NEOPLASIA

Definition: is formation of mass due to multiplication of cells. This multiplication is without cause ,without limit, without function and without control.

Neoplasms may be 'benign' when they are slow-growing and localised without causing much difficulty to the host, or 'malignant' when they proliferate rapidly, spread throughout the body and may eventually cause death of the host.

All tumours have 2 basic components:

1. Parenchyma comprised by proliferating tumour cells and it determines the nature and of the tumour.
2. Supportive stroma composed of fibrous connective tissue and blood vessels. It provides the framework on which the parenchymal tumour cells grow..

The tumours are named with suffix '-oma' to denote benign tumours. Malignant tumours of epithelial origin are called carcinomas, while malignant mesenchymal tumours are named sarcomas.

Normally growing cells in an organ are related to the neighbouring cells—they grow under normal growth controls, perform their assigned function and there is a balance between the rate of cell proliferation and the rate of cell death including cell suicide (i.e. apoptosis). Thus, normal cells are socially desirable. However, cancer cells exhibit anti-social behaviour as under:

i) Cancer cells disobey the growth controlling signals in the body and thus proliferate rapidly.

ii) Cancer cells escape death signals and achieve immortality.

iii) Imbalance between cell proliferation and cell death in cancer causes excessive growth.

iv) Cancer cells lose properties of differentiation and thus perform little or no function.

v) Due to loss of growth controls, cancer cells are genetically unstable and develop newer mutations.

vi) Cancer cells overrun their neighbouring tissue and invade locally.

vii) Cancer cells have the ability to travel from the site of origin to other sites in the body where they colonise and establish distant metastasis.

Cancer cells originate by clonal proliferation of a single progeny of a cell (monoclonality). There is evidence to suggest that cancer cells arise from stem cells normally present in the tissues in small number and are not readily identifiable.

These stem cells have the properties of prolonged self-renewal, asymmetric replication and transdifferentiation (i.e. plasticity). These cancer stem cells are called tumour-initiating cells.

***Differences between pathologic hyperplasia and neoplasia:**

-Induced by stimulus and corrected by its removal.	-Induced by stimulus but usually unknown
-It is self limited	-Uncontrolled
-The degree of hyperplasia is related to the degree of stimulation.	-After initiation, it becomes independent
-It usually produces function.	-It is usually functionless purposeless
-Hyperplastic cells resemble tissue of origin (normal in shape and pattern) Normal mitosis	-Malignant lesion differ from the original tissue and abnormal in shape and pattern. Abnormal mitosis if malignant

CHARACTERISTICS OF TUMOURS

Majority of neoplasms can be categorised into benign and malignant on the basis of certain clinical features, biologic behaviour and morphological characteristics.

However, there are exceptions—a small proportion of tumours have some features suggesting innocent growth while other features point towards a more ominous behaviour. Therefore, it must be borne in mind that based characteristics of neoplasms, there is a wide variation in the degree of deviation from the normal in all the tumours.

The characteristics of tumours are described under the following headings:

I. Rate of growth
II. Cancer phenotype and stem cells
III. Clinical and gross features
IV. Microscopic features
V. Spread of tumours
   a. Local invasion or direct spread
   b. Metastasis or distant spread

Based on these characteristics, contrasting features of benign and malignant tumours are summarised in the coming Table

Classifications of neoplasms :

1- According to tissue of origin: epithelial, mesenchymal,.....
2- According to behavior: benign, locally malignant, and malignant.
3- According to cytology (degree of differentiation)

Classification and nomenclature of common neoplasms

Tissue of origin	Benign tumours	Locally malignant tumours	Malignant tumours
Epithelium: 1- Covering epithelium: -Squamous -Transitional -Columnar 2- Glandular epithelium:	-Squamous cell papilloma -Transitional cell papilloma -Columnar cell papilloma Adenoma Cystadenoma	-Basal cell carcinoma -Carcinoid	-Squamous cell carcinoma -Transitional cell carcinoma -Adenocarcinoma -Cystadenocarcinoma
Mesenchymal tissue: -Fibrous tissue -Fat -Smooth muscle -Striated muscle -Cartilage -Bone -Blood cells -Lymphoid tissue. -Mesothelium -Meninges -Peripheral nerves -**Neuroglia**	-Fibroma -Lipoma -Leiomyoma -Rhabdomyoma -Chondroma -Osteoma -Mesothelioma -Meningioma -Neurofibroma	-Giant cell tumour -Low Grade astrocytoma	-Fibrosarcoma -Liposarcoma -Leiomyosarcoma -Rhabdomyosarcoma -Chondrosarcoma -Osteosarcoma -Leukaemias -Lymphomas -Malignant mesothelioma -Malignant meningioma -Neurofibrosarcoma -Astrocytoma grade III& Glioblastoma multiforme.
Foetal trophoblast	-Hydatidiform mole	-Invasive mole	-Choriocarcinoma
Germ cell (*totipotent*)	-Mature teratoma (Dermoid cyst)		-Malignant teratoma
Embryonic tissue *Pluripotential cell* -Kidney -Liver *Unipotintial cell* -Retina -Sympathetic ganglia and adrenal medulla			-Nephroblastoma -Hapatoblastoma -Retinoblastoma -Neuroblastoma -Medulloblastoma
Hamartomas -Blood &lymph vessels -Lung -Cartilage -Peripheral nerves -Melanocytic	-Angiomas. -Lung hamartoma -Enchondromatosis -Neurofibroma -Melanocytic nevus		-Angiosarcoma & Kaposi sarcoma. -Chondrosarcoma -Neurofibrosarcoma -Melanoma

CHARACTERISTICS OF BENIGN TUMOURS

- **Origin:** From the normal cells of the tissue **(de novo).**
- **Size:** Usually smaller than malignant, but some are huge as uterine tumours.
- **Rate of growth:** Less rapid than malignant ones.
- **Mode of growth:** By expansion. They grow as cohesive expansile masses that compress the surroundings.
- **Gross appearance:**
    1. Usually solitary
    2. Well circumscribed
    3. The margins are usually well defined
    4. The cut surface is smooth
    5. Usually no hemorrhage or necrosis.
    6. It is usually firm or soft in consistency and not hard.
    7. **Capsule:** usually encapsulated except for those of surface epithelium.
- **Microscopic picture:**
    1. Usually resemble the tissue origin.
    2. Mitotic figures are absent or few (if present they are normal).
    3. The stroma is well formed.
    4. No hemorrhage or necrosis.
- **Distant spread (metastasis):** Benign tumours do not metastasize.
- **Recurrence after removal:** do not recur if completely removed.
- **Effects and complications of benign tumours:**

    1- Usually do not endanger life except those arising in vital organs as brain or heart.

    2- Those of intestine may cause intestinal obstruction.

    3- Large tumours may cause pressure symptoms on surroundings.

    4- Twisting of pedunculated tumours may produce infarction and necrosis.

    5- Tumours of endocrine glands are usually functioning as gigantism occurs in acidophil adenoma of pituitary gland.

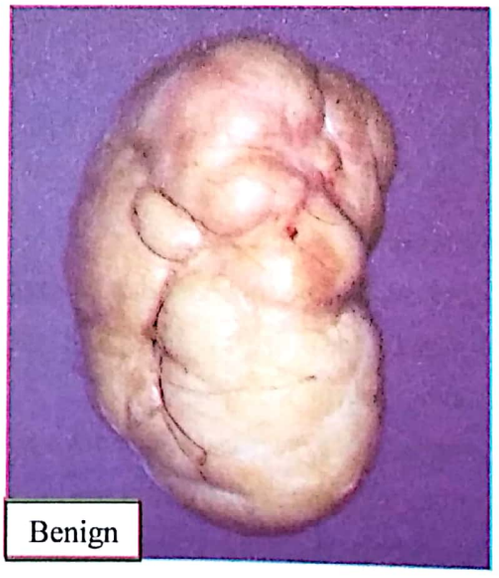
    6- May change malignant as evidenced by rapid rate of growth, capsular invasion, necrosis, hemorrhage and microscopic features of malignancy.

CHARACTERS OF MALIGNANT TUMOURS

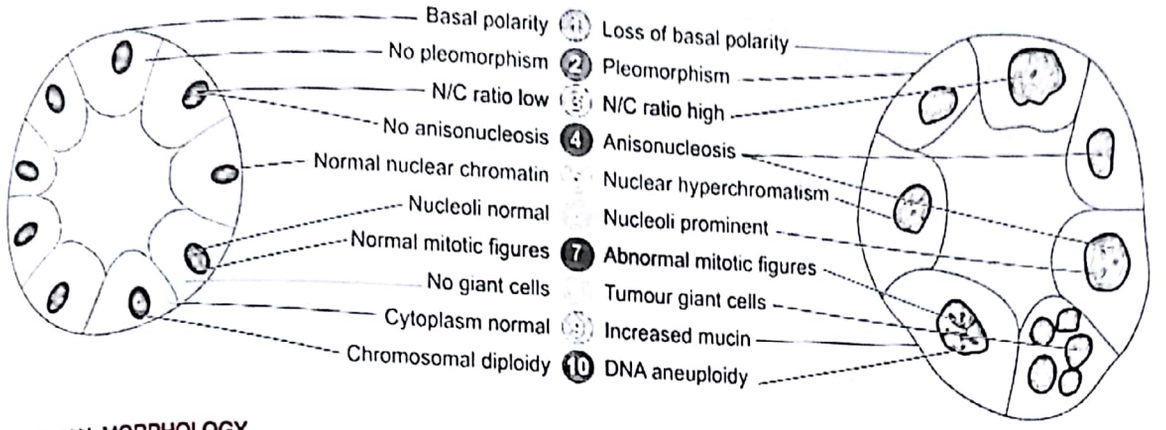
- **Origin:** Either de novo or from premalignant lesion as chronic ulcers or as a malignant transformation of benign tumour.
- **Size:** ***Variable but may reach large size in short time.***
- **Rate of growth:** Growth rate correlates with degree of differentiation and thus most malignant tumours grow more rapidly than benign ones.
- **Mode of growth:** Grow by progressive infiltration, invasion, and destruction of the surrounding tissues.
- **Gross appearance:**
  1. Usually ill-defined mass
  2. Mostly vague margin.
  3. Usually hemorrhage and necrosis are present because of rapid cell proliferation which exceeds the blood supply of the tumour.
  4. **Capsule:** usually unencapsulated.
- **Microscopic picture:**
  1. Cellular anaplasia in the form of pleomorphism, nuclear enlargement, hyperchromasia, increased N/C ratio, prominent nucleoli, abundant and irregular atypical mitoses, abnormal differentiation, and loss of polarity with haphazard arrangement of the cells.
  2. Blood vessels are numerous and poorly formed.
- **Distant spread (metastasis):** With few exceptions all malignant tumours metastasize.
- **Behavior and prognosis:** Recurrence is very common. 5- Years survival rate after treatment without recurrences is curative standard.
- **Causes of death and effects of malignant tumours:**
  1. Malignant tumours may produce the same effects as benign tumours but they are more serious owing to their rapid rate of growth and their highly invasive and destructive nature.
  2. **Anemia**: diet deficiency, hemorrhage and bone marrow invasion.
  3. **Malnutrition** due to obstruction of the alimentary tract.
  4. **Cachexia** accompanied by weakness and wasting.
  5. **Organ failure as** C.N.S. failure due to increased intracranial tension and pressure. Renal, cardiac, liver, or respiratory failure results from compression, invasion, obstruction or infection.
  6. **Infections and toxemia,** pneumonia, septicemia, and peritonitis
  7. **Immunologic effects:** lymphomas can depress the immune system.
  8. **Pain** in advanced malignancy secondary to invasion of perineural lymphatics.

Differences between benign and malignant tumours

Feature	Benign	Malignant
-Origin	-De novo	-De novo , on top of premalignant or benign lesion
-Size	-Usually small in size	-Usually reach large size in short time
-Rate of growth	-Usually slow	-Usually rapid
-Mode of growth	-Expansion	-Infiltration and invasion
-Gross picture	-Well defined margin, uniform cut surface, no hemorrhage or necrosis	-Ill defined or irregular margin, cut surface show areas of hemorrhage and necrosis
-Capsule	-Usually present	-Absent
-Consistency	-Soft to firm	-Usually hard
-Microscopic picture	- Monomorphic cells - monmorphic nucleus - Mitosis very few - Normal N/C ration - B.VS well formed	- Pleomorphic cells - Pleomorphic nucleus - Many mitosis (abnormal) - increased N/C ratio - B.VS badly formed
-Metastasis	-Absent	-Present
-Recurrence	-No	-Very common


Benign


Malignant



A. NORMAL MORPHOLOGY

B. CYTOMORPHOLOGY IN CANCER

METHODS OF SPREAD OF MALIGNANT TUMOURS

The mechanisms of spread include the following:

(I) Invasion of extracellular matrix (ECM): *4 steps are included:*

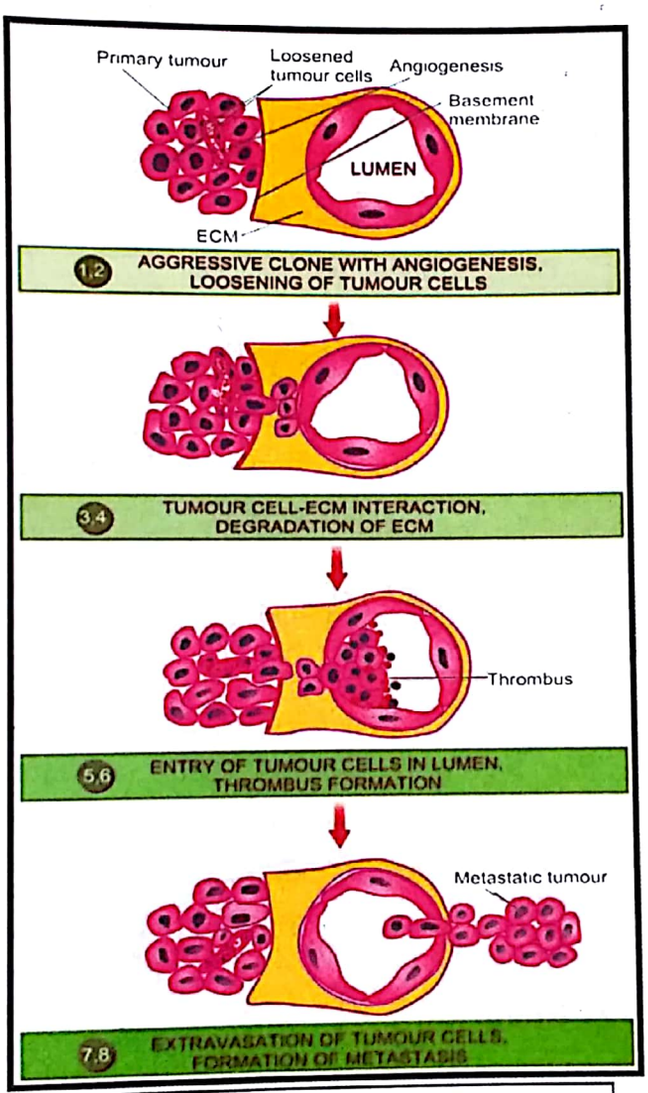
1. *Detachment* or loosing of tumour cells from each other due to down- regulation or diminution of *E-cadherins* leading to decreased cell cohesiveness.
2. *Attachment* of the tumour cells to matrix components of basement membrane; mainly to *laminin* receptors and to *fibronectin* and *collagen*.
3. *Degradation* of the basement membrane by *proteolytic enzymes* secreted by tumour cells.
4. *Migration or locomotion* of tumour cells through the degraded ECM.

(II) Vascular dissemination and homing of tumour cells:

1-By similar mechanisms, tumour cells cross the vascular basement membrane.

2-In the blood stream, some tumour cells form emboli by adhering to lymphocytes and platelets.

3- They adhere to the endothelium, cross the basement membrane (settle in the new site and proliferate forming a metastatic deposit).



Mechanism of spread of malignant tumour

ROUTES OF SPREAD

A) Local or direct spread:

1- Direct infiltration of the surrounding tissues is common in malignant tumours.

2- The microscopic extent of tumour exceeds its macroscopic boundaries [safety margin].

B) Distant spread (metastasis): metastasis means the development of secondary malignant implants away from the primary tumour.

ROUTS OF METASTASIS ARE:

1) Lymphatic spread: carcinoma shows a great tendency for lymphatic invasion early than sarcoma.

Two methods are included:

A) Lymphatic embolism:

- Malignant cells invade the walls of lymphatics.
- Detached tumour cells are carried as tumour emboli and arrested in the subcapsular sinus of the lymph node.
- The malignant cells proliferate and gradually destroy and replace the nodal tissue.
- Capsular invasion occur and the node become fixed.
- Spread of malignancy occurs from node to another through the efferent lymphatics.
- Tumor emboli reach the main *thoracic duct* or cisterna chyli from which tumour emboli reach the venous circulation causing haematogenous spread.

B) Lymphatic permeation:

- The malignant tumour cells may grow inside the lumen of the lymphatics as solid column.
- There is marked lymphatic obstruction and tissue edema as in case of breast cancer (peau d'orange appearance).
- Retrograde tumour embolism in the reverse direction.
- The best example is involvement of the **left** supraclavicular lymph node ***(Virchow's node)*** in carcinoma of the stomach.

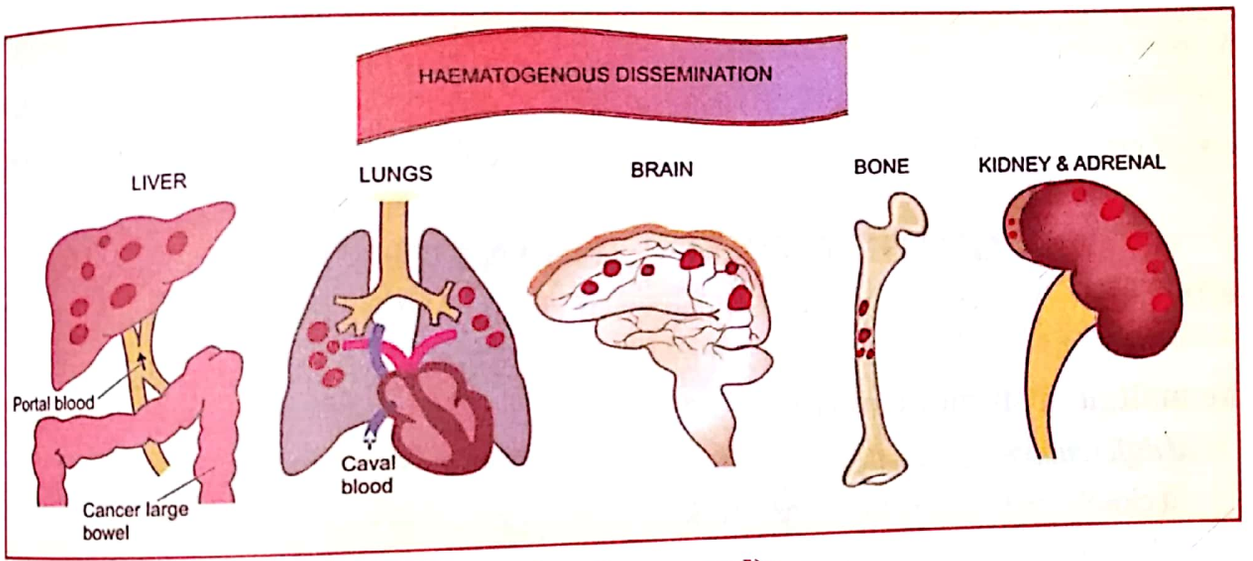
2) Blood spread:

- Common in all sarcomas.
- Some carcinomas may spread early by blood and lymphatics as those of placenta (Choriocarcinoma), lung, breast, thyroid and liver.
- Because of their thinner wall, veins are frequently invaded than arteries.

- Lymphatic spread leads to blood spread.
- There is formation of thrombus containing malignant cells. The thrombus break into particles which circulate in the blood as emboli containing malignant cells.
- The most common sites of metastasis : liver, lung, bone and brain.
- Metastases are rare in muscle, spleen, pancreas and intestine.

Organs affected by metastasis:

- Tumour emboli derived from tumours originating in organs drained by **systemic circulation** are carried to the **lung**.
- Tumour emboli derived from tumours originating in organs drained by **portal circulation** are carried to the **liver**
- Metastasis reach the **brain, spinal cord and vertebra** without lung affection via the **vertebral system of veins** from tumours of the pelvic, abdominal or thoracic organs (prostate, stomach, lung, breast and thyroid cancers) by retrograde venous spread, where there are direct venous communications, helped by increased intra-abdominal and intrathoracic pressures.
- Bone secondaries are *osteolytic* , while secondaries from ***prostatic*** carcinoma usually cause bone thickening due to new bone formation or ***osteoblastic*** **reaction**.
- Bone metastases may cause pathologic fracture or bone marrow destruction causing anemia, leucopoenia and thrombocytopenia.



3) Spread by serous sacs (transcoelomic spread):

- This occurs in tumours that reach the serous sac surface, like that of the peritoneum, pleura and pericardium from near-by organs.
- *Transperitoneal spread* occurs in carcinomas of the stomach, colon & pancreas. Carcinoma of the stomach in the **females** is usually associated with **bilateral ovarian** metastasis termed ***Krukenberg tumour*** which is mainly due to transcoelomic spread.

4) Spread by implantation:

- ***Transluminal spread and implantation:***
  1- Malignant cells may spread along ***natural passages*** from the renal pelvis to be implanted in the mucosa of the urinary bladder or from the bronchi, to be implanted in the terminal alveoli.
  2- Carcinoma of the lower lip may be implanted over the opposite upper lip.
- ***Surgical implantation:*** Cancer cells may be implanted in the needle track following the aspiration of malignant ascites or implanted into the surgical wound through instruments contaminated with malignant cells causing secondary tumour deposits.

CANCER INCIDENCE:

Table 7.3 Five most common primary cancers in the world.

	MEN	WOMEN	CHILDREN (UNDER 20)
1.	Prostate (oral cavity in India)	Breast (cervix in India)	Acute leukaemia
2.	Lung	Lung	Gliomas
3.	Colorectal	Colorectal	Bone sarcoma
4.	Urinary bladder	Endometrial	Endocrine
5.	Lymphoma	Lymphoma	Soft tissue sarcoma

The most commonly cancer KILLERS:

- Males (in descending order): lung, prostate , colon
- Females (in descending order): lung , breast , colon

GRADING OF MALIGNANT TUMOURS

Definition: it is the evaluation of the degree of cytological similarity (resemblance) of the malignant tissue to the tissue origin (degree of differentiation).

The malignant tumour may be:

1- ***Well differentiated (grade I):***

It closely resembles to the tissue of origin. In this grade more than three forths of the cells *(75%-100%)* are differentiated.

2- ***Moderately differentiated (grade II):***

(50%-75%) are differentiated and resemble tissue of origin.

3- ***Poorly differentiated (grade III):***

(25%-50%) are differentiated.

4- ***Undifferentiated (Grade IV):***

(0%-25%) are differentiated and the tumour hardly resembles the tissue of origin.

N.B:

- ***A total loss of resemblance to the original tissue is termed anaplasia (anaplastic tumour).***
- ***The criteria for grades vary with each tumour. In glandular tumors, the grading depends on tubular differentiation, nuclear size and shape and number of mitosis.***

STAGING OF MALIGNANT TUMOURS

Definition: is the evaluation of anatomical extension of the malignant tissue.

e.g.: insitu ⟶ ***invasion*** ⟶ ***local infiltration*** ⟶ ***regional metastasis*** ⟶ ***distant metastasis)***

The stage of a malignant tumour is based on:

1. the size of tumour,
2. the spread to the regional lymph nodes
3. the presence or absence of blood born metastasis.

The most popular method for malignant tumour staging is the staging system of American Joint Committee (AJC) of cancer staging, where:

- **T** represents tumour size and extent of local tumour spread.
- **N** represents the absence or presence of regional lymph node metastasis
- **M** represents distant metastasis.

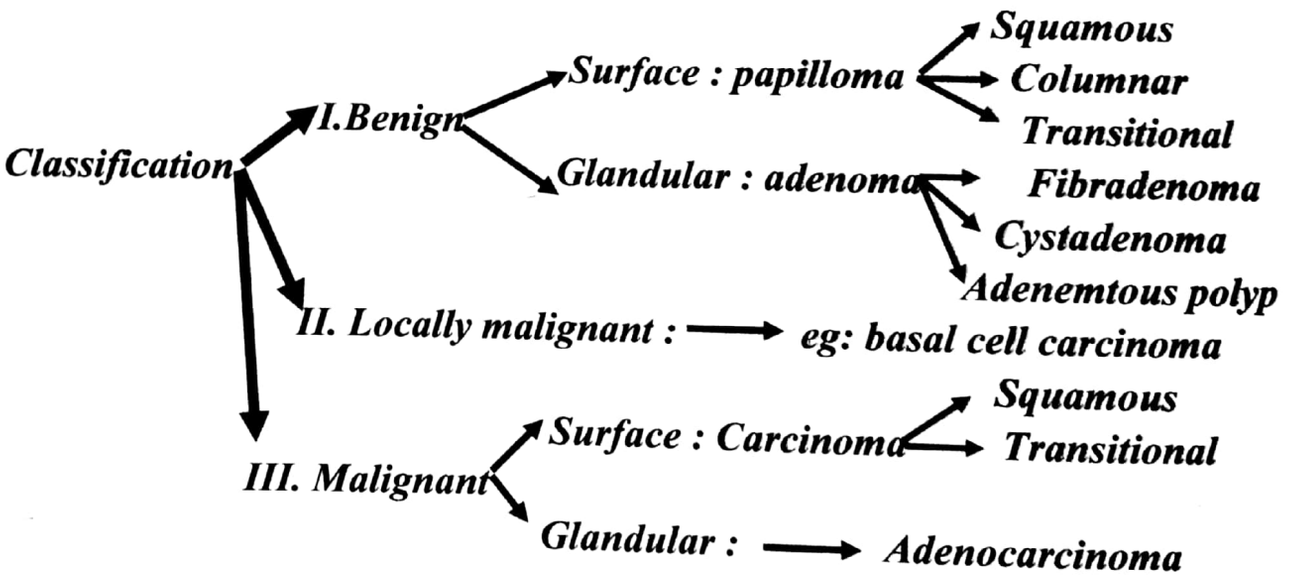
According to this staging tumour estimated as T1 N0 M0 has better prognosis than other staging as T4 N3 M1.

- **Primary tumour size (T)**:
  - T0: no evidence of primary tumour.
  - Tis: carcinoma in situ
  - T1,T2, T3 and T4: Indicating the size of tumour and its extent of local spread.
- **Regional lymph node (N):**
  - N0: no regional lymph nodes metastasis.
  - N1, N2, and N3: Extent of regional lymph node metastasis.
- **Distant metastasis (M):**
  - M0: no distant metastasis.
  - M1: distant metastasis.

PROGNOSTIC FACTORS OF MALIGNANT TUMOURS

1- **Age:** Poor prognosis in patients with colorectal and lung cancer who are less than 40 years age, while younger age group patient with thyroid carcinoma have favorable prognosis.
2- **Sex:** The prognosis of some tumours as colorectal and liver carcinomas is favorable in females than males. On the other hand the prognosis of lung carcinoma is favorable in males than females.
3- **Tumour type:** e.g. most sarcomas have poorer prognosis than carcinomas.
4- **Tumour site:** e.g. superficial tumours are diagnosed earlier than deeply seated tumours and brain tumours.
5- **Differentiation or grading:** Well differentiated tumours are of favorable prognosis as they grow slower.
6- **Tumour stage:** *T1 N0 Mo* tumours have much better prognosis than other stages, and tumours assessed as *T4 N3 M1* have the worst prognosis.
7- **Prognostic tumour markers:** To be discussed later.
8- **Stromal fibrosis:** Associated with a favorable or good prognosis.
9- **Efficiency of the immune system:** Cancer cells are capable of producing an immune response. Both cell- mediated and humoral immunity may be involved in the defense mechanisms against cancer as they have anti-tumour activity. Disturbances of the immune mechanisms can predispose to cancer.

EPITHELIAL TUMOURS



BENIGN EPITHELIAL TUMOURS

A) PAPILLOMA

Definition: benign tumour of surface epithelium.

Grossly: unencapsulated finger like projecting mass from the surface. It may be simple or compound, either sessile or pedunculated.

Microscopically: central connective tissue core containing vessels covered with benign proliferating surface epithelium.

Types:

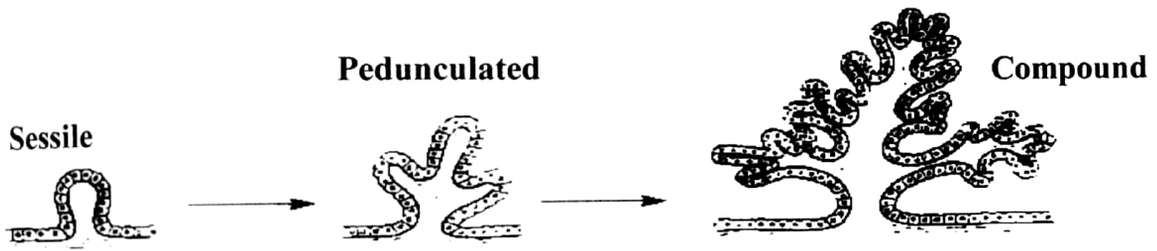
1-Squamous cell papilloma: from skin, tongue, mouth, larynx, vagina& esophagus. ***Microscopic picture:*** vascular connective tissue core covered by hyperplastic stratified squamous epithelium showing basal cell hyperplasia, acanthosis and hyperkeratosis.

2-Columnar cell papilloma: **It may be:**

a- ***Duct papilloma*:** It arises from the epithelial lining of the large duct as in the breast.

b- ***Mucous cell papilloma (Adenopapilloma or adenomatous polyp):*** arises from the mucosa of gastrointestinal tract (stomach, intestine).

3-Transitional cell papilloma: arises from uretheral cells of the urinary bladder, renal pelvis, prostatic urethra and nasopharynx.



Papilloma

B) ADENOMA

Definition: benign tumour of glandular epithelium.

Grossly: well encapsulated, rounded, variable-sized tumour that may be lobulated due to fibrous septae.

Microscopically: several patterns are known.

Types of adenoma:

I. According to functional capacity:

a) ***Functioning adenomas*:** adenomas of the thyroid.

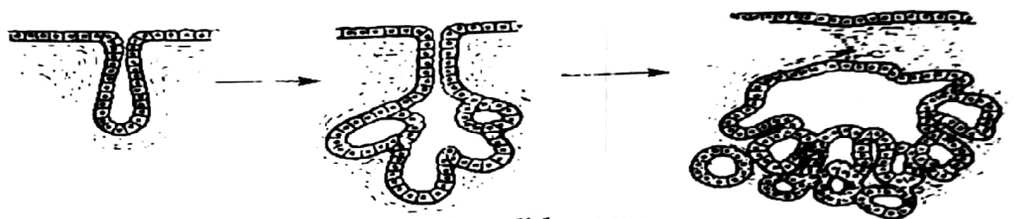
b) ***Non- functioning adenomas.***

II. According to the histology: (see special pathology)

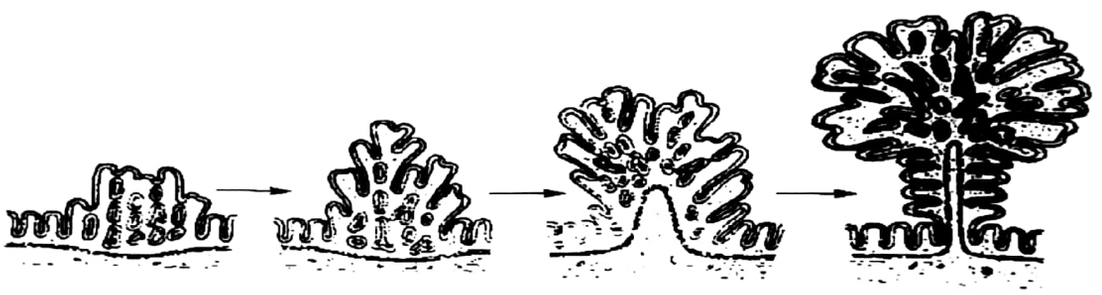
a) Simple adenoma (tubular adenoma): proliferating glands arranged in acinar or solid patterns lined by cubical epithelium and separated by delicate fibrovascular stroma. e.g. pancreatic adenoma.

b) Fibroadenoma: mixed adenoma showing proliferation of both and glandular and fibrous tissues as in breast. There are two types: ***Pericanalicular fibroadenoma*** and ***intracanalicular fibroadenoma.***

c) Cystadenoma: Common in the ovary and appears as cystic structure due to accumulation of secretion. There are two types*:* ***Serous cystadenoma*** and ***Mucinous cystadenoma***



Adenoma in solid organs



Adenoma in hollow organs

MALIGNANT EPITHELIAL TUMOURS (CARCINOMAS)

Definition: malignant tumour of epithelial tissues.

General characters:

(1) Age: middle and old age (usually >40 years).

(2) Rate of growth: rapidly growing but slower than sarcomas.

(3) Mode of growth: by infiltration of the surrounding tissues.

(4) Grossly:

- Less vascular than sarcomas.
- The shape of the tumour mass may be polypoidal (fungating), ulcerating, diffuse infiltrating, or displays an annular growth pattern.
- The consistency may be firm to hard.
- The cut surface shows haemorrhage & necrosis.

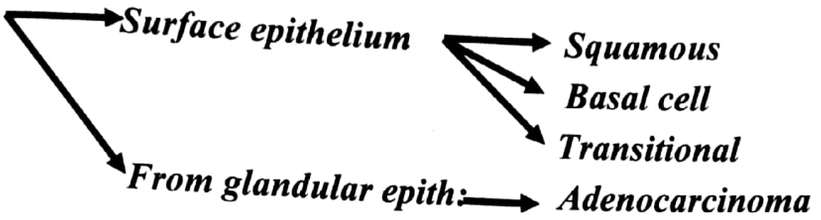
(5) Microscopically:

- Masses of malignant cells separated by fibrous stroma.
- The cells are arranged in sheets, clusters or acini.
- They show all malignant characters (pleomorphism, hyperchromatism, mitotic figures, and disturbed polarity).

(6) Spread: slower than sarcomas. Early by lymphatics and late by blood.

(7) Differentiation (grading): well, moderately, poorly differentiated or undifferentiated (anaplastic).

(8)Types of carcinoma:



SQUAMOUS CELL CARCINOMA

(see special pathology)

Definition: Malignant tumour of stratified squamous epithelium.

BASAL CELL CARCINOMA

(see special pathology)

Definition: Locally malignant tumour arising from the basal cell layer of the epidermis of the skin and its appendages as hair follicles.

TRANSITIONAL CELL CARCINOMA

(see special pathology)

Definition: Malignant tumour of transitional epithelium.

CARCINOMA OF GLANDULAR EPITHELIUM

1-ADENOCARCINOMA

Definition: Malignant tumour of glandular epithelium.
Origin: Glandular epithelium of mucous membranes and glands.
Sites: Breast, GIT, liver, pancreas, endometrium, ovary, prostate, thyroid and lung,....

Gross picture:

1-In endocrine and exocrine glands the tumour may appear as irregular infiltrating growth.

2- In mucous membranes, the tumour may be:

a. Polypoidal fungating mass protruding into the lumen.

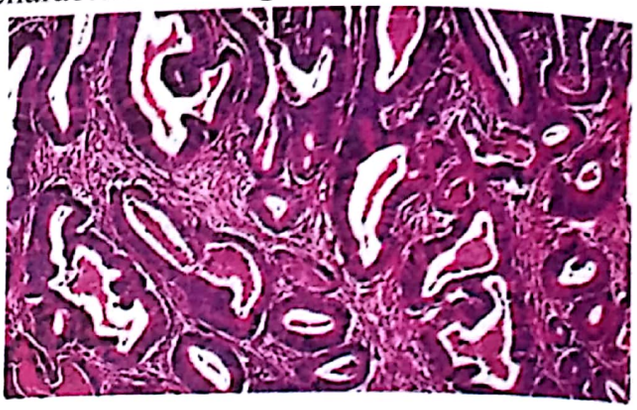
b. Diffuse annular infiltrating mass.

c. Ulcerative growth with characters of malignant ulcer.

Microscopic picture:

**In well differentiated adenocarcinoma:*

- The malignant cells show acinar pattern but the acini are irregular and showing malignant features.
- The neoplastic glands infiltrate the underlying structures as submucosa and muscle layer and sending distant metastasis.



Well differentiated adenocarcinoma

- the acini may be distended with secretions forming cysts which may form papillae (cystadenocarcinoma & papillary cystadenocarcinoma).

**In less differentiated adenocarcinoma:*

Variable degrees of glandular differentiation.

Grading: adenocarcinoma is graded into 3 grades according to:

- Tubule formation.
- Size and shape of the nuclei.
- Number of mitotic figures.

Grade I: Well differentiated tumour that shows tubule formation, slight variation in glandular and nuclear size and shape, and few mitotic figures.

Grade II: Moderately differentiated tumour (in between grade I & III).

Grade III: Poorly differentiated with poor tendency to acinar formation, variability in size and shape of nuclei and many mitotic figures.

2- MUCOID CARCINOMA

Definition: rapidly growing highly malignant tumour arising from mucous secreting tissues as: stomach, large intestine and breast.

Gross picture: translucent soft jelly like bulky masses.

Microscopic picture: groups of spheroidal cells containing mucin. The mucin pushes the nuclei to the periphery giving "*Signet ring*" appearance.

3- ANAPLASTIC CARCINOMA

Definition: highly undifferentiated tumour of glandular origin.
Sites of origin: Common in breast and less common in ovary, stomach, prostate.
Types:

1) *Scirrhous carcinoma:* firm to hard tumour with slow rate of growth. *Microscopically*, masses of polygonal cells separated by dense fibrous tissue.
2) *Medullary (Encephaloid) carcinoma:* rapidly growing large soft tumour brain-like in consistency showing areas of haemorrhage and necrosis. *Microscopically*, masses of polygonal cells separated by few fibrous tissue.

CARCINOMA IN SITU
(INTRAEPITHELIAL OR PREINVASIVE CARCINOMA)

Definition: Is an early intraepithelial malignant changes without invasion to the basement membrane.

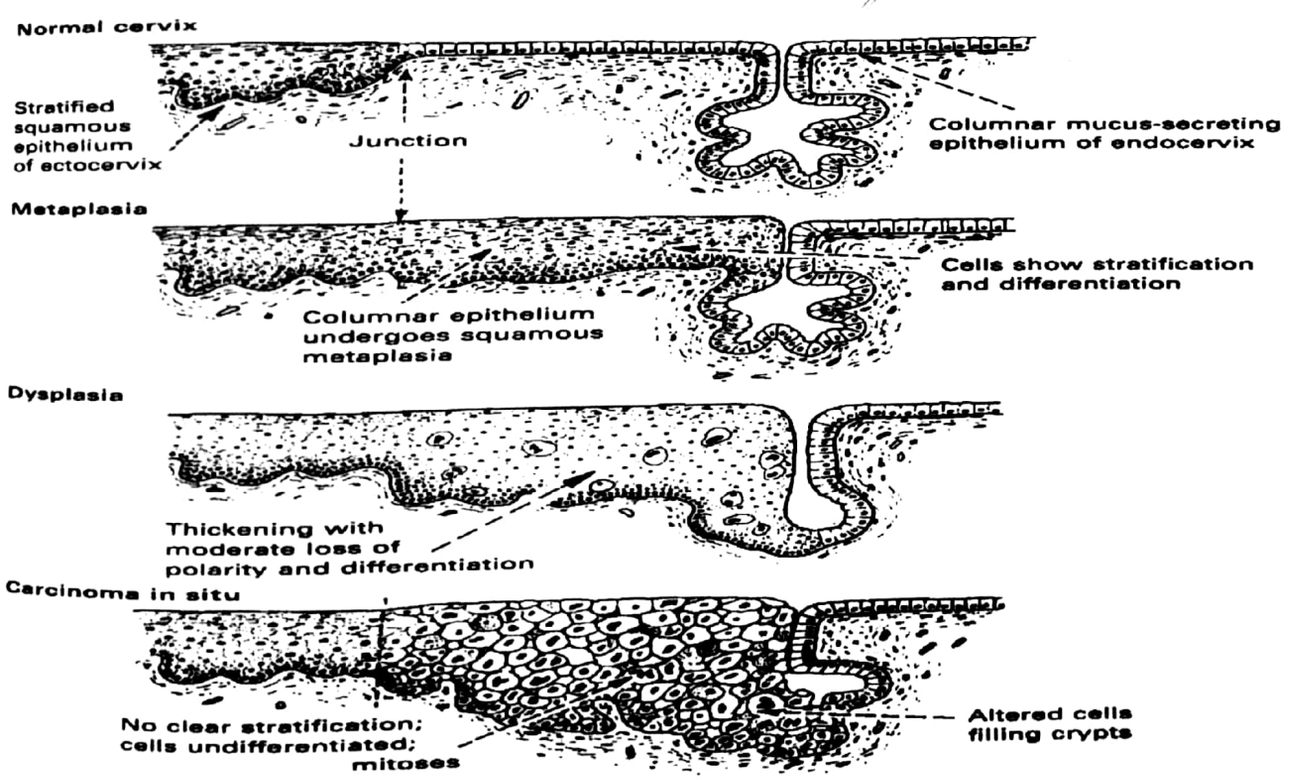
Microscopic picture:

Malignant epithelial changes occurring in the full thickness of the affected sites. The cells show all features of malignancy as pleomorphism, hyperchromasia, disturbed polarity, nuclear enlargement and excess mitotic figures.

Sites : May occur in the skin, cervix, bladder, glands or eye.

NB: - there is no invasion of the basement membrane.

- CIS may progress to invasive carcinoma after years.



LOCALLY MALIGNANT AND LOCALLY DESTRUCTIVE TUMOURS

Definition: group of ***intermediate tumours*** characterized by:

1-A slow rate of growth than other malignant tumours.

2-Local invasion and destruction by infiltration only without distant metastasis.

3-Microscopic features of malignancy.

4-Prognosis: may recur especially after incomplete removal

Examples of locally malignant tumours are:

1- Basal cell carcinoma.
2- Giant cell tumour of bone (osteoclastoma).
3- Adamantinoma of the mandible.
4- Craniopharyngioma at the region of the anterior pituitary
5- Intermediate grade astrocytoma.
6- Carcinoid tumours of the intestine and bronchi.
7- Ameloblastoma

MESENCHYMAL TUMOURS

A-BENIGN MESENCHYMAL TUMOURS

1-LIPOMA

Definition: benign tumour of fatty tissue.

Sites of origin: subcutaneous fatty tissue as that of the back, shoulder region & buttocks,

Gross picture: Capsulated, rounded or lobulated, yellowish and soft.

Microscopic picture:

- Lobules of mature adult fat cells separated by delicate fibrous tissue septae
- Adult fat cells are large and vacuolated.
- The nuclei are flat and compressed against the cell wall giving a signet ring appearance.
- Malignant transformation is rare.

2-FIBROMA

Definition: a benign tumour arising from fibrous connective tissue

Sites of origin: subcutaneous tissue, fascia, tendons and sometimes in the ovary, kidney, breast, and intestine.

Gross picture:

- Capsulated rounded to oval in shape.
- Soft or hard according to fibrous tissue content and cellularity.

Microscopic picture: interlacing bundles of fibrous collagenous connective tissue mixed with fibroblasts having spindle shaped nucleus with tapering ends.

Desmoid tumour: special type of fibromatosis arising from the muscular aponeurosis of the abdominal wall especially that of the rectus abdominus muscle.

Predisposing factors: trauma and repeated pregnancy.

It is locally infiltrative, non capsulated, and recurs after surgical removal but does not show any microscopic evidences of malignancy or distant metastasis.

3-MYXOMA

Definition: rare benign tumour composed of myxomatous tissue. It is uncommon in the pure form but common as myxomatous degeneration in other tumours.

Sites of origin: muscle sheaths, and atrial septum of the heart.

Gross picture: ill defined round mass with translucent soft, jelly like consistency.

Microscopic picture: small elongated and stellate cells with interlacing slender branches. The cells are separated by faint blue mucoid matrix.

4-CHONDROMA

(see special pathology)

Definition: Benign tumour composed of hyaline cartilage.

5-OSTEOMA

(see special pathology)

Definition: Benign tumour of bone.

Types:

1- Compact or ivory osteoma.

2- Osteoid osteoma

3-Cancellous osteoma (Osteochondroma, exostosis or ecchondoma)

6-LEIOMYOMA

(see special pathology)

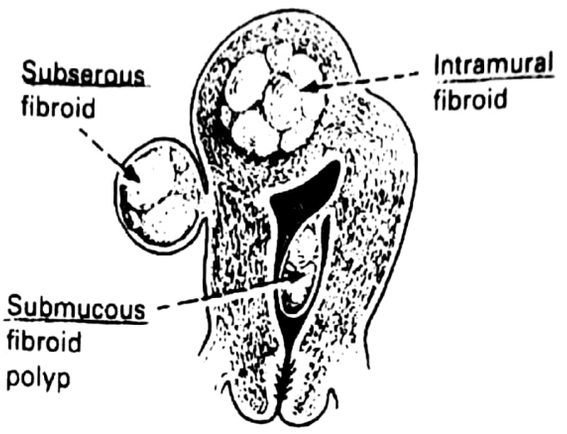
Definition: It is common benign tumour of smooth muscle.

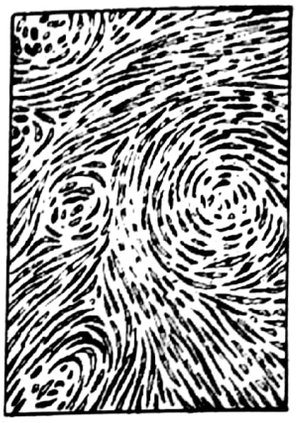
Sites of origin:

- Uterus (the commonest site).
- Gastrointestinal tract as the stomach, esophagus and intestine.
- Any sites have smooth muscle tissue. as blood vessels

Gross picture: circumscribed, firm mass surrounded by compressed muscle tissue forming a pseudocapsule. The cut surface shows a whorled pattern.

Microscopic picture: interlacing bundles of smooth muscle fibrous with fibrous stroma containing blood vessels.





LEIOMYOMA

7- RHABDOMYOMA

Very rare benign tumour of striated skeletal muscles and heart muscle. It appears as rounded brown mass that may or may not be capsulated.

Microscopically: formed of branched striated muscle cells.

8-BENIGN TUMOURS OF VESSELS (ANGIOMAS)

(see special pathology)

These are considered to be hamartomatous (tumour-like) malformations rather than true neoplasms. They are detected early in life. They are noncapsulated lesions .

I. Haemangioma: benign tumours of vascular endothelium

II. Lymphangioma: benign tumours of lymphatic vessels filled with coagulated lymph.

9-BENIGN TUMOURS OF PERIPHERAL NERVES

(see special pathology)

I. Schwannoma :

Benign capsulated tumour originating from *Schwann cells*, attached to peripheral nerves. Within the skull, the VIII cranial nerve is commonly involved.

II. Neurofibroma

Unencapsulated, tumours originating from Schwann cells, fibroblast and perineurial cells, which cause a fusiform expansion of the affected nerves.

MALIGNANT MESENCHYMAL TUMOURS (SARCOMAS)

Definition: malignant tumour of connective (mesenchymal) tissue.

Characters of sarcoma:

1. **Incidence:** Less common than carcinoma.
2. **Age:** usually younger age than carcinoma .
3. **Grossly: bulky masses, fleshy with** areas of haemorrhage & necrosis.
4. **Microscopically:** the tumour is very cellular and the individual cells are arranged singly show the malignant characters. The tumour is highly vascular with thin-walled, ill-formed vessels.
5. Metastasis occurs early by blood (commonly to the lung).

Classification of sarcomas:

A) Differentiated sarcoma: classified according to the tissue of origin e.g.: fibrosarcoma, liposarcoma, chondrosarcoma,…..

B) Undifferentiated sarcoma: named according to the shape of predominating cells e.g. round cell sarcoma, spindle cell sarcoma or giant cell sarcoma.

EXAMPLES OF SOME DIFFERENTIATED SARCOMAS

1-FIBROSARCOMA:

Definition: malignant tumour of fibrous tissue.

Sites of origin: any fibrous tissue particularly the deep fascia, subcutaneous tissue and periosteum.

Gross picture: large grayish soft or firm mass with areas of hemorrhage and necrosis.

Microscopic picture: malignant fibroblasts showing varying degrees of malignancy and separated by collagen fibers.

2-LEIOMYOSARCOMA:

Definition: malignant tumour of smooth muscle origin.

Sites of origin: smooth muscles any where particularly the uterus.

Microscopic picture: spindle-shaped smooth muscle cell showing features of malignancy with hemorrhage and necrosis.

3-LIPOSARCOMA:

Definition: malignant tumour of fatty tissue.

Sites of origin: retroperitoneal fat, intermuscular septa or on top of lipoma.

Gross picture: bulky mass, soft, yellow with hemorrhage and necrosis.

Microscopic picture: in well differentiated liposarcoma the malignant cells contain abundant fat. The undifferentiated pleomorphic liposarcoma contains pleomorphic

large spindle shaped cells and large giant cells. Myxoid liposarcoma is characterized by myxomatous background and arborized vessels.

MELANOCYIC TUMOURS

(see special pathology)

These tumours originated from the melanocytes which normally present in the skin, mucous membranes, eye and leptomeninges. They include benign melanocytic lesions (nevi) and malignant melanocytic lesions (melanomas).

Differences between carcinoma and sarcoma

Item	*Carcinoma*	*Sarcoma*
Definition	Malignant tumour of epithelial origin	Malignant tumour of mesenchymal origin
Age	Middle& old	All ages especially young
Incidence	More common	Less common
Rate of growth	Less rapid	More rapid than carcinoma
Size	Usually smaller	Usually large, variegated
Microscopic picture	Sheets, cords of cell or acini separated by fibrous stroma.	Cellular and the individual cells are separated by intercellular stroma
Stroma	Well formed	Poorly formed stroma
Hemorrhage& necrosis	less than sarcoma	More than carcinoma
Differentiation	less anaplastic	Usually more anaplastic
Metastasis	Early by lymphatic& late by blood	Early by blood and rarely by lymphatics
Radiosensitivity	Usually radiosensitive	Usually radio resistant
Prognosis	Usually better	Usually bad

DEVELOPMENTAL TUMOURS

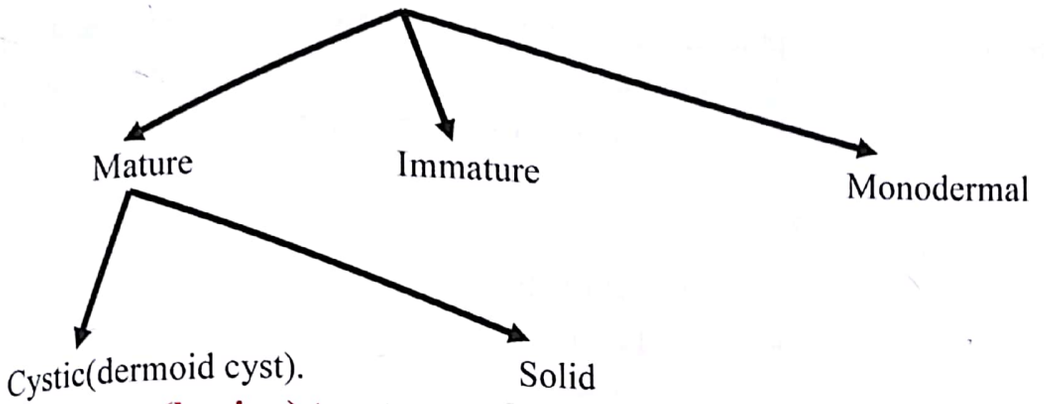
TERATOMAS

- **Definition:** tumours containing structures arising from totipotent germ cells and are composed of tissues which are foreign to the site of origin of tumour. The totipotent cell gives rise to the three embryonic cell types, ectoderm, endoderm and mesoderm.
- **Sites of teratoma:**

1-Gonadal: from testis and ovary.

2-Extragonadal: from the anterior mediastinum, retroperitoneum, base of the skull and sacrococcygeal region (midline structures).

- **Types of teratoma:**

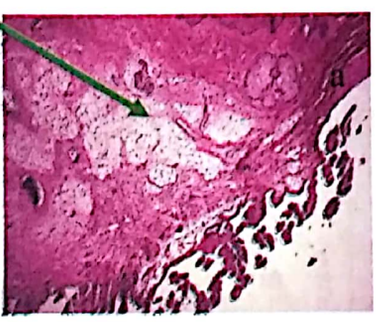


(I) Mature (benign) teratoma:

Two types are present:

A- Cystic teratoma (Dermoid cyst):

- The most common type of teratoma.
- The ovary is the commonest site.
- It appears as thick walled rounded cyst lined by stratified squamous epithelium and contains sebaceous material.
- The cyst may also contains hair, teeth, bone cartilage, respiratory or nerve elements .
- The tumour tissue projects in the cyst cavity as nipple-like protrusion known as *dermoid ridge*.

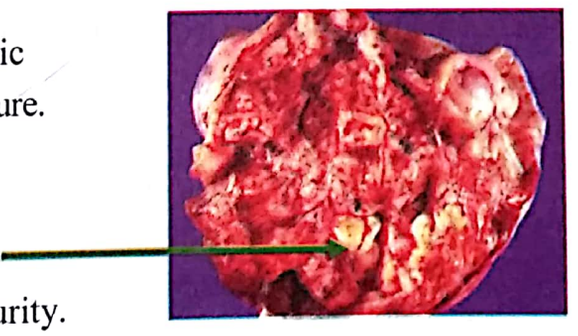


–About 1% of cases undergoes malignant transformation of any one of the component elements, and mostly gives rise to squamous cell carcinoma (teratoma with malignant transformation)

B- Solid teratoma:

The tumour contains mixture of tissues similar to cystic teratoma but with excessive amount giving solid feature.

a rare type.



(II) Immature (malignant) teratoma:

rare tumours composed of a wide variety immature tissue elements varying stages of immaturity.

HAMARTOMAS

Definition: tumour-like developmental malformation composed of noncapsulated irregular mature tissues of the affected organ arranged haphazardly or in an abnormal arrangement. Hamartoma is present at birth and its growth stop at puberty. Some of them are precancerous.

Examples of hamartoma:

1- Lung hamartoma: composed of a mixture of cartilage
, blood vessels, smooth muscles, connective tissue and bronchial tissue.

2- Some tumour-like lesions as Haemangioma, nevi, enchondromas, neurofbromatosis.

Hamartoma	True neoplasm
• developmental abnormality	• new growth
• Present and often visible at birth	• Usually in adults
• Its growth continues until puberty	• Not related to body growth
• Is essentially benign	• May be malignant

CHORIOSTOMA

Definition: resembles hamartoma but contain tissues that are not normally present in its site of origin.

Example: gastric choriostoma: presence of smooth muscles, pancreatic acini and ducts in the wall of the stomach.

EMBRYONIC TUMOURS

Definition: highly malignant tumours which are detected early life within the first 5 years. They are derived from embryonic remnants. They are composed of one or more types of undifferentiated tissues.

Examples:

1. Neuroblastoma from adrenal medulla and sympathetic ganglion.
2. Nephroblastoma from the kidney.
3. Hapatoblastoma from the liver.
4. Retinoblastoma from the eye.
5. Medulloblastoma from the cerebellum

OCCULT (LATENT, HIDDEN) CANCER

It is a clinically silent (no symptoms and signs) malignant tumour. It is discovered accidentally during investigations of other disease or during autopsy, e.g. nasopharyngeal carcinoma, thyroid carcinoma and prostatic carcinoma.

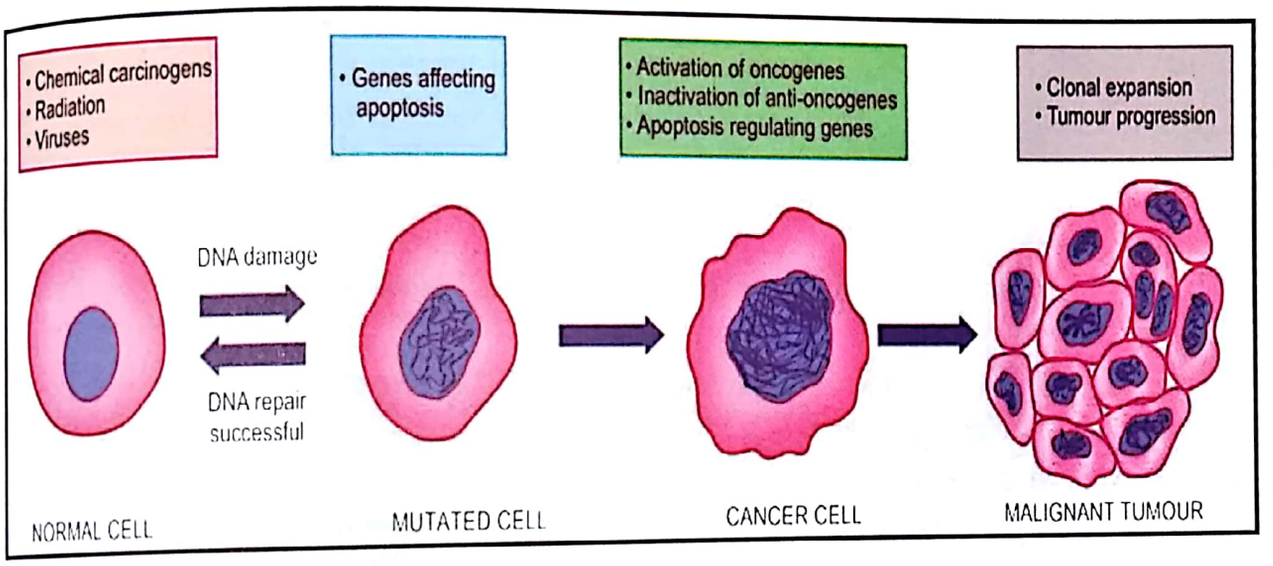
DORMANT CANCER

It is the appearance of metastasis many years after (up to 30 years) successful surgical removal of the primary malignant tumour, e.g. breast carcinoma, thyroid carcinoma.

MOLECULAR BASIS OF CANCER

For tumorigenesis to occur, there is the necessity for nonlethal genetic damage. Tumors arise by clonal expansion of a single genetically damaged precursor cell {they are monoclonal).

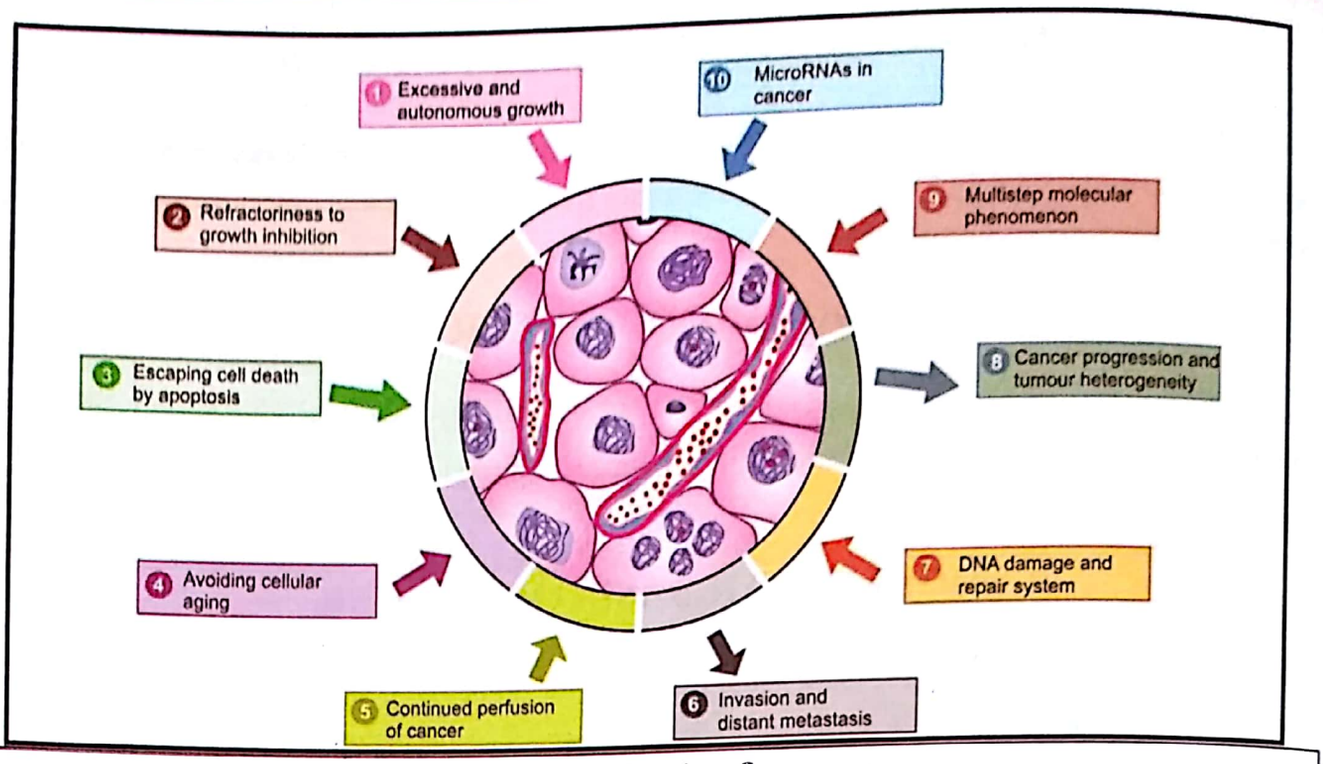
Note: Mistakes made in DNA replication are normally corrected by DNA repair genes.



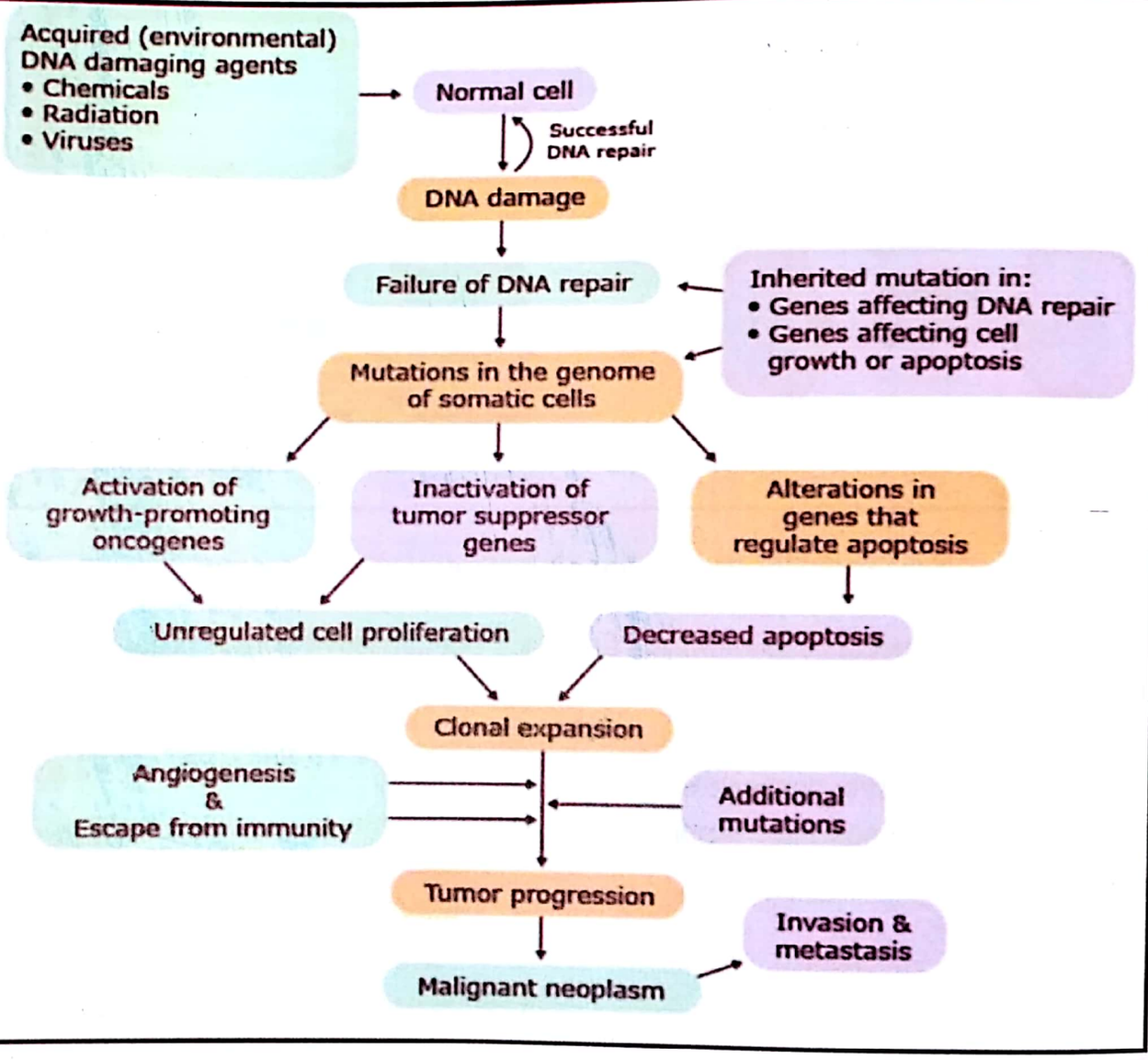
Schematic illustration to show molecular basis of cancer.

Tumorigenesis occurs as a multistep process. Four classes of normal regulatory genes are often damaged:

- DNA repair genes
- Growth-promoting oncogenes
- Growth-inhibiting tumor suppressor genes
- Apoptosis-regulating genes



Molecular basis of cancer



CARCINOGENESIS (AETIOLOGY OF CANCER)

A large number of agents *cause genetic damage* and induce neoplastic transformation of cells. The factors that can participate in such genetic damage include:

(I) **Chemical carcinogenesis**: mechanism of neoplastic transformation in response of carcinogenic agents occurs in two steps:

A) **Initiation:** means induction of certain irreversible change in the genome of the cell on exposure to carcinogenic agent. Initiation causes permanent DNA damage (gene mutation) and the cells are called *latent tumour cells*.

B) **Promotion:** subsequent irritation of the initiated latent tumour cells by various hormones, drugs and the latent tumour cells undergo subsequent proliferation.

Examples of chemical carcinogens are:

1-**Aromatic hydrocarbons** (3, 4 penzpyrene) present in *coal tar derivatives* and in *cigarette smoke* cause carcinoma of the lung and skin.

2-**Aromatic amines** as ß-naphthylamine present in aniline dye, rubber and cable industry and benzedine cause urinary bladder carcinoma.

3-**Nitrosamines and amides** derived from combination of nitrosable amines present in foods with nitrates present in food preservatives which is converted to nitrites by the action of bacteria cause carcinoma of the stomach and urinary bladder.

4-**Azo dyes** used in color food as scarlet red and butter yellow cause hepatocellular carcinoma.

5-**Asbestos** causes mesothelioma and bronchogenic carcinoma.

6-**Aflatoxins** produced by Aspergillus flavus fungus infection of stored grains and nuts cause hepatocellular carcinoma.

7-**Vinyl chloride** present in plastic industry causes hepatic angiosarcoma.

8-**Alkylating** (anticancer) agents may cause leukemia and lung carcinomas.

9-**Arsenic** compounds cause carcinoma of the skin on chronic exposure.

10-**Nickel and chromium** causes lung carcinomas.

(2) **Radiation carcinogenesis (Physical):** by direct effects on DNA or by activating cellular oncogenes.

A) Ultraviolet rays: sun rays predispose to different skin cancers.

B) Ionizing radiation:

1-***Radiotherapy*** induces malignant neoplasms, commonly sarcomas. Thyroid carcinoma occurs in 9% of those exposed during infancy to neck radiation.

2-***Radio diagnostic*** abdominal x-rays during pregnancy may slightly increase the risk of leukemia in the foetus.

3-***Radio isotopes*** as radium containing paints to produce luminous watch faces causes osteosarcoma.

4-***Radioactive minerals*** are associated with increased incidence of lung cancer.

5-***Atomic bomb*** explosion in *Hiroshima* and *Nagasaki* caused acute and chronic myelocytic leukemia after 7 years.

(3) Viral carcinogens:

A) DNA viruses:

1. *Human papilloma virus (HPV):* causes squamous cell carcinoma of the cervix and anogenital region. Low risk virus is responsible for the development of juvenile laryngeal papilloma and skin papilloma (verruca valgaris).
2. *Epstein-Barr virus (EBV):* Burkitt's lymphoma and nasopharyngeal carcinoma.
3. *Herpes viruses* : carcinoma of the cervix.
4. *Cytomegalovirus (CMV)* : Kaposi sarcoma.

B) RNA oncogenic viruses:

1. *Human T-cell lymphoma / leukemia virus (retrovirus):* Causes T-cell lymphoma and leukemia.
2. *Human immunodeficiency virus (HIV):* B-cell lymphoma and Kaposi sarcoma.
3. *Hepatitis C virus (HCV)* : hepatocellular carcinoma.

(4) Hormones and neoplasia: The relation of hormones and neoplasia is complex.

a- Induction of neoplasms by hormones:

1. **Estrogen:** Patients with estrogen producing tumours of the ovary (granulosa cell tumour) or those taken exogenous estrogen have high risk of development of **endometrial cancer**.
2. Young female children whose mother has taken **Diethylstilbestrol** in treatment of threatened abortion my get clear cell adenocarcinoma of the **vagina.**

b- Hormonal dependence of neoplasms:

1- **Prostatic carcinoma:** It is always dependent on androgen.

2- **Breast carcinoma:** usually dependents on estrogen and progesterone.

3- **Thyroid carcinoma:** Well differentiated thyroid cancer is dependant constantly on thyroid stimulating hormone (TSH).

(5) Other factors (co-carcinogens):

1. *Age:* increased risk in old age owing to diminished efficiency of the immune system and prolonged exposure to carcinogens as in prostatic carcinoma.
2. *Sex:* Males are generally more susceptible to cancer, however some carcinomas predominates in females as thyroid and breast cancer.
3. *Environmental factors:* Air pollution and smoking predispose to lung cancer.
4. *Heredity:* retinoblastoma, neurofibromatosis, familiar polyposis coli, breast cancer and colon cancer.
5. *Race:* white races are more susceptible for skin cancer.

6. *Dietary factors* as high intake of smoked foods, food preservative, food additives, Aflatoxins, pesticides and low fiber diet predisposed to cancer.

ONCOGENES AND CANCER

Definition: cancer causing genes and they are derived from *proto-oncogenes*. The proto-oncogenes are normal cellular genes that affect the proliferation and differentiation of normal cells through the regulation of certain growth factors production. The transformation of proto-oncogenes into oncogenes occurs by one of three mechanisms:

1-Mutation: permanent change in DNA. Certain environmental factors such as chemicals, viruses and irradiation increase the rate of mutation.

2-Chromosomal translocation: where during cell division a part of certain chromosome with its genes is translocated into another chromosome leading to gene fusion or change in the sequence of genes.

3-Gene amplification: This is reduplication of proto- oncogenes leads to over-expression of carcinogenic activity.

4- Chromosomal deletions.

PRECANCEROUS LESIONS

A- Hereditary Precancerous lesions:

1. ***Neurofibromatosis:*** inherited as autosomal dominant gene and affected patient are predisposed to get gliomas of the brain and optic nerve or meningioma or acoustic neuroma in the future.
2. ***Xeroderma pigmentosum:*** inherited as autosomal recessive disorder and affected patients are predisposed to get skin squamous cell carcinoma, basal cell carcinoma, or malignant melanoma.
3. ***Familial polyposis coli:*** Inherited as autosomal dominant disorder and affected patient are predisposed to get adenocarcinoma of the colon.
4. ***Agamaglobulinemia: Inherited*** as X- linked disorder and the patient is predisposed to get lymphoma and leukemia.

B- Acquired precancerous lesions:

1-Atypical endometrial hyperplasia predispose to endometrial carcinoma.

2-Atypical breast ductal and lobular hyperplasia predispose to breast cancer.

3-Liver cirrhosis predisposes to carcinoma of the liver.

4-Chronic atrophic gastritis and chronic gastric ulcer predispose to gastric adenocarcinoma.

5-Ulcerative colitis predispose to carcinoma of the colon.

6-Leukoplakia predispose to squamous cell carcinoma

7-Dysplasia and metaplasia of bronchial epithelium and cervix predispose to carcinoma.

8-The undescended testis is liable to tern malignant (seminoma).

9-Benign tumours as colonic adenoma, neurofibroma and villous bladder papilloma may turn malignant.

10-Women having iron deficiency anaemia and atrophy of the mucosa of the mouth are liable to get post-cricoid carcinoma later on.

11-Paget's disease of the bone may predispose to osteosarcoma in old age.

12-Bilharziasis of the urinary bladder and gall bladder stones especially if associated with squamous metaplasia owing to chronic irritation.

13-Chronic infections such as chronic osteomyelitis, cholecystitis, chronic varicose ulcer and dermatitis.

CLINICAL ASPECTS OF NEOPLASIA

THE DEFENSE MECHANISMS AGAINST CANCER (TUMOUR IMMUNOLOGY)

It has long been known that body's immune system can recognize tumour cells as 'non-self' and they attempt to destroy them and limit the spread of cancer.

Basis for this concept:

1. Certain cancers evoke significant lymphocytic infiltrate and such tumours have somewhat better prognosis e.g. medullary carcinoma breast (as compared with infiltrating ductal carcinoma), seminoma testis (as compared with other germ cell tumours of testis).
2. Rarely, a cancer may spontaneously regress partially or completely, probably under the influence of host defense mechanism. For example, rare spontaneous disappearance of malignant melanoma temporarily from the primary site which may then reappear as metastasis.
3. It is highly unusual to have primary and secondary tumours in the spleen due to its ability to destroy the growth and proliferation of tumour cells.
4. Increased frequency of cancers in immunodeficient host e.g. in AIDS patients, or development of post-transplant lymphoproliferative disease.

The concept of immunology of cancer which is discussed under the following headings:

1. TUMOUR ANTIGENS

Tumour cells express surface antigens which have been seen in animals and in some human tumours. Identifiction of tumour antigens is based on their recognition by the host immune cells, i.e. CD8+ T cells (CTL), and by the molecular structure of the tumour antigens.

Currently, various groups of tumour antigens are as follows:

i) Oncoproteins from mutated oncogenes e.g. products of RAS, BCL/ RABL and CDK4.

ii) Protein products of tumour suppressor genes e.g. mutated proteins p53and b-catenin.

iii) Overexpressed cellular proteins e.g. in melanoma the tumour ntigen is structurally normal melanocyte specific protein, tyrosinase, which is overexpressed. Similarly, HER2/neu protein is overexpressed in many cases of breast cancer.

iv) Abnormally expressed cellular proteins e.g. MAGE gene silent in normal adult tissues except in male germ line but MAGE genes are expressed on surface of many tumours such as melanoma (abbreviation MAGE from 'melanoma antigen' in which it was first found), cancers of liver, lung, stomach and oesophagus.

v) Tumour antigens from viral oncoproteins e.g. viral oncoproteins of HPV (E6, E7) in cervical cancer and EBNA proteins of EBV in Burkitt's lymphoma.

vi) Tumour antigens from randomly mutated genes Mutated cells elaborate protein products targeted by CTL.

vii) Cell specific differentiation antigens e.g. various CD markers for various subtypes of lymphomas, prostate specific antigen (PSA) in carcinoma of prostate.

viii) Oncofoetal antigens e.g. AFP in liver cancer and CEA in colon cancer.

ix) Abnormal cell surface molecules e.g. abnormal expression of mucin in ovarian cancer (CA-125) and in breast cancer (MUC-1).

2. ANTI-TUMOUR IMMUNE RESPONSES

Include the following:

i) **Cell-mediated mechanism:** This is the main mechanism of destruction of tumour cells by the host. It can destroy tumour cells and induce tumour immunity in humans via:

a) Specifically sensitized cytotoxic T lymphocytes (CTL) (CD8+ T cells) are directly cytotoxic to target cell and require contact between them and tumour cells.

b) Natural killer (NK) cells are lymphocytes which after activation by IL-2, destroy tumour cells without sensitisation, either directly or by antibody dependent cellular cytotoxicity (ADCC).

c) Macrophages are activated by interferon-g secreted by T-cells and NK cells, and therefore there is close collaboration of these two subpopulations of lymphocytes and macrophages.

ii **Humoral mechanism** As such there are no anti-tumour humoral antibodies which are effective against cancer cells in vivo. However, in vitro humoral antibodies may kill tumour cells by complement activation or by antibody-dependent cytotoxicity.

3. CANCER IMMUNOTHERAPY

It is a generally-accepted that the best defense against human diseases is our own immune system. In cancer the immune system starts failing and requires to become more effective in fighting against cancer. Immunotherapy has been used as treatment against cancer in combination with other therapies (surgery, radiatation, chemotherapy) through the following:

i) Non-specific stimulation of the host immune response.
ii) Specific stimulation of the immune system.
iii) Current status of immunotherapy is focused on following three main approaches:
   a) Cellular immunotherapy
   b) Cytokine therapy
   c) Monoclonal antibody therapy

PARANEOPLASTIC SYNDROMES

Definition: cancer associated various *endocrine* and *metabolic* (non-metastatic) signs and symptoms that can not be explained either by the location of the tumour or its distant metastases.

Examples:

1- ***Cushing syndrome*:** due to the elaboration of ACTH by certain tumours as small cell (oat cell) carcinoma of the lung.
2- ***Hypercalcaemia*:** is the most common paraneoplastic syndrome occurs owing to bone resorption from elaboration of bone lytic substances by squamous cell bronchogenic carcinoma of the lung and by carcinomas of breast and ovary.
3- ***Hypoglycemia*:** Mesothelioma and liver cancer.
4- ***Hyperthyroidism*:** hydatidiform mole and choriocarcinoma due to secretion of specific thyroid hormone by these tumours.
5- ***Acanthosis nigricans***: It is verrucous hyperkeratotic pigmented skin lesions associated with stomach malignancy.
6- ***Disseminated intravascular coagulation (DIC)***: Occurs due to the elaboration of thromboplastine-like substances by certain tumours as carcinomas of the pancreatic, lung and stomach.
7- ***Pruritus*:** Occurs with Hodgkin's disease.
8- ***Myasthenia gravis and peripheral neuropathy*:** Associated with thymomas, visceral tumours due to autoimmune mechanism.
9- ***Polycythaemia***: Associated with renal cancer and hepatoma due to the production of erythropoietin like substances by the tumour.
10- ***Clubbing of the fingers and hypertrophic osteoarthropathy (periosteal new bone formation)***: Secondary to lung cancer and other intrathoracic neoplasm.

TUMOUR MARKERS

Definition: biochemical indicators for the presence of cancer. They include surface antigens, cytoplasmic proteins, enzymes and hormones. Tumour markers help in **diagnosis, differential diagnosis, prognosis, response to therapy** and **follow up** of tumours. They can be assessed in tissues, blood and other body fluids. . They are divided into:

1-**Prognostic tumour markers:** estrogen receptors (ER) and progesterone receptors (PR) for breast cancer. PCNA, Ki-67 and Her 2/neu markers are used to estimates the Proliferative growth fraction in many cancers as those of breast, prostate and lung.

2-**Diagnostic tumour markers:** Such as:

1. ***Carcinoembryonic antigen (CEA):*** carcinoma of the colon, pancreas and lung
2. ***Prostatic specific antigen (PSA):*** prostatic cancer.
3. ***Alpha –Fetoprotein (AFP)*:** cancer of the liver and testicular germ cell tumours.
4. ***Vimentin and desmin*** : mesenchymal and muscle tumours
5. ***Cytokeratin and epithelial membrane antigens (EMA)***: epithelial tumours.
6. ***Factor VIII – associated antigen***: vascular tumours.
7. ***T-cell markers*** as CD3, CD5, CD8 and ***B-cell markers*** as CD19, CD20, CD23.
8. ***Hormones as calcitonin***: medullary carcinoma of the thyroid.
9. ***Neural antigens as S-100 protein***: melanoma and neural tumours.
10. ***chromogranin*** **and** ***neuron-specific enolase (NSE)***: Neuroendocrinal tumours

DIAGNOSIS OF NEOPLASIA

1. A complete clinical history.
2. Clinical examination including site, signs and symptoms, rate of growth, and the nature of the surrounding structures.
3. Fine needle aspiration of tumour cells.
4. Cytological diagnosis: exfoliated or detached malignant cells can be detected in sputum, urine and body fluids as ascitis, pleural effusion, and CS.F.
5. Biopsy specimens: Stained paraffin sections or frozen sections.
6. Tumor markers.
7. Serologic diagnosis by detecting cancer cells products in the serum (serological tumour markers eg: AFP…liver, CA125….ovary, CA15.3…breast, PSA…prostate).

8 Radiologic diagnosis: Including CT and MRI.

9 Flow cytometry: measuring of the DNA content of tumour cells.

10 Electron microscopy.

RADIATION INJURY

- Radiation is energy that travels in the form of waves or high-speed particles.
- It can be divided into:
  - **Non ionizing Radiation:**
    -Its energy can move atoms in a molecule or cause them to vibrate but is not sufficient to displace electrons from atoms.
    -Such as ultraviolet (UV) and infrared light, microwaves, and sound waves.
  - **Ionizing Radiation:**
    -Has sufficient energy to remove tightly bound electrons. Crash of these free electrons with other atoms releases additional electrons, in a reaction cascade referred to as ionization.
    -The main sources of ionizing radiation are: x – rays, Beta, or Gamma rays.
    -They are used in medical practice but constitute a two-edged sword.

Radiosensitivity of tissues and tumours

The mature and differentiated tissues are less susceptible to radiation injury than embryonic and immature tissues.

According to radiosensitivity tissues are divided into:

- ***Highly radiosensitive tissues***:
  Lymphoid cells, hematopoietic cells, spermatogonia, gastrointestinal and mucosal epithelium, lung and kidney tissues.
- ***Highly radiosensitive tumours***:
  Leukemia, lymphoma, seminoma, dysgerminoma, squamous cell carcinoma of the skin and cervix, and adenocarcinoma of the breast. They are destroyed by doses of radiation which does not affect the normal adjacent tissue.
- ***Low radiosensitive tissues***:
  Mature cartilage, muscles, peripheral nerves, and fibroblasts.
- ***Radioresistant tumours***:
  Gliomas(except glioblastoma multiforms), large sarcomas, melanoma, renal cell carcinoma, and osteosarcomas. These tumours could be damaged only by doses of radiation which equally destroy the normal adjacent tissue.

Effects of ionizing radiation on the cells:

1- Nuclear changes:

- Due to interference with the nucleoprotein metabolism.
- There is nuclear breaking down into fragments.
- The synthesis of DNA is inhibited.

2- **Cytoplasmic changes:**
- Due to interference with enzymes such as cloudy swelling, hydropic degeneration…etc.

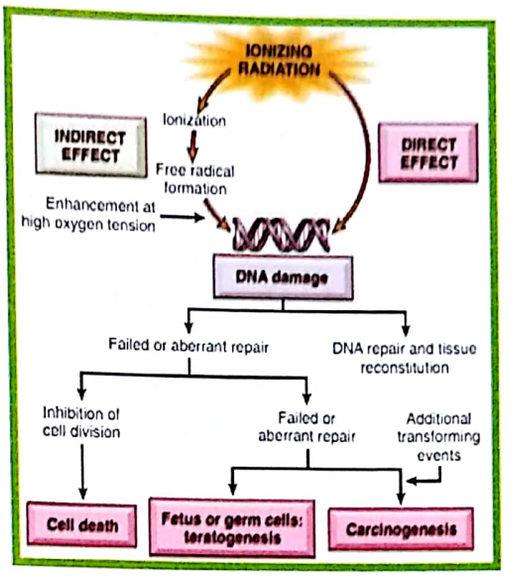
3- **Inhibition of cell division and mitosis.**

4- **Cell death in heavy dose** (10,000 rad or more).

5- **Chromosomal abnormalities and malformations:** Such as skull defect and spina bifida.

6- **Neoplasia:** Such as bone sarcoma and leukaemia.

7- **Inflammation of the irradiated tissues and fibrosis:** This leads to permanent structural changes.



Effects of total body irradiation

Depend on the total *dose* and the *area* exposed to radiation.

I. Immediate effects:

1) ***Cerebral manifestations*:**
- Nausea, vomiting, tremors, convulsions, and shock.
- This occurs within few hours after administration of high dose due to the occurrence of acute vascular dilatation, meningitis and encephalitis.

2) ***Gastrointestinal Symptoms:***

Vomiting and diarrhea resulting in dehydration and shock.

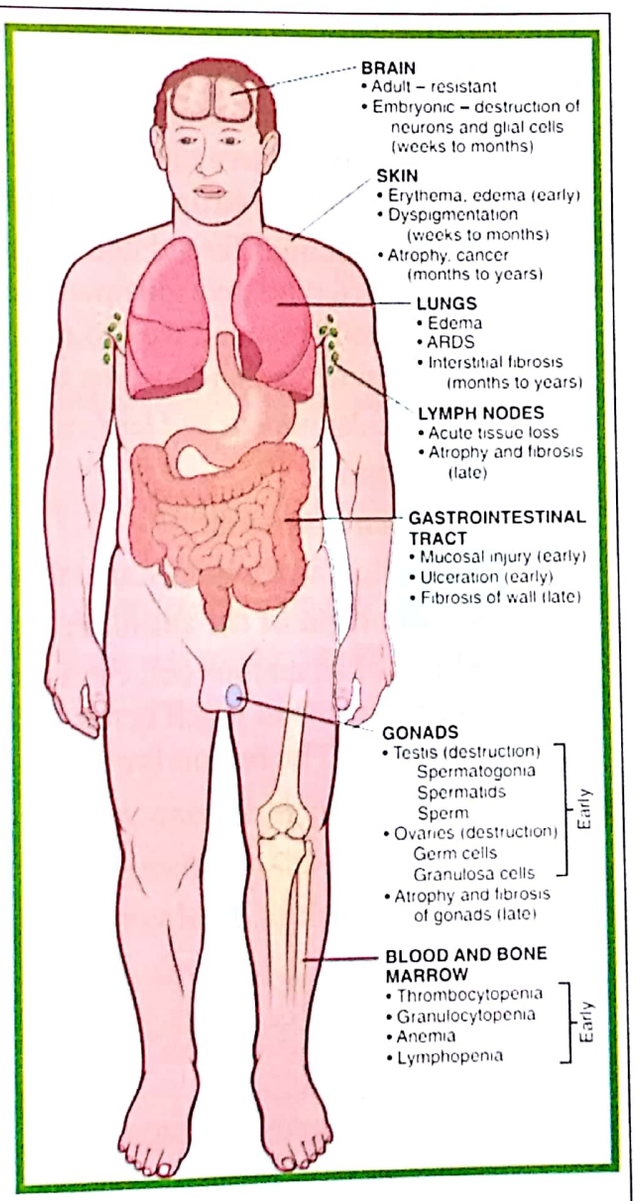
These symptoms occur with moderate dose due to the occurrence of necrosis of the gastrointestinal epithelium.

3) ***Haematopoietic and lymphoid tissue affection*:**

Bone marrow depression occurs with low doses and is manifested by neutropenia, anaemia, and thrombocytopenia leading to haemorrhage and infections.

II. Late effects:

They occur in individuals exposed to sublethal doses of radiation and are manifested by cataract, sterility, fetal abnormalities, fibrosis, neoplasia, and genetic changes.



Carcinogenic effects of radiation:

The following malignant tumours may occur as a result of exposure to radiation:

1- **Lung cancer:** Occupational exposure to radioactive minerals.
2- **Acute leukemia:** atomic bombs in Japan.
3- **Papillary thyroid cancer:** occur in children later on after therapeutic radiation of the neck to decrease the size of the thymus.
4- **Osteosarcoma:** in those employed in painting the dial of watches with paints containing radium.
5- **Skin cancer:** in those exposed to ultraviolet radiation; mainly in fair-skinned individuals.
6- **Angiosarcoma and cholangiocarcinoma of the liver:** in those exposed to radioactive isotopes.

RADIOTHERAPY

The sensitivity of tumours to ionizing radiation depends on:

1- The tissue of origin:

- It is known that seminoma, lymphoma, dysgerminoma, and leukaemias are radiosensitive tumours (see before).

2- Degree of differentiation and mitotic activity:

- The most undifferentiated tumours are the most radiosensitive. However, well differentiated squamous cell carcinoma of the skin, anus, and tongue frequently respond well to radiotherapy.

3- The tumour bed and oxygen tension:

- Avascular tumour bed leads to tumour hypoxia and so, it is more resistant to irradiation.

4- Recurrent tumours:

- They are more radioresistant than the original one.

5- Site of origin of the tumour:

- Most of squamous cell carcinomas of the skin, mucous membrane and cervix respond much better to irradiation than squamous cell carcinoma of the lung. The reason for this is not apparent.

NUTRITIONAL DISORDERS

VITAMIN DEFICIENCIES

Vitamins are organic substances that are essential in very small amounts for the maintenance of the normal metabolic functions of the body.

I-VITAMIN B COMPLEX

Group of vitamins present together, in nature, particularly in Liver and yeast.

1-Vitamin B1 (Thiamin, Aneurine):

Its deficiency produces **Beri Beri** characterized by peripheral neuritis, weakening of cardiac muscle with heart failure, and mental disturbances as irritability.

2-Vitamin B2 (Riboflavin): Its deficiency is manifested by:

- Roughness and scaliness of the skin **(seborrheic dermatitis).**
- **Angular stomatitis or cheilosis.**
- Enlarged tender inflamed tongue **(glossitis).**
- **Keratitis** and lacrymation.

3-Nicotinic acid (Niacin): Deficiency may be:

- **True deficiency:** inadequate intake in diet as occurring in poor classes of farmers consuming flour of maize.
- **Conditioned deficiency:** Due to lack of absorption in diarrhea, and steatorrhea.

Nicotinic acid deficiency leads to pellagra, characterized by (the three D):

- **Dermatitis:** redness, roughness and scaliness of the exposed parts of the skin.
- **Diarrhea**.
- **Dementia:** begins as anxiety, depression, confusion, and terminates by mental disorders. This is due to degeneration in the nerve cells, demylination of the lateral and posterior column of the spinal cord and peripheral neuritis.

4-Vitamin B6 (Pyridoxine):

Its deficiency leads to ulceration of the mouth and tongue, convulsions, dermatitis, peripheral neuritis and anemia.

5-Vitamin B12 and folic acid:

The main clinical manifestation of folate and B12 deficiency is megaloblastic anemia (see blood diseases)

II- VITAMEN C (ASCORBIC ACID)

Vitamin C concerned with the formation of intercellular material such as collagen, bone, and cartilage.

Effects of deficiency (Scurvy):

1- Impairment of bone formation
2- Irregular dentition.
3- Delayed wound repair.
4- Swelling of gums, bleeding, and ulceration.

III- VITAMEN A (RETINOL)

Deficiency causes hyperkeratosis and roughness of skin, night blindness, Keratomalacia and squamous metaplasia of epithelium of the bronchi and urinary system. Renal calculi can occur.

IV- VITAMEN D (CHOLECALCIFEROL)

Vitamin D deficiency leads to ***Rickets*** in **children** and to ***Osteomalacia*** in **adults**.

RICKETS:

A disease resulting in softening of bone from deficient deposition of calcium salts. Three forms of Rickets are known, infantile rickets, adolescent rickets, and renal rickets.

1-Infantile rickets:

Affects infants and children from 6 months to 2 years. Black races are more liable to disease, probably due to non-absorption of sun rays by their thick dark skin.

Pathology (Bone changes in rickets):

1- Swelling at the ends of bones at the epi-metaphyseal junction.
2- Broadening and irregularity of epiphyseal line.
3- Deformities in shape.

- In the *skull*, there is delayed closure of fontanels and deficient ossification of the vault (craniotabes).
- The teeth show delayed eruption, irregularity of edges, softening, and decay.

- The *thorax*: pigeon shaped appearance with thick prominent costochondral junctions *(Rachitic Rosary)*.
- The vertebral column shows *Scoliosis*.
- The *pelvis* assumes a (*trifoil appearance)* due to pressure of the heads of femora on the acetabula, pushing them onwards.
- The *lower limb* shows outward bend femurs, knock-knee and forward bent tibia *(bow legs)*.
- There is also splenomegally and abdominal distension.

2-Adolescent rickets:

This form occurs in children at ages of 9-12 years. It is due to relative deficiency of Vitamin D and calcium. The bone at this age is rapidly growing and the demand for Vitamin D is increased. The bony changes are the same as in infantile rickets.

3-Renal rickets:

This results from excessive secretion of calcium in urine in cases of chronic renal failure.

OSTEOMALACIA

Softening of bone occurs in adult female due to increased demand to Vitamin D, because of multiple pregnancy and lactation. The disease is common in poor classes.
Pathologically: there is failure of calcification and deformity in vertebrae, pelvis (trifoil), and limbs. Muscles are hypotonic and weak

V-VITAMIN K

It is concerned with production of prothrombin, and normal liver is necessary for its function.

Effects of deficiency:

1. Punctate hemorrhage in the skin and mucous membranes,
2. Decreased prothrombin formation in blood.
3. Prolonged clotting time.

Protein -Energy malnutrition (Marasmus, kwashiorkor)

Marasmus and kwashiorkor are part of a clinical spectrum of protein energy malnutrition. Kwashiorkor being the most extreme disorder, and affects infants and children.

Clinically: *the developmental effects can be seen as:*

- Growth retardation
- Immunologic deficiency
- Intellectual impairment.
- Extreme wasting
- Generalized oedema
- Fatty liver due to abnormal fat metabolism
- Rashes and increased desquamation of the skin.

NB:

1-Young children tend to be more affected mainly in the developing countries including Egypt.

2- The common cause of death is secondary bacterial infection.