

# *Neoplasia*

# Neoplasia

- “New growth”
- Neoplasm = tumor (swelling in inflammation initially)
- Greek word; Neo=New+ plasma=thing formed
- Oncology (Greek, oncos=tumor) = study of tumor or neoplasm

# Neoplasm

## According to Willis Definition:

A neoplasm is "an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the change."

# Neoplasia

- Disorder of cell growth that is triggered by a series of acquired mutations affecting a single cell and its clonal progeny.

# Tumor

- Clonal proliferation
- Autonomous growth
  - Independent of physiologic growth stimuli

# Types

- Benign neoplasm
- Malignant neoplasm

# Benign tumour

- Localized
- Does not spread
- Very good prognosis and Surgical removal is curative
- Well differentiated: cells closely resemble their tissue of origin.

# Malignant tumour

- “Cancer”
- Invade and destroy adjacent structures
- Spread to distant sites (metastasis)  
exception: Basal cell carcinoma which is rarely metastasize to distant site And Glioma is malignant tumor of CNS.
- Tumors cause Death

# Components of tumour

## Parenchyma – neoplastic cells

Cell type:

- Epithelial origin
- Mesenchymal origin

## Non neoplastic stroma

Supportive connective tissue and blood vessels and cells of immune system

Desmoplasia- abundant fibrocollagenous stroma in tumour-- hard consistency  
“schirrhous”

# Nomenclature : Benign tumours

- Suffix –**oma** added to the parenchymal cell type

## Mesenchymal tumours

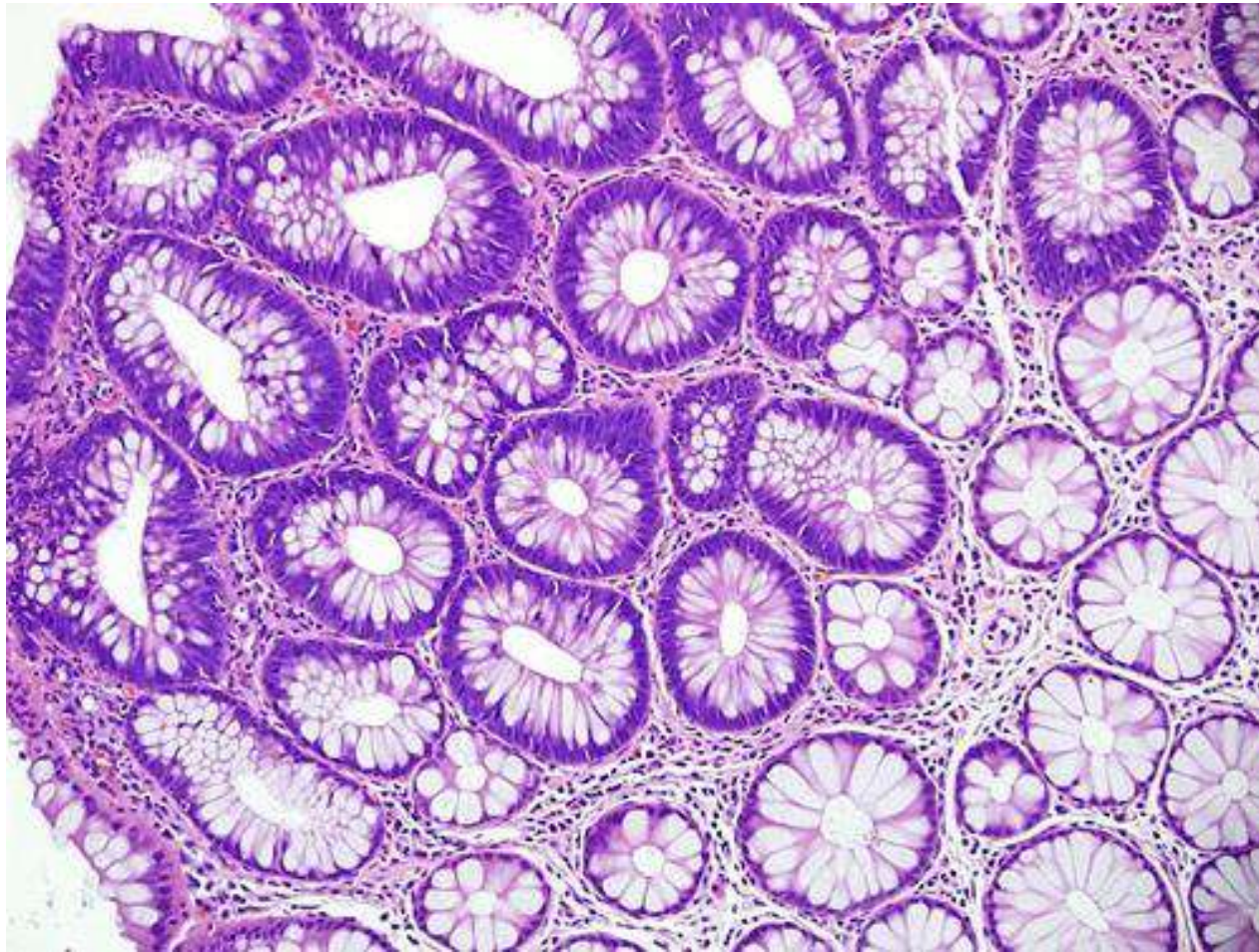
- Fibrous tumour(fibroblasts)- fibr**oma**
- Cartilage(chondrocytes)-chondr**oma**
- Bone tumours(osteocytes)-oste**oma**

# Nomenclature : Benign tumours

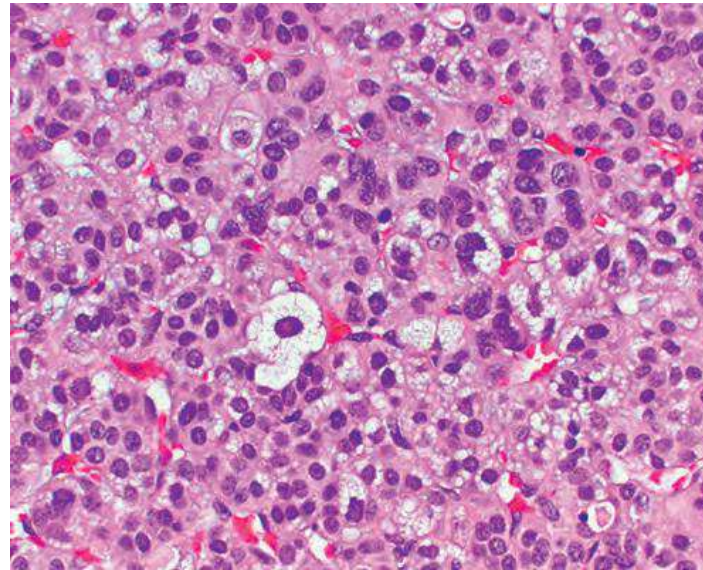
## Epithelial tumours

1. Derived from glands-- Adenoma
  - Microscopy:- glandular pattern may or may not be present
  - GI epithelial tumours e.g. Colonic adenoma- glandular pattern arrangement
  - Adrenal gland tumour e.g. Adrenocortical adenoma- solid sheet pattern

# Adenoma -- benign epithelial tumour arranged in glandular pattern



# Adrenocortical adenoma



# Nomenclature : Benign tumours

❑ Based on morphology (gross and microscopic features)

## 2. Papillomas

Gross: Tumour with finger like projections;

Microscopy- finger like projections lined by epithelium with fibrovascular core

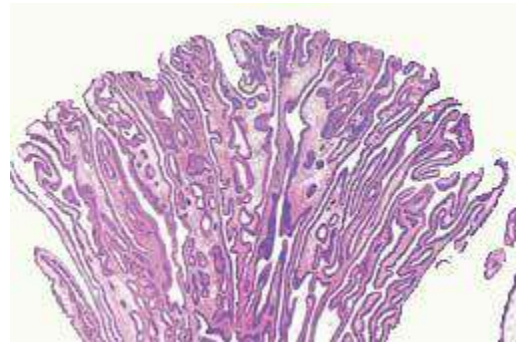
## 3. Cystadenoma

Tumour derived from glands with cystic appearance

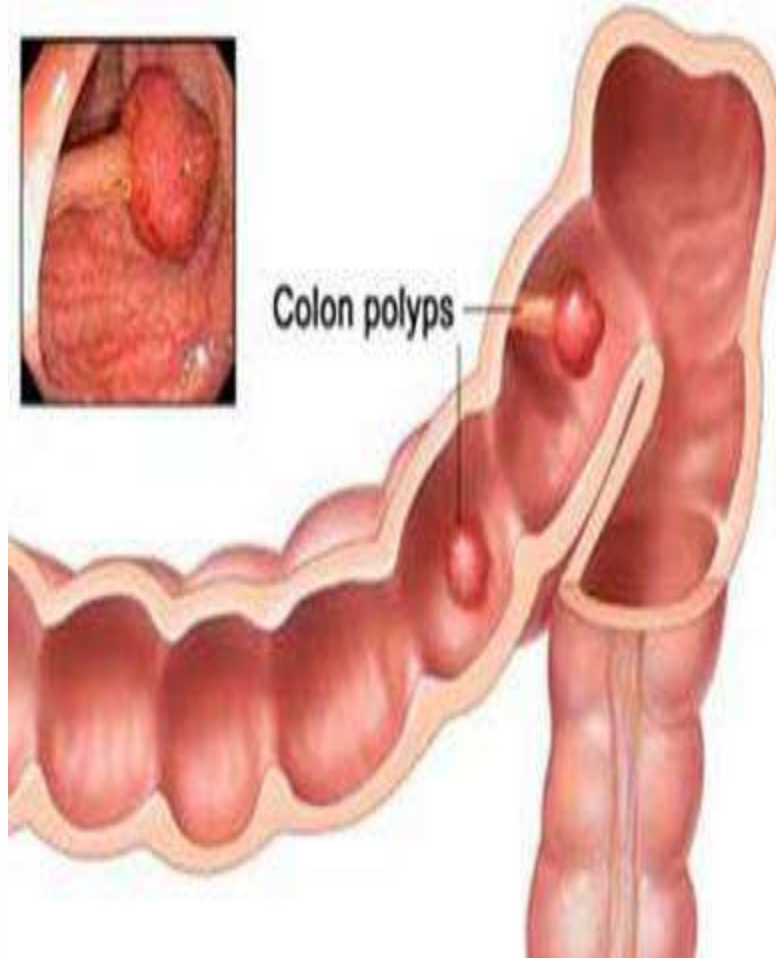
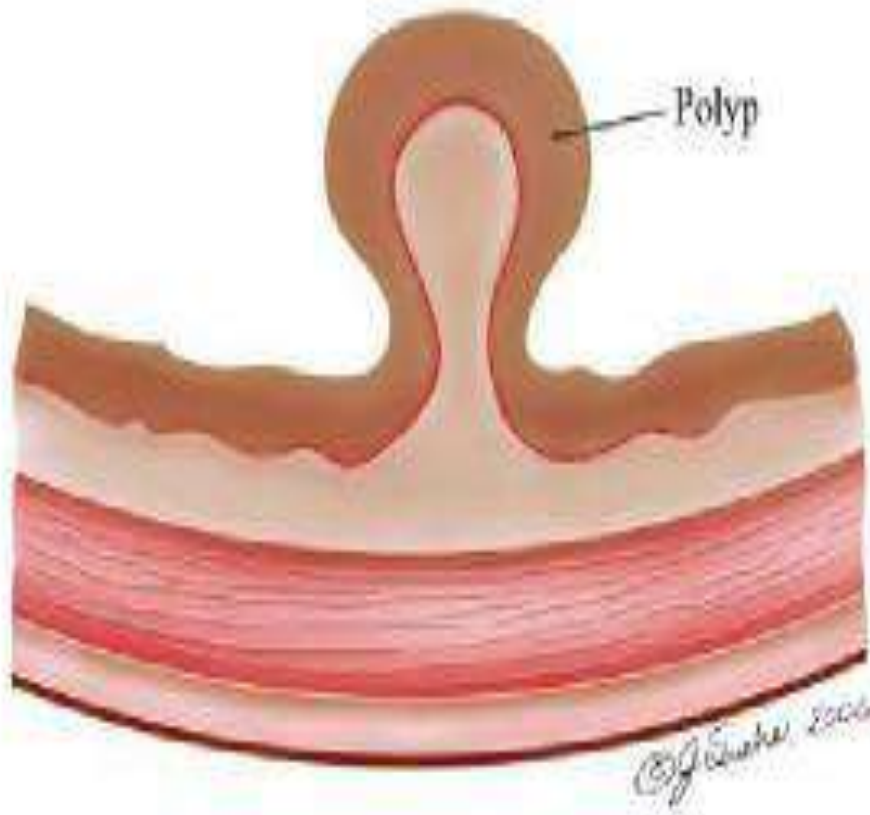
## 4. Polyp

Gross:- mass that projects above a mucosal surface  
e.g. colonic polyp.

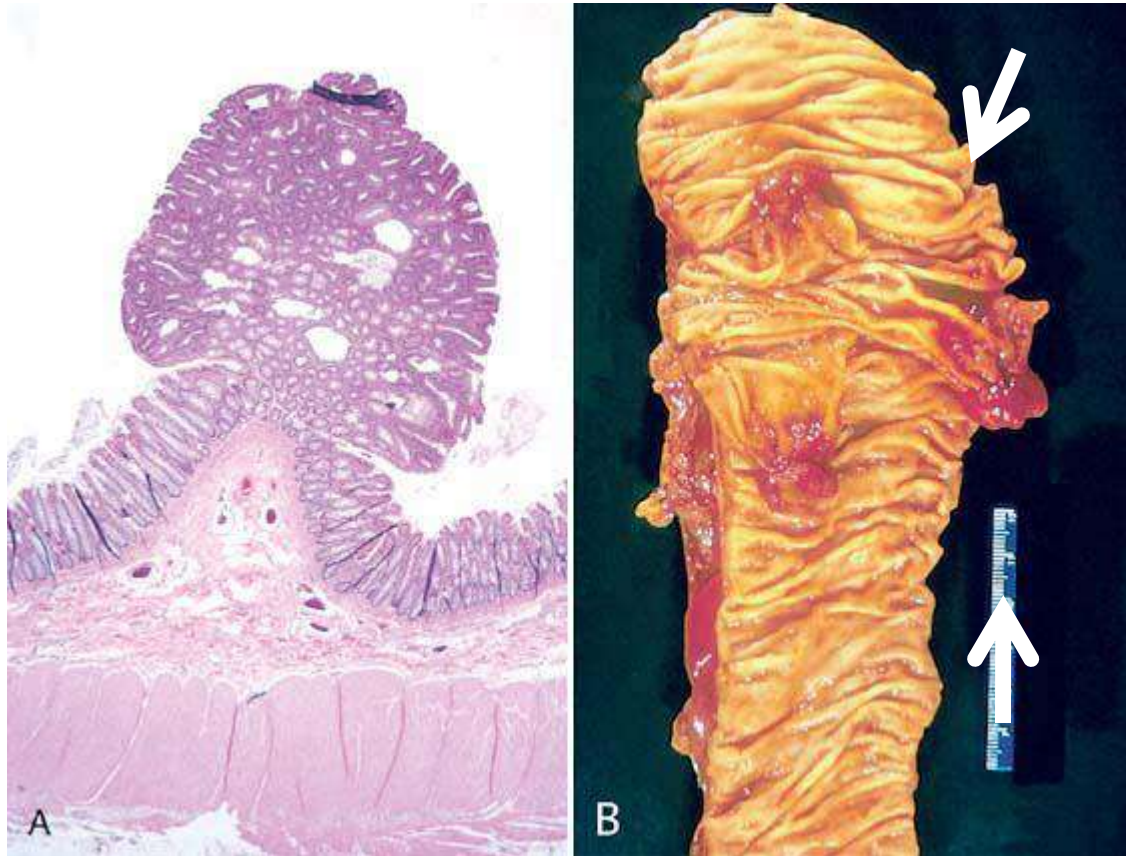
# Papilloma of the colon



# Polyp



# Colonic polyp

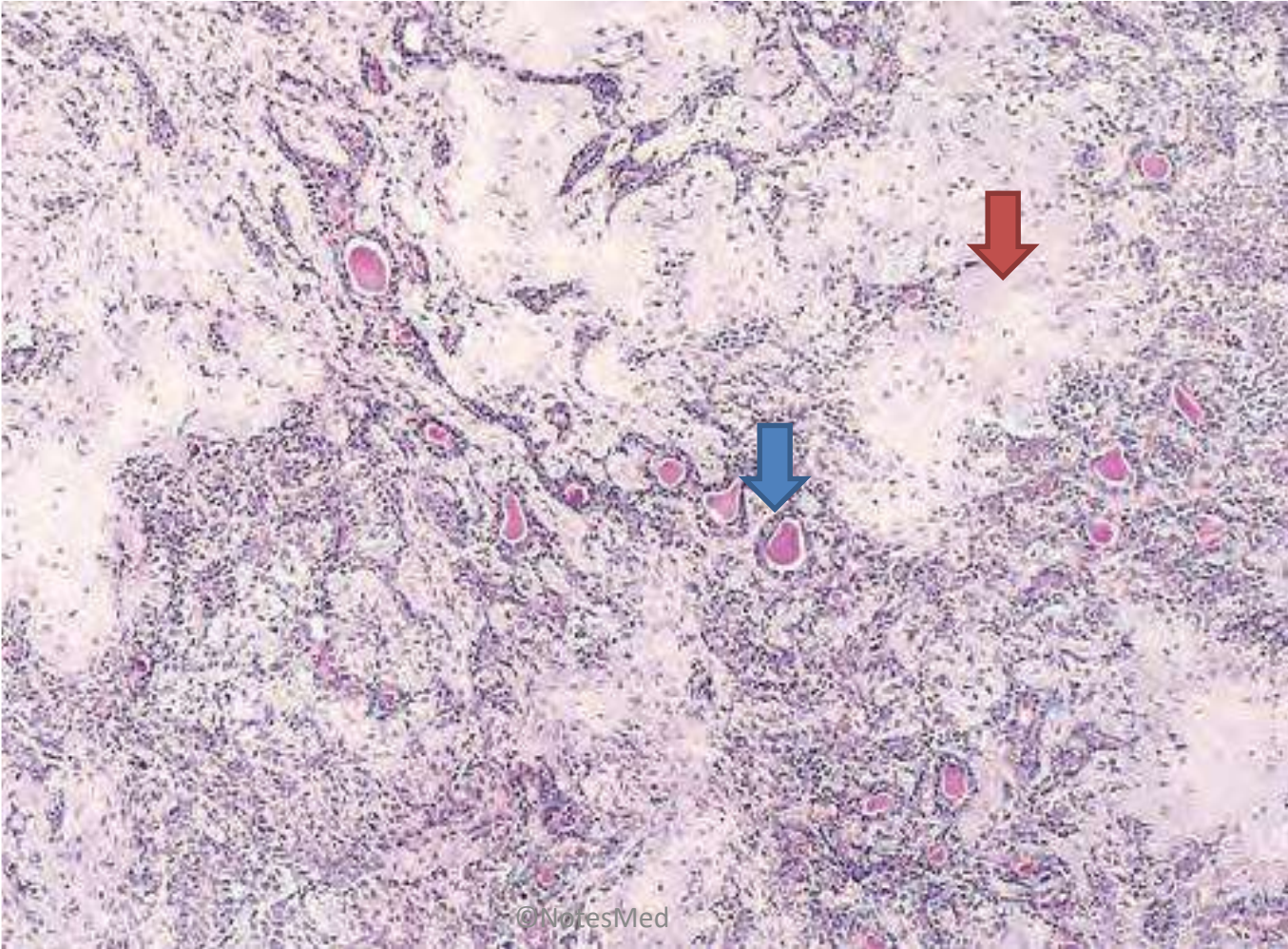


# Nomenclature : Benign tumours

## Mixed tumour

- Arise from single neoplastic clone that differentiate into two different lineages
  - E.g. pleomorphic adenoma of salivary gland
  - Composed of neoplastic epithelial and mesenchymal component (bone, cartilage)
  - Derived from single germ cell layer

# Mixed tumour- pleomorphic adenoma



# Nomenclature : Benign tumours

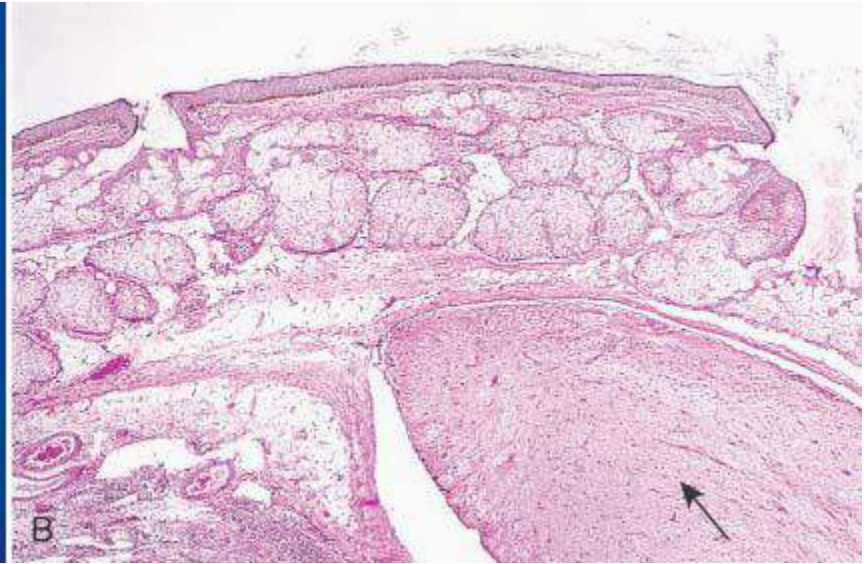
## Teratoma

- Tumour arising from totipotential stem cells that can differentiate into different cell types representing the derivatives of more than one germ layer
- Present in ovary, testes or abnormally sequestered in midline embryonic rests

❖ **Mature Teratoma- benign**

❖ **Immature teratoma- malignant**

# Teratoma, ovary



# Nomenclature : Malignant tumours

- Epithelial cell origin-**Carcinoma**
  - Derived from glands - **Adenocarcinoma**
- Organ or tissue origin added
  - Gastric adenocarcinoma
  - Renal cell adenocarcinoma
- Squamous cell origin
  - Squamous cell carcinoma
- Transitional cell origin
  - Transitional cell carcinoma

# Nomenclature : Malignant tumours

- Epithelial cell origin-**Carcinoma**
- Cell or tissue type difficult to identify due to poor differentiation-
  - Undifferentiated **carcinoma**
  - Poorly differentiated **carcinoma**

# Nomenclature : Malignant tumours

- Mesenchymal origin: **Sarcoma**
  - Bone – **osteosarcoma**
  - Cartilage- **chondrosarcoma**
  - Fibrous tissue- **Fibrosarcoma**

# Nomenclature : Malignant tumours

- Derived from blood forming cells
  - Leukemia
  - lymphoma

Tissue of origin	Benign	Malignant
Composed of one parenchymal cell type		
Mesenchymal origin		
Connective tissue	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	chondrosarcoma
	Osteoma	Osteosarcoma
Blood vessels	haemangioma	Angiosarcoma
Smooth muscle	Leiomyoma	Leiomyosarcoma
Skeletal muscle	Rhabdomyoma	Rhabdomyosarcoma

Tissue origin	Benign	Malignant
Tumours of epithelial origin		
Stratified squamous	Squamous papilloma	Squamous cell carcinoma
Epithelial lining of glands and ducts	adenoma	adenocarcinoma
	Papilloma	Papillary carcinoma
	Cystadenoma	Cystadenocarcinoma
Respiratory airways	Bronchial adenoma	Bronchogenic carcinoma
Renal tubules	Renal tubular adenoma	Renal cell carcinoma
Liver hepatocytes	Hepatic adenoma	Hepatocellular carcinoma
Urothelial tract lining epithelium	Transitional papilloma	Transitional cell carcinoma

# Nomenclature : Malignant tumors

- Malignant tumors with suffix-**oma**
  - Lymphoma- lymphoid malignancy
  - Mesothelioma- mesothelial cells lining the serous cavities
  - Melanoma– melanocytic origin
  - Seminoma – malignant germ cell tumour of testis

# Not all lesions with suffix –oma are tumors

- **Choristoma**

- Heterotopic rest of cells
- i.e. normal cells but present in the tissue other than its usual site
- e.g. ectopic pancreatic tissue in the stomach

- **Hamartoma**

- Disorganized tissue indigenous to the particular site
- Previously- malformation—now, neoplasm
- e.g. lung hamartoma
  - Nodule in the lung containing mature cartilage, bronchi, and blood vessels

# Characteristics of benign and malignant neoplasms

- Differentiation and anaplasia
- Local invasion
- Distant metastasis

# Differentiation

Refers to extent or degree of  
Morphologic and functional resemblance of  
the neoplastic cell to the corresponding normal  
cell

Well  
differentiated

Moderately  
differentiated

Poorly  
differentiated

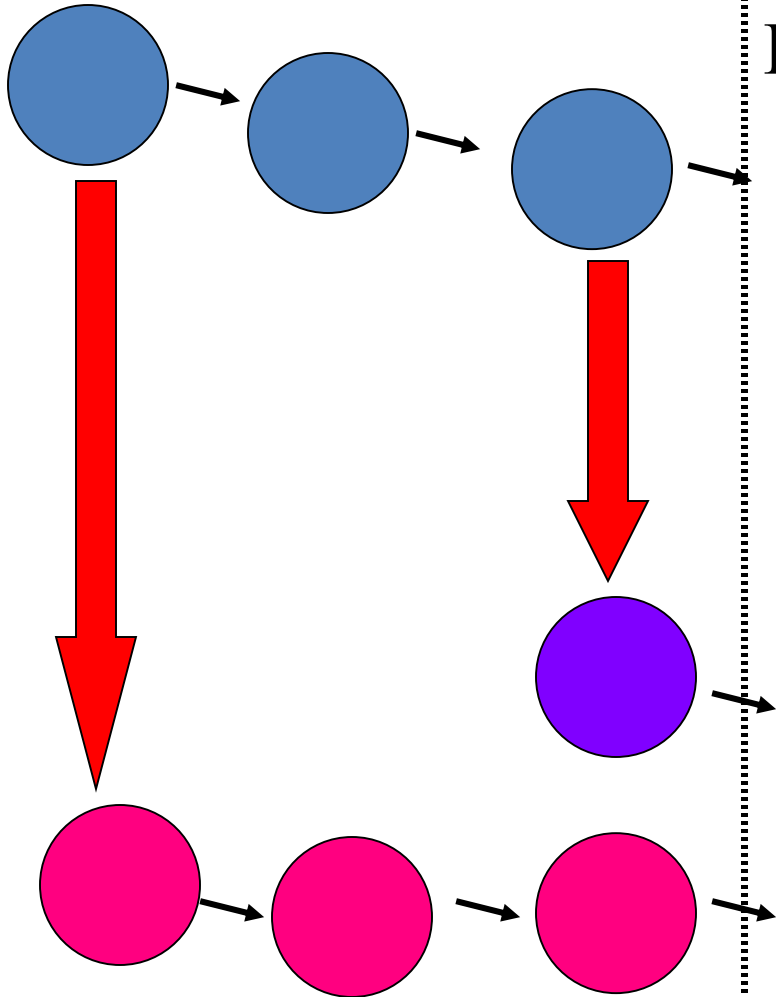
# Differentiation

- **Benign tumor**
  - Well differentiated
  - Individual cell resemble normal cells
  - Presence of discrete mass that differentiate it from normal tissue
  - Mitoses- scanty

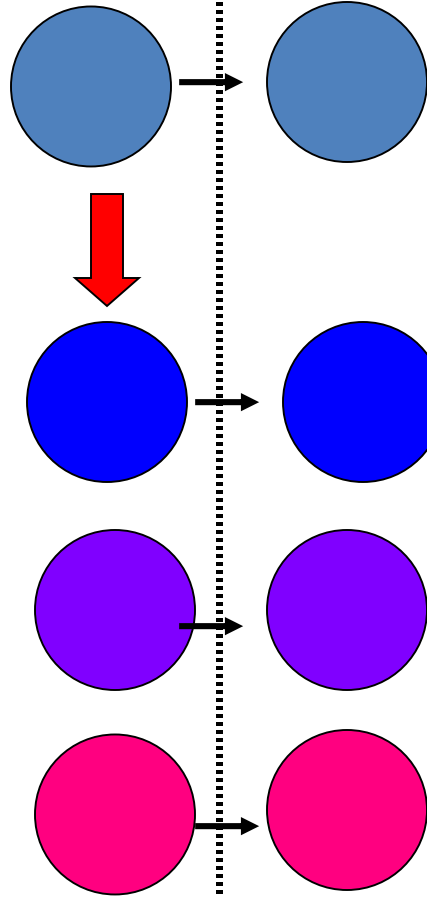
# Differentiation

- Malignant tumour
  - Well to poorly differentiated or undifferentiated
  - Anaplasia- poorly differentiated
    - Lack of differentiation

Stem cell



Differentiated



Post mitotic

Normal  
senescent  
differentiated  
cell

**Benign  
tumor**

**Grade 2  
malignancy**

**Grade 3 or 4  
malignancy**

# Anaplasia : Morphologic changes

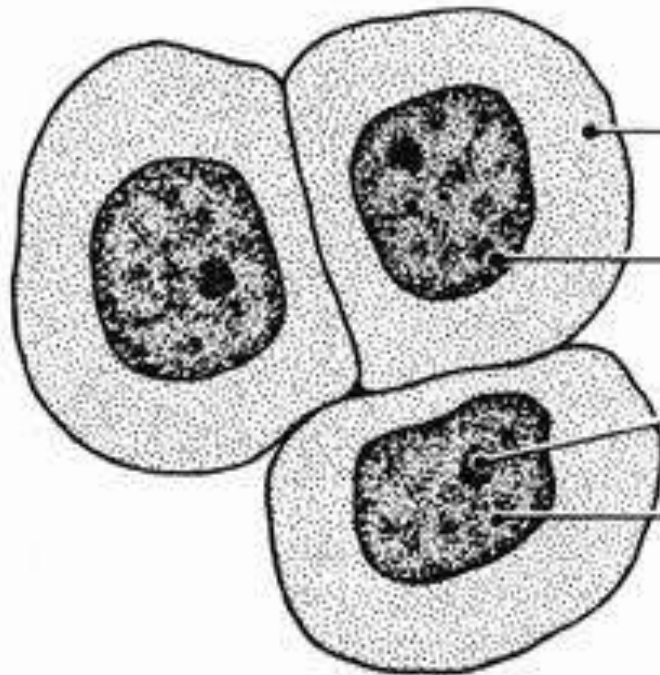
1. Pleomorphism- variable size and shape
2. Abnormal nuclear morphology
  - ↑ N:C ratio- 1:1 (normal 1:4 to 1:6)
  - Nuclear membrane- usually irregular
  - Hyperchromatic nuclei-- increased chromatin content and dark staining
  - Chromatin – coarse clumping
  - Nucleolus- prominent

# Anaplasia : Morphologic changes

3. Loss of polarity
  - orientation of cells are disturbed
4. Mitoses
  - Increased number
  - Abnormal mitotic figures e.g. tripolar, quadripolar
5. Tumour giant cells- huge single irregular nucleus or multinucleated cells
6. Ischemic necrosis

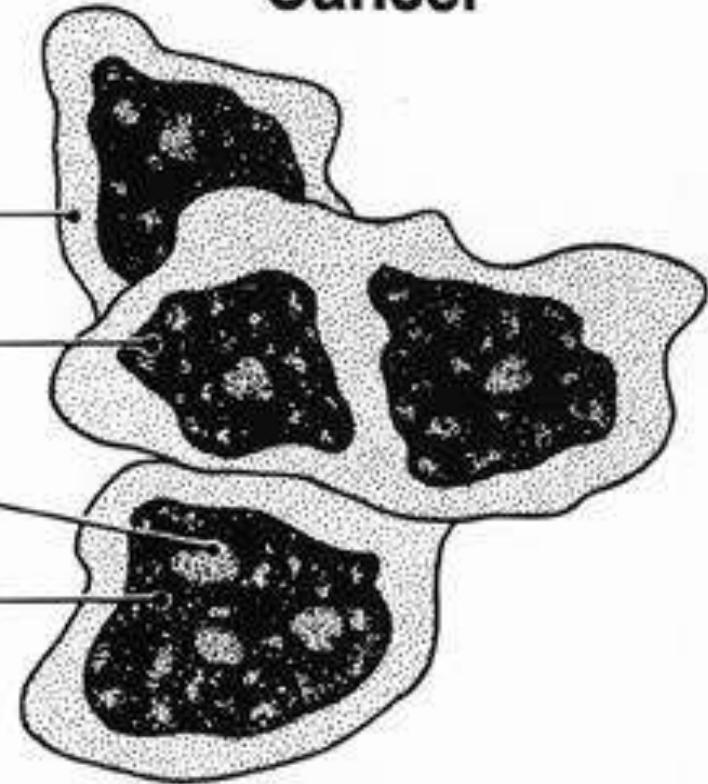
# Normal and Cancer Cells Structure

## Normal



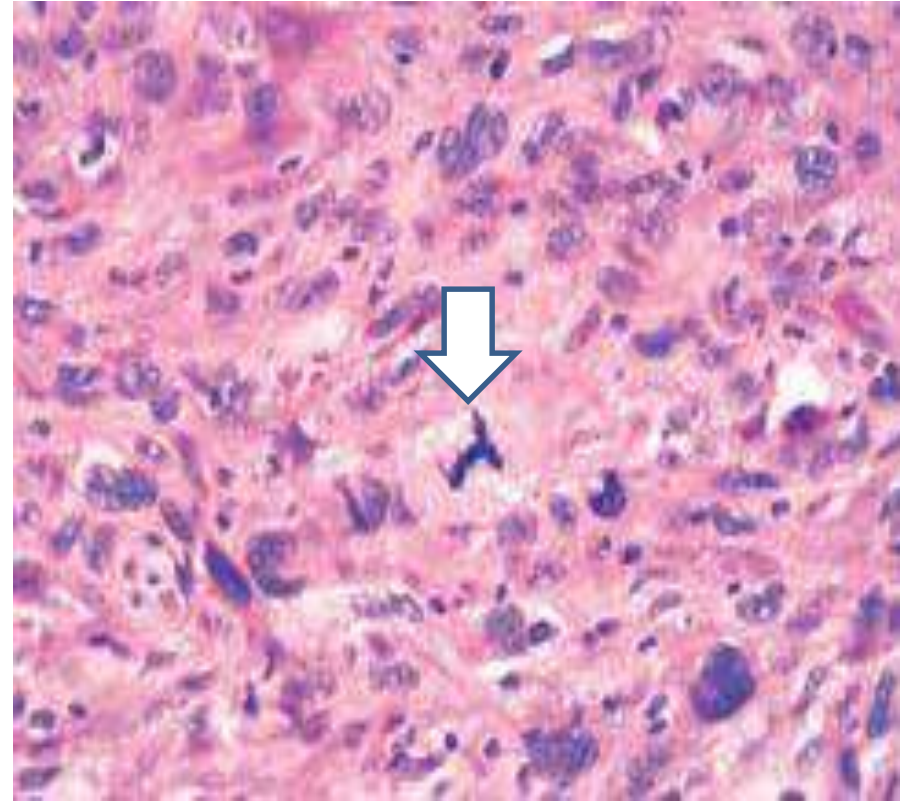
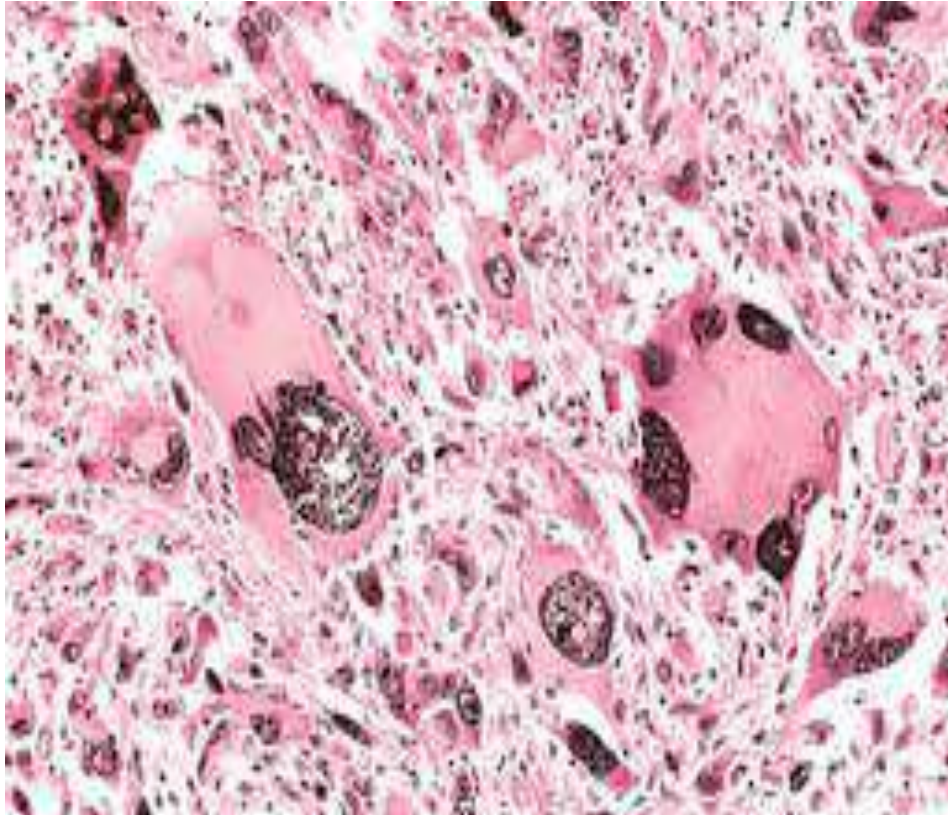
- Large cytoplasm
- Single nucleus
- Single nucleolus
- Fine chromatin

## Cancer



- Small cytoplasm
- Multiple nuclei
- Multiple and large nucleoli
- Coarse chromatin

# Anaplasia



- Functional capacities decreases with less differentiation
  - Well differentiated tumour-
    - e.g. Benign and well differentiated malignant endocrine tumour- secrete hormone
    - Well differentiated squamous cell carcinoma- keratin synthesis- keratin pearl formation
  - Poorly differentiated malignancy-
    - loss of normal function
    - May acquire new function
      - e.g. express fetal proteins –  $\alpha$ -fetal protein by malignant hepatocytes
    - e.g. bronchogenic carcinoma producing ACTH

# Dysplasia

- **Disordered growth confined to the epithelium**
  - **Disoriented architectural pattern**
  - **loss in the uniformity of the individual cells**

# Dysplasia: morphology

- **Pleomorphism**
- **large hyperchromatic nuclei with a high N:C ratio**
- **Architectural disorientation**
  - Loss of polarity
  - Maturation defect
- **↑ ↑ normal mitotic figures present at abnormal locations within the epithelium**

# Dysplasia

Depending upon the severity

- Mild
- Moderate
- Severe

# Dysplasia:- carcinoma in situ

- Severe form of dysplasia involving entire thickness of the epithelium
- Preneoplastic lesion
- ❖ Penetration of the basement membrane by neoplastic cells and invasion into the underlying stroma

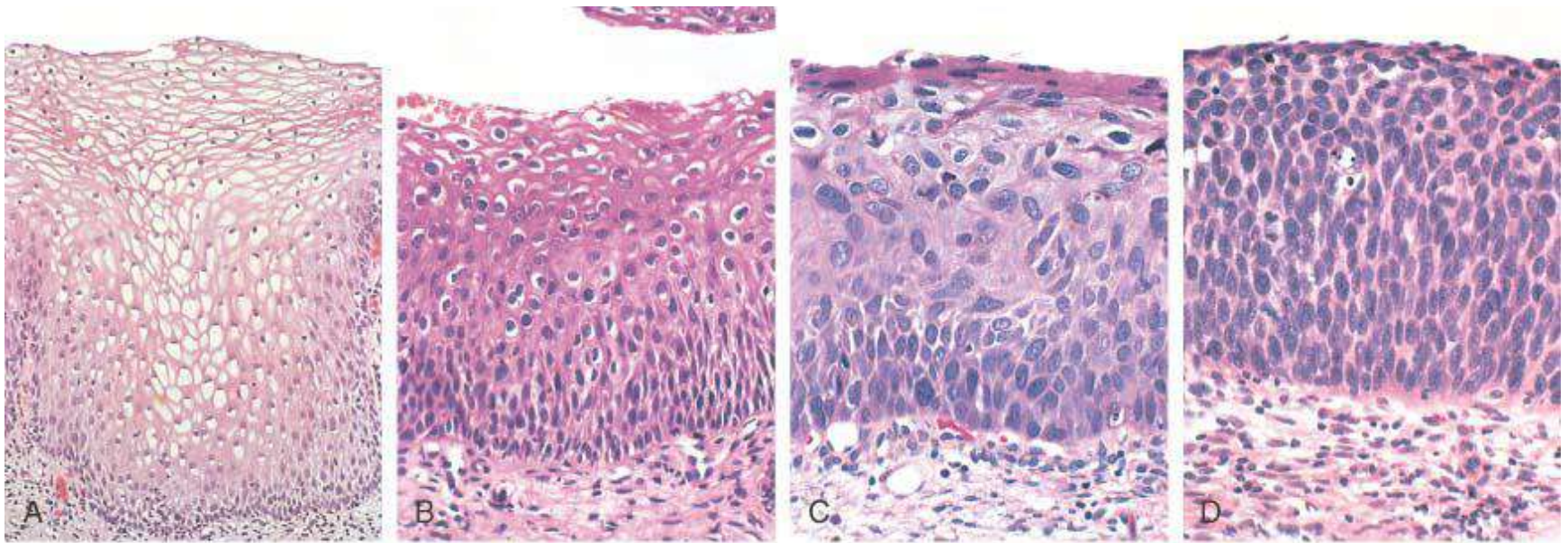


Invasive carcinoma

# Dysplasia

- Dysplastic lesions are usually present adjacent to invasive carcinoma
- Not all dysplastic lesion progress to malignancy
- Mild and moderate dysplasia may revert back to normal if stimulus is removed

# Dysplasia



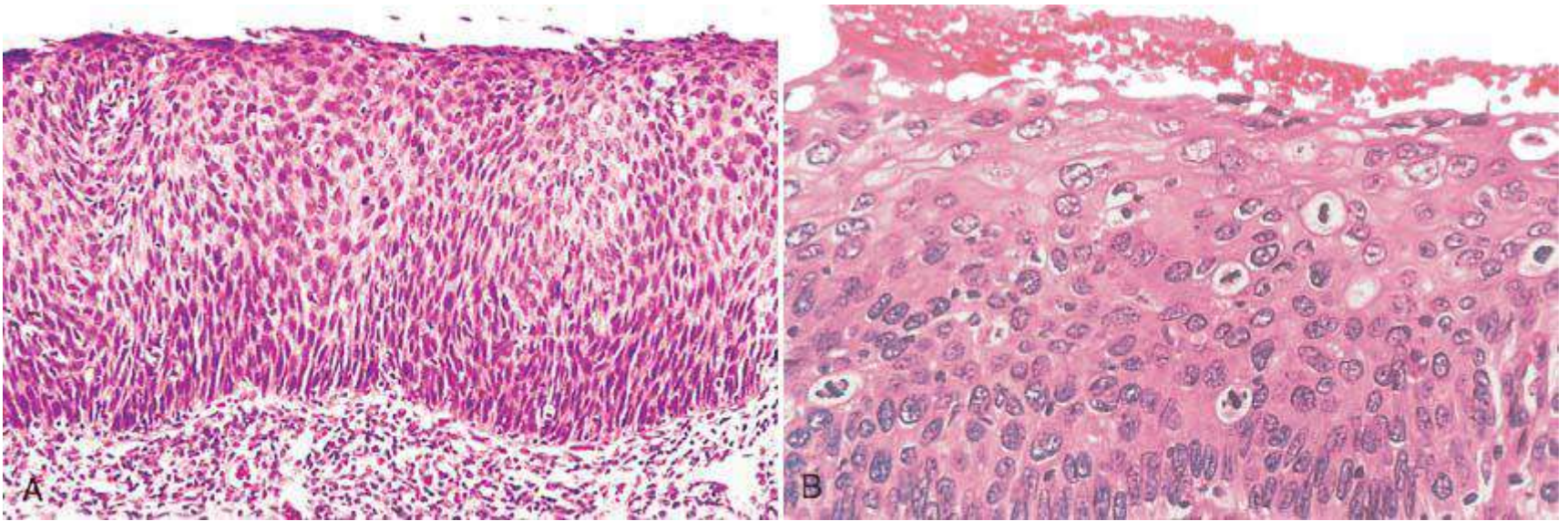
Normal

CIN I

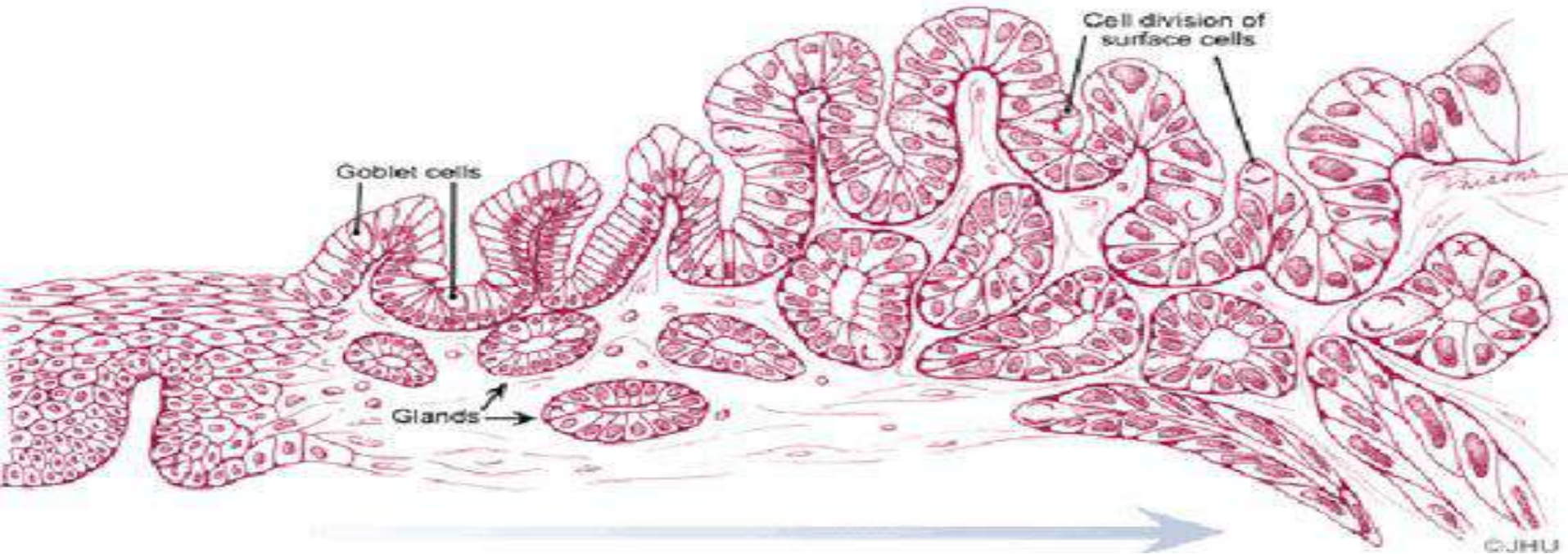
CIN II

CIN III

# Carcinoma in situ



# sequence of events in development of cancer e.g oesophageal cancer



Normal  
squamous cell



columnar  
metaplasia



Dysplasia



cancer

# Rate of growth

- Growth rate may not be constant
- Benign tumours- - grow slowly
- Malignant tumours- wide range of growth; common- rapid growth
- Factors affecting growth
  - hormonal stimulation
  - Blood supply
- Cancer stem cells- tumour initiating cells

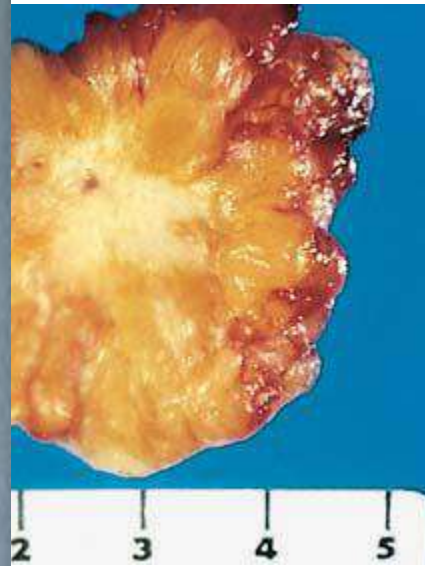
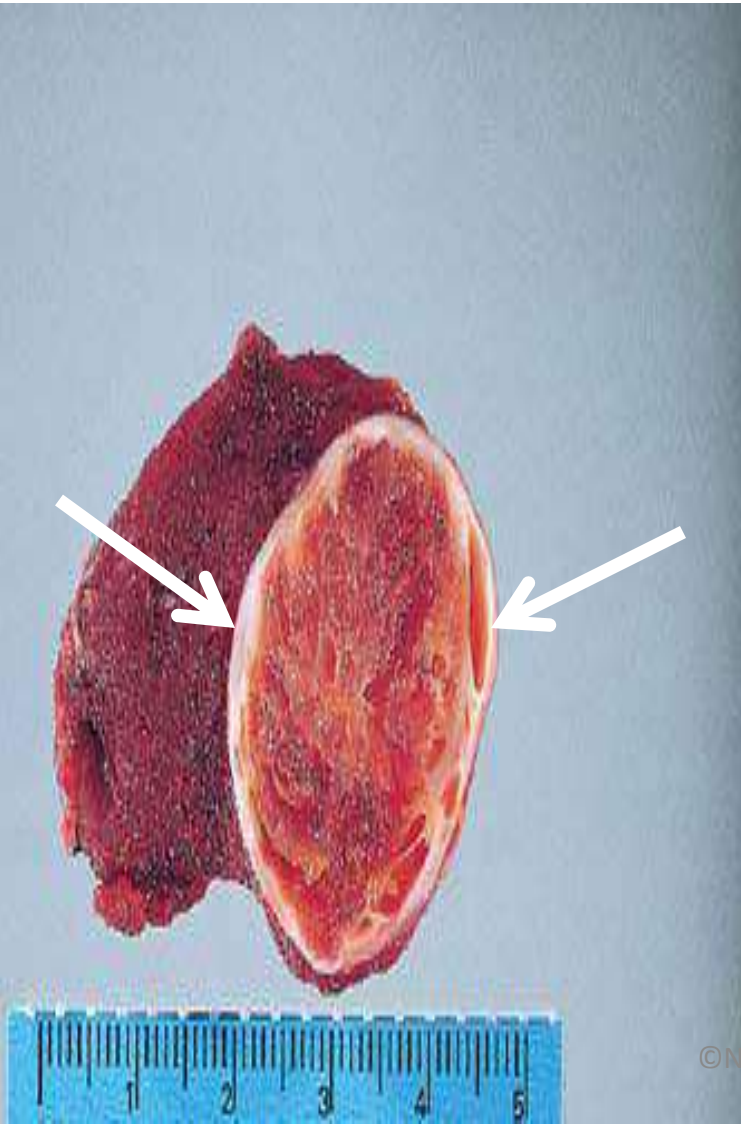
# Local invasion

- **Benign tumours**
  - **No invasion or infiltration**
  - **Localized**
  - **Encapsulated**
    - **Derived from connective of the native tissue**
  - **Capsule makes tumour a discrete, well circumscribed, easily palpable mobile mass**
  - **surgically enucleated**
- **Capsule may be lacking in some tumours**

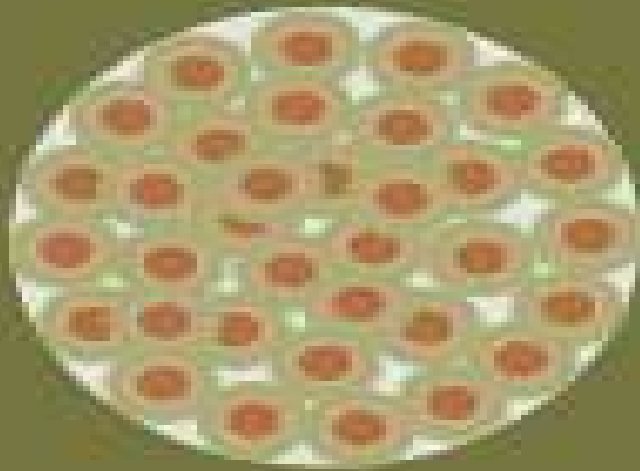
# Local invasion- Malignant tumours

- Locally invasive with destruction of surrounding tissue
- Poorly demarcated from surrounding tissue with irregular margin
- Slowly growing- pseudoencapsulated or pushing margin infiltrating adjacent tissue
- Surgical removal quite difficult

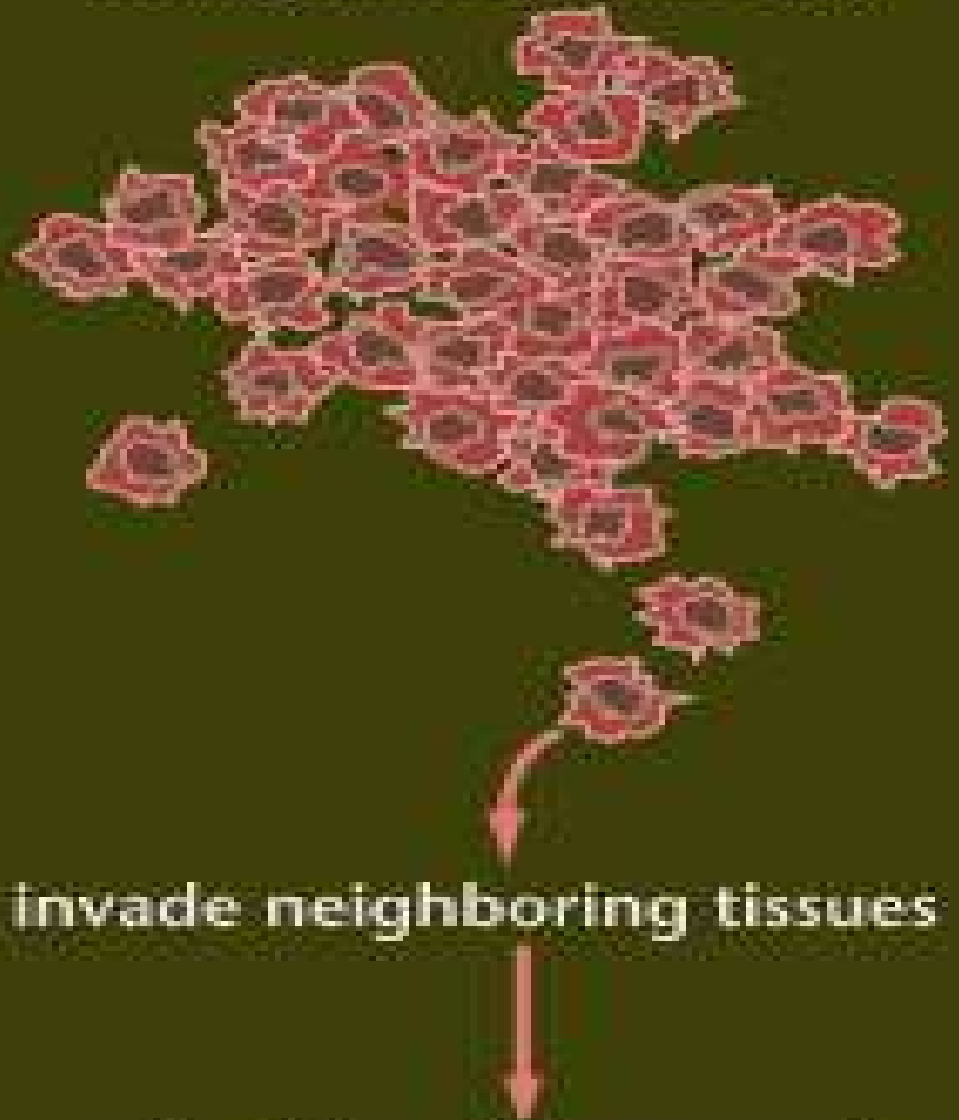
# Benign and malignant tumour



## Benign



## Malignant (Cancer)



invade neighboring tissues

enter bloodstream and metastasize to different sites

# Local invasion



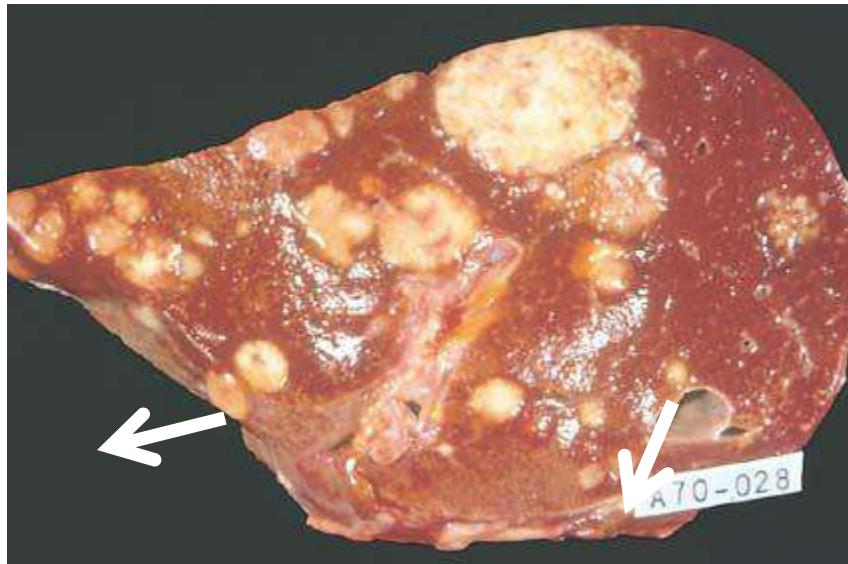
# Metastases

- Spread of tumour to a site, physically discontinuous with the primary tumour
- Most cancers have capacity to metastasize
- Larger and undifferentiated rapidly growing -- more likely to metastasize
- mostly incurable

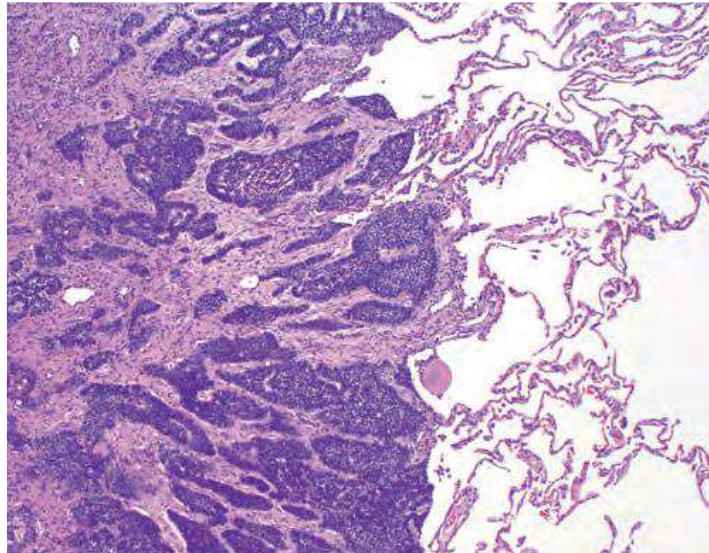
# Metastasis: Pathways of Spread

1. Seeding of body cavities and surfaces e.g. ovarian tumour seeding over the peritoneal surface
2. Lymphatic
  - Carcinomas more common
  - Regional lymph nodes involved
3. Haematogenous
  - Sarcomas but also carcinomas
  - Usual initial involvement – Liver , lung

# Metastases to liver



# Metastasis of colonic cancer in lung

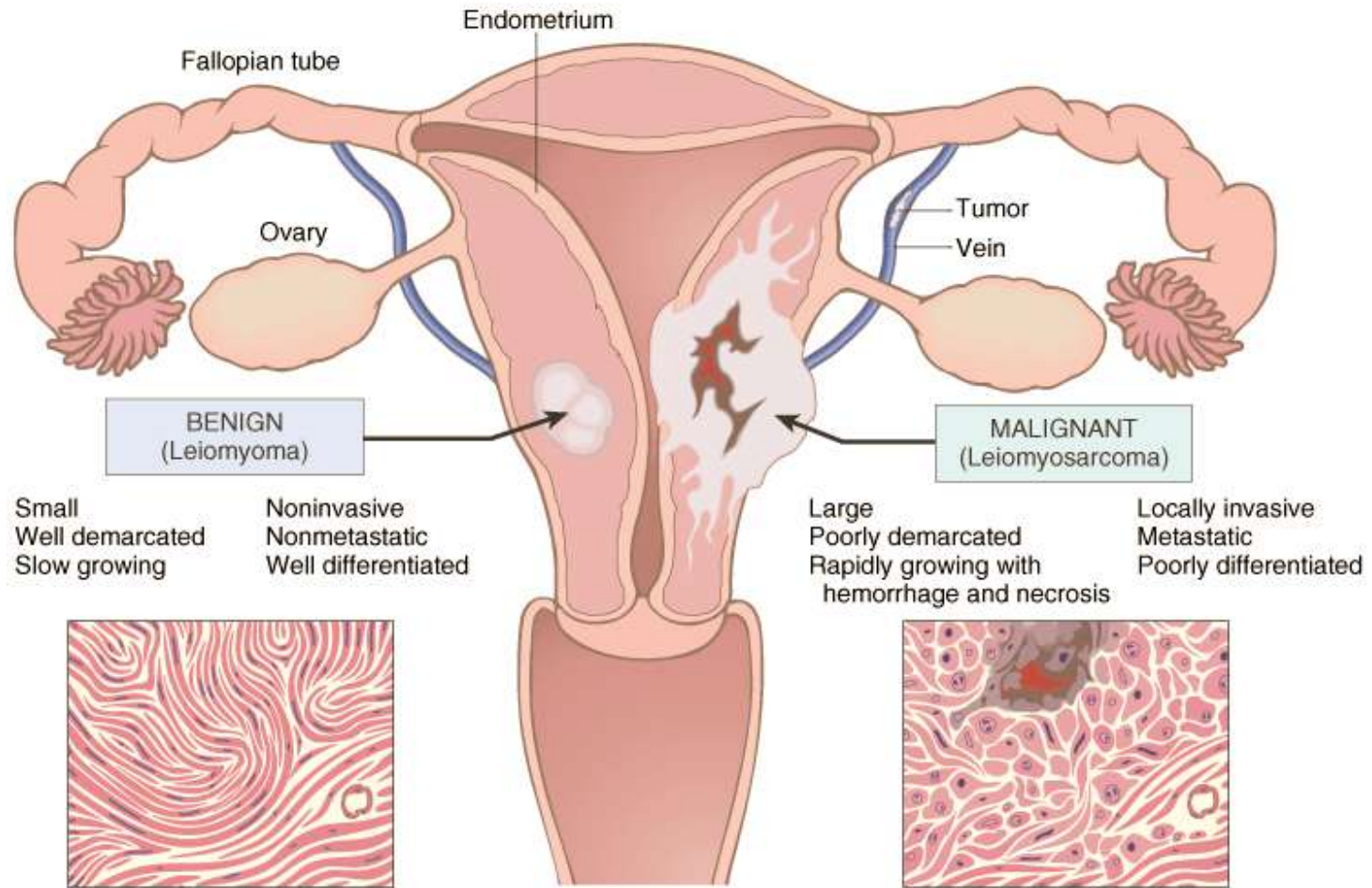


Distinguishing Features	Benign	malignant
Rate of growth	Slow growing	Slow to rapid growing
size	Smaller	Usually large at presentation
Function	retained	Lost in poorly differentiated tumour or acquire new function
Local invasion	absent	Locally invasive
Capsule	Usually encapsulated	absent
Margin	Well circumscribed	Poorly circumscribed; irregular margin

Distinguishing features	Benign	Malignant
Degree of differentiation	Well differentiated	Poorly differentiated ; undifferentiated
Pleomorphism	Absent	Present
N:C ratio	normal	Increased
Nuclear features: Chromatin	Fine chromatin	Hyperchromatic,  Coarsely clumped
nucleolus	inconspicuous	prominent
Mitotic activity	Absent or low	Increased with often abnormal mitotic figures

<b>Distinguishing features</b>	<b>Benign</b>	<b>Malignant</b>
Loss of polarity(epithelial tumours)	No	Yes
Necrosis and haemorrhage	Absent	Usually present
Distant metastasis	Never	Frequently present

# Benign and malignant tumours



# Cancer: Epidemiology: Incidence

	Developed countries	Developing countries
<b>Men</b>	Prostate	lung
	Lung	Stomach
	Colorectum	liver
<b>Women</b>	Breast	Breast
	Lung	Cervix
	colon and rectum	Lung

# Neoplasia: Predisposing factors

- Geographic and environmental factors
- Age
- Genetic factors
- Acquired predisposing conditions

# Geographic and environmental factors

- **Geographic variation**

- stomach carcinoma is 7-8x higher in Japan>>> US
- carcinoma of the lung-US>> Japan
- Developed countries- men – prostate; female– breast
- Developing countries- men-- liver stomach, bladder; female– breast cancer incidence less than in developed countries

# Environmental factors

- **Exposure to Carcinogens**
  - occupational exposure- asbestosis- mesothelioma
  - Diet, alcohol, cigarette smoking
  - Infection- viral– HPV infection and cervical cancer
  - Radiation
  - Chemical agents, drugs
- Obesity
- Reproductive history: exposure to estrogen stimulation - breast and endometrial cancer

# Age

- Cancers—commonly in the elderly age group (>55 years)
- common neoplasms of infancy and childhood
  - leukaemias
  - primitive tumours of CNS -small round blue cell tumors e.g. retinoblastoma

# Genetic factors

- Hereditary

3 categories

1. Autosomal Dominant Inherited Cancer Syndromes
2. Autosomal recessive syndromes of Defective DNA-Repair
3. Familial Cancers

# Autosomal Dominant Inherited Cancer Syndromes

- Autosomal dominant inheritance
- Inheritance of single mutant gene  
e.g RB gene – retinoblastoma,  
osteosarcoma
- Specific marker phenotype
  - Nonneoplastic markers-- café au lait spot  
in neurofibromatosis type I

# Familial cancers

- No clearly defined inheritance pattern
- Onset-- early age
- Tumours in two or more close relatives
- multiple or bilateral tumors
- No specific marker phenotype
- E.g. breast cancer

# Genetic predisposition to cancer

- Hereditary forms of cancers- Only 5 – 10% of all cancers
- Interaction between environmental and inherited factors
  - Genetic predisposition -- ↑ risk of development of **environmentally induced cancers**
- e.g. lung cancer in **chronic smoker** increased if
  - **Genetic polymorphism** in drug metabolizing enzymes- p450-- converts procarcinogens into carcinogens
  - Genetic variants - nicotinic acid receptor

# Acquired predisposing conditions

- Clinical conditions prone to develop into cancer
  - **Chronic inflammations**
  - **Precursor lesions**
  - **Immunodeficiency states**
- FERTILE SOIL for malignant transformation
- Proliferating cells - at risk for accumulating the genetic lesions → carcinogenesis

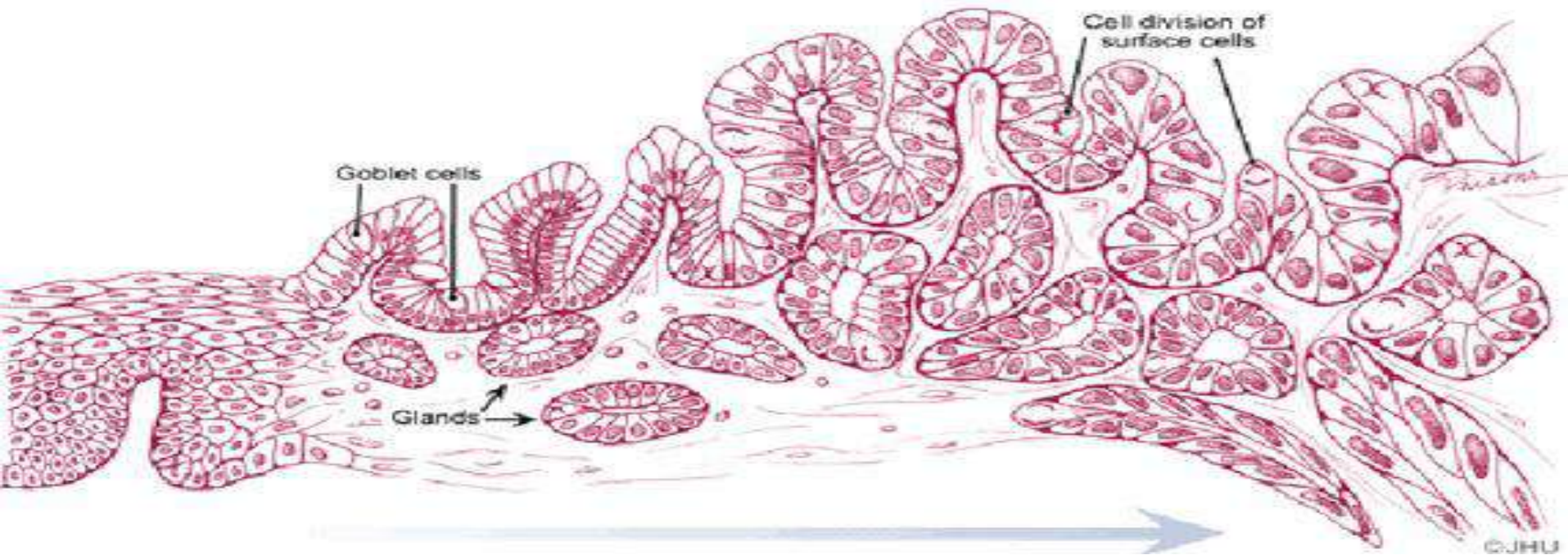
# Acquired predisposing conditions: Chronic inflammation

- Chronic inflammation
  - Tissue injury → repair- proliferation of cells
  - ↑ pool of stem cells– malignant transformation
  - Inflammatory cells
    - ROS—genotoxic
    - Inflammatory mediators → promote survival of mutated cells
  - Metaplasia → long term → survival of cells with oncogenic mutations → cancer

# Precursor lesions

- localized morphologic changes associated with a high risk of cancer
- Epithelial lesions → carcinoma
- Metaplasia, dysplasia, hyperplasia, some benign tumours

# sequence of events in development of cancer e.g oesophageal cancer



Normal  
squamous cell



columnar  
metaplasia



Dysplasia



adenocarcinoma

	<b>Acquired predisposing conditions</b>	<b>Cancer</b>
<b>1. Chronic inflammation</b>	Chronic atrophic gastritis	Gastric carcinoma
	Hashimoto thyroiditis	Lymphoma
<b>2. Precursor lesions</b>	Atypical endometrial hyperplasia	Endometrial carcinoma
	Barrett esophagus (intestinal metaplasia)	Adenocarcinoma of esophagus
	Villous adenoma of colon (benign neoplasm)	Colonic adenocarcinoma

# "What is the risk of malignant change in a benign neoplasm?"

- ?? Precancerous
- The answer is “NO”
- Exceptions exist
- Each type of benign tumor is associated with a particular level of risk, ranging from high to virtually nonexistent

# Acquired predisposing conditions: immunodeficiency states

- Deficits in T-cell immunity--↑ risk for cancers
- caused by oncogenic viruses
  - Lymphoma--e.g. EBV-- lymphomas
  - Carcinomas- e.g. HPV- cervical carcinoma
  - Sarcoma- KSHV- Kaposi sarcoma

# Molecular basis of carcinogenesis

- **Nonlethal genetic damage → carcinogenesis**
- The initial damage (or mutation) ---may be due to
  - environmental factor (carcinogens)– viruses, chemical, radiation (somatic mutation)
  - Germline mutation
  - spontaneous and random

## Somatic mutations

- Occur in nongermline tissues
- Are nonheritable



Nonheritable

Somatic mutation  
(e.g., breast)

## Germline mutations

- Present in egg or sperm
- Are heritable
- Cause cancer family syndrome



Mutation in  
egg or sperm

All cells  
affected in  
offspring

# Tumors Are Clonal

Normal cell



First mutation



Second mutation



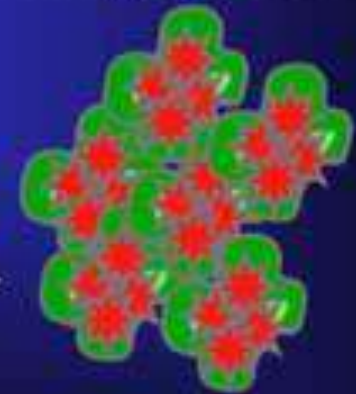
Third mutation



Fourth or later mutation



Malignant cells



Adapted by American Society of Cell Biology

# The principal targets of genetic damage “*Normal regulatory genes*”

1. Growth-promoting protooncogenes

2. Growth-inhibiting tumor suppressor genes

3. Genes that regulate programmed cell death (apoptosis)

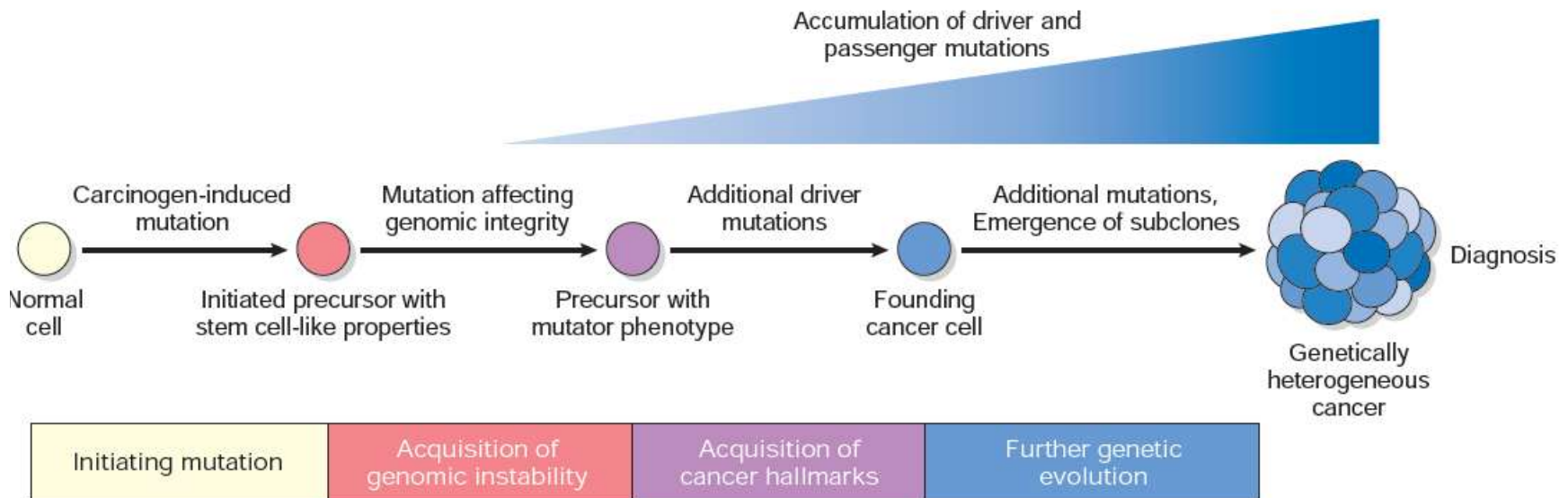
4. Genes for DNA repair

- **malignant phenotype** : Malignant neoplasms with genomic alteration which gives rise to malignant characteristics or cancer hallmarks
- **Cancer hallmarks- e.g.** excessive growth, local invasiveness, ability to form distant metastases
- **Driver mutation:** Mutations giving rise to malignant phenotype
- **Initiating mutation:** First driver mutation that starts a cell on the path to malignancy & present in all of the cells of the subsequent cancer (inherited in daughter cells)

- **Cancer stem cells** : initiating mutation → generation of cell with stem cell like properties-- capacity for self-renewal and long-term persistence
- **Mutator phenotype**: cell with mutation affecting **DNA repair genes (loss of function)**
  - Cells unable to repair non lethal genetic damage in other genes
  - Prone to undergo mutations in accelerated rate → **Genomic instability**
- **Passenger mutations** - mutations that have no phenotypic consequence

# Molecular basis of carcinogenesis:

Carcinogenesis results from the accumulation of complementary mutations in a stepwise fashion over time



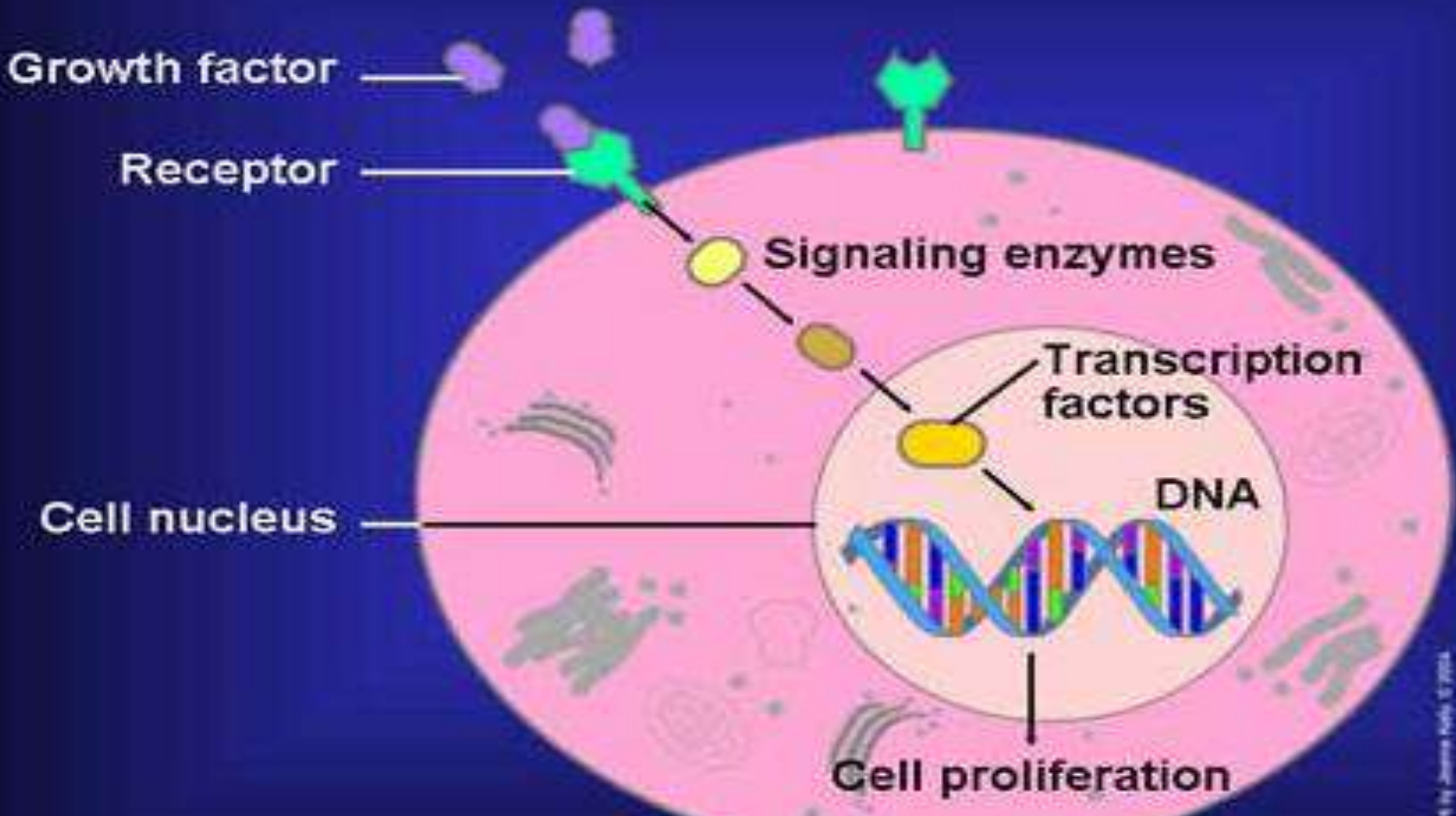
# Tumour progression

- Tendency of tumors to become more aggressive over time
- Occurs as a result of selection of the fittest cells among tumour cells through genetic evolution (Darwinian selection)
- Tumours are monoclonal however subclones develop & are genetically heterogenous having different malignant phenotype such as
  - Invasiveness
  - Rapid growing
  - Metastatic ability
  - nonantigenic

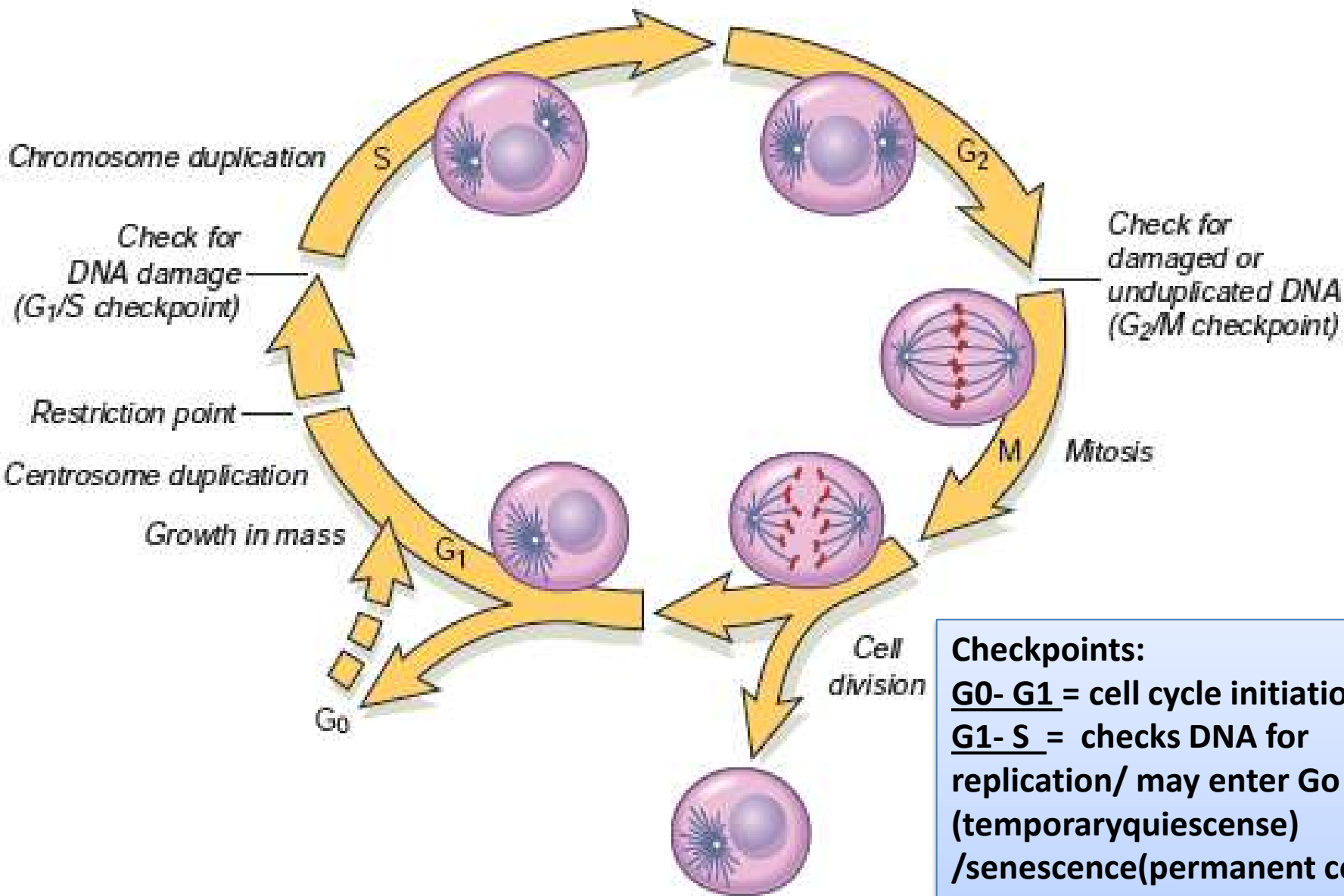
# Molecular basis of carcinogenesis

- **Epigenetic aberrations** also gives rise to malignant properties of cancer cells
  - DNA methylation—silence gene expression
  - modifications of histones--  $\uparrow / \downarrow$  gene expression

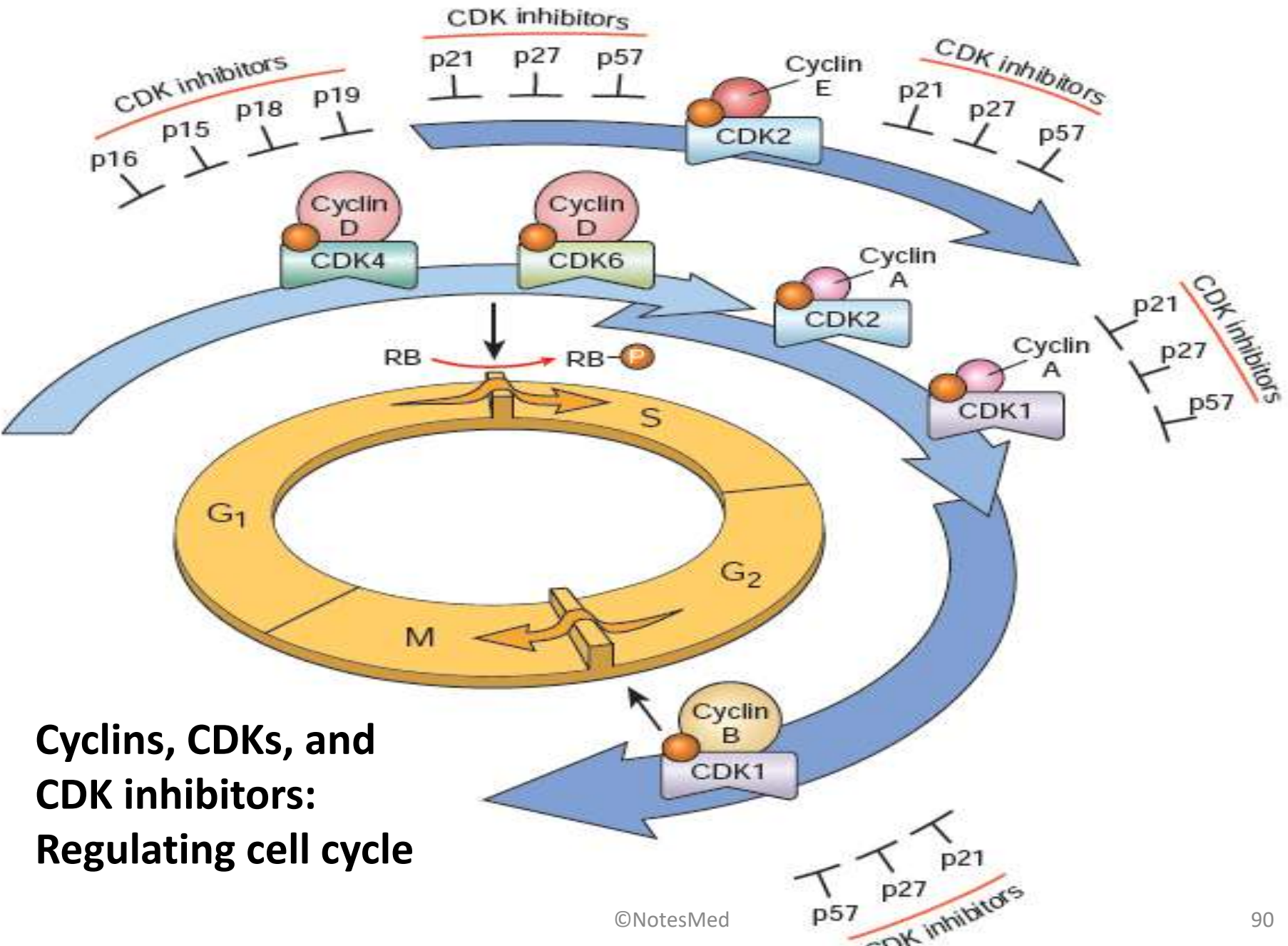
# Normal Growth-Control Pathway



cell cycle progression, controlled by  
**Cell cycle proteins**



**Checkpoints:**  
**G<sub>0</sub>- G<sub>1</sub>** = cell cycle initiation  
**G<sub>1</sub>- S** = checks DNA for replication/ may enter G<sub>0</sub> (temporary quiescence) /senescence(permanent cell cycle arrest)  
**G<sub>2</sub>- M** = Damaged DNA – repaired or undergo apoptosis



**Cyclins, CDKs, and CDK inhibitors: Regulating cell cycle**

# Genetic lesions in cancer

- **Point mutation**
- **Balanced Translocation**
  - Results in:
    - Overexpression of protooncogenes e.g. t(8;14) → **MYC gene overexpression** → Burkitt's Lymphoma
    - Fusion genes → increased growth promoting activity e.g. t(9;22) → Ph chromosome → BCR-ABL fusion gene → **increased tyrosine kinase activity** → CML
- **Deletions**
  - Result in loss of tumour suppressor genes e.g. del ch 13q → loss of RB gene → retinoblastoma

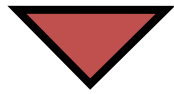
# Genetic lesions in cancer

- **Gene amplifications**
  - Increased copies of protooncogenes e.g. HER2/NEU overexpression → breast cancer
- **Aneuploidy** – error of mitotic check point → autonomous growth
- **Chromothrypsis**- chromosome shattering
  - dozens to hundreds of chromosome breaks occur within a single chromosome or several chromosomes
  - haphazard DNA repair
  - chromosome rearrangements
    - result in the loss of some chromosome
    - activate oncogenes and inactivate tumor suppressors

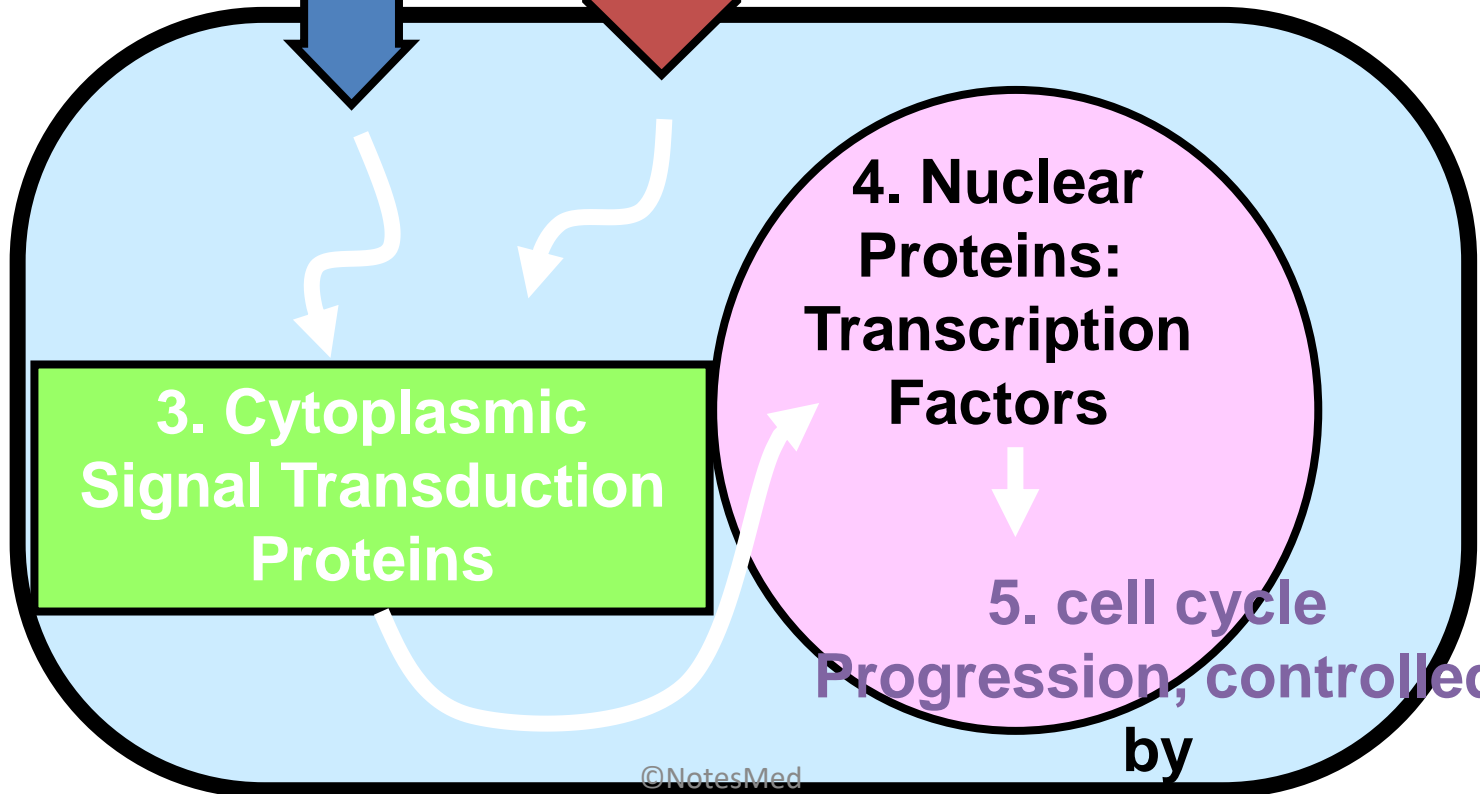
- **MicroRNAs**- non coding single stranded RNAs- negative regulator of gene expression
  - Upregulation → reduce tumour suppression gene
  - Downregulation → overexpression of oncogene
- **Epigenetic changes**- posttranslational modification of histones and DNA methylation-silencing of tumour suppressor genes or activate oncogenes

# Cellular Protooncogenes: encode protein --Promote cell growth and proliferation

1. Secreted Growth Factors



2. Growth Factor Receptors



3. Cytoplasmic Signal Transduction Proteins

4. Nuclear Proteins: Transcription Factors

5. cell cycle Progression, controlled by

Cell cycle proteins

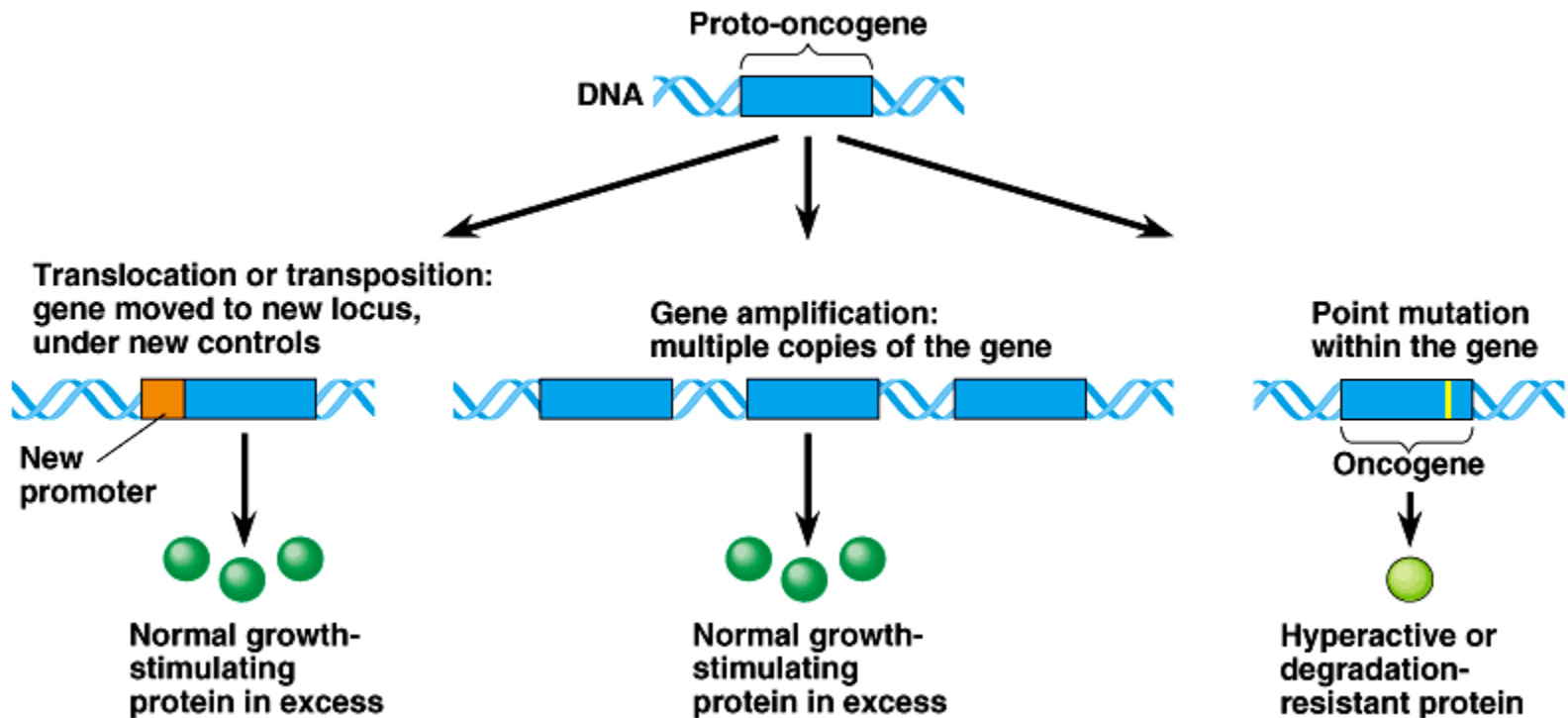
# Oncogenes

- Mutated forms of cellular proto-oncogenes
- Mutation → Gain of function
- promote autonomous cell growth in the absence of growth promoting signals

Mechanisms of activation of Protooncogenes into oncogenes:

- Point mutation
- Translocation/ gene rearrangements
- Gene amplification and overexpression

# Mechanisms of conversion of protooncogene into oncogene



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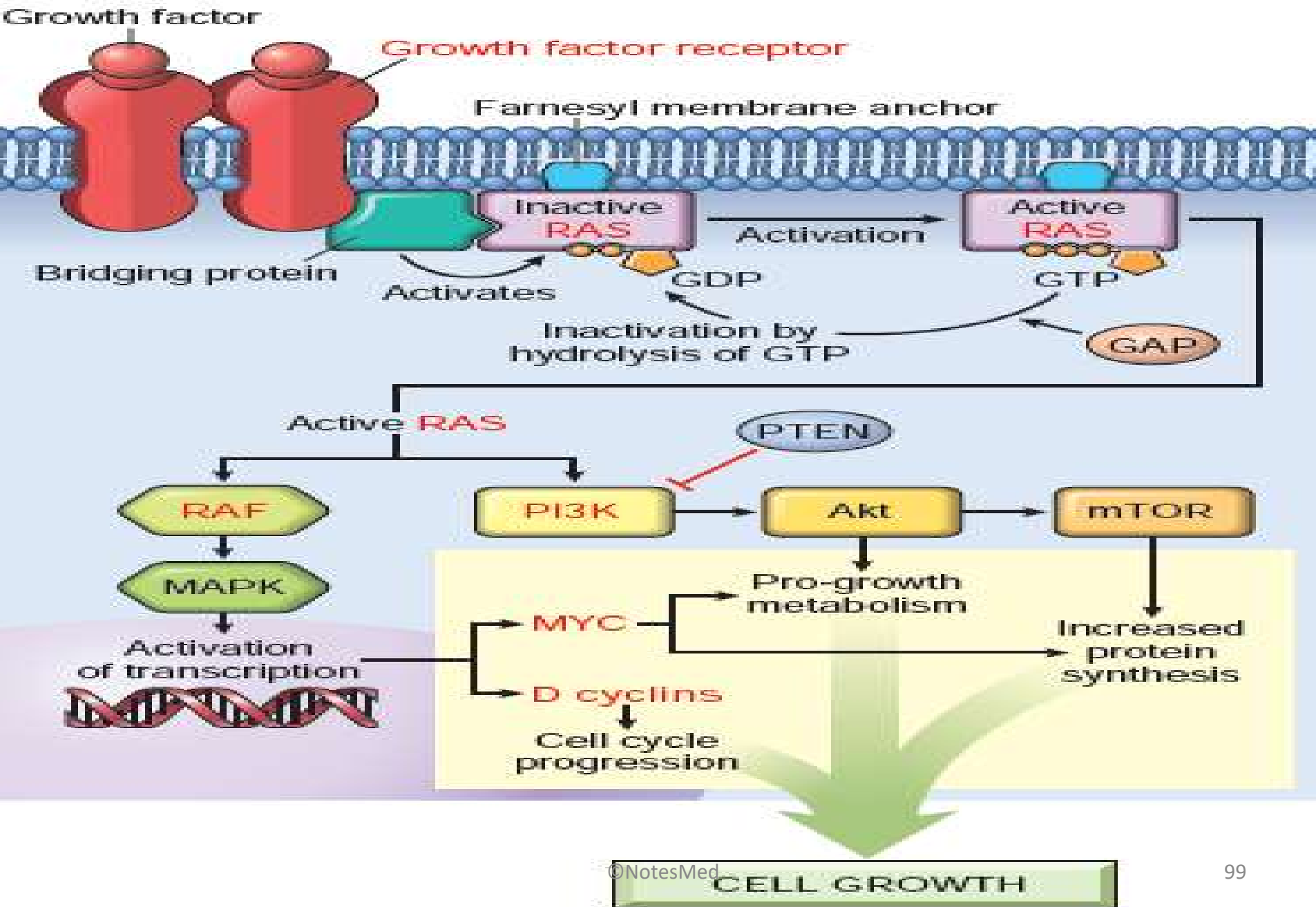
# Oncogenes

- **Growth factors:**
  - Cancer cells secrete growth factor and also express its receptor- self sufficient (autocrine loop)
    - E.g. PDGF- PDGFR- Glioblastomas
- **Growth factor receptors- receptor tyrosine kinases:**
  - Continuous mitogenic signals to cells even in the absence of growth factor
  - E.g. ERBB1 gene- point mutation- EGFR- lung adenocarcinoma
  - ERBB2 gene- amplification-HER2NEU- breast cancer
  - Del of ch 5-- EML-ALK fusion gene- ↑ALK tyrosine kinase activity ↑-- lung adenocarcinoma

# Genes for Signal transducing proteins

- **RAS gene:**
  - Ras protein – family of small G protein (*HRAS, KRAS, NRAS*)
  - GDP bound Ras- inactive state → Ras bound to GTP- active state
  - Stimulated by growth factor on binding to its receptor
  - Signal transduction thru' messenger molecules to nucleus
  - **Point mutation** → Results in RAS trapped in active state due to failed GTP hydrolysis
    - e.g. colon and pancreatic adenocarcinoma
- **ABL gene:** non receptor tyrosine kinase activity
  - BCR-ABL fusion gene- constitutive tyrosine kinase activity -- e.g. CML

# RAS pathway



# Oncogenes: Genes for nuclear transcription factors

- **MYC gene:** MYC protein
  - Activated by signal transduction proteins (RAS/MAPK)
  - Activate transcription of growth promoting genes such as **cyclins** & Repress expression of **cell cycle inhibitors**
  - Also regulates intermediate metabolism e.g. aerobic glycolysis and increased utilization of glutamine
  - Upregulates telomerase expression
  - Reprogram somatic cells into pluripotent stem cells
  - e.g.
    - Burkitt lymphoma – t(8;14)
    - Breast, colon, lung- amplification
    - *N-MYC*, *L-MYC*- neuroblastoma, small cell carcinoma of lung

# Oncogenes: Cyclins and cyclin-dependent kinases

- Cell cycle regulated by **cyclin proteins and cyclin dependent kinases (CDK)**
- **CDK- cyclin complexes** phosphorylate target proteins that regulate cell cycle transition such as Rb protein and drives the cell cycle further
- **CDK inhibitors-** regulate activity of CDK- cyclin complexes e.g, p21, p27; p15, p16 at check points
- **Mutation of cyclin and CDKs- abnormal proliferation**
  - E.g. mutation of cyclin D- cancer of breast
  - CDK4 mutation- melanoma, sarcoma

# Oncogenes

Protein Products	Oncogenes	Mode of activation	Tumours
Growth factor PDGF	<i>sis</i>	overexpression	Brain tumours
Growth factor receptor EGFR	<i>HER2/NEU</i>	overexpression	Breast
Signal transducing protein	<i>Ras</i>	Point mutation	colon
Nuclear regulator proteins: Transcription factors	<i>myc</i>	Translocation, amplification	Burkitt lymphoma
Cell cycle regulators	<i>Cyclin D</i>	Translocation, amplification	Esophageal cancers, mantle cell lymphoma

# Tumour suppressor genes

- Normal function - inhibit cell proliferation
- Inhibitory effects at different stages of normal cell growth
  - Cell surface receptors inhibitors
  - Signal transduction inhibition
  - Nuclear transcription regulator inhibitors
  - Cell cycle inhibitors
- Requires loss or mutation of both normal allele
- associated with suppression of any of the various hallmarks of cancer

# Prototypes of Tumour suppressor genes

- RB gene
- p53 gene

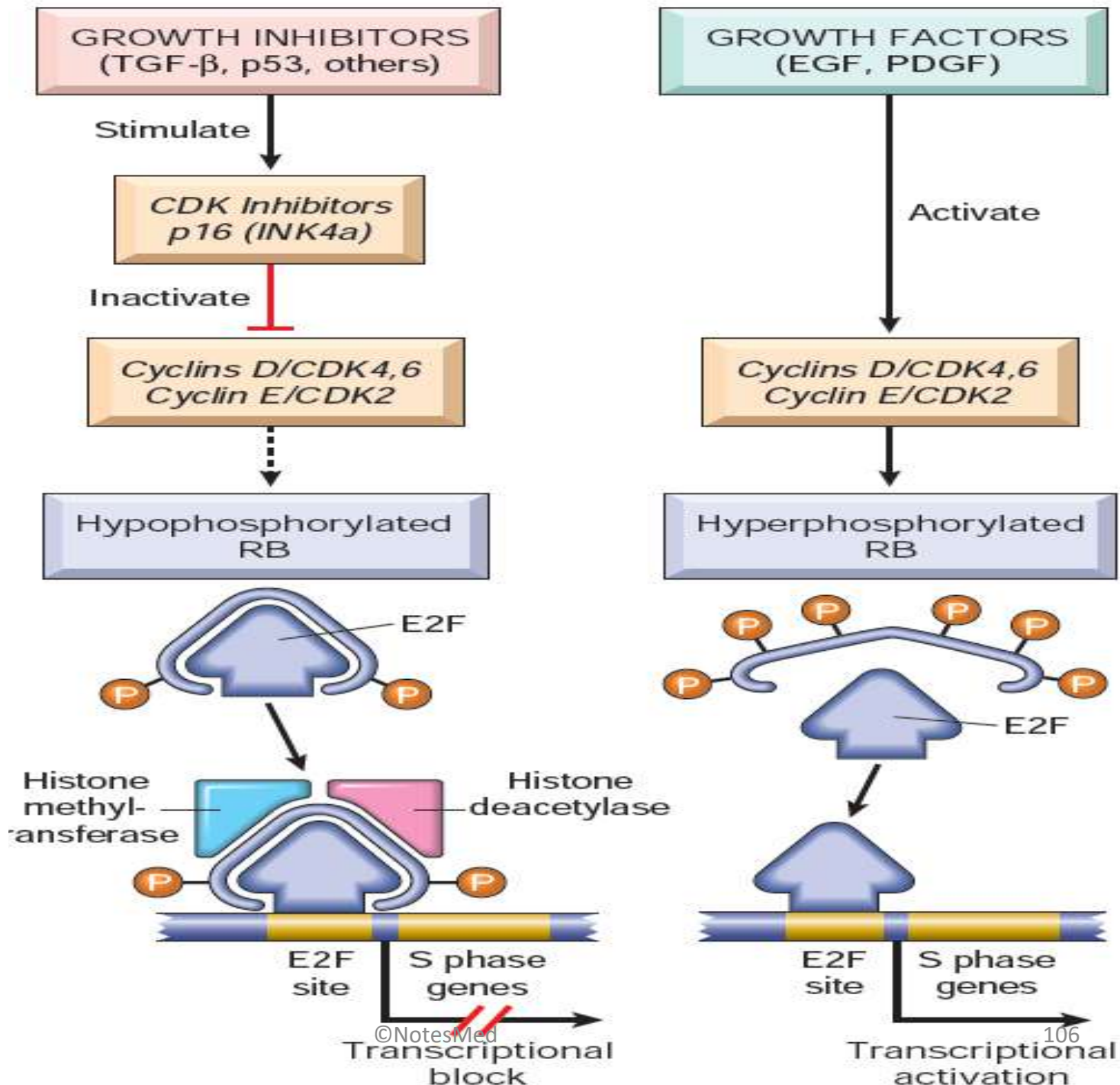


**Cycle cycle  
Inhibitors–  
Molecular brakes  
On cell cycle**

# RB gene

- **Governer of the cell cycle**
- Locus Ch 13
- Inhibit cell cycle at  $G_1 / S$  transition
  - Imp. Check point → once cross it → mitosis occurs
- active hypophosphorylated state-- quiescent cells
- inactive hyperphosphorylated state-- pass through the  $G_1 / S$  cell cycle transition

cell cycle  
regulator  
at G1-S  
check  
point-  
Cyclin D,  
CDK4,  
p16INK4  
a,Rb



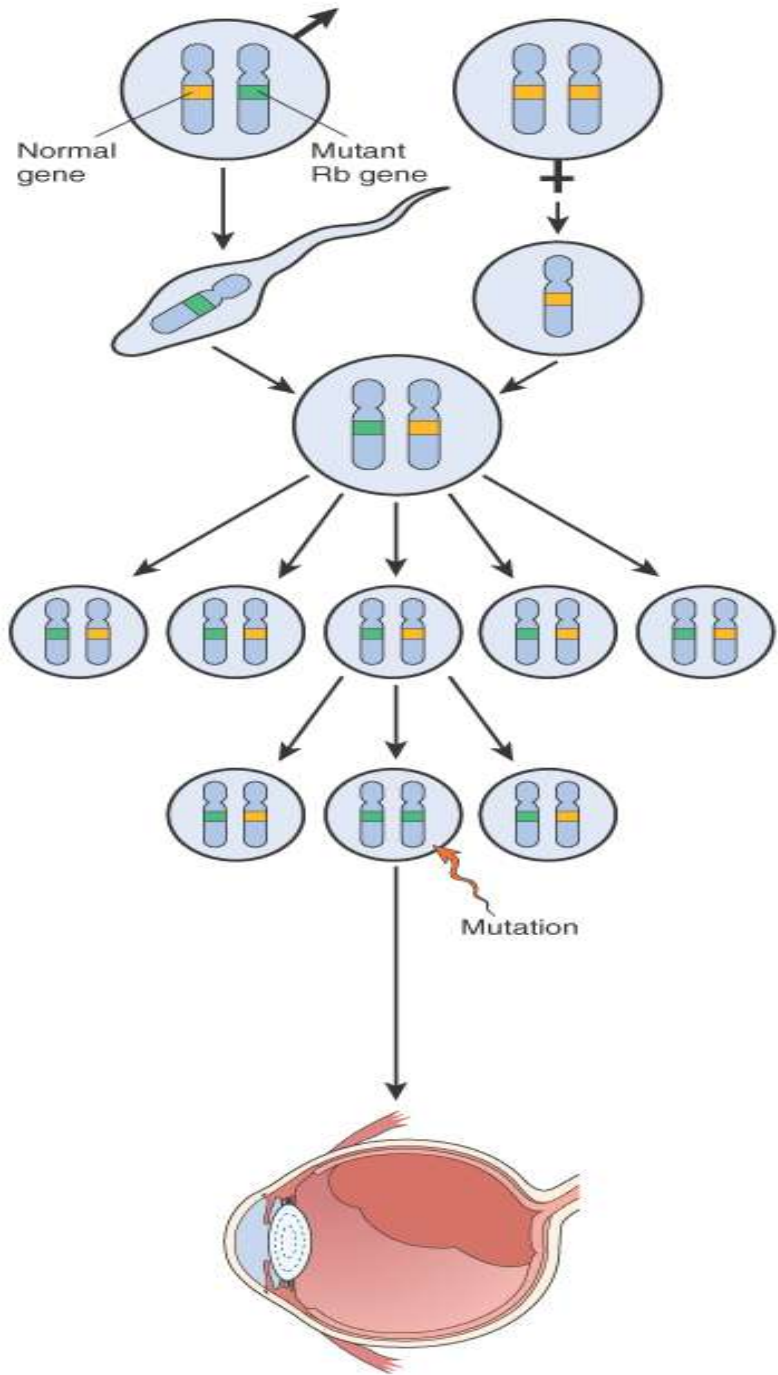
# RB gene

- Mutated RB gene– retinoblastoma
- Knudson Two hit hypothesis for familial and sporadic tumour occurrence
- Autosomal dominant inheritance
- Homozygous loss- other cancers-
  - Sporadic- breast, small cell cancer of lung, bladder cancer
  - Familial- osteosarcoma
- HPV – E7 protein binds to Rb protein → functional loss → uncontrolled growth

FAMILIAL FORM

PATHOGENESIS OF RETINOBLASTOMA

SPORADIC FORM



Somatic cells of parents

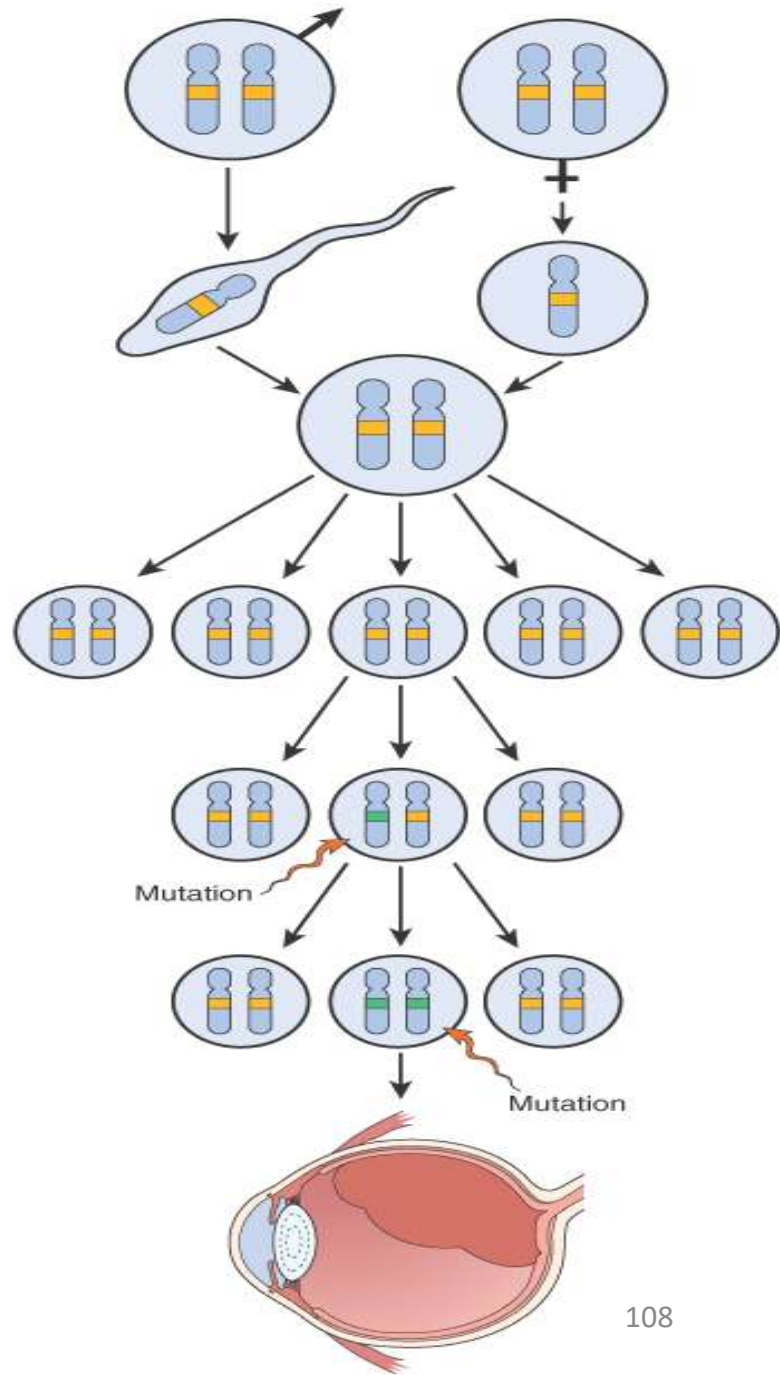
Germ cells

Zygote

Somatic cells of child

Retinal cells

Retinoblastoma



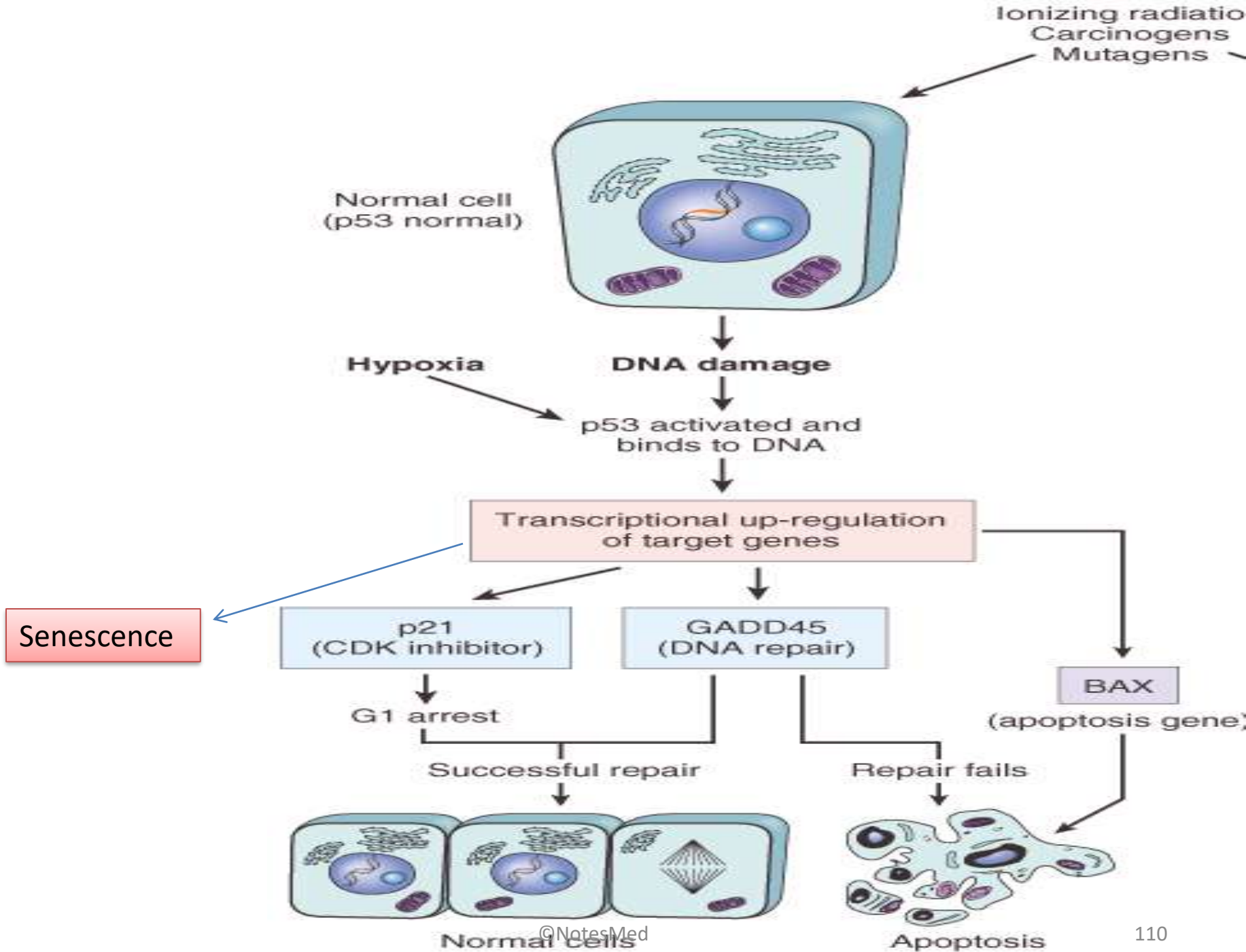
## TP53 gene

Located at  
chromosome  
**17p**

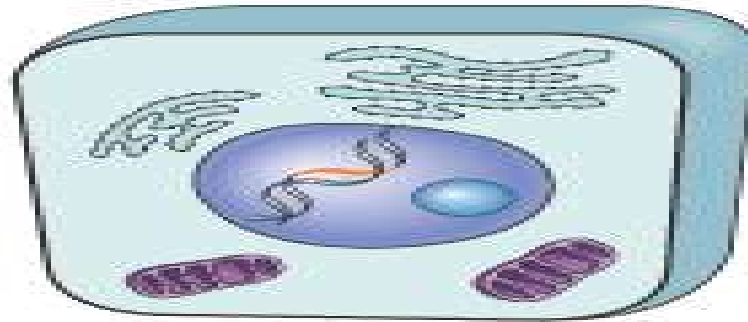
**Guardian of  
the genome**

Tu  
sup  
g

- Sense genomic damage
  - Activated by anoxia, DNA damage, telomere shortening, inappropriate oncogenic signaling
- ↓
- Temporarily inhibit cell cycle progression
  - DNA repair
  - Cellular senescence
  - Apoptosis
- 
- Normal cell- p53 undetectable- MDM2 promote its degradation



Radiation,  
carcinogens



Cell with  
mutations or  
loss of p53

Mutation  
or loss of  
p53

DNA damage

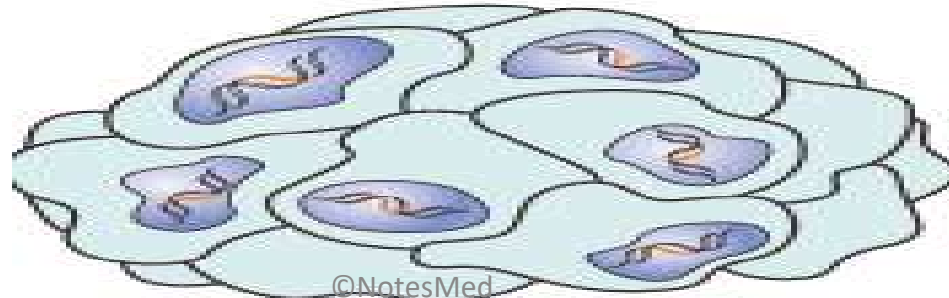
p53-dependent genes  
not activated

No cell  
cycle  
arrest

No DNA  
repair

Mutant cells

Expansion and  
additional  
mutations  
Driver



Malignant tumor

# p53 gene

- Cancer- biallelic loss of p53 gene
- > 70% of cancer e.g. lung, colon and breast
- Autosomal dominant cancer syndrome- one mutant allele inherited
  - E.g. Li Fraumeni syndrome- multiple primary tumours at early age-like- sarcoma, leukaemia, breast tumour etc.
- Oncogenic DNA virus infection → HPV, EBV, HBV bind to p53- functionally inactive → cancer

# Tumour suppressor genes

- **Inhibitors of mitogenic signaling pathways**
  - **APC gene**- inhibitor of WNT signaling pathway-  
**Cancer of colon**
- **Inhibitors of Cell Cycle Progression**
  - **RB gene**- Inhibitor of G1/S transition-  
**retinoblastoma, osteosarcoma**
  - **CDKN2A gene**- p16/INK4a and p14/ARF p16:  
negative regulator of CDK- cyclin complex–  
**melanoma, Pancreatic, carcinoma**

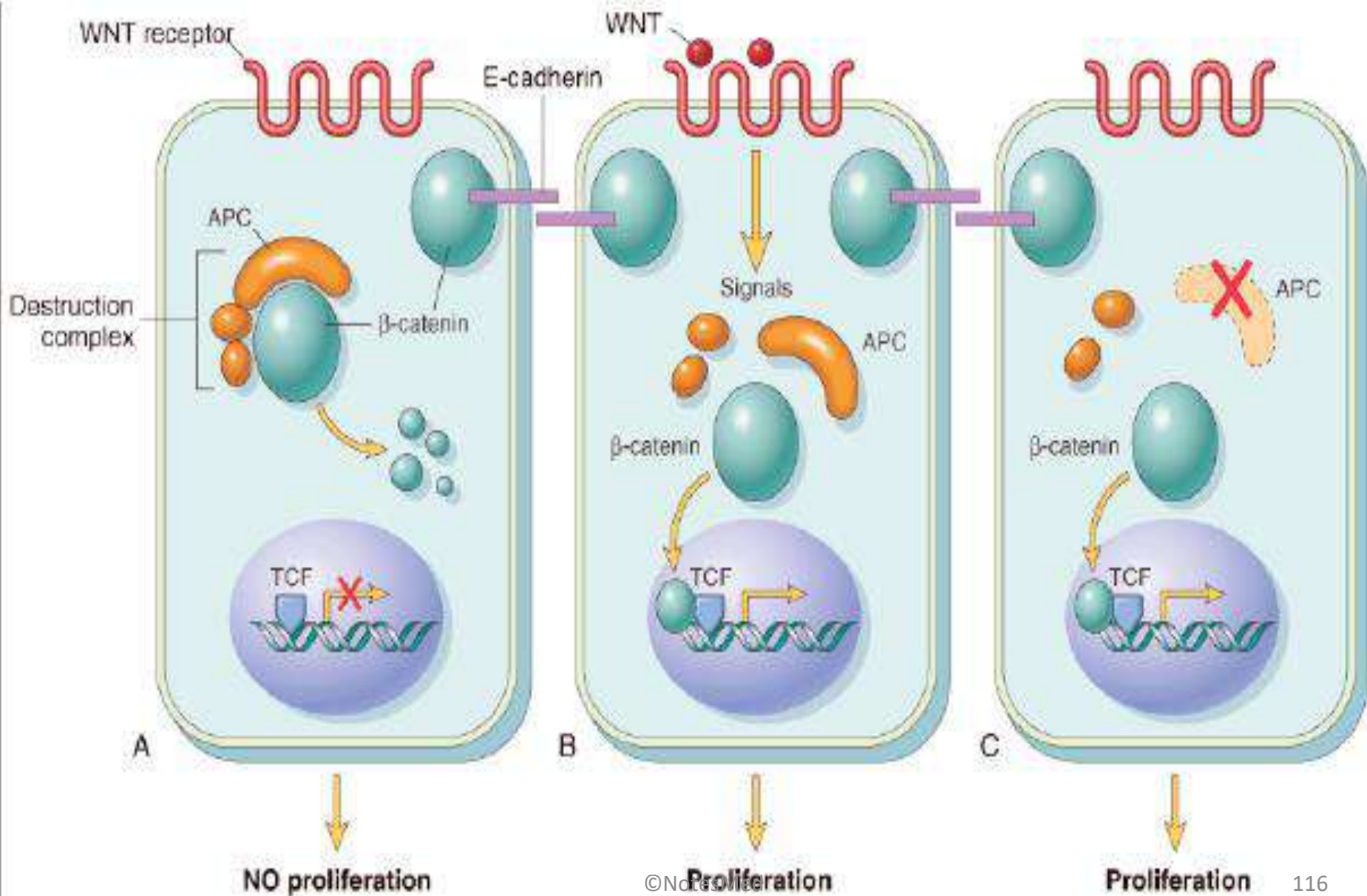
# Tumour suppressor genes

- **Enablers of Genomic Stability**
  - ***TP53 gene***-- Cell cycle arrest and apoptosis-Li-Fraumeni syndrome (diverse cancers) and many sporadic cancers
- **Inhibitors of “Pro-growth” Programs of Metabolism and Angiogenesis**
  - ***VHL gene***- inhibitor of transcription factors HIF1 $\alpha$ - **RCC**; VHL syndrome

# Tumour suppressor genes

- **Inhibitors of Invasion and Metastasis**
  - ***CDH1***- E-cadherin Cell adhesion, inhibition of cell motility- **Familial gastric cancer**
- **DNA Repair Factors**
  - ***BRCA1, BRCA2*** -Repair of double-stranded breaks in DNA- **Familial breast and ovarian carcinoma**
  - ***MSH2, MLH1, MSH6*** - DNA mismatch repair- **Hereditary nonpolyposis colon carcinoma**
- **Unknown Mechanisms**
  - ***WT1 gene***- Transcription factor - **Wilms tumor**, certain leukemias

# WNT SIGNALLING PATHWAY

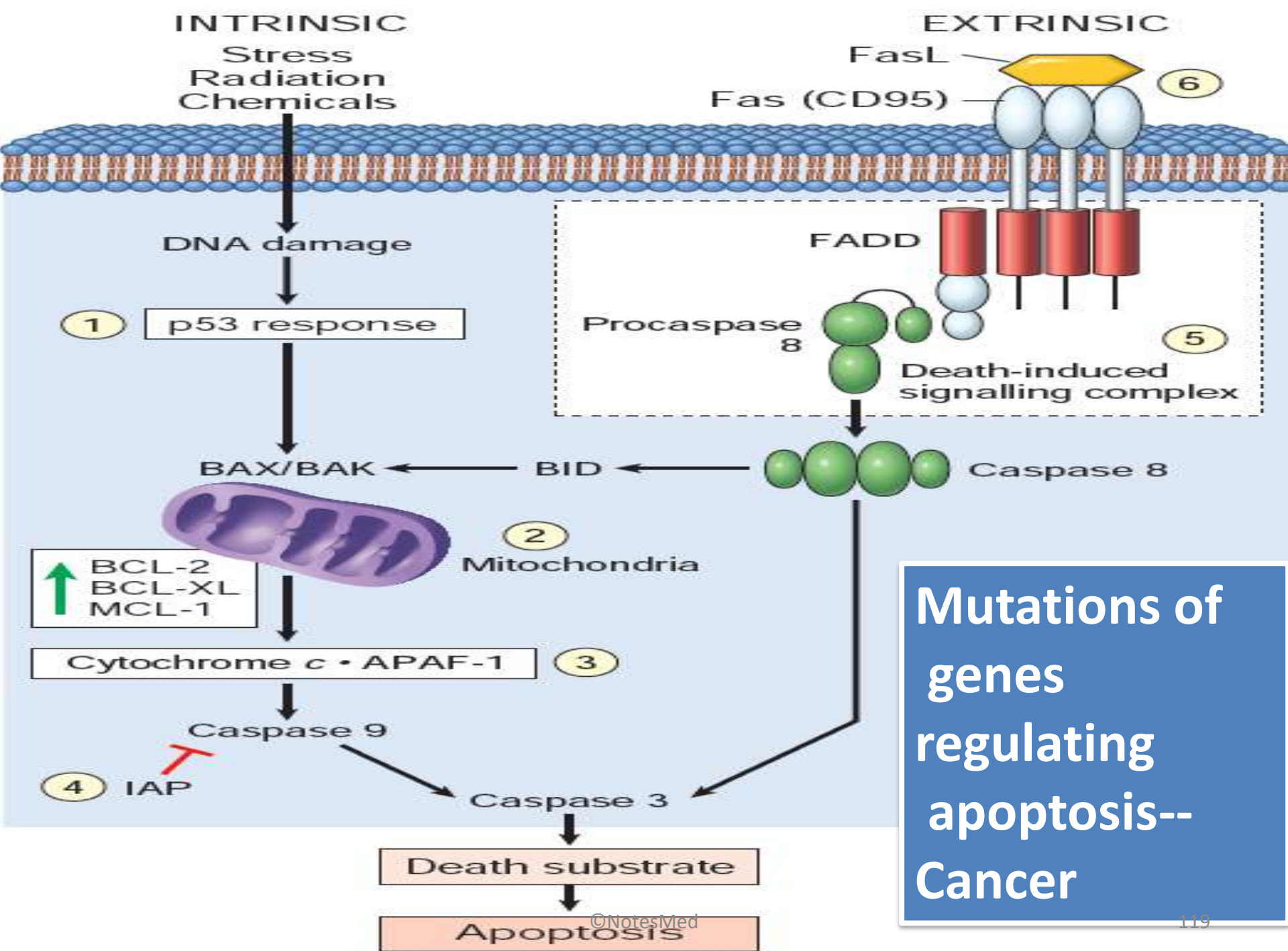


# Other Tumour suppressor genes:

- ***NF-1*** gene: protein product- neurofibromin
  - GTPase activating protein (GAP)
  - Promote conversion of RAS from active to inactive state by activating GTPase -- negative regulator of signal transduction
  - Loss of NF-1 gene- neurofibroma
  - Inherited form- neurofibromatosis type 1 (multiple neurofibroma, café au lait spots, lisch nodule- pigmented iris hamartoma )
- ***PTEN*** gene- (*phosphatase and tensin* homologue)
  - membrane-associated phosphatase; Ch 10q23
  - brake on the PI3K/AKT arm of the receptor tyrosine kinase pathway.
  - Del, epigenetic silencing
  - Cowden syndrome: AD disorder--skin appendage tumors, epithelial cancers- breast, endometrium, and thyroid

# Genes that regulate apoptosis

- **BCL2 family genes encoding**
  - Pro - apoptotic protein- BAX/BAK
  - Anti- apoptotic proteins- BCL-2
    - t(14;18)- overexpression of *BCL2* gene-- follicular B-cell lymphomas
  - BH-3 proteins- BAD, BID- neutralizes the action of anti- apoptotic proteins
- **TP53 gene** – induces apoptosis by promoting pro-apoptotic gene expression – BAX, PUMA



# Genes for DNA repair

- DNA damage → normally repaired
  - Environmental agents- radiation, dietary carcinogens, ROS from cell metabolism
  - Errors during replication
- **Inherited defect** in DNA repair genes
- **Sporadic**-defects in repair mechanisms—  
some cancers
- not oncogenic but allow mutations in other genes and carcinogenesis
- **Genomic instability**- both alleles are lost

# DNA repair mechanism

- Mismatch repair
- Nucleotide excision repair
- Recombination repair
- Defect in DNA repair systems → genomic instability

# Defective DNA mismatch repair genes

- Proofreading of DNA sequences
- Repair mismatch of bases e.g. mismatch pairing of A to C
  - Defective repair--Mutated protooncogenes and tumour suppressor genes
  - Defective mismatch repair in microsatellites → **microsatellite instability** -contraction or expansion of repeats
  - E.g. HNPCC (hereditary nonpolyposis colonic cancer) syndrome- germline mutation in mismatch repair genes e.g. MSH2, MLH1

(Microsatellites – short DNA sequences -- tandem repeats of 1 to 6 nucleotides)

# Defect in DNA repair genes

## ❑ Defect in genes for nucleotide excision repair (NER)

- UV radiation → cross linking of pyrimidine- repaired by NER pathway
- Inherited loss of these genes → **xeroderma pigmentosum**

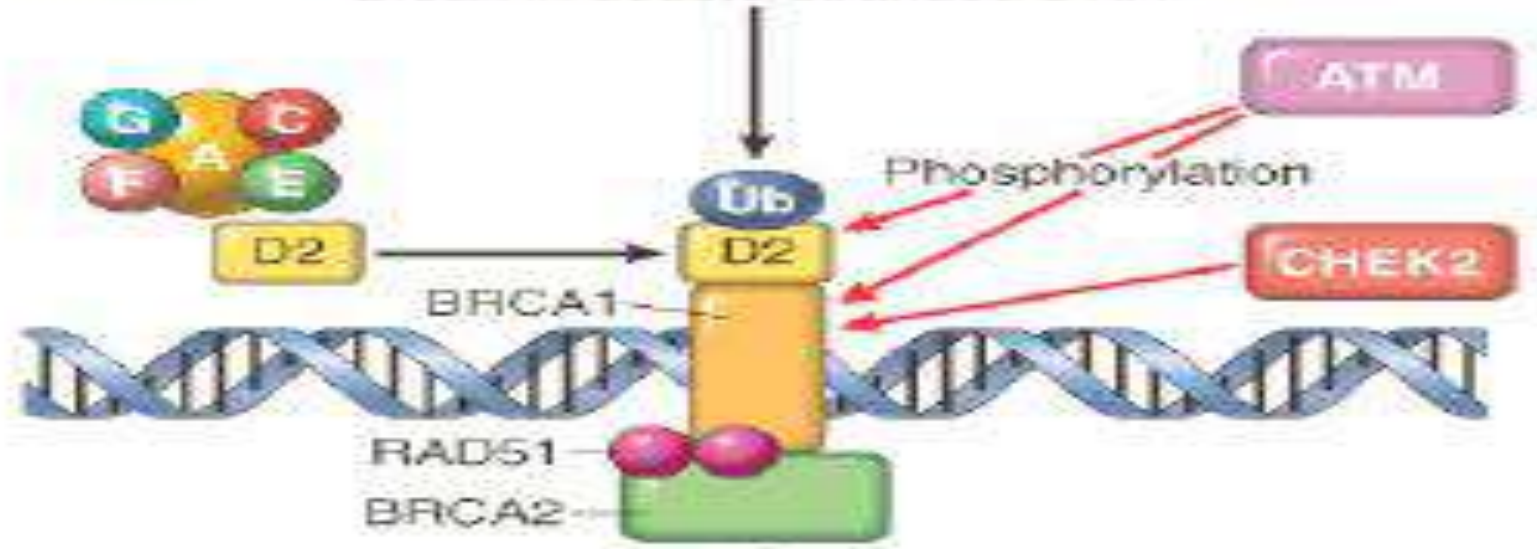
## ❑ Defects in DNA repair by homologous recombination

- BRCA1, BRCA2 along with ATM, CHEK2, RAD51, - repair break in double stranded DNA
- Inherited mutation in BRCA1 - breast cancer, ovary, prostate , colon
- Inherited mutation in BRCA2- breast, ovary, melanoma, pancreatic tumours

DNA

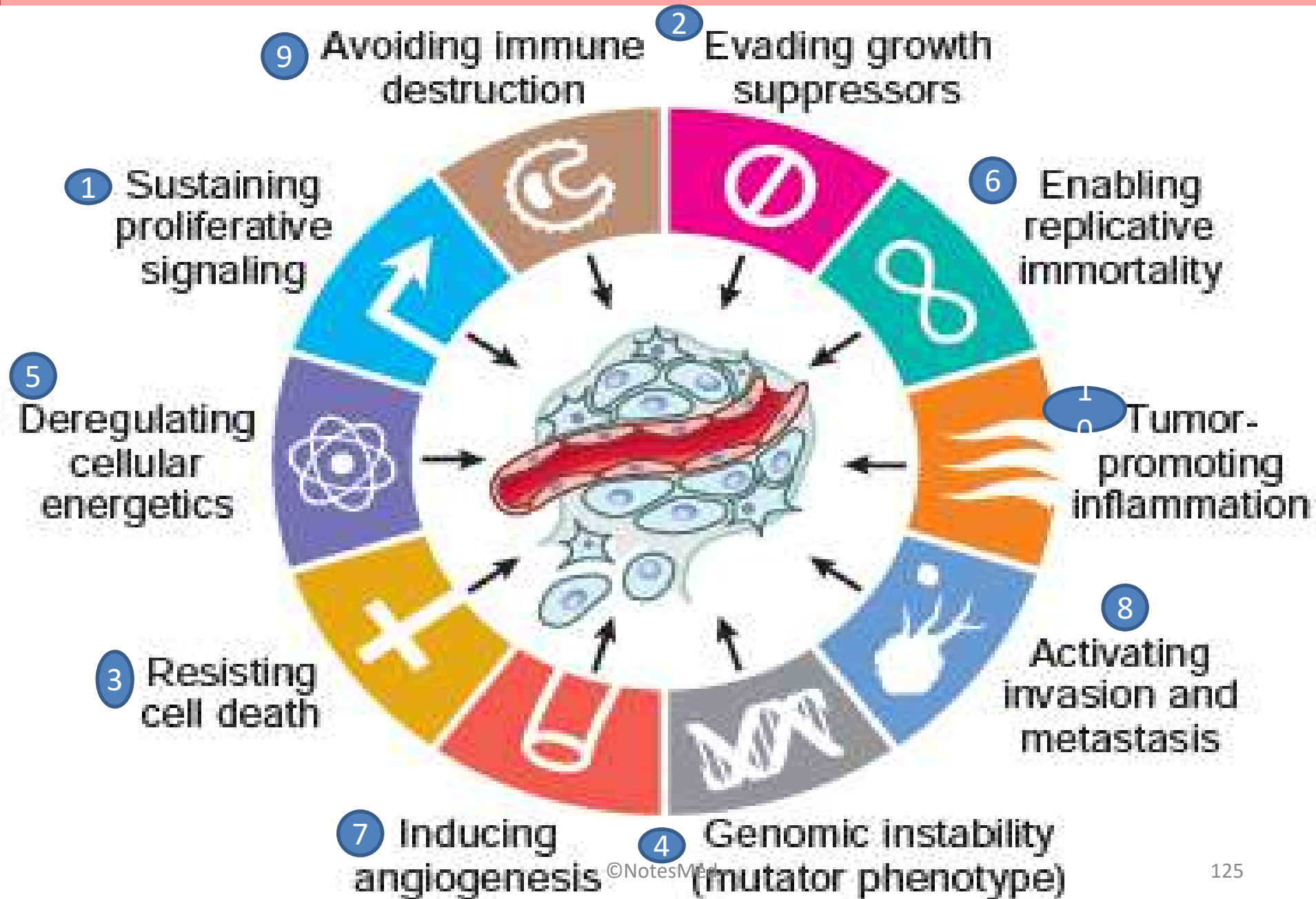


Break in double-stranded DNA



Error-free DNA repair by recombination

# Essential alteration for malignant transformation



# Additional alterations or hallmarks of cancer

- Reprogramming of energy metabolism
- Evasion of the immune system
- Genomic instability
- Tumour promoting inflammation

# Self-sufficiency in Growth Signals: oncogenes

## Unregulated proliferation (accelerators )

- **Overproduction of growth factors** e.g. *PDGF*—overexpression-- astrocytoma
- **Growth factor receptors**
  - *EGFR*- point mutation- lung adenocarcinoma
- **Increased transduction signals**
  - e.g. G protein- *KRAS*- point mutation- colon cancer
- **Nuclear regulatory proteins**
  - Transcriptional activators-*MYC*- Translocation –Burkitts Lymphoma
- **Cell cycle regulators**
  - *Cyclin D1*- translocation- mantle cell lymphoma

# Inensitivity to inhibitory growth signals: tumour suppressor genes

- Loss or inactivation of tumour suppressor genes (act as brakes to cell growth) → malignant transformation
- Both gene alleles must be defective

# Evasion of apoptosis

- Increased anti-apoptotic molecules (BCL2)

E.g. Follicular B-cell lymphomas:-

anti-apoptotic gene *BCL2* is activated by t(8;14)

- Mutation of antiapoptotic gene—p53

# Growth-Promoting Metabolic Alterations: Warburg Effect

- metabolic switch to aerobic glycolysis

– glucose-----pyruvate→ lactate

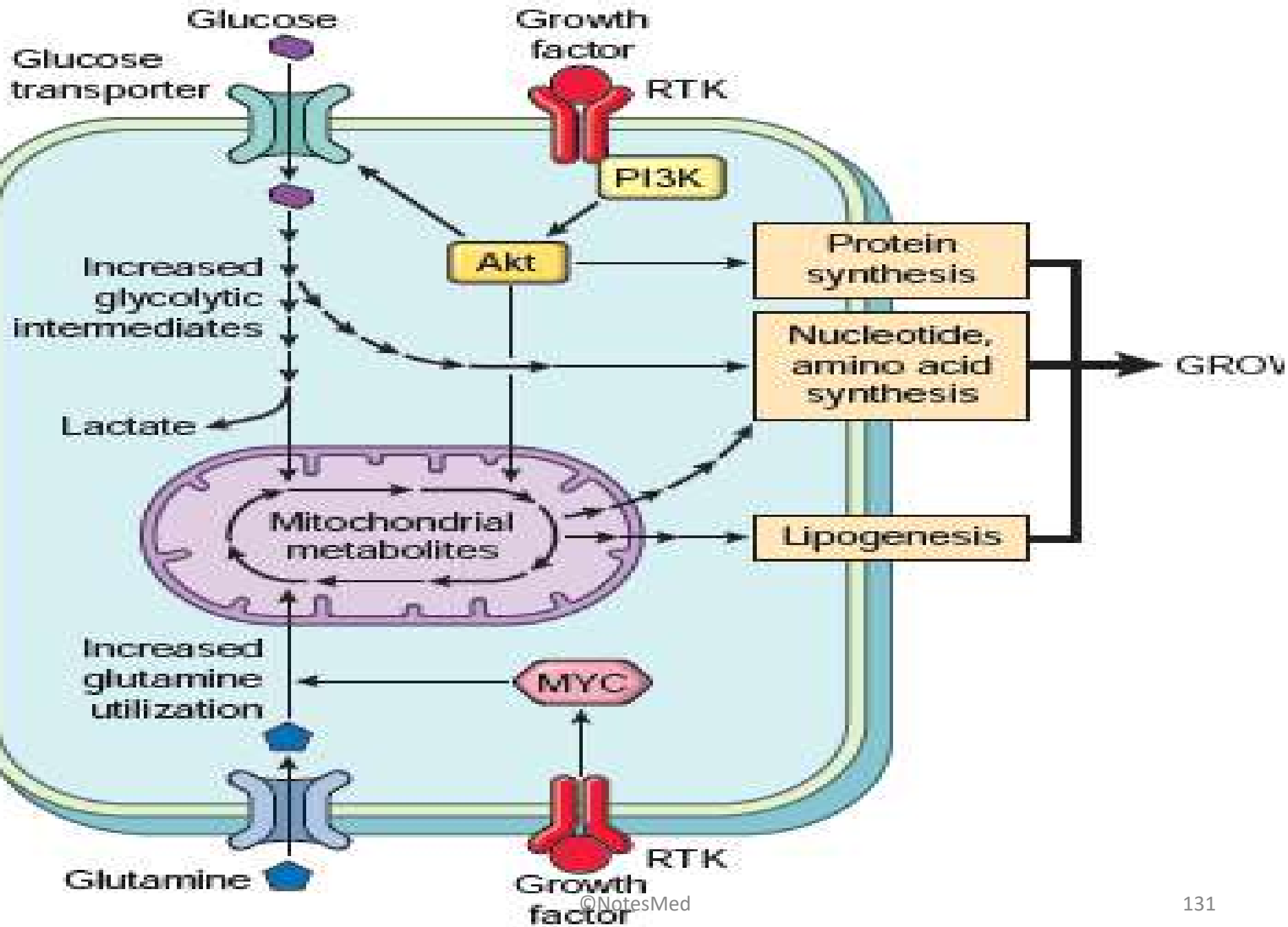
– Provides metabolic intermediate ←→ Krebs cycle

– synthesis of the macromolecules and organelles required for rapid cell growth

- **metabolic reprogramming**—due to persistent **signaling cascades** provided by oncogenes/ due to loss of tumour suppressor genes

– e.g. PI3K/AKT signaling—promote glycolytic activity; lipid biosynthesis and protein synthesis

# GROWING CELL (NORMAL OR TUMOR)



- Tumor suppressors inhibit metabolic pathways.
- PTEN--“braking” effect on PI3K/AKT signaling
  - Mutation -- Warburg effect
- STK11 –mutation-- produce Warburg metabolism
- p53—normally upregulates target genes that collectively inhibit glucose uptake, glycolysis, lipogenesis, and the generation of NADPH (a key cofactor needed for the biosynthesis of macromolecules)

- **Receptor tyrosine kinase activity--**
  - phosphorylate the M2 isoform of pyruvate kinase
  - attenuates its enzymatic activity inhibiting conversion of phosphoenol pyruvate to pyruvate
  - glycolytic intermediates– siphoned off for synthesis of DNA, RNA, and protein
- **MYC--gene expression--**
  - glycolytic enzymes and glutaminase

# cell

- ***Autophagy. State of nutrient deficiency*** cannibalize their own organelles, proteins, and membranes as carbon sources for energy production if fails cell dies
- Tumor cells –pathways that induce autophagy are deranged
- Tumor suppressors promote autophagy
- In contrast severe nutrient deprivation tumor cells may use
- Autophagy to become “dormant,” a state of metabolic hibernation that allows cells to survive hard times for long periods.
- Resistant to therapies that kill actively dividing cells-- therapeutic failures

# Limitless replicative potential: The Stem cell–Like properties of cancer Cells

- DNA damage
- **P53/p16**
- Cell cycle arrest at G1/S

## Senescence

**Normal mortal cells**

After multiple rounds of replication

**Cells that are resistant to senescence**

**Telomere shortening**

(DNA sequences at the end of chromosome that bind to protective protein complexes)

**Eroded telomeric end of DNA**

**Detected as double stranded DNA break by p53**

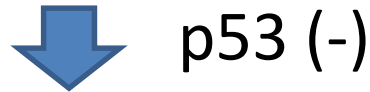
**Apoptosis**

# Limitless replicative potential: The Stem cell–Like properties of cancer Cells

- All cancer
  - limitless replicative potential
  - Some cells are immortal- Cancer stem cells
- Mechanisms:
  - **Evasion of senescence**
    - Most of the cancers- mutation of tumour suppressors-- disruption of RB dependent **G1-S checkpoint**
  - **Evasion of mitosis crisis**
  - **Self re-newel capacity**

# limitless replicative potential

Cancer cells with shortened telomere



Inappropriate DNA repair pathway: Fusion of non homologous chromosomes at telomere ends



Double stranded DNA breaks during cell cycle  
(anaphase)



Repeated bridge-fusion- breakage cycle



Genomic instability

**Telomerase activation**

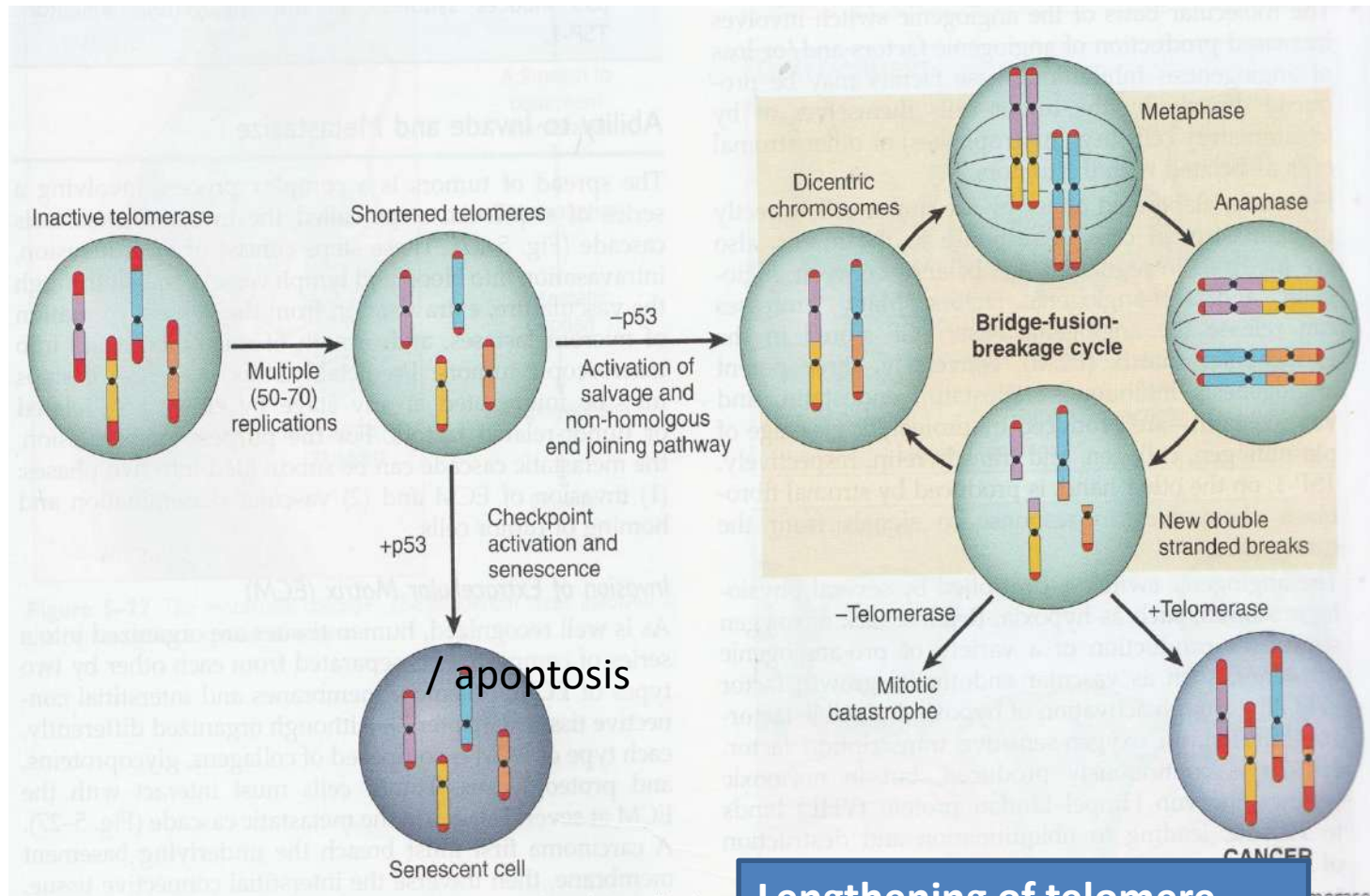
**Lengthening of telomere ends**

**Prolonged life, accumulations  
of mutations**

Cell death

**Cancer**

# Evasion of mitosis crisis- Telomerase activity in cancer



**Lengthening of telomere  
+ accumulation of  
mutation**

# Self renewal of Cancer stem cells

- Some of the cancer cells- stem cells
  - Express telomerase → escape mitosis crisis and senescence
  - **Capacity for self renewal**
    - During division, one daughter cell → stem cells (low rate of cell division)
  - Somatic cells → transformed cell- acquires stemness (de- differentiated )
  - Stem cell → transformed cells

# Sustained angiogenesis

- Vascularization of tumors is essential for their growth
  - provides nutrients and oxygen
  - Endothelial cells-> secrete growth factors
  - Provides access for metastasis
- Occurs later – angiogenic switch-> ↑ angiogenic factors;  
↓ antiangiogenic factors

# Sustained angiogenesis

- Angiogenic factors- VEGF , bFGF
  - Hypoxia-> activates HIF-1 $\alpha$  (TF)-> synthesis of VEGF
- Antiangiogenic factor- TSP-1
- Promoting and inhibiting factors secreted by
  - tumour cells
  - stromal cells/ inflammatory cells
    - released from ECM by proteases

# Sustained angiogenesis

- Promoted by mutated oncogene and tumour suppressor genes
  - Oncogene--RAS-MAPK pathway → ↑ VEGF
  - Tumor suppressor gene inhibits angiogenesis
    - VHL: binds to HIF-1 $\alpha$  (TF) → destruction → (-) VEGF expression; germ line mutation → VHL syndrome
    - p53 : VEGF ↓ ; TSP1 ↑

# Invasion and metastasis

- Hallmark of malignant tumour
- Complex interaction of tumour cells and stromal cells
- Additional mutations in the tumour clones leads to formation of subclones with metastatic potential
- These subclones are responsible for tumour invasion and metastasis

# Invasion and metastasis: mechanism

1. Invasion of extracellular matrix(local invasion)
2. Vascular dissemination and homing of tumour cells

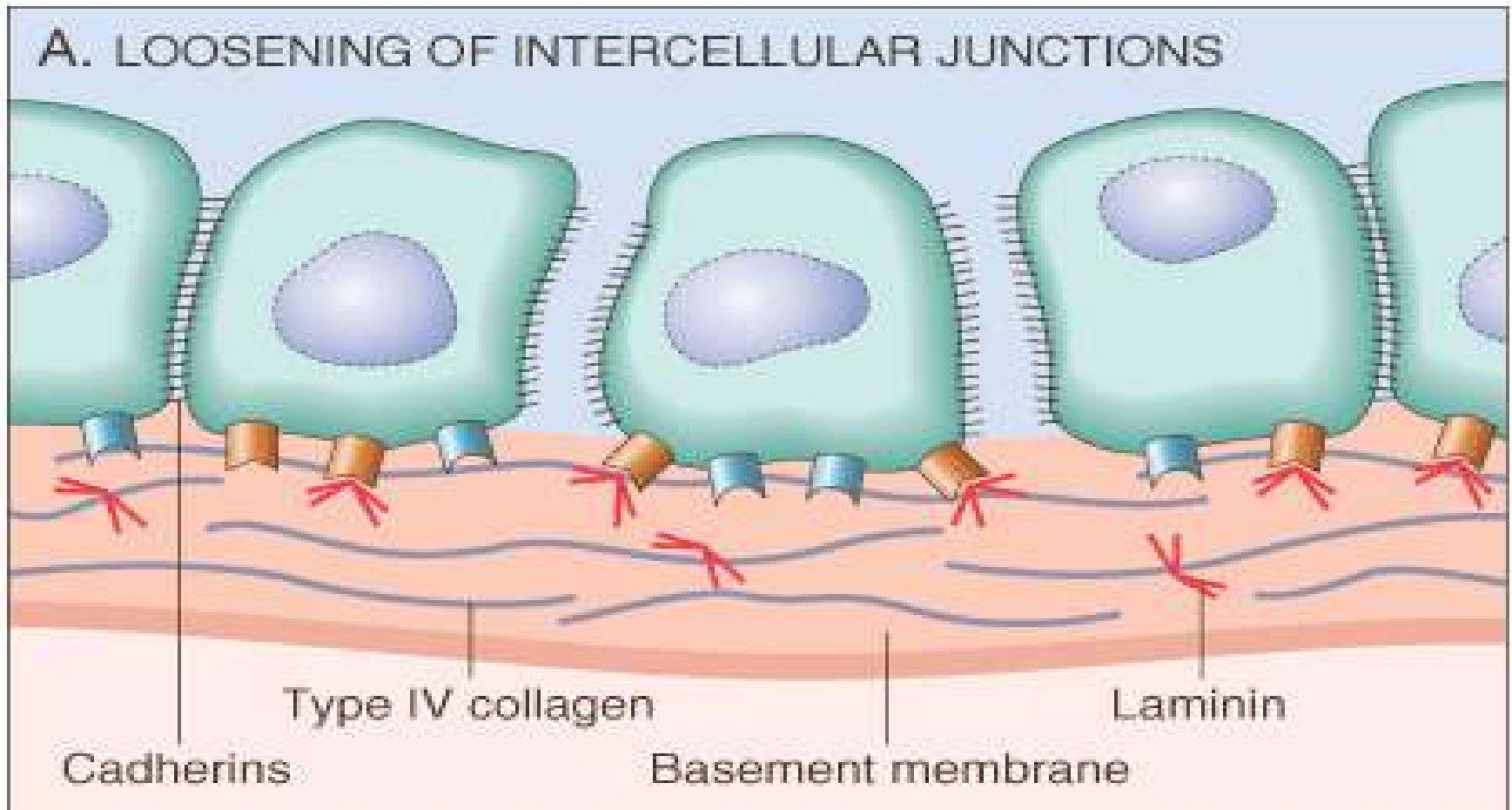
# 1. Invasion of ECM (basement membrane and interstitial connective tissue)

- **Detachment of tumour cells from each other**
  - E-cadherin- intercellular glues
  - Loss of E- cadherin (mutation of E- cadherin, activation of  $\beta$ -catenin genes)
- **Degradation of ECM**
  - Release of proteases by tumour cells or stromal cells like MMPs

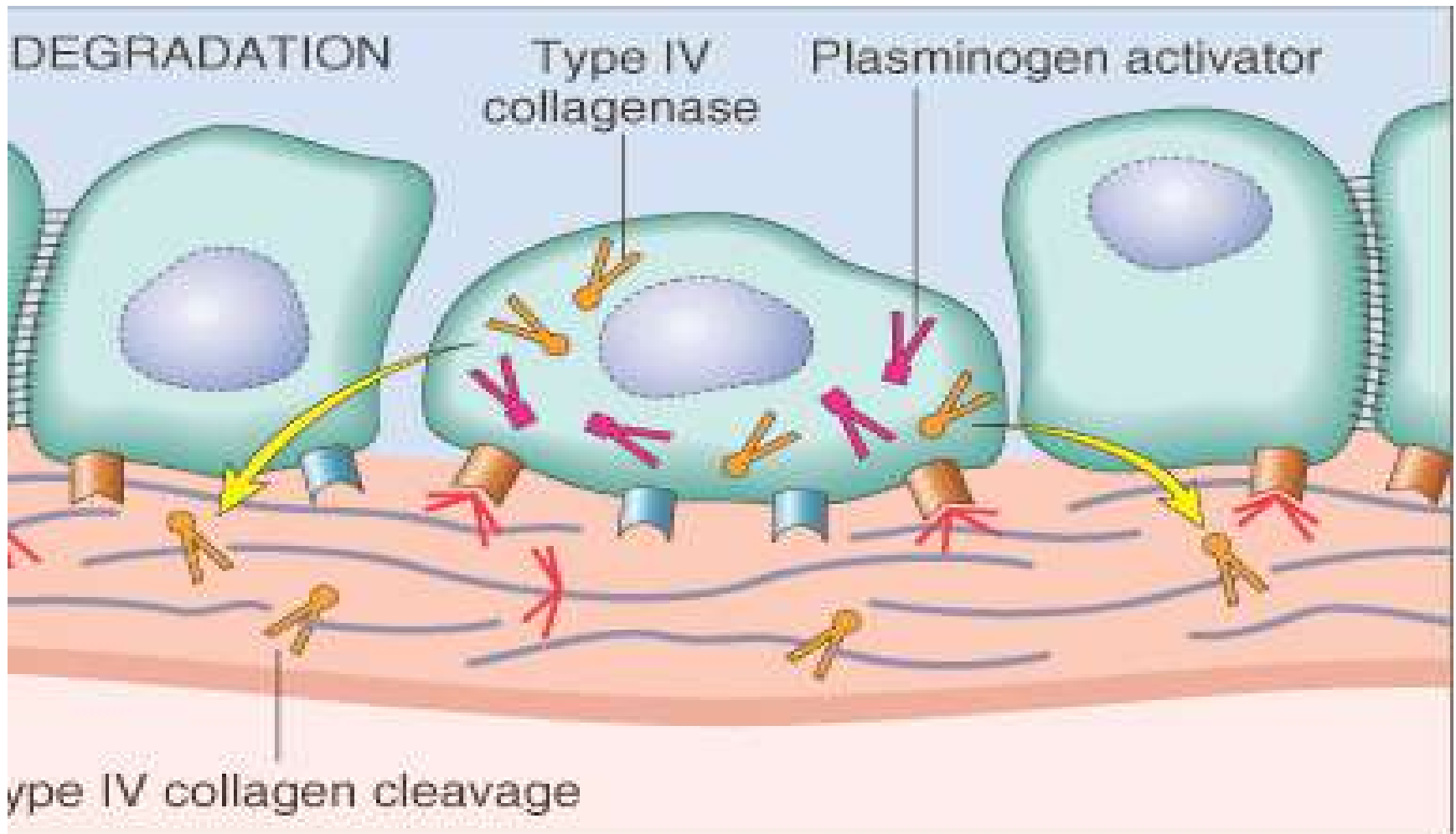
# 1. Invasion of ECM (basement membrane and interstitial connective tissue)

- **Changes in attachment of tumour cells to ECM proteins**
- **Migration of tumour cells via actin**
  - Release of tumour cell derived cytokines
  - Stromal cell derived factor- hepatocyte growth factor
  - By product of cleaved ECM act as chemotactic factor

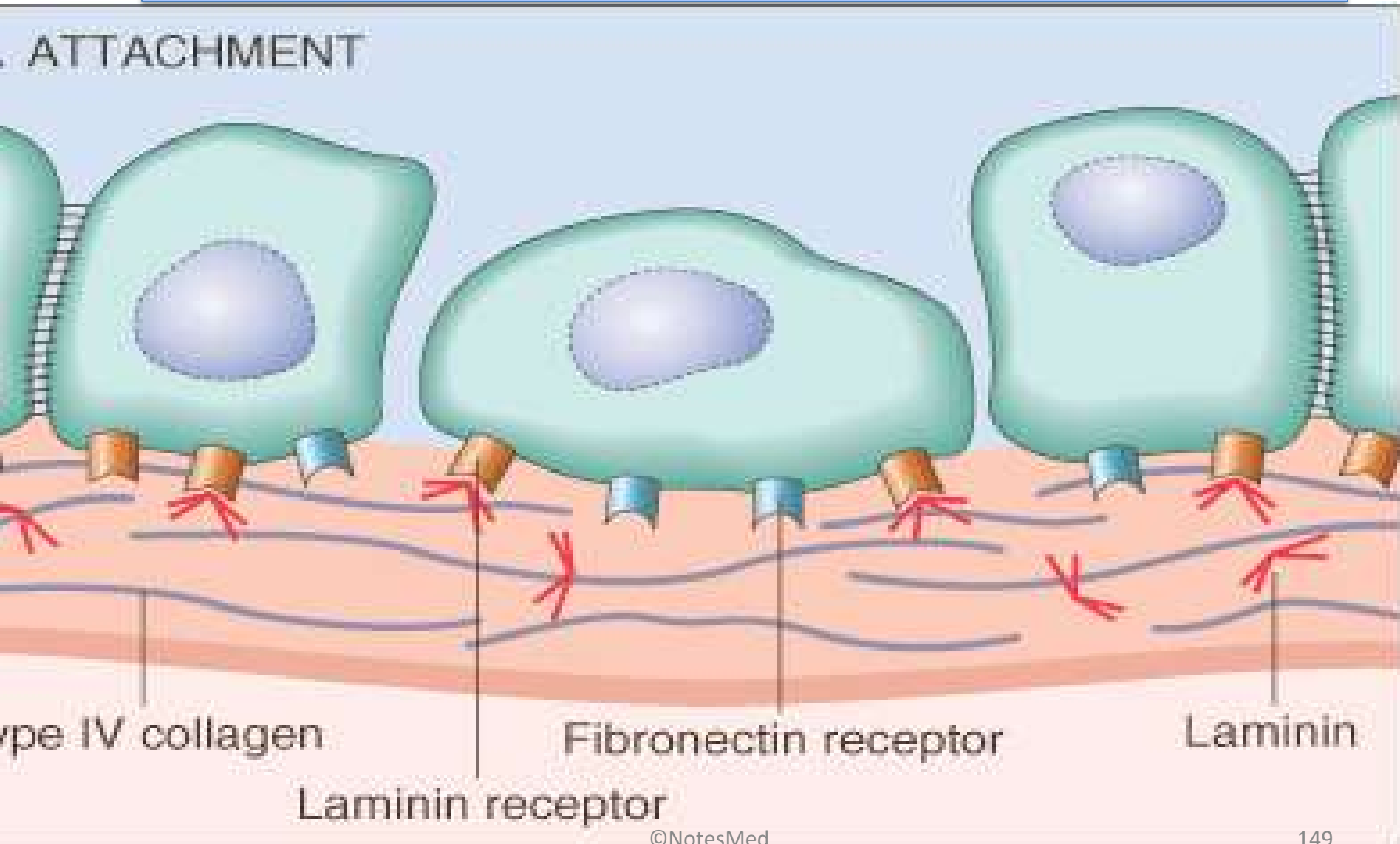
# Invasion of ECM: detachment



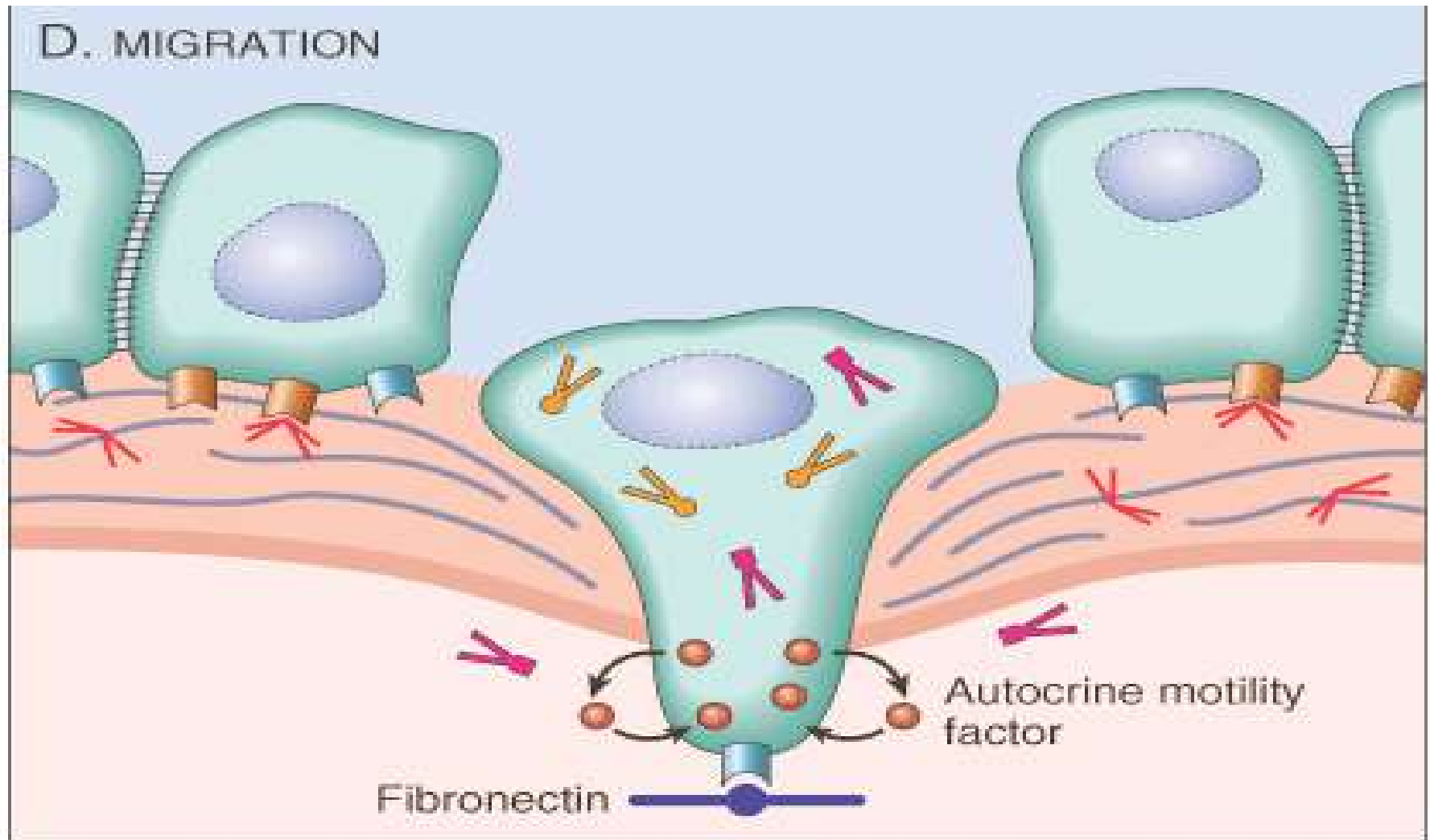
# Invasion of ECM: degradation



# Invasion of ECM: attachment



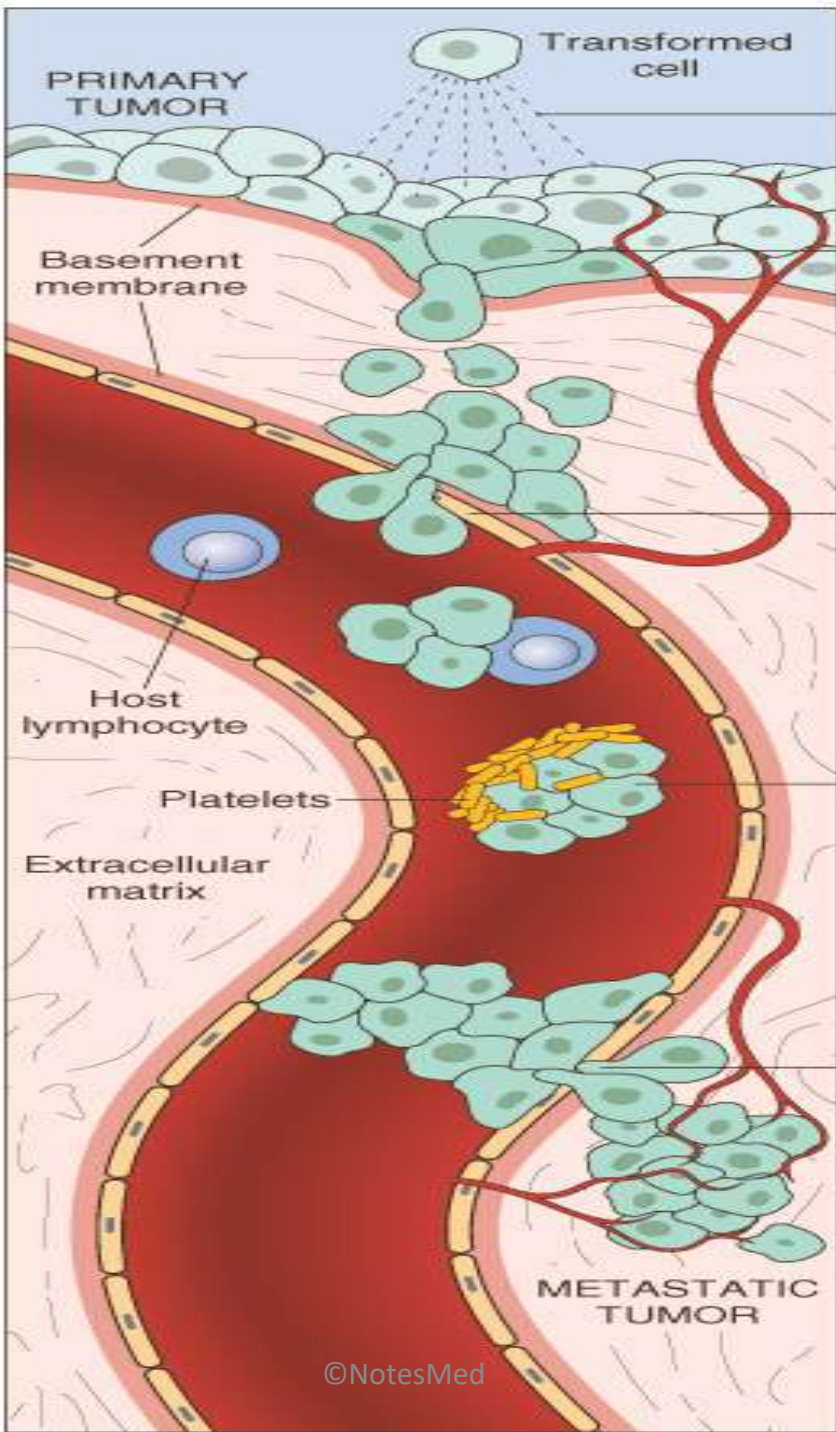
# Invasion of ECM: migration



# Vascular dissemination and homing of tumour cells

- ❖ Intravasation into blood and lymph vessels: adhesion & invasion of BM
- ❖ Transit through the vasculature: Within the circulation tumour cells adhere to each other or leucocytes and platelets forming aggregates (emboli)
- ❖ Extravasation from the vessels: adhesion to endothelial cells and invasion of BM
- ❖ Formation of micrometastases
- ❖ Growth of micrometastases into macroscopic tumours

# Metastasis: mechanism



- Clonal expansion, growth, diversification, angiogenesis
- Metastatic subclone
- Adhesion to and invasion of basement membrane
- Passage through extracellular matrix
- Intravasation
- Interaction with host lymphoid cells
- Tumor cell embolus
- Adhesion to basement membrane
- Extravasation
- Metastatic deposit
- Angiogenesis
- Growth

# Site or organ of metastases

- Depend upon the lymphatic and vascular drainage pathway
- Role of organ tropism by tumour cells

Tumour cells express adhesion molecules and chemokines receptors



Corresponding ligands are expressed by endothelial cells of the metastatic sites

# Invasion and metastases

- After tumour deposition at distant sites, tumour cells are dependent on a receptive stroma for growth
  - secrete cytokines, growth factors and ECM molecules- act on stromal cells at the site of metastasis and modify them to suit their growth

# Evasion of host defense

- Host immune system can recognize tumour cells as foreign Ag and destroy them- **immune surveillance**
- Cancer subclones are able to survive by avoiding immune elimination

# Tumour antigen

- Protein products of **oncogenes and tumour suppressor genes**
- **Over expressed or aberrantly expressed** sequestered normal proteins E.g. tyrosinase, tumour testis ag
- **Tumour ag produced by oncogenic viruses** e.g. HPV- E6
- **Oncofetal ag-** e.g. CEA, alpha feto protein- tumour markers
- **Altered cell surface glycolipids and glycoproteins** e.g. CA125 in ovarian carcinoma

# Tumour antigen

- **Cell type-specific differentiation antigens**
  - normal self-ag specific for particular lineages or differentiation stages of various cell types- no host immune response
  - Helpful to identify cell origin of the tumour and targeted therapy

# Anti-tumour effector mechanism

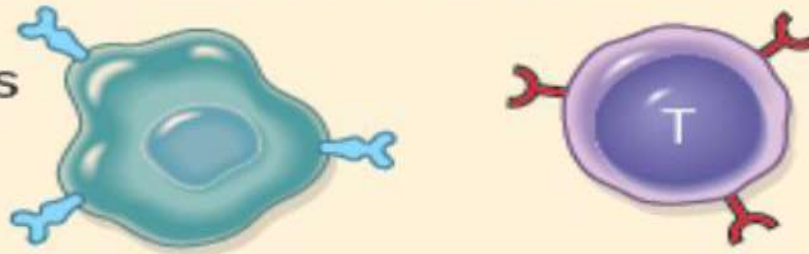
- **Cell mediated immunity**
- **CD8+ CTLs** -- protective role against virus asso tumours
  - CD8+ CTLs recognized tumor antigens presented on the cell surface by MHC class I molecules
  - recognized by
- **Natural killer cells**- first line of defense against tumor cells
- **Macrophages**

# Mechanisms to escape immunity

- Selective outgrowth of **antigen-negative variants- cancer immunoediting**
- **Loss or reduced expression of HLA class I** molecules by tumor cells
- **Activation of immunoregulatory pathways**
  - Downregulate the expression of costimulator receptor-B7 on APC
  - Activate inhibitory receptor CTLA-4, PD-1 on tumour specific T cells
- Secretion of **immunosuppressive factors** by cancer cells e.g. TGF  $\beta$
- Induction of **immunoregulatory T cells**

### Failure to produce tumor antigen

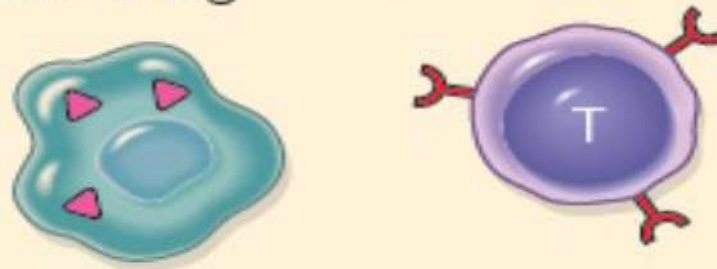
Antigen-loss variant of tumor cell



Lack of T cell recognition of tumor

### Mutations in MHC genes or genes needed for antigen processing

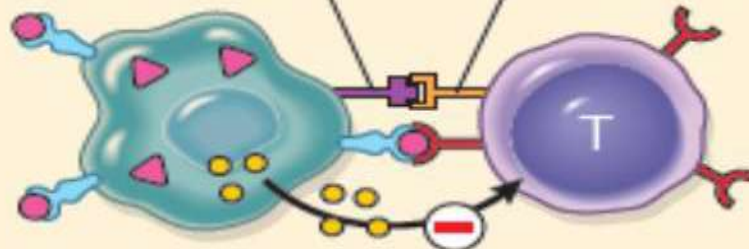
Class I MHC-deficient tumor cell



Lack of T cell recognition of tumor

### Production of immunosuppressive proteins or expression of inhibitory cell surface proteins

Inhibitory ligand      Inhibitory receptor



Inhibition of T cell activation

Immunosuppressive cytokines

# Cancer enabling inflammation

- Inflammatory cells modify the tumor microenvironment in favor of cancer

# Cancer enabling effects of inflammatory cells and stromal cells

- Release of growth promoting factors from ECM
  - e.g. EGF
- Removal of growth suppressors
  - Adhesion molecules that suppresses growth by cell- cell and cell-ECM interaction
- Enhanced resistance to cell death
  - Expression of adhesion molecules that bind to tumour cells and prevent its death after loss of cell-cell interaction and cell-BM interaction

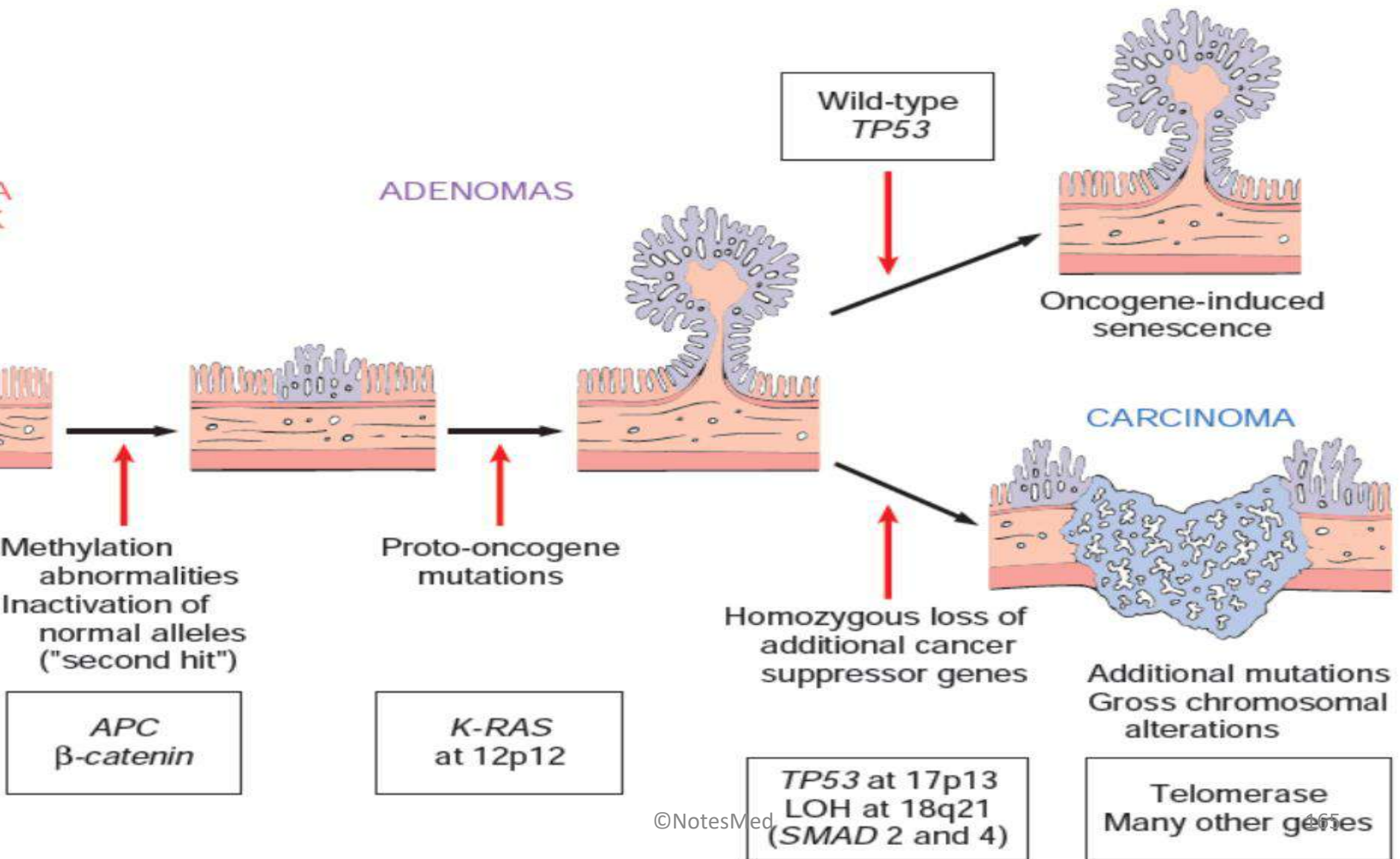
# Cancer enabling effects of inflammatory cells and stromal cells

- Inducing angiogenesis by releasing proangiogenic factor—VEGF
- Activating invasion and metastasis
- Evading immune destruction

# Molecular basis of multistep carcinogenesis

- Each cancer must result from **stepwise accumulation of multiple mutations** and acquire **multiple cancer hallmarks** resulting in development of fully malignant tumour

# Multistep carcinogenesis



# Carcinogens

# ETIOLOGY OF CANCER: CARCINOGENIC AGENTS

- (1) Chemicals
- (2) Radiation
- (3) Microbial agents

# Mechanism of action of chemical carcinogens

1. Initiation
2. Promotion

## Carcinogens

- Initiator
- Promoter

# Chemical carcinogens: initiators

- Direct acting agents
- Indirect acting agents

# Initiators: Direct acting agents

- No requirement for metabolic conversion to carcinogens
- Weak carcinogens
- Alkylating agents
  - Cyclophosphamide
  - Busalphan
- Acylating agents
  - Dimethylcarbamyl chloride

# Indirect acting agents

- Procarcinogens : Metabolic conversion to active carcinogen is needed
- Active forms are highly potent carcinogens
- E.g. polycyclic hydrocarbon (cigarette smoking)

# Indirect-Acting Agents

## **1. Polycyclic and heterocyclic aromatic hydrocarbons**

- Benzo(a)pyrene

## **2. Aromatic amines, amides, azo dyes**

- 2-Naphthylamine ( $\beta$ -naphthylamine)
- Benzidine

## **3. Natural Plant and Microbial Products**

- Aflatoxin B<sub>1</sub>
- Betel nuts

## **4. Others**

- Nitrosamine and amides
- Vinyl chloride, nickel, chromium
- Insecticides
- Occupational exposure – Asbestos

# Initiation- promotion sequence

## Initiator:

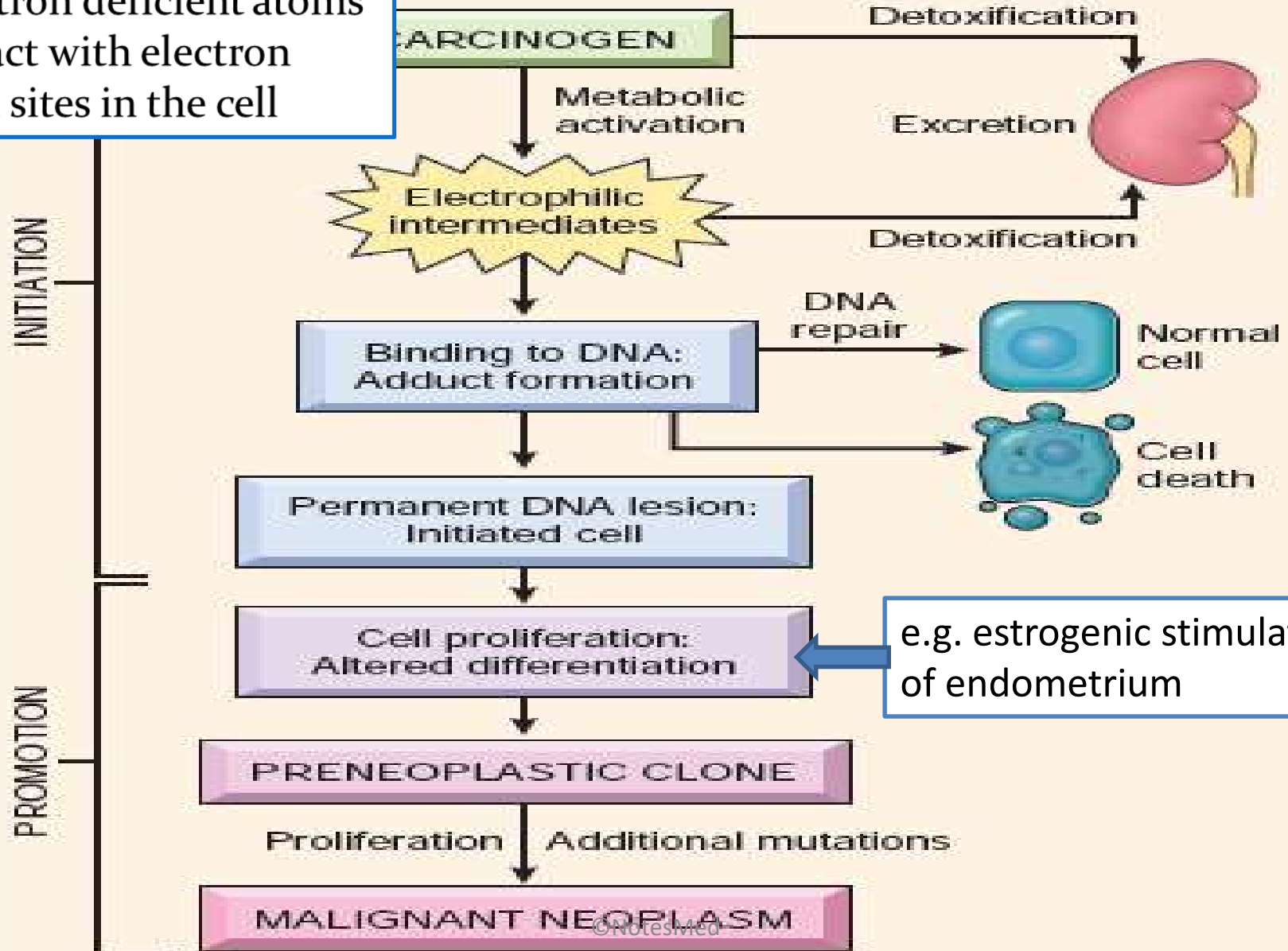
- Initiates tumour development
- Highly reactive electrophiles (have electron-deficient atoms) that can react with nucleophilic (electron-rich) sites in the cell
- Can bind to DNA, proteins and RNA
- Exposure to a sufficient dose of a initiator results in permanent DNA damage (mutation)
- Initiated cell has potency to become a tumour but not yet a tumour cell

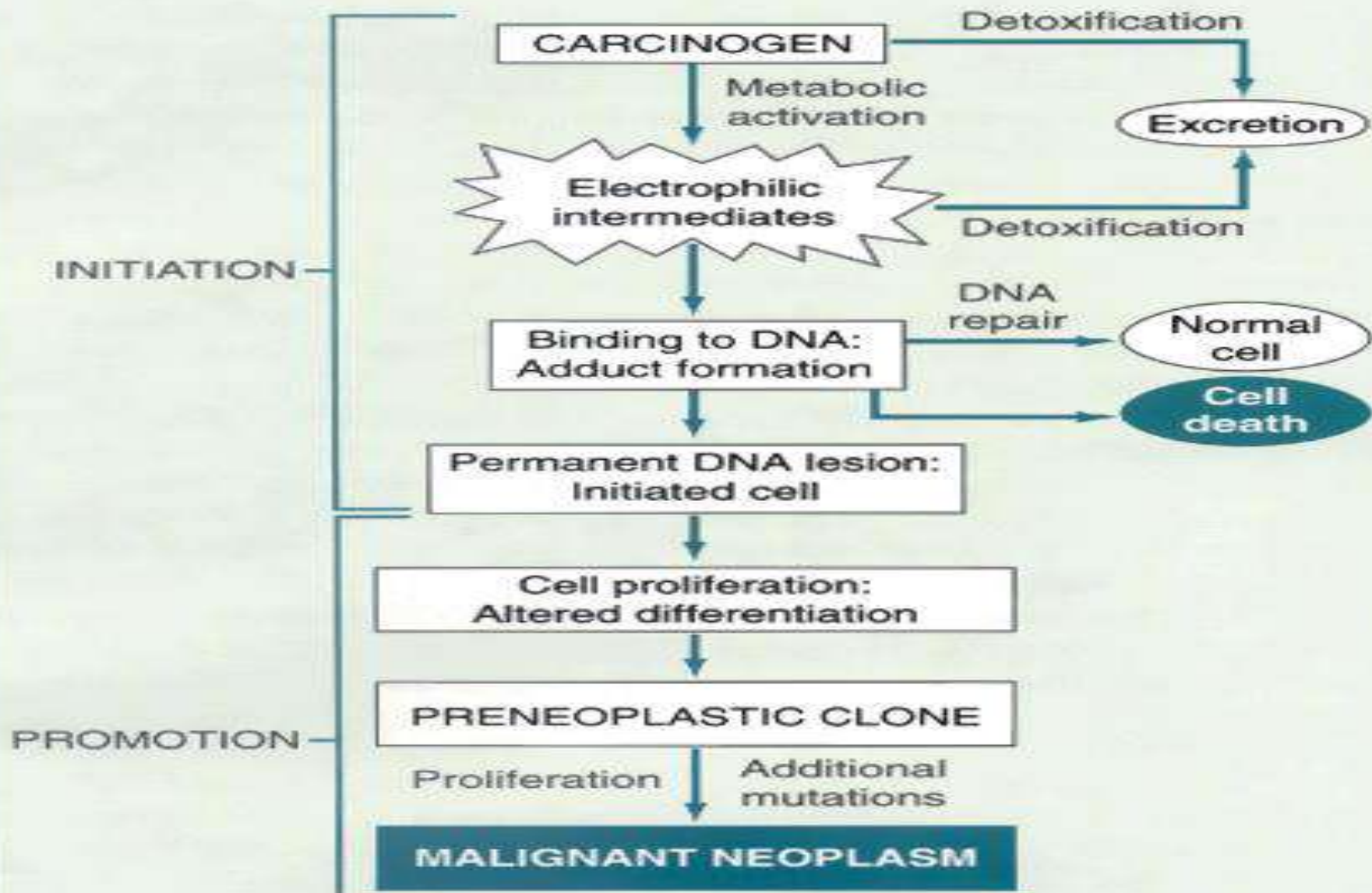
# Promoters

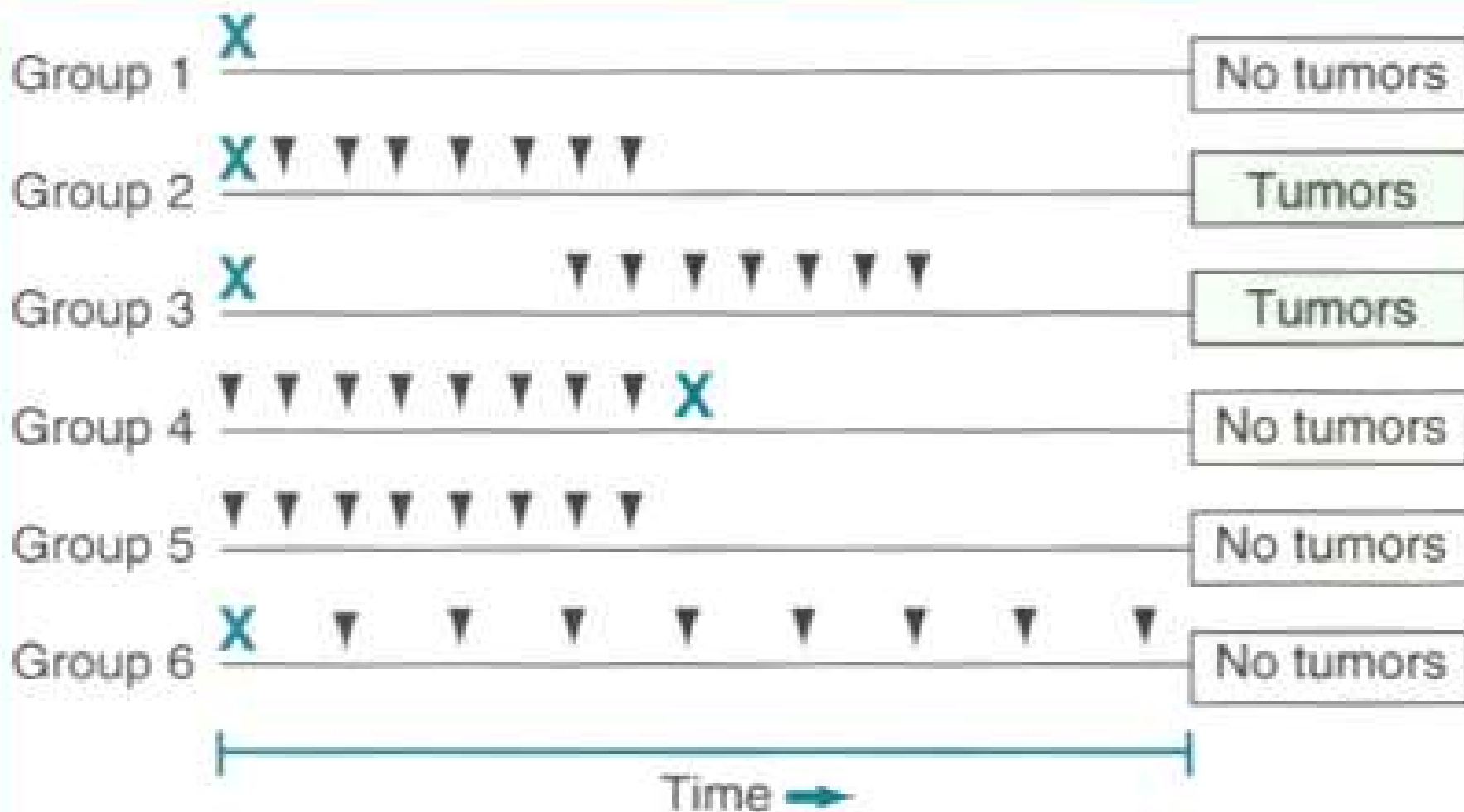
- Act on initiated cells
- Promotes tumour development and progression
- Nontumorigenic --do not affect DNA directly
- Enhance the proliferation of initiated cells which leads to additional mutations and malignant transformation
- Effects may be reversible
- E.g. endogenous and exogenous
  - Estrogen- promote liver cancer
  - bile acids in excess- colon cancer
  - Alcohol- oral cancers

# Initiation-promotion sequence

Electron deficient atoms  
--react with electron  
rich sites in the cell







**X** = Application of initiator (polycyclic hydrocarbon)      ▼ = Application of promoter (Croton oil)

# Radiation carcinogenesis

Carcinogen- radiant energy

- UV rays
- Ionizing electromagnetic or particulate radiation

# Ultraviolet radiation

- Exposure--Skin cancers
  - Squamous cell carcinoma
  - Basal cell carcinoma
- Carcinogenesis depends upon
  - Type of UV rays- UV- B rays (280-320nm)
  - Intensity of exposure
  - Quantity of protective melanin in skin; fair skin– increased risk of malignancy

# UV Radiation carcinogenesis

- Formation of pyrimidine dimers--covalent bonds between bases on the same strand
- Repaired by nucleotide excision repair pathway
- Excess sun exposure → NER pathway overwhelmed → some DNA may not be repaired → MUTATION
- Xeroderma pigmentosum
  - Defective NER
  - High risk of skin malignancy with sunexposure

# Ionizing radiation

## Carcinogens:

- Electromagnetic (x-rays,  $\gamma$  rays)
- Particulate ( $\alpha$  particles,  $\beta$  particles, protons, neutrons) radiations

# Ionizing radiation

Survivors of the atomic bombs dropped on Hiroshima and Nagasaki

- latent period of about 7 years –developed acute and chronic myelogenous leukemia
- longer latent periods --many solid tumors (e.g., breast, thyroid)

# Microbial carcinogenesis

- Oncogenic viruses
- Bacteria

# Oncogenic viruses

- Oncogenic RNA virus
  - Human T-Cell Leukemia Virus Type 1 (HTLV-1)
  - **HCV**
- Oncogenic DNA Viruses
  - 1. HPV**
  - 2. Epstein-Barr virus (EBV)**
  - 3. Hepatitis B virus (HBV)**
  - 4. Kaposi sarcoma herpesvirus (human herpesvirus 8)**
  - 5. Merkel cell polyomavirus**

# Oncogenic RNA Virus: Human T-Cell Leukemia Virus Type 1

- T cell leukaemia / lymphoma
- Route of transmission- sexual/ breast feeding/ blood products
- Tropism for CD4+T cells

## **Mechanism of tumour clone formation**

- HTLV – 1-- contains **tax gene**-- required for viral replication
- alters the transcription of several host cell genes
  - Activation of PI3K/AKT pathway; activate NF- $\kappa$ B;  $\uparrow$ Cyclin D2
- Development of cancer hallmarks

# DNA VIRUSES: HPV virus

- About 70 variants of HPV
- Low risk type
  - 1,2,4--squamous cell papilloma of skin (wart)
  - 6,11( benign anogenital warts)
- High risk type
  - 16, 18
  - Acquired by Sexual transmission
  - Cervical cancer (squamous cell carcinoma)-  
form of STD

# HPV high risk types

- Express oncogenic proteins (E6 & E7)
- Inactivate proteins of tumour suppressor genes, proto-oncogenes or inhibit apoptosis
  - E6 & E7 bind to RB protein and p53 protein and degrade them

# High risk HPV

- Infection with HPV-initiator
- **Additional Ras gene mutation** required
- Other environmental cofactors have **promotion effect**
  - Cigarette smoking
  - Coexisting microbial infections
  - Dietary deficiencies
  - Hormonal changes

# Helicobacter pylori

- Gastric adenocarcinoma
- MALT lymphoma

## **Mechanism– multifactorial**

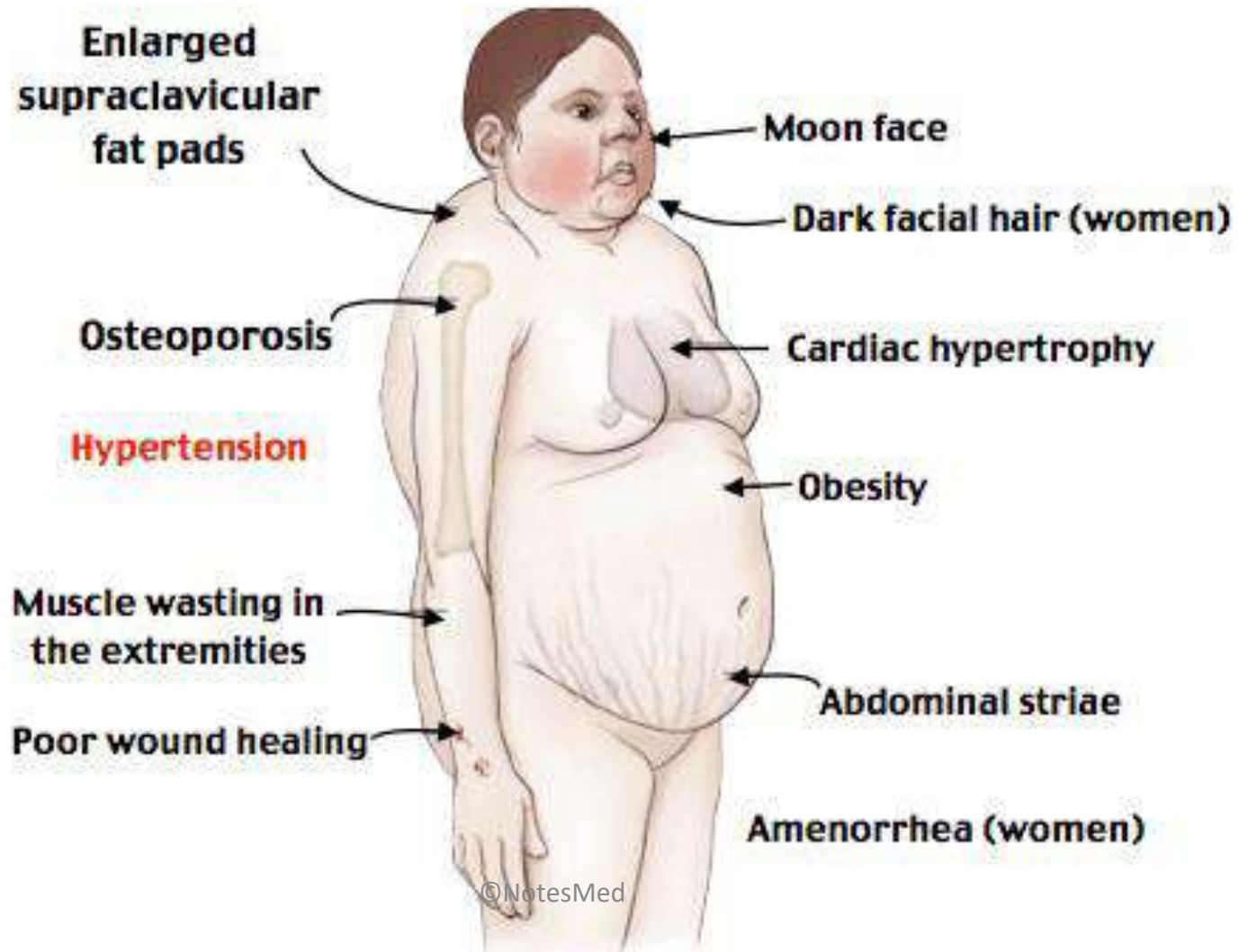
1. Chronic inflammation → glandular atrophy → intestinal metaplasia → dysplasia → cancer
  - Ch inflammation--Stimulation of gastric cell proliferation
  - ROS production– DNA damage and mutations
2. CagA genes– stimulates signaling cascade.
  - CagA gene– Cytotoxin associated A gene product and penetrates cell- stimulates signaling cascade → unregulated growth factor stimulation

# Paraneoplastic syndrome

- Symptom complexes not readily explained by local or distant spread of tumour or by elaboration of hormone indigenous to the tissue from which the tumour arose
- 10% to 15% of cancer patients

# Cushing's syndrome

↳ Due to **excess cortisol-like medication** (prednisone) or **tumor** that produces or results in production of **excessive cortisol**  
[Cases due to a pituitary adenoma = **Cushing's disease**]



# Paraneoplastic syndrome

- May be the earliest clinical manifestation of an occult neoplasm
- May even be lethal
- May mimic metastatic disease and therefore confound treatment.

# Paraneoplastic syndromes

- Endocrinopathies
- Neuromuscular syndromes
- Vascular and Hematologic syndromes
- Bones and joint and soft tissue involvement
- Dermatologic abnormalities

# Paraneoplastic syndrome

## 1. Endocrinopathies:

- **Hypercalcemia**

- Secretion of **PTHrP**
- Not related with bone metastasis
- Associated with squamous cell carcinoma of lung, breast carcinoma, renal carcinoma, Adult T-cell leukemia/lymphoma

- **Cushing's syndrome**

- **Ectopic ACTH** production and hypercortisolism
- Associated with Small cell carcinoma of lung, pancreatic carcinoma

# Neuromuscular syndromes

Mechanism: immune mediated

Associated with Small cell carcinoma of lung

- Lambert-Eaton Myasthenic syndrome
- Peripheral neuropathy- sensory

# Hematologic syndromes

- Migratory thrombophlebitis – venous thrombosis (trousseau phenomenon)
  - Mucin released into the circulation that activate coagulation cascade
  - E.g. Pancreatic carcinoma; adenocarcinoma of lung
- DIC- e.g. acute promyelocytic leukemia

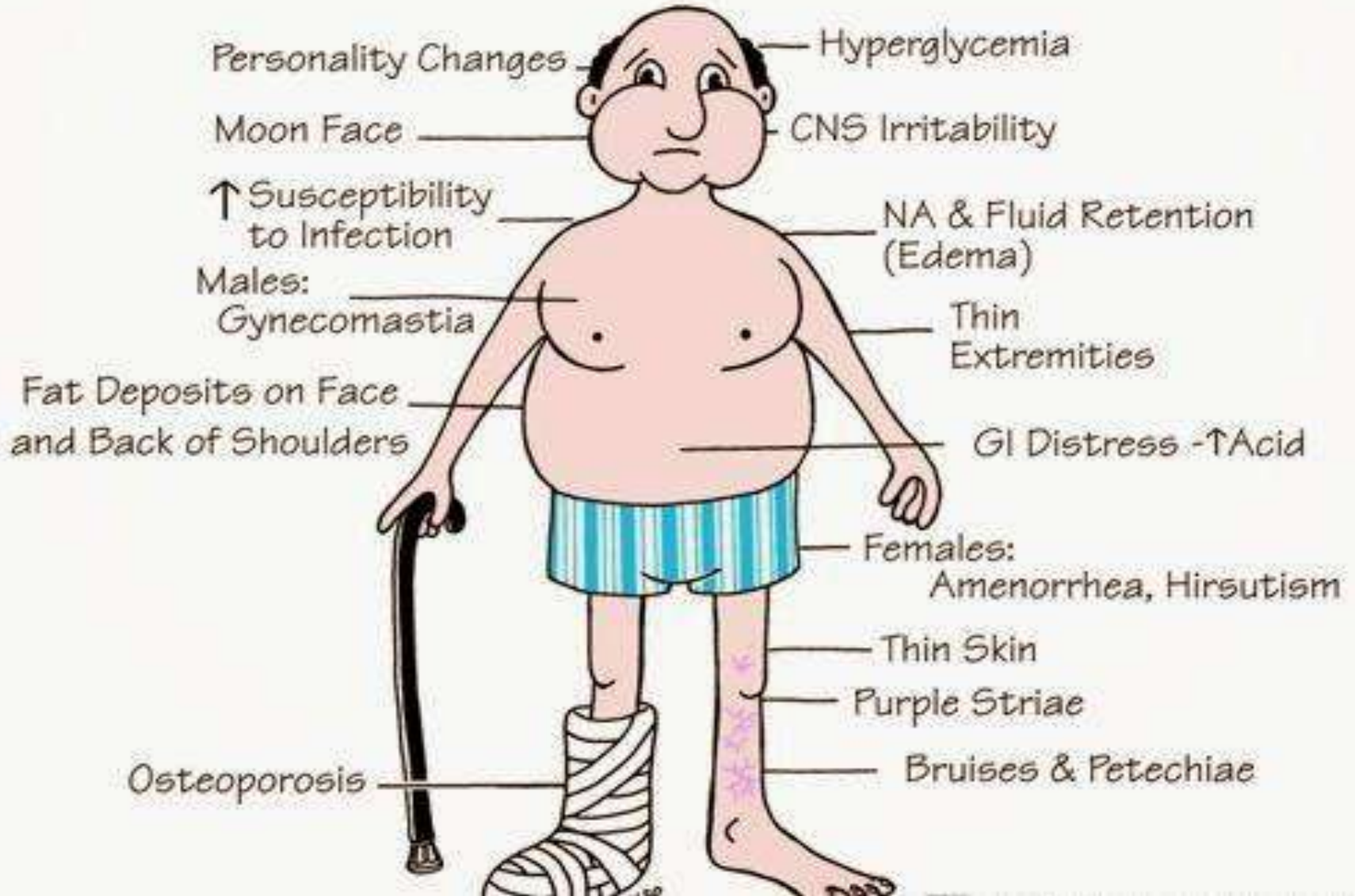
# Involvement of bones, joints and soft tissues

- Clubbing of the fingers
- Hypertrophic osteoarthropathy
  - E.g. bronchogenic carcinoma
- Mechanism is unknown

# Dermatologic abnormalities

- Acanthosis nigricans
  - e.g. gastric carcinoma
  - Mechanism: Immunologic- secretion of epithelial growth factors

# CUSHING'S SYNDROME



# Hypertrophic osteoarthropathy



clubbing of the digits, periostitis of the long (tubular) bones,  
and arthritis

**TABLE 7-11 – Paraneoplastic Syndromes**

Clinical Syndromes	Major Forms of Underlying Cancer	Causal Mechanism
<b>ENDOCRINOPATHIES</b>		
Cushing syndrome	Small-cell carcinoma of lung	ACTH or ACTH-like substance
	Pancreatic carcinoma	
	Neural tumors	
Syndrome of inappropriate antidiuretic hormone secretion	Small-cell carcinoma of lung; intracranial neoplasms	Antidiuretic hormone or atrial natriuretic hormones
Hypercalcemia	Squamous cell carcinoma of lung	Parathyroid hormone–related protein (PTHrP), TGF- $\alpha$ , TNF, IL-1
	Breast carcinoma	
	Renal carcinoma	
	Adult T-cell leukemia/lymphoma	
Hypoglycemia	Ovarian carcinoma	Insulin or insulin-like substance
	Fibrosarcoma	
	Other mesenchymal sarcomas	
Carcinoid syndrome	Hepatocellular carcinoma	Serotonin, bradykinin
	Bronchial adenoma (carcinoid)	
	Pancreatic carcinoma	
Polycythemia	Gastric carcinoma	Erythropoietin
	Renal carcinoma	
	Cerebellar hemangioma	
	Hepatocellular carcinoma	

## NERVE AND MUSCLE SYNDROMES

Myasthenia	Bronchogenic carcinoma	Immunological
Disorders of the central and peripheral nervous system	Breast carcinoma	

## DERMATOLOGIC DISORDERS

Acanthosis nigricans	Gastric carcinoma	Immunological; secretion of epidermal growth factor
	Lung carcinoma	
	Uterine carcinoma	
Dermatomyositis	Bronchogenic, breast carcinoma	Immunological

## OSSEOUS, ARTICULAR, AND SOFT-TISSUE CHANGES

Hypertrophic osteoarthropathy and clubbing of the fingers	Bronchogenic carcinoma	Unknown
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## VASCULAR AND HEMATOLOGIC CHANGES

Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma	Tumor products (mucins that activate clotting)
	Bronchogenic carcinoma	
	Other cancers	
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability
Red cell aplasia	Thymic neoplasms	Unknown

## OTHERS

Nephrotic syndrome	Various cancers	Tumor antigens, immune complexes
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ACTH, adrenocorticotrophic hormone; IL, interleukin; TGF, transforming growth factor; TNF, tumor necrosis factor.