# Fundamental Concepts of Neoplasia: Benign Tumors and Cancer

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- The term neoplasia (from Greek, neo = new and plasis = a moulding) indicates the formation of new tissue or a tumor (from Latin for swelling) that may be benign or malignant.

- The first recognition of microscopic differences between malignant and benign cells is attributed to Johannes Müller (1836).
- The observations on microscopic makeup of cancer subsequently led to the recognition of precursor lesions or precancerous states.

# BENIGN TUMORS

**Definition**

- Benign tumors are focal and limited proliferations of morphologically normal or nearly normal cells, except for their abnormal arrangement and quantity.
- Benign tumors may occur in any tissue or organ and are characterized by:
    - Limited growth
    - A connective tissue capsule
    - The inability to either invade adjacent tissue or metastasize

## Classification

- Epithelial origin
  - squamous epithelium orurothelium) : papillomas,
  - Glandular epithelia: adenomas or polyps
  - Papillomas and polyps are visible to the eye of the examiner as pale or reddish protrusions from the surface of the epithelium of the affected organ.
- Fat, muscle, bone: lipoma, myoma, or osteoma respectively.

# CLASSIFICATION AND NOMENCLATURE OF HUMAN TUMORS

| Tissue Origin | Benign | Malignant (Cancer) |
|---|---|---|
| Stratified protective epithelium | Papilloma | Squamous or epidermoid carcinoma; urothelial carcinoma |
| Columnar epithelium, including that of glands | Adenoma or polyp | Adenocarcinoma, mucoepidermoid carcinoma Occasionally epidermoid carcinoma |

| Mesothelia Supportive tissues of mesodermal origin | Benign mesothelioma …omas according to the type of tissue involved (i.e., fatlipoma, bone-osteoma) | Malignant mesothelioma Sarcoma (with designation of tissue type; i.e., liposarcoma, osteogenic sarcoma) |
|---|---|---|
| Lymphoid tissues | Hyperplasia | Malignant lymphomas |
| Blood cells | | Leukemia |
| Tumors composed of several varieties of tissue | Benign teratomas | Malignant teratomas |

# MALIGNANT TUMORS (CANCERS)

**Definition**

- Fully developed primary malignant tumors are characterized by several fundamental features that apply to all cancers:
- Autonomous proliferation of morphologically abnormal cells results in abnormal, often characteristic tissue patterns and leads to the formation of a visible or palpable swelling or tumor.

- Spread of cancer through blood vessels is known as hematogenous spread and may result in metastases to any organ in the body, whether adjacent to the tumor or distant.
- The terms recurrent cancer and recurrence indicate a relapse of a treated tumor.

## Classification

- Cancers originating from epithelial structures or glands are known as carcinomas, whereas cancers derived from tissues of middle embryonal layer origin (such as connective tissue, muscle, bone) are classified as sarcomas.

- The names of yet other cancers of highly specialized organs or tissues may reflect their origin, for example, thymus = thymoma and mesothelium = mesothelioma.
- Cancers of blood cells are known as leukemias, and cancers of the lymphatic system as lymphoma.

- Carcinomas and sarcomas may be further classified according to the type of tissue of origin, which is often reflected in the component cells.
- Carcinomas derived from squamous epithelium, or showing features of this epithelial type, are classified as squamous or epidermoid carcinomas.

- In this text, the term “squamous carcinoma” will be applied to tumors with conspicuous keratin formation, whereas tumors with limited or no obvious keratin formation will be referred to as “epidermoid carcinomas.”
- Carcinomas derived from gland-forming epithelium or forming glands are classified as adenocarcinomas.

- There are also carcinomas that may combine the features of these two types of cancer and are, therefore, known as adenosquamous or mucoepidermoid carcinomas.
- Carcinomas of highly specialized organs may reflect the tissue of origin, for example, hepatoma, a tumor of liver cells.

- Sarcomas are also classified according to the tissue of origin, such as bone (osteosarcoma), muscle (myosarcoma), and connective tissue or fibroblasts (fibrosarcoma).
- Again, tumors derived from highly specialized tissues may carry the name of the tissue of origin, for example, glial cells of the central nervous system (glioma) or pigment-forming cells, melanoblasts (melanomas).

- Yet other tumors may show combinations of several tissue types (hamartomas and teratomas), or reflect certain common properties, such as production of hormones (endocrine tumors).
- In certain age groups, tumors that show similar morphologic characteristics (although not cells of origin) have been grouped together as small-cell malignant tumors of childhood.

**Risk Factors and Geographic Distribution**

- Age
- Immunosuppression (E.g.: AIDS)
- Environmental factors
- Viruses and Bacteria
- Smoking
- Alcohol

## Grading and Staging

- Description of the histologic (and sometimes cytologic) level of deviation from normal tissue or cells of origin.
- Grading is expressed in Roman numbers or equivalent phrases.

- Well differentiated, or grade I: histologic pattern of a cancer resembles closely the makeup of the normal tissue,
- Poorly differentiated, or grade III: cells differ significantly from normal.
- Most cancers fall somewhere between the two extremes and are therefore classified as moderately well differentiated, or grade II.

- **Staging**
- It is based on an internationally accepted code to assess the spread of cancer at the time of diagnosis.
- The TNM system includes tumor size and extent of invasion (T), the involvement of the regional lymph nodes by metastases (N), and the presence or absence of distant metastases (M).

- The T group is usually subclassified and ranges from Tis (tumor in situ) or To, indicating a cancer confined to the tissue or organ of origin, to T1, T2, T3 and T4, indicating tumor size and, in some instances, the depth of invasion.

- Something missing :N,M

- Clinical staging is based on the results of inspection and palpation, now usually supplemented by radiologic techniques, such as magnetic resonance imaging (MRI) or ultrasound.
- Pathologic staging is based on examination of tissues surgically removed from the patient.

# PRECURSOR LESIONS OF HUMAN CANCER

**The general characteristics:**

- The lesions are confined to the epithelium of origin.
- They are composed of cells showing abnormalities that are similar but not necessarily identical to fully developed cancers.

**Progression of Intraepithelial Lesions to Invasive Cancer**

- Epidemiologic studies have shown that, as a general rule, precursor lesions occur in persons several years younger than persons with invasive cancer of the same type.

- Hence, it is assumed that several years are required for an intraepithelial lesion to progress to invasive cancer.
- For invasion to take place, the cells of the precursor lesion must break through the barrier separating the epithelium from the underlying connective tissue and, hence, must breach the basement membrane.

**One of two possible events must be assumed:**

- The cells composing the precancerous lesions acquire new characteristics that allow them to breach the basement membrane.
- The basement membrane becomes altered and becomes a porous barrier to the cells.

- There is evidence that some of the genes involved in carcinogenesis affect the adhesion molecules on cell membranes.

# MORPHOLOGIC CHARACTERISTICS OF CANCER CELLS

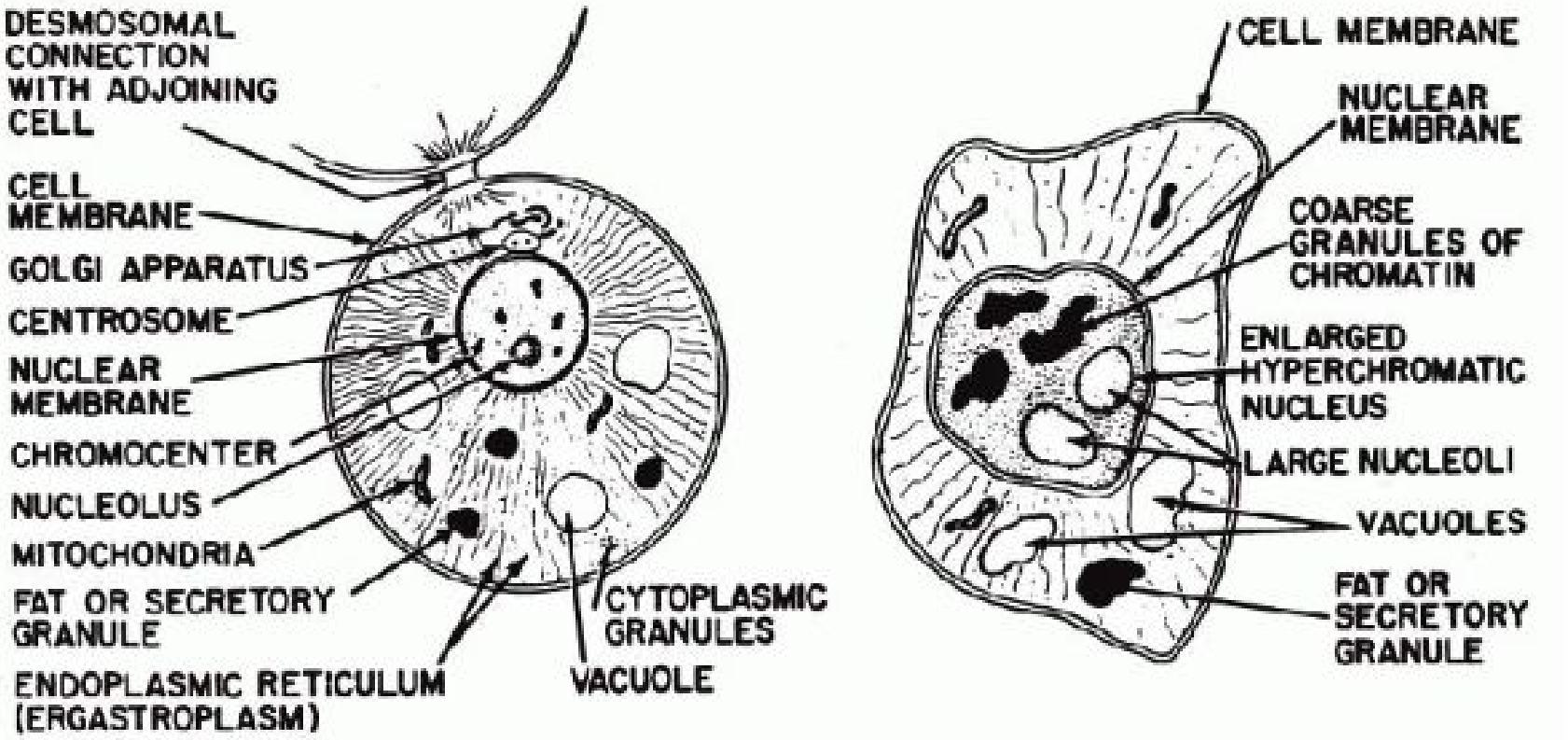
- Identification of cancer cells by a light microscopic examination is an accepted means of cancer diagnosis
- Cancer cells, like normal cells, are composed of a nucleus and a cytoplasm.
- The differences are based on cell size and configuration, interrelationship of cells, cell membrane, characteristics of the nucleus, and mitotic activity.

## The Cytoplasm

## Cell Size

- The size of cancer cells usually differs from normal cells of the same origin.
- Extreme size changes may be occasionally recorded; very large, sometimes multinucleated giant cells and very small cancer cells may occur.

- More importantly, a population of cancer cells is rarely made up of cells of equal size (anisocytosis).
- However, cell size alone is not a sufficient criterion for the diagnosis of cancer in the absence of nuclear abnormalities.




- Schematic representation of the principal differences between a hypothetical benign cell (left) and a malignant cell (right). The differences, detailed in Table below, pertain to cell configuration; nuclear size, shade, and texture; nucleolar size and shape; and the cell-to-cell relationship. The last is symbolized by the desmosome present on the benign cell and absent on the malignant cell to emphasize the reduced adhesiveness among cancer cells.

# PRINCIPAL MORPHOLOGIC DIFFERENCES BETWEEN NORMAL CELLS AND CANCER CELLS

| | Benign Cells | Cancer Cells |
|---|---|---|
| Cell size | Variable within physiologic limits | Variable beyond physiologic limits |
| Cell shape | Variable within physiologic limits and depends on tissue type | Abnormal shapes frequent |
| Nuclear size | Variable within limits of cell cycle | Significant variability (anisonucleosis) |
| Nucleocytoplasmic ratio | Variable within physiologic limits | Commonly altered in favor of nucleus |
| Nuclear shape | Generally spherical, oval, or kidney-shaped | Aberrations of shape and configuration |
| Chromatin texture (nondividing nucleus) | Finely granular texture, “transparent” | Coarsely granular texture, “opaque” |
| Hyperchromasia | Rare | Common |
| Multinucleation | Not characteristic | Not characteristic |
| Nucleoli | Small, regular in shape, limited in number | Enlarged, of irregular configuration, increased in number |

| | Benign Cells | Cancer Cells |
|---|---|---|
| Nucleolini | Small and of constant size | Enlarged and of variable sizes |
| Adhesiveness | Excellent (except in lymph nodes, spleen, bone marrow) | Poor |
| Cell junctions | According to tissue type | No conclusive evidence of abnormalities |
| Growth pattern in culture | Contact inhibition | No contact inhibition |
| Number of cell generations in culture | ± 50 | Unlimited |
| Effects of lectins | Not agglutinable* | Agglutinable |
| Ultrastructure of cell surface in scanning electron microscope | Ridges, ruffles and blebs (microvilli in specific sites only)* | Microvilli of variable configuration on the entire surface† |
| Mitotic rate | As needed for replacement* | Elevated |
| Mitoses | Bipolar* | Aberrant forms |
| Placement of mitoses in epithelium | Basal layer only* | Not confined to basal layer |
| Cell cycle duration | 16-22 hr | Normal or longer |

**Cell Configuration**

- bizarre configuration in human tissue or in cells growing freely in effusions.
- Nuclear and clinical features must be always considered before rendering the diagnosis of cancer.

## Cell Adhesiveness

- One of the principal traits of cancer cells is their poor adhesiveness to each other.
- Thus, in smears prepared from an aspirated sample of a malignant tumor, the abundant cancer cells may appear singly or in loosely structured aggregates.

- Generally speaking, cancer cells of epithelial origin tend to form clusters and aggregates, even when allowed to proliferate freely.
- On the other hand, the cells of most nonepithelial tumors, particularly malignant lymphomas and sarcomas, rarely, if ever, form clusters and tend to remain single.

## Cell Membranes

- In general, the surfaces of benign cells, such as squamous cells, lymphocytes, macrophages, or mesothelial cells, display either ridges, blebs, or uniform microvilli.
- The surfaces of most (but not all) malignant cells of epithelial origin (carcinomas) are covered with microvilli of variable sizes and configuration.

- In benign epithelial cells of glandular origin, the microvilli are polarized (i.e., confined to one aspect of the normal cell, usually that facing the lumen of a gland or organ) and are of uniform and monotonous configuration.
- The microvilli of epithelial cancer cells cover the entire cell surface, vary in size and length, sometimes forming clumps of very long microvilli.

**The Nucleus**

**The key changes observed are:**

- Altered nucleocytoplasmic (N/C) ratio in favor of the nucleus.
- Irregularity of the nuclear configuration and contour
- Altered nuclear texture; hyperchromasia and coarse granulation of chromatin
- Abnormalities of sex chromatin in females
- Changes in nuclear membrane
- Nucleolar abnormalities
- Abnormalities of cell cycle and mitoses

**Size**

- The size and, hence, the area of the nucleus in smear and other cytologic preparations depends on DNA content.
- For example, the doubling of the amount of DNA that occurs during the S-phase of the normal cell cycle results in doubling of the nuclear volume, however, the nuclear diameter increases by only 40%.

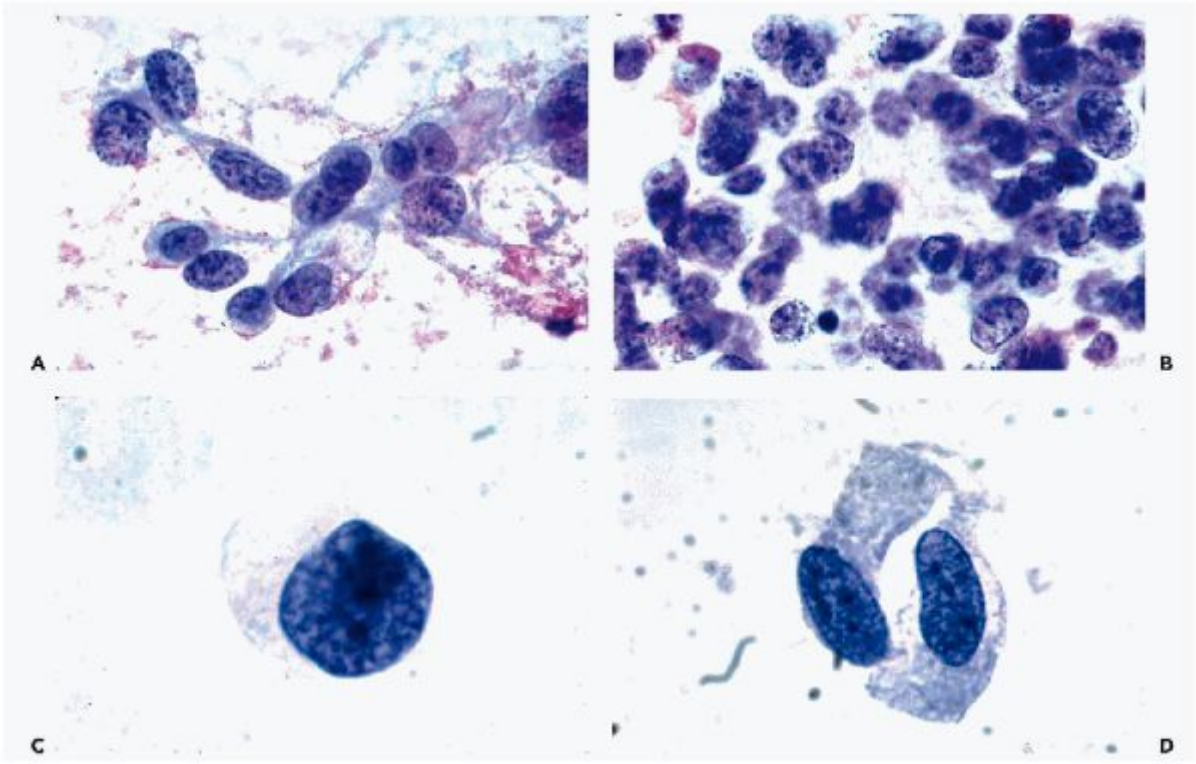
- Because the nucleus in smears is flattened on the surface of the glass slide, the nuclear diameter, corresponding approximately to the largest cross section of the nucleus, is the dominant feature observed under the microscope.

**Irregularities of the Nuclear Configuration and Contour**

- The configuration of the nuclei in normal cells usually follows the shape of the cytoplasm.
- Most nuclei, in benign spherical or polygonal epithelial cells, are spherical.
- In cells of columnar shape, the nuclei are usually oval.
- Nuclei of elongated epithelial cells, fibroblasts, or smooth muscle cells are often elongated and sometimes spindle-shaped.

- The configuration of the nuclei of cancer cells also generally follows the configuration of the cells.
- Thus, most spherical or polygonal cancer cells have approximately spherical or oval nuclei.
- Elongated or “spindly” cancer cells have elongated nuclei.
- However, these nuclei often show abnormalities of the nuclear contour, best observed in spherical or oval nuclei.

# Abnormalities of the nucleus in cancer cells.




Abnormalities of the nucleus in cancer cells. A. Aspirate of pancreatic carcinoma. B. Aspirate of neuroblastoma. C,D. Urothelial carcinoma. Coarse granulation of chromatin and subtle abnormalities of nuclear contour (notches and protrusions) may be observed in all photographs. (Pap stain; A: high magnification; B-D: oil immersion.)

- In elongated cancer cells and most nonepithelial cells with elongated nuclei, the abnormalities of the nuclear contour are more difficult to recognize, although sometimes spinelike protrusions may be observed at one pole.
- In bizarre cancer cells that are sometimes multinucleated, bizarre configuration of nuclei may be observed.

**Nuclear Texture: Hyperchromasia and Coarse Granulation of Chromatin**

- Dark staining of interphase nuclei of cancer cells with appropriated dyes, such as hematoxylin or acetic orcein, is known as hyperchromasia.
- Hyperchromasia is usually associated with changes in configuration of nuclear chromatin, which shows coarse granulation and may be associated with a thickening of the nuclear membrane .

## Abnormalities of Nuclear Membrane

- It has been previously mentioned that in many cancer cells displaying coarse granularity of chromatin, the nuclear membrane appears thickened.
- On close scrutiny, the thickness of the nuclear membrane is variable and irregular.

**Multinucleation in Cancer Cells**

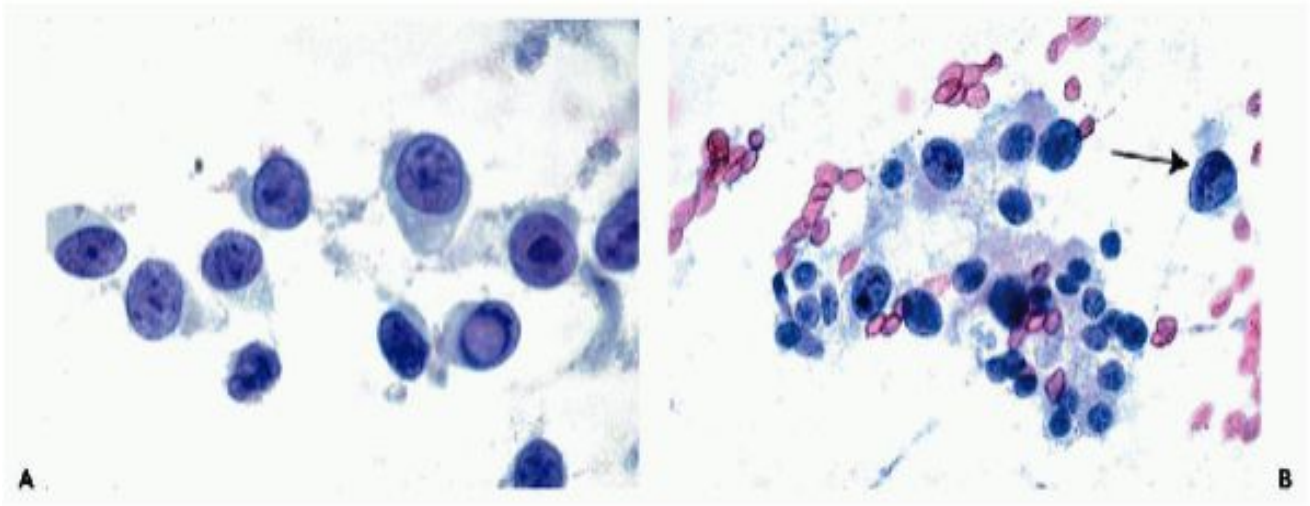
- Cancer cells with two or more nuclei are fairly common.
- In some cells, such as the Reed-Sternberg cells in Hodgkin's disease, the finding of the specific arrangement and configuration of the nuclei is of great diagnostic significance.
- However, in other tumors, the phenomenon is fairly common and of little diagnostic significance.

## Other Nuclear Changes in Cancer Cells

- In some malignant tumors, nonspecific nuclear abnormalities may occur that may be of diagnostic help.
- For example, in some thyroid carcinomas, malignant melanomas, and occasionally other cancers, cytoplasmic intranuclear inclusions appear as clear areas within the nucleus (nuclear cytoplasmic invaginations, Orphan Annie nuclei).

- In electron microscopy, the clear zones contain areas of cytoplasm with cytoplasmic organelles, such as mitochondria.
- Another nuclear abnormality is nuclear “creases,” “grooves,” or folds.

# Abnomalities of nuclear membrane

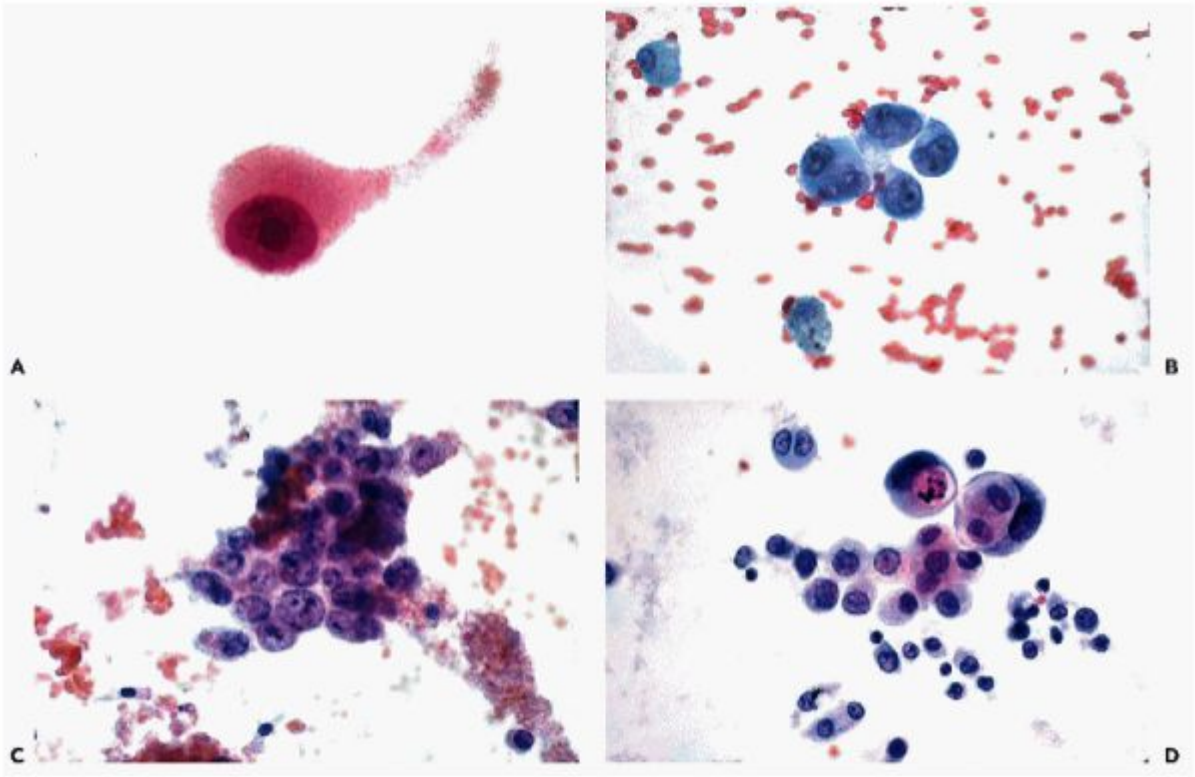



Intranuclear cytoplasmic inclusions (nuclear “holes”) and nuclear grooves or creases. A. Intranuclear cytoplasmic inclusions. Note the sharp borders of the clear intranuclear space. Metastatic malignant melanoma to liver. B. Smear of a Hürthle cell tumor of thyroid. Nuclear folds or creases are seen as a diagonal line (arrow). (A: Oil immersion; B: high magnification.)

**Nucleolar Abnormalities**

- Nucleolar abnormalities are an important feature of cancer cells.
- The number and size of nucleoli in cancer cells is often increased and their configuration may be abnormal.
- It is logical that, in cancer cells with rapid growth and, therefore, high requirements for proteins, the nucleoli should be large and multiple.

# Nuc abn




Nucleoli in cancer cells. A. Huge nucleolus of somewhat irregular shape in a cell of a malignant melanoma. B. Large, irregularly shaped and multiple nucleoli in cells of a spindle- and giant cell carcinoma of lung. C. Large, irregular nucleoli in a poorly differentiated tumor of anterior mediastinum. Cells of a metastatic gastric cancer. D. Large cancer cells of signet ring type are accompanied by smaller macrophages and still smaller leukocytes in pleural effusion. (

## Cell Cycle and Mitoses

## Cell Cycle

- The principal characteristic of cancer cells is their uninhibited proliferation. Clinically, the rate of proliferation of a cancer can be measured as doubling time of tumor volume, using either clinical judgment or radiologic data.
- The doubling time may vary significantly from one cancer to another.

- There are two possible explanations for this phenomenon:
  - (1) either the duration of the cell cycle is shortened, resulting in more frequent replication of the same cells, or
  - (2) the number of cells undergoing mitosis is increased.

- It is commonly and erroneously assumed that the duration of the cell cycle (time required for replication of the DNA, for the mitosis) is much shorter in cancer cells than in normal cells. This is not true.
- Both in the experimental systems and in humans, the duration of the cell cycle in cancer cells is variable, very rarely shorter, and usually very much longer than normal.

**Mitotic Rate**

- In general, the mitotic rate of malignant tumors exceeded significantly the rate for normal tissues of origin.
- However, the mitotic rate of regenerating or stimulated normal tissues (for instance, the breast in pregnancy or the regenerating liver after partial hepatectomy) could exceed the mitotic rate of cancer.

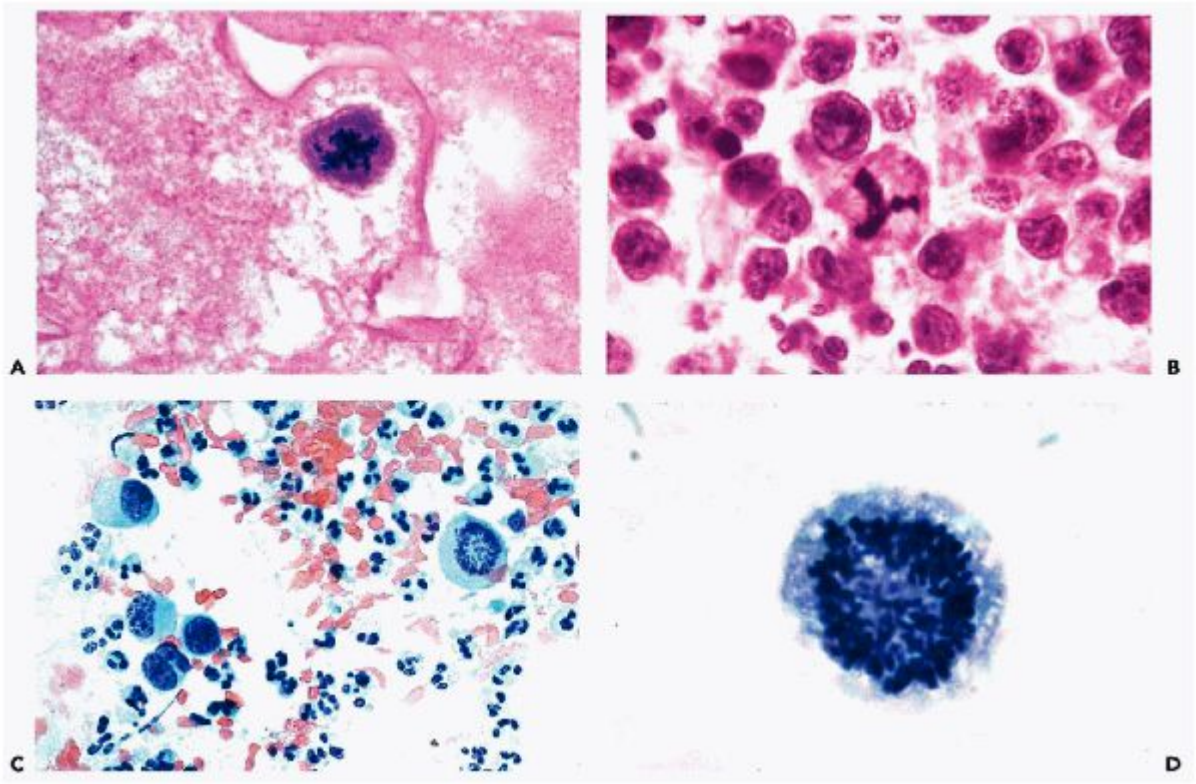
- The high mitotic rate of regenerating or stimulated benign tissues is a temporary phenomenon, followed by a return to normal values once the reparative events have taken place or the stimulus has ceased.
- In cancer, the high mitotic rate is usually a sustained phenomenon.

- In proliferating normal tissues, the mitotic rate usually matches the rate of cell loss.
- The mitotic rate in cancer is not offset by an equivalent cell loss.
- The phenomenon of apoptosis, regulating normal cell growth, is reduced in cancer.

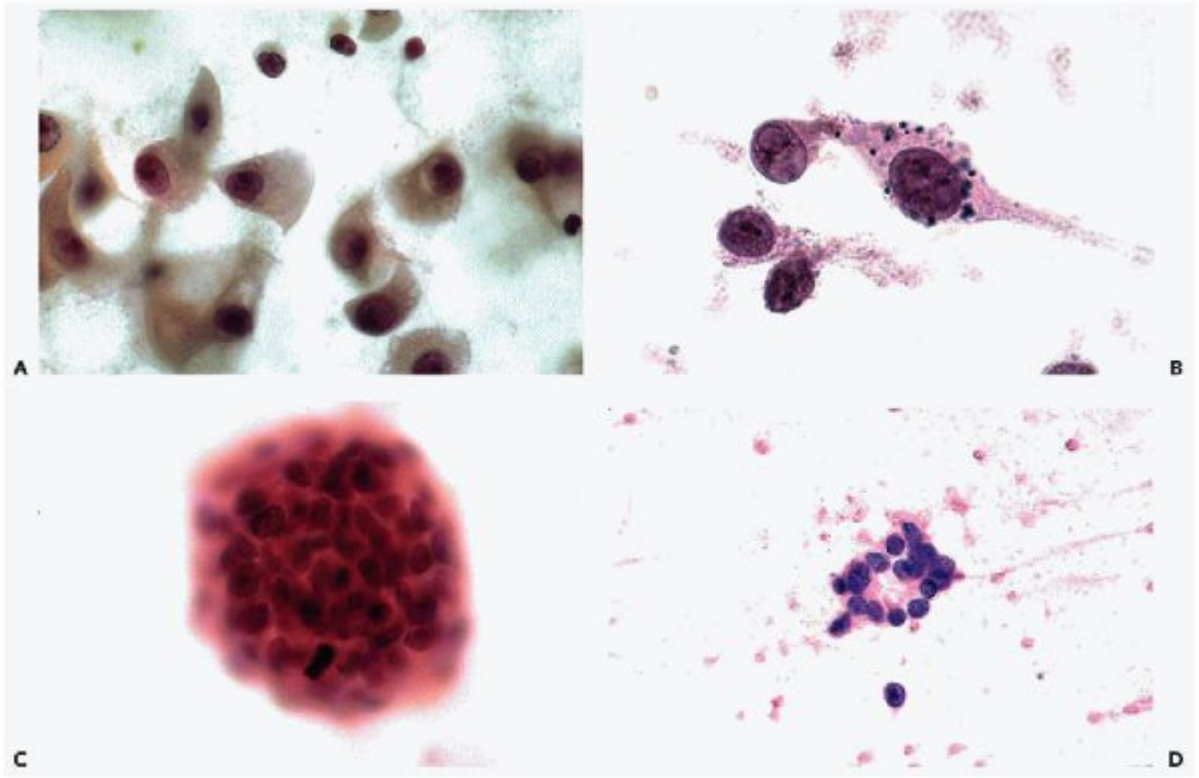
**Abnormal Mitoses**

- Mitotic abnormalities have been recognized for many years as a common occurrence in malignant tumors.
- The term abnormal mitoses refers to mitotic figures with abnormal number or distribution of chromosomes or an excessive number of mitotic spindles, hence, more than two mitotic poles (multipolar mitoses).

# Mitosis diag




Mitotic abnormalities in cancer cells. A. Quadripolar mitosis, metastatic carcinoma to pericardial fluid. B. Tripolar mitosis, embryonal carcinoma, testis. C. Lung cancer, bronchial brush. Note a metaphase with numerous chromosomes next to cancer cells. D. Carcinoma of bladder, voided urine sediment with a tumor cell metaphase containing numerous chromosomes




Examples of differentiation of cancer cells. A. Metastatic bronchogenic adenocarcinoma in pleural fluid. The cancer cells mimic bronchial epithelial cells. B. Metastatic malignant melanoma to liver. Melanin pigment granules in the cytoplasm are enhanced with Fontana-silver stain. C. Metastatic mammary adenocarcinoma in pleural fluid. The cells form a 3-dimensional spherical papillary cluster with evidence of mitotic activity. D. Lung brushings. Gland formation by cells of adenocarcinoma. (B: Oil immersion; C: high magnification.) (B: Courtesy of Prof. S. Woyke, Warsaw, Poland.)

# RECOGNIZING THE TYPE AND ORIGIN OF CANCER CELLS

- Although the recognition of the malignant nature of cancer cells is based primarily on the nuclear features, the cytoplasmic features often reflect their origin and derivation of these cells.
- The issue is important because the recognition of cell derivation may be of significant diagnostic and clinical value, particularly in the classification of metastatic tumors of unknown origin.

- As a general principle, cancer cells attempt, at all times, to mimic the tissue of origin with variable success and these attempts are expressed in the cytoplasm.
- Thus, cancer cells of bronchial origin may mimic bronchial cells
- Cancer cells of squamous epithelial origin often contain an abundance of keratin filaments of high molecular weight; this is reflected in rigid polygonal shape and intense eosinophilic staining of the cytoplasm, easily recognizable under the microscope.

- The formation of squamous “pearls,” i.e., spherical structures composed of squamous cells surrounding a core of keratin, is commonly observed in squamous cancers.
- The cytoplasm of cancer cells originating in the glandular epithelium may show evidence of production and secretion of mucin or related substances in the form of cytoplasmic vacuoles; such cells may also retain the columnar configuration of cells of the epithelium of origin.

- Cancer cells derived from striated muscle may display cytoplasmic striations and cells derived from pigment-producing malignant tumors, such as melanomas, may produce cytoplasmic deposits of melanin pigment.
- It is not uncommon for differentiated cancer cells to form three-dimensional structures mimicking the structure of the tissue of origin.
- Thus, formation of gland-like or tubule-like structures is fairly common in adenocarcinomas, as is the formation of spherical or oval three-dimensional clusters of cancer cells, mimicking the formation of papillary structures of the tumor observed in tissue sections.

- In many cancer cells, however, the efforts at differentiation are stymied, resulting in cells that have very few or no distinguishing features under the light microscope.
- Such cells are classified as “poorly differentiated” or “anaplastic” (from Greek, ana = again and plasis = a moulding), suggesting a reversal to a more primitive, embryonic type of cell.
- Still, even such cells may display features of sophisticated differentiation by electron microscopy or by immunostaining.

- For example, cells derived from poorly differentiated tumors of the nervous system, such as neuroblastomas, may show ultrastructural evidence of formation of characteristic cell junctions (synapses), and of neurofibrils.
- Cells derived from tumors with endocrine function may show evidence of hormone formation in the form of the characteristic cytoplasmic vesicles in electron microscopy.

- The endocrine function may also be revealed by immunocytochemistry with antibodies to the endocrine granules in general or to the specific cell product.
- Many such examples could be given, may be applied in an attempt to determine the origin on undifferentiated cancer cells.
- The issue of cell differentiation in cancer is further complicated by the fact that the expressions of differentiation may vary, not only from cell to cell within the same tumor, but may depend on the clinical presentation of the same tumor.

- As an example, a poorly differentiated primary carcinoma of squamous or glandular lineage may become fully differentiated in a metastatic focus and vice versa; a well differentiated primary tumor may form poorly differentiated metastases.

- Further, a tumor that may appear to be of a single lineage in its primary presentation may form metastases showing two or sometimes more families of cancer cells.
- In general, during the natural history of a cancer, recurrent or metastatic tumors tend to be less well differentiated than the primary but there are many exceptions to this rule.

Thanks.