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: “Tumours: epithelial, neuroendocrine, melanocytic neoplasms”

Duration: 3 hours

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EDUCATIONAL AND INSTRUCTIONAL GOALS, OBJECTIVES, AND MOTIVATION FOR MASTERING THE TOPIC

Educational Goal:

- To study the classification, morphology, and clinical features of epithelial, neuroendocrine, and melanocytic neoplasms. To analyze benign and malignant epithelial tumours (papillomas, adenomas, carcinomas) with emphasis on the most common types: squamous cell carcinoma, adenocarcinoma (including variants such as tubular, papillary, mucinous), transitional cell carcinoma, and basal cell carcinoma. To examine the spectrum of neuroendocrine neoplasms, from well-differentiated neuroendocrine tumours (carcinoids) to poorly differentiated neuroendocrine carcinomas (small cell carcinoma, large cell neuroendocrine carcinoma). To analyze melanocytic neoplasms, including benign nevi (junctional, compound, intradermal, dysplastic) and malignant melanoma (superficial spreading, nodular, lentigo maligna, acral lentiginous types). To discuss the histological grading, immunohistochemical profiles (e.g., cytokeratins, chromogranin, synaptophysin, S-100, HMB-45, Melan-A), and prognostic factors for each group.

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 classification of epithelial tumours (benign and malignant);
- The morphological features of common carcinomas (squamous cell carcinoma, adenocarcinoma, transitional cell carcinoma, basal cell carcinoma);
- The classification and morphological features of neuroendocrine neoplasms;
- The classification and morphological features of melanocytic neoplasms (nevi and melanoma);
- The immunohistochemical markers used to diagnose epithelial, neuroendocrine, and melanocytic tumours;
- The prognostic factors and outcomes for common malignant tumours in these categories.

Be able to:

- Identify benign and malignant epithelial tumours on histological specimens;
- Diagnose neuroendocrine neoplasms based on microscopic appearance (organoid nesting, rosettes, trabecular patterns);
- Distinguish benign nevi from malignant melanoma using histological criteria (asymmetry, border irregularity, colour variation, diameter, elevation – ABCDE rule, plus cytological atypia, mitotic activity, deep invasion);
- Diagnose pathological processes and diseases based on the description of macroscopic and microscopic changes in organs and tissues of the body.

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:

Epithelial malignancies (carcinomas) account for approximately 80–90% of all human cancers, including lung, breast, colorectal, prostate, and gastric cancers, which are leading causes of cancer death worldwide. Neuroendocrine neoplasms, though less common, present unique diagnostic challenges due to their varied clinical behaviour and histological appearance. Melanoma, while representing only a small percentage of skin cancers, causes the majority of skin cancer deaths due to its high metastatic potential. Knowledge of the morphological and immunohistochemical features of these tumours is essential for accurate diagnosis, appropriate treatment selection, and prediction of patient outcomes. This topic is critical for all physicians involved in cancer diagnosis and management.

QUESTIONS

1. Tumors from squamous epithelium: papilloma, squamous cell carcinoma, basal cell carcinoma. Definition. Classification. Most frequent localization. Pathological features.
2. Adenoma. Definition. Classification. Types and localization. Pathological features.
3. Adenocarcinoma. Definition. Classification. Types and localization. Pathological features.
4. Urothelial tumors. Definition. Classification. Most frequent localization. Pathological features.
5. Neuroendocrine tumor and carcinoma. Carcinoid. Definition. Classification. Most frequent localization. Pathological features.
6. Melanocytic tumors: nevus. Definition. Classification. Types and localization. Pathological features.

7. Melanocytic tumors: melanoma. Definition. Classification. Types and localization. Pathological features. Metastatic pathways.

8. Mesothelioma. Definition. Classification. Types and localization. Pathological features.

9. Teratoma. Definition. Classification. Types and localization. Pathological features.

COURSE OF THE SESSION

Tumors of epithelial tissues

Depending on epithelium type benign epithelial tumors are subdivided into papillomas (the tumors of **squamous** and **transitional** epithelium) and adenomas (tumors of **glandular** epithelium).

Papilloma occurs in the skin and mucous membranes, covered with squamous or transitional epithelium; it looks like a ledge or a bush of ranching papillae. It is a good example of an exophytic tumor. The center of the tumor usually consists of connective tissue containing blood vessels.

Adenoma is a benign epithelial tumor from the epithelium of the glands and mucous membranes covered with columnar epithelium. More often they can be found in the breast, thyroid gland, ovaries, prostate gland, uterus, and gastrointestinal tract.

According to the histological structure adenoma may be tubular, trabecular, papillary and alveolar. In some adenomas glandular cavities form cysts filled with the serous fluid or mucus (**cystadenomas**).

Tumors of epithelial tissues

Carcinoma in situ is a frequent variant of cancer which is characterized by severe atypia, active cellular proliferation while infiltrative growth is absent, and basement membrane is not invaded.

Depending on the epithelium differentiated carcinomas histologically are subdivided into following types:

1. **Squamous cell carcinoma** may arise in any part of the skin or mucous membranes lined by squamous epithelium (oral cavity, esophagus, larynx, vagina, uterus cervix, etc.). It can arise on glandular or transitional epithelium too after preceding metaplasia. Microscopically, squamous cancer is characterized by irregular downward proliferation of epithelial cells into derma or underlying tissues with the formation of epithelial «nests». Masses of tumor cells show atypical features such as variation in cell size and shape, nuclear hyperchromatism, absence of intercellular bridges, atypical mitoses, individual cell keratinization or whorled arrangement of malignant squamous cells forming horn pearls.

2. **Transitional cell carcinoma** arises on transitional epithelium of mucous membranes of urethra, urinary bladder, etc. Microscopically, it is characterized by irregular downward proliferation of epithelial cells into underlying tissues. Masses of tumor cells show all atypical features too.

3. **Adenocarcinoma** arises appears on prismatic epithelium of mucous membranes or epithelium of glands. It has a structure similar to adenoma but differs from it in presence of atypia, variation in cell and nucleus size and shape, nuclear hyperchromatism, atypical mitoses and infiltrative growth. There are acinar, tubular and papillary variants of adenocarcinoma.

Papillomas are **benign epithelial tumors** characterized by finger-like projections known as papillae, which may appear as fronds or warts.

Morphologically, papillomas often exhibit a **fibrovascular core** covered by **hyperplastic epithelium**. These tumors can occur in various organs and tissues, including the skin, mucous membranes, and internal organs.

Common localizations include the **skin**, where they may present as **warts**, and the respiratory tract, where they can occur in the nasal passages, larynx, or trachea.

Clinical manifestations of papillomas depend on their specific location. Cutaneous papillomas may manifest as small, elevated skin lesions with a rough surface. Respiratory papillomas can lead to symptoms such as hoarseness, coughing, or difficulty breathing.

While most papillomas are benign, some may exhibit a tendency for recurrence, and in rare instances, those in the respiratory tract may have malignant potential.

Treatment involves surgical excision or other appropriate interventions to manage symptoms and reduce the risk of complications.

Squamous carcinoma in situ, also known as squamous intraepithelial neoplasia (SIN) or **Bowen's disease**, is an early, non-invasive form of squamous cell carcinoma.

Morphologically, it is characterized by **abnormal proliferation of squamous cells confined to the epithelial layer without invasion** into the underlying tissue.

The cells often exhibit **nuclear atypia**, increased **mitotic activity**, and **disordered maturation**.

Commonly localized in the **skin**, especially sun-exposed areas, squamous carcinoma in situ can also affect mucosal surfaces, such as the **cervix**, **vulva**, **anus**, or **oral cavity**.

Clinical manifestations depend on the specific location; in cutaneous lesions, it may present as red, scaly patches or plaques, while mucosal involvement can manifest as visible changes or may be asymptomatic. Although squamous carcinoma in situ is considered a **precursor to invasive squamous cell carcinoma**, early detection and intervention offer a favorable prognosis, often involving local excision or ablative techniques to prevent progression to invasive disease.

Invasive squamous cell carcinoma is a **malignant neoplasm** characterized by the infiltration of squamous cells beyond the epithelial layer into the surrounding tissue.

Morphologically, it presents with **atypical**, **infiltrating squamous cells** that invade the underlying stroma, often exhibiting features such as **keratinization** and **cellular pleomorphism**.

Commonly localized in various tissues, invasive squamous cell carcinoma frequently arises in the **skin**, especially in sun-exposed areas, as well as in mucosal surfaces like the **oral cavity**, **esophagus**, **cervix**, and **anus**.

Clinical manifestations vary depending on the specific site, but commonly include the development of a persistent, enlarging mass or ulceration, accompanied by symptoms such as bleeding, pain, or changes in skin color. **Early diagnosis is crucial for effective treatment**, which often involves surgical excision, radiation

therapy, or chemotherapy depending on the extent and location of the tumor. The prognosis can range from favorable in cases of early-stage disease to more challenging in advanced or metastatic conditions, underscoring the importance of timely detection and intervention.

Basal cell carcinoma (BCC) is the **most common type of skin cancer**, and its morphology is characterized by **nests of basaloid cells with peripheral palisading** and often a **central area of ulceration or crusting**.

This cancer typically arises in sun-exposed areas of the **skin**, especially on the **face**, **neck**, and **head**. Basal cell carcinoma tends to grow slowly and is **locally invasive**, with a low likelihood of metastasis.

Clinical manifestations of BCC include the development of pearly or translucent nodules, pinkish growths, or open sores that may bleed or ooze. These lesions often have a rolled border and may exhibit telangiectasias.

Although BCC rarely spreads to distant organs, early detection and treatment are crucial to prevent local tissue destruction and disfigurement.

Urothelial cell papilloma

Urothelial cell papilloma is a **benign epithelial tumor** arising from the urothelial lining of the **urinary tract**, commonly found in the bladder.

Morphologically, these papillomas are characterized by **finger-like projections** covered with **normal-appearing urothelial cells**, creating a wart-like appearance. While typically benign, these lesions share some histological similarities with urothelial carcinomas, necessitating careful examination and differentiation.

Urothelial cell papillomas are most commonly localized in the **bladder**, particularly on the urinary bladder wall, and may also occur in the **renal pelvis** or **ureter**, albeit less frequently.

Clinical manifestations are often absent or mild, with patients occasionally presenting with painless hematuria or lower urinary tract symptoms. Though generally non-invasive and unlikely to progress to malignancy, proper diagnosis through imaging studies, endoscopy, and histopathological examination is crucial to distinguish urothelial cell papillomas from potentially more aggressive lesions.

Urothelial cell carcinoma (UCC), also known as transitional cell carcinoma, is a **malignant tumor originating from the urothelial lining** of the urinary tract.

Morphologically, UCC can exhibit a range of patterns, including **papillary**, **solid**, or **infiltrating** configurations, and is characterized by atypical urothelial cells with enlarged, hyperchromatic nuclei.

Commonly localized in the **bladder**, UCC can also affect the **renal pelvis**, **ureters**, and **urethra**.

Clinical manifestations depend on the tumor's location and extent but often include hematuria, frequent urination, urgency, and pelvic or flank pain. UCC is known for its potential to recur and progress to invasive disease.

Treatment strategies involve a combination of surgery, chemotherapy, and immunotherapy, with the prognosis varying based on the tumor's stage and grade at diagnosis.

Adenomas

In **tubular** adenoma, there are glandular cavities resembling tubes in the connective tissue with vessels. In **alveolar** adenoma, numerous foci bedded with cylindrical or cubic epithelium are observed in the connective tissue with vessels. **Trabecular** adenoma consists of cellular cords, while **papillary** type of adenoma is composed of papillary structures.

Adenomas: Morphology

Adenomas are **benign tumors** that originate from **glandular epithelial tissues**.

Morphologically, adenomas often exhibit **well-differentiated glandular structures**, resembling the tissue of origin.

The cells forming these glands may be arranged in a **tubular** or **papillary pattern**, and the nuclei usually maintain a relatively uniform appearance.

While adenomas are generally considered benign, they can occasionally show dysplastic changes or atypia, raising concerns about potential malignant transformation.

The **classification of adenomas often depends on the specific tissue** involved, such as tubular adenomas in the colon or pituitary adenomas in the brain.

Adenomas: Clinical Manifestations

The common localization of adenomas is **diverse** and depends on the type of glandular tissue from which they arise. For example, **colorectal adenomas** are frequently found in the lining of the colon or rectum, representing precursors to colorectal cancer. **Pituitary adenomas** arise from the pituitary gland in the brain and may affect hormone production. **Adrenal adenomas** can develop in the adrenal glands, and thyroid adenomas can occur in the thyroid gland. **Localization determines the clinical significance** and potential complications associated with adenomas.

Clinical manifestations of adenomas are often related to the specific organ or gland involved. **Colorectal adenomas** may not cause noticeable symptoms initially but can lead to **gastrointestinal bleeding**, changes in bowel habits, or even progress to colorectal cancer. **Pituitary adenomas** may cause **hormonal imbalances**, resulting in issues such as headaches, visual disturbances, or endocrine dysfunction. **Thyroid adenomas** can lead to thyroid nodules, sometimes causing compression symptoms or **thyroid dysfunction**.

Adenocarcinomas: Morphology

Adenocarcinomas are **malignant tumors** that arise from **glandular epithelial tissues**.

Morphologically, these cancers are characterized by the presence of **abnormal glandular structures** and an **invasive growth pattern**. The cells

forming the glands often exhibit varying degrees of differentiation, and the nuclei may show features of dysplasia, including increased size, irregular shape, and prominent nucleoli.

Adenocarcinomas **can arise in various organs**, including the lungs, gastrointestinal tract, breast, prostate, and pancreas.

The **localization of adenocarcinomas is crucial** in determining their clinical behavior and potential treatment options. For example, colorectal adenocarcinomas are common and often arise from adenomatous polyps, while lung adenocarcinomas are a prevalent subtype of non-small cell lung cancer.

Adenocarcinomas: Clinical Manifestations

The clinical manifestations of adenocarcinomas depend on the specific organ affected and the stage of the cancer at the time of diagnosis.

In **colorectal adenocarcinomas**, patients may present with symptoms such as changes in bowel habits, **rectal bleeding**, **abdominal pain**, or unintentional **weight loss**.

Lung adenocarcinomas can cause respiratory symptoms like **cough**, **shortness of breath**, or **chest pain**.

Breast adenocarcinomas may present as palpable **breast lumps** or changes in breast appearance, while **prostate adenocarcinomas** can lead to **urinary symptoms** such as difficulty in urination.

The clinical course varies widely, and early detection is crucial for optimal treatment outcomes.

Management of adenocarcinomas often involves a combination of surgery, chemotherapy, radiation therapy, and targeted therapies, depending on the specific characteristics of the tumor and its stage. Regular surveillance and follow-up are essential to monitor for recurrence and guide ongoing treatment decisions.

NET: Morphology

Neuroendocrine tumors (NETs) are a diverse group of neoplasms that arise from cells of the **neuroendocrine system**, which includes cells that share features of both **nerve cells** and **hormone-producing endocrine cells**.

Morphologically, NETs can display a broad spectrum of appearances, ranging from **well-differentiated**, indolent tumors to poorly differentiated, aggressive **carcinomas**.

Well-differentiated NETs often form small, uniform nests or trabeculae and may produce characteristic "**salt-and-pepper**" **chromatin patterns** under the microscope.

Commonly localized in the gastrointestinal tract, pancreas, lungs, and less frequently in other organs, **NETs exhibit unique clinical manifestations** depending on their site of origin and functional activity.

NET: Clinical Manifestations

The localization of neuroendocrine tumors is diverse, with the gastrointestinal tract being a prominent site. **Carcinoid tumors**, a subtype of NETs, often originate in the **gastrointestinal tract**, particularly the appendix, small intestine, and rectum. Pancreatic NETs can occur in the **pancreas** and may produce various hormones,

leading to distinct clinical syndromes. **Bronchial carcinoids** are another subset that originates in the lungs. *Functioning NETs*, which produce hormones, can cause specific clinical manifestations related to hormone excess, such as flushing, diarrhea, wheezing, or abdominal pain. *Non-functioning NETs*, lacking hormone production, may go unnoticed until they cause symptoms due to their size or location, often presenting as mass effects or compressive symptoms.

Clinical manifestations of neuroendocrine tumors can be diverse and depend on factors such as the tumor's size, location, functional status, and potential for metastasis. **Carcinoid syndrome**, associated with the release of serotonin and other vasoactive substances, can cause symptoms such as **flushing**, **diarrhea**, and **bronchospasm**. Insulinomas, a type of pancreatic NET, may lead to hypoglycemia, while gastrinomas can cause **Zollinger-Ellison syndrome**, characterized by peptic ulcers and gastric hyperacidity. The slow growth of some NETs may result in the absence of symptoms until advanced stages. Diagnosis involves imaging studies, hormonal assays, and histopathological examination.

Nevus

Nevi, commonly referred to as moles, are **benign growths** on the skin originating from **melanocytes**, the pigment-producing cells.

Morphologically, nevi can vary widely in appearance, from **flat**, **pigmented spots** to **raised**, **dome-shaped lesions**. They may exhibit **different colors**, including shades of brown, tan, black, or pink. The borders of a nevus are **typically well-defined**, and the size can range from **tiny specks to larger patches**.

Nevi can be localized on **any part of the skin** and may appear during childhood or adolescence. Common sites include the face, neck, chest, and extremities, but they can be found on the scalp, genital area, and mucous membranes as well. The number of nevi varies among individuals, and some people may have only a few, while others may develop numerous nevi. While **most nevi are harmless**, certain types, such as dysplastic nevi, have an increased risk of transforming into melanoma.

Clinical manifestations of nevi are **typically asymptomatic**, and individuals may only notice them by appearance. It is essential to monitor nevi for any changes in size, shape, color, or other features, as alterations may raise concerns about potential malignancy, prompting further evaluation.

Pathological classification of nevi

1) **Compound Nevus** involve both the epidermis and dermis. They typically consist of nests of melanocytes at the junction between these two layers, as well as deeper within the dermis.

Histological Features: Compound nevi display melanocytic proliferation in both the epidermis and dermis. The junctional component often consists of melanocytes arranged in nests along the basal layer of the epidermis, while the dermal component contains nests of melanocytes in the dermis.

2) **Junctional Nevi** are confined to the junction between the epidermis and dermis.

Histological Features: These nevi are characterized by nests or clusters of melanocytes along the basal layer of the epidermis. The melanocytes are typically uniform in size and shape, and their proliferation is limited to the junctional zone.

3) **Intradermal Nevi** are primarily located within the dermis.

Histological Features: Intradermal nevi exhibit nests of melanocytes within the dermis, lacking a significant junctional component. The melanocytes are often more scattered and may not extend into the epidermis.

4) **Dysplastic Nevi** (Atypical Nevi) are considered atypical, and they may have features that resemble melanoma, posing a slightly higher risk for malignant transformation.

Histological Features: Dysplastic nevi often exhibit architectural and cytological atypia, such as irregular nesting patterns, varying cell sizes, and increased melanocytic proliferation. While they share some characteristics with melanoma, dysplastic nevi are still benign lesions.

Melanoma

Melanoma is a **malignant tumor** that arises from the pigment-producing cells called **melanocytes**.

Morphologically, melanomas often exhibit **asymmetry**, **irregular borders**, **varied colors**, a **diameter larger than 6 millimeters**, and **evolving characteristics** — commonly referred to as the **ABCDE** criteria.

A - Asymmetry: In benign moles, both halves typically look similar and symmetrical. Asymmetry refers to the unevenness or irregular shape of a lesion. In melanomas, one half may differ from the other, suggesting potential malignancy.

B - Border Irregularity: Benign moles often have smooth, well-defined borders. Melanomas, on the other hand, may exhibit irregular or jagged edges. Blurred or poorly demarcated borders can be an indicator of malignant growth.

C - Color Variation: Benign moles usually have a uniform color, whereas melanomas often display diverse colors within the same lesion. This variation might include shades of brown, black, red, white, or blue. The presence of multiple colors in a single lesion raises concern for malignancy.

D - Diameter: While benign moles are typically smaller in diameter, melanomas often exceed 6 millimeters (about the size of a pencil eraser). However, it's essential to note that melanomas can be smaller, and the guideline serves as a general reference for assessing size.

E - Evolution or Change: Any change in the appearance of a mole or pigmented lesion should be carefully monitored. This includes changes in size, shape, color, or symptoms like itching or tenderness. An evolving or changing lesion may indicate potential malignancy.

Melanocytes may form nests or clusters within the epidermis, and the presence of **atypical melanocytes with irregular nuclei** is a hallmark feature.

Melanoma has various subtypes: 1) **nodular melanoma** may present as a rapidly growing, elevated nodule with a uniform color; 2) **superficial spreading melanoma**, the most common subtype, typically shows radial growth along the skin surface before invading deeper layers.

Melanomas can occur **anywhere on the skin**, and their localization is often associated with **sun-exposed areas**. In individuals with fair skin, melanomas frequently develop on the trunk, back, legs, and face. In those with darker skin types, melanomas may appear on the palms, soles, or mucous membranes. Additionally, melanomas can arise in areas not exposed to the sun, such as the **eyes** (ocular melanoma) or **internal organs**. The malignant cells can invade the dermis and, if left untreated, may metastasize to regional lymph nodes and distant organs.

Clinical manifestations of melanoma often involve changes in the appearance of existing moles or the development of new pigmented lesions. Early detection is crucial, and individuals should be vigilant for alterations in size, shape, color, or the presence of symptoms like itching, tenderness, or bleeding. As melanomas progress, they may become **elevated**, **ulcerated**, or **exhibit irregular borders**.

Regional lymph node involvement can lead to lymphadenopathy, and distant metastasis may cause systemic symptoms such as weight loss and fatigue. Regular skin self-examinations and professional screenings are essential for identifying suspicious lesions early, improving the prognosis and facilitating timely intervention, which may include surgical excision, immunotherapy, or targeted therapies.

INFORMATIONAL AND METHODOLOGICAL PART

MAIN LITERATURE

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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.

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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.

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