Disturbances of growth & Neoplasia
2013-2014
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Acknowledgement
- To the memory of my dear professor
  Prof. Abdel Fattah EL Bedeiwy (May our great Allah bless his Soule)
- This work is based upon the lectures prepared by him, my knowledge are also based upon what he taught me… So I just want to say to him….
  Thank You

Objectives
- Recognize patterns, pathogenesis, types and morphology of growth disturbances
- Identify steps of carcinogenesis, origin and morphological features of different types of neoplasms and know the molecular basis of cancer..

Growth disturbances are considered under 3 headings:
1- Abnormalities of cell growth and differentiation
   A. Hereditary & Congenital
   B. Acquired
2- Adaptations
3- Neoplasia

1 - Abnormalities of cell growth
   A. Hereditary & Congenital anomalies
      - Hereditary means abnormal germ cell (sperm or ovum)
      - Congenital means normal germ cell with a lesion occurring after fertilization

• Causes of congenital anomalies
  • Nutritional
  ✓ Exposure to Radiation
  ✓ Chemicals and Drugs
  ✓ Infections e.g German measels
  ✓ Increased maternal age (above 35 years)

• Types of congenital anomalies:
  1- Agenesis: Complete absence of an organ.
2- Aplasia: The organ is replaced by fibrous tissue.
3- Hypoplasia: Underdevelopment or incomplete development of a tissue or organ.
4- Atresia: Failure of canalization of a hollow organ
5- Heterotopia (choristoma): Normal tissue in abnormal site e.g. pancreatic tissue in the wall of the stomach
6- Hamartoma.

**Hamartoma**
- **Definition:**
  A developmental malformation formed of non-capsulated mass composed of mature tissues of the locality which show variation in arrangement or quantity. It manifests at birth or shortly after and usually stops growing when general body growth stops

**Examples**
- Pigmented naevi
- Haemangioma & lymphangioma
- Osteo-chondroma
- Multiple neurofibromatosis
- Hamartoma of the lung and liver.

*Prognosis:*
- Usually stops at puberty
  - Some may turn malignant e.g. Osteo-chondroma can change into Chondrosarcoma

Hemangioma of the tongue  
M/E: vascular spaces lined by endothelium and filled with blood
B-Acquired

- **Dysplasia**
- **Definition**
  - Disorder of cellular growth, usually associated with epithelium
  - Loss in the uniformity of individual cells as well as loss of architectural orientation. Cells show
  - Pleomorphism
  - Hyperchromasia
  - Abnormal N:C ratio
  - When the entire thickness of the epithelium is involved, it is called carcinoma in situ

![Image of dysplasia progression](image)

**Prognosis**

Epithelial dysplasia is a **premalignant lesion**

- The risk of developing invasive cancer varies with
  - (1) the grade of dysplasia—the more severe, the greater the risk;
  - (2) the duration of dysplasia—the longer the duration, the greater the risk; and
  - (3) the site of dysplasia. Dysplasia in the urinary bladder is associated with a more imminent risk of cancer than is cervical dysplasia, in which several years may elapse before invasive carcinoma develops.
** What are the differences between dysplasia and neoplasia???

2- Adaptation

- Atrophy
- Hypertrophy
- Hyperplasia
- Metaplasia

Atrophy

*Definition*
Decrease in size and weight of a tissue or organ due to reduction in size and/or number of its component parenchymal cells. It may be physiological or pathological

*Types of atrophy:-*
1- Physiological  or  2- Pathological

- 1-Physiological
  i- General: Senility
  ii- Local:  a. New born: Ductus arteriosus, Umblical Vessels, Adrenal cortex
  b. Adult ... thymus at puberty
  c. Menopause  Female genital tract

Atrophy of breast tissue after menopause
2- Pathological:
   A- General:
      Starvation
      Toxic: Tuberculosis or cancer
      Hormonal: Decreased pituitary trophic hormones
   B- Local:
      Disuse: atrophy of the muscles of a limb put in plaster cast.
      Neurogenic: Poliomyelitis causes muscle atrophy
      Ischemic: Reduction in blood flow of an organ.
      Pressure:
         Exogenous: atrophy of vertebrae by an aortic aneurysm
         Endogenous: atrophy of liver cells by a hydatid cyst.
      Thermal: Testicular atrophy in a undescended testicle.
      Immunologic: Autoimmune atrophic gastritis.
      Hormonal: Adrenal atrophy due to absence of ACTH.

   Hypertrophy

   Definition:- It is increased size and weight of an organ due to increased size of its component cells.
   - It is related to muscles. May be physiological or pathological
Types:

Physiologic:

a. Excess functional demands
b. Hormonal...smooth muscles of a pregnant uterus

Pathologic:

1- Hormonal: Acromegaly, gigantism.
2- Adaptive hypertrophy
   Occurs in muscular hollow organs usually to overcome a distal obstruction …
   a- Heart
      - Right ventricle: in mitral stenosis, or pulmonary hypertension
      - Left ventricle: In aortic valve lesions
   b. GIT
      - Pyloric stenosis
      - Intestinal obstruction.
   C. Urinary bladder: in prostatic hyperplasia
3- Compensatory hypertrophy

- Occurs in paired organs when one of them is lost, the remaining one hypertrophies to carry on the extra work e.g.
  - Kidney
  - Lung
  - Adrenal gland

Hypoplastic, Hypertrophic kidney
Hyperplasia

1- Definition

2- Types (physiological & pathological)

3- Clinical significance

4- Differences between it and neoplasia

Definition

- It is increase size and weight of an organ or tissue due to increased number of its specialized cells in response to a particular stimulus.
- It can only occur in organs or tissues composed of cells capable of mitotic division in the postnatal life i.e. labile and stable cells.
- It may be physiological or pathological

Types

1- Physiological Hyperplasia

- Glandular Hyperplasia of the female breast at puberty, pregnancy & during lactation.
- Smooth muscles of a gravid uterus.
- Thyroid gland in girls at puberty & during lactation.

2- Pathological Hyperplasia

- A. Compensatory
- B. Hormonal
- C. Irritative.

A) Compensatory Hyperplasia:

- Liver cells & thyroid epithelial cells after partial destruction or removal.
- The remaining kidney after nephrectomy.
- Bone marrow after hemorrhage.
Bone marrow hyperplasia

**B) Hormonal Hyperplasia**
- Estrogen: endometrial hyperplasia in females
- Prostatic hyperplasia in males.
- Anterior pituitary trophic H: hyperplasia of thyroid, adrenal cortex

**C) Irritative hyperplasia**
- Epidermal hyperplasia seen in chronic irritation or abrasions of the skin or mucous membranes

**Clinical significance of hyperplasia:**
1. Mass (breast, prostate, thyroid).
2. Uterine bleeding in endometrial hyperplasia
3. Increased risk of neoplasia (atypical endometrial hyperplasia)

Hyperplasia is...
- Physiological or pathological
- Usually reversible,
- Normal cytology and histology
- May have useful function
- May progress to malignancy, as in surface epithelium.

**Metaplasia**

- Definition
- Types and examples
- Causes
- Clinical significance

![Normal Metaplasia](image)

**Definition**
* It is an adaptive substitution of one type of adult or fully differentiated cell for another type of adult cell of the same category (i.e. epithelial to epithelial & C.T. to C.T. in response to changes in the environment
- It occurs only in cells capable of proliferation in the post natal life i.e. in labile & stable cells.

**Types:**
* Epithelial  * Connective tissue  * Mesothelial
  Epithelial metaplasia:
  **Causes:**
  a. Chronic irritation  
  b. Avitaminosis A
  c. Gene activation  
  d. Unknown causes.
  a. Squamous metaplasia:
  - Transformation of columnar epithelium (of bronchi, endocervix, gall bladder in chronic cholecystitis or stones) into stratified squamous epithelium.
Transformation of transitional epithelium of urinary bladder into stratified squamous epithelium as occurs with bilharziasis or stones.

- **Metaplasia**
  - Squamous metaplasia

**b. Glandular metaplasia:**
- Intestinal metaplasia of the gastric mucosa in auto immune atrophic gastritis.
- Glandular metaplasia of transitional epithelium in case of cystitis glandularis.
- Barrett’s esophagus: transformation of the lower end of esophagus (stratified squamous epithelium) to intestinal epithelium as occurs with reflux esophagitis.

**B) Connective tissue metaplasia:-**
- **Cartilaginous metaplasia:-** seen in healing fractures especially with immobilization
- **Bone metaplasia:-** In laryngeal & tracheal cartilage in old age.
- **Myositis ossificans:-** In a traumatized muscle, the fibrosis replacing the haematoma changes to bone.
  - **Irreversible.**
C) Mesothelial metaplasia:-
- Affects flattened cells that line the serous sacs.
- Chronic irritation may change them to cubical, columnar, glandular, or stratified squamous.

prognosis of metaplasia

1- Reversib 2- Epithelial metaplasia may be precancerous
Summary

- Abnormal differentiation
- Replacement of mature cells of one type with cells of another type
- Regular organization of tissue maintained
- Reversible

- Abnormal differentiation and maturation
- Partial loss of control and organization
- Slight increase in cell number
- Cytologic abnormalities
- Partially reversible

- Abnormal differentiation and maturation
- Marked increase in cell number
- Complete loss of control
- Variable loss of organization
- Cytologic abnormalities
- Irreversible

Metaplasia          Dysplasia          Neoplasia

Normal tissue

Atrophy          Hypertrophy          Hyperplasia

Decrease in cell size  Decrease in cell number  Increase in cell size  Increase in cell number
Neoplasia

Objectives
- Definition
- Classification
- Nomenclature

Definition
- Abnormal mass of tissue the growth of which exceeds and is uncoordinated with normal tissue and that persists in the same excessive manner after cessation of the stimuli which evoked the change.

(Autonomous new growth)

* General features of neoplasm:
  - Tumor arises as a result of mutation (genetic damage) either acquired by environmental factors or inherited in germ cell line.
  - The tumor is formed by monoclonal proliferation of a single precursor cell that has incurred the genetic damage (i.e., tumors are monoclonal).
  - Any cell can give rise to tumor, but more frequent in labile cells, followed by stable cells, and then least in the permanent cells.
Any tumor- benign or malignant- has 2 basic components:
  a. Parenchyma:  
  b. Supporting stroma: 

1- Parenchyma
   * Made of transformed or neoplastic cells
   • It determines the biological behavior of the tumor (benign or malignant)
     *From it the tumor derives its name.
   * The tumor results from clonal proliferation of a single cell (Monoclonal). Therefore, the
     more the cell divides, the more its chance for tumor production. (more in labile cells, next in stable cells then least in permanent cells)

2-Supporting stroma
   • It is host derived, non-neoplastic component of the tumor.
     *It is made of connective tissue and blood vessels of the tumor.
     * Its amount is responsible about the consistency of the tumor
     * Vascularity of the stroma is related to tumor-angiogenesis factors e.g vascular endothelial growth factor (VEGF) which is mainly produced by the tumor cells.

Classification of tumors

According to the biological behavior
A) Benign           B) Malignant
   C) Locally malignant

According to the tissue of origin
A) Epithelial (Adenoma, papilloma - Carcinoma)
   B) Mesenchymal (…oma - Sarcoma)
   C) Miscellaneous

Differences between benign and malignant tumors
Benign versus Malignant tumors
<table>
<thead>
<tr>
<th>Differences between benign and malignant tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benign tumor</strong></td>
</tr>
<tr>
<td><strong>1. Definition</strong></td>
</tr>
<tr>
<td>A single mass formed of mature tissue, grows slowly and remains localized.</td>
</tr>
<tr>
<td><strong>2. Origin</strong></td>
</tr>
<tr>
<td>Normal cells of the parent tissue. (de novo)</td>
</tr>
<tr>
<td><strong>3. Rate of growth</strong></td>
</tr>
<tr>
<td>Slow.</td>
</tr>
<tr>
<td><strong>4. Mode of growth</strong></td>
</tr>
<tr>
<td>By expansion</td>
</tr>
<tr>
<td><strong>5. Gross features</strong></td>
</tr>
<tr>
<td>a. Number: single.</td>
</tr>
<tr>
<td>b. Size: usually small.</td>
</tr>
<tr>
<td>c. Capsule: capsulated. (Some exceptions).</td>
</tr>
<tr>
<td>d. Cut section: uniform, no hemorrhage or necrosis.</td>
</tr>
<tr>
<td>e. Shape: according to the site;</td>
</tr>
<tr>
<td><em>Inside a solid organ</em>... it is globular or ovold surrounded by fibrous capsule.</td>
</tr>
<tr>
<td><em>From surface epithelia</em>... it forms a noncapsulated polyp (papilloma)</td>
</tr>
<tr>
<td><strong>1. Polypoid (fungating) mass</strong>: grayish white bulging mass like cauliflower, hard in consistency with irregular outer surface &amp; fixed broad base.</td>
</tr>
<tr>
<td><strong>2. Ulcerative pattern (malignant ulcer)</strong>:</td>
</tr>
<tr>
<td><strong>Margins</strong>: irregular.</td>
</tr>
</tbody>
</table>
**6. Microscopic features**

<table>
<thead>
<tr>
<th>No cellular atypia; (well differentiated)</th>
<th>Cellular atypia is characteristic of cancer: Tumor cells show changes in cellular morphology (cytology) and cellular pattern of arrangement (histology)</th>
</tr>
</thead>
<tbody>
<tr>
<td>the tumor cells resemble the parent tissue cells in both cytology and histology.</td>
<td><strong>1. Cytology:</strong> the cells show <em>cytologic criteria of malignancy</em>;</td>
</tr>
<tr>
<td><strong>1. Cytology:</strong></td>
<td>a. <strong>Pleomorphism:</strong> variability in size &amp; shape of cells and nuclei.</td>
</tr>
<tr>
<td>▶ The cells are mature.</td>
<td>b. <strong>Hyperchromatism:</strong> increased D.N.A.</td>
</tr>
<tr>
<td>▶ Resemble the mother cell of origin.</td>
<td>c. <strong>Increased nuclear/cytoplasmic (N/C) ratio to 1:2 (N=1:4).</strong></td>
</tr>
<tr>
<td>With minimal mitoses.</td>
<td>d. <strong>Increased mitotic figures</strong> with abnormal forms.</td>
</tr>
<tr>
<td><strong>2. Histology:</strong></td>
<td>e. <strong>Tumor giant cells.</strong></td>
</tr>
<tr>
<td>▶ The pattern of arrangement of the tumor cells is similar to the tissue of origin e.g. thyroid adenoma is formed of thyroid acini similar to the normal thyroid acini.</td>
<td>f. <strong>Prominent nucleoli</strong></td>
</tr>
<tr>
<td><strong>3. Stroma:</strong></td>
<td><strong>2. Histology:</strong></td>
</tr>
<tr>
<td>▶ Excess with few well formed blood vessels.</td>
<td>The pattern of arrangement of the tumor cells is variable and depends on the tumor grade.</td>
</tr>
<tr>
<td><strong>Tumor Grade</strong> (differentiation): the degree of resemblance of the tumor tissue to the tissue of origin as regard morphology and function. It may be</td>
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</tr>
<tr>
<td>▶ Well differentiated (grade I),</td>
<td>▶ Well differentiated (grade I),</td>
</tr>
<tr>
<td>▶ Moderately differentiated (Grade II),</td>
<td>▶ Moderately differentiated (Grade II),</td>
</tr>
<tr>
<td>▶ Poorly differentiated (grade III)</td>
<td>▶ Poorly differentiated (grade III)</td>
</tr>
<tr>
<td>▶ Undifferentiated (grade IV).</td>
<td>▶ Undifferentiated (grade IV).</td>
</tr>
<tr>
<td><strong>3. Stroma:</strong></td>
<td><strong>3. Stroma:</strong></td>
</tr>
<tr>
<td>▶ Poor, with prominent vascularity.</td>
<td>▶ Poor, with prominent vascularity.</td>
</tr>
<tr>
<td>▶ 2ry changes are common e.g. hyaline deg.,</td>
<td>▶ 2ry changes are common e.g. hyaline deg.,</td>
</tr>
<tr>
<td>2ry changes: less common</td>
<td>calcification, hemorrhage and necrosis</td>
</tr>
<tr>
<td>--------------------------</td>
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</tr>
</tbody>
</table>

### 7. Behavior & Prognosis

- Does not spread.
- Does not recur if well excised.
- Don’t endanger patient life except in the following conditions:
  - Located in vital organ.
  - Located in tubular organ (obstruction).
  - Hormones production.
  - Malignant transformation

- Spreads locally and sends distant metastases.
- Recurs after excision.
- May be fatal:

  **Causes of death in malignant tumors**
  - X. Local organ destruction due to direct spread.
    - Destruction of distant organs by distant spread.
    - Obstruction of hollow organs. e.g. intestine or urinary bladder.
    - Cachexia.
    - Paraneoplastic syndrome

**Benign tumor (thyroid adenoma)**

- Capsule

**Malignant tumor (breast carcinoma)**

- No capsule

**Benign tumor (lipoma)**

- Capsule, mature fat cells
- Few well formed blood vessels

**Malignant tumor**

- Pleomorphism, increased N/C ratio
- Abnormal mitoses (arrows)
Grading of Tumors

- **Tumor Grade** = degree of resemblance of the tumor to mother tissue as regards morphology, function, and relationship to themselves and other cells.
- It may be: *Well differentiated*
  - Moderately diff. *Poorly diff.* *Undifferentiated or anaplastic.*
- The degree of malignancy increases with decreased differentiation.

1. well differentiated
2. Moderately differentiated

3. Poorly differentiated
4. Anaplastic

**LOCALLY MALIGNANT TUMORS**

*Def:* Tumors which infiltrate locally but don’t send distant metastases.

*Characters:*
- Slower rate of growth than malignant tumors but more rapid than benign tumors.
- Grow by infiltration.
- No blood or lymphatic spread.
- Microscopically, the cells are malignant.
- May turn malignant (metastasizing).
- Recur after incomplete excision.

*Examples:*
1. Basal cell carcinoma of skin.
2. Giant cell tumor of bone “osteoclastoma”.
3. Adamantinoma of the mandible.
4. Brain tumors as astrocytoma & craniopharyngioma.
5. Carcinoid tumor.

**Prognosis:**
- May recur after removal
- May turn malignant and give distant metastasis

**Spread of malignant tumors**

A. Local spread (direct invasion):
B. Distant spread metastasis: by;
   1. Blood (hematogenous) spread
   2. Lymphatic spread
   3. Transcelomic spread
   4. Inoculation
   5. Implantation

**A. LOCAL SPREAD (INVASION)**

*Definition:*
- Presence of tumor cells away from the primary tumor mass without loss of continuity with it.
- Done by Invasion of the extracellular matrix “E.C.M” (basement membrane & interstitium).
- **Next to development of metastases, invasiveness is the most reliable feature that differentiates malignant from benign tumors.
Local invasion occurs through a four step process that includes

a) Detachment of tumor cells from each other
b) Attachment of tumor cells to the E.C.M
c) Degradation of the E.C.M
d) Migration

a) **Detachment of tumor cells from each other**

*This occurs due to loss of the intercellular glue substance (E.cadheren)*

*It results in loosening up of tumor cells*

![Diagram of detachment](image1)

b) **Attachment of tumor cells to E.C.M**

The E.C.M. includes
- Basement membrane which contains laminin and
- Interstitial connective tissue which contains fibronectin.
  - Tumor cells develop laminin & fibronectin receptors which cause them to adhere to the B.M. & interstitial C.T

![Diagram of attachment](image2)

c) **Degradation of the extra cellular matrix**

- Tumor cells then secrete proteases which causes degradation of the E.C.M e.g. type IV collagenase. 
  N.B Protease inhibitors can be used as therapeutic agents

d) **Migration**

*This step occurs under the effect of certain chemo tactic factors e.g. tumor cell derived cytokines, cleavage products of matrix components and some growth factors*
Distant spread = Metastasis

It is the presence of a tumor cells away of its primary tumor site without continuity with it.
Distant spread can occur by:-
a. Blood,
b. Lymphatic,
c. Transcoelomic,
d. Through natural Passages
e. Implantation and inoculation.

a. Blood (Hematogenous) Spread

-Typical of sarcomas, can be used by carcinomas
   (renal, hepatocellular, choriocarcinoma, breast, follicular thyroid, prostatic & lung small cell).
- Veins, with thinner walls are more susceptible to penetration than arteries.
- Liver and lungs most frequent secondarily involved sites
  - All portal area drainage flows to liver
  - All caval blood flows to the lungs.
- Vertebral system of veins.
* **Mechanism:**

- **Intravasation:** the malignant cells invade the E.C.M & wall of the blood vessel to get inside it.
- **Embolization:** The malignant cells pass with blood stream as tumor emboli. They are covered by host platelets (so the tumor cells are hidden from the immune system).
- **Extravasation:** The tumor emboli are impacted in a narrow blood vessel in a distant organ and invade its basement membrane.
- **Homing:** the tumor cells proliferate again, develop new vascular supply and form a new tumor mass.

**Homing of tumor cells**

The site of extravasation of tumor emboli and hence the organ distribution of metastases depends upon

1. The site of the 1ry tumor and its vascular and lymphatic drainage.
2. The affinity of certain tumor cells to certain metastatic sites which may be related to the presence of adhesion molecules on tumor cells to the endothelium of blood vessels of the organ e.g. 1ry lung tumor to the adrenal glands.

On the other hand, some organs e.g. spleen and skeletal muscles are rarely affected by metastatic tumors.
- This may be due to the presence of high concentrations of protease inhibitors which prevent the establishment of a tumor colony.

**According to the anatomical factors:**

1. **Emboli derived from 1ry tumors drained by systemic veins,** causing **lung metastasis,** however, there are some exceptions;

- **Paradoxial embolism** to systemic organs due to ASD or VSD.
- The tumor cells are small enough to pass through lung capillaries without arrest.
- Metastasis of some pelvic, abdominal or thoracic tumors through the **paravertebral system** of veins directly to brain & spinal cord.
- Metastasis of cancer kidney to left testis through left testicular vein after thrombosis of the renal vein (**retrograde hematogenous spread**).

2. **Emboli derived from tumors of the lung cause systemic metastasis.**

3. **Emboli derived from tumors drained by portal blood cause liver metastases.**
4. **Emboli reaching the paravertebral system of veins** from tumors of pelvic, abdominal or thoracic organs lead to metastases in *brain, spinal cord and vertebrae* without causing lung metastasis.

* **Morphology of metastatic deposits:**
  - **N/E:**
    - **Nodules:** multiple, peripheral in position, round, of slightly variable sizes, hard in consistency, grayish white in color
    - **C/S:** shows areas of hemorrhage and necrosis.
  - **M/P:** Metastatic deposits resemble the lary tumor

**Bone metastasis**

**Liver metastasis**

**Metastasis in the lungs**

**Brain metastases**
b. Lymphatic Spread

-Most common pathway of spread for dissemination of carcinoma

-Pattern of lymph node involvement follows natural routes of drainage
  
  -Breast carcinoma, upper outer quadrant, axillary nodes
  
  -Breast carcinoma, inner quadrant, internal mammary nodes

Lymphatic Spread

Metastatic deposit in a L.N

- Tumor passes with the afferent lymphatic…..sucapsular sinus…progress to replace the structure of the LN

Lymphatic permeation

- Affects small lymphatic channels.
  
  -It is best seen in
  
  A) serous sacs and

B) Perineural lymphatics especially in cases of cancer prostate. & biliary tract

- Tumor cells multiply in the lumen to produce a cord-like structure.
  
  - Nerve compression produces severe pain.
3- Transceolomic (Seeding of Body Cavities)
Occurs whenever a malignant neoplasm penetrates into an “open field”
- peritoneal cavity
- pleural cavity
- pericardial cavity
- subarachnoid space

Common in carcinomas arising in the stomach or GIT giving metastatic deposits on the surface of the ovary (Krukenberg tumor)

- Metastasis through cranial cavity: Brain tumors send to the base of the skull and the dorsal aspect of the spinal cord

- Metastasis through Pleural cavity: Malignant cells from cancer bronchus are deposited on the surface of the diaphragm

4. INOCULATION
- Direct transplantation of tumor cells by surgical instrument.
- Extremely rare.

5. IMPLANTATION
Spontaneous transfer of malignant cells in opposing surface e.g. from lower to upper lip.
Histogenetic classification of tumors

- **A. Epithelial tumors**
  - **I- Benign**
    - a. Surface epithelium…… Papilloma
    - b. Secretory epithelium…… Adenoma
      - Cystadenoma
      - Papillary cystadenoma
    - c. Protective secretory epithelium…Adenopapilloma
  - **II- Malignant…… Carcinoma**
    - Surface epithelium…squamous cell, transitional carc.
    - Secretory epithelium … Adenocarcinoma
    - Cystadenocarcinoma & papillary cystadenocarcinoma

<table>
<thead>
<tr>
<th>Tissue of origin</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous tissue</td>
<td>Fibroma</td>
<td>Fibrosarcoma</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipoma</td>
<td>Liposarcoma</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Chondroma</td>
<td>Chondrosarcoma</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoma</td>
<td>Osteogenic sarcoma</td>
</tr>
<tr>
<td>Smooth muscle</td>
<td>Leiomyoma</td>
<td>Leiomyosarcoma</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Hemangioma</td>
<td>Angiosarcoma</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>Rhabdomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Squamous epithelium</td>
<td>Squamous cell papilloma</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Transitional epithelium</td>
<td>Transitional cell papilloma</td>
<td>Trans. Cell carcinoma</td>
</tr>
<tr>
<td>Glandular epithelium</td>
<td>Adenoma</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td></td>
<td>Cystadenoma</td>
<td>Cystadenocarcinoma</td>
</tr>
<tr>
<td>Melanocytes</td>
<td>Nevus</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Mesothelium</td>
<td></td>
<td>Mesothelioma</td>
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<tr>
<td>Hematopoietic cells</td>
<td>Lymphoid cells</td>
<td>Leukemia</td>
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<td></td>
<td></td>
<td>Lymphoma</td>
</tr>
</tbody>
</table>

**Benign epithelial tumors**

1-**Protective epithelium:-**

- **Papilloma:-** It is a benign tumor of protective epithelium.
- **Etiology:-** human papilloma virus (HPV) types I,II,IV and VII
- **Pathology:-**
  - **Gross:-** The tumor projects above the surface. -It is non capsulated.
  - It may be sessile or pedunculated, simple or compound.
The tumor is made of two main components:

1. A central fibrous core which carries the blood vessels, lymphatics, and nerves of the tumor.
2. A hyperplastic epithelial covering which may be

* Stratified squamous epithelium.... Squamous cell papilloma.
* Transitional epithelium...... Transitional cell papilloma.
* Lining of large ducts "breast or pancreas"........ Duct papilloma.

Complications:

1. Bleeding (nipple and urinary bladder papillomas)  
2. Hoarseness of voice (larynx) 
3. Malignant transformation to squamous cell carcinoma, transitional cell carcinoma and duct carcinoma

Benign tumors of secretory epithelium Adenoma

- Adenoma: A benign tumor of secretory and glandular epithelium.

* Pathology

  - Gross: Size Variable
  - Shape Well defined, rounded, oval or lobulated.
  - Color The same as its origin or may be paler.
  - Capsulated May be solid, cystadenoma, or papillary cystadenoma

Adenoma M/E

A* Solid Adenoma: It is formed of tumor acini separated by fibrous stroma.
The acini may be

- Opened with a central lumen & lined by one or two layers of benign epithelial cells.
- Solid acini formed of groups or masses of epithelial cells without a central lumen e.g. liver and ant. Pituitary.

B *- Cystadenoma

C* Papillary Cystadenoma

Complications
- Excessive secretion of hormones.
- Pressure effects (pituitary adenoma)
- Malignant transformation (Adenocarcinoma)

Protective -secretory epithelium

Adenopapilloma
A benign tumor of protective-secretory epithelium.
- It is related to colo-rectal mucous membrane.

*Pathology:-

Gross:- Uncapsulated tumor "like papilloma"

ME:- Open acini lined by columnar epithelium and separated by fibrous stroma "like adenoma"

"The surface is covered by epithelium.

-Complications:- Malignant transformation :"adenocarcinoma

Carcinoma (malignant epithelial tumor)

1) CARCINOMA

➢ Malignant tumor of the surface epithelium.
➢ More common and occur in older age group than sarcoma.
➢ It has slower rate of growth than sarcoma.

N/E A) Surface epithelium:

- Fungating (polypoid) mass
- Infiltrating mass
■ Malignant ulcer

**B) In solid organs:**
- Non capsulated mass, hard, fixed
- Grey white cut surface.
- With areas of hemorrhage and necrosis.

**Histology:**
The tumor cells are arranged in groups or sheets. They show features of malignancy:

  **Pleomorphism of the cells, loss of polarity, hyperchromatic nuclei, increased N/C ratio, frequent mitosis.**
  - The groups of malignant cells are separated by abundant stoma that contains blood vessels
- Different grades of differentiation:
  Well, moderately, poorly differentiated, completely undifferentiated (anaplastic).

**Behavior:**
- Carcinoma grows by infiltration.
- Spreads: Early by lymphatics Late, by blood.

**Cancer Stage**
- Reflects degree of spread, for an individual cancer patient
- Assigned at the time of diagnosis, may be updated as patient progresses

**TNM Staging**

| T  | Tumor characteristics |
| N  | Nodal involvement     |
| M  | Metastasis            |
T= Primary tumor

N= lymph node

M= distant metastasis

Squamous cell carcinoma

It is a malignant tumor of stratified squamous epithelium.

*Sites:-
   a) Skin
   b) Squamous mucous membranes.
   c) muco- cutaneous junctions & d) Squamous metaplasia "bronchus U.B., G.B. & endocervix

*Predisposing factors
   a) Chronic irritation by U.V. rays, Ionizing irradiation, chemicals, & chronic inflammation (chronic skin ulcer, ch. Sinus), leukoplakia
   b) Hereditary diseases...Xeroderma pigmentosa
   c) Benign tumors e.g. squamous cell papilloma.
   d) The tumor may arise de novo

Grossly

A hard nodule on the surface that may be
   a. Fungating  b. Infiltrating  c. Ulcerating
M/E

Early squamous cell carcinoma (In situ carcinoma)

1- In situ changes, down growth of the surface epithelium into the deeper tissue can be detected, cells are malignant but the basement membrane is still intact.

Variable sized columns and groups of malignant epithelium cells invade the deeper parts. They are separated by fibro-vascular stroma. The tumor may be well, moderately or poorly differentiated

Well differentiated tumors

They show concentric arrangement of different layers of the epidermis with central keratin formation " cell nests or epithelial pearls"

-Cells of the outer layer of the cell nest are small with hyperchromatic nuclei.
-Next layers (prickle cells) are large, polyhedral cells wit intercellular bridges. The nuclei are pale with prominent nucleoli.
-Towards the center, the cells become flattened with granular cytoplasm and small, dense nuclei.
-In the center of the group, there are laminated, eosinophilic, keratin layers.

Moderately & poorly differentiated squamous cell carcinoma.

a) Less cell nest formation. & b) More anaplastic changes
Broder's classification

It is related to the degree of differentiation or anaplasia of squamous cell carcinoma and according to the % of cell nests to the whole tumor

- Gr. I :75-100% cell nests
- Gr. II :50-75% cell nests.
- Gr. III :25-50% cell nests
- Gr. IV : 0-25% cell nests

- Spread: Local, Lymphatic or hematogenous
- Prognosis… Depends upon .Grade and stage

- Adenocarcinoma

It is a malignant tumor of

a) Secretory( glandular) epithelium. "including malignant A.P.U.D omas“
b) Secretory-protective epithelium. And
c) Mucous membrane of ....endometrial, resp.tract, stomach & biliary tract.

Gross:

- On the surface , it may be
  • Fungating     Ulcerating or      Infiltrating

- Inside solid organs it may be
  a. solid hard mass with irregular infiltrating borders
  • b. Cystadenocarcinoma e.g. ovary, pancreas & kidney.
  • c. Papillary cystadenocarcinoma e.g. ovary ,thyroid ,kidney

M/E

• A) Classical Adenocarcinoma:-
  • Formed of glandular acini of variable sizes separated by thin fibrous stroma.
  • The acini are lined by malignant epithelial cells which may show stratification with no basement membrane.
• The acini may be open” having a lumen” or closed formed of groups of malignant epithelial cells without a lumen.
• The tumor may be well, moderately or poorly differentiated

![Image of Well, Moderate, Poorly, Anaplastic differentiation](image)

- **B) Mucoid adenocarcinoma**
  - It is an adenocarcinoma in which mucous secretions usually marked.
  - **NE:** The tumor appears as a jelly-like mass.
  - **MÆ:** -No acini. -tumor cells are dispersed, may be signet ring.
  - - they float in lakes of mucous.
  - **Sites** -Colon "commonest” -stomach -breast
  - **Prognosis**  Bad.

- **C) Cystadenocarcinoma:-**
  - It is a cyst lined by many layers of malignant cubical or columnar epithelium which invades the wall of the cyst.
- **D) Papillary Cystadenocarcinoma:-**
  - Cellular papillary processes project into the cyst. They are covered by several layers of malignant epithelium

**Malignant (Apud Omas) "Neuroendocrine Adenocarcinoma**
- These are endocrine cells which produce regulatory polypeptide hormones. These cells are distributed in different parts of the body and tumors arising from them are called (Apudomas). These cells are found in:
  1. Anterior pituitary - Adenoma & very rarely carcinoma.
  2. C-cells (parafollicular) cells in the thyroid medullary carcinoma of the thyroid gland.
3-Pancreatic islet cells - Islet cell tumors.
4-Adrenal medulla& paraganglia Pheochromocytoma& paraganglioma
5-Argentaffin cells in the G.I.T & bronchus - Carcinoid tumor

**Locally malignant tumors**

**Basal cell carcinoma**
- It infiltrates locally, does not metastasize
  - Origin: from the basal cells of epidermis and skin adnexa.
  - Occurs only in skin.
  - It occurs after the age of 40 years in those with fair skin
  - Predisposing factors: UVR exposure- arsenic and xeroderma pigmentosa.
  - Site: face: above a line drawn from the angle of the mouth to the lobule of the ear. Mainly inner canthus, nasolabial fold.

**N/E:**
- Starts as small papule with dilated blood vessels on it, gradually ulcerate,
- The ulcer (Rodent ulcer) has:
- It infiltrates soft and bony tissues

M/E
- Starts with groups of small, dark . basaloid cells apparently sprouting from the undersurface of intact epidermis
- Later on, the dermis is infiltrated by variable sized groups of spherical or elongated cells with darkly stained nuclei showing variable numbers of mitotic figures.
- The cells at the periphery of the sheets are arranged parallel to each other in a **palisade manner**
- The sheets may contain cystic cavities or melanin pigment.
  - The sheets of epithelial cells are separated by vascular, fibrous stroma.

**Prognosis**
* Locally infiltrates the surrounding soft, bony tissues.
* No distant metastasis.
Other locally malignant tumors

2 - Fibromatosis

* A group of lesions of fibrous tissue that may be neoplastic. Their behavior & histological features are intermediate between fibroma and fibro sarcoma. They include
  a) Keloid
  b) Desmoid tumor (abdominal & extra abdominal)

3 - Giant cell tumor of bone

4 - Adamantinoma (jaw)

5 - Neuro ectodermal tumors (nervous system)

Benign mesenchymal tumors

1 - Benign connective tissue tumors:

General characters:

- They have a capsule formed by compression & atrophy of the surrounding tissue.
- They may be multiple.
- Tumors may reach a large size e.g. lipoma, & they are liable for secondary changes.
- We add the suffix oma to the name of the original tissue
  - Fibrous tissue……  ...Fibroma
  - Fatty tissue.........  ....lipoma
  - Osseous tissue…….Osteoma
  - Cartilage…………....Chondroma
  - Smooth muscle…….Leiomyoma
  - Striated muscles……Rhabdomyoma
Lipoma

- Benign tumor of fatty tissue.
- **Incidence:** Common.
- **Sites:** Subcutaneous tissue of the neck, shoulders, back, & buttocks. Intramuscular septa. Mediastinum & retroperitoneum.
- **N\E:-** Capsulated - soft & lobulated.

- may reach a large size.
- **C\S:-** is bulging, pale yellow, greasy to touch.
- **M\E:-** *The capsule sends fibrous septa lobulation.*
- *Formed of lipocytes + fibrous tissue stroma which contains blood vessels.*

Lipoma Gross M/E

Osteoma

- A benign bone tumor
- It grows slowly till formed then remains static
  - **Types:** 2Types 1- Compact 2- Osteoid osteoma.
  1- **Compact osteoma:** *Occurs in young persons.
- **Sites:** Membranous bones of the skull, inner or outer tables (vault, face, orbit & air sinuses)
- **N\E:-** Hemispherical, broad based, smooth, hard non capsulated mass.
- **M\E:-** Formed of one or mixture of three elements
  - Lamellar bone with few Haversian systems. - Woven bone and osteoblastic connective tissue.
- **Complications:** Pressure symptoms

2- **Osteoid osteoma**

*Affects adolescents and young adults (10-25 Ys) - males > females.
- **Sites:** Near the articular surface of long bones of L.L (femur & tibia)
- **N\E :-** Sharply circumscribed lesion. - Brown or gray.
  - Not more than one cm. in diameter.
- **M/E:** A center of osteoid tissue surrounded by atypical, dense calcified bone.

- **S&S:** Severe pain

![Image of Osteoid Osteoma](image)

**Chondroma**

1- **Enchondroma**
   - A true benign tumor of cartilage. *It affects young adults.*

**-Sites:** The medullary cavity of

   a) Short bones of hands & feet.
   b) Long tubular bones esp. femur & humerus.
   c) Flat bones "pelvis, shoulder girdle, ribs, sternum". These sites are considered to be malignant even when histologically benign.

- They tend to grow faster than chondromas of other sites.

**-N/E:** - A capsulated tumor. It causes expansion thinning of the
cortex. - Hard in consistency. - Rounded.

- **C/S:** lobulated, bluish-gray, semi translucent.

**M/E:** The tumor is formed of:

   a) Islets of cartilage made of hyaline pale blue matrix chondrocytes arranged irregularly and often singly.
   b) A fibrous capsule that sends fibrous septa inside the tumor

![Image of Enchondroma](image)
2-Osteochondroma

* The commonest benign bone lesion. *It is a hamartoma.

*Occurs in children & adolescents

- **NE:** - May be single, more common, they are multiple" familial"

- Uncapsulated.

- Formed of a small projecting bone covered by a cap of proliferating epiphyseal cartilage.

- The outer shell and medulla of the tumor are continuous with that of the mother bone

![Image of Osteochondroma]

**Osteochondroma**

- **ME:** Woven bone covered by a cap of cartilage.

- **Fate:** The tumor stops growing with closure of epiphyses. By that time, the cartilaginous cap of the tumor ossifies

- **Complications:** - Pressure on the surroundings.

- Malignancy "Chondrosarcoma" especially with multiple lesions.

Leiomyoma

- *It is a benign tumor of smooth muscle.

- *It is the commonest B. mesenchymal tumor.

- **Sites:**
  a) Female genital tract "more in the uterus, ovary, fallopian tube, & broad ligament
  b) Alimentary tract.
  c) Urinary bladder. d) Erector pilae muscle of hair follicles.

- **NE:**
  - A pseudocapsulated tumor. - May reach a large size.
- Firm in consistency. - C\S: shows a wholly pattern

Leiomyoma

**M/E:**--Bundles of leimyocytes"smooth muscle cells" running in various
directions with a predominant whorled pattern.
- The bundles have intervening fibrous tissue.

Leiomyosarcoma

1.3 % of malignant tumors of the uterus

**Gross:** intramural in 75 % of cases

**M/E:**--

Three criteria are useful for the diagnosis

- Cellular density
- Pleomorphism
- Mitosis > 5M/10HPF

Vascular tumors

1- **Capillary hemangioma**--

* skin "face, head, trunk, limbs" *M.M."nose, lip, tongue, rectum" *C.N.S."brain"* Single or multiple

*Size: variable*

*Colour: deep red or purple. Well defined*

*Consistency: soft*

**M/E**

*Capillary spaces lined by prominent endothelium and contain blood.*

*Endothelial capillary buds may have no lumen.*

*Clusters of capillaries are separated by fibrous tissue*
2-Cavernous haemangioma
Less common* liver *skin" face" *M.M."lip,tongue" *vertebra,muscle, brain

M/E:-
*Wide, intercommunicating, endothelial lined spaces, containing blood.
*They are separated by fibrous tissue.

Cavernous lymphangioma
*It is a hamartoma composed of lymphatic vascular spaces.

-Sites:- a) Lips" macrochelia" b) Tongue" macroglossia"
   c) Skin & subcutaneous tissue. d)Mesentery , retroperitoneum, spleen , kidney.

Malignant mesenchymal tumors  (SARCOMA)

Origin:  Mesenchymal tissue (Bone, cartilage, muscles)

Incidence:  Less common than carcinoma. Usually affects younger age group.

N/E:  Bulky soft fleshy uncapsulated mass with delineated borders because it grows more by expansion than by infiltration.

M/E  - Individual tumor cells separated by matrix
   -Stroma is scanty with rich blood vessels. It surrounds each individual cell (not groups of cells as in carcinoma)

Histological types ( classification of sarcoma):

Differentiation is estimated by the type of matrix,e.g. :
   Collagen fibers  fibrosarcoma.
   Hyaline matrix  chondrosarcoma.
Osteoid matrix osteosarcoma.

* Undifferentiated (if No matrix):

  It is named according to the shape of the tumor cells e.g: spindle cell sarcoma, round cell, giant cell sarcoma.

**Spread:** Early by blood so it has a worse **prognosis**

**Miscellaneous tumors**

I. Melanocytic tumors

*Melanocytes are* :
- Rounded cells, with abundant, clear cytoplasm, contain variable amount of melanin pigment.
  *In the skin, melanocytes lie among the basal layer of the epidermis in a ratio of 1:10 to 1:5 according to the anatomical site.

They can be divided into:
1) Common acquired naevi. 2) Blue naevus. 3) Dysplastic naevi.

1) Common acquired naevi.

It is focal developmental aberration of melanocytes (hamartomas).

  **Incidence** … Common. A normal person usually has many nevi.

  **Nature** ….

  The lesion is due to proliferation of melanocytes. It starts at birth and passes into various stages till it matures about puberty.

  - Proliferation may stop at any stage.
  - Similar stages of proliferation can occur in adults.
A. Lentigo  
- Melanocytes replace the basal cells of the epidermis in a given area.
- Macrophages in the dermis contain melanin

B. Junctional nevus

- Melanocytes produce a sharply demarcated focal collection deep in the epidermis at the epidermo-dermal junction

C. Compound nevus

- The melanocytes are seen both in the epidermis and dermis.

D. Intradermal nevus

- It occurs in adults.
- It represents the mature, quiescent stage of the lesion. The epidermal proliferation and migration of melanocytes to the dermis stops. The dermis is occupied by groups of melanocytes + some fibrosis.

2) **Blue nevus**
It is a blue spot commonly seen at the buttocks of children.  
- Etiology… it is due to failure of melanoblasts during the embryonic period to reach their final site at the basal layer of the epidermis and remains deep in the dermis.  
- M/E…. groups of immature spindle shaped nevus cells in the deep dermis.

3) **Dysplastic nevus:**
* Etiology: arise de novo or evolve from common acquired nevi.  
* Characters: May be familial (familial dysplastic nevus syndrome).  
Higher incidence of malignant transformation than common nevi.  
* N/E: larger macules more than 6 mms, have irregular border and variegated tan to dark brown color.  
* M/P: groups of dysplastic nevus cells either junctional or compound

**Malignant Melanoma**

**Criteria of malignant transformation (in benign nevus)**

1- Rapid increase in size.  
2- Deepening of pigmentation.  
3- Ulceration and hemorrhage.  
4- Loss of hair &  
5- Enlarged regional lymph nodes

**M&E:**  
* Malignant melanoblasts which have one of two growth patterns

A) **Radial growth (superficial spreading melanoma):**  
Malignant cells are confined to the epidermis and upper dermis.

B) **Vertical growth (nodular growth):**  
- Malignant cells infiltrate deep in the dermis and ulcerate on the surface.  
- Depth of infiltration is an important prognostic criterion.
* Malignant cells may be arranged in groups of rounded cells separated by fibrous stroma (*melanocarcinoma*), or in a sarcomatous pattern formed of spindle-shaped cells.

**Spread:**
- *Local* limited
- Lymphatic to the regional lymph nodes.
- Blood spread to the lung and every other organ in the body.

Melanin pigment may reach the blood (*Melanaemia*) and excreted in urine (*Melanuria*).

**Staging:** Clark's staging according to the depth of infiltration

**Prognosis:** Depends upon the depth of infiltration.

**Composite tumors**

**These include:**
- b. Embryonal tumors.
- c. Teratoma.

**a. Mixed tumors**

These tumors are formed of more than one neoplastic cell types.

**Examples:**

1- True mixed tumors  
**Fibro adenoma** of the breast.

In this tumor, both the ducts and fibrous stroma are neoplastic.

![Fibroadenoma of the breast](image)

2- Metaplasia
   a) Of tumor cells e.g. adenoacanthoma formed of adenocarcinoma + benign squamous metaplastic areas.

   adenosquamous carcinoma.---- formed of adenocarcinoma + malignant squamous element

   b) Of stroma---- **pleomorphic adenoma** of salivary gland.

3) Tumors of multipotent cells as nephroplastoma.
b. Embryonal tumors
They are derived from persisting immature multipotent cells (usually derived from single germ layer).

Characters of embryonal tumors:
- Highly malignant
- Radiosensitive
- Occur mostly before age of 4 years.

*They include:-

a) Medulloblastoma group - medulloblastoma (cerebellum)
   - Retinoblastoma (retina)
   - Neuroblastoma (supra renal)

b) Nephroblastoma (kidney)
c) Hepatoblastoma (liver) &

d) Embryonal rhabdomyosarcoma (nose, vagina)
c. Teratoma
- A composite tumor that originate from totipotent germ cell

**Teratoma**
Tumor composed of tissues derived from all 3 embryonic germ cell layer

**Pathogenesis:**
*Arises from totipotent cells.*
Parthenogenesis (auto fertilization) or segregation of totipotent cell

Sites:

* Gonads.
* Extra-gonadal (base of skull, lower end of vertebral column and mediastinum).

Types:

1) Mature teratoma: solid and cystic
2) Immature teratoma (malignant)
3) Monodermal and highly specialized teratoma i.e. teratoma is formed of only one tissue for example; stroma ovarii formed only of thyroid tissue.

1) Mature teratoma

Gross :-

1- Cystic teratoma: More common in the ovary ….mostly benign (dermoid cyst).
2- Solid teratoma: the commonest site is the testis

Mature cystic teratoma (dermoid cyst)

M/E

(1) Cystic teratoma:

■ Cyst lined by stratified squamous epithelium.
■ Contains different tissues derived from:

* Ectoderm   * Endoderm   * Mesoderm.

(2) Solid mass    Contain different tissues
Mature cystic teratoma

2) Immature teratoma (Malignant)
- Commonest site is the testis.
- N/E: Solid mass with areas of hemorrhage and necrosis.
- M/E:
  - *Immature embryonic tissue* or tissues which show malignant criteria.
- Prognosis: Malignant tumor especially if it contains syncytiotrophoblast and yolk sac tumor.

Precancerous lesions

Non malignant lesions that may turn malignant. They are related to the epithelium (pre-carcinomatous).

They include
1. Chronic irritation.
2. Hyperplasia
3. Metaplasia especially atypical metaplasia
4. Some benign tumors or hamartomas
5. Undescended testis.
6. Dysplasia
7. Carcinoma in situ

Prognosis
- Precancerous lesions show extremely variable malignant potential. Therefore, they are classified as
- **1- High risk lesions:** In which the development of cancer is invariable (100%) e.g.
  * Multiple familial polyposis & * Xeroderma pigmentosa.
- **2- Low risk lesions:** In which the incidence of malignancy is so low (3-5%) e.g.
  * Leukoplakia, ulcerative colitis, endometrial hyperplasia, Dysplasia.
**Molecular basis of cancer**

**Carcinogenesis** = The process of transformation of normal cell to malignant cell.
**Carcinogenic agents** = Substances which induce carcinogenesis

**Carcinogenic agents**

These are agents which can produce cancer.

They can be classified into three main groups

1- **Internal**
2- **External**

a) Chemical  b) Radiant  c) Viral ,  d) Parasites. and  e) Bacterial

3- **Unknown factors:**-

1- **Internal Carcinogens**

These include

i) **Smegma**: in uncircumcised persons  Cancer penis

ii) **Bile acids & cholesterol**  Carcinogenic to the colon.

iii) **Hormones**:-

   A hormone dependent tumor is a tumor whose growth is affected (increased or decreased) by certain hormones e.g.

   a) **Breast carcinoma**

   b) **Carcinoma of the body of the uterus**:-

   c) **Clear cell carcinoma of the vagina**

   d) **Cancer prostate**: - They are related to androgens.

   e) **Well differentiated carcinoma of the thyroid**: - It is T.S.H. dependent tumor.

   *In all cases, hormones act as **promoters**.*

2- **External Carcinogens**

1- Physical carcinogens  2- Chemical carcinogens.

3- Viral carcinogens &

4- Parasitic carcinogens  e.g **Bilharziasis**  carcinoma of the U.B.

5- Bacteria…**Helicobacter pylori**….. Gastric carcinoma and B- cell lymphoma of the stomach
Ionizing radiation
- Leukemias – survivors of atomic blast
- Secondary tumors from therapeutic irradiation
- X-ray treatment for benign head and neck conditions (enlarged thymus, tinea capitis)
- Fluoroscopic X-rays – TB patients

*Ultraviolet rays:* These are related to skin cancer e.g. squamous cell carcinoma, basal cell carcinoma, & malignant melanoma

Chemical carcinogens

These are either

a. Direct acting agents e.g. alkalating agents
b. Indirect acting agents that need metabolic convergence e.g. polycyclic hydrocarbons

They include

☉ Polycyclic hydrocarbons(mainly, benzepyrene)
☉ Aromatic amines (aniline & azo dye)
☉ Dietary factors
☉ Alkalating agents
☉ Others …chromium, cobalt, cadmium, uraniumAsbestos.

Aflatoxin B1 A common contaminant of grains and peanuts Africa and Asia

- A probable factor in the high incidence of hepatocellular carcinoma in Africa and Asia (along with Hepatitis B infection)
Viral carcinogens

<table>
<thead>
<tr>
<th>Virus</th>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein–Barr virus</td>
<td>Burkitt's lymphoma</td>
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<tr>
<td></td>
<td>Nasopharyngeal carcinoma</td>
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<tr>
<td></td>
<td>Other B-cell lymphomas and some cases of Hodgkin's disease</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Cervical carcinoma</td>
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<tr>
<td></td>
<td>Some forms of carcinoma of the skin</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>T-cell leukaemia/lymphoma</td>
</tr>
</tbody>
</table>

*Fig. 4.14 Viruses implicated in human neoplasia.*

**Human papilloma virus**

* high risk HPVs (subtypes 16 and 18) are currently considered to be the single most important factor in cervical oncogenesis

*skin wart & juvenile papilloma of the larynx (Types 1, 2, 4, and 7)

- **HTLV-1 can produce T-cell leukemia/lymphoma**
Carcinogenesis
Neoplastic changes occur as a result of non-lethal genetic changes which are then transmitted to each new generation of cells within the neoplasm.

Carcinogenesis is a multistep process, it passes through 3 steps

A-Initiation:
The first step that will induce the irreversible but not lethal change in the genetic material of the affected cell.

B-Promotion:
The second step in tumor formation.
- It promotes the proliferation of the initiated cells.
- Promoters can not induce cancer by their own ,they must act on initiated cells.

C-Progression:
The third phase of tumor formation.
- At his stage the growth of the tumor becomes autonomous.
**Genes controlling cancer**

1- Growth promoting genes (proto-oncogene) which when transformed are called oncogenes.
2- Growth inhibiting genes (tumor suppressor gene).
3- Genes regulating apoptosis.
4- Genes controlling repair of DNA damage.

**1 - Oncogenes**

- Proto-oncogenes are genes found in normal cells and are responsible for controlling normal growth and proliferation. When they are transformed, they are called oncogenes.
- Proto-oncogenes are dominant genes and changes that affect them are usually acquired.
- Commonly, more than one oncogene abnormalities are seen in a single tumor.

**Proto-oncogenes** are genes that control normal cell growth and proliferation. When transformed, they change to oncogenes.

**Growth promoting genes (proto-oncogene)**

Proto oncogenes control normal cell growth via :-

1- Production of growth factor (GF).
2- Growth factors bind to cell surface receptors.
3- Binding results in the formation of transduction signals which reach the nucleus that produces….
4- Transcription factors that initiate DNA synthesis
5- Regulation of cyclin-cyclin dependant kinases that push the cell into the cell cycle.

2- Tumor suppressor genes
- These genes code the production of proteins that inhibit cell proliferation.
- Absence of tumor suppressor genes promotes neoplasia.
- Tumor suppressor genes act as recessive genes and absence of both copies is required for transformation.
- Mutations of tumor suppressor genes may be inherited or acquired

Tumor suppressor genes include
a- Retinoblastoma (Rb gene)
* The first tumor suppressor gene discovered was retinoblastoma gene (Rb), homozygous loss of this gene leads the development of retinoblastoma which may be familial in 40% of cases.

b. P53 Gardian of the genome
- This tumor suppressor gene is mutated in more than 50% of malignant tumors.
  - When there’s damage of the DNA, P53 causes cell cycle arrest at G1 providing time for DNA repair then the cell re-enter the cell cycle again.
  - If DNA repair is not successful, P53 activates BAX the proapoptotic gene and the cell dies by apoptosis.
  c. NF-1..... Neurofibroma       d. BRCA-1, BRCA-2...... Breast cancer
  e. APC, DCC...... Colonic cancer   f. WT-1..... Wilm’s tumor
3- Genes controlling apoptosis

- BCL2 family controlling apoptosis
- Mitochondrial genes
- 2 types
  - Proapoptotic bax
  - Antiapoptotic bc12
  - Activation of antiapoptotic genes leads to prolongation of life span of genetically mutated cells and development of malignant tumors

4- DNA mismatch repair genes

- Normal human DNA is subjected to daily minor damage by body heat & ultraviolet rays, however, repair of this damage takes place by a group of DNA repairing enzymes called DNA ligases.
- Mutation in genes that control the expression of DNA ligases lead to the development of tumors

Example: 1- Xeroderma Pigmentosa:
A skin disease "inherited" characterized by multiple & early development of skin cancers "squamous cell carcinoma, basal cell carcinoma & malignant melanoma

2- Hereditary Non-Polyposis Colon Cancer. (HNPCC)
- Leading to familial right sided colo-rectal carcinoma and increased incidence of other carcinoma.
- HNPCC Predisposes to mutations in other genes more directly related to transformation

Carcinogenesis is a multistep process
**Karyotypic changes in tumor:**

i) Not detected by karyotype: as point mutation  
ii) detected by karyotype:  
a) Balanced translocation.  
b) Deletions.  
c) gene amplification.  
d) Whole chromosome may be gained or lost.

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**Biology of tumor growth**

After neoplastic transformation of a certain cell, clonal expansion occurs with local invasion & ultimately metastasis.

• Clonal expansion & formation of tumor mass from the transformed cell is controlled by many factors.

The most important of which are:

1. **Kinetics of tumor growth**.
2. **Tumor angiogenesis**.
3. **Tumor progression & heterogeneity**.

1. **Kinetics of tumor growth**:

   The time taken by a single transformed cell to appear clinically as a mass depends upon:

   a- **Doubling time of tumor cells**: It was found that the total cell cycle time of many tumor cells is equal to or even longer than that of normal cells.
   
   b- **Growth fraction**: Is the proportion of tumor cells that are capable of proliferation. In most tumors, it does not exceed → 20%.
   
   c- **Cell production & cell loss**: ↑↑ cell production & ↓↓ cell loss → tumor growth.
In transformed cells, cell loss is very few because of 2 factors:

I- ↓ cell loss by apoptosis (Bcl-2).
   II- ↑ed activity of telomerase: Telomerase is an enzyme responsible for synthesis & maintenance of telomeres which are structures present at the end of each chromosome that shorten with each mitotic cell cycle till they are lost & at this point, the cell stops dividing.

- In tumor cells, telomerase protects telomeres from shortening & so, tumor cells continue to live & divided i.e.: they become Immortal.

d- Cancer chemotherapy: It affects tumor with high growth fraction.

2. **Tumor angiogenesis:**
   - A tumor can not grow more than 2 mms without blood supply.
   Angiogenesis factors can be produced:
   × By tumor cells e.g.: fibroblastic growth factor FGF and VEGF.
   × By macrophage TGF, EGF & TNF.

3. **Tumor progression & heterogeneity:**
   tumor progression means that aggressiveness of tumors increase with time & acquire more malignant characters.
   Although the tumor is monoclonal, by time it is clinically evident, its constituent cells are very heterogeneous due to multiple mutation of different tumor cells.

**Tumor - Host Interactions**

1- Effect of the host on the tumor…. tumor immunity
2- Effect of tumor on the host
   a. Neoplastic syndrome.
   b. Para-neoplastic syndrome

**What is the evidence for tumor antigenecity?**
- Regression - Lymphocytic infiltration
What are tumor antigens?
1 -Tumor specific antigens (TSA)
2 -Tumor associated Antigen (TAA)
   a. Differentiation specific Ag
      Peculiar to the differentiation state of cancer cells
      * e.g. CD 10 is expressed in early B lymphocytes
      * Prostate specific antigen (PSA)
      * S-100 in neural crest tumors and melanoma

   b. Oncofetal Ag:
      * alpha-Foeto proteins in cancer liver and teratocarcinoma.
      * Carcino-embryonic antigen (CEA): in cancer colon

What are anti-tumor mechanisms?
 a- Cytotoxic lymphocytes,  b-Natural killer
  c-Macrophages    d-Humoral mechanisms.

Escape mechanisms:
 a-Antigen negative cells      b-Loss of MHC.
 c-Modulation of antigen      d-Immune suppression.

Effectors of tumor immunity
Systemic Effects of Cancer in the Host

- Most symptoms of cancer are due to local effects of primary tumor or its metastases. 
  - **Neoplastic syndrome.**

- In some patients, cancer produces remote effects not attributable to invasion or metastases
  Collectively called **Paraneoplastic syndromes.**

  ➢ **Neoplastic Syndromes include:**
    i- Local effects
    ii- Hormonal effects
    iii- Cachexia

  **Local effects**

Complicate both benign and malignant tumors:

1) Compression and obstruction: 2) Ulceration and hemorrhage.
3) Rupture and perforation. 4) Hormone production

Cachexia - characteristic wasting syndrome seen in cancer patients. It manifests as anorexia, weight loss, lethargy

- **Causes…**
  a. Inadequate food intake
  b. Impaired digestion, absorption
  c. Altered taste in cancer patient
  d. Increased energy requirement of cancer patient - elevated metabolic rate
  e. TNF, other cytokines

B. Paraneoplastic syndromes

  ➢ Appears in (20%) of patients with cancer
  ➢ Can not be explained by tumor spread or by elaboration of hormones
  ➢ Importance:

May be the earliest manifestation of cancer, may cause major clinical problems.

**Manifestations of Paraneoplastic syndromes**

1. Cushing's syndrome with oat cell carcinoma
2. Hypercalcemia with sq. c. carcinoma of esophagus
3. Hypercoagulability (migrating thrombophlebitis) with cancer pancreas
4. Non bacterial thrombotic endocarditis with advanced malignancy
5. Clubbing of fingers and osteoarthropathy
6. Amyloidosis
7. Cutaneous Syndromes:
8. Neurologic syndromes:
9. Hematological disorders:
   10. Autoimmune reaction

4) Laboratory diagnosis of cancer
a) Histologic and cytologic methods

Specimen
* Adequate, representative and properly preserved.

Approach: * Excision, needle aspiration, and cytologic smear.

* Fine needle aspiration is used with palpable lesions, modern imaging technique enabling
  reaching deeper organs

Methods of examination:
- Paraffin section, stained with ordinary or special stains.
- Frozen section …at the time of operation for rapid diagnosis
- Electron microscopy

   b) RECENT TECHNIQUE:
   ➢ Immunohistochemistry

- To detect the tumor using specific mono-clonal Ab
- Can be done on both histologic and cytologic slides
- Important to define origin of tumor eg.
  - Desmin in muscle tumor
  - CytoKeratin and EMA in epithelial tumors
   ➢ Flow cytometry,
   ➢ DNA probe, analysis
C) TUMOR MARKERS
Substances produced by the neoplastic cells and can be demonstrated in tissues, serum, or bodyfluids

Importance:
Support diagnosis, assessment of therapy and follow up (to detect tumor recurrence)

Examples:
- Enzymes: Acid phosphatase in cancer prostate
- Hormones: PTH in parathyroid tumors
  - HcG in choriocarcinoma
- Immunoglobulin: M protein in multiple myeloma
- Onco-fetal antigens:
  - α-feto proteins in liver tumor, germ cell
  - CEA in cancer colon
- Specific Antigens:
  - Prostatic Specific Antigen (PSA) cancer prostate
- Mucins and Glycoproteins:
  - CA/125 in ovarian cancer
  - CA/19-9 in colon cancer
  - CA/15-3 in breast cancer
- Chromosomes: Philadelphia chromosom in CML
- Molecular Markers: P53 in cancer colon, P53+ras in lung cancer

EPIDEMIOLOGY OF CANCER

CANCER INCIDENCE
- The incidence rate differs among developed and developing countries depending on many factors as geographical and environmental factors

GEOGRAPHIC FACTORS
- Individual cancers show differences among different nations of the world.
- Cancer breast has high incidence in western countries while it is low in Japan.
- Cancer stomach incidence is higher in Japan than in western countries.
- Liver carcinoma is infrequent in USA but it is number one lethal cancer in Africa.
Cancer urinary bladder is common in Egypt.

ENVIRONMENTAL INFLUENCES

- **Age:** cancer increases with age due to accumulated mutations and decreased immunity.
- **Sex:** cancer breast is more common in females and cancer lung in males.
- **Heredity:** some cancers are inherited such as retinoblastoma and some inherited lesions are premalignant as xeroderma pigmentosa and familial polyposis coli.
- **Diet:** may contain carcinogenic agents as aflatoxin and food additives.
- **Trauma:** may predispose to osteosarcoma.
- **Personal habits:** cigarret smoking increase lung cancer and alcoholism may increase cancer oesphagus.
- **Marital status:** early age of marriage may predispose to cancer cervix.