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.

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.

Classification of neoplasms
According to histogenesis:

TISSUE	BENIGN TUMORS	MALIGNANT TUMORS
Epithelial tissues:	**Epithelial neoplasms**	**Epithelial neoplasms**
Stratified	Papilloma	Squamous cell carcinoma
Simple and glandular	Adenoma	Adenocarcinoma
Neoplasms from neuro-endocrine cells	Carcinoid	Atypical carcinoid
Tissues mesenchymal (or mesodermal) in origin:	**Mesenchymal neoplasms**	**Mesenchymal neoplasms**
Fibrous connective tissue	Fibroma	Fibrosarcoma
Vascular tissue	Hemangioma	Hemangioarcoma
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 Medullablastoma
Neural tissue of CNS	Astrocytoma Oligodendroglyoma	
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

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.

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.

Features of Malignant Tumors

Major:

- Metastases (hematogenous, lymphogenous, etc.)
- Invasion (into the basement membrane, into the blood and/or lymphatic vessels, capsule, neighboring organs, etc.)

Minor:

- Atypia (tissue, cellular, nuclear, subcellular, etc.), polymorphism
- The number of mitoses

Classification of epithelial neoplasms

The classification of neoplasms from the epithelium is based on the generally accepted criteria, according to which there are:

- benign tumors of the epithelium (epithelioma);
- malignant (cancer, carcinoma).

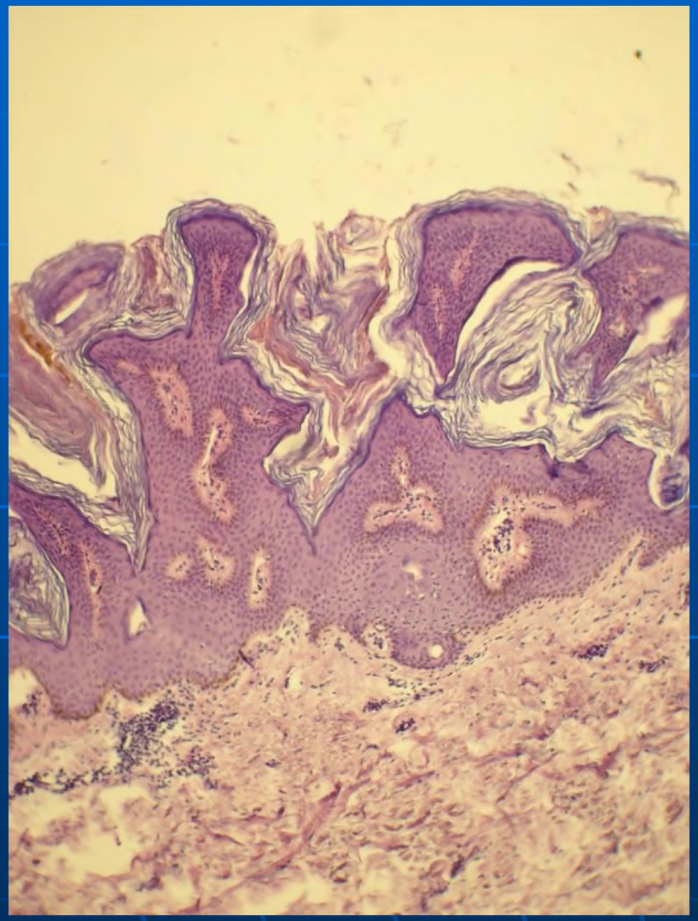
According to histogenesis:

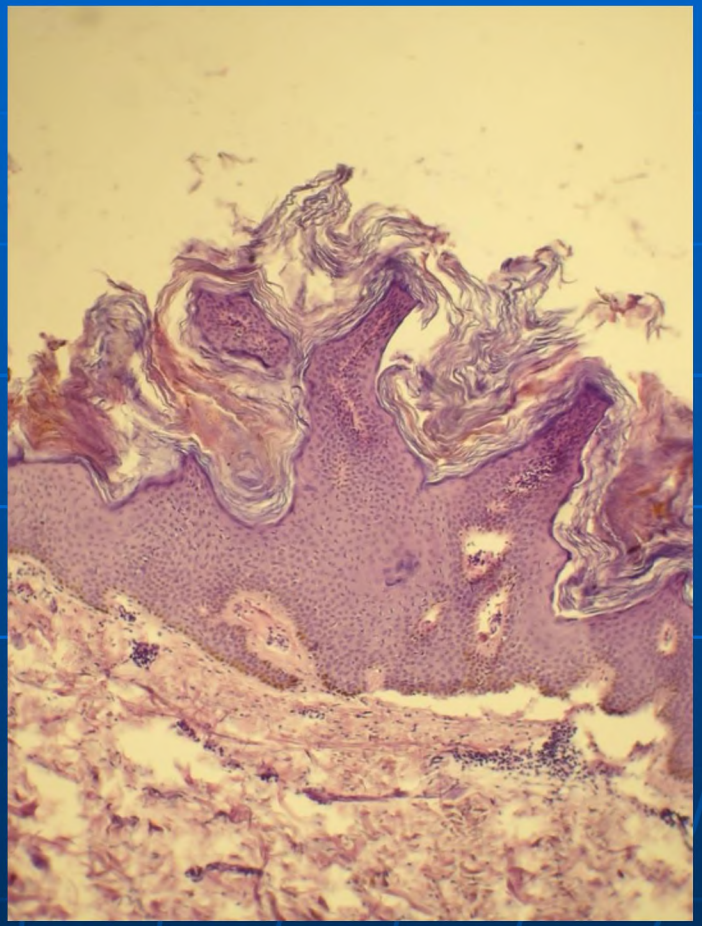
- from the surface epithelium (squamous and transitional - papilloma and squamous and transitional cell carcinoma);
- from glandular epithelium (adenomas, adenomatous polyps and adenocarcinomas);
- according to the grade of differentiation adenocarcinomas 3 grades of differentiation are distinguished.

Papilloma

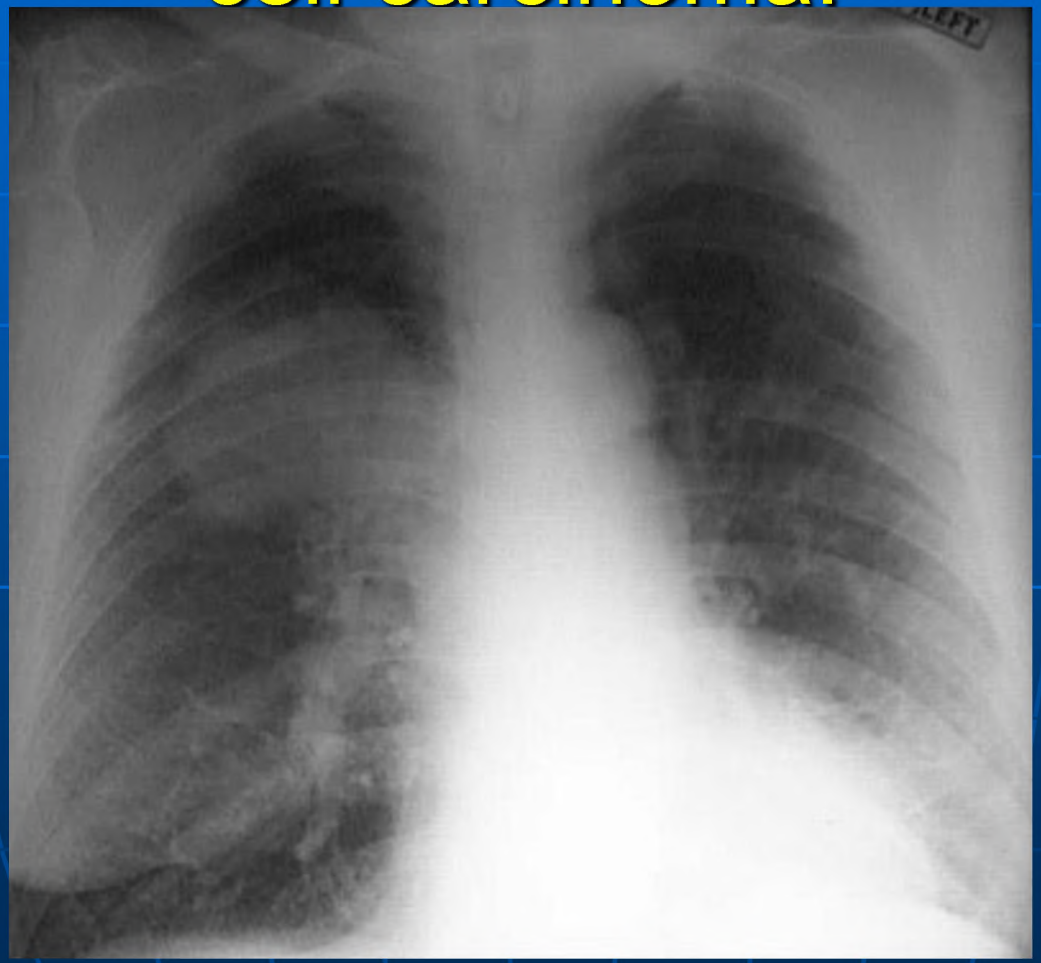


Papilloma

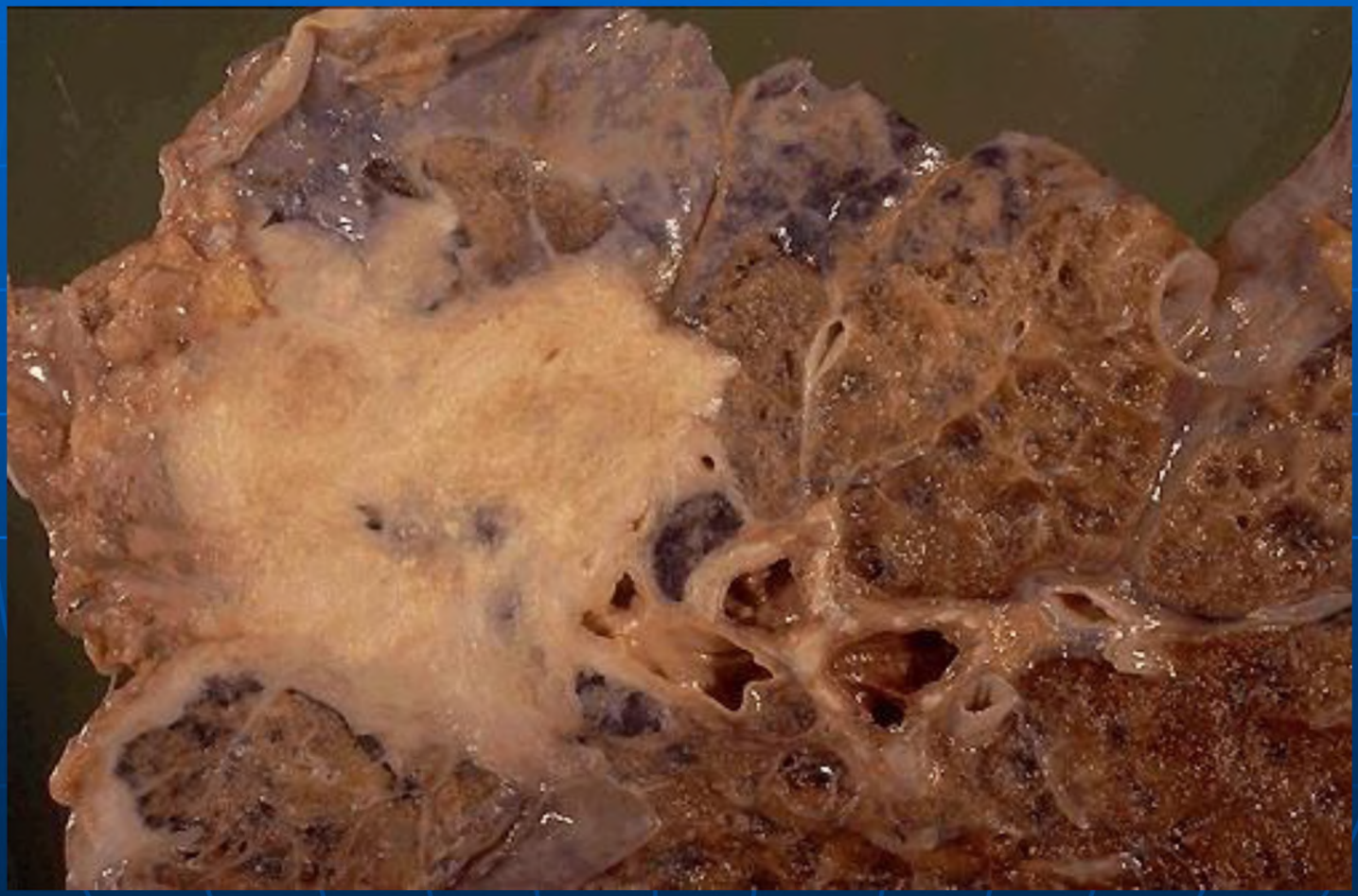




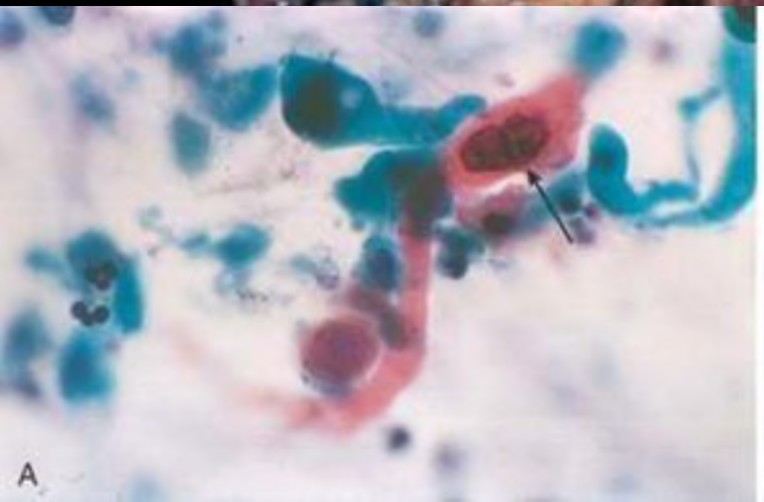
This solitary lung mass is near the hilum and proved to be a squamous cell carcinoma.

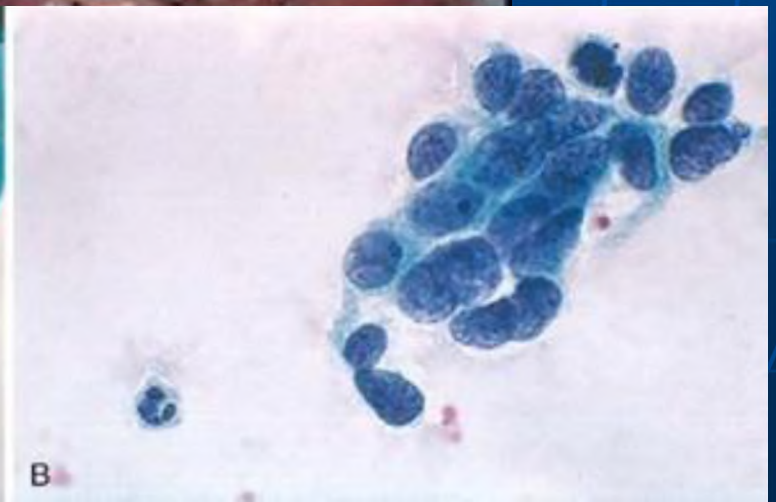


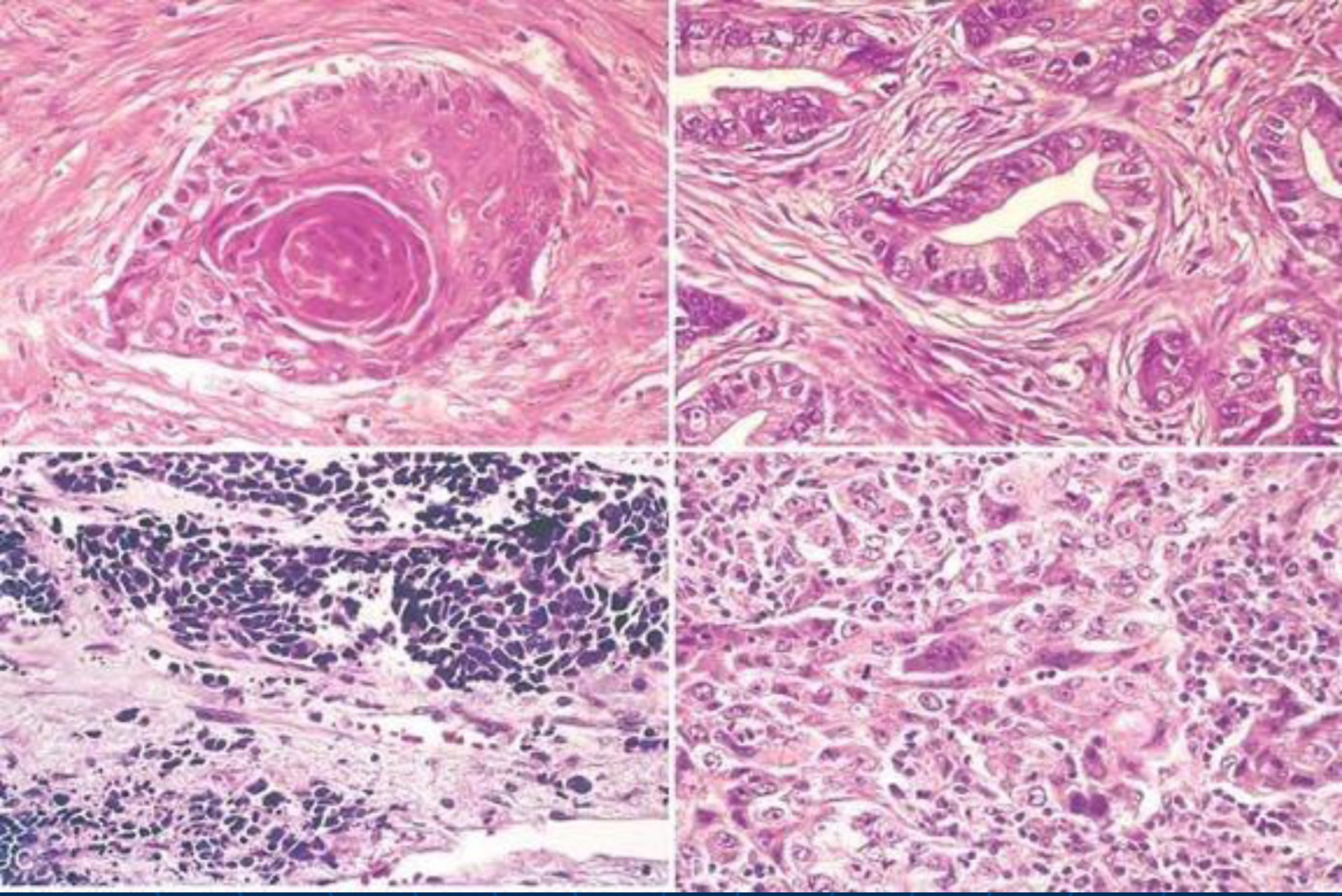
This is a squamous cell carcinoma of the lung. It is a bulky mass that extends into surrounding lung parenchyma.



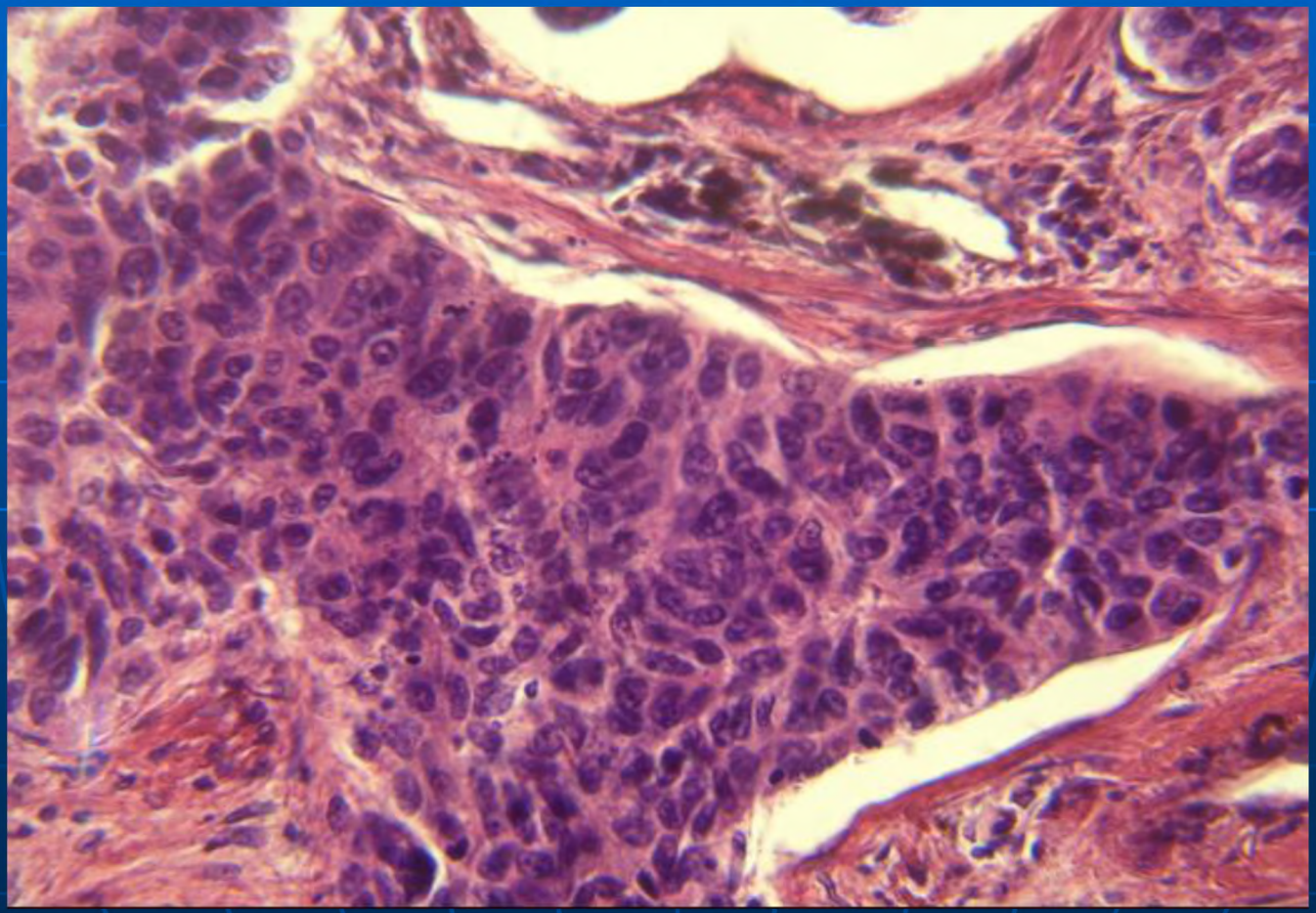



A


B



squamous cell carcinoma





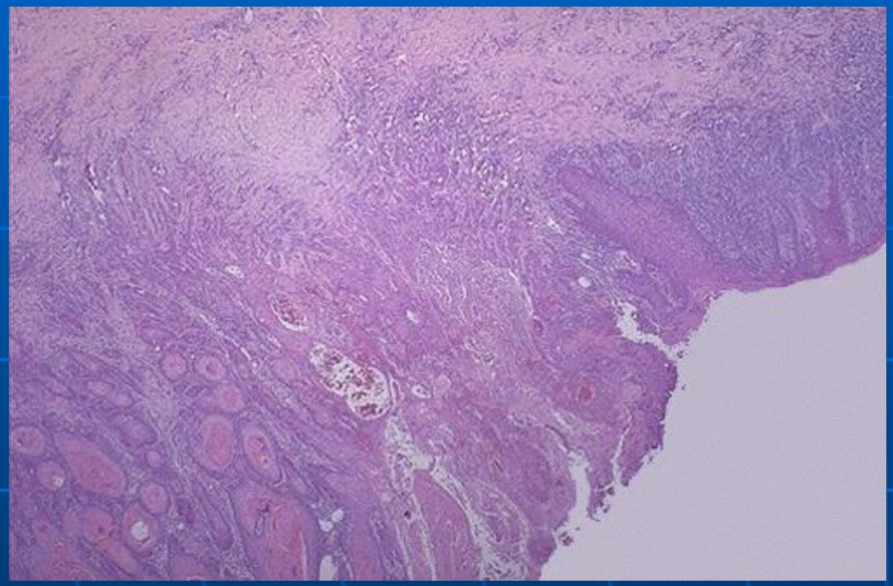
- This is a squamous cell carcinoma arising on the dorsum of the hand. Besides sun exposure, risk factors for squamous cell carcinoma arising in skin include carcinogens such as tars, chronic ulcers, burn scars, arsenic poisoning, and radiation exposure. In this case there was a history of both sun exposure as well as exposure to carcinogens.

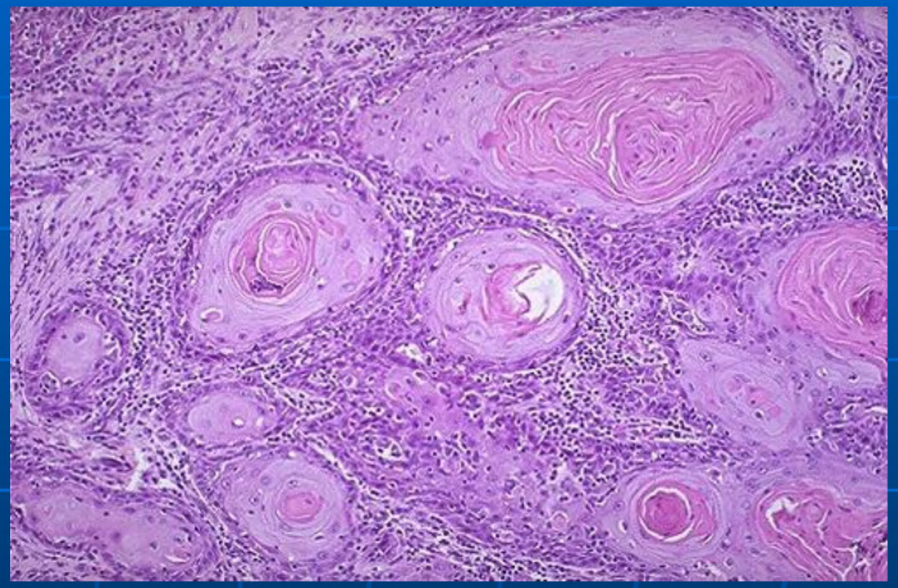
Squamous cell carcinoma of uterine cervix



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.

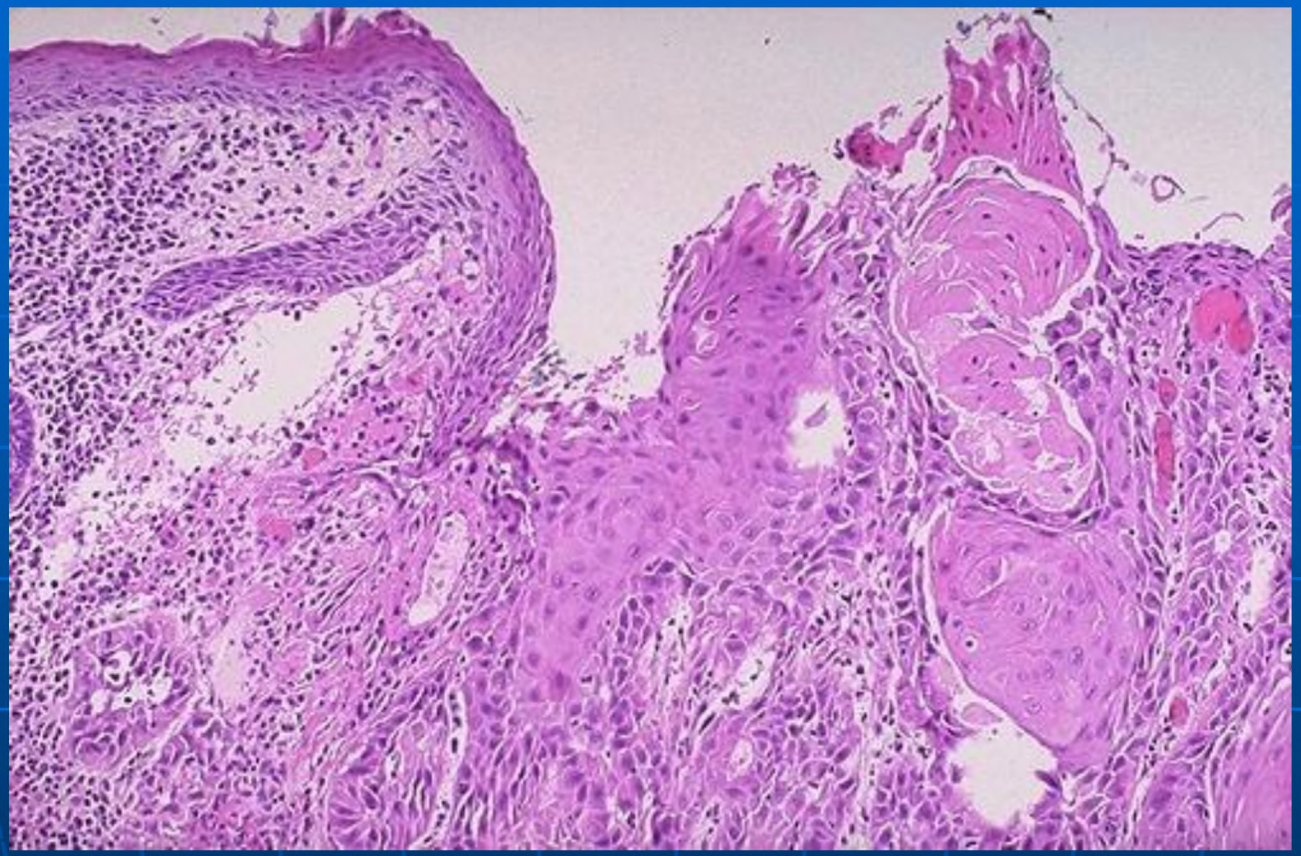
Squamous cell carcinoma of uterine cervix





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.

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.

Adenomas - benign neoplasms of glandular epithelium.

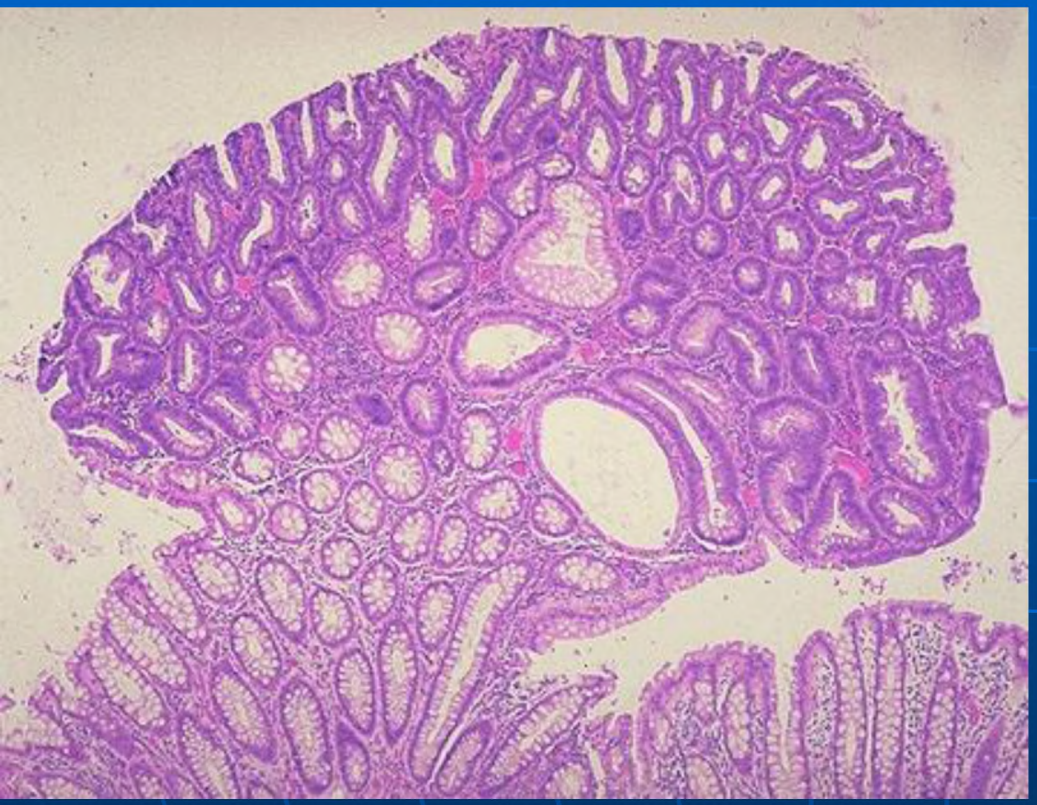
Types of adenomas:

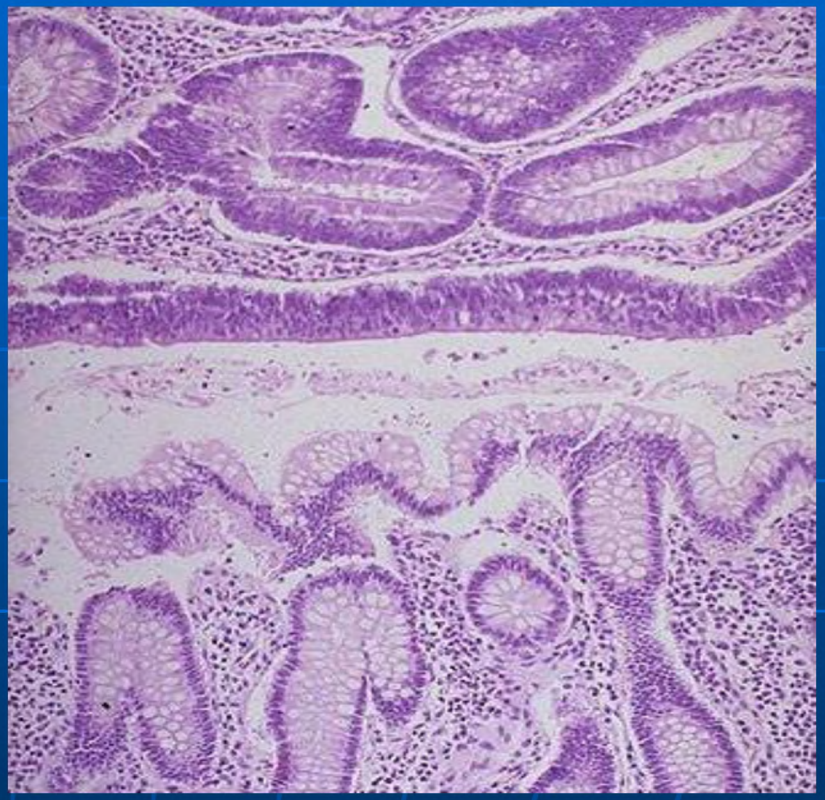
- tubular (tubular structures);
- trabecular (beam structures);
- alveolar;
- papillary (papillary);
- cystadenomas (cystic).

Colon polyposis



Adenoma (adenomatous polyp) of the colon





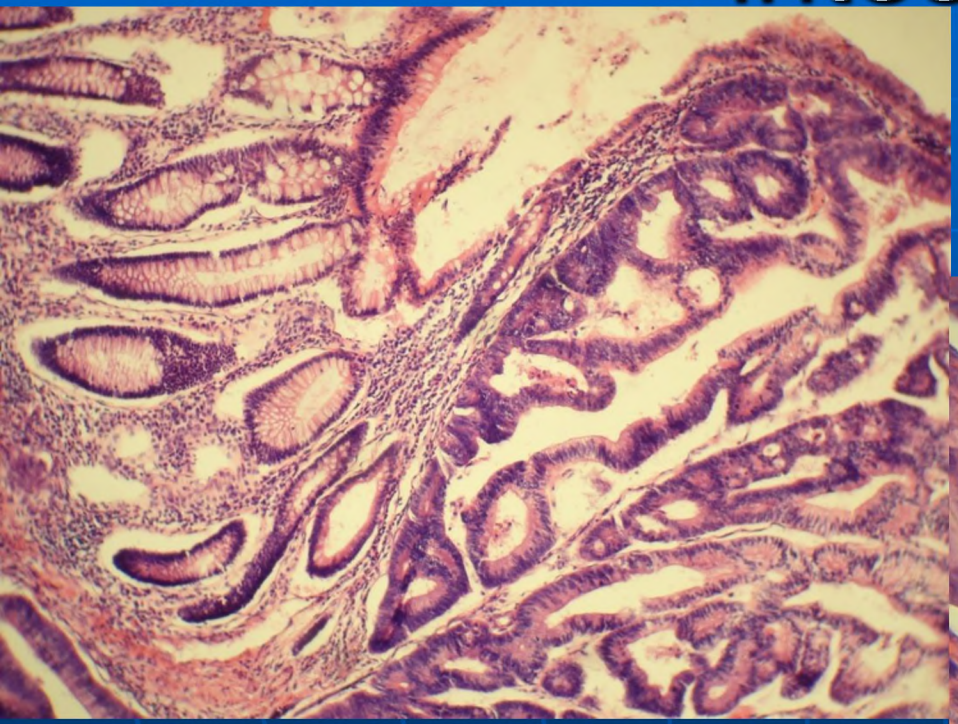
The concept of differentiation is demonstrated by this small adenomatous polyp of the colon. Note the difference in staining quality between the epithelial cells of the adenoma at the top and the normal glandular epithelium of the colonic mucosa below.

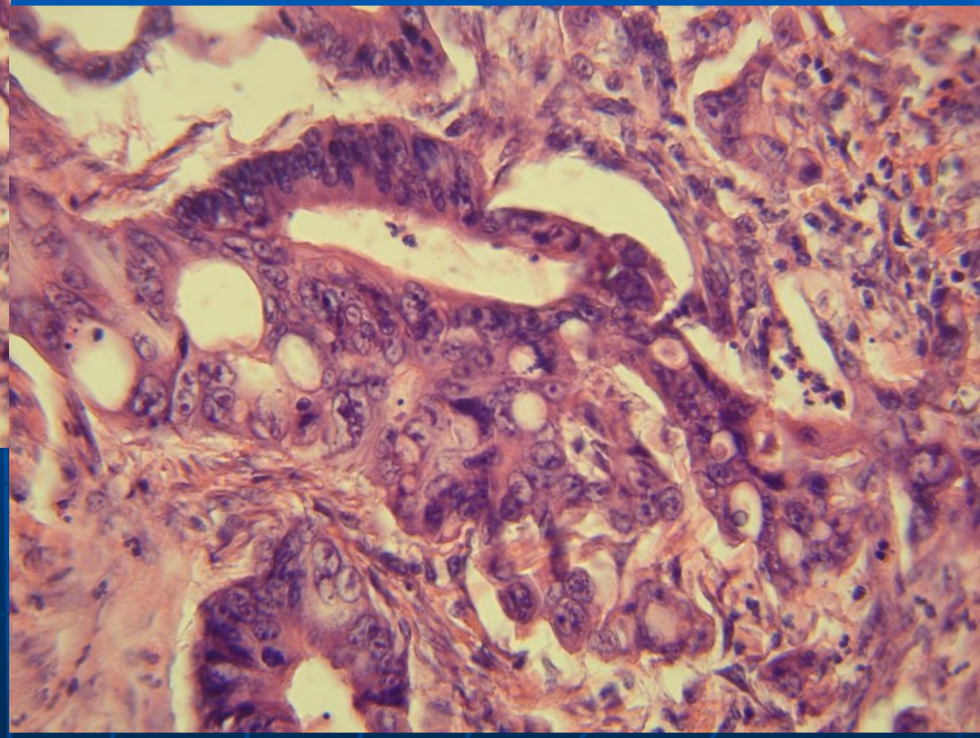
Adenocarcinoma is a malignant organ-non-specific tumor of glandular epithelium.

Types of adenocarcinoma:

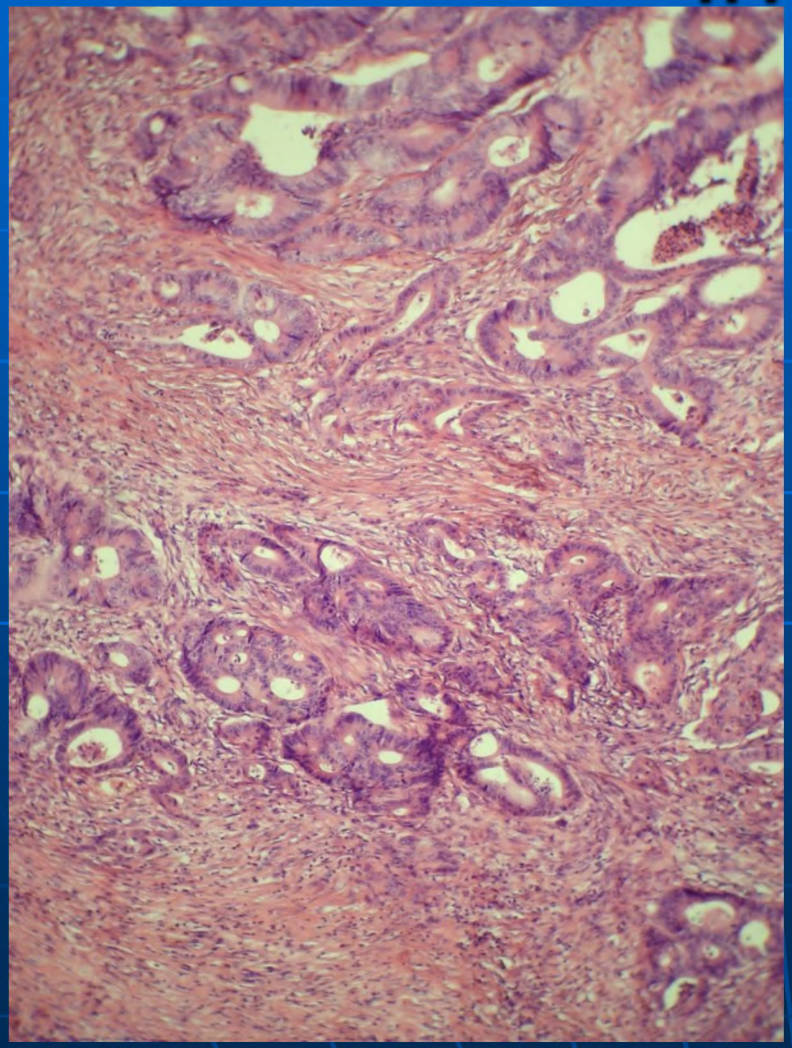
- tubular (tubular structures);
- trabecular (cord-like structures);
- alveolar;
- papillary (papillary);
- cystadenomas (cystic).

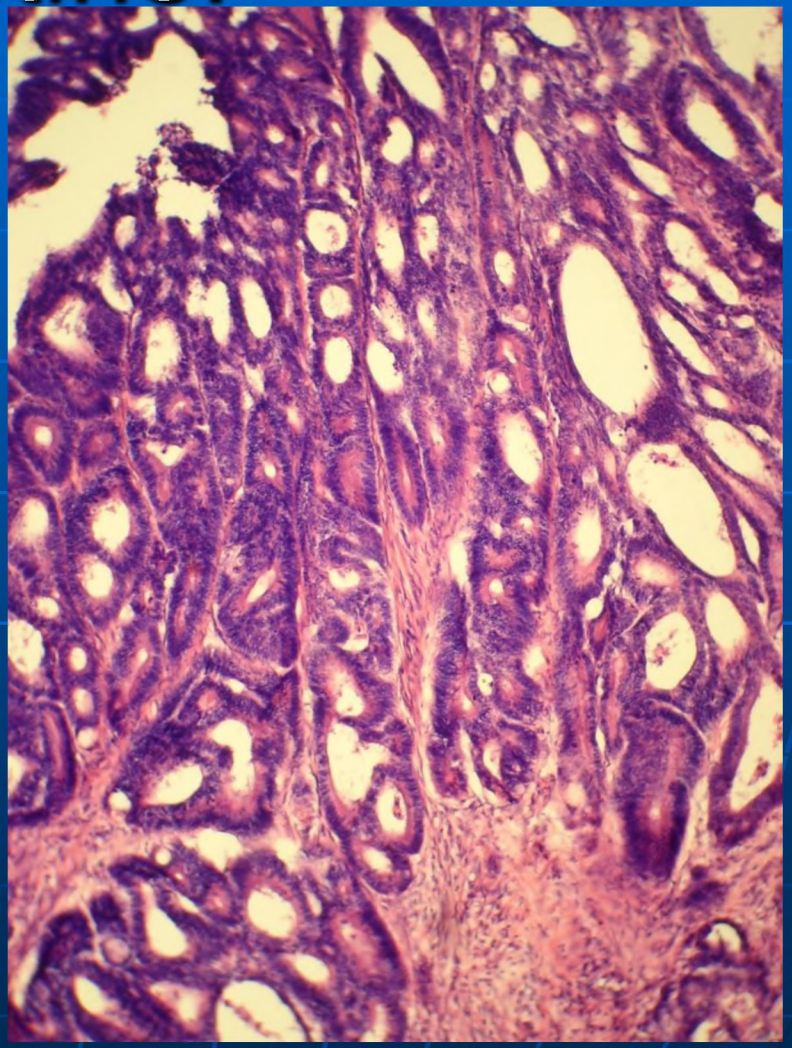
Adenocarcinoma of large intestine.



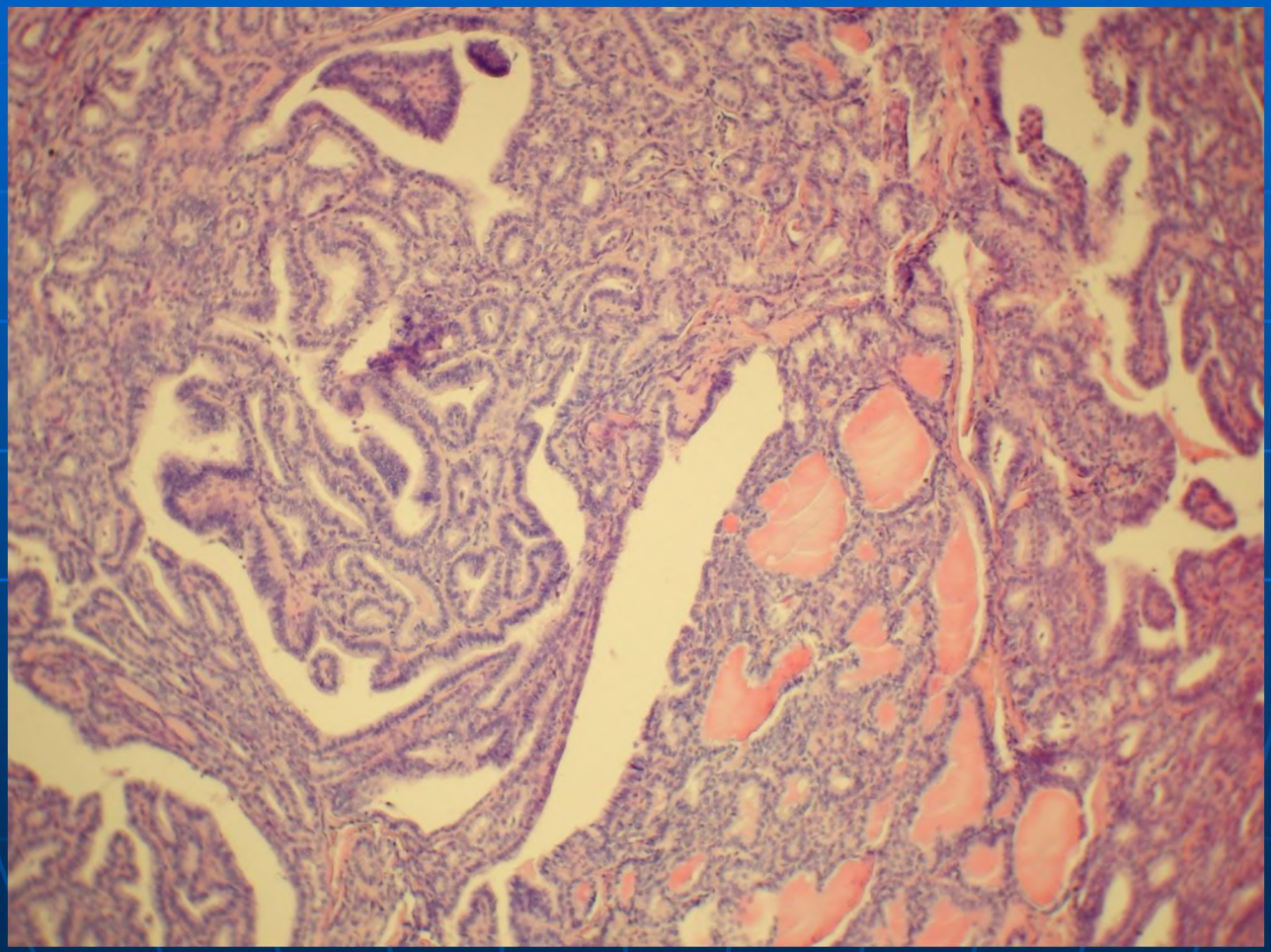


Adenocarcinoma of large intestine.

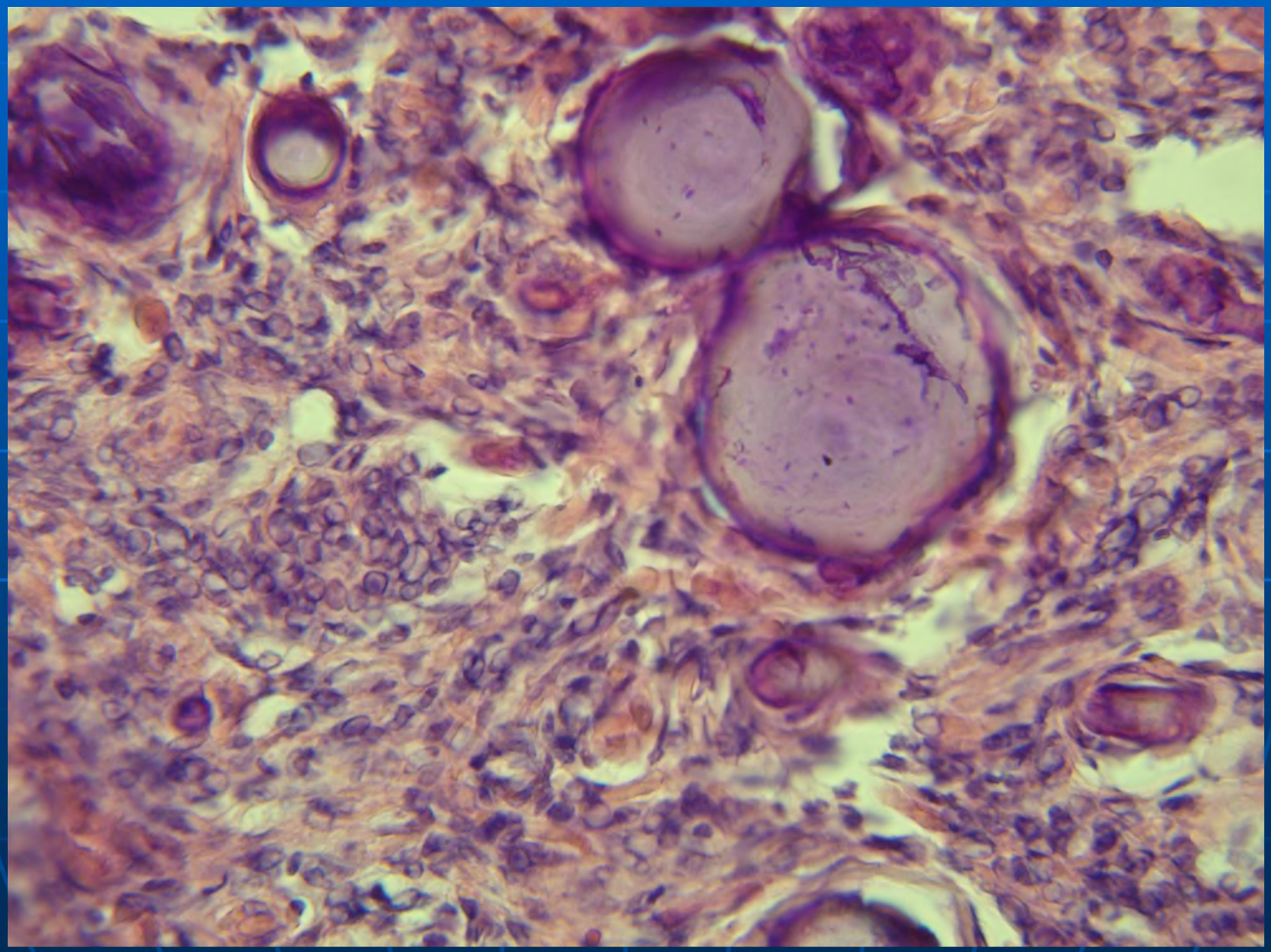




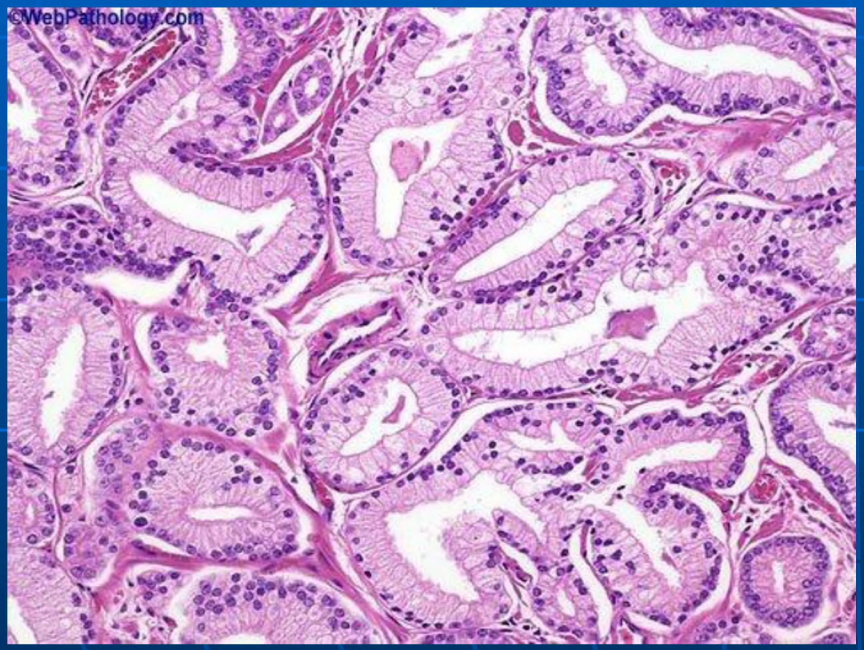
Adenocarcinoma of thyroid gland (papillary cancer).

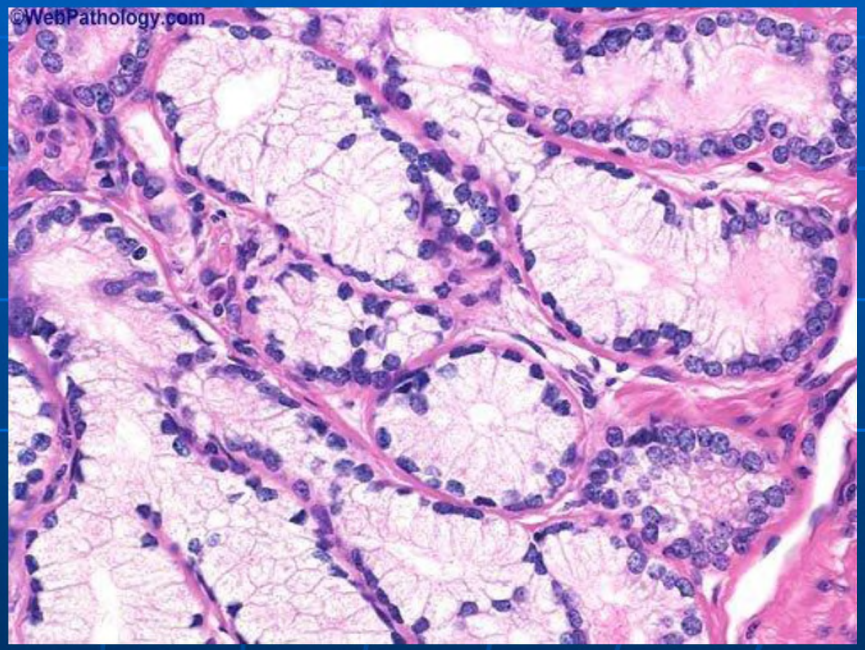


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Risk factors: alcohol addiction, smoking

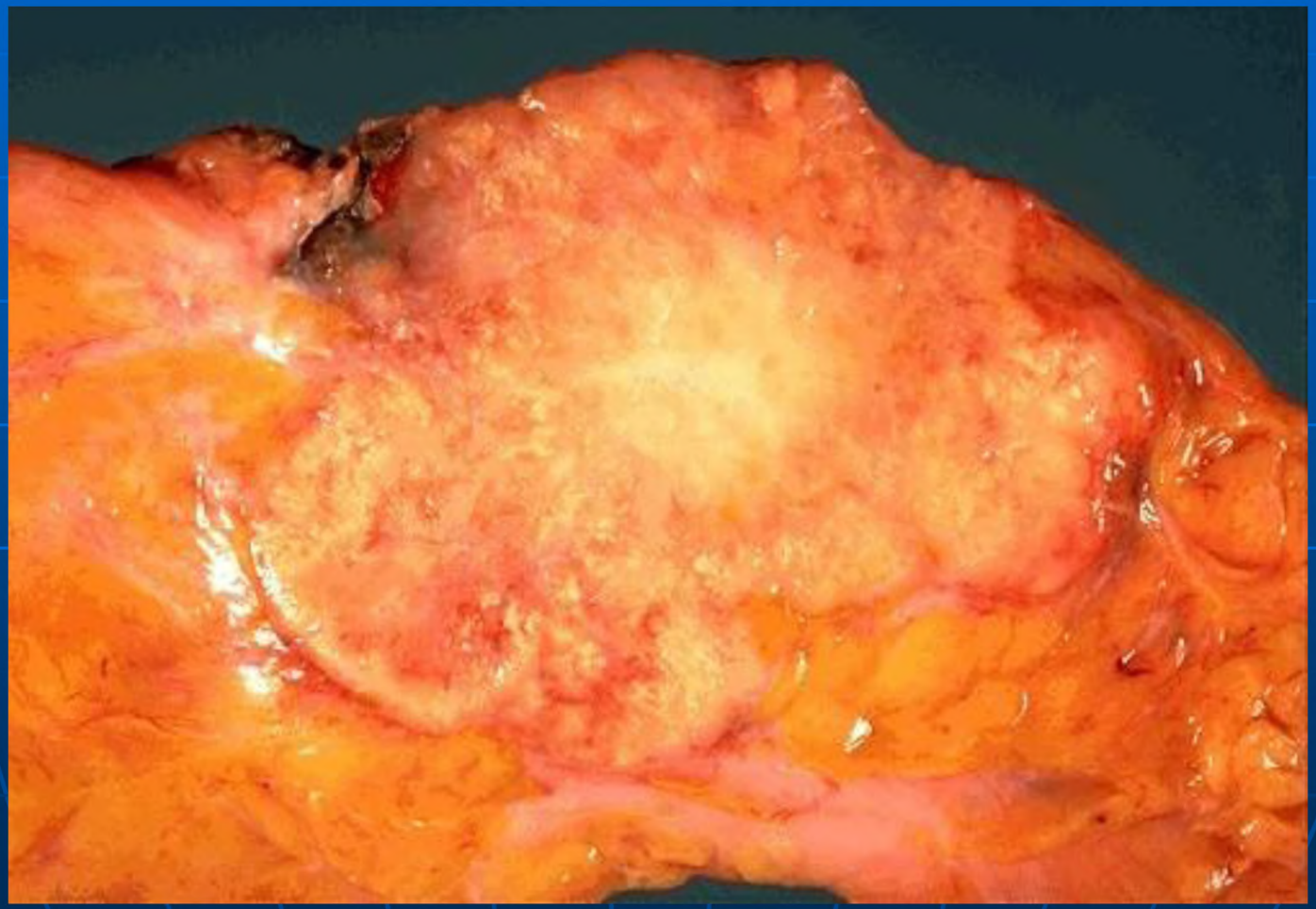




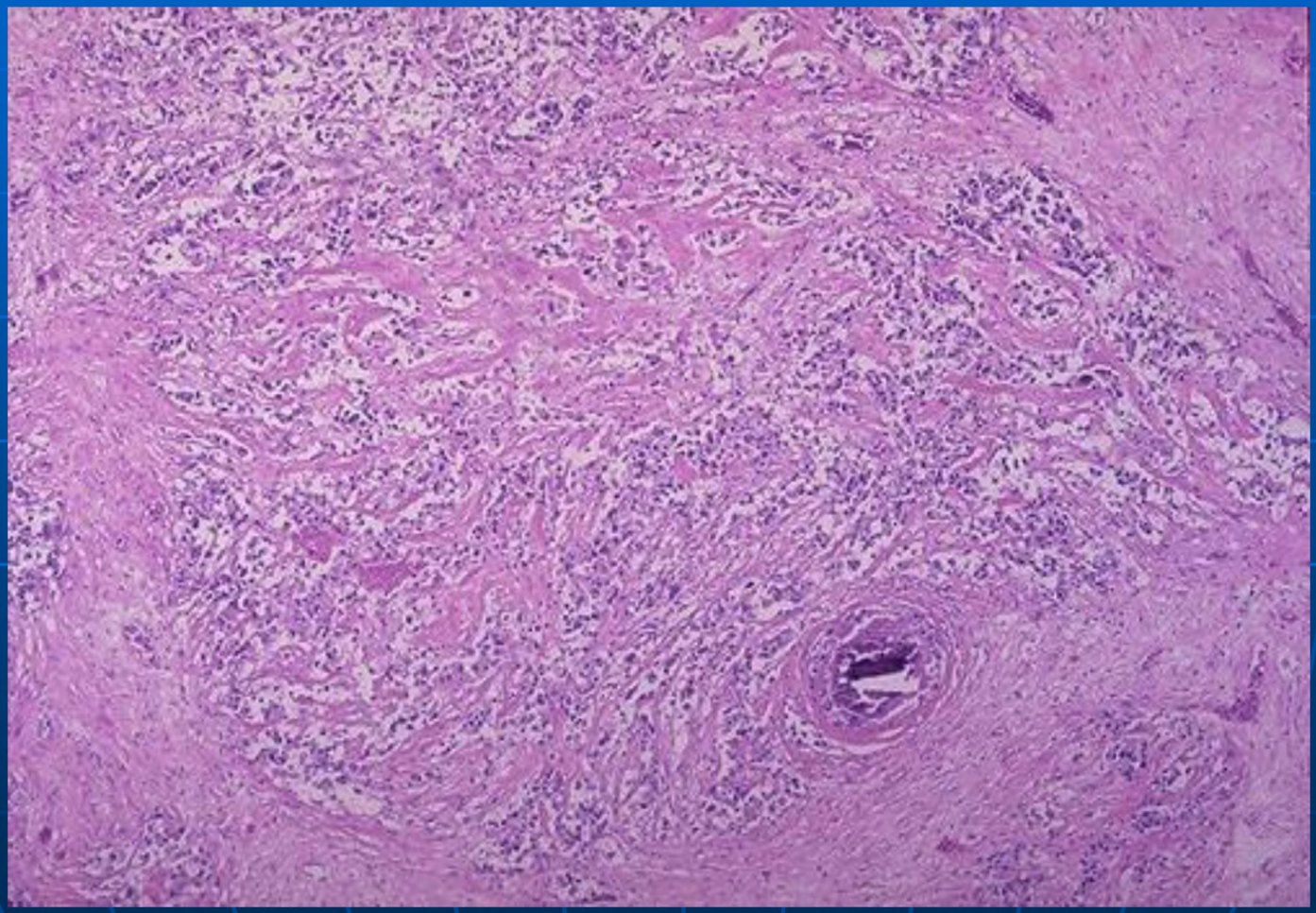


- Comparison of common features of classic invasive ductal breast cancer on the left and benign fibroadenoma on the right.

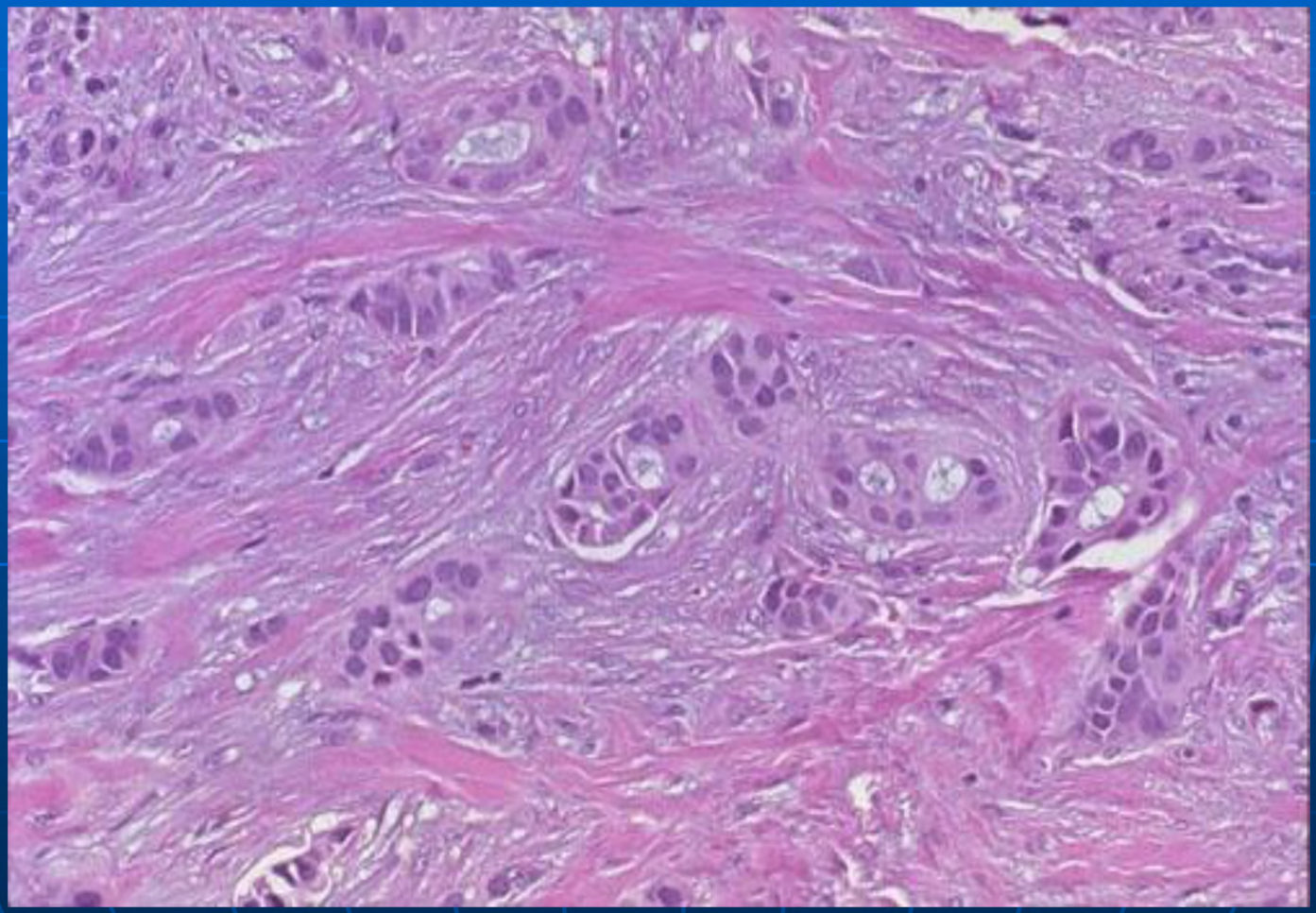
Breast carcinoma



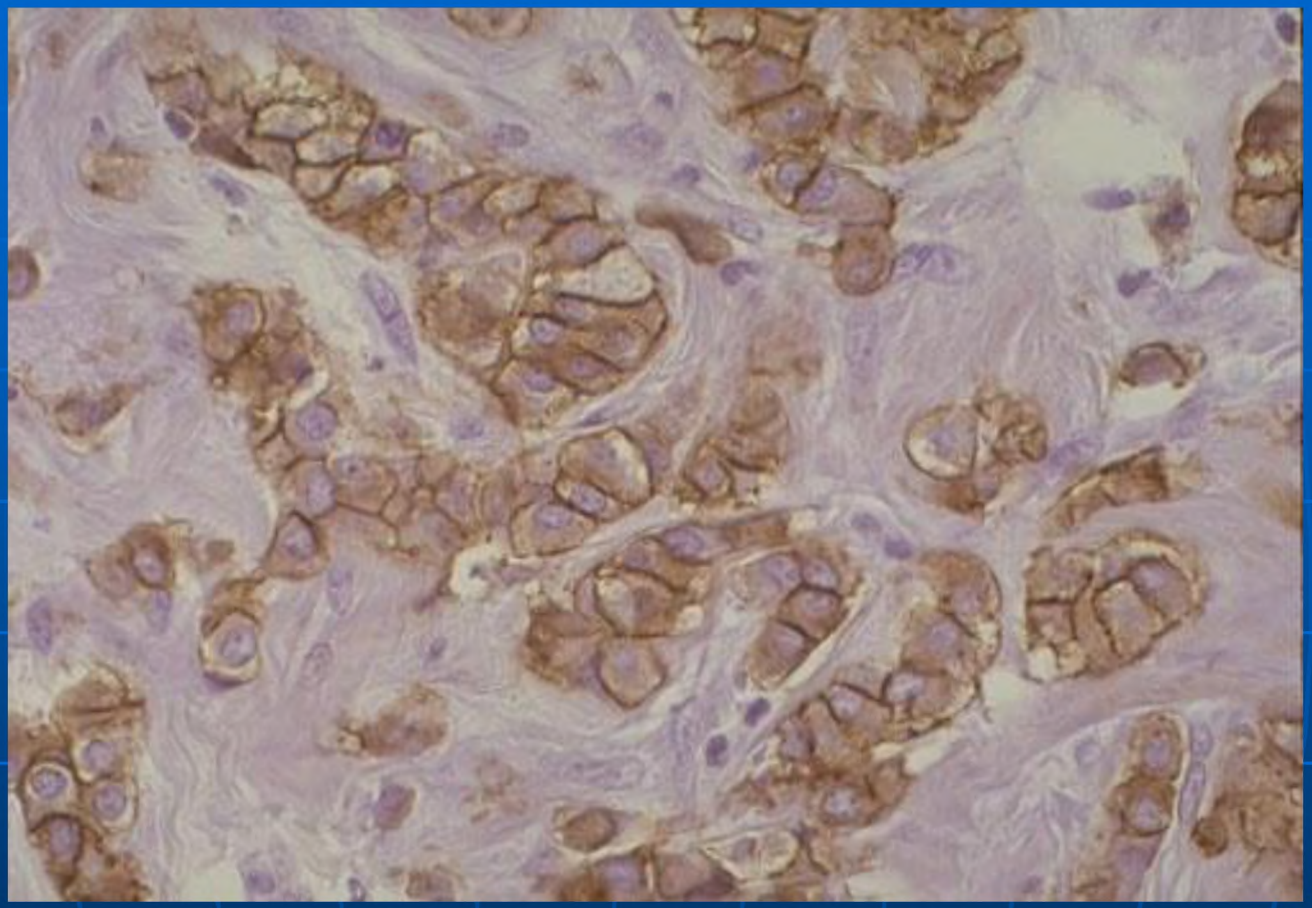
Infiltrating ductal breast carcinoma



Infiltrating ductal breast carcinoma

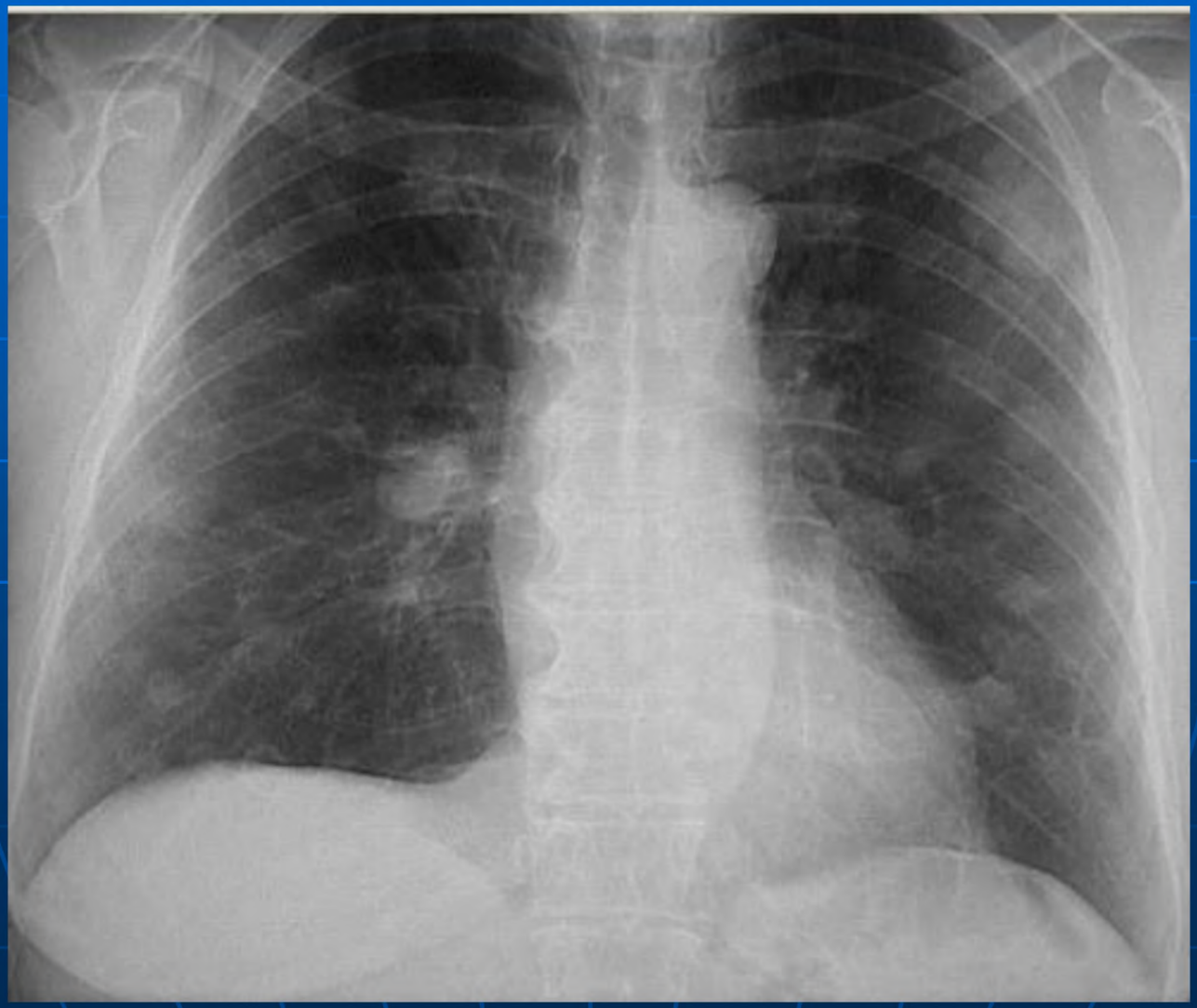


breast carcinoma

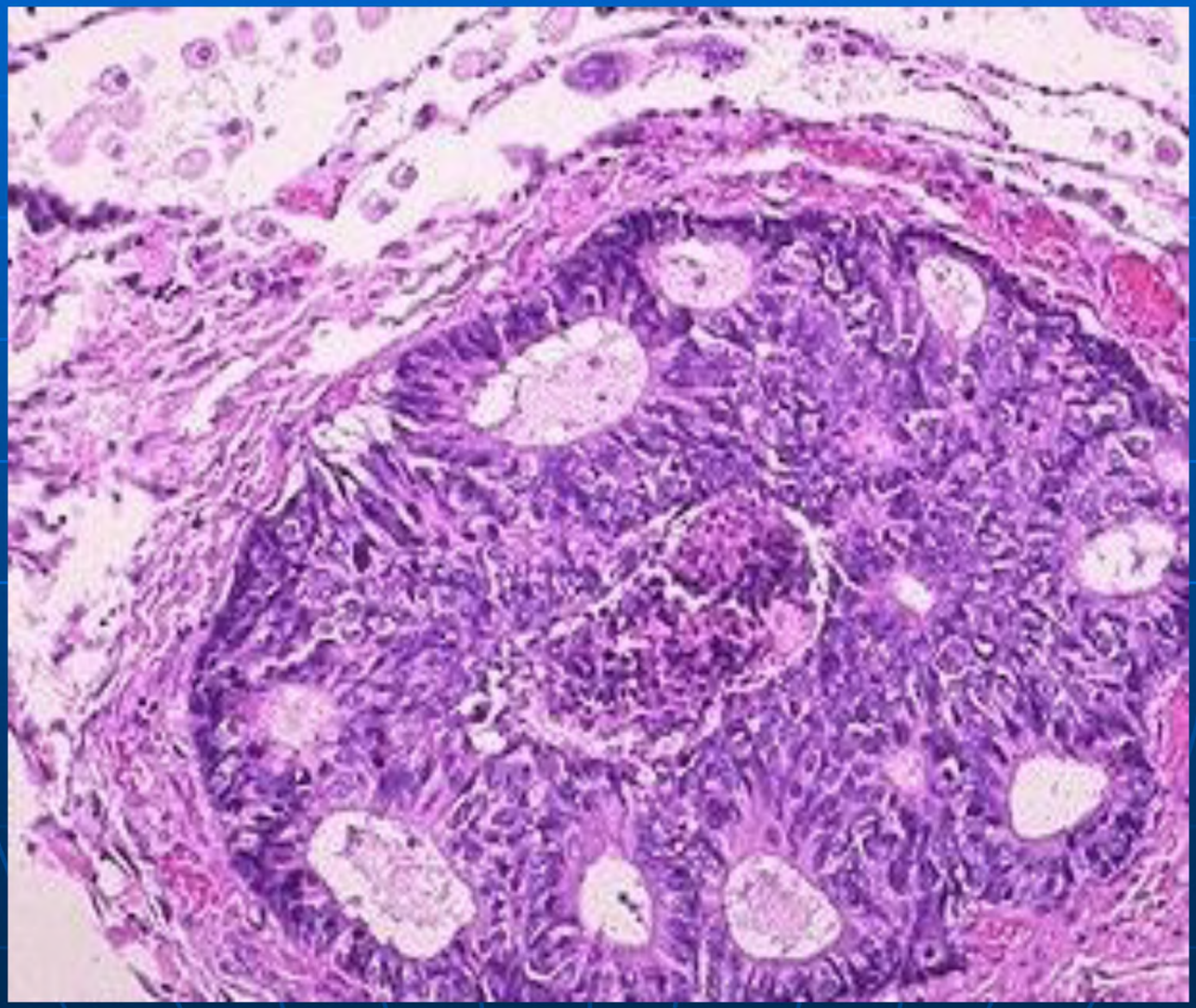


Here is an example of c-erb-B2 positivity in a breast carcinoma. This oncogene acts via reduplication of the normal proto-oncogene hundreds of times, leading to production of a protein product that drives unregulated cell growth. This is detected here by immunoperoxidase staining with the brown reaction product concentrated in a perimembranous pattern around the cells.

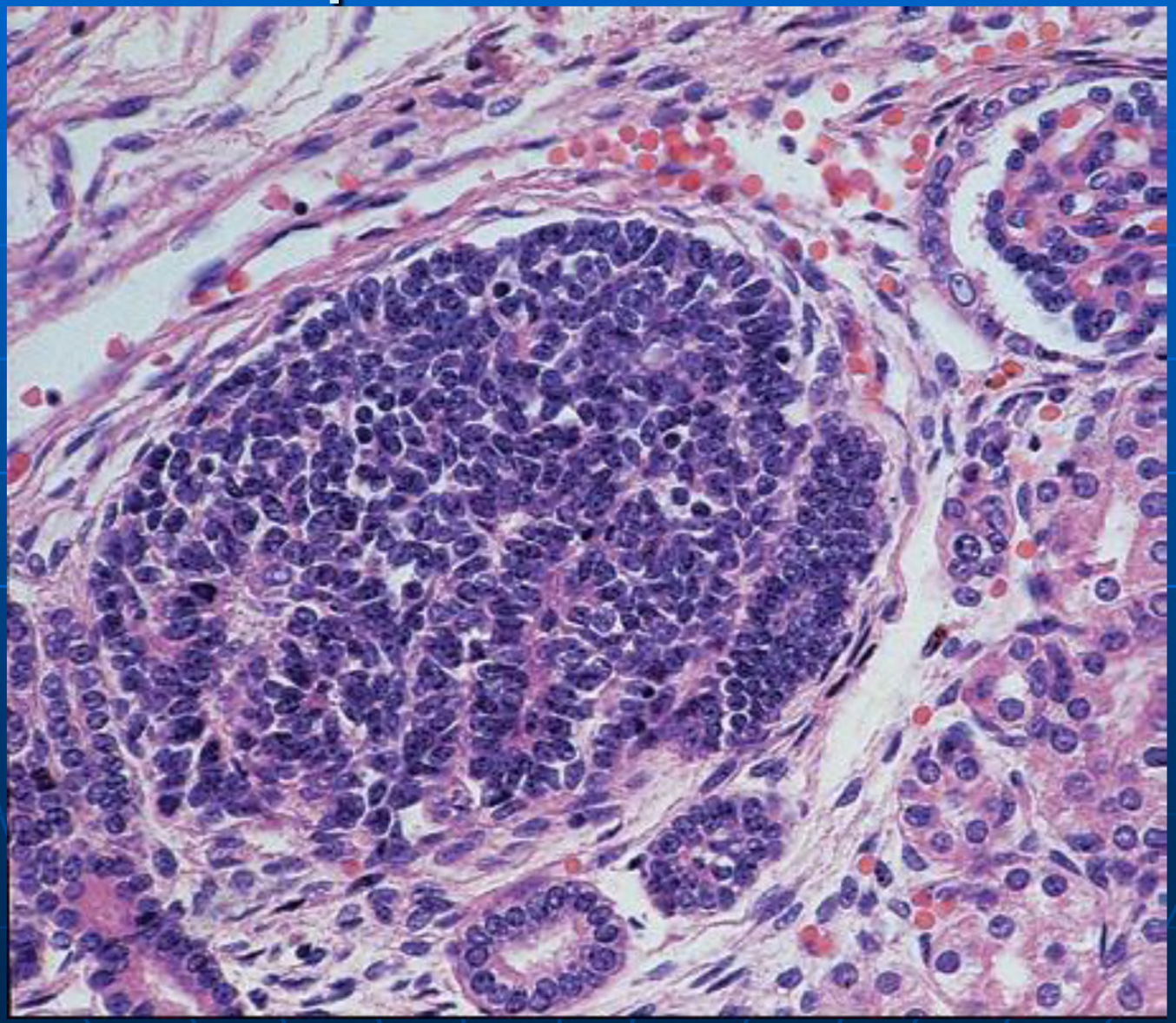
Mts of breast carcinoma



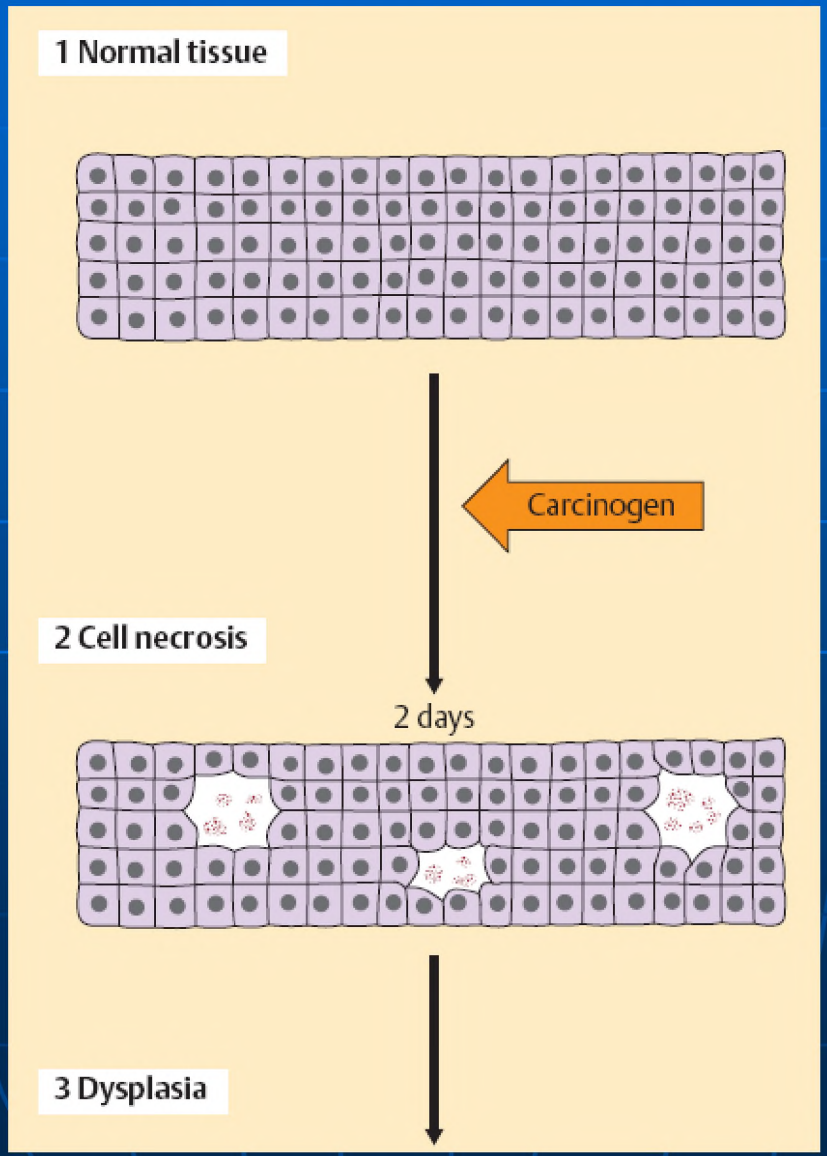
Mts of breast carcinoma in lung



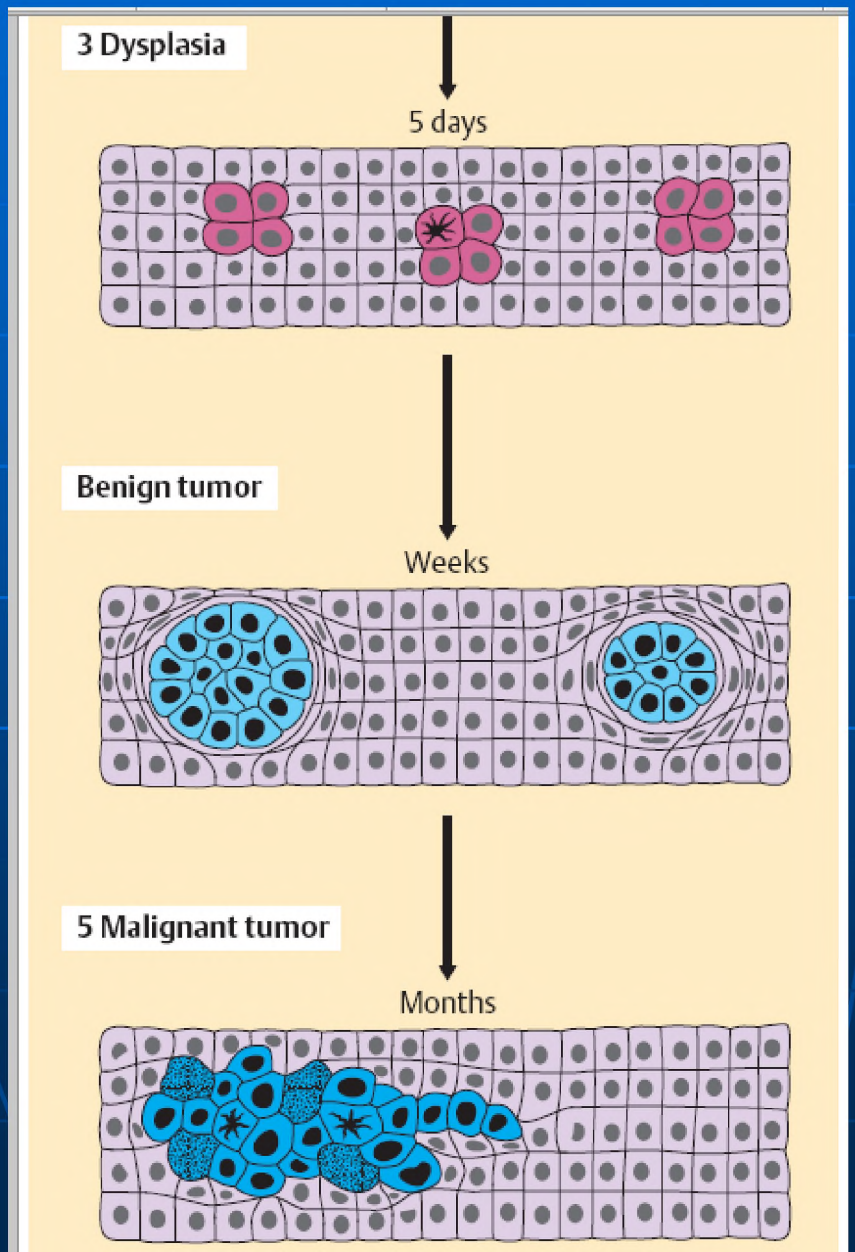
Nephroblastoma



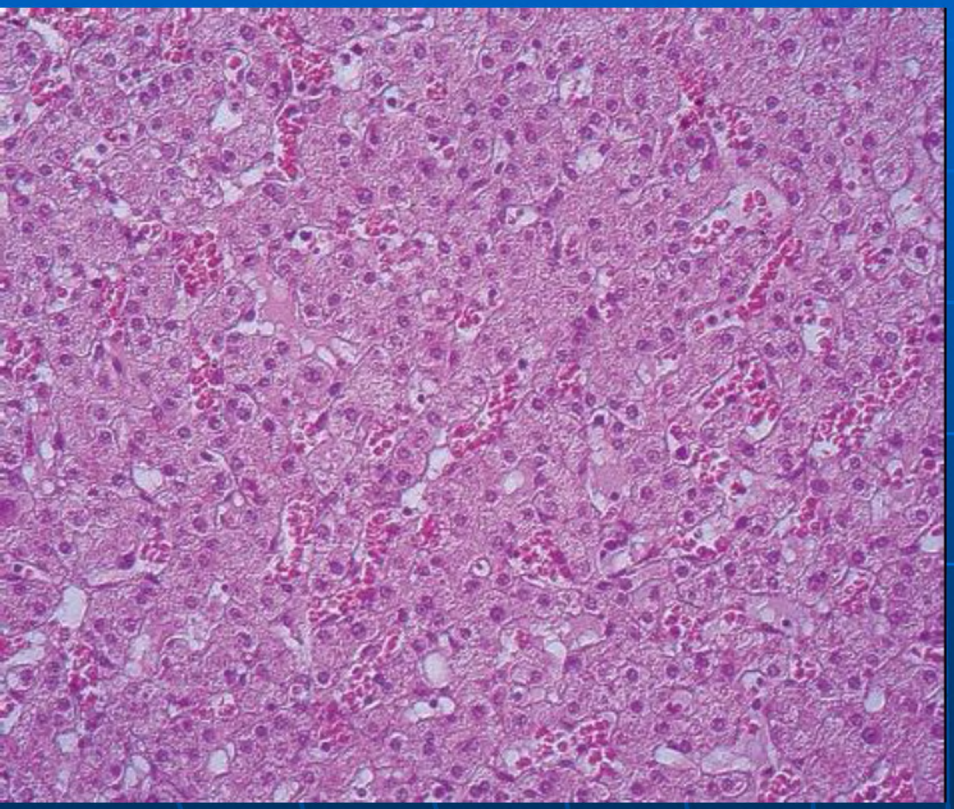
Carcinogenesis in the liver



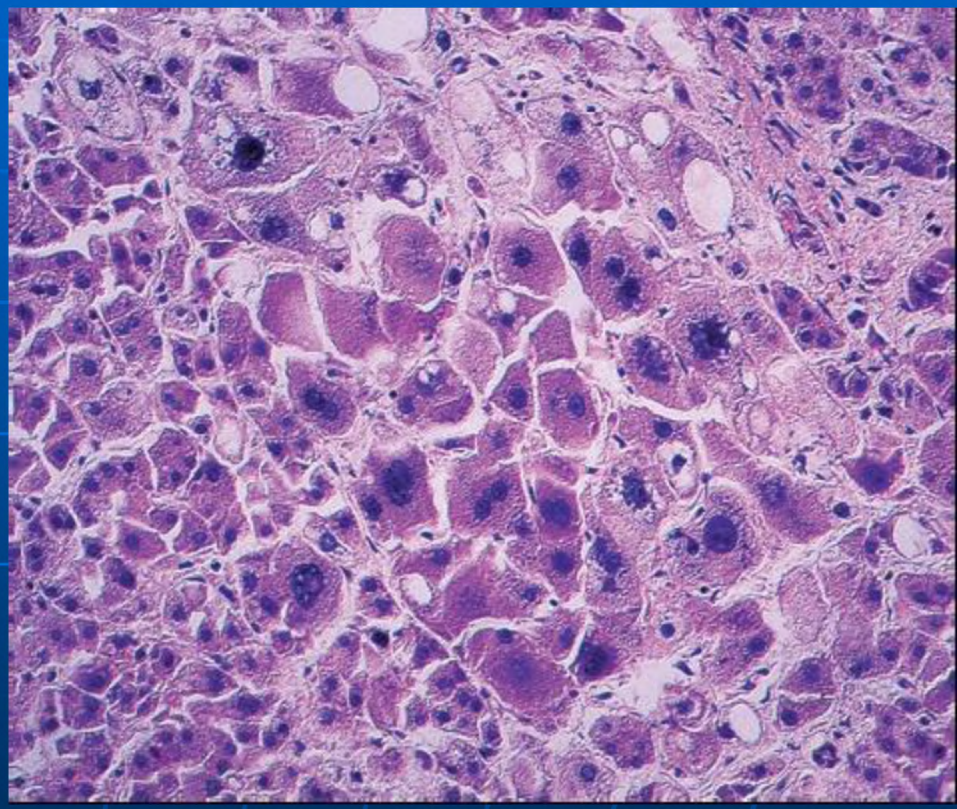
Carcinogenesis in the liver



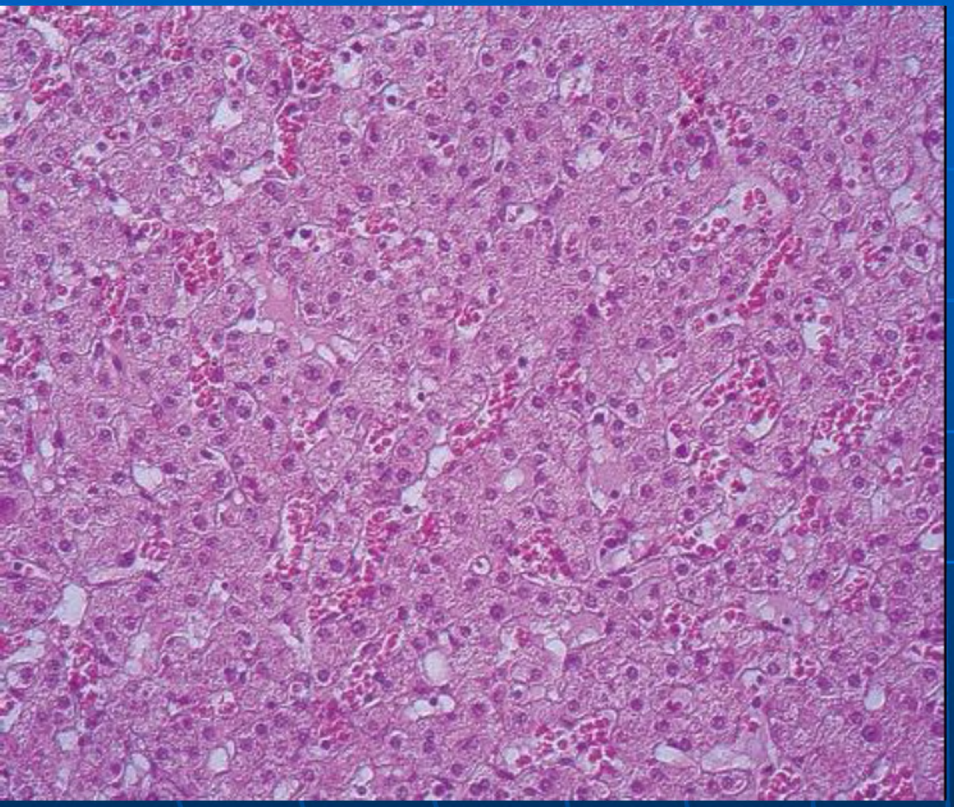
Normal liver



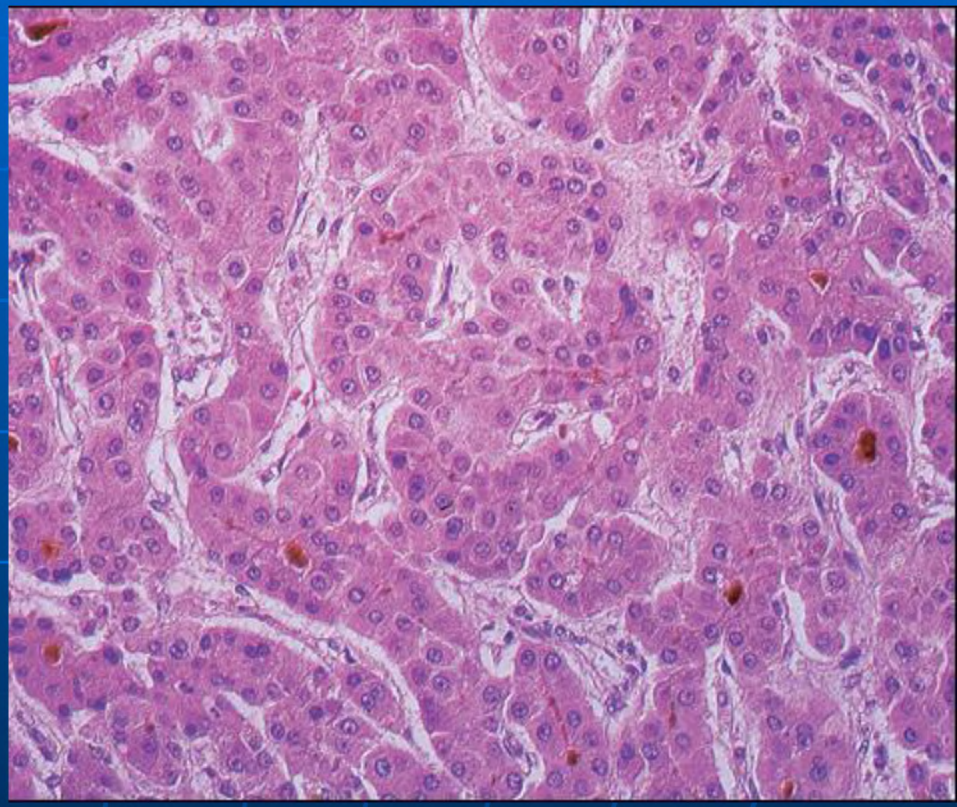
Liver dysplasia



Normal liver

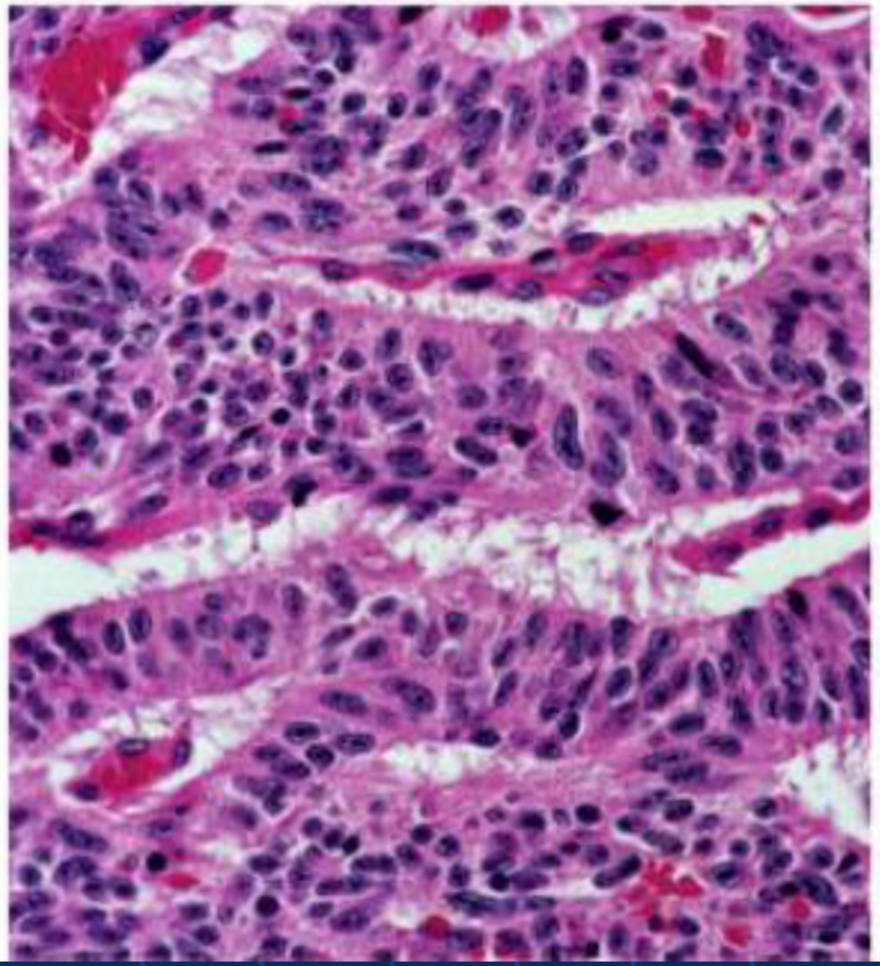


Hepatocellular carcinoma

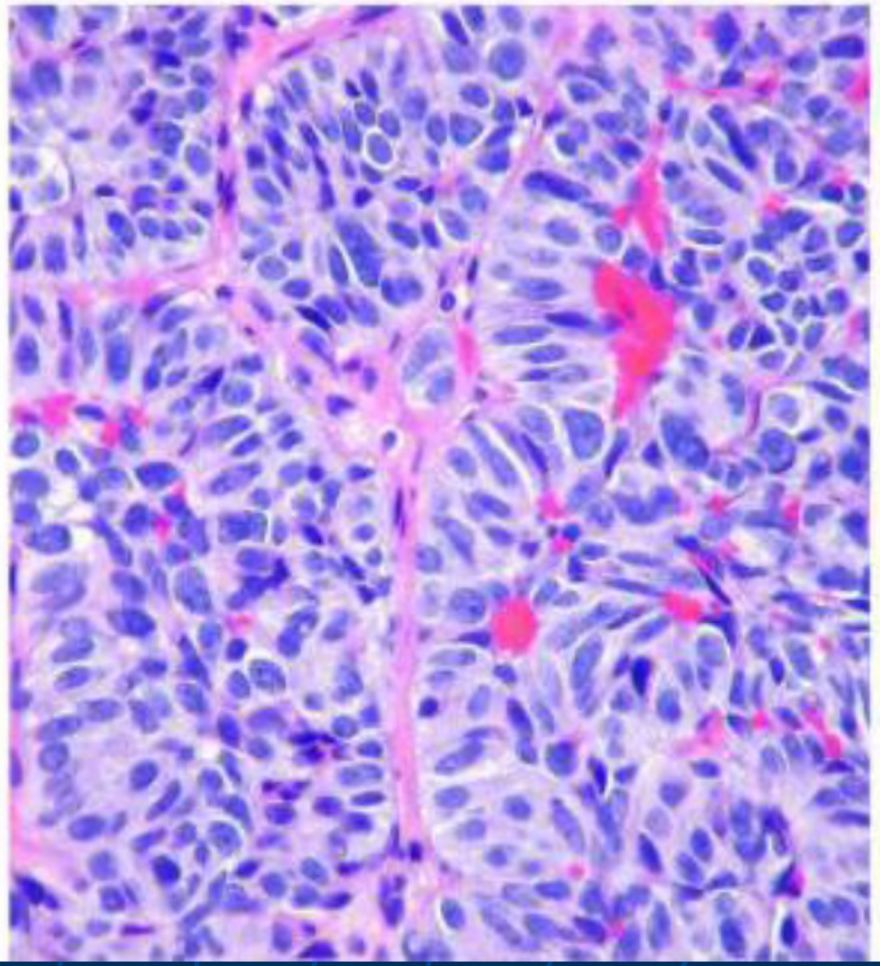


NEUROENDOCRINE TUMORS

- Neuroendocrine tumors develop from APUDcyte precursor cells located in almost all organs and having a common origin with the epithelial cells of the organ.
- Tumors from neuroendocrine cells are called APUDomas. They can be benign - carcinoids, and also malignant - atypical carcinoid, highly differentiated and poorly differentiated neuroendocrine carcinomas. Often their name is associated with a hormone that is produced, for example, gastrinoma, insuloma.



typical carcinoid of lung



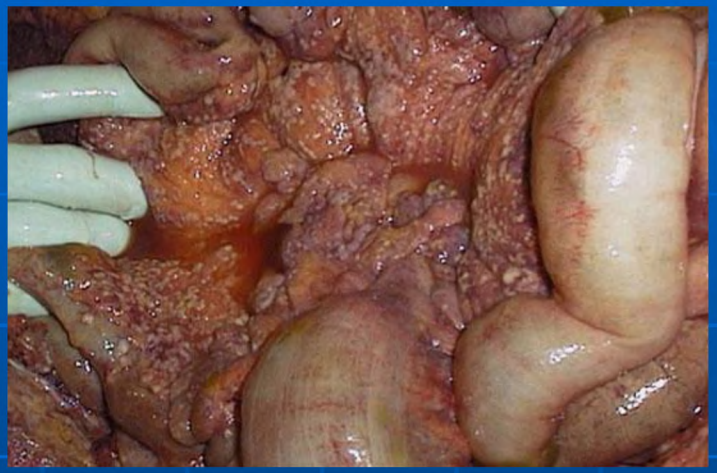
atypical carcinoid of lung

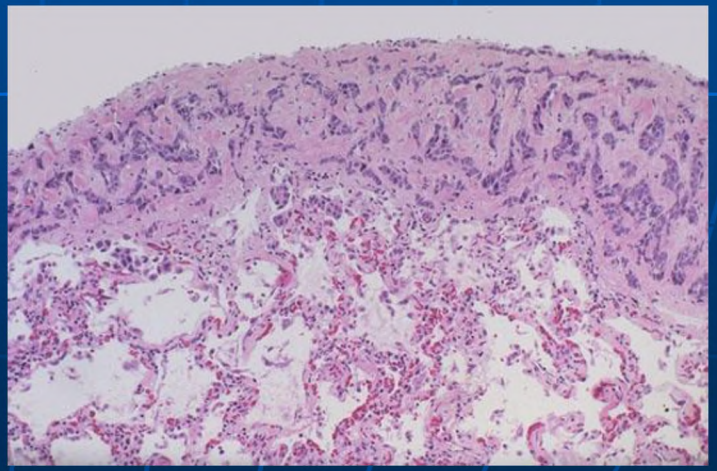
Dissemination of cancers may occur through one of **four pathways**:

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

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.





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.

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.

SOFT TISSUE TUMORS

- The histological classification of soft tissue tumors combines more than 50 variants of tumors and is based on generally accepted criteria, according to which there are:

- • benign tumors of mesenchymal derivatives, whose name is formed from the root of the name of the tissue and the suffix "-om" (fibroma, lipoma, etc.);
- • malignant tumors - sarcomas.

Thank You…