Волгоградский государственный медицинский университет

Кафедра патологической анатомии

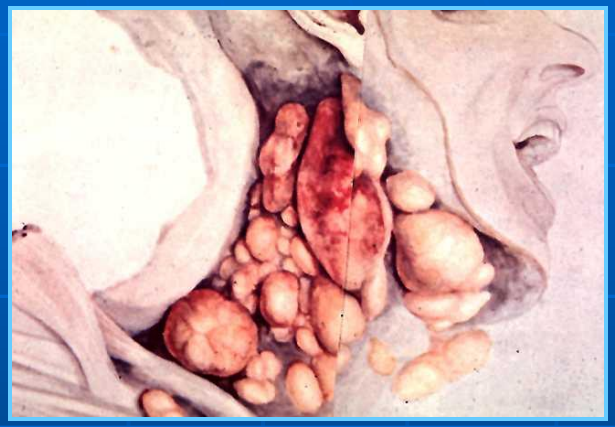
LECTURE. NEOPLASIA

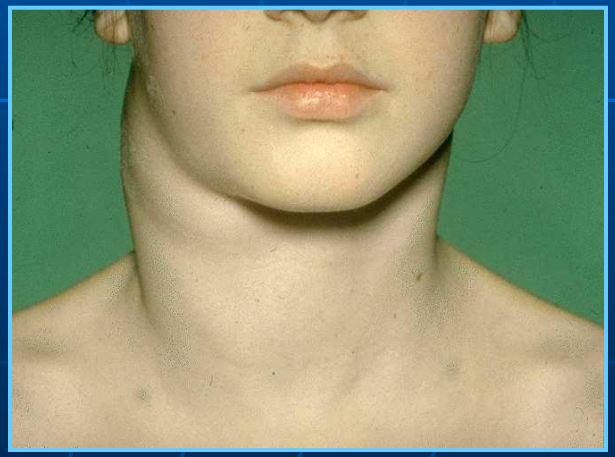
Neoplasia

- is the autonomous proliferation of cells without response to the normal control mechanisms governing their growth. As used by investigators, clinicians, and the laity alike, neoplasia is often equated with cancer. However, neoplasia may be benign or malignant.

Hodgkin Lymphoma: Clinical

- Neoplasia literally means "new growth" and the new growth is a "neoplasm". The term "tumor" is, literally, any swelling, including an inflammatory mass (e.g., an abscess), but the term has become a synonym for neoplasm, to the point of being equated often with the term.





There are several conditions, when there is increased growth of cells and tissues.

1. **Hypertrophy** is an enlargement in **individual cell size,** causing a corresponding increase in tissue mass. Cellular proliferation is controlled.
2. **Hyperplasia** is an increase in the **number of cells,** causing a corresponding increase in tissue mass.
3. **Metaplasia** is the replacement of one adult tissue type by another; usually the replacement (i.e., the metaplastic tissue) is simpler in form.
4. **Dysplasia** literally means any abnormal growth. However, the term has come to have several more restricted meanings.
   a. It is applied to certain congenital defects such as dysplastic (malformed) kidneys.
   b. More commonly, however, dysplasia connotes cytologic abnormalities that are believed to be precursors of malignant neoplastic changes. These include disorderly architectural changes and pleomorphism (a multiplicity of sizes and shapes); frequent mitoses, often in odd locations; and unusually large, hyperchromatic (deeply staining) nuclei.

- **5. Anaplasia** is a loss of the cell's normal morphologic and functional characteristics. In practice, anaplasia is equated with malignancy (i.e., with cancer).
- a. Anaplastic cells resemble more primitive cells of similar tissue. The more primitive (embryonic) the cells appear, the more anaplastic they are said to be.
- b. Anaplasia literally means "backward formation." However, the anaplastic process is a failure to develop into a differentiated cell, and not a progressive loss, or dedifferentiation, of cellular specialization. Hence the earlier concept of malignancy as being due to dedifferentiation has been abandoned.

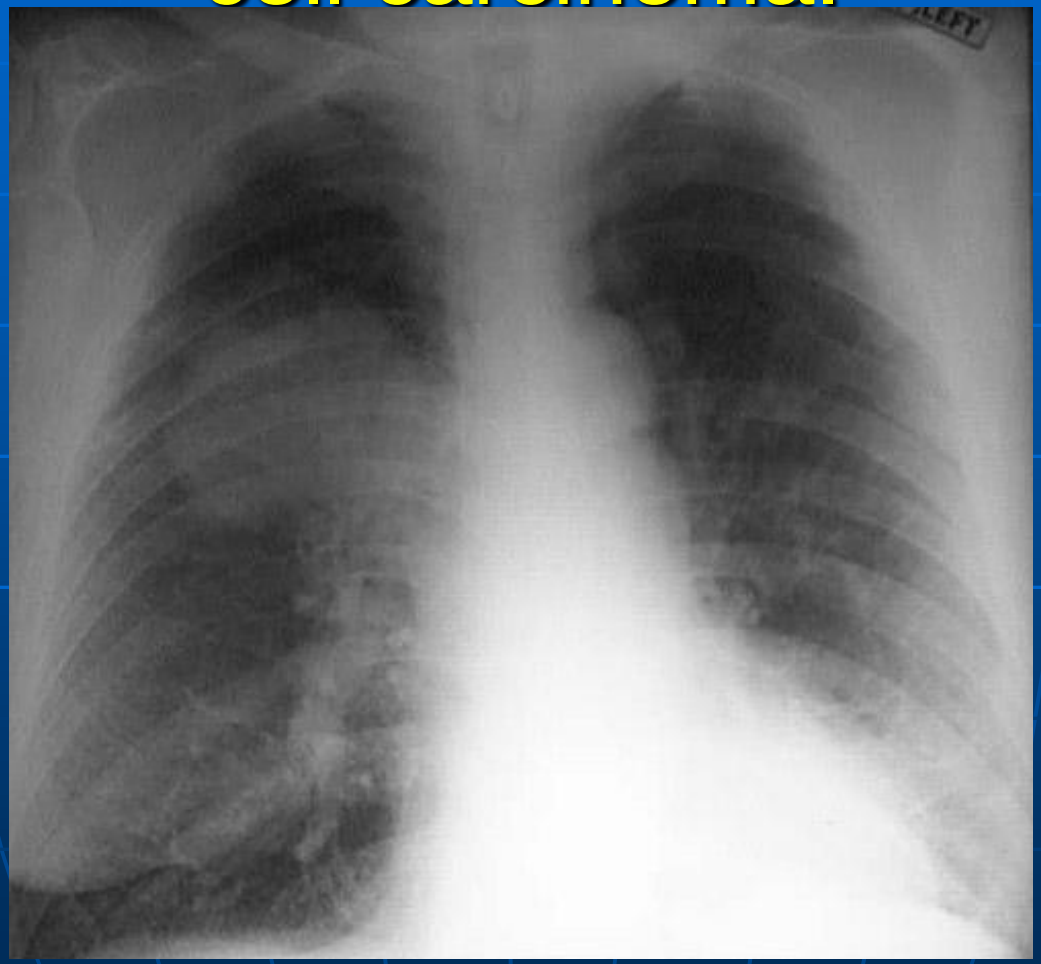
Types of tumor growth are the following:

- expansive - the tumor grows "from its own" moving aside the surrounding tissues;
- appositional - the growth at the expense of neoplastic transformation of normal cells in the tumor cells;
- infiltrative (invasive) -- tumor cells grow into surrounding tissues and destroy them;
- endophytic - infiltrative growth; tumor penetrates deep into the wall of the hollow organ;
- exophytic - expansive growth into the cavity of the hollow organ;
- unicentric - the growth of the tumor from one focus;
- multicentric - the growth of the tumor from plural foci;
-systemic growth is typical for tumors of the blood.

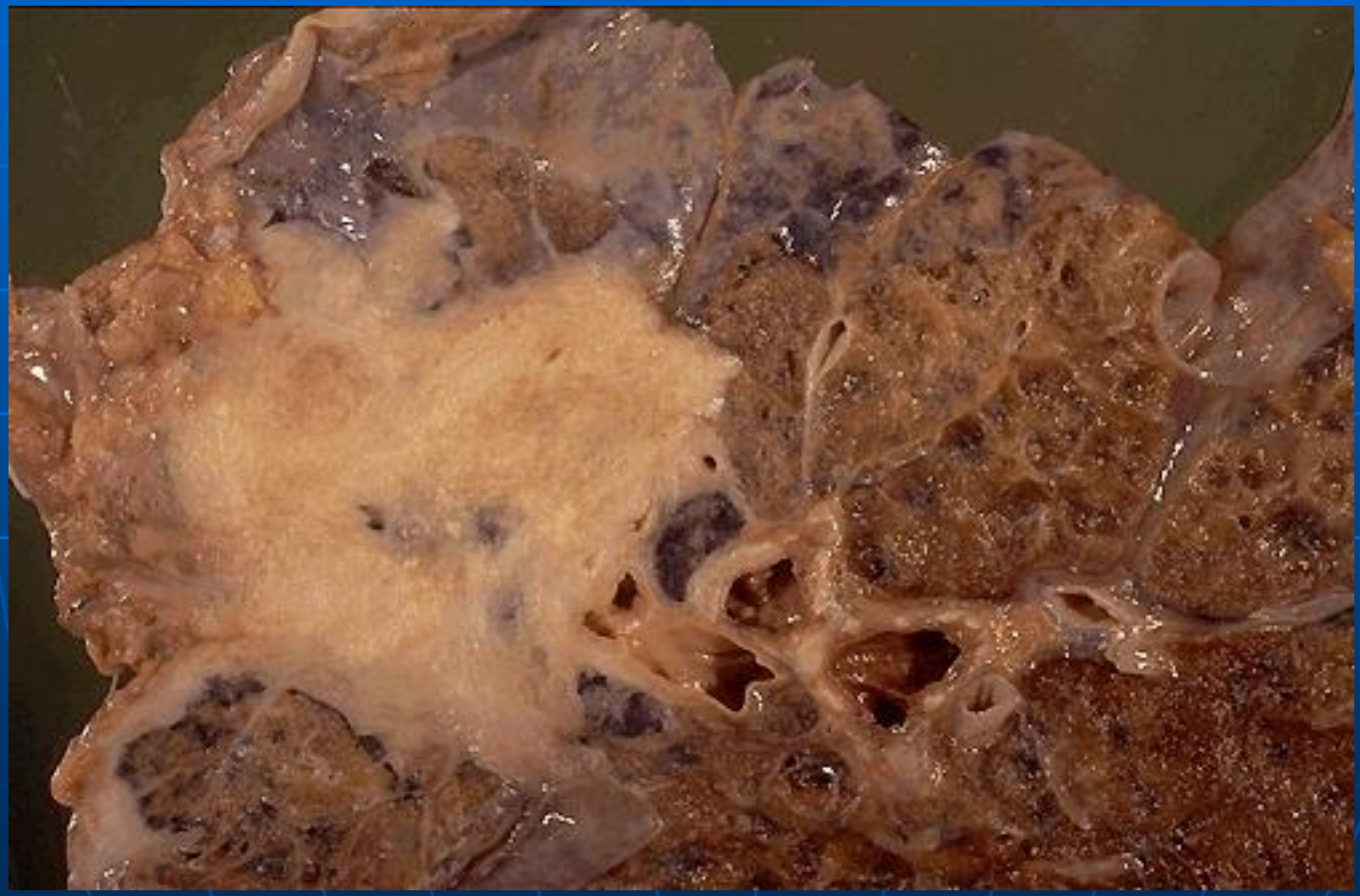
There are two principle types of tumors: benign and malignant.

Here is an osteosarcoma of bone. The large, bulky mass arises in the cortex of the bone and extends outward.

This solitary lung mass is near the hilum and proved to be a squamous cell carcinoma.



This is a squamous cell carcinoma of the lung. It is a bulky mass that extends into surrounding lung parenchyma.



Classification of neoplasms

I. Epithelial neoplasms without specific localization (organo-non-specific).

II. Epithelial neoplasms of specific localization in some endo- and exocrine glands, covering epithelia (organo-specific).

III. Mesenchymal neoplasms .

IV. Melanin-producing tissue neoplasms.

V. Neoplasms of neural tissue and meninges.

VI. Neoplasms of hemopoietic and lymphoid tissues.

VII. Teratomas.

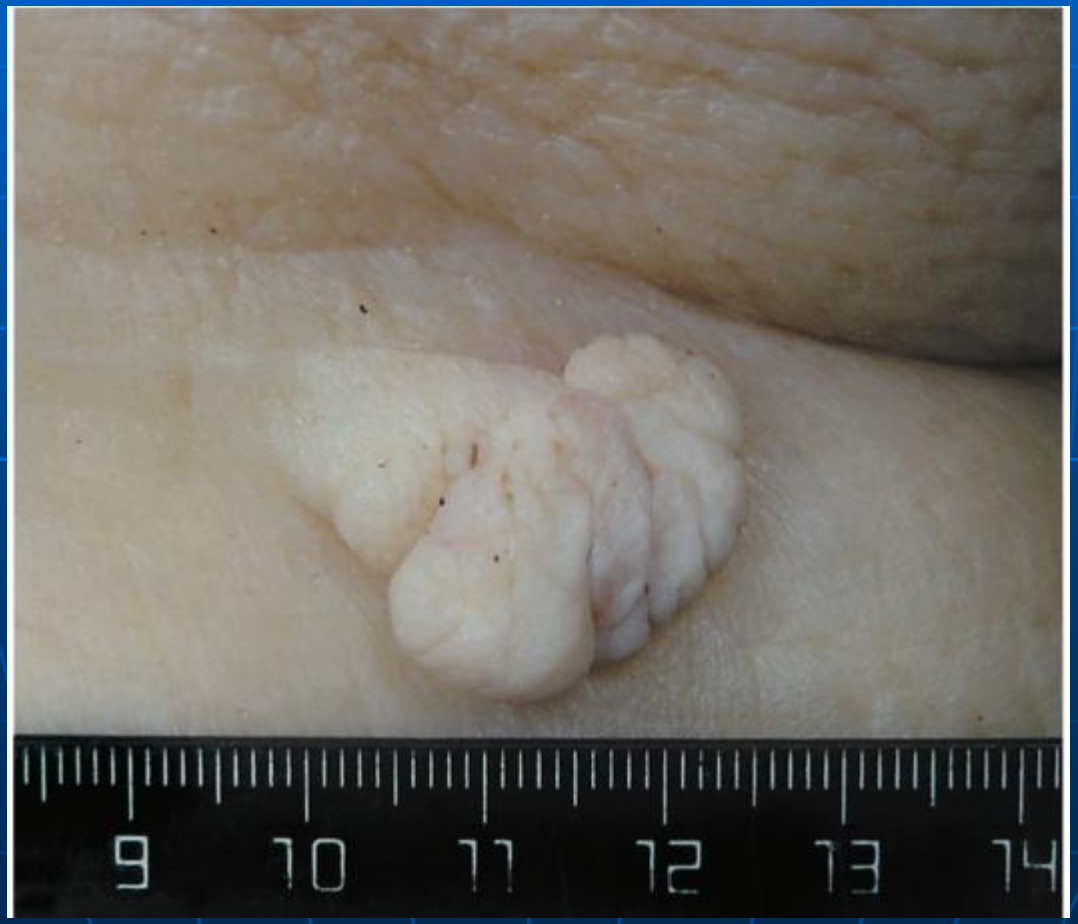
Classification of neoplasms

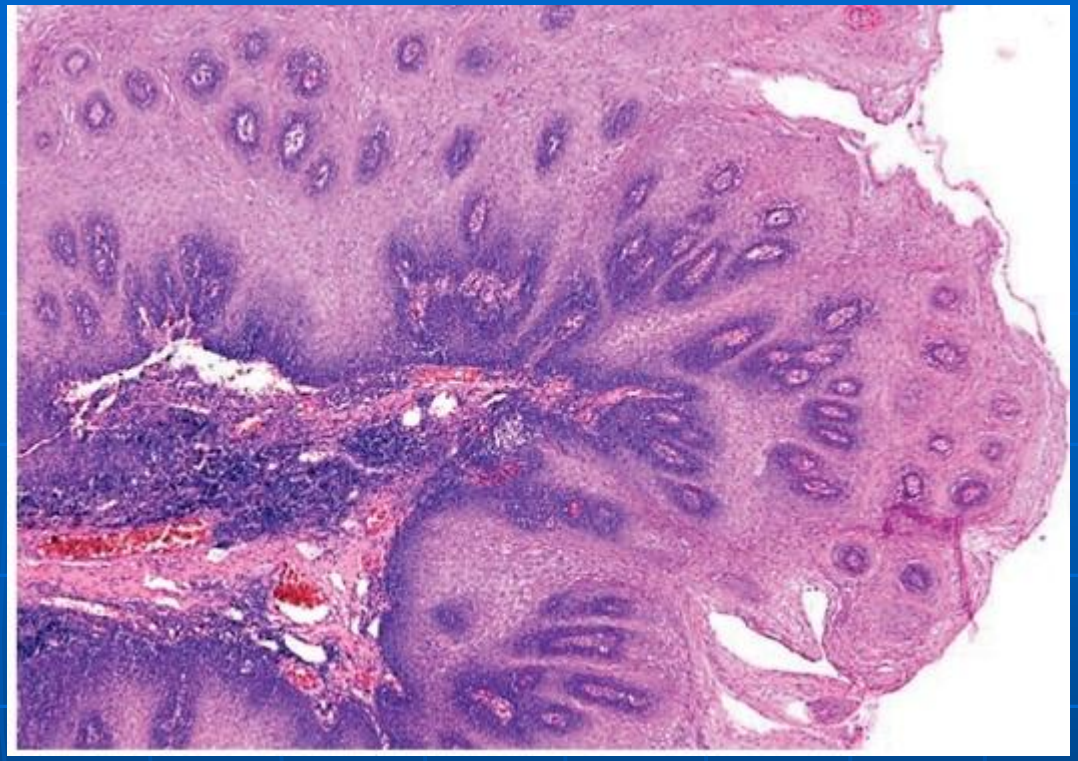
According to clinical and morphological features:

1. BENIGN TUMORS. In general these are designated by attaching the suffix "oma" to the cell of origin: fibroma, chondroma, osteoma, etc.

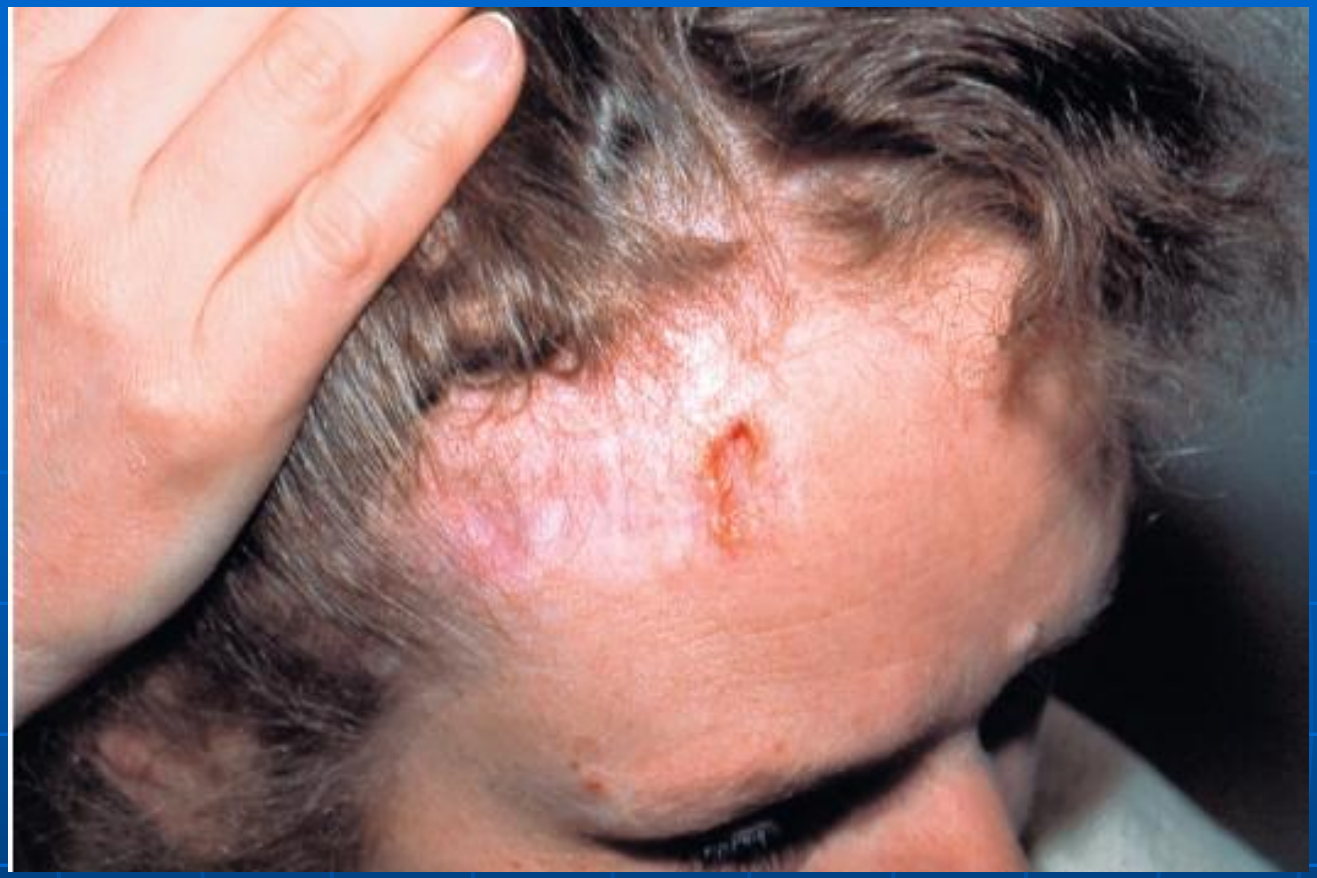
2. MALIGNANT TUMORS The nomenclature of the **MALIGNANT TUMORS** essentially follows the same scheme used for benign neoplasms, with certain additions. Thus malignant tumors arising in mesenchymal tissue are usually called sarcomas: fibrosarcoma, liposarcoma, leiomyosarcoma, etc.

Skin papilloma. Skin tumor with a diameter of about 1.5 cm, on a thin stalk, with a papillary surface in the form of cauliflower, soft consistency, with an unconsolidated base, the color of normal skin (can be pigmented).

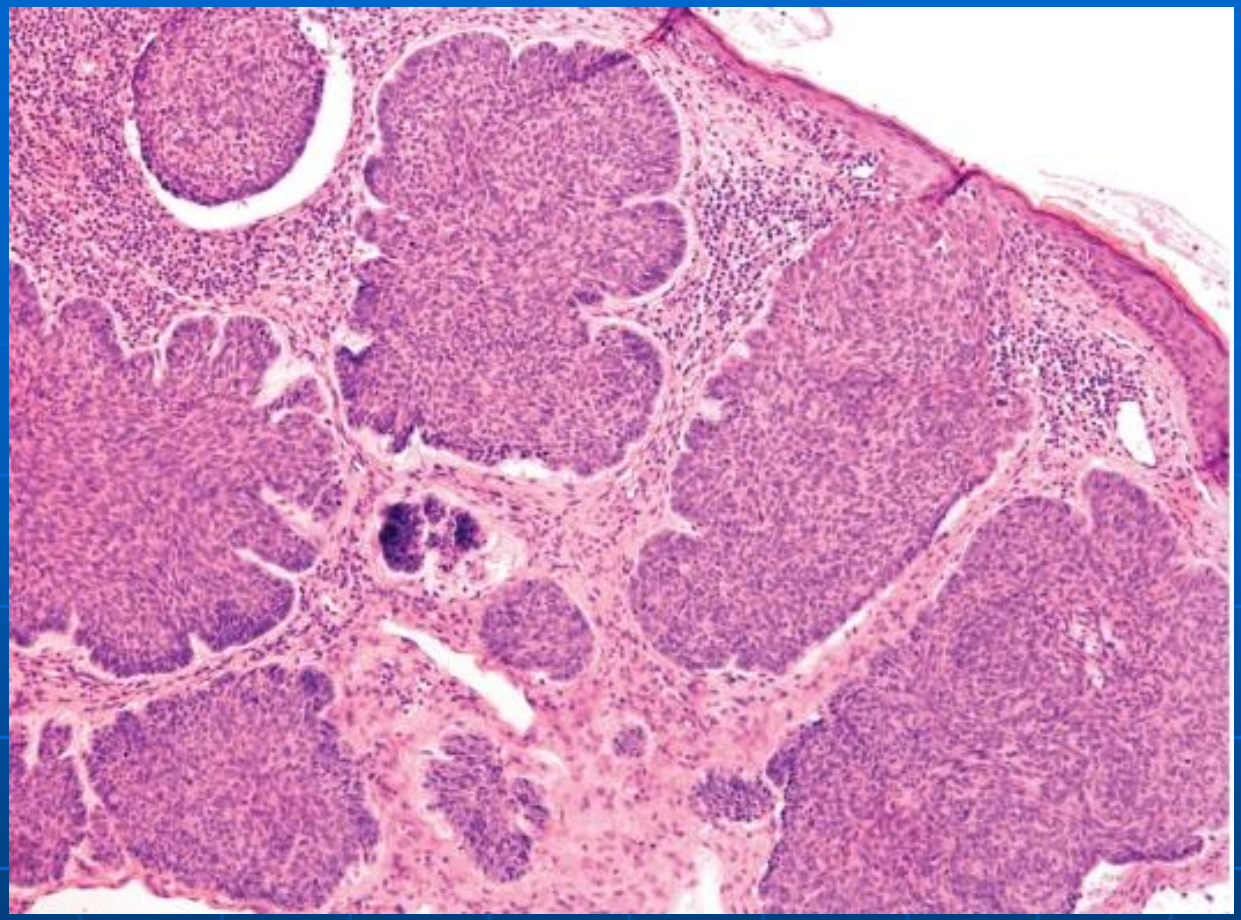




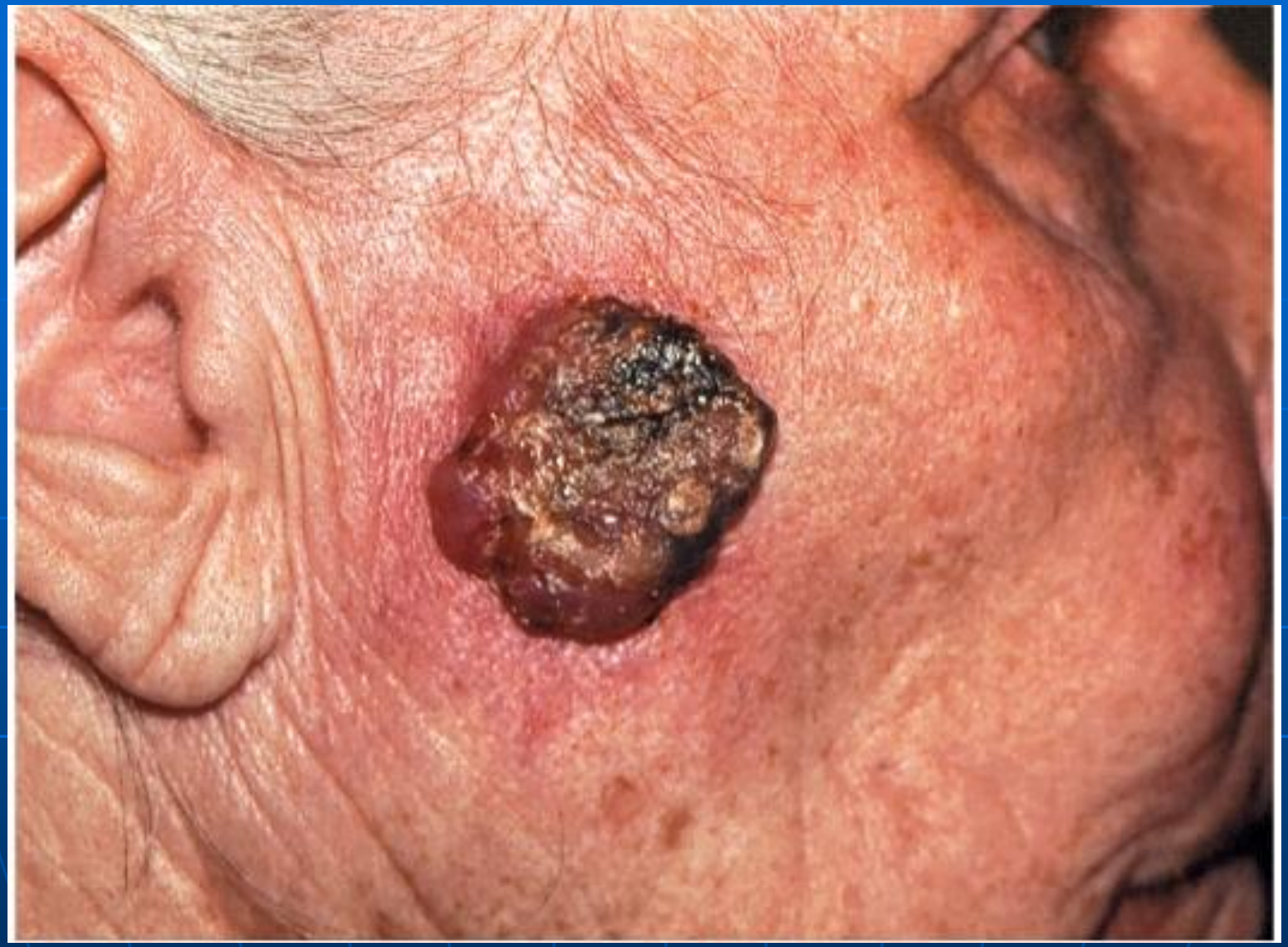
Micropreparation. Skin papilloma. The tumor grows in the form of papillae with hyperkeratosis of a stratified squamous epithelium (tumor parenchyma), which covers connective tissue papillae with vessels (fibrovascular core - tumor stroma), the basal membrane, polarity, stratification, epithelial complexity are preserved. In some places there is an increase in the number of melanocytes, in the stroma there may be foci of inflammatory infiltration; x100



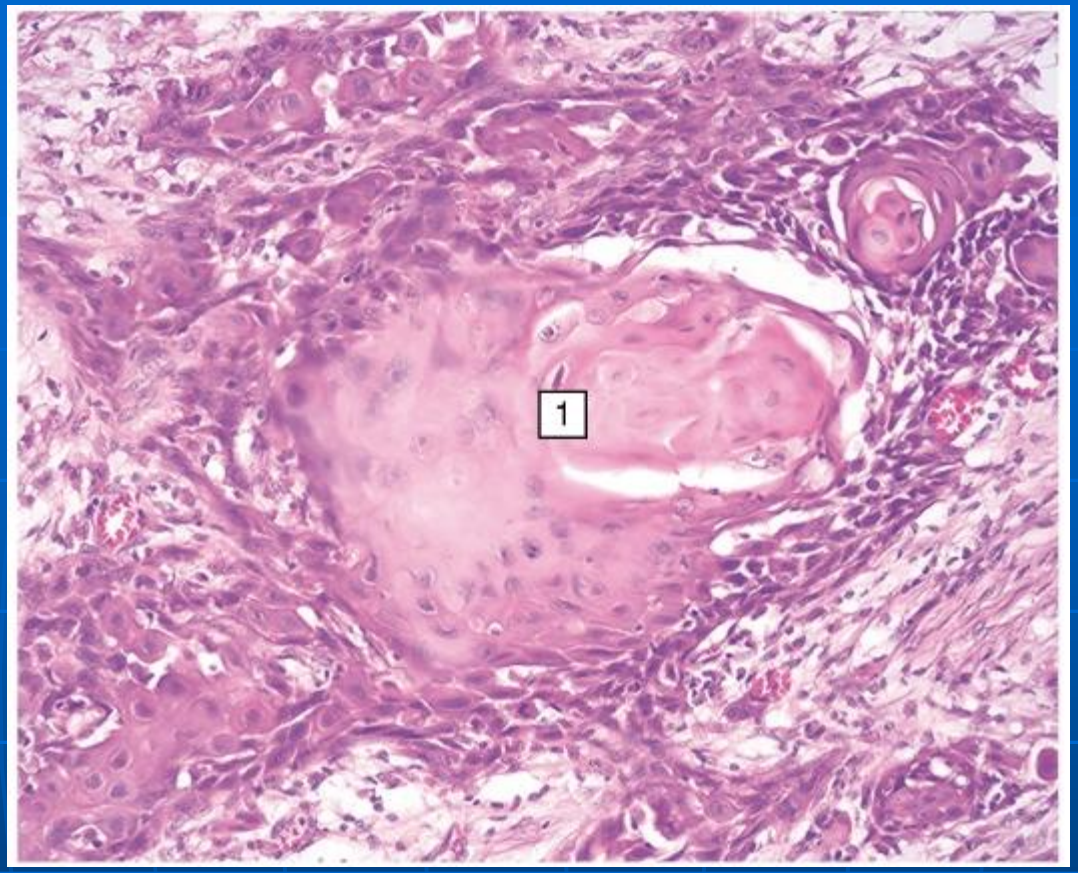
- Basal cell carcinoma of the skin. The tumor is represented by a lesion with ulceration, the bottom of the ulcer is uneven, “dirty”, partially covered with a brown or gray crust. The edges of the ulceration have the appearance of a thickened cushion or consist of small nodules of whitish color.



Basal cell carcinoma of the skin. Tumor complexes have the form of cords or nests (tissue atypia) located in the thickness of the dermis under the epidermis. Tumor cells are similar to the basal cells of the epidermis (basaloid cells), round or oval, with a narrow rim of basophilic cytoplasm, darkly colored oval nuclei, in the peripheral areas of the tumor complexes they are palisadoobrazno (in the form of "palisade"). A moderately pronounced polymorphism of cells and their nuclei (cell atypia); x100



Squamous cell carcinoma of the skin. Ulcerated knot with wide and compacted base, ulcerous defect with uneven, “dirty” bottom, covered with brown crusts.



Micropreparation. Squamous cell carcinoma of the skin with keratinization. Strands of stratified squamous epithelium, penetrating deep into the dermis (with signs of tissue atypia). Tumor cells and their nuclei are polymorphic, hyperchromic nuclei (cellular atypia). Patterns of pathological mitoses are detected. Many cells with eosinophilic keratin inclusions in the cytoplasm, among the cords of tumor cells are rounded clusters of keratin (cancer pearls - 1); x200.

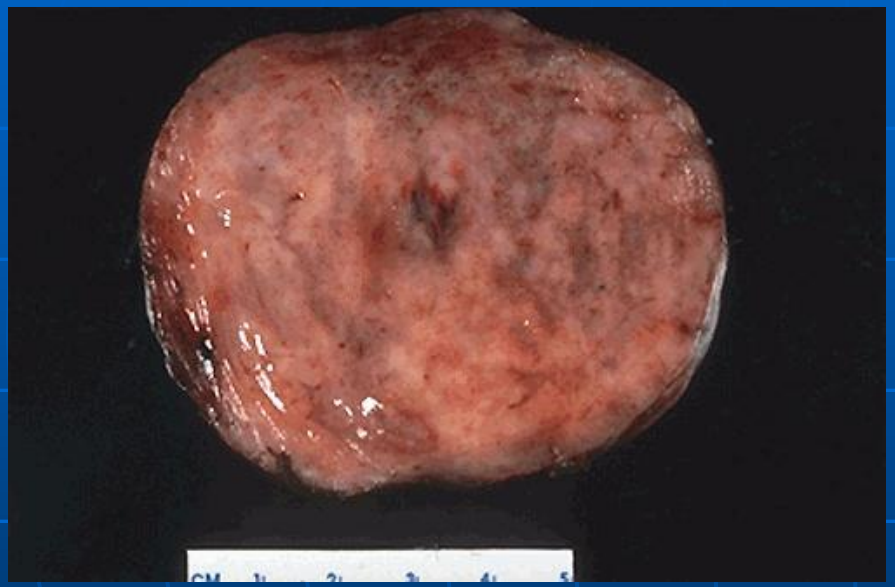
Classification of neoplasms According to histogenesis:

TISSUE	BENIGN TUMORS	MALIGNANT TUMORS
Epithelial tissues:		
Stratified	Papilloma	Squamous cell carcinoma
Simple and glandular	Adenoma	Adenocarcinoma
Tissues mesenchymal (or mesodermal) in origin:		
Fibrous connective tissue	Fibroma	Fibrosarcoma
Vascular tissue	Hemagioma	Hemagioarcoma
Adipose tissue	Lipoma	Liposarcoma
Smooth muscular tissue	Leiomyoma	Leiomyosarcoma
Skeletal striated muscular tissue	Rhabdomyoma	Rhabdomyosarcoma
Cartilage	Chondroma	Chondrosarcoma
Bone	Osteoma	Osteosarcoma
Hemopoietic tissue		Leukemia
Lymphoid tissue		Lymphoma

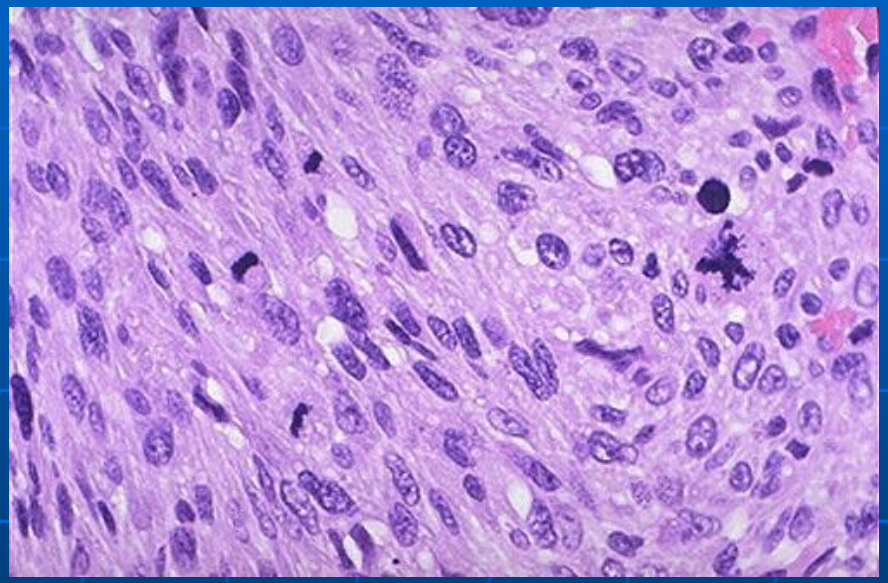
Classification of neoplasms According to histogenesis:

TISSUE	BENIGN TUMORS	MALIGNANT TUMORS
Tissues neural in origin:	Glyomas (biologically malignant):	Glyoblastoma
Neural tissue of CNS	Astrocytoma Oligodendroglyoma	Medullablastoma
Neural tissue of PNS	Neurilemmoma	Malignant neurilemmoma
Melaninproducing tissue		Melanoma
Different tissues:		
Epithelial and connective tissues	Fibroadenoma (mixed tumor)	Malignant fibroadenoma (mixed tumor)
Different germ layers	Teratoma	Malignant teratoma

Sarcoma



This large fleshy mass arose in the retroperitoneum and is an example of a sarcoma. Sarcomas arise from mesenchymal tissues.



This sarcoma has many mitoses. A very large abnormal mitotic figure is seen at the right.

Risk factors.

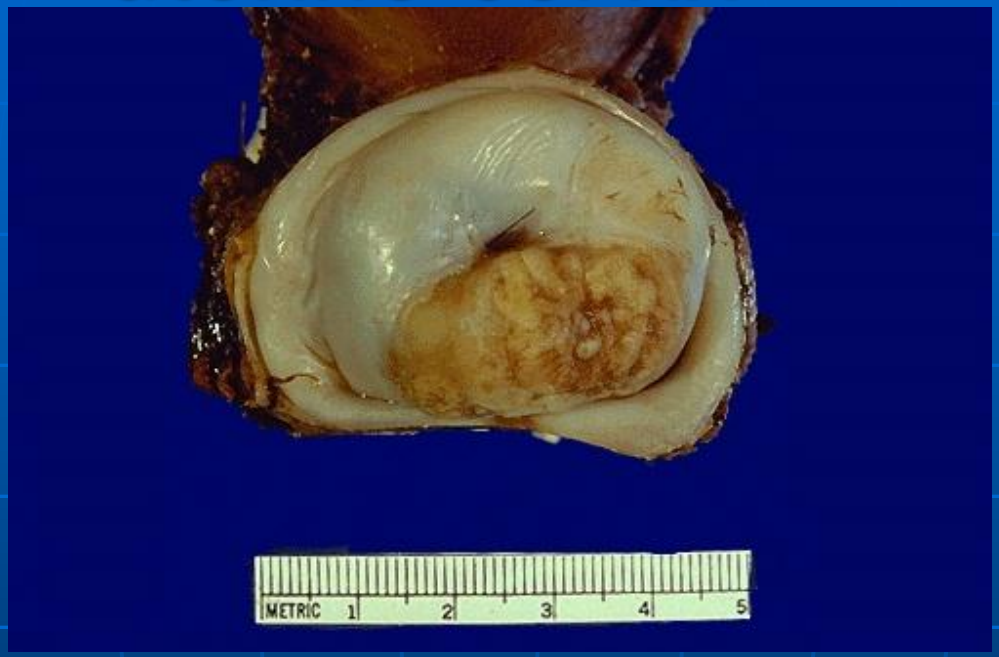
Four important factors believed to be associated with the increasing incidence of cancer are

- age,
- diet,
- environment, and
- genetic makeup.

Environment.

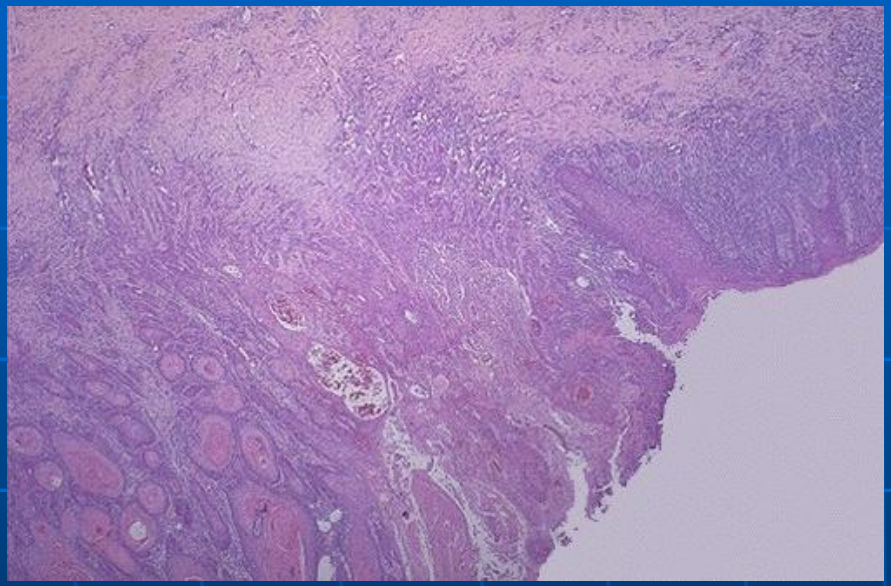
- The environmental agents associated with a high incidence of cancer include radiation and chemical pollution. Industrialization and development, along with the conquest of infection and malnutrition, bring an increase in cancer incidence.
- An urban setting, with its greater air and water pollution than in a rural environment, leads to higher cancer rates, especially for lung cancer.
- Smokers get lung cancer much more frequently than do nonsmokers. Smoking has also been linked to oral, pharyngeal, laryngeal, and bladder carcinoma.
- Industrial workers exposed to certain agents (e.g., asbestos or vinyl chloride) develop cancer more often than do nonexposed groups.
- Sexual activity may be related to cancer.

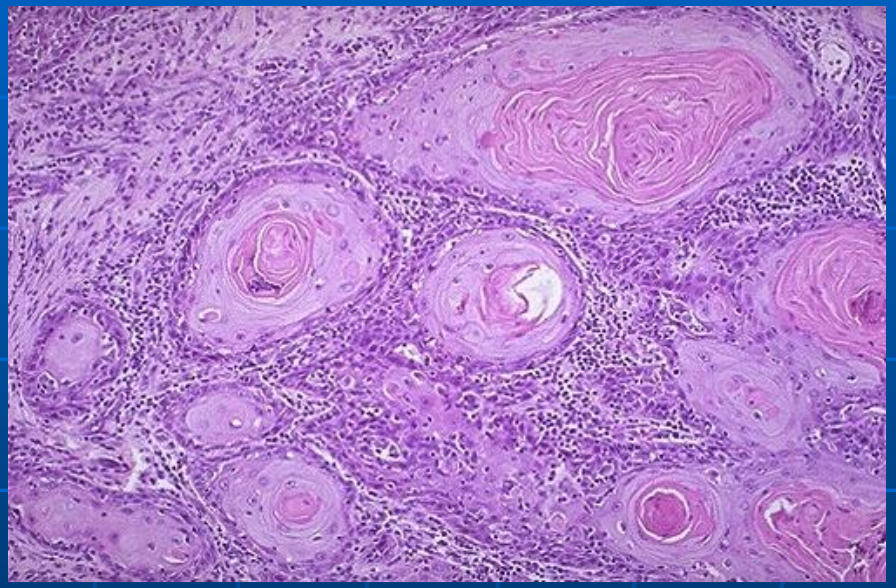
Squamous cell carcinoma of uterine cervix



This is a neoplasm. Neoplasia is uncontrolled new growth. Note the mass of abnormal tissue on the surface of the cervix. The term "tumor" is often used synonymously with neoplasm, but a "tumor" can mean any mass effect, whether it is inflammatory, hemodynamic, or neoplastic in origin. Once a neoplasm has started, it is not reversible.

Squamous cell carcinoma of uterine cervix





This is the microscopic appearance of neoplasia, or uncontrolled new growth. Here, the neoplasm is infiltrating into the underlying cervical stroma. Of course, there can be carcinoma in situ in which a full-fledged neoplasm is present, but has not yet invaded.

MECHANISMS OF CARCINOGENESIS

A. **Role of genetic instability**

1. **Role in initial transformation**

- **a. Because of genetic instability (apparently greater in the neoplastic state), mutant cells are produced. Some of these are destroyed by either metabolic disadvantage or immune mechanisms, but an occasional cell will express a selective advantage over the original neoplastic cells and will give rise to the predominant subpopulation.**
- **b. In time, this selection process leads to increasingly abnormal cells with the acquired properties of the fully developed cancer.**

MECHANISMS OF CARCINOGENESIS

- 2. Subsequent role
- a. The cancerous phenotype itself is unstable. In time, with continued cell division and progression of the neoplastic process, a variety of subclones may appear as the progeny of a single cancer.
- b. This clonal heterogeneity may be manifested morphologically or biochemically. Each of the subclones can show differences in morphology, special product elaboration, and antigenicity.
- c. Cancer cells display a type of clonal evolution that allows for the insidious selection of the most aggressive, rapidly growing, and invasive clones. It is this feature that gives rise to subclones that are fiercely resistant to all known modes of therapy and eventually prove lethal.

MECHANISMS OF CARCINOGENESIS

- 3. The mutation hypothesis
- a. Most neoplasms are associated with a heritable alteration in the involved cells. That is, the transformation of a normal to a neoplastic cell involves changes within the genetic apparatus of the cell (mutation). Heredity, chemicals, physical agents, radiation, and viruses may be involved in this change.
- b. Most investigators feel that neoplasia involves a multifactorial, multistage process of progressive mutation in the genetic makeup of cells. The mutation hypothesis is favored by several arguments.
- All carcinogens (including chemicals, radiation, and viruses) are mutagenic.
- Defective DNA repair mechanisms, as occur in xeroderma pigmentosa, are associated with an increased risk of neoplasia.
- Neoplasia is a clonal disease.

MECHANISMS OF CARCINOGENESIS

- Role of carcinogens
- A constant feature of all agents that are known carcinogens is their demonstrated interaction with DNA. This interaction is obvious for the three major classes of carcinogens, namely chemicals, viruses, and ionizing radiation. Each of these classes can intercalate with nuclear DNA and induce miscoding of genetic information.
- Many carcinogens (often chemicals by nature) must be metabolically activated by cellular enzymes. In the absence of the appropriate enzymes, transformation cannot occur.
- Neoplasia is at least a two-stage process (at least in experimental settings): initiation (primary insult) and promotion (requiring other agents for full expression of the neoplasm).
- a. An initiator causes alterations in DNA structure and is mutagenic.
- b. A promoter stimulates replication of the mutant cells, apparently by acting on cell membranes. Alone, promoters are not carcinogens, and they must act after the initiator to produce cancer.
- c. Two or more initiators, acting in combination, can induce transformation (cocarcinogenesis).

MECHANISMS OF CARCINOGENESIS

- **Role of viruses**
- **1. General concepts**
- **a. Functionally speaking, viruses are blocks of genetic material. Thus, once inside a cell, a virus can change the genetic information that the cell transmits to all its progeny.**
- **b. Neoplastic transformation can be caused by viruses of either the DNA or RNA type, and in some experimental systems, the viral genes seem necessary to maintain the transformed state. The neoplastic change involves the integration of new genetic information from the virus—in the form of DNA nucleotide sequences—into the host's cellular genome.**

MECHANISMS OF CARCINOGENESIS

- **Retroviruses and oncogenes**
- **a. Retroviruses are RNA viruses. They replicate by forming a proviral DNA that integrates into host-cell DNA. The integrated provirus then acts just like host-cell genes, transmitting genetic information to the cell's progeny.**
- **Some retroviruses contain one or more nucleotide sequences capable of inducing malignant transformation. These sequences are called viral oncogenes (v-oncs). Several v-oncs have proved to induce cancers in experimental systems; none is definitely known to produce cancer in humans, although for some viruses there is strong evidence that this is so in humans.**
- **Eukaryote cells contain genes with nucleotide sequences that are identical or closely similar (homologous) to v-oncs. These proto-oncogenes, or cellular oncogenes (c-oncs), are thought to be the precursors of v-oncs, picked up by retroviruses in the course of evolution.**

MECHANISMS OF CARCINOGENESIS

- b. Oncogenes probably confer a selective growth advantage on the transformed cell, since many *v-oncs* are genes that code for protein kinase enzyme systems, which appear to bind to cell membranes and serve as growth factor receptors.
- c. The proto-oncogene (c-onc) sequences found in the DNA of normal cells may be involved in normal cellular differentiation and in growth control, since their evolutionary conservation suggests an important natural function.
- d. Retrovirus genomes (even those without *v-oncs)* also contain long repeated nucleotide sequences at both ends of the integrated DNA. These long terminal repeat (LTR) sequences regulate transcription. LTRs may be capable of activating nearby c-oncs, converting them to oncogenes and causing the breakdown of control mechanisms. (Gene amplification, gene rearrangements, and chromosomal translocations are suggested mechanisms of oncogene activation.)
- e. Possibly, other etiologic (perhaps exogenous) factors also act by activating *c-oncs.*

MECHANISMS OF CARCINOGENESIS

- f. Certain c-oncs have been found in patients with specific human cancers, although causation has not been proved.
- The oncogene c-myc is associated with a translocation between chromosomes 8 and 14 in Burkitt's lymphoma.
- The oncogene c-ras is associated with loss of the small arm of chromosome 11 in Wilms' tumor.

MECHANISMS OF CARCINOGENESIS

- 3. DNA viruses. Less is known about the role of DNA viruses in tumorigenesis.
- a. Carcinogenic DNA viruses code for certain proteins that are prerequisites for the transformation of cells, such as the SV40 virus T antigens. These substances, like the protein products of v-oncs, are membrane-associated and have protein kinase activity.
- b. Moreover, the SV40 virus genome also has repeat sequences like the LTRs of retroviruses; these sequences are required for the transcription of T antigens.
- D. Role of endogenous factors

CHARACTERISTICS OF NEOPLASMS.

- Components. All neoplasms have a parenchyma and a stroma.
- The parenchyma comprises the neoplastic proliferating cells. Parenchymal morphology underlies the name assigned to a neoplasm, and parenchymal behavior determines whether a neoplasm is benign or malignant.
- The stroma comprises the supporting connective tissue and blood supply that allows the neoplasm to grow.

CHARACTERISTICS OF NEOPLASMS.

- **Clonality. In theory, a neoplasm represents the progeny of one cell, a clone, and in many neoplasms all cells show the same abnormal karyotype. Even when several chromosome patterns are present, marker chromosomes in each cell suggest that the different subpopulations derive from a common stemline. The following are examples.**
- **Immunoglobulins from a myeloma (a plasma cell neoplasm) display a homogeneity that is characteristic of a single clone.**

CHARACTERISTICS OF NEOPLASMS.

- C. Autonomy. Neoplastic cells exhibit uncontrolled proliferation; that is, they are autonomous.
- Normally, inhibitory influences control cell growth and proliferation; this accounts for the stoppage of cell movement that occurs when two cells growing in tissue culture collide. Neoplastic cells, in contrast, tend to grow over one another.
- The property of autonomy is probably related to the fact that neoplastic cells show changes in morphology and membrane composition and, hence, in receptor sites.

CHARACTERISTICS OF NEOPLASMS.

- D. Blood supply. Solid neoplastic growth requires the development of a blood supply to the neoplasm; that is, neovascularization. Without such a blood supply, solid neoplasms cannot grow beyond 2 to 3 mm in diameter.
- Various experiments have shown that neovascularization does not require direct cell-to- cell contact either between neoplastic cells or between these cells and endothelial cells in blood vessels near the lesion.
- A protein called tumor angiogenesis factor that stimulates endothelial cell mitosis and new vessel growth has been discovered.

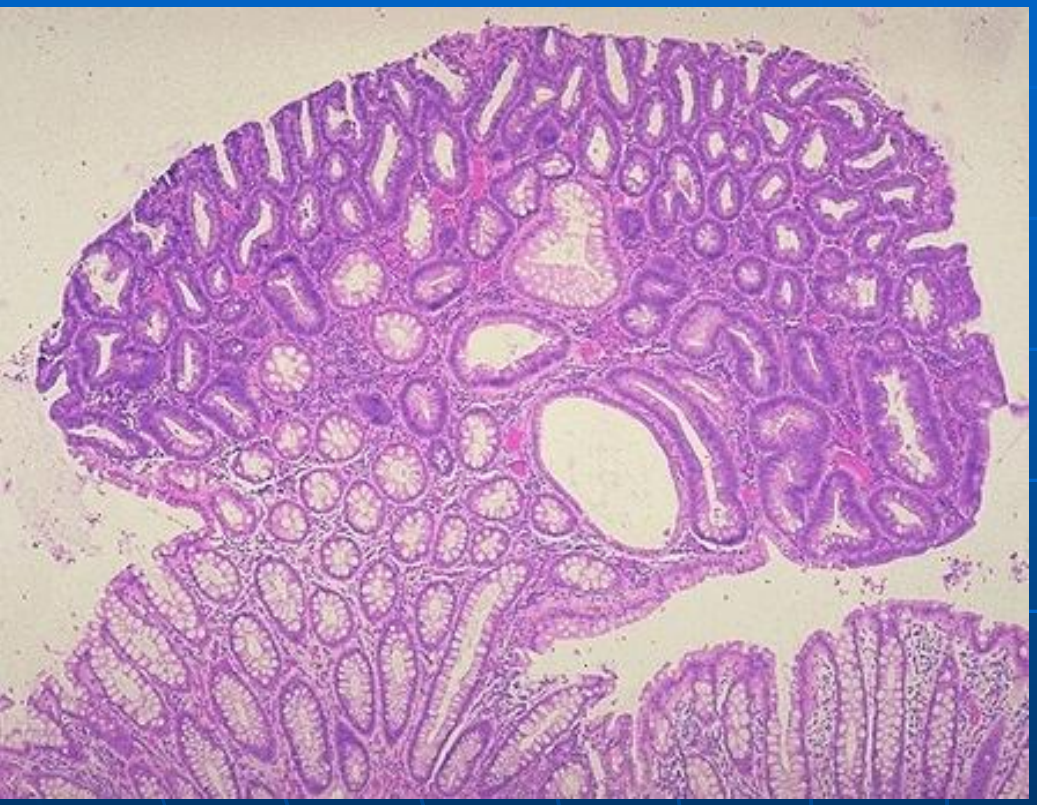
CHARACTERISTICS OF NEOPLASMS.

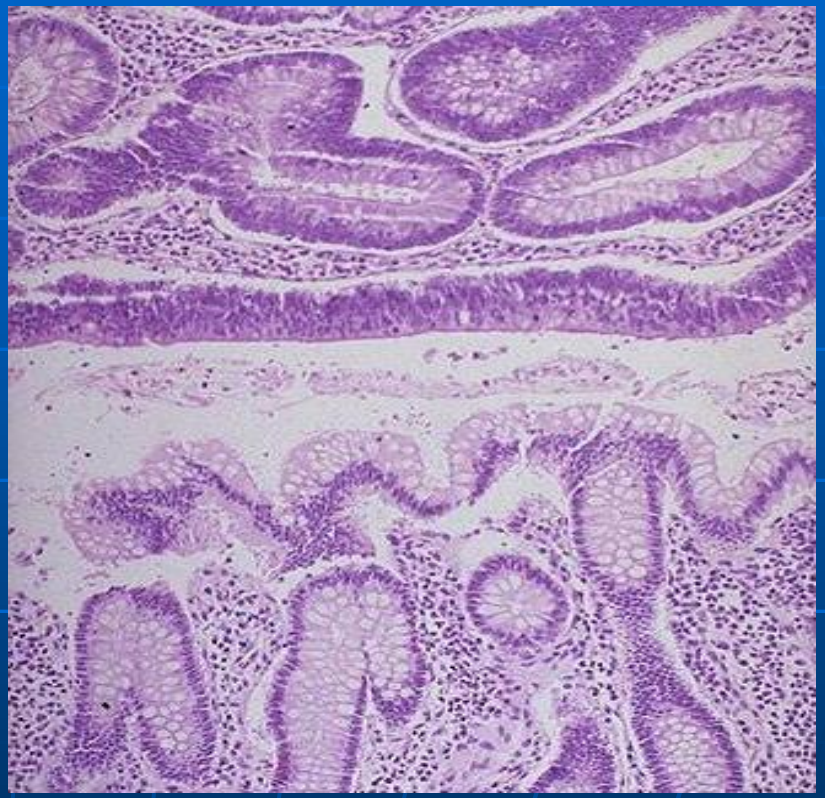
- E. Metastasis. The major characteristic of cancer is the capacity to metastasize.
- As the neoplastic clone undergoes mutation, the more aggressive subpopulations selected tend to be those with metastasizing potential.

The differences between benign and malignant tumors can be discussed under the following headings:

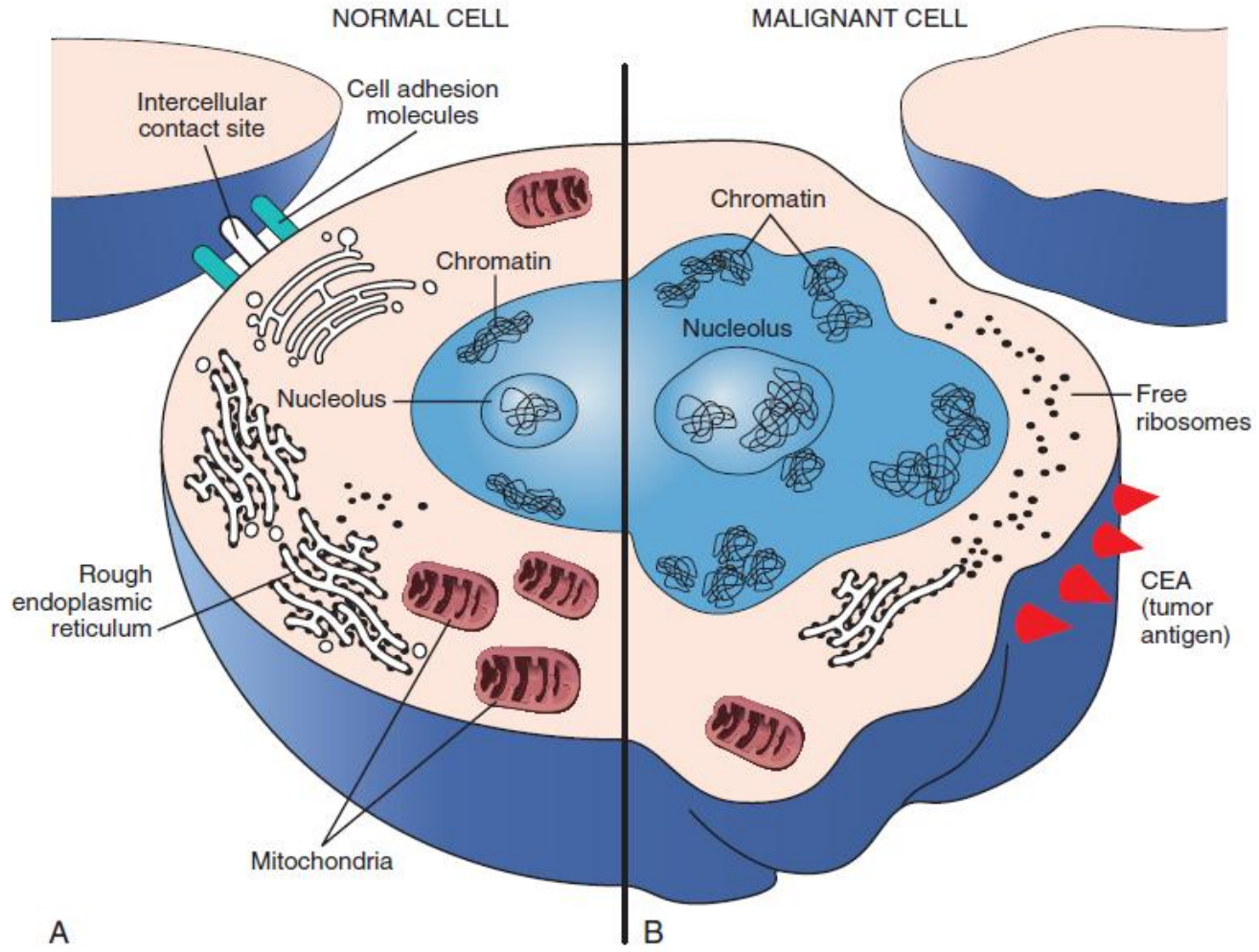
- **- differentiation and anaplasia,**
- **– rate of growth,**
- **- local invasion (throw basement membrane, into blood or lymph vessels and into the capsule);**
- **- metastasis.**

differentiation and anaplasia

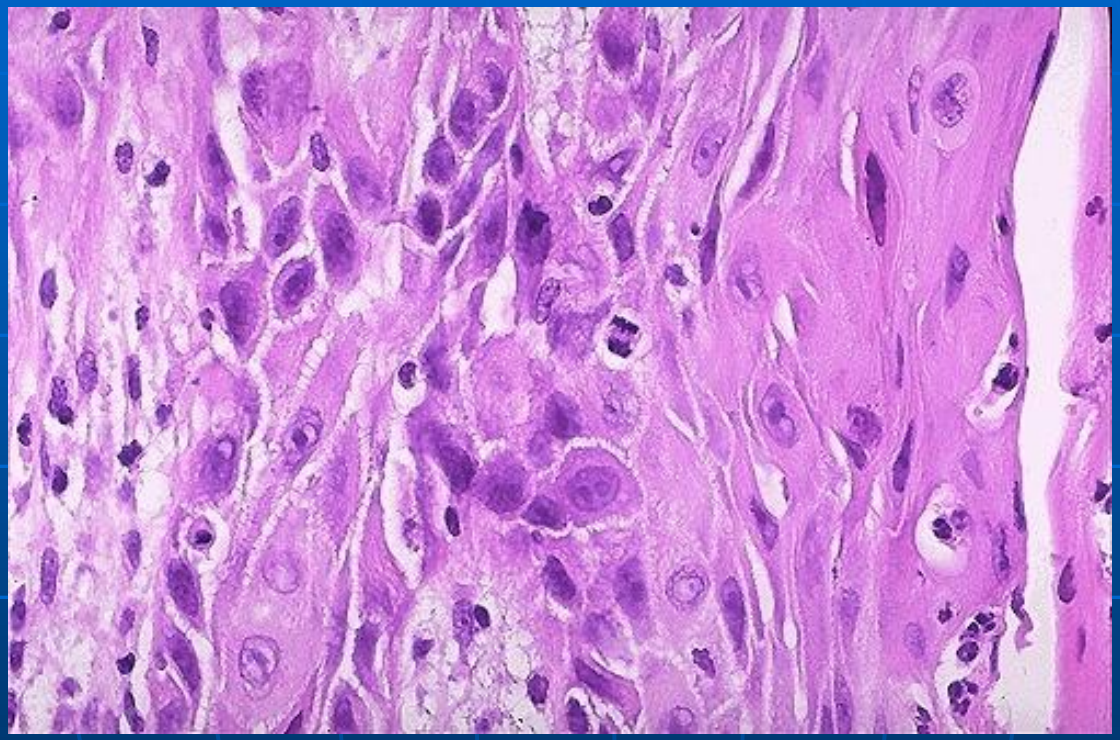




The concept of differentiation is demonstrated by this small adenomatous polyp of the colon. Note the difference in staining quality between the epithelial cells of the adenoma at the top and the normal glandular epithelium of the colonic mucosa below.

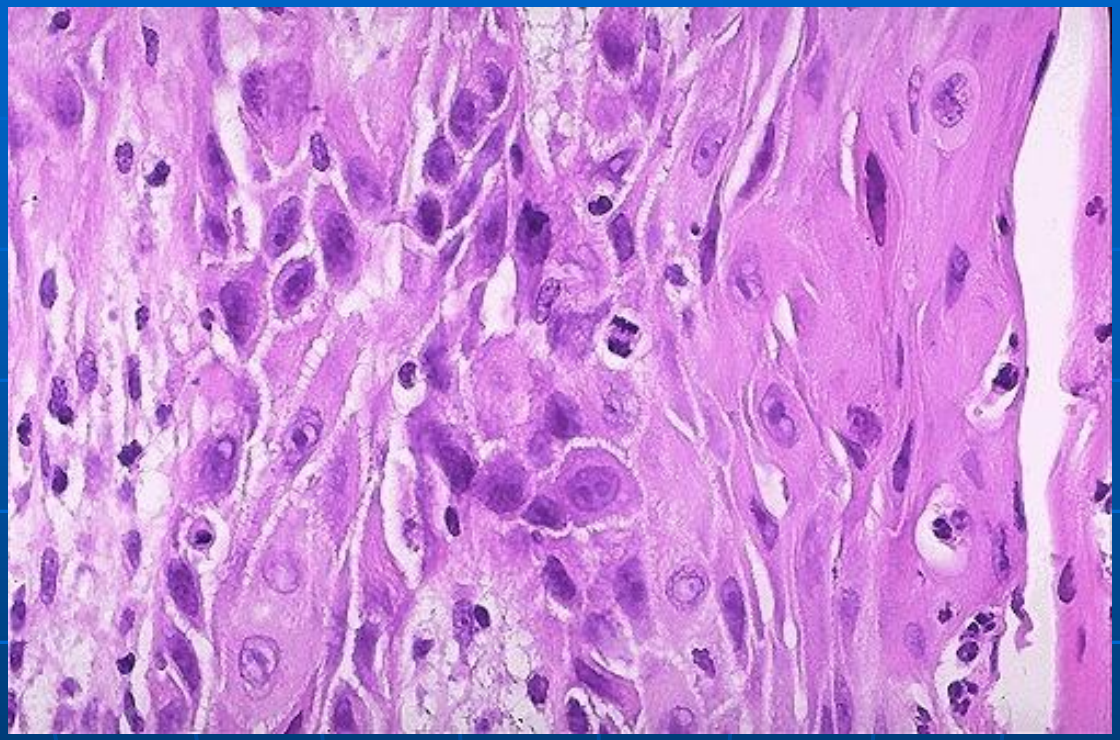

NORMAL CELL
MALIGNANT CELL
Intercellular contact site
Cell adhesion molecules
Chromatin
Nucleolus
Rough endoplasmic reticulum
Mitochondria
Chromatin
Nucleolus
Free ribosomes
CEA (tumor antigen)
A
B

differentiation and anaplasia



Both the cells and nuclei characteristically display pleomorphism - variation in size and shape.

Rate of growth.



Undifferentiated tumors usually possess large number of mitosis, but it should be noted, however, that the presence of **mitosis** does not necessarily indicate that a tumor is malignant or that the tissue is neoplasmic. More important as a morphologic feature of malignant neoplasia are **atypical mitotic figures** sometimes producing tripolar, quadripolar or multipolar spindles.

Cell organelles in malignant versus normal cells

- 1. Organelles in the cytoplasm when compared to a normal cell
- a. Fewer mitochondria
- b. Less prominent rough endoplasmic reticulum (RER)
- c. Loss of cell-to-cell adhesion molecules (cadherins)

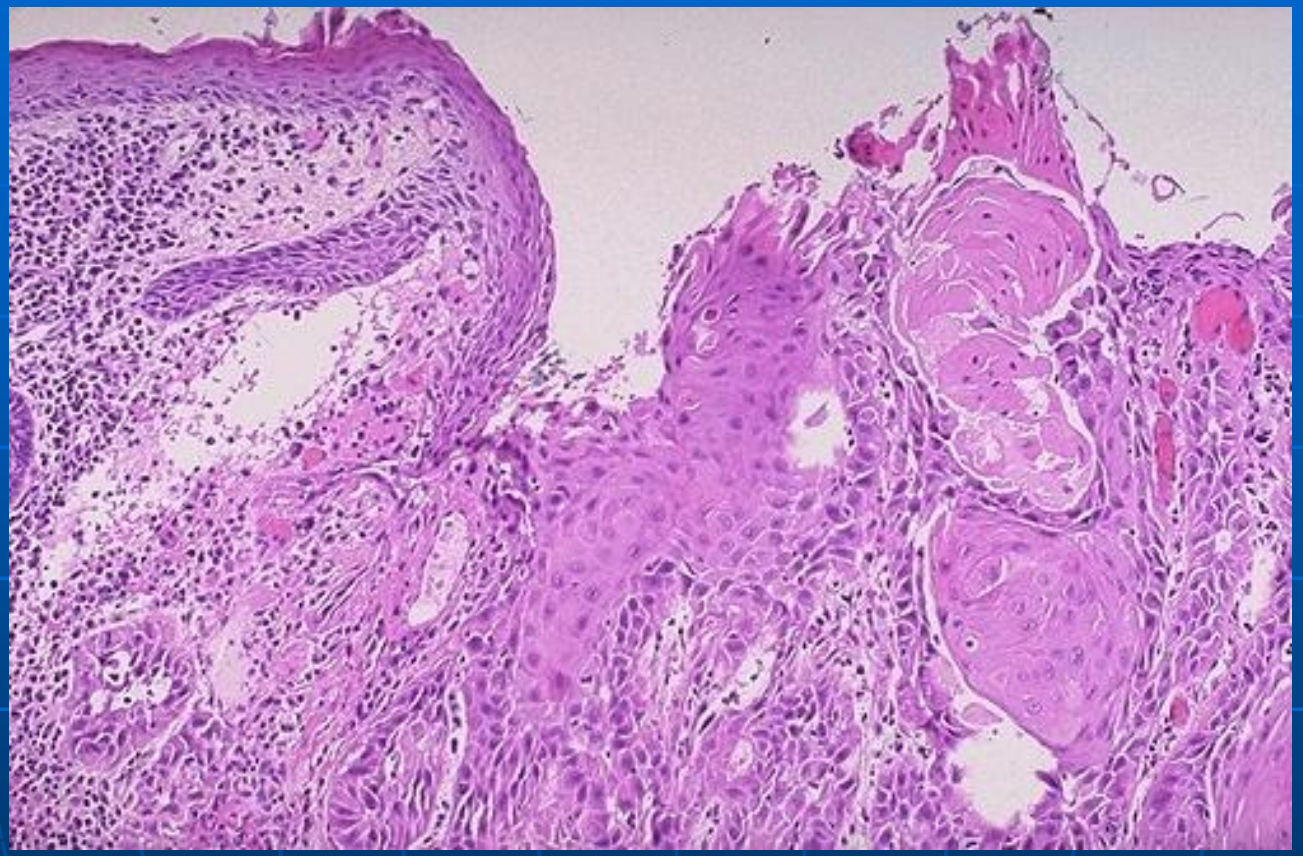
Cadherins are a group of calcium-dependent transmembrane proteins that play an important role in cell-to-cell adhesion.

- 2. Nuclear features when compared to a normal cell
- a. Nucleus is larger, has irregular borders, and has more chromatin (hyperchromatic)
- b. Nucleolus is larger and has irregular borders
- c. Mitoses have normal and atypical mitotic spindles

Growth rate in benign and malignant tumors

- 1. Benign tumors usually have a slow growth rate.
- 2. Malignant tumors have a variable growth rate.
- a. Growth rate correlates with degree of differentiation of the malignant tumor.
- b. Example—anaplastic (high-grade) cancers have an increased growth rate, whereas low-grade cancers have a slow growth rate.
- 3. Clinically detectable tumor mass must have 30 population doublings to produce 109 cells, which equals 1 g of tissue.
- 4. Malignant cells with an increased growth rate (e.g., acute leukemia) are treated with cell cycle–specific chemotherapy agents.
- a. Methotrexate inhibits the S phase of the cell cycle (duplication of DNA), whereas vincristine inhibits the mitotic (M) phase of the cell cycle.
- b. When malignant cells are killed, other malignant cells quickly enter the cycle, and the cycle repeats itself so that the size of the tumor begins to shrink (this is called debulking of the tumor).

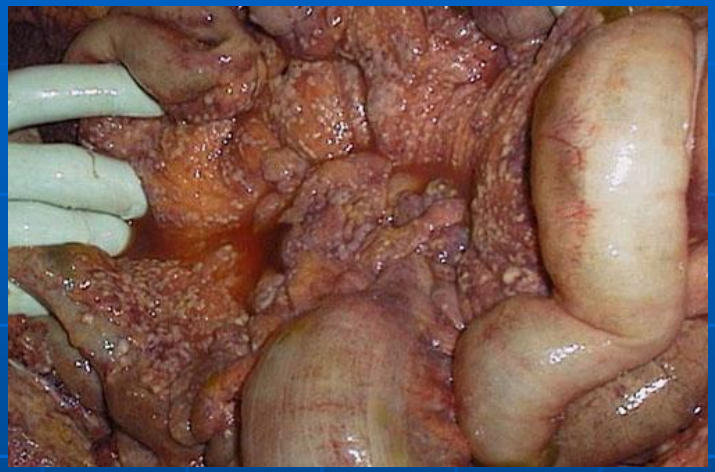
Local invasion.

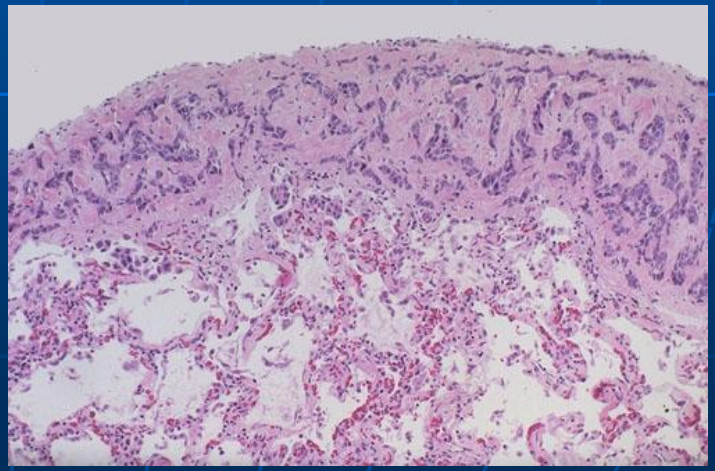


The growth of cancers is accompanied by progressive infiltration, invasion and destruction of the surrounding tissue. In general, they are poorly demarcated from the surrounding normal tissue, and thus they are obviously invasive and can be expected to penetrate the wall of colon or uterus, for example, or fungate through the surface of the skin.

Metastases.

- The development of metastases is the most reliable feature that differentiates malignant from benign tumors.
- Metastases are tumors implants discontinuous with the primary tumor. Metastasis marks tumor as malignant because benign neoplasms do not metastasize. The invasiveness of cancers permits them to penetrate into blood vessels, lymphatics, and body cavities, producing the opportunity of spread. With few exceptions, all cancers can metastasize.





Dissemination of cancers may occur through one of **four pathways**:

- - direct seeding of body cavities or surfaces,
- - lymphatic spread,
- - hematogenous spread and
- - mixed pathway.

IV. IMMUNE HOST RESPONSES TO MALIGNANT NEOPLASMS.

- At least in animal studies, autoimmune reactions to cancer cells are common. However, the ability of cancer cells to stimulate the immune mechanism in humans is usually quite small and is probably inconsequential as a defense mechanism.

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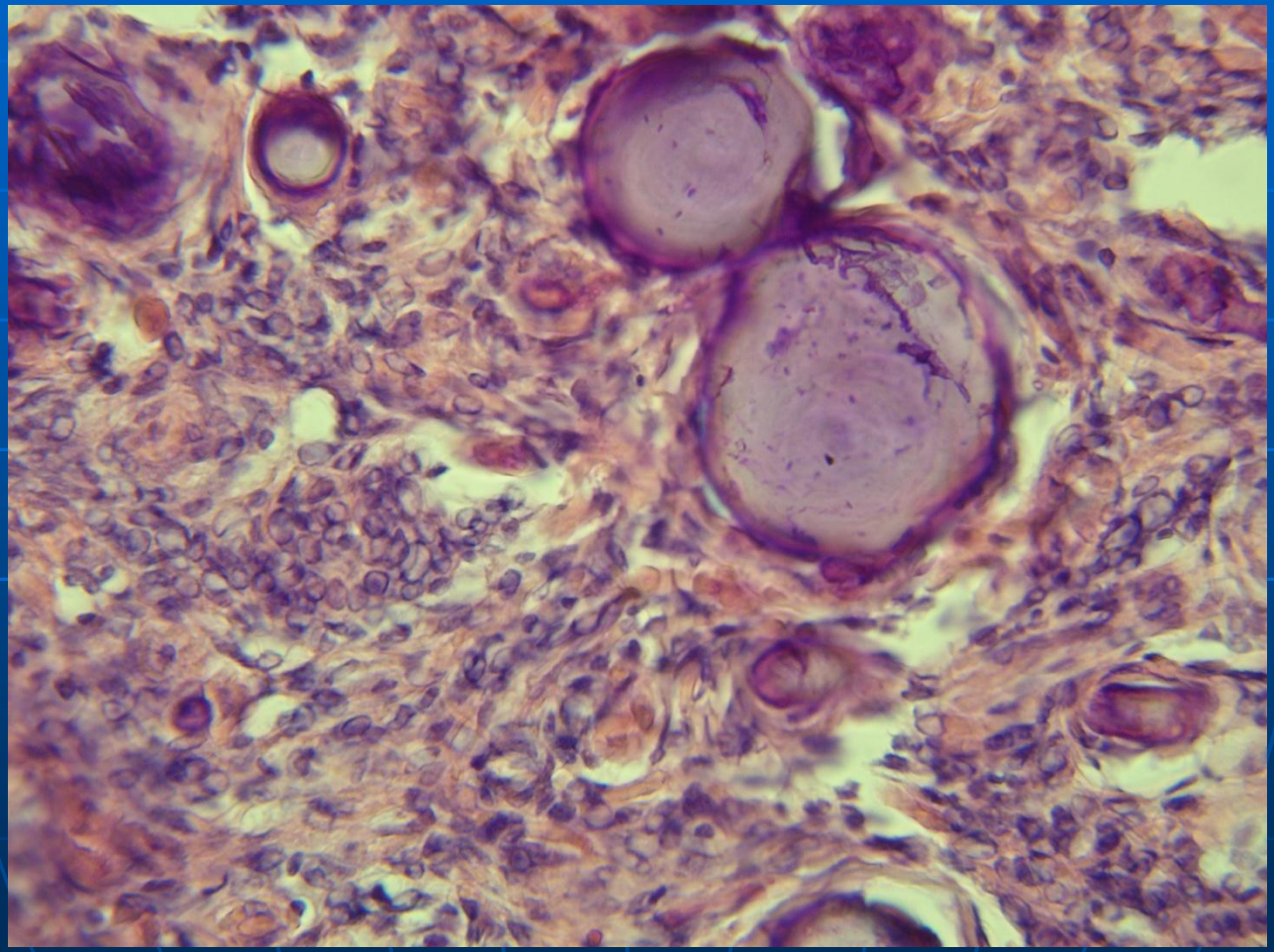

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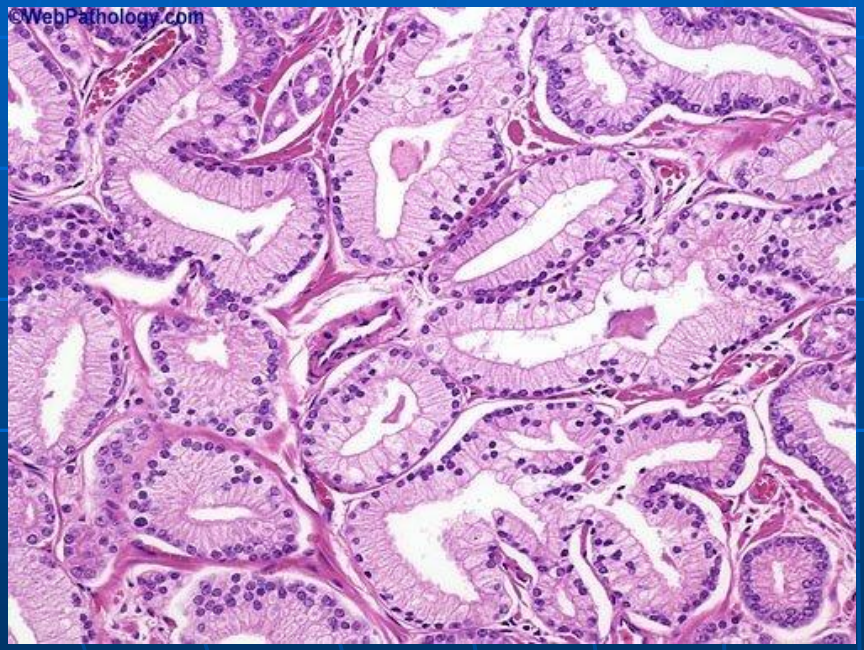
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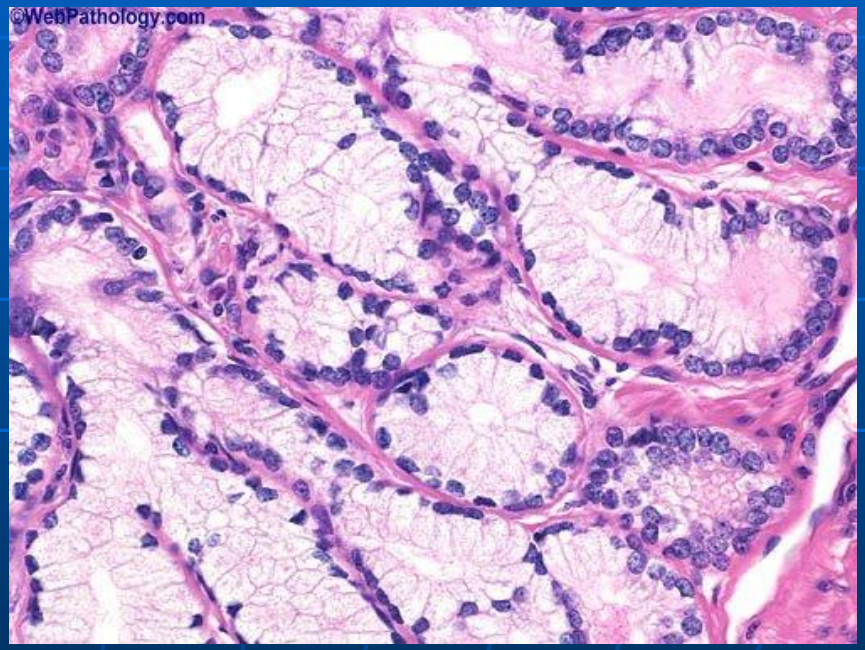
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