa that protects it against the caustic effect of its own secretion are, as follows:

1. a dense mucous tunic that covers the gastric surface, protecting the mucous membrane against the action of HCl and preventing cellular autodigestion by digestive enzymes
2. epithelium that secretes HCO_3 ions - which will diffuse to the mucus level, where they will buffer the H+ ions (prostaglandins are an important stimulant of this alkaline secretion)
3. the presence of tight junctions between the cells, thus preventing the penetration of gastric juice into the gastric wall
4. rapid cell renewal due to the increased ability of cells to divide
5. good blood irrigation of the mucosa (blood quickly carries H+ ions or provides the intake of HCO_3-ions).

The stomach has two types of secretions:

1. Exocrine secretion: the secretion product is discharged directly into the gastric cavity, where it acts on the food content, in the form of gastric juice. Gastric juice consists of: water, electrolytes (sodium chloride, sodium bicarbonate), HCl, pepsin and mucus. It has a very acidic pH of 1.5-3.5.

2. Endocrine secretion is represented by hormones that are discharged into the blood, and through the blood will act on the targeted organs. The main gastric hormone is gastrin secreted by G cells located in the pyloric-antrum region. Discharged into the blood, gastrin attaches to the specific receptors of parietal cells and stimulates the secretion of HCl. In addition, gastrin stimulates pancreatic and biliary secretion and favors gastric and intestinal motor skills.

Gastric secretion is under neuro-hormonal dependence. It contains in 3 phases:

1. Cephalic phase: triggered by smell, sight or thought of food, by its presence in the oral cavity and by the feeling of hunger. These excitations cause vagal stimulation with acetylcholine release that activates acid secretion: directly, via muscarinic M1 receptors on the surface of parietal cells that secrete HCl and indirectly, via the H cells that secrete histamine. In turn, the histamine released into the blood is fixed on the histamine H_2 receptors on the surface of parietal cells. The two (histamine and gastrin) stimulate acid secretion.
2. Gastric phase: triggered by the contact of gastric contents with the lower part of the stomach (pyloric-antrum region). This excitation triggers the secretion of gastrin. At this level, gastrin causes directly but also indirectly (by amplifying vagal activity) the increase of gastric juice secretion.
3. Intestinal phase: the entry into the duodenum of the gastric chimney that has a low pH, as well as the presence of chyme fats, will inhibit gastric secretion by releasing various duodenal hormones (such as secretin).

Small intestine

It is a duct that stretches from the level of the pyloric sphincter to the level of the ileocecal valve, with a length of 4-6 m, being the longest portion of the digestive tract. It consists of 3 subdivisions, duodenum, jejunum and ileum. Digestion and absorption are favored by the considerable amplification of the exchange surface between the external and internal environment, due to: the considerable length of the small intestine that is folded into intestinal loops and due to the presence of intestinal villi lining on the internal surface of the entire intestine (numerous tiny sacs in the form of glove fingers, having a thickness of about 1mm).

The duodenum is the initial segment, the fixed portion of the small intestine. In its middle portion Vater's ampulla is located, which represents the place where the choledochal canal (through which bile flows into the

duodenum) and the Wirsung pancreatic canal (through which pancreatic juice is poured into the duodenum) opens; their orifice is bounded by the sphincter of Oddi. The duodenum is of short length, so its crossing is extremely rapid, and the food does not have the time to undergo important chemical processes. However, a single pass of the food will trigger the hormonal secretion necessary for the preparation of food by the main secretions of the annexed glands: bile (produced by the liver) and pancreatic juice (produced by the pancreas).

The Jejune-ileum is the mobile portion, folded into about 15 intestinal loops in the abdominal cavity. It is the long portion of the small intestine, its crossing is slow (in 3-4 hours); the food prepared by the pancreatic-biliary secretions have the necessary time to undergo important changes (fragmentation into simpler elements) and for the intestinal absorption process; a process in which the elements necessary for the organism are passed into the blood vessels that surround the small intestine.

At the level of the small intestine, pancreatic juice, bile and intestinal juice act on the gastric chyme, which continue the digestion processes, the result being the transformation of the gastric chyme into intestinal chyme:

(i) the food is degraded into smaller compounds so that nutrients or metabolites can overcome the intestinal barrier and pass into the blood and lymphatic circulation;

(ii) the undigested residues will remain in the intestinal lumen constituting fecal matter.

Throughout the entire digestive tract, for each segment separately, the intestine has two fundamental actions:

1. motricity or peristalsis, which allows the progression of food
2. glandular secretion, which acts on food to continue the process of digestion and to extract substances useful to the body.

At duodenal level, 2 hormones are secreted:

- secretin - stimulates pancreatic secretion and inhibits acid gastric secretion

- cholecystokinin-pancreozymin (CCK-PZ) secreted by contractions of the gallbladder - eliminates bile in the duodenum through the choledochal duct and stimulates pancreatic secretion.

At the level of the jejune-ileum, glandular secretion is represented by the intestinal juice released by enterocytes. Intestinal juice contains water, bicarbonate and mucin, providing a basic pH necessary for the activation of pancreatic enzymes.

Intestinal digestion

The first phase in the duodenum is called the intraluminal phase in which pancreatic enzymes and bile act transforming carbohydrates into disaccharides, proteins into smaller peptides and lipids are emulsified into monoglyceride complexes or fatty acid complexes with bile salts.

The second phase takes place in the jejune-ileum, namely the intracellular phase performed with the help of enzymes secreted by enterocytes: disaccharidases, peptidases and lipases. Now the complete degradation of the food is achieved, generating the appropriate compounds that can be absorbed through the intestinal wall: monosaccharides, amino acids and absorbable fatty acids.

Intestinal absorption

Enterocytes, through the enzymes they secrete, provide the final stages of digestion, representing the place of absorption of nutrients, water, mineral salts and vitamins.

The absorption of nutrients begins in the duodenum, but the important headquarters is represented by the jejune-ileum (at the level of which there is a larger area of exchanges).

Large intestine

It frames the small intestine from 3 sides and stretches from the ileocecal valve to the anal canal. Compared to the small intestine, its larger in diameter, but shorter.

Its major function is to absorb water from undigested remnants of food, and to remove the food debris in the form of semi-solid feces.

The ascending colon is located in the right portion of the abdominal cavity and makes a curve to the right (right colic curvature), then it crosses

the abdominal cavity forming the transverse colon, bends at the level of the spleen forming the left colic curvature and descends into the left abdomen forming the descending colon. In the lower part, the colon penetrates into the pelvis where it turns into the sigmoid colon. The sigmoid colon joins with the rectum that is located right in front of the sacrum. The anal canal is the last segment of the large intestine and begins where the rectum penetrates the anal lift muscle from the pelvic floor. The anal canal presents an involuntary internal sphincter consisting of smooth muscle and a voluntary external sphincter made up of skeletal muscle.

Processes in the Large Intestine:

1) Motricity - the main function. There are 2 types of peristaltic movements:

- mixing movements necessary for homogenization of intestinal contents
- propulsion movements important to ensure the progression of the fecal bowl. The feces thus reach the terminal portion of the colon and will be stored in the sigmoid canal in the interval between the defecation processes.

2) Digestive function - less important than that of the small intestine:

- water absorption by converting liquid food residues from the small intestine into a semi-solid material, fecal matter.
- digestion - provided exclusively by the physiological saprophytic intestinal flora, responsible for the degradation of food residues. At this level the transformation of bilirubin (the main biliary pigment) into stercobilin, pigment that ensures the color of feces occurs. Also, here it takes place the synthesis of certain vitamins (vitamins of group B, vitamin K, folic acid).

Liver

The liver is the largest gland of the body and consists of 4 lobes, right, left, caudate and square. The gallbladder is located on the lower surface of the right hepatic lobe. Due to its privileged position in the blood circulation it receives all the blood that comes from the various organs of the digestive tract through the portal vein, thus the liver constitutes the metabolic headquarters indispensable for life.

The liver parenchyma consists of microscopic units, hepatic lobules (50000), separated by connective spaces, port spaces. The hepatic lobule represents the histological unit of the liver. The hepatic lobule has a hexagonal shape in cross-section:

- hepatocytes, the specific cells of the liver are grouped in concentric lamellae, having as a starting point the center of the lobe occupied by the centrilobular vein
- Sinusoid capillaries composed from 2 types of cells: endothelial cells and macrophages (called Küpffer cells). Sinus capillaries provide the centripetal circulation of blood (mixture of blood from the hepatic artery and from the portal vein), converging to the level of the centrilobular vein.
- The bile ducts that do not have their own walls. Their role is to circulate the bile in a centrifugal manner, in the direction of the port spaces, to then discharge it into the bile ducts.

The liver has a double vascularization, one provided by the portal vein (75% of the afferent blood) that circulates to the liver the blood coming from the digestive tract, rich in absorbed food nutrients and the other vascularization, represented by the hepatic artery (25% of the afferent blood), which provides the necessary oxygen to the multiple liver cells. The liver is the largest mixed gland with two functions:

- exocrine: discharges into the duodenum, through the bile ducts a continuous secretion, bile.
- endocrine: discharges into the blood the metabolic products it develops.

Bile leaves the liver through several bile ducts that join together and eventually form the common liver duct that goes to the duodenum. It joins the cystic duct that drains the gallbladder, and together forms the choledochal duct that flows into the duodenum. Bile is an alkaline solution of greenish-yellow color, which contains bile salts, bile pigments, cholesterol, neutral fats, phospholipids and electrolytes. Of these, only bile salts and phospholipids are involved in the digestion process. Bile salts are derived from cholesterol, and their major function is the emulsification of fats. The major bile pigment is bilirubin. The gallbladder is a muscle sac with thin walls, green in color, the size of a kiwi, located in a fossa on the

ventral face of the liver. It stores the bile and concentrates it by absorbing water and ions. When the muscle wall contracts, the bile is evacuated into the cystic canal connected with the choledochal duct. Bilirubin comes from the hemoglobin degradation, being released after the death or destruction of red blood cells in the cells of the reticulo-endothelial system. This form of bilirubin is called indirect or unconjugated bilirubin that, being insoluble in water, cannot be eliminated in the urine, so it circulates in the blood bound to plasma albumin, until it reaches the hepatocytes. At the hepatic level, indirect bilirubin will be conjugated with glucuronic acid, resulting the direct or conjugated bilirubin. Direct bilirubin thus becomes soluble and can be eliminated. Bile is discharged into the intestine, where, under the action of the intestinal flora, direct bilirubin is converted into urobilinogen.

Most of urobilinogen oxidizes, turning into stercobilinogen that is eliminated by means of feces (the pigment that gives the color of feces). The rest of the urobilinogen is reabsorbed at the level of the intestinal mucosa and passes into the blood, from where most of it returns to the liver constituting the hepatic-entero-hepatic circuit. A small fraction of this remaining urobilinogen, which is water soluble, is eliminated through the urine (it is the pigment that gives the urine its characteristic color).

Metabolic function

The liver intervenes in all 3 food metabolisms (carbohydrate, lipid, protein).

1. Glycogenic function

Glycogen is a reserve substance stored in the liver and manufactured by it, starting from food glucose, through a process called glycogenogenesis. Glycogen can be easily converted by the liver back into glucose following the process of glycogenolysis. These processes allow the liver to practically adapt to the needs of the body (e.g. during muscle labor), as well as to ensure the stability of blood glucose levels.

2. Fat storage

The liver is the storage place of excess fats, resulting from a chronic overeating or alcoholism (fatty liver), at the same time it is also the deposit place for iron and several vitamins (B12, folic acid, A, D, E, K).

3. The deamination of amino acids (release of the NH_2 radical) leads to the formation of ammonia, which is a toxic substance. In the liver,

following complex biochemical processes, ammonia is converted into urea; urea is quickly eliminated through the kidneys, in the urine.

4. Hematopoietic function:

The liver intervenes in the formation of blood by synthetizing plasmatic proteins (especially albumins). Moreover, the liver stores and regulates the iron metabolism, indispensable for the synthesis of hemoglobin. Also, it intervenes in the destruction of aged red blood cells, a process that also takes place in other hematopoietic organs (bone marrow, spleen). Also, the liver intervenes in blood coagulation, by ensuring its synthesis of most coagulation factors.

5. Antitoxic function

The liver filters and blocks the passage of toxic substances (and drugs). The liver immediately converts these substances into less toxic products, which will be eliminated through the bile and especially through the urine.

The pancreas

The pancreas is a parenchymal organ of soft consistency. It is composed of three parts: the caudal part reaches up to the spleen, the cephalic part is surrounded by the duodenum and the body of the pancreas that is in intimate contact with the posterior part of the stomach. The pancreas lies transversally in the upper left part of the abdominal cavity. It is a mixed gland, with both endocrine and exocrine function:

The endocrine pancreas is represented by the islands of Langerhans, disseminated inside the exocrine parenchyma. Langerhans Islets present β cells (75%) that secrete insulin which is a hypoglycemic hormone and α cells (25%) that secrete glucagon with a hyperglycemic role.

The exocrine pancreas consists of pancreatic acini placed in bunches of cells that surrounds ducts. Each acinus is formed out of simple epithelium that consists in several pyramidal cells with a broad base and a narrow apical pole that delimit a small central cavity called lumen. The cells secrete pancreatic juice rich in digestive enzymes. Their secretory function is due to the presence of acidophilic zymogen granules (are large secretory organelles). The byproducts of acinar cells and zymogen granules are inactive enzymes, named zymogens or proenzymes. The

zymogens are activated upon stimulation and then released by exocytosis and the acinar cells release their secretions by way of exocytosis. The pancreatic juice is drained from the pancreas via the pancreatic duct, also named the Wirsung duct. The pancreatic duct joins with the choledochal and penetrates the duodenum at the level of the hepatopancreatic ampulla (the ampulla of Vater).

4.2 Pathology of the stomach

4.2.1 Gastritis

Gastritis is an acute or chronic gastric inflammation, characterized by a superficial lesion that affects only the layer of the gastric mucosa. The common mechanism of gastritis is the alteration of the thin layer of mucus that covers the gastric surface and protects the mucous membrane against the action of HCl. Consequently, the H+ ions secreted into the lumen can retro-diffuse into the gastric wall, triggering an inflammatory lesion.

Classification:

A. erosive and hemorrhagic gastritis
B. chronic active non-corrosive gastritis
C. atrophic gastritis

Causes

- administration of nonsteroidal anti-inflammatories
- alcohol abuse or ingestion of caustic products
- radiation treatment
- acute stress
- local trauma (gastric probe, accidental ingestion of a foreign body). The prognosis is favorable, after the removal of the causative agent.

Atrophic gastritis is localized mainly at the bottom level, the main cause is the presence in gastric juice and blood of autoantibodies directed against parietal cells. These cells will atrophy, while the secretion of HCl and intrinsic factor diminish greatly (the consequences will be achlorhydria and pernicious anemia). The main danger of this type of gastritis is the malignant transformation, due to the frequent evolution of atrophic gastritis towards gastric carcinoma.

4.2.2 Ulcers

The ulcers represent a loss of substance in the gastric or duodenal mucosa, accompanied by a deep lesion that also interests the submucosa and muscularis.

Classification

1. Duodenal ulcer

Duodenal ulcer mainly affects young men, 20-40 years old, with the main localization at the level of duodenal bulb, the risk of malignant transformation being null.

2. Gastric ulcer

Gastric ulcer mainly affects elderly people over 50 years of age, frequent localization is at the level of the small curvature of the stomach, the risk of malignant transformation is high.

Pathogenesis

The appearance of the ulcer is the result of an imbalance, in a precise point at the level of the mucosa, between the aggression factors (acid and peptic secretion) and the defense factors (mucus, epithelium, mucosal vascularization, HCO_3, prostaglandins). It was unanimously accepted that in duodenal ulcer the dominant factor is chlorhydro-peptic aggression (mandatory condition: "no acid, no ulcer"), while in gastric ulcer the dominant factor is the alteration of the gastric mucosa.

Causes

a) Helicobacter pylori infection is the most frequent cause, the risk of ulcers in patients with this type of infection being 10 times higher. The infection favors the appearance of:

- gastric ulcer: due to the gastritis it causes, the alteration of the barrier function of the epithelium and the chemical aggression of the oxygen free radicals produced by H. pylori
- duodenal ulcer: as a result of colonization mainly of the anthro-pyloric area, there is an increase in gastric secretion; In addition, H. pylori stimulates the secretion of pepsinogen.

b) Administration of nonsteroidal anti-inflammatories (NSAIDs): aspirin, indomethacin, diclofenac in high doses; represents the second most common cause of ulcer development. NSAID's have the ability to inhibit cyclooxygenase and thus they block also the synthesis of prostaglandins

that in turn causes a decrease in the secretion of HCO_3 ions, as well as an increase in acid secretion. Taking into account the inhibitory action of NSAIDs on platelet aggregation, the bleeding risk of ulcers is increased.

c) other causes of ulcers:

- acute stress: after major surgery, following burns, or following the onset of shock
- psychological stress induces the psychogenic increase of acid secretion levels or bicarbonate
- smoking diminishes the secretion of bicarbonate
- alcohol in large quantities or at high concentrations causes damage to the mucous membrane

Complications

- Hemorrhage - if a blood vessel is eroded; its manifestation includes hematemesis (sanguinolent vomiting), melena (black, sanguinolent feces) or occult hemorrhages (blood is not visible in the feces)
- Perforation - due to the deep erosion of all layers of the gastric wall, with the realization of a direct communication with the peritoneal cavity and the appearance of peritonitis
- Pyloric stenosis - due to fibrous and retractile scarring of a pyloric ulcer can be complicated with severe vomiting, followed by hypovolemia and ionic imbalances.

Therapeutic principles

Treatment of ulcers consists in:

1. eradication of H.pylori infection with specific antibiotic therapy
2. inhibition of chlorhydro-peptic secretion by administration of proton pump inhibitors (omeprazole), histamine H2 receptor inhibitors (ranitidine, famotidine), vagal stimulation inhibitors (anticholinergic medication, M1 receptor inhibitors)
3. neutralization of gastric acidity (by administering antacids that act as pH buffers in the intestinal lumen).

The eradication treatment contains 2 antibiotics associated with an antisecretory. The most commonly used associations are: proton pump inhibitors, amoxicillin and clarithromycin/metronidazole, for 7, 14 or 21 days.

4.3 Jaundice

Jaundice is a clinical and paraclinical syndrome characterized by yellow pigmentation of the skin and by the increase of blood bilirubin over more than 2.5 mg% (normal, 1 mg).

Etiological classification

1. Prehepatic jaundice occurs after an increase in the production of indirect bilirubin (IB) due to hemolysis (hemolytic anemia). This type of jaundice is called hemolytic jaundice and translates into increased IB.

2. Intrahepatic jaundice occurs due to the genetic alteration of:

- bilirubin capture by the liver cells
    - deficit in bilirubin conjugation
    - decrease of bilirubin secretion in the bile ducts

In the first two cases in the plasma IB is predominantly increased, while in the case of secretion alteration direct bilirubin (DB) predominantly increases BD. This occurs in liver diseases such as: acute viral hepatitis, alcoholic hepatitis, post-treatment with isoniazid, phenytoin, or in advanced cirrhosis.

3. Post-hepatic jaundice occurs when the post-hepatic bile ducts are blocked as a result of a calculus (cholelithiasis) or a tumor (pancreatic carcinoma that compresses the choledochal duct). This type of jaundice is called obstructive or mechanical jaundice, in which predominantly BD increases.

4.4 Cirrhosis

It is an irreversible and diffuse disease of the liver characterized by 4 simultaneous phenomena:

- hepatocellular necrosis
- inflammation followed by fibrosis
- nodal regeneration of normal neighboring cells that causes the lobular architecture to change
- the formation of vascular anastomoses (ways of derivation represented by the vessels surrounding the liver).

Causes:

- Alcoholism
- viral infection with B or C hepatitis virus.

4.5 Acute pancreatitis

Acute pancreatitis is the inflammation of the pancreas characterized by the abnormal local release of pancreatic enzymes, responsible for the necrosis of the pancreas. It occurs in a few days; hence the rapidity of its occurrence leads to an increased mortality rate. Alcoholism and obstruction of the bile ducts by calculi are the main causes. Gallstones lead to the incompetence of the sphincter of Oddi, secondary to the passage of calculi through the sphincter of Oddi that leads to duodeno-pancreatic reflux. The result is obstruction of the bile duct, especially of the choledochal with bile-pancreatic reflux. Increased alcohol ingestion stimulates pancreatic secretion of enzymes associated with Oddi sphincter incompetence that leads to bile-pancreatic reflux. Secondary to this reflux, the pancreatic enzymes, and especially trypsin (resulted from trypsinogen activation), phospholipase and elastases are releases and activated locally leading to the digestion and destruction of pancreatic and extra-pancreatic tissue.

The destruction of pancreatic cells and the release of their enzymatic contents gives rise to a vicious circle, which produces autodigestion of the pancreas.

4.6 Chronic pancreatitis

Chronic pancreatitis is an inflammatory process that damages pancreatic tissue in an irreversible, progressive manner and induces fibrosis.

It is characterized by the appearance of protein deposits that are calcified at the level of the excretory ducts, which are replaced either by fibrous tissue or are dilated thus forming cysts. Chronic alcoholism is the most common cause.

Evolution occurs in two phases:

1. first: lasts for several years and is marked by painful abdominal crises, malabsorption, weight loss and acute complications (acute pancreatitis, cysts)
2. the second phase: dominated by the onset of exocrine pancreatic insufficiency (steatorrhea) and endocrine (diabetes mellitus).

5. THE URINARY SYSTEM

5.1 Anatomy of the urinary apparatus

5.1.1 The kidneys

The kidneys are paired organs located retroperitonally, on either side of the lumbar spine and under the lungs.

Topography:

- *laterally* are delimited by the transverse muscle of the abdomen, *posterior* – by the square lumbar muscle, *medial* – by the psoas and *superior* – by the diaphragm
- in relation to the vertebrae: - left kidney: vertebrae $T_{11\text{-}T\ 12} \rightarrow$ L 1-L_2
  - right kidney: $T_{12} \rightarrow$ L 1-L_3

Color: red-brown

Dimension:

- children: 6-7 cm (L); 3-4 cm (l); 1.5-2 cm (h)
- adults: 10-12 cm (L); 5-6 cm (l); 3 cm (h)

Weight:

- children: 35-40 g
- Adults: 115-150 g

Consistency: firm

External morphology:

The kydneys have 2 faces (anterior and posterior) and 2 edges (convex lateral and medial concave). The renal parenchyma is divided into segments and lobes. In the kidneys we distinguish five segments: upper, anterior upper, anterior lower, lower and posterior. Each segment consists of 2-3 renal lobes. A renal lobe includes a renal pyramid with the adjacent cortical substance and is delimited by the interlobary arteries and veins.

In the area of the concave edge there are found the renal hilum and pedicle in which the renal vessels (the renal artery and vein), the ureter and vegetative nerve fibers are entering/exiting the kidney. On the outside, the kidneys are wraped in a fibrous capsule that protects the kidney.

Internal morphology:

Cutting the kidney along the midline, from the convex side to the concave one, one can observe:

1. a fibrous capsule: the thin translucent membrane (0.2 mm) consisting of fibro-connective tissue and rare elastic fibers that give the kidney a reduced extensibility and high strength
2. renal parenchyma
   - cortical zone (external part)
   - medullary area (internal part)
3. urinary tract: renal papilla → small calyx (6-12 / kidney) → large calyxes (2-3, formed by the union of 2-3 small calyx) → pelvis / renal pelvis (shows an intrarenal / sinus portion and an extrarenal portion - which narrows and continues with the ureter)

The cortical zone is mainly made up of the renal corpuscule, renal tubules and blood vessels. It has a yellowish/grayish-brown color, 5-7 mm thick and intertwines between the pyramids of the medullary area through the renal columns.

The medullary area consists of 6-18 renal pyramids (Malpighi). The pyramids have a triangular shape with the base facing towards the cortical zone, and with the tip towards the renal sinus. At this level, the pyramids end with a convex surface, called the renal papilla that is punctured by 15-20 papillary orifices (or urinary pores) and form a riddled structure called a cribrous (riddled) area.

Urine produced in the kidneys circulates through the ureters, being further discharged and stored in urinary bladder. As a result of urination, it will be eliminated on the outside by the urethra.

The vascularization is performed as follows:
abdominal aorta → renal artery → (kidneys) → segmental arteries → interlobular arteries → arcuate arteries → → interlobular arterioles (nephron) → *arteriola glomerular afferent to* → *glomerular capillaries* → *arteriola glomerular efferenta* → *peritubulary capillaries* → interlobular (descending) venules + right (ascending) venules → arched veins → interlobed veins → segmental veins → renal vein → inferior vena cava

5.1.2 Nephron

The nephron represents the morpho-functional unit of the kidneys that performs all the complex processes that will result in the formation of urine.

In the structure of the kidney we distinguish two types of nephrons :

1. **80% are cortical** nephrons - renal corpuscles are located in the external area of the cortical substance; the Henle loop is located in the peripheral portion of the pyramid.
2. **20% are juxtamedular nephrons** - renal corpuscles are located at the border between the internal area of the cortical and the medullary substance; the Henle loop is much longer and reaches close to the papillary orifice.

Structure

1. renal corpuscle (the Malpighi corpuscule)
2. proximal convoluted tube (PCT)
3. Henle loop
4. distal convoluted tube (DCT)
5. collector tube (TC)

A kidney has about 1.3 million nephrons and after the age of 40 years the number is reduced by 10% every 10 years; the nephrons cannot regenerate.

I. Malpighi corpuscle is a spheroidal formation with a diameter of 150-250 μm; located exclusively in the cortical zone. It has a vascular pole and a urinary pole.

It is composed of:

1. The Bowmann capsule (the closed end of the nephron) that envelops the capillary ball, with a double wall: the internal, visceral wall adhering to the glomerular capillaries and the external, parietal wall that continues with the proximal tube. Between the two walls is the urinary space (Bowman).

2. The glomerulus – the capillary ball. It is located in the concavity of the Bowmann capsule located at the end of each nephron. The glomerus represents the filtration unit of the kidneys. It consists of a ball of 4-12 capillary loops, resulting from the division of the afferent arteriole and which come together at the exit of the capsule, in the efferent arteriola, surrounded by the Bowmann capsule. The Bowman capsule continues with the PCT, through which urine passes with a role in glomerular filtration and the production of primary urine.

The renal corpuscle Malpighi has a vascular pole (the place of entry of the afferent arteriole and exit of the efferent arteriole) and a urinary pole (the exit place of the primary urine from the Bowmann capsule to the PCT)

II. The renal tubules are adapted for the processes of reabsorption and secretion and have several segments:

1. The proximal convoluted tubule (PCT) of the uriniferous tube consists of a metered portion, the proximal contorted tube (which is located in the renal cortical) and consists of a layer of cells whose membrane, towards the lumen, has an "edge in the brushes", formed by microvili, which greatly enlarge
the surface of the membrane, it receives all the glomerular ultrafilter and has an increased role in reabsorption and secretion.

2. The intermediate tubule (Henle loop), is thin and has two arms (descending and ascending) joined to each other by a loop, hasthe flattened epi telium, without microvili. Cthey 2 arms of the loop have different permeability. Theducks of the Henle loops have a trajectory parallel to the straight arterioles and venules (vasa recta). Role in the concentration of urine.

3. The distal convoluted tubule (DCT) consists of a straight, ascending portion, which reaches the cortical in the vicinity of the own glomerulum, in immediate contact with the afferent arteriole. At this level, the tubular epithelia, as well as the smooth muscle cells, of the afferent arteriole, shows changes and forms the juxtaglomerular apparatus that secretes renin.

4. Collecting tube (CT)*:* numerous DCT join together and open into the collecting tube in the structure of the Malpighi pyramids.

Juxtaglomerular apparatus

The DCT is located in the immediate vicinity of the Malpighi corpuscle. At this level is formed the juxtaglomerular apparatus. It consists of: the walls of the afferent arterioleof the glomerulum and the wall of the TCD. Here is a high density of cells that act as baroreceptors that detects with high sensitivity the changes in blood pressure. TCD contains modified, specialized cells, with a role in the self-regulation of glomerular filtration (dense macula),whose function is as a chemoreceptor for the urinary concentration of Na^+.

The kidneys play an essential role in the regulation of TA through the juxtaglomerular apparatus through the synthesis of renin involved in SRAA.

5.2 Kidney function

The kidneys have two main functions: exocrine (urine formation) and endocrine (secretion of certain hormones: renin, erythropoietin, prostaglandins).

5.2.1 The exocrine function

The mechanism of urine formation comprises three fundamental processes:

A. plasma ultrafiltration at the glomerular level
B. reabsorption
C. secretion of certain constituents in the tubules

A. Glomerular filtration

It's the first process in urine formation that takes place through the passive passage of water and micromolecular plasma components from the glomerular capillaries into the Bowman capsule with the formation of primary urine.

Primary urine is an ultrafiltered deproteinized plasma, with a composition similar to that of plasma, but without proteins and isotonic (300 mOsm/l).

By its structure, the filter membrane allows the filtration of a large amount of fluid and micromolecules from plasma (hundreds of times more than normal capillaries):

- those with small molecular weight (MW) (<6,000 Da) are easily filtered: water, ions, small organic compounds (e.g. glucose),
- those with large MW are less and less filtered, up close to 0: albumin, globulins, blood cells.
- the positive charged substances are more easily filtered than the negative ones, even at the same size, due to the negativity of the filter membrane.

Thus in the urine formed in the urinary space, called primary urine, all plasma elements except proteins are found at the same concentration as in plasma (deproteinized plasma).

At the glomerular level, metabolic wastes are filtered, especially the nitrogenous residues of proteins, amino acids and nucleotides:

- urea (it is formed in the liver),
- creatinine
- uric acid
- some medications

The glomerular filter (barrier) is composed of three elements, each of which has a selective permeability:

1. capillary endothelium or fenestrate lamina with pores that prevent the passage of blood cells
2. Glomerular membrane containing 3 layers: rare internal lamina - to the endothelium, dense lamina – in the middle and rare external lamina - to the podocyte layer; achieving an effective barrier for proteins with MW > 50.000 Da.
3. the internal (visceral) layer of the Bowman capsule, with podocytes (cells with extensions/podocyte processes), which envelop the capillaries but also leave lacunae spaces through which the primary urine passes. It has a negative charge → is impermeable for albumins (negatively charged) and for proteins with MW > 150.000 Da.

The glomerular filtration rate is equal to the filtered volume of glomeruli per unit of time (120 ml/min → 180 l/day being normally filtered by the kidneys). At the tubular level, the primary urine undergoes the processes of reabsorption and secretion, so that the kidneys will excrete on average 1.5 l/ day, which represents the definitive urine.

B. Tubular reabsorption

During this process almost all elements in the primary urine will be reabsorbed at the tubular level (except creatinine). Reabsorption is the passage of the substances contained from the tubular lumen into the capillaries. It is the process by which certain substances useful to the body are recovered from glomerular ultrafilter, thus maintaining their plasma homeostasis. The process is selective, in the sense that it is maximally performed for each substance in a tubular segment through the action of specific cellular mechanisms, being conditioned by the flow rate of the respective substance and by the needs of the body:

1. Glucose and aminoacids are reabsorbed about 100%

2. Na^+, Cl^-, HCO_3^- have increased but variable reabsorption rate, depending on the needs of the body
3. Urea has a low reabsorption and increased excretion
4. The water is reabsorbed in all segments of the tube, with various intensities, based on the laws of diffusion and osmosis, so that out of the 125 ml glomerular filtrates per minute, only 1ml / min reaches the bladder (so 124 ml are absorbed). In the DCT and especially in the collector tube, the optional reabsorption of water and Na^+ is performed under the control of antidiuretic hormone (ADH) and aldosterone, adjusting the elimination on the hydration state of the body.

The reabsorption (transport) of different constituents from primary urine through the wall of the renal tubules is made by active and passive mechanisms.

Active transfer is performed against the concentration or electrical gradients, requiring a consumption of energy supplied by ATP hydrolysis.

The mechanisms of active transport have limited capacity per unit of time and intervene in the reabsorption of glucose, certain amino acids, uric acid, some vitamins (B_{12}, C), inorganic phosphates, sulfates and the main ions of the filtrate (Na^+, K^+, HCO_3^-).

Passive transport is done under the action of physico-chemical gradients so it does not require energy consumption and is not limited by a maximum capacity; it contributes to the resorption of three main constituents of ultrafiltration: water, urea and Cl^-

C. Tubular secretion

Tubular secretion is the reverse process of reabsorption, which ensures the transport of blood substances to the tubular urine. It has the role of eliminating both foreign substances (such as drugs) and substances usually present in the blood (K^+, uric acid), some only when they are in high concentrations (creatinine). It is carried out through active and passive mechanisms.

The active secretion, occurs especially at the level of the proximal and distal tubules, and is made against some electrochemical gradients, therefore requiring a high energy consumption. The secretion of H^+ takes place by active transport; by eliminating the H^+ tubules hold a fundamental role in maintaining the acid-base balance of the body.

Passive secretion involves the transport of constituents as their concentration gradients and therefore, does not require direct energy consumption. This mechanism intervenes in the secretion of K^+, bases and weak acids.

Tubular cells are capable of eliminating even substances that accidentally reach the internal environment: toxic substances - accidental intoxication or drugs (e.g., penicillin). This explains why the renal tube (more than the glomerulus) will be affected in case of severe poisoning (mercury, carbon tetrachloride), or by so-called nephrotoxic drugs. Posology depends on kidney function, and the administration of medicines must be strictly controlled

5.2.2 Endocrine function

The kidney is a real endocrine organ, capable of synthesizing a large number of hormones:

Renin, secreted by juxtaglomerular, plays an important role in regulating blood pressure: renin diffuses into the blood and hydrolyzes the angiotensinogen secreted by the liver that is transformed into inactive angiotensin I (ATI); in the lungs, a conversion enzyme converts AI into ATII that leads to increase in aldosterone secretion, Na^+ reabsorption and secondary reabsorption of water, at the level of DCT, that in turn increases the plasma volume and blood pressure. The ensemble of these mechanisms constitutes the RAAS. Renin is a proteolytic enzyme synthesized in the aa walls of the renal glomeruli, in response to:

- reduction of renal perfusion,
- decreased renal excretion of sodium and
- sympathetic stimulation.

Erythropoietin, glycoproteic hormone (90% of renal origin, 10% of hepatic origin) that plays an important role in the process of erythropoiesis (differentiation and proliferation of erythrocytes in the hematogenous bone marrow). The lack of blood oxygen (hypoxemia) causes an increase in the secretion of erythropoietin, and thus of the proliferation of red blood cells. There are anemias of renal origin (absence of erythropoietin due to various nephropathies and chronic renal insufficiency).

Renal prostaglandins, especially PGI2, PGE2 (vasodilators) play an important role in the adaptation of renal circulation in case of hypovolemia and in renal excretion of sodium.

At the same time, the kidneys, under the action of an enzyme existing in the cells of the proximal tubules, ensure the transformation of inactive *vitamin D* (the hydroxylated 25-OH-cholecalciferol from the liver), into 1,25-dihydroxylated -cholecalciferol which represents the active form.

5.3 Quantification of metabolism and elimination. The notion of clearance

The clearance (Cl) represents the body's overall ability to remove a foreign molecule. It represents the volume of plasma totally purified, per unit of time and is expressed as a flow rate in ml/min. The total clearance is equal to the sum of the clearances of each organ likely to intervene in the elimination of a substance:

- Cl renal
- Cl hepatic
- Cl intestinal
- Cl pulmonar

Of particular importance is the hepatic Cl and the renal Cl.

The renal clearance of a substance represents the volume (ml) of plasma that can be totally purged/filtered of that substance (/min), provided that the substance would be fully extracted at the first passage. In order to determine the glomerular filtration rate, a substance must therefore be used which can be freely filtered at the glomerular level, but which cannot be reabsorbed or secreted at the tubular level such as creatinine. The measurement of creatinine in the blood and the determination of creatinine Cl are thus essential investigations in order to explore the kidney function.

5.4 Diuretics

Diuretics are medicinal substances that inhibit the renal reabsorption of Na^+, thus causing urinary elimination of sodium chloride and water.

Indications

1. AHT
2. IC (main)
3. Hypokalemia (only those that save potassium)
4. Oedema

Classification

1. Loop diuretics (furosemide, bumetanid, pyrethaneid) block the reabsorption of NaCl at the level of the Henle loop, causing a marked elimination ofsalts and a marked diuresis. They have a quick action and can be used in the insufficiency of the ounce.

Since an increased amount of Na reaches the distal segment of the nephron, one part will be reabsorbed under the influence of aldosterone, which is responsible for the mandatory elimination of K^+. This explains the hypokalemiant action of loop diuretics.

2. Thiazide diuretics (hydrochlorothiazide, chloraligone, indapamide) block the reabsorption of NaCl in the proximal portion of the distal tube, causing diuresis and natrireasis. The natriuretic effect is less important than that of loop diuretics, but in this case too there is an increase in the concentration of Na at the level of the distal metered tube and collector, which will lead to an increased secretion of aldosterone, responsible for hypokalemia. They are not used in renal failure.

3. *K^+-sparing diuretics*

a. Anti-aldosteronic (spironolactone, canrenone). The most important representative is spironolactone, a steroid structurally analogous to aldosterone, which thus achieves a competitive antagonism at the level of the distal tube (spironolactone blocks the aldosterone receptors at the TCD and TCP levels). Anti-aldosteronics cause moderate natriumresesis, in exchange for K^+ that is reabsorbed. They lose their effectiveness in patients with renal insufficiency, their use becoming even dangerous daoritis of hyperkalemia that occurs.

b. Pseudo anti-aldosteronic (triamterene, amilorid). They have the same mechanism as spironolactone, but there is no competition.

5.5 Pathophysiology of the urinary system

5.5.1 Urinary bacterial infections

Bacterial urinary tract infections are extremely common in medical practice.

Urethritis is the inflammation of the urethra, which occurs only in men and is manifested by stinging during urination and a purulent discharge at the level of the urethral meatus, in the period between urinations. A particular form is gonococcal urethritis/blenorrhagia which

is a sexually transmitted condition and does not manifest itself in women carrying the neisseria gonorrhae germ .

Cystitis is inflammation of the bladder, more common in women, most commonly caused by E. Coli. It is manifested by the appearance of stinging during urination, frequent and imperative urinations with the elimination of only a few splashes of urine (polakiuria).

Acute pyelonephritis is determined by the existence of an infection that affects the pelvis and interstitial renal tissue. It is manifested by the appearance of unilateral low back pain, associated with bacteriuria and pyuria (the presence of pus in the urine). It is mandatory antibiotherapy performed following the antibiogram.

Chronic pyelonephritis is chronic inflammation with sclerosis of the renal interstitial and tubular atrophy. In most of the cases, it represents the evolutionary stage of a urinary tract infection that complicates an abnormality of the urinary tract and/or of the renal parenchyma. It accounts for 10-20% of the causes of chronic renal failure.

5.5.2 Glomerular nephropathies (glomerulonephritis)

Glomerulonephritis are inflammatory reactions induced by immune mechanisms that involve the deposition of Ag-Ac complexes in the glomeruli, which will trigger lesions locally. Blockage of glomerular capillaries leads to increased resistance in aa and ae, while blood flow decreases, as well as glomerular filtration with oliguria (urinary flow < 500 ml / day).

Alteration of renal irrigation will stimulate renin secretion, so RAAS is stimulated with the production of AHT. Glomerular filter lesionsleduced loss of selective permeability with the appearance of edema, proteinuria and hematuria (plasma proteins, and even erythrocytes can cross the glomerular barrier)

The glomerular filter (barrier) is composed of three elements, each of which has a selective permeability:

1. capillary endothelium or phenestrata lamina with phenestrates (pores): prevents the passage of blood cells
2. Glomerular MB containing the 3 layers: rare internal lamina - to endothelium, dense lamina - central and rare external lamina - to

the podocytic layer; achieves an effective protein barrier with GM > 500 000 D.

1. the internal (visceral) foitis of the Bowman capsule, with podocytes that are cells with extensions/podocite processes, which envelop the capillaries but also leave gaping spaces through which the FG passes. It has a negative charge, it is waterproof for albumins (negatively charged) and for Pr with GM > 150000 D.

Glomerulonephritis is presented as 2 clinical syndromes (syndrome meaning the association of several symptoms):

Nephrotic syndrome – syndrome with brutal onset, with endothelial cell damage, characteristic foracute glomerular n efropatiile: oliguria, hematuria, einurie prot, edema, azotemia and AHT.

Nephrotic syndrome – syndrome with progressive onset, affects especially the basal membrane, characteristic foracute, but also chronic glo merular nephropathies: proteinuria > 3 g / day, hypoalbuminemia, edema, hyperlipidemia.

Causes

1. Primitive glomerulonephritis

Characteristic is the absence of extrarenal signs or of an obvious etiological agent. The diagnosis is put on the renal biopsy. There are several types: glomerulonephritis with minimal lesions, segmental and focal hyalinosis, glomerulonephritis with mesangial iga deposits.

2. Secondary glomerulonephritis

Toappear within another condition, or there is a clear etiology with are DZ, lupus erythematosus (auto-immune condition characterized by increased levels of AutoAc), malignancy,
infections (after a streptococcal angina), drugs (D-penicillin, NSAIDs).

5.5.3 Acute renal failure

Acute renal failure (IRA) is characterized by a sharp decrease (several hours to several days) in renal functions, which is manifested by a sharp decrease in the flow of the glomerular filtrate. The decrease in FG is estimated by the rapid increase of urea and blood creatinine (retention of nitrogenous waste). In IRA, hydro-electrolytic and acido-base homeostasis and/or accumulation of organic waste are lost.

Classification

1. Depending on the *diuresis:*

1. Preserved IRA diuresis where diuresis > 500 ml/day
2. Oliguric IRA where diuresis < 500 ml/day.
3. Anuric IRA where diuresis < 100 ml/day.

4. Depending on the cause:

1. Prerenal IRA *(functional IR*) consequence of renal hypoperfusion occurring as a result of digestive loss (vomiting and severe diarrhea), renal loss (excessive diuretic treatment, osmotic polyuria from decompensated DZ), real hypovolemia (from IC, hypotension, cirrhosis of the liver) or the administration of some drugs (diuretics, NSAIDs or IECA)
2. Renal IRA *(parenchymal or organic IR)*, secondary to a lesion affecting one or more components of the renal tissue that is triggered by: acute tubular necrosis (septic shock, anaphylactic, hemorrhagic), anticancer treatment (cisplatin, methotrexate), antifungal treatment (amphotericin B)
3. Postrenal IRA (*obstructive* IR) is due to an obstacle in the urinary tract, excretory pathways, or intratubular pathways, often being the consequence of a tumor pathology: adenoma or prostate cancer, tumor of the VU.

5.5.4 Chronic renal failure

Chronic renal failure (IRC) is characterized by a progressive, most commonly irreversible, decrease in exocrine and endocrine kidney functions; represents the final stage of chronic, evolutionary renal diseases. It is expressed especially by the decrease of glomerular filtration, with the increase of creatinemia and uremia by decreasing FG (and Clcr). The evolution is towards terminal renal failure, which requires hemodialysis or kidney transplantation.

Mechanism

IRC is due to the decrease in the number of functional nephrons by the initial destruction is determined by the condition in question and compensatory, there is a hyperfunction of the remaining nephrons, which over time leads to glomerulosclerosis

Evolutionary stages

Depending on the severity of the decrease in the value of Clcr (N : 120 ml / min) we have:

1. Compensated IRC – Clcr 80-40 ml/min (asymptomatic)
2. Decompensated IRC – Clcr 40-10 ml/min

Symptomatology is related to the decrease of exocrine function with the retention of nitrogenous waste (urea and creatinine) and hydro-electrolyte disorders: hyperkalemia, acidosis, hypocalcemia, hyperphosphatemia and endocrine function with anemia (deficiency of erythropoietin synthesis) and bone demineralization or osteomalacia (lack of vitamin D activation).

If Clcr< 40 ml/min, the posology of renal elimination drugs should be adapted. The medication prescribed should take into account the pharmacokinetic changes related to IRC.

In chronic terminal IRC (uremia), Clcr <10 ml/min, dialysis or kidney transplantation is required.

6. THE ENDOCRINE SYSTEM

6.1 General notions about the endocrine system

The endocrine system represents the totality of the endocrine glands that secrete the hormones necessary for internal regulation and maintenance of homeostasis. It works closely with the nervous system, coordinates cellular activity and regulates all functions of the body, thus ensuring its functioning as a whole.

The endocrine system intervenes in:

1. maintaining the homeostasis of the internal environment and its interaction with the external environment
2. metabolic processes of the body: carbohydrate, lipid, protein, hydro-electrolyte and mineral metabolism
3. the process of reproduction, sexual behavior and the development of sexual characters
4. growth, development and defenses of the body
5. malignant transformation and promotion of the growth of some tumors

6.2 General structure of the endocrine system

Glands are very well differentiated organs or tissues and specialize in the synthesis and secretion of a chemical substance that has specific property. Depending on the place of discharge of the secretion product, the glands are divided into: ***endocrine glands*** (the secretion product is discharged directly into the blood that irrigates the gland, e.g. thyroid, hypothalamus), ***exocrine glands*** (the glandular secretion product is discharged to the outside of the gland, e.g. salivary, sweating) and ***mixed glands*** (e.g. pancreas, ovaries, testicles).

The endocrine system consists of: *i)* centrally located endocrine glands: hypothalamus, pituitary, epiphysis, *ii)* peripherally located endocrine glands: thyroid, parathyroid, adrenal glands, *iii)* glands with a mixed role located peripherally: testicle, ovary, pancreas, placenta and *iv)* diffuse endocrine glands: isolated cells that are hormone-producing.

6.3 Hormones

Hormones are chemicals secreted by specialized cells, discharged into the bloodstream and circulated by circulation (bound to plasma proteins) to exert an exciting action (positive or negative) on various target

cells located locally or remotely. Ahormonal action is possible by the presence of specific receptors that are found on the target cells; the cell response differs depending on the type of cell/tissue, so a hormone may have different actions on different cells/tissues. Hormones do not show species specificity, only slight variations in structure from one species to another. The blood concentration of hormones is very low and they are quickly catabolized, within a few hours.

The mechanisms of hormonal action involve:

1. accelerating or slowing down normal cellular processes
2. change in permeability or membrane electrical charge
3. protein synthesis and activebad/inactivation of some enzymes
4. stimulation of mitosis

Classification according to solubility:

1. Hydrophobias (fat soluble) – Steroids and thyroids

To be able to circulate in plasma they need transport proteins. The formed complex, hormone-protein transport, is also a form of hormone storage; in the form related to the transport protein, the hormone is inactive.

- diffuses through the plasma membrane
- in the cytoplasm it binds to the receptor, forming a hormone-receptor complex
- the complex penetrates into the nucleus and causes DNA transcription into the mRNA
- the synthesis of new proteins that influence cellular activity is triggered

2. Water solubles - Peptides, protein crops and amino acid derivatives

- can not penetrate into the cell
- binds to receptors on the plasma membrane
- binding causes the activation of a G protein which then causes the activation of an enzyme and the production of a secondary messenger (cAMP)
- cAMP activates protein kinase
- protein kinase phosphorylases and activates cytoplasmic proteins that then influence cellular activity

Effect on cellular function

- A hormone can have several different target cells (e.g.: estrogen)
- A hormone can have different effects depending on the target cell (e.g.: Ach)
- The target cell may react differently at different times
- The external environment can act on the production of a hormone (e.g. melatonin)

Regulation of hormonal release

The hormonal level is controlled by **feedback** mechanism: as the blood level of a hormone increases, the body tries to decrease its serum concentration and vice versa. The stimulus can be:

- Hormonal: increasing the concentration of the hormone inhibits its own production
- humoral: inhibition by variations in the blood concentration of certain ions
- Nervous: inhibition by nervous influx

Hormonal secretions are controlled at the higher level by the nervous system, the hypothalamus being the one that plays a predominant role. For almost all hormones, the hypothalamus is an indispensable intermediate: its neurons secrete substances with hormonal functions, which influence the secretion of hormones of the anterior lobe of the pituitary. Neurosecrations (hypothalamic neuro-hormones) are of 2 types: *i)* ***releasing factors*** of pituitary hormones ("releasing factors" - RF) and *ii)* ***inhibitory factors*** ("inhibiting factors" - IF). Hypothalamic hormones, called hypophysiotropic (active on the pituitary), pass into the bloodstream through a vein that connects the hypothalamus to the pituitary, constituting the ***hypothalamopophysical port system.*** Due to the infuence of the hypothalamus on the other endocrine glands, through the pituitary, ***we are talking about the hypothalamopophysical axis.***

Table 2. Hypothalamic release hormones and inhibitory hormones that control pituitary secretion

Hormone	The effect on anterior hypophysis (pituitary gland)
Thyrotropin-releasing hormone **(TRH/TRF)**	Stimulates the secretion of thyroid-stimulating hormone (TSH) of thyrotrope cells
Gonadotropin-releasing hormone **(GnRH)**	Stimulates the secretion of follicle-stimulating hormone (FSH) and luteotropic hormone (LH) of gonadotrope cells
C-releasing hormone of orticotropine **(CRH/CRF)**	Stimulates the secretion of adrenocorticotrp hormone (ACTH) of corticotropic cells
Growth hormone-releasing hormone **(GHRH/SRF)**	Stimulates the secretion of growth hormone (STH) of somatotropic cells
Prolactin-releasing hormone **(PRH)**	Stimulates the secretion of prolactin (PRL)
Hormonul de inhibare a eliberării de STH **(somatostatină)**	Inhibits the secretion of STH in somatotropic cells
Prolactin inhibiting hormone **(PIH)**	Inhibits PRL secretion

6.4 Pituitary

It is a small, complex gland, located in a cavity in the structure of the sphenoid bone (one of the median bones at the base of the skull), called the Turkish saddle. The pituitary has 2 lobes: an anterior one (adenohypophysis) and a posterior one (neurohypophysis), which in reality constitute two distinct glands (with different origin, structure and function), glued to each other. The form is ellipsoidal, the size of a bean grain, weight 0.5-0.8 g.

1. Adenohypophysis
   - Represents the bulk of the gland (2/3)
   - Regulates the activity of several endocrine glands
   - Secretes 7 hormones:2 with effects on non-endocrine target cells (growth hormone/somatotropic hormone- **STH** and prolactin - **PRL**) and 5 stimulators (thyroid stimulating hormone - **TSH**, adrenocorticotropic hormone - **ACTH**, melanocytostimulator hormone - **MSH,** follicle-stimulating hormone - **FSH** and luteotropic hormone - **LH**)

2. Neurohypophysis
   - Does not secrete hormones
   - It only stores 2 hormones produced by the hypothalamus: **oxytocin** and antidiuretic hormone - **ADH**

6.4.1 Growth hormone or somatotropic hormone (somatotrophic hormone - STH, growth hormone - GH)

Growth hormone/ somatotropic hormone/ somatotropin - **STH** is a hormone made up of a single chain of 191 amino acids. STH acts on all tissues of the body stimulating the increase in cell size and the growth of mitosis, as well as the specific differentiation of some cell types. However, STH is not the only hormone that influences growth. Thyroxine, prolactin, androgens and insulin exert a synergistic action, while ACTH and adrenal steroids have opposite effects.

Actions

- increase in protein anabolism (increase in the rate of protein synthesis)
- stimulating the mobilization of fatty acids in adipose tissue → increasing the blood concentration of free fatty acids and using them to obtain energy
- decrease in the rate of utilization of glucose in the body and stimulation of hepatic glycogenolysis → hyperglycemic effect
- maturation of growth cartilages → increase in length of bones
- the formation of the periosteum → the growth of the bone in thickness

Physioptaology

The insufficiency of the secretion of STH leads to the child the dwarfism called harmonious dwarfism because the deficiency occurs before the closing of the cartilages and all the elements of the skeleton are affected. In adults, *insufficiency* of STH induces severe asthenia and cachexia (Simmonds' casexia). STH deficiency can be the consequence of lesions present in hormone-secreting cells (produced by tumors, hemorrhage, irradiation) or as a result of a decrease in hypothalamic stimulation.

The excess of STH causes gigantism by the child and in the adult, given that the cartilages of the long bones are welded, the excess of STH causes disharmony: the excess growth of the nose, tongue, lips and extremities (the disease called acromegaly, from Greek: acro = extremity and megalos = large).

6.4.2 Prolactin

Prolactin acts on the mammary glands during lactation, stimulating the development of lactogenic tissue of the mammary glands and the production of dairy secretion. Its secretion by adenohypophysis increases progressively during pregnancy but its action on the mammary glands is blocked by placental hormones: estrogens and progesterone. After birth and removal of the placenta, the released prolactin can act on the mammary glands, triggering the secretion of milk that becomes manifest 2-3 days after birth. The sucking process can sometimes trigger the release of prolactin that will stimulate breast secretions and. at the same time, stimulate the release of ocytocin that causes the gland to empty. Prolactin at the same time has a blocking effect on other adenohypophysis hormones, physiologically responsible for anovulation during the period of breastfeeding.

The secretion is provoked by a nervous reflex whose starting point is located at the level of the sensory endings of several peripheral organs: uterus, vulva, nipple.

• Simulates secretion: TRH, endorphins, angiotensin II, stress and hypoglycemia, drugs (phenothiazines, haloperidol, metoclopramide, alpha-methyldopa, opiate derivatives, antagonists for histamine type H2).

• Inhibits the secretion: dopamine; this phenomenon explains why drugs such as neuroleptics that block dopamine receptors can cause hyperprolactinemia, while bromocriptine, a dopamine agonist, is the treatment used in hyperprolactinemia.

6.4.3 Trophic hormones (ACTH, MSH, TSH, FSH, LH)

1. ACTH stimulates the secretion of adrenal corticals (glucocorticoids, mainly cortisol)
2. MSH stimulates the synthesis of melanin (skin pigment) in skin cells – melanocytes
3. TSH stimulates thyroid hormonal secretion (thyroxine)
4. FSH stimulates follicular maturation and secretion of estrogens in women; gametogenesis (spermatogenesis) in men
5. LH triggers ovulation and stimulates the secretion of progesterone in women, while ICSH (its equivalent in men), stimulates the secretion of testosterone by testicular interstitial cells.

The hypothalamus regulates pituitary secretions, by means of secretion of corresponding neuro-hormones (Table 2).

6.4.4 Oxytocin

Polypeptide made up of 9 amino acids.

Actions

1. *Strong ocitocic effect* on the pregnant uterus, especially towards the end of the gestation period; stimulates uterine contractions during labor. Its role is essential in relation to the expulsion of the fetus during childbirth. It is used in daily obstetrical practice in the form of natural extracts or synthetic derivatives.

2. *Lacctogenic effect* (facilitcase ejection of milk from the mammary glands): the suction of the nipple by the newborn causes a nervous reflex that causes the release of oxytocin by neurohypophysis. Oxytocin transported by blood to the mammary glands causes the contraction of the mammary glandular lobes, so that the milk is expelled through the galactophore ducts to the level of the nipples. It has no effect on the formation of milk.

3. *Vasoconstrictor effect* - increased blood pressure.

6.4.6 Antidiuretic hormone ADH (vasopressin)

Polypeptide made up of 9 amino acids.

Actions

1. *Antidiuretic effect* (reduction of diuresis), via renal V2 receptors, by increasing the optional water reabsorptation at the level of the distal convoluted tube (the most important). By regulating water reabsorption, ADH thus controls the concentration of electrolytes in plasma and interstitial fluids. As this concentration increases, certain particular receptors of the hypothalamus, called osmoreceptors (addition sensitive to osmotic pressure) send nerve inflows to neurohypophysis, which secrete increased amounts of ADH.

2. Vasoconstrictor effect (increases blood pressure), via vascular V1 receptors, by acting on vascular smooth muscle - relatively weak action.

Regulation

Hypovolemia and/or hyperosmolarity (the increase in osmotic pressure of the blood and interstitial fluid that stimulates the osmorceptors) are the major stimuli that increase the secretion of ADH by the hypothalamus. This secretion is inhibited by hypervolemia and a decrease in osmotic pressure.

Pathophysiology

The deficiency of ADH leads to diabetes insipidus characterized by: polyuria (increased diuresis); polydipsia (permanent, imperative feeling of thirst). The lack of ADH causes the impossibility of the renal tube to normally reabsorb the water filtered by the glomerulum, with the excretion of significant amounts of poorly concentrated urine and the development of hypertonic dehydration. Renal water losses are thus compensated by an increase in water consumption. If the osmorreceptors present in the hypothalamus are destroyed, the deficiency of ADH is also associated with hypodipsia and massive hypertonic dehydration.

By etiology, the following are distinguished:

1. central insipidus diabetes: related to a hypothalamic-pituitary pathology: destruction of the hypothalamus (e.g. following an auto-immune disease or as a result of neurohypophysis lesions)
2. Renal insipidus diabetes (nephrogenic): despite a normal secretion of ADH, the kidneys are insensitive to the effects of ADH. It can be hereditary or secondary (e.g. chronic kidney disease, abnormalities in the receptors or following a drug treatment: amphotericin B, lithium salts, anesthesia with methoxyflurane)

Excess ADH is determined by increased hypothalamic synthesis, as a result of which injuries to the central nervous system (of traumatic, infectious, hemorrhagic origin) are caused by increased hypothalamic synthesis, as a result of which injuries to the central nervous system (of traumatic, infectious, hemorrhagic origin). The ADH can be synthesized in an ectopic manner (from outside the hypothalamus) by tumors (certain bronchial carcinomas) or by lung diseases that lead to an inadequate secretion of ADH (Schwartz-Bartter syndrome). Hypersecretion of ADH is characterized by a decrease in the excretion of water (oliguria) and an increased concentration of easily soluble urinary constituents, which can lead to the formation of calculi (urolithiasis). Simultaneously, extracellular osmolarity decreases (hypotonic hyperhydration) causing swelling of the cells, the most dangerous consequence is the development of cerebral edema.

6.5 Thyroid

6.5.1 General

The thyroid is an odd organ, located in the anterior and lower part of the neck, in front of the trachea. It has the shape of the letter H, being composed of 2 lateral lobes (pyramid-shaped) united in the lower part by an isthmus, which passes in front of the trachea.

Weight: 25-50 g, transverse diameter: 5-7 cm.

Vascularization of the thyroid is very rich: the middle thyroid artery - from the aorta cross, 2 lower thyroid arteries - branches of the sub-clavicular, and 2 upper thyroid arteries - from the external carotids.

From a structural point of view, the thyroid consists of a shell (a fibrous capsule), a schrome (conjunctival septa) and glandular parenchyma. The glandular parenchyma is formed by the thyroid lobules, formed in turn from the thyroid follicles (which together with the stroma make up the morpho-functional unit of the gland). Thyroid follicles are vesicles that contain/secrete in the central portion a colloidal substance in which iodine and thyroid hormones accumulate. Vesicles contain two types of cells: i) follicular cells - which form the walls of the vesicles and secrete triiodothyronine and thyroxine, and ii) parafolicular cells - which secrete calcitonin.

6.5.2 Iodine metabolism

The total content of the body in iodine is approx. 50 mg, of which 15 mg are found in the thyroid gland. Food intake (0.2 mg/day) is carried out in the form of iodide, of which 2/3 are excreted by the kidneys. Iodine is concentrated in the thyroid, being actively transported thanks to a pump stimulated by TSH. The next step involves the oxidation of iodide in iodine by a peroxidase, and then the iodization of tyrosine (which is transported by thyroglobulin - a dimeric glycoprotein synthesized by thyrocytes that serves as a matrix for the synthesis of thyroid hormones), with the formation of iodothyrosine (can be: mono-, di-, tri- or tetraiodata). This is then stored in the follicle along with thyreoglobulin. The increase in TSH stimulates pinocytosis that allows the reuptake of substances stored in the colloid. They get into lysosomes; it is here that their hydrolysis takes place, which *leads to the release of the main thyroid hormones, tri-iodothyronine (T3) and tetra-iodothyronine (T4 or thyroxine)*, into the blood. The transport of T3 and T4 in the blood is carried out by proteins , the main transporting protein being "Thyroxin Binding Globulin" (TBG).

6.5.3 Action of thyroid hormones

-Accelerates the overall metabolism of the body, which leads to increased basal metabolism (by 60-100%) above the normal value.
- Stimulates the active transport of ions through cell membranes.
- It influences the growth, the effects being manifested mainly in children in the process of development.
- Increase oxygen consumption (oxidation) at the level of all cells with the use of reserves:

- carbohydrates: by stimulating glycogenolysis, hepatic gluconeogenesis and increasing the absorption of carbohydrates from the intestine → have hyperglycemic effect

- lipids: mobilizes the lipids in the adipose tissue → with the decrease of fat deposits but also with the consequent increase of the plasma concentration of free fatty acids

- proteins: by muscle loss and bone loss (protein sieve)

- Cresc schimble respiratory
- Cresc circulating blood volume, heart rate and cardiac output
- Cresc forcesof myocardial cotractil
- Acceleracceler treats gastric atheist motilit and the rate of secretion of gastric juices
- Stimulating appetite and food intake
- Effects on muscle functions (thrombus/ stiffness, depending on the concentration of hormones)
- Influences sleep and sexual function
- Thermoregulation of the cold area. Being hypermetabolizers, thyroid hormones are by definition calorigenic and intervene in the body's lult against caloric loss in cold areas.

Calcitonin is another peptide hormone (made up of 32 amino acids) secreted by the thyroid gland, more specifically in nicelule parafolicular cells (also called C cells) in the interstitial fluid between the thyroid follicles. It is responsible for the decrease in plasma calcium concentration and has effects opposite to those induced by parathormone.

6.5.4 Regulation of thyroid hormone secretion

Regulation of the synthesis of thyroid hormones occurs at the cerebral level and is carried out by feed-back mechanisms that act at the hypothalamic (through TRH) and pituitary (TSH) levels. TRH is

transported from the hypothalamus to the anterior pituitary via the intenneium of the hypothalamic-pituitary port system. TSH (thyrotropin) is a glycoproteic honnon secreted by the anterior pituitary. It then stimulates the secretion of thyroxine and triiodothyronine of the thyroid gland. Increased concentrations of thyroid honnons in the body (1.75 times from the normal value) then produce a decrease in TSH secretion (near zero) of the anterior pituitary = inhibitory feedback.

6.5.5 Thyroid pathology

Hyperthyroidism

Hyperthyroidism (thyrotoxicosis) is defined as an increase in the production of T3 and T4 of the thyroid gland. In most patients with hyperthyroidism, an increase of 2-3 times above normal values in the size of the thyroid gland occurs, hyperplasia also associated with an increase in the rate of homononic secretion. The clinical picture of thyrotoxicosis includes:

- General signs: asthenia, fatiguability, increased appetite, moderate hyperthermia, thirst, profuse sweating and thermophobia
- Heart disorders: tachycardia, rhythm disturbances (tachyarrhythmia, palpitations), heart failure
- Muscle disorders: exercise fatiguability / muscle weakness
- Digestive disorders: diarrheal syndrome
- Nervous disorders: trembling, irritability, hyperexcitability, nervousness, insomnia, sometimes confusion

The main causes of hyperthyroidism and the pathogenic mechanisms involved are:

1. Basedow-Graves disease – present stimulating antibodies (anti-TSH-R) that stimulate follicular cells to produce T3 and T4 in excess. In this disease, in addition to the specific symptoms of thyrotoxicosis, the appearance of exophthalmos (protrusion of the eyeballs) and diffuse indolore goiter (its increase) is described.
2. Pituitary adenoma – produces hypersecretion of TSH
3. Toxic multinodular goiter – thyroid nodules act independently of TSH regulation and secrete excess thyroid hormones
4. Thyrotoxicosis produced by drugs – excessive consumption of thyroid hormones

Hypothyroidism

Hypothyroidism is the most common thyroid pathology. It is characterized by a decrease in the synthesis of T3 and T4. The clinical picture of hypothyroidism includes:

- Heart disorders: bradycardia, decreased cardiac output, angore of exertion, changes in ecg
- Muscle disorders: hard and painful muscles, delay in muscle deconditioning, cramps
- Digestive disorders: constipation
- Nervous disorders: sluggish and inadvertent gestures, drowsiness, paresthesia
- Amenorrhea or infertility

Other signs and symptoms:

- asthenia
- weight gain
- compared to the full moon
- hair loss and depilation
- dry skin
- brittle nails
- elastic and firm edematous face
- deafness

The main causes of hypothyroidism and the pathogenic mechanisms involved are:

1. Primary hypothyroidism (increased TSH and low T4) can be: congenital, drug-induced (lithium, amiodarone, methimazole), Hasimoto's thyroiditis (by autoimmune mechanism) and produced as a result of thyroid ablation
2. Secondary hypothyroidism (low TSH and low T4): as a result of hypopituitarism – deficiency of secretion of TSH
3. Tertiary hypothyroidism occurs as a result of a hypothalamic condition – with decreased secretion of TRH

6.6 Parathyroid glands

The parathyroid glands are vital glands; their total extirpation leads to death. Parathyroids are small glands with oval or lenticular shape (they rise 4-8 mm, the size of a grain of wheat, weight 50 g) in number of 4 (no ranges 2-4). Two parotids (upper, right and left) are located in the middle

of the postero-lateral face of the thyroid lobes, and two other parotids (lower right and left) are located at the base of the thyroid lobes.

The parathyroid glands secrete a hypercalcinate hormone, parathormone (PTH).

PTH – actions:

1. at the level of bones: bone resorption, mobilization of bone calcium
2. in the kidneys: increased tubular reabsorption of calcium
3. in the intestine: increased intestinal absorption of calcium

Parathyroid pathology

Hyperparathyroidism is the excessive production of PTH with the consequent onset of hypercalcemia (>2.6mmol/l). The clinical picture includes:

- General signs: asthenia, fatiguability to exertion, polydipsia
- Cardio-vascular signs: AHT, tachyarrhythmia, QT shortening
- Digestive signs: anorexia, nausea, vomiting, abdominal pain
- Urinary signs: nephrotic colic
- Osteoarticular signs: bone pain, fractures, swelling
- Neurological signs: PSY disorders, apathy, hypotonia, osteotendinous areflexia

Etiology of hypercalcemia

Primitive hyperparathyroidism (in over 55% of cases) produced by: single adenoma (benign tumor), hyperplasia of the 4 glands, parathyroid cancer (very rare).

Secondary hyperparathyroidism produced by: *i)* severe deficiency of Ca^{2+} and vitamin D → hypersecretion of PTH → diffuse glandular hyperplasia → hypercalcemia; ii) most commonly (in chronic renal failure): decrease in production of 1.25-(OH)2D, decreased intestinal calcium absorption, skeletal resistance to PTH and renal retention of phosphate → diffuse glandular hyperplasia → hypercalcemia.

Hypoparathyroidism represents the insufficiency of PTH. The clinical picture includes:

- Neuro-muscular signs: tetany crisis, hand in the claw, carpopedal spasm
- Seizures, depressive or confusing syndrome
- Cortical cataract (frequently)

- Disorders of the appendages (chronic hypocalcemia)
- Heart disorders: rhythm (atrial fibrillations, elongation of QT)

Etiology of hypocalcemia: vitamin D deficiency, renal failure, thyroid surgery (thyroidectomy), idiopathic (sporadic, familial or autoimmune), secondary to a hypomagnesemia.

Calcium and vitamin D

Vitamin D facilitates intestinal resorption of Ca^{2+}. In moderate doses, it favors bone calcification, but in excessive doses, it can cause osteolysis.

There are 2 forms: ergocalciferol (vitamin D2), provided by food, and cholecalciférol (vitamin D3), produced in the skin under the influence of ultraviolet rays. The 2 forms undergo a first hydroxylation (activation) in the liver → 25-hydroxy D3. The second hydroxylation occurs in the kidneys → 1,25 (OH)2 D3 = the active form of vitamin D3.

The last stage is under the control of PTH and STH, which increase the speed of the 2nd hydroxylarum and the plsmatic concentration of 1,25 (OH)2 D3.

Calcium exists in the body in 2 forms: in bound form and in free form. Over 99% of Ca^{2+} is related and associated with bone structures. Free calcium is found in intra- and extracellular environments. Total chalcemia is divided into:

a) A fraction bound to plasma proteins (especially albumin) = non diffusible fraction;
b) A fraction not related to plasma proteins = diffusible fraction: ionized calcium and calcium complexes

Normal plasma concentration of calcium: 9 - 11 mg% .

Calcium plays a crucial role in numerous biological processes:

- muscle contraction
- activation of coagulation
- nervous conduction
- skeletal composition
- various extracellular actions (e.g. activation of coagulation);
- numerous intracellular actions.

The regulation of calciumemia is carried out by the action of 2 antagonistic hormones: PTH and calcitonin, thus: the decrease in calcium

increases the secretion of PTH and decreases the secretion of calcitonin; increased calcium decreases the secretion of PTH and increases the secretion of calcitonin.

6.7 Adrenal glands

The adrenal glands are 2 small flattened glands, shaped like a hat, located above the 2 kidneys. It has a central part (called the adrenal medulla/inner medulla) and a peripheral part (cortical / adrenal cortex) that secrete adrenal hormones indispensable for life.

The *adrenal medulla* secrete 2 catecholamines: adrenaline and norepinephrine, also called epinephrine and norepinephrine. The actions of the 2 hormones are similar and differ only in quantitative terms.

The adrenal cortex presents from the periphery to the depth 3 cellular zones, each ensuring a specific hormonal secretion:

1. The glomerular area (zona glomerulosa) secretes mineralocorticoid hormones, necessary to maintain the concentration of ions (sodium, potassium, chlorine) in extra-cellular liquids (plasma and interstitial fluids): ALDOSTERONE.

2. The fascicular area (zona fasciculata) secretes glucocorticoid hormones, necessary to control the metabolism of glucose, proteins and lipids: CORTISOL. In addition, they have an important anti-inflammatory effect and also act on hydro-electrolyte metabolism.

3. The reticular area (zona reticularis) secretes androgens.

Catecholamines – actions and regulation:

- Cardio-vascular actions: generalized vasoconstriction, tachycardia, increased cardiac output, AHT
- Metabolic, intense actions: carbohydrate metabolism (hyperglycemia), lipid metabolism (mobilization of reserve fats)
- Actions on smooth muscles and viscera: bronchial dilation, slowing gastric and intestinal peristalsis, contraction of visceral sphincters (bladder, digestive tract)
- Mydriasis
- Regulation: reacts quickly to emergency situations: hypotension (hemorrhage, shock), muscle effort, cold, emotions, pain, hypoglycemia; the onset of secretion is carried out exclusively by the nervous way (sympathetic path)

Aldosterone – actions and adjustment:

- acts mainly at the level of the distal tubules and the collecting tubules of the nephrons
- stimulates the absorption of Na^+ and water, as well as the excretion of K^+
- acts independently of pituitary activity; dependent on the volume of circulating blood and the value of blood pressure, activated by the renin-angiotensin-aldosterone system

Glucocorticoids – actions and regulation:

- catabolizing effect on the bone system and protein metabolism
- maintain sympathetic vasomotor tone and control vascular permeability
- produce immunodepression by decreasing the number of eosinophils, basophils and circulating lymphocytes
- causes the inhibition of the release of histamine
- stimulates the central nervous system
- increase gastric secretion of HCl
- causes hydrosaline retention and loss of K^+
- produce hyperglycemia by increasing gluconeogenesis, increasing liver glycogenolysis and decreasing peripheral glucose consumption
- stimulates lipolysis→ ↑concentration of plasma free fatty acids
- adjustment by pituitary control, by ACTH

Adrenal pathology

Adrenal insufficiency is characterized mainly by a lack of cortisol and aldosterone.

Signs and symptoms:

- Marked, global asthenia
- Melanoderma (hyperpigmentation of the discovered areas)
- Weight loss and anorexia
- Hypotension and hypoglycemia
- Digestive disorders: abdominal pain, diarrhea

Acute adrenal insufficiency can be discovered accidentally (clinical symptomatology + biochemical changes) or in case of major stress (trauma, surgery, other severe conditions) or as a result of lack of treatment. Acutesupra-renal failure is an emergency, cardio-vascular collapse, extreme adynamics, nausea and profuse vomiting are associated.

Etiology:

- Adrenal tuberculosis: extremely rare at present
- Addison's disease : cortical atrophy of auto-immune origin (women aged 30-40 years)
- Secondary to long-term corticotherapy

Cushing's syndrome represents the hyperproduction of glucocorticoid hormones (mainly cortisol) and androgens by the adrenal glands.

Signs and symptoms:

- Facio-troncular obesity: face with the appearance of a full moon, erythrosic, with an abnormal distribution of fat.
- Amyotrophy with major muscle asthenia
- Cutaneous signs: purplish stretch marks, acne, hyperpilosity, hirsutism (baldness in the temporal lobes, hypertrophy of the clitoris).
- Sometimes melanoderma
- The patient may also present AHT, latent diabetes mellitus, osteoporosis, amenorrhea, mental disorders

Etiology:

- Cushing's disease in 3/4 of the cases - corticotropic adenoma (secreting acth)
- Benign or malignant adrenal tumors
- Iatrogenic, produced by corticoids

7. THE HYDROELECTROLYTIC METABOLISM

7.1 Water balance

Water balance is the difference between water inflow and water excretion from the body. Under normal conditions, the body maintains its water balance (water hometasia). The water in the body comes from two main sources: food & liquids (about 2100 ml / day) and metabolic (about 200 ml / day, water formed in the body by oxidation of carbohydrates). The total fluid in the body (60%) is distributed in two compartments: intraceular fluid (40%) and extracellular fluid (20%) - which in turn comprises: interstitial fluid (75%) and blood plasma (25%).

The elimination of water occurs by sweating (100-200 ml/day), urine (1200-1500 ml/day), faeces (100-200 ml/day), perspiration (at the cutaneous level, 350 ml/day) and at the lung level (350 ml/day). The amount of total water in the body varies with age and sex: in newborn children it is 80% but decreases to 65% by the age of 1 year, in young male adults the amount of water is 60%, while in the female sex it is 50%.

The roles of water in the body:

- Solvent for organic and inorganic substances
- Environment for carrying out biosynthesis and biodegradation processes
- Keeps the normal body temperature
- Ensures mechanisms of homeostasis
- Elimination of metabolic by-products and toxins

Disorders of the water balance

Dehydration

Causes:

- hemorrhage, plasmoragia
- osmotic diuresis from diabetes mellitus
- loss of digestive fluids (diarrhea, vomiting, digestive fistulas)
- skin loss (fever, exposure to an overheated environment)

Symptomatology:

- feeling thirsty
- hypotonic eyeballs
- dry skin and mucous membranes

- decrease in skin turgor
- weight loss
- hemodynamic disorders (⬆ TA, ⬆ FC, weak pulse) up to hypovolemic shock

Consequences:

- hemoconcentration
- increased plasmatic osmolality

Hyperhydration

Causes:

- congestive heart failure with an increase in the ingestion of Na^+
- nephropathies with increased retention of Na and water
- liver failure
- corticotherapy, Cushing's syndrome

Symptomatology:

1. weight gain
2. jugular turgidity
3. local edema
4. pulmonary edema (breathlessness)
5. systemic oedema

Consequences:

1. hemodilution
2. decrease in plasmatic osmolality

Pathology – edema

Edemas are isotonic hyperhydrations located in the interstitial space. They are produced by extravasation of fluid from capillaries or lymphatic obstruction, of various causes:

1. Increased capillary pressure
   - excessive renal retention of water and salt (renal failure, excess mineralocorticoids)
   - high venous pressure (heart failure, venous stasis, insufficiency of venous pumps)
2. Decrease in plasma proteins
   - protein loss through urine
   - losses due to lack of skin (burns, wounds)
   - Insufficient protein synthesis (liver disease, intake deficiency)
3. Increased capillary permeability

- immune reactions that cause release of histamine or other immune substances
-Toxins

4. Blockage of lymphatic drainage

Clinical elements:
- enlargement of the region (volume increase)
- erasing the anatomical reliefs
- dimple/pit (when pressed usually on a bone plane)

Description:
1. Localization: general edemas initially appear in certain areas of choice and then generalize
2. Color: inflammatory or allergic edema - red
- renal edema – white
- cardiac and venous edema – cyanotic (ocra dermatitis)

3. Appearance: In the constitution stage: stretched, glossy. Then fine longitudinal folds are formed, and stretch marks appear on the thighs and abdomen. Chronic edema leads to thickening and cardboardization of the skin.
4. Temperature: - increased - inflammatory edema
- normal in renal edema
- low in cardiac edema

5. Consistency: - renal edema - soft fluffy, slightly leave a dimple
- inflammatory edema and venous - tougher, leaves harder or not at all well when pressing
- chronic edema, especially cardiac and venous edemas are accompanied by a fibroblastic proliferation that causes the edema to become cardboard

7.2 Electrolyte balance

Normal values for adults:
Calcium: 4.5 to 5.5 mEq/L
Chloride: 97 - 107 mEq/L
Potassium: 3.5 to 5.3 mEq/L
Magnesium: 1.5 - 2.5 mEq/L
Sodium: 136 - 145 mEq/L

Sodium is the main extracellular cation, with a role in regulating the osmotic activity of the extracellular fluid and regulating the acid-base balance (sodium bicarbonate).
Elimination: renal, gastro-intestinal (losses increase in case of diarrhea, vomiting), transpiration - negligible losses (increased just in the case of physical exertion), cutaneous (increased losses in case of stretched burns).

Dyselectrolythemics:

1. *Hyponatremia*

Occurs when Na^+ <135 mEq/l
Causes:

- By renal loss of Na+
- When increasing the extracellular volume (excessive fluid intake)
- Digestive losses

Manifestations:

- Edema with well
- Cramps, muscle weakness
- Headache,lethargy
- Nausea, vomiting

2. *Hypernatremia*

Occurs when Na^+ > 150 mEq/l
Causes:

- Diabetes insipidus
- Water loss in excess of sodium
- Excessive salt intake
- Insufficient water intake in old people, newborns, comatoses, with an abolite thirst reflex

Manifestations:

- Dry skin, dry mucous membranes
- Headache, agitation
- Decrease in volemia
- Hypotension

Potassium is the main intracellular cation, with a role in regulating the acid-base balance, in the nerve conduction and excitability of skeletal muscles, in the transformation of glucose into glycogen and in the transformation of amino acids into proteins.

Dyselectrolythemics:

1. *Hypokalemia*

Occurs when K^+ <3 mEq/l

Causes:

- Intracellular capture of K^+ : metabolic alkalosis, insulin administration
- Renal loss: increased diuresis (administration of loop diuretics and thiazide), excess of glucocorticoids (Cushing's syndrome), renal tubular diseases, gastrointestinal loss, reduction of food intake

Manifestations:

- Intense feeling of thirst
- Muscle cramps, paralysia
- Nausea, vomiting
- Confusion, depression
- Arrhythmias, orthostatic AHT

2. *Hyperkalemia*

Occurs when K^+ > 5.3 mEq/l

Causes:

- Increased intake of antibiotics that contain K^+ , IECA administration/ sartans
- Release of K^+ from cells: metabolic acidosis, burns, antitumor chemotherapy, insulin deficiency
- Deficient renal elimination: acute/ chronic renal failure, administration of diuretics that save K^+

Manifestations:

- Muscle cramps
- Risk of cardiac arrest
- Diarrhea, intestinal cramps
- Weakness, dizziness

8. THE NERVOUS SYSTEM

8.1 General considerations

A. *The central nervous system (CNS),* also called the nevrax, comprises two segments: *i) the encephalon,* which is located intra-cranially and consists in turn of several portions: the brain (the two cerebral hemispheres and the diencephalon), the brainstem and cerebellum, and *ii) the spinal cord,* which is located intra-spinal and separates the encephalus from the spinal bulb.

B. *Peripheral nervous system (PNS)*, represented by nerves that originate in the nevrax. These nerves are grouped into: *i) cranial nerves* belonging to the brainstem – 12 pairs of nerves that innervate the cephalic extremity and *ii) spinal nerves* belonging to the spinal cord – are destined for the trunk and limbs

The SNP has 2 types of paths:

1. The sensory or afferent pathway: related somatic neurofibers (skin, skeletal muscles and joints) and visceral (viscera). Transport to the CNS of impulses from sensory receptors
2. Motor or efferent pathway: motor neurofibers that transmit to the effector organs (muscles and glands) the inflows coming from the CNS that trigger motor responses.

The motor path can be subdivided into 2 parts:

A. Somatic or voluntary nervous system (SNS): The body's relationship with the environment

B. Autonomic or vegetative nervous system (ANS/VNS): is an involuntary system represented by the ensemble of centers and nerves that control the viscera, glands, blood vessels and the balance of the internal environment (homeostasis). Subdivided into two antagonistic and complementary components:

- *parasympathetic nervous system*
- *sympathetic nervous system*

8.1.1 Functions of the nervous system (NS)

The nervous system ensures the functioning of all the organs necessary for maintaining life, through the different receptors located throughout the body (skin, viscera, muscles) that transmit impulses

through the sensory afferent nerves and through the central conduction pathways – the white substance. The CNS then elaborates an effector response by means of synapses located at the level of the gray substance, a response transmitted at the level of the effectors (muscles, secretory glands) through the motor efferent nerves.

- Reception of stimuli and their transformation into nervous signal
- Conduction of the nervous influx to the brain on the nerve pathway that constitutes the PNS
- Integration of related information to develop a tailored response
- Transmission of the response to the effectors

The NS has three fundamental functions:

Sensory function: through millions of sensory receptors, it receives sensory information on changes that occur both inside and outside the body.

Integrative function: sensory information analysis and determination of action accordingly; integration of messages.

Motor function: response to the integration that activates the effectors (muscles or glands).

8.1.2 Receptors

A receptor is a structure capable of transforming a physical or a chemical stimulus into a nervous message, a process also called transduction. The receptors are disseminated in the body and thus integrated into the sensory devices.

Classification:

By type of sensitivity:

I. Superficial sensitivity receptors (or exteroceptors): are located in the skin and sense organs and are stimulated by changes in the environment. They are formed from cells specialized in the perception of minimal environmental changes and in the transmission of this information to the related nerve pathways.

1. Contact receptors
    - mechanoreceptors of the skin, responsible for the tactile sensation

- skin nociceptors, which are either thermoreceptors (heat/cold) or algoreceptors (pain)
- chemoreceptors, located at the level of the olfactory mucosa (odour) or at the level of the tongue (taste)

2. Telereceptors
   - photoreceptors of the eye, sensitive to light
   - mechanoreceptors of the ear, sensitive to either sounds or balance
   - skin thermoreceptors, sensitive to infrared radiation

II. Deep sensitivity receptors (or proprioceptors):

1. Receptors of the musculoskeletal system:
   - joint receptors: sensitive to movements and to the position of joints
   - muscle receptors: sensitive to movement and to the position of skeletal muscles
2. Baroreceptors: are pressure-sensitive receptors
3. Chemoreceptors: they test the chemical composition of the body's liquids and intervene in the regulation of certain biochemical constants.

8.2 Structural organization – neurons, nerves and nervous influx

The NS is composed of billions of nerve cells (neurons) and support cells (glial cells) that form a complex and rigorously organized network.

The neuron is the structural and functional unit of NS. Neurons are non-reproducing cells with high longevity and curtailed metabolism (they account for 5% of body weight and 20% of energy consumption). Each neuron consists of:

1. A cellular body or soma:
   - contains the cellular nucleus, cytoplasm and classical cellular organelles
   - variable form
   - directional and metabolic center of the neuron
   - ensures the synthesis of a large number of constituents necessary for the structure and functions of the neuron
2. Fine extensions = axon and dendrites

- dendrites: are extensions of irregular shape, numerous and short; is the receiving pole of information
- axon: represents the output pole of the neuron; it has a smooth appearance and uniform diameter along the entire length of the route or origin at the level of the emerging cone located at the base of the somei; has variable length. The axon is wrapped on the outside by an "insulating" shell, Schwann's sheath. Most axons also have a thick outer shell, another sheath, called myelin, a white fatty substance.

Types of neurons:

- *Sensory neurons:* relatively long - captures the messages of sensory receptors and communicates them to the central nervous system
- *Motor neurons*: long - conduct the motor command of the cortex to the spinal cord or from the marrow to the muscles
- *Interneurons*: the most numerous – make the interconnections between the different neurons inside the brain or spinal cord

Nerves

Nerve ← Bundles ← Nerve fibers ← Axon + dendrites

Nerve fibers can be, depending on the presence of myelin sheath, myelin and amelin fibers. The myelin sheath is a good electrical insulator because it prevents parasitizing with nerve messages from other fibers and also allows an effective way of propagating the impulse, by jumping conduction (from ranvier node to node). Most of the nerves of the central nervous system, as well as the nerves of the parasympathetic autonomic nervous system, are formed from white or myelin fibers, with a thick myelin sheath and showing a rapid conduction of the nervous influx. The rest of the nerves of the central nervous system, as well as most of the nerves of the sympathetic autonomic nervous system, are formed from gray or amiline fibers, with a thin myelin sheath and showing a slow conduction of the nervous influx.

After the direction of the nerve influx:

- *Sensory afferent nerves:* circulate the information from the periphery (skin, muscles, joints or organs) to the steering center (spinal cord or brainstem) - centripetal influx.

- *Motor efferent nerves:* circulate the information from the center (nevrax) to the effector organs (muscles and glands) - centrifugal influx.
- *Peripheral nerves:* are often small, sensitive and motor (and also vegetative).

Glial cells

Glia is the supporting tissue, being the medium that neurons need. There are 2 types of glial cells:

1. Glial cells of the central nervous system (central glia) comprising:
   - macroglia (nutritional and blood brain barrier role)
   - oligodendroglia (provides the formation of myelin at the level of the CNS)
   - microglia (role in phagocytosis)
2. Glial cells of the peripheral nervous system (peripheral glia) comprising:
   - Schwann cells (provide the formation of myelin at the snp level).

Synapse

Communication between two neurons is done at the level of the synapse (from Greek sun = with, and aptein = together) or through the junction between the terminal arborisions of the axon of a neuron with the dendrites of the neighboring neuron. It is the synapse that determines the meaning of the nervous influx. The nerve synapse is the junction between two nerve cells: an axon (more rarely a dendritis) belonging to a neuron called presynaptic joins with a dendritis, another axon or the neural body of another neuron, called the postsynaptic. It is the place of information transfer between these two neurons.

Classification (by mode of operation):

1. *Electrical synapse (rarer):* it is an open junction, the communication between the two neurons being performed through channels of a protein nature. These structures are also called "gap-junctions" in English. The signal transmission in this type of synapse is very fast (several microseconds) either in one direction or in both directions (two-way). There is no latency time between the recording of the presynaptic and the postsynaptic current.
2. *Chemical synapse*: consists of:

- Synaptic button: small synaptic vesicles, suspended in the cytoplasm – contain neurotransmitters

- Receiving region – several types of specific receptors. Each type of receptor corresponds to a certain type of neurotransmitter. These receptors are located on the membrane of a dendritis/on the cell body of the postsynaptic neuron. Between the 2 regions there is the synaptic slit, a space filled with interstitial fluid that prevents direct contact between the 2 regions. The transmission of the nervous influx is unidirectional and involves: nervous influx → synaptic button → the vesicles release the neurotransmitters into the synaptic slit → this interactions with specific post-synaptic receptors → nervous influx (post-synaptic). A few seconds after exerting their effect, the neurotransmitters are degraded by enzymes in the synaptic slit, recovered in the synaptic button, or absorbed into the blood.

The reflex act

The fundamental mechanism of nervous system function is the reflex act or reflex. The reflex act represents the response reaction of the nerve centers when a receiving area is stimulated. A reflex arc is a neural chain interposed between the receptor (R) and the effector (E), which passes through a nerve center. The simplest reflex arc presupposes the existence of two neurons: one sensory and one motor. The first (afferent) neuron is located in the spinal or sensory ganglion of the cranial nerve. Through central extensions the afferent neuron connects with the intercalar neuron located in the posterior horns of the gray substance of the spinal cord. The axons of this neuron then connect with the third neuron, the motor (effector). The extensions of this neuron leave the CNS (in the structure of the spinal nerve or cranial nerve), through which they reach the effector.

The anatomical basis of the reflex act is the reflex arch consisting of five components: R, the afferent path, the nerve centers, the efferent path and E.

Neurotransmitters

A neurotransmitter is a chemical released by a neuron at the level of the synapse and that specifically alters the activity of another cell. It is either stored or synthesized at the level of presynaptic endings and released into the synaptic slit in response to the stimulation of a presynaptic element

(calcium-dependent release). The release is carried out in sufficient quantities to induce a response of a postsynaptic element. The neurotransmitter has specific postsynaptic receptors (application of the molecule to the postsynaptic membrane reproduces the effect of the endogenous neurotransmitter) and is specifically inactivated (by reuptake or degradation).

Examples:

1. **Acetylcholine:** the first neurotransmitter discovered is released at the level of synapses of neurons of the peripheral nervous system. These synapses that use Acetylcholine as a neurotransmitter are called cholinergic synapses. Acetylcholine attaches to the receptors present at the surface of the postsynaptic neuron. These receptors are of two main types: nicotinic and muscarinic.
2. **Monoamines:** they are synthesized starting from amino acids, they are represented by:

2.A catecholamines (derived from tyrosine): dopamine, norepinephrine and adrenaline (or norepinephrine, epinephrine) - synthesized by medullaosuprarenal cells and postganglionar neurons of the sympathetic nervous system. Adrenaline acts both as a neurotransmitter in the central nervous system and as a hormone in blood circulation. Norepinephrine is mainly a neuroransmitistor of the peripheral sympathetic nervous system, but it is also found in the blood

2.B Serotonin (or 5-hydroxy-tryptamine, derived from tryptophan) - works by binding to specific receptors located in the membrane of the target cells (serotonin receptors: 5-HT1 to 5-HT7). It intervenes in the regulation of functions such as thermoregulation, eating and sexual behavior, the wake-sleep cycle, pain, anxiety or in motor control.

2.C Histamine (derived from histidine)

3. **Amino acids:**
    - excitatory: glutamic acid, aspartic acid
    - inhibitors: GABA (gamma-amino butyric acid), glycine
4. **Endorphins** (*endogenous morphines*) are opioid-like molecules.

Nervous influx

Like all excitable cells, the nerve fiber is characterized by a resting potential (-70mV) due to the difference in electrical charges present on the outside of the axonal membrane (positively charged), and the inside of the

fiber (negatively charged). This difference in electrical charge is due to the difference in ionic composition between extra and intracellular liquid media.

Communication of the nervous influx implies the existence of a transient variation of the membrane potential, triggered by a stimulation. It propagates at the level of the axon. Neurons do not have the same triggering threshold. The action potential propagates only in one direction and does not decrease in intensity with the increase in distance.
The potential for action involves several stages:

1. Depolarization

The opening of the Na^+ channels decreases the membrane potential and the permeability of the membrane for sodium increases. The inside of the membrane is less negative and the membrane potential is approaching zero.

2. Repolarization

It occurs at the same level where the initial depolarization took place. The K^+ channels open, initially closed. The output of the potassium ions restores the distribution of the electric charge. The outside of the membrane becomes positive again.

3. Hyperpolarization

It occurs while the increased membrane potential becomes more negative than your resting potential.

The nerve influx or action potential is an inversion wave of polarity at each successive point of the fiber. The current will propagate from point to point to the end of the axon at a slow speed of 0.1-2 m/s. This polarity inversion (or depolarization) allows sodium to enter the cell quickly while the inside of the cell becomes positive and the outside negative. Between the excited point on the surface of the cell (i.e. negatively charged) and the point located just before it, not yet excitated (and therefore positively charged) a very localized current appears. This current will induce inversion of cellular permeability at the level of the point located just before. Thus, the current will propagate from point to point to point to the end of the axon. Immediately after the passage of the action potential, the output of sodium occurs through the intervention of the sodium cell pump, with the return of the polarity to the normal resting value, the repolarization being always slightly slower than the depolarization or inversion of the polarity.

8.3 Structural organization - Central nervous system (CNS)

CNS protection is carried out by:

1. **Meninges**
   - *Dura mater*: in Latin, dura mater means "hard mother." Dura mater is the outer, thick, solid meninges layer located directly under your skull and vertebral column. Dura mater contains a drainage system, called the venous sinuses
   - *Arachnoid*: located between the two. It doesn't contain blood vessels or nerves. It consists of two sheets:
   - parietal foita: adherent to the dura mater
   - visceral foita: in contact with pia mater
   - *Pia mater:* in close contact with the nervous system. It is the innermost layer and is a thin layer.
2. **Cerebrospinal fluid (CSF):**
   - produced by the choroid plexuses → fills the ventricles →flowing into the subarachnoid space through the spaces at the level of the 4th ventricle → umple the subarachnoid space where it forms a pillow of fluid; it is reabsorbed by blood at the level of the meninges
   - role of mechanical protection of the encephalon and spinal cord.
   - composition - similar to that of plasma, but contains only 0.5g carbohydrates/l and contains no cells at all.
3. **Blood-brain barrier:** represented by the existence of tight, almost airtight, junctions between endothelial cells of the capillaries of the encephalon. The tight junction forms a barrier with selective permeability and allows only certain substances as well as glucose, alcohol, some drugs and drugs to pass into the CSF.

The central nervous system/ nevrax consists of two main components:

1. Encephalon (brain)

- telencephalon (cerebral hemispheres)
- diencephalon
- cerebellum
- brainstem

2. Spinal cord

3.3.1 Encephalon (brain)

The encephalon is formed by the ensemble of nerve formations contained in the skull. It is the place of superior psychic faculties, self-awareness, voluntary actions, memory, reflection and various psychological states. The brain contains a number of neurons rated at about 10 billion.

Telencephalon - Cerebral Hemispheres

The telencephalon is the most voluminous part of the encephalon. It consists of two cerebral hemispheres (right and left) that are separated by the longitudinal fissure of the brain. In the middle portion the right and left hemispheres are joined by a portion of white matter, called the corpus callosum.

On the outside, the two cerebral hemispheres have a creased appearance, presenting three more accentuated grooves, called sulcus. The sulcus divide each hemisphere into four lobes (frontal, temporal, parietal, occipital), each containing a number of circumvolutions.

1. *Frontal lobe:* reasoning, planning, modulation of emotions, implications in personality, initiation of voluntary movements (posterior part), transformation of ideas into words.
1. *Parietal lobe:* sensory perception (taste, touch, temperature, pain), integration of auditory and visual signals in relation to memories, understanding written and spoken language.
2. *Temporal lobe:* the tonality of sounds, understanding the meaning of words (the upper part), the formation and remembrance of memories, visual and verbal memory (left temporal).
3. *Occipital lobe:* decoding of visual information (shape, color, movement).

On the inside, the cerebral hemispheres are organized into the brain substance (*with the gray substance and the white substance*) and the *ventricular system*.

A. *The gray substance* consists of: the cerebral crust (cerebral cortex) and the deep nuclei (central nuclei: the striated nucleus/body, the claustrum nucleus and the amygdala). Clinically, within the central nuclei, along with the striated nucleus, the following are associated: (i) the diencephalon (subtalamic nucleus) and (ii) the midbrain (the black substance).

B. *The white substance* is arranged in the center. It is made up of ascending pathways and descending pathways that connect the brain with the lower regions of the body: the brainstem, the cerebellum, the spinal cord. There are also association pathways, which connect the various parts of the cortex, as well as commissural pathways.
C. *Ventricular system:* is made up of four ventricles: two lateral ventricles, located at the level of the hemispheres, which stretch from the frontal to the occipital lobe; the 3rd ventricle, which is found at the level of the diencephalon and which communicates through the aqueduct of Sylvius with the 4th ventricle, located at the level of the brainstem.

Diencephalon

The diencephalon surrounds the IIIrd ventricle, being located in the continuation and above the midbrain, under the corpus callosum. It is covered on both sides by the cerebral hemispheres. The gray substance forms the nuclei of the vegetative nervous system, and through the white substance pass all the ascending and descending conductive pathways. In the structure of the diencephalon we distinguish: hypothalamus, thalamus, epithalamus, metathalamus and epiphysis.

Hypothalamus – role: control of all vegetative organs through the ANS. The ANS has a role in adjusting: emotions, temperature, appetite, thirst and control of the hormonal system (by controlling the pituitary).

The thalamus is the main subcortical center of integration of the general sensitivity: tactile, deep sensations, pain and temperature, as well as visual and olfactory functions. It thus constitutes an important center of motor skills, controlling especially the affective tonality that is expressed through gestures and mimicry.

Epiphysis: is a small, conical endocrine gland attached to the posterior part of the 3rd ventricle. It is responsible for the production of melatonin (derived from serotonin) with a central role in regulating the biological rhythm.

Cerebellum

The cerebellum is located in the posterior fossa of the skull, posteriorly from the brainstem. It consists of three lobes covered by parallel creases: a thin median lobe (vermis) and two larger lateral lobes (cerebellar hemispheres). The vermis is separated from the cerebellar hemispheres by the paramedian ditch. The cerebellum is connected to the brainstem by means of three pairs of peduncles.

The cerebellum is the main center for coordinating movements. In this regard, it receives information from the organs of balance located at the level of the inner ear, as well as tactile and proprioceptive sensations. The cerebellum maintains muscle tone, thus keeping the muscles ready for action. He ensures the balance of the body in a purely reflex way, especially during orthostatism. It also coordinates voluntary or semi-voluntary movements such as walking, catching objects, etc., therefore disorders of the cerebellum function are manifested by incoherent and disordered gestures.

Brainstem

The brainstem is the portion of the nevrax between the spinal cord and the brain. It consists of three floors that are, from top to bottom: the midbrain, the deck of Varolio (protuberance) and the spinal bulb.

The spinal bulb (medulla oblongata), stretches from the spinal cord to the bridge. It controls the autonomous functions of the body and transmits information from the brain, via the spinal cord. Its structure is similar to that of the spinal cord, with the gray substance located in the middle and the white substance on the outside. The spinal bulb is the center of homeostasis, intervening in:

- transmission of information between the brain and the spinal cord;
- control of reflex functions of the air and digestive tract: coughing, sneezing, mastication, salivation and swallowing;
- control of autonomic functions - regulation of respiratory and heart rhythm, as well as blood pressure by contraction of vessels.

Most of the brainstem is occupied by the cross-linked formation that stretches from the spinal bulb to the base of the 3rd ventricle. The cross-linked formation is a nervous structure of the brainstem, located at the interface of the autonomous, motor and sensory systems. It intervenes in the regulation of vital functions (such as the wakefulness-sleep cycle), in the control of reflex or stereotypical motor activities, such as walking or postural tone, and in cognitive functions such as attention. Due to its central role in regulating alertness, the lesions of the cross-linked formation often determine the state of coma.

3.3.2 Spinal cord

External configuration

The spinal cord is the portion of the central nervous system that occupies the spinal canal. It is faithful to the curvatures of the spine along its entire length and is surrounded by the meninges. The marrow is a white cord, about 45 cm long with an average diameter of 1-1.2 cm.

The spinal cord is located in the vertebral canal, and its upper limit is at the level of the occipito-atlantis joint and ends sharply at the level of the second lumbar vertebra where it branches into numerous nerves called "ponytail"- terminal filum.

From the right of each space located between the vertebrae, a pair of nerves is detached, at the level of the right and left portion of the marrow (spinal nerves, 31 pairs). The two nerves, originating on each side, join into a single spinal nerve that opens through the conjugation holes and then divides into an anterior motor branch and a posterior sensory branch.

Internal configuration

The cross-section through the spinal cord indicates the presence of the gray substance inside, placed specifically in the shape of a "butterfly" and surrounded on the outside by white substance.

The gray substance has three portions: the anterior horns, the hind horns and an intermediate bridge, the gray commissure (or the lateral horns).

At the center of the gray substance is the ependimar canal, very tight and which follows in the extension of the 4th ventricle.

The white substance consists of myelinated fibers, distributed in several parallel bundles, grouped in six cords: two anterior, two posterior and two lateral.

Functions:

1. *Binder between the brain and all organs related to the spinal nerves*

The spinal cord continues at the level of the brain through the spinal bulb, thus communicating with different nerve centers of the brain. It conducts nerve inflows originating from the posterior roots. The portions of the marrow that achieve this sensory communication are the ascending pathways because they go up to the brain. The ascending pathways start at the level of the sensitive endings of the skin and the muscles, penetrate into the marrow and then ascend to the brain. The direct ascending pathways

cross at the level of the bulb, and from here they reach the level of the cerebral cortex. The indirect or cerebellar ascending paths first reach the level of the cerebellum, which is the coordination center of movements. They then move towards the cerebral hemispheres on the opposite side. The descending pathways transmit the motor influx that the brain sends to the body.

2. *Integration of certain functions: simple reflexes*

The reflex represents the simplest nervous activity. It is a quick and involuntary response to an excitation (e.g., when the hand touches an object that is too hot). The reflex presupposes the presence of a sensory excitation reached to the marrow through the posterior root of a spinal nerve. This influx is transmitted, in the marrow, to one or more motor neurons that transmit inflows to the muscles through the anterior roots.

8.4 Structural organisation – Peripheral nervous system (PNS)

Peripheral nervous system (PNS), represented by nerves that originate in the nevrax. These nerves are grouped into:

1. spinal nerves belonging to the spinal cord – are intended for the trunk and limbs.
2. cranial nerves belonging to the brainstem – 12 pairs of nerves that innervate the cephalic extremity;

Spinal nerves:

Each spinal nerve is formed from the union of a dorsal root with a ventral root. The spinal nerves are formed at the level of the spinal canal. They are divided into 31 pairs:

- eight cervicals
- twelve dorsals
- five lumbar
- five sacrats
- a coccygeal one

Cranial nerves:

The cranial nerves, after leaving the brain, cross all the holes in the bony walls of the skull. They are arranged bilaterally and symmetrically, forming 12 pairs (numbered from I to XII). They especially innervate the head and neck, but not only.

I - the olfactory nerve: its endings leave from the upper part of the nasal cavities and reach the level of the olfactory bulb where it communicates with the olfactory area.
II – optic nerve: it starts through the ganglion cells of the retina and partially crosses at the level of the optic chiasma, before the pituitary.
III – the oculomotor nerve: controls the motor muscles of the eyeball.
IV – trochlear nerve: innervates the lifting muscle of the eyelid.
V – trigeminal nerve: collects information from the eye, nose and forehead; innervates the teeth, gums and lip of the upper and lower jaw.
VI – the abduces nerve: determines the rotation of the eye outwards.
VII – facial nerve: innervates the sublingual and sub-maxillary salivary glands and the lacrimal glands
VIII – the auditory nerve: the cochlear branch that collects the acoustic sensations and the vestibular branch for balance
IX – glosso-pharyngeal nerve: collects sensations from the posterior portion of the tongue and from the pharynx; controls the movements of the pharynx and secretion of the parotids.
X – the vagus nerve: through the parasympathetic fibers, it acts on the heart, on the digestive secretions and on various other organs
XI – accessory nerve: innervates the muscles of the pharynx, shoulder and arm.
XII – hypoglossal nerve: command the movements of the tongue.

The SNP has 2 types of paths:

The sensory or afferent pathway consists of somatically afferent neurofibers (skin, skeletal muscles and joints) and visceral (viscera). It carries impulses from sensory receptors to the CNS.

The motor or efferent pathway is formed by motor neurofibers that transmit to the effector organs (muscles and glands) the inflows coming from the CNS that trigger motor responses. The motor pathway can be subdivided into 2 parts: the somatic or voluntary nervous system (SNS) and the autonomic or vegetative nervous system (ANS/VNS). The somatic nervous system only innervates the striated muscles and causes contraction.

Vegetative nervous system (VNS)

The vegetative nervous system (VNS) regulates and coordinates the function of internal organs, adapts it to the needs of the moment and controls the vegetative functions of the organism. Because the function of the vegetative nervous system is independent of the will, it is also called autonomous NS (ANS). Most organs also have an intrinsic or intraparietal nervous system, which controls their motor or secretory activity, as well as an extrinsic nervous system, which can modulate this characteristic activity of the organ through stimulation or inhibition.

At the periphery, the VNS is anatomically and functionally separated from the peripheral NS, having its own centers, its own motor pathways that reach up to the muscles or glands; on the contrary, there are close links between the two systems at the central SN level. VNS is distinguished from the CNS by the route of its motor fibers. At the CNS level, the motor fibers leave the marrow and move directly towards the muscles without another ganglion relay. On the contrary, the motor fibers of the VNS, after leaving the marrow, always stop at the level of a ganglion where they perform synapses; preganglionary fibers and postganglionary fibers are thus distinguished. The sensory fibers of VNS follow the same path as the sensory cerebro-spinal fibers.

The VNS actually comprises two more or less antagonistic systems of action:

1) The sympathetic (orthosympathic) system whose terminal fibers contain the neuromediator norepinephrine. Its nerve centers are found in the thoracic portion of the spinal cord and in the ganglia of the sympathetic chain. It is a system that puts the body on alert with the predominance of relationship functions. Neurotransmitter: norepinephrine. Active in case of emergency.

Norepinephrine is synthesized from L-Tyrosine, stored in the presynaptic vesicles and released when the action potential reaches the synapse. The action of NA ceases as a result of reuptake of NA in presynaptic endings and as a result of degradation by COMT (catecol-o-methyl transferase) and MAO (mono-amino oxidase).

Sympathetic /adrenergic receptors are divided into two types: **alpha** (*α: 1 and 2*) and **beta** (β: *1, 2 and 3*), as follows:

- **adrenergic α receptors are of two types:**
  - *α1 receptors* that predominate in smooth muscles; their stimulation determines the vasoconstriction and constriction of the bronchioles, uterus, sphincters of the urinary and digestive tract;
  - *α2 receptors* are found in mast cells (degranulation), platelets (aggregation), pancreas (insulin release).
- **adrenergic β receptors are of three types:**
  - *β1 receptors* located in the heart, kidneys, digestive tract; Their stimulation is responsible for the inotropic cardiac effects, chronotropic and dromotrope positive, the release of renin;
  - *β2 receptors* located in blood vessels, bronchi, uterus, gastrointestinal and urinary tract, adipose tissue; Their stimulation induces vasodilation, bronchodilation, relaxation of the sphincters and glycogenolysis (liver)
  - *β3 receptors* located in the adipose tissue; stimulation leads to increased lipolysis in adipocytes.

2) The parasympathetic system uses acetylcholine as a neuromediator. Its centers are found in the brainstem and in the sacral portion of the spinal cord. It puts the body at rest and favors vegetative functions. Neurotransmitter: acetylcholine $\Longrightarrow$ Active at rest.

Acetylcholine is synthesized in the nerve endings from the precursors choline and acetyl-CoA, stored in the presynaptic vesicles and released into the synaptic slit after the arrival of the action potential. The effect of acetylcholine stops at the time of its cleavage through the action of acetylcholinesterases.

Parasympathetic/cholinergic receptors are divided into two types: nicotinic receptors (present at the level of postsynaptic ganglion cells and medulla), are stimulated by acetylcholine and nicotine, and muscarinic receptors present in the target organs at the level of cholinergic fibers, are stimulated by muscarin (but also by acetylcholine).

8.5 Pathophysiology of the nervous system

8.5.1 Pain

Pain is a disagreeable sensory and emotional experience due to real or potential tissue damage. There are mediators that sensitize nociceptors (painful sensitivity receptors) directly or indict. Tissue lesions and inflammation cause the production of a sea of pain mediators (algogene substances). Among these we mention: substance P (it is found in the receptor neurons of the spinal ganglia), bradykinin, histamine, serotonin, K^+, H^+, prostaglandins.

Depending on the duration of evolution, the pain can be: acute pain, "wake-up call", or chronic pain, "disease pain".

Acute pain

Pain that lasts < 6 months, with sudden, recent appearance.

It is well located and always associated with a primary injury that can be: an acute disease, an acute trauma, surgery, a therapeutic maneuver, etc.

The clinical picture in acute pain is dominated by the sympathocton vegetative reaction ("fight or flight"): tachycardia, hypertension, mydriasis, sweating, etc. The affective-emotional reaction is intense: anxiety and agitation. Acute pain disappears with the removal of the primary lesion and responds well to common analgesics.

Chronic pain

Pain that lasts > 6 months, with continuous or intermittent appearance, and which is becoming more and more weakly localized. It can also exist in the absence of the primary lesion that sometimes can no longer be identified. The clinical picture is dominated by emotional affective reaction characterized by depression, irritability, sleep and behavioral disorders, while the vegetative reaction is usually absent. The evolution of pain is variable (it may increase or diminish). The level of substance P is very high (especially in cancer patients), and the titer of endorphins is low. Thus, chronic pain responds well to treatment with tricyclic antidepressants and anticonvulsants.

Antalgic therapy

Preventing the formation of the nervous influx, in the sensory endings is achieved by the administration of: local anaesthetics,

myorelaxants, antispasmodics, antianginal or anti-inflammatory. Preventing the transmission of nervous influx through the sensory fibers is carried out by taking local anaesthetics. The prevention of the perception of pain, at the level of the integration centers is carried out either non-selectively, by the administration of general anaesthetics, or selectively, by taking analgesic-antipyretics (which influence the perception of pain) or analgesic-morphineomimetics (which influence perception and reaction to pain).

The World Health Organization (WHO) has defined a hierarchical scale of use of analgesics on three successive levels, as follows:

1. Level 1: Non-opioid analgesics: do not cause physical or mental dependence and do not induce respiratory depression. These are:

- antipyretic analgesics: paracetamol, metamizole sodium
- non-steroidal anti-inflammatory drugs (NSAIDs):

❖ **Classic:**

- *salicylic acid derivatives:* acetylsalicylic acid, diflunisal,
- *acetic acid derivatives:* diclofenac,indomethacin, sulindac
- *propionic acid derivatives:* ibuprofen, naproxen, ketoprofen
- *oxicami:* piroxicam, tenoxicam

❖ **COX-2 selective:**

- meloxicam, nimesulide, colecoxib, etorcoxib

2. Level 2: they can be associated with step 1 drugs

- pethidine
- tramadol
- codeine

3. Level 3:

- morphine
- pentazocine
- buprenorphine
- methadone
- dihydrocodein
- oxycodone

8.5.2 Parkinson's disease

Parkinson's disease is a disease characterized by a degeneration of dopaminergic neurons in the substantia nigra responsible for the degradation of movements.

Causes:

- hereditary predisposition
- trauma (in boxers)
- inflammation (encephalitis)
- atherosclerosis

Pathophysiology:

Parkinson's disorders are caused by the degeneration/death of dopaminergic neurons, mainly by apoptosis, in the substantia nigra, degeneration of the nigrostriatal bundle and decreased dopamine levels in the corpus striatum (caudate nucleus and putamen). The significant reduction of dopaminergic influx at the level of striated considerably disrupts the voluntary motor activity. Thus, patients move with difficulty with a rigid posture, movements that require a lot of effort. A regular tremor occurs in the hands. The muscle tone of the face is sometimes reduced, which gives the typical appearance of stereotypical expression.

The major clinical signs of Parkinson's disease are:

- Tremor at rest with a frequency of 4-7 cycles/s
- Hypokinesia
- Bradykinesia
- Muscular ridicity
- Posture in flexion and walking with small steps

Other signs:

- sleep disorders
- difficulties in swallowing
- drooling
- micrography (written small, unreadable)
- hypophony (diminished, monotonous voice) and difficulty articulating words
- urinary incontinence and constipation, due to alteration in bowel and bladder function
- confusion, memory loss

- loss of swinging of the arms while walking
- orthostatic hypotension
- personality disorders

Therapeutic principles:

1. Antiparkinsonian anticholinergics: trihexyphenidyl, orphenadine, biperiden, procycline
2. Antiparkinsonian antiglutamatergics, NMDA antagonists rec. : amantadine, memantadine
3. Antiparkinsonian drugs that stimulate dopaminergic transmission:
   - Antiparkinsonian drugs that influence dopamine metabolism: increase biosynthesis (levodopa); stimulate dopamine release (amantadine); inhibitors of dopamine catabolism (selegiline, tolcapone, entacapone)
   - Antiparkinsonian agonists of dopamine D2 receptor: lisuride, pergolide, bromocriptine, ropinirole, pramipexole

8.5.3 Alzheimer's disease

It is a chronic neurodegenerative disease involving acquired impairment of cognitive function, which progressively leads to impairment of social, family and occupational activities and loss of autonomy.

The Alzheimer's Association has identified 10 warning signs of Alzheimer's disease. These are*:*

- memory loss, forgetting recently stored information
- language disorders, forgetting words or substituting unusual words
- temporo-spatial disorientation
- judgment disorders
- problems with abstract thinking, such as the impossibility of interpreting numbers
- putting certain objects in unusual places
- mood disorders, as rapid changes in their mood: from calm to crying, and then to anger seemingly for no reason
- changes in personality, from confusion, suspicion, fear, addiction
- lack of initiative manifested by continuous drowsiness

Non-cognitive symptoms:

- Agitation and physical or verbal aggression
- Psychotic disorders: hallucinations, usually visual, delusional ideas (of persecution, jealousy, abandonment, etc.).
- Disorders of eating behavior: reduction or exaggerated increase in appetite, unkempt nutrition, ingestion of non-food substances.
- Sexual disinhibition: comments on sexual topics, obscene gestures, less often sexual aggression.
- Urinary and faecal incontinence, meeting physiological needs in inappropriate places or in the presence of other people.

Morphological changes in the brain:

On macroscopic examination (by CT and MRI) of the brain, a sharp reduction in the cerebral volume prevalent in the frontal, parietal and temporal region is observed (due to atrophy of the cerebral crust). At the histopathological examination by using staining techniques with argentic impregnation, the presence of the following characteristic lesions is observed:

1. Senile plates:

They occur due to the accumulation at the level of presynaptic nerve endings of beta-amyloid (Aβ) that form insoluble plaques that will cause disruption of the transmission of the nervous influx.

2. Neurofibrillary degeneration:

Inside neurons, fascicles are accumulated, consisting mainly of the tau protein (which normally enters the composition of the microtubules and have a role in the feeding of the neuron) = > abnormal tau protein with consequent damage to the structure of the microtubules and the abnormal functioning of the neuron.

3. Granulo-vacuolar degeneration

In the cytoplasm of neurons, located especially in the hippocampus, vacuoles will appear that contain granules of as yet unknown nature and affect neuronal functioning.

All these changes that have occurred progressively cause the death of neurons, especially those in areas intended for cognitive functions: the frontal cerebral crust, the hippocampus and the basal nucleus.

Therapeutic principles:

1. Anticholinesterases: donepezil, rivastigmine, galantamine
2. NMDA (N-methyl-D-aspartate) receptor antagonists: memantine (blocks the effects of pathologically increased concentrations of glutamate the main excitatory neurotransmitter)
   They slow down evolution without stopping it.

8.5.4 Epilepsy

It is a convulsive disorder produced by an abnormal, irregular electrical discharge (electrical hyperactvity) at the level of the gray substance, discharge that temporarily interrupts the normal functioning of the brain. This exaggeration of electrical activity can interest the whole brain or only part of it and manifests itself in the form of more or less violent seizures, associated or not with the loss of consciousness.

Seizures are classified into:

I. *Generalized seizures:* aberrant elecric discharge involves the entire cortex of both hemispheres.
   1. The grand mal crisis (the great evil): the patients lose consciousness, the body suddenly becomes tense (the tonic phase) then the patient presents violent contradictions (the clonic phase). It ends in a period of confusion and sleep lasting up to several hours.
   2. The petit mal crisis (the little bad) corresponds to an abnormal electrical activity of short duration (5-15 sec) with the repetition of this period several times during the day. The patient loses consciousness of the environment in which he is located (period of absence) and does not remember the events unfolding during the crisis. There are no specific muscle contractions, the patient simply stops all his motor activities and has a lost look.

II. *Partial/focal seizures:* are the result of structural abnormalities and can be generalized. It is not associated with loss of consciousness. The nature of the symptoms of the crisis depends on the cerebral

focus involved. For example, motor focal seizures are manifested by repetitive movements, time seizures cause strange sensory impressions.

Causes:

The causes of this abnormal electrical activity are very varied: brain trauma, poisoning, metabolic abnormalities (symptomatic epilepsy). There are also forms of epilepsy that occur in the absence of brain damage, idiopathic epilepsy. Within this last group, etiopathogenic factors are genetic in nature.

Pathophysiology:

The seizures consist in the synchronized excitation of vast groups of neurons that constitute epileptic foci. Genetic mutations have been discovered that encode voltage-dependent sodium channels and encode GABA receptors. As for the Na^+ channels (responsible for triggering and propagating the action potential) mutations lead to a prolonged entry of Na^+ into the neuron. The consequence is the increase in the frequency of neuronal discharge and thus hyperexcitation. As for the GABA receptor, the main inhibitory neurotransmitter of the brain, mutations produce a significant decrease in the hyperpolarizing current of Cl^- and thus a decrease in the inhibitory action of GABA.

These two forms of mutations lead to the appearance of a group of hyperactive neurons that constitute the epileptic focus from which will start strong and abnormal stimuli that discharge impulses propagated over greater or lesser distances from the brain. This results in partial or generalized epileptic seizures.

It has been found that at the cellular level, the first seizures destroy some of the gabaergic neurons by overstimulation, neurons that regulate telencephalic neurons. This destruction triggers a process of physiological compensation aimed at restoring the lost synapses, the so-called process of budding the neighboring neurons with the injured neurons. Thus, after the crisis, the synapses made by inhibitory GABAergic neurons are lost and replaced by excitatory synapses. After that, from crisis to crisis, the overstimulated neurons will necrosis, increasing the area of stretching of neuronal lesions, potentially causing permanent functional deficits: the repetition of seizures leads to brain damage.

Therapeutic principles:

According to pharmacodynamic and pharmacotherapeutic criteria:

- Tonic-clonic or convulsive seizures: phenobarbital, valproic acid, phenytoin, lamotrigine, topiramate, carbamazepine
- Absence seizures: ethosuximide, valproic acid, lamotrigine, acetazolamide
- Myoclonic seizures: valproic acid, clonazepam, lamotrigine, topiramate
- Partial epilepsy: all antiepileptics useful in grand mal seizures + antiepileptics: lamotrigine, gabapentin, vigabatrin, tiagabin, topiramate, zonisamide, levetiracetam
- Broad spectrum: phenacemide

9. THE CARBOHYDRATE, LIPIDIC AND PROTEIC METABOLSIM

9.1 Carbohydrate metabolism

Glucose is an organic compound with six carbon atoms (one of which is a carbonyl group) that belongs to the aldohexose class. Glucose is a source of energy: by the reactions of the citric acid cycle, it is oxidised to form CO2 and H2O, also resulting in energy, mainly in the form of ATP. Also, glucose has a precursor role being essential in the production of proteins and in the metabolism of lipids.

As a result of digestion processes, part of the carbohydrates are converted into glucose. The level of glucose in the blood directly influences the production of insulin from the pancreas. Insulin stimulates the capture of glucose by cells and its transformation into glycogen in the liver. Blood sugar is the concentration of glucose in the blood and has the following normal values: 70-100 mg/dl (a fasting) and below 140 mg/dl (1 hour postprandial). Blood glucose regulation is done through substances, anabolic hormones that lower blood sugar – insulin or catabolics that lower blood sugar – glucagon, cortisol, catecholamines.

The pancreas is a parenchymal organ located on the left side of the abdominal cavity, under the stomach, made up of: head, body and tail. Its head is surrounded by the duodenum, the tail reaches the spleen. It is a mixed digestive gland, having an endocrine and exocrine role:

Endocrine pancreas : it consists of the islets of Langerhans that are spread in the exocrine parenchyma. Langerhans islets show β cells - insulin secretants and α cells - secreting glucagon.

The exocrine pancreas represents the rest of the parenchyma and is made up of pancreatic acini of spherical shape. In the structure of the acini there are sero-zymogenic cells (containing zymogen granules) that provide intermittent secretion of pancreatic juice containing digestive enzymes.

Insulin is the main hormone of the postprandial period (after eating), its release being induced by hyperglycemia.

It has a metabolic action on the three metabolisms: carbohydrate, lipid and protein, which translates into the formation of energy reserves, being therefore an anabolic hormone.

Insulin - actions:

Carbohydrate metabolism:

- Increases the speed of transport of glucose
- Increases glucose consumption at the cellular level (oxidation): increases glycolysis
- Increases glucose reserves in the liver and muscles in the form of glycogen: increases glycogenogenesis
- Inhibits neoglucogenesis (glucose synthesis from protidic and lipid precursors)

Lipid metabolism:

- Blocks lipolysis in adipose tissue (inhibits enzymes that catalyze triglyceride degradation)
- Increases lipogenesis in adipose tissue and also in the liver, where in addition, accelerates the synthesis of triglycerides and lipoproteins, as well as the release of VLDL

Protein metabolism:

- Increases the assimilation of amino acids by forcing cells to absorb them from the bloodstream
- Stimulates protein synthesis
- Decreases proteolysis in muscle, liver and adipose tissue

Antagonistic hormones are catabolizing hormones, which have a metabolic action opposite to insulin. They are represented by: glucagon, somatotropin (STH / growth hormone), adrenaline, glucocorticoids (cortisol) and thyroid hormones.

Pathophysiology – Diabetes mellitus

Diabetes mellitus occurs due to an absolute or relative deficiency in insulin, which leads, among other things, to an increase in the plasma concentration of glucose. The diagnosis is made on the basis of blood glucose, when fasting blood sugar > 126 mg%, or at any time of the day > 200 mg%.

Classification:

I. Primary diabetes mellitus: two types 1, 2

II. Secondary diabetes mellitus

Diabetes can occur secondary to other conditions, such as:

1. Severe chronic pancreatitis
2. Increased secretion of antagonistic hormones, which generate diseases associated with diabetes:
    1. somatotropin – hypersecretion induces acromegaly/gigantism – in adults/young people,
    2. glucocorticoids – hyperfunction of the adrenal cortex or Cushing's disease (steroid diabetes).
    3. adrenaline – tumor of the adrenal medulla (pheochromocytoma).
3. Diabetes-induced drugs: thiazide diuretics and steroids.

III. Gestational diabetes (transient diabetes mellitus, which occurs in the third trimester of pregnancy; after childbirth may disappear, may turn into a decrease in glucose tolerance, or into diabetes mellitus).

Type I diabetes mellitus (DM)

It is also called juvenile diabetes because the onset of the disease occurs under 20 years of age. The patient has a normal weight. Type I diabetes mellitus is characterized by an absolute deficiency of insulin, the patients being dependent on an exogenous intake of insulin.

At the origin of this type of diabetes is the damage to the cells of pancreatic β generally caused by an auto-immune disease (triggered by chance by a viral infection). Anti-insular cell antibodies appear that cause damage to beta cells and thus produce a severe deficiency in insulin production.

Type II diabetes mellitus (DM)

The onset of type II DM is usually after the age of 30, but it is diagnosed more and more frequently in adolescents. The patient shows obesity. Type II diabetes mellitus is determined by a relative deficiency of insulin, patients not being obliged to receive exogenous insulin; treatment consists of dietary regimen, physical activity, and, where appropriate, administration of oral hypoglycemic agents. However, insulin secretion may be normal or even increased (at the beginning of the disease), but the target organs have a diminished sensitivity vis-à-vis insulin, a phenomenon called insulin resistance, which considerably decreases the transport of glucose to the target cells.

Genetic predisposition plays an important role in the occurrence of this disease, anti-cell antibodies do not appear β.

Symptoms:

Insulin insufficiency has the following effects (opposite to those caused by normal, physiological insulin secretion):

- blocking the use of glucose (glycolysis) of the body (because carbohydrate metabolism is insulin-dependent).
- this impossibility of using the available glucose causes an increase in its concentration in the blood – hyperglycemia;
- hyperglycemia leads to the excretion of glucose in the urine – glycosuria (occurs when blood sugar exceeds the renal threshold of elimination of glucose – 180mg%);
- glycosuria causes by osmotic mechanism increased elimination of water – polyuria, which causes polydipsia.

The last 2 symptoms + polyphagia (increased appetite appeared to compensate for the decrease in glucose use as a source of energy) = the classical symptomatic triad of DM.

Other symptoms include:

- fatigue
- frequent urination
- sudden weight loss (initially)
- slow wound healing
- paraesthesia

Complications:

Acute:

1. Metabolic: hyperglycaemic coma (ketoacidosis - main acute complication of type I DM and hyperosmolar - main acute complication of type II DM) and hypoglycaemic coma
2. Infectious complications

Chronic:

1. Microangiopathy: diabetic glomerulopathy (the first cause of chronic renal failure) and diabetic retinopathy (damage to the blood vessels in the retina at risk of blindness)

2. Macroangiopathy:
   - Atherosclerosis - DM accelerates the formation of atheroma plaques (deposition of cholesterol in the arterial walls) which will cause the calibre of the arteries (atherosclerosis) to decrease, an increased risk of acute myocardial infarction or brain.
   - Diabetic neuropathy: disrupts the conduction of the nervous influx: with bilateral and symmetrical touch of the lower limbs. Nerve fibers are affected, which leads to paresthesia (tingling) and even to loss of sensitivity in the extremities (hands, fingers, calves, feet). Neuropathy associated with a deficiency of blood circulation in the calves favors the development of ulcers in the foot (diabetic foot). If the ulcers are poorly treated, the complications are extremely serious: gangrene and amputation.
3. Infectious complications: patients with diabetes have an increased sensitivity to infections, especially bacterial and mycotic, the consequences of which may be skin infections (folliculitis, boils) and candidiasis (genital and / or digestive).

Therapeutic principles:

Treatment consists in the control of blood glucose levels and ensuring a balance between the type and amount of food ingested and the limited amount of insulin available.

Insulin is injected subcutaneously because in the case of oral administration, digestive enzymes prevent the absorption of insulin in the digestive tract. The purpose of administration is to stimulate as well as possible the physiological secretion of insulin and to achieve a massive diffusion of it at rest, as well as postprandial. Fast-acting, intermediate insulins, retard insulins (slow and ultralent) are distinguished, as well as biphasic insulins, which allow a mixed action: initially rapid, then slow.

These types of insulin induce physiological blood glucose in diabetic patients, being preserved a relative comfort of life. Insulin is also indicated in gestational diabetes (because oral hypoglycemic agents cannot be administered – risk of malformations in the fetus), as well as in type II diabetes, during episodes of decompensation and complications.

Patients with type II diabetes mellitus are treated with oral hypoglycemic agents (after establishing an appropriate diet) and in certain situations, even with insulin. Oral antidiabetic medication includes:

1. *Biguanides:* the main representative is *metformin*. These drugs favor the action of insulin in the body. They decrease the production of glucose in the liver and delay its absorption in the intestine.
2. *Hypoglycaemic sulfonamides*: glibenclamide, gliclazide, glycolysis, glimepiride - acts directly on the pancreas stimulating insulin secretion.
3. *Glinides*: reglinide, nateglinide - act in the same way as sulphonamides, stimulating insulin secretion, but through a mechanism dependent on blood glucose, which allows a more adequate regulation of postprandial blood glucose.
4. *Alpha-glucosidase inhibitors:* acarbose, miglitol, voglibosis. Alpha-glucosidase is an enzyme located on the surface of the villi of the large intestine, whose action is to convert food polysaccharides into absorbable monosaccharides. Inhibiting this enzyme slows down the digestion of carbohydrates, their absorption is thus slowed down, which leads to a decrease in postprandial blood glucose.
5. *Glitazones*: rosiglitazone, pioglitazone - are insulin-sensitisers: the newest class of oral hypoglycaemic agents. These drugs reduce blood glucose levels by decreasing insulin resistance in adipose tissue and skeletal muscle, due to activation of nuclear receptors in fat and muscle cells.

9.2 Lipid metabolism

Lipids or fats are represented by: cholesterol (Col, the main atherogenic factor) and triglycerides (TG, neutral fats). *Triglycerides* are used as an energy substrate. *Cholesterol* has many roles in the human body: it is involved in the metabolism of fat-soluble vitamins (A, D, E and K), is a major precursor of vitamin D, steroid hormones (cortisol and aldosterone in the adrenal glands), sex hormones (progesterone, oestrogen and testosterone), enters into the structure of cell membranes, is involved in bile synthesis (bile acids), regulates the viscosity of cellular fluids (blood) and in the immune system.

Plasma transport of Col and TG, insoluble molecules, is carried out in the form of lipoproteins. Lipoproteins (LP) are macromolecules made up of: central nucleus (fomat in turn from: triglycerides, esterified cholesterol; has hydrophobic properties) and external shell (consisting of phospholipids, unsterified cholesterol and apolipoproteins; it has hydrophilic properties).

There are 5 classes of LP:

1. Chilomicrons (Chy): contain 90% TG of exogenous origin
2. Very low density lipoproteins (VLDL): carry 60% of TG of endogenous origin
3. Intermediate density lipoproteins (IDL): contain residual TG and Col
4. Low density lipoproteins (LDL): transports Col from the liver to the arterial walls
5. High density lipoprotein (HDL): captures Col from the arterial walls and transports it to the liver

Apolipoproteins:

There are 4 classes of APO: A, B, C and E with the following functions:

- Structural role = maintaining stability and ensuring plasma solubility of lipids
- Role of ligands = for cellular receptors (provide lipids to cells)
    - apo E (from VLDL and IDL) and B100 (from LDL) for the corresponding liver receptors
- Role of enzymatic activators = co-factors of enzymes involved in the metabolism of LP:
    - apo CII (from CHY and VLDL) for endothelial lipoproteinlipase
    - apo AI and II (from HDL) for lecithin-cholesterol-acyltransferase (LCAT)
- Role of markers/ predictors of disease:
    - apo CIII (VLDL, IDL): marker of TG-rich atherogenic LP
    - apo B (LDL, VLDL): predictor of atherosclerosis
    - apo AI (HDL): inversely proportional to risk of coronary heart disease

Pathophysiology – Dyslipidemias

Dyslipidemias are qualitative and quantitative alterations of lipid metabolism that are manifested by increases or decreases in blood lipid levels. In medical practice, the term is restricted to hyperlipidemias that are accompanied by a decrease in HDL-cholesterol.

Hyperlipidemia (HLP) is the increase in blood of cholesterol and/or triglycerides above normal values.

Causes:

- Genetic
- Lifestyle-related: unhealthy diet, lack of physical activity, smoking, excessive alcohol consumption
- Associated diseases: however, they can also occur in the case of diabetes mellitus, renal failure, hypothyroidism or following certain treatments.

Classification:

1. Current classification: primary and secondary: HLP from DM, hypothyroidism, chronic alcoholism, liver diseases, kidney disease and HLP as a result of treatment with oestrogenic contraceptive pills.
2. Old classification (Fredrickson): HLP type I, IIa, IIb, III, IV, V (Table 3)

Table 3. Clasificare Fredrickson a HLP

Type	***Name***	***LP class involved***	***Lipids that increase***	***Cardi-ovascular risk***	***Pancreatitis***
I	Familial hyper-kylomicronia	Chy	TG	-	+
IIa	Familial hyper-cholesterolemia	LDL	Col	+	-
IIb	Combined familial hyperlipidemia	VLDL + LDL	TG and Col	+	-
III	Familial dysbetali-poproteinemia	LDL + IDL	TG and Col	+	-
IV	Familial hyper-triglyceridemia	VLDL	TG	+	-
V	Mixed hyper-triglyceridemia	VLDL + Chy	TG	-	+

Therapeutic principles:

Hypercholesterolemia, and especially the increase in LDL-cholesterol, is a risk factor for cardiovascular diseases. Main classes of lipid-lowering drugs:

1. ***Inhibitors of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase*** – enzyme involved in the synthesis of Col (Statins): *simvastatin, fluvastatin, atorvastatin, rosuvastatin, lovastatin*

   Effect:

   - LDL-c ↓ 18-55%
   - HDL-c ↑ 8-10%
   - TG ↓ 10-20%

   - Are more effective in terms of decreasing LDL-Col compared to the effect on TG; are preferred in the treatment of pure hypercholesterolaemia or in mixed hyperlipidaemia with moderate increase in TG.

2. ***Fibrates:*** *fenofibrate, gemfibrozil, ciprofibrate, benzafibrate*

   - have a hypotriglyceridemic action by combined effects on the production and catabolism of VLDL.

     Effects:

     - LDL-c ↓ 5-15%
     - HDL-c ↑ 10-20%
     - TG ↓ 20-50%

   - are effective on cholesterol and triglycerides.
   - may be proposed in the treatment of mixed hyperlipidaemia.
   - represent an alternative in statin-intolerant hypercholesterolemia.

3. Nicotinic acid:

- it is a water - soluble vitamin that inhibits, in high doses, lipolysis from adipose tissue, causing a decrease in the hepatic synthesis of VLDL and LDL

Effects:

- LDL-c ↓ 20-30% (associated with cholestyramine)
- HDL-c ↑ 15-30%
- TG ↓ 35-45%
- Total cholesterol ↓ 25%

- indicated for the treatment of familial or polygenic hypertriglyceridaemia (alone or associated with statins or fibrates), familial or polygenic hypercholesterolaemia (alone or associated with statins or cholestyramine) and type V hypertriglyceridaemia (resistant to fibrates).

4. ***Resins*** : *cholestyramine, colestipol*

Effects:

- LDL-c ↓ 15-20%
- HDL-c ↑ modest
- Total cholesterol ↓ 15-20%

- are indicated in familial and polygenic hypercholesterolaemia (IIa and IIb)
- have a synergistic effect with statins, so they can be associated with them, if their effect is not enough

9.3 Protein metabolism

Proteins are also more important compounds of living matter and especially of the animal kingdom. The basic constituent of proteins is aminate acid or amino acid (AA). Proteins are macromolecules composed of a chain (or sequence) of AA bound by peptide bonds. Conventionally, a protein containing less than 50 AA is called a peptide.

Peptides are grouped together to form more complex elements, polypeptides. Similarly, polypeptides come together to form proteins (they contain more than 100 AA). Following digestion the proteins are converted again into absorbable AA.

Functions:

- the movement and locomotion of cells and cellular organelles depend on contractile proteins
- enzymes contain proteins
- the structure of cells and extracellular matrices is largely made up of proteins (e.g. collagen)
- the transport of various substances into the body's fluids depends on proteins
- there are hormone receptors and other signaling molecules
- have a nutritional function
- participates in the realization of colloid-osmotic pressure

- are important in maintaining acid-based balance
- intervene in the body's defense mechanism

The main ways of production and use of AA and proteins are:

- Protein synthesis: starting from a very small free AA pool (compartment)
- Proteolysis (or protein degradation) that releases AA

The 2 phenomena of protein synthesis and proteolysis are simultaneous and constitute the protein turnover (renewal). A synthesis superior to proteolysis will cause an inadequate excess of protein: protein anabolism. A proteolysis superior to synthesis, protein catabolism, will cause a decrease in protein mass.

Protein electrophoresis:

Electrophoresis is based on the property of electrically charged particles to migrate to the positive or negative pole, at the passage of an electric current.

Amino acids, having the amino group and carboxyl in their molecule, have an amphoterial character. Subject to the action of an electric current, amino acids in the solution will migrate to one of the poles, and the direction of migration will be depending on the pH of the environment. In acidic environment, amino acids behave as bases and migrate to the cathode, and in alkaline medium, they behave like acids and migrate to the anode. Amino acids, being components of proteins, will also print the same characters to them.

On the electrophoregram, after staining, the proteins appear in the form of strips that are measured optical density, each band having a maximum absorption. By electrophoresis, under the conditions mentioned above, five fractions are obtained: serum albumin, α_1, α_2, β, γ – globulins.

- **Albumins: 3,5-5,5 g% (50-70%)** - major plasma protein, facilitates the transport of various substances (eg: bilirubin, hormones, drugs).
- **Globulins: 2.0-3.5 g% (40-50%):**

1. *Alpha 1-globulins: 0.2-0.4 g% (3-6%).* The high level of α-1 globulins may indicate: chronic inflammatory disease (rheumatoid arthritis); acute inflammatory disease.
    - α1-antichimotrypsin inhibits serum enzymes - α1-antitrypsin

- α1-fetoprotein: tumor marker

2. *Alpha 2-globulins: 0.5-0.9 g% (7-10%).* The increased level of α-2 globulin indicates the presence of acute or chronic inflammation. Low level is an indicator for hemolysis.
   - α2-macroglobulin
   - haptoglobulin

3. *Beta-globulins: 0.5-1.1 g% (11-14%).* The increased level occurs in hyperlipoproteinemia and oestrogen treatments, and the low level occurs in hereditary dysfunction of coagulation factors; disseminated intravascular coagulation.
   - transferrin: transport Fe
   - C-reactive protein: inflammatory marker
   - β2-microglobulin: component of the HLA I system
   - fibronectin: intercellular adhesion

4. *Gamma-globulins: 0.7-1.7 g% (15-23%).* The increased level of γ-globulins may indicate: chronic inflammatory disease; hyperimmunization; acute infection; chronic liver disease.
   - Immunoglobulins (IgA, IgD, IgE, IgG and IgM) essential part of the γ - globulins. They constitute the immune substances in plasma (antibodies) that intervene in the body's defense processes.

<u>Pathological changes of serum proteins:</u>

1. Hyperproteinemia (increased proteinemia over 8 g%)

They can be real, as a result of an accentuated catabolism or synthesis of monoclonal proteins, or apparent (false), as a result of haemoconcentration (in dehydration). True hyperproteinaemias are rare.

Pseudohyperproteinaemia occurs in situations of marked dehydration (severe diarrhea, vomiting, excessive diuresis, sweating) or in case of determination errors (evaporation of the serum sample in the laboratory).

Real hyperproteinaemia occurs in autoimmune diseases.

2. Hypoproteinemia (Decrease in proteinemia below 5.5 g%)

They occur as a result of deficits of intake, absorption, synthesis, excessive losses (renal, burns, haemorrhages) or hormonal insufficiencies (pituitary, adrenocortical).

Pseudohypoproteinemia occurs in massive infusions, the third trimester of pregnancy, in nocturnal clinostatism.

Real hypoproteinemia occurs in protein loss: renal (nephrotic syndrome), digestive (protein-losing enteropathies), cutaneous (burns), repeated paracentesis, low synthesis: severe protein deficiency, malnutrition, malabsorption, chronic liver disease, increased catabolism: severe infections, malignant tumors.

3. Dysproteinemias

Change in the ratio of the different protein fractions separated by electrophoresis is called dysproteinemia.

Pathological variations in:

- Acute inflammation
- Chronic inflammation
- Nephrotic syndrome
- Chronic liver disease (cirrhosis of the liver)
- Exudative enteropathy (loss of protein in the intestine)
- Hypogammaglobulinemia

4. Paraproteinemias

These diseases are characterized by the presence, in serum or urine, of monoclonal immunoglobulins (Ig) also called paraproteins or the M component (monoclonal). Monoclonal proteins are immunoglobulins normal in structure, but produced in excess.

Alterations in the metabolism of purines – Hyperuricemia

Uric acid comes from the degradation of nucleic acids: deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), present at the cellular level in the form of purines (adenine, guanine, xanthine and hypoxanthine). Uric acid also comes from the digestion of certain foods rich in purines/nucleic acids: red meat, internal organs (liver, kidneys), fish meat. Uric acid and urate are molecules characterized by a poor solubility, solubility that decreases even more in cold, therefore, uric acid will precipitate with sodium, thus generating sodium urate crystals (precipitation occurs in aqueous solutions such as urine or synovial fluid). Increased concentrations of serum urate (hyperuricemia) occur when its concentration increases above 6 mg% (normal value: 3-6 mg).

Hyperuricemia is thus produced either by increasing the formation of urate (degradation of endogenous or exogenous purines) or by decreasing its excretion.

Gout

It is a syndrome caused by an inflammatory response with the formation of monosodium urate crystals, secondary to a chronic hyperuricemia. It starts most commonly at an average age and affects men more. Crystalline deposits (tophi or gouty microtophi) are formed very slowly in the joints because the extremities are the coldest parts of the body. Gout shows 4 stages: asymptomatic stage, acute arthritis, intercritical period and chronic gout with gouty tophi deposition. The attack of gout is determined by the deposition of sodium urate crystals in the joints, triggering an acute inflammatory reaction. They usually occur at night and are accompanied by atrocious pain, swelling, erythema, local tension. The attack can affect: knees, elbow, wrists and feet and rarely hips.

Among the chronic consequences produced by gout we find: chronic arthropathies, the appearance of kidney stones and nepholithiasis.

Therapeutic principles:

Treatment has three important stages: i) treatment of acute attack of gout, ii) treatment of hyperuricemia (background treatment) and iii) treatment of kidney complications. Treatment of acute crisis is symptomatic, while background treatment is a pathophysiogenic treatment.

The treatment of acute attack is aimed at diminishing the inflammatory process by:

- bed rest – the affected joint is protected: rest will last until the painful manifestations are calmed down;
- diet - light diet based on vegetables, fruits, carbohydrates and hydration with mineral water to alkalise the urine;
- drugs - colchicine and NSAIDs (in case of intolerance or resistance to colchicine)
  - glucocorticoids administered intra-articularly

Background treatment is aimed at reducing excess urat by:

- diet - prohibition of foods rich in nucleoproteins (veal, turkey, goose, ham, venison, mollusks, liver, kidneys, sardine, pork, mushrooms, peas,) and alcohol

• drugs that increase the elimination of uric acid - benzbromarone; probenecid, sulfinpirazone (acts by inhibiting the tubular resorption of uric acid)

• drugs that inhibit the endogenous production of uric acid: allopurinol.

(inhibits the enzyme xanthine oxidase that intervenes in the stages of uric acid formation)

Treatment of kidney complications

By maintaining in a soluble state uric acid in the urine, the development of uric nephropathy is prevented. It is achieved by supplementing the water intake

(2-3 liters / day) and by alkalization of urine (by taking baking soda possibly associated with acetazolamide). To increase renal diuresis can be given furosemide.

Alterations in amino acid metabolism – Phenylketonuria

Phenylketonuria is a metabolic disorder caused by a genetic defect, more precisely by the absence or by a low level of the enzyme phenylalanine hydroxylase, an enzyme that catalyzes the transformation of phenylalanine to tyrosine. As a result, phenylalanine accumulates in the blood and brain tissue. In the absence of treatment, the serum concentration of phenylalanine exceeds 20 mg%.

Early symptoms of phenylketonuria occurring in 50% of cases:

- the smell of mold of the skin, hair and urine
- vomiting and diarrhea that lead to weight loss
- irritability
- skin conditions: dryness, hives, eczema
- sensitivity to light (photosensitivity)
- clinically: progressive and serious mental disorders occur: cretinism, as well as depigmentation of the hair and skin

The diagnosis of phenylketonuria is made in the neonatal period by a screening test called the Guthrie bacterial inhibition test. Treatment for phenylketonuria consists in the permanent reduction of the amount of protein in the diet. The regime must be respected all its life.

Alterations in amino acid metabolism – Albinism

Albinism is a genetic condition characterized by diminishing the pigmentation of the eyes, skin, hair, produced by a congenital anomaly of melanin metabolism (the pigment that gives color to the skin and protects it).

The absence of melanin in melanocytes causes characteristic morphological changes:

- very light white or blonde hair,
- grey or blue irises,
- pupils with more or less visible red reflexes
- discolored skin, sensitive to solar radiation.
- In people affected by albinism there is an increased risk of developing skin carcinomas or melanomas. Thus, it becomes mandatory to protect the eyes and skin, especially during sunny periods.

10. THE REPRODUCTIVE SYSTEM

10.1 Male reproductive system

The male reproductive apparatus consists of structures that produce, transport, protect and provide sperm nutrition. Male reproductive organs are the external genitalia (penis and scrotum) and internal genitalia: the testicles, the epididymis, the deferens and ejaculatory ducts, the seminal vesicles, the prostate and the bulbourethral glands also called Cowper's Gland.

Penis

It is the male copulatory organ, consisting of erectile tissue, which favors the erection of the penis during sexual arousal. It consists of: the glans, the most voluminous portion and the foreskin, the integumentary shell of the glans. By cross-section of they describe: 2 cavernous bodies (cavernous corpus), 1 corpus spongiosum – surrounding the urethra, on the outside they are covered by an albuginea tunica. Its role is the insertion of spermatozoa into the vagina for possible fertilization.

Scrotum

The scrotum is a bag of skin and subcutaneous cellular tissue located at the bottom of the abdominal wall, under the root of the penis, being suspended from the pubic region. On its antero-inferior face there is a median longitudinal groove, which corresponds to the scrotal raffe that separates inside the scrotal into two compartments - the two testicular lodges. At the level of the subcutaneous cellular tissue there are smooth muscle fibers that have the role of contracting or relaxing (depending on the temperature) to maintain the viability of the spermatozoa.

Testicles

The testicles represent the male reproductive gland; produce male sperm and sex hormones. The testicles have an ovoid shape, hard consistency, 4-5 cm in length, 2 cm in thickness and a width of 3 cm. On the outside the testicular parenchyma is covered the tunica albuginea. Each testicle contains 250-300 lobules, and each lobe comprises 2-4 channelicule (tubules) seminiferous contorted (length of 70-80 cm). Among the contorted seminiferous canalicles are the Leydig interstitial cells - the endocrine cells of the testicle.

Epididymis and vas deferens

The epididymis is a long and twisted tube (about 6 m in size), covered by a fibrous tunic; contains smooth muscle fibers. It stores the sperm produced in the contorted seminiferous tubes and secretes a large part of the seminal fluid (activates the stored spermatozoa). The vas deferens (60 cm) represents a continuation of the epididymis duct, it crosses the inguinal canal and ends with the confluence with the excretory duct of the seminal vesicles. It has a role in the conduction of sperm from the epididymis to the level of the ejaculatory canal.

Appendage glands

The prostate is an odd glandular muscular organ located around the initial portion of the urethra and secretes a whitish alkaline fluid that gives the sperm color.

The seminal vesicles are 2 glands located lower than the bladder, lateral to the deferent duct. The excretory ducts join with the terminal portion of the deferent canal, forming the ejaculatory duct (which then penetrates the prostate). They secrete an alkaline liquid with fructose, the main energy product for spermatozoa.

Cowper's glands (bulboureth rale) are 2 glands located on the sides of the urethra, inferior to the prostate. They produce a clear, slippery, alkaline liquid that lubricates the urethra and neutralizes the remnants of urine.

Sperm

Sperm is the male sex cell. Spermatozoa are formed in the epithelium of the seminiferous tubules in the testicle. The seminiferous tube shows cells with a trophic role (Sertoli cells) between which germ cells are found in various stages of development. It consists of the head (acrosom + nucleus), neck and flagella. The number is between 60,000,000 -120,000,000/cm3 sperm.

Male sex hormones: testosterone

- stimulates the development of external genitalia
- influences the linear growth of the body
- increase in bone density and muscle mass
- stimulates the maturation of sperm
- development of the larynx and alteration of the voice
- determines the secondary male sexual characters
- facilitates libido and sexual potency

Pathology

1. Prostate cancer is the most common cancer in beards after lung cancer. It has a slow development, but is generally curable if it is discovered in the early stages.
2. Prostate adenoma affects men over 50 years of age, causing urination disorders. It is a benign and non-censorious tumoration of the prostate.
3. Penile agenesis is a congenital defect in which the penis is missing
4. Phimosis is a condition that localizes at the level of the foreskin, characterized by abnormal straiting of the prepuţial ring that causes a painful or even impossible decalottion.
5. Priapism is a genital condition, characterized by a painful and persistent erection, not being conditioned by physical or mental arousal.

10.2 Female reproductive system

The female genital organs are: internal (ovaries, uterus, fallopian tubes and vagina) and external (pubic mountain labia majora, labia minora, large and small vestibular glands, vestibule bulbul vestibule, clitoris, hymen).

Ovaries

The ovaries (2 glands) represent the female sex glands, which produce the sex cells (ovules) and the female sex hormones. At birth, the ovaries contain millions of primary ovarian follicles. At puberty, the development of follicles is stimulated by hormones, each develops and releases a mature egg at each menstrual cycle. The ovaries have an anteroposterior flattened ovoid shape, length: 2.5 – 4 cm, mass: 5 – 8 g. They are covered with an embryonic epithelium under which the tunic albuginea (dense connective tissue) is located. The parenchyma of the ovary is made up of the cortical substance (located on the periphery) and the medullary substance (in the center of the ovary)

Uterus

The uterus is a smooth muscular organ with walls about 1 cm thick. During pregnancy, this cavity grows greatly. It is lined on the inside by a mucous membrane, rich in blood vessels and glands, called an endometrium. Under the hormonal influence it increases in view of a

possible nidation of the fertilized egg. In the absence of fertilization, this mucosa takes off in about 2 weeks after ovulation, the blood vessels rupture, causing bleeding (menstruation). The ova is 8-9 cm long; width: 4-5 cm.

Cervix

The cervix is less mobile than the body of the uterus. The cervix is a fibromuscular portion of 3 cm that surrounds the cervical canal, covered by a mucous membrane. The cervical canal communicates upwards with the uterine cavity through the internal orifice of the cervix and down with the vagina through the external orifice. The boundary between the uterine body and the cervix is called the uterine isthmus.

Fallopian

The fallopian tubes (oviducts) are two musculo-membranous channels with a length of 10 to 12 cm and the lumen between 2 and 4 mm, through which the oocyte is driven from the peritoneal cavity into the cavity of the uterus. The fallopian tube communicates with the cavity of the uterus through the hole called the uterine bone. Consisting of 2 regions, the pavilion (the fringed extremity of the tube that almost entirely surrounds the ovary and receives the ovum at the time of ovulation) and the ampulla (the enlarged region of the tube that is located close to the ovary, in the first third of the length of the tube – is the place where the fertilization takes place).

Ova

The ovum is the female reproductive cell, also called the female gamete. The size of the ovules is 200-250 μm and the service life after ovulation is 12-24 hours. Its nucleus contains 23 chromosomes. If, as a result of fertilization, the ovum merges with a sperm, the one that nucleus also contains 23 chromosomes, they will form a zygote of 46 chromosomes.

Female sex hormones and hormonal regulation of ovarian activity

The endocrine cells of the ovary are found in the interstitial substance of the gland and in the yellow body, coming from the follicles after their bursting, the expulsion of the ovum and the follicular fluid. The cells of the follicular epithelium develop the hormone estrogen (folliculin),

and the cells of the yellow body secrete the hormone progesterone. For the ovary, the cyclic production of estrogens and progesterone is characteristic

In women, the function of the ovary ceases around the age of 50 years; the ovary no longer responds to the stimulations of the hypothalamus and pituitary gland.

In the case of pregnancy, an important source of hormones is the placenta, especially after the 3rd month of pregnancy. The placenta secretes relaxin, progesterone, estrogen, chorionic growth hormone, prolactin and chorionic gonadotropin.

1. *Important biological activities of estrogen:*
   - development of primary and secondary female sexual characters
   - differentiation and development of genital organs
   - stimulating the growth of myometrium and endometrium
   - stimulating the growth and development of mammary glands
   - deposition of subcutaneous fat
2. *Important biological activities of progesterone:*
   - prepares the endometrium for the implantation of the fertilized egg and the development of the embryo
   - placenta formation, retention of growth and development of new follicles

The regulation of ovarian function involves the action of releasing hormones (releasing factors), gonadotropins from the hypothalamus and hormones, folliculostimulin (FSH) and luteinizing hormone (LH), produced by the pituitary gland. Growth and maturation of a follicle requires FSH, LH and estrogens; adequate levels of these hormones are responsible for the ovarian cycle and follicular development. In the first part of the cycle the concentration of estrogens is only slightly increased. As the follicular development develops, the secretion of estrogens increases little by little (follicular cells are one of the first sources of estrogens).

Ovarian cycle

It consists of a series of changes that occur in the ovary:

1. **follicle development:** under the influence of adequate hormonal stimulation, a few primary follicles continue their development and become secondary follicles. Depending on their growth, a noncellular translucent membrane, the zona pellucida, is formed in

certain secondary follicles. If one of these follicles increases in size, a cavity (antru) filled with fluid is formed, which increases in size and moves to the surface of the ovary where it forms a protuberance. This mature follicle is called the De Graaf follicle (period of development: 10-14 days).

2. **release of an egg coming from a mature follicle following ovulation:** under appropriate hormonal conditions, the De Graaf follicles break and release the egg, a process called ovulation. After ovulation, the ovum passes into the pavilion, where the ciliary movements of the fringes of the flag of Fallope's tube produce a stream of peritoneal fluid, which pushes the egg through The Fallope's tube.
3. **the formation of a structure called the yellow body:** after ovulation and the loss of follicular fluid, the De Graaf follicle tightens. The cells of the ruptured follicle then hypertrophy, turn yellow and turn into the yellow body. The exit of the yellow body depends on that of the ovum, thus: if the ovum is not fertilized, the yellow body, after 14 days, degenerates and forms a thin white scar formed by connective tissue, the white body; if the egg is fertilized, the yellow body continues to develop and remains in the same place until the end of pregnancy.

The duration of the ovarian cycle varies between 20-40 days, with an average of 28 days. The menstrual cycle involves repetitive changes in the inside of the uterine mucosa and, to a lesser extent, in the vaginal mucosa. It is closely related to the ovarian cycle.

10.3 Hormonal contraception

Definition: a method that allows to prevent the conception of a child. Oral contraceptives contain ovarian hormones that produce a negative feed-back on the hypothalamus, inhibiting the production of GRH and pituitary gonadotropins (LH and FSH), thus ovulation is no longer stimulated. Oral contraceptives contain estrogen and progesterone or only progesterone (to avoid side effects associated with estrogens or if taking estrogen is contraindicated).

Mechanisms of contraception

• inhibition of follicular growth with the absence of ovulation (the main effect of the pill)
• absence of the maximum value of LH and FSH - estrogens and progestogens
• change in the consistency of cervical mucus – it becomes thick, preventing the passage of spermatozoa - progestogens
• atrophy of the endometrium that thus becomes unfit for nidation - progestogens.

Classification:

Depending on the dose of estrogens :

- normodoses (50 μg ethinyl estradiol)
- minidoses (30 μg ethinyl estradiol)
- microdoses (20 μg ethinyl estradiol)

Depending on the proportion of estrogen/progesterone in the pills:

- Fixed, single-phase combinations: release the same amount of estrogen and progesterone during the 21 days of taking the pill. A 7-day break follows
- Sequential, biphasic or three-phase combinations, containing an estrogen and different doses of progestogen

Side effects

- Increase by 40% the frequency of cardiovascular diseases by favoring coagulation (increase the synthesis of coagulation factors: VII, VIII, IX, X and fibrinogen)
- They increase cholesterol and triglycerides → produce dyslipidemia → atherosclerosis
- Decrease glucose tolerance → can induce diabetes
- Headache, nervous depression, decreased libido, irritability
- May trigger epileptic seizures
- Can cause excess hair to appear, profuse sweating
- Decrease bile flow and may favor the onset of cholelithiasis and jaundice
- Weight gain
- Hypertension and edema
- Skin rashes and photosensitization

Contraindications

- DZ
- Obesity
- Tumors
- Hepatic or renal insufficiency
- Cholelithiasis
- Smokers
- Over 35 years

11. THE MUSCULOSKELETAL SYSTEM

The musculoskeletal system consists of bones (with connections called joints) and muscles. The totality of the bones forms the skeleton, which constitutes a kind of "scaffold" that generates the general shape and proportion of the human body. Bones are connected to each other by various kinds of connective structures (joints) that provide them with mobility. On the bones are fixed skeletal striated muscles that act on the bones and joints and print some movements of the bone segments.

11.1 Bone system

Bones are hard and hardy organs of yellowish-white color. Their ensemble (about 206 bones) constitutes the skeleton.
The skeleton is divided into: *i) axial skeleton*: skull, verterbral spine (33-34 bones), thoracic box and *ii) the skeleton complementing the* bones of the upper limbs and lower limbs. 33-34 of them are odd: vertebrae, sacrum, coccyx, sternum and some bones of the skull, the other bones are even.

Functions

1. determines the shape, dimensions and proportions of the body
2. serve as a support for the whole body and for the soft parts
3. make up cavities that protect organs
4. are deposits for mineral substances
5. locomotion

External configuration

In general, bones are assigned the shape of geometric bodies with three dimensions: length, width and thickness:

6. Long bones - the length exceeds the width and thickness
7. Flat - length and width are approx. equal, but exceed the thickness
8. Short - have the 3 almost equal sizes

Internal configuration

By cutting the bones and examining the section, it is noticed the presence of a bone substance (bone tissue) proper (whitish, of hard-woody consistency). Bone tissue is a tissue of a conjuctive nature composed of an *interstitial substance* (made up of fundamental substance / ossein -

impregnated with mineral substances and collagen) and *3 types of cells: osteoblasts, osteoclasts, osteocytes.*

According to the microscopic disposition of cells, fundamental substance and fibers we distinguish 2 kinds of bone tissue: compact and spongy.

Compact bone tissue (substance) is found in the diaphyses of long and short bones and on the surface of epiphyses. It consists of bone blades (thin collagen fibers, embedded in the fundamental calcified substance). Between the bone slats or in their thickness there are osteoblasts (lenticular pantries) that contain osteocytes. The assembly formed by a centrally located Havers canal, by the bone lamellae that surrounds it and by the components located in these formations constitutes a morphological and functional unit called the osteon or haversian system. The Havers ducts contain blood vessels and nerves. They anastomose each other through volkmann channels. They open into the bone marrow cavity of the bone and to its surface, into the subperiost.

Spongy bone tissue (substance) is found in the epiphyses of long bones and vertebrae; it has the appearance of a sponge, with cavities of different sizes, filled with bone marrow, surrounded by compact bone tissue.

The periosteum is a fibrous membrane that envelops the bones all over their outer surface. At the level of the joints, the periosteum continues with the joint capsule. Its thickness varies depending on the size of the bones, age, sex. It consists of 3 layers: external (rich in blood vessels, nerves and receptors), intermediate (fibroelastic, rich in connective and elastic fibers) and internal (osteogenous, represents the proliferating layer). The periosteum has a role in the formation of bone tissue during the period of osteogenesis in children, and in adults it provides nutrition and growth of bone in thickness.

Marrow

The cavities of the spongy substance and the medullary cavity of the long bones, are filled with a soft, semifluid substance, rich in blood elements. Bone marrow has several important roles: it participates in the formation of bone tissue, during ossification (osteogenic role); contributes to the formation of figurative elements of the blood (hematopoietic role);constitutes a mechanical factor, diminishing the weight of the bones;

like any adipose tissue, it serves as a reserve substance. 3 types of bone marrow are distinguished:

1. **Red marrow:** red osteogenic marrow – with a leading role in osteogenesis, and red hematogenous marrow – with a leading role in hematopoiesis.
2. **Yellow marrow:** it is found in most of the bones of the adult and represents for the body a reserve of lipids.
3. **Gelatinous marrow (grayish):** it is found in the elderly and does not perform any role in the body.

The human skeleton

I. The skeleton of the head

4. **Neurocranium:** - the upper and posterior portion of the skull
   - consisting of 8 bones: frontal, ethmoid, sphenoid, occipital, 2 parietal bones and 2 thermoporal bones
5. **Viscerocranium (face):** consisting of 14 bones of which 6 are pairs (maxilla, zygomatic, nasal, lacrimal, palatine and lower nasal cornea) and 2 odd: the mandible and the vomit.

II. Skeleton of the trunk

6. Backbone:
   - 7 cervical vertebrae
   - 12 thoracic vertebrae
   - 5 lumbar vertebrae
   - 5 fused sacrum vertebrae
   - 4-5 fused coccygeal vertebrae
2. Thoracic cage:
   - 12 vertebrae
   - 12 pairs of ribs
   - Sternum

III. Skeleton of the upper limbs:

1. It consists of a portion that connects it to the bony trunk – the scapular belt (formed by the collarbone and shoulder blade) and a portion in its continuation – the free upper limb
2. The skeleton of the free upper limb consists in its turn of:
   - skeleton of the arm: humerus
   - skeleton of the forearm: radius and ulna

- skeleton of the hand: 27 bones divided into the bones of the carpal, the bones of the metacarpus and the bones of the fingers of the hand

IV. Skeleton of the lower limbs

3. Pelvic girdle (coxal bones):
   - Ilion
   - Ischium
   - Pubis
4. Skeleton of loose lower limbs
   - Skeleton of the thigh: femur
   - Skeleton of the lower leg: tibia and fibula (fibula)
   - Skeleton of the foot: 26 bones arranged in 3 groups: tarsal, metatarsal, bones of the fingers

Joints

A joint consists of:

- ***cartilage***: white coating covering the articular surfaces. It is hydrated and elastic; with a role in the protection of the bone.
- ***capsule:*** fibrous sleeve that maintains the articular surfaces.
- ***ligaments***: made up of fibrous tissue; unite 2 bones bordering each other.

Types of bonds between the bones:

5. **Syndesmosis:** the binding of 2 bones is made by means of a fibrous tissue (the articular bone surfaces are joined by fibrous tissue)
6. **Synchondrosis**: binding is done by means of hyaline cartilage. (the articular surfaces are joined by hyaline cartilage very adherent to them)
7. **Symphysis**: the binding is made by fibrous cartilage and connective tissue (the connecting tissue is fibrocartilage)
8. **Diarthrosis:** the most common joint. It is a discontinuous joint, consisting of articular surfaces, the joint capsule and an articular cavity between the articular fragments.

Pathophysiology

1. Fractures

It represents an interruption or discontinuity in a bone as a result of a trauma. General signs include agitation, anxiety, pallor, and local

signs: pain at a fixed point, ecchymosis, local deformation, anormular mobility, bone crepitation, disruption of bone continuity.

2. Sprains:

They are traumatic injuries to the joints, without changing the normal anatomical ratio between the articular surfaces. They occur as a result of over-escalation; as a result of the injury, the stretching or rupture of the ligaments in the joint occurs.

3. Dislocations

It is a traumatic condition, which consists in the premanent displacement of the bone extremities of a joint. Damage to the joint capsule, ligaments, vascular destructions, nerve and muscle damage occur. Clinical signs include: strong pain, functional impotence, deformation of the region, ecchymosis, hematoma, hemarthrosis.

4. Head trauma

Among the most common disorders of the nervous system. Principal causes of occurrence of head trauma include: road accidents, aggressions, traumas occurred during the practice of sports branches and accidents at work

Depending on the intensity of the shock, head trauma can be both scalp injuries (wounds, swellings), bone injuries (skull fractures) and internal (brain) injuries.

Concussion is a short abolition of the state of consciousness through the "functional" involvement of the cross-linked formation of the brainstem; this is considered a momentary interruption of the alertness function that occurs due to the brutal depolarization of the component neurons. The condition is transient and reversible, lasting around a minute.

Cerebral contusion is characterized by alteration or loss of consciousness and the installation of neurological signs of focus. It occurs due to a traumatism that causes a necrosis of the brain tissue at the point where the shock has the maximum effect, to which can be added a arterial or venous hemorrhages, hematomas, vasoparalysis, vasodilation or cerebral edema.

Brain abscess is the main infectious complication that can occur both in closed traumas, through a possible crack of the meningeal and open layers, in which the mechanism of circulating the infection is clarified.

5. Osteomyelitis

It represents inflammation of the bone marrow, with propagation has on the compact and spongy substance of the bone and periosteum. After the evolutionary character, osteomyelitis can be acute and chronic, and after the mechanism of infection of the bone marrow may be primary or secondary hematogenous osteomyelitis (complication of trauma).

The main role in the appearance of osteomyelitis belongs to pyogenic microorganisms: hemolytic staphylococcus (60-70%), streptococci (15-20%), coliform bacilli (10-15%), pneumococci, gonococci. Sometimes pathogens can be fungi. The source of hematogenous propagation of the infection can be the inflammatory focus in any organ, but most of the time the primary focus cannot be detected. It is assumed that in these patients there is a transient bacteremia generated by an instestinal lesion, diseases of the teeth, infections of the upper respiratory tract.

The peculiarities of vascularization of bone tissue contribute to the localization of infection in the long tubular bones. The purulent process usually begins in the medullary interstitium of the metaphyses, where the blood flow is slow. Subsequently, it can expand, causing vast necrosis, spreading on the cortical layer of the bone, the periosteum and the adjacent tissues. The purulent inflammation extends through the osteo-medullary canal, affecting new portions of the bone marrow. In children, especially in newborns, because of the weak fixation of the periosteum and the peculiarities of the vascularization of the cartilages of the epiphyses, the purulent process often spreads over the joints, causing purulent arthritis.

Complications: hemorrhages from fistulas, spontaneous fractures of bones, formation of pseudoarthrosis, pathological dislocations, sepsis.

6. Osteoarthrosis

It is one of the most common degenerative/dystrophic joint diseases. It occurs predominantly in women of old age. Osteoarthrosis can be: primary (idiopathic) and secondary (for example, in endocrine diseases). The most affected are the joints of the lower limbs: coxophemural, knee, ankle, less often, large joints of the upper limbs. In the development of osteoarthrosis are important the predisposing factors - hereditary (genetically determined disorder of the joint cartilage metabolism) and acquired (mechanical trauma).

Three stages of osteoarthrosis are described:

1) *in the first stage* there are pains in the joints during effort, radiologically it is found the narrowing of the articular slit and osteophytes,
2) *in the second stage* the pains in the joints become permanent, the narrowing of the articular slit and the development of osteophytes at the radiological examination are more pronounced and
3) *in the third stage*, besides permanent joint pain, the functional insufficiency of the joints is found.

11.2 Muscular system

The muscular system comprises all formations that have contractile cells. It consists of somatic, cardiac and visceral musculature. There are 3 types of muscle cells: striated (striated fibers, polynuclear), smooth (fusiform, single nucleus arranged centrally) and striated cardiac (striated fibers, uninuclear). This describes several types of muscles:

1. skeletal muscles: they have an intense metabolism; large energy producers; respond quickly and accurately to stimuli
2. smooth muscles: it enters the structure of cavitary viscera, glanular cells, blood vessels; works involuntarily; performs motor visceral functions; intervated by the autonomic nervous system; react more slowly to stimuli and produces little energy
3. heart muscle: it enters the structure of the heart, it is a particular type of striated muscle; works involuntarily; intervated by the vegetative nervous system;

The structure of the muscle

The muscle consists of a conjunctival component and a muscular one.

The connective tissue forms the outer shell of the muscle (epimisium), the sheathing of the bundles of muscle fibers (perimisium) and the shell of each muscle fiber (endomisium). At the level of connective tissue there are blood, lymphatic and nerve vessels, thus having a role in ensuring the mechanical, nutritional and biological integrity of muscle fibers and bundles.

Muscle tissue is made up of specialized contractile cells (muscle fibers, also called myocytes) in muscle contraction. Each fiber contains several myofibriles made up in turn of 2 types of structures called myofilaments: some thick (myosin) and some thin (actin). The portion

located between 2 Z lanes is called a sarcomer. The sarcomer represents the functional, contractile unit of the skeletal muscle.

Sarcomere

The sarcomere contains two types of proteins, contractile proteins and regulating proteins.

The contractile proteins are arranged in parallel along the entire axis of the sarcomere and are represented by the fine actin filaments and the thick filaments of myosin. Actin myofilaments are fixed with one end directly on the Z-lines. Actina is presented in the form of long polymers whose monomers are in the form of a bean. Myosin myofilaments are arranged in the middle of the sarcomere and are indirectly fixed on the Z-lines by means of a protein, protein titin. Myosin has the form of a golf stick.

There are 2 types of regulating proteins: troponin and tropomiosin.

Neuro-muscular junction and muscle contraction mechanism

The neuro-muscular junction (or neuro-muscular ending) is where an axonal ending (terminal buttons) comes into contact with the muscle fiber sarcolema. The motor plate represents the place where the surface of the sarcoleme forms a hollow in which the neuromuscular junction will be made.

The actin filaments belonging to the two successive Z-bands are located among the myosin filaments, with their free ends overlapping a little, when the sarcomere is relaxed. The release of a neurotransmitter (acetylcholine) from the level of the axonal ending in the motor plate, causes the generation of an electrical impulse at the level of the sarcolemma of the muscle fiber and the creation of an action potential. Thus, the initiation of the contraction of the skeletal muscle takes place. The electric currents also spread to the inside of the fiber, where they cause the release of calcium ions from the sarcoplasmic reticulum. The penetration of the electric current in the vicinity of each myofibrils is achieved by transmitting ap through the T tubules. T tubules are very narrow, they start at the level of the cell membrane and penetrate the muscular fiber, crossing it completely from one side to the other. The calcium ions will then initiate the contraction.

Calcium is necessary to allow the heads of myosin to fix to actin. The actin filaments are then drawn among the myosin filaments so that

they will overlap almost completely. At the same time, the Z-bands are pulled by the actin filaments to the vicinity of the ends of the myosin filaments. So, muscle contraction occurs through a mechanism of sliding filaments.

Muscle tissue - properties

Excitability is the property of the geranium to react to certain stimuli.

Contractility is the property of the muscle to change its shape under the action of an excitation and exert traction to its extermities.

Elasticity is the property of the myocardium to return to its original form after the cessation of contraction.

Classification of muscles

1. **Head muscles:**
   1) *Masticatory muscles*: temporal, masseter
   2) *Mimicry muscles, facial*: they are located superficially (leathery muscles), thin, fine. They also have a role in mastication, breathing, speech.
      - cranial m.: epicranial
      - eyelids m.: eyebrow, orbiculari, descenders of the eyebrow
      - nose m.: nasal
      - mouth m.: orbicular of the mouth, zygomatic, lift of the upper lip, lowering
      - external ear m.: auricularis
2. **Neck muscles:** influences the movements of the head, mandible, hyoid bone, cervical segment of the spine, the first 2 ribs; changes the shape and position of the tongue, pharynx and larynx.
   - sternocleidomastoid
   - suprahioids
   - infrahioids
3. **Deep muscles:**
   - scalians
4. **Back muscles:**
   1) *superficial m.:*
      - trapezoid
      - dorsal

- rhomboids

2) deep m.:

- spinal
- semispinal

5. Chest muscles

6. M. acting on the scapular belt and the arm:

- m. pectoral large / small
- subclavian
- previous tooth

7. Thoracic cage m.:

- external/internal intercostals
- transverse of the chest
- lifters of the ribs

8. Muscles of the abdomen :

- right abdominal
- oblique
- transverse

9. Upper limb muscles

a) scapular belt:

- deltoid
- subscapular

b) arm m.:

- flexors
- biceps
- triceps

c) forearm m.:

- pronounces
- substitutes

d) hand m.

10. Muscles of the lower limb

1) basin m.

- piriform
- gluteals
- gemellus

2) thigh m.

- femoral quadriceps

- tailor
- pectincine
- adductor/abductor
- semitendinos/semimembranos

3) *shin m.*
   - solear
   - gastrocnemian
   - peroneal
   - tibial
4) *foot m.*

Pathophysiology of the muscular system

1. Muscle atrophy

It occurs most often in muscles that are not in use. They lose their strength and decrease their size. Possible causes include prolonged bed immobilization and stroke.

2. Myalgia

It can occur in isolation, at the level of a certain muscle or at the level of the whole body. Possible causes include: muscle damage, intense physical exertion, stress, autoimmune diseases (lupus, polymyositis), viral infections, some drugs.

3. Hernia

It is a rupture that occurs in a region of a weak muscle wall, accompanied by the exit of an organ or part of it, through the structure or muscle that contains it. It occurs due to an increased pressure in the abdomen, in obesity, with aging or it can be congenital.

4. Splay foot

It occurs as a result of the weakening of the leg muscles that make up the curvature of the foot. It is of 2 types: flexible (asymptomatic and painless) and rigid (due to abnormal development of the foot, painful, requires treatment)

5. Tetanus

It is an infectious disease, characterized by muscle spasms. It is provoked by toxin from Clostridium tetani, which penetrates the body by way of open wounds, burns. It's not contagious! Symptoms include

stiffening of the jaws, abdominal and back muscles, fever, sweating, swallowing problems, painful muscle spasms.

6. Myasthenia gravis

It is an autoimmune chronic disease represented by a progressive weakening and pathological fatiguability of the striated muscles leading to paralysis. The development of the disease is related to the decrease of up to 90% of the number of acetylcholine receptors at a unit of motor plaque, which is determined by autoimmune reactions. Antibodies to acetylcholine receptors were extracted from the thymus and identified in the blood of 85-90% of patients. The cause of its occurrence is a defect in the transmission of the nerve impulse to the effector muscle due to the decrease in the number of receptors for acetylcholine. This occurs when normal communication is interrupted at the level of the neuromuscular junction. Any muscles can be affected, but in particular, damage to the m. of the eyes, m. masticators, m. of the arm and of the femur occurs. The normal contraction of the muscles after the active functioning loses its strength and volume and may be completely interrupted. After rest, the function of the muscles is restored. In the advanced stage of the disease the rest time is increased, the impression of paralysis of the muscles is created. The disease occurs at any age (the peak of morbidity is at 20 years) and is three times more common in women compared to men. The exact cause of the disease is not known, but a correlation has been found between thymus abnormalities and myasthenia; timectomy often leads to a positive effect. Complications occur more frequently in the case of respiratory muscle damage. Inadequate pulmonary ventilation leads to the development of pneumonia and asphyxia, which are usually the cause of death.

12. CELL SIGNALING AND RECEPTORS

Cell signaling is the way cells can communicate with each other, exchange information.

Cell signaling = transmembrane signaling (the message necessarily crosses the cell membrane).

It occurs regardless of the distance at which the cells are located; the signaling routes are classified as follows:

1. *endocrine:* cells are at a great distance and signal molecules must be transported through humors
2. *paracrine:* the cells that communicate are in the immediate vicinity
3. *autocrine:* the signal is transmitted and received by the same cell
4. *juxtracrine:* cells are attached, bound; both transmit and receive signals

The mechanism and stages of cellular signaling:

Cell signaling takes place with the mandatory participation of 2 components:

1. **ligand** (signal molecule)
2. **receiver**

The binding of the ligand to the receiver induces conformational changes at its level → the induction/initiation of a mechanism by which the cell receives and processes the signal → triggering various cellular processes.

The response T is that the cell creates and is dependent on the set of effector proteins (those that take the signal from the receptor and contribute to the intracellular processes that constitute the response).

Stages:

1. Signaling initiation: occurs by binding the ligand to the receiver. Ligand binding presupposes the existence of an affinity interaction, of high specificity.

2. Signal transduction and receiver activation

Ligand binding induces conformational changes of the receptor (at the level of the polypeptide chain) → the propagation of information through

the transmembrane domain of the receiver, up to the endosome in the cytosol → the activation of the receptor

3. Activating the effector and amplifying the signal

Receptor activated binds the molecule of the first effector → activation of the first effector → activation of effectors 2 ..... and so on

! the signaling process involves a large number of conventionally acting effector types, each of which picks up the signal from the previous (upstream) effector and then transmits it to the next (downstream) effector = > signal amplification increases at the end of the cellular response.

4. Signal attenuation and desensitization of the cell: after the completion of the cell response, inactivation of the effectors occurs, dissolution of the receptor ligand and intracellular degradation of the ligand (by lysis, metabolism, dephosphorylation)

Classification of ligands:

1. After solubility:

A. **Hydrophilias (lyophobes):** amino acids (AA), peptides, catecholamines, serotonin (5-HT), histamine

B. **Hydrophobes (lyophilic):** h thyroids , steroids, eicosanoids

2. According to the chemical structure:

1. **AA**: glutamate, aspartate, glycine, gamma amino butyric acid(GABA)
2. **Amines**: catecholamines (DA, EPI, NA); serotonin (5-HT), h. thyroid and histamine
3. **Peptide**e (polypeptides, proteins): cytokine
4. **Steroids**: glucocorticoids, progesterone, estrogens, androgens, mineralocorticosteroids
5. **Arachidonic acid derivatives**: prostaglandins, prostacyclins, thromboxanes, leukotrienes
6. **Acetylcholine (Ach)**
7. **Medicines**

+ physical stimuli that can activate receptors

Types of cellular responses:

1. *Differentiation:* self-regeneration (e.g. stem cell, tissue regeneration, hematopoiesis)

2. *Survival*: the most common effect; the cell receives stimuli that help it adapt to new conditions; the cell responds through normal functioning and survival
3. *Proliferation:* cellular homeostasis, the ability to restore tissues
4. *Apoptosis*: programmed cell death

Factors that influence the cellular response

1. Ligand concession

The increase in the concentration of ligand causes the increase in no. of occupied receptors; the effect lasts until the cold stature of the receptor (when all the receptors are bound/occupied).

2. Affinity of the receiver

The greater the affinity of the receptor for the ligand, the higher the cellular response.

Ligands that bind to the receptor and produce a cellular effect/response = **AGONISTS** (binds to the receptor and activate the receptor triggering a biological response).

Classification:

5. **Selective agonist:** it is selective for a certain type of receptor.
6. **Full agonist:** binds and activates the receptor with the production of the maximum response that can be obtained from that receptor.
7. **Partial agonist :** binds and activates a receptor, but only with partial efficacy.
8. **Inverse agonist/Antagonist** : it is an agent that binds to the same receptor as an agonist but exerts a pharmacological effect opposite to that of that agonist.

Ligands that bind to the receptor but do NOT produce an effect/response celular = **ANTAGONISTS** (binds specifically to a particular receptor and blocks it with the aim of significantly diminishing its activity).

Classification:

1. **competitive antagonist** binds to the same site as the endogenous ligand => decrease in the potency of the ligand. They can be **reversible** and **irreversible**.
2. **the uncompetitive antagonist** binds to a different site on the receptor, which diminishes the maximum effectiveness of the endogenous ligand.

3. Number of receptors

Increase no. of receptors causes the cellular effect/response to increase.

Agonists and antagonists can influence the number and functionality of receptors suitable for binding. Thus, 2 phenomena occur:

1. **UP-REGULATION:** increasing the number of receptors when the concentration of ligand is low:
   - Appears at a reduction in receptor stimulation (absence of an agonist or blockage of the receptor by an antagonist).
   - Is achieved by: decreasing the degradation of the receptor (the receptor will withdraw into the cytoplasm) or sensibilization of the receptor (increases the number of receptors expressed at the surface of the membrane).

2. **DOWN-REGULATION**: decrease in the receptors number when the concentration of ligand is increased:
   - Appears as a measure of defense of the body in the presence of an excess agonist that has leads to an overstimulation of the receptor.
   - Is achieved by : increasing the degradation, desensitization and internalization of the receptors.

Types of receptors

Receptors are membrane proteins or glycoproteins that receive external signals/bind to signal molecules and undergo structural changes that trigger various cellular activities.

Classification according to the physico-chemical properties of the signal molecule:

1. Receptors for lipophilic/ fat-soluble ligands
2. Receptors for hydrophilic/water-soluble ligands

1. Receptors for lipophilic/ fat-soluble ligands

Receptors for lipophilic ligands:

- Cortisol
- Estrogen
- Progesterone
- Vitamin D
- Thyroid hormones
- Retinoic acid

Tosell lipophilic properties, they can tighten the cell membrane by simple diffusion, and through intracellular space, they are transported using a carrier protein. The receptors for lipophilic ligands are located in the cytosol or nucleus and take over the ligand after its diffusion through the membrane.

- if the receptors are located in the cytosol, the activation of the ligand-receptor complex will also occur in the cytosol. Well, the passage of the complex in the nucleus then takes place through the nuclear pores.
- if the receptors are located in the nucleus, the ligands are led into the nucleus with the help of carrier proteins where the activation of the ligand-receptor complex will take place.

The activated ligand-receptor complex will bind to a specific sequence of DNA (response element) that causes the gene transcription/inhibition of the transcription of that gene. This will then lead to the stacking/disabling of the mRNA translation, and implicitly, to the activation/disabling of the synthesis of proteins that produces a cellular response.

2. Receptors for hydrophilic/water-soluble ligands

Receptors for hydrophilic ligands are the most numerous and are located in the cell membrane.

Classification:

1. Receptors with ionic channel function (ionotropic rec. / ion channel with ligand)
2. Receptors coupled with G proteins
3. Receptors with enzymatic function or enzyme coupling

2.2.1 Receptors with ionic canal function

They are fast ionic channels that close/open as a result of coupling a ligand. The formation of the ligand-ion channel complex causes the gates to open and the ions to enter the cell. This process causes two effects:

- change of membrane potentially: depolarization or hyperpolarization
- passage Na^+, K^+,Ca^{2+},Cl^-

2.2.1 Receptors coupled with G-proteins (GPCRs)

Are integral membrane proteins that are used by cells to convert extracellular signals into intracellular responses. In order to bind to the G protein, they must cross the cell membrane formed by seven transmembrane helices (TM) are connected to three extracellular loops and three intracellular loops.

Transmembrane organization of the receiver:

- at the surface of the cell is exposed to the amino-terminal head
- on the citosolic front is exposed the carboxi-terminal head
- the seven transmembranare domains (TM1 - TM7) provide the formation of three external loops (also called ectodomain) and three internal loops (also called endodomain)

The domain of the receiver is large and contains sites for binding of divers ions and ligands.

The endodomain of the receptor represents the place of interaction with the G proteins, but also the place of phosphorylation necessary for desensitization of the situation.

Mechanism of action/stages:

1. Binding of the ligand to the receiver -> activation of the receiver

- protein G presents 3 subunits (α,β,γ) - the subunit of the α binds to guanosine diphosphate (GDP) in inactive state.

2. Activation of the receptor => detachament of GDP and binding of GTP => activation of the G protein

3. Signal transmission to the downstream effector: it can have either enzymatic function (adenylate-cyclase, phospholipase C, cGMP) or the role of ionic channel. Through different mechanisms/pathways the *cellular effect* occurs. The effect produced differs depending on the type of heterotrimeric G protein involved and depending on the set of stimulated cell effectors.

4. Deactivation of heterotrimeric G protein: by hydrolysis of GTP -> return to initially, inactive conformation with bound GDP.

Types of G proteins:

1. *G-stimulating proteins (Gs, with αs subunit):* activates adenylate-cyclase and Ca^{2+} channels
2. *Inhibitory G proteins (Gi with subunit αi):* inhibition adenylate-cyclase and activate K^{+} channels
3. *Gq proteins (Gq with subunit αq):* activates phospholipase C
4. *Proteins Gt (transducin, with subunit αt):* activates cGMP-phosphodiesterase in photosensitive cells with the stick

Effectors :

1. slow ligand ionic channel that produces changes in the potentiallly membrane when activated
2. activation/inhibition of an **amplifying protein (Phospholipase C and adenylate cyclase)**, by means of the alpha-GTP subunit -> catalyzes the synthesis of a **second messenger** - > activation of a protein kinase - > phosphorylation of a protein - > cellular response.

Types of second messenger :

1. Ca^{2+} : the influx of Ca^{2+} into the cell (as a result of the opening of the ionic channel of Ca^{2+} or at the Ca^{2+} input by other mechanisms) → badly bind to calmodulin → the activation of their protein kinases → phosphorylation of a protein → cell response (contraction, transport or influenceof cellular metabolism)

Activation of **phospholipase C** causes production of the following second messengers:

2. inositol triphosphate (IP3) reaches the cytosol → triggers the release of Ca^{2+} from the endoplasmic reticulum and binds to calmodulin (see Ca^{2+} as the second messenger)
3. diacylglycerol (DAG) remains in the membrane → activating protein kinase C → phosphorylation of a protein → cell response

Activation **of adenylate cyclase** causes the production of the following second messengers:

1. Cyclic adenosine monophosphate (cAMP) → activation of protein kinase A → phosphorylation of a protein → cellular response
2. Cyclic guanosine monophosphate (cGMP) → activation of protein kinase G→ phosphorylation of a protein → cellular response

1 2.2.1 Receptors with enzymatic function or coupled with enzymes

Receptors with tyrosine-kinase activity

They're the most numerous and of great structural diversity. They're single-step transmembrane proteins, when interacting with the ligand, they're going to dimerize (in the free state they're monomers. The endodomain presents an area with tyrosine-kinase activity (also called the tyrosine-kinase domain) with multiple tyrosines that will trans-autophosphorylate after dimerization. Phosphorylated tyrosines then cling to signaling proteins that eventually produce a cellular effect.

Receptors for:

- Growth factors
- Cytokines
- Insulin

13. SPECIFIC AND NON-SPECIFIC DEFENSE

The body's defense against external invaders/ ANTIGENS (**Ag**) (micro-organisms: viruses, bacteria and other pathogens or macromolecules present in the air, water, food) implies the existence of two systems:

1) **the non-specific** defense system (which cannot differentiate the pathogens from each other) and

2) **the specific** defense system (which reacts specifically to each type of invader: *humoral and cellular immunity*).

13.1 Non-specific defence

Comprising the first and second lines of defense of the body:

1. First line

- Skin, mucous membranes and secretions (physical barrier)

2. Second line

1. Phagocytosis (neutrophils, macrophages)
2. NK lymphocytes ("natural killer")
3. Inflammatory reaction
4. Antimicrobial proteins (interferons, complement)

Nonspecific defense encompasses the body's totality of defense mechanisms against foreign agents that do not require the specific recognition of an Ag and thus, immune cells (which have specific receptors for Ag) are not involved.

13.1.1. The first line of defense

Features:

- develop an immediate response to aggression
- does not produce immunological memory
- does not have specificity (does not distinguish "self" from "non-self")
- the effectiveness of is average
- if is intact, constitutes a physical barrier for bacteria and viruses
- the mucous membrane (epithelial tissue secreting mucus) line the digestive, respiratory and urogenital pathways, protecting the body against the micro-organisms that penetrate these pathways

- in addition to their role as a physical barrier, the skin and mucous membranes can fight against ag with the help of chemical weapons:

    - Sweat and sebum: maintain an acid pH in the skin (pH 5) which prevents the growth and spread of their micro-organisms.
    - Mucus (secreted by mucosal cells) is a viscous liquid that physically retains micro-organisms = > facilitates their phagocytosis by macrophages.
    - Secretions (tears, saliva and vaginal secretions) contain lysozyme (an enzyme that can destroy the wall of certain bacteria)
    - The increased acidity of the stomach prevents the growth of bacteria
    - Normal flora (saprophyte) prevents the development of pathogens at this level through competition for the substrate.

13.1.2 Second line of defense (native, innate immunity)

Features:

- has low specificity, recognizes the "self" of "non-self" but not the Ag between them
- presents an immediate response (minutes, hours)
- the response is identical with each exposure
- the effectiveness of it is high
- does not present immunological memory

Phagocytosis (neutrophils, macrophages)

Phagocytosis is a non-specific defense reaction during which specialized cells (*neutrophils*/ microphages and *monocytes*/macrophages) ingest foreign particles and destroy them through an intracellular digestion process.

Phagocytes are leukocytes that have the ability to phagocytosis. Microphages intervene early in the acute inflammatory reaction and macrophages intervene late in acute inflammation and predominate in chronic inflammation. By releasing preformed (existing in cytoplasmic granules) and neo-formed (synthesized "de novo") cellular mediators, phagocytes also participate in the inflammatory reaction.

Stages of phagocytosis:

1. Migration of phagocytes near Ag and preparation of lysosomes (cellular organelles containing proteolytic enzymes)
2. Formation of cytoplasmic expansions (pseudopods) and surrounding the Ag
3. Membrane invagination with the formation of an intracellular membrane vesicles called phagosome (vacuole containing Ag)
4. Phagosome unites with lysosomes, forming the phagocytosome
5. Stacking of bacteriolytic mechanisms (i) lysosomal enzymes and (ii) oxidants such as hydrogen peroxide and oxygenated free radicals (superoxide, hydroxyl) which determine the distribution of the content
6. Elimination of degradation products

NK lymphocytes ("natural killer")

They are a subset of the lymphocytes that destroy:

- their own modified cells that lack MCH class I molecules (major histocompatibility complex antigens)
- tumor cells
- cells infected with intracellular pathogens.
- cells that have fixed antibodies (**Ac**)

Features:

- Are responsible for Ac-dependent cytotoxicity
- NK fixation on IgG-coated target cells causes release from the grain of:
  1. perforations→ form transmembrane pores in the membrane of the target cell → penetrate: Na+ and water → osmotic cytolysis
  2. → granzyme apoptosis

Inflammatory reaction

ACUTE INFLAMMATION

Definition: defense reaction of the body, of the living / vascularized tissues adjacent to an area of tissue injury or necrosis, against harmful stimuli.

Etiology:

• Non-specific factors: biological (bacteria, fungi, viruses), chemicals (insect venom, caustic substances), physical (ionizing radiations), mechanical (incisions, traumas, foreign bodies)

• Specific (immunological) factors: autoimmune diseases, hypersensitivity reactions

Role: defense of the body (elimination of the causative agent and prevention of the extension of lesions).

Duration: less than 2 weeks.

Stages:

1. Release / activation of inflammatory mediators:

Mediators may have the origin of:

A. cellular (released by cells participating in the inflammatory reaction):

- preformed: stored in the granules of cells participating in the inflammatory reaction (*histamine, lysosomal enzymes, chemotactic factors for neutrophils and eosinophils*)
- neo-formed synthesized de novo as a result of stimulation of cells participating in inflammation (*arachidonic acid derivatives, platelet activation factor, interferon, interleukins, chemokines*)

B. plasma-derived (from the activation of plasma constituents as a result of the action of etiological factors): *the complement system, the kinin system, the coagulation and fibrinolysis system*

2. Vascular reaction with the formation of inflammatory exudate
3. Cell reaction with formation of an inflammatory cell infiltrate
4. Installing of repair processes

CHRONIC INFLAMMATION

Definition: a pathological process characterized by the existence, to varying degrees, of inflammation with tissue destruction and or reparative processes.

Features:

- vascular changes are reduced / absent
- inflammatory cell infiltrate: rich in plasma cells, lymphocyte macrophages
- tissue destruction occurs as a result of the persistence of the lesion agent and the influx of inflammatory cells
- reparative processes are characterized by proliferation of connective tissue (with stretched fibrosis) and local angiogenesis

Etiology:

- infection with intracellular microorganisms (tuberculosis)
- delayed-type hypersensitivity reaction (IV)
- autoimmune diseases
- chronic exposure to an exogenous injury agent
- the presence of an irritating physical agent

Duration: weeks-months

Antimicrobial proteins (interferons, complement)

C-REACTIVE PROTEIN (CPR)

It is synthesized exclusively in the liver, a few hours after an infection. Binds specifically to bacteria, stimulating their phagocytosis. It is a specific marker of inflammation and increases proportionally with its intensity. Increased levels of CRP are found in severe trauma, bacterial infections, inflammation, surgery and during tumor growth.

INTERFERON (IFN)

A cytokine with a major role in the body's antiviral defense. It is a small protein that diffuses to neighboring cells (it is unchanged in virus-infected cells), where it causes increased antiviral defense. Thus, interferon prevents the multiplication of the virus and its propagation.

Classification:

• IFN-α and IFN-β: are released by macrophages or virally infected cells. They cause increased production of antiviral proteins by neighboring cells.

• IFN-γ: produced by lymphocytes. It increases the bactericidal and virucidal capacity of macrophages.

COMPLEMENT SYSTEM

Consisting of 20 plasma proteins that circulate in the blood in an inactive form. Activation occurs on the classical path within the specific defense or on the alternate path within the non-specific defense. Activation causes the formation of active fragments that determine:

1. lysis of foreign particles (a membrane attack complex C5b-C9 is formed, which then causes osmotic cytolysis)
2. facilitation of phagocytosis (C3b that produces opsonization of phagocyte particles)
3. chemotaxis (attraction of phagocytes - C5a, C3a)
4. stimulating the inflammatory reaction (C3a and C5a)

13.2 Specific defense (Adaptive/acquired immunity)

It comprises the body's third line of defense: the *immune system* (*immune response*: humoral and cellular).

The specific defense is the production of antibodies **(Ab**) and the generation of specialized lymphocytes against specific antigens (**Ag**). Ag are substances that can mobilize the specific immune system and cause a response; are recognized by T and B lymphocytes as "non-self" and have *immunogenicity* (the ability to stimulate the production of lymphocytes and specific Ac)

Immunity is the ability of an organism to recognize and protect itself against Ag. Immunity can be: ***naturally acquired*** (the immunity with which an organism is born, genetically determined) or ***artificially acquired*** (the immunity that an organism develops during life and is not genetically determined).

Naturally acquired immunity can be:

1. active: by effective infection with bacteria or viruses
2. passive: by transmitting of the Ac from mother to fetus (placenta or breast milk)

Acquired artificial immunity can be:

1. active: by vaccination
2. passive: by injection of serum containing Ac (rabies, snakebite, botulism)

Specific defence – characteristics:

- maybe: recognizes the "self" of "non-self"
- is oriented against a specific Ag
- the response is triggered:
    - with a latency (days, weeks) at the first contact with the antigen in the primary immune response (first contact with Ag)
    - immediately, rapidly and more effectively on subsequent exposures to the same antigen in the secondary immune response (on subsequent contacts with Ag)
- has high efficacy
- has immunological memory

Components:
1. Antigens (immunogenic, Ag)
2. Effector cells
3. Soluble mediators – immunoglobulins or antibodies (Ig or Ab)

13.2.1 Antigens

Antigens are structures recognized as foreign/"non-self" that generate a humoral and/or cellular immune response in the body.

It can be: drugs, food, fungi, bacteria, parasites, viruses, insect venom, vaccines, transplanted tissues or organs, canned blood.

The antigenic determinant (epitope) is the portion of the structure

Ag has a role in recognition and fixation on:

- Ab (Fab fragment of it)
- B lymphocytes (on their Ag receptor - BCR)
- T lymphocytes (on their Ag receptor - TCR)

Antigens HLA Antigens /Molecules of the Major Compatibility Complex (MHC)

These are structural proteins, characteristic of each individual, located on the surface of the body's cells. They have an essential role in the transplantation of some tissues or organs because they can be recognized as antigens by the host organism.

There are 2 classes (I and II). HLA class I binds to cytotoxic T lymphocytes => can initiate a cellular immune response; HLA class II binds to helper T lymphocytes=> can initiate a humoral immune response. *Role* in the double recognition by lymphocytes of endogenous and exogenous Ag.

13.2. 2 Effector cells

Antigen-presenting cells (APC)

Macrophages: the tissue form of the monocyto-macrophage system.

Dendritic cells: a population of monocytes (differentiated at the level of peripheral lymphoid organs) that presents Ag expressed on both types of MHC = > can initiate a humoral and cellular immune response.

Immunocompetent cells (lymphocytes)

B and T lymphocytes form in the hematogenous bone marrow. B lymphocytes mature (become immunocompetent) in the bone marrow,

and T lymphocytes mature in the thymus (the place where positive and negative selection occurs; T lymphocytes responding to self antigens will be destroyed).

***T lymphocytes* (LTs)** are the effectors of cellular immunity (mediated by subpopulations of T lymphocytes modulating the secretion of antibodies). Cellular immunity is mediated by living cells that attack compromised cells – usually those that have become cancer cells or have been infected. There are 2 major classes of LT:

1. **T helper lymphocytes (LTh,CD4+):** recognize the Ag expressed by APC after which they proliferate + differentiate into LTh with immunological memory and LTh1 and LTh2. LTh secretes IL-2 (activates LTc), secretes IFN-γ (activates macrophages), stimulates the differentiation of LB in plasma cells (which secrete Ac), secretes IL-5 (for the recruitment and activation of eosinophils)
2. **Cytotoxic T lymphocytes (LTc, CD8+):** recognize the Ag expressed by nucleated cells carrying APC Ag after which they proliferate + differentiate into LTc with immunological memory and directly release perforins and granzymes (similar to the action of NK lymphocytes) thus producing cytotoxicity.

B-lymphocytes (LBs) are the effectors of humoral immunity (antibody- mediated). Humoral immunity is achieved by antibodies present in the "humors" or body fluids (blood, lymph, tears, saliva, etc.). These antibodies are produced by PLASMA CELLS. LBs expresses receptors for Ag (BCR) that bind circulating (extracellular) Ag; a single type of BCR ensures the binding of a single type of antigen. The contact with Ag specific to naive LB proliferates + differentiates (it is activated with the participation of LTh2); thus initiates the clonal selection that will result in thousands of daughter cells: of the type of plasmocites that secrete Ab or of the type of LB with immunological memory.

13.2.3 Antibodies

Structure:

Antibodies are formed from 4 polypeptide chains (2 heavy chains and 2 light chains) forming an Ac monomer. Each of the 4 chains has a variable region (the binding site of Ag) and a constant region (determines the Ac class).

Describe 3 areas (fragments) of the Ac:
- two identical fragments: Fab (antigen binding) that recognise and bind Ag
- one fragment: Fc (crystallisable): provides activation of serum complement by the classical pathway, activates phagocytosis and is important in the transport of IgG from mother to fetus.

Role:

The binding of the Ag-Ab leads to the formation of the antigen-antibody complex that causes:

- Precipitation (for soluble Ag)
- Lysis (by the action of the complement: IgG + C3b has the role of opsonin that makes the bacterium susceptible to phagocytosis)
- Agglutination (for Ag milled on cells)
- Neutralization (Ag-Ac complexes prevent toxins from settling on cellular receptors and exerting their pathological effects)

Classification:

1. **IgG**
   - Single monomer
   - Capable of activating the complement system
   - The only one who can cross the placental barrier
   - Anti-toxin (neutralising toxins)
   - Opsonine (phagocytosis)
2. **IgA**
   - Monomer or dimer
   - Defense in the mucous membranes
3. **IgM**
   - Pentamer
   - First class of antibodies released by plasma cells
   - Capable of activating the complement system
4. **IgD**
   - Single monomer
   - Related only to the surface of cell B where it acts as receiver for Ag, which initiates clonal selection (role of BCR)
5. **IgE**
   - Single monomer
   - IgE-Ac complexes bind to mast cells and basophils and cause the release of histamine; therefore has a role in allergic reactions and anti-parasitic defenses

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