Ministry of Health of the Republic of Belarus
Educational Institution
“Gomel State Medical University”

Department of Pathological Anatomy

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METHODICAL GUIDELINES

for conducting a practical class
in the academic discipline “Pathological Anatomy”
for students
of the 3rd year, Faculty of International Students (instruction in English),
enrolled in the specialty
7-07-0911-01 “General Medicine”

Topic: “Necrosis and apoptosis”

Duration: 3 hours

Approved at the meeting of the Department of Pathological Anatomy
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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To study the causes, morphology, and outcomes of various types of necrosis. To distinguish between the concepts of necrosis and necrobiosis. To emphasize the diversity of etiological factors of necrosis (direct necrosis – traumatic, toxic; and indirect necrosis – vascular, allergic, trophoneurotic). To analyze the clinical and anatomical forms of necrosis – coagulative, liquefactive, gangrene (dry, wet) and its variants – infarct, sequestrum, bedsore. To relate the features of necrosis to the structural and blood supply characteristics of the organ in which it develops. To study the microscopic changes in the cell nucleus (karyopyknosis, karyorrhexis, karyolysis), cytoplasm (coagulation, plasmorexis, plasmolysis), and fibrous structures. To pay attention to the destructive changes in necrotized tissues resulting from enzymatic autolysis and the staining properties of tissue detritus. To examine the changes occurring at the border between necrotized and living tissue, as well as the outcomes of necrosis (organization, encapsulation, petrification, cyst formation, ossification, aseptic and purulent liquefaction) depending on the type, location, and reactivity of the organism. To determine the significance of necrosis based on the localization and size of the necrotic area. To examine the phenomenon of apoptosis, determine its role in the vital activity of the organism, study the morphological differences from necrosis, and name the structural elements involved in apoptosis.

Instructional Goal:

- Within the framework of the educational process for this academic discipline, the student must acquire not only theoretical knowledge, practical skills and abilities in the specialty but also develop their personal potential. They should cultivate qualities of responsibility and patriotism, be prepared to actively participate in the economic, socio-cultural, and public life of the country, recognize the social significance of their future professional activity, understand the norms of medical ethics and deontology, and learn to observe academic and labor discipline. In the course of studying the educational material, students should realize the importance of maintaining a healthy lifestyle and, as an example in the future, when performing professional duties, set an example for those around them and their patients.

Objectives: Upon completion of the practical session, the student must:

***Know*:**

- The causes, mechanisms, and morphological features of typical general pathological processes;
- The etiology, pathogenesis, and morphology of diseases at different stages of their development (morphogenesis), the structural basis of recovery, complications, outcomes, and long-term consequences of diseases, as well as the causes and mechanisms of dying (thanatogenesis).

Be able to:

- Define necrosis and explain its essence;
- Explain the dynamics of the necrotic process;
- Identify macroscopic, microscopic, and ultrastructural signs of necrotic changes;
- Identify and characterize the etiological types and clinical-morphological forms of necrosis;
- Identify the outcomes of various forms of necrosis and assess their functional significance;
- Define apoptosis, state its causes, morphological criteria distinguishing it from necrosis, and mechanisms of development;
- Determine the significance of apoptosis in the vital activity of the macroorganism.

***Master*:**

- Basic techniques for working with a microscope;
- Skills in clinical-anatomical analysis;
- The fundamentals of synthetic generalization of morphological diagnostic signs of diseases and their correct interpretation in cause-and-effect relationships.

Motivation for Mastering the Topic:

Necrosis is an irreversible process characterized by the death of individual cells, parts of organs, and tissues in a living organism. Under pathological conditions, necrosis is observed in various diseases. Knowledge of the general patterns of this process, its morphological and clinical features, will aid in the diagnosis and treatment of diseases involving tissue necrosis. Therefore, representatives of various medical specialties are engaged in the study of necrosis. The main goal of studying this topic is the possibility of managing necrotic processes and searching for means that would prevent the progressive destruction of cells, tissues, and organs under the influence of the body's own enzymes. Naturally, particular interest lies in studying the morphogenesis and pathogenesis of necrosis, as well as the genotypically programmed cell death under physiological conditions (apoptosis), with an emphasis on the earliest changes and initial stages. In this regard, the study of necrosis and apoptosis at various levels opens up prospects for a deeper understanding of the processes of dying. It is important to recognize the causes, mechanisms of manifestation, outcomes, as well as the specificity of necrosis depending on the structural and functional features of organs, tissues, cells, and the individual characteristics of the macroorganism.

During the session, students are invited to study the structural-pathogenetic changes in organs and tissues in necrosis; analyze the morphogenetic aspects of the development of specific types of necrosis.

QUESTIONS

1. Necrosis. Definition. Etiology. Nuclear and cytoplasmic changes. Classification. Outcomes. Difference between apoptosis and necrosis.
2. Apoptosis. Definition. Etiology. Nuclear and cytoplasmic changes. Classification. Outcomes. Difference between apoptosis and necrosis.
3. Gangrene. Definition. Etiology. Classification. Clinical examples.
4. Pressure ulcers. Definitions. Etiology. Clinical examples.
5. Sequestrum. Definitions. Etiology. Clinical examples.
6. Death. Medical definition. Difference between clinical and biological death. Clinical and physiological criteria.

COURSE OF THE SESSION

Necrosis is a form of cell injury which results in the premature death of cells in living tissue by autolysis.

Necrosis is caused by factors external to the cell or tissue, such as **infection**, or **trauma** which result in the unregulated digestion of cell components.

In contrast, apoptosis is a naturally occurring programmed and targeted cause of cellular death. While apoptosis often provides beneficial effects to the organism, necrosis is almost always detrimental and can be fatal.

Etiological types of necrosis:

1. Traumatic - occurs under the action of physical and chemical factors.
2. Toxic - occurs under the action of toxins of a bacterial and other nature.
3. Trophoneurotic - associated with impaired microcirculation and tissue innervation.
4. Allergic - develops with immunopathological reactions.
5. Vascular - associated with impaired blood supply to an organ or tissue.

Depending on the **mechanism of action** of the etiological factor, there are:

1. **Direct** necrosis (with direct action on the tissue of a traumatic or toxic agent).
2. **Indirect** (mediated action through the vascular, nervous and immune systems).

In the development of necrosis, the following **stages of development** are distinguished:

1. **Paranecrosis** - reversible changes.
2. **Necrobiosis** - irreversible dystrophic changes.
3. **Cell death**.
4. **Autolysis** - decomposition of a dead substrate under the action of hydrolytic enzymes released from a damaged cell.

Microscopic features are found in the nucleus and the cytoplasm of cells, as well as the extracellular matrix.

1. Nucleus:

a) **karyopyknosis** - wrinkling of nuclei due to condensation of chromatin;

b) **karyorrhexis** - disintegration of the nucleus into lumps;

c) **karyolysis** - dissolution of the nucleus due to the activation of hydrolases.

2. Cytoplasm:

a) **plasma coagulation** - denaturation and coagulation of the protein with the manifestation of bright pink clumps in the cytoplasm;

b) **plasmorhexis** - the disintegration of the cytoplasm into clumps;

c) **plasmolysis** - hydrolytic melting of the cytoplasm.

3. Changes in the extracellular matrix are manifested in the splitting of reticular, collagen and elastic fibers under the action of proteases, lipases.

Necrosis is manifested by various clinical and morphological changes. The differences depend on the structural and functional features of organs and tissues, the type of necrosis and its etiology.

Coagulative (dry) necrosis and **liquefactive** (wet) necrosis are distinguished.

Coagulative necrosis: In this type of necrosis, dead cells retain their shape for several days. Cells lacking a nucleus look like a mass of coagulated, homogeneous, pink cytoplasm. Coagulation of cytoplasmic proteins makes them resistant to the action of lysosomal enzymes and, as a result, their liquefaction slows down. Coagulative necrosis usually occurs in organs rich in proteins and poor in fluids, usually as a result of insufficient circulation and anoxia, the action of physical, chemical and other damaging factors, for example, coagulative cell necrosis liver with viral damage or under the action of toxic agents of bacterial and non-bacterial origin. Coagulative necrosis is also called dry, since it is characterized by the fact that the dead areas that occur with it are dry, dense, crumbling, white or yellow.

Liquefactive necrosis

Liquefactive necrosis is characterized by the melting of dead tissue. It develops in tissues that are relatively poor in proteins and rich in fluid, where there are favorable conditions for hydrolytic processes. Cell lysis occurs as a result of the action of its own enzymes (autolysis). A typical example of wet colliquative necrosis is a focus ischemic infarction of the brain.

Caseous necrosis

Caseous necrosis develops in tuberculosis and leprosy. This is a mixed type of necrosis, in which both the parenchyma and the stroma (both cells and fibers) die at the same time. Microscopically, such a tissue area looks like a structureless, homogeneous, stained pink with hematoxylin and eosin, clumps of nuclear chromatin (karyorrhexis) are clearly visible.

Fibrinoid necrosis

Fibrinoid necrosis is seen in allergic and autoimmune diseases (rheumatism, rheumatoid arthritis, and systemic lupus erythematosus). Collagen fibers and smooth muscles of the middle membrane of the blood vessels are most severely damaged. This necrosis is characterized by the loss of normal collagen fiber structure and the accumulation of a homogeneous, bright pink necrotic material that mimics fibrin microscopically. Note that "**fibrinoid**" is different from "**fibrinous**", as the latter refers to the accumulation of fibrin, such as in blood clotting or inflammation. Areas of fibrinoid necrosis contain varying amounts of immunoglobulins and complement, albumin, breakdown products of collagen and fibrin.

Fat necrosis (steatonecrosis)

Fat necrosis most commonly occurs in **acute pancreatitis** and **pancreatic injury**, when pancreatic enzymes leak from the ducts into the surrounding tissues.

Non-enzymatic fat necrosis is observed in the **breast**, **subcutaneous adipose tissue** and in the **abdominal cavity**. Most patients have a history of trauma. It is also called traumatic fat necrosis, even if trauma is not identified as the underlying cause.

Non-enzymatic fat necrosis causes an inflammatory response characterized by the presence of numerous macrophages with foamy cytoplasm, neutrophils, and lymphocytes.

This is followed by fibrosis, and this process can be difficult to distinguish from a tumor.

Gangrene

Gangrene is the necrosis of tissues that communicate with the external environment and change under its influence. The term "gangrene" is widely used to denote a clinical and morphological condition in which tissue necrosis is often complicated by a **secondary bacterial infection** of varying severity or, being in contact with the external environment, **undergoes secondary changes**.

Dry gangrene is necrosis of tissues in contact with the external environment, proceeding without the participation of microorganisms. Dry gangrene most often occurs on the extremities as a result of **ischemic coagulative tissue necrosis**. Necrotic tissue appears black, dry, and is **clearly demarcated** from adjacent viable tissue. On the border with healthy tissues, demarcation inflammation occurs. The color change is due to the transformation of hemoglobinogenic pigments in the presence of hydrogen sulfide into iron sulfide. Treatment consists of surgical removal of dead tissue, with the demarcation line serving as a guide.

Wet gangrene

Wet gangrene develops as a result of the addition of a **severe bacterial infection** to necrotic tissue changes. Under the action of microbial enzymes, secondary colliquation occurs. The type of microorganisms depends on the localization of gangrene.

Wet gangrene usually develops in tissues rich in fluid. Acute inflammation and bacterial growth cause the necrotic area to become edematous and red-black, with extensive liquefaction of dead tissue.

In wet gangrene, spreading necrotizing inflammation can occur that is **not clearly demarcated** from adjacent healthy tissue and thus is difficult to treat surgically.

Gas gangrene

Gas gangrene occurs when a wound becomes infected with anaerobic flora, such as **Clostridium perfringens** and other microorganisms of this group. It is characterized by extensive tissue necrosis and gas formation as a result of bacterial enzymatic activity. The main manifestations are similar to wet gangrene, but with the additional presence of gas in the tissues.

Crepitus (a crackling phenomenon on palpation) is a common clinical symptom in gas gangrene.

Pressure ulcers

Pressure ulcers (also known as pressure sores or bedsores or decubitus) are injuries to the skin and underlying tissue, primarily caused by prolonged pressure on

the skin. Bedsores often appear in the region of the sacrum, the spinous processes of the vertebrae, and the greater trochanter of the femur. This is a trophoneurotic necrosis, as vessels and nerves are compressed, which exacerbates tissue trophic disorders in seriously ill patients suffering from cardiovascular, oncological, infectious or nervous diseases.

Sequestrum

Sequestrum is an area of necrosis that has not undergone autolysis and sclerosis.

A sequestrum is a medical term referring to a fragment of dead bone tissue (necrotic bone) that has become separated or detached from the surrounding healthy bone. This condition typically occurs as a result of various underlying diseases or conditions that disrupt blood supply to the bone, leading to bone tissue death and subsequent fragmentation.

Sequestrum etiology

1) **Osteomyelitis**: This is one of the most common causes of sequestrum formation. Osteomyelitis is a bacterial infection of the bone that can lead to the death of bone tissue. The body's immune response to the infection may cause an area of necrotic bone to become isolated and form a sequestrum.

2) **Trauma**: Severe bone fractures or injuries can sometimes result in a loss of blood supply to a portion of the bone, leading to bone tissue death and subsequent sequestrum formation.

3) **Vascular Insufficiency**: Conditions that affect blood flow to the bone, such as atherosclerosis or vascular diseases, can cause insufficient oxygen and nutrient supply to the bone, resulting in tissue death and sequestrum formation.

Apoptosis

Apoptosis is the process of programmed cell death.

Morphologically, apoptosis is manifested by the death of single, randomly arranged cells, which is accompanied by the formation of rounded bodies surrounded by a membrane (**apoptotic bodies**), which are immediately phagocytosed by the surrounding cells.

Apoptosis vs Necrosis

Table 1. Comparative characteristics of necrosis and apoptosis

Sign	Apoptosis	Necrosis
Induction	Activated by physiological or pathological stimuli	Different depending on the damaging factor
Prevalence	Single cell	Group of cells
Biochemical changes	Energy dependent DNA fragmentation by endogenous endonucleases. Lysosomes are intact .	Violation or termination of ion exchange. Enzymes are released from lysosomes.
DNA decay	Intranuclear condensation with splitting into fragments	Diffuse localization in a necrotic cell

Cell membrane integrity	Saved	Violated
Morphology	Shrinkage of cells and fragmentation with the formation of apoptotic bodies with compacted chromatin	Swelling and cell lysis
Inflammatory response	No response	Usually present
Removal of dead cells	Absorption by neighboring cells	Phagocytosis by neutrophils and macrophages

Death is the irreversible cessation of all vital functions and processes in an organism, leading to the permanent and complete loss of consciousness, brain function, and the ability to sustain life.

It is a fundamental concept in medicine and is typically determined through **clinical and physiological criteria**.

1) CARDIAC CRITERIA:

a. **Absence of Heartbeat**: One of the primary clinical criteria for death is the absence of a heartbeat or cardiac activity. When the heart stops beating and cannot be restarted through resuscitation efforts, it is a strong indicator of death.

b. **Asystole**: Asystole, or the flatline on an electrocardiogram (ECG or EKG), indicates the absence of electrical activity in the heart. It is a crucial physiological sign of cardiac arrest and, when persistent, suggests death.

2) RESPIRATORY CRITERIA:

a. **Absence of Breathing**: The cessation of spontaneous breathing is another critical clinical indicator of death. This is typically confirmed by the absence of chest rise and fall.

b. **Arterial Blood Gases**: Blood gas analysis may reveal severe hypoxemia (low oxygen levels) and hypercapnia (high carbon dioxide levels) in cases of respiratory failure associated with death.

3) CORE BODY TEMPERATURE:

a. **Hypothermia**: Extremely low core body temperature may lead to the suspension of vital bodily functions, mimicking death. Therefore, temperature must be taken into account when assessing whether an individual is deceased.

4) NEUROLOGICAL CRITERIA:

a. **Brain Function**: The assessment of brain function is a fundamental component of determining death. Brain death involves the irreversible loss of all brain functions, including consciousness and brainstem reflexes. Neurological examinations and tests, such as EEG (electroencephalogram), are used to confirm brain death.

b. **Absence of Pupillary Reflexes**: The absence of pupillary reflexes, such as the pupillary light reflex, can be indicative of brainstem dysfunction and is considered a clinical sign of severe neurological impairment.

5) REFLEX CRITERIA:

a. **Absence of Reflexes**: The absence of certain reflexes, such as the gag reflex, corneal reflex, and deep tendon reflexes, can be observed as a result of brain or spinal cord injury and may indicate death.

Classification of Death

Clinical death refers to the moment when vital signs such as heartbeat, breathing, and brain activity cease. However, it may still be **possible to reverse** clinical death through immediate medical intervention, such as cardiopulmonary resuscitation (CPR) or defibrillation.

Biological death refers to the point at which **irreversible damage** occurs to the body's cells and tissues due to oxygen deprivation. This process **begins with clinical death and progresses to biological death** as cells and organs fail to function due to lack of oxygen.

Brain death is a specific classification of death in which all brain functions, including consciousness, brainstem reflexes, and electrical activity, have irreversibly ceased. This is typically determined through clinical and neurologic examinations, including EEG (electroencephalogram) readings, and it is considered legally and medically equivalent to death in many jurisdictions.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

1. Pathomorphology : textbook / ed. by I.V. Sorokina, V.D. Markovskyi, D.I. Halata. - 2nd ed. - Kyiv : AUS Medicine Publishing, 2020. - 327 p., [10] col. inserts : tab.

2. Klatt, E. C. Robbins and Cotran Atlas of Pathology : [with Student Consult Online Access] / Edward C. Klatt. - third edition. - Philadelphia : Elsevier, 2015. - 587 p. : il.

3. Robbins Basic pathology / [ed. by] Vinay Kumar, Abul K. Abbas, Jon C. Aster. - 9th ed. - [Philadelphia] : Elsevier ; Saunders. - 910 p. : ill., scheme, tab.

ADDITIONAL LITERATURE

1. Sobotta. Atlas of human anatomy. [V. 1]. General anatomy and musculoskeletal system / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 400 p. : ill., col. ill.

2. Sobotta. Atlas of human anatomy. [V. 2]. Internal organs / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 259 p. : ill., col. ill.

3. Sobotta. Atlas of human anatomy. [V. 3]. Head, neck, and neuroanatomy / ed. by F. Paulsen, J. Waschke. - 15th ed. - München : Elsevier. Urban & Fischer, 2011. - 370 p. : ill., col. ill.

4. Weir & Abrahams' imaging atlas of human anatomy / ed.: J. D. Spratt [and oth.] ; consultant eds.: J. Weir, P. H. Abrahams. – 5th ed. - [S.l.] : Elsevier, 2017. - xvi, 263 p. : ill.

NORMATIVE LEGAL ACTS AND DOCUMENTS

1. Order of the Ministry of Health of the Republic of Belarus No. 111 of 06/01/1993 "On further improvement of the pathological service of the Republic of Belarus"

Access mode: http://patan.by/menyu/administrativnyie-proczeduryi.html - The date fccess: 20.03.2022.

ELECTRONIC DATABASES

1. Physician's consultant. Electronic Medical Library = Consultant of the doctor. Electronic medical library [Electronic resource] / Publishing group "GEOTAR-Media", LLC "IPUZ". – Access mode: http://www.rosmedlib.ru/ . – Access date: 03/15/2022.

2. Springer Link [Electronic resource] / Springer International Publishing AG. – Access mode: https:link.springer.com. – Date of access: 03/15/2022.