

Ukrainian Medical Stomatological Academy

THE DEPARTMENT OF PATHOLOGICAL ANATOMY
WITH SECTIONSL COURSE

MANUAL
for the foreign students

GENERAL PATHOMORPHOLOGY

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Навчально-методичні рекомендації англійською мовою, розроблені на кафедрі патологічної анатомії з секційним курсом ВДНЗУ УМСА асистентом Ніколенко Д.Є., професором Старченко І.І., доцентом Прилуцьким О.К.

У рекомендаціях в достатньому обсязі для кожного заняття представлені цілі вивчення теми, основні питання теми, практичні навички, які повинні бути освоєні студентами, алгоритми опису макро- і мікропрепаратів, ситуаційні задачі.

Формулювання тестів, їх кількість і варіабельний рівень труднощів, достатній обсяг для кожної теми дозволяє рекомендувати їх в якості підготовки студентів до складання ліцензованого інтегрованого іспиту «КРОК-1».

TOPIC I: Introduction to pathomorphology. Content and task of pathological anatomy. The main stages of its development. Methods of pathological anatomy diagnostic. Methods of pathomorphological investigations. .

1. Actuality of the problem.

PATHOLOGY is the study (logos) of suffering (pathos). Pathomorphology is a discipline involving both basic science and clinical practice and is devoted to the study of the structural and functional changes in the cells, tissues, and organs that underlie “diseases”. The discipline of pathomorphology forms a vital bridge between initial learning phase of preclinical sciences and the final phase of clinical subjects. Pathomorphology studies cause of the disease (etiology), the mechanisms of its development (pathogenesis), the structural alterations induced in the cells and organs of the body (morphological changes), and the functional consequences of the morphologic changes (clinical significance). It also studies the reasons and mechanisms of death - pathogenesis, pathomorphosis (variability of diseases), pathology of treatment (iatrogenic pathology, i.e. the diseases caused by wrong medical tactics).

Methods of pathomorphological researches: autopsy, biopsy, research of operating material, experimental modeling. We use the following methods of research: macroscopic, microscopic (with the help of a light, electronic, luminescent microscope), histochemical and immunohistochemical. With the help of these methods of research we can know: “what changes and in what sequence they develop, what causes of them, and also what outcomes”. Aim of studies. Study the main methods of morphology’s research; learn the description’s schema of the macro- and micropreparations, to explain the significance of the pathology.

2. Aim of studies and competence .

Study the main methods of morphology’s research; learn the description’s schema of the macro- and micropreparations, to explain the significance of the pathology.

Competence.

Integral:

It’s ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it’s characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge’s on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge’s and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of inner organs of a human. 2. To draw normal structure of the inner organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs of a human.
Physiology and pathophysiology	1. Be able to use knowledge's about different kinds of interactions of inner organs in human body. 2. To use knowledge's about disturbance of regulation of the interactions.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Pathomorphology	is a discipline involving both basic science and clinical practice and is devoted to the study of the structural and functional changes in the cells, tissues, and organs that underlie "diseases"
Etiology	is cause of the disease
Pathogenesis	is mechanisms of the disease development
Morphological changes	Is the structural alterations induced in the cells and organs of the body
Clinical significance	is the functional consequences of the morphologic changes
Tanathogenesis	Is the reasons and mechanisms of death
Pathomorphosis	is variability of diseases
Jatrogenic pathology	is the diseases caused by wrong medical tactics
Pathological Anatomy	is anatomy of an unhealthy body
Disease	is a complex social and biological phenomenon occurring due to different causes in the human organism at interaction with the environment
General pathological anatomy	is the branch of Pathological Anatomy. It studies general pathological processes. It deals with information about the signs of death, disturbances of local and general circulation, disturbance of metabolism, inflammation, morphology of immune reactions, disturbances of growth and development, compensatory processes and tumors.
Special Pathological Anatomy	studies morphology, etiology and pathogenesis of diseases, their complications, outcomes, as well as classification of the diseases and phenomena of pathomorphism.

4.2 Theoretical questions for the practical class:

Questions for self-studying:

1. Pathomorphology: its maintenance, tasks, objects of research, place in the medical science and practical health protection, relations with other sciences.
2. Tools of pathological anatomy. Biopsy: determination, purpose, basic kinds according to the methods and time of realization, clinical value.
3. Autopsy: modern tasks and methods of conducting, clinical value.
4. Modern understanding of humoral, cellular and molecular aspects of pathology. Dialectical unity of structure and function in development of pathological process.
5. Knowledge of the pathological process and diseases. Etiology, pathogenesis and pathomorphosis.

6. Organ-pathological, syndromological and nosological principles of classification of diseases.
7. Diagnosis: principles of constructions, notion about the basic disease, its complications, direct and immediate cause of death.
8. Periods of tanathogenesis. Early signs of clinical and biological death. Morphological signs of biological death and postmortem changes.
9. History of development of pathological anatomy. Works by Morgani, Rokitansky, Virhov. Theory of cellular pathology and its importance for the medical science.

Practical skills:

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate passible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Tasks of the studies:

1. To explain the role of pathological anatomy as sciences, fields of medicine and educational object. To master the methods of research of pathomorphology.
2. To analyze making stages of pathomorphology and payment of scientists in development of world pathomorphology.
3. Get acquaint with the help of the teacher with the basic forms of work in the department of pathomorphology. Trace basic stages of preparation and conducting of biopsy research (undersection of the biopsy and operative material, its fixing, preparation of the paraffinic cuts, their coloring, study of sections and formation pathohistological diagnosis), acquaints with apparatus, which are used for preparing of the biopsy.
4. Acquaints with the modern methods of pathomorphological diagnostics: common-histological, immunohistochemistry, computer morphometry, and express diagnostic of operative material.
5. In the electron-microscopic laboratory acquaints with the modern tools of ultra-structural analysis (electronic microscopic investigations, histochemistry, radioautography), trace basic stages of preparation of material for research.
6. Acquaints with the method of conducting an autopsy in the sectional hall, clinical-anatomic analysis, formation of the pathological diagnosis and conclusions about the cause of death.

Topic content:

Pathological Anatomy is one of the most important subjects in the system of physician training. During the first years you studied Human Anatomy and Physiology. Before entering the clinic, which is a temple where an unending struggle against diseases is carried on day and night, you have to understand the essence of pathological conditions (diseases), thus, it is necessary to know pathological anatomy.

Literally pathology means the study of suffering. More specifically, Pathological Anatomy deals with the material basis of the disease and its morphology. It is impossible to understand the development and consequences of the disease without the knowledge of the changes in the organism which accompany it.

Pathological Anatomy is anatomy of an unhealthy body. The word pathological originates from a Greek word with the meaning «ill». «Pathological Anatomy» means a field of

medicine dealing with the problems connected with a sick organism that is clinical features of the disease, its signs and symptoms, disturbances of physiological functions, structural changes in the organs and tissues as well as treatment and preventive measures.

Thus, Pathological Anatomy is complex knowledge about a sick person; the role of Pathological Anatomy is to study the structural changes which occur during the disease. It is closely connected with the other sciences, i.e. clinical medicine and Pathological Physiology which study the disturbances of physiological functions during the disease as well as with Microbiology, Hygiene which deal with the causes and prevention of the diseases.

Disease is a complex social and biological phenomenon occurring due to different causes in the human organism at interaction with the environment. There is no exact definition of this term but there exists a common opinion that during the disease disturbances of cellular structures and functions develop. They bring about changes in the regulatory systems which provide homeostasis, i.e. the property of the organism to adapt to the constantly changing environment. The human organism has powerful defensive and adaptive mechanisms which protect it from the disease development. That is why it is sometimes very difficult to draw a boundary between health and disease. A lot depend on the pathogenic factor influence, its duration and the whole totality of the conditions of this action, e.g. it is well known that blood clotting is a physiological process. Any injury of the vessel is accompanied by formation of a blood clot which results in arrest of the hemorrhage. On the other hand, formation of a clot in the coronary artery causes a severe disease, i.e. myocardial infarction. This example shows that a serious and dangerous pathological process occurs on the basis of normal physiological reactions and regularities but causes a new, different from the norm pathological process with special localization. The art of treatment consists in the ability to see the new quality, i.e. disease, as well as to find the means of the fight against the disease.

Pathological Anatomy studies not only the manifestations of the disease but also the reactions of the organism aimed at the protection from the disease. Thus, Pathological Anatomy studies functional morphology, i.e. functional structure of the sick organism. Every disease is accompanied by various changes in the organs and tissues. Sometimes these changes are considerable; they are well seen during the examination with a naked eye. Such changes are observed when the disease is neglected, they are difficult to treat. As the very primary manifestations of the disease may be inconsiderable, it may seem that at the beginning of the disease structural changes do not develop, and only functional changes are present. But modern methods of investigation (electronic microscopy, luminescent microscopy, histochemical and enzyme techniques, autoradiography) allow concluding that the disease begins with the changes of the cellular structures, changes in the state of mitochondria, endoplasmic reticulum, ribosomes, lysosomes, Golgi's apparatus etc. The newest methods of study allow to investigate the structure and function

as entity. There are no functional changes which are not connected with structural ones. There are no purely functional diseases, that are diseases which are not accompanied by the changes in the cell structure.

Pathological Anatomy studies outcomes of diseases. Each disease may have different outcomes: recovery, development of the pathological state which is compensated by the organism and death (arrest of vital functions and systems of the organism, i.e. central and vegetative nervous and endocrine).

Pathological Anatomy is not limited to study of morphological changes which occur in the organism of a sick person. It uses the information about morphology to reveal the etiology and pathogenesis of the disease.

Etiology and pathogenesis

The term «etiology» is purely medical one. It appeared in ancient times. For many centuries the essence of the term has been changing. Thus, Claudius Galen used it as a synonym to «pathology», but he also considered that etiology is a sum of internal and external factors as

well as pathological changes. Contemporary specialists consider that it is only a cause of a disease (microbe, virus, and trauma).

Literary «etiology» means study of the causes of the disease, thus its philosophical concept is equal to cause.

Pathogenesis is a mechanism of development of the pathological process (disease). The basis of this genesis is common biological laws of regulation of physiological processes. The mechanisms include proper physiological processes (reflex) and biochemical shifts which are the base of physiological processes. These shifts are reflected in structural transformations. In other words, pathogenesis of the process is closely connected with its histogenesis, the latter allows to conclude about functional aspect of the process. Morphological changes have definite regularities of development; they illustrate separate phases of the process (usually stereotypical and cyclic) and make the process stable. Thus, pathogenesis means not only functional (physiological, biochemical, immunological) shifts but also structural changes in definite tissues and organs. Pathogenesis also means localization of the process which is reflected in the clinical picture of the disease. Pathogenesis is connected with the etiology of the disease (its internal and external causes). Very often individuality and heredity determine the ways of interaction of the organism and the environment as well as interorgan correlations. The ability of the organs and the whole organism to rebuild the rhythm of its excitement to change its properties creates a very sophisticated mechanism. The problem of pathogenesis is very complicated. At present it is one of the most important aspects of the theory of disease. The knowledge of the pathogenesis enables the physician to interfere the disease development. The mechanisms and reactions of pathogenesis have adaptive and compensatory character. Neural and humoral mechanisms are the most important. The primary regularity of pathogenesis is self-development, self-movement, and self-regulation. It means that once the process appeared, it develops in chain-like manner, like a chain consisting of many links which manifest themselves consequently. This regularity embraces all physiological phenomena. At present it is known as a new branch of science, cybernetics: theories, hypothesis and viewpoints about general questions of management and communication in automatic machines and living organisms.

Tasks of Pathological Anatomy

The changes which occur in the organism in different diseases can be divided into several categories. It means that the changes in different organs and tissues are similar, they develop in different cells no matter where they are located: in the liver, kidneys, heart. These common pathological processes are studied by the branch of Pathological Anatomy which is called general course (general pathological anatomy). It deals with information about the signs of death, disturbances of local and general circulation, disturbance of metabolism, inflammation, morphology of immune reactions, disturbances of growth and development, compensatory processes and tumors. All these processes are the subject of general pathological anatomy which studies general regularities of the processes.

Special Pathological Anatomy also studies morphology, etiology and pathogenesis of diseases, their complications, outcomes, as well as classification of the diseases and phenomena of pathomorphism.

The changes in the morphological picture of the disease under the influence of medicinal preparations and improvement in the life conditions are called pathomorphism.

Pathological Anatomy has its methods of investigation: autopsy (dissection), biopsy, experiment.

Autopsy allows to reveal the cause of death, peculiarities of the course of the disease, to evaluate the efficiency of the drugs, instruments that is to perform clinical anatomical testing to improve the quality of diagnosis and thus to improve the qualification of a specialist. An autopsy demonstrates neglected disease which caused death. But it also gives information about morphological manifestations of the disease in case the pathologist studies the changes in the systems and organs which are not involved by the process. For example, all stages of tuberculosis which are well known to the physician were studied in this manner. This method

was also used to study the manifestations of cancer and pre-cancerous states. Dissection of the corpse is not the purpose but means of investigation, it is necessary to enrich medical practice with new knowledge or to aid justice. Ethical duties of the pathologist include professional secret about everything found during the study.

An autopsy is performed on a cadaver or on organs removed in toto. First of all, the topographic relationships of individual organs are examined before their removal. This is followed by a macroscopic assessment, description of findings, and diagnosis. This method enables the autopsy to be performed quickly. After samples have been taken for histologic study, the organs are replaced in the body cavities. This autopsy technique is not suitable to demonstrate topographic relationships to a clinician (particularly a surgeon) or to a student.

Biopsy is also very important to study the disease pathology. It consists in visual examination of pieces of tissue or entire organs removed surgically. Biopsy includes research of the material taken from a living organism. This term was introduced in 1879 by E. Besnier. The first biopsy investigation was done in 1864 by Dushen de Boulogne for diagnosis of pseudohypertrophic mastopathy.

Biopsy is performed with the purpose of early diagnosis of the tumour, verification of the tumour, ascertainment of the histogenesis and anaplasia degree for tumours, determination of efficacy for operative procedures and prognosis for tumor, determination of characteristics of non neoplastic processes.

Biopsy of tissues can be performed by several techniques and material processed for histology.

- a) **Excision biopsy** — total dissection of the injured tissue or organ with subsequent study.
- b) **Incision biopsy** — taking of a part of the injured tissue for studying.
- c) **Open (operative) biopsy** — taking biopsy after surgical opening of the injured focus.
- d) **Needle (aspiration) biopsy** — taking of the specimen by drawing it off through a needle or trochar.
- e) **Endoscopic biopsy** — taking of the specimen by instrument through the endoscope or by needle under endoscopic control.
- f) **Puncture biopsy**—taking of the small cylindrical specimen through puncture or small incision.
- g) **Brush biopsy**—taking of the biopsy material with help of the brush catheter with subsequent study of the attached specimen.
- h) **Shave biopsy**—taking the material with the help of the razor or surgical edge (is used for biopsy of the tissue which is prominent above the skin or upper layers of the derma).
- i) **Trepanobiopsy**, curettage, smear, smear-imprint, forceps biopsy, biopsy by wash-out of operative wound and ulcerative defect, casual biopsy are also used.

Samples can also be assessed by electron microscopy.

Experiment is performed in scientific research to reveal distinctive features of the diseases, as well as the efficiency of the drugs and other.

Evolution of Pathological Anatomy

Ancient history of diseases dates back to the time of Hippocrates (460—377 B.C.). He first affirmed that disease was alteration in the body and not due to some curse or evil spirit.

As dissection was prohibited for many centuries, Pathological Anatomy began to develop as a separate branch of science only in the 16th century. The first scientific book in pathology was the work of an Italian anatomist

J. Morgagni (1682—1771) «On site and causes of diseases revealed by anatomist» (published in 1761). The author had studied 700 corpses.

The first textbook on Special Pathological Anatomy written by A.Beily (1799—1858) was published in the middle of the 18th century.

In the 19th century pathology departments were founded in Berlin, Paris, Vien, Moscow, Petersburg. Such prominent scientists as M. Schleiden (1804— 1881), T. Schwann (1810—1882), K.Rokitansky (1804—1878), R. Virchow (1821—1902). K.Rokitansky and R.Virchow

being pathologists contributed much to pathology development. K.Rokitansky was the last representative of the humoral theory of pathology which reigned during many centuries but it did not have any scientific base.

R. Virchow, the greatest German pathologist, brought the changes in the body to the level of cells by his famous publication of «Cellular pathology» in 1858. This theory proved true by microscopical study of sections cut by microtomes made possible by technological advances in machine manufacture.

In the 20th century pathology has been developing rapidly. This century, further studies in medical sciences have made possible cellular study at molecular, ultrastructural level using new modern methods of investigation (electronic and luminescent microscopy, histochemical and enzyme techniques, autoradiography).

Self-check materials:

1. The most important kind of pathologist's activity is:
 - a) participation of medical conference
 - b) establishment of diagnosis in one's life
 - c) embalming of body
 - d) taking of section material for research
 - e) notice of case report
2. Basic direction of pathological development is:
 - a) clinical
 - b) structural
 - c) laboratory and diagnostic
 - d) clinicoanatomic
 - e) macromicroscopic
3. The problem of the bioptic researches is
 - a) writing of clinical epicrisis
 - b) writing of anatomic epicrisis
 - c) construction of differential diagnosis
 - d) writing of clinicoanatomic epicrisis
 - e) discovering of primary cause of death
4. The kind of biopsy is:
 - a) exophytic
 - b) foliaceous
 - c) incisional
 - d) endophytic
 - e) correlative
5. Dissection of body start from:
 - a) dissection of head
 - b) dissection of organs of neck
 - c) dissection of organs of abdominal cavity
 - d) examination of body
 - e) acquaintance with case report

TOPIC II: Morphological changes of cells in response to stress and toxin induced injury (parenchymatous degenerations / cells degenerations): protein, fatty and carbohydrate intracellular accumulation.

1. Actuality of the problem.

Intracellular accumulations (parenchymal degenerations or dystrophies) are the accumulation of abnormal amounts of various substances in the cells.

Parenchymatous degenerations occur in functional cells such as: cells of a liver, kidneys, a myocardium and are characterized by accumulation of proteins, fats and carbohydrates in their cytoplasm. It is accompanied by decrease (reduction) of function of enzyme systems and occurrence of structural changes in cells.

Knowledge of these processes is necessary for understanding of the pathogenesis of the diseases and for the clinic-anatomical analysis of the autopsy.

2. Aim of studies and competence. Learn the morphological features of the intracellular accumulations; to explain the causes and mechanisms of their development; to estimate outcomes and determine the significance for organism.

- To interpret morphology of stereotyping and specific injury of cellular organelles and cellular-interstitial cooperations.
- To explain morphology of reversible and irreversible damage of cells and tissues.
- To explain the intracellular mechanisms of trophics and causes of their disturbances.
- To interpret morphology of intracellular accumulation of proteins, carbonhydrates, lipids and their consequences.
- Learn the classification of the intracellular accumulations according to prevalence of morphological changes, to the prevalence of that or another type of metabolism, to the influence of genetic factors and to the spreading of the process.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological

	structure of parenchyma and stroma of inner organs. 2. To draw normal structure of inner organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of inner organs parenchyma reactions in response to neuro-humoral stimulation. 2. To use knowledge's about disturbance in parenchyma trophic function due to influence from pathological factors.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Lesion (alteration)	is a change in the cell structure, intercellular substance, tissues, and organs accompanied by disturbances in their vital activity.
Translation	means transfer of a segment of one chromosome to another nonhomologous chromosome.
Deletion	means loss of part of the DNA from a chromosome
Trophism	is the entity of mechanisms responsible for nourishing of the definite structure and determining its metabolism
Infiltration	abundant invasion of metabolic products from the transportation system to the cell followed by their accumulation
Decomposition	this is destruction of cellular ultrastructure (lipoprotein complex from cellular membranes) with accumulation within a cell
Disturbed synthesis	intracellular synthesis of the substances which are not produced normally (e.g. amyloid, glycogen in renal tubular epithelium in diabetes)
Transformation	formation of products of one type of metabolism from the common primary products, e.g. increased polymerization of glycogen from glucose.
Pyknosis	is condensation of nucleus chromatin
Karyolysis	is dissolution of the nucleus
Cell death	is that state in which cells are incapable of any function, including energy generation, homeostatic control, motility, uptake of materials, synthesis, export cell communication and excitability, and reproduction

4.2 Theoretical questions for the practical class:

1. Pathology of cell as an integrative concept.
2. Pathology of cellular nucleus, of mytosis, chromosomal aberrations and chromosomal diseases.
3. Stereotyping injury of ultrastructures in reply to the varied influencing.
4. Pathological changes of cellular membranes and cells during the damage of cytolemma, endoplasmic reticulum, Goldgy complex, mitochondria, lysosomes, peroxisomes.
5. Pathological changes of the cytoskelet (microfilaments, microtubules). Specific changes of ultrastructures: "diseases" of receptors, lysosomal, mitochondria, peroxisomal "diseases".
6. Intracellular accumulations: causes, morphological mechanisms of development (infiltration, transformation, decomposition, perverted synthesis).
7. Classification: according to prevalence of morphological changes in specialized parenchymatous or stromal elements (parenchymatous, stromal-vascular and mixed);

8. Classification: according to the prevalence of that or another type of metabolism (proteins, lipids, carbohydrates, minerales);
9. Classification: according to the influence of genetic factors (hereditary and acquired) and to the spreading of the process (diffuse and local).
10. Intracellular accumulations of proteins: hyaline-droplet, balloon (hydropic) and keratinous degenerations. Morphologic characteristics, causes and pathogenesis.
11. Intracellular accumulations of lipids (fatty dystrophies): fatty degeneration of the myocardium, liver, kidneys. Morphologic characteristics, causes, pathogenesis. Steatosis.
12. Intracellular accumulations of carbohydrates. Degenerations associated with disorders of glycogen's metabolism. Morphologic characteristics, causes, pathogenesis of glycogen metabolic disorders in diabetes mellitus.
13. Colloid dystrophy. Morphologic characteristics, pathogenesis. Cystic fibrosis.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **“Fatty degeneration of the Myocardium (“Tiger’s Heart”)**”. Pay attention to the organ’s size, expansion of the chambers, soft texture. Characterize the appearance of the sectioned myocardium, pay attention to the greenish-yellow color. Describe the appearance from endocardial side. *What morphological changes develop in cardiomyocytes and intracellular organelles?*
2. **“Lipoid nephrosis”**. Pay attention to the organ size, flabby texture and white color of the parenchyma. Such kidney is called “large white Kidney”. *How do you characterize the type of the sectioned tissue? What are the causes of such changes?*
3. **“Fatty degeneration of the Liver”**. Pay attention to the organ size, flabby texture, yellowish-ochre color of the parenchyma on the cut. Such liver is called “Goose Liver”. *In what cases such changes may be? What are possible outcomes?*
4. **“Fatty degeneration of the Liver (“False Nutmeg Liver”)**”. Pay attention to the organ size, flabby texture. The liver looks lumpy coloration with appearance yellowish-gray spots on the brown background. *How do you characterize the type of the sectioned tissue? What are the causes of such changes?*

Microslides

Slide 1. Fatty degeneration of the Liver (ought to be drawn)

Small optically empty vacuoles are diffusely seen in the cytoplasm of hepatocytes. They are created on the place of fatty droplets, which had been soluted with alcohol during preparation of the slide.

Slide 2. Kidney in Diabetes Mellitus (ought to be drawn)

The red color granules of glycogen can be found with large magnification in the epithelial cells of Henley’s loops and in the lumen of kidney’s tubules.

Slide 3. Keratinized dystrophy of an epidermis (ought to be drawn)

It is seen an excess of keratin material in keratinizing layer of skin epidermis. It looks as bright pink broad layer on the surface of the epidermis.

Slide 4. Hyaline-droplets degeneration of Kidney (ought to be drawn)

Epithelial cells of renal tubules are increased. Cytoplasm of these cells contains large bright pink hyaline-like inclusions.

Topic content:

Lesion (alteration) is a change in the cell structure, intercellular substance, tissues, and organs accompanied by disturbances in their vital activity.

There are different morphological manifestations of a lesion in the cells and tissues. Subcellular alteration, which largely occurs as a response to more or less constant stimuli and intracellular accumulation of a number of substances, due to the disturbances in cellular metabolism or excessive storage, as well as cell death (necrosis and apoptosis) have been described in the cells.

CELLULAR INJURY

Visible changes occur in the cells as a result of noxious agents, the degree of changes varying with the severity of the damaging processes: with minor damage the repair mechanisms change, more severe damage results in cell death. There are a lot of genetic and acquired causes of cell injury.

Genetic causes of cellular injury producing disease may result from one of the following abnormalities:

1. Abnormalities of chromosomes.
2. Abnormalities of genes carried by chromosomes.
3. Disorders with multifactorial inheritance.
4. Disorders with variable genetic pattern.

Abnormalities of chromosomes

There are abnormalities in the number and/or morphology of chromosomes. During meiosis in gametogenesis, two homologous chromosomes rather than moving to the opposite poles of the dividing cell, instead move to the same side so that one germ cell receives both chromosomes and the other germ cell none. This is referred to as *chromosomal disjunction*. The main examples of chromosomal nondisjunction are: Turner's syndrome (monosomy 45, XO), Klinefelter's syndrome (trisomy 47, XXY), Down's syndrome (trisomy 21 involving autosome 21).

When one homologous chromosome in meiosis or one chromatid in mitosis fails to reach the pole of dividing cell and is left out of the nucleus of the daughter cell, it is called **anaphase lag**. This results in one normal daughter cell and the other with monosomy.

A great deal of inherited and acquired structural abnormalities of the chromosomes have been described.

Translocation means transfer of a segment of one chromosome to another nonhomologous chromosome.

It may be of either of the following types: 1) balanced translocation, when the two fragments of chromosomes exchange material without any loss of material; 2) Robertsonian translocation, when two acrocentric chromosomes lose their short arms and fuse at the centromere so that eventually the cell is left with 45 chromosomes.

Deletion means loss of part of the DNA from a chromosome. Deletion may be from terminal or middle portion of the chromosome. When both ends of a chromosome are lost and the two damaged ends join together, they form a ring chromosome.

Abnormalities of genes carried by chromosomes

Mendelian disorders are the result of mutation of a single gene of large effect. The term mutation refers to heritable alteration in the genome, more often affecting a single base in the gene so that protein synthesis is interfered with. The common types of mutations are point mutation and frameshift mutation. Mutations may be inherited from a parent, or may occur as a result of environmental influence such as radiation, chemicals and viruses as occurs in carcinogenesis.

The inheritance pattern of genetic abnormalities may be dominant or recessive, autosomal

or sex-linked. A dominant gene produces its effects, whether combined with similar dominant or recessive gene. Recessive genes are effective only if both genes are similar. However, when both alleles of a gene pair are expressed in heterozygote state, it is called codominant inheritance. A single gene may express in multiple allelic forms known as polymorphism. Genes on Y-chromosome are determinant for testis and are not known to cause any sex-linked disorder. Therefore, all sex-linked disorders are, in fact, X-linked disorders. All people carrying abnormal gene pairs for a character are affected differently. Penetrance means mathematical expression of mutant gene-character as present in the individual, while variable expressivity is variable expression of mutant gene in the different individuals.

Disorders with multifactorial inheritance. These are disorders which result from the combined effect of genetic composition and environmental influences. Some normal phenotypic characteristics have also multifactorial inheritance, e.g. the colour of hair, eye, skin, height and intelligence. Some examples of disorders where environmental influences unmask the mutant genes are:

- 1) autosomal recessive inheritance: beta-thalassaemia, sickle cell anemia, albinism, Wilson's disease etc;
- 2) autosomal codominant inheritance: HLA antigens, blood group antigens;
- 3) autosomal dominant inheritance: family polyposis coli, hereditary spherocytosis, neurofibromatosis, Marfan's syndrome etc;
- 4) sex-(X) linked recessive inheritance: haemophilia A, diabetes insipidus etc;
- 5) sex-(X) linked dominant inheritance: hypophosphataemic rickets, Incontinentia pigmentosa etc.

The causes of acquired damage of cells are various. Their main groups are the following:

1. Reduced oxygen supply (respiratory disease, cardiovascular disease, anemia).
2. Physical agents (mechanical trauma, excessive heat or cold radiations).
3. Chemical agents (these continue to increase enormously with the complexity of industrial processes).
4. Toxins (bacteria, plants, animals e.g. snakes).
5. Viruses.
6. Abnormal immunological reaction (hypersensitivity states, glomerulonephritis).
7. Nutritional deficiencies (vitamin deficiency and malabsorption syndromes).

Cellular or tissue metabolism is called trophism. **Trophism** is the entity of mechanisms responsible for nourishing of the definite structure and determining its metabolism.

Trophism mechanisms are cellular and extracellular:

- 1) cellular: autoregulation within a cell (enzymes);
- 2) extracellular: transportation systems (blood, lymph); endocrine regulation; nervous regulation.

There are several morphogenetic mechanisms of degenerations:

- 1) ***infiltration***: abundant invasion of metabolic products from the transportation system to the cell followed by their accumulation;
- 2) ***decomposition***: this is destruction of cellular ultrastructure (lipoprotein complex from cellular membranes) with accumulation within a cell;
- 3) ***disturbed synthesis***: intracellular synthesis of the substances which are not produced normally (e.g. amyloid, glycogen in renal tubular epithelium in diabetes);
- 4) ***transformation***: formation of products of one type of metabolism from the common primary products, e.g. increased polymerization of glycogen from glucose.

Organ dependence has been found according to different morphogenetic mechanisms. Infiltration is more characteristic for the renal epithelium; but decomposition for the heart, transformation and disturbed synthesis are more characteristic for the liver.

Cellular reactions to damage depend on the type, duration, and severity of injury induced. The response can range from a minimal and reversible disturbance of cell volume to massive irreversible swelling with a concomitant loss of cell function, followed by death. When

injury develops rapidly, it is conventionally referred to as «acute injury». The factor that ultimately determines whether a cell will survive or succumb after injury remains to be unequivocally established. Irreversibility is probably attributable to the effect of the loss of several vital functions coupled with increased degradation of intracellular components.

Recent studies indicate that in the early stages of cell injury there are significant losses of phospholipids from cell membranes. This leads to functional alterations of the cell, presumably resulting from activation of intracellular phospholipases.

If stress is sufficiently prolonged, the cells will certainly die; perhaps this occurs when the synthesis of a certain vital molecule or molecules is sufficiently compromised that the renewal of cell substance is critically impaired. In less intense and prolonged forms of stress, termed «chronic injury», cells are able to adapt to environmental abnormalities to the extent that they are capable of augmented rather than diminished function.

Cells may adapt to a pathological (disease) stimulus by extending the three normal physiological adaptive responses: 1. Increased cellular activity — increased functional demand on a tissue can be met by increase in cell number (hyperplasia), as well as by increase in cell size (hypertrophy). 2. Decreased cellular activity — cell atrophy. 3. Alteration of cell morphology (degeneration, apoptosis, necrosis).

The response of cells to an adverse environment is conditioned by numerous intracellular and extracellular factors. These can be classified into four broad categories: extracellular and intracellular milieu, pattern and degree of metabolic activity, level of cell differentiation, and amount, and expression of information contained in the genome.

Studies of acute injury caused by a variety of noxious agents on both isolated cells and tissue have shown a striking similarity in the types and sequence of morphologic changes, regardless of the nature of the injurious agent. The initial event, occurring almost immediately after exposure of a cell to a noxious environment, is a loss of cell volume control, which is rapidly followed by a decrease in the optical density of the cytoplasm because of intracellular swelling (*hydropic change*) and eventual accumulation of lipid droplets (*fatty change*). If the noxious agent is particularly toxic, additional alterations are seen: violent movements of the plasma membrane followed by the development of bizarre pseudopodia and blebs of the plasma membrane, nuclear swelling, condensation of nucleus chromatin (*pyknosis*), dissolution of the nucleus (*karyolysis*), and finally lysis of the cell (*cytolysis*).

Cell death is that state in which cells are incapable of any function, including energy generation, homeostatic control, motility, uptake of materials, synthesis, export cell communication and excitability, and reproduction.

Protein intracellular accumulation

Hyalin drop accumulation occurs when hyalin-like protein drops filling the entire cytoplasm are formed. We usually observe this accumulation in the kidneys, liver, myocardium. Macroscopic study does not reveal any changes. The outcome is unfavorable because of coagulative necrosis.

In hydropic change vacuoles of cytoplasmic fluid appear in the cytoplasm. It develops in the kidneys, skin, liver, muscles, nerves.

Macroscopic study does not reveal any changes.

Microscopic findings are as follows: the nucleus is displaced to the peripheral areas and there are vacuoles in the cytoplasm. It is often caused by viral herpes and cachexia.

The outcome of this cellular change is unfavorable because of colliquation necrosis.

Intracellular fatty accumulation

It is known that cellular cytoplasm is mainly formed of lipids, which, together with proteins form lipoprotein complexes (cellular membranes). Besides, there is neutral fat, it is localized in the fat depots, i.e. subcutaneous fat, mesentery, subepicardial fat etc.

For identification of different kind of fats we usually use special reactions (staining): Sudan III — stains fat red, Sudan IV — black, Nile blau sulfat — stains fatty acids blue and neutral fats red.

Disturbance of fat metabolism may manifest as:

- appearance in the place where it does not appear under normal conditions (e.g. in the myocardium);
- appearance of fat of unusual composition;
- increase of fat amount in the places where it is present under normal conditions (e.g. in the fat depots).

The main cause of fatty change is hypoxia which may be due to:

- a) disturbances in transportation systems (e.g. in patient with chronic cardiovascular and chronic pulmonary insufficiency);
- b) chronic intoxications (e.g. alcoholism);
- c) cachexia, avitaminosis;
- d) infections (e.g. Diphtheria, tuberculosis). The heart, liver, kidneys are damaged most frequently.

Its manifestations in the myocardium are impressive. It is called «tiger's heart». Microscopically in «tiger's heart» we can see dust-like or small-capsule adiposity on the cardiomyocytes. It is observed in the papillary muscles and trabecules of the ventricles in the form of bands (surrounding the veins), because of hypoxia, which is more express surrounding the veins (when compared with the arteries). Macroscopically the heart is enlarged; the chambers are stretched, flabby.

The liver also has impressive appearance. It is called 'goose's liver' *Macroscopically* the liver is enlarged, flabby. Fat drops are seen on incision. The colour is ochre yellow.

Microscopically dust-like, small- and large drops in the liver's cells are observed.

The kidneys look like «large white kidney». They are enlarged, flabby. The cortical substance is gray with yellow drops.

The outcome of fatty change depends on the stage. It is seldom reversible. Necrosis and sclerosis usually develop.

Intracellular carbohydrate change

Carbohydrates are divided into 3 groups:

- 1) polysaccharides (glycogen);
- 2) mucopolysaccharides;
- 3) glycoproteides (mucin, mucoid).

There are several special reactions for identification of these carbohydrates, PAS or SHIK reaction and carmine according to Best are used for identification polysaccharides (glycogen) and mucopolysaccharides. Polysaccharides and mucopolysaccharides are stained dark pink or red. Staining according to Haile — for identification glycoproteides. Glycoproteides are stained blue.

Glycogen metabolism disturbance is significant in the human pathology. It is known that glucose which enters the organism with the food polymerizes to glycogen which accumulates in the liver and muscles and is called labile glycogen.

Glycogen in the nervous cells, endothelium, connective tissue, cartilages and other cells is called stable glycogen.

Disturbance of glycogen amount manifests with:

- increase or reduction in the amount in the tissues where it is present under normal conditions;
- its appearance in the areas where it is not present under normal conditions.

Glycogen metabolism disturbance occurs in diabetes mellitus. In this disease insulin insufficiency causes glucosuria and hyperglycemia. Glycogen amount in the tissues reduces sharply (e.g. in the liver) which causes its fat infiltration (fatty liver degeneration). Glucosuria causes changes in the kidneys. Glycogen infiltration of the tubular epithelium develops (we observe glycogen in the cells and lumens). In the glomeruli, microangiopathy develops due to their increased permeability for sugar and protein. It's called intercapillary (diabetic) glomerulonecrosis.

Storage diseases

There are a lot of diseases which are due to hereditary factors and connected with metabolism disturbance. Those diseases are called storage diseases or enzymopathy.

A few general comments can be made about all storage diseases:

1. All the storage diseases occur as a result of autosomal recessive, or sex-(X)linked recessive genetic transmission.
2. Most of the storage diseases are lysosomal storage diseases. Out of the glycogen storage diseases, only type II (Pompe's disease) is due to lysosomal enzyme deficiency.

According to the type of metabolism disturbance storage diseases have been classified into proteinoses, lipidoses and glucogenoses. The type of proteinoses, lipidoses and glucogenoses depends on the defect in the enzyme.

The most frequent of them are described in the above diagrams.

PROTEINOSES

Disease	Enzyme	Organs in which pathologic proteins accumulate
Cystinosis	-	Liver, kidney, spleen, eyes, skin
Tyrosinosis	Tyrosine-aminotransferase	Liver, kidney, bones
Phenylpyruvic oligophrenia	Phenylalanines-hydroxylase	Central nervous system, muscles, skin, blood, urine

Cystinosis is a rare metabolic disease with an autosomal recessive inheritance. It is characterized by deposition of an extraordinary amount of cystine in different organs of the body, particularly the kidneys. In children, cystinosis is the most common cause of proximal renal tubular acidosis as seen in Fanconi syndrome. Deposition of cystine may also occur in brain, bones, liver, lymph nodes, fibroblasts, leukocytes, cornea, conjunctiva, thyroid, pancreas and intestines. Depending on the degree of involvement, there are different types of cystinosis: infantile (nephropathic), adolescent (intermediate) and adult (benign) type (Schneider JA, Katz B, Melles RB., 1990).

Nephropathic cystinosis is transmitted as an autosomal recessive trait with an incidence of 1 in 200 000 live births. The actual defect is located at the level of lysosomal transportation. The infantile or nephropathic cystinosis involves many organs and systems particularly kidneys which are the first to get involved leading to renal insufficiency. In adolescent type nephropathy is mild and renal involvement progresses very slowly. In the adult type renal involvement is not seen. Recently the disease is classified into two types: nephropathic cystinosis and non-nephropathic cystinosis. The nephropathic type is progressive, starting with symptoms between 6 and 18 months of age whereas non-nephropathic type is found in childhood at the age of 4—5 years and in adolescent 12—15 years.

The extrarenal signs of cystinosis are numerous and are caused by intracellular accumulation of cystine in various organs, which continues even after renal replacement therapy. The most prominent features are rickets and growth retardation. Despite intensive supplementation with fluids, electrolytes, vitamins and calories, it is not possible to achieve a normal growth rate. The eyes are involved early extensively. Patchy retinal depigmentation, sparkling crystal in the cornea and abundant crystals in the conjunctiva are observed.

Phenylketonuria (PKU, phenylpyruvic oligophrenia) with its associated hyperphenylal-aninemia (HPA) and mental retardation, is a classic genetic disease. The disorder is caused by a mutant allele at the phenylalanine hydroxylase (PAH) locus that results in lack of functional PAH, the liver enzyme required for hydroxylation of phenylalanine. The disease is environmental in that the clinical phenotype is produced by the presence in food of L-phenyl-alanine, an essential amino acid. Thus, combining dietary

phenylalanine with lack of phenylalanine catabolism produces hyperphenylalaninemia, and this leads to mental retardation. Successful treatment requires control of the hyperphenylalaninemia. The relationship between hyperphenylalaninemia and brain dysfunction in PKU is indisputable, even though the proximate cause of the brain damage is unknown. Children born with even the most severe form of PKU can have normal cognitive development when dietary treatment begins in early infancy and the blood phenylalanine concentration is maintained at near normal or normal levels .

Woolf and Vulliamy in 1951 were the first to suggest that the levels of phenylalanine and the biochemical byproducts of hyperphenylalaninemia could be reduced by restricting the dietary intake of phenylalanine. Two years later, Bickel et al. followed this suggestion by constructing a phenylalanine-restricted diet and using it to treat a child with PKU who was mentally retarded. They demonstrated that the diet produced both a marked reduction in the blood phenylalanine concentration and improvement in behavior.

During the next few years, a number of infants known to be at risk for PKU were diagnosed and begun on the diet soon afterbirth. Follow-up studies of these infants indicated that, under these conditions, the diet could prevent mental retardation. This led to newborn screening for PKU which, by the mid-1960s, was routine throughout the United States and, by the early 1970s, was routine throughout most of the developed world. Over 150 million infants now have been screened, and over 10,000 have been detected with PKU and have been treated with diet.

Some important forms of lipidoses are described below.

LIPIDOSES

Disease	Enzyme	Organs in which pathologic lipids accumulate
Gaucher disease - cerebrosid-lipidosis	Glycocerebrosi-dase	Liver, spleen, bone marrow, central nervous system
Niemann-Pick disease (sphingo-myelinlipido-sis)	Sphingomyelinase	Liver, spleen, bone marrow, central nervous system
Tay-Sachs disease (amaurotic idiopathy)	Hexosaminidase	Central nervous system, retina, spleen, liver
Normann-Landing disease (generalized gangliosidosis)	B-galactosidase	Central nervous system, nervous bands, liver, spleen, bone marrow, kidneys

Gaucher's Disease

This is an autosomal recessive disorder in which there is deficiency of lysosomal enzyme, gluco-cerebrosidase, which normally cleaves glucose from ceramide. This results in lysosomal accumulation of glucocerebroside (ceramide-glucose) in phagocytes of the body and sometimes in the neurons. The main sources of glucocerebroside in phagocytes are the membrane glycolipids of old leukocytes and erythrocytes, while the deposits in the neurons consist of gangliosides.

Clinically, there are 3 types of Gaucher's disease:

Type I or classic form is the adult form of the disease in which there is storage of

glycocerebrosides in the phagocytes of the body, principally involving the spleen, liver, bone marrow and lymph nodes. This is the most common type comprising 80% of all cases of Gaucher's disease.

Type II is the infantile form in which there is progressive involvement of the central nervous system.

Type III is the juvenile form of the disease having features in between type I and type II, i.e. they have systemic involvement like in type I and progressive involvement of the CNS as in type II.

The clinical features depend upon the clinical subtype of Gaucher's disease. In addition to involvement of different organs and systems (splenomegaly, hepatomegaly, lymphadenopathy, bone marrow and cerebral involvement), a few other features include pancytopenia, or thrombocytopenia secondary to hypersplenism, bone pains and pathologic fractures. Microscopically large number of characteristically distended and enlarged macrophages called Gaucher cells which are found in the spleen, liver, bone marrow and lymph nodes, and in the case of neuronal involvement, in the Virchow-Robin space. The cytoplasm of these cells is abundant, granular and fibrillar resembling crumpled tissue paper. They have mostly a single nucleus but occasionally may have two or three nuclei. Gaucher cells are positive with PAS, and Prussian-blue reaction indicating the nature of accumulated material as glycolipids admixed with haemosiderin. These cells often show erythro-phagocytosis and are rich in acid phosphatase.

Niemann-Pick Disease

This is also an autosomal recessive disorder characterized by accumulation of sphingomyelin and cholesterol. Majority of the cases (about 80%) have deficiency of sphingomyelinase which is required for cleavage of sphingomyelin, while a few cases probably result from deficiency of an activator protein.

The condition presents in infancy and is characterized by hepatosplenomegaly, lymphadenopathy and physical and mental underdevelopment. About a quarter of patients present with familial amaurotic idiocy with characteristic cherry-red spots in the macula of the retina.

The storage of sphingomyelin and cholesterol occurs within the lysosomes, particularly in the cells of mononuclear phagocyte system. The cells of Niemann-Pick disease are somewhat smaller than Gaucher cells and their cytoplasm is not wrinkled but is instead foamy and vacuolated which stains positively with fat stains. These cells are widely distributed in the spleen, liver, lymph nodes, bone marrow, lungs, intestine and brain.

GLUCOGENOSES

Disease	Enzyme	Organs in which pathologic products accumulate
Gierke's (type 1)	Glucose-6-phosphatase	Liver, kidneys
Pompe's (type 2)	Acid -L-glucosidase	Muscles
MacArdle's (type 5)	System of muscles's phosphorilase	Muscles
Hers' (type 6)	Liver's phosphorilase	Liver
Forbes-Cori (type 3)	Amylo-1,6-glucosidase	Liver, muscles, heart
Andersen's (type 4)	Amylo-1,4—1,6-trans-glucosidase	Liver, spleen, lymphatic glands

In the type 1, 2, 5, 6 — the structure of glycogen in the tissues is not changed. In the type 3,4 — glycogen structure is changed.

Gierke's disease (type 1)

This condition is inherited as an autosomal recessive disorder due to deficiency of enzyme, glucose-6-phosphatase. In the absence of glucose-6-phosphatase, excess of normal type of glycogen accumulates in the liver and also results in hypoglycaemia due to reduced formation of free glucose from glycogen. As a result, fat is metabolized for energy requirement leading to hyperlipoproteinemia and ketosis. Other changes due to deranged glucose metabolism are hyperuricaemia and accumulation of pyruvate and lactate.

The disease manifests clinically in infancy with failure to thrive and stunted growth. Most prominent feature is enormous hepatomegaly with intra-cytoplasmic and intranuclear glycogen. The kidneys are also enlarged and show intracytoplasmic glycogen in tubular epithelial cells. Other features include gout, skin xanthomas and bleeding tendencies due to platelet dysfunction.

Pompe's disease (type II)

This is also an autosomal recessive disorder due to deficiency of a lysosomal enzyme, acid maltase, and is the only example of lysosomal storage disease amongst the various types of glycogenoses. Acid maltase is normally present in most cell types and is responsible for the degradation of glycogen. Its deficiency, therefore, results in accumulation of glycogen in many tissues, most often in the heart and skeletal muscle, leading to cardiomegaly and hypotonia.

McArdle's disease (type V)

The condition occurs due to deficiency of muscle phosphorylase resulting in accumulation of glycogen in the muscle (deficiency of liver phosphorylase results in type VI glycogenoses). The disease is common in 2nd to 4th decades of life and is characterized by painful muscle cramps, especially after exercise, and detection of myoglobinuria in half the cases.

The outcome of storage diseases is unfavorable because of insufficient development of the respective organ.

Self-check materials:

1. External examination of a newborn revealed dry dull pale skin with uneven surface and presence of gray scaling plates. Which type of degeneration is this pathology associated with?
 - A. Hydropic
 - B. Hyalin-drop
 - C. Horny*
 - D. Fibrinoid swelling
 - E. Mucoid swelling
2. Autopsy of the patient who had been ill with leukemia and died of increasing chronic anemia revealed an enlarged heart, dull, flabby, pale gray myocardium. There were yellow plaques and bands under the endocardium. Which pathologic process is observed in the heart?
 - A. Vacuole degeneration
 - B. Hyalin-drop degeneration
 - C. Mesenchymal fatty degeneration
 - D. Parenchymal fatty degeneration*
 - E. Functional hypertrophy
3. Microscopic study of the biopsy material from the female patient who suffers from diabetes mellitus has revealed that the epithelium of narrow and distal segments of the tubules is high with light foamy cytoplasm. Staining with Best's carmine revealed red grains in the cytoplasm of the epithelium and tubules. Which parenchymatous dystrophy is present?
 - A. Protein
 - B. Fat
 - C. Hyalin-drop
 - D. Mucous
 - E. Carbohydrate*

4. Autopsy of the patient who had suffered from hypertension disease revealed considerable enlarged flabby heart with widened cavities. The myocardium was dull, clay-like, with white strips from the side of the myocardium which were more pronounced in the papillary muscles and trabeculas of the heart ventricles (tiger's heart). Which parenchymatous dystrophy was present?

- A. Fat*
- B. Horny
- C. Mucous
- D. Protein
- E. Carbohydrate

5. Microscopy of the kidneys from the dead patient who had suffered from chronic glomerulonephritis showed enlarged epithelial cells of the renal tubules, their cytoplasm was filled with vacuoles with transparent fluid, the nucleus was displaced to the periphery. Which parenchymatous dystrophy was present?

- A. Protein
- B. Horny
- C. Hyalin drop
- D. Hydropic *
- E. Fatty

TOPIC III: Morphological changes of extracellular matrix (stroma) in response to injury. (Stromal-vascular degenerations). Morphology of complex proteins (hyalinosis) and lipids accumulation. Cachexy.

1. Actuality of the problem.

Extracellular accumulations or mesenchymal (stromal-vascular) degenerations of the proteins, lipids, carbohydrates develop in the connective tissue as a result of metabolic disturbances in it. Proteinous mesenchymal degenerations occur as mucoid swellings, fibrinoid changes, hyalinosis. These pathological processes are successive stages of disorganization of the connective tissue. Knowledge of these processes is necessary for understanding of the pathogenesis of the diseases and for the clinic-anatomical analysis of the autopsy.

2. Aim of studies and competence . Learn the morphological features of the extracellular accumulations; to explain the causes and mechanisms of their development; to estimate outcomes and determine the significance for organism.

- To explain the extracellular mechanisms of trophic and causes of their disturbances.
- To interpret morphology of the extracellular accumulation of proteins, carbonhydrates, lipids and their consequences.
- Learn the classification of the extratracellular accumulations according to prevalence of morphological changes, to the prevalence of that or another type of metabolism, to the influence of genetic factors and to the spreading of the process.
- Study the mechanisms of the various types of mesenchymal degenerations.
- Learn the morphology and functional manifestations of the mucoid swelling, hyaline changes and fatty growth.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of parenchyma and stroma of inner

	organs. 2. To draw normal structure of inner organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of inner organs stroma reactions in response to neuro-humoral stimulation. 2. To use knowledge's about disturbance in stroma trophic function due to influence from pathological factors.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Stroma	the connective, functionally supportive framework of a biological cell, tissue, or organ
Mucoid swelling	is superficial reversible disorganization of the connective tissue.
Fibrinoid	is a complex substance consisting of decomposed collagen fibers, proteins, blood plasma, main substance, cellular nucleoproteids, fibrin
Hyalinosis	is formation of semitransparent dense masses (hyalin) resemble hyaline cartilage in the connective tissue.

4.2 Theoretical questions for the practical class:

1. Extracellular accumulations: causes, morphological mechanisms of development (infiltration, transformation, decomposition, perverted synthesis).
2. Call the definition, classifications, causes and mechanisms of the development of mesenchymal (extracellular) degenerations.
3. Call types of proteinogenic mesenchymal (extracellular) degenerations. Describe morphological signs of the mucoid swelling, and hyaline changes. What stages of the disorganization of connective tissue do you know? What functional significance of hyaline changes takes place?
6. Call causes and mechanisms of fatty growth. Common obesity: causes, pathogenesis, morphologic characteristics; classification.
7. Cachexia. Causes, pathogenesis, morphological features.
8. Lipomatosis and partial lipodystrophy.
9. Stromal-vascular carbohydrates degenerations associated with metabolic disturbances of glycoproteins and mucopolysaccharides. Mucopolysaccharidosis.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **"Lipomatosis of the Aorta".** Note the localization, size, shape, color of the aorta. *What are the causes of such changes? What possible outcomes may be?*

2. “Adipose Heart”. Determine the dimensions of the organ. Pay attention to the quality of the fat under the epicardium. Pay attention to the growth of fatty tissue in the heart wall on the section, more developed in the right portions. *Characterize the type of dysfunctional fatty metabolism. Name the etiology and mechanisms of development of the general obesity, its significance, and outcome.*

3. “Hyaline change in the Spleen’s capsula”(“Glazed Spleen”). Pay attention to the organ enlargement, changes in color of capsula, texture of organ tissue, appearance of surface on the section. *What are the causes of such changes?*

4. “ Sclerosis and hyalinosis of Mitral valve (Reumatic defect of the heart). Pay attention on the leaflets of the valve are thickened, firm, rigid, deformed and loss their transparency; the greater thickening along the line of closure is seen. Chordae tendineae are thickened and shortened. *What are the causes of such changes?*

Micropreparations:

Slide 1. Hyaline change in the spleen’s vessels

The arterioles at the center of lymphoid follicles have narrow lumen and thicken homogenous walls of pink color.

Slide 2. Adipose Heart (ought to be drawn)

Masses of adipose tissue can be found between muscle fibers. These masses look like large optically empty vacuoles. Muscle fibers are suppressed and atrophic.

Slide 3. Muroid swelling of leaflet of Mitral Valve in rheumatic fever (toluidin-blue-staining)

The tissue of leaflet lost its fibrillary structure due to swelling and homogenization of collagen fibers and is colored in violet colour in contrast with normal dark-blue stained tissue (phenomenon of metachromatism).

Slide 4. Atherosclerosis of the coronary artery with its thrombosis. The wall of the vessel is thickened everywhere, but much more it is thickened because of the formation of the atherosclerotic plaque, which are composed with lipids and fibrotic tissue. Thrombus can be seen in the artery’s lumen. It is closely connected with the vessel’s wall because of the growth of the connective tissue. Here and there the areas of petrification can be seen among thrombotic masses.

Slide 5. Hyaline change in the vessels of the renal glomerulies. Pay attention to deposition of the hyaline masses in the capillaries of the renal glomeruli, and their thickness.

Topic content:

STROMAL CARBOHYDRATE CHANGES

Stromal carbohydrate changes develop due to disturbance of glycosaminoglycans and glycoproteids metabolism. When glycoprotein metabolism is disturbed, chromotropic substances are released from the protein bonds. They accumulate in the main substance of the connective tissue. Collagen fibers change into mucus-like mass.

The most frequent cause of this is endocrinopathy (thyroid hypofunction, i.e. myxedema). It may be observed in cachexia. The condition results in colliquation, necrosis with formation of cavities filled with mucus.

Mucopolysaccharidoses (MPS). Disturbance of GAG (earlier called mucopolysaccharids) is due to hereditary factors as in a storage disease, thesaurismosis. This group of the diseases is called mucopolysaccharidoses. Mucopolysaccharidoses are a group of six inherited syndromes numbered from MPS I to MPS VI. Each of these results from deficiency of specific lysosomal enzyme involved in the degradation of mucopolysaccharides or glycosaminoglycans, and are, therefore, a form of lysosomal storage diseases. Mucopolysaccharides which accumulate in the MPS are chondroitin sulfate, dermatan sulfate, heparan sulfate and keratan sulfate. All these syndromes are autosomal recessive disorders except MPS II (Hunter's syndrome) which has X-linked recessive transmission.

Syndrome of MPS manifests in infancy or early childhood and involves multiple organs and tissues, chiefly connective tissues, liver, spleen, bone marrow, lymph nodes, kidneys, heart and brain. The mucopolysaccharides accumulate in mononuclear phagocytic cells, endothelial

cells, intimal smooth muscle cells and fibroblasts. The material is finely granular and PAS-positive by light microscopy. By electron microscopy, it appears in the swollen lysosomes and can be identified biochemically as mucopolysaccharide.

The most frequent of them are Pfaundler-Hurler disease, or gargolism. Its cause is congenital defect of the enzyme determining GAG metabolism. This disease is characterized by irregular skeleton growth, «massive» skull, heart defects, inguinal and umbilical hernias, hepato- and splenomegaly, keratoleukoma (retina opacity).

STROMAL VASCULAR PROTEIN CHANGES

Stromal vascular protein changes develop in the connective tissue as a result of metabolic disturbances in it. Pathological process develops in a structural unit of connective tissue, i.e. histion. Histion is formed by a segment of microcirculatory channel with the surrounding elements of connective tissue and nerve fibers.

Connective tissue elements are collagen, reticular and elastic fibers, cells: fibroblasts, which producing collagen, macrophages, fibrocytes as well as the main substance. It should be mentioned that in addition to collagen, fibroblasts produce glycosami-noglycanes of the main substance.

Albuminous (protein) changes manifest as

- mucoid swellings,
- fibrinoid changes,
- hyalinosis
- amyloidosis.

The first three types are the stages of connective tissue disorganization. Their development is based on blood plasma protein accumulation in the main substance due to increased vascular permeability (plasmorrhagia). Besides, connective tissue elements destruction accompanied by formation of protein-polysaccharide complexes is present. In amyloidosis the protein-polysaccharide complex includes abnormal fibril protein.

Mucoid swelling is superficial reversible disorganization of the connective tissue. The amount of hyaluronic acid and its derivatives (HAH), possess which hydrophilic properties increases. Increased vascular permeability (due to HAH action) and plasmorrhagia develop resulting in HAH, globulin, and blood glycoproteides accumulation in the main substance and hydration and swelling of the main substance.

Microscopic examination shows meta-chromasia. Under normal conditions the main substance is basophilic. In this case staining with toluidine blue demonstrates reddish coloring. Collagen fibers are swollen though band structure is preserved.

Macroscopic study does not reveal any changes. The outcome may be reversible. In other cases development of fibrinoid swelling is possible.

The causes of mucoid swelling, fibrinous changes and hyalinosis are the same as they are the stages of one process. They are immunopathological and autoimmune states, hypoxia, infections. These types of connective tissue disorganization are frequently observed in hypertension, rheumatism and other diseases of the connective tissue accompanied by immune disturbances as well as in allergic diseases, etc.

In the majority of cases the arterial walls, heart valves, endocardium, epicardium, articular connective tissue are involved.

Fibrinoid changes. There are two stages in the fibrinoid changes.

Stage 1 is fibrinoid swelling which is deep and irreversible connective tissue disorganization.

Stage 2 is fibrinoid necrosis. As a result of the main substance destruction and sharp increase in vascular permeability, fibrinoid is formed. It is a complex substance consisting of decomposed collagen fibers, proteins, blood plasma, main substance, cellular nucleoproteids, fibrin. In different diseases histochemical composition of fibrinoid is different and very often is a diagnostic criterion (e.g. in lupus erythematosus). The appearance of the organs is changed a little. The main signs are revealed microscopically: the bands of collagen fibers are homogenous,

impregnated with plasma proteins. Metachromasia is not marked due to HAH depo-lymerization of the main substance. Fibrinoid swelling may be generalized (in systemic diseases of the connective tissue) and localized (in chronic inflammations, e.g. in the bed of chronic ulcer). The outcome is fibrinoid swelling followed by fibrinoid necrosis, sclerosis or hyalinosis.

Hyalinosis (greek «hyalos»—transparent, glass-like) is formation of semitransparent dense masses (hyalin) resemble hyaline cartilage in the connective tissue.

Hyalinosis develops as a result of plasma impregnation, fibrinoid swelling, inflammation, necrosis, sclerosis. Hyalinosis are classified according to their localization (vascular hyalinosis, connective tissue hyalinosis) and propagation (generalized and localized). Each of the above forms may be generalised and localized.

Vascular hyalinosis involves the arterioles and small arteries. In their walls, endothelium, basal membranes, and smooth muscle cells are damaged. Impregnation of the wall with plasma is observed. Microscopic study of the arteries demonstrates thickened walls with a sharply narrowed or obliterated lumina. At first, hyalin is accumulated in subendo-thelial areas of the vascular wall, then it destroys elastic plate and middle membrane. Vascular hyalinosis is generally a systemic process. It characterizes hypertension and diabetic cardiomyopathy. The vessels of the brain, kidneys, retina are the most frequently involved.

Three types of vascular hyalin are distinguished depending on the pathogenetic character of its formation:

- 1) simple,
- 2) lipohyalin,
- 3) compound-hyalin.

Connective tissue hyalinosis is usually a localized condition, it develops in scars, adhesions, in the areas of chronic inflammation (e.g. «glazed spleen»).

The outcome of hyalinosis is irreversible as a rule, but in the scars called keloids hyalin can loosen and resolve (e.g. in the breast).

Functional significance of hyalin is different. Thus, vascular hyalinosis is fatally dangerous, rupture or occlusion of the vessel may result in infarct, insult, nephrosclerosis. Local hyalinosis in the cardiac valves results in heart defects.

Self-check materials:

1. Skin biopsy of the patient with allergic vasculitis demonstrated a thickened homogenic, pyroninophilic vascular walls at Brachet's reaction, PAS-positive, stained yellow with picrofuchsin. Name the type of mesenchymal degeneration.

- A. Fibrinoid swelling*
- B. Amyloidosis
- C. Muroid swelling
- D. Hyalinosis
- E. Lipidosis

2. The patient who had suffered from hypertension disease died of brain hemorrhage. Microscopy of the arteriole walls supplying this area of the brain showed that they are homogenic, eosinophilic, PAS-positive. Which substance is responsible for the changes in the walls of the vessels?

- A. Lipohyalin
- B. Amyloid
- C. Complex hyalin
- D. Simple hyalin*

3. Histology of the deformed mitral valve revealed marked basophilic reaction at staining with hematoxylin-eosin of the connection tissue, staining with toluidin blue showed metachromasia reaction. Which changes in the connective tissue can be revealed by these reactions

- A. Amyloidosis
- B. Fibrinoid swelling
- C. Hyalinosis

- D. Muroid swelling*
 - E. Fibrinous necrosis
4. Autopsy of the man revealed the signs of rheumatic heart defect, i.e. thickened deformed cartilage-like valves with luster surface. Which process is present in the valves:
- A. Amyloidosis
 - B. Fibrinoid necrosis
 - C. Fibrinoid swelling
 - D. Hyalinosi*
 - E. Degenerative calcification
5. A 45-year old man died of sudden cardiac arrest. Symmetrical stage III obesity, rupture of the wall of the right ventricle with hemopericardium, excessive fat under the epicardium were revealed. Microscopy showed that fatty tissue of the epicardium involved the myocardium causing muscular fiber atrophy. Which pathological process is most probable?
- A. Fatty degeneration of the myocardium
 - B. Acute myocardial infarction
 - C. Coronary artery disease
 - D. Obesity of the heart
 - E. Hypertension disease

TOPIC IV:Morphology accumulation of disturbed metabolism products. Disturbance of iron and hemoglobingenic pigments metabolism. Morphological features of disturbed metabolism melanin as well as nucleoproteins and cuprum. Calcinosis.

1. Actuality of the problem.

Pigments are colored substances, some of which are normal constituents of cells where as others are abnormal and collect in cells only under special circumstances. Pigments are generally classified into two broad categories: endogenous pigments, which are normal constituents of cells and tissues, and exogenous pigments introduced into the body from without. Impairment of metabolism of the endogenous pigment may lead to various pathological processes, especially: hemosiderosis, hemochromatosis, jaundice, melanosis, etc.

Minerals play an active role in metabolic processes of the human organism. They are components of structural elements of cells, enzymes, hormones, vitamins, and pigments. Therefore in medical practice the most frequent are disturbances in the metabolism of calcium, copper, potassium, and iron.

Knowledge of these processes is necessary for understanding of the pathogenesis of some diseases and for the clinic-anatomical analysis of the autopsy.

2. Aim of studies and competence. Study the mechanisms of development, morphology and outcomes of the impairment of metabolism of the endogenous and exogenous pigments. Estimate the consequences of metabolism's impairment of calcium, copper, and iron in organism.

- Know classifications of endogenous and exogenous pigments.
- Explain and estimate role of hemoglobinogenous pigments in organism.
- Tell apart about these processes according to morphological features.
- Study the mechanisms and morphologic features of the various types of jaundice. Give examples.
- Know classifications, mechanisms of development and appearance of calcification. Give examples.
- Learn the morphology, functional manifestations and complications of the stone's formation in different organs.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.

- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of parenchyma and stroma of inner organs. 2. To draw normal structure of inner organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of inner organs reactions in response to minerals and pigments in fluid. 2. To use knowledge's about disturbance in inner organs function due to abnormal metabolism of minerals and pigments.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Bilirubin	an orange-yellow pigment formed in the liver by the breakdown of haemoglobin and excreted in bile
Hydrochloride	hematin is found in the erosions and ulcers of the stomach, its color is brown-black. It is formed from hemosiderin in the presence of HCl.
Formalin pigment	looks like dark brown grains, it can be found in the tissues preserved with formalin.
Melanin	a dark brown to black pigment occurring in the hair, skin, and iris of the eye in people and animals. It is responsible for tanning of skin exposed to sunlight
Lipofuscin	a brownish pigment staining with certain fat stains. It is most common in the cells of heart muscle, nerves, and liver and is normally contained within the lysosomes.
Calcium	is a soft white element which is found in bones and teeth, and also in limestone, chalk, and marble.
Copper	is reddish brown metal that is used to make things such as coins and electrical wires.
Potassium	is a soft silvery-white chemical element, which occurs mainly in compounds. These compounds are used in making such things as glass, soap, and fertilizers.

4.2 Theoretical questions for the practical class:

1. Classification of endogenous pigment and exogenous pigments.
2. Metabolic disturbance of iron and hemoglobinogenic pigments. Metabolism and pathogenic action of iron, formation of anabolic and catabolic ferritin. Toxic forms of ferritin: causes and effects of their formation.
3. Classification of hemoglobinogenic pigments. Disorders of hemoglobin-derived pigments metabolism: hemosiderosis, hemochromatosis, hemomelanosis. Mechanisms of their development. Evolution of bruise according to changes of pigments

4. Types of jaundice: Intrahepatic jaundice (hepatocellular jaundice), posthepatic jaundice (obstructive jaundice, hemolytic, prehepatic jaundice (hemolytic jaundice); mechanisms of their development and morphological features.
5. Porphyria: causes, morphological and clinical manifestations.
6. The proteinogenous pigments: classification, role of proteinogenous pigments in the physiology and pathology.
7. Disorders of proteinogenous pigments metabolism. Morphological description of hypopigmentation (leucoderma, vitiligo, albinism) and hyperpigmentation (diffuse and local melanosis, nevus). Addison's disease.
8. Disorders of nucleoproteins metabolism. Gout and gout arthritis: classification, etiology, pathogenesis, stages and morphological characteristics of changes of joints, clinical manifestations, complications, outcomes. Gout nephropathy. Clinical-morphological manifestations.
9. The lipidogenous pigments: classification, biological role of lipofuscin, lipofuscinosis.
10. Disorders of mineral metabolism. Mineral dystrophies, their types. Disorders of copper metabolism. Hepatolenticular degeneration (Wilson's disease).
11. Disorders of calcium metabolism – calcinosis. Types of calcifications (dystrophic, metastatic and metabolic calcification). Causes, pathogenesis and morphological characteristics.
12. Causes and mechanisms of the formation of stones. Types of stones. Consequences of stones formation.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **“Hemosiderosis of the Spleen in hemolytic disease of newborn”**. Pay attention to the shape of organ, its size, color, texture, appearance of surface on the section. Indicate the nature of process. *What are the causes of such changes?*
2. **“Brown induration of the Lung”**. Pay attention to the shape of organ, its size, color, texture, the appearance of surface on the section. *Why are the lungs firm and brown? What type of hemosiderosis takes place? In what cases else such changes take place?*
3. **“Brown atrophy of the Myocardium”**. Pay attention to the size, shape, and quantity of subendocardial fat, color of the cardiac muscles. *What are the causes of such changes? Why is the heart brown?*
4. **“Renal stones”**. Pay attention to the appearance of the stones, their shape, size and surface. Pay attention to the changes in renal tissues. *What are possible complications of renal stones?*
5. **“Metastasis of melanoblastoma in the Skin, Larynx, and Liver”**. Pay attention to localization, size, shape, condition of boundary between metastases and surrounding tissue. *What pigment is present in metastasis?*
6. **“Hemorrhage in the Brain (hematoma)”**. Pay attention to localization, size, shape, color, and consistency of the hematoma. Describe boundaries of the hematoma. What pigment deposits in hematoma? What type of hemosiderosis takes place?

7. **“Pigment nevus”**. Pay attention to the size, color, texture, appearance of surface and state of surrounding skin. *What pigment deposits in nevus?*

Micropreparations:

Slide 1. Ghon’s focus (ought to be drawn)

It is an area of caseation necrosis with massive petrification. This focus is separated from the lung tissue with fibrotic capsule (incapsulation).

Slide 2. Local hemosiderosis of ovarium (ought to be drawn)

In ovarium stroma visible yellow-brown pigment (hemosiderin), follicular cyst, fibrous tissue and white bodies.

Slide 3. Skin in gout (ought to be drawn)

The salts of uric acid are accumulated in derma in the manner of amorphous masses or needle-like crystals. The reactive proliferation of giant multinuclear foreign body cells around a postponing of uric salts is noted.

Slide 4. Yellow softening of the Brain (ought to be drawn)

The glial macrophages with the granules of yellow-brown pigment in cytoplasm accumulate around the area of necrosis (softening of brain tissue – pink color) on the border of saved tissue.

Slide 5. Skin in Addison’s disease (ought to be drawn)

In the basal layer of epidermis the melanocytes carrying the brown-black pigment (melanin) are seen.

Slide 6. Hemosiderosis of the Spleen in leukemia (Prussian blue reaction)

The excessive amount of hemosiderin as intracellular as free locating amongst the tissues is noted everywhere within the Spleen. The granules of iron-containing hemosiderin is colored to greenish blue color because of Prussian blue reaction in which colorless potassium ferrocyanide is converted by iron to blue-greenish ferric ferrocyanide.

Slide 8. Intra dermal nevus

There are clear visible nevus cells in derma of skin. Several cells contain black-brownish granules of melanin. Hair follicles and sebaceous glands are also visible.

Topic content:

HAEMOSIDERIN

The iron derived from red cell breakdown is held in the spleen, liver and bone marrow, combined with apoferritin. In the plasma it is transported by transferrin. The two mechanisms maintain an equilibrium between the iron contents in these three sites. When the amount of iron within the cells becomes excessive and overloads the ferritin system, it is deposited in a brown granular form - haemosiderin. This occurs in 2 situations:

Morphological manifestations of the disturbed metabolism are observed both in the cells and stroma (connective tissue), as well as in the walls of the vessels.

Pathology of pigments occur at disturbances of metabolism of conjugated proteins (chromoproteins, nucleoproteids, lipoproteins) and minerals.

Disturbances of chromoproteins metabolism

Chromoproteins are endogenic pigments, that is colored proteins.

They participate in the following functions of the organism:

- a) respiration (hemoglobin, cytochromes),
- b) re-stocking of iron (ferritin),
- c) secrete production (bile),
- d) organism protection from radiation (melanin),
- e) vitamin balance maintenance (lipochromes).

Classification of endogenic pigments

Endogenic pigments are divided into 3 groups:

- 1) hemoglobinogenic,
- 2) proteinogenic, or tyrosinogenic,
- 3) lipidogenic (lipopigments).

Disturbances in hemoglobinogenic pigments

Normally conditions, the following pigments are formed due to physiological decomposition of erythrocytes and hemoglobin: ferritin, hemosiderin, bilirubin. In pathological conditions, when erythrocyte decomposition increases, new pigments are synthesized except for the increase of the amount of the above pigments. They are hematin, hematin, porphyrin.

The most important disturbance is hemosiderosis, i.e. abundant production of hemosiderin.

Hemosiderosis may be general and local.

General (generalized) hemosiderosis is noted at intravascular hemolysis of erythrocytes (intravascular hemolysis).

It occurs at

- 1) transfusion of rhesus- or group-incompatible blood,
- 2) poisoning with hemolytic poisons (mushrooms),
- 3) infections (malaria, relapsing fever),
- 4) diseases of blood (anemia, hemo-blastoses).

Hemosiderin is accumulated in monocyte-macrophage cells, histiocytes, endotheliocytes, epithelial cells of the liver, spleen, bone marrow, lymphatic nodes, lungs. The organs become enlarged, dense, brown-rusty.

Local hemosiderosis develops in extravascular hemolysis of erythrocytes (extravascular hemolysis), as a rule in the foci of hemorrhages, e.g., brown induration of the lungs which develops in the patients with rheumatic heart defects, cardiosclerosis in chronic cardiac insufficiency. In all respects the knowledge in morphogenesis of brown induration of the lungs is important for physician.

Morphogenesis of brown induration of the lungs

Chronic venous congestion in the lungs causes hypoxia which results in increase of vascular permeability, development of diapedetic hemorrhages, erythrocytes occur in the interalveolar septa, alveoles, where they are destroyed and turn into hemosiderin. The erythrocytes are partially phagocytized by the alveolar macrophages. In this case, hemosiderin is formed in them. These cells are called sideroblasts. More often macrophages phagocytize ready hemosiderin, in this case they are called siderophages. Connective tissue begins to grow around the hemosiderin deposits. The lung becomes dense, enlarged and rusty-brown.

Hemochromatosis may be primary (hereditary) and secondary.

Primary hemochromatosis is associated with the defect of the enzymes of the small intestine, secondary — with the damage of these enzymes during the lifetime (after stomach resection, in alcoholism).

In hemochromatosis, iron absorption increases, the iron is deposited in the form of hemosiderin in the liver, pancreas, endocrine glands, heart, eye retina, the mucous membrane of the intestine. Ferritin and melanin amount increases simultaneously. Therefore, the main features of the disease are bronze skin, bronzed diabetes (diabetes mellitus), pigment cirrhosis of the liver, pigment cardiopathy with cardiac insufficiency. When the level of ferritin in the blood decreases, ferritinemia develops (it may be observed in hemosiderosis). It is dangerous because SH-ferritin acts as adrenaline antagonist and may cause vascular collapse, resulting in irreversible shock.

Bilirubin. Hyperbilirubinemia refers to an increased serum bilirubin concentration (i.e., > 1.2 mg/dl). At serum bilirubin concentrations above 2 to 2.5 mg/dl, the skin, sclerae, mucous and serous membranes turn yellow — a condition known as *jaundice*.

Increase of its amount in the blood causes jaundice, i.e. yellow coloring of the skin, sclera.

According to the mechanism of its development, there are 3 types of jaundice:

Prehepatic (hemolytic, unconjugated hyperbilirubinemia) jaundice occurs as a result of the increased production of bilirubin at erythrocyte hemolysis. The liver produces increased amount of bilirubin. This disorder is characterized by elevated serum levels of unconjugated bilirubin; levels of conjugated bilirubin are within normal limits. This finding typifies conditions

associated with increased red blood cell destruction (e.g., hemolytic anemia, ineffective erythropoiesis), reduced hepatic bilirubin uptake (e.g., as from such drugs as rifampin), and impaired bilirubin conjugation (e.g., Crigler-Najjar and Gilbert's syndromes). This condition is observed in intoxications, infections, autoimmune processes, etc. It results from failure of hepatocytes to conjugate bilirubin and inability of bilirubin to pass from the liver to the intestine.

Hepatocellular (parenchymatous) jaundice occurs in hepatocyte damage (acute and chronic hepatitis, liver cirrhosis, autointoxications in gestosis).

Posthepatic(conjugated hyperbilirubinemia) or obstructive jaundice results from obstruction to the outflow of conjugated bilirubin (cholelithiasis, cancer of bile ducts, etc.). Levels of both conjugated and unconjugated bilirubin rise in this disorder. Intrinsic liver disease and extrahepatic biliary obstruction are the underlying causes of conjugated hyperbilirubinemia. Cholestasis is usually, but not always, present.

Hematin.Hemomelanin(malaria pigment) is produced from hemoglobin due to the Plasmodium vital activity. While circulating in the blood, it is phagocytized by macrophages of the spleen, liver, bone marrow, lymphatic nodes, brain and causes hemomelanos. The organs became bright grey, dense and enlarged.

Hydrochloride hematin is found in the erosions and ulcers of the stomach, its color is brown-black. It is formed from hemosiderin in the presence of HCl.

Formalin pigment looks like dark brown grains, it can be found in the tissues preserved with formalin.

Porphyria develops when porphyrin metabolism is disturbed. It is characterized by increase of porphyrin amount in the blood (porphyria) and urine (porphyria), sharp increase of sensitivity to ultraviolet radiation (photophobia, erythema, dermatitis). It may be congenital and developed. Developed porphyria is observed in intoxications (lead, sulfasol, barbiturates), avitaminosis (pellagra), pernicious anemia, diseases of the liver.

Disturbances in proteinogenic (tyrosinogenic) pigments.

Proteinogenic pigments are melanin, pigment of enterochromatous cell grains, adrenochrome.

Melanin is produced by melanocytes: epidermis, dermis, iris, retina, pia mater. Disturbance of melanin metabolism has different forms, either its increased production or disappearance. These disturbances may be congenital or developed, local or general (generalized).

Generalized developed hypermelanos(melanoderma) characteristic for Addison's disease. It is caused by bilateral destruction of adrenal glands (tuberculosis, tumor). Hyperpigmentation of the skin is caused by melanin synthesis stimulation which, in turn, is due to the abundant production of ACTH by the pituitary body in response to the deficiency of adrenaline and other adrenal hormones (ACTH is responsible for melanin synthesis). Melanoderma also occurs in hypogonadism, pellagra, scurvy, cachexia.

Generalized congenital hypermelanos(xeroderma pigmentosum) is associated with increased sensitivity of the skin to ultraviolet radiation and manifests by spot-like skin pigmentation with hyperkeratosis and edema.

Local acquired melanosis manifests by:

- 1) melanosis of the large intestine in elderly people suffering from chronic constipation;
- 2) blackacanthosis (black acanthosis means skin areas with increased pigmentation) in hypophyseal adenoma, hyperthyroidism, diabetes mellitus;
- 3) pigmented nevi;
- 4) melanomas (malignant tumors). Generalized hypomelanosis (albinism) is due to tyrosinase deficiency. Albinism is characterized by absence of melanin in the hair bulbs, epidermis, dermis, retina and iris. Focal hypomelanosis(vitiligo) occurs in the persons with disturbed endocrine regulation of melanogenesis(hyperparathyroidism, diabetes mellitus, Hasimoto's goiter, skin inflammation (syphilis)).

Disturbances of lipidogenic pigments (lipopigments) metabolism

Lipopigments include lipofuscin, pigment of vitamin E insufficiency, ceroid, lipochromin. The first three have similar physicochemical properties, which allows to unite them under a common name, lipofuscin. Lipopigment of mesenchymal cells (macrophages) is called ceroid. In pathological conditions, cellular lipofuscin amount increases sharply and causes **lipofuscinosis** development. It can be primary (hereditary) and secondary.

Primary lipofuscinosis is characterized by accumulation of the pigment in the cells of a definite organ or system, e.g. hereditary hepatosis (Dabin-Johnson syndrome); neuronal lipofuscinosis (Bielschowsky-Jansky syndrome).

Secondary lipofuscinosis develops at an old age, in cachexia (brown atrophy of myocardium, liver), at increased functional load (lipofuscinosis of myocardium in heart defects), analgetics abuse, vitamin E deficiency.

Disturbances in ceroid and lipochromes metabolism are of less significance.

Nucleoproteins metabolism disturbances

When the metabolism of nucleoproteins is disturbed (they consist of protein, DNA (deoxyribonucleic acid), and RNA (ribonucleic acid) and the production of uric acid and its salts is abundant, gout, urolithiasis and uric acid infarct develop.

Gout is characterized by periodic sedimentation of sodium urate in the joints, which is accompanied by pains. Uric acid amount in the blood and urine is increased (hyperuricemia and hyperuricuria). The salts accumulate in the cartilages, synovial membranes of the small joints of feet, hands, knees, talocrural articulation, in the tendons, in the cartilage of the auricle floor. The tissues where the salts accumulate necrotize with the development of aggranulomatous reaction and accumulation of giant cells around them. The process is followed by connective tissue growth with formation of gouty nodes. In the kidneys, uric acid accumulates in the tubules and collecting tubes obstructing their lumina, which causes inflammation and atrophy (gouty kidney). The most frequent cause of gout is congenital metabolic disturbance, in rare cases, gout is a complication of nephrocirrhosis, blood diseases.

Urolithiasis is characterized by urates (stones) formation in the kidneys.

Uric acid infarction occurs in newborns living not less than 2 days. It manifests by sedimentation of amorphous masses of sodium urate and ammonium urate in the tubules and collecting tubes. On incision accumulation of the salts looks like yellow-red bands joining together near the papillae of the medullary layer. This pathological condition is due to intensive metabolism in the first days of life and is an adaptation process.

MINERAL METABOLISM DISTURBANCE

Minerals play an active role in metabolic processes of the human organism. They are components of structural elements of cells, enzymes, hormones, vitamins, pigments.

In medical practice the most frequent are disturbances in the metabolism of calcium, copper, potassium, and iron.

Calcium metabolism disturbances

Most part of calcium is located in the bones (bones are calcium depot) where it is bound to the organic substance of the bone tissue. It is stable in the compact bone substance and labial in the spongy substance of epiphyses and metaphyses. Calcium metabolism is regulated by nervous and humoral systems. The most important for this are Parathormone of parathyroid gland and Calcitonine of thyroid gland. Parathormone stimulates washing out calcium from the bone. Calcitonine vice versa contributes to the transition of calcium from the blood to the bone.

In parathyroid hypofunction and thyroid hyper-function, blood calcium amount decreases, in parathyroid hyperfunction and thyroid hypofunction, calcium is washed out from the bones. This may be of two types: lacunar and sinusal. Lacunar one takes place with the help of osteoclasts when large cavities in the bone tissue are formed. In sinusal resorption, the bones are dissolved without the participation of the cells, in this case so-called «liquid bone» when small-cell structures are formed. Such complications as spontaneous (unexpected) bone fractures can be observed.

Disturbances of calcium metabolism are called calcinosis, calcium degeneration, or calcification.

According to the location calcinosis may be intracellular, extracellular and of both locations.

According to propagation calcinosis are divided into systemic and local.

According to the mechanism of its development, calcinosis may be metastatic, degenerative, metabolic.

Staining with H&E demonstrates calcium salts as deeply basophilic, irregular and granular clumps. For identification of calcium salts we usually use special reaction called silver impregnation method or Kossa's method. Calcium deposits are stained black.

Metastatic calcinosis (calcium metastases) is of systemic character. Its main cause is hypercalcemia, which may be of endocrine origin in hyperproduction of Parathormone or hypoproduction of Calcitonine. It may be associated with the reduction of calcium excretion from the organism. That is why calcium metastases develop in multiple fractures of the bones, multiple myeloma, osteomalacia (when the bone becomes soft), lesions of the large intestine (the place of Ca excretion), vitamin D abundance. Calcium salts precipitate in different organs, more frequently in the lungs, gastric mucosa, kidneys, myocardium, arterial walls. Sedimentation in the lungs and stomach is due to acid products, in myocardium and arteries because they are washed with poor with carbon dioxide arterial blood.

In degenerative calcification, or petrification, calcium salts are deposited in the tissues with marked degeneration changes or in necrotic zones: caseous foci in tuberculosis (necrosis looks like cottage cheese-curd), in syphilitic gummas, infarction places, tumors, foci of chronic inflammation as well in the scars, cartilages, dead parasites (echinococci), dead fetus (lythopedion).

Metabolic calcification (calcium gout) develops in instability of buffer systems (pH and protein colloid) when calcium is not retained in the blood and tissue fluid even at its low concentration as well as in calcemia, i.e. increased sensitivity of the tissues to calcium. Metabolic calcinosis may be systemic and local. In interstitial systemic calcinosis, calcium is accumulated in the skin, subcutaneous fat, along the sinews, fasciae, aponeuroses, in the muscles, nerves, vessels, in local calcinosis in the skin of the fingers and toes in the form of plates.

The outcome is unfavorable, calcium does not resolve.

Copper metabolism disturbance

This appears in Wilson's disease (hepatocerebral degeneration, hepatolenticular degeneration). It is a hereditary disease in which liver ceruloplasmin production decreases. The responsible gene, which is located on chromosome 13, is inherited in an autosomal-recessive fashion. The precise excretory defect and the mechanism of copper-induced cellular injury are unknown. Ceruloplasmin is alpha-2-globulin and can bind copper in the blood. As a result, copper becomes free from unstable bonds with plasma proteins and sediments in the tissue.

The clinical features are dominated by hepatic and neuropsychiatric manifestations as well as hemolytic anemia. Patients can present acutely, with fulminant hepatic failure, or, more commonly, with evidence of chronic hepatitis and cirrhosis. Kayser-Fleischer rings represent rings of copper deposited in Descemet's membrane of the cornea at the periphery of the iris (in the cornea it looks like green-brown ring on its margin of the cornea). They are found in all patients with central nervous system (CNS) involvement but are less frequent in patients without CNS effects. Occasionally, Kayser-Fleischer rings are seen in disorders associated with chronic cholestasis, such as primary biliary cirrhosis. Serum free copper, urine copper, and hepatic copper levels are all elevated, whereas the total serum copper and serum ceruloplasmin levels nearly always are decreased.

Copper accumulates in the liver, brain, kidneys, pancreas, testes, etc. The state is characterized by development of liver cirrhosis, degenerative symmetrical changes in the brain in

the area of lens nuclei, caudal body, pale globe, cortex. There are 3 forms of the disease: hepatic, lenticular, hepatolenticular.

The outcome is unfavorable.

Potassium metabolism disturbances

Increased blood (hyperpotassemia) and tissue potassium amount is observed in Addison's disease and is associated with the lesion of the adrenal cortex, the hormones of which regulate electrolyte exchange.

Potassium deficiency characterizes periodic paralysis, hereditary disease for which attack of weakness and motor paralysis are typical.

Iron metabolism disturbances are observed in disorders of hemoglobinogenic pigments metabolism. (*See Pathology of Pigments*).

Stones

Stones, or calculi are dense formations freely lying in the cavities of the organs or in the ducts. Their shape depends on the organs in which they are formed: round in the urinary bladder, facet in the gallbladder (their faces are lapped to each other), branching in the kidneys. Their surface may be either smooth or rough. The color depends on their chemical composition: white (phosphates), yellow (urates), dark brown or green (pigment). On saw cut they may be crystalloid (radial structure), colloid (stratified structure) and colloid-crystalloid (radial-stratified). Their chemical composition is different, i.e. biliary calculi may be cholesterol, pigment, calcium and combined, urinary — urates, phosphates, oxalates (calcium oxalate), cystin, xantin. Bronchial calculi consist of mucus inlaid with calcium. Calculi are most frequently formed in the bile ducts and urinary tract in cholelithiasis, urolithiasis, in the excretory ducts of the pancreas, salivary glands, bronchi, crypts of the tonsils, veins (phlebolith), intestine (coprolith).

Both general and local factors are important for pathogenesis of calculus formation. General factors are the main ones, they are acquired or hereditary disturbances of metabolism. Local factors are secrete congestion, inflammation of an organ. The immediate mechanism of calculus formation consists of two processes: formation of organic matrix and salt crystallization. Each of these may be primary.

Compression with a stone may result in necroses in renal pelvis, gallbladder etc., bedsores, perforations, inflammation (pyelocystitis, cholecystitis, cholangitis etc.).

Self-check materials:

1. The patients with hypernephroid cancer of the kidney with multiple metastases developed bronze coloring of the skin, weakness, hypotension, adynamia. Which pigment is responsible for the changes in the color of the skin:

- A. Melanin*
- B. Hemosiderin
- C. Porphyrin
- D. Lipofuscin
- E. Biliverdin

2. Gastroscopy revealed an ulcer with dense herders and black-brown bed in the gastric mucosa. Microscopy revealed black-brown pigment on the necrotic layer in the ulcer bed. Which pigment is it?

- A. Porphyrin
- B. Hydrochloric hematin*
- C. Bilirubin
- D. Ferritin
- E. Hemosiderin

3. After a snake bite a woman developed hemolytic anemia, in spite of the intensive therapy the patient died on the 7th day. The autopsy showed brown spleen, bone marrow and lymph nodes. Microscopy revealed Pearls- positive pigment in the cytoplasm of macrophages of these organs. Which pigment was present in the tissues?

- A. Hematoidin
- B. Hematin
- C. Lipofuscin
- D. Bilirubin
- E. Hemosiderin*

4. Histological study of the organs from a woman aged 42 who had had breast cancer with multiple metastases to the spine revealed small-foci calcifications in the lungs, kidneys, gastric mucosa, heart, walls of the arteries. Which type of calcification is most probable?

- A. Metastatic
- B. Dystrophic *
- C. Generalized interstitial
- D. Focal interstitial
- E. Metabolic

5. Autopsy of the patient who died of cancer cachexia demonstrated atrophy of the skeletal muscles, diminished heart and yellow-brown liver. Microscopy revealed small perinuclear grains of brown Perls-negative pigment in the cytoplasm of the myocytes and hepatocytes. Metabolism of which pigment is disturbed most probably?

- A. Lipofuscin*
- B. Hemosiderin
- C. Hematoidin
- D. Bilirubin
- E. Hemomelanin

TOPIC V: Basis of thanatology. Necrosis. Clinical and morphological forms of necrosis. Selective death of highly specialized cells: pathogenic induced apoptosis, cell death caused by immune system and activated complement.

1. Actuality of the problem.

Necrosis and apoptosis are irreversible cell injuries. Necrosis is cellular death in the living body in the disease. Apoptosis is a programmed (physiological) death of the cell in the living body. These pathological processes were accompanying a lot of diseases, which are very often meeting and also they are selfish diseases. Research of the mechanisms, morphology of necrosis and apoptosis is important task in practical medicine because it may help to diagnose and treat the different diseases.

2. Aim of studies and competence. Study the morphological features of necrosis and apoptosis; to explain the causes and mechanisms of their development; estimate outcomes and determine the significance for organism.

Tasks of the studies:

- Explain the role of necrosis and apoptosis in organism.
- Know the terminology and definitions these processes.
- Know the classification of necrosis according to its causes and mechanisms of influence of pathogenic factor.
- Learn the morphology and functional manifestations of necrosis and apoptosis.
- Explain the morphologic features of the various types of necrosis and to estimate their functional significance.
- Study the signs of death, postmortem changes.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of inner organs. 2. To draw normal structure of inner organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of inner organs metabolism. 2. To use knowledge's about disturbance in inner organs morphology and function due to pathological agents' action.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Necrosis	is death of cells and tissues in a living organism.
Coagulative necrosis	is the conversion of normal cells into their «tombstones» i.e., the outlines of the cells are retained so that the cell type can still be recognized but their cytoplasmic and nuclear details are lost.
Colliquative necrosis	occurs due to ischaemic injury and bacterial infections, because of hydration and colliquation of tissue by the action of powerful hydrolytic enzymes.
Gangrene	is a form of necrosis of tissue with superadded putrefaction
Bedsore	is a kind of gangrene, death of the tissue under the influence of pressure (sacral area, spinous processes, great trochanter). It is trophoneurotic necrosis in severity ill patients.
Sequestration	is an area of dead tissue which does not experience autolization, does not sclerotize and is freely located in the living tissue
Infarct	(originates from Latin «stuff, fill») is vascular necrosis, the most frequent form of necrosis.
Caseous necrosis	looks like cottage cheese (curd), the tissue is soft, granular and yellowish. As a rule it is observed in the center of tuberculous infection.
Fibrinoid necrosis	develops due to fibrinoid swelling in mesenchymatous albumin degeneration.
Apoptosis	is controlled pattern of cell death termed programmed cell death is very different from that which occurs as a direct result of a severe, damaging stimulus to cells.

4.2 Theoretical questions for the practical class:

1. Definition of necrosis as local cellular death. Conception of paranecrosis, necrobiosis and autolysis.
2. Causes, mechanisms of development and morphological characteristics of necrosis and apoptosis; morphological differences between necrosis and apoptosis. Peculiarities of necrosis in children.
3. Classification of necrosis according to its causes (traumatic, toxic, trophoneurotic, allergic, vascular) and mechanisms of influence of pathogenic factor (direct and indirect).
4. Clinical and morphological types of necrosis: coagulative (dry), liquefactive (wet), fatty, caseous, gangrene, infarction and sequester. Their characteristics. Significance of necrosis and its consequences.
5. Immune elimination of cells: morphological manifestations. Phagocytosis: definition, main cell-phagocytes, microscopic manifestations of phagocytosis.

6. Death, signs of death, postmortem changes. Causes of death. Natural death, violent death and death because of the disease.
7. Clinical and biological death. Tanathogenesis and signs of death. Postmortem changes, their morphological characteristics. Early and late signs of biological death and death of reanimating patient.
8. Conception of tanathogenesis and reanimatology. Pathology of reanimatology (iatrogenic pathology).
9. Causes, molecular-metabolic and structural mechanisms of stopping of activity of vitally-important organs at the natural course of disease. Nearest consequences of stopping of work of heart, lungs, brain, kidneys and liver.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate passible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **“Gangrene of the Foot”. “Atherosclerotic gangrene of the Foot”.** Pay attention to the changes in the color, surface of skin, extent of necrotic tissue, texture. *What is gangrene? Call the causes of gangrene.*

2. **“Ischemic infarction of the Spleen”.** To note the localization, size, shape, color of the area of necrosis *What type of necrosis takes place and what are the causes and mechanisms, which caused its development?*

3. **“Ischemic infarction of the Kidneys”.** To note the localization, size, shape, color of the necrotic area.

What type of necrosis takes place and what are the causes and mechanisms, which caused its development?

4. **“Tuberculoma of the Lung”.** To note the localization, size, shape, color of the area of necrosis. *What type of necrosis takes place and what are the causes and mechanisms, which caused its development?*

5. **“Caseouse pneumonia in tuberculosis”.** Pay attention to the changes in the color, size and texture of necrotic tissue in the lung. *What type of necrosis takes place? Call other diseases with this type of necrosis.*

Microslides:

Slide 1. Coagulative necrosis of skeletal muscles in aseptic gangrene (ought to be drawn)

The muscles fibers are in condition of cytolysis, their nuclei are absent. Stroma is edematous.

Slide 2. Ischemic infarction of the Spleen (ought to be drawn)

The area of necrosis is bordered from saved tissues by zone of hyperemia and leukocytic infiltration (demarcation zone). The necrotic zone looks as homogenized pinkish masses, the nuclei of cells are absent.

Slide 3. Necrotic nephrosis (ought to be drawn)

Nephrocytes of proximal ducts are enlarged in sizes, their nuclei aren't defined (karyolysis); the nuclei of nephrocytes of distal ducts are saved. Glomeruli are saved.

Slide 4. Gangrene of the Appendix

Zone of necrosis is characterized by lysis of cells as homogeneous pinkish masses. Leukocytic infiltration is seen in serosa. Edema, dilation of vessels is visible too.

Slide 5. Tuberculoma of the Lung

It is an area of pink color masses without any structure but with many dark blue grains (the result of karyorrhexis and karyopycnosis). The dark violet areas of petrification can be found. The necrotic area is surrounded with fibrotic capsule.

Topic content:

Necrosis is death of cells and tissues in a living organism.

Necrosis can be caused by various factors such as

- hypoxia (ischaemia),
- chemical and physical agents,
- microbial agents,
- immune injury,
- disturbances of nervous trophism.

Two essential changes bring about irreversible cell injury, cell digestion by lytic enzymes and denaturation of proteins. These processes are morphologically identified by characteristic cytoplasmic and nuclear changes in necrotic cells.

Microscopic study demonstrates characteristic changes both in the nucleus and cytoplasm of the cell and intracellular substance.

Nuclear changes. At first nucleus becomes wrinkled, the process is called karyopycnosis. After that karyorrhexis develops. Karyorrhexis is decomposition of the nucleus into small grains. And after that karyolysis develops, when the nucleus dissolution is observed.

In the cytoplasm, protein denaturation and coagulation, or hydration and colliquation take place. Coagulation completes in plasmorrhesis. Plasmorrhesis, that is when cytoplasm decomposition into lumps are

observed. Then plasmolysis takes place. Plasmolysis is hydrolytic fusion of cytoplasm. Sometimes we can observe vacuolization and calcification in the cytoplasm.

In the interstitial (base) substance of the intercellular space depolymerization with glucosamine glycane and saturation with blood plasma proteins develops. As a result interstitial substance becomes swollen and fuses. The same happens to the collagen fibers. Elastic fibers are fused (elastolysis).

Reticular fibers are preserved longer than the other structures. Then they dissociate to lumps.

There are several stages in necrosis morphogenesis:

- 1) paranecrosis reversible changes; as a rule, reversible degeneration;
- 2) necrobiosis irreversible degenerative changes;
- 3) cell death;
- 4) cell autolysis decomposition of dead ultra-structures with hydrolytic enzymes.

Necrosis classification

I. According to the cause:

- 1) traumatic (caused by chemical or physical factors);
- 2) toxic (toxins of bacteria);
- 3) trophoneurotic (in disturbances of nervous trophism), e.g. bedsore;
- 4) allergic (develops in the sensibilized organism as hypersensitivity reaction of immediate type);
- 5) vascular (infarction).

II. According to the clinico-morphological forms:

- 1) coagulation (dry) necrosis;
- 2) colliquative (liquefactive) necrosis;
- 3) gangrene (originates from Greek «gangraina» fire) necrosis of tissue adjacent to the outer environment:
 - a) dry,

- b) wet,
- c) gas;
- 4) sequestration;
- 5) infarction.

III. According to mechanism of its development it may be direct and indirect.

Direct necrosis may be toxic and traumatic, indirect necrosis may be vascular and trophoneurotic.

Necrosis zone is limited from a healthy tissue by a demarcation inflammation.

Microscopically we observe a wide zone of leukocytes between the normal area and necrosis. The normal area is bordered by a hemorrhagic belt. In the area of necrosis the tissues are homogenous and the nuclei are absent.

Some forms of necrosis

Coagulation necrosis. This is the most common type of necrosis which is caused by ischaemia, and less often by bacterial and chemical agents. The organs commonly affected are the heart, kidney and spleen.

Macroscopically the foci of coagulative necrosis in the early stage are pale, firm and slightly swollen. With progression, they become more yellowish, softer and shrunken. The hallmark of coagulative necrosis is the conversion of normal cells into their «tombstones» i.e., the outlines of the cells are retained so that the cell type can still be recognized but their cytoplasmic and nuclear details are lost. The necrotized cells are swollen and appear more eosinophilic than the normal, along with nuclear changes. This pattern of microscopic change probably results from denaturation of structural and enzymatic proteins but cell digestion and liquefaction fail to occur. Eventually, the necrotized focus is infiltrated by inflammatory cells and the dead cells are phagocytosed leaving granular debris and fragments of cells.

Colliquative necrosis occurs due to ischaemic injury and bacterial infections, because of hydration and colliquation of tissue by the action of powerful hydrolytic enzymes. The common examples are brain infarct and abscess cavity.

Macroscopically, the affected area is soft and swollen. Late a cyst wall is formed.

Microscopically, the cystic space contains necrotic cell debris and macrophages filled with phagocytosed material. The cyst wall is formed by proliferating capillaries, inflammatory cells, and gliosis (proliferating glial cells) in the case of brain, and proliferating fibroblasts in the case of abscess cavity.

Gangrene is a form of necrosis of tissue with superadded putrefaction. The type of necrosis is usually coagulative due to ischemia. In either case, the coagulative necrosis undergoes liquefaction by the action of putrefactive bacteria.

There are 3 main forms of gangrene dry, wet and gas gangrene.

Dry gangrene begins in the distal part of a limb due to ischaemia. The typical example is the dry gangrene in the toes and feet of an old patient due to arteriosclerosis. The gangrene spreads slowly upwards until it reaches a point where the blood supply is adequate to keep the tissue viable. A line of separation is formed at this point between the gangrenous part and the viable part.

Macroscopically, the affected part is dry, shrunken and dark black, resembling the foot of a mummy. It is black due to liberation of hemoglobin from hemolysed red blood cells which is acted upon by the hydrogen disulfide (H₂S) produced by the bacteria resulting in formation of black iron sulfide. The line of separation usually brings about complete separation with eventual falling off of the gangrenous tissue if it is not removed surgically.

Microscopically, there is necrosis with smudging of the tissue. The line of separation consists of inflammatory granulation tissue.

Wet gangrene occurs in naturally moist tissues and organs such as the mouth, bowel, lung, cervix, vulva, etc. Diabetic foot is another example of wet gangrene due to high sugar content in the necrosed tissue which favors growth of bacteria. Bedsores occurring in a bed-

ridden patient due to pressure on sites like the sacrum, buttocks and heels are the other important clinical conditions included in wet gangrene. In wet gangrene, the tissue is effected by saprogenic microorganisms (*Bac. perfringes*, *fusiformis*, *putri-ficans*, etc.), becomes swollen and emits fetid smell. It develops in the tissues rich in water: lungs, intestine, noma (water cancer) gangrene of cheek in children at measles. Wet gangrene usually develops rapidly due to blockage of venous and/or arterial blood flow. The affected part is stuffed with blood which favours the rapid growth of putrefactive bacteria. The toxic products formed by bacteria are absorbed causing systemic manifestations of septicemia, and finally death. The spreading wet gangrene lacks clear cut line of separation and may spread to peritoneal cavity causing peritonitis. Macroscopically, the affected part is soft, swollen edematous, putrid, rotten and dark. The part is stained dark due to the same mechanism as in dry gangrene. Microscopically, there is coagulative necrosis with stuffing of affected part with blood. There is ulceration of the mucosa and intensive inflammatory infiltration. The lumen of the bowel contains mucus and blood. The line of separation

between gangrenous segment and viable intestine is generally not clear cut.

Gasgangrene is a special form of wet gangrene caused by gas-forming *Clostridia* (gram-positive anaerobic bacteria) which gain entry into the tissues through open contaminated wounds, especially in the muscles, or as a complication of operation on the colon which normally contains *Clostridia*. *Clostridia* produce various toxins which cause necrosis and edema locally and are also absorbed producing profound systemic manifestations. Macroscopically, the affected area is swollen, edematous, painful and crepitant due to accumulation of gas bubbles within the tissues. Subsequently, the affected tissue becomes dark black and foul-smelling. Microscopically, the muscle fibers undergo coagulative necrosis with liquefaction. Large number of gram-positive bacilli can be identified. At the periphery, a zone of leucocytic infiltration, edema and congestion are found. Capillary and venous thrombi are common.

Bedsore is a kind of gangrene, death of the tissue under the influence of pressure (sacral area, spinous processes, great trochanter). It is trophoneurotic necrosis in severity ill patients.

Sequestration is an area of dead tissue which does not experience autolization, does not sclerotize and is freely located in the living tissue. It is characteristic for osteomyelitis (purulent inflammation of the bone).

Infarct (originates from Latin «stuff, fill») is vascular necrosis, the most frequent form of necrosis. It may be wedge-shaped or it may have an irregular shape.

According to the propagation it may be total (when the whole organ is affected), subtotal (when only a part of the organ is affected), microinfarct (when observed only microscopically).

According to the color it is divided into white, white with hemorrhagic rim and red. The color of infarct depends on the peculiarities of the blood supply of the organ. When an organ is supplied through the main vessel (spleen), infarct is white.

If under the background of the supply through the main vessel, microcirculatory system is well developed, infarct is white with hemorrhagic rim (kidney).

In the lungs, infarct is red as the lungs are supplied through the system of two arteries (pulmonary and bronchial).

The causes of infarction are

- a) prolonged stasis,
- b) thrombosis,
- c) embolism.

There are several special forms of necrosis. They are: caseous, fat and fibrinoid necrosis.

Caseous necrosis looks like cottage cheese (curd), the tissue is soft, granular and yellowish. As a rule it is observed in the center of tuberculous infection.

Fat necrosis is a special form of cell death occurring in two anatomically different locations but morphologically similar lesions. They are acute pancreatic necrosis and traumatic fat necrosis commonly in breasts.

Macroscopically fat necrosis appears as yellowish-white and firm deposits. Calcium

usually accumulates in these areas.

Fibrinoid necrosis develops due to fibrinoid swelling in mesenchymatous albumin degeneration.

The outcome of necrosis may be either favorable or unfavorable. Favorable outcomes:

- 1) organization, replacement by connective tissue with formation of a scar or a capsule;
- 2) petrification;
- 3) ossification, formation of bone;

4) aseptic autolysis. Unfavorable outcome- saprogenic fusion of necrosis focus followed by sepsis.

APOPTOSIS

This pattern of cell death has long been recognized by pathologists, but only recently it has been appreciated as a distinctive and important mode of cell injury, which should be differentiated from the common coagulative necrosis.

Apoptosis is an important means of reducing the number of cells in a tissue. It is a process which brings about death of established cells in an organ or tissue, causing a reduction in the number of functioning cells. There is activation of specific genes, which act to bring about cellular dissolution. One of the morphological manifestations of this type of cell death is termed apoptosis.

Apoptosis of cells is a programmed and energy-dependent process designed specifically to switch cells off and eliminate them. This controlled pattern of cell death termed programmed cell death is very different from that which occurs as a direct result of a severe, damaging stimulus to cells.

Apoptosis is thought to be responsible for numerous physiologic and pathologic events including the following: the programmed destruction of cells during embryogenesis (including implantation, organogenesis, developmental involution) and metamorphosis, hormone-dependent involution in the adult, cell deletion in proliferating cell populations, such as intestinal crypt epithelia; cell death in tumors, most frequently during regression but also in tumors with active cell growth; death of immune cells; pathologic atrophy of hormone-dependent tissues and parenchymal organs after duct obstruction, cell injury in certain viral diseases; cell death produced by a variety of injurious stimuli.

The following morphologic features, best seen with the electron microscope, characterize cells undergoing apoptosis.

The cell shrinkage is observed. The cell is smaller in size: the cytoplasm is dense; and the organelles, although relatively normal, are more tightly packed.

The chromatin condensation develops. This is the most characteristic feature of apoptosis. The chromatin aggregates peripherally, under the nuclear membrane, into well-delimited dense masses of various shapes and sizes. The nucleus itself may break up, producing two or more fragments.

Formation of cytoplasmic blebs and apoptotic bodies is observed. The apoptotic cell first shows extensive surface blebbing, then undergoes fragmentation into a number of membrane-bound apoptotic bodies composed of cytoplasm and tightly packed organelles, with or without a nuclear fragment.

Phagocytosis of apoptotic cells or bodies by adjacent healthy cells, either parenchymal cells or macrophages. The apoptotic bodies are rapidly degraded within lysosomes, and the adjacent cells migrate or proliferate to replace the space occupied by the now deleted apoptotic cell.

Microscopically, in tissues stained with hematoxylin and eosin, apoptosis involves single cells or small clusters of cells. The apoptotic cell appears as a round or oval mass of intensely eosinophilic cytoplasm with dense nuclear chromatin fragments. Because the cell shrinkage and formation of apoptotic bodies are rapid, and the fragments are quickly phagocytosed, degraded, or extruded into the lumen, considerable apoptosis may occur in tissues before it becomes apparent in histologic sections.

Thus, apoptosis is a distinctive form of cell death manifested by characteristic chromatin

condensation and DNA fragmentation, whose function is the deletion of cells in normal development, organogenesis, immune function, and tissue growth, but which can also be induced by pathologic stimuli.

Self-check materials:

1. Liver biopsy of a woman with viral hepatitis revealed hepatocytes with balloon degeneration Councilman's bodies in the sinusoid capillaries which, according to electron microscopy, are cell fragments surrounded by a cellular membrane, contained densely positioned organelles as well as nuclei fragments. Which process can be suggested by Councilman's bodies?
 - A. Necrosis
 - B. Necrobiosis
 - C. Apoptosis*
 - D. Paraneurosis
 - E. Degeneration
2. Histological study of an enlarged lymph node of the patients with tuberculosis showed irregular small chromatin grains in the focus of caseous necrosis. Which pathological process caused grain formation?
 - A. Karyolysis
 - B. Nuclear pyknosis
 - C. Mitotic activity of the nuclei
 - D. Karyorrhexis*
 - E. Apoptosis
3. Autopsy of a man who had suffered from gastric cancer showed soft tissue necrosis in the zone of the sacrum, buttocks and calcaneus. Which is a most probable etiology of necrosis?
 - A. Traumatic
 - B. Toxic
 - C. Trophoneurotic*
 - D. Allergic
 - E. Vascular
4. A patient with tuberculosis died of cardiopulmonary insufficiency. Autopsy revealed acute tuberculosis sepsis with multiple miliary necrotic tubercles in all organs. Which is a most probable etiology of necrosis?
 - A. Trophoneurotic
 - B. Toxic*
 - C. Traumatic
 - D. Vascular
 - E. Allergic
5. The patient with atherosclerosis developed gangrene of the lower extremity. The study of the vessels of the amputated extremity showed an obturating thrombus in the iliac artery. Which is the main etiological factor in this case?
 - A. Trophoneurotic
 - B. Traumatic
 - C. Toxic
 - D. Vascular*
 - E. Allergic

TOPIC VI: Acute systemic disturbance of blood circulation (acute coronary insufficiency, shock), systemic disturbance of blood circulation caused by chronic heart insufficiency and their outcomes. Regional disturbance of blood circulation: hyperemia, ischemia, plasmorrhagia, hemorrhage, hematoma). Disturbance of lymph formation and circulation.

1. Actuality of the problem.

Hemodynamic disturbances are considered under 2 broad headings: disturbances in the volume of the circulating blood (hyperemia and congestion, hemorrhage and shock) and circulatory disturbances of obstructive nature (thrombosis, embolism, ischemia and infarction). Research of the mechanisms, morphology of pathological processes in blood and lymphatic system may help to diagnose and treat the different diseases. These hemodynamic disturbances often are causes or complications of other diseases and in the majority of cases can become the cause of death. Different types of hemodynamic disorders accompany practically all known diseases; therefore study of these processes is important task in practical medicine. Thrombosis and embolism also can lead to serious clinical manifestations and are accompanied by occlusion of vessels, ischemia and infarction. These hemodynamic disturbances often are causes or complications of other diseases and in the majority of cases can become the cause of death. Therefore, the study of these pathological processes has big clinical significance. Knowledge of the mechanisms of development, morphologic manifestations, may help to diagnose the disease, prevent the spread of probable complications and treat them.

2. Aim of studies and competence. Study the morphological features of hemodynamic disturbances and their complications; to explain the causes and mechanisms of their development; to estimate probable outcomes and determine the significance for organism.

Tasks of the studies:

- Know the terminology and definitions of hemodynamic disturbances.
- Learn the morphology and functional manifestations of hemodynamic disturbances.
- Study the causes, mechanisms of development, morphologic characteristics of hyperemia and congestion.
- Study the causes, mechanisms of development, and morphologic characteristics of ischemia.
- Explain the morphologic features of the lymphodynamic insufficiency. Study the causes, mechanisms of development, and morphologic characteristics of edema.
- Know the terminology and definitions of hemodynamic disturbances (thrombosis and embolism, Infarction, DIC-syndrome).
- Learn the morphology and functional manifestations of thrombosis and embolism, Infarction, DIC-syndrome.
- Study the causes, mechanisms of development, morphologic characteristics of thrombosis, outcomes and significance for organism.
- Study the causes, mechanisms of development, and morphologic characteristics of the various types of embolism.
- Learn the morphology and functional manifestations of infarction.
- Explain the morphologic features of the disseminated intravascular coagulation syndrome.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology

- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure blood and lymph circulation system. 2. To draw normal structure of the system organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs of blood and lymph circulation system.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of blood and lymph stream. 2. To use knowledge's about disturbance in inner organs morphology and function due to disturbance of their blood and lymph circulation 3. Be able to use knowledge's about peculiarity of blood stream. 4. To use knowledge's about disturbance in blood stream due to influence of different factors.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Arterial hyperemia	is increased blood filling of the organ or tissue due to increased flow of the arterial blood.
Venous hyperemia	is increased filling with blood of the organ or tissue due to difficulties with blood outflow when blood supply is not changed or decreased.
Ischemia	is decreased filling with blood of the tissue, organ, part of the body due to insufficient blood flow.
Hemorrhage	is exit of the blood from the lumen of the vessel or from the heart cavity.
Hematoma	is accumulation of clotted blood in the tissues with disturbance of their entity.
Hemorrhagic saturation	is accumulation of the blood in the tissue when its entity is

	preserved.
Plasmorrhagia	is exit of plasma from the circulatory system. This can be caused by vascular spasm, tissue hypoxia, immune pathology.
Stasis	is arrest of blood flow in the vessels of microcirculatory system (capillaries).
Hemostasis	is a striking example of circulation adaptation failure. Short stasis is reversible, long one causes hyaline thrombi formation, vascular permeability increase, edema, bleeding.
Thrombosis	is a pathologic manifestation of homeostasis, i.e. intravital coagulation of blood with formation of a blood clot called thrombus in the lumen of the vessel.
Embolism	circulation in the blood or lymph of particles which do not normally occur and obstruction of the vessels with them.
Thromboembolic syndrome	is separation of a thrombus or a part of it and circulation of these particles in the blood of general system with obstruction of lumina of different arteries accompanied by multiple infarctions.
Disseminated intravascular coagulation	is pathological syndrome which is characterized by formation of disseminated blood clots in the micro-circulatory bed (often in combination with simultaneous reduction of blood coagulability) causing hemorrhages.
Shock	is a special reaction of the organism to a stimulus. It is fulfilled with nervous mechanisms and characterized by peculiar «shock» disturbance of circulation

4.2 Theoretical questions for the practical class:

1. Conception of general and local hemodynamic disorders, their intercommunication, classification. Hyperemia. Arterial hyperemia: causes, types, morphology.
2. Congestion (venous hyperemia): general and local; acute and chronic.
3. Changes in organs in acute congestion (asphyxia of fetus and newborn; acute cardiac insufficiency). Their consequences.
4. Morphological changes in organs in chronic congestion (chronic cardio-vascular insufficiency). Morphogenesis of congested sclerosis.
5. Ischemia. Causes, types, morphology and consequences.
6. Hemorrhage: causes, types, morphology, consequences, significance for organism. Hemorrhagic diathesis.
7. Clinical-pathomorphological peculiarities features and consequences of postischemic-reperfusion damages of organs.
8. Plasmorrhagia. Causes, mechanisms of development, morphologic characteristics.
9. Morphological manifestations of disturbances of lymph circulation.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
1. To indicate Latin name of a preparation.	1. To indicate used staining method for the organ tissue.
2. To describe macroscopic features of an organ (size, color, consistence)	2. To name both tissue and organ
3. To indicate pathological process	3. To indicate changes in the tissue of the organ
4. To indicate possible outcomes of the pathological process	4. To name the pathological process
5. What disease does the pathological process	5. To indicate the pathological process

correspond to	outcomes
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Macropreparations:

1. **“Cyanotic induration of the Spleen”**. Pay attention to the size, consistency and color of the organ. *Explain etiology and morphogenesis of cyanotic induration.*
2. **“Cyanotic induration of the Kidneys”**. Pay attention to the size, consistency and color of the organ. *Explain etiology and morphogenesis of cyanotic induration.*
3. **“Brown induration of the Lung”**. Pay attention to the size, consistency and color on the cut surface. *Explain the origin of the term “brown induration of the lung” and morphogenesis of brown induration of the lung.*
4. **“Nutmeg Liver”**. Pay attention to the size and consistency of the liver, color on the section. *Why liver is called “nutmeg”? What diseases can lead to formation of “nutmeg liver”? Give definition and name possible outcomes of this pathologic process.*
5. **“Hemorrhage in the Brain (hematoma)”**. Pay attention to localization, size, shape, color, and consistency of the hematoma. Describe boundaries of the hematoma. *Give definition and name possible outcomes of this pathologic process.*

Microslides:

Slide 1. “Nutmeg” liver (ought to be drawn)

The capillaries in the central areas of lobules are dilated and filled with blood. The emigrated erythrocytes are under hemolysis. The liver’s beams here and there are thinned or absent. The brown pigment hemosiderin locates in the cells.

Slide 2. Brown induration of the lung (ought to be drawn)

The alveolar macrophages with the presence of hemosiderin in their cytoplasm can be seen in the alveolar spaces. Inter-alveolar septa are thicken because of the dilation of their capillaries and proliferation of the septal cells. The growth of the connective tissue takes place between lobules.

Slide 3. Cyanotic induration of the spleen

The hyperemia of the organ with the development of connective tissue takes place. Capsule and trabecules are thickening.

Slide 4. Petechial hemorrhages in the brain tissue (ought to be drawn)

The small clusters of erythrocytes are seen here and there in the brain tissue. These blood clusters surround small vessels like muffs. The walls of vessels are saved. The spots of hemorrhages around small vessels with saved walls are the result of diapedesis of erythrocytes.

Topic content:

There are three types of fluid in the organs of human internal environment. They are blood, lymph, tissue fluid. Metabolism in these fluids, their qualitative and quantitative changes are closely connected with each other and are regulated by complicated neurohumoral mechanisms. The factors which cause the failure in these mechanisms as well as the disturbances of blood and lymph circulation and those appearance in the tissue are numerous.

All the disturbances of blood circulation can be divided into three groups:

1) disturbances of blood filling or disturbances in the volume of the circulating blood (hyperemia and anemia),

2) disturbances of blood vessel wall permeability (hemorrhage, plasmorrhagia),

3) disturbances of blood rheology (stasis, sludge, thrombosis, embolism).

Disturbance of blood circulation is the cause of such phenomena as disseminated intravascular coagulation (DIC), thromboembolic syndrome, shock, acute or chronic cardiac insufficiency.

Hyperemia (plethora) can be arterial and venous.

Arterial hyperemia is increased blood filling of the organ or tissue due to increased flow of the arterial blood. It may be general or local. General arterial hyperemia develops at increase of circulating blood volume or at increase of erythrocyte amount.

Clinically, general arterial hyperemia manifests by elevation of arterial pressure and skin reddening. Local arterial hyperemia occurs more often and can be physiological and pathological. Physiological arterial hyperemia is due to increase in the organ function or as a

result of shame and rage.

Pathological arterial hyperemia may be:

- 1) angioneurotic,
- 2) collateral,
- 3) postanemic(hyperemia after anemia),
- 4) vacant,
- 5) inflammatory,
- 6) caused by arteriovenous fistula.

Angioneurotic hyperemia is caused by irritation of vasodilatory nerves or by paralysis of vaso-constrictory nerves.

Collateral hyperemia is caused by obstruction to the blood flow in the main arterial trunk (thrombosis, embolism). In this case the blood gains entry to the collateral vessels and they dilate.

Postanemic hyperemia is observed when the factor causing anemia (tumor, fluid in the cavity) is eliminated. The vessels of anemic tissue are overfilled which may cause their rupture and hemorrhage as well as anemia in the brain. That is why manipulations aimed at removal of a tumor, fluid or ligature should be performed slowly.

Vacant hyperemia is observed at reduction of barometric pressure. It may be general (in divers) or local (on the place of cups).

Inflammatory hyperemia is caused by inflammation.

Hyperemia caused by arteriovenous fistula is observed at injury, when anastomosis between an artery and vein is formed and the arterial blood enters the vein.

The significance of arterial hyperemia is different. In some cases it is a protective or adaptive reaction but vacant hyperemia is an important factor in caisson disease morphogenesis, postanemic hyperemia may cause death.

Venous hyperemia is increased filling with blood of the organ or tissue due to difficulties with blood outflow when blood supply is not changed or decreased. It may be general or local. General venous hyperemia develops in acute or chronic cardiovascular insufficiency. Local venous hyperemia develops when there are difficulties with venous blood outflow from the organ or a part of the body (tumor, thrombus, embolus). Morphogenesis of the both types of venous hyperemia is similar, the only difference is the range of the lesion. In general venous hyperemia a number of organs are damaged, in local only one organ.

General venous hyperemia may be acute or chronic.

Acute venous hyperemia is a manifestation of a syndrome of acute cardiac insufficiency (e.g. in myocardial infarction) and is characterized by edematous plasmorrhagia, hemorrhage and degeneration.

Chronic venous hyperemia develops in chronic cardiovascular insufficiency. It is accompanied by tissue hypoxia development which increases vascular permeability, which in turn results in development of edema, plasmorrhagia, diapedesis of erythrocytes, degeneration in surrounding parenchymatous cells, with outcomes like necrosis and sclerosis. Sclerosis results in congestive induration of the organ. One of the final links in chronic venous hyperemia morphogenesis is formation of capillary parenchymatous block due to thickening of basement endothelial and epithelial membranes because of increase in collagen fibroblast production. It's known that collagen fibroblast production increases due to hypoxia.

The most prominent changes develop in parenchymatous organs.

The liver is called «nutmeg» liver, it is enlarged, dense, its borders are rounded, it has «nutmeg» appearance at incision. In this case you can see gray-yellow and dark-red areas.

Microscopically, the veins and sinusoids are plethoric, diapedesis of erythrocytes and fat degeneration of hepatocytes in the peripheral regions are observed.

Morphogenesis of «nutmeg» liver at first congestion of the venous blood develops, it is accompanied by tissue hypoxia development which increases vascular permeability, as a result diapedesis of erythrocytes and fat degeneration in hepatocytes are observed. Due to hypoxia

sclerosis and pathologic regeneration develop.

In «brown induration» of the lungs. The organs are dense, brown with multiple hemorrhages, besides sclerosis is observed.

In the kidneys and spleen cyanotic induration is observed. Morphogenesis of cyanotic induration in the kidney and spleen is similar to liver one.

Ischemia (originates from Greek ischo — delay) is decreased filling with blood of the tissue, organ, part of the body due to insufficient blood flow.

Depending on the cause and conditions ischemia can be classified into:

- 1) angiospastic caused by arterial spasm because of irritation, e.g. pain;
- 2) obturation, i.e. due to closure of the artery lumen with a thrombus or embolus or growth of connective tissue in inflammation, arteriosclerosis;
- 3) compression, i.e. squeezing of the artery with a tumor, fluid, tourniquet, etc.;
- 4) ischemia as a result of blood redistribution in case of postanemichyperemia.

If the duration of ischemia is short, the structure and the function of tissue may be restored. When the lesion is continuous, infarct, atrophy or sclerosis may develop.

Hemorrhage is exit of the blood from the lumen of the vessel or from the heart cavity. This may be external (to the environment) such as from the nose (epistaxis), vomiting of blood (hemotenesis) and other or internal (in the body cavity) such as hemoperi-cardium, hemothorax, hemoperitoneum.

Hemorrhage is also defined as accumulation of blood in the tissues.

Hematoma is accumulation of clotted blood in the tissues with disturbance of their entity. Large extravasations of blood into the skin and mucous membranes are called **ecchymoses**.

Hemorrhagic saturation is accumulation of the blood in the tissue when its entity is preserved.

According to the mechanism, bleeding can result from:

- 1) rupture of the vessel (per rhexin);
- 2) corrosion of the vessel (per diabrosin);
- 3) diapedesis (per diapedesin).

The hemorrhage can be caused by:

1. Trauma to the vessel wall, e.g. penetrating wound in the heart or great vessels.
2. Spontaneous hemorrhage, e.g. rupture of an aneurysm, septicemia, acute leukemias, pernicious anemia.
3. Inflammatory lesions of the vessel wall, e.g. bleeding from chronic peptic ulcer from tuberculous cavity in the lungs.
4. Neoplastic invasion e.g., hemorrhage following vascular invasion in cancer.
5. Vascular diseases, e.g., atherosclerosis.
6. Elevated pressure within the vessels, e.g. cerebral hemorrhage in systemic hypertension.

Outcomes: blood resorption, cyst formation (brain), encapsulation, organization, suppuration.

Plasmorrhagia is exit of plasma from the circulatory system. This can be caused by vascular spasm, tissue hypoxia, immune pathology. As a result, vascular permeability increases, plasma saturates the vessel and the surrounding tissues, plasma saturation occurs resulting in fibrous edema, fibrous necrosis and sclerosis. Plasmorrhagia is significant in morphogenesis of hypertension, infectious and allergic diseases, autoimmune diseases.

Disturbances in lymph circulation

Lymphostasis lymph congestion due to mechanical, resorption or dynamic insufficiency of lymph circulation.

Mechanical insufficiency is caused by increase in venous pressure, compression or obstruction of the lymph vessels. Dynamic insufficiency is due to discrepancy between the abundance of the fluid in the interstitial tissue and the rate of its outflow. Resorption insufficiency is due to disturbances in lymphatic capillaries permeability or changes in tissue

protein composition. Lymphostasis results in lymphedema, edema accompanied by chylosis when the fluid becomes milk white. There are mesothelial or tumor cells in chylous ascites. Prolonged lymphostasis results in lymphogenic sclerosis (according to experimental data it develops on the 20th day), e.g. elephantiasis of the extremities. In contrast to inflammatory sclerosis, lymphosclerosis develops without formation of granulation and inflammatory infiltration, it is called «non-cellular». Hyalinosis often develops in the connective tissue.

Disturbances in interstitial fluid amount

Interstitial fluid is located in the intercellular substance. The amount of interstitial fluid is controlled by neurohumoral system (aldosterone and pituitary antidiuretic hormone). It depends on the state of blood and lymph circulation as well as the level of vascular-tissue permeability.

Disturbances in interstitial fluid amount may be of the following types: increase (*edema*) and reduction (*dehydration, exicosis*).

Increase in interstitial fluid amount. Edema when transudate (which contains not more than 2% of protein) accumulates in the tissues or the cavities of the body. If transudate accumulates in subcutaneous fat it is called anasarca, in the heart cavity hydroperi-cardium, in the pleural cavity hydrothorax, in the abdominal cavity ascites, in the testis hydrocele. Edemas develop in the patients with cardiovascular, kidneys, liver, allergic diseases, infections, pathologic conditions of pregnancy (hestosis), in vein thrombosis, lymph congestion, disturbances of nervous trophism, etc.

In these diseases, the following changes are observed:

- 1) those in hydrostatic blood pressure,
- 2) those in colloid osmotic pressure of blood plasma,
- 3) vascular wall permeability increases,
- 4) retention of water and electrolytes.

These factors accompany each other in the majority of cases, but as a rule one of them prevails, e.g.

mechanical or congestive edema develops as a result of increase in hydrostatic pressure in micro-vessels and in fluid filtration.

Oncotic edema results from reduction in colloid-osmotic pressure in the blood plasma.

Membranogenic edema is associated with the increase in capillary permeability which results in plasma protein exit and its accumulation in the tissues.

Electrolyte edema results from retention of water and electrolytes.

Lymphogenic edema is caused by lymph congestion.

According to the disease responsible for the edema and its cause, it can be:

1. Congestive (in thrombophlebitis, vein compression, lymphostasis). Most frequently edema is local. This is due to venous congestion resulting in increase in venous pressure, hypoxia, damage of endothelium and basement membranes of the capillaries, increase in vascular permeability, transudation of some amount of blood to the tissue.
2. Cardiac (in cardiac decompensation). This case edema is characterized by combination of pathogenesis of congestive edema as well as accompanying blood redistribution, increase in aldosterone secretion and reduction in its destruction by the liver. Aldosterone is known to retain Na and water resulting in edema.
3. Hepatic. The pathogenesis consists of oncotic factor and Na retention.
4. Degenerative. Protein deficiency. Hypo-proteinemia develops and oncotic blood pressure reduces.
5. Inflammatory edema develops in the focus of inflammation where vascular permeability increases.

The outcome of edema is favorable, the fluid resolves, but prolonged edema can result in degeneration, atrophy, sclerosis.

Reduction in interstitial fluid amount (exicosis) may occur in rapid loss of great amount of fluid (cholera, prolonged diarrhea).

... **Stasis** (stasis — stop) is arrest of blood flow in the vessels of microcirculatory system

(capillaries). It is preceded by slowing the blood flow which is called prestasis.

Sludge syndrome (phenomenon) is regarded as a type of stasis. It is characterized by sticking of erythrocytes, leukocytes and thrombocytes to each other, which is accompanied by blood viscosity increase. Stasis may be discirculatory as a result of venous hyperemia or ischemia.

It develops due to:

- 1) physical factors (temperature elevation, cold);
- 2) chemical factors;
- 3) infection;
- 4) infectious-allergic factors;
- 5) autoimmune factors.

SHOCK

According to N. A. Kraievsky, «shock is a special reaction of the organism to a stimulus. It is fulfilled with nervous mechanisms and characterized by peculiar «shock» disturbance of circulation» (1944). But one of the founders of shock theory, W. Cannon (1943) believed that the role of nervous reaction in shock development is not significant. According to him, main feature of shock is peculiar disturbance in blood circulation due to exit of the blood from the circulation but not from the body.

Later it was called «hemorrhage into the vessels» or «blood depot». Recently this point of view became predominant owing to the achievements in microcirculation study. Shock is nonspecific clinical syndrome caused by reduction in tissue perfusion with blood. Shock believed to be based not so much on the primary disturbance of central neuro-regulatory mechanisms as disturbance of autoregulation in microcirculatory system due to the release of abundant biologically active substances.

In contemporary textbooks the following definition can be found: «Shock is acute pathologic process due to development of extrapowerful stimuli and characterized by disturbances in CNS function, metabolism and microcirculatory system autoregulation resulting in destructive changes in the organs and tissues».

According to etiology and pathogenesis shock is classified as:

1. Hypovolemic (blood loss, trauma, peritonitis, cholera).
2. Cardiogenic (caused by the reduction in cardiac output in myocardial infarction, vascular insufficiency).
3. Bacterial (caused by endotoxins).
4. Anaphylactic (immediate reaction of hypersensitivity).
5. Neurogenic (in intoxication with hypnotic preparations, ganglioblockers, narcotics).
6. Shock developing as a result of obstruction to the blood flow (pulmonary thromboembolism).
7. Shock developing in hormonal insufficiency (thyrotoxic shock, myxedema, adrenal insufficiency).

Shock morphology

- Three main pathological processes are observed in shock:
- DIC (disseminated intravascular coagulation) syndrome,
- hemorrhagic diathesis,
- liquid cadaver blood.

Microscopically it is characterized by generalized spasms of the vessels, microthrombosis, signs of increased vascular permeability in microcirculatory system, hemorrhages, degenerations, necroses connected with hypoxia and damaging effect of endotoxins.

Some examples of changes in the different organs in shock are:

- **shock kidney**, degeneration and necrosis in proximal canals with development of necrotic

nephrosis (or symmetrical cortical necroses are possible) which results in acute renal insufficiency,

- **shock liver**, glycogen amount in the hepatocytes decreases, hydropic degeneration and centrilobular necroses resulting in acute hepatic insufficiency develop. Combination of renal and hepatic insufficiency is called hepatorenal syndrome,
- **shock lung**, atelectasis foci, serous-hemorrhagic edema, stases and thromboses in the microcirculatory bed resulting in acute respiratory insufficiency,
- **shock heart**, degeneration and necrosis in cardiomyocytes, reduction in glycogen amount, fat degeneration, necrosis foci.

Similar changes occur in gastrointestinal tract, nervous, endocrine systems, immune organs.

Shock morphology depends not only on the cause of the shock but also on its stage. At the early stage, disturbances of hemodynamics and DIC (disseminated intravascular coagulation) syndrome are noted. At the last stages degenerative and necrotic process occur.

Intensive transfusion therapy of shock masks clinico-morphological picture. But the constant features are liquid cadaver blood irrespective of the composition of transfused fluids. Blood clots in the cardiac cavities and vessels are characteristic for terminal states of nonshock origin. So blood composition is a criterion for differential diagnosis

Self-check materials:

1. A patient with hepatic cirrhosis developed a collapse and hyperaemia of the peritoneum after removal of 10 litres of ascitic fluid from his abdominal cavity. Determine the kind of arterial hyperaemia of the peritoneum.

- | | |
|----|---|
| A. | Inflammatory |
| B. | Hyperaemia after anaemia* |
| C. | Vicarious |
| D. | Collateral |
| E. | On the ground of an arteriovenous shunt |

2. An autopsy revealed a diverse big liver with a picture of a nutmeg on section. In the lumens of the hepatic veins there were parietal thrombi. Name the kind of a circulatory disturbance in the liver.

- | | |
|----|-------------------------|
| A. | General venous plethora |
| B. | Anaemia |
| C. | Haemorrhage |
| D. | Local venous plethora* |
| E. | Bleeding |

3. An autopsy revealed a diverse big liver with a picture of a nutmeg on section. In the lumens of the hepatic veins there were parietal thrombi. Name the kind of a circulatory disturbance in the liver.

- | | |
|----|-------------------------|
| A. | General venous plethora |
| B. | Local venous plethora* |
| C. | Anaemia |
| D. | Haemorrhage |
| E. | Bleeding |

4. An autopsy of a male, who died from a profuse bleeding after numerous gunshot injuries, revealed large accumulation of coagulated blood in the soft tissues of his left thigh with an impairment of the structure of the muscles. Which of the processes listed below was the most probable?

- | | |
|----|-----------------------------------|
| A. | Haemorrhagic infiltration |
| B. | Microfocal haemorrhage (petechia) |
| C. | Bruise |
| D. | Ecchymoses |

E.

Haematoma*

5. A male patient with multiple fractures of his long tubular bones suddenly died under the phenomena of acute pulmonary insufficiency. An autopsy did not reveal any pathological changes in the internal organs. Microscopically, there were some diffuse sudanophilous inclusions in the lumens of small branches of the pulmonary artery and capillaries. What kind of embolism was the most probable?

- A. Thrombembolia
- B. Air
- C. Tissue
- D. Fat*
- E. With foreign bodies

TOPIC VII:Disturbance of hemostasis: hemorrhagic syndrome, thrombosis, disseminated intravascular coagulation. Embolism. Thromboembolism of lung artery.

1. Actuality of the problem.

Hemodynamic disturbances are considered under 2 broad headings: disturbances in the volume of the circulating blood (hyperemia and congestion, hemorrhage and shock) and circulatory disturbances of obstructive nature (thrombosis, embolism, ischemia and infarction). Research of the mechanisms, morphology of pathological processes in blood and lymphatic system may help to diagnose and treat the different diseases. These hemodynamic disturbances often are causes or complications of other diseases and in the majority of cases can become the cause of death. Different types of hemodynamic disorders accompany practically all known diseases; therefore study of these processes is important task in practical medicine. Thrombosis and embolism also can lead to serious clinical manifestations and are accompanied by occlusion of vessels, ischemia and infarction. These hemodynamic disturbances often are causes or complications of other diseases and in the majority of cases can become the cause of death. Therefore, the study of these pathological processes has big clinical significance. Knowledge of the mechanisms of development, morphologic manifestations, may help to diagnose the disease, prevent the spread of probable complications and treat them.

2. Aim of studies and competence. Study the morphological features of hemodynamic disturbances and their complications; to explain the causes and mechanisms of their development; to estimate probable outcomes and determine the significance for organism.

Tasks of the studies:

- Know the terminology and definitions of hemodynamic disturbances.
- Learn the morphology and functional manifestations of hemodynamic disturbances.
- Study the causes, mechanisms of development, morphologic characteristics of hyperemia and congestion.
- Study the causes, mechanisms of development, and morphologic characteristics of ischemia.
- Explain the morphologic features of the lymphodynamic insufficiency. Study the causes, mechanisms of development, and morphologic characteristics of edema.
- Know the terminology and definitions of hemodynamic disturbances (thrombosis and embolism, Infarction, DIC-syndrome).
- Learn the morphology and functional manifestations of thrombosis and embolism, Infarction, DIC-syndrome.
- Study the causes, mechanisms of development, morphologic characteristics of thrombosis, outcomes and significance for organism.
- Study the causes, mechanisms of development, and morphologic characteristics of the various types of embolism.
- Learn the morphology and functional manifestations of infarction.
- Explain the morphologic features of the disseminated intravascular coagulation syndrome.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction

- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of blood and lymph circulation system. 2. To draw normal structure of the system organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of different organs of blood and lymph circulation system.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of blood and lymph stream. 2. To use knowledge's about disturbance in inner organs morphology and function due to disturbance of their blood and lymph circulation 3. Be able to use knowledge's about peculiarity of blood stream. 4. To use knowledge's about disturbance in blood stream due to influence of different factors.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Term	Determination
Stasis	is arrest of blood flow in the vessels of microcirculatory system (capillaries)
Sludge syndrome	is regarded as a type of stasis. It is characterized by sticking of erythrocytes, leukocytes and thrombocytes to each other, which is accompanied by blood viscosity increase
Hemostasis	is a striking example of circulation adaptation failure
Thrombosis	is a pathologic manifestation of homeostasis, i.e. intravital coagulation of blood with formation of a blood clot called thrombus in the lumen of the vessel.
Embolism	circulation in the blood or lymph of particles which do not normally occur and obstruction of the vessels with them.
Thromboembolic syndrome	is separation of a thrombus or a part of it and circulation of these particles in the blood of general system with obstruction of lumina of different arteries accompanied by multiple infarctions.

Disseminated intravascular coagulation	is pathological syndrome which is characterized by formation of disseminated blood clots in the micro-circulatory bed (often in combination with simultaneous reduction of blood coagulability) causing hemorrhages.
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4.2 Theoretical questions for the practical class:

10. Thrombosis: clinical - morphologic manifestation, significance and consequences of thrombosis.
11. Local and general factors of creation of thrombus.
12. Thrombus: definition, types and morphological characteristics, distinguishing features of arterial and venous thrombi
13. Syndrome of disseminated intravascular coagulation (DIC).
14. Embolism. Causes, types, morphologic characteristic, consequences, significance of embolism.
15. Orthograde, retrograde and paradoxical embolism.
16. Thromboembolism of pulmonary artery.
17. Infarction: definition, types, morphological features and outcomes.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. "Cyanotic induration of the Spleen". Pay attention to the size, consistency and color of the organ. *Explain etiology and morphogenesis of cyanotic induration.*

1. "Thromboembolism of pulmonary artery". Pay attention to character and consistence of thrombotic masses. Describe the localization of thromboembolus, size and color. *Name the most frequent origin of pulmonary thromboembolism.*

2. "Obtured thrombus of vena cava inferior". Pay attention to shape, color, consistence and localization of thrombus into lumen of vessel. *What are the causes of such changes?*

3. "Chronic cardiac aneurysm with thrombosis". Pay attention to the brown thrombotic masses, their localization on the surface of chronic cardiac aneurysm. *What are the causes of such changes?*

4. "Embolic purulent nephritis". Pay attention to the size of the kidney, its shape, color, consistency. Note numerous areas of reddish color. It's secondary nephritis appearing due to septic embolism. *Give definition and name possible outcomes of this pathologic process.*

5. "Tamponade of cavity of pericardium". Pay attention to the cavity of pericardium. It is filled by flat brownish clots which were formed due to hemorrhage within the cavity in result of rupture of myocardium. *What are the causes of such changes? What are the possible outcomes?*

Microslides:

Slide 1. "Red thrombus"(ought to be drawn)

The lumen of the vein is filled with fresh masses of red thrombus with fibrin and erythrocytes.

Slide 2. "Intertrabecular mixed thrombus in atrium"

The red color areas are the areas of crowded erythrocytes. Blue color areas – leukocytes; violet color – thrombocytes and fibrin.

Slide 3. “White thrombus” (ought to be drawn)

The thrombus contains fibrin in form of firm fibrillary pinkish masses or thin fibers similar to network. There are leukocytes and lymphocytes among the fibrin. Thrombocytes look as a pale granular agglutinated homogenized masses.

Slide 4. Organization and recanalization of thrombus (ought to be drawn)

The lumen of artery is obliterated by thrombus. Fibrillar connective tissue with multiple clefts and young vessels, brownish granules of hemosiderin are visible in thrombus.

Slide 5. “Mixed thrombus” (ought to be drawn)

Thrombotic masses contain pinkish fibrin, leukocytes, erythrocytes, with hemolysis. Agglutinated masses of thrombocytes are visible among fibers of fibrin.

Topic content:

Hemostasis is a striking example of circulation adaptation failure. Short stasis is reversible, long one causes hyaline thrombi formation, vascular permeability increase, edema, bleeding.

Isolated vein spasm may cause leukostasis, accumulation of erythrocytes within venules (small veins) and capillaries. It is observed in hypoxia.

In shock, leukostasis may be generalized, but as a rule it is localized in the venules. Microcirculation disturbances.

There are four links in microcirculation:

- 1) the link of inflow and distribution of the blood (arterioles and precapillaries);
- 2) intermediate (exchange) link (capillaries);
- 3) depot link (postcapillaries and venules);
- 4) drainage link (lymphatic capillaries and postcapillaries).

The function of microcirculation is exchange between the blood and tissue. Pathology of microcirculatory system is formed of vascular, intravascular and extravascular changes.

Vascular changes are those in the thickness and shape of the vessels, angiopathies with disturbance of vascular permeability as a result of hypoxia.

Intravascular changes manifest as different disturbances of blood rheology (sludge, prestasis, stasis). They are observed in shock of different origin.

Extravascular changes are perivascular edema, hemorrhage, lymphostasis on the lymph vessels.

Thrombosis (originates from Greek thrombus — blood clot) is a pathologic manifestation of homeostasis, i.e. intravital coagulation of blood with formation of a blood clot called thrombus in the lumen of the vessel. The thrombus may partially or completely close the lumen and cause serious disturbances of blood circulation.

At the same time homeostasis is a protective mechanism and it becomes active at the vessel rupture. The mechanism of thrombus formation includes four consequent stages: thrombocytes agglutination, fibrinogen coagulation and fibrin formation, erythrocyte agglutination and plasma protein precipitation. Thrombosis pathogenesis includes local and general factors which cause thrombus formation.

Local factors are changes in the vascular wall, slowing the blood flow and disturbance of turbulent motion. General factors include disturbances of regulation of coagulation and anticoagulation systems and changes in the blood composition.

Morphology. The thrombus is attached to the vascular wall, it is dense, with corrugated surface. It is composed of branching bars of stuck thrombocytes and bands of fibrin with erythrocytes and leukocytes located between them.

Thrombi may be white, red, mixed and hyaline. Hyaline thrombus consists of precipitating plasma proteins, destructed erythrocytes, leukocytes and thrombocytes. They do not contain fibrin. They resemble hyaline and are located in the microcirculatory bed.

According to the degree of the lumen obliteration, thrombi may be parietal or obstructive.

Parietal thrombi develop in large arteries and heart cavities. Obstructive thrombi most commonly develop in small arteries and veins.

The thrombus enlarges with adding new masses to the primary one. It may grow both with the blood flow and against it.

If the thrombus which appeared in the veins (e.g. leg) enlarges with the flow and reaches the collecting veins (e.g. inferior vena cava), thrombosis is called progressive. The thrombus in the aneurysm is called dilatation. Thrombi in the veins can be revealed in 31.0 — 22.0% of autopsies, those in the heart in 45.8%.

Thrombosis is the main factor in morphogenesis of disseminated intravascular coagulation (DIC) syndrome and is the basis of thromboembolic syndrome.

The outcome of thrombosis may be favorable: aseptic thrombus autolysis or growth of connective tissue from vascular intima with formation of clefts and channels, covered with endothelium, so called thrombus canalization. Then these canals turn into vessels with restored blood flow, it is so called vascularization of the thrombus. Calcification of thrombus with stones (phlebolith) formation is possible.

Unfavorable outcome: thromboembolism, septic thrombus autolysis, thrombobacterial vascular embolism in sepsis.

Embolism (originates from Greek emballein — to cast into) circulation in the blood or lymph of particles which do not normally occur and obstruction of the vessels with them. These particles are called emboli.

Depending of the way of their movement embolism may be:

1) orthograde (with the flow):

- from the veins of general circulation to the vessels of pulmonary circulation,
- from the left part of the heart, aorta, large arteries to the arteries of the heart, brain, kidneys, spleen, etc.,
- from the veins of the portal system to the portal vein of the liver;

2) retrograde embolism, movement of embolus against the flow with his own weight (e.g. through inferior vena cava to femur vein);

3) paradoxical embolism, in defect of atrial or ventricular septum when the embolus enters the arteries from the general circulation.

According to the type of embolus the following types of embolism are distinguished:

1) thromboembolism, the most frequent form occurring when a thrombus or its part separate. It may be either venous or arterial;

2) air embolism is caused by the air entering the venous system in injuries of the veins located near the heart. Air embolism may be caused by injection of air to the uterine cavity at criminal abortion, at intravenous injections if the air has not been evacuated from the syringe.

Diagnosis: at autopsy, the right heart is punctured without taking it out. The cavity of the cardiac sac

should be preliminary filled with water. Air discharge and foamy blood are observed;

3) gas embolism occurs as a result of exudation of bubbles of the gas dissolved in the blood, e.g. at rapid transition from high atmospheric pressure to normal in caisson disease, gas gangrene, in pilots;

4) fat embolism occurs in bone injuries when the fat is crushed and turned into emulsion;

5) tissue embolism occurs in the fetus during delivery if amniotic fluid and chorion enter the veins of the uterus. The other examples are tumor cells and septic thrombus;

6) foreign bodies (fragments of shells, bullets), embolism with lime, cholesterol crystals.

Thromboembolic syndrome is separation of a thrombus or a part of it and circulation of these particles in the blood of general system with obstruction of lumina of different arteries accompanied by multiple infarctions. Infarct is vascular necrosis. Most frequently it is caused by thrombi in aortic or mitral valves, intratrabecular thrombi of the left ventricle and auricle of the left atrium, the thrombi of aorta and large arteries which turn into thromboemboli. All these develops in rheumatic and bacterial endocarditis, atherosclerosis, cardiac aneurysm, heart

defects.

In thromboembolic syndrome, infarcts frequently develop in the kidneys (white with hemorrhagic rim), spleen (white), brain (white and red), heart (white with hemorrhagic rim), intestine (red), gangrene of extremities. A variety of thromboembolic syndrome is pulmonary thromboembolism. Thromboemboli formed in the veins of the general system and in the right heart and enter the pulmonary artery. They may enter small branches of the pulmonary artery causing hemorrhagic lung infarction. If the embolus enters a large branch of the artery, the patients die suddenly because of pulmonocoronary reflex. This condition is characterized by spasm of bronchial tree, branches of pulmonary artery and coronary arteries.

Thromboembolic syndrome may complicate infectious, cardiovascular, and oncological diseases, it may occur after different operations.

Disseminated intravascular coagulation (consumption coagulopathy, defibrination, throm-bohemorrhagic syndrome or phenomenon) is pathological syndrome which is characterized by formation of disseminated blood clots in the micro-circulatory bed (often in combination with simultaneous reduction of blood coagulability) causing hemorrhages. It often develops in complicated pregnancy, profuse uterine bleedings, Cesarean section, large injuries, anemias, thrombocytopenias, leukosis, in 36—50% of cases of asphyxia in premature children.

The causes of its development are numerous, the mechanisms of development are different.

The most important are:

1. Massive formation of thromboplastin or its activators. It may be thromboplastin of erythrocytes in intravascular hemolysis (hemolytic disease of newborn, massive blood transfusions, poisoning, infections) or thromboplastin of amniotic fluid at massive aspiration of amniotic fluid by the fetus, tissue thromboplastin in injury (especially that of brain and lungs).

2. Generalized disturbance of microcirculation accompanied by changes in blood rheology and its clotting which is observed in hypoxia and shock of different origin. Bacterial toxins and immune complexes act similarly. They activate factor XII which plays the most important role both in blood coagulation and anticoagulation activation. The same mechanism regulates disseminated intravascular coagulation syndrome in thrombosis of large arteries or at severe loss of fibrinogen at formation of hyaline membranes in the lungs of newborns.

3. Reduction of the number of thrombocytes (consumption thrombocytopenia in Kasabach-Merritt syndrome).

4. Generalized angiopathy in infectious diseases and hemolytic disease of newborn also causes disseminated intravascular coagulation syndrome. At the first stage it is characterized by generalized increase of blood coagulation in the microvessels. Large number of fibrin clots are formed. They close the vessel (fibrinoembolism).

At the second stage the amount of thrombocytes, fibrinogen, protrombin in the blood decreases sharply because they have already been used at the first stage with the resultant consumption coagulopathy. Thus, hemorrhagic syndrome develops.

At the third stage fibrinolysis activation takes place in response to generalized increase of coagulation occurring at the first stage which makes hemorrhagic syndrome more severe.

In severe cases the three stages develop simultaneously. Disturbance in blood clotting is accompanied by stasis, opening of arteriovenous shunts, capillary paralysis, decrease in arterial pressure. Degenerative and necrotic changes develop in parenchymatous organs.

Morphological changes in disseminated intravascular coagulation (DIC) syndrome:

- 1) large amount of fibrin thrombi and emboli in the small vessels of the liver, red pulp of spleen, adrenals, brain, lungs, kidneys, placenta, thymus,
- 2) mucoid swelling, fibrinous swelling and fibrinous necrosis with endothelium desquamation in the walls of small arteries,
- 3) thromboses of large vessels are possible. Often the thrombi occur in the sinuses of the dura mater, hepatic veins, aorta,
- 4) in thrombosis of microcirculatory bed, vital processes of blood-tissue metabolism stop. Under

these conditions organ pathology is not distinct, general changes (like toxicosis or shock) develop,

5) in thrombosis of larger arteries, organ pathology prevails, i.e. acute renal or hepatic insufficiency, shock lung, brain edema, myocardial infarction,

6) DIC (disseminated intravascular coagulation) results in hemorrhages in different organs, those in the capsule are most frequent.

SHOCK

According to N. A. Kraievsky, «shock is a special reaction of the organism to a stimulus. It is fulfilled with nervous mechanisms and characterized by peculiar «shock» disturbance of circulation» (1944). But one of the founders of shock theory, W. Cannon (1943) believed that the role of nervous reaction in shock development is not significant. According to him, main feature of shock is peculiar disturbance in blood circulation due to exit of the blood from the circulation but not from the body.

Later it was called «hemorrhage into the vessels» or «blood depot». Recently this point of view became predominant owing to the achievements in microcirculation study. Shock is nonspecific clinical syndrome caused by reduction in tissue perfusion with blood. Shock believed to be based not so much on the primary disturbance of central neuro-regulatory mechanisms as disturbance of autoregulation in microcirculatory system due to the release of abundant biologically active substances.

In contemporary textbooks the following definition can be found: «Shock is acute pathologic process due to development of extrapowerful stimuli and characterized by disturbances in CNS function, metabolism and microcirculatory system autoregulation resulting in destructive changes in the organs and tissues».

According to etiology and pathogenesis shock is classified as:

1. Hypovolemic (blood loss, trauma, peritonitis, cholera).
2. Cardiogenic (caused by the reduction in cardiac output in myocardial infarction, vascular insufficiency).
3. Bacterial (caused by endotoxins).
4. Anaphylactic (immediate reaction of hypersensitivity).
5. Neurogenic (in intoxication with hypnotic preparations, ganglioblockers, narcotics).
6. Shock developing as a result of obstruction to the blood flow (pulmonary thromboembolism).
7. Shock developing in hormonal insufficiency (thyrotoxic shock, myxedema, adrenal insufficiency).

Shock morphology

- Three main pathological processes are observed in shock:
- DIC (disseminated intravascular coagulation) syndrome,
- hemorrhagic diathesis,
- liquid cadaver blood.

Microscopically it is characterized by generalized spasms of the vessels, microthrombosis, signs of increased vascular permeability in microcirculatory system, hemorrhages, degenerations, necroses connected with hypoxia and damaging effect of endotoxins.

Some examples of changes in the different organs in shock are:

- **shock kidney**, degeneration and necrosis in proximal canals with development of necrotic nephrosis (or symmetrical cortical necroses are possible) which results in acute renal insufficiency,
- **shock liver**, glycogen amount in the hepatocytes decreases, hydropic degeneration and centrilobular necroses resulting in acute hepatic insufficiency develop. Combination of renal and hepatic insufficiency is called hepatorenal syndrome,
- **shock lung**, atelectasis foci, serous-hemorrhagic edema, stases and thromboses in the

microcirculatory bed resulting in acute respiratory insufficiency,

- **shock heart**, degeneration and necrosis in cardiomyocytes, reduction in glycogen amount, fat degeneration, necrosis foci.

Similar changes occur in gastrointestinal tract, nervous, endocrine systems, immune organs.

Shock morphology depends not only on the cause of the shock but also on its stage. At the early stage, disturbances of hemodynamics and DIC (disseminated intravascular coagulation) syndrome are noted. At the last stages degenerative and necrotic process occur.

Intensive transfusion therapy of shock masks clinico-morphological picture. But the constant features are liquid cadaver blood irrespective of the composition of transfused fluids. Blood clots in the cardiac cavities and vessels are characteristic for terminal states of nonshock origin. So blood composition is a criterion for differential diagnosis

Self-check materials:

1. A 52-year-old woman has a history of urinary tract infections. Recently, one of these episodes was complicated by acute pyelonephritis involving her kidneys. She became septic, and a blood culture grew *Escherichia coli*. She developed severe hypotension. She had purpuric areas on her skin. A stool for occult blood was positive. She had a prothrombin time of 50 sec (control 12), partial thromboplastin time of 100 sec (control 25), platelet count of 20,000/microliter, and D-dimer of 4 microgm/mL. These findings are most characteristic for which of the following conditions:

- A. Hemophilia A
- B. Von Willebrand disease
- C. Antiphospholipid syndrome
- D. Disseminated intravascular coagulation *
- E. Acute fulminant hepatitis

2. A male patient with multiple fractures of his long tubular bones suddenly died under the phenomena of acute pulmonary insufficiency. An autopsy did not reveal any pathological changes in the internal organs. Microscopically, there were some diffuse sudanophilous inclusions in the lumens of small branches of the pulmonary artery and capillaries. What kind of embolism was the most probable?

- F. Thrombembolia
- G. Air
- H. Tissue
- I. Fat*
- J. With foreign bodies

3. An autopsy of a 70-year-old male, who suffered from hypertensive disease and died of a disturbance in the cerebral circulation, revealed in his brain stem some cavity which was 2 cm in diameter and filled with blood clots. Name the mechanism of the impairment of the vascular wall which most likely could result in a haemorrhage.

- A. Rupture*
- B. Spasm
- C. Erosion
- D. Oedema
- E. Diapedesis

4. Following an injury of his cervical veins, a male suddenly died under the phenomena of an acute respiratory insufficiency. An autopsy revealed that his right heart cavities were distended and contained some foamy liquid blood, the major veins contained the blood of the same kind. Microscopically, the lumens of small branches of the pulmonary arteries and capillaries revealed numerous embolic masses. Which of the kinds of embolism listed below was the most probable?

- A. Tissue
- B. Gaseous

- C. Thrombembolia
- D. Air*
- E. Fat

5. An autopsy of a woman, who died from acute myocardial infarction, a thrombus in a vein of her left shin was found out. A microscopic study of the thrombus revealed that it was substituted with a connective tissue having some cracks and channels with an endothelial lining. Indicate the most probable outcome of the thrombosis.

- A. Aseptic autolysis
- B. Petrification of the thrombus
- C. Organization and canalization of the thrombus*
- D. Septic autolysis
- E. Transformation into thromboembolism

TOPIC VIII:Inflammation: reasons, morphogenesis. Morphology of exudative inflammation.

1. Actuality of the problem.

Inflammation is fundamentally a protective response whose ultimate goal is to rid the organism of both the initial cause of cell injury and the consequences of such injury, the necrotic cells and tissues. Acute inflammation is the immediate and early response to an injurious agent. The account of acute inflammation given above is based on local tissue responses. However, acute inflammation is associated with systemic effects. Knowledge of these processes is necessary for understanding of the pathogenesis of the diseases and for the clinic-anatomical analysis of the autopsy.

2. Aim of studies. Study the morphological features of the acute; to explain the causes and mechanisms of its development; to estimate outcomes and determine the significance for organism.

Tasks of the studies:

- inflammation in organism. Explain the role of
- inflammation. Know the terminology of
- processes of alteration, exudation and proliferation. Tell apart the inflammatory
- and functional manifestations of different types of exudative inflammation, their outcomes. 4 Learn the morphology

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of immune system.

	2. To draw normal structure of immune system's organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of immune system's inner organs as well as its cells.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of work activity of immune system. 2. To use knowledge's about disturbance in immune system due to influence of different factors.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Inflammation	is defined as the local response of living tissues to injury caused by any agent. It is body defense reaction in order to eliminate or limit the spread of injurious agent.
Serous exudate	when the fluid exudate resembles serum or is watery, e.g. pleural effusion in tuberculosis, blister formation in burns.
Fibrinous exudate	when the fibrin content of the fluid exudate is high, e.g. in pneumococcal and rheumatic pericarditis. Two types may be croupous and diphtheroid fibrinous inflammation.
Purulent exudate	or suppurative exudate is formation of creamy pus as seen in infection with pyogenic bacteria, e.g. abscess, acute appendicitis, phlegmon.
Hemorrhagic exudate	when there is vascular damage, e.g. acute hemorrhagic pneumonia in influenza.
Catarrhal exudate	when the surface inflammation of epithelium produces increased secretion of mucus, e.g. common cold.
Phlegmon	is unbounded purulent inflammation in which pus spreads diffusely between different components of tissue owing to fusion and tissue lysis.
Empyema	is appearance of purulent exudate in the human cavities
Furuncle	is an acute inflammation via hair follicles in the dermal tissues.
Cellulitis	is a diffuse inflammation of soft tissues resulting from spreading effects of substances like hyaluronidase released by some bacteria.
Bacteremia	is presence of small number of bacteria in the blood which don't multiply significantly.
Septicemia	means presence of rapidly multiplying, highly pathogenic bacteria in the blood, e.g. pyogenic cocci, bacilli of plague, etc.
Pyemia	is the dissemination of small septic thrombi in the blood which cause their effects at the site where they are lodged.

4.2 Theoretical questions for the practical class:

1. Definition. Essence and biological significance of inflammation.
2. Causes and mechanisms of development of inflammation.
3. Phases of inflammation, their morphological features.
4. Classification of Inflammation.
5. Morphological patterns of acute inflammation.
6. Classification of exudative inflammation.
7. Suppurative inflammation. Types of suppurative inflammation (abscess and phlegmon). Outcomes and complications.
8. Fibrinous (pseudomembranous) inflammation. Croupous and diphtheric inflammation. True and false croup. Examples of diseases.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to	1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **“Croupous pneumonia in the stage of grey hepatization”**. Describe the appearance of the lungs, aeration, pleura state, the character of exudates. *Call the etiological factors, the outcomes of the inflammation and possible complications.*
2. **“Purulent meningitis”**. Characterize the type of inflammation in the pia mater of the brain: swelling, color, condition of sulcus, convolutions and vessels. *What type of inflammatory process takes place?*
3. **“Fibrinous Pericarditis (“corvillosum”)**. Pay attention to the appearance of the epicardium, its surface. *How do you characterize the type of inflammation? What are the causes of such changes? What are the possible outcomes?*
4. **“Phlegmonous appendicitis”**. Pay attention to the size, color, and surface of appendix. *Characterize the type of inflammation.*
5. **“Abscess of the Liver”**. Pay attention to the appearance of the abscess walls and the content of the cavity. *What type of inflammatory process takes place? What are the causes of such changes?*
6. **“Diphtheritic Colitis”**. The wall of large intestine is thickened with some areas of ulceration. Mucosa is rough, covered by dense fibrinous yellowish-grayish masses, which closely connected with sublying layers. If those masses are come off ulcers appear in their sites. *Characterize the type of inflammation, its complications.*

Microslides:

Slide 1. Phlegmonous inflammation of the Thigh (ought to be drawn)

The edema, hemorrhages and diffuse infiltration of the cellular tissue with leukocytes take place.

Slide 2. Fibrinous pericarditis (ought to be drawn)

The pink-purple masses of fibrin with red blood cells, leukocytes are noted on the surface of pericardium.

Slide 3. Fibrinous pericarditis (ought to be drawn)

The pink-purple masses of fibrin with red blood cells, leukocytes are noted on the surface of pericardium.

Slide 4. Acute purulent bronchopneumonia

There are many neutrophils in the lumens of alveoli, bronchi and bronchioles. The small abscesses with necrosis of pulmonary tissue are seen here and there. Hyperemia of vessels is noted.

Topic content:

Inflammation is defined as the local response of living tissues to injury caused by any agent. It is body defense reaction in order to eliminate or limit the spread of injurious agent.

Causes. The agents causing inflammation may be as follows:

1. Physical agents (heat, cold, radiation, mechanical injury).
2. Toxic chemical agents (organic and inorganic poisons).
3. Microbiological agents (bacteria, viruses, parasites, fungi).

4. Immunological agents (cell-mediated, immune complex and antigen-antibody reactions).

Clinico-morphological signs of inflammation. There are 5 main clinico-morphological signs of inflammation:

1. rubor (redness);
2. tumor (swelling);
3. calor (heat),
4. dolor (pain)
5. functiolaesa (loss of function).

The word «inflammation» means burning. This nomenclature has its origin in old times but now we know that burning is only one of the signs of inflammation. The condition develops on the histion.

Types of inflammation

There are 3 phases in inflammation:

- 1) alteration,
- 2) exudation
- 3) proliferation.

The first phase is alteration, degeneration and necrosis of the cells, tissue.

The second phase is exudation, formation of exudate. There are several stages in exudation:

- a) microcirculation reaction with disturbance of blood rheo-logy,
- b) increased vascular permeability,
- c) exudation of main blood components,
- d) emigration of blood cells,
- e) phagocytosis,
- f) formation of exudation
- g) development of inflammatory infiltration.

According to prevailing one of these phases, inflammation is classified into 2 groups. We distinguish exudative and proliferative inflammations.

Depending upon the defense capacity of the host and duration of the response, inflammation can be classified as acute and chronic.

Exudative inflammation usually develops as acute inflammation, proliferative inflammation develops as chronic one.

Acute inflammation is of short duration and represents the early body reaction and is usually followed by repair.

Chronic inflammation is of longer duration and occurs either after the causative agent of acute inflammation persists for a long time, or the stimulus is such that it induces chronic inflammation from the beginning.

Cells involved in inflammation

Neutrophils (also known as polymorphonuclear neutrophils), are the predominant cells in acute inflammation as well as in abscess formation, loculation, and empyema. They are the white blood cells (WBCs) most responsible for the leukocytosis that occurs in response to an inflammatory or infectious crisis. Neutrophils are granular leukocytes with a multilobate nucleus and fine cytoplasmic granules that stain readily with neutral dyes. In the inflammatory response, neutrophils are the first cells to arrive at the injured area. The major activity of neutrophils is phagocytosis of invading bacterial cells, with subsequent destruction of the cells through the release of lysosomal enzymes.

Eosinophils (eosinophilic granulocytes) have a characteristic bilobate nucleus and

cytoplasmic granules that stain orange with Romanovsky's stain and red-orange with eosin. The granules contain hydrolytic enzymes (e.g., histaminase, which inactivates histamine; arylsulfatase B, which inactivates SRS-A). The granules also contain a poorly understood major basic protein. Although they also can be found in peripheral blood, a number of the body's eosinophils exist in hypersensitivity sites within the tissues, where they can abort hypersensitivity reactions. Eosinophils are increased in the peripheral blood in the presence of allergy and parasitic infestation. Eosinophils are readily chemotactic upon the release of eosinophil chemotactic factor (ECF) from IgE-sensitized mast cells—an occurrence in anaphylaxis. Eosinophils are also phagocytic, although phagocytosis is a minor function.

Basophils (basophilic granulocytes) contain granules that stain blue with Wright's stain. The granules contain histamine, heparin, and slow-reacting substance of anaphylaxis. Basophils are involved in type I immediate, or immunoglobulin E (IgE)-mediated hypersensitivity reactions. When an IgE-specific antigen enters the body, basophils stimulate the formation of IgE, which binds to the surface of the antigen. The basophilic granules then release histamine and other vasoactive substances to produce anaphylactic reactions in susceptible persons. Basophils also play a role in type IV (i.e., delayed) hypersensitivity reactions, such as contact dermatitis.

Macrophages. The mononuclear phagocyte system (also known as the monocyte-macrophage system and reticuloendothelial system) is an extensive network of macrophages that exists throughout the body. Pulmonary alveolar macrophages, Pleural and peritoneal macrophages, Kupffer cells of the liver, Histiocytes of mesenchymal and connective tissue, Mesangial cells of the kidney, Both fixed and mobile macrophages in the lymph nodes, spleen, and bone marrow. Macrophages in the body tissues develop from monocytes that have left the peripheral blood. The monocytes originally derive from bone marrow precursors. Monocytes in the bone marrow and the peripheral blood can be converted rapidly into additional macrophages when needed.

Macrophages dispose of noxious matter within tissues, for example, microorganisms and necrotic tissue or other debris. Macrophages also appear to serve in tumor cell killing. In phagocytosis, the cytoplasmic membrane extends around particles and engulfs them, forming an intracellular vacuole. In pinocytosis, the cell membrane engulfs extracellular fluid along with the particles. The lysosomes of macrophages contain degradative substances similar to those in neutrophils. Macrophages have surface receptors for the Fc segment of the immunoglobulin G (IgG) molecule and for complement component C3b. These aid the macrophage in phagocytosis of opsonized microorganisms.

Macrophages are important components of the immune system. Their involvement begins with the initiation of the immune response, and they interact closely with T-lymphocytes. B-cell activation requires IL-1, which is secreted by macrophages (and some other cells). B-cell activation also requires that antibody on the B-cell surface match its specific antigen. Antigen on the macrophage surface can serve this purpose.

Mast cells resemble basophils in both structure and function.

Whereas basophils are present mainly in the peripheral blood and at sites of inflammation, mast cells are connective tissue cells found close to small blood vessels. Mast cells contain numerous granules that stain metachromatically with basic dyes. Like basophilic granules, mast cell granules release histamine, heparin, and SRS-A during type I reactions. In addition, mast cell granules release. Agents that cause inflammation (e.g., physical factors, drugs, immunoglobulins, complement components C3a and C5a, cationic proteins) may cause histamine release from mast cells.

Lymphocytes and their derivatives are found in the tissues in all types of inflammation, especially after the acute ingress of neutrophils. All lymphocytes are derived from bone marrow stem cells. Stem cells differentiate into lymphocytes in the primary lymphoid organs (thymus and bone marrow). From these locations, some lymphocytes migrate — via the circulation — to

secondary lymphoid organs, namely, the spleen, lymph nodes, and lymphoid germinal centers throughout the body.

Lymphocytes are divided into two types — T-cells and B-cells — which serve different functions (*See Immunopathology*).

ACUTE INFLAMMATION

Morphological manifestations of inflammation depend upon a number of factors and processes. They are factors of the organisms and the host, type of exudation, cellular proliferation.

Factors involving the organisms

1. Type of injury and infection. For example, skin reacts to herpes simplex infection by formation of a vesicle and to streptococcal infection by formation of a boil; lung reacts to pneumococci by occurrence of lobar pneumonia while to tubercle bacilli it reacts by granulomatous inflammation.

2. Virulence. Many species and strains of organisms may have varying virulence e.g. the three strains of *C. diphtheriae* (gravis, intermedius and mitis) produce the same diphtherial exotoxin but in different amount.

3. Dose. The concentration of organism in small doses produces usually local lesions while a larger dose results in more severe spreading infections.

4. Portal of entry. Some organisms are infective only if administered by particular route, e.g. *Vibrio cholerae* is not pathogenic if injected subcutaneously but causes cholera if swallowed.

5. Product of organisms. Some organisms produce enzymes that help in spread of infections, e.g. hyaluronidase by *CI. welchii*, streptokinase by *Streptococci*, staphylokinase and coagulase by *Staphylococci*.

Factors involving the host

1. General health of host. For example, starvation, hemorrhagic shock, chronic debilitating diseases like diabetes mellitus, alcoholism, etc. render the host more susceptible to infections.

2. Immune state of host. Immunodeficiency helps in spread of infections rapidly, e.g. in AIDS.

3. Leukopenia. Patients with low WBC count with neutropenia or agranulocytosis develop spreading infection.

4. Site or type of tissue involved. For example, the lung has loose texture as compared to bone and thus both tissues react differently to acute inflammation.

5. Local host factors. For instance, ischemia, presence of foreign bodies and chemicals cause necrosis and are thus harmful.

Type of exudation. The appearance of escaped plasma determines the morphological type of inflammation. These are:

1. Serous, when the fluid exudate resembles serum or is watery, e.g. pleural effusion in tuberculosis, blister formation in burns.

2. Fibrinous, when the fibrin content of the fluid exudate is high, e.g. in pneumococcal and rheumatic pericarditis. Two types may be croupous and diphtheroid fibrinous inflammation.

3. Purulent or suppurative exudate is formation of creamy pus as seen in infection with pyogenic bacteria, e.g. abscess, acute appendicitis, phlegmon.

4. Hemorrhagic, when there is vascular damage, e.g. acute hemorrhagic pneumonia in influenza.

5. Catarrhal, when the surface inflammation of epithelium produces increased secretion of mucus, e.g. common cold.

Cellular proliferation. Variable cellular proliferation is seen in different types of inflammations.

1. There is no significant cellular proliferation in acute bacterial infections except in typhoid fever in which there is intestinal lymphoid hyperplasia.

2. Viral infections have the ability to stimulate cellular proliferation, e.g. epidermal cell proliferation in herpes simplex, chickenpox and smallpox.
3. In glomerulonephritis, there is proliferation of glomerular capsular epithelial cells resulting in formation of «crescents».
4. In chronic inflammation, cellular proliferation of macrophages, fibroblasts and endothelial cells occurs.

Necrosis. The extent and type of necrosis in inflammation is variable. In gas gangrene, there is extensive necrosis with discolored and foul smelling tissues. In acute appendicitis, there is necrosis as a result of vascular obstruction. In chronic inflammation such as tuberculosis, there is characteristic caseous necrosis.

Morphology of acute inflammation

Inflammation of an organ is usually named by adding the suffix «itis» to its Latin name e.g. appendicitis, hepatitis, cholecystitis, meningitis, etc. A few morphologic varieties of acute inflammation are described below:

1. **Catarrhal inflammation.** A surface inflammation associated with greatly increased secretion of clear mucus. Later, polymorphs appear (common cold and some forms of colitis).
2. **Hemorrhagic inflammation.** Where the damage is severe, actual rupture of all blood vessels occurs, with hemorrhage the most striking feature (acute hemorrhagic pneumonia occasionally occurring in fatal cases of influenza).
3. **Suppuration.** There are several types of suppuration: an abscess, phlegmon, furuncle, carbuncle, cellulitis, bacterial infections of the blood.

When acute bacterial infection is accompanied by intense neutrophilic infiltrate in the inflamed tissue, it results in tissue necrosis. A cavity is formed which is called an abscess and contains purulent exudate or pus and the process of abscess formation is known as suppuration. The bacteria which cause suppuration are called pyogenic. Pus is creamy or opaque in appearance and is composed of numerous dead as well as living neutrophils, some red cells, fragments of tissue debris and fibrin. In old pus, macrophages and cholesterol crystals are also present. The wall of abscess is called pyogenic membrane. An abscess may be discharged to the surface due to increased pressure inside or may require drainage by the surgeon. Due to tissue destruction, resolution does not occur but instead healing by fibrous scarring takes place.

Phlegmon is unbounded purulent inflammation in which pus spreads diffusely between different components of tissue owing to fusion and tissue lysis. Phlegmon frequently occurs along the muscular bands, tendons, fascias, vascular-nerves bands and in subcutaneous fat. Two types of phlegmon have been described: soft and dense.

If purulent exudate appears in the human cavities it is called **empyema**.

Furuncle is an acute inflammation via hair follicles in the dermal tissues.

Carbuncle is seen in untreated diabetics and occurs as a located abscess in the dermis and soft tissues of the neck.

Cellulitis. It is a diffuse inflammation of soft tissues resulting from spreading effects of substances like hyaluronidase released by some bacteria.

Bacterial infections of the blood. This includes the following 3 conditions: bacteremia, septicemia, pyemia.

Bacteremia is defined as presence of small number of bacteria in the blood which don't multiply significantly. They are commonly not detected by direct microscopy. Blood culture is done for their detection, e.g. infection with *Salmonella typhi*, *Escherichia coli*, *Streptococcus viridans*.

Septicemia means presence of rapidly multiplying, highly pathogenic bacteria in the blood, e.g. pyogenic cocci, bacilli of plague, etc. Septicemia is generally accompanied by systemic effects like toxemia, multiple small hemorrhage, neutrophilic leucocytosis and disseminated intravascular coagulation (DIC).

Pyemia is the dissemination of small septic thrombi in the blood which cause their effects

at the site where they are lodged. This can result in pyemic abscesses or septic infarcts. Pyemic abscesses are multiple small abscesses in various organs such as in cerebral cortex, myocardium, lungs and renal cortex, resulting from very small emboli fragmented from septic thrombus.

Microscopy of pyemic abscess shows a central zone of necrosis containing numerous bacteria, surrounded by a zone of suppuration and an outer zone of acute inflammatory cells. Septic infarcts result from lodgment of larger fragments of septic thrombi in the arteries with relatively larger foci of necrosis, suppuration and acute inflammation, e.g. septic infarcts of the lungs, liver, brain, and kidneys from septic thrombi of leg veins or from acute bacterial endocarditis.

4. Serous inflammation. Serous inflammation is marked by the outpouring of a thin fluid that, depending on the size of injury, is derived from either the blood serum or the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. The skin blister resulting from a burn or viral infections represents a large accumulation of serous fluid, either within or immediately beneath the epidermis of the skin.

5. Fibrinous inflammation. With more severe injuries and the resulting greater vascular permeability, larger molecules such as fibrin pass the vascular barrier. A fibrinous exudate develops when the vascular leaks are large enough or there is a pro-coagulant stimulus in the interstitium (e.g., cancer cells). A fibrinous exudate is characteristic of inflammation in body cavities, such as the pericardium and pleura.

Microscopically, fibrin appears as an eosinophilic meshwork of threads, or sometimes as an amorphous coagulum. Fibrinous exudates may be removed by fibrinolysis, and other debris by macrophages. This process, called resolution, may restore normal tissue structure, but when the fibrin is not removed it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to scarring. Conversion of the fibrinous exudate to scar tissue (organization) within the pericardial sac will lead either to opaque fibrous thickening of the pericardium and epicardium in the area of exudation or, more often, to the development of fibrous strands that bridge the pericardial space.

According to the type of epithelium on which inflammatory process develops and depth of necrosis there are two types of fibrinous inflammation croupous and diphtheroid fibrinous inflammation. Usually croupous inflammation develops on the columnar epithelium. In this case the fibrinous membranes unfix easily, without any effort. Diphtheroid fibrinous inflammation develops on the squamous or intermediate epithelium, when the fibrinous membranes unfix with difficulties.

6. Pseudomembranous inflammation. It is inflammatory response of mucous surface (oral, respiratory, bowel) to toxins of diphtheria or irritant gases. As a result of denudation of epithelium, plasma exudes on the surface where it coagulates, and together with necrosed epithelium, forms false membrane that gives this type of inflammation its name.

7. Ulcer. Ulcer is a local defect on the surface of an organ produced by inflammation. In the acute stage, there is infiltration by polymorphs with vasodilatation while long-standing ulcers develop infiltration by lymphocytes, plasma cells and macrophages with associated fibroblastic proliferation and scarring.

The acute inflammatory process can culminate in one of the following 4 outcomes:

- a. resolution,
- b. healing by scarring,
- c. progression to suppuration,
- d. progression to chronic inflammation.

Outcome. This means complete return to normal tissue following acute inflammation. It occurs when tissue changes are slight and the cellular changes are reversible, e.g. resolution in lobar pneumonia.

Healing by scarring. This takes place when the tissue destruction in acute inflammation is extensive so that there is no tissue regeneration but actually there is healing by fibrosis.

Progression to suppuration. When the pyogenic bacteria causing acute inflammation

result in severe tissue necrosis, the process progresses to suppuration. Initially, there is intense neutrophilic infiltration. Subsequently, mixture of neutrophils, bacteria, fragments of necrotic tissue, cell debris and fibrin comprise pus which is contained in a cavity to form an abscess. The abscess, if not drained, may get organized by dense fibrous tissue, and in time, get calcified.

Progression to chronic inflammation. Acute inflammation may progress to chronic one in which the processes of inflammation and healing proceed side by side.

Self-check materials:

1. For a histological examination, a vermiform process (appendix) was sent. Its size is increased, the serous membrane is dim, plethoric and covered with greyish films, the wall is thickened and some pus is discharged from the lumen. Microscopically, a plethora of the vessels, an oedema of all the layers and their diffuse infiltration by leukocytes are observed.

Name the kind of inflammation in the vermiform process.

- A. Catarrhal
- B. Putrid
- C. Mixed
- D. Fibrinous
- E. Phlegmonous*

2. An examination of a 7-year-old child, who was referred to infectious department with complaints about a sharp pain in his throat, difficult swallowing, an elevated body temperature up to 39°C, an oedema of his neck, revealed that the tonsils were enlarged, their mucosa was plethoric and covered with a large number of yellow-whitish films which were closely adjacent to the mucosa. An attempt to remove a film results in a deep bleeding defect. What kind of inflammation takes place?

- A. Suppurative
- B. Serous
- C. Croupous
- D. Diphtheritic*
- E. Haemorrhagic

3. A male was treated for purulent otitis. On the 9th day of his staying at an inpatient department he died from a brain oedema. On autopsy, the temporal region of the left hemisphere revealed a cavity with uneven rough inner edges which was filled with some yellowish-greenish thick dull fluid. The outer wall of the cavity was represented with the cerebral tissue. What pathological process was it?

- A. Acute abscess*
- B. Colliquative necrosis
- C. Phlegmon
- D. Empyema
- E. Chronic abscess

4. An autopsy of a 58-year-old male, who suffered from croupous pneumonia during his lifetime and died of cardiopulmonary insufficiency, revealed 900 ml of some yellow-greenish dull fluid in his right pleural cavity. The pleural leaves were dull and plethoric. Name the clinical-morphological form of the inflammation in the pleural cavity.

- A. Dry pleurisy
- B. Empyema*
- C. Plegmon
- D. Chronic abscess
- E. Acute abscess

5. A 63-year-old male patient, who suffered from cancer of the stomach, developed a sharp pain in the epigastric region, tachycardia, loss of consciousness. Some time later the patient died. On autopsy, about 1000 ml of some yellow-greenish dull fluid in the abdominal cavity, as well as greyish thread-like deposits on the visceral and parietal leaves of the peritoneum, were revealed. What kind of inflammation takes place in the peritoneum?

- A. Catarrhal
- B. Serous
- C. Haemorrhagic
- D. Productive
- E. Fibrinous-purulent*

TOPIC IX: Proliferative (productive) inflammation: with formation of pointed condyloma, productive inflammation caused by parasites, interstitial inflammation, granulomatous inflammation

1. Actuality of the problem. Proliferative (productive) inflammation is considered to be inflammation of prolonged duration, in which active inflammation, tissue destruction, and attempts in healing are proceeding simultaneously. Proliferative inflammation may have nonspecific and specific morphologic characteristics, therefore knowledges of this topic are necessary in practical medicine because it may help to diagnose and treat such diseases.

2. Aim of studies. Study the morphological features of the proliferative (productive inflammation); to explain the causes and mechanisms of its development; to estimate outcomes and determine the significance for organism.

Tasks of the studies:

- Explain the role of proliferative (productive) inflammation in organism.
- Know the terminology and definitions of the types of proliferative inflammation.
- Learn the morphology and functional manifestations of granulomatous inflammation, estimate outcomes and significance for organism.
- Study the morphology of interstitial inflammation.
- Explain the morphologic features of the various types of chronic inflammation and estimate their functional significance.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of immune system. 2. To draw normal structure of immune system's organs.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of immune system's

	inner organs as well as its cells.
Physiology and pathophysiology	<ol style="list-style-type: none"> 1. Be able to use knowledge's about peculiarity of work activity of immune system. 2. To use knowledge's about disturbance in immune system response due to influence of different factors.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Inflammation	is defined as the local response of living tissues to injury caused by any agent. It is body defense reaction in order to eliminate or limit the spread of injurious agent.
Chronic inflammation	is defined as prolonged process in which tissue destruction and inflammation occur at the same time.
Polyp	a growth, usually benign, protruding from a mucous membrane. Polyps are commonly found in the nose and sinuses, giving rise to obstruction, chronic infection, and discharge. They are often present in patients with allergic rhinitis, in whom they may develop in response to long-term antigenic stimulation. Other sites of occurrence include the ear, the stomach, and the colon, where they may eventually become malignant.
Granuloma	is defined as a circumscribed, tiny lesion, about 1 mm in diameter, composed predominantly of collection of modified macrophages called epithelioid cells, and rimmed at the periphery by lymphoid cells.
Pointed condyloma	is a sexually transmitted disease that appears externally on the genitalia, in the anal area, internally in the upper vagina or cervix, and in the male urethra. The lesion is typically raised and pinkish.

4.2 Theoretical questions for the practical class:

9. Definition of proliferative (productive) inflammation, its localization, main morphological types.
10. Mononuclear cell infiltration (local and diffuse).
11. Polyps and condylomas. Causes and morphological appearances.
12. Acute and chronic granulomatous inflammation
13. Granulomas and granulomatous diseases (examples); typical cellular composition of granulomas, their classifications depending on etiology and pathogenesis; morphological appearances depending on the type of immunologic answer.
14. Histological structure of tuberculous, lepromatous, and syphilitic granuloma.
15. Relationship of productive inflammation with sclerosis and cirrhosis of organs, definition of these processes, their appearances and difference.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process

correspond to	outcomes
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Macropreparations:

1. **“Polyps of the Stomach”**. Pay attention to the appearance of polyps, its size, the character of the growth. Name the localization of polyp. *Call other kinds of the productive inflammation.*
2. **“Miliary pulmonary tuberculosis”**. Pay attention to the appearance of the nodule and nature of the process. Describe the color, size, and quantity of them. *Give the definition with the regard of the character of the pathological process and its morphological form, etiology and degree of the prevalence. Translate the term “miliary”. In what forms of tuberculosis is it observed? Call the possible outcomes of granuloma; the causes of the death.*
3. **“Echinococcus of the Liver”**. Pay attention to cavity, shape, and its internal layer, cyst contents. Describe the appearance of the external layer of the cyst side. *Name the sequence of changing the tissue reaction to the zone of parasitical inculcation.*
4. **“Mesaortitis in Syphilis”**. Pay attention to the localization of the pathological process with regard of the aorta part. Describe the appearance of the aorta in the place of the localization of the pathological process. *Give the definition with the regard of the character of the pathological process and its morphological form, kind of the productive inflammation. To call the etiological factors, the outcomes of the inflammation and possible complication.*

Microslides:

Slide 1. Productive caseous lymphadenitis (ought to be drawn)

In the tissue of lymph node numerous tubercles (tubercular tumors) are seen. They consist of caseous necrosis surrounded with epithelioid cells among which the giant Langhans-type cells and some lymphocytes can be found.

Slide 2. Scleroma

In rhinoscleroma of nose, the granuloma (scleroma) consists of the plasma cells, epithelioid cells, lymphocytes, and hyaline sphere. Large macrophages with light cytoplasm containing Klebsiellarhinoscleromatis (Mikulicz’s cells), sclerosis and hyalinoses take place.

Slide 3. Leproma

In tuberculoid leprosy, the epidermis contains confluent granulomas composed of macrophages, plasma cells, and leprous Virchow’s cells. Leprous Virchow’s cells (or leprosy cells) refer as large foamy macrophages within fatty vacuoles containing leprous mycobacteriums.

Slide 4. Proliferative inflammation around echinococcus of the Liver

The area of the liver’s tissue with destructive rose color shined chitinous membrane and surrounded necrotic tissue are seen. In peripheral areas crowded lymphocytes, plasma cells, fibroblasts and single “giant cells of the foreign bodies” can be found. In the outside – fibrous capsule.

Topic content:

Chronic inflammation is defined as prolonged process in which tissue destruction and inflammation occur at the same time.

Chronic inflammation can be caused by one of the following 3 ways:

1. Chronic inflammation following acute inflammation — when the tissue destruction is extensive, or the bacteria survive and persist in small numbers at the site of acute inflammation, e.g. in osteomyelitis, pneumonia terminating in lung abscess.
2. Recurrent attacks of acute inflammation — when repeated bouts of acute inflammation culminate in chronicity of the process, e.g. in recurrent urinary tract infection leading to chronic pyelonephritis, repeated acute infection of gall bladder leading to chronic cholecystitis.
3. Chronic inflammation starting de novo—when the infection with organisms of low pathogenicity is chronic from the beginning, e.g. infection with *Mycobacterium tuberculosis*.

Though there may be differences in chronic inflammatory response depending upon the tissue involved and causative organisms, there are some basic similarities amongst various types of chronic inflammation. ***These general features characterize any chronic inflammation.***

1. *Mononuclear infiltration.* Chronic inflammatory lesions are infiltrated by mononuclear inflammatory cells like phagocytes and lymphoid cells. Phagocytes are represented by circulating monocytes, tissue macrophages, epithelioid cells and sometimes, multinucleated giant cells. The macrophages comprise the most important cells in chronic inflammation.
2. *Tissue destruction and necrosis.* Tissue destruction and necrosis are common in many chronic inflammatory lesions and are brought about by activated macrophages by release of a variety of biologically active substances.
3. *Proliferative changes.* As a result of necrosis, proliferation of small blood vessels and fibroblasts is stimulated resulting in formation of inflammatory granulation tissue. Eventually, healing by fibrosis and collagen laying takes place.

Main classifications of chronic inflammation

Conventionally, chronic inflammation is subdivided into 2 types.

1. *Nonspecific*, when the irritant substance produces a non-specific chronic inflammatory reaction with formation of granulation tissue and healing by fibrosis, e.g. chronic osteomyelitis, chronic ulcer.
2. *Specific*, when the injurious agent causes a characteristic histologic tissue response, e.g. tuberculosis, leprosy, syphilis.

However, for a more descriptive classification, histological features are used for classifying chronic inflammation into 3 corresponding types.

1. *Chronic nonspecific interstitial inflammation.* This is characterized by nonspecific inflammatory cell infiltration, e.g. chronic osteomyelitis, lung abscess. A variant of this type of chronic inflammatory response is chronic suppurative inflammation in which infiltration by polymorphs and abscess formation are additional features, e.g. actinomycosis. The inflammatory cell infiltration consist of lymphocytes, monocytes, plasmocytes, eosinophils and other cells.
2. *Chronic nonspecific interstitial inflammation with formation of polyps and pointed condyloma.* It occurs on the mucous membranes and in the areas borderline with squamous epithelium.

Polyps are the end result of prolonged chronic irritation. Nasal, cervical, colorectal polyps are common.

Macroscopically they are gelatinous masses with smooth and shining surface.

Microscopically they are composed of loose edematous connective tissue containing some mucous glands and varying number of inflammatory cells (lymphocytes, plasmocytes, eosinophils).

Condyloma is commonly located on the coronal sulcus on the penis or the perineal area.

3. *Chronic granulomatous inflammation.* This is characterized by formation of granulomas, e.g. tuberculosis, leprosy, syphilis, actinomycosis, sarcoidosis, etc. Granuloma is defined as a circumscribed, tiny lesion, about 1 mm in diameter, composed predominantly of collection of modified macrophages called epithelioid cells, and rimmed at the periphery by lymphoid cells. The word «granuloma» is composed of granule meaning circumscribed granule-like lesion, and -oma which is a suffix commonly used for true tumours but here indicates inflammatory mass or collection of macrophages. The epithelioid cells, so called because of their epithelial cell-like appearance, are modified macrophages which are somewhat elongated, having pale-staining abundant cytoplasm, lightly-staining nucleus and the cell membrane of adjacent epithelioid cells is closely apposed. Besides the presence of epithelioid cells and lymphoid cells, granulomas may have giant cells, necrosis and fibrosis. The giant cells are formed by fusion of adjacent epithelioid cells or by internal nucleate division without cytoplasmic division and may have 50—100 nuclei. These nuclei may be arranged at the periphery like horse-shoe or ring or clustered at the two poles (Langhans' giant cells), or they may be present centrally (foreign body giant cells). The former are commonly seen in tuberculosis while the latter are common in foreign body tissue reactions.

Necrosis may be a feature of some granulomatous conditions, e.g. central caseous necrosis of tuberculosis, so called because of cheese-like appearance and consistency of necrosis.

Fibrosis is due to proliferation of fibroblasts at the periphery of granuloma.

The following two factors favor the formation of granulomas:

1. Presence of poorly digestible irritant which may be organisms like *Mycobacterium tuberculosis*, particles of talc, etc.
2. Presence of cell-mediated immunity to the irritant, implying thereby the role of hypersensitivity in granulomatous inflammation.

A fully-developed tubercle is about 1 mm in diameter with central area of caseous necrosis, surrounded by epithelioid cells and one to several multinucleated giant cells (commonly Langhans's type), surrounded at the periphery by lymphocytes and bounded by fibroblasts and fibrous tissue.

Granulomatous inflammation is typical of reaction to poorly digestible agents elicited by tuberculosis, leprosy, fungal infections, schistoso-miasis, foreign particles, etc.

The outcomes of chronic inflammation depend on the type of inflammation, morphofunctional characteristic of the definite organ or tissue, where inflammation develops. Frequently sclerosis and hyalinosis may develop.

Self-check materials:

1. A microscopic examination of the tissue dissected from some postoperative infiltrate revealed granulomata with giant multinucleate cells around the suture material. What kind of granulomata did they belong to ?
 - A. Tuberculous
 - B. Rheumatic
 - C. Lepromatous
 - D. Foreign-body*
 - E. Mycotic
2. An examination of a renal biopsy revealed some mostly perivascular and periglomerular lymphocytic, plasmacytic and macrophagal infiltration of the interstice against a background of its sclerosis. Name the most probable kind of inflammation.
 - A. Productive diffuse
 - B. Productive focal*
 - C. Granulomatous
 - D. Exudative diffuse
 - E. Exudative focal
3. A microscopic examination of the aorta in a male, who died from a rupture of its aneurysm, revealed in the medial coat of the aorta some foci of destruction of elastic fibres and an inflammatory infiltrate consisting of lymphoid and plasma cells around the «vasa vasorum». Which of the diagnoses listed below was the most probable?
 - A. Tuberculosis
 - B. Atherosclerosis
 - C. Syphilis*
 - D. Leprosy
 - E. Rheumatism
4. An autopsy of a 60-year-old male revealed numerous whitish miliary nodules in the lungs and liver. A microscopic examination revealed granulomata with foci of necrosis in their centre and epithelial, lymphoid, plasma cells, as well as macrophages and a large number of Pirogov-Langhans cells on the periphery. Indicate the granuloma which corresponds to the description.
 - A. Macrophagal
 - B. Phagocytoma
 - C. Epitheliocellular
 - D. Giant cell*
 - E. Foreign-body

5. A 46-year-old male patient complains of difficult nasal breathing. A biopsy of his thickened nasal mucosa revealed Mikulicz's cells, clusters of epithelioid cells, plasmacytes, lymphocytes, hyaline balls. What is your diagnosis?

- A. Scleroma*
- B. Adenovirus rhinitis
- C. Allergic rhinitis
- D. Rhinovirus infection
- E. Meningococcal nasopharyngitis

TOPIC X:Regeneration. Structural basis of visceral organs and cells physiological adaptation. Morphology of cells accommodation processes. Adaptation and compensation processes.

1.Actuality ofthe problem.As explained earlier, cells must constantly adapt, even under normal conditions, to changes in their environment. These *physiologic adaptations* usually represent responses of cells to normal stimulation by hormones or endogenous chemical substances. *Pathologic adaptations* may share the same underlying mechanisms, but they provide the cells with the ability to modulate their environment and perhaps escape injury. Cellular adaptation, then, is a state that lies intermediate between the normal, unstressed cell and the injured, overstressed cell.

Knowledge of these processes is necessary for understanding of the pathogenesis of the diseases and for the clinic-anatomical analysis of the autopsy.

2. Aim of studies.Study the morphological features of adaptive and compensative processes; to explain the causes and mechanisms of their development; to estimate outcomes and determine the significance for organism.

Tasks of the studies:

- Explain the role of adaptive and compensative processes in organism.
- Know the terminology and definitions of these processes
- Distinguish the processes of hypertrophy, hyperplasia and atrophy.
- Learn the morphology and functional manifestations of atrophy, hypertrophy and hyperplasia.
- Study the mechanisms of the various types of regeneration.
- Explain the morphologic features of the various types of regeneration and estimate their functional significance.
- Study the mechanisms, morphological features of the wound healing.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge'sandskills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of a human's inner organs. 2. To draw their normal structure.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of a human's inner organs. 2. Give characteristic of peculiarity of regeneration processes in different organs.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of physiological restore both structure and function of inner organs. 2. To use knowledge's about disturbance in regeneration of different kinds of cells and tissues.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Healing	the process of making or becoming sound or healthy again
Regeneration	the action or process of regenerating or being regenerated, in particular the formation of new tissue.
Adaptation	the process of change by which an organism or species becomes better suited to its environment
Hyperplasia	is an increase in the number of cells in a tissue caused by increased cell division.
Hypertrophy	is an increase in the size of existing cells, accompanied by increase in their functional capacity.
Hypertrophy	in the absence of hyperplasia is typically seen in muscle where the stimulus is an increased demand for work.
Cell atrophy	is reduction in cell number or cell size due to reduced their functional demand.
Metaplasia	is a change in cell or tissues differentiation for adapt to environmental stimuli.

4.2 Theoretical questions for the practical class:

1. Importance of adaptation and compensation.
2. Atrophy: definition, essence, causes, types, macro- and microscopical signs. Examples of the physiologic and pathologic atrophy.
3. Hypertrophy and hyperplasia: causes, types and macro- and microscopical manifestations, their resemblance and difference. Examples of hypertrophy and hyperplasia.
4. Phases of development of adaptive-compensative processes. Morphological features of the compensation and decompensation in the heart due to cardiac insufficiency.
5. Regeneration: essence and the biological meaning, definition, morphogenesis (proliferation and differentiation of cells), types.
6. Physiologic regeneration. Examples of physiological regeneration of organs and tissues.
7. Pathologic regeneration. Causes, examples.
8. Particularities of the regeneration of the connective, vascular and bone tissues and some parenchymatous organs.
9. Reparative regeneration: determination, essence, types, morphological features in myocardium and liver. Importance of restitution and regenerative hypertrophy.
10. Metaplasia and dysplasia: causes, morphological signs, clinical significance. The difference from tumorous and proliferative processes.
11. Morphology of processes of organization in the damaged tissue: sclerosis, cirrhosis, incapsulation, petrification, and formation of cysts.

12. Wound healing. Morphology of healing by first (primary) and secondary intention.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to	1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

Slide 1. Granulation tissue (ought to be drawn)

The parallel vessels can be seen here and there. Between them leukocytes and immature cells of connective tissue are located.

Slide 2. Glandular hyperplasia of the Endometrium

The glands of endometrium have corkscrew-like twisting forms. The pictures “gland into gland” can be found in cross-cuts. Parallely the proliferation of endometrial stroma takes place.

Slide 3. Metaplasia of bronchial epithelium into squamous cell epithelium (ought to be drawn)

Cilliary epithelium transforms into squamous cell epithelium as the result of chronic inflammation and regeneration.

Slide 4. Epidermization of cervix's erosion

At the edge of erosion the proliferative basal cells of squamous cell epithelium grow under columnar epithelium. During differentiation this proliferative epithelium transforms into squamous cell epithelium.

Slide 5. Hypertrophy of the Myocardium

The muscle fibers are thicken; their nuclei are enlarged and hyperchromic; the hardened stroma also takes place. These changes are strongly expressed in subendocardial areas.

Slide 6. Glandular hyperplasia of the Endometrium (ought to be drawn)

The glands of endometrium have corkscrew-like twisting form. The pictures “gland into gland” can be found out in cross-section. At the same time the proliferation of endometrial stroma with edema and hyperemia takes place.

Topic content:

Injury to tissue may result in cell death and tissue destruction. Healing on the other hand, is the body response to injury in an attempt to restore normal structure and function.

The process of healing involves 2 distinct processes:

1. Regeneration when healing takes place by proliferation of parenchymal cells and usually results in complete restoration of the original tissues.
2. Repair when healing takes place by proliferation of connective tissue elements resulting in fibrosis and scarring.

Some parenchymal cells are short-lived while others have a longer lifespan. In order to maintain proper structure of tissues, these cells are under constant regulatory control of their cell cycle. These include growth factors, e.g. brain, epidermis-, macrophage-, nerve-, and platelet, derived growth factors.

Depending upon their capacity to divide, the cells of the body can be divided into 3 groups: labile cells, stable cells and permanent cells.

1. Labile cells. These cells continue to multiply throughout life under normal physiologic conditions. These include surface epithelial cells of epidermis,

alimentary tract, respiratory tract, urinary tract, vagina, cervix, uterine endometrium, hemopoietic cells of bone marrow and cells of lymph nodes and spleen.

2. Stable cells. These cells decrease or lose their ability to proliferate after adolescence but retain the capacity to multiply in response to stimuli throughout adult life. These include parenchymal cells of kidneys, liver, adrenal glands; mesenchymal cells of smooth muscles.

3. Permanent cells. These cells lose their ability to proliferate around the time of birth. These include: neurons of nervous system, skeletal muscle and cardiac muscle cells.

Regeneration of any type of parenchymal cells involves the following 2 processes.

1. Proliferation of original cells from the margin of the injury with migration so as to cover the gap.
2. Proliferation of migrated cells with subsequent differentiation and maturation so as to reconstitute the original tissue.

There are 3 types of regeneration

1. physiological,
2. reparative
3. pathological.

Physiological regeneration is observed during the human life.

There are 2 types of reparative regeneration **restitution** and **substitution**. In restitution, reconstruction of the original tissue in the definite organ is observed. In substitution (so called «repair») connective tissue or fat appear instead of original tissue (e.g. sclerosis develops in the area of the myocardial infarction).

The pathological regeneration may be of one of the following types: hyperregeneration, hyporegeneration and metaplasia.

Contraction of Wounds. The wound starts contracting after 2—3 days and the process is completed by the 14th day. During this period, the wound is reduced by approximately 80% of its original size. Contracted wound results in rapid healing since lesser surface area of the injured tissue has to be replaced.

In order to explain the mechanism of wound contraction, a number of factors have been proposed.

These are as follows:

1. Dehydration as a result of removal of fluid by drying of wound was first suggested but without being substantiated.
2. Contraction of collagen was thought to be responsible for contraction but wound contraction proceeds at a stage when the collagen content of granulation tissue is very small.
3. Discovery of myofibroblasts appearing in active granulation tissue has resolved the controversy surrounding the mechanism of wound contraction.

These cells have features intermediate between those of fibroblasts and smooth muscle cells. Their migration into the wound area and their active contraction decreases the size of the defect.

Wound Healing

Healing of skin wounds provides a classical example of combination of regeneration and repair described above. This can be accomplished in one of the following two ways: healing by first intention (primary union) and healing by second intention (secondary union).

Healing by first intention (primary union). This is defined as healing of a wound which has the following characteristics: clean and uninfected, surgically incised, without much loss of cells and tissue, edges of wound are approximated by surgical sutures.

The sequence of events in primary union is described below.

Immediately after injury, the space between the approximated surfaces of incised wounds is filled with blood which then clots and seals the wound against dehydration and infection.

Acute inflammatory response occurs within 24 hours by appearance of polymorphs from the margins of incision. By the 3rd day, polymorphs are replaced by macrophages.

The basal cells of epidermis from both the cut margins start proliferating and migrating towards incisional space in the form of epithelial spurs. A well-approximated wound is covered

by a layer of epithelium in 48 hours. The migrated epidermal cells separate the underlying viable dermis from the overlying necrotic material and clot, forming scab which is cast off. The basal cells from the margins continue to divide. By 5th day, a multilayered new epidermis is formed which is differentiated into superficial and deeper layers.

By the 3rd day, fibroblasts also invade the wound area. By the 5th day, new collagen fibrils start forming which dominate till healing is completed. In 4 weeks, the scar tissue with scanty cellular and vascular elements, a few inflammatory cells and epithelialised surface is formed.

Each suture track is a separate wound and incites the same phenomena as in healing of the primary wound, i.e. filling the space with hemorrhage, some inflammatory cell reaction, epithelial cell proliferation along the suture track from both margins, fibroblastic proliferation and formation of young collagen. When sutures are removed around the 7th day, much of epithelialised suture track is avulsed and the remaining epithelial tissue in the track is absorbed. However, sometimes the suture track gets infected or the epithelial cells may persist in the track.

A sutured wound, thus takes a little longer to heal but the scar formed is neat due to close apposition of the margins of wounds. The use of adhesive tapes avoids this complication.

Healing by second intention (*secondary union*). This is defined as healing of a wound having the following characteristics: open with a large tissue defect, at times infected; having extensive loss of cells and tissues; the wound is not approximated by surgical sutures but is left open.

The basic events in secondary union are similar to primary union but differ in having a larger tissue defect which has to be bridged. Hence healing takes place from the base upwards as well as from the margins inwards. The healing by second intention is slow and results in a large, at times ugly, scar as compared to rapid healing and neat scar of primary union.

The sequence of events in secondary union are as follows.

As a result of injury, the wound space is filled with blood and fibrin clot which dries.

There is an initial acute inflammatory response followed by appearance of macrophages which clear off the debris as in primary union.

As in primary healing, the epidermal cells from both the margins of wound proliferate and migrate into the wound in the form of epithelial spurs till they meet in the middle and re-epithelialise the gap completely. However, the proliferating epithelial cells do not cover the surface fully until granulation tissue from base has started filling the wound space. In this way, preexisting viable connective tissue is separated from necrotic material and clot on the surface, forming scab which is cast off. In time, the regenerated epidermis becomes stratified and keratinised.

The main bulk of secondary healing is by granulations. Granulation tissue is formed by proliferation of fibroblasts and neovascularisation from the adjoining viable elements. The newly-formed granulation tissue is deep red, granular and very fragile. With time, the scar on maturation becomes pale and white due to increase in collagen and decrease in vascularity. The specialized structures of skin like hair follicles and sweat glands are not replaced unless their viable residues remain which may regenerate.

Contraction of wound is an important feature of secondary healing, not seen in primary healing. Due to the action of myofibroblasts present in granulation tissue, the wound contracts to one-third to one-fourth of its original size. Wound contraction occurs at a time when active granulation tissue is being formed.

Bacterial contamination of an open wound delays the process of healing due to release of bacterial toxins that provoke necrosis, suppuration and thrombosis. Surgical removal of dead and necrosed tissue, debridement, helps in preventing the bacterial infection of open wounds.

During the course of healing, following complications may occur: infection of wound due to entry of bacteria delays the healing; implantation (epidermal) cyst formation may occur due to persistence of epithelial cells in the wound after healing; pigmentation, when healed wounds may at times have rust-like colour due to staining with hemosiderin; deficient scar formation may occur due to inadequate formation of granulation tissue; incisional hernia—a weak scar, especially after a laparotomy, may be site of bursting open of a wound (wound dehiscence) or an

incisional hernia; hypertrophied scars and keloid formation; excessive contraction; rarely scar may be the site for development of carcinoma later, e.g. squamous cell carcinoma in scar.

Two types of factors influence the wound healing: those acting locally and those acting in general. Local factors: infection; poor blood supply to wound, foreign bodies including sutures interfere with healing and cause intense inflammatory reaction and infection; exposure to ionizing radiation; exposure to ultraviolet light; type, size and location of injury. Systemic factors: age, nutrition, systemic infection, uncontrolled diabetes, hematological abnormalities.

HEALING IN SPECIALIZED TISSUES Fracture healing

Healing of fracture by callus formation depends upon some clinical considerations whether the fracture is traumatic (in previously normal bone), or pathological (in previously diseased bone); complete or incomplete like green stick fracture; simple (closed), comminuted (splintering of bone) or compound (communicating to skin surface).

Primary union of fractures occurs occasionally in a few special situations when the ends of fracture are approximated like by application of compression clamps. In these cases, bony union takes place with formation of medullary callus without periosteal callus formation.

Secondary union is the more common process of fracture healing. Though it is a continuous process, secondary bone union is described under the following 3 headings:

1. Procallus formation. There are following steps involved in the formation of procallus.

Hematoma forms due to bleeding from torn blood vessels, filling the area surrounding the fracture. Loose meshwork is formed by blood and fibrin clot which acts as framework for subsequent granulation tissue formation.

Local inflammatory response occurs at the site of injury with exudation of fibrin, polymorphs and macrophages. The macrophages clear away the fibrin, red blood cells, inflammatory exudate and debris. Fragments of necrosed bone are scavenged by macrophages and osteoclasts.

Ingrowth of granulation tissue begins with neovascularisation and proliferation of mesenchymal cells from periosteum and endosteum. A soft tissue callus is thus formed which joins the ends of fractured bone without much strength.

Callus composed of woven bone and cartilage starts within the first few days. The cells of inner layer of the periosteum have osteogenic potential and lay down the collagen as well as osteoid matrix in the granulation tissue. The osteoid undergoes calcification and is called woven bone callus. A much wider zone over the cortex on either side of fractured ends is covered by the woven bone callus and united to bridge the gap between the ends, giving spindle-shaped or fusiform appearance to the union.

2. Osseous callus formation. The procallus acts as scaffolding on which osseous callus composed of lamellar bone is formed. The woven bone is cleared away by incoming osteoclasts and the calcified cartilage disintegrates. In their place, newly-formed blood vessels and osteoblasts invade, laying down osteoid which is calcified and lamellar bone is formed by developing Haversian system concentrically around the blood vessels.

3. Remodeling. During the formation of lamellar bone, osteoblastic laying and osteoclastic removal are taking place, remodeling the united bone ends, which after sometime, is indistinguishable from normal bone. The external callus is cleared away, compact bone (cortex) is formed in place of intermediate callus and the bone marrow cavity develops in internal callus. These are following complications of fracture healing: fibrous union, non-union, delayed union.

Healing of Nervous Tissue

Central nervous system. The nerve cells of brain, spinal cord and ganglia once destroyed are not replaced. Axons of CNS also do not show any significant regeneration. The damaged neuroglial cells, however, may show proliferation of astrocytes called gliosis.

Peripheral nervous system. In contrast to the cells of CNS, the peripheral nerves show regeneration, mainly from proliferation of Schwann cells and fibrils from distal end. Briefly, it consists of the following:

- myelin sheath and axon of the intact distal nerve undergo Wallerian degeneration up to the next node of Ranvier towards the proximal end;
- the degenerated debris are cleared away by macrophages;
- regeneration in the form of sprouting of fibrils takes place from the viable end of axon. These fibrils grow along the track of degenerated nerve so that in about 6—7 weeks, the peripheral stump consists of tube filled with elongated Schwann cells;
- one of the fibrils from the proximal stump enters the old neural tube and develops into new functional axon.

Healing of Muscle

All three types of muscle fibres have limited capacity to regenerate.

Skeletal muscles. The regeneration of striated muscle is similar to peripheral nerves. On injury, the cut ends of muscle fibres retract but are held together by stromal connective tissue. The injured site is filled with fibrinous material, polymorphs and macrophages. After clearance of damaged fibres by macrophages, one of the following two types of regeneration of muscle fibres can occur. If the muscle sheath is intact, sarcolemmal tubes containing histiocytes appear along the endomysial tube which, in about 3 months time, restores properly oriented muscle fibres e.g. in Zenker's degeneration of muscle in typhoid fever. If the muscle sheath is damaged, it forms a disorganized multinucleate mass and scar composed of fibrovascular tissue, e.g. in Volkman's ischaemic contracture.

Smooth muscles. Non-striated muscle has limited regenerative capacity, e.g. appearance of smooth muscle in the arterioles in granulation tissue. However, in large destructive lesions, the smooth muscle is replaced by permanent scar tissue.

Healing of Mucosal Surfaces

The cells of mucosa have very good regeneration and are normally being lost and replaced continuously, e.g. mucosa of alimentary tract, respiratory tract, urinary tract, uterine endometrium, etc. This occurs by proliferation from margins, migration, multilayering and differentiation of epithelial cells in the same way as in the epidermal cells in healing of skin wounds.

Healing of Solid Epithelial Organs

Following gross tissue damage to organs like kidney, liver and thyroid, the replacement is by fibrous scar, e.g. in chronic pyelonephritis and cirrhosis of liver. However, in parenchymal cell damage with intact basement membrane or intact supporting stromal tissue, regeneration may occur. For example, in tubular necrosis of kidney with intact basement membrane, proliferation and slow migration of tubular epithelial cells may occur to form renal tubules; in viral hepatitis if part of the liver lobule is damaged with intact stromal network, proliferation of hepatocytes may result in restoration of liver lobule.

ADAPTATION

Cells as adaptable units. Cells are constantly exposed to changes in their environment. The conditions to which cells are exposed are subject to constant change as a result of normal physiological processes, and also because of changes in the external environment, including the effects of medical treatment. If cells were static and rigid systems, these changes in the cellular environment would profoundly affect function of tissues, but there are homeostatic mechanisms which allow cells and tissues to cope with such stresses. Cells adapt to acceptable changes in their environment by modifying metabolism or growth pattern.

To maintain normal function, cells have a physiological ability to adapt to acceptable environmental changes. Many of these modifications are physiological metabolic adaptations, and represent fine regulation of metabolic function at a biochemical level.

Other cell adaptations to environmental change are (physiological structural adaptations) caused by a change in the normal pattern of growth and accompanied by easily detectable structural changes.

The cell stress response to injury. Damaged cells produce proteins which protect them from damage. In response to some pathological stimuli, cells exhibit a series of metabolic

changes known as the cell stress response, which is an important basic cellular mechanism that enables cells to survive environmental insults. Stressed cells turn down the genes coding for normal structural proteins (housekeeping genes) and show high levels of expression of genes coding for a set of proteins which have cell-organizing and protective functions (cell stress genes). Many of the cell stress proteins were originally described in response to experimental heat shock, hence a major group is termed the heat shock proteins (HSPs). The general terms «heat shock protein» and «cell stress protein» are synonymous. Cell stress proteins are vital for cell viability. The stress proteins are expressed at low levels in normal cells, where they have important roles, but levels increase following exposure to damaging stimuli. Their increased production in a cell stress response provides the extra stress proteins needed in pathological conditions.

In certain cells which undergo chronic stress, permanent aggregates of abnormal cell constituents and ubiquitin form visible masses known as inclusion bodies within the cytoplasm. One example of this phenomenon is when liver cells are chronically exposed to alcohol and form masses of the intermediate filament cytokeratin and ubiquitin, visible as pink-stained inclusion bodies. These are eponymously termed Mallory's hyaline. Another example is the Lewy body in nerve cells. Production of the cell stress proteins following exposure to a damaging stimulus is a rapid response that minimizes cell damage and ensures cell viability. Cell stress proteins can only protect against certain levels of damage, with more severe stimuli leading to cell degeneration or death.

ADAPTIVE RESPONSES IN DISEASE

Cells respond to damaging stimuli by extending adaptive processes. As well as mounting an immediate cell stress response, cells can adapt to damaging stimuli, becoming modified to achieve a new, steady state of metabolism and structure that better equips them for survival in the abnormal environment. Cells may adapt to a pathological (disease) stimulus by extending the three normal physiological adaptive responses: increased cellular activity, decreased cellular activity, alteration of cell morphology.

Inability to adapt successfully to an environmental change leads to failure of cellular function and may result in sublethal cellular damage or cell death. Change in cellular growth pattern is an adaptive response in disease. Cells can adapt to certain pathological stimuli by altering their pattern of growth. This may be reflected in changes in the size, number or differentiation of cells in affected tissue.

Certain organs or tissues may adapt to a disease process by increasing functional cell mass. There are two mechanisms of increase. Increased functional demand on a tissue can be met by increase in cell number (hyperplasia), as well as by increase in cell size (hypertrophy).

Hyperplasia is an increase in the number of cells in a tissue caused by increased cell division. As this type of change can occur only in tissues that have the capacity for cell division, hyperplasia is not an adaptive response seen in skeletal muscle, cardiac muscle or nerve cells, which are non-dividing cell populations. Hormonal influences are important in this growth response.

Hypertrophy is an increase in the size of existing cells, accompanied by increase in their functional capacity. Cell enlargement is brought about by increased synthesis of structural components, associated with accelerated activity of cellular metabolism and rises in levels of RNA and organelles required for protein synthesis. Hypertrophy is particularly seen as a response to increased demand in tissues composed of cells which are unable to divide (skeletal and cardiac muscle). Hypertrophy and hyperplasia may occur independently of each other or together to meet a demand for increased function, and are usually associated with an increase in the size and weight of the organ or tissue concerned. Increased functional demand or endocrine stimulation is the stimulus that usually causes hypertrophy and hyperplasia. These new patterns of growth are stable while the causative stimulus persists, but once it is removed the tissue returns to a normal pattern of growth.

An increase in functional cell mass through hypertrophy or hyperplasia may be physiological.

Hypertrophy in the absence of hyperplasia is typically seen in muscle where the stimulus is an increased demand for work. Increased cell mass in a tissue can result from physiological stimuli and as a response in disease states. If the serum calcium is abnormally low, the parathyroid glands increase the number of parathormone-secreting cells (hyperplasia). If the aortic valve outflow is severely narrowed by disease, the muscle of the left ventricle of the heart responds with an increase in the size of cardiac muscle cells (hypertrophy) to overcome the resistance to flow and to ensure an adequate blood pressure. This is also seen in myocardial muscle when systemic hypertension causes an increased on cardiac function. The increased mass of the left ventricle is due to enlargement of cardiac muscle cells as a result of hypertrophy. This can be seen by comparing the diameter of fibres from the normal heart with those from the diseased heart. Note that the size of nuclei in the hypertrophied cardiac muscle is also increased; it has been found that such nuclei are frequently polyploid.

According to the stage of adaptation two types of myocardial hypertrophy have been described; concentric and eccentric. In concentric hypertrophy (clinically, no insufficient) the musculature is clearly enlarged, measuring till 1.8 cm, but chambers of the heart are not dilated. In eccentric hypertrophy myocardium is enlarged but chambers of the heart are dilated. This leads to a hemodynamic deterioration with cardiac insufficiency develops.

If a kidney is removed or ceases to function, the remaining healthy kidney increases in size and weight to compensate for the loss. The process of hyperplasia leads to enlargement of structures such as glomeruli, and is often termed compensatory hyperplasia.

Hyperplasia may not be uniform and sometimes occurs as nodules.

Hyperplasia may not occur uniformly throughout a tissue; instead, nodules of excessive cell growth hyperplastic nodules develop between areas of normal tissue, giving rise to the term B nodular hyperplasia. Most examples of nodular hyperplasia occur in tissues in which cells are responding to a trophic hormone. It is likely that the hyperplasia seen in these conditions is a result of a disturbance in the hormone responsiveness of the target tissue. Nodular hyperplasia is seen most commonly in the prostate gland thyroid gland, adrenal gland and the breast.

Following removal of the stimulus causing hyperplasia or hypertrophy, tissue reverts to normal.

Cell atrophy. Reduced functional demand leads to reduction in cell number or cell size. When the mass of functioning cells in a tissue becomes reduced, the tissue is said to have undergone atrophy. There are two mechanisms of reduction.

Reduced functional demand, reduction in trophic stimuli, or reduction in nutrients are the usual stimuli which cause involution or cell atrophy. Atrophic or involuted tissues are stable patterns of growth that persist while the lack of stimulation or demand causing them remains. However, once appropriate stimulation or demand returns, the tissue reverts to a normal pattern of growth.

In cellular atrophy, structural proteins and organelles of a cell are destroyed, with a parallel reduction in the size and functional capacity of the cell. This is an adaptive response as it allows the cell to survive in adverse conditions by reducing its metabolic overheads.

Cell constituents are eliminated by a process of autophagy: unwanted cell organelles become enwrapped by membrane derived from the endoplasmic reticulum (ER), forming an autophagic body which subsequently fuses with vesicles containing lysosomal acid hydrolases. The action of the hydrolases brings about degradation of the organelles. Cells which are actively undergoing atrophy can be seen ultrastructurally to contain numerous autophagic vacuoles. These bodies become electron dense, but have internal tubular or vesicular profiles (derived from membrane-fusion events) that have earned them the alternative name of tubulovesicular bodies. Late autophagic bodies become more electron dense and may form residual bodies containing lamellar undigested lipid-rich cell material called lipofuscin.

Reduction in cell mass occurs in some pathological states. Many disease processes lead to a reduction in functional demand, hormonal or nervous stimulation, or nutrition of tissues; atrophy or involution occurs as an adaptive response.

Atrophy may be physiological and pathological. The former is observed during the human life, e.g. atrophy of thymus and sex glands in elderly people. The latter may be general and local. General atrophy is observed in cachexia.

There are several types of local atrophy: 1. Disuse atrophy. 2. Ischaemic atrophy. 3. Denervation atrophy. 4. Atrophy due to pressure. 5. Atrophy due to chemical and physical influences.

E.g. skeletal muscle fibres in the leg undergo cellular atrophy if the leg is immobilized, when splinting is used in the treatment of a fracture (disuse atrophy). Gradual reduction in blood supply to a tissue results in loss of functional cells through involution, as well as through cellular atrophy (ischemic atrophy). Damage to axons supplying muscle causes atrophy of affected muscle fibres (denervation atrophy)

Metaplasia. Tissues may adapt to environmental stimuli by a change in cell differentiation termed metaplasia.

Certain long-standing environmental stimuli render the environment unsuitable for some specialized cell types and, as an adaptive response, the proliferating cells change their pattern of differentiation. These cells can adapt to a change in environment by differentiating to a new, mature, stable type of cell, which better equips them to withstand environmental stress. This process is termed metaplasia.

Metaplasia occurs in many tissue types. In the bronchi, under the influence of chronic irritation by cigarette smoke, the normal ciliated columnar mucus-secreting respiratory epithelium is replaced by squamous epithelium (squamous metaplasia). In the cervix, the normal columnar epithelium of the lower endocervix changes to squamous epithelium in response to exposure to the acid vaginal environment (squamous metaplasia). In the urinary bladder, the normal transitional epithelium may be replaced by squamous epithelium in response to chronic irritation by bladder stones or infection (squamous metaplasia). The esophageal squamous epithelium is replaced by columnar epithelium in response to exposure to gastric acid in cases of gastric reflux.

Metaplasia most commonly occurs in epithelial tissues, but may also be seen elsewhere. For example, areas of fibrous tissue exposed to chronic trauma may form bone (osseous metaplasia). In many settings, metaplasia co-exists with hyperplasia; e.g., the squamous epithelium that arises by metaplasia in response to stone in the bladder may also be hyperplastic.

Adaptive responses in disease occur only with tolerable environmental changes. The adaptive responses of hyperplasia, hypertrophy, atrophy, involution and metaplasia occur only if the damaging stimulus is tolerable to the affected cells. Failure to adapt leads to cell damage and, if the stimulus is severe or prolonged, may result in cell death. Adaptive responses allow cells to survive in the face of a change in the cellular environment. Failure to adapt is associated with cell damage or cell death.

Self-check materials:

1. Ten years ago a male patient's right lung was removed because of a tumour, since then the capacity of his left lung has increased by 50 %. What process has developed in the left lung?

- A. Vicarious hypertrophy*
- B. Neurohumoral hypertrophy
- C. Atrophy
- D. Work hypertrophy
- E. Hypertrophic vegetations

2. An autopsy of a male patient, who died from hypertensive disease, revealed an enlarged heart weighing 600 g, with a thickened left ventricular wall up to 2 cm and a dilated cavity of the left ventricle. Name the kind of an adaptive reconstruction in the heart.

- A. Eccentric atrophy
- B. Concentric hypertrophy
- C. Vicarious hypertrophy
- D. Eccentric hypertrophy*

- E. Vicarious hypertrophy
3. An autopsy of a male, who suffered from hypertensive disease for a long period of time, revealed a sharply enlarged heart weighing 800.0 g. Name the kind of compensatory hypertrophy of the heart.
- A. Hypertrophic vegetations
 - B. Vicarious
 - C. Neurohumoral
 - D. Work*
 - E. Vicarious
4. As a result of falling down, a small abrasion formed of the knee of a child and some time later it epithelialized completely without formation of any scar. What form of regeneration took place in this case?
- A. Physiological
 - B. Restitution*
 - C. Substitution
 - D. Pathological
 - E. Intracellular
5. A 20-year-old male patient with a posttraumatic variceal dilation and thrombosis of the subcutaneous vein in the middle third part of the shin underwent its surgical removal. Histologically, an obstructive thrombus was found in the lumen of the vein with growing of a connective tissue into the thrombus from the side of the vascular wall. What process did the changes in the thrombus result from?
- A. Organization*
 - B. Reconstruction
 - C. Canalization
 - D. Revascularization
 - E. Repair

TOPIC XI:Oncogenesis. Anatomical and microscopical features and kinds of tumor grow. Morphological characteristic of malignant tumors development basis stages.Nomenclature of tumors.

1.Actuality ofthe problem.Oncologic processes are pathological states, which are associated with disturbances of structure and function in organisms and may lead to death. The term “**neoplasia**” means new growth; the new growth produced is called “neoplasm” or “tumor”. However, all “new growth” is not neoplasms since examples of new growth of tissues and cells also exist in the processes of embriogenesis, regeneration on repair, hyperplasia and hormonal stimulation. Neoplastic cells lose control and regulation of replication and form an abnormal mass of tissue. Research of the etiology, mechanisms, morphology, secondary appearance of the tumors is important task in the practical medicine because it may help to diagnose and treat these diseases. In clinical practice the knowledge of the oncomorphology is necessary for the comparison of the clinical dates with the result of the biopsy research and postoperative materials, and also for the clinic-anatomical analysis of the autopsy.

2. Aim of studies.Receive the notion about the essence of tumors and the principle of the classification. Learn the etiology, morphogenesis, growth; morphological features of tumors and estimate the outcomes (complications) and determine the significance for organism.

Tasks of the studies:

- Explain the role of the oncologic processes in organism.
- Know the definition of neoplasia and terminology.
- To interpret the modern concepts of etiology (cancerogenesis) and pathogenesis of benign and malignant tumors.
- To interpret the pre-tumors (pre-cancerous) states and changes, their essence and morphology.
- To interpret the general morphologic features of benign and malignant tumors.
- To interpret a morphogenesis and histogenesis of tumors.
- Know the histogenic classification of tumors and the morphological classification is based on differentiation of the tumor cells.
- To explain mechanisms (metastatic cascade) and routes of metastasis.
- To explain the major clinical-pathological manifestations of tumorous growth.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.

- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of a human's inner organs. 2. To draw their normal structure.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of human's inner organs. 2. Give characteristic of regeneration processes peculiarity in different organs.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of physiological restore both parenchyma and stroma of inner organs. 2. To use knowledge's about disturbance in regeneration of different kinds of cells and tissues.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Tumor (neoplasm, blastoma)	is a pathological process characterized by unrestrained cell multiplying.
Benign tumors (mature)	consist of differentiated mature cells.
Malignant (immature)	tumors consist of undifferentiated cells. These tumors produce metastases.
At expansive growth	the tumor grows from itself moving away the surrounding tissues. This type of growth is slow, and is characteristic benign tumors.
Apposition growth	is due to transformation of normal cells to tumor ones.
In infiltrating growth	the cells of the tumor invade normal tissues and destroy them (so called destructive growth).
Endophytic growth	is infiltrating growth of the tumor deep into the wall of the organ.
Exophytic growth	is expansive growth of the tumor to the cavity of the organ.

4.2 Theoretical questions for the practical class:

1. Risk factors of tumor growth. Influencing of geographical areas, factors of environment.
2. Modern theories of carcinogenesis. Influencing of senescence of human. Heredity: inherited tumors syndromes, family forms of neoplasia, syndromes of RNA broken reparation.
3. Pre-tumors (pre-carcinomatous) states and changes, their essence, morphology.
4. Biology of tumor growth. Morphogenesis of tumors. Tumor's angiogenesis. Progression and heterogeneity of tumors. Features of cellular population in tumor focus.
5. Nomenclature and principles of classification.
6. Stages of carcinogenesis. Carcinogenic agents and their co-operation with cells. Major groups of chemical carcinogens. Radiation carcinogenesis. Viral carcinogenesis. Histogenesis (cytogenesis) and differentiation of tumors.
7. Basic properties of tumor. Structural features, parenchyma and stroma of tumor.
8. Tumor's cytomorphology (Differentiation and Anaplasia). Morphology of cellular and tissue atypia (homo- and heterological tissue).
9. Types of tumor growth: expansive, infiltrating and appositional; exophytic and endophytic.

10. Major clinical-pathological appearance of tumor growth. Description of the neoplastic process. Local influence of tumor.
11. Metastasis: types, conformities to the law, mechanisms. Metastatic cascade.
12. Disturbance of homeostasis of organism. Secondary changes in a tumor. Cancer cachexia, paraneoplastic syndromes.
13. Role of biopsy in oncology.
14. Clinical-morphological appearances.
15. Antitumor immunity. Antigens of tumors. Immune supervision. Antitumor effector mechanisms (cellular and humoral).
16. Dysplasia: stages, morphological features, clinical significance, their role in cancerogenesis.
17. Contrasting Features of Benign and Malignant Tumors.
18. Clinical aspects of neoplasia, effect of tumor on host.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **“Fibromyoma of the Uterus”**. Pay attention to appearance of the tumor: size, color, shape, presence of the nodules, localization, type of growth; flexibility of the tumor; the condition of tumor on cut section (necrosis and hemorrhages). *Name the macroscopic forms and the possible histological types. Call the most frequent localization, outcomes and significance for organism.*
2. **“Papilloma of the Skin”**. Describe the appearance of the tumor, its connection with the skin, type of the growth, color and structure on cut section. *Determine the pathologic process. Call histogenic type of tumor.*
3. **“Primary hepatocellular carcinoma”**. Diagnose the tumor, describe the appearance: size, color, localization, type of growth; the condition of tumor on cut section. *Determine the pathologic process. Name the malignant type.*
4. **“Central bronchogenic cancer of the Lungs”**. Describe a tumor: size, shape, surface, color, localization (growth of tumor relatively to bronchus's lumen), condition of bronchial wall, and structure on cut. Describe the peribronchial lymphatic nodules. *What histological types of central bronchogenic cancer of the lung take place usually? What changes in the adjacent lung tissue and pleura can be found?*
5. **“Breast's Cancer”**. Pay attention to appearance of the tumor: size, color, shape, presence of the nodules, localization, type of growth; flexibility of the tumor and its attitude to the skin; the condition of tumor on cut section (necrosis and hemorrhages). *Name the macroscopic forms and the possible histological types. Call the ways of spreading (possible metastases). What pre-cancer conditions do you know?*
6. **“Gastric polyps”**. Describe the appearance of the formations: size, color, surface, and quantity, type of growth. *Determine the pathologic process. Name the malignant type.*

Micropreparations:

Slide 1. Benign Hyperplasia of the Prostate gland (ought to be drawn).

Number of glands is increased. They are variable in size, shape and location in fibrous-muscular stroma. Hyperplastic glandular epithelium does not have signs of cellular atypism.

Slide 2. Papilloma

The tumor consists of the growing squamous cell epithelium and strongly pronounced connective tissue stroma with vessels. The atypia is manifested because of the presence of papillas and different ratio between parenchyma and stroma. The layers of keratinizing epithelium can be found on the surface of tumor.

Slide 3. Squamous non-keratinizing cell carcinoma of the Cervix (ought to be drawn)

The carcinomatous areas look like fields of polymorphous atypical squamous cells. The tumor's stroma is made up with immature proliferative connective tissue.

Slide 4. Metastases of mucinous carcinoma in the Lung (ought to be drawn)

Vessels and alveoli are filled by large atypical cells with foamy cytoplasm and localization on nuclei in periphery of cells.

Slide 5. Adenocarcinoma of the Rectum

Atypical tumoral glands grow in submucosa of rectum. Carcinomatous cells have pleomorphism and hyperchromatic nuclei. They are located in several layers. Many mytoses are seen here and there.

Topic content:

NEOPLASIA

Tumor (neoplasm, blastoma) is a pathological process characterized by unrestrained cell multiplying. Annually, malignant tumors cause 575 000 deaths from gastric cancer, 600 000 from lung cancer, 250 000 from breast cancer. The highest frequency of malignant tumors (242.3—361.1 per 100 000 persons) was registered in Italy, France, Denmark, the USA, Brazil.

The tumors are classified according to histogenetic principles with the account of their morphological structure, localization, peculiarity of their structure in a definite organ, benign or malignant character.

The classification was suggested as an international one by the Committee on Tumor Nomenclature of the International Anticancer Union. According to this classification, there are 7 groups of tumors, their total number exceeds 200.

1. Epithelial tumors without specific localization (nonorganspecific).
2. Tumors of endocrine and exocrine glands as well as epithelial integument (organspecific).
3. Mesenchymal tumors.
4. Tumors of melanin-forming tissue.
5. Tumors of nervous system and brain membranes.
6. Tumors of blood system.
7. Teratomas.

According to their clinico-morphological characteristics the tumors are divided into 3 groups:

- 1) benign,
- 2) malignant,
- 3) tumors with local destructive growth.

Benign tumors (mature) consist of differentiated mature cells. They are characterized by

1) tissue atypism, that is a property which distinguishes cells and tissues from their normal condition;

- 2) slow expansive growth;
- 3) the tumor does not usually influence the organism in general;
- 4) the tumor does not produce metastases;
- 5) the relapses are rare. Benign tumors may become malignant.

Malignant (immature) tumors consist of undifferentiated cells. These tumors produce metastases. Metastasis is separation of the tumor cells from the bulk and their transportation to the other organs.

Metastases can be:

- 1) *lymphogenic* (they are carried through the lymphatic vessels to regional lymphatic nodes);
- 2) *hematogenic* (they are carried with the blood flow to distant organs);
- 3) *implantation* (contact), when the tumor disseminates through the serous layers (peritoneum,

pleura) and grow to the adjacent organs).

Malignant tumors often relapse. Relapse is appearance of the tumor on the place from which it was removed.

Malignant tumors produce both local and general effect on the organism. A local effect manifests with squeezing and destruction of the surrounding tissues. General effect on the organism is characteristic for all malignant tumors, it manifests with metabolic disturbances and cachexia development.

The tumors with local destructive growth occupy the intermediate place between benign and malignant. They have the features of infiltrating growth but do not give metastases. Malignant tumors are characterized by tissue, cellular, biochemical, histochemical and antigenic atypism as well as that of the ultra-structure.

Depending on the degree of the tumor differentiation, there are different types of its growth: expansive, apposition, infiltrating (invasive).

At expansive growth the tumor grows from itself moving away the surrounding tissues. This type of growth is slow, and is characteristic benign tumors.

Apposition growth is due to transformation of normal cells to tumor ones.

In *infiltrating growth* the cells of the tumor invade normal tissues and destroy them (so called destructive growth).

In relation to the lumen of the hollow organ, the growth of the tumor may be endophytic or exophytic.

Endophytic growth is infiltrating growth of the tumor deep into the wall of the organ.

Exophytic growth is expansive growth of the tumor to the cavity of the organ.

According to the number of foci of tumor development, they can be unicenter (one focus) and multicenter (several foci).

Structure of tumor

The appearance of the tumor is various.

Its shape may resemble a node, a mushroom cap or cauliflower, a saucer.

Its surface may be smooth, bumpy, papillary.

The tumor may *grow as a node* with distinct borders, it may have *a limb or a capsule*.

The size of the tumor can be different.

Its consistency depends on prevalence of parenchyma or stroma in it. It may be either soft or solid (dense).

Secondary changes in the tumor result from disturbances of blood circulation in it as well as from chemo- or radiotherapy. They manifest by foci of necrosis, hemorrhages, inflammation, formation of mucus, calcification.

The etiology of tumors is various, 4 theories are recognized.

1. **Virogenetic theory.** It states integration of the genomes of the virus and the normal cell, that is combination of nucleic acid of the virus with genetic apparatus of the cell which turns into tumor cell. Oncogenic viruses are those containing DNA and RNA (Epstein-Barr virus, herpes virus, hepatitis B virus, etc.).

2. **Physicochemical theory** suggests that tumor appears under the influence of different physical and chemical substances, so called carcinogens.

3. **Dysontogenetic theory** was created by J. Cohnheim. According to his theory, tumors appear from embryonic tissue and abnormally developed tissues under the influence of different causative agents.

4. **Polyetiological theory** emphasizes the importance of different factors, i.e. chemical, physical, viral, parasite, dyshormonal.

Self-check materials:

1. In 40-year-old patient, the tumor, which grew under skin of spine was resected. The histologic diagnosis: a lipoma. What principle of the tumors' classification did the pathologist use when created his conclusion?

- A. Gistogenesis *
 - B. Of biochemical features
 - C. Of ultrastructural features
 - D. Of physico-chemical features
 - E. Macrostructure of an organ
2. During the laparotomy in 49 year-old male patient, the tumor has been found out in the field of a sigma with growth through all its layers and an occlusion of the lumen of an intestine. The biopsy has been taken and colonostoma has been overlapped. The clinical diagnosis after operation: a cancer of sigma. What kind of tumor is growth in relation to tissues?
- A. Infiltrative*
 - B. Expansive
 - C. Endophytic
 - D. Exophytic
 - E. Multicentric
3. A clinical study is performed with patients who had a diagnosis of breast cancer. Characteristics of the grade, stage, molecular biology, and histologic type are analyzed. Of the following characteristics, which is most likely to be associated with the best prognosis for these patients?
- A. Decreased nuclear/cytoplasmic ratio *
 - B. Increased expression of laminin receptors
 - C. Increased cathepsin expression
 - D. Decreased apoptosis
 - E. Decreased doubling time
4. A 45-year-old healthy woman has a routine check of her health status. She has no chest pain, cough, or fever. A chest x-ray taken and shows a peripheral 2.5 cm diameter "coin lesion" in the right mid-lung field. Which of the following biologic characteristics best distinguishes this lesion as a neoplasm, rather than a granuloma?
- A. Uncontrolled (autonomous) growth *
 - B. Recurrence following excision
 - C. Rapid increase in size
 - D. Sensitivity to radiation or chemotherapy
 - E. Necrosis
5. A 55-year-old man dies after a year-long illness. At autopsy the liver contains multiple tumor masses from 2 to 5 cm in size that are mostly firm and tan and that grossly exhibit umbilication with central necrosis. Which of the following statements would best characterize the significance of such an appearance?
- A. The neoplasm has an advanced stage. *
 - B. There is multicentric origin of a benign neoplasm.
 - C. The neoplasm has a high grade.
 - D. The primary neoplasm is in the stomach.
 - E. A carcinogen was the underlying cause for the neoplasm.

TOPIC XII:Epithelium origin tumors. Malignant and benign organospecific epithelium origin tumors. Peculiarities their development, metastasis, histological forms.

1. Actuality of the problem. Oncologic processes are pathological states, which are associated with disturbances of structure and function in organisms and may lead to death. Research of the etiology, mechanisms, morphology, secondary appearance of the epithelial tumors is important task in the practical medicine because it may help to diagnose and treat these diseases. In clinical practice the knowledge of the oncomorphology is necessary for the comparison of the clinical data with the result of the biopsy research and postoperative materials, and also for the clinic-anatomical analysis of the autopsy.

2. Aim of studies. Receive the notion about the essence of tumors and the principle of the classification. Learn the etiology, morphogenesis, growth; morphological features of epithelial tumors and estimate the outcomes (complications) and determine the significance for organism.

Tasks of the studies:

- Explain the role of the oncologic processes in organism.
- Know the definition of epithelial neoplasia and terminology.
- Know the histogenic classification of tumors and the morphological classification is based on differentiation of the tumor cells.
- Tell apart the benign and malignant epithelial tumors.
- Learn the morphology and functional manifestations of the benign and malignant epithelial tumors.
- Learn the morphology and functional manifestations of the benign and malignant epithelial tumors in lungs, stomach, large intestine, uterus and breast, prostate gland.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of a human's inner organs.

	2. To draw their normal structure.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of inner organs' parenchyma. 2. Give characteristic of morphological and functional peculiarities of different kinds of epithelium.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of physiological restore parenchyma of inner organs. 2. To use knowledge's about regeneration disturbance of different kind's epithelial cells.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Papilloma	is a tumor originating from the skin and mucous membranes, it looks like a ledge or a bush of branching papillae.
Adenoma	is a benign epithelial tumor from the epithelium of the glands and glandular organs.
Carcinoma	is a cancer arising in the epithelial tissue of the skin or of the lining of the internal organs.
Adenocarcinoma	a malignant tumour formed from glandular structures in epithelial tissue
Carcinosarcoma	a malignant tumour of the cervix, uterus, or vagina containing a mixture of adenocarcinoma, sarcoma cells, and stroma. Sarcomatoid differentiation of epithelial cancers often indicates a poor prognosis.
Carcinoma in situ	the earliest stage of cancer spread, in which the neoplasm is confined by the basement membrane of the epithelium. Surgical removal of the growth should lead to cure.

4.2 Theoretical questions for the practical class:

1. Epithelial tumors: definition, the nomenclature, principles of the classification.
2. The morphogenesis of epithelial tumors: pre-tumorous processes, and progression of tumors.
3. The characteristic of epithelial tumorous growth.
4. Benign epithelial tumor: types according to histological structure, microscopical and macroscopical features.
5. Malignant epithelial tumor: types according to histological structure, precancerous states, microscopical and macroscopical features of the distinctive types.
6. Metastases: definition, types of spreading. Peculiarities of cancer's dissemination.
7. Clinical aspects of neoplasia, effect of tumor on host.
8. Lung carcinoma: etiology, pathogenesis, classification, morphology, complications, causes of death.
9. Carcinoma of stomach: etiology, pathogenesis, classification, morphology, complications, causes of death
10. Carcinoma of the Prostate gland: etiology, pathogenesis, classification, morphology, complications, causes of death.
11. Carcinoma of large intestine: etiology, pathogenesis, classification, morphology, complications, causes of death.
12. Carcinoma of breast: etiology, pathogenesis, classification, morphology, complications, causes of death.

13. Carcinoma of cervix and body of uterus: pretumoral processes, classification and morphologic appearances.
14. Significance of biopsy in diagnostics of tumors.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate passible outcomes of the pathological process 5. What disease does the pathological process correspond to	1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. “Polyposis of the Stomach and Colon”. Describe the appearance of the formations: size, color, surface, and quantity, type of growth.

Determine the pathologic process. Name the malignant type.

2. “Central bronchogenic cancer of the Lungs”. Describe a tumor: size, shape, surface, color, localization (growth of tumor relatively to bronchus’s lumen), condition of bronchial wall, and structure on cut. Describe the peribronchial lymphatic nodules.

What histological types of central bronchogenic cancer of the lung take place usually? What changes in the adjacent lung tissue and pleura can be found?

3. “Peripheral cancer of the Lungs”. Describe a tumor: size, shape, surface, color, localization, and attitude to the pleura, state of the surrounding tissue, type of tumor’s growth in the pulmonary tissue.

Select the signs of malignization. What is the difference between this tumor and central cancer? Call the possible histological types of the peripheral cancer?

4. “Cancer of the Stomach, Intestine”. Diagnose malignant epithelium tumors, describe the appearance: size, color, localization, type of growth; the condition of tumor on cut section (necrosis and hemorrhages).

Name the macroscopic forms and the possible histological types. Call the ways of spreading (possible metastases). What pre-cancer condition do you know?

5. “Breast’s Cancer”. Pay attention to appearance of the tumor: size, color, shape, presence of the nodules, localization, type of growth; flexibility of the tumor and its attitude to the skin; the condition of tumor on cut section (necrosis and hemorrhages).

Name the macroscopic forms and the possible histological types. Call the ways of spreading (possible metastases). What pre-cancer conditions do you know?

Macropreparations:

Slide 1. Intraduct’s fibroadenoma of the Breast (ought to be drawn)

The growth of connective tissue is much more pronounced than the growth and branching out of glandular tubules. The connective tissue suppresses the glandular ducts and that’s why the last whimsically branch out in different directions creating epithelial streaks with numerous protuberances look like antlers.

Slide 2. Schirrus of the Breast (ought to be drawn)

It is undifferentiated malignant tumor. In Breast there are ingrowths of connective tissue (stroma of tumor) in which the large areas of atypical epithelial cells with hyperchromic nuclei and mitoses are visible

Slide 3. Gastric adenocarcinoma (ought to be drawn)

The growth of atypical glandular structures of different shape and size (stretched, round, with irregular outlines, small or large) into mucosa and submucosa of the gastric wall takes place. The carcinomatous structures are irregularly located in the middle of fibrous tissue. The epithelial cells are atypical too: their nuclei are polymorphous with various maintenance of chromatin and mitoses; the cells have various shape and size; not rare the cells are arranged in some layers.

Slide 4. Adrenal cortical carcinoma

Here is an adrenal cortical carcinoma seen microscopically at high power to demonstrate cellular pleomorphism with nuclear hyperchromatism. Tumor consists of polymorphic mononuclear and multinuclear giant cells with grainy or by a vacuolated cytoplasm and large hyperchromic nuclei. Both benign and malignant endocrine neoplasms demonstrate some degree of cellular pleomorphism, so it is not easy to tell benign from malignant on histologic grounds alone. The larger the neoplasm, the more likely it is malignant, but the best indicators are invasion and metastasis.

Slide 4. Squamous cell carcinoma with keratinization in the Skin (ought to be drawn)

A numerous accumulations of atypical squamous epithelial cells are located in derma. Polymorphism, and mitoses of cells are seen. Appearance of keratinizing islands, so-called "carcinomatous pearls" (pink color) amongst atypical tumorous cells takes place.

Slide 5. Adenocarcinoma of the Large intestine (ought to be drawn)

The growth of atypical glandular structures of different shapes and sizes (stretched, round, with irregular outlines small or large) into mucosa and submucosa of the colon takes place. The atypical cells have diverse shapes and sizes; their nuclei are polymorphous with various maintenance of chromatin and mitoses.

Topic content:

EPITHELIAL TUMORS

First, it is necessary to emphasize that epithelial tumors are the most frequent ones in the man, they involve chiefly people of middle and old age. Every 6th person over 40 dies from this tumor. In Europe, cancers are 4 times more frequent than in Asia. For instance, stomach cancer affects around 8000 people per year in the UK, although the incidence is declining. It affects more men than women. It is rare under the age of 40 and becomes more common with increasing age. The decline in the rate of stomach cancer is thought to be associated with improvements in diet.

Skin cancer is very rare in children but is more common as people get older. At the age of 20 only about 1 person in 100 000 has non-melanoma skin cancer, whereas at the age of 80 about 200 per 100 000 have it.

The incidence of kidney cancer is increasing and now accounts for approximately 6 000 new cases per year.

Cancer of the ovary is more common in women who have never had children than in those who have. It may occur at any age but is most usual between the ages of 50 and 80. Before age 30, the incidence is less than 1 in 50 000. After 55 it is about 1 in 2000 women. The incidence peaks in women in their seventies.

Benign epithelial tumors are subdivided according to their origin from different types of epithelium into the tumors of integumentary epithelium (papillomas), tumors of glandular epithelium (adenomas).

Papilloma is a tumor originating from the skin and mucous membranes, it looks like a ledge or a bush of branching papillae. It is a good example of an exophytic tumor. The base of the tumor consists of connective tissue containing blood vessels. It is a continuation of subepithelial connective tissue covered with epithelium like with a glove.

Depending on the stage of the development and the character of stroma, papilloma may be either hard or soft.

Hard papillomas are benign, they grow slowly, seldom become ulcerative and seldom bleed. They appear on the skin and mucous membranes covered with multilayer squamous

epithelium (mouth, larynx, pharynx).

Soft papillomas are tender, their stroma is loose, swollen, consists of thin fibers with thin-walled vessels. They are covered with cylindrical transition or ciliated epithelium. Their thin branching papillae can be easily injured and bleed.

These papillomas more often occur on the mucous membranes (nose, uterus, gastrointestinal tract, fallopian tubes) and are associated with chronic irritation of the mucous membrane. The most dangerous are papillomas of the urinary bladder. They grow quickly, relapse, may be the cause of bleeding resulting in general anemia, they often become malignant turning into cancer. These papillomas are mainly found in the neck of the urinary bladder and in the region of the triangle. It is necessary to admit that in papilloma both epithelium and stroma are subjected to tumor growth, they are characterized by anaplasia, therefore papillomas are considered fibroepithelial tumors.

Adenoma is a benign epithelial tumor from the epithelium of the glands and glandular organs. More often they can be found in the breast, thyroid gland, liver, ovaries, prostatic gland, gastrointestinal tract. According to the histological composition adenoma may be tubular and alveolar. In tubular adenoma, there are glandular cavities resembling tubes in the connective tissue with vessels. In alveolar adenoma, numerous bubbles bedded with cylindrical or cubic epithelium are observed in the connective tissue with vessels. In this cases, the epithelium is separated from the surrounding tissue by its own membrane.

Adenomas from compact organs (liver, adrenal gland) can be made of groups of respective cells separated from each other by a thin layer of stroma. Thus, the structure of adenomas is similar to that of the original organ which is the cause of their functional similarity (ability of adenoma cells to produce respective secreted) e.g. — adenomas of mucous membranes — mucus, adenomas of eosinophilic cell of the anterior lobe of pituitary — somatotrophic hormone, medullar layer of adrenal gland — norepinephrine, beta cells of pancreas — insulin, etc. This peculiarity must be always taken into account by a physician as it may contribute timely diagnosis of these tumors and correct treatment tactics. But, alone with similarity, adenomas (being tumors) have atypical structure which manifests in absence of ducts, variety of shape, size and location, parenchyma and stroma ratio (fibroadenoma, adenofibroma) in the glandular tubules and vesicles.

Sometimes papilloid growth of epithelium, bedding glandular cavities, is observed.

In some adenomas glandular cavities are widened and form large cavities, cysts filled with serous fluid or mucus. These cyst-like adenomas are called cystadenomas.

Sometimes epithelial integument of glandular cavities begin to grow in a cyst-like manner. The papillae fill cyst-like cavities with masses resembling cauliflower.

Sometimes epithelial growth is so intensive that the papillae invade the walls of the cyst, involve the peritoneum, produce metastases, relapse, cause cachexia and may cause severe consequences. These adenomas are termed papillary adenocystomas.

They develop in ovaries, thyroid gland. Adenocystomas may become malignant more frequently than the other adenomas.

Immature, or malignant, tumors of epithelium are also called cancers. The term came to us from the time of Hippocrates and Galen.

The popularity of this term can be explained by the increase of the cancer incidence in the 20th century when compared with previous centuries.

This fact can be explained by the increase of the life expectancy by 20 years, that is the group of people of «cancer age» enlarged (due to increased possibility to be exposed to carcinogenic factors, accumulation of the total number of precarcinogenic processes and increased chance to develop latent cancer with long duration). Besides, increase of the number of tumors can be associated with improvements in diagnosis. But the above does not exclude objective causes of cancer development, especially in the population of the developed countries due to increase of the number of industrial tumors (cancer of lungs, skin, urinary bladder) associated with exposure to chemical carcinogens (at present there are about 300 of them, mainly

polycyclic aromatic hydrocarbon, azo- or aminocompounds).

The morphological classification is based on differentiation of the tumor cells.

According to it all cancers can be divided into 3 groups:

- 1) **poorly-differentiated**: small-cell or basal cell, medullar, scirrhous, solid;
- 2) **well-differentiated**: squamous-cell, with keratinization, without keratinization, adenocarcinoma (trabecular, alveolar, papillary, mucous);
- 3) **special kinds**: chorionepithelioma, seminoma, hypernephroid cancer.

This classification is important because main clinico-morphological peculiarities of different cancers are due to the degree of differentiation, or anaplasia of their cellular elements: intensity and character of the primary tumor growth, secondary changes, sensitivity to radiotherapy which is higher in undifferentiated, character, rate and terms of metastases appearance. Squamous-cell cancer of skin, bronchi, i.e. highly differentiated cancers, do not produce metastases for a prolonged period of time. Vice versa undifferentiated cancers, e.g. medullar, small-cell cancer of bronchi, even small in size, gives early and abundant metastases. This may be accounted by the location of the cellular complexes in medullar cancers forming pure cultures of free cells easily penetrating lymphatic and blood vessels. It is necessary to remember about the association of the type and character of the metastases with the age of the patient. Thus, the size of the primary tumor does not influence metastases appearance, its histological structure and the degree of anaplasia are more important.

As to metastases, it is important to know that invasion of the tumor cells to the veins is difficult because they become narrowed in the rapidly growing tumor and due to increase of intravenous pressure. Blood vessels in the tumors look differently. Usually they have the structure of capillaries. As a rule, vessels in tumors are new structures but they are connected with general circulation. The tumors may be connected with the sources of nutrition in different ways. The more directly they contact, the more intensive is the growth of the tumor, the more rapidly it produces metastases (e.g., chorionepithelioma, seminoma, hypernephroid cancer).

If both stroma and parenchyma of the tumor are anaplastic, they characterize combination tumors, termed sarcomas or carcinosarcomas.

Together with tissue and cellular atypism, malignant tumors are characterized by infiltrating tumor growth.

Clinico-anatomical practice suggests that tumor, as a rule, does not appear at once, its development is preceded by different processes characterized by:

- 1) prolonged chronic course,
- 2) association with cell multiplying,
- 3) failure of conservative treatment.

These kind of processes or states are called precancerous. There are a large number of them: defects of development, including lost embryonic germs, chronic inflammatory diseases, chronic ulcers, disturbed tissue regeneration (abundant granulation, metaplasia), hormonal hyperplasias, polyposis of mucous membrane, leukoplakias of the mucous membrane. The problem of the terms of transition of

pre-cancerous states into cancers is disputable. It is thought that the period of malignization (latent period) may last for 15—20 years (gastric cancer). Clinical observations show that some precancerous states turn into cancers more often than the other. The former are called obligatory precancers (polyposis of the mucous membrane of the stomach, intestine, uterus, chronic gastric ulcer, cystic mastopathy, erosion of the uterine cervix), the latter are optional.

CANCERS OF DEFINITE ORGANS

Gastric carcinoma

Gastric carcinoma comprises more than 90% of all gastric malignant tumors. The men at the age of 40—60 suffer more often than women.

Pre-cancer changes in the gastric mucosa.

1. Atrophic gastritis.
2. Adenomatous polyps of the stomach.

3. Chronic gastric ulcer.

Gastric carcinoma is most commonly located in the region of gastric canal (prepyloric region), less common localization are the body, cardia and fundus.

Classification

According to the deepness of the lesion in the gastric wall there are 2 types of carcinoma:

1. *Early gastric carcinoma*, when carcinoma confined only mucosal layers.
2. *Advanced gastric carcinoma*, when it penetrates the muscular layer or beyond.

According to the location gastric carcinoma may be:

1. Pyloric (50%) gastric carcinoma.
2. Lesser curvature of the stomach (27%).
3. Cardial gastric carcinoma (15%).
4. Greater curvature of the stomach (3%).
5. Fundal gastric carcinoma (2%).
6. Total gastric carcinoma (3%).

According to the peculiarities of growth there are the following types of gastric carcinoma:

1. Carcinoma with exophytic and expansive growth:
 - a) Fungating (resembling a mushroom) type;
 - b) Superficial spreading type;
 - c) Polypoid type;
 - d) Ulcerative type:
 - primary-ulcerative,
 - like source (Cancer-ulcer),
 - cancer from chronic ulcer (Ulcer-cancer).
2. Carcinoma with endophytic — infiltrating growth:
 - a) Ulcerative-invasive (infiltrating) type;
 - b) Diffusely spreading type (Linitis plastica).
3. Carcinoma with exophytic and endophytic growth. (Mixed types of carcinoma).

According to the histological signs there are the following types of gastric carcinoma:

1. Adenocarcinoma: papillary, mucoid, trabecular (well-differentiated).
2. Signet-ring cell carcinoma, scirrhus carcinoma, solid carcinoma (poorly-differentiated).
3. Squamous-cell carcinoma.
4. Adenosquamous carcinoma.

Early gastric carcinoma is the term used to describe cancer limited to the mucosa and submucosa. The diagnosis of this condition has been made possible by extensive work on histogenesis of gastric cancer by Japanese pathologists by the use of fiberoptic endoscope and gastrocamera.

Macroscopically, the lesions of early gastric carcinoma may have 3 patterns—superficial, polypoid and ulcer-associated. The superficial type may further be of flat, elevated to depressed subtypes.

Microscopically, early gastric carcinoma is a typical glandular adenocarcinoma, usually well-differentiated.

Early gastric carcinoma must be distinguished from certain related terms: epithelial dysplasia (cellular atypia seen in intestinal metaplasia such as in atrophic gastritis and pernicious anemia); carcinoma in situ in the stomach (a state of severe cellular atypia or dysplasia, without invasion across the basement membrane of the glands).

Advanced gastric carcinoma. When the carcinoma crosses the basement membrane into the muscular propria or beyond, it is referred to as advanced gastric carcinoma. Advanced gastric carcinoma has following patterns:

1. Ulcerative carcinoma. This is the most common pattern. The tumour appears as a flat, infiltrating and ulcerative growth with irregular necrotic base and raised margin. It is seen more commonly in

the region of gastric canal. Macroscopically, ulcerative carcinomas are poorly-differentiated adenocarcinomas, which invade deeply into the stomach wall. Tubular and acinar patterns are seen more commonly.

2. Fungating (polypoid) carcinoma. The second common pattern is a cauliflower growth projecting into the lumen, similar to what is commonly seen in the large intestine. It is seen more often in the fundus. The tumor undergoes necrosis and infection commonly. Microscopically, fungating or polypoid carcinomas are well-differentiated adenocarcinomas, commonly papillary type.

3. Scirrhus carcinoma. In this pattern, the stomach wall is thickened due to extensive desmoplasia giving the appearance as «leather bottle stomach» or «linitis plastica». The involvement may be localized to pyloric antrum, or diffuse affecting whole of the stomach from the cardia to pylorus. The lumen of the stomach is reduced. There are no ulcers but rugae are prominent. Microscopically, it may be an adenocarcinoma or signet-ring cell carcinoma, extensively infiltrating the stomach wall, but due to marked desmoplasia cancer cells may be difficult to find.

4. Colloid (mucoid) carcinoma. This pattern is usually seen in the fundus. The tumour grows like masses having gelatinous appearance due to secretion of large quantities of mucus. Microscopically, mucoid carcinoma contains abundant pools of mucin in which are seen a small number of tumor cells, sometimes having signet-ring appearance.

5. Ulcer-cancer. Majority of ulcer-cancers are malignant lesions from the beginning. For confirmation of cancer in a pre-existing gastric ulcer, the characteristic microscopic appearance of peptic ulcer should be demonstrable with one portion of the base or the margin of the ulcer showing carcinomatous changes. Microscopically, ulcer-cancers are adenocarcinomas without any specific features.

Metastases can be:

1. Lymphogenic. There are 2 types of them: orthograde (with the lymph flow) and retrograde (against the lymph flow). In orthograde metastases, they are carried through the lymphatic vessels to regional lymphatic nodes — along the lesser and greater curvature, around the cardiac and suprapancreatic lymph nodes.

In retrograde metastases they are carried through the lymphatic vessels to the left supraclavicular lymph node (Virchow's gland), ovaries (Krukenberg tumor), pararectal tissue (Shnitsler metastases).

2. Hematogenic metastases are carried with the blood flow to the liver, lungs, brain, bones, kidneys and adrenal glands.

3. Implantation (contact), when the carcinoma disseminates through the peritoneum or penetrates to the pancreatic glands.

Carcinoma of lung

95% of all primary lung tumors is bronchogenic carcinoma.

According to the peculiarities of their growth there are following types of pulmonary carcinoma:

1. Exophytic (endobronchial) type.
2. Endophytic (exobronchial and peribronchial) type.

According to the macroscopical signs there are following types of pulmonary carcinoma:

1. Superficial spreading type.
2. Polypoid type.
3. Endobronchial diffusely spreading type.
4. Nodular type.
5. Branching type.
6. Nodular-branching type.

According to the WHO, there are following histological types of bronchogenic carcinoma:

1. Squamous-cell carcinoma.
2. Adenocarcinoma:
 - a) acinar carcinoma;
 - b) papillary carcinoma;
 - c) bronchiolo-alveolar carcinoma;
 - d) solid carcinoma with mucos formation.
3. Small cell carcinoma:
 - a) oat cell carcinoma;
 - b) small cell carcinoma, intermediate cell type;
 - c) combined oat-cell carcinoma.
4. Large cell carcinoma.
5. Adenosquamous carcinoma.

According to its location, bronchogenic carcinoma may be hilar and peripheral.

Hilar type. Most commonly, the lung cancer arises in the main bronchus or one of its segmental branches in the hilar parts of the lung, more often on the right side. The tumour begins as a small roughened area on the bronchial mucosa at the bifurcation. As the tumour enlarges, it thickens the bronchial mucosa producing nodular or ulcerated surface. As the nodules coalesce, the carcinoma grows into a friable spherical mass, 1 to 5 cm in diameter, narrowing and occluding the lumen. The cut surface of the tumour is yellowish-white with foci of necrosis and hemorrhages which may produce cavitory lesions. It is common to find secondary changes in the lungs such as bronchopneumonia, abscess formation and bronchiectasis as a result of obstruction and accompanying infections. The tumour soon spreads within the lungs by direct extension or by lymphatics, and to distant sites by lymphatic or hematogenous routes, as described later.

Peripheral type. A small proportion of lung cancers, chiefly adenocarcinomas including bronchioloalveolar carcinomas, originate from a small peripheral bronchiole but the exact site of origin may not be discernible. The tumour may be a single nodule or multiple nodules in the periphery of the lung producing pneumonia-like consolidation of a large part of the lung. The cut surface of the tumour is grayish and mucoid.

Squamous cell (epidermoid) carcinoma. This is the most common type of bronchogenic carcinoma found more commonly in men, particularly with the history of tobacco smoking. These tumors usually arise in a large bronchus and are prone to massive necrosis and cavitation. The tumour is diagnosed microscopically by identification of either intercellular bridges or keratinization. Usually the spread of squamous cell carcinoma is more rapid than the other histologic types. Frequently, the edge of the growth and the adjoining uninvolved bronchi show squamous metaplasia, epithelial dysplasia and carcinoma in situ.

Adenocarcinoma is the most common bronchogenic carcinoma in women and is slow-growing. Adenocarcinoma is further subclassified into 4 types:

1. Acinar adenocarcinoma which has predominance of glandular structure and often occurs in the larger bronchi.
2. Papillary adenocarcinoma which has a pronounced papillary configuration and is frequently peripherally located in the lungs and is found in relation to pulmonary scars (scar carcinoma).
3. Bronchioloalveolar carcinoma is characterized by cuboidal to tall columnar and mucus-secreting epithelial cells growing along the existing alveoli and forming numerous papillary structures.
4. Solid carcinoma is a poorly-differentiated adenocarcinoma lacking acini, tubules or papillae but having mucus-containing vacuoles in many tumour cells.

Small cell carcinomas are frequently hilar or central in location, have strong relationship to cigarette smoking and are highly malignant tumors. They are most often associated with ectopic hormone production because of the presence of neurosecretory granules in majority of tumour cells which are similar to those found in argentaffin or Kulchitsky cells normally found in bronchial epithelium. Small cell carcinomas may be:

1. Oat-cell carcinoma is composed of uniform, small cells, larger than lymphocytes with dense, round or oval nuclei having diffuse chromatin, inconspicuous nucleoli and very sparse cytoplasm. These cells are organized into cords, aggregates and ribbons or around small blood vessels forming pseudorosettes.

2. Small cell carcinoma, intermediate cell type is composed of cells slightly larger than those of oat cell carcinoma and have similar nuclear characteristics but have more abundant cytoplasm. These cells are organized into lobules.

3. Combined oat-cell carcinoma is a tumour in which there is a definite component of oat cell carcinoma with squamous cell and/or adenocarcinoma.

Large cell carcinoma. These are undifferentiated carcinomas which lack the specific features by which they could be assigned into squamous cell carcinoma or adenocarcinoma. Large cell carcinomas are more common in men, have strong association with cigarette smoking and are highly malignant tumors. The tumour cells have large nuclei, prominent nucleoli, abundant cytoplasm and well-defined cell borders.

Adenosquamous carcinoma. These are a small proportion of peripheral scar carcinomas having clear evidence of both keratinisation and glandular differentiation.

Metastases can be:

1. Lymphogenic — through the lymphatic vessels to regional lymphatic nodes — hilar, mediastinal, cervical, supraclavicular and paraaortic lymph nodes.

2. Hematogenic metastases are carried with the blood flow to the liver, pancreas, brain, bones, kidneys, adrenal and thyroid glands.

3. Implantation (contact) when the carcinoma disseminates through the pleura or penetrates to the peribronchial lung tissue.

In carcinoma, irrespective of its location patients die from metastases and secondary complications, i.e. hemorrhages, necrosis of the tumor as well as cachexia.

Esophageal cancer

Esophageal cancer occupies special place as in the majority of cases the death of the patients is caused by hunger long before the disease becomes incompatible with the life. Even gastrostomy cannot save the patient, it only slows down the rate of cachexia. This cancer is on the 2nd—3rd place in occurrence. Men suffer more often than women (70 to 30). The tumor is localized mainly in the middle and lower part of the esophagus.

Carcinoma of the oesophagus is mainly of 2 types — squamous cell (epidermoid) and adenocarcinoma.

Squamous cell (epidermoid) carcinoma. Squamous cell or epidermoid carcinoma comprises 90% of primary esophageal cancers. The sites of predilection are the three areas of esophageal constrictions. Half of the squamous cell carcinomas of esophagus occur in the middle third, then in the lower third, and then in the upper third part of esophagus.

Macroscopically, 3 types are recognized: 1) Polypoid fungating type is the most common form. It appears as a cauliflower-like friable mass protruding into the lumen; 2) Ulcerating type is the next common form. It looks grossly like a necrotic ulcer with everted edges; 3) Diffuse infiltrating type appears as an annular, stenosing narrowing of the lumen due to infiltration into the wall of esophagus.

Microscopically, the majority of squamous cell carcinomas of the esophagus are well- or moderately-differentiated. Prickle cells, keratin formation and epithelial pearls are commonly seen. However, non-keratinising and anaplastic growth patterns can also occur.

Adenocarcinoma. The common locations of adenocarcinomas are lower and middle third of the esophagus.

Macroscopically, esophageal adenocarcinoma appears as nodular, elevated mass in the lower esophagus.

Microscopically, adenocarcinoma of the esophagus may be:

1) Intestinal type (adenocarcinoma with a pattern similar to that seen in adenocarcinoma of intestine or stomach);

- 2) Adenosquamous type (the pattern in which there is an irregular admixture of adenocarcinoma and squamous cell carcinoma);
- 3) Adenoid cystic type (an uncommon variety and is akin to similar growth in salivary gland i.e. a cribriform appearance in an epithelial tumour).

Besides the two main histological types of esophageal cancer, a few other varieties are occasionally encountered. These are as under:

1. Mucoepidermoid carcinoma is a tumour having characteristics of squamous cell as well as mucus-secreting carcinomas.
2. Malignant melanoma is derived from melanoblasts in the epithelium of the esophagus.
3. Oat-cell carcinoma arises from argyrophil edit in the basal layer of the epithelium.
4. Undifferentiated carcinoma is an anaplastic carcinoma which cannot be classified into any recognizable type of carcinoma.
5. Carcinosarcoma consists of malignant epithelial as well as sarcomatous components.
6. Secondary tumors rarely occur in the esophagus from carcinomas of the breast, kidney and adrenals.

Metastases are lymphogenic. Hematogenic metastases are rare, chiefly to the liver, lungs, adrenal glands.

Complications: involvement of trachea, stomach, aspiration pneumonia, lung gangrene, etc.

Breast cancer

Breast cancer is a frequent disease but as it is diagnostically and surgically accessible, it appears in surgical material more frequently than in autopsy. In women with malignant tumors, breast cancer occurs in 18% (S.A. Kholdin). In unmarried and nuliparous women it occurs 3 times more often. In men this cancer is rare (100 times rarer than in women). It is frequent in gynecomastias which is believed to be a precancerous state in women.

There are cancer of ducts, parenchyma, nipple and areola. In 95% of cases it develops from ductal epithelium near the base of the nipple, which frequently causes its pulling in (e.g. cancer of large and medium ducts). Cancer from the parenchyma as well as from small and medium ducts develops deep in the organ Breast cancer may at first develop in the axillary region. These aberrant cancers occur in 10% of cases. The most frequent location of the tumor is upper external quadrant of the breast.

According to the WHO, carcinoma of the breast are subdivided on 2 main types non-invasive carcinoma and invasive one. Non-invasive carcinoma may be intraductal carcinoma and lobular carcinoma. There are several types of invasive carcinoma. They are infiltrating ductal carcinoma-NOS, invasive lobular carcinoma, medullary carcinoma, colloid carcinoma, papillary carcinoma, tubular carcinoma, adenoid cyst carcinoma, secretory carcinoma, inflammatory carcinoma and carcinoma with metaplasia.

Non-invasive (in situ) carcinoma. In general, noninvasive or in situ carcinoma is characterized histologically by presence of tumour cells within the ducts or lobules without evidence of invasion. Two types of carcinoma in situ are described: intraductal carcinoma and lobular carcinoma in situ. Intraductal carcinoma. Carcinoma in situ confined within the larger mammary ducts is called intraductal carcinoma. The tumour initially begins with atypical hyperplasia of ductal epithelium followed by filling of the duct with tumour cells. Macroscopically, the tumour may vary from a small poorly-defined focus to 2.5—5.5 cm diameter mass.

On cut section, tumor shows cystically dilated ducts containing cheesy necrotic material (comedo pattern), or the intraductaltumour may be polypoid and friable resembling intraductal papilloma (papillary pattern). Microscopically, the proliferating tumour cells within the ductal lumina may have 4 types of patterns in different combinations: solid, comedo, papillary and cribriform. Solid type is characterized by filling and plugging of the ductal lumina with tumour cells. Comedo type is centrally placed necrotic debris surrounded by neoplastic cells in the duct. Papillary type has formation of intraductal papillary projection of tumour cells which lack a

fibrovascular stalk so as to distinguish it from intraductal papilloma. Cribriform type is recognized by neat punched out fenestrations in the intraductal tumour.

Lobular carcinoma in situ is identified only microscopically. In situ lobular carcinoma is characterized by filling up of terminal ducts and ductules or acini by rather uniform cells which are loosely cohesive and have small, rounded nuclei with indistinct cytoplasmic margins.

Invasive carcinoma. Infiltrating ductal carcinoma-NOS (not otherwise specified) is the classic breast cancer. Macroscopically, the tumor is irregular, 1—5 cm in diameter, hard cartilage-like mass that cuts with grating sound. The sectioned surface of the tumour is gray-white to yellowish with chalky streaks and often extends irregularly into the surrounding fat. Microscopically, as the name NOS suggests, the tumour is different from other special types in lacking a regular and uniform pattern throughout the lesion. There are 3 histological types of this carcinoma:

- anaplastic tumour cells forming solid nests, cords, poorly-formed glandular structures and some intraductal foci;
- infiltration by these patterns of tumour cells into diffuse fibrous stroma and fat;
- invasion into perivascular and perineural spaces as well as lymphatic and vascular invasion.

Infiltrating (invasive) lobular carcinoma. Invasive cancers in being more frequently bilateral; and within the same breast, it may have multicentric origin.

Macroscopically, the appearance varies from a well-defined scirrhous mass to a poorly-defined area of induration that may remain undetected by inspection as well as palpation.

Microscopically, there are 2 characteristics: 1) Pattern — a characteristic single file (Indian file) linear arrangement of stromal infiltration by the tumour cells with very little tendency to gland formation is seen. Infiltrating cells may be arranged concentrically around ducts in a target-like pattern ; 2) Tumour cytology — individual tumour cells resemble cells of in situ lobular carcinoma. They are round and regular with very little pleomorphism and infrequent mitoses. Some tumors may show signet-ring cells distended with cytoplasmic mucus.

Medullary carcinoma has a significantly better prognosis than the usual infiltrating duct carcinoma, probably due to good host immune response in the form of lymphoid infiltrate in the tumour stroma. Macroscopically, the tumour is characterized by a large, well-circumscribed, rounded mass that is typically soft and fleshy brain-like and hence the alternative name of «encephaloid carcinoma». Cut section shows areas of hemorrhages and necrosis. There are 2 histological characteristics of this tumor. The first — pleomorphic tumour cells with abundant cytoplasm, large vesicular nuclei and many bizarre and atypical mitoses are diffusely spread in the scanty stroma. The second — the loose connective tissue stroma is scanty and usually has a prominent lymphoid infiltrate.

Colloid (mucinous) carcinoma contains large amount of extracellular epithelial mucin and acini filled with mucin. Cuboidal to tall columnar tumour cells, some showing mucus vacuolation, are seen floating in large lakes of mucin.

Paget's disease of the nipple. The nipple bears a crusted, scaly eczematoid lesion with a palpable subareolar mass in about half the cases.

Macroscopically, the skin of the nipple and areola is crusted, fissured and ulcerated with oozing of serosanguineous fluid from the erosions. Microscopically, the skin lesion is characterized the presence of Paget's cells singly or in small clusters in the epidermis. These cells are larger than the epidermal cells, spherical, having hyperchromatic nuclei with cytoplasmic halo that stains positively with mucicarmine. In these respects, Paget's cells are adenocarcinoma-type cells. In addition, the underlying breast contains invasive or non-invasive duct carcinoma which shows no obvious direct invasion of the skin of nipple.

The metastases are either local or distant, the former to the lymphatic nodes of the breast base, axilla, subclavicular, parasternal nodes. Distant metastases are hematogenous ones, 40—50% to the bones, lungs, liver. Late metastases and relapses occur 5—20 years after the operation.

Self-check materials:

1. A histological examination of a scrape from the mucous coat of the uterus made in a female patient, who complained of a disorder in the ovariomenstrual cycle, revealed vegetation of the glandular structures consisting of atypical epithelial cells with hyperchromatic nuclei and pathological mitoses. The changes in the glandular structures were accompanied by an impairment in the integrity of the basal membrane of the cells. Make a diagnosis.

- A. Adenocarcinoma*
- B. Glandular hyperplasia of endometrium
- C. Chorionepithelioma
- D. Mucinous carcinoma
- E. Dimorphic carcinoma

2. A microscopic examination of a biopsy from a large intestine revealed some tumour made of the columnar epithelium that formed atypical glandular structures of various shapes and size. The epithelial cells were polymorphous and with hyperchromatic nuclei, there were pathological mitoses. What is your diagnosis?

- A. Basal cell carcinoma
- B. Solid carcinoma
- C. Adenocarcinoma*
- D. Mucinous carcinoma
- E. Carcinoma simplex

3. A male patient, who suffered from chronic bronchitis for a long period of time, revealed a pulmonary tumour, which was closely connected with the bronchial wall and grew in the form of a polyp. Microscopically, the tumour consisted of complexes of polymorphous epithelial cells with a large number of mitoses. Among the tumour cells there were stratified concentric oxyphilic structures. Name the histological type of the tumour.

- A. Mucinous carcinoma
- B. Solid carcinoma
- C. Nonkeratinizing squamous cell carcinoma
- D. Adenocarcinoma
- E. Keratinizing squamous cell carcinoma*

4. A histological examination of a biopsy from a uterine cervix revealed that its tissue was covered with a wide layer of the stratified squamous epithelium having foci of proliferation of atypical cells with pathological mitoses, but the basal membrane of the epithelium was not affected. What is your diagnosis?

- A. Nonkeratinizing squamous cell carcinoma
- B. Keratinizing squamous cell carcinoma
- C. Carcinoma in situ*
- D. Leukoplakia
- E. Epithelial dysplasia

5. A histological examination of some spherical neoplasm located under the surface of the skin, revealed papilliform vegetations of the epithelium with phenomena of acanthosis and hyperkeratinization. The tumour stroma consisted of a large amount of the connective tissue and vessels. What tumour took place?

- A. Keratoacanthoma
- B. Papilloma*
- C. Carcinoma in situ
- D. Keratinizing squamous cell carcinoma
- E. Nonkeratinizing squamous cell carcinoma

TOPIC XIV: Morphological features of benign and malignant mesenchyme origin tumors. peculiarities of sarcoma development and metastasis. Fibroblastic, myofibroblastic and fibrohistiocytic origin tumors. Tumors of fat and muscle tissue. Tumors from blood vessels. Morphological features of melanin-producing tumors. Nomenclature and morphological features of nervous tissue origin tumors (astrocyte, oligodendroglia, ependymal, neuronal and meningovascular tumors). Cranial and spine nervous origin tumors.

1. Actuality of the problem. Mesenchymal tumors and tumors derived from melanin-producing tissue are widespread ones, which have very important significance. These tumors have different localization in mesenchymal tissue. It may lead to secondary changes. All sarcomas have hematogenous metastasis and can become the cause of death. Research of the etiology, mechanisms of the development, morphology, secondary appearance of the mesenchymal tumors can help timely to diagnose and treat these diseases. In clinical practice the knowledge of the oncomorphology is necessary for the comparison of the clinical dates with the result of the biopsy research and postoperative materials, and also for the clinic-anatomical analysis of the autopsy.

Tumors of nervous tissue are widespread ones, which have very important significance. These tumors have different localization in mesenchymal tissue; it may lead to secondary changes. All sarcomas have hematogenous metastasis and can become the cause of death. Research of the etiology, mechanisms of the development, morphology, secondary appearance of the mesenchymal tumors can help timely to diagnose and treat these diseases. In clinical practice the knowledge of the oncomorphology is necessary for the comparison of the clinical dates with the result of the biopsy research and postoperative materials, and also for the clinic-anatomical analysis of the autopsy. Research of the etiology, mechanisms of the development, morphology, secondary appearance of these tumors can help timely to diagnose and treat these diseases.

2. Aim of studies. Receive the notion about the essence of mesenchymal tumors, the principle of their classification. Learn the pretumorous processes, growth, and morphological features of mesenchymal tumors. Estimate the outcomes (complications) and determine the significance for organism.

Tasks of the studies:

- Know the terminology of the mesenchymal tumors and tumors derived from melanin-producing tissue.
- Explain the role of this oncologic process in organism.
- Know the histogenic classification of mesenchymal tumors and the morphological classification, based on differentiation of the tumor cells.
- Tell apart the benign and malignant mesenchymal tumors.
- Learn the morphology and functional manifestations of the benign mesenchymal tumors.
- Explain the role of this oncologic process in organism.
- Know the histogenic classification of tumors and the morphological classification, based on differentiation of the tumor cells.
- Tell apart the benign and malignant tumors.
- Learn the morphology and functional manifestations of the benign tumors.
- Learn the morphology and functional manifestations of the malignant tumors

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology

- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge's and skills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Received knowledge's
Normal anatomy	1. To describe normal morphological structure of an inner organs. 2. To draw their normal structure.
Histology, cytology and embryology	1. Be able to use knowledge's about histological structure of inner organs' stroma. 2. Give characteristic of morphological and functional peculiarities of different kinds of connective tissue cells and nervous cells .
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of physiological restore stroma and nervous tissue of inner organs. 2. To use knowledge's about regeneration disturbance of different kind of stromal cells.

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Fibroma	is a node of differentiated connective tissue with different direction of the bands
Desmoid fibroma	is a kind of dense fibroma and characterized by infiltrating growth and relapses.
Dermatofibroma (histiocytoma)	consists of capillaries and connective tissue with fibrous structures and fibroblasts, fibrocytes, histiocytes, macrophages. There are giant polynuclear cells with lipids and hemosiderin between cells.
Protruding dermatofibroma (malignant histiocytoma)	numerous polymorphic fibroblast cells with metastases. It grows slowly, its growth is infiltrating, the relapses of metastases are very rare
Lipoma	a node, sometimes in a capsule, yellow, made of lobules of different size. It may develop in every site where there is fat tissue.
Hybernoma	a rare tumor of brown fat. This consists of large round cells with granular or foamy cytoplasm (fat vacuoles).
Liposarcoma (lipoblastic myoma)	a rare, large tumor, which is built of lipocytes of different degree of maturity and lipoblasts.

Leiomyoma	consists of smooth muscle with chaotic location of the muscular tissue bands, the stroma with vessels and nerves.
Rhabdomyoma	consists of striated muscles. It resembles embryonic muscular fibres and myoblasts.
Leiomyosarcoma	(malignant leiomyoma) with cellular and tissue atypism, a large number of mitoses (high mitotic index) are characteristic.
Rhabdomyosarcoma	is characterized by extreme polymorphism, loss of tissue characteristic (it is necessary to use special immune antibodies to verify the tumor).
Malignant granular-cell tumor (malignant myoblastoma)	resembles malignant rhabdomyoma but the cytoplasm is granular.
Hemangioma	is a tumor from blood vessels.
Glomus tumor (glomus angioma)	More often develops in hands and feet (fingers and toes). There are vessels with endothelium, surrounded by mounds of epithelioid (glomus) cells, rich in nerves it is usually painful.
Lymphangioma	of growth lymphatic vessels in different direction with formation of a node or enlargement of the organ.
Benign synovioma	develops in the tendons and tendon sheath. It contains a lot of stroma with hyalinosis, and a little number of vessels. There may occur xanthomic cells and clefts.
Synovial sarcoma (malignant synovioma)	develops in the large joints. It has polymorphic structure. Some tumors have polymorphic cells and pseudoepithelial gland formations with cysts, the other have fibroblastoid atypical cells and collagen fibers, structures resembling tendons.
Benign mesothelioma	resembles a dense node in serous membrane (pleura), its structure is similar to fibroma (fibroid mesothelioma).
Malignant mesothelioma (peritoneum, pleura, pericardium)	microscopically looks like atypical large cells with vacuolized cytoplasm.
Osteoma	develops as a rule in spongy and tubular bones, skull
Osteoid osteoma	appears as a maze of irregular bone trabeculae, fibrous tissue, and vessels. The center of the tumor is rich in osteoblasts, calcification, and multinucleate giant cells.
Benign osteoblastoma	predominantly affects the vertebrae and long bones of young males in the first three decades of life. Macroscopically, the lesions vary in size from a few to several centimeters. Microscopically, osteoblasts proliferate and osteoid production increases. Osteoclasts and multinucleate giant cells may be very numerous, especially in areas of blood extravasation.
Osteosarcoma (osteogenic sarcoma)	from osteogenic tissue rich in atypical cells of osteoblastic type with a lot of mitoses, the bone is primitive.
Benign chondroblastoma	consists of chondroblasts, interstitial substance, marked osteoclast reaction. Chondroblastoma is a rare cartilaginous tumor that almost always involves the epiphyseal portion of the long bones.
Chondrosarcoma	is a malignant cartilaginous tumor. Microscopically, there are islands of immature or poorly developed cartilage in which anaplastic cells with two or more nuclei are present within the lacunar space.
Nevi	are benign tumors of skin consisting of melanocytes of epidermis

	and derma.
Melanoma	is one of the most malignant tumors, it spreads through the lymphatic and hematogenic routs.
Astrocyte tumors	are the most frequent brain tumors. They develop from astrocytes and can be found in all brain portions.
Oligodendroglial tumors	consist of homogeneous small cells with round nuclei and narrow outline of cytoplasm which is poorly colored. They are mainly localized in the large hemispheres of the brain, more seldom in the region of visual tuber and in the trunk
Oligodendro-glioblastoma	is a malignant type of the oligodendrogliomas. One is characterized by special cell location, marked polymorphism with giant cells. It is also characterized by numerous mitoses and necrosis foci.
Ependymoma	is a cerebral tumour derived from the glial (non-nervous) cells lining the cavities of the ventricles of the brain. It may obstruct the flow of cerebrospinal fluid, causing a hydrocephalus .
Ependymoblastoma	is a malignant type of ependymoma. This is characterized by marked cellular polymorphism. It grows quickly, metastases spread through the liquor system.
Choroid papilloma	is a tumor from the epithelium of vascular plexus, looking like a villous node in the cavity of the brain ventricle. It consists of numerous villous structures of cubic or prismatic epithelial cells.
Choroid carcinoma	is a malignant type of choroid papilloma. It is made of anaplastic cells covering the vascular plexus.
Ganglioneuroma	is a rare mature tumor. Most frequently it is localized in the bed of the 3th ventricle, rarer in the hemispheres of the brain.
Cerebellum ganglioma	is characterized by proliferation of large nervous elements of Purkinjer's cell type.
Ganglioneuroblastoma	is a malignant analogue of ganglioneuroma
Neuroblastoma	is a rare highly malignant brain tumor. The tumor is formed from large cells with bubble-like nucleus. Mitoses are numerous. The cells grow like syncytium. There are a lot of vessels.
Medulloblastoma	is a tumor made by immature cells, medulloblasts, therefore it is highly malignant. The most frequent localization is vermis cerebelli.
Glioblastoma	is characterized by marked polymorphism. The cells are located disorderly (cellular chaos), their size and shape are various, from small lymphocyte-like to giant poly-nuclear. Necroses, hemorrhages and vascular growths are typical. Mitoses and centers of atypical division are frequent. It is situated in the white substance of the brain
Arachnoidendothelioma	is the most frequent type of meningovascular tumors. It is characterized by large endothelium like cells. The cells usually form groups (plate-like, curl-like, band-like), so-called endotheliomatous structures.
Meningeal sarcoma	is a malignant type of the arachnoidendothelioma. It resembles fibrosarcoma, polymorphocellular sarcoma, diffuse sarcomatosis of the meninges.
Ganglioneuromas	are localized in the medullar substance of the adrenal gland, sympathetic trunks, cerebrospinal nerves. The tumor differs from normal ganglia as it has the signs of atypism (polynuclear cells, tigrolysis, nuclear decentralization.

Malignant ganglioneuroblastoma	is a combination of neuroblastoma and ganglioneuroma.
Nonchromophilicparagan glioma	is a benign variant. It resembles the tumors of APUD system (APUDomas). It can produce ACTH and serotonin.
Schwannoma	is atumors of peripheral nervous system originate from the nerve membranes. The tumor is formed of spinder-like cells with rod-shaped nuclei. The cells and fibers form rhythmical structures.
Neurofibromatosis	is a systemic disorder characterized by development of multipleneurofibromas associated with different development defects. This may be peripheral and central.

4.2 Theoretical questions for the practical class:

1. Modern histogenetic classification of mezenchymal tumors.
2. Peculiar properties of the growth and spreading of sarcomas.
3. Connective tissue tumors: benign and malignant, morphological appearances, metastases.
4. Tumors of fatty tissue: benign and malignant, morphological appearances, metastases.
5. Tumors of bone and cartilage: benign and malignant, morphological appearances, metastases.
6. Tumors of vessels: classification, morphologic appearances and spreading. Kaposi's sarcoma.
7. Value of pre-tumorous changes. Modern histogenetic classification of nevus.
8. Modern histogenetic classification of melanoma. Peculiar properties of the growth and spreading of sarcomas.
9. Tumors of nervous tissue: classifications, influence in organism.
10. Tumors of CNS: neuroectodermal (astrocytic, oligodendroglial, ependimoglia tumors of choroidal epithelium, neuronal, low-differentiated and embryonic), meningovascular. Morphologic features and features of metastatic spreading.
11. Tumors of the autonomic nervous system.
12. Tumors of the peripheral nervous system.
13. Tumors from cambial embryonic tissues: meduloblastoma, retinoblastoma, neuroblastoma.

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate passible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **"Fibromyoma of the Uterus"**. Pay attention to appearance of the tumor: size, color, shape, presence of the nodules, localization, type of growth; flexibility of the tumor; the condition of tumor on cut section (necrosis and hemorrhages). *Name the macroscopic forms and the possible histological types. Call the most frequent localization, outcomes and significance for organism.*

2. **“Liposarcoma”**. Describe the tumor: size, shape, surface, color, localization, growth of tumor and structure on cut. *Name the macroscopic forms and the possible histological types. Call the ways of spreading (possible metastases).*

3. **“Metastases of sarcoma in the Lung”**. Diagnose anatomic signs of metastases: number of nodules, their shape, color, consistency, the boundary between metastases and brain tissue. *What type of metastases takes place?*

4. **“Hemangioma of the Intestine”**. Pay attention to appearance of the tumor: size, color, shape, presence of the nodules, localization, type of growth; flexibility of the tumor. *Where is localization of this tumor else?*

5. **“Tumor of the Brain with hemorrhage”**. Describe a tumor: size, shape, surface, color, localization, state of the surrounding tissue. *What classification of CNS tumor do you know?*

Micropreparations:

Slide 1. Giant cell tumor (osteoblastoclastoma) (ought to be drawn)

It is a benign tumor developing in bones and sometimes in tendons. It consists of oval and round cells like fibroblasts. Between these cells the giant multinuclear cells (osteoclasts) can be found.

Slide 2. Polymorphous cell sarcoma (ought to be drawn)

It is a malignant tumor. It has histioid structure. The heavy cell's atypia and polymorphism (different shape and size, various color of nuclei) take place. Besides, the giant multinuclear cells can be found here and there.

Slide 3. Spindle-cell sarcoma.

There are cellular neoplasm composed of radially oriented (“storiform”) fibroblasts, showing spindled and polygonal cells; mitoses are not as numerous as in fibrosarcoma. The overlying epidermis is thinned and there often is microscopic extension into subcutaneous fat.

Slide 4. Lipoma

It is a benign tumor. The mature adipose tissue in which the lobules have irregular shape and size can be seen. This neoplasm is so well-differentiated that, except for its appearance as a localized mass, it is impossible to tell from normal adipose tissue.

Slide 5. Angiosarcoma

The tumor is well-differentiated masses of proliferating endothelial cells around well-formed vascular channels, to poorly-differentiated lesions composed of plump, anaplastic and pleomorphic cells in solid clusters with poorly identifiable vascular channels.

Topic content:

MESENCHYMAL TUMORS

In ontogenesis, mesenchyma gives the beginning to:

- 1) connective tissue,
- 2) vessels,
- 3) muscles,
- 4) tissues of musculoskeletal system,
- 5) serous membranes
- 6) hemopoietic system.

Mesenchymal tumors develop from:

- 1) connective (fibrous) tissue,
- 2) fat tissue,
- 3) muscular tissue,
- 4) blood and lymphatic vessels,
- 5) synovial tissue,
- 6) mesothelial tissue,
- 7) bone tissue.

They may be benign (name of the tissue + oma) and malignant (name of the tissue + sarcoma). There are also special terms (e.g. desmoid, granular-cell tumor).

Connective (fibrous) tissue tumors

Main benign connective (fibrous) tissue tumors are:

1. Fibroma—a node of differentiated connective tissue with different direction of the bands:

- a) dense-fibrous structures prevail over the cellular elements;
- b) soft (loose connective tissue with great amount of stroma cells — fibroblasts and fibrocytes).

Localization of fibroma is various: skin, breast, on the skin it may have a limb, cranial base, spinal canal, orbit.

2. Desmoid fibroma is a kind of dense fibroma and characterized by infiltrating growth and relapses. More often it is located on the anterior abdominal wall.

3. Dermatofibroma (histiocytoma) consists of capillaries and connective tissue with fibrous structures and fibroblasts, fibrocytes, histiocytes, macrophages. There are giant polynuclear cells with lipids and hemosiderin between cells.

Malignant connective (fibrous) tissue tumors are characterized by atypical cells, including loss of the structure.

Macroscopically sarcoma looks like fish flesh. As a rule sarcoma metastases are disseminated hematogenically.

1. Fibrosarcoma looks like node or indistinct formation. There are 3 types of fibrosarcoma:

- a) Differentiated fibrosarcoma, termed cellulofibrous, when fibrous component prevails cellular component;
- b) Poorly differentiated fibrosarcoma, termed cellular sarcoma. It produces metastases more frequently;
- c) Round-cell tumors of unknown origin, termed unclassified tumor.

2. Protruding dermatofibroma (malignant histiocytoma) — numerous polymorphic fibroblast cells with metastases. It grows slowly, its growth is infiltrating, the relapses of metastases are very rare.

Tumors of fat tissue

Benign

1. Lipoma: a node, sometimes in a capsule, yellow, made of lobules of different size. It may develop in every site where there is fat tissue.

Intramuscular infiltrating lipoma is a tumor without distinct borders, it infiltrates to intermuscular connective tissue.

2. Hybernoma: a rare tumor of brown fat. This consists of large round cells with granular or foamy cytoplasm (fat vacuoles).

Malignant

1. Liposarcoma (lipoblastic myoma) — a rare, large tumor, which is built of lipocytes of different degree of maturity and lipoblasts.

There are several types of liposarcoma:

- a) mainly highly differentiated;
- b) mainly myxoid (embryonic);
- c) mainly round-cell;
- d) mainly polymorphocellular.

It grows slowly, the metastases develop late.

2. Malignant hybernoma is a very rare tumor with cellular polymorphism and a lot of giant cells.

Tumors from the muscles

Benign

1. Leiomyoma consists of smooth muscle with chaotic location of the muscular tissue bands, the stroma with vessels and nerves. If stroma prevails this tumor is termed fibromyoma. Secondary changes: necrosis, hemorrhages, cysts, hyalinosis, petrification are characterized for leiomyoma.

2. Rhabdomyoma consists of striated muscles. It resembles embryonic muscular fibres and myoblasts. It appears against a background of tissue shifts and is accompanied by other development defects (large masses of striated muscles).

3. Granular-cell tumor (Abrikosov's tumor): this is small tumor in a capsule. It is located in the tongue, esophagus, skin. The cells are round, large with granular cytoplasm (no lipids).

Malignant

1. Leiomyosarcoma (malignant leiomyoma) with cellular and tissue atypism, a large number of mitoses (high mitotic index) are characteristic.
2. Rhabdomyosarcoma (malignant rhabdomyoma) is characterized by extreme polymorphism, loss of tissue characteristic (it is necessary to use special immune antibodies to verify the tumor).
3. Malignant granular-cell tumor (malignant myoblastoma) resembles malignant rhabdomyoma but the cytoplasm is granular.

Tumors from blood and lymph vessels

Benign tumors from blood vessels

1. Hemangioma is a tumor from blood vessels. There are several types of hemangioma:
 - a) capillary which develops in the skin, mucous membranes, gastrointestinal tract, liver, more often in children. It looks like cyanotic node of capillaries, branching with a narrow lumen;
 - b) venous: vascular bands with smooth muscles, resembles veins;
 - c) cavityhemangioma in the liver, skin, bones, muscles, gastrointestinal tract, brain;
 - d) benignhemangiopericytoma in the skin, intramuscular spaces of the extremities.
2. Glomus tumor (glomus angioma). More often develops in hands and feet (fingers and toes). There are vessels with endothelium, surrounded by mounds of epithelioid (glomus) cells, rich in nerves it is usually painful.

Malignant tumors from blood vessels Angiosarcoma which may be:

- a) malignanthemangioendothelioma;
- b) malignanthemangiopericytoma: highly malignant, early metastases (skin, liver, muscles).

Benign tumors from lymph vessels

Lymphangioma: growth of lymphatic vessels in different direction with formation of a node or enlargement of the organ. If lymphangioma develops in the tongue, it is termed macroglossia, if lymphangioma develops in the lip it is termed macrocheilia. Microscopically it looks like cavities filled with lymph. *Malignant tumors from lymph vessels* Lymphangiosarcoma. This appears as a result of chronic lymphatic stasis.

Tumors from synovial tissue

1. Benign synovioma develops in the tendons and tendon sheath. It contains a lot of stroma with hyalinosis, and a little number of vessels. There may occur xanthomic cells and clefts.
2. Synovial sarcoma (malignant synovioma) develops in the large joints. It has polymorphic structure. Some tumors have polymorphic cells and pseudoepithelial gland formations with cysts, the other have fibroblastoid atypical cells and collagen fibers, structures resembling tendons.

Tumors of mesothelial tissue

1. Benign mesothelioma resembles a dense node in serous membrane (pleura), its structure is similar to fibroma (fibroid mesothelioma).
2. Malignant mesothelioma (peritoneum, pleura, pericardium) microscopically looks like atypical large cells with vacuolized cytoplasm. Malignant mesothelioma may have tubular and papillary structures. Mesothelioma with tubular and papillary structures is called epithelial mesothelioma.

Bone tumors

Benign

1. Osteoma develops as a rule in spongy and tubular bones, skull. 2 types of osteoma are known:
 - a) spongy osteoma, b) compact osteoma.

This benign tumor almost exclusively involves the skull and facial bones; the frontal sinus is the most common location. Males are affected more often than females, the lesion can occur at any age. Although osteoma is predominantly a solitary lesion, multiple osteomas can occur in association with intestinal polyposis and soft tissue tumors. The tumor of normal dense and mature bone originates from the periosteum. There is little evidence of osteoblastic activity.

2. Osteoid osteoma is common in young persons, mostly males. Macroscopically, an osteoid osteoma appears as a small round or oval mass containing a central red-brown, friable area. Microscopically, the tumor appears as a maze of irregular bone trabeculae, fibrous tissue, and vessels. The center of the tumor is rich in osteoblasts, calcification, and multinucleate giant cells.
3. Benign osteoblastoma predominantly affects the vertebrae and long bones of young males in the first three decades of life. Macroscopically, the lesions vary in size from a few to several centimeters. Microscopically, osteoblasts proliferate and osteoid production increases. Osteoclasts and multinucleate giant cells may be very numerous, especially in areas of blood extravasation.

Malignant

1. Osteosarcoma (osteogenic sarcoma) from osteogenic tissue rich in atypical cells of osteoblastic type with a lot of mitoses, the bone is primitive. 2 types of osteosarcoma are known: a) osteoblastic type (bone formation), b) osteolytic type (bone destruction).

Osteosarcoma is a highly malignant bone tumor characterized by the production of osteoid and bone. Most osteosarcomas arise in the metaphyseal end of long bones (predominantly the femur, humerus, and tibia), but they can involve any bone, including the small bones of the hands, feet and face. Osteosarcoma is the most common primary malignant tumor of bone (next to multiple myeloma), accounting for approximately 16% of all bone malignancies. The disease predominantly affects young males between age 10 and 20.

Macroscopical appearance. The tumor appears as a large necrotic and hemorrhagic mass. The lesion usually ends in the epiphyseal cartilage and rarely extends into the nearby joint space.

Microscopic appearance. Three types of osteosarcomas have been differentiated according to their predominant histologic patterns: osteoblastic, fibroblastic and chondroblastic. The hallmark of the tumor is the presence of a malignant stroma that contains osteoid and bone. The stroma shows bizarre pleomorphic cells, with hyperchromatic, irregular nuclei and abundant mitoses. Multinucleate giant cells are seen most often near zones of necrosis and calcification. Malignant cartilage may be present in small foci or as a large proportion of the tumor.

2. Giant cell tumor of bone (osteoclastoma) is an uncommon malignant tumor characterized by multinucleate giant cells. It occurs predominantly in women over age 19 and peaks in the third decade of life. The lesion almost always is localized in the distal portion of the long bones (femur or humerus), and 50% of these tumors occur in the area of the knee. Occasionally, the tumor involves the skull, pelvis, or small bones of the hands and feet.

The tumor is believed to originate from the mesenchymal cells of connective tissue.

Macroscopically, the tumor characteristically appears as multiple hemorrhagic cystic cavities that destroy the adjacent bone and are enclosed by a thin shell of new bone formation.

Microscopically, a vascularized stroma composed of spindle cells that contain multinucleate giant cells intermixes with areas of hemorrhage, inflammation, and hemosiderin deposits. Mitoses are present.

Cartilage tumors

Benign

1. Chondroma derives from hyaline cartilage in the feet, spine, breastbone, pelvis. If tumor is located in the peripheral area of the bone it is termed exchondroma, if in the center area of the bone, enchondroma.

Ollier's disease (enchondromatosis) is a rare, nonhereditary disorder in which multiple chondromas are present in the metaphysis and diaphysis of various bones.

Maffucci's syndrome is a congenital disease characterized by dyschondroplasia and multiple hemangiomas in the skin and viscera.

This neoplasm is thought to originate from heterotopic cartilaginous cell; nests in the medullary cavities of bones. Macroscopically, the lesion appears as a confluent mass of bluish hyaline cartilage with a lobular configuration. Microscopically, the cartilage appears moderately cellular, with occasional binucleate cells. Mitoses are absent.

2. Osteochondroma is the most common benign tumor of bone affecting patients under age 21. The lesions may be single or multiple and predominantly involve the metaphysis of long bones. Macroscopically, the tumor may range in size from 1 to several centimeters and appears as a stalked protuberance, with a lobulated surface jutting from the affected bone. The periosteum of the adjacent bone covers the lesion. Microscopically, the cartilaginous cells appear lined up, mimicking the orientation of cartilaginous cells in a normal epiphysis. No mitoses are present.

3. Benign chondroblastoma consists of chondro-blasts, interstitial substance, marked osteoclast reaction. Chondroblastoma is a rare cartilaginous tumor that almost always involves the epiphyseal portion of the long bones. The tumor predominantly affects males in the second decade of life. Macroscopically, the tumor is round or oval in shape, with areas of cystic degeneration and hemorrhage. Microscopically, proliferation of chondroblasts is intermixed with varying amounts of fibrous stroma and chondroid material. Multinucleate giant cells and calcifications are present. Mitoses are virtually absent.

4. Chondromyxoid fibroma is most commonly located in the metaphysis of long bones but occasionally can involve the epiphysis. It primarily affects males in the first and second decades of life. Macroscopically, the tumor is a well-circumscribed, solid mass with a cartilaginous appearance. The cortex of the bone is expanded by the tumor, which is limited by the periosteum. Microscopically, a variety of fibrous, myxomatous, and chondroid elements are seen together with multinucleate giant cells and macrophages that contain hemosiderin. When the tumor forms lobules, a condensation of nuclei occurs beneath the rim of the compressed adjacent tissue.

Malignant

Chondrosarcoma is a malignant cartilaginous tumor. The most common locations are the spine, pelvic bones, and upper ends of the femur and humerus. The tumor may arise de novo (primary chondrosarcoma) or originate from a preexisting benign cartilaginous lesion (secondary chondrosarcoma). Chondrosarcomas comprise between 7% and 15% of all bone neoplasms. The tumor occurs in patients between age 30 and 60 and in men three times more often than in women.

Macroscopically, a chondrosarcoma appears as a lobulated white or gray mass that contains mucoid material and foci of calcification.

Microscopically, there are islands of immature or poorly developed cartilage in which anaplastic cells with two or more nuclei are present within the lacunar space.

The neoplasm is slow growing and can remain locally aggressive for years, with a high tendency to recur and implant in soft tissues. Hematogenous dissemination to the lungs, liver, and kidneys takes place over the years, with eventual death of the patient. The 10-year survival rate ranges from 50% to 60%.

TUMORS OF MELANIN-PRODUCING TISSUE

Melanin-producing cells (melanocytes) are of neurogeneous origin. They may become the origin of tumor-like formations (nevi) and melanomas.

Nevi are benign tumors of skin consisting of melanocytes of epidermis and derma. Neurogeneous origin of melanocytes is generally recognized. Nevi are defects of development of neuroectodermal pigment elements. They look like brown spots of different size, and may be either flat or elevated over the surface or be wartlike. Sometimes their size is enormous (giant pigmented nevus).

According to the WHO classification (1974), there are the following types of nevi: 1) junction nevus, 2) compound nevus, 3) intradermal, 4) epithelioid nevus (intracellular), 5) balloon-cell nevus, 6) halo-nevus, 7) giant pigmented nevus, 8) involution nevus (fibrous papule of the nose), 9) blue nevus, 10) cellular blue nevus.

Junction nevus. Nests of nevus cells are found on the border of epidermis and dermis. The nests are round or oval. Their cytoplasm is homogeneous, slightly granular. The nevus cells are localized in the area of reticular layer apices.

Compound nevus. Together with the nevus cells located on the border of dermis and epidermis, there are nests of nevus cells in derma itself.

Intradermal nevus. Nevus cells are located only in derma. Some of them can be found on the border between derma and epidermis. They resemble nests. The nevus cells look like compact mass. The cells in mature nevi may be polynuclear. Macroscopically they have papillomatous appearance and may contain hairs.

Epithelioid nevus can often appear on the face, especially in children. It looks like flat or ball-like node. The surface of the skin is smooth, sometimes papillomatous changes are observed. Microscopically it looks like compound nevus with borderline changes.

Sometimes marked acanthosis is present. The amount of melanin is small, it may also be absent. The cells have light basophilic cytoplasm and hyperchromic nuclei. Epithelioid cells with large foamy light cytoplasm may be present. Mitoses are not numerous. Uni- or polynuclear cells resemble Touton's cells. There are a lot of vessels.

Blue nevus. Macroscopically this looks like bluish or bluish-brown or bluish-gray spot, its shape is round or oval, it does not elevate over the surface of the skin. Microscopic examination reveals stretched melanocytes.

Melanoma. In the case of malignant melanoma, at the age of 20, only one person per 300 000 (0.3 per 100 000) has the cancer, and at the age of 80 about 30 per 300 000 (10 per 100 000) have it. The numbers of skin cancers rise with age because the main cause of all types of skin cancers is sunlight exposure. Sunlight contains ultraviolet light (UV), and this is what does the harm, particularly to the skin of babies and young children. The numbers of skin cancers vary from country to country. In tropical countries with large white populations, the numbers are proportional to the amount of sunlight. Australia, South Africa and the Southern American states all have a very high incidence of skin cancer in their white populations. Black people are better protected by their skin colouring.

Melanoma is one of the most malignant tumors, it spreads through the lymphatic and hematogenic routs. 70% of melanomas develop on the skin of the face, body and extremities.

Two kinds of melanoma are known.

1. Melanoma against a background of pigmented Hutchinson's sport (freckles) or malignant lentigo.
2. Superficially disseminated melanoma (invasive melanoma, nodular melanoma). Melanomas may not contain pigments. In the tumor, there are a lot of mitoses, hemorrhages and necroses. At the tumor decomposition, a great amount of melanin and chromelanin enter the bloodstream, which is accompanied by melaninemia and melaninuria. The tumors are localized on the skin, pigment membrane of the eye, meninges, medullar layer of adrenal glands, in rare cases mucous membranes.

TUMORS OF THE NERVOUS SYSTEM AND BRAIN MEMBRANES

Tumors of nervous system are various. They develop from different elements of the nervous system:

- 1) central;
- 2) vegetative;
- 3) peripheral;
- 4) mesenchymal elements, which are also a part of this system.

The etiology and prognosis of brain tumors are poorly studied.

According to many authors, there are six etiological groups of tumor and tumor-like diseases of human and animal nervous system:

- 1) genetically dependent (hereditary);
- 2) con-genital;
- 3) radiation;
- 4) chemically-induced;
- 5) meta-bolic (including dyshormonal);
- 6) viral.

Recklinghausen's neurofibromatosis is an example of a human hereditary tumor. Some authors believe that neurodermal melanosis belongs to this group. Congenital tumors and tumor-like diseases are medulloblastoma and astrocytoma in children. Radiation tumors of brain were described in experimental animals as well as in the people who were administered intensive radiotherapy or exposed to high-dose ionizing radiation due to accidents (Hiroshima and Nagasaki). Brain tumors caused by exogenic administration of pure carcinogenic substances were observed in experimental animals. It is believed that some brain tumors occur as a result of disturbed metabolism, so-called hormone-depending tumors. Hormone-depending tumors are observed both in people and animals, e.g. arachnoidendothelioma. These tumors become active during pregnancy. In some cases, they disappear after delivery of a child. Virus-induced tumors are known only in animals. Thus, polyoma virus may cause hemorrhagic sarcomatosis of pia mater. Some adenoviruses may cause ependymoblastoma in hamsters. Some authors (L.I. Smirnov, A.P. Avtsin, B.S. Khominsky, A.N. Age-eva) introduced the idea about preblastoma (in particular focal proliferation with them).

According to the degree of maturity, brain tumors may be more or less mature (benign) or immature (malignant).

Special attention should be paid to the characteristic features of brain tumors.

1. The term «benign» is not suitable in this case as they are located in the brain and indeed are always malignant. Even slow growth affects vitally important centers and causes their dysfunction.

2. Neuroectodermal (neuroepithelial) tumors of brain originating from neuroectoderm derivatives are dysontogenetic, i.e. develop from the cells which are known as precursors of mature CNS elements. Therefore, it may be difficult to determine their histological type. More often their cellular composition corresponds to definite stages of development of neuronal and glial elements.

3. Brain tumors produce metastases within the skull, that is with the help of liquor.

4. Their microscopic appearance is characterized by prolonged fascicular structures, lying either in wave-like or curl-like manner.

Neurodermal tumors are subdivided into astrocyte, oligodendroglial, ependymal tumors and those of choroid epithelium, neuronal, poorly differentiated and embryonic.

Astrocyte tumors or gliomas are the most frequent brain tumors. They develop from astrocytes and can be found in all brain portions. The highest incidence is observed between the age 25—45. The diameter of the tumor is about 5—10 cm. They do not always have distinct boundaries with the surrounding tissue. It is homogeneous on incision. As a rule, considerable enlargement of the brain portions is observed. Astrocytoma is characterized by cyst formation (one or several). They contain colloid substance or yellowish fluid with large amount of protein.

There are three histological types of astrocytoma: 1) fibrillar, 2) protoplasmatic, 3) fibrillar-protoplasmatic.

Fibrillar tumor is rich in glial fibers looking like parallel bands, it contains small amount of astrocytes.

Protoplasmaticastroma consists of different in size cells with processes which resemble astrocytes, their processes form thick interlacing.

A *fibrillar-protoplasmatic tumor* is characterized by even location of astrocytes and glial cells.

Cerebellar astrocytoma and subependymal astrocytoma are separate subtypes.

A malignant type is astroblastoma characterized by rapid growth, polymorphism and necroses in the tumor. This tumor is rare, it disseminates through the liquor routs.

Oligodendroglial tumors. In the majority of cases these are benign. The highest incidence is observed at the age of 30—40. In rare cases, they occur in children. They are mainly localized in the large hemispheres of the brain, more seldom in the region of visual tuber and in the trunk. Very seldom, they develop in the area of cerebellum and spinal cord. Primary multiple oligodendrogliomas of meninges and visual nerves were also described.

Macroscopically, the tumor is pinkish-gray, resembles brain substance and is diagnosed by the enlargement of the brain portion. Its consistency may be paste-like, when calcifications are present it may be dense.

Microscopically it consists of homogeneous small cells with round nuclei and narrow outline of cytoplasm which is poorly colored. Sometimes it is characterized by the structure resembling honeycombs. The tumor is usually poor in vessels. Hyalinosis and calcification may also be observed.

The types of oligodendrogliomas are: 1) fusiform cell, 2) polymorphocellular.

A malignant type of the tumor is oligodendro-glioblastoma characterized by special cell location, marked polymorphism with giant cells. It is also characterized by numerous mitoses and necrosis foci. The metastases spread through the liquor routs, more often along the walls of the ventricles. Symmetrical location of the tumor nodes in the walls of the ventricles is typical.

Ependymal tumors and tumors of choroid epithelium. According to L.I. Smirnov, three types of ependymal tumors are distinguished.

Ependymoma (glioma connected with ventricular ependymoma) looks like intra- or extraventricular node. The foci of necrosis and cysts can be found in it. Clusters of uni- and bipolar cells around the vessels (so-called pseudorosettes) and cavities covered with epithelium (true rosettes) are typical. Most frequently they are located in caudal portions of rhomboid fossa. Ependymoma may go down the spinal canal (craniospinal tumors). Ependymoma is usually localized in the bed of the 4th ventricle and in the 3th ventricle. In the area of the spinal cord, they first grow intramedullary, then become extramedullary. Macroscopically they look like nodes of different size with tuberous (4th ventricle) or villous (lateral ventricle) surface. The color is pinkish-gray, the consistency is soft. Microscopic study reveals peri-vascular structures of radially located cells. Their processes form a fibrous ring between the body of the cell and the wall of the vessel and over the body of the cell. In the rest of the tumor tissue, the cells are located in mosaic manner. Single and multiple clefts and tubes bedded with cylindrical epithelium are common.

Ependymoblastoma is a malignant type of ependymoma. This is characterized by marked cellular polymorphism. It grows quickly, metastases spread through the liquor system.

Dedifferentiated ependymoma is a transitory form between the two types.

Choroid papilloma is a tumor from the epithelium of vascular plexus, looking like a villous node in the cavity of the brain ventricle. It consists of numerous villous structures of cubic or prismatic epithelial cells. It is mainly observed in young people. It is located within the brain ventricles. Heterotopic types are rare (horse's tail).

Macroscopic study demonstrates well-outlined nodes of various size. The surface of the tumor is small or large-villous, has cauliflower- or mulberry-like appearance. Its consistency is either dense or soft, the color is pinkish-gray.

Microscopically it consists of villi, their connective tissue stroma is covered with cubic or cylindrical epithelium. Hyalinosis can be frequently observed.

Choroid carcinoma is a malignant type of choroidpapilloma. It is made of anaplastic cells covering the vascular plexus. Papillary cancer is a rare tumor.

Neuronal tumors

Ganglioneuroma is a rare mature tumor. Most frequently it is localized in the bed of the 3th ventricle, rarer in the hemispheres of the brain. It usually occurs in children and juveniles. The tumor consists of mature ganglionic cells divided with the bands of glial stroma. Macroscopically ganglioneuroma looks like a limited node. In the medulla oblongata it is diffuse, in the cerebellum it looks like hyperplastic folds.

Cerebellum ganglioma is characterized by proliferation of large nervous elements of Purkinjer's cell type.

Ganglioneuroblastoma is a malignant analogue of ganglioneuroma (malignant gangliocytoma). This is an extremely rare tumor of CNS. It is characterized by cellular polymorphism and similar to malignant glioma.

Neuroblastoma is a rare highly malignant brain tumor. It occurs mainly in children. The tumor is formed from large cells with bubble-like nucleus. Mitoses are numerous. The cells grow like syncytium. There are a lot of vessels.

Poorly differentiated and embryonic tumors

Medulloblastoma and glioblastoma belong to this group. The latter occurs in children. Medulloblastoma is a tumor made by immature cells, medulloblasts, therefore it is highly malignant. The most frequent localization is vermis cerebelli. Macroscopically, it is pinkish-gray.

Microscopically medulloblastoma consists of homogeneous small cells with dark round or oval nucleus and poorly seen rim of cytoplasm. The cells are located close to each other. Rosette, so-called collar, structures are typical. Mitoses are numerous. Vessels are not numerous. Metastases spread through the liquor routes.

Glioblastoma is the second (after astrocytoma) in the incidence. It occurs at the age of 40—60. It is situated in the white substance of the brain. This tumor is mainly located in the large hemispheres of the brain, sometimes in the trunk. It is characterized by rapid infiltrative growth without distinct boundaries. Glioblastoma usually produces regional metastases, those to the inner organs are rare (lungs). Macroscopically it is motley-colored due to necroses and hemorrhages. Microscopically the tumor is characterized by marked polymorphism. The cells are located disorderly (cellular chaos), their size and shape are various, from small lymphocyte-like to giant poly-nuclear. Necroses, hemorrhages and vascular growths are typical. Mitoses and centers of atypical division are frequent. (Synonyms: multiform glioblastoma, glioblastoma, spongioblastoma).

Meningovascular tumors

These tumors appear from the meninges. The most frequent is meningioma and its malignant variant meningeal sarcoma.

Arachnoidendothelioma (meningioma) is the most frequent type of meningovascular tumors. They mainly occur in adults over 30, while in children, they are rare. They are characterized by slow expansive growth. Arachnoidendothelioma is usually localized in: 1) longitudinal sinus and Pacchionian bodies, 2) convex, 3) falxiform process, 4) olfactory region, 5) wings and body of main bone, 6) tubercle of the saddle, 7) the region of semilunar node of trigeminal nerve, 8) tentorium cerebelli, 9) vascular plexi, 10) meninges of spinal cord.

Macroscopically, arachnoidendothelioma looks like well-limited solitary (in rare cases, multiple) nodes, their consistency is dense, elastic. The tumor is on incision they are grayish-pink with light bands.

Microscopically it is characterized by large endothelium like cells. The cells usually form groups (plate-like, curl-like, band-like), so-called endotheliomatous structures. In these tumors, there are secondary changes (calcifications, psammoma bodies, cysts). It is also termed psammoma. Types of arachnoidendotheliomas: 1) endotheliomatous; 2) fibrous arachnoidendothelioma with plenty of connective tissue fibers; 3) meningotheliomatous characterized by microcirculatory structures; 4) alveolar; 5) xanthomatous.

Malignant type of the tumor is meningeal sarcoma. Histologically it resembles fibrosarcoma, polymorphocellular sarcoma, diffuse sarcomatosis of the meninges.

Thus, morphogenetic variety of CNS tumors, difficult diagnosis and differential diagnosis as well as their localization allow to include them into a separate group. Special attention should be paid to development of secondary signs which appear due to the influence on the craniobasal and distal regions of the brain. Secondary syndromes are dislocation syndromes which are dangerous for the life of the patient; entrance of the temporal lobe to the tentorial foramen with strangulation of the midbrain; vasomotor vascular crises, heart failure; wedging of cerebellum tonsil to the great foramen; regional foci of circulation disturbance (infarcts and hemorrhages); epileptiform attacks. Only correct diagnosis helps to determine the tactics of treatment for such patients.

Tumors of vegetative nervous system

Tumors of vegetative nervous system originate from ganglionic cells of different degree

of maturity (sympathogonias, sympathoblasts, ganglioneurocytes) in sympathetic ganglia as well as from the cells of nonchromophilic paraganglia (glomes) genetically connected with sympathetic nervous system. Such benign tumors as ganglioneuroma, paraganglioma (glome tumor, chemodentoma) belong to this group.

Ganglioneuromas are localized in the medullar substance of the adrenal gland, sympathetic trunks, cerebrospinal nerves. It usually develops in young

patients. The tumor differs from normal ganglia as it has the signs of atypism (polynuclear cells, tigrolysis, nuclear decentralization).

Schwann's glia is represented by satellite cells. The tumor does not produce metastases.

Malignant ganglioneuroblastoma is a combination of neuroblastoma and ganglioneuroma. The tumor develops intrauterinely or during the first years of life. It may be localized in any region of vegetative nervous system, small intramural ganglia of the inner organs, medullar layer of adrenal glands and sympathetic trunks. Sometimes it matures and turns into ganglioneuroma.

Nonchromophilic paraganglioma is a benign variant. It resembles the tumors of APUD system (APUDomas). It can produce ACTH and serotonin. The tumor is localized in the middle ear, retroperitoneally. It may be large, its histological structure is alveolar and trabecular with large number of sinusoid vessels.

Malignant variant is paraganglioma. This is characterized by cellular polymorphism, infiltrating growth, lymphogenic metastases. Thus, the tumors of peripheral ganglia correspond to different stages of their embryonic structure. The least mature is neuroblastoma, the most mature is ganglioneuroma. Ganglioneuroblastoma occupies an intermediate place.

Tumors of peripheral nervous system

Tumors of peripheral nervous system originate from the nerve membranes. Neurilemma (Schwannoma), neurofibroma, neurofibromatosis (Recklinghausen's disease) are benign ones.

Schwannoma is formed of spindle-like cells with rod-shaped nuclei. The cells and fibers form rhythmical structures. Neurofibroma is a tumor connected with the nerve membrane. It consists of connective tissue with nervous cells, bodies and fibers.

Neurofibromatosis is a systemic disorder characterized by development of multiple neurofibromas associated with different development defects. This may be peripheral and central.

Malignant neurilemma is neurogenic sarcoma. Polymorphocellular atypism, polynuclear symplasts, garden-like structure are characteristic.

Self-check materials:

1. An epidemiologic study is performed to determine risk factors for development of malignant neoplasms. A statistical analysis of pre-existing medical conditions is done. Some pre-existing conditions are observed to precede development of malignant neoplasms, while others do not. Which of the following conditions is most likely to be statistically unrelated to subsequent malignancy?

- A. Uterine leiomyomas *
- B. Endometrial atypical hyperplasia
- C. Chronic alcoholism with hepatic cirrhosis
- D. Cervical squamous dysplasia
- E. Chronic ulcerative colitis

2. A histological examination of a neoplasm originating from the gastrocnemius muscle revealed some cells which resembled embryonal muscles without any signs of cellular atypism. What is your diagnosis?

- A. Rhabdomyoma*
- B. Leiomyoma
- C. Fibromyoma
- D. Hibernoma
- E. Rhabdomyosarcoma

3. In a male patient, a visual examination of the skin of his back revealed some spherical tumour, 2 cm in diameter, which was thick in consistency and had clear borders with the surrounding tissues. Microscopically, the tumour consisted of some chaotically interlaced bundles of collagenous fibres and a small number of connective tissue cells. Name the tumour.

- A. Leiomyoma
- B. Fibroma*
- C. Haemangioma
- D. Melanoma
- E. Lipoma

4. A 45-year-old male underwent surgical removal of a tumour, 4 x 3 cm in size, from the lateral ventricle of his brain; the tumour surface had small papillae, and it was connected with a vascular plexus. Microscopically, the tumour consisted of villus-like vegetations covered with epithelial cells of the cubical and columnar shape and the monomorphous kind. Which of the tumours listed below was the most probable?

- A. Ependymoma
- B. Ependymoblastoma
- C. Choriocarcinoma
- D. Glioblastoma
- E. Choriopapilloma*

5. A 40-year-old male patient underwent removal of a tumour, 2 cm in diameter, which was localized in the region of the cerebellopontine angle of the brain stem and tended to grow into the auditory meatus. Histologically, the tumour consisted of spindle cells with rod-shaped nuclei; the tumour cells and fibres formed rhythmic structures. Name the kind of the tumour.

- A. Medulloblastoma
- B. Meningioma
- C. Schwannoma*
- D. Oligodendroglioma
- E. Astrocytoma

TOPIC XV:Haemopoetic and lymph tissue origin tumors.

1.Actuality ofthe problem.Hemoblastoses are pathological conditions, which are associated with disturbances of structure and function of lymphatic system. Research of the mechanisms, morphology of pathological processes in lymphatic system is important task in practical medicine because it may help to diagnose and treat the different diseases. Anemias, thrombocytopenias, thrombocytopathies and coagulopathies are pathological conditions, which are associated with disturbances of structure and function of blood system. Research of the mechanisms, morphology of pathological processes in blood system is important task in practical medicine because it may help to diagnose and treat the different diseases.

2. Aim of studies andcompetence.To learn the morphological features of injury of lymphatic system; to explain the causes and mechanisms of their development; to estimate outcomes and determine significance for organism. To learn the morphological features of injury of the blood system; to explain the causes and mechanisms of their development; to estimate outcomes and determine significance for organism; to explain principles of classification of nosological forms of diseases.

Tasks of the studies:

- Explain the role of blood and lymphatic systems in organism.
- Explain the mechanisms of clinical manifestations, complications, causes of death.
- Learn the morphology and functional manifestations of different forms of leukemia, lymphogranulomatosis (Hodgkin's disease).
- Learn the morphology and functional manifestations of different forms of anemias.

Competence.

Integral:

It's ability to decide standard and complex routine and practical problems in process of teaching. The competence provide for research conducting as well as innovations realization and it's characteristic is complexity and definiteness of terms and requirements.

General:

- Ability to use knowledge's on pathomorphology in concrete situations
- Knowledge and understanding of pathomorphology
- Ability to choice of communication; ability to team-work; skills of interpersonal interaction
- Ability to communicate in native language both verbally and in writing; ability to communicate in a second language
- Skills in using information and communication technologies
- Ability to abstract thinking, analysis and synthesis, the ability to learn and be modern-trained
- Ability to assess and ensure the quality of work performed
- Certainty and perseverance in the set tasks and responsibilities

Special (professional, subject):

- Ability to evaluate the results of autopsy, biopsy and sectional material studies.
- Ability to analyze morphological manifestations of diseases.
- Ability to analyze the structural basis for the development of diseases and their clinical manifestations, the structural bases of recovery, complications and consequences.
- Ability to assimilate pathomorphological research methods: autopsy, biopsy.

3. Basic knowledge'sandskills you need to learn the topic (interdisciplinary integration)

Name of previous discipline	Receivedknowledge's
Normal anatomy	1. To describe normal morphological structureof hematopoieticorgans. 2. To draw their normal structure.
Histology, cytology and embryology	1. Be able to use knowledge's about

	histological structure of hematopoietic organs. 2. Give characteristic of morphological and functional peculiarities of different kinds of blood cells.
Physiology and pathophysiology	1. Be able to use knowledge's about peculiarity of physiological restore stroma of blood cells . 2. To use knowledge's about regeneration disturbance of blood cells

4. Tasks for self-studying during practical class prepare.

4.1. List of basic terms, characteristics, which a student must take over at practical class:

Anemia	is a symptom-complex which is characterized by changes in the number of erythrocytes and reduction of hemoglobin amount in a unit of blood volume.
Acute anemia	is massive hemorrhage of the vessels of the stomach and intestines in ulcer of the stomach and duodenum, from the ulcers in typhoid fever, in ectopic pregnancy, pulmonary hemorrhage in tuberculosis, rupture of aortic aneurysm.
Anemias due to increased destruction of blood	This group includes the conditions which develop when hemolysis prevails over hemopoiesis.
Sickle-cell anemia and thalassemia	are hemoglobinopathies (conditions due to abnormal hemoglobin in the erythrocytes).
Thalassemia (target cell anemia, Cooley's anemia)	is characterized by: progressive anemia with erythroblastemia, enlargement of the spleen and liver,) increased hemolysis, osteoporosis causing changes in the facial bones.
Leukemias	are malignant neoplasms of the hematopoietic stem cells characterized by diffuse replacement of the bone marrow by neoplastic cells.
Lymphomas	are malignant neoplasms characterized by the proliferation of cells native to the lymphoid tissues, that is, lymphocytes, histiocytes, and their precursors and derivatives.
Lymphogranulomatosis (Hodgkin's disease)	is a chronic (in rare cases acute) disease, the growth of the tumor cells takes place mainly in the lymphatic nodes.

4.2 Theoretical questions for the practical class:

1. Leukemias are the primary tumors growth in bone marrow.
2. Determination, etiology, classification, general clinical-morphologic description of leukemias.
3. Cytogenetic and cytochemical methods of differentiation of cellular variants of leukemias.
4. Acute leukemia: types, stages in course of diseases, clinical-morphologic description, complications, medical pathomorphosis, causes of death.
5. Chronic leukemia: types, stages in course of diseases, clinical-morphologic description, complications, medical pathomorphosis, causes of death.
6. Common description, methods of diagnostics of tumors from plasma cells.
7. Multiple Myeloma: etiology, pathogenesis, morphological description, clinical manifestations, prognosis, causes of death.
8. What mechanism of clinical manifestations, complications and causes of death of leukemia, the signs of leukemia in children do you know?
9. Reactive conditions of lymphatic nodes (histiocytosis, angiofollicular hyperplasia of lymphatic nodes).
10. Hodgkin's disease: clinical stages, histological types, morphological description, diagnostic methods, clinical manifestations, prognosis, causes of death.

11. Non-Hodgkin's Lymphomas: common description, localization, prognosis, differentiation and classification.
12. Tumors from T- and B-lymphocytes: kinds, morphological description, immunophenotypic variants, clinical manifestations, prognosis, causes of death.
13. Anemia, definition, classification.
14. Call the clinical-morphological manifestations, diagnostics of anemia by blood loss, complications
15. Clinical-morphological manifestations, diagnostics of anemia caused by impaired red cells production, complications, and causes of death.
16. What are the clinical-morphological manifestations, diagnostics of anemia due to increased rate of destruction, complications, and causes of death?

4.3 Practical work students do at class:

Students must be able to learn macro- and micropreparations by use their diagnostic algorithms

Test algorithm for macropreparation diagnosis	Test algorithm for micropreparation diagnosis
<ol style="list-style-type: none"> 1. To indicate Latin name of a preparation. 2. To describe macroscopic features of an organ (size, color, consistence) 3. To indicate pathological process 4. To indicate possible outcomes of the pathological process 5. What disease does the pathological process correspond to 	<ol style="list-style-type: none"> 1. To indicate used staining method for the organ tissue. 2. To name both tissue and organ 3. To indicate changes in the tissue of the organ 4. To name the pathological process 5. To indicate the pathological process outcomes

Macropreparations:

1. **"The Spleen in lympholeukemia"**. Pay attention to size of the Spleen, color of cutting surface. Indicate normal size and weight of Spleen. *Name the cause of this enlargement.*
2. **"The Liver in undifferentiated leukemia"**. Pay attention to size of the Liver, color and architecture of cutting surface. *What microscopical changes in liver can be found out?*
3. **"Necrotic tonsillitis in leukemia"**. Pay attention to size, color, and cutting surface of Tonsils. *What type of leukemia can characterize these changes?*
4. **"Spleen in chronic myelocytic leukemia"**. Pay attention to increased size and weight of Spleen, thickened capsule, color of cutting surface. *Describe stages of the development of this leukemia.*
5. **"The Spleen, and the Lung in Hodgkin's disease"**. Describe size, color of cutting surface, and multiple whitish spots there. Explain origin of these spots. *Name the type of Hodgkin's disease with these changes.*

Micropreparations:

Slide 1. Liver in chronic lymphoid leukemia (ought to be drawn)

Leukemical infiltrates look like nests and are located in triads.

Slide 2. Lymph node in Hodgkin's disease (ought to be drawn)

Lymph node lost its usual structure and it was replaced with tissue consisting of polymorphonuclear cells. Pay attention to big reticulous cells, small lymphoid cells, endothelial cells, giant Reed-Sternberg cells and eosinophils. The growth of connective tissue takes place here and there.

Slide 3. The Bone marrow of the Thigh in myeloblastic leukemia (ought to be drawn)

The bone marrow looks like immature myeloid tissue. Here and there some adipose cells are kept.

Slide 4. The Liver in undifferentiated leukemia

Among hepatic lobules in triads the nesting proliferation of hemocytoblasts and other immature myeloid cells can be seen.

Slide 5. The Liver in chronic lympholeukemia (ought to be drawn)

Leukemic infiltrates are disposed locally predominantly in portal tracts. Lymphocytes are atypical with hyperchromatic nuclei.

Topic content:

DISEASES OF HEMOPOIETIC AND LYMPHORETICULAR TISSUES

Anemia literary means «without blood, blood-less». But indeed this term denotes a complicated symptom-complex which is characterized by changes in the number of erythrocytes and reduction of hemoglobin amount in a unit of blood volume.

In anemia, qualitative changes of erythrocytes (their size, shape and color) are noted in the peripheral blood. In some types of anemia nuclear forms of erythrocytes (erythroblasts, normoblasts, megaloblasts) appear in the blood. Immature erythrocytes (poly-chromatophils) can also be observed.

In anemias erythrocytes change their shape (anisocytosis), size (poikilocytosis), color (hyperchromia, hypochromia).

True anemia should be differentiated from hemodilution (hydremia), i.e. liquefaction of blood due to abundant amount of interstitial fluid (e.g. when edema becomes less).

Blood mass in anemia may be normal, increased or decreased. These conditions are called normovolemia, hypervolemia and hypovolemia, respectively.

It is known that erythrocytes and hemoglobin are necessary to transport oxygen to the tissues. Thus, decrease in the number of erythrocytes may cause oxygen deficiency in the tissues, i.e. hypoxia development. Not only the degree of anemia but also the rate of its development as well as the degree and quickness of the organism adaptation are important. Physicians often observe discrepancy between the severity of anemia and active condition of the patient, which can be explained by compensation mechanisms, providing physiological need of the tissues in oxygen. Only in cases of severe anemia or at high rate of adaptation, hypoxia may develop.

Numerous neurohumoral factors participate in compensation of anemic state. They stimulate blood and hemopoietic systems. Hypoxia causes appearance of incompletely oxygenated metabolic products. They affect central regulation of blood system as well as neuromuscular apparatus of the heart causing increase in the heart rate and acceleration of the blood flow. As a result, minute blood volume discharged by the left ventricle increases twice (up to 8 liters instead of 4). Besides, spasm of peripheral vessels develops in anemia and blood reserve from the tissue depot (mainly from subcutaneous tissue) enter the blood circulation.

Classification of anemias

Common mechanisms of anemias at different conditions allows to divide all significant clinical forms of anemia into several groups. The task of the physician is to find the main pathogenetic (and if possible, etiologic) factor and to administer proper treatment.

At present anemias are classified according to pathogenetic principle with the account of etiological and clinico-morphological forms.

According to modern classification there are 3 groups of anemias:

- 1) anemias caused by blood loss (posthemorrhagic),
- 2) anemias caused by disturbances of blood circulation (deficient),
- 3) anemias due to increased blood destruction (hemolytic). Each group is subdivided into several groups.

Posthemorrhagic anemias are caused by the blood loss. They are caused by traumas, pathological processes, accompanied by damage of the vessel or hemorrhage from the inner organs. Depending on the size of the injured vessel and the rate of the blood loss it may be acute or chronic.

Acute anemia

This is massive hemorrhage of the vessels of the stomach and intestines in ulcer of the stomach and duodenum, from the ulcers in typhoid fever, in ectopic pregnancy, pulmonary hemorrhage in tuberculosis, rupture of aortic aneurysm.

The larger is the vessel, the closer it is to the heart, the more dangerous is the hemorrhage. In rupture of the aortic arch, loss of less than 1 liter of blood causes death due to sudden drop of arterial pressure. The death occurs before exsanguination of the organism, therefore anemia in the organs is not marked. In hemorrhages from small vessels, death occurs when half of the blood is lost. The patients develop the signs of hemorrhage: pale skin, oligohemia of organs, collapse signs. If the hemorrhage is not fatal, the blood loss is compensated due to regeneration processes, taking place in the tissue of the bone marrow. The bone marrow of the flat bones proliferates and becomes bright. The yellow bone marrow is replaced by red (hemopoietic) one. In repeated hemorrhages, extra-medullary hemorrhage may occur in the spleen, liver, lymphatic nodes and other organs. The prognosis of posthemorrhagic anemia depends on the rate of blood flow. Rapid blood loss of 1/4 of the total blood volume may cause shock, loss of 1/2 of the total blood volume is incompatible with the life. Loss of 3/4 of the total circulating blood does not cause death if it occurs slowly during several days. In healthy persons, even at considerable blood loss, its composition restores in 4—5 weeks, in weak ones it restores for a longer period of time.

Chronic posthemorrhagic anemia

It frequently develops after long, repeated slow blood loss, in the majority of cases at hemorrhages from gastrointestinal tract (ulcer, cancer, hemorrhoids), uterine bleedings, in hemophilia, hemorrhagic diathesis, in ankylospondylosis.

Clinical sign of anemia is pale skin and visceral organs. In some cases, the source of hemorrhage is inconsiderable, it is very difficult to reveal it. Severe iron-deficient anemia develops.

Anemias caused by disturbances of hemopoiesis occur in those cases when the organism amount of a definite substance (e.g. iron, vitamin B12) is insufficient. Therefore, these anemias are called deficiency anemias. Disturbances of hemopoiesis can occur in helminthic invasions, toxic effect on the organism, in hypoplasia of the bone marrow.

There are different types of iron deficiency anemia, their etiology is various, but the main pathogenetic factor is iron deficiency in the organism (sideropenia, hyposiderosis). All types of iron deficiency anemia may be divided into the following clinico-anatomical forms:

1. Iron deficiency anemia of early age.
2. Early and late chlorosis.
3. Symptomatic chloranemia which develops at different pathological conditions of gastrointestinal tract (achylic, agastric, anenteral etc.) in infections (tuberculosis).
4. Hypochromic anemia of pregnancy.
5. Posthemorrhagic anemia which indeed is iron deficiency anemia.
6. Chlorosis (called so because of pale greenish color of skin in this disease).

There are two types of chlorosis: early and late. Early chlorosis occurs in women at the age of 15—20, that is at the period of sexual maturation. Late chlorosis is observed in women aged 35—45, sometimes before climax.

Iron deficiency anemias are iron-insaturated (sideroachrestic) anemias in which erythrocytes contain small amount of iron due to the fact that iron is not used by the bone marrow for hemoglobin synthesis.

Anemias due to vitamin B12 deficiency (pernicious anemias). Pathogenetic mechanisms of B12 deficient anemia development are different, that is why there are different forms:

1. Pernicious anemia (Addison-Biermer) due to deficiency of gastromucoprotein in the gastric juice.
2. Pernicious anemia after stomach resection for cancer, polyposis.
3. Pernicious anemia in diseases of small intestine due to disturbed absorption of vitamin B12.
4. Helminthic pernicious anemia.
5. Pernicious anemia of pregnancy due to fetal growth and increased consumption of vitamin B12 and folic acid.
6. B12 achrestic anemia due to disturbances of B12 utilization in the bone marrow.

Classical form of B12 deficiency anemia is Addison-Biermer malignant or pernicious anemia first described by Addison in 1855.

Pathology of Addison-Biermer disease

Autopsy demonstrates pale skin and mucous membrane, poorly marked cadaveric spots, oligohemia of inner organs, at good nutrition there is fatty degeneration of myocardium (tiger's heart), kidneys and liver.

Hemosiderosis of liver, kidneys, lymphatic glands, spleen and bone marrow is observed. The alimentary organs have characteristic changes. Papillae of the tongue are atrophic, the tongue is smooth, looks as if varnished. Its tip and edges are inflamed (Hunter's glossitis). Similar changes are observed in the pharynx and esophagus. Atrophy is observed in the mucous membrane of the stomach and intestines (anadenia). The mucous membrane of the stomach is thin, smooth, without folds. Typical signs of pernicious anemia are crimson juicy bone marrow, not only in the flat but also in tubular bones where it looks like raspberry jelly. Foci of extramedullar hemopoiesis are seen (accumulations of erythroblasts and megaloblasts) in the spleen, liver, lymphatic nodes. The most characteristic are megaloblasts, which participate in normal erythropoiesis only at an early embryonic period, in the bone marrow and peripheral blood. Biological peculiarity of megaloblasts is loss of capability to turn into normal erythrocyte due to disturbed processes of hemoglobin formation. Megaloblastic way of blood formation is close to embryonic type. It suggests serious changes in erythropoiesis due to vitamin B12 insufficiency. Thus, increased hemo- and erythropoiesis take place, but the latter is not complete, erythrocytes are not of full value, they are destroyed by macrophages (erythrophagia) of the bone marrow, spleen, liver, lymphatic glands which results in hemosiderosis.

Hypoplastic and aplastic anemias

Hypoplastic or aplastic anemias are total or partial inhibition of hemopoietic processes. Any hypo- and aplastic anemia is accompanied by leuko- and thrombocytopenia. When speaking about anemia we only emphasize the main syndrome (anemic) which determines clinical manifestations.

There are congenital and developed anemias.

According to their course they are divided into acute, subacute, chronic hypo- and aplastic anemias.

The etiology is different. The factors causing it may be exogenic and endogenic.

Endogenic:

1. Endocrine (hypothyroidism, thymus tumors).

2. Genuine (Ehrlich's aplastic anemia).

3. Osteomyelosclerosis. Exogenic:

1. Radiation lesions (x-rays, radium radiation, atomic energy).

2. Chemical (benzene, cytostatic preparations, etc).

3. Toxicallergic:

a) medicinal (pyrimidin, barbiturates, sulfanilamides);

b) antibiotics (Chloromycetin).

4. Infectious.

Congenital hypo- and aplastic anemias include:

Family anemia. It develops in childhood and occurs against the background of clearly marked endocrine insufficiency (dwarfism, infantilism, undeveloped thumb phalanges, testis atrophy).

Pathology: Clearly marked oligemia of all organs, bone marrow aplasia, atrophy of testes, thyroid and pituitary glands. The etiology is unknown.

Ehrlich's aplastic anemia It is a rare condition, mainly occurring in the young people. It is characterized by progressive anemia, hemorrhages, necrotic phenomena and sepsis. The disease has either acute or subacute course.

The etiology is unknown.

Osteosclerotic anemia. There are two forms:

a) Marble disease which develops in childhood and is accompanied by obliteration of the bone marrow cavity. The bone looks like a solid mass resembling marble. The etiology and pathogenesis are unknown but is considered that the course is parathyroid gland dysfunction.

b) Osteomyelosclerosis is observed mainly in elderly people, it is chronic subleukemic myelosis. Anemia develops due to substitution of bone-marrow spaces by osseous and osteoid tissues, i.e. due to osteosclerosis.

Aplastic and hypoplastic anemias can occur at destruction of the bone marrow by cancer metastases.

Anemias due to increased destruction of blood (hemolysis)

This group includes the conditions which develop when hemolysis prevails over hemopoiesis. There are congenital (family) and developed types of the disease.

One forms are due to hereditary defects of erythrocytes (erythrocytopathy or hemoglobinopathy), the other occur in persons due to different extra-erythrocyte causes which cause hemolysis. Therefore, there are two groups of hemolytic anemias: erythrocyte and extra-erythrocyte. Erythrocyte (intracellular) are

characterized by extravascular hemolysis and splenomegaly (splenic hemolysis).

Extra-erythrocyte anemias develop due to intravascular hemolysis and are accompanied by hemoglobinuria (renal hemolysis).

Hemolytic anemias due to extravascular hemolysis are congenital, hereditary conditions.

Destruction of erythrocytes occurs mainly in macrophages of the spleen, in the bone marrow, liver and lymphatic nodes. Therefore, splenectomy is indicated in such patients. This group of anemias is characterized by three signs: jaundice, splenomegaly, anemia. It includes the following forms of the disease: congenital (family) spherical-cell anemia, sickle-cell anemia, thalassemia, or Cooley's anemia.

Spherical-cell anemia is characterized by congenital spherocytosis (erythrocytes are small, spherical, brightly colored, without light center, with decreased resistance. These abnormal erythrocytes are destroyed in cells of reticuloendothelial system (mainly in the spleen).

The first sign of the disease is jaundice, it is followed by splenomegaly and anemia.

Sickle-cell anemia and thalassemia are hemoglobinopathies (conditions due to abnormal hemoglobin in the erythrocytes).

The cause of sickle-cell anemia is congenital insufficiency of erythrocytes due to presence of S-hemoglobin (S-corresponds to sickle). The condition is characterized by presence of sickle-like erythrocytes revealed during crisis, they cause stasis, hemorrhages, infarctions. Siderofibrosis caused by hemosiderin accumulation develops due to increased decay of sickle-like erythrocytes in the spleen.

Thalassemia (target cell anemia, Cooley's anemia) was described in the USA in the emigrants from the Mediterranean basin. It occurs in children and is characterized by: 1) progressive anemia with erythroblastemia, 2) enlargement of the spleen and liver, 3) increased hemolysis, 4) osteoporosis causing changes in the facial bones.

Acute hemolytic anemia develops in poisoning with hemolytic poisons (those of snakes and mushrooms, phosphorus, etc.), in burns, sepsis, malaria, transfusion of incompatible blood, fetal erythroblastosis. The latter occurs due to rhesus incompatibility of the mother's and fetus's blood.

Fetal erythroblastosis is a reaction of the bone marrow to the blood decay caused by maternal anti-rhesus agglutinins. In fetus, there is jaundice, enlargement of liver, spleen and hemorrhagic diathesis. The blood is characterized by anemia with great amount of erythroblasts (up to 50%), leukocytosis.

There are 3 types of hemolytic disease of newborn: 1) edematous, 2) with jaundice, 3) without jaundice.

Favism is acute hemolytic anemia caused by eating beans (*Vicia fava*) or inhalation of their pollen. It may be observed in Italy. Hemosiderosis in favism is connected with congenital deficiency of enzymic system of erythrocytes with deficiency of glucoso-6-phosphate.

Recently, autoaggressive hemolytic anemia has been described. Under the influence of a number of medicines, bacteria, viruses, autoantibodies with specific agglutinating properties develop in the organism.

Hemolytic anemias are characterized by jaundice, hemoglobinuria, hemosiderosis.

LEUKEMIAS

Leukemias are malignant neoplasms of the hematopoietic stem cells characterized by diffuse replacement of the bone marrow by neoplastic cells.

Hemoblastoses (tumors of blood system) are divided into 2 groups:

1) leukemias — systemic tumors diseases of hemopoietic tissue;

2) lymphomas — regional tumorous diseases of hemopoietic and/or lymphatic tissue.

Etiology is not completely known. There is no doubt that leukemia is polyetiologic disease. It develops due to a number of mutagenic factors:

- viruses (retrovirus HTLV-1, HTLV-2, Epstein-Barr DNA virus);
- ionizing radiation;
- chemical substances (benzopyren, dibenz-antracen);
- hereditary factors (in chronic myeloid leukoses, reduction of autosome of the 22nd pair of leukoses cell chromosome is observed).

Thus, mutation theory of leukoses pathogenesis may be the most probable.

Classification

1. Leukemias.

1.1. Acute leukemias: 1) undifferentiated, 2) myeloblast, 3) lymphoblast, 4) plasmoblast, 5) monoblast, 6) erythromyeloblast; 7) megacaryo-blast.

1.2. Chronic leukoses.

a) of myelocyte origin: 1) chronic myeloid, 2) chronic erythromyelosis, 3) erythremia, 4) true polycythemia (Vaquez-Osler syndrome).

b) of lymphocyte origin: 1) chronic lympho-leukosis, 2) skin lymphomatosis (Sezary's disease), 2) para-proteinemic leukoses: a) myeloma, b) primary macroglobulinemia (Valdenstrem's disease), c) heavy chain disease (Franklin's disease).

c) of monocyte origin: 1) chronic monocyte leukoses, 2) histiocytosis.

2. Lymphomas — regional tumors: 1) lymphosarcoma: lymphocyte, prolymphocyte, lymphoblast, immunoblast, lymphoplasmocyte, African lymphoma (Burkitt's); 2) mycosis fungoides; 3) Sezary's disease; 4) reticulosarcoma; 5) lymphogranulomatosis (Hodg-kin's disease).

The above classification is based on histogenetic principles, that is the type of the proliferating cell clone is taken into account.

The division into chronic and acute leukemia is based on the presence of blasts (immature) or cytic (mature) cells. If blasts are revealed, acute leukemia is diagnosed, if mature cells are found, the disease is chronic. The type of acute and chronic leukemia is established on the basis of cytochemical peculiarities of tumor cells.

In addition to histogenetic classification, there is classification based on the number of leukoses cells in 1 microl of blood:

- 1) leukemic (tens and hundreds thousand leukosis cells per 1 microl);
- 2) subleukemic (not more that 15.000 — 25.000 per 1 microl);
- 3) leukopenic (leukocyte count is reduced but leukosis cells can be found);
- 4) aleukemic (leukosiscells in the blood are absent).

Acute and chronic leukemias are characterized by the following pathomorphological syndromes:

1. Pyoid bone marrow due to proliferation of the tumor cells (mature or immature, respectively) in the bone marrow with displacement of the red sprout. Macroscopically, bone marrow is grayish-whitish.
2. Leukoses infiltration of hemopoietic organs (bone marrow, spleen, lymphatic glands) at first, then of the other organs (mucous membranes, myocardium, kidneys, brain, etc., vessels).
3. The displacement of the red sprout of the bone marrow causes anemia.
4. Severe hemorrhagic syndrome in combination with anemia and destruction of the vascular walls with leukoses infiltration develop as a manifestation of thrombocytes formation in the bone marrow.
5. Necrotic tonsillitis, gingivitis develop due to leukoses infiltration of the oral mucosa and tonsils against the background of immunogenesis inhibition.
6. Secondary infection often accompanies the process, sepsis may develop.
7. Foci of extramedullar hemopoiesis develop in the liver, spleen, kidneys, lymphatic glands as compensatory adaptation reaction directed to restoration of the red sprout.

Distinctive features of acute and chronic leukaemias are:

1. Bone marrow and blood picture (In acute leukoses the blasts are observed, in chronic leukoses the mature cells are found).
2. Leukemic failure (hiatus leucemicus) characterizes acute leukoses. It is sharp increase of blast count and single mature elements while transitional forms are absent.
3. Sharp enlargement of the spleen, liver, kidneys and lymphatic glands characterizes chronic leukoses while in chronic leukoses it is less marked. The spleen can weigh 6—8 kg, the liver 5—6 kg.

Complications and causes of death: 1) hemorrhage to vital organs (brain); 2) ulcerative necrotic and septic complications (sepsis).

Paraproteinemic leukemia

The most important of this group is myelomic disease, first described by O. Rustitsky (1873) and Kahler (1887). The disease consists in growth of tumor lymphoplasmocytic cells (myeloma cells in the bone marrow and other organs). Bone marrow myelomatosis causes bone destruction. Flat bones (ribs and skull) are the most frequently involved, tubular bones (humerus and femur) are involved less frequently. Sinusal resorption of the bone results in osteolysis and osteoporosis. The bones become fragile. Hypercalcemia develops due to their destruction, it may be followed by development of calcific metastases. Myelomic-cell infiltration develops in the inner organs: spleen, lymphatic nodes, liver, kidneys, lungs, etc. A number of changes is connected with secretion of paraprotein by the tumor cells. These changes are amyloidosis, paraproteinemic nephrosis or myelomic nephropathy resulting in contracted kidney.

Depending on the character of myelomic cells, myelomas are divided into: 1) plasmocyte, 2) plasmoblast, 3) polymorphocellular, 4) small-cell.

Morphologically, depending on the character of myelomic infiltrations the following forms are distinguished: 1) diffuse, 2) diffuse nodular, 3) multiple nodular.

Causes of death: uremia, sepsis, necrotic changes, amyloidosis.

MALIGNANT LYMPHOMAS

Lymphomas are malignant neoplasms characterized by the proliferation of cells native to the lymphoid tissues, that is, lymphocytes, histiocytes, and their precursors and derivatives. The term «lymphoma» is something of a misnomer, since these disorders are lethal unless controlled or eradicated through therapy. There are no «benign» lymphomas. Within the broad group of malignant lymphomas, Hodgkin's disease (Hodgkin's lymphoma) is segregated from all other forms, which constitute the non-Hodgkin's lymphomas.

NON-HODGKIN'S LYMPHOMAS (NHL)

The usual presentation of NHL is as a localized or generalized lymphadenopathy. NHLs are divided into three prognostic groups, designated as low-grade, intermediate-grade, and high-grade, based on survival statistics.

Low-Grade Lymphomas

This category includes three tumors: small lymphocytic lymphoma; follicular, predominantly small cleaved cell lymphoma; and follicular, mixed (small cleaved and large cell) lymphoma.

Small Lymphocytic Lymphoma (SLL)

This pattern makes up approximately 4% of all NHLs and is the only low-grade lymphoma that does not have a follicular architecture.

Morphology. SLL consists of compact, small, apparently unstimulated lymphocytes with dark-staining round nuclei, scanty cytoplasm, and little variation in size. Mitotic figures are rare, and there is little or no cytologic atypia. Involvement of bone marrow to present in almost all cases, and in about 60% of patients the neoplastic cells spill over into blood, evoking a chronic lymphocytic leukemia-like picture.

Follicular Lymphomas

There are two cytologic subgroups of low-grade follicular lymphomas: follicular small cleaved cell and follicular mixed cell type.

Morphology. The neoplastic B cells tend to recapitulate normal lymphoid follicles, and hence they resemble the cells seen within normal germinal centers. Small cleaved cells are slightly larger than normal lymphocytes, with scanty cytoplasm. The most distinctive feature that differentiates the tumor cells from small normal lymphocytes is their irregular «cleaved» nuclear contour, characterized by prominent clefts, indentations, and linear infoldings. The nuclear chromatin is coarse and condensed, and nucleoli are indistinct. Mitoses are infrequent. Follicular, mixed lymphomas constitute a small proportion of all follicular center cell tumors.

Intermediate-Grade Lymphomas

There are four tumors in this category — one with a follicular architecture and the other three with a diffuse pattern. The diffuse intermediate-grade lymphomas are distinguished on the basis of their cellular composition.

Follicular, Predominantly Large Cell Lymphoma Morphology. In contrast to the low-grade follicular lymphomas, the majority of the neoplastic cells are large, with cleaved or noncleaved nuclei. Mitotic figures are also more numerous. **Diffuse Small Cleaved Cell Lymphoma** This type is composed of small cleaved cells that are morphologically and phenotypically similar to those that are present in the follicular small cleaved cell lymphoma.

Diffuse Mixed Small and Large Cell Lymphoma Morphology. These tumors contain a mixture of small cleaved cells already described and large cells that may be cleaved or noncleaved. The nuclei of large cleaved cells are irregular in contour, indented, and larger than nuclei of normal histiocytes or endothelial cells (often used as a reference in evaluating size). The nuclear chromatin is slightly more dispersed than in a normal small lymphocyte, and nucleoli are inconspicuous. The cytoplasm is scant and pale. Large noncleaved cells are up to four times the size of normal lymphocytes, with a round or oval nucleus and one to two prominent nucleoli. The nuclear chromatin is vesicular, and mitoses are prominent. The amount of cytoplasm is greater than in large cleaved cells and stains pale blue.

Diffuse Large Cell Lymphoma

This variant is the most common of intermediate-grade lymphomas. Morphologically, these tumors contain predominantly large cells of the cleaved and noncleaved types described above. It should be noted that the distinction between diffuse large cell lymphomas and the diffuse mixed variant is difficult and somewhat arbitrary.

High-Grade Lymphomas

There are 3 types of lymphomas in this category: 1) large cell immunoblastic lymphomas; 2) lymphoblastic lymphoma, a tumor that occurs in adolescents and is associated with a characteristic clinical presentation; 3) small noncleaved lymphomas, which include Burkitt's lymphoma and related B-cell neoplasms.

Large Cell Immunoblastic Lymphoma Morphology. In some cases the tumor cells have plasmacytoid features. These cells are four to five times larger than small lymphocytes and have a round or oval large nucleus that appears vesicular owing to margination of chromatin at the

nuclear membrane. One or two centrally placed prominent nucleoli are usually seen. In other cases, the tumor cells may contain large multilobated (polymorphous) nuclei, or the nucleus may be round with a clear cytoplasm. Although features such as plasmacytoid appearance and clear cytoplasm or polymorphous nucleus are suggestive of B- and T-immunoblasts respectively, these distinctions are not absolute.

Lymphoblastic Lymphoma

Morphology. The tumors are fairly uniform in size, with scanty cytoplasm and nuclei that are somewhat larger than those of small lymphocytes. The nuclear chromatin is delicate and finely stippled, and nucleoli are either absent or inconspicuous. In many, but not all, cases the nuclear membrane shows deep subdivision. Imparting a convoluted (lobulated) appearance. In keeping with its aggressive growth, the tumor shows a high rate of mitosis, and as with other tumors having a high mitotic rate (e.g., Burkitt's lymphomas), a «starry sky» pattern is produced by the interspersed benign macrophages.

Small Noncleaved Cell Lymphoma

Morphology. These tumors consist of a sea of strikingly monotonous cells, with round or oval nuclei containing two to five prominent nucleoli. The nuclear size approximates that of benign macrophages within the tumor. There is a moderate amount of faintly basophilic cytoplasm, which also is intensely pyroninophilic and often contains small, lipid-filled vacuoles (better appreciated on stained imprints of the tumor). A high mitotic index is very characteristic, as is cell death, accounting for the presence of numerous tissue macrophages with ingested nuclear debris. Since these benign macrophages, which are diffusely distributed among the tumor cells, are often surrounded by a clear space, they create a «starry sky» pattern.

HODGKIN'S DISEASE

Lymphogranulomatosis (Hodgkin's disease) is a chronic (in rare cases acute) disease, the growth of the tumor cells takes place mainly in the lymphatic nodes. Morphologically, local and generalized lymphogranulomatosis are distinguished. In isolated lymphogranulomatosis, one group of lymphatic nodes is involved (cervical, mediastinal, retroperitoneal).

In generalized form, the growth of the tumor cells occurs not only in the primary focus but also far from it. As a rule the spleen is involved. Its pulp is red with numerous white-yellow foci of necrosis and sclerosis, so called «diffuse waxy spleen». The process becomes generalized due to metastases from the primary node.

Clinico-morphological classification: variant 1: with prevail of lymphoid tissue (lymphohistiocyte); variant 2: nodular sclerosis variant; 3: mixed-cell variant; 4: with inhibition of lymphoid tissue.

Microscopic study of tumor nodes demonstrates proliferation of lymphocytes, histiocytes, reticulocytes, eosinophils, plasmoblasts and plasmocytes, neutrophils. These cells form accumulations of the nodes with necrotic and sclerotic changes. Atypical cells (small Hodgkin's cells, mononuclear giant cells or large Hodgkin's cells) are revealed. The causes of death and complications: 1. Renal amyloidosis followed by contracted kidney and uremia. 2. Intoxication. 3. Septic complications.

Self-check materials:

1. A death of a 7-year-old boy resulted from acute posthaemorrhagic anaemia caused by a profuse bleeding from the gastrointestinal tract. A postmortem examination revealed: macroscopically - an anaemia of the internal organs, an enlargement of lymph nodes in different groups, thymomegaly, a moderately manifested hepatosplenomegaly, a bright red bone marrow; microscopically - a hypercellular bone marrow with some monomorphous infiltrate of blast cells, diffuse-focal tumour infiltrates in the liver, spleen, lymph nodes, meninges and substance of the brain. Make a diagnosis for this form of leukaemia.

- A. Acute lymphoblastic*
- B. Acute myeloblastic
- C. Acute stem cell

- D. Acute monoblastic
 - E. Acute plasmablastic
2. A 70-year-old male patient with an expressed hepatosplenomegaly and cachexia underwent a diagnostic puncture biopsy of his liver. A histological examination revealed that along the portal tracts there were numerous infiltrates of monomorphous round cells verified as prolymphocytes and B-lymphocytes. What disease are the above changes characteristic of ?
- A. Lymphosarcoma
 - B. Acute lymphoplasmic leukaemia
 - C. Lymphogranulomatosis
 - D. Chronic lymphatic leukaemia*
 - E. Casari's disease
3. A male patient, who worked for a long period of time with benzene, develops progressing anaemia and the haemorrhagic syndrome. A biopsy of his breastbone reveals prevalence of a fatty tissue, and there are some small islets of haemopoiesis with solitary cells of myelopoiesis. What is your diagnosis?
- A. Chronic myeloleukaemia
 - B. Pernicious anaemia
 - C. Haemolytic anaemia
 - D. Hypoplastic anaemia*
 - E. Aplastic anaemia
4. A histological examination of an enlarged lymph node revealed a proliferation of lymphocytes, histiocytes, reticular cells, acidophilic leukocytes, small and large Hodgkin's cells, multinuclear Reed-Sternberg cells. Which of the diseases Listed below do the described morphological data correspond to?
- A. Lymphosarcoma
 - B. Metastasis of carcinoma
 - C. Chronic leukaemia
 - D. Acute leukaemia
 - E. Lymphogranulomatosis*
5. A patient with acute myeloblast leukemia has developed liver and spleen enlargement, anemia, myeloblasts in peripheral blood. What principal morphological sign allows differing myeloblast leukemia from chronic one?
- A. Blast cells in peripheral blood *
 - B. Thrombocytopenia
 - C. Pancytopenia
 - D. Anemia
 - E. Leukemic collapse

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