

CANCER

Nomenclature - Histopathology

Why it is important to give the right name to a CANCER disease

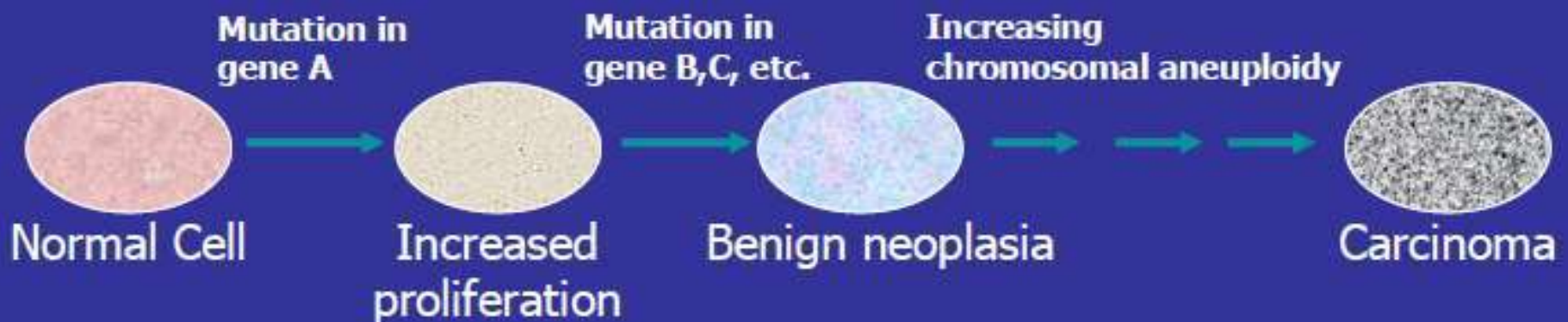
understanding the pathology and/or histology of cancer helps you:

- to make a correct diagnosis (fundamental step for a correct therapy)
- to formulate a better research question (fundamental for studying the etiology, the molecular pathogenesis, and the progression of the disease)
- to design novel targeted therapeutic strategies

Neoplasia

- Benign tumours :
 - Will remain localized
 - **Cannot (by definition= DOES NOT) spread to distant sites**
 - Generally can be locally excised
 - Patient generally survives
- Malignant tumours:
 - Can invade and destroy adjacent structure
 - **Can (and OFTEN DOES) spread to distant sites**
 - Cause death (if not treated)

Cancer is not a single static state
but a progression and mixture of
phenotypic and genetic/epigenetic
changes that proceed toward
greater aggressive biological
behavior



Cancer Hystopathology Diagnosis

- Biopsy
- Fine-Needle aspiration (FNA)
- Exfoliative cytology (pap smear)
- Biochemical markers (PSA, CEA, Alpha-fetoprotein)

Neoplasia

- two basic components:
 - **Parenchyma:** made up of neoplastic cells
 - **Stroma:** made up of non-neoplastic, host-derived connective tissue and blood vessels

The parenchyma:

Determines the biological behavior of the tumor

From which the tumour derives its name

The stroma:

Carries the blood supply

Provides support for the growth of the parenchyma

NOMENCLATURE

The most basic classification of human cancer is the organ or body location in which the cancer arises

1. Principle of nomenclature

(1) Benign tumors

Attaching the suffix “-oma” to the type of cell (glandular, muscular, stromal, etc) plus the organ: e.g., adenoma of thyroid.

More detail:

The name of organ and derived tissue/
cell + morphologic character + oma

e. g. skin papilloma, ovarian cyst
adenoma

(2) Malignant tumors (cancers)

① **Carcinoma:** Malignant tumors of epithelial cell origin

The name of organ and derived tissue/ cell + carcinoma.

e. g. adenocarcinoma of thyroid.

More details:

The name of organ and derived tissue/ cell + morphologic features + carcinoma

e. g. papillary carcinoma of skin, ovarian cystadenocarcinoma, oat (small) cell carcinoma of lung, signet ring cell (cell with a large vacuole) carcinoma of stomach

② **Sarcoma:** malignant tumors arising in mesenchymal tissue or its derivatives

The name of organ

and derived tissue/ cell + sarcoma

e. g. leiomyosarcoma of uterus

(3) Special nomenclature

- ① Blastoma: tumours arising in immature tissue or nervous tissue, most of them are malignant
e.g. medulloblastoma, retinoblastoma, nephroblastoma
- ② Some tumors attaching the suffix-oma. But malignant
e. g. seminoma, lymphoma, melanoma, dysgerminoma, endodermal sinus tumor

- ③ Some malignant tumors, but called disease.
e. g. leukemias, paget's disease
- ④ Some malignant tumors nominated by
scientists' name
e. g. Hodgkin's disease, Ewing's tumor
- ⑤ Mixed tumors: tumors which derived from
one germ layer may undergo divergent
defferentiation creating
e. g. mixed tumor of salivery gland

- ⑥ **Teratomas:** tumors containing mature or immature cells or tissues representative of more than one germ layer and sometimes all the three layers.
- ⑦ **Hamartoma:** tumor-like malformation composed of a haphazard arrangement of tissues indigenous to the particular site, which is totally benign.

Neoplasia nomenclature

- historic eponyms – “first described by...”

Hodgkin's disease	Malignant lymphoma (HL) of B Ly cell origin
Burkitt tumor	NHL – B Ly cell in children (jaw and GIT)
Ewing tumor	Bone tumor (PNET)
Grawitz tumor	Kidney tumor - clear cell adenocarcinoma
Kaposi sarcoma	Malignant tumor derived from vascular epithelium (AIDS)
Brenner tumor	Ovarian tumor derived from Brenner cells
Askin tumor	Malignant chest wall tumor of PNET
Merkel tumor	Skin tumor derived from Merkel cell

Mesenchymal – connective tissue & endothelial related

Benign

- Fibroma
- Lipoma
- Chondroma
- Osteoma
- Hemangioma
- Meningioma

Malignant

- Fibrosarcoma
- Liposarcoma
- Chondrosarcoma
- Osteogenic sarcoma
- Angiosarcoma
- Invasive meningioma
- Synovial sarcoma
- Mesothelioma

Epithelial origin

Benign

- Adenoma
- Renal tubular adenoma
- Liver cell adenoma
- Hydatidiform mole

Malignant

- Squamous cell carcinoma
- Basal cell carcinoma
- Adenocarcinoma
- Renal cell carcinoma
- Hepatocellular carcinoma
- Choriocarcinoma
- Seminoma
- Embryonal carcinoma

Macroscopic Criteria for Classification of:

<h2>Benign</h2>	<h2>Malignant</h2>
-----------------	--------------------

- Structure typical of tissue of origin
- Encapsulated
- Slow growth
- No metastasis

- Atypical structure
- Locally invasive, infiltrating
- Rapid & erratic growth
- Metastasis

Microscopic Criteria for Classification of:

Benign	Malignant
--------	-----------

- Well differentiated
- Uniform
- N:C = 1:4 or 1:6
- Rare *normal* mitotic figures
- Normal orientation
- Abundant stroma

- Generally less well differentiated to undifferentiated (anaplastic)
- Pleomorphic
- N:C = 1:1
- Hyperchromatic
- More mitoses, abnormal & bizarre
- Loss of polarity
- Tumor giant cells

The first step toward epithelial neoplasia is cellular transformation

Traditionally, two forms of cellular transformation have been recognized that are potentially reversible, but may be steps toward a neoplasm. These are:

- **Metaplasia**: the exchange of *normal epithelium* for another type of epithelium. Metaplasia is reversible when the stimulus for it is taken away.
- **Dysplasia**: a *disordered growth and maturation of an epithelium*, which is still reversible if the factors driving it are eliminated.

However, **Hyperplasia**: *an increase in the number of phenotypically normal cells*, may also reflect an early stage of transformation.

Dysplasia

- “*disordered growth*”
- Loss in uniformity of the individual cells
- Loss of architectural orientation
- Pleomorphism
- Hyperchromatic
- Increased mitoses (normal)

Carcinoma in situ

- Dysplastic changes involve entire thickness of epithelium
- If left untreated, will progress to invasive cancer

Neoplasia

- Dysplasia :
 - Definition: a loss in the uniformity of the individual cells and a loss in their architectural orientation.
 - Non-neoplastic
 - Occurs mainly in the epithelia
 - Dysplastic cells shows a degree of : pleomorphism, hyperchromasia, increased mitosis and loss of polarity.

Dysplasia

- Clinical significance:
 - It is a premalignant condition.
 - The risk of invasive cancer varies with:
 - ✓ grade of dysplasia (mild, moderate, severe)
 - ✓ duration of dysplasia
 - ✓ site of dysplasia

Neoplasia

- Dysplasia does not mean cancer
- Dysplasia does not necessarily progress to cancer
- Dysplasia may be reversible
- If dysplastic changes involve the entire thickness of the epithelium it is called :

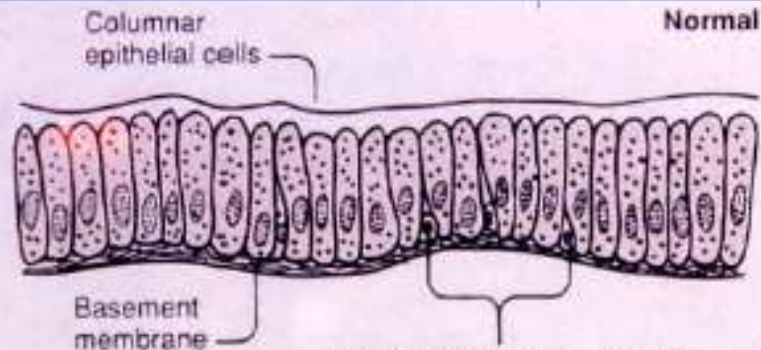
CARCINOMA IN-SITU

Dysplasia Features:

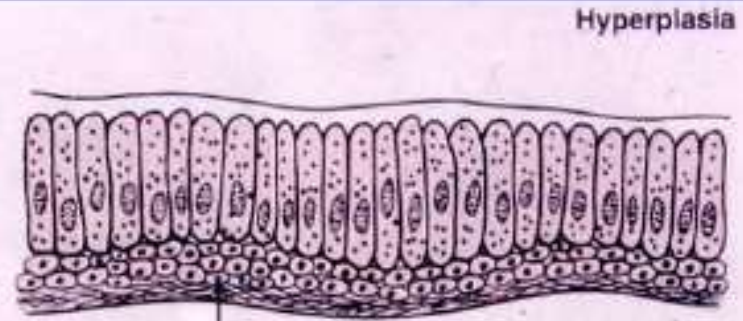
- Increased rate of multiplication.
- Disordered maturation.

- **Nuclear abnormality**
 - Increased N/C ratio
 - Irregular nuclear membrane
 - Increased chromatin content
- **Cytoplasmic abnormalities**
due to failure of normal

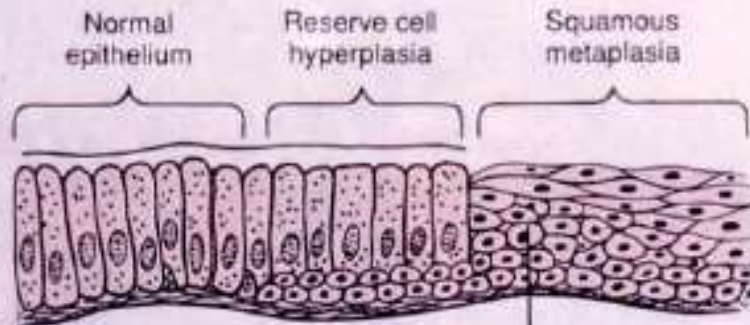
CHANGES IN UTERINE CERVIX



Reserve cells (stem cells of endocervical epithelium) normally divide and differentiate into glandular epithelial cells that replace exfoliated surface cells.



Hyperplastic reserve cells differentiate into normal glandular epithelial cells.



Squamous metaplasia

Reserve cells differentiate into normal appearing mature squamous epithelium that replaces glandular epithelium. (Similar changes occur in squamous metaplasia of the bronchus.)



Dysplasia

Squamous epithelial cells show abnormal maturation and cytologic abnormalities.

Neoplasia

- Carcinoma in-situ
 - Definition: an intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration of the basement membrane.
 - Applicable only to epithelial neoplasms.

Metastases

- A primary neoplasm is more likely to appear within an organ as a solitary mass.
- The presence of metastases are the best indication that a neoplasm is malignant. The original clone of cells that developed into a neoplasm may not have had the ability to metastasize, but continued proliferation of the neoplastic cells and acquisition of more genetic mutations within the neoplastic cells can give them the ability to metastasize.

Spread of Tumors

- Direct invasion – infiltration & destruction of surrounding tissue
- Metastasis – noncontiguous spread to other organ/body locations
 - Lymphatics – carcinomas, lymphatic drainage
 - Veins & arteries – sarcomas, *renal cell carcinoma, hepatocellular carcinoma*
 - Implantation – “open field”, ovarian carcinomas, appendix = *pseudomyxoma peritonei*

Nomenclature of tumors

Tissue of Origin	Benign	Malignant
<p>Composed of One parenchymal cell Type</p> <p>Mesenchymal tumors</p> <p>Connective tissue and derivatives</p>	<p>Fibroma</p> <p>Lipoma</p> <p>Chondroma</p> <p>Osteoma</p>	<p>Fibrosarcoma</p> <p>Liposarcoma</p> <p>Chondrosarcoma</p> <p>Osteogenic sarcoma</p>
<p>Endothelial and related tissues</p> <p>Blood vessels</p> <p>Lymph vessels</p> <p>Synovium</p> <p>Mesothelium</p> <p>Brain coverings</p>	<p>Hemangioma</p> <p>Lymphangioma</p> <p>Meningioma</p>	<p>Angiosarcoma</p> <p>Lymphangiosarcoma</p> <p>Synovial sarcoma</p> <p>Mesothelioma</p> <p>Invasive meningioma</p>

Nomenclature of tumors

Tissue of Origin	Benign	Malignant
Blood cells and related cells Hematopoietic cells Lymphoid tissue Muscle Smooth Striated	Leiomyoma Rhabdomyoma	Leiomyosarcoma Rhabdomyosarcoma
Epithelial tumors Stratified squamous Basal cells of skin or adnexa Epithelial lining Glands or ducts	Squamous cell papilloma Adenoma Papilloma Cystadenoma	

Nomenclature of tumors

Tissue of Origin	Benign	Malignant
Epithelial tumors Stratified squamous Basal cells of skin or adnexa Epithelial lining Glands or ducts	Squamous cell papilloma Adenoma Papilloma Cystadenoma	Squamous cell or epidermoid carcinoma Basal cell carcinoma Adenocarcinoma Papillary carcinoma Cystadenocarcinoma

Nomenclature of tumors

Tissue of Origin	Benign	Malignant
Respiratory passages Neuroectoderm Renal epithelium Liver cells Urinary tract epithelium (transitional) Placental epithelium (trophoblast) Testicular epithelium (germ cells)	Nevus Renal tubular adenoma Liver cell adenoma Transitional cell papilloma Hydatidiform mole	Bronchogenic carcinoma Bronchial adenoma (carcinoid) Malignant melanoma Renal cell carcinoma Hepatocellular carcinoma Transitional cell carcinoma Choriocarcinoma Seminoma Embryonal carcinoma

Nomenclature of tumors

Tissue of Origin	Benign	Malignant
<p>More Than One Neoplastic Cell Type- Mixed Tumors, Usually Derived From One Germ Layer</p> <p>Salivary glands</p>	<p>Pleomorphic adenoma (mixed tumor of salivary origin)</p>	<p>Malignant mixed tumor of salivary gland origin</p>
<p>Breast</p> <p>Renal anlage</p>	<p>Fibroadenoma</p>	<p>Malignant cystosarcoma phyllodes</p> <p>Wilms tumor</p>

Nomenclature of tumors

Tissue of Origin	Benign	Malignant
<p><i>More Than One Neoplastic Cell Type Derived From More Than One Germ Layer- Tera- fogenous</i></p> <p>Totipotential cells in gonads or in embryonic rests</p>	<p>Mature teratoma, dermoid cyst</p>	<p>Immature teratocarcinoma, teratoma,</p>

Neoplasia

- **Adenoma** : benign epithelial neoplasms producing gland pattern....OR ... derived from glands but not necessarily exhibiting gland pattern
- **Papilloma** : benign epithelial neoplasms growing on any surface that produce microscopic or macroscopic finger-like pattern

TERATOMA

- Teratoma:
 - Teratoma contains recognizable mature or immature cells or tissues representative of more than one germ-cell layer and some times all three.
 - Teratomas originate from totipotential cells such as those normally present in the ovary and testis.

If all the components parts are well differentiated, it is a benign (mature) teratoma.

If less well differentiated, it is an immature (malignant) teratoma.

TERATOMA

- **Such cells have the capacity to differentiate into any of the cell types found in the adult body. So they may give rise to neoplasms that mimic bone, epithelium, muscle, fat, nerve and other tissues.**
- **Most common sites are: ovary & testis**

TERATOMA

- If all the components parts are well differentiated, it is a benign (mature) teratoma.
- If less well differentiated, it is an immature (malignant) teratoma.

WHAT ARE HAMARTOMAS AND CHORISTOMA?

Hamartoma: a mass composed of cells native to the organ

e.g. pulmonary hamartoma.

Choristoma: a mass composed of normal cells in a wrong location

e.g. pancreatic choristoma in liver or stomach.

- Malformation and not neoplasm.

Hamartoma and Choristoma

- They are distinguished from neoplasms by the fact that they do not exhibit continued growth. they are group of tumor-like tissue masses which may be confused with neoplasms

Staging and Grading

Staging and Grading

- Devised for malignant neoplasms
- The stage and/or grade generally determine the treatment and the prognosis
- In general, the higher the stage, the larger a neoplasm is and the farther it has likely spread.
- In general, the higher the grade, the more likely it is that the tumor is rapidly growing and will invade and metastasize.

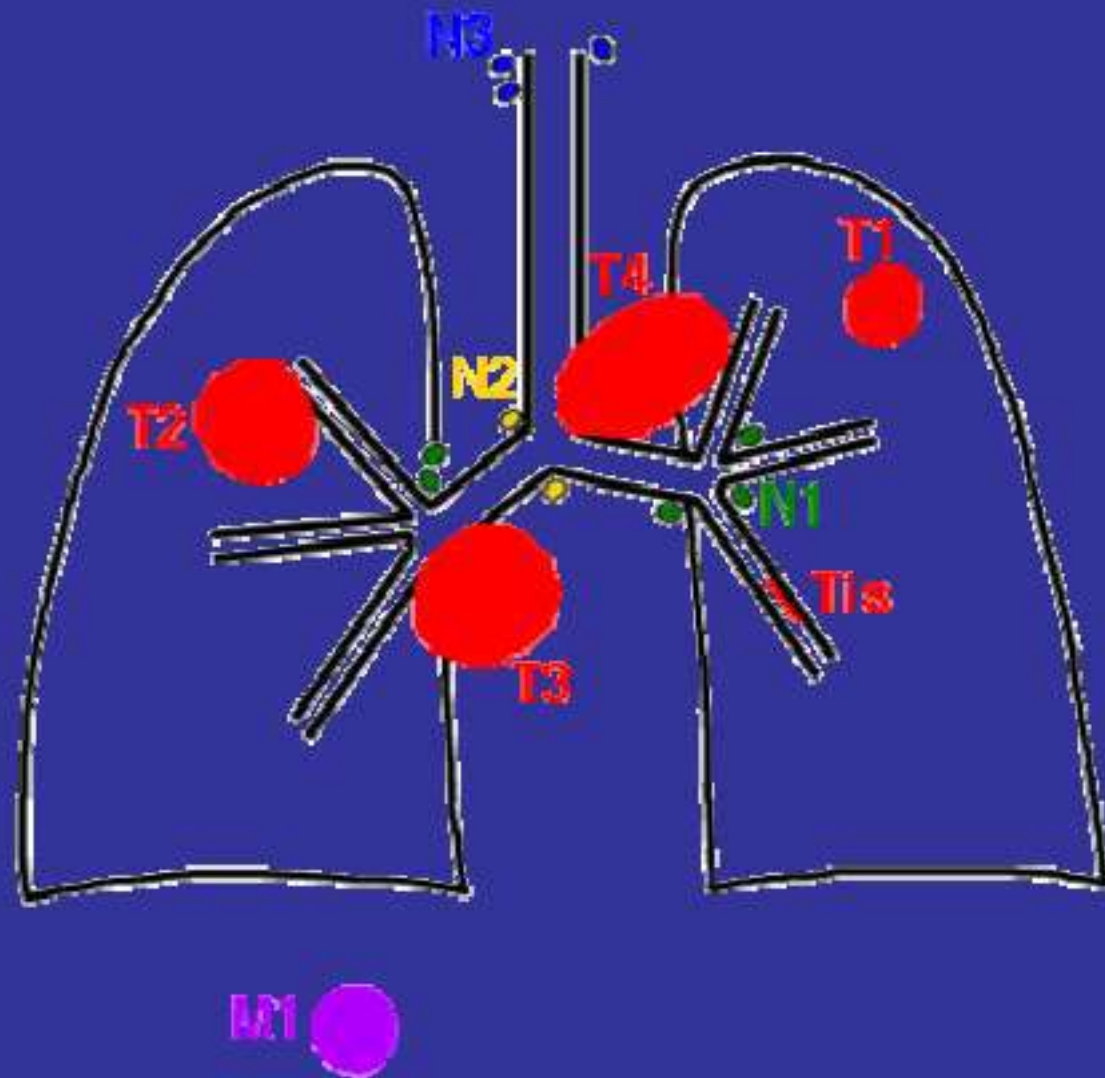
Staging Tumors:

Extent of Spread

- Generally correlates better with prognosis than histopathologic grading
- Used in therapy selection
- Union Internationale Centre Cancer (UICC)
 - TNM system
- American Joint Committee (AJC) on Cancer Staging
 - Stages 0 – IV

Staging of Malignant Neoplasms

Stage	Definition
Tis/T0	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present



In the diagram above utilizing a lung carcinoma as an example, the principles of staging are illustrated:

Grading

= degree of differentiation

- Grading schema are based upon the microscopic appearance of a neoplasm with H&E staining.
- In general, a higher grade means that there is a lesser degree of differentiation and the worse the biologic behavior of a malignant neoplasm will be.
- A well-differentiated neoplasm is composed of cells that closely resemble the cell of origin
- A poorly differentiated neoplasms have cells that are difficult to recognize as to their cell of origin.
- Grading schema have been devised for many types of neoplasms, mainly carcinomas.
- Most grading systems have three or four grades (designated with numbers or roman numerals).

Grading of Malignant Neoplasms

Grade	Definition
I	Well differentiated
II	Moderately differentiated
III	Poorly differentiated
IV	Nearly anaplastic

Tumor markers

Tumor markers

- Tumor markers are usually proteins which are produced from cancer cells or as response to cancer
- Cancer specific
- Tissue specific

Tumor markers

- **Cancer specific** of certain cancerous tissue BUT large overlap (low specificity)
- **Tissue specific** i.e PSA, AFP, B-HCG, thyroglobulin

In oncology tumor markers are used:

- Screening i.e PSA
 - Monitoring i.e AFP
- Diagnosis (when biopsy is not feasible)
- Determine prognosis

Tumor markers: CEA

- Complex glycoprotein that is associated with the plasma membrane of tumor cells, from which may be released in the blood
- Elevated specially in Colon cancer, But Also in Pancreatic, Gastric, Lung, breast and Ovarian cancer
- ALSO in cirrhosis, inflammatory bowel disease, chronic lung disease, pancreatitis, 19% of smokers, 3% of healthy population

Tumor markers: CEA

- NOT satisfactory for screening for a healthy population
- Monitor of recurrence
- Monitor of treatment

Tumor markers: Ca-125

- 80% of nonmucinous ovarian cancer detected by monoclonal antibody
- Elevated in Ovarian, Endometrial, Pancreatic, Lung, Breast, Colon, Menstruation, Pregnancy, Endometriosis and other gynecological and non conditions.

Tumor markers: Ca-125

- Useful in monitoring ovarian cancer recurrence & treatment
- Not useful for screening
- Screening of high risk population (BRCA1-2 Carriers)

Tumor markers: CA 19-9

- 21-42% elevated in gastric ca
- 20-40% elevated in colonic ca
- 71-93% elevated in pancreatic
- Useful for differentiated benign from malignant disease

Tumor markers: PSA

- Prostate Specific Antigen: Glycoprotein
- Ideal for tumor marker, high tissue specificity
- High sensitivity for prostate cancer, also elevated in benign prostate hypertrophy & prostatitis
- Useful in diagnosis

Tumor markers: PSA

Useful for:

- Diagnosis of prostate cancer
- Prognostic factor
- Monitor recurrence & response to treatment
- ?Screening of prostate cancer (+rectal examination)

Tumor markers: AFP

- Normal serum fetal protein synthesized by the liver, yolk sac, gastrointestinal tract
- Hepatocellular cancer: diagnosis (>500) screening of high risk population

Tumor markers: AFP

- Testicular germ cell tumor (embryonal or endodermal):
 - diagnosis
 - monitor of recurrence & response
 - prognostic marker (>100.000 –high risk)
- Less frequent elevated: pancreatic ca
 - Gastric ca
 - Colonic ca
 - Bronchogenic ca

TREATMENT OF CANCER

OVERVIEW

- There are many types of cancer treatment. The types of treatment that patient receive will depend on the type of cancer, stage of cancer and how advanced it is.
- Some people with cancer will have only one treatment. But most people have a combination of treatments, such as surgery with chemotherapy and/or radiation therapy.

Treatment of cancer can involve any of several modalities:

Surgical interventions

Radiation therapy

Chemotherapy

Gene therapy

Stem cell and bone marrow transplants

Immunotherapy

SURGERY

- Surgical removal of the entire cancer remains the ideal and most frequently used treatment method.
- Surgery may be the primary method of treatment, or it may be prophylactic, palliative, or reconstructive.

Factors that increase operative risk in cancer patients include

- 1. Age**
- 2. Comorbid conditions**
- 3. Debilitation due to cancer**
- 4. Paraneoplastic syndrome** (associated with cancer occur when a cancer causes unusual symptoms due to substances that circulate in the blood stream) For E.g. Lung tumor, renal carcinoma, hepatocellular carcinoma, breast, ovarian cancer and pancreatic cancer.

WHAT IS RADIATION THERAPY

- Sometimes radiation therapy is the only treatment a patient needs.
- Other times, it is combined with other treatments, like surgery and chemotherapy.

Radiation therapy

- Radiation therapy is the use of **high-energy ionizing rays** to destroy a cancer cell's ability to grow and multiply.
- The goal of radiation therapy is to deliver a precisely measured dose of irradiation to a defined tumor volume with minimal damage to surrounding healthy tissue.
- This results in eradication of tumor, high quality of life, prolongation of survival, and allows for effective palliation or prevention of symptoms of cancer, with minimal morbidity.

The total number of fractions administered depends on:

- Tumor size and location
- Cancer type
- Reason for treatment
- Patient's overall health
- Other treatments the patient is receiving.

Complications

- Complications depend on the site of radiation therapy, type of radiation therapy (brachytherapy or teletherapy), total radiation dose, daily fractionated doses, and overall health of the patient.

Side Effects of Radiation Therapy

- Side effects, like skin tenderness, are generally limited to the area receiving radiation. Unlike chemotherapy, radiation usually doesn't cause hair loss or nausea.
- Most side effects begin during the second or third week of treatment. Side effects may last for several weeks after the final treatment.

CHEMOTHERAPY

- Chemotherapy-is the use of chemicals to treat disease.
- **-Paul Erlich**, considered to be the father of chemotherapy,

What is Chemotherapy.

- Chemotherapy is the use of antineoplastic drugs to promote tumor cell destruction by interfering with cellular function and reproduction.
- It includes the use of various chemotherapeutic agents and hormones.

- Chemotherapy is a term used to describe any treatments that utilizes the introduction of chemical agents to an organism to help control, stop and or terminate the rapid growth of cells.
- There are 60 types of chemotherapy currently available and new ones being developed all the time.

HOW DO THE DRUGS WORK

- The drugs enter the bloodstream and reach all parts of the body
- Cytotoxic drugs destroy cancer cells by damaging them so that they can't divide and grow.
- The drugs can also affect normal cells.

HOW DO THE DRUGS WORK

- In order to damage and kill the cancer cells, the drugs must be absorbed into your blood and carried throughout your body.
- The way chemotherapy is given depends on the type of cancer.
- The drugs. (for example, some must be injected and some can be taken by mouth).

TOXICITY

- Toxicity associated with chemotherapy can be acute or chronic.
- Cells with rapid growth rates (eg, **epithelium, bone marrow, hair follicles, sperm**) are very susceptible to damage, and various body systems may be affected as well.

Nursing Management in Chemotherapy

- The nurse has an important role in assessing and managing many of the problems experienced by the patient undergoing chemotherapy.
- Requires knowledge about the treatment -, skill in assessment - technical expertise, - ability and desire to support the client physically and emotionally

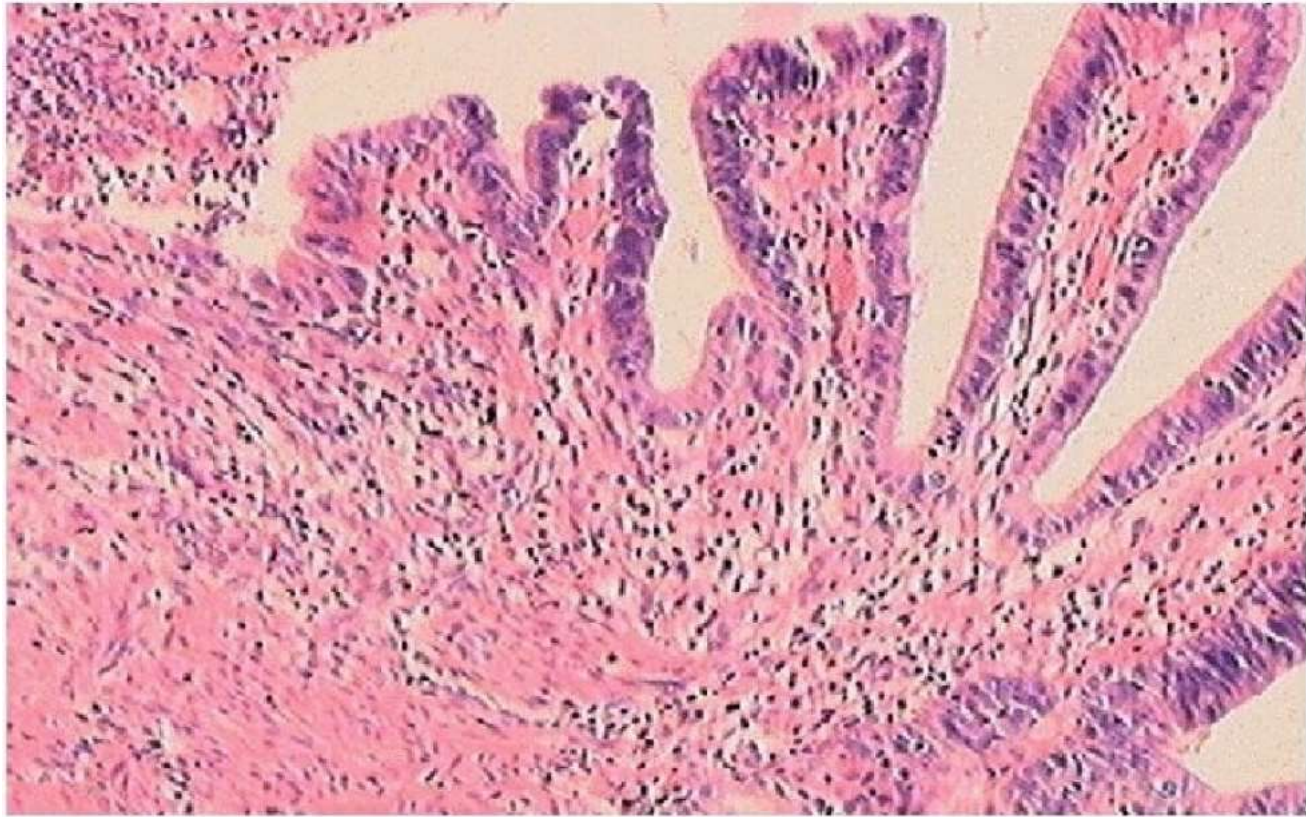
Repair

- Completely regeneration: Regeneration of injured tissue by parenchymal cells of the same type.
- Fibrous repair: Replacement by connective tissue
- In other words
 - Regeneration
 - Scar

Proliferative Potential

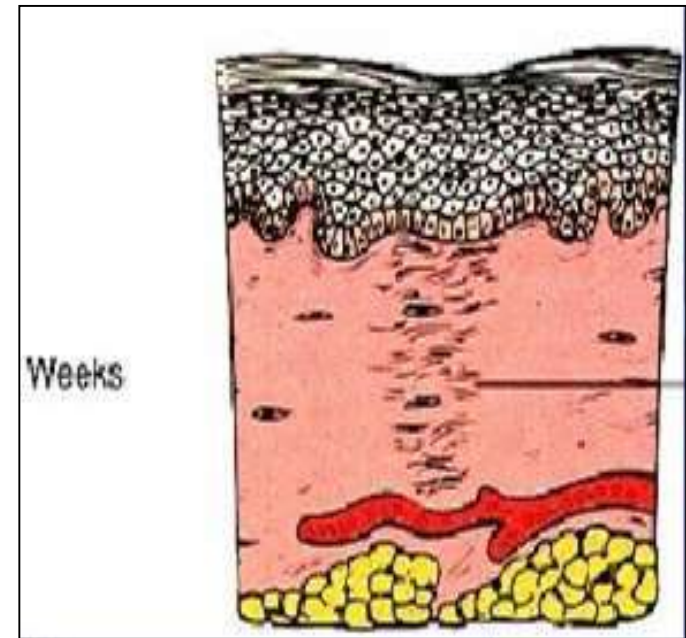
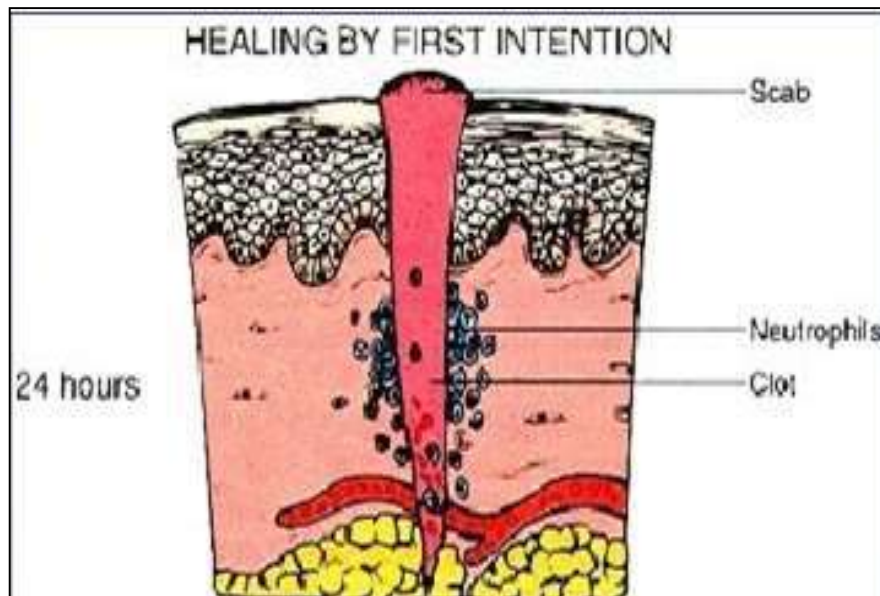
- **Labile cells** - continuously dividing
 - Epidermis, mucosal epithelium, GI tract epithelium etc
- **Stable cells** - low level of replication
 - Hepatocytes, renal tubular epithelium, pancreatic acini
- **Permanent cells** - never divide
 - Nerve cells, cardiac myocytes, skeletal mm





1. Regeneration of epithelial tissues

- ❑ Skin regeneration : BM not breached, repaired by the proliferation of epithelial cells



❑ Regeneration of renal tubular cells and hepatocytes :

2. Renal tubular cells: repaired by surviving renal tubular epithelial cells.

If the basic framework is not intact, massive scar tissue is formed.

3. Hepatocytes are analogous to the above

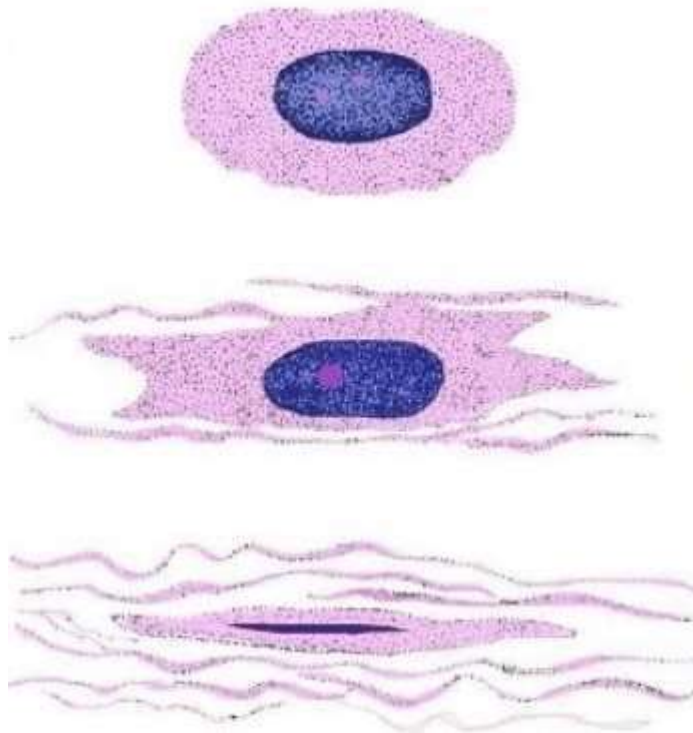
1. Regeneration of connective tissue

- connective tissue includes:

3. inactive fibroblasts(fibrocyte),

4. activated fibroblasts

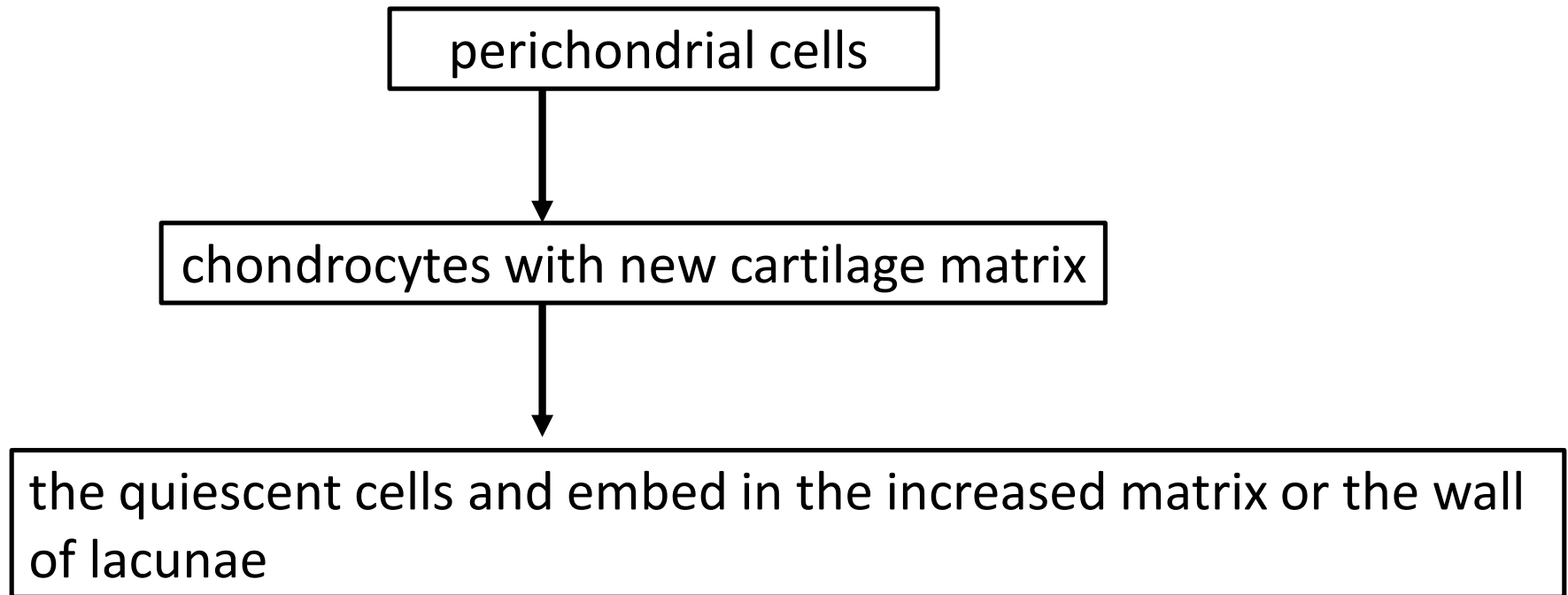
5. extracellular matrix



□ Fibroblasts produce collagen, elastic, and reticular fibers and amorphous material

1. Regeneration of cartilage and bone

- Cartilage regeneration: weak of repair capability



- Bone tissue: a strong regenerative ability

1. Angiogenesis:
by two processes:
3. Vasculogenesis: from angioblasts
4. Angiogenesis: capillary sprouts

1. Muscle

2) Cardiac muscle fibers and skeletal muscle :

- scar tissue.
- skeletal muscle: Repair may be possible only when sarcolemma keeps alive and portion of myofibrils destroy in muscle fiber.

5) Vascular smooth muscle: a limited replicative protential, new small vessels can be formed.

- Sarcolemma: a coating of BM-like material adhering to the plasma membrane

Fibrous Repair

Granulation tissues:

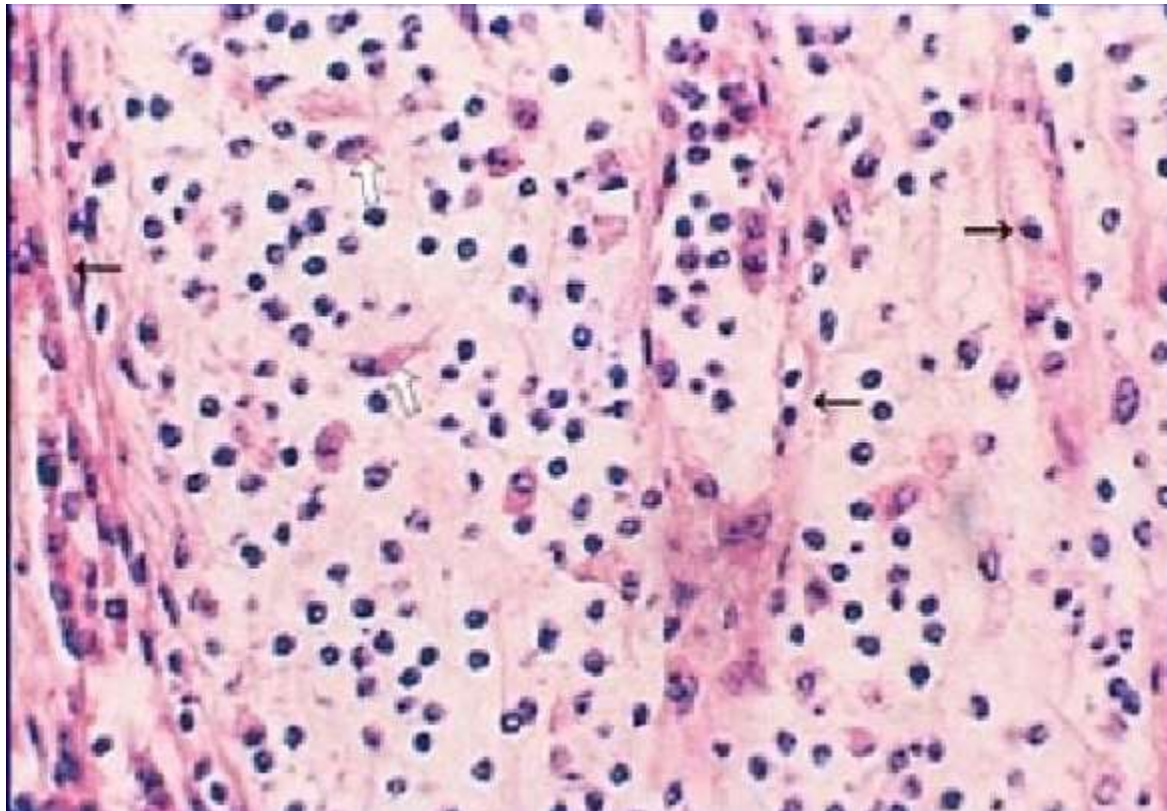
- Newly formed capillaries
- Fibroblasts
- Inflammatory cells

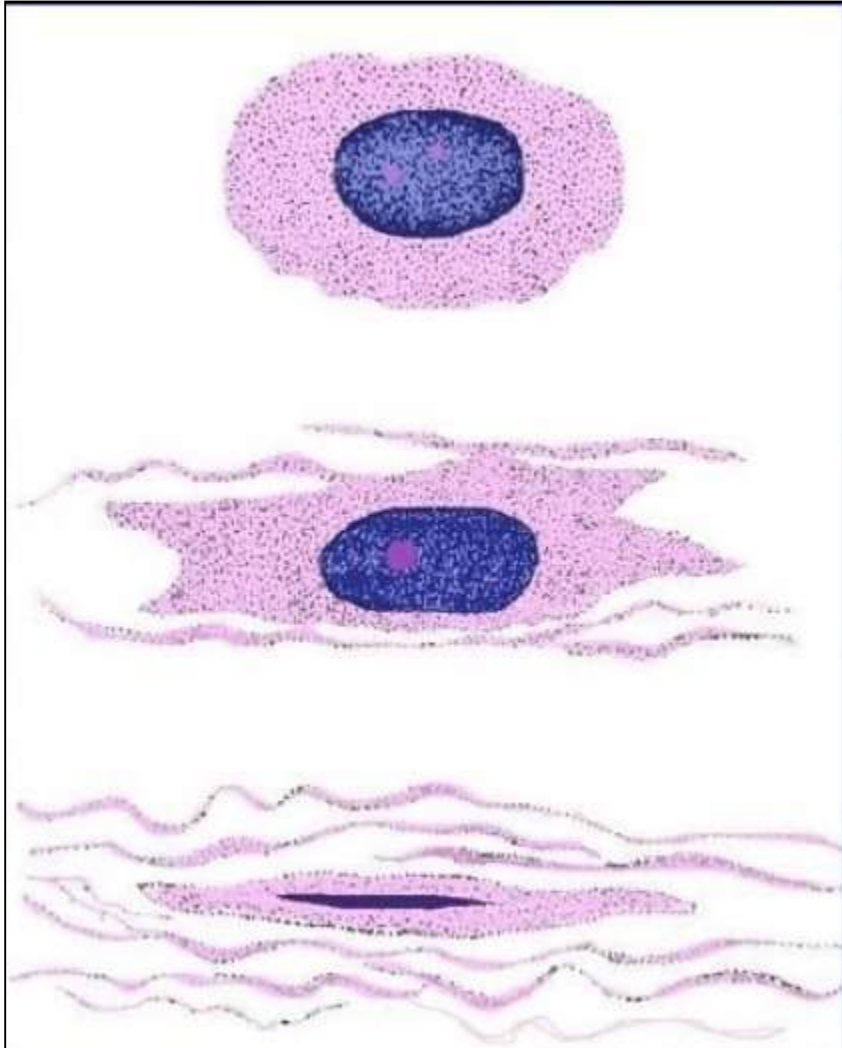
Repair by connective tissue

- Occurs when repair by parenchymal regeneration alone cannot be accomplished
- Involves production of Granulation Tissue
- replacement of parenchymal cells with proliferating fibroblasts and vascular endothelial cells

❑ Granulation tissue

- Gross: soft, pink, and granular.
- LM: fibroblasts, new thin-walled capillaries and inflammatory cells in a loose ECM with edema





- Fibroblasts -- divide and secrete collagen.
- Eventually results in fibrosis with connective tissue matrix

❑ Scar formation (Fibrosis)

Angiogenesis - New vessels budding from old

Fibrosis: emigration and proliferation of fibroblasts and deposition of ECM.

Scar remodeling: tightly regulated by proteases and protease inhibitors

Scar tissue

- a pale, avascular scar with largely inactive fibroblasts, dense collagen, fragments of elastic tissue, and other ECM components.
- may undergo a reduction in size of 90 percent

Advantage of scar:

- 2) provides a resilient permanent patch
- 3) provides a tensile strength and can keep the reparative site solid

Wound healing

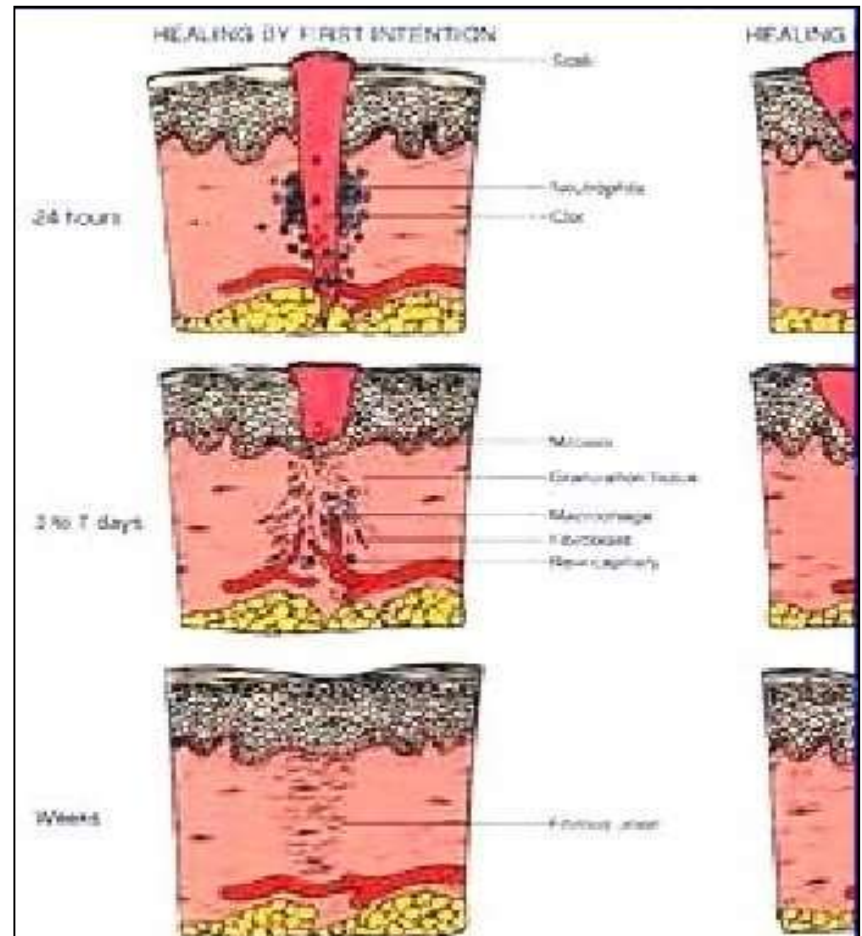
- Induction of acute inflammatory response by an initial injury
- Parenchymal cell regeneration
- Migration and proliferation of parenchymal and connective tissue cells

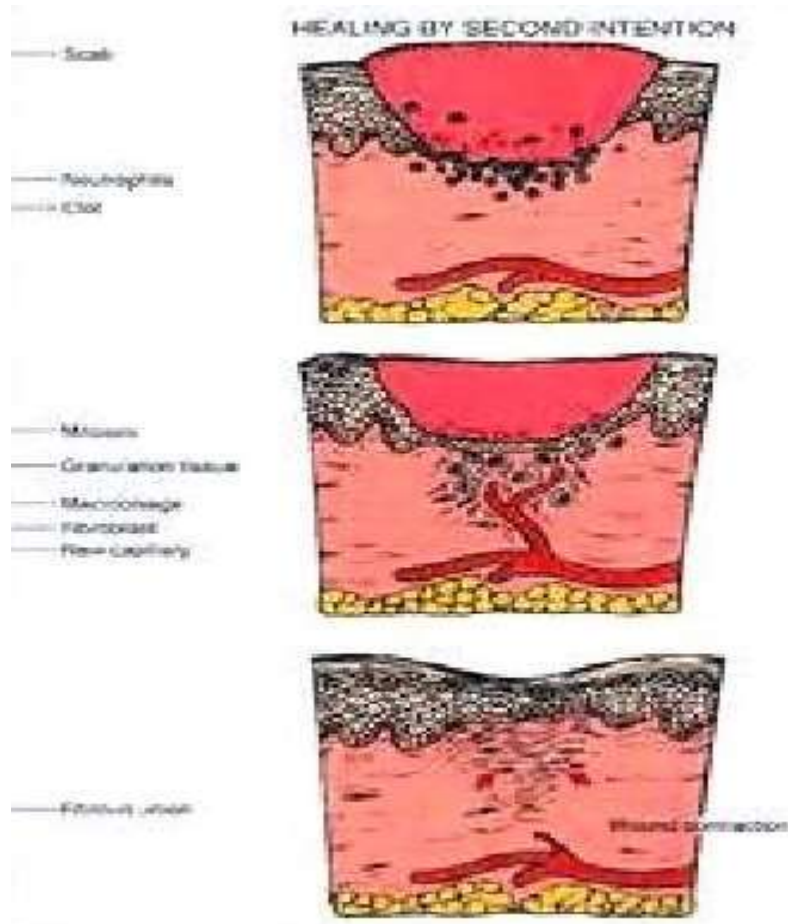
Wound healing (cont'd)

- Synthesis of ECM proteins
- Remodeling of parenchymal elements to restore tissue function
- Remodeling of connective tissue to achieve wound strength

Healing by **First Intention**

Focal Disruption of
Basement Membrane
and loss of only a few
epithelial cells e.g.
Surgical Incision





Healing by **Second Intention**

Larger injury, abscess,
infarction

Process is similar but
Results in much larger
Scar and then
CONTRACTION

Factors affecting Healing:

Systemic

- Age
- Nutrition
- Vitamin def.
- Immune status
- Other diseases

Local

- Infection
- Size or extent.
- apposition
- Blood supply
- Mobility
- Foreign body

Pigments and minerals

Classification of pigments

1. Artefact pigments

- * usually as a result of fixation eg formalin pigment

2. Exogenous pigments

- * pigments or minerals that are formed externally and taken into the body eg coal dust, copper

3. Endogenous pigments

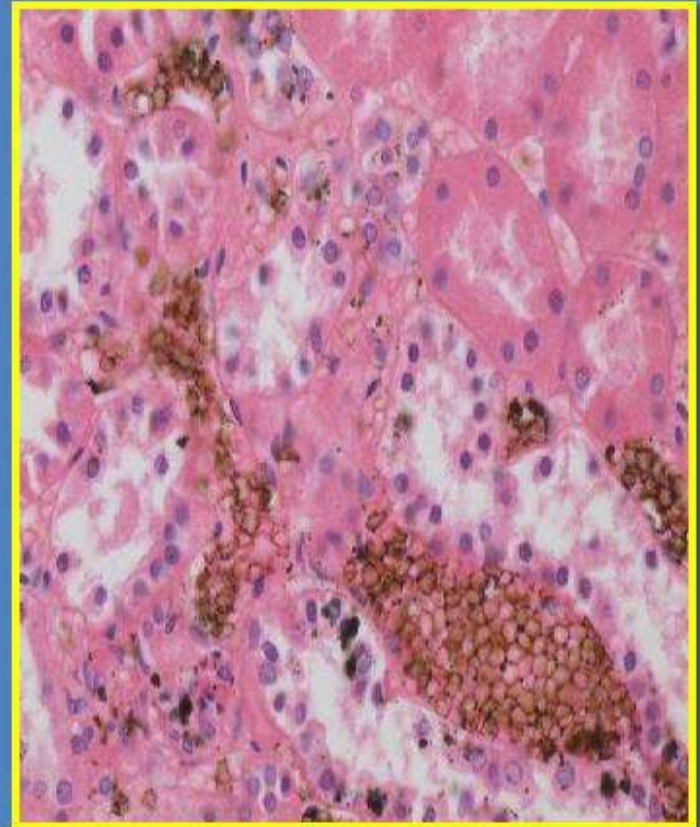
- * pigments that are formed within the body
 - i. haematogenous - haemosiderin, bile
 - ii. non-haematogenous - melanin, lipofuscin

1. Artefact pigments

- Most commonly as a result of fixation
- Normally lie on top of tissues and not within cells
 - Formalin
 - Mercury
 - Chrome
 - Picrates

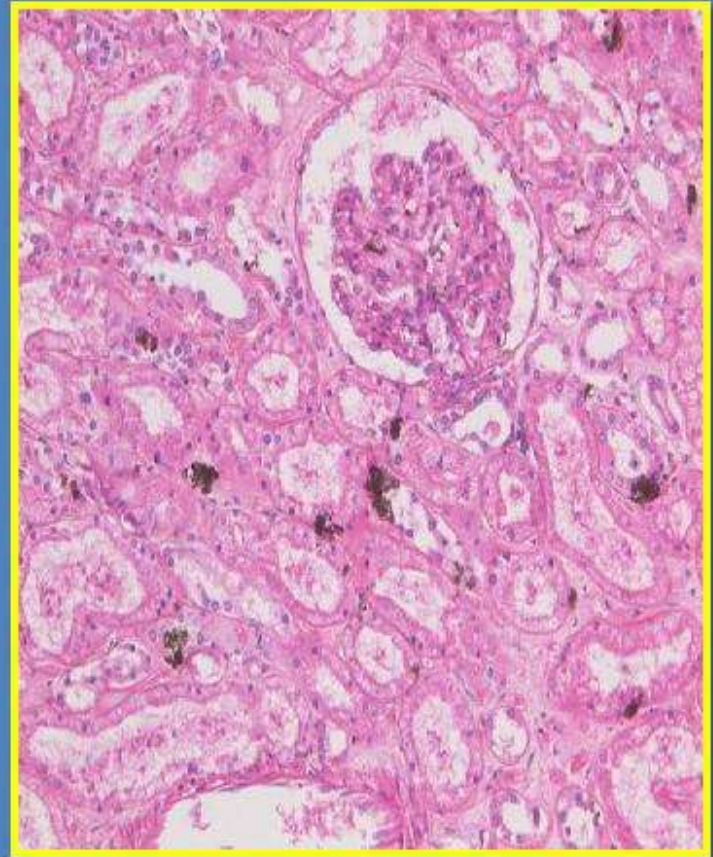
Formalin pigment

- Result of fixation of tissue in acid formalin
- Also called acid haematin
- Resistant to strong acids
- Usually associated with blood-containing tissues
- Can be removed from sections using alcoholic picric acid



Mercury pigment

- Occurs with mercury-containing fixatives such as Zenker's and Heidenhain's Susa
- Can be removed from sections using iodine followed by sodium thiosulphate (Hypo) solution



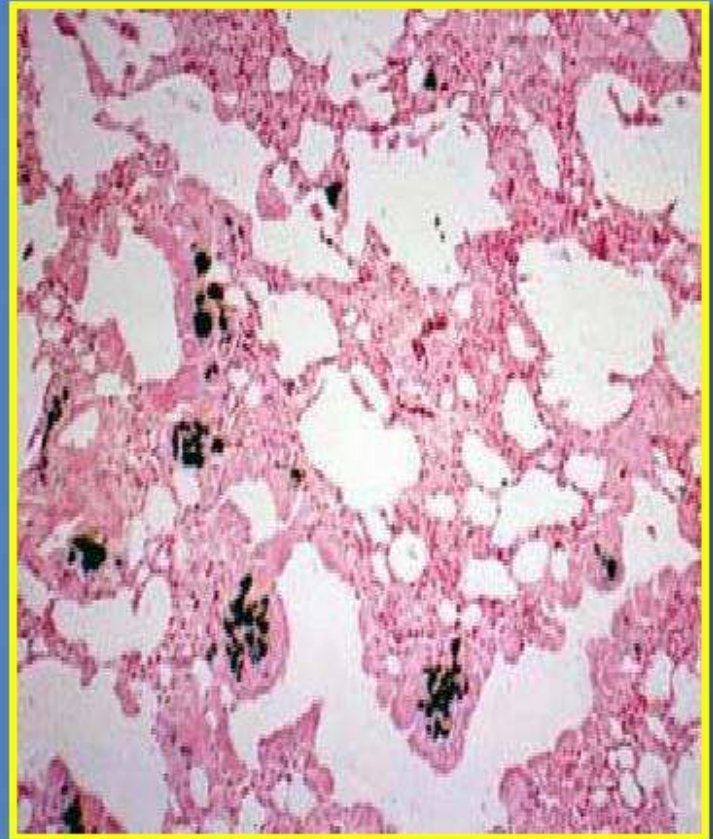
Chrome and picric acid pigments

- Chrome pigment
 - Consequence of fixation in solutions containing potassium dichromate eg Zenker's fixative
 - Can be removed from sections by thoroughly washing in water prior to dehydration
- Picrate pigment
 - Consequence of fixation in solutions containing picric acid eg Bouin's fixative
 - Can be removed with saturated aqueous lithium carbonate

2. Exogenous pigments

Pigments that are formed externally and taken into the body

- Carbon is the most common as a result of accumulation from inhaled pollution, coal dust and cigarette smoke
- It resists bleaching and is insoluble in acid



Exogenous pigments

- Tattoo

- Found in skin and associated lymph nodes



- Asbestos

- Become coated with iron in the lungs (bodies) and stain positive with Perl's

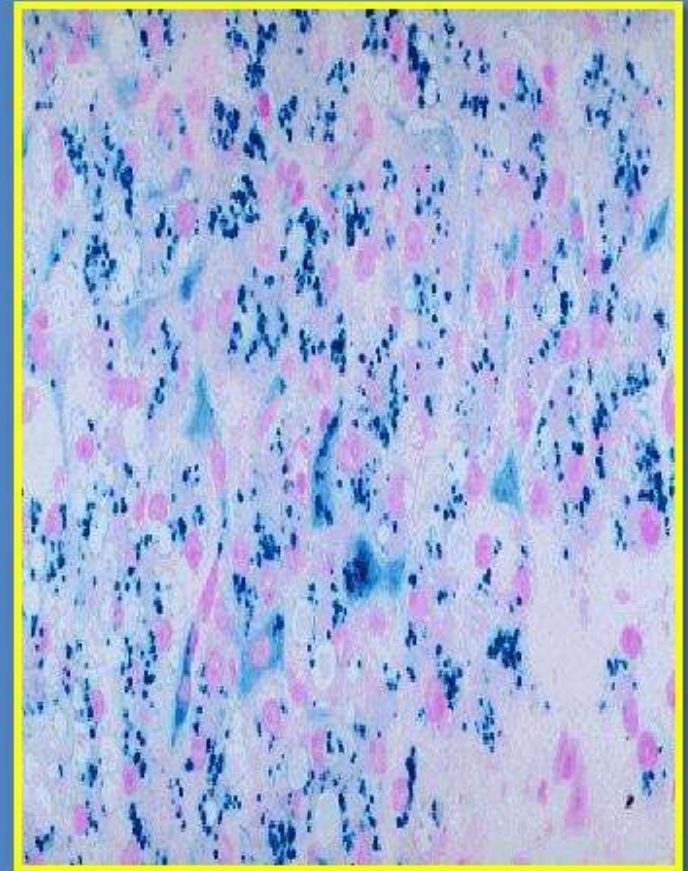


Haematogenous pigments

- Endogenous pigments derived from blood
- Main ones are haemoglobin, iron, haemosiderin, haematoidin and bile pigments
- Haemoglobin breaks down into two parts: globin and haem (iron-containing pigment part)
- The haem portion further splits into iron (haemosiderin) and bile pigments (biliverdin)
- Haematoidin (similar to bilirubin) is formed in tissue as a result of haemorrhage

Haematogenous pigments

- Haemosiderin
- Stored as ferric iron in bone marrow and spleen
- Can be demonstrated using Perl's prussian blue stain which detects ferric iron
- Excessive absorption of dietary iron causes haemochromatosis
- Ferrous iron is demonstrated by Turnbull's blue



Haematogenous pigments

- Bile and bilirubin
- Biliverdin also results from destruction of RBCs
- Biliverdin (green) is transported to the liver
- Undergoes reduction to bilirubin (yellow-brown)
- Can be demonstrated by Hall's method which uses Fouchet's reagent

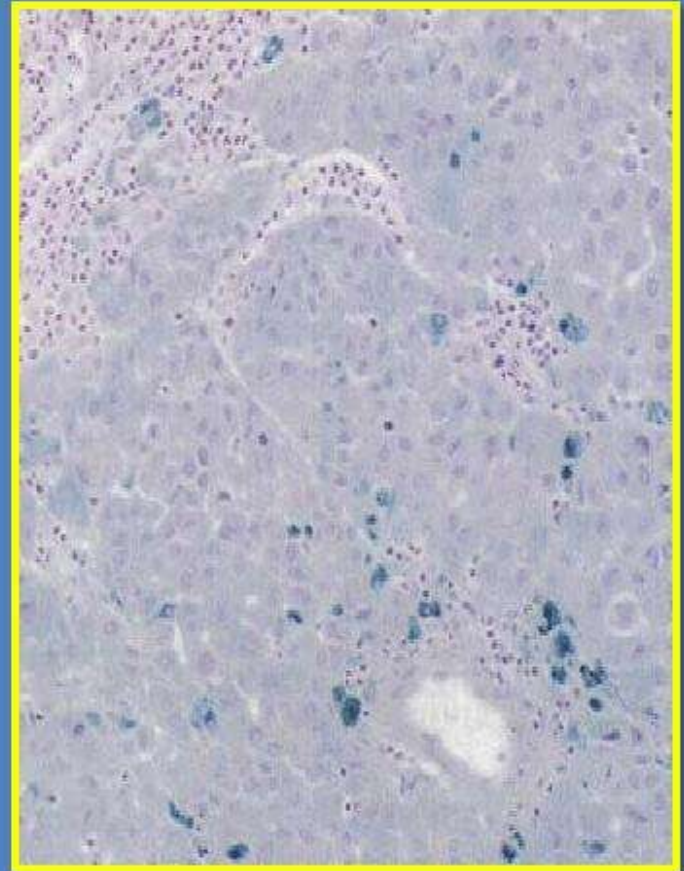


Non-haematogenous pigments

- Endogenous pigments not derived from blood
- There are two types of non-haematogenous pigment
- Lipidic (lipofuscin and ceroid)
- Non-lipidic (melanin)

Lipidic pigments

- Lipofuschin
- Wear and tear pigment, usually found in the heart and liver
- Stain with Schmorl's stain. Also use oil red O, aldehyde fuchsin, Sudan black B and PAS
- Ceroid stains similar but can be differentiated by staining positive with ZN



Non-lipidic pigments

- Melanin is the most important and is found in skin, hair, retina and parts of the CNS
- Melanin can be bleached in the tissue section by treatment with hydrogen peroxide or potassium permanganate and oxalic acid
- Pathologically, melanin is found in the cells of malignant melanomas and various benign naevi
- Melanin reduces silver nitrate to metallic silver in the Masson Fontana method (argentaffin)

Molecular Basis of Cancer

What Is Cancer?

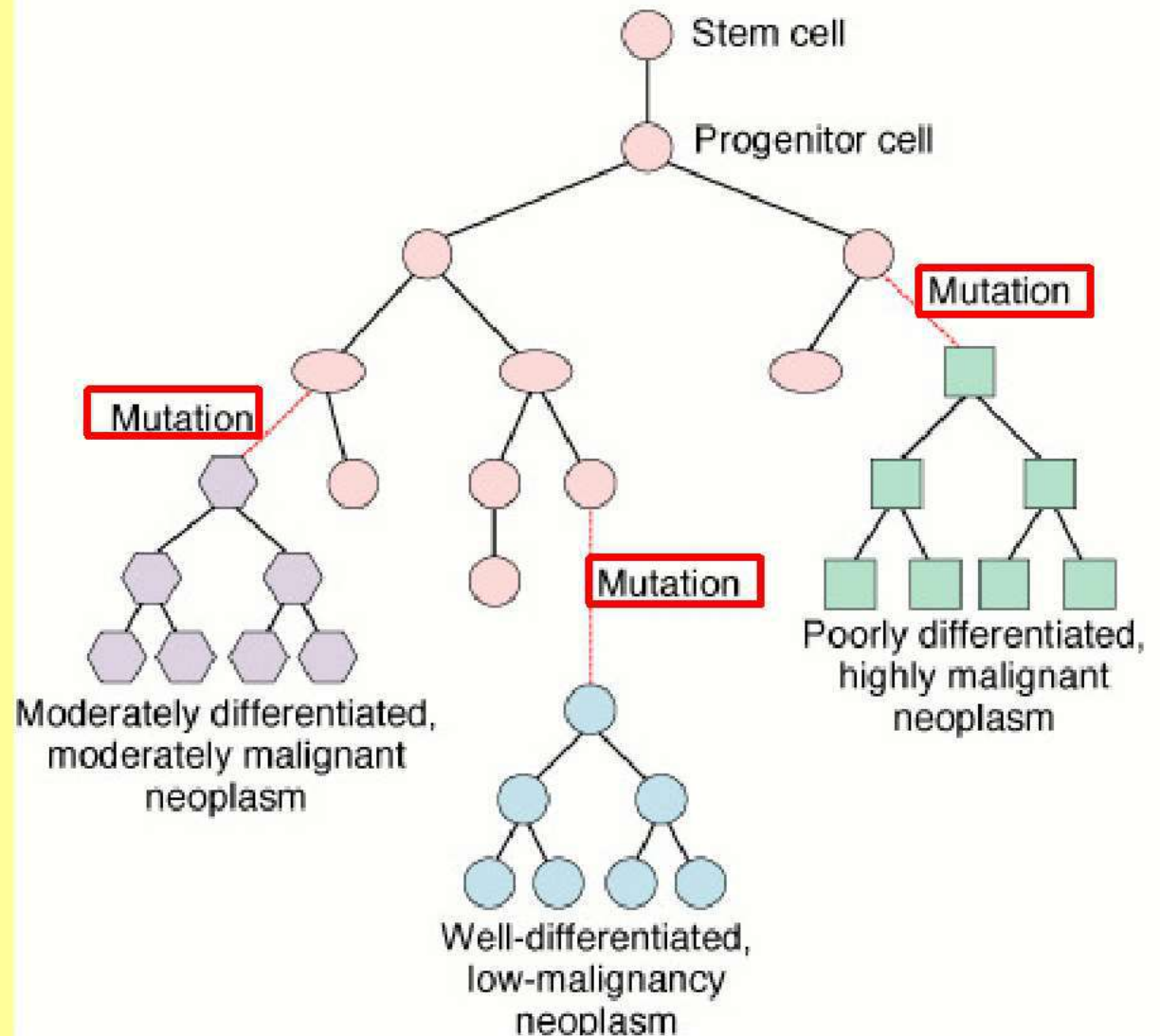
- Cancer is a group of diseases caused by the uncontrolled multiplication of abnormal cells in the body, a process called **neoplasia**.
- Abnormal new tissues called **neoplasms** are formed.
- **Neoplasms** usually form masses called **tumors** that may be **benign** (non cancerous) or **malignant** (cancerous).
- **Malignant** or **cancerous tumors** grow rapidly, are **invasive** (to surrounding tissue) and **metastatic** (traveling via blood/lymph to invade distant tissues).
- Cancers destroy healthy tissues causing loss of function and death.
- Cancer is the 2nd major killer in populations of developed countries & the leading cause of death in children 3-15 (US).
- Cancers are genetic disorders caused by accumulation of somatic mutations (gene & chromosome) in a person's cells.
- Inherited mutations give a predisposition for certain cancers.

Characteristics of Cancer Cells

- **Cancer cells are genetically altered** via gene or chromosome mutations so:
 - **lack normal controls** over cell division or apoptosis.
 - **may express inappropriate genes** (e.g. for telomerase, enzyme that maintains length of DNA for continued division)
 - **are genetically unstable due to loss of DNA repair mechanisms** (so are more susceptible to radiation damage than normal cells).
- **Divide excessively** (proliferate) & indefinitely producing neoplasms.
- **Live indefinitely** (do not show apoptosis).
- **Lose the normal attachment to other cells so become metastatic** (travelling via blood/lymph to invade distant sites).
- **Secrete signals for angiogenesis** (growth of blood vessels into tumor).

Cancer Cells are Undifferentiated & Malignant

- **Cancer cells are undifferentiated** to varying degrees (even anaplastic, like stem cells) so divide & do not perform the normal function of mature cells.
- **The less differentiated the cancer cell the more malignant the cancer** (the more rapidly growing is the tumor).



What Causes Cancer?

Inherited mutations in genes that affect cell cycle, DNA repair, or apoptosis: these mutations give a genetic predisposition for cancer.

Somatic mutations to these same genes caused by:

- **Exposure to risk factors**
 - environmental mutagens (carcinogenic chemicals, radiation)
 - hormones
 - weakening of immune system (as in AIDS).
- **Oncogenic (tumor) Virus infections**
 - **Epstein Barr virus** (causes **Burkitt lymphoma**)
 - **Human Papilloma Virus** (causes **cervical cancer**).

Tumor viruses transform human cells into cancer cells by:

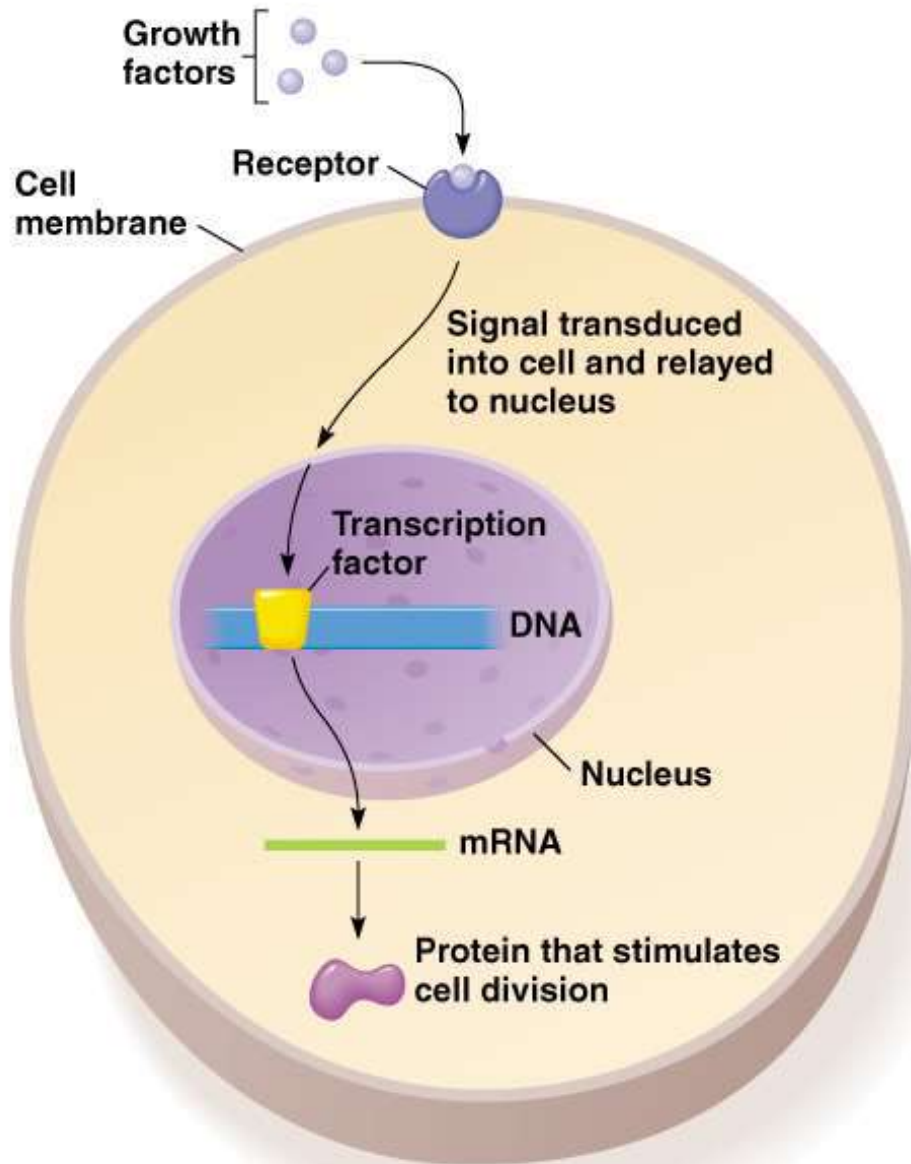
- Introducing viral cancer - causing oncogenes into host cell DNA
- Causing Translocation and overexpression of host protooncogenes.

Normal cell cycle is controlled by signal transduction:

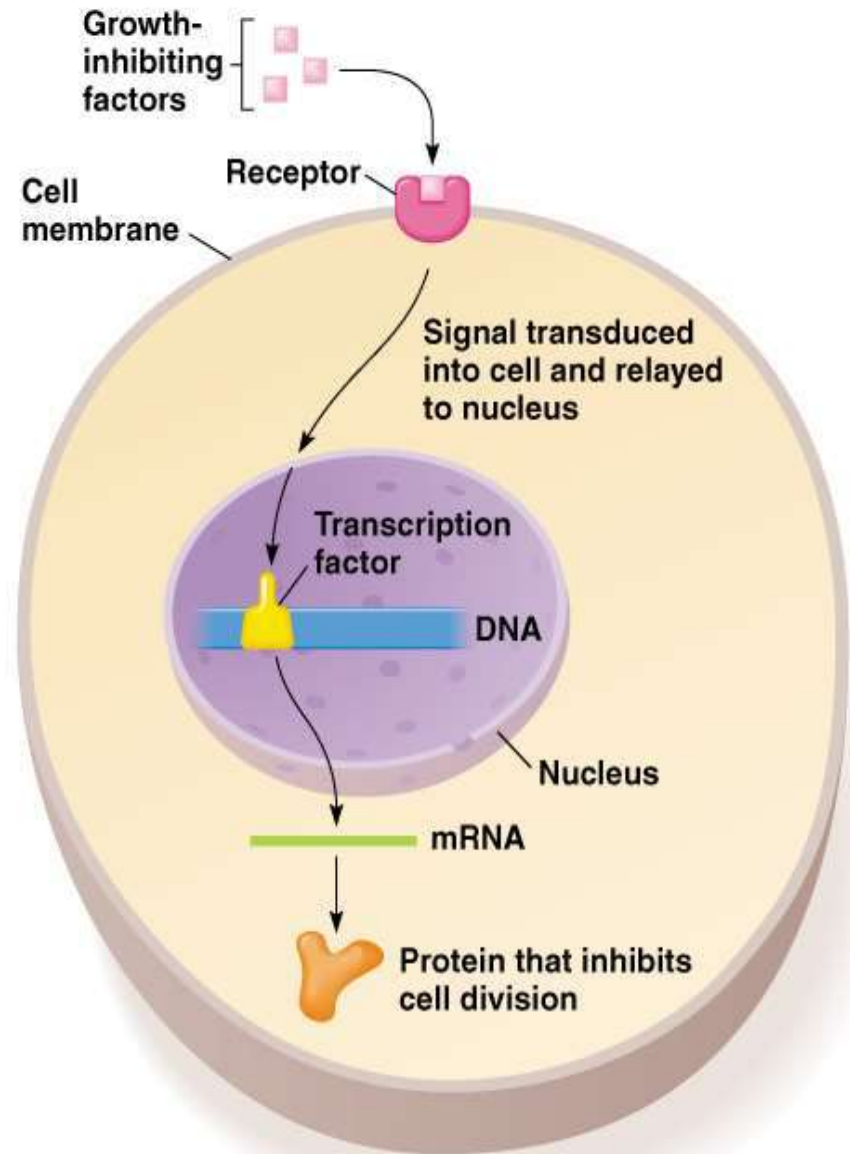
- Growth factors bind to surface receptors on the cell; transmembrane proteins relay signals into the cell.
- Two types of growth factors:
 1. Growth factors stimulate cell division.
 2. Growth-inhibiting factors inhibit cell division.
- Healthy cells divide only when growth factor and growth-inhibiting factor balance favors cell division.
- Cancer cells divide without constraint (e.g., mutations in growth and growth-inhibiting factor genes).

Regulation of cell division by signal transduction.

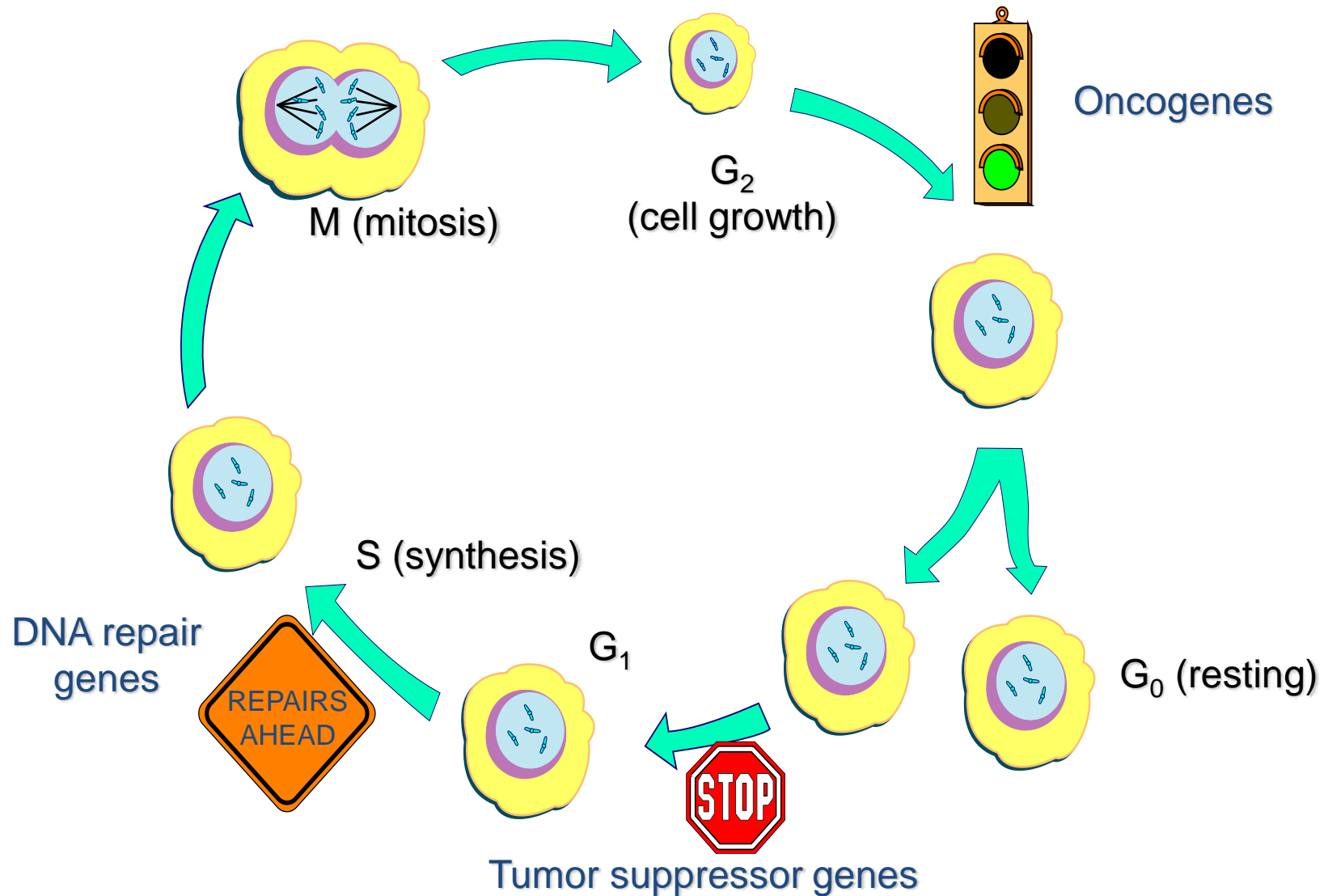
a) Stimulation of cell division induced by growth factor



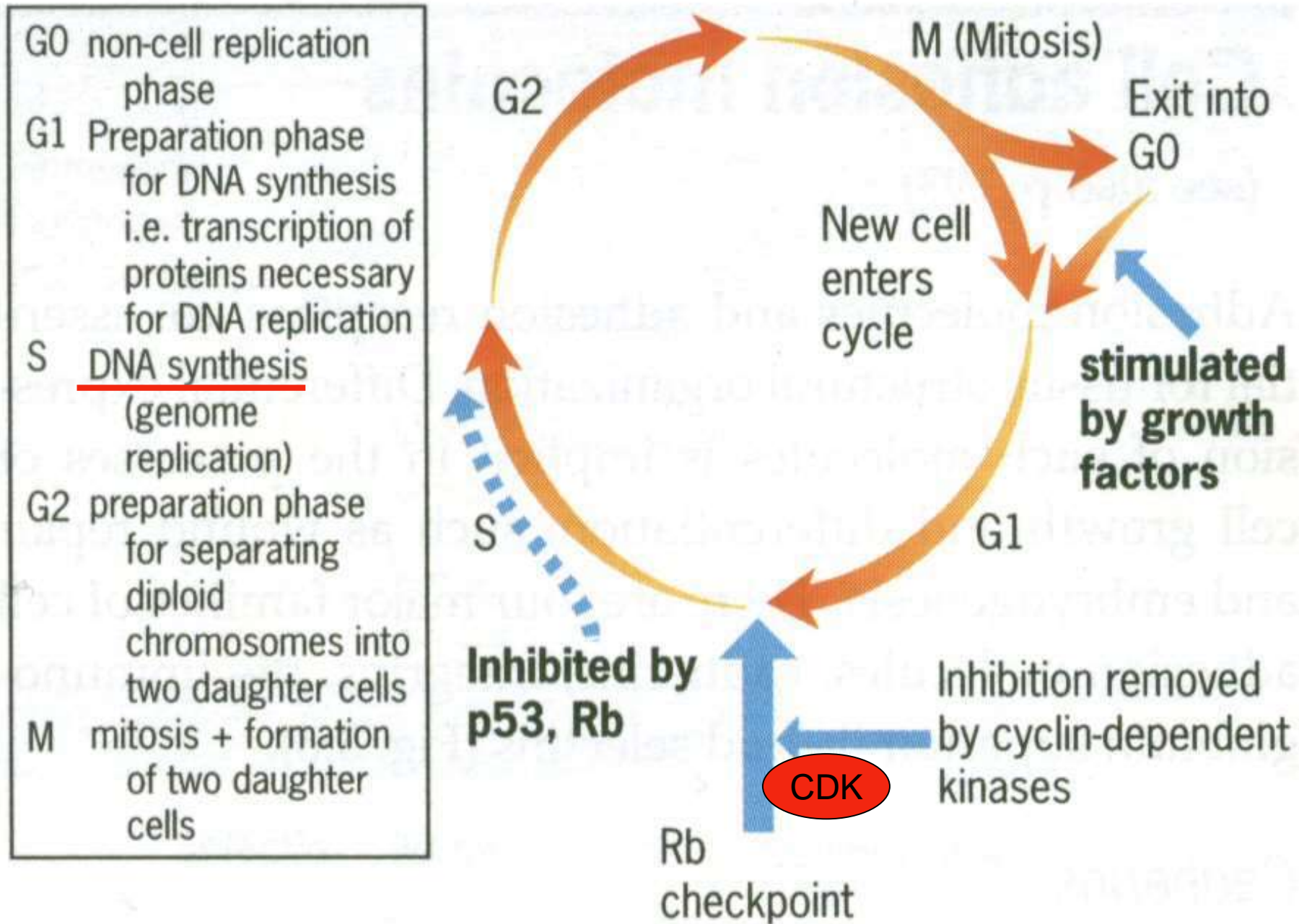
b) Inhibition of cell division induced by growth-inhibiting factor



The Cell Cycle



Cell cycle



p53 is known as the 'guardian of the genome'

Cancer and genes:

Three classes of genes are frequently mutated in cancer:

- Proto-oncogenes (\Rightarrow oncogenes)
- Tumor suppressor genes
- Mutator genes

Proto-oncogenes \Rightarrow oncogenes:

Proto-oncogenes

- Proto-oncogenes are genes that possess normal gene products and stimulate normal cell development.

Oncogenes

- Oncogenes arise from mutant proto-oncogenes.
- Oncogenes are more active than normal or active at inappropriate times and stimulate unregulated cell proliferation.

Some tumor viruses that infect cells possess oncogenes:

- RNA tumor viruses = possess viral oncogenes (derived from cellular proto-oncogenes) capable of transforming cells to a cancerous state.
- DNA tumor viruses = another class of tumor viruses; do not carry oncogenes, but induce cancer by activity of viral gene products on the cell (no transformation per se).

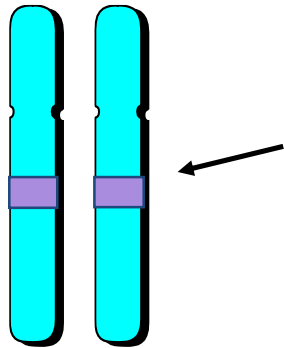
Types & effects of different types of mutations:

1. **Point mutations**: occur in protein coding or controlling sequences.
2. **Deletion**: frameshifts may lead to defective proteins.
3. **Gene amplification**: random over-replication of small segments of DNA results in extra copies (up-regulates cell growth).

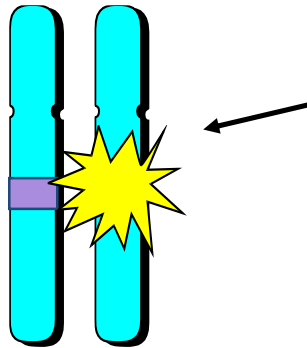
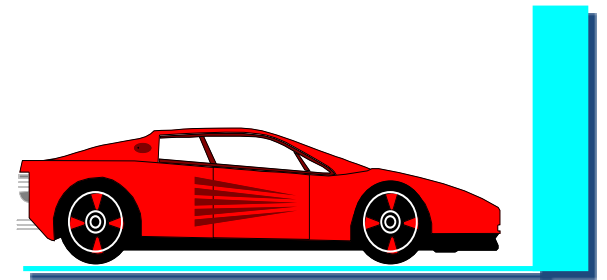
Mutator genes:

- Mutator gene increases spontaneous mutation rate of other genes.
- Mutator gene products are involved in DNA replication and repair; mutations make the cell error prone.

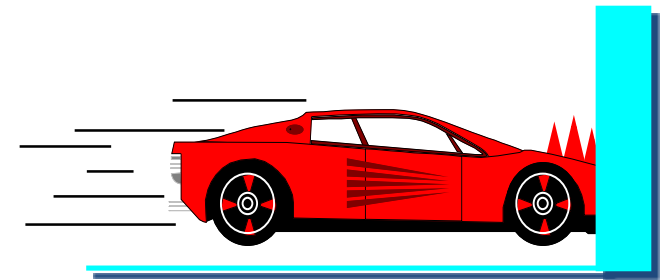
Oncogenes



Normal genes
(regulate cell
growth)



1st mutation
(leads to
accelerated cell
division)



1 mutation sufficient for role in cancer development

Genetic Abnormalities Associated With Hematologic Malignancies

A- Point Mutation

Mutations within the RAS oncogenes or P53 tumor-suppressor gene are common in many haemopoietic malignancies. The point mutation may involve several base pairs. In 35% of cases of AML the nucleophosmin gene shows an insertion of 4 base pairs.

B- Translocation

Includes two main mechanisms:

- 1- Fusion of parts of two genes to generate a chimeric fusion gene that codes a novel fusion protein. Ex: BCR- ABL in t(9; 22) in chronic myeloid leukaemia.
- 2- Overexpression of a normal cellular gene. Ex: overexpression of BCL-2 in the t(14; 18) translocation of follicular lymphoma or MYC gene in Burkitt's lymphoma.

C- Deletions

May involve a small part of a chromosome, the short or long arm or the entire chromosome. Losses most commonly affect chromosomes 5, 6, 7, 11, 20 and Y. The critical event is probably loss of a tumor suppressor gene.

D- Duplication or amplification

Gains are common in chromosomes 8, 12, 19, 21 and Y. It is not a common feature in haematologic malignancy but has been described involving the MLL gene.

E- Epigenetic alterations

Means alterations in the mechanism by which genes are transcribed and are stably inherited with each cell division so they are passed on as the malignant cell divides. The most important mechanisms are methylation of cytosine residues in DNA and enzymatic alterations such as acetylation or methylation of the histone protein that package DNA.

Etiology of Breast Cancer

Breast cancer is most common cancer in women & 2nd most common in cancer deaths in women (after lung cancer).

Risk Factors for Breast Cancer

- Prolonged exposures to **estrogens** (early menarche & late menopause). Breast cancers that are estrogen receptor +ve are treated with drugs (e.g. tamoxifen) that bind to these receptors.
- **Late Childbearing** (having first child after age 30)
- Breasts with a high proportion of **lobular (milk producing) and ductal tissue** density.
- **Not** breast feeding babies increases post menopausal BC.
- Exposure to **radiation**.
- High **alcohol** consumption.
- **Family History of BC & Genetic Predisposition** in 5-20% of cases (inheriting mutated breast cancer susceptibility genes, BRCA-1 or BRCA-2).

Diagnostic methods used to study malignant cells

1- Karyotype analysis: It is a direct morphological analysis of chromosomes from tumor cells under the microscope.

2- Fluorescent in situ hybridization analysis

FISH analysis involves the use of fluorescent- labelled genetic probes which hybridize to specific parts of the genome. This can detect extra copies of genetic material or reveal chromosomal translocation.

3- Southern blot analysis: It involves extraction of DNA from leukaemic cells followed by restriction enzyme digestion, gel electrophoresis and transfer by blotting to a suitable membrane. The DNA is then hybridized to a probe complementary to the gene of interest.

4- Polymerase chain reaction: Can be performed on blood or bone marrow for a number of specific translocations such as t(9; 22) and t(15; 17). It is very sensitive and can detect one abnormal cell in one million normal cells. It is of great value to diagnose minimal residual disease.

5- DNA microarray: Allows rapid and comprehensive analysis of cellular transcription by hybridizing labelled cellular mRNA to DNA probes which are immobilized on a solid support. This approach can rapidly determine mRNA expression from a large number of genes and may be used to determine the mRNA expression pattern of different leukaemia or lymphoma subtypes.

6- Flow cytometry: Normal cells each have a characteristic profile but malignant cells often express an aberrant phenotype that can be useful in allowing their detection.

7- Immunohistochemistry: Antibodies can be used to stain tissue sections with fluorescent markers.

Value of using these methods:

- a- Initial diagnosis.
- b- Establishing treatment protocol.
- c- Monitoring response to therapy.

Cell Injury, Death, Inflammation, and Repair

Cellular Adaptation to Injury or Stress

Injury or Stress

Adaptation

Increased demand



Hyperplasia or hypertrophy

Decreased stimulation or lack
of nutrients

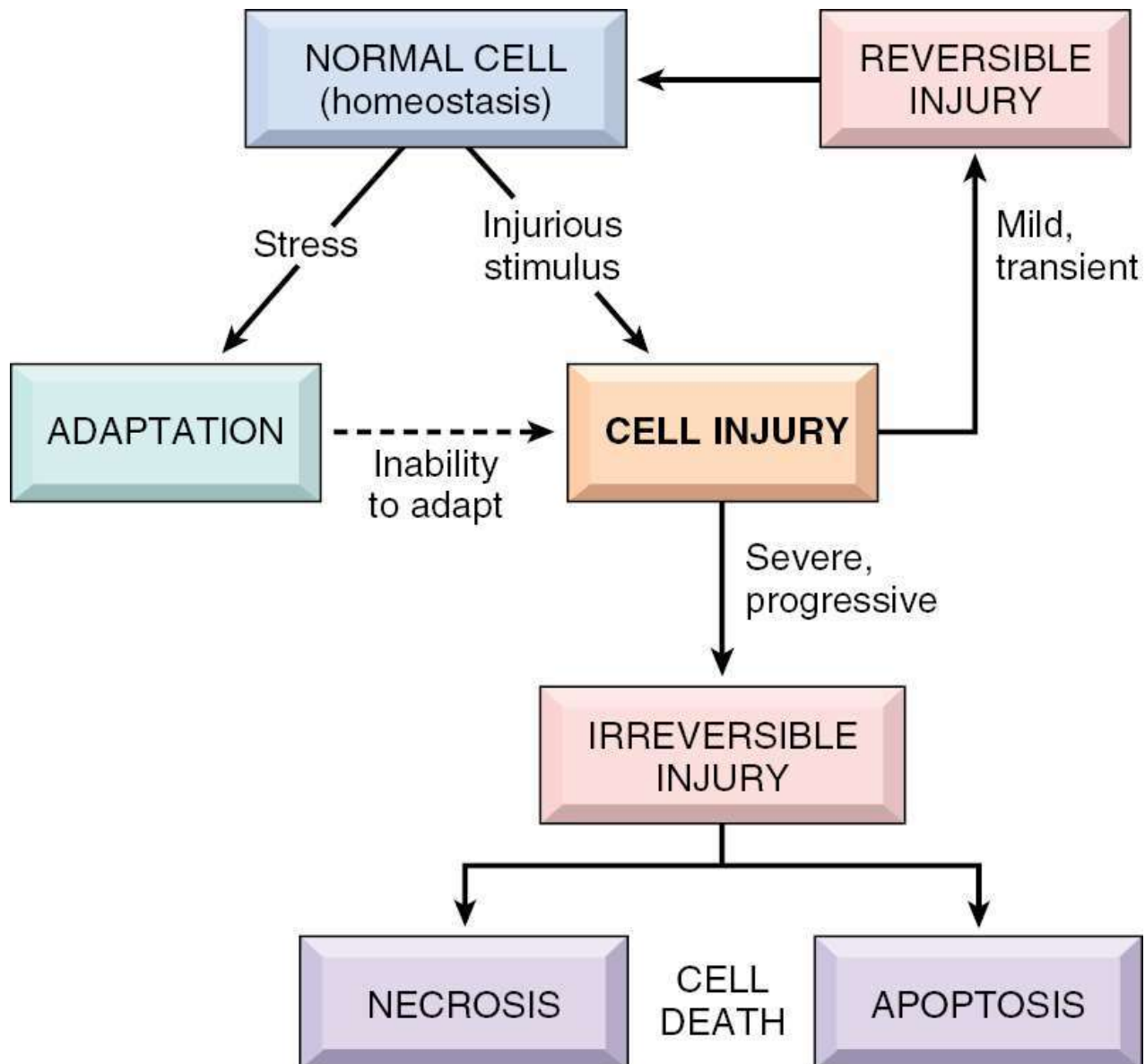


Atrophy

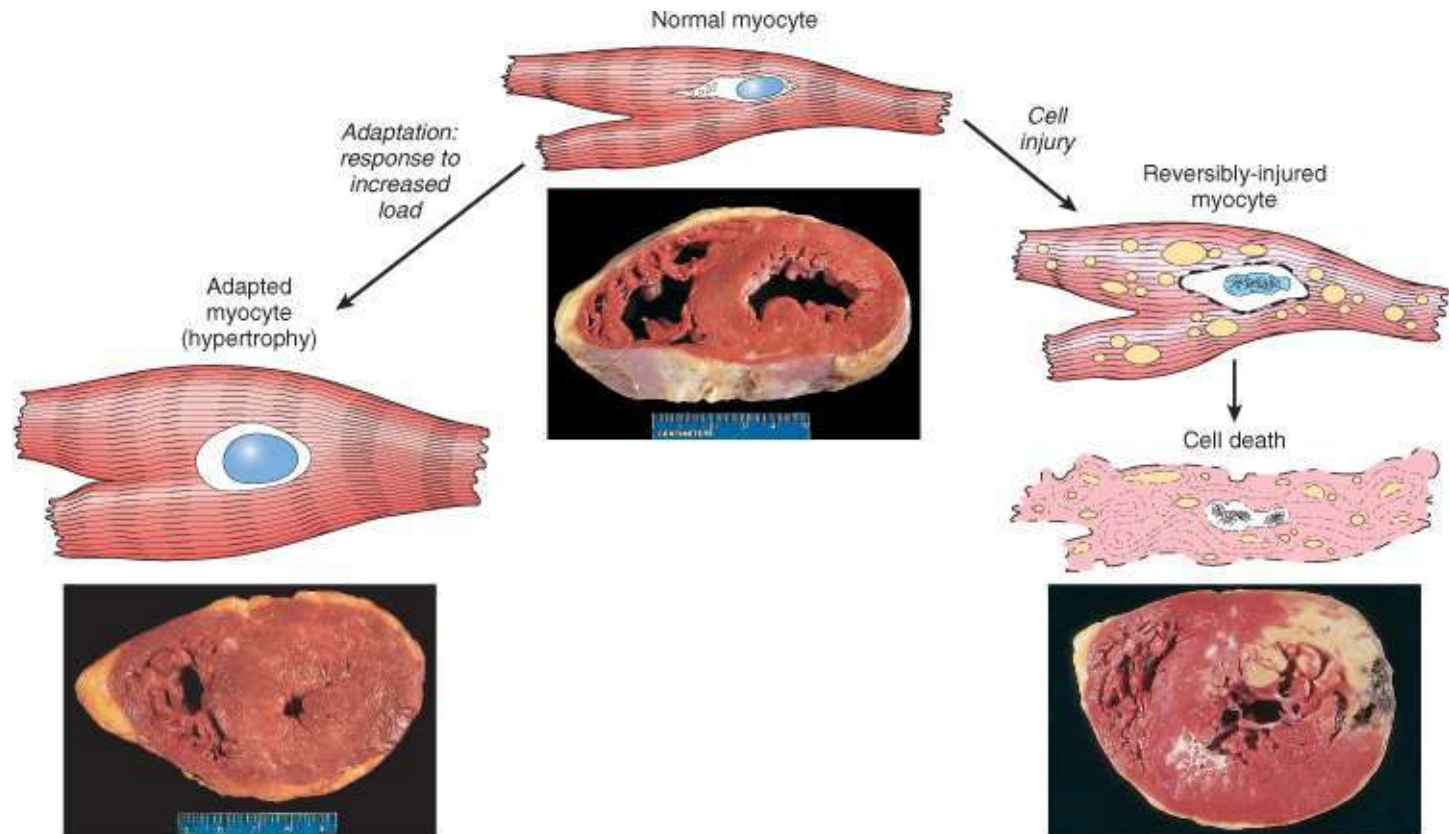
Chronic irritation



Metaplasia



Adapted - Normal - Injured Cells



Adaptations

- **Hypertrophy**
- Hyperplasia
- Atrophy
- Metaplasia

Hypertrophy

**Increase in the size of cells results
in increased size of the organ**

May be Physiologic or Pathologic

Examples of Physiologic Hypertrophy

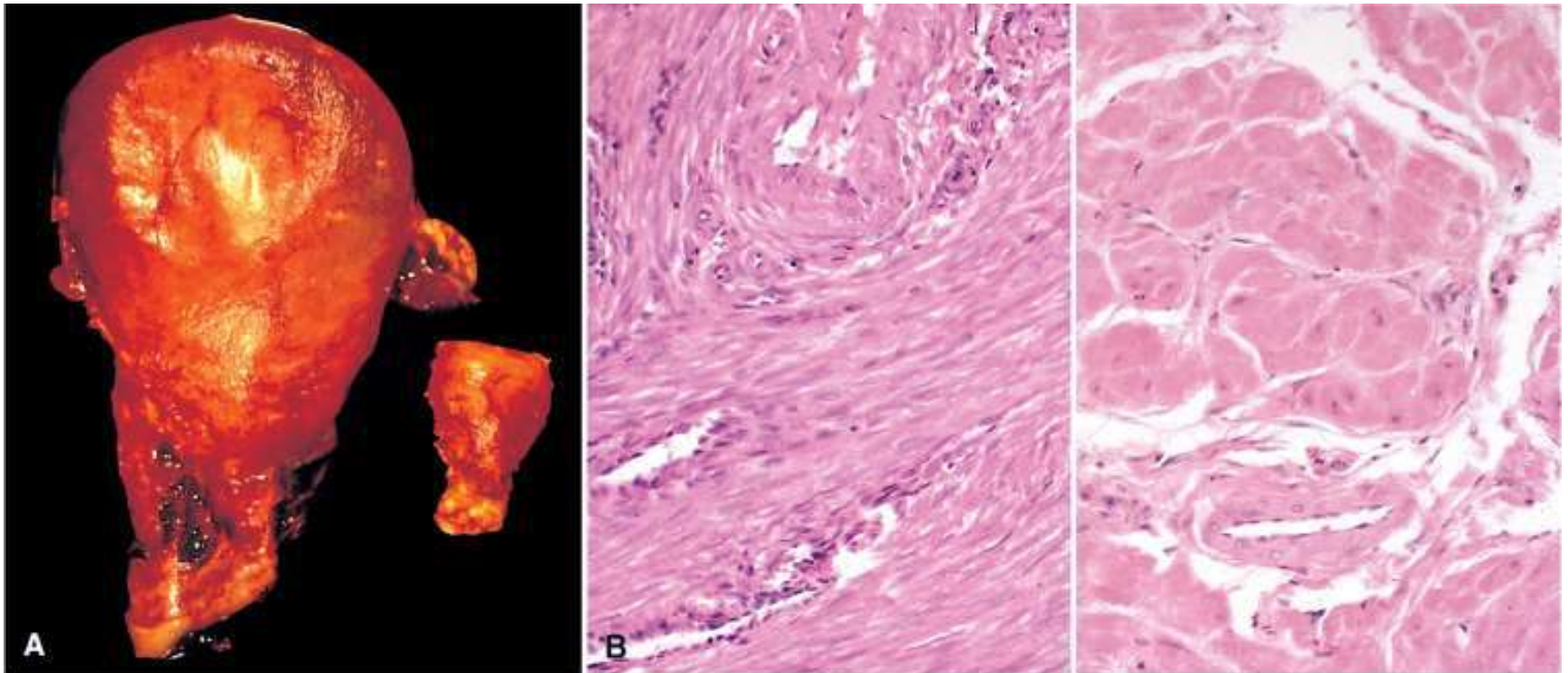
Increased workload - skeletal muscle

cardiac muscle

Hormone induced –pregnant uterus

Physiologic hypertrophy

Gravid uterus and Normal uterus



Hyperplasia

Increase in the number of cells results in increase in size of the organ.

May be Physiologic or Pathologic.

Physiologic Hyperplasia

- **Hormonal hyperplasia**

Female breast; puberty and pregnancy

- **Compensatory hyperplasia**

Prometheus

Unilateral nephrectomy

**Erythroid hyperplasia of bone marrow
in chronic hypoxia (mountain climbers).**

Pathologic Hyperplasia

- **Excessive hormone stimulation**
 - Endometrial hyperplasia**
 - Prostatic hyperplasia**
- **Viral infections**
 - Papilloma virus (warts)**

Atrophy

- **Reduced size of an organ due to a decrease in cell size and number.**
- **Physiologic atrophy – notochord, post partum uterus**
- **Pathologic atrophy – local or generalized**

Causes and Examples of Atrophy

- **Decreased workload (disuse atrophy)**
- **Loss of innervation (denervation atrophy)**
- **Diminished blood supply (ischemia)**
- **Inadequate nutrition (marasmus, cachexia)**
- **Loss of endocrine stimulation (menopause)**
- **Aging (senile atrophy)**
- **Pressure (enlarging benign tumor)**

Normal



Copyright © 2010 by Saunders, an imprint of Elsevier Inc.

Atrophy



Copyright © 2010 by Saunders, an imprint of Elsevier Inc.

Metaplasia

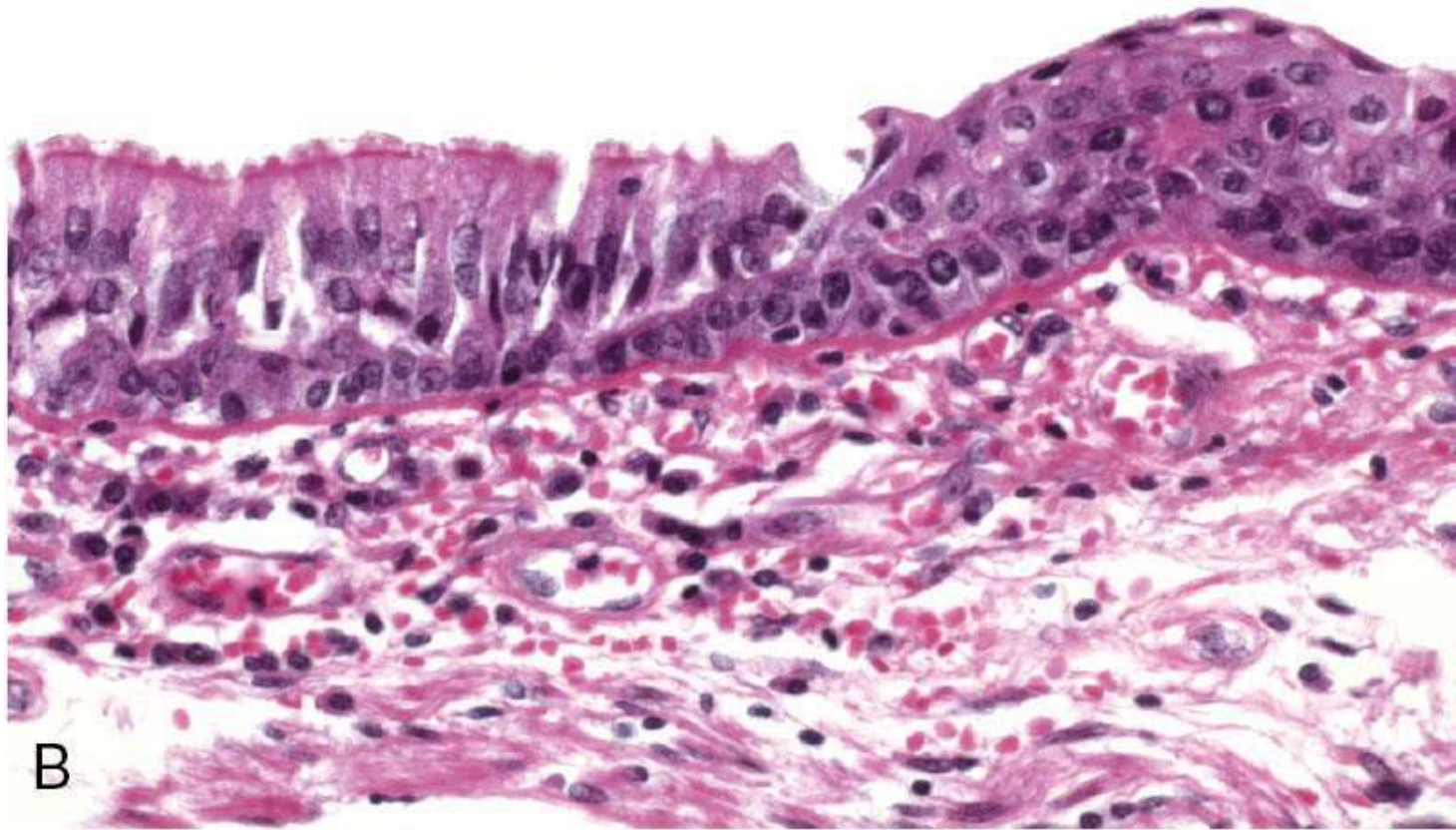
Reversible change in which one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type.

Usually occurs in response to stress or chronic irritation.

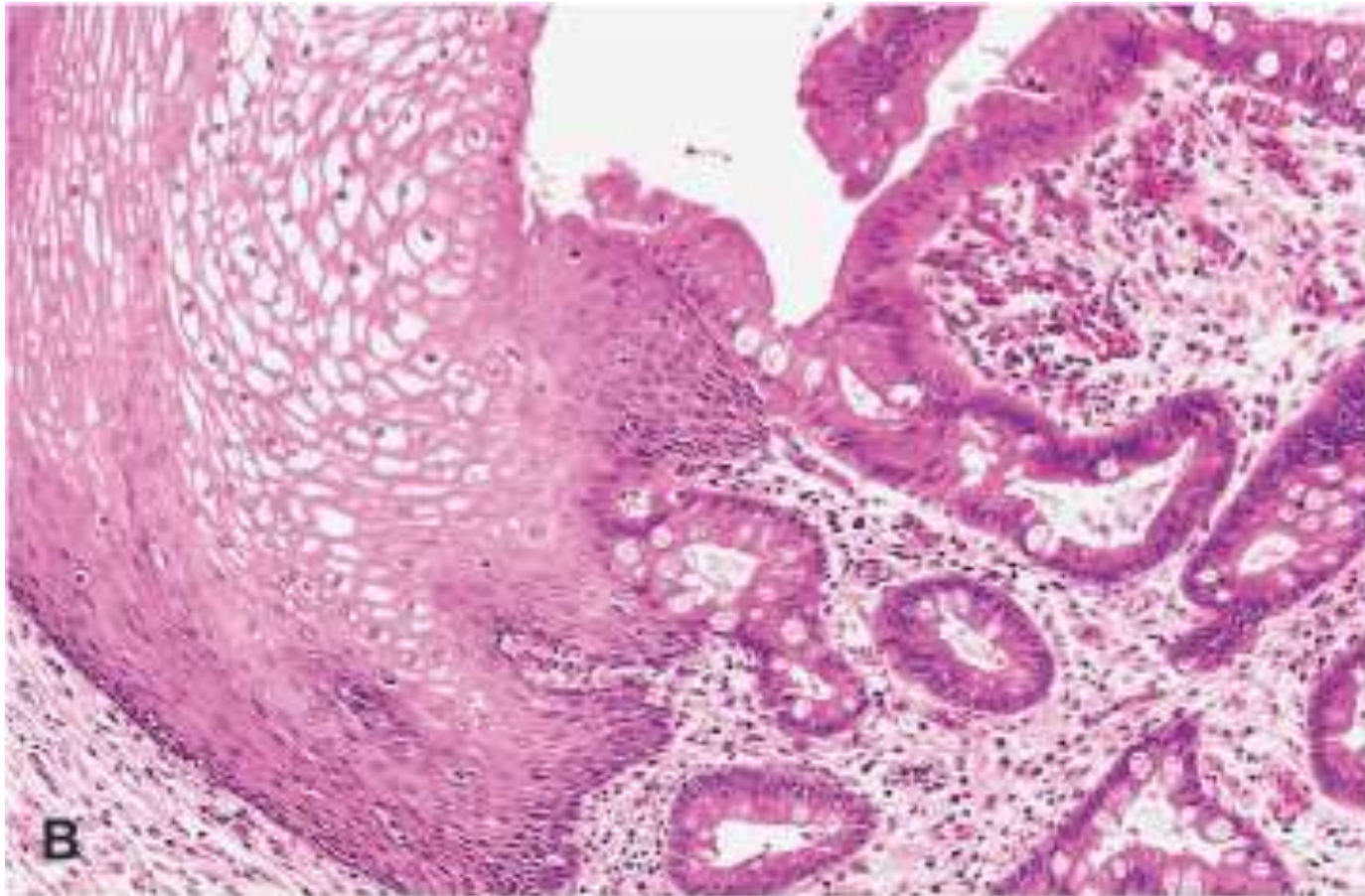
Causes and Examples of Metaplasia

- **Tobacco smoke - Squamous metaplasia in the respiratory tract, most common.**
- **Gastric acid reflux - Gastric metaplasia of distal esophagus; Barrett esophagus.**
- **Repeated skeletal muscle injury with hemorrhage- muscle replaced by bone; myositis ossificans.**

Bronchus with Columnar to Squamous Metaplasia



Esophagus with Squamous to Columnar metaplasia



Mechanisms of Metaplasia

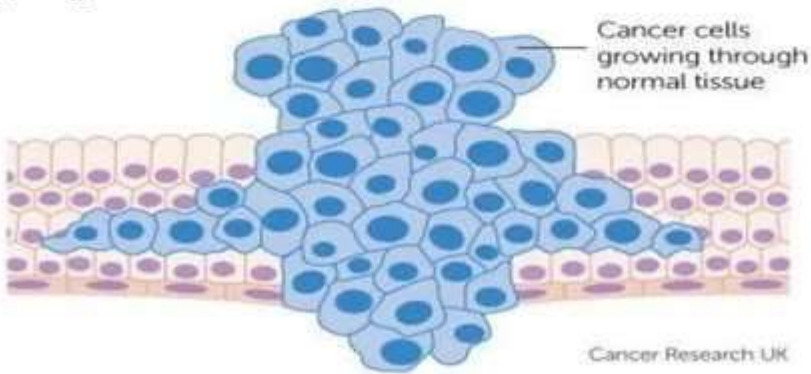
- **Re-programing of stem cells that exist in normal tissue.**
- **Induced by cytokines, growth factors and other environmental signals**
- **Retinoic acid may play a role.**
- **Exact mechanism is unknown.**

Characteristics of Normal cells

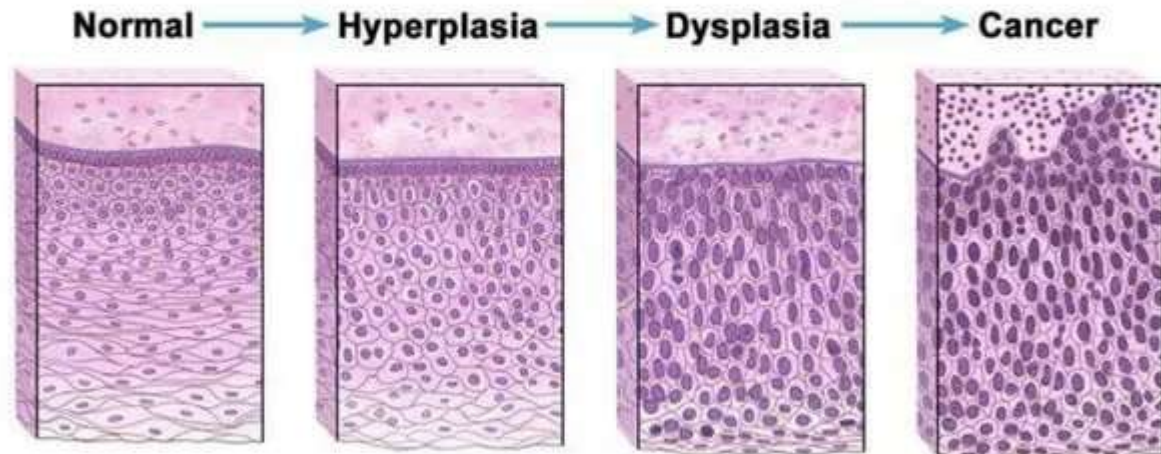
- These 'normal' cells act as the body's basic building blocks.
- Normal cells control their growth using external signals, meaning they only grow and divide when required.
- They undergo programmed cell death (apoptosis) as part of normal development, to maintain tissue homeostasis, and in response to unrepairable damage.
- They 'stick together' by maintaining selective adhesions that they progressively adjust which ensures they remain in their intended location.
- Normal cells differentiate into specialized cells with specific functions meaning they can adopt different physical characteristics despite having the same genome.

What is CANCER?

- An uncontrolled division of abnormal cells in a part of the body is called cancer.
- Abnormal cells divide without control and can invade nearby tissues.
- Loss of Cell-cycle Control.
- Before a cell divides, the DNA is checked to make sure it has replicated correctly. (If DNA does not copy itself correctly, a gene mutation occurs.



Normal Cells May Become Cancer Cells



© 2014 Terese Winslow LLC
U.S. Govt. has certain rights

Essential alterations in cell physiology that characterized malignancy

*In 2000 cancer biologists Robert Weinberg and Douglas Hanahan published an article entitled "**The Hallmarks of Cancer.**"*

- Self-sufficiency in growth signals: cancer cells acquire an autonomous drive to proliferate - pathological mitosis - by virtue of the activation of oncogenes such as ras or myc.
- Insensitivity to growth-inhibitory (antigrowth) signals: cancer cells inactivate tumor suppressor genes, such as Rb, that normally inhibit growth.
- Evasion of programmed cell death (apoptosis): cancer cells suppress and inactivate genes and pathways that normally enable cells to die.

Essential alterations in cell physiology that characterized malignancy

*In 2000 cancer biologists Robert Weinberg and Douglas Hanahan published an article entitled "**The Hallmarks of Cancer.**"*

- Limitless replication potential: cancer cells activate specific gene pathways that render them immortal even after generations of growth.
- Sustained angiogenesis: cancer cells acquire the capacity to draw out their own supply of blood and blood vessels - tumor angiogenesis.
- Tissue invasion and metastasis: cancer cells acquire the capacity to migrate to other organs, invade other tissues, and colonize these organs, resulting in their spread throughout the body.

Normal Cell vs Cancer Cell – The Key Differences

- Cell shape

➤ cancer cells are misshapen and irregular in shape.

➤ Normal cell of same cell type will look extremely similar, maintaining a uniform shape. But cancer cells differ.



Normal Cell



Cancer Cell

Normal Cell vs Cancer Cell – The Key Differences

- Nucleus

- In normal cells the nucleus has a smooth appearance and maintains a uniform, spheroid shape.
- Cancer cell nuclei are frequently misshapen and bulges known as “blebs”.



Normal Cell

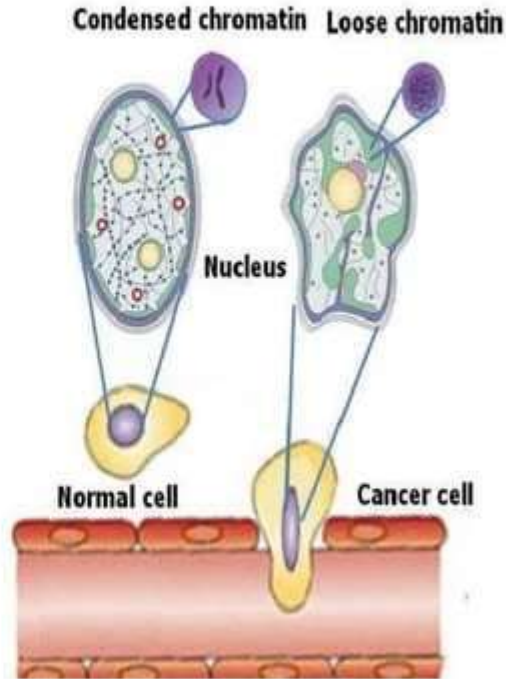


Cancer Cell

Normal Cell vs Cancer Cell – The Key Differences

- Chromatin

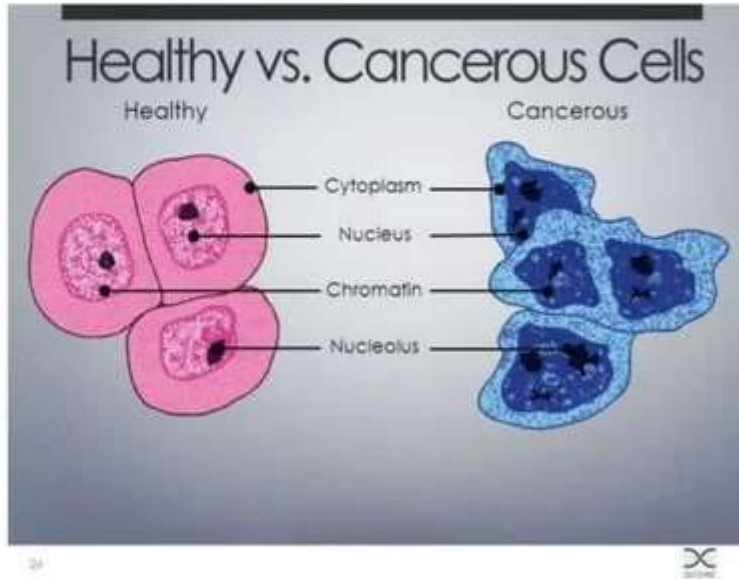
- The fine, evenly distributed chromatin found in normal cells.
- coarse, chromatin are found in cancer cells aggregating into irregular clumps that vary in both size and shape.



Normal Cell vs Cancer Cell – The Key Differences

- Nucleolus

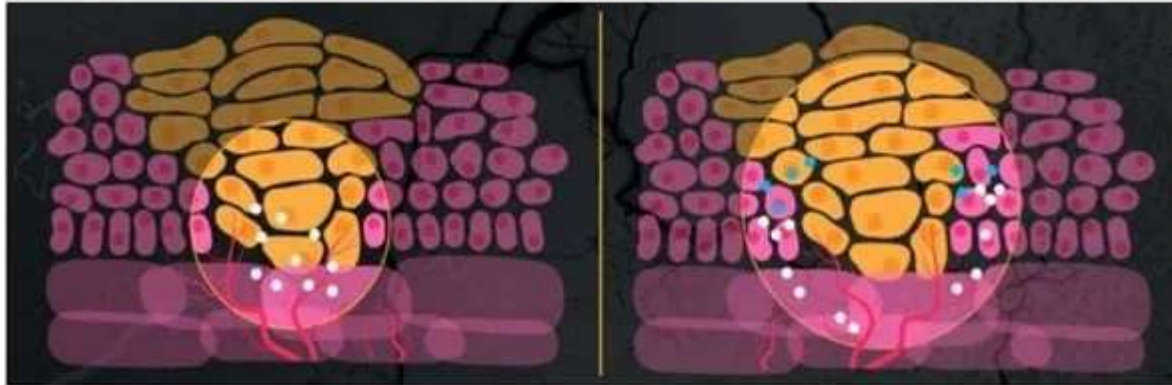
- The nucleolus becomes increasingly enlarged and more irregular in cancer cells – cells can have multiple nucleoli within the nucleus.



Normal Cell vs Cancer Cell – The Key Differences

- Blood supply

- Angiogenesis is a vital process in normal cells that occurs during development, growth, and wound healing.
- Tumors have the ability to secrete chemical signals that stimulates angiogenesis



Inflammation Acute & chronic

What is Inflammation?

- Response to injury (including infection)
- Reaction of blood vessels leads to:
 - Accumulation of fluid and leukocytes in extravascular tissues
- Destroys, dilutes, or walls off the injurious agent
- Initiates the repair process
- Fundamentally a protective response
- May be potentially harmful
 - Hypersensitivity reactions to insect bites, drugs, contrast media in radiology
 - Chronic diseases: arthritis, atherosclerosis
 - Disfiguring scars, visceral adhesions
- Consists of two general components
 - Vascular reaction
 - Cellular reaction
- Controlled by a variety of chemical mediators
 - Derived from plasma proteins
 - Derived from cells inside and outside of blood vessels

Types of Inflammation

- Acute inflammation
 - Short duration
 - Edema
 - Mainly neutrophils
- Granulomatous inflammation
 - Distinctive pattern of chronic inflammation
 - Activated macrophages (epithelioid cells) predominate
 - +/- Multinucleated giant cells
- Chronic inflammation
 - Longer duration
 - Lymphocytes & macrophages predominate
 - Fibrosis
 - New blood vessels (angiogenesis)

Acute Inflammation

- Three major components:
 - Increase in blood flow (redness & warmth)
 - Edema results from increased hydrostatic pressure (vasodilation) and lowered intravascular osmotic pressure (protein leakage)
 - Leukocytes emigrate from microcirculation and accumulate in the focus of injury
- Stimuli: infections, trauma, physical or chemical agents, foreign bodies, immune reactions

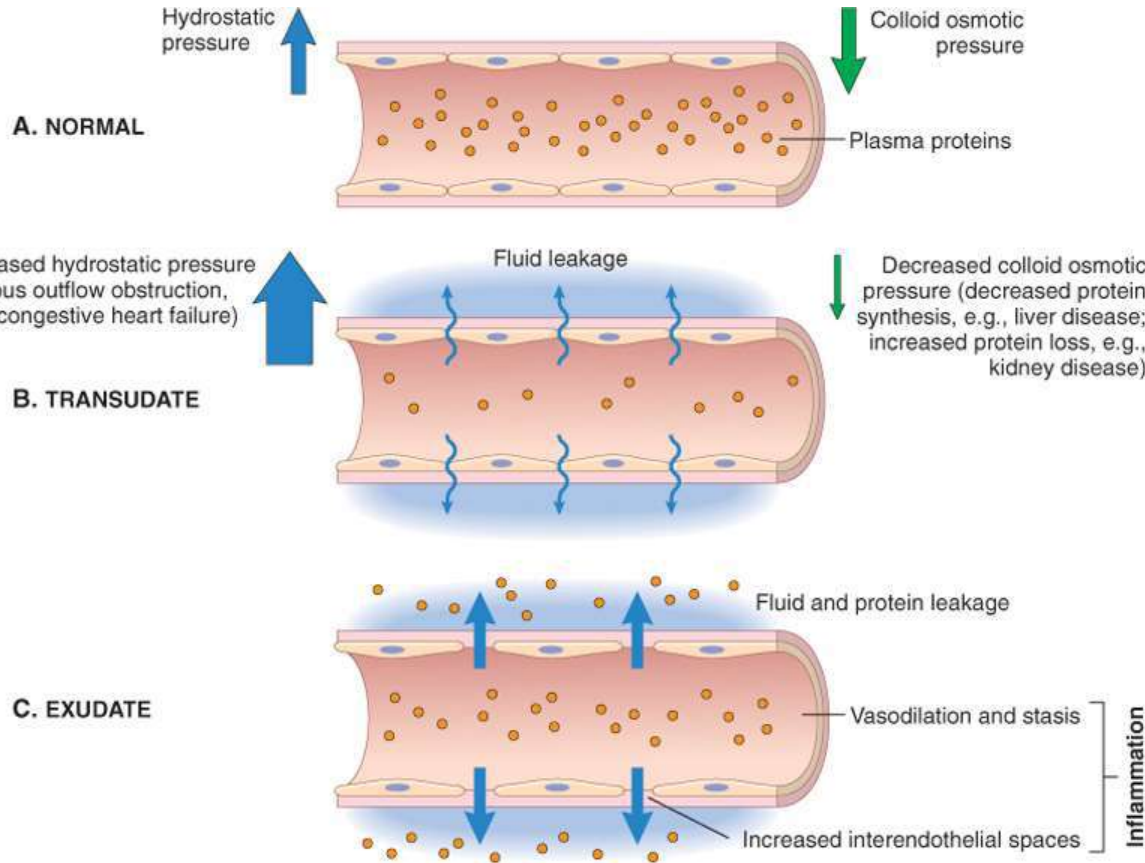
Edema in inflammation

Edema is a general term for swelling (usu. due to fluid)

Plasma proteins in blood maintain a “colloid osmotic pressure” to help draw fluid that leaks out into tissue bed via hydrostatic pressure

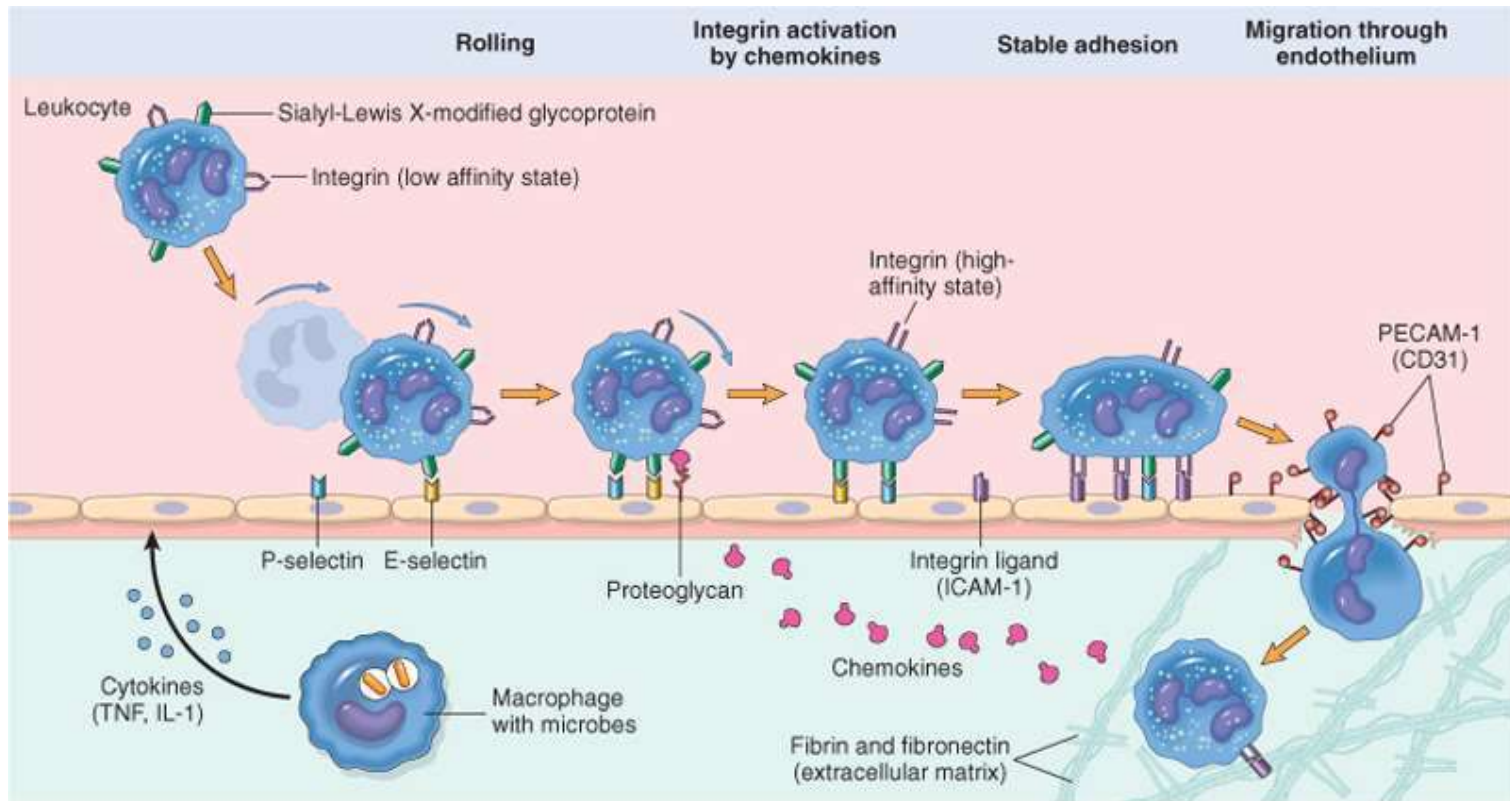
Dysregulation of hydrostatic pressure (e.g. heart failure) and/or colloid pressure (decreased protein synthesis/retention) pushes out more fluid (transudate) into tissue bed

Inflammation causes endothelial cells to separate, thus allowing fluid + protein (exudate) to enter tissue bed.



Leukocyte Extravasation

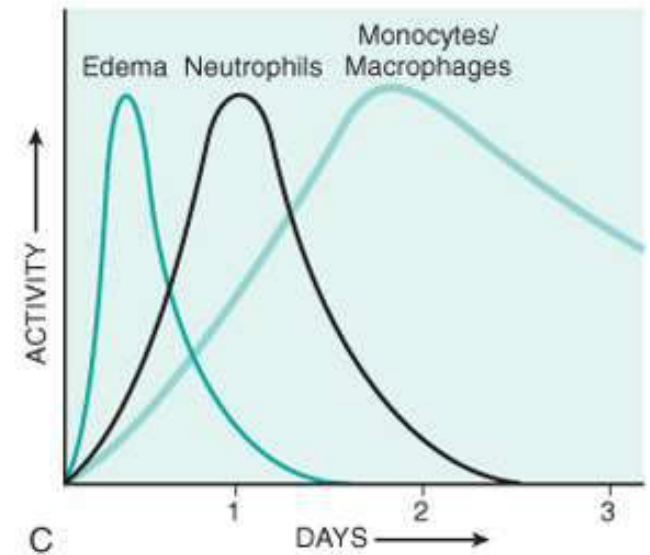
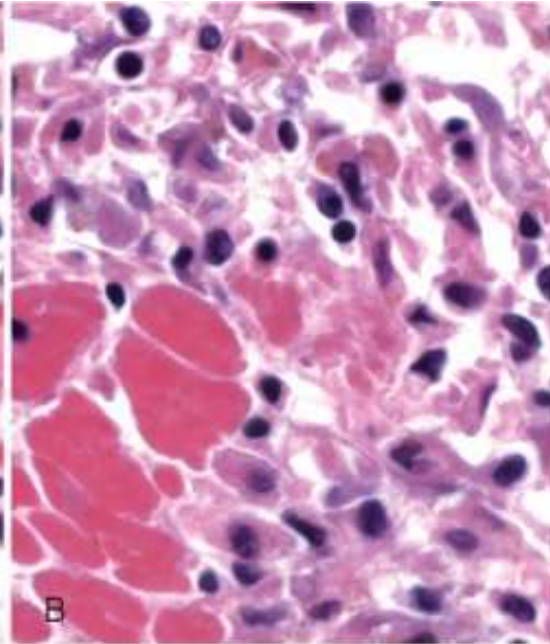
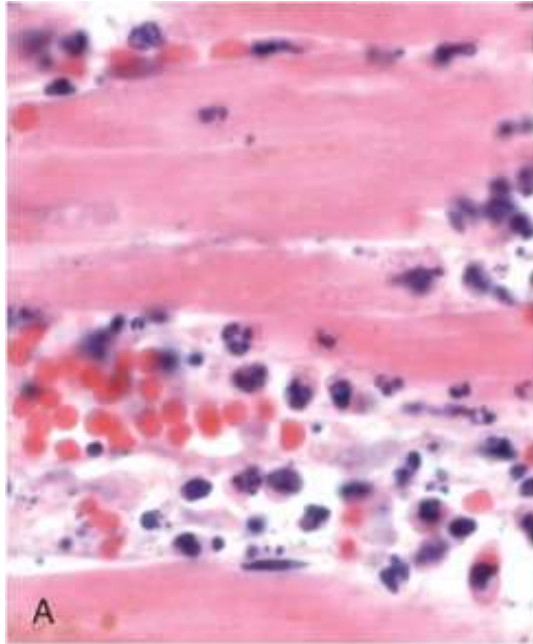
- Extravasation: delivery of leukocytes from the vessel lumen to the interstitium
 - In the lumen: margination, rolling, and adhesion
 - Migration across the endothelium (*diapedesis*)
 - Migration in the interstitial tissue (*chemotaxis*)
- Leukocytes ingest offending agents (phagocytosis), kill microbes, and degrade necrotic tissue and foreign antigens
- There is a balance between the helpful and harmful effects of extravasated leukocytes



Sequence of Leukocyte Emigration

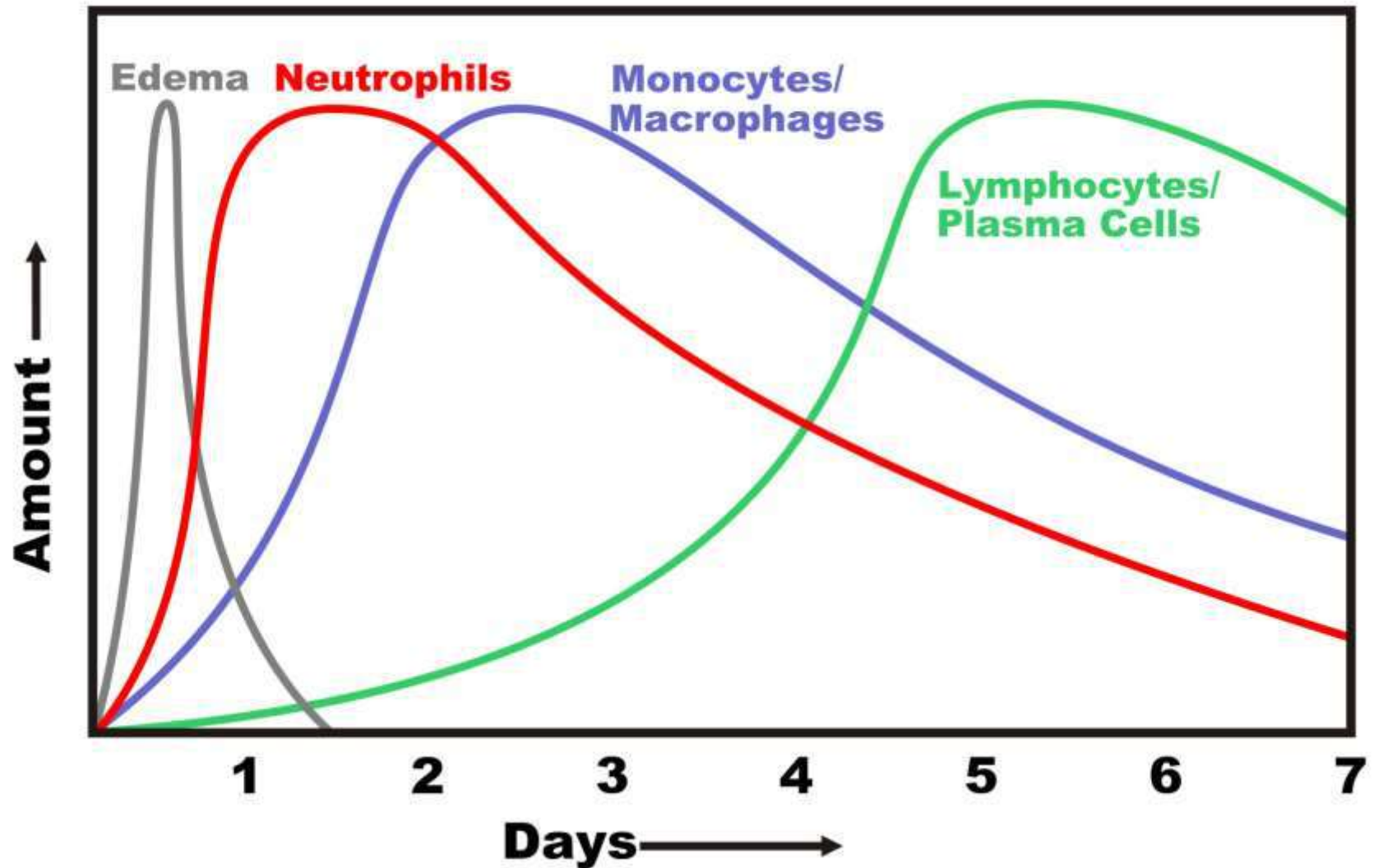
- Neutrophils predominate during the first 6 to 24 hours
- Monocytes in 24 to 48 hours
- Induction/activation of different adhesion molecule pairs and specific chemotactic factors in different phases of inflammation

Sequence of Events - Injury



© Elsevier. Kumar et al: Robbins Basic Pathology 8e - www.studentconsult.com

Sequence of Events - Infection

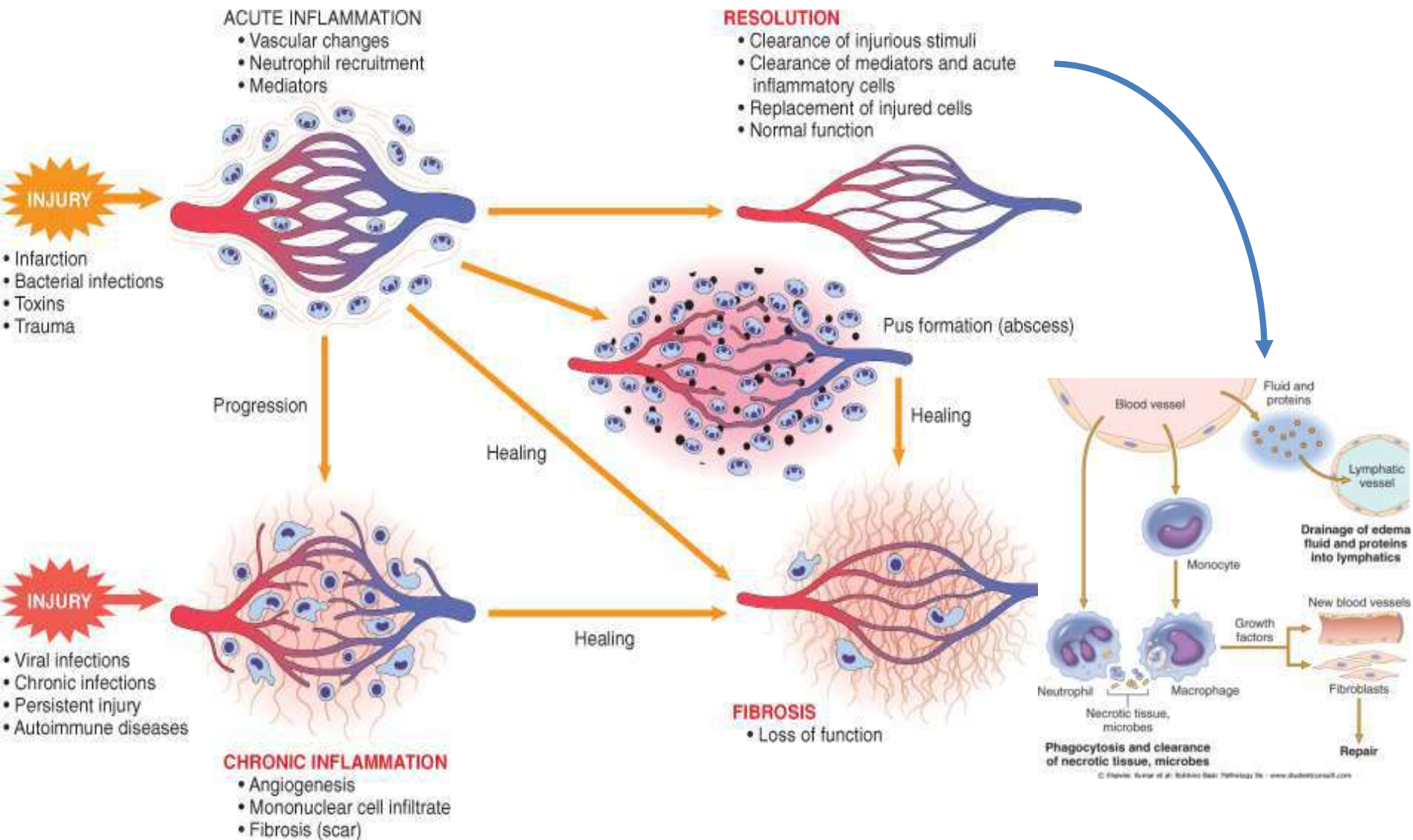


Outcomes of Acute Inflammation

- Complete resolution
- Abscess formation
- Fibrosis
 - After substantial tissue destruction
 - In tissues that do not regenerate
 - After abundant fibrin exudation, especially in serous cavities (pleura, peritoneum)
- Progression to chronic inflammation

Types of Inflammation: acute vs. chronic

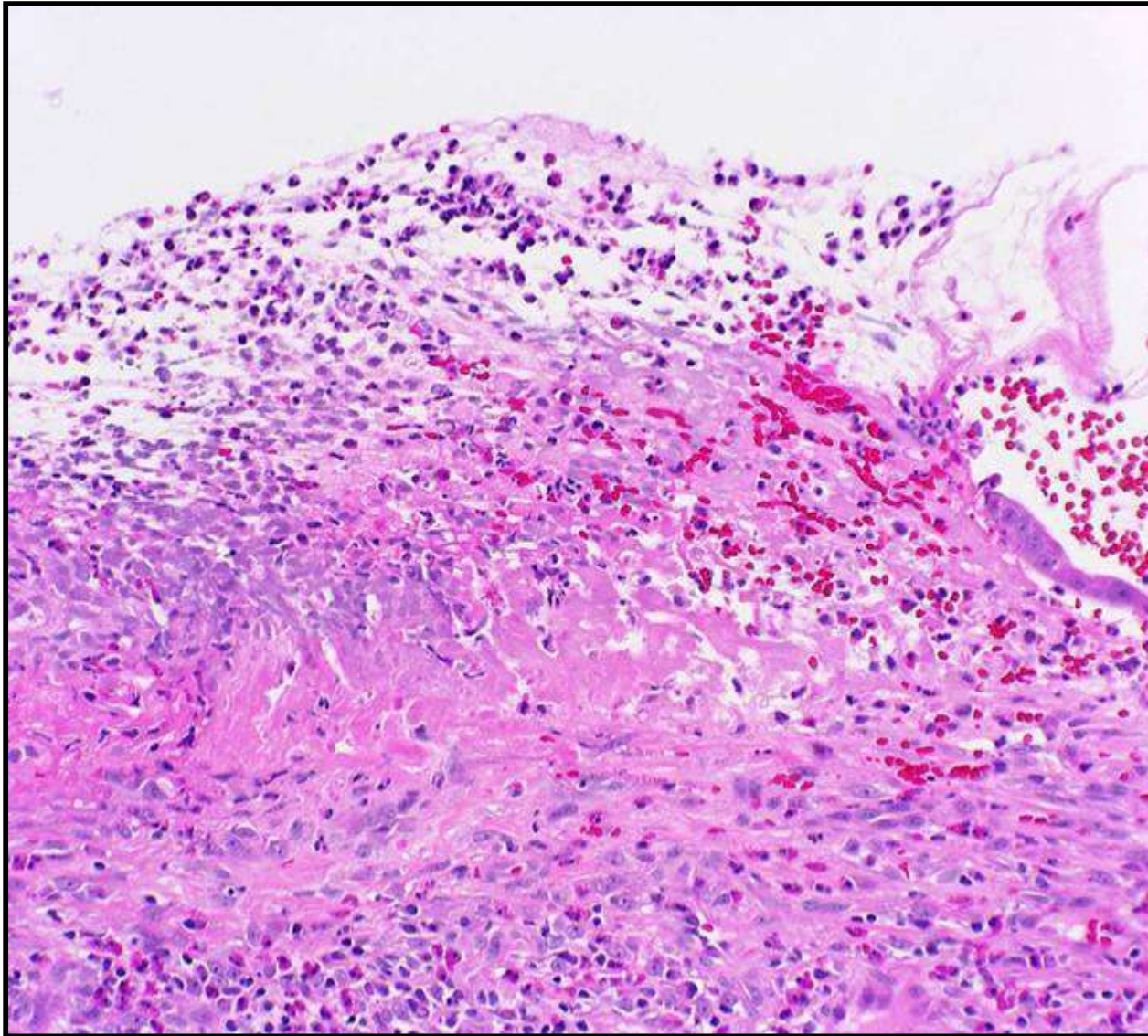
Types of repair: resolution vs. organization (fibrosis)



Morphologic Patterns of Acute Inflammation

- Serous inflammation: Outpouring of thin fluid (serous effusion, blisters)
- Fibrinous inflammation: Body cavities; leakage of fibrin; may lead to scar tissue (adhesions)
- Suppurative (purulent) inflammation: Pus or purulent exudate (neutrophils, debris, edema fluid); abscess: localized collections of pus
- Ulcers: Local defect of the surface of an organ or tissue produced by the sloughing (shedding) of inflammatory necrotic tissue

Gastric Ulcer



Systemic Manifestations

- Endocrine and metabolic
 - Secretion of acute phase proteins by the liver
 - Increased production of glucocorticoids (stress response)
 - Decreased secretion of vasopressin leads to reduced volume of body fluid to be warmed
- Fever
 - Improves efficiency of leukocyte killing
 - Impairs replication of many offending organisms

Systemic Manifestations

- Autonomic
 - Redirection of blood flow from skin to deep vascular beds minimizes heat loss
 - Increased pulse and blood pressure
- Behavioral
 - Shivering (rigors), chills (search for warmth), anorexia (loss of appetite), somnolence, and malaise

Systemic Manifestations

- Leukocytosis: increased leukocyte count in the blood
 - Neutrophilia: bacterial infections
 - Lymphocytosis: infectious mononucleosis, mumps, measles
 - Eosinophilia: Parasites, asthma, hay fever
- Leukopenia: reduced leukocyte count
 - Typhoid fever, some viruses, rickettsiae, protozoa

Chronic Inflammation

- Inflammation of prolonged duration (weeks or months)
 - Active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously
- May follow acute inflammation or begin insidiously and often asymptotically
 - Persistent infections, exposure to toxic agents such as silica (silicosis), or by autoimmunity

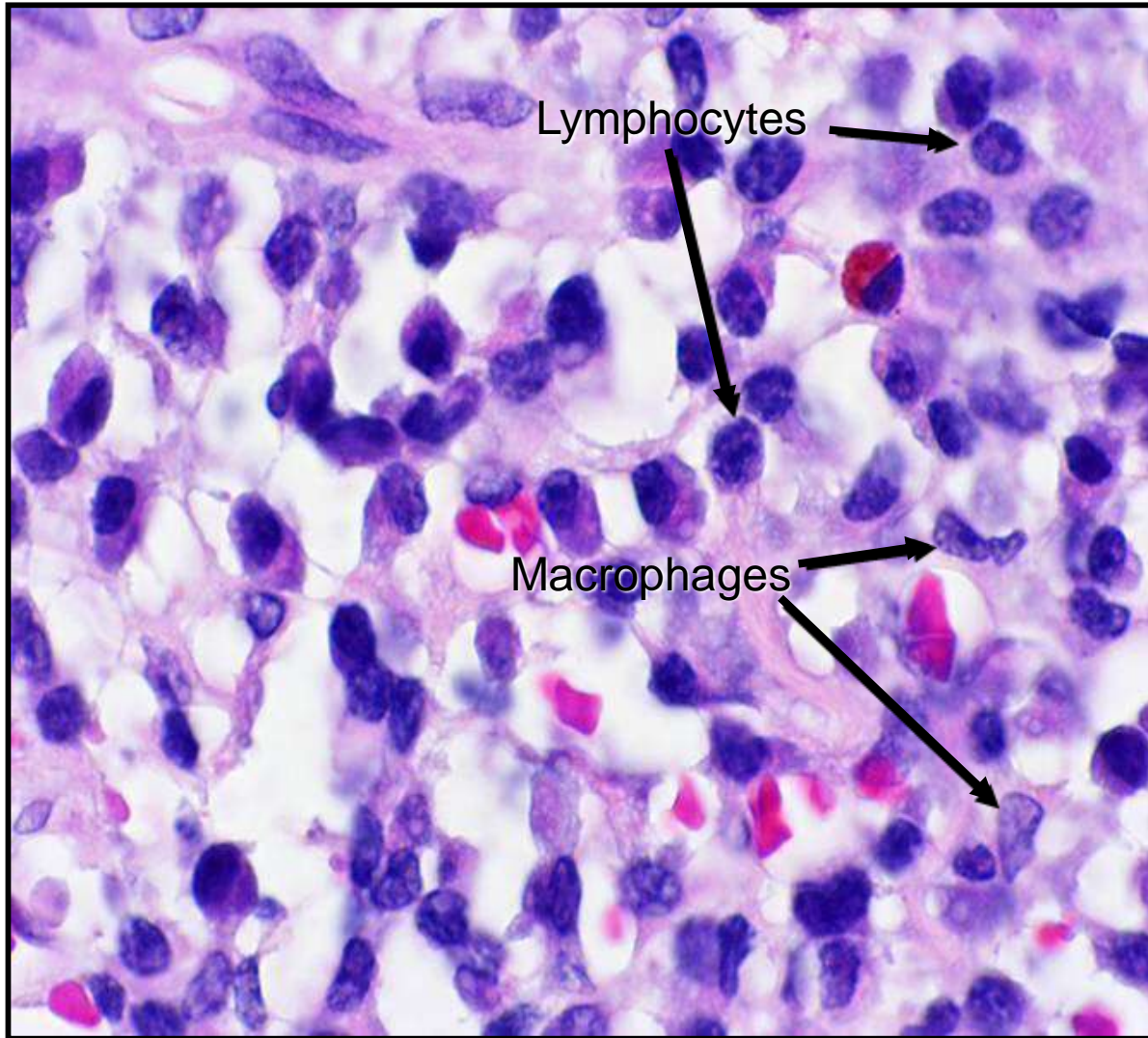
Chronic Inflammation

- Persistent infections
 - *Treponema pallidum* [syphilis], viruses, fungi, parasites
- Exposure to toxic agents
 - Exogenous: silica (silicosis)
 - Endogenous: toxic plasma lipid components (atherosclerosis)
- Autoimmunity
 - Rheumatoid arthritis, systemic lupus erythematosus

Chronic Inflammation

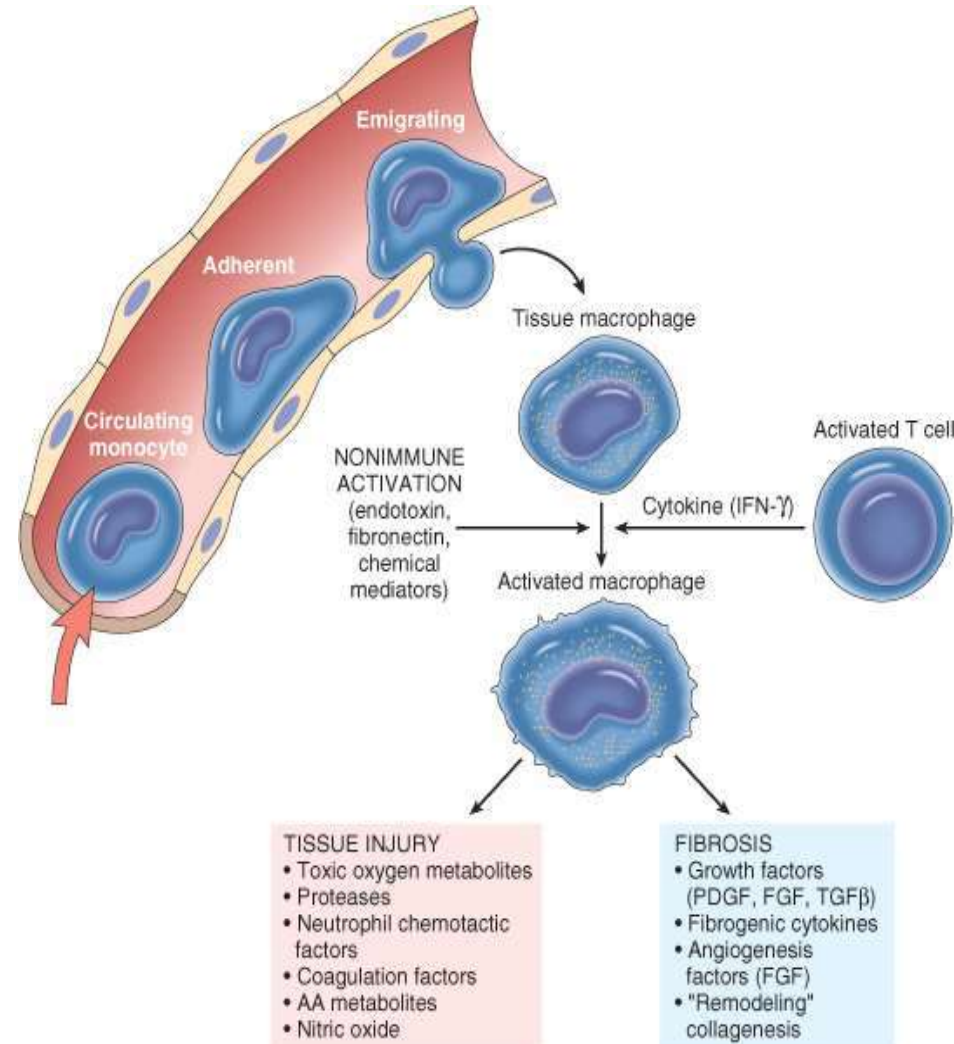
- Histological features
 - Infiltration with mononuclear cells
(macrophages, lymphocytes, and plasma cells)
 - Tissue destruction
(induced by the inflammatory cells)
 - Healing by replacement of damaged tissue by
connective tissue (fibrosis)
and new blood vessels (angiogenesis)

Chronic Inflammatory Cells



Macrophages

- Monocytes begin to emigrate into tissues early in inflammation where they transform into the larger phagocytic cell known as the macrophage
- Macrophages predominate by 48 hours
 - Recruitment (circulating monocytes); division; immobilization
- Activation results in secretion of biologically active products



Other Cells in Chronic Inflammation

- Lymphocytes
 - Produce inflammatory mediators
 - Participate in cell-mediated immune reactions
 - Plasma cells produce antibody
 - Lymphocytes and macrophages interact in a bi-directional fashion

Other Cells in Chronic Inflammation

- Eosinophils
 - Immune reactions mediated by IgE
 - Parasitic infections
 - Eosinophil granules contain a protein that is toxic to parasites
- Mast cells
 - Release mediators (histamine) and cytokines

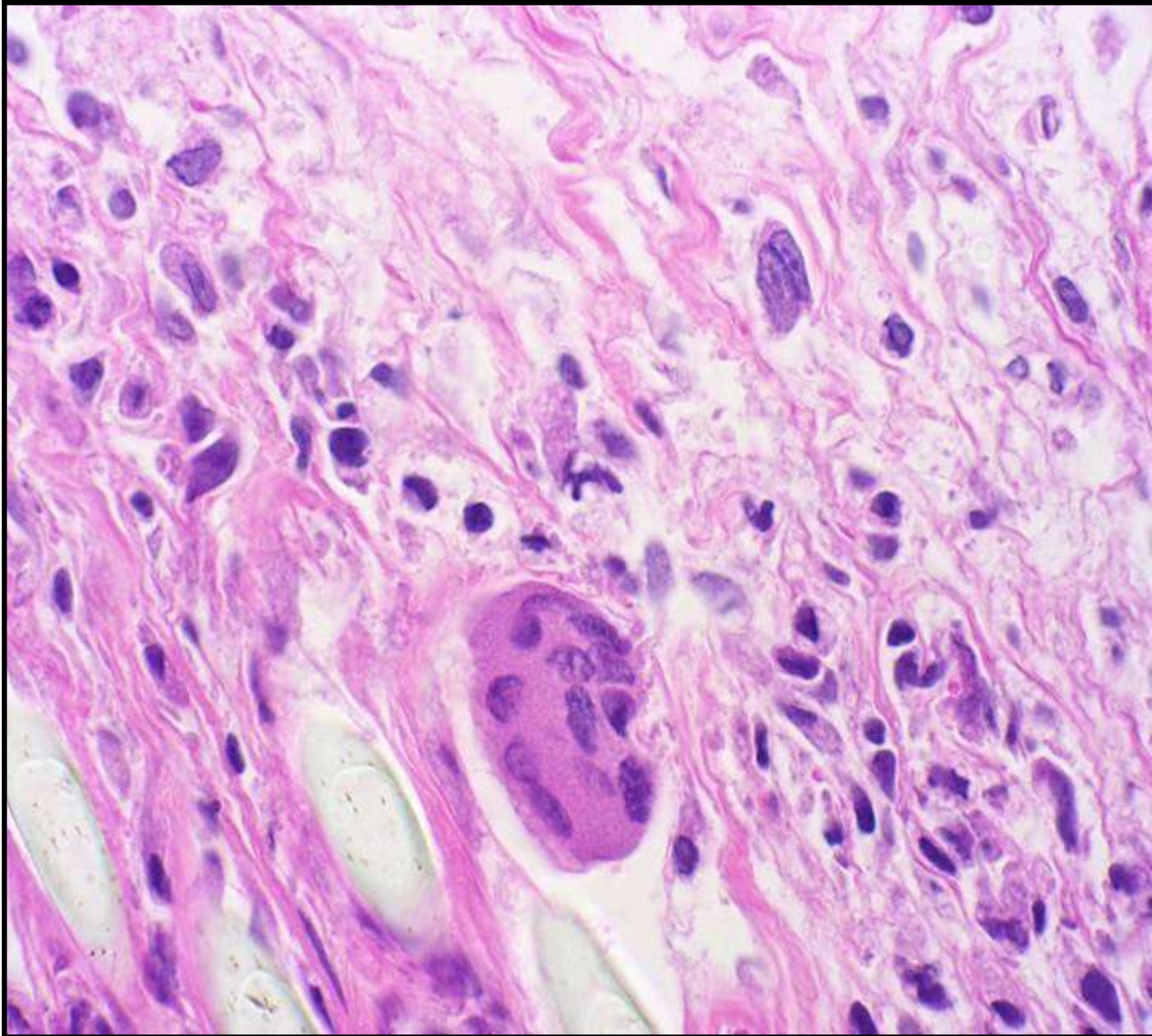
Granulomatous Inflammation

- Distinctive pattern of chronic inflammation
 - Predominant cell type is an activated macrophage with a modified epithelial-like (epithelioid) appearance
 - Giant cells may or may not be present
- Granuloma:
Focal area of granulomatous inflammation

Granulomatous Inflammation

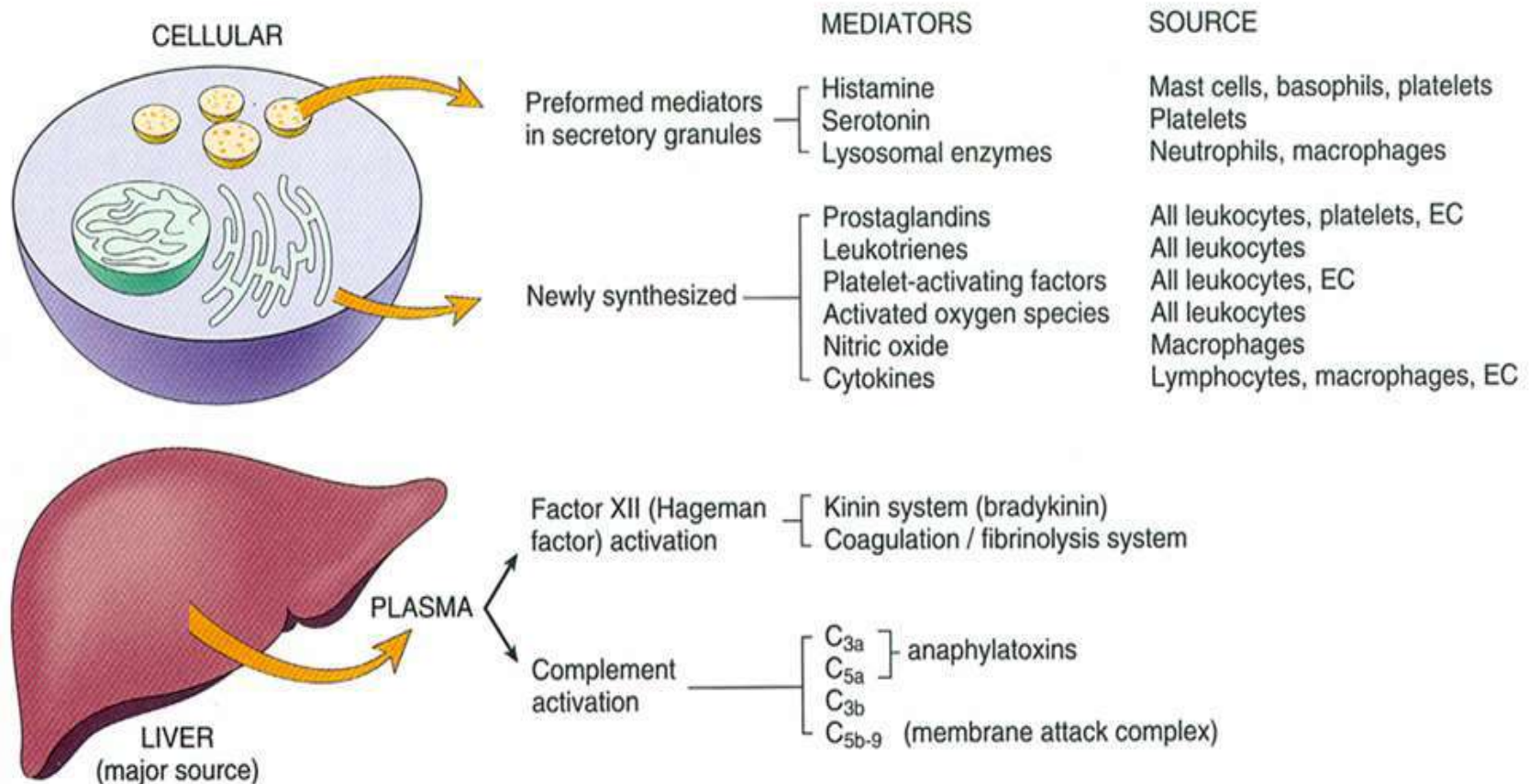
- Foreign body granulomas:
Form when foreign material is too large to be engulfed by a single macrophage
- Immune granulomas:
Insoluble or poorly soluble particles elicit a cell-mediated immune response

Granulomatous Response to Suture



Chemical Mediators of Inflammation

- General principles of chemical mediators
 - May be derived from plasma or cells
 - Most bind to specific receptors on target cells
 - Can stimulate release of mediators by target cells, which may amplify or ameliorate the inflammatory response
 - May act on one or a few target cells, have widespread targets, and may have differing effects depending on cell and tissue types
 - Usually short-lived
 - Most have the potential to cause harmful effects



Chemical Mediators of Inflammation

- Vasoactive mediators

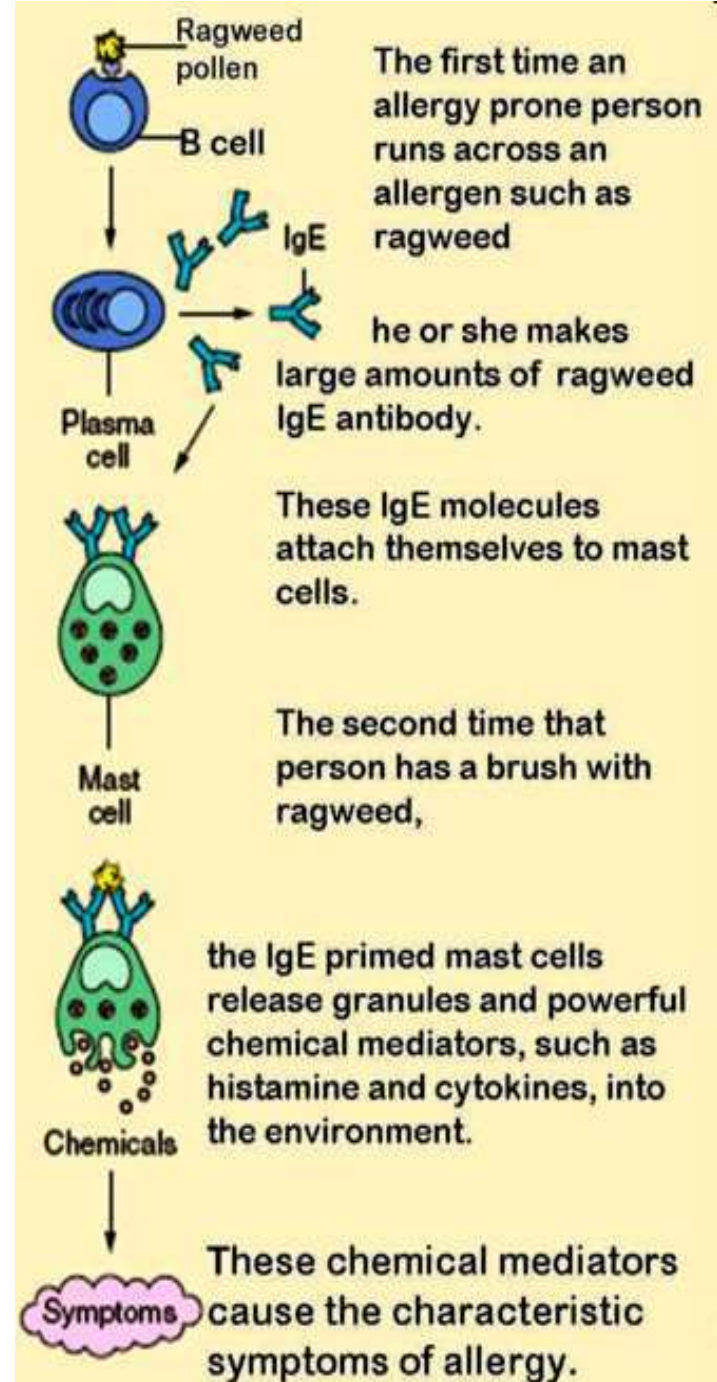
- Histamine
- Bradykinin
- Complement (C3a, C5a)
- Prostaglandins/leukotrienes
- Platelet activating factor
- Nitric oxide

- Chemotactic factors

- Complement (C5a)
- Leukotriene (B4)
- Platelet activating factor
- Cytokines (IL-1, TNF)
- Chemokines
- Nitric oxide

Histamine

- Mast cells (also basophils and platelets)
- Release mechanisms
 - Binding of antigen (allergen) to IgE on mast cells releases histamine-containing granules
 - Release by nonimmune mechanisms such as cold, trauma, or other chemical mediators
 - Release by other mediators
- Dilates arterioles and increases permeability of venules (wheal and flare reaction)



Complement

- Proteins found in greatest concentration in the plasma
- Require activation
- Increase vascular permeability and cause vasodilation
 - Mainly by releasing histamine from mast cells
- Increase leukocyte adhesion, chemotaxis, and activation
- C3b attaches to bacterial wall and enhances phagocytosis by neutrophils & macrophages

Bradykinin

- Small peptide released from plasma precursors
- Increases vascular permeability
- Dilates blood vessels
- Causes pain
- Rapid inactivation

Arachidonic Acid Metabolites

- Prostaglandins
 - Vasodilators: prostacyclin (PGI_2), PGE_1 , PGE_2 , PGD_2
 - Vasoconstrictors: thromboxane A_2
 - Pain (PGE_2 makes tissue hypersensitive to bradykinin)
 - Fever (PGE_2)
 - Production blocked by steroids and nonsteroidal anti-inflammatory agents (NSAIDs)
- Leukotrienes
 - Increase vascular permeability: leukotrienes C_4 , D_4 , E_4
 - Vasoconstriction: leukotrienes C_4 , D_4 , E_4
 - Leukocyte adhesion & chemotaxis: leukotriene B_4 , HETE, lipoxins
 - Production blocked by steroids but not conventional NSAIDs

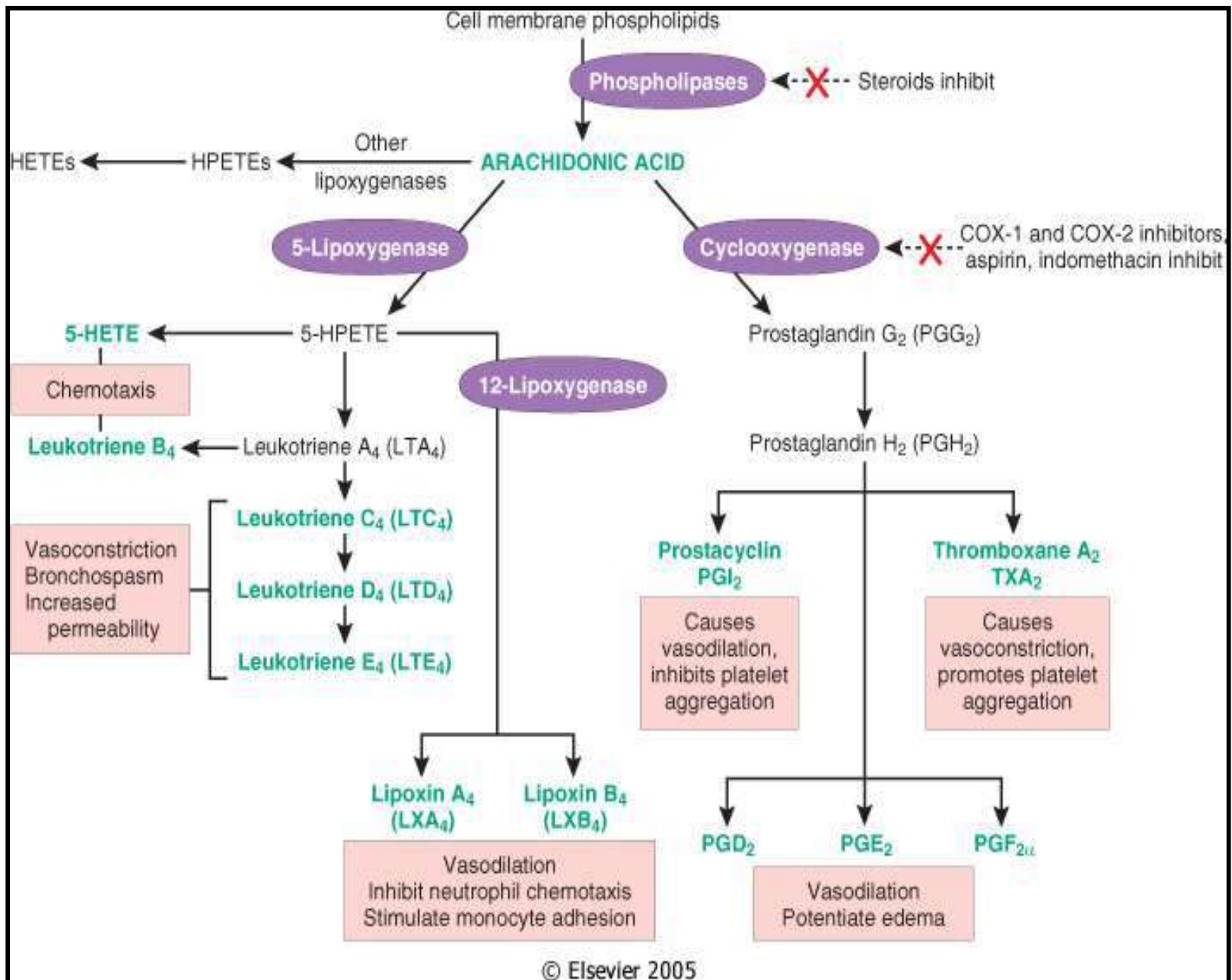


Figure 2-16 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Platelet Activating Factor

- Subclass of phospholipids
- Synthesized by stimulated platelets, leukocytes, endothelium
- Inflammatory effects
 - Stimulates platelet aggregation
 - Vasoconstriction and bronchoconstriction
 - Vasodilation and increased venular permeability
 - Increased leukocyte adhesion to endothelium, chemotaxis, degranulation, and oxidative burst
 - Increases synthesis of arachidonic acid metabolites by leukocytes and other cells

Cytokines

- Proteins produced by many cell types (principally activated lymphocytes & macrophages)
- Modulate the function of other cell types
- Interleukin-1 (IL-1) and tumor necrosis factor (TNF) are the major cytokines that mediate inflammation

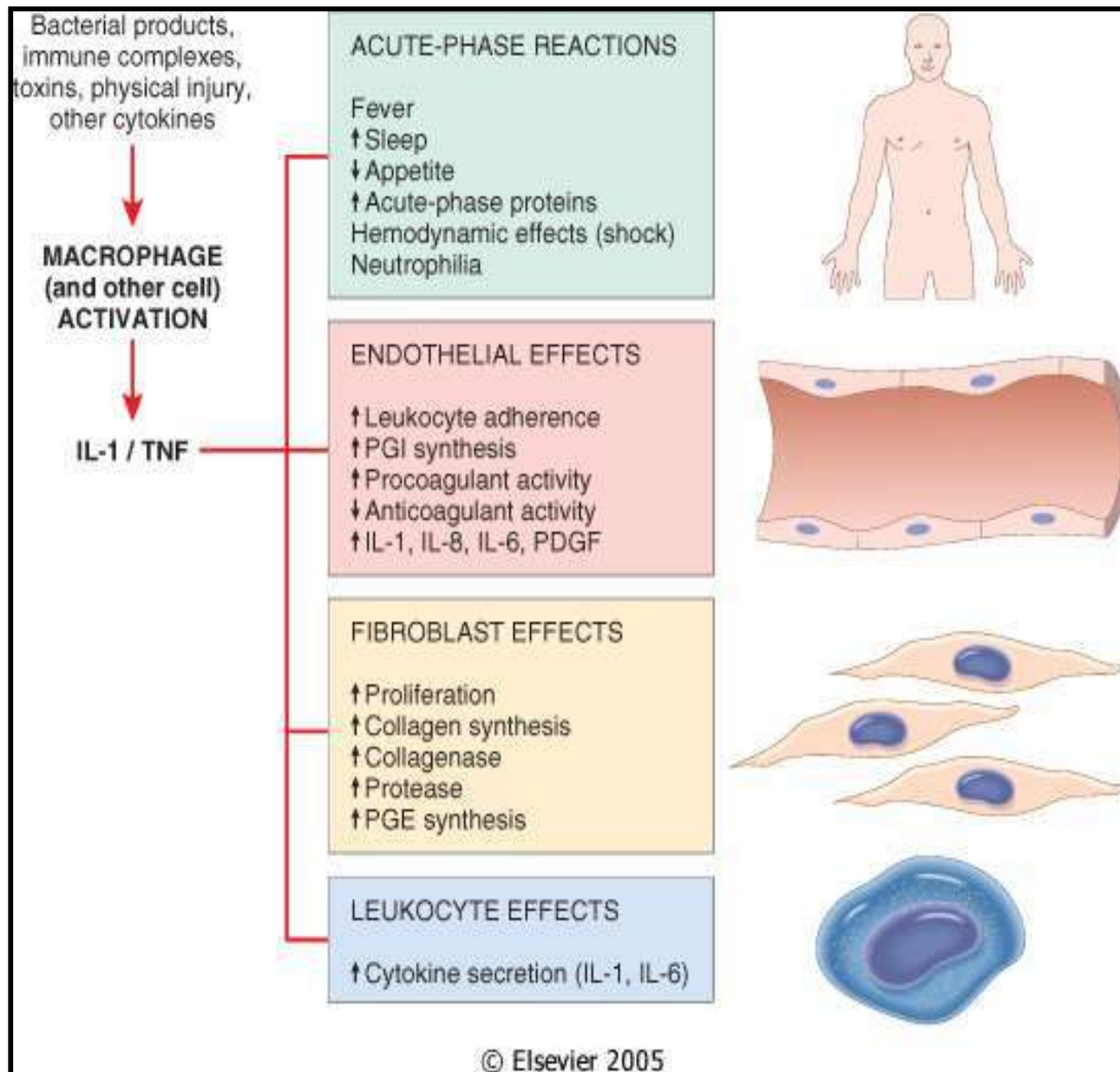


Figure 2-18 Robbins and Cotran Pathologic Basis of Disease, 7th Ed.

Chemokines

- Small proteins that act primarily as chemoattractants for specific types of leukocytes (approximately 40 known)
- Stimulate leukocyte recruitment in inflammation
- Control the normal migration of cells through tissues (organogenesis and maintenance of tissue organization)
- Examples: IL-8, eotaxin, lymphotactin

Other Mediators

- Neutrophil granules:
 - Cationic proteins increase vascular permeability, immobilize neutrophils, chemotactic for mononuclear phagocytes
 - Neutral proteases generate other mediators and degrade tissue
- Oxygen-Derived Free Radicals:
 - Produced during phagocytosis by neutrophils (“respiratory burst”)
 - Tissue damage including endothelium

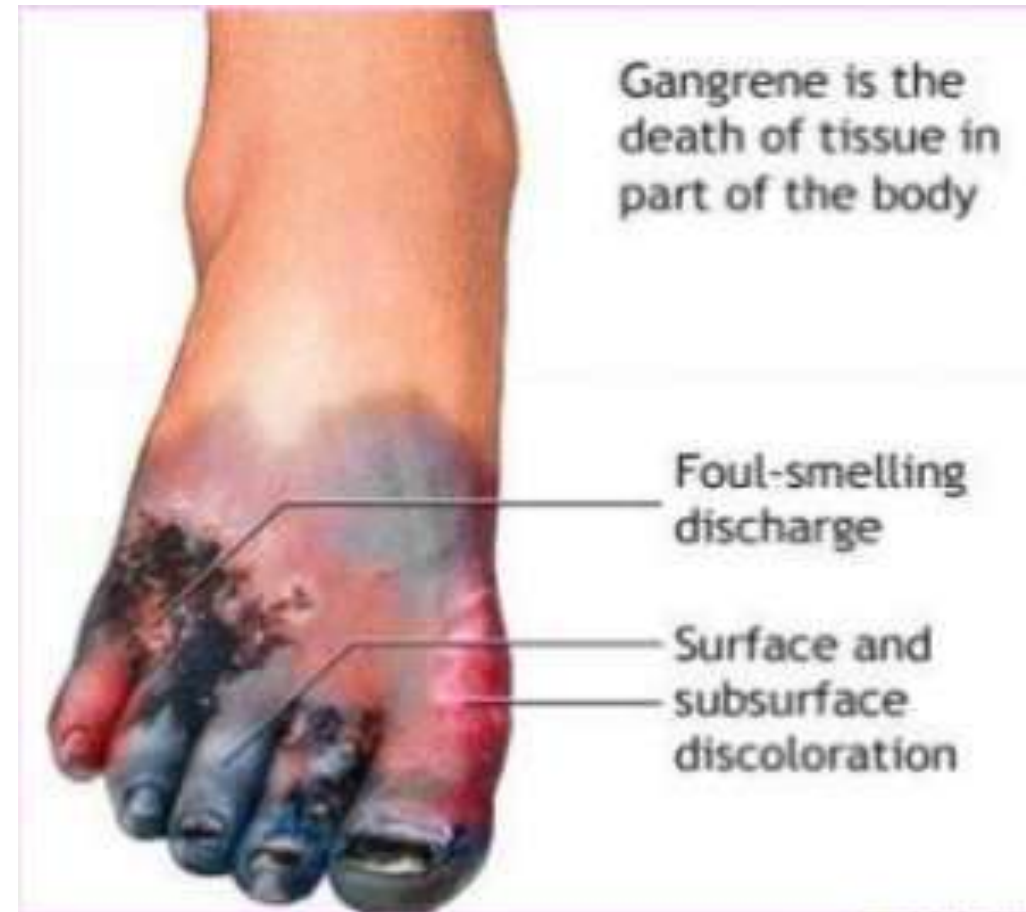
Gangrene

- A form of necrosis of tissue with superadded putrefaction.
 - All types of gangrene, necrosis undergoes liquefaction by the action of putrefactive bacteria.
 - It may be caused either **ischemic** or **inflammatory**
- Coagulative Necrosis due to ischaemia
 - gangrene of the bowel,
 - gangrene of limb

- **Gangrenous or necrotising inflammation:** primarily inflammation provoked by virulent bacteria resulting in massive tissue necrosis.
 - Gangrenous appendicitis,
 - Gangrenous stomatitis (noma, cancrum oris)

Types of Gangrene

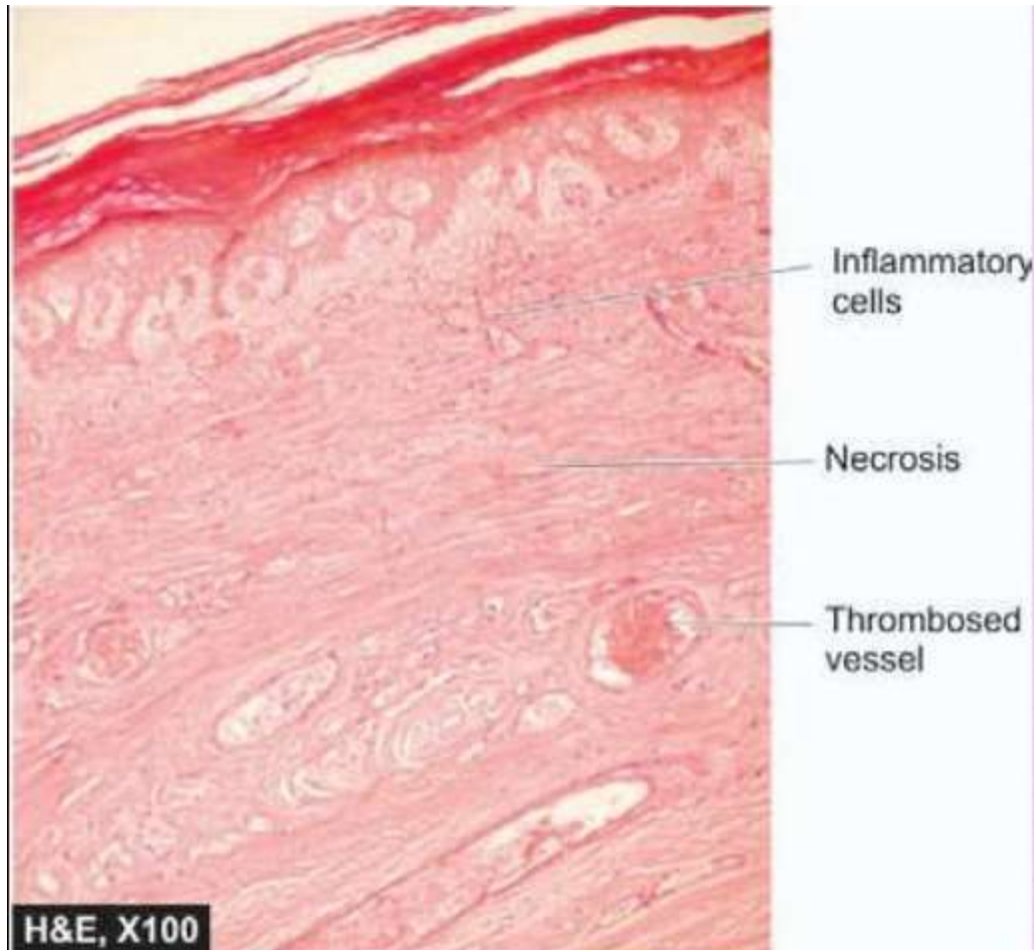
- 2 main forms of gangrene
- **Dry gangrene**
- **Wet Gangrene**
 - **Gas gangrene:**
a kind of wet gangrene



Dry Gangrene

- begins in the distal part of a limb due to ischaemia.
 - The gangrene spreads slowly upwards until it reaches a point where the blood supply is adequate to keep the tissue viable.
 - A **line of separation** is formed at this point between the gangrenous part and the viable part.
 - Toes and feet of an old patient due to **arteriosclerosis**.
 - Thromboangiitis obliterans (Buerger's disease),
 - Raynaud's disease,
 - Trauma
 - Ergot poisoning

Morphology



- **Grossly**

- the affected part is dry, shrunken and dark black, resembling the foot of a mummy.
- It is black due to liberation of haemoglobin from haemolysed red blood cells which is acted upon by hydrogen disulfide (H_2S) produced by bacteria resulting in formation of black iron sulfide.
- The line of separation usually brings about complete separation with eventual falling off of the gangrenous tissue if it is not removed surgically

- **Histologically**

- Necrosis with smudging of the tissue.
- The line of separation consists of inflammatory granulation tissue

Wet Gangrene

- Naturally moist tissues and organs such as the mouth, bowel, lung, cervix, vulva.
- develops rapidly due to blockage of venous, and less commonly, arterial blood flow from thrombosis or embolism.
- The affected part is stuffed with blood which favours the rapid growth of putrefactive bacteria.
- The toxic products formed by bacteria are absorbed causing profound systemic manifestations of septicaemia, and finally death.

Wet Gangrene

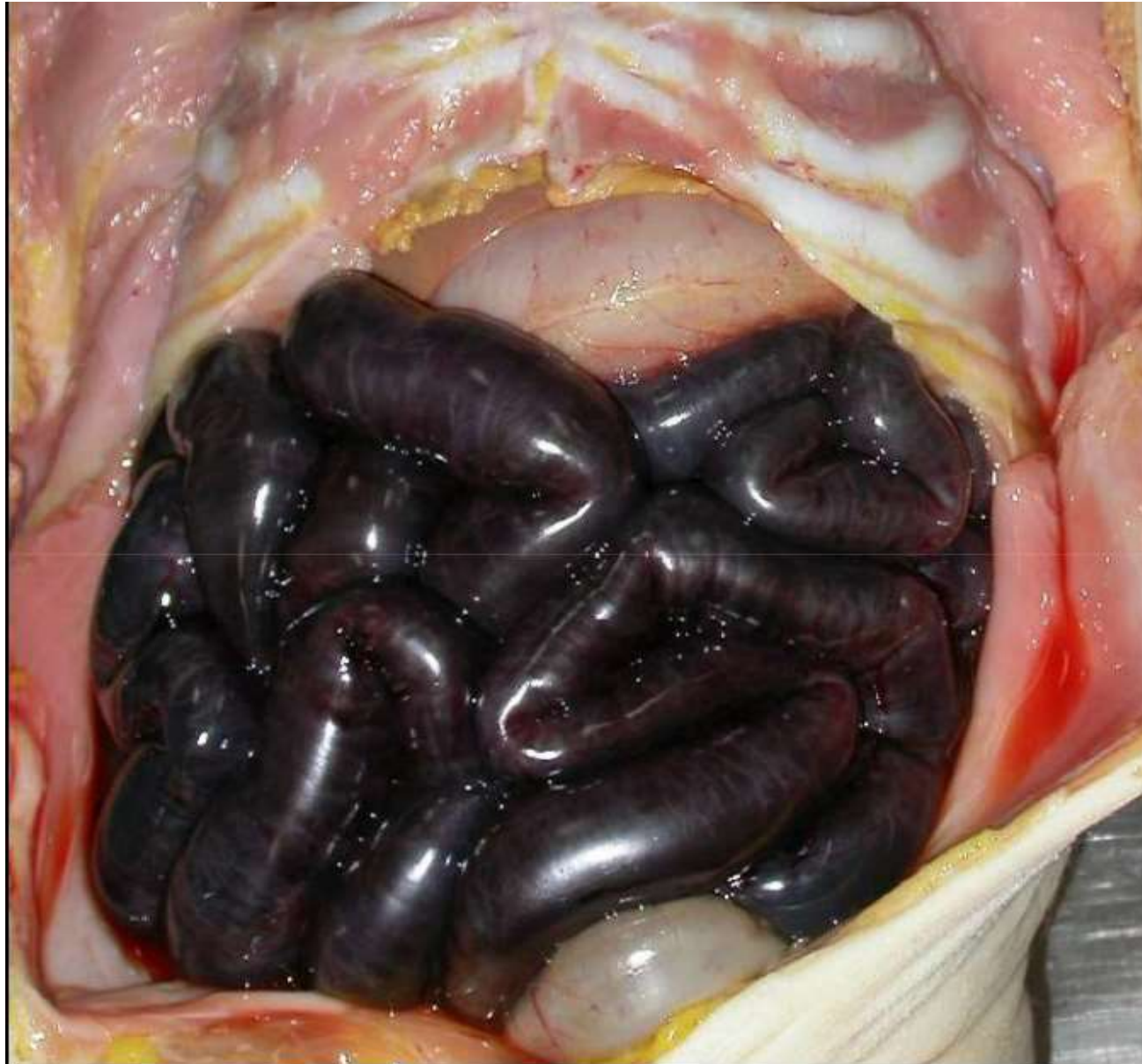
- **Diabetic foot**

- high sugar content in the necrosed tissue which favours growth of bacteria.of bacteria.

- **Bed sores**

- bed-ridden patient due to pressure on sites like the sacrum, buttocks and heels





**Wet
gangrene
Intestine**

MORPHOLOGIC FEATURES

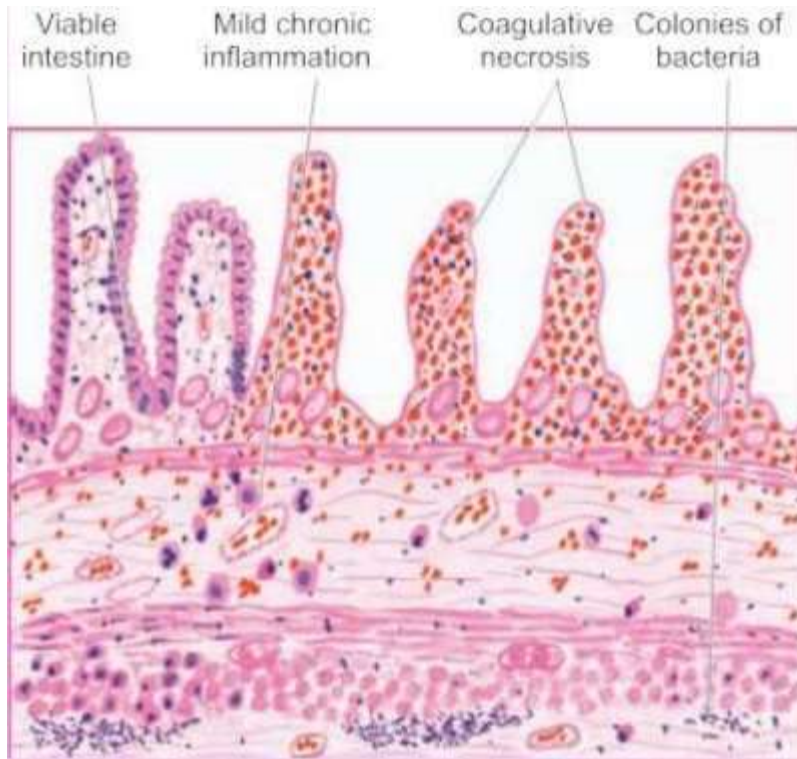
- **Grossly,**

- the affected part is soft, swollen, putrid, rotten and dark.
- The classic example is gangrene of bowel, commonly due to strangulated hernia, volvulus or intussusception.
- The part is stained dark due to the same mechanism as in dry gangrene

- **Histologically,**

- coagulative necrosis with stuffing of affected part with blood.
- There is ulceration of the mucosa and intense inflammatory infiltration.
- Lumen of the bowel contains mucus and blood.
- The line of demarcation between gangrenous segment and viable bowel is generally not clear-cut

Wet gangrene of the small bowel



- Coagulative necrosis of the affected bowel wall and thrombosed vessels while the junction with normal intestine is indistinct and shows an inflammatory infiltrate

Contrasting Features of Dry and Wet Gangrene

Feature	Dry Gangrene	Wet Gangrene
Site	Commonly limbs	More common in bowel
Mechanisms	Arterial occlusion	More commonly venous obstruction, less often arterial occlusion
Macroscopy	Organ dry, shrunken and black	Part moist, soft, swollen, rotten and dark
Putrefaction	Limited due to very little blood supply	Marked due to stuffing of organ with blood
Line of demarcation	Present at the junction between healthy and gangrenous part	No clear line of demarcation
Bacteria	Bacteria fail to survive	Numerous present
Prognosis	Generally better due to little septicaemia	Generally poor due to profound toxemia

GAS GANGRENE

- Special form of wet gangrene caused by gas-forming **clostridia** (gram-positive anaerobic bacteria).
 - gain entry into the tissues through open contaminated wounds,
 - especially in the muscles, or as a complication of
 - especially in the muscles, or as a complication of operation on colon which normally contains clostridia.
- It produce various toxins which produce necrosis and oedema locally
- Also absorbed producing profound systemic manifestations.

MORPHOLOGIC FEATURES

- **Grossly**

- the affected area is swollen, oedematous, painful and crepitant due to accumulation of gas bubbles within the tissues.
- Subsequently, the affected tissue becomes dark black and foul smelling.foul smelling.

- **Microscopically**

- the muscle fibres undergo coagulative necrosis with liquefaction
- Large number of gram-positive bacilli can be identified.
- At the periphery, a zone of leucocytic infiltration, oedema and congestion are found.
- Capillary and venous thrombi are common.

GAS GANGRENE

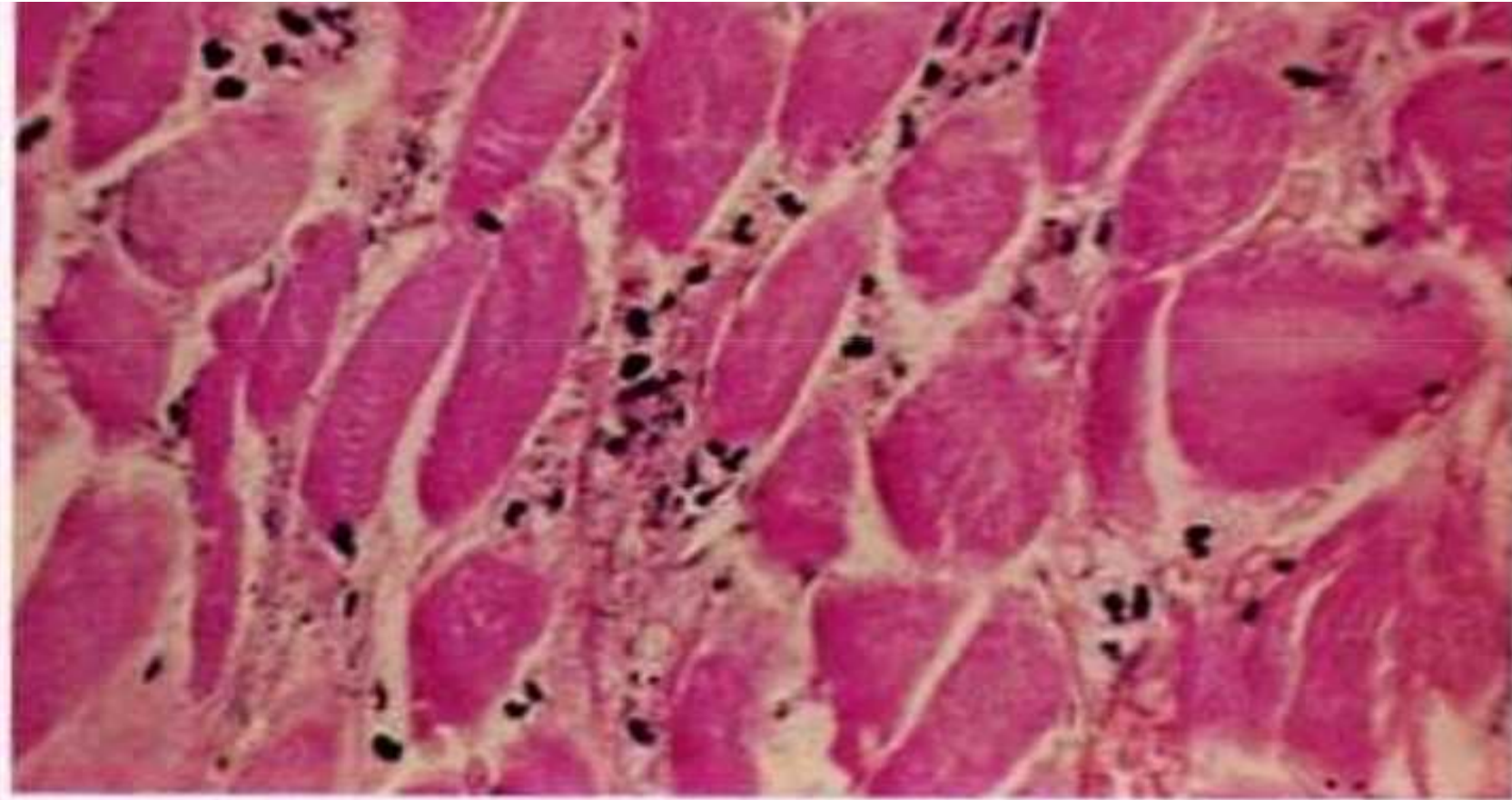


Figure 8. Histological section from a case of gas gangrene showing myonecrosis and gas in tissues.

References

- Robinson's basic pathology 8 ed
- Harsh Mohan - Textbook of Pathology 6th Ed.
- Color atlas of pathology

Diagnosis of cancer

- ☐ There are several methods of diagnosing cancer with advantages in technologies that understand cancer better
- ☐ There are rises of number of diagnostic tools that can help detect cancers
- ☐ Diagnosis is usually made by pathologist and oncopathologist.
- ☐ Some type of cancers, particularly lymph nodes, can be hard to classify even for an expert. Most cancer needs a second opinion regarding diagnosis before being sure of diagnosis or stage & type.

Main methods of cancer diagnosis

1. Radiological diagnosis
2. Cytological diagnosis
3. Histological diagnosis
4. Frozen section
5. Hematological diagnosis
6. Immunohistochemistry
7. Molecular diagnosis
8. Tumour markers

1.RADIOLOGICAL DIAGNOSIS

- It include,
- X-ray
- Ultrasound
- CT scan
- MRI
- These are one of the best early, non-invasive methods of cancer diagnosis.
- **X-ray** – it is a most common technique. These is used for detection of stomach & small intestinal growths & cancer.

- **Ultrasound**- an exam in which the sound waves are bounced off tissue and echoes are converted into picture
- **CT scan** – (computerized tomography)
It uses radiographic beams to create detail computerized picture.
It is more precise than a standard X-ray .
- **MRI**- (Magnetic resonance imaging)
It uses powerful magnetic field to create detail computerized images of the body's soft tissue, large blood vessels & major organs.

2.CYTOLOGICAL DIAGNOSIS

- **1. Fine needle aspiration cytology (FNAC)**
- Fine needle aspiration cytology is a popular method of tumor diagnosis particularly for palpable tumors
- Lymph nodal tumors
- Breast tumors
- Salivary gland tumors
- Thyroid tumors

- **Procedure :** the skin over the area is cleaned with antiseptic solution like spirit. Tumor is fixed by holding it.
A 24 g needle is pushed inside the tumor and
The material is sucked by a syringe is prepared
from the aspirated material.
It is increased by putting the needle under CT
or Ultrasound guidance. The smear is stained
Giemsa Stain.

3.HISTOLOGICAL DIAGNOSIS :

- For histological diagnosis the following methods of sampling is done:
- **Biopsy**- biopsy is a surgical removal of small piece of tissue For microscopic examination for the presence of cancer cell.

There are three ways tissues can be removed for

- **Biopsy:-**
- Endoscopy
- Needle biopsy
- Surgical biopsy

- **Endoscopy**- in this process ,
A thin, flexible tube with a tiny camera on the end is inserted into the body cavity. This allows the doctor to view the abnormal area.
- **Needle biopsy** - the doctor takes a small tissue sample by Inserting a needle into abnormal area. Different types of needles are used, EX: Vim Silverman needle for liver biopsy
- Renal biopsy needle for renal tissue
- True cut biopsy needle for prostatic Tissue or breast tissue

Surgical Biopsy:-

- There are two types of surgical biopsies.
- **An excisional biopsy** :it is performed when the doctor removes the entire tumor, often with some surrounding normal tissue.

- **An incisional biopsy:** it is performed when the doctor removes just a portion of the tumor. If cancer is found to be present, the entire tumor may be removed immediately or during another operation.

The processing of tissue and its diagnosis takes a two or three days.

4. FROZEN SECTION:-

- Frozen section is quick diagnosis method. The tissue is quickly frozen at around -20° c in frozen section
- cryostant which makes the tissue hard.
 - tissue is immediately sectioned & stained
 - the whole process from receiving, staining to diagnosis can be completed within 10 to 15 days.

5. HAEMATOLOGICAL DIAGNOSIS:-

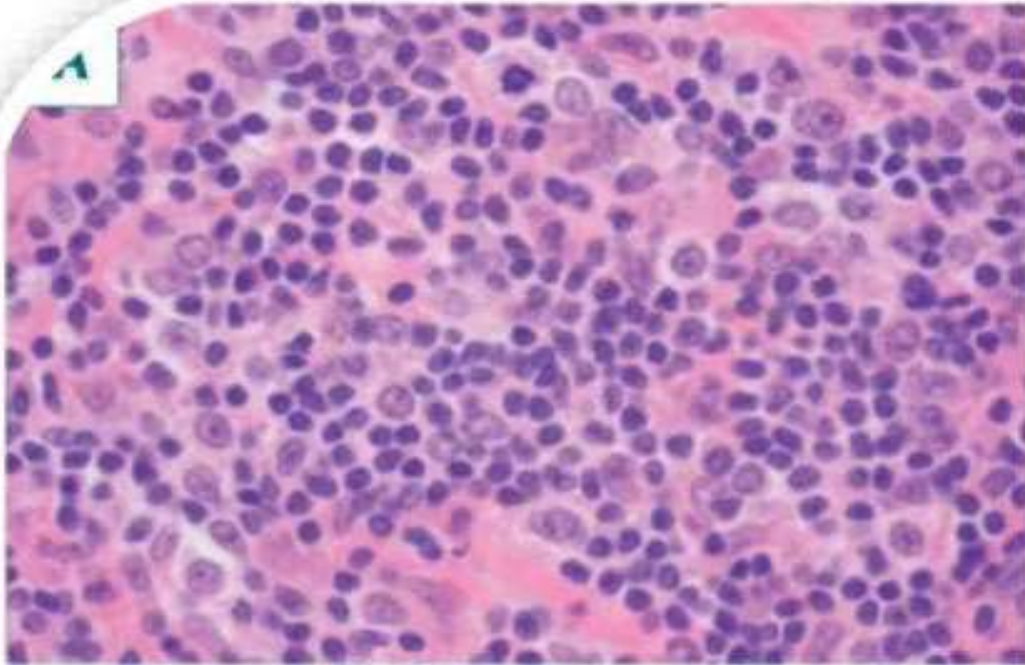
- -Marrow is aspirated by bone marrow aspiration needle biopsied by trephine needle. It is useful in the diagnosis of Leukemia
- Metastasis from lymphoma or solid tumors. This is needed for staging
- Leukemia

6.IMMUNOHISTOCHEMISTRY

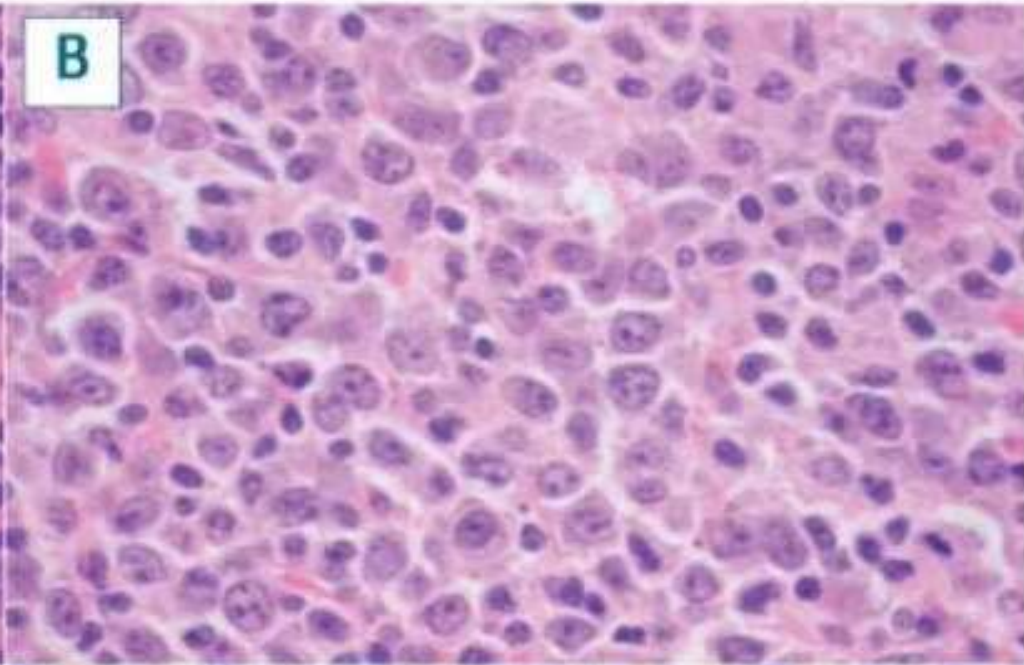
Large number of monoclonal antibodies are available which are useful for:

- typing of a malignant tumour. Poorly differentiated tumours are difficult to morphologically type but if it shows positivity for cytokeratin antibody then it can be typed as carcinoma.
- T cell or B cell monoclonal antibody positivity in the T cell or B cell lymphoma.
- classification of leukemia and lymphomas.
Determination of site of primary in metastatic tumour.

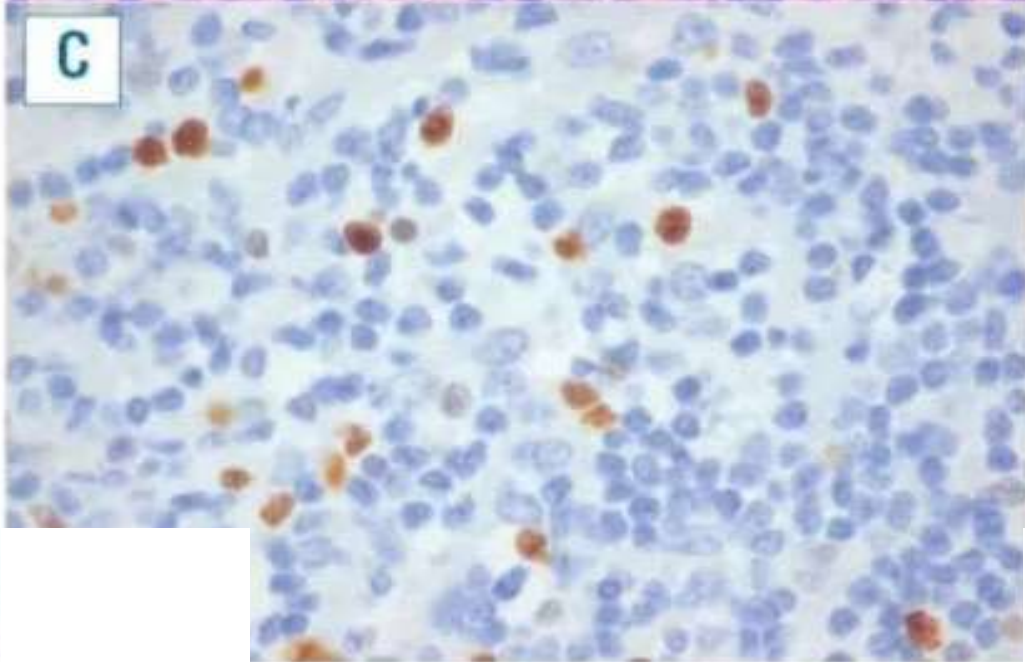
A



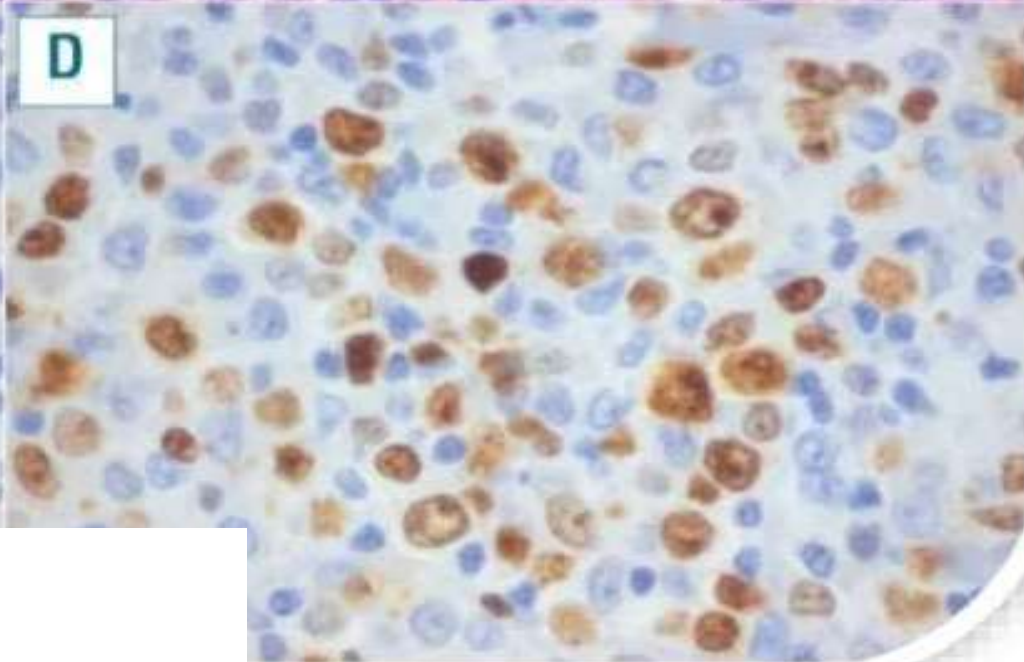
B



C

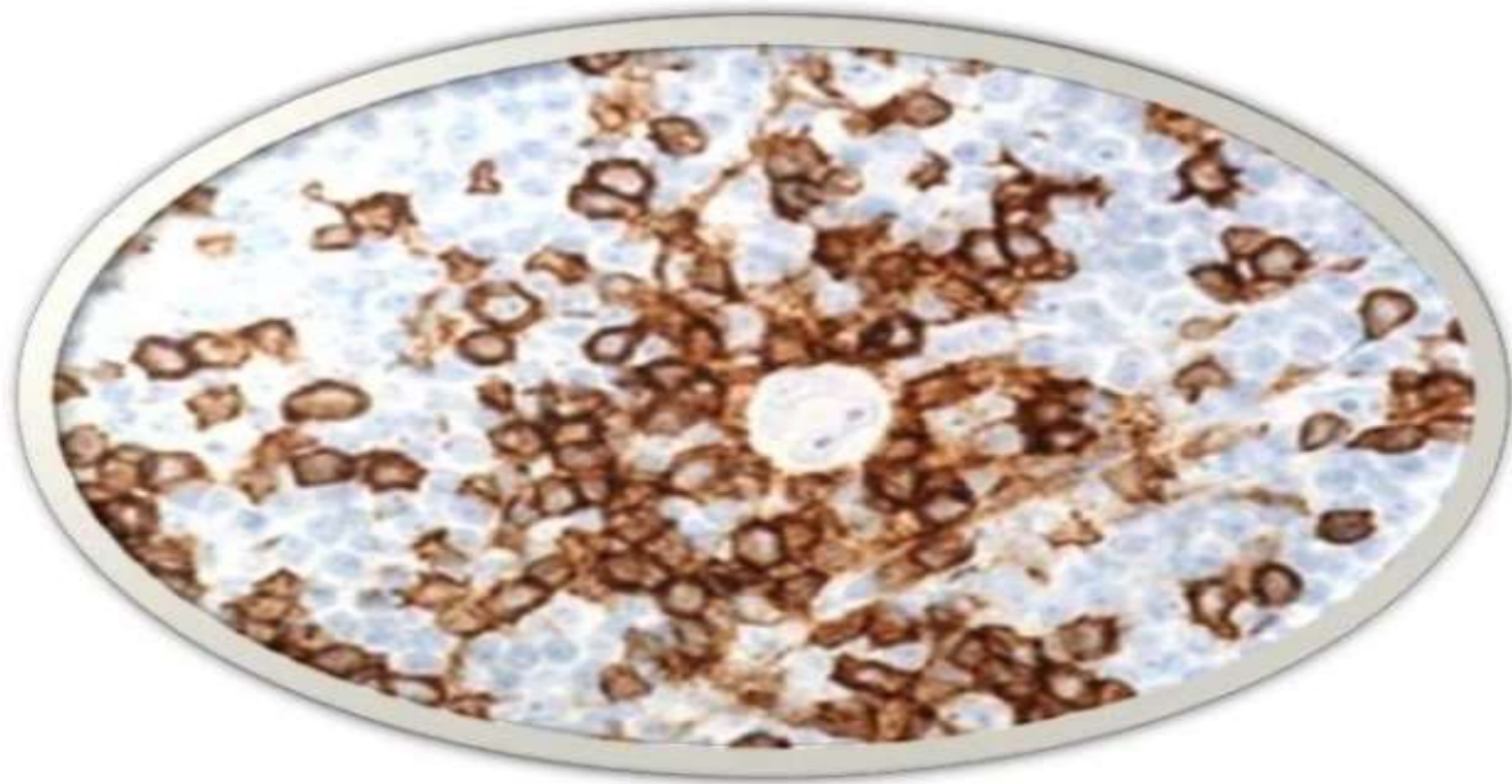


D



7. MOLECULAR DIAGNOSIS

- Molecular diagnosis is an ever emerging field.
- These are useful in detection of : Minute translocations Minimal residual disease.





8. TUMOR MARKER:-

- Some tumors release substance is called **tumor markers**
- Blood test can be performed to detect the blood Cells as well as for specific tumor markers
- Tumor marker is biochemical indicators of Tumors .these may be:
 - Antigens
 - Cytoplasmic proteins
 - Enzymes
 - Hormones
 - Use in support diagnosis

DEGENERATION & REGENERATION

DEGENERATION:

- When a nerve fibre is cut or severely crushed, **degenerative changes** take place at **3** levels:
 1. Changes in the **nerve cell body**
 2. Changes in the **central/proximal** stump
(RETROGRADE DEGENERATION)
 3. Changes in the **distal stump**
(WALLERIAN DEGENERATION also called the Secondary Degeneration)

1. Changes in the nerve cell body:

- Cell body swells
- Nissl granules undergo dissolution (CHROMATOLYSIS)
- Nucleus is pushed to one side
- Mitochondria, Golgi apparatus, ribosomes & lysosomes show structural changes
- If the axon is cut quite close to the cell body, the neuron may die....

2. RETROGRADE DEGENERATION

- This is the degeneration that occurs in the central or proximal segment.
- Degenerated area may extend upwards for one or more nodes.
- Degeneration may be followed by repair..... As this part is still attached to the cell body.

Wallerian Degeneration

In less than 24 hours	Neurofilaments break up; axons break up into short lengths
Within 10 days	Myelin sheath breaks down into lipid droplets around the axon
Within a month	Myelin gets denatured chemically
Within three months	Macrophages from the endoneurium invade the degenerating myelin sheath and axis cylinder and phagocytose the debris

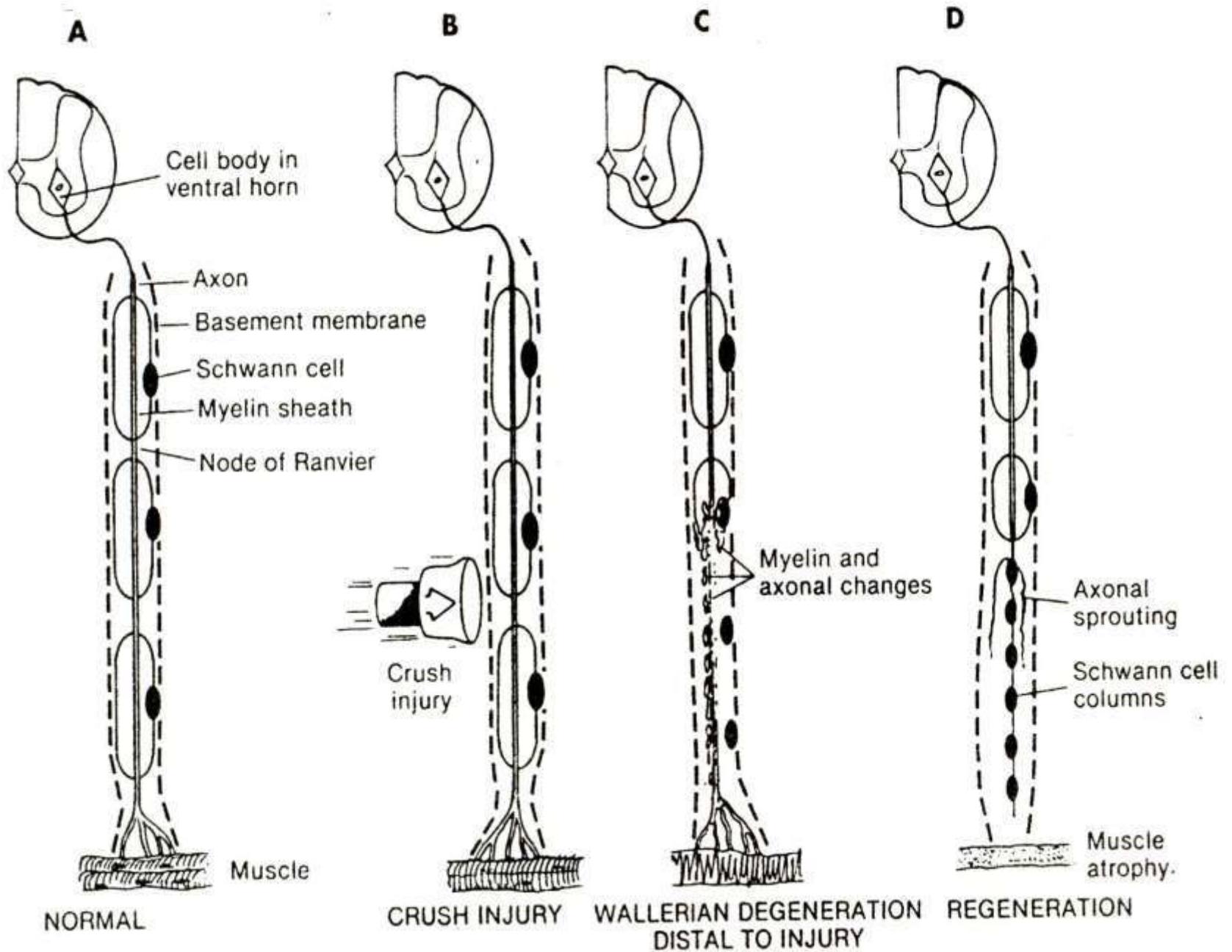
REGENERATION:

Regeneration of injured nerve fibres will take place in 2 cases:

1. If the injury was slight and/ or away from the cell body.
2. If the injured nerve fibre was part of the PNS.

WHAT HAPPENS:

- The nissl granules reappear & the nucleus resumes its central position.
- Full recovery may take upto 3-6 months.
- The endoneural tube is formed by the Schwann cells themselves. This tube guides the regenerating nerve fibre to its proper destination.
- At the beginning of the process, axon in the central end of the cut nerve fibers elongate & give rise to large no. Of fibrils that enter into the endoneural tube.



Nerve Injury

Nerve will begin to
degrade

Axon and surrounding
myelin break down

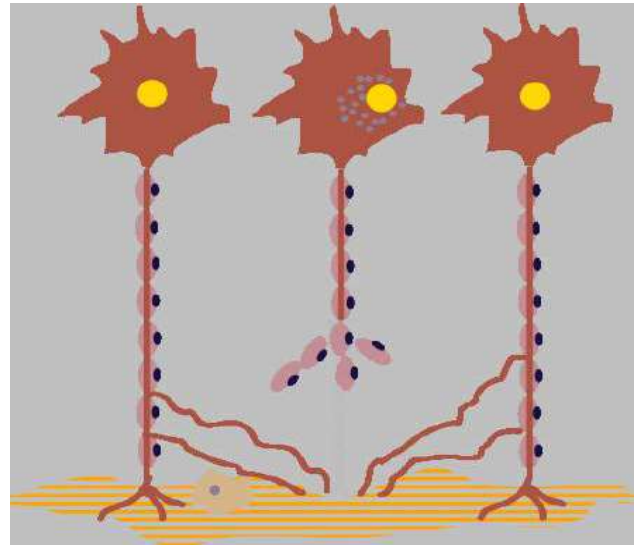
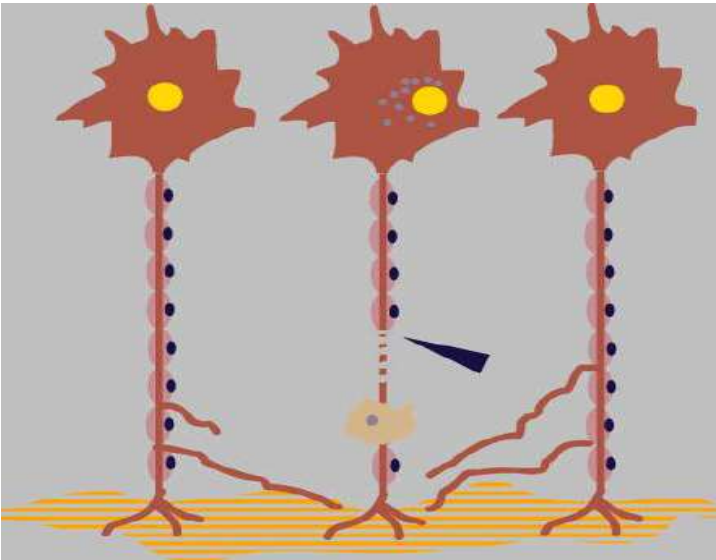
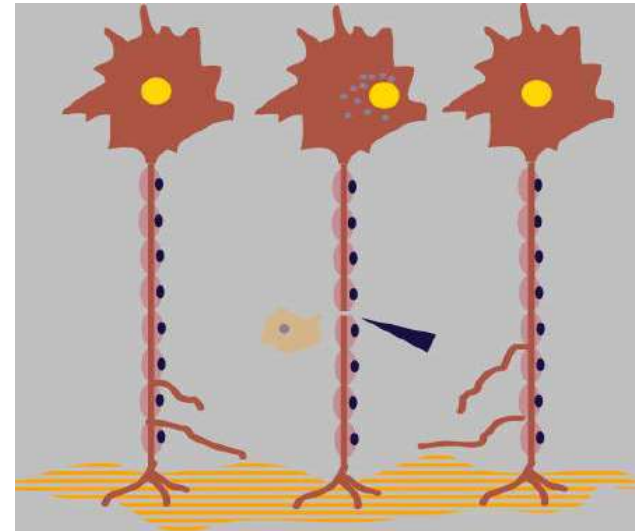
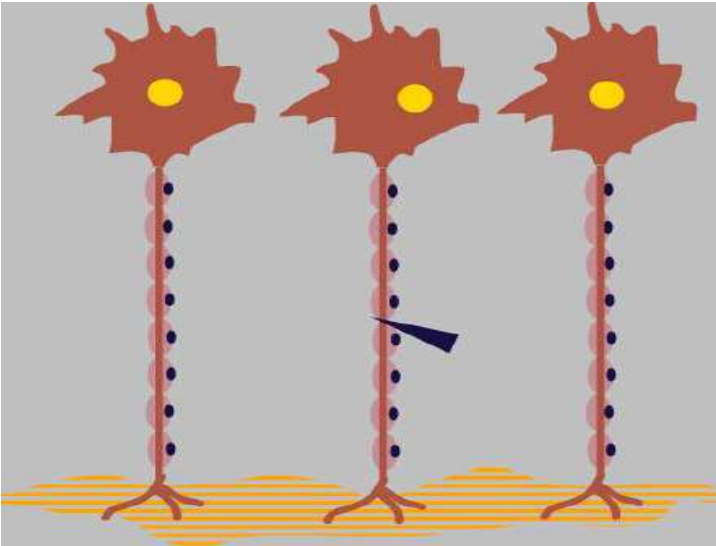
Phagocytic macrophages
interact with Schwann cells to
remove the injured tissue debris

Connection with the target muscle
is lost, leading to muscle atrophy
and fibrosis

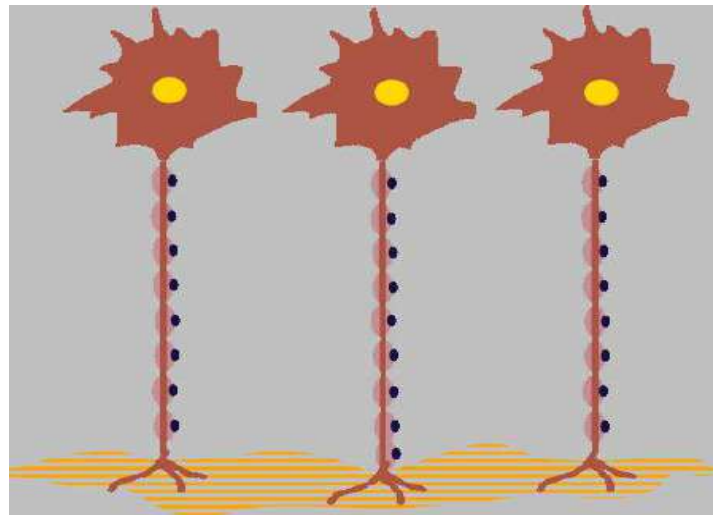
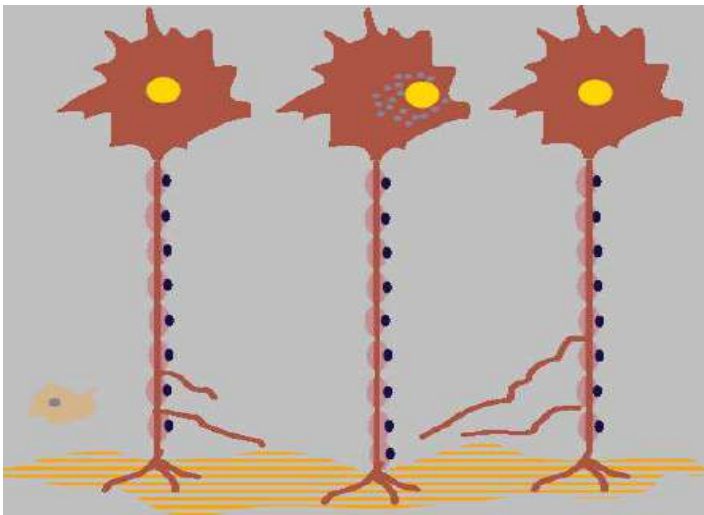
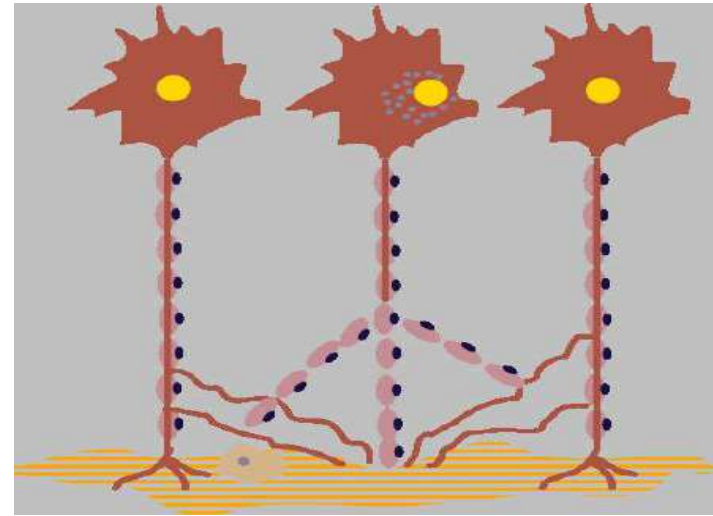
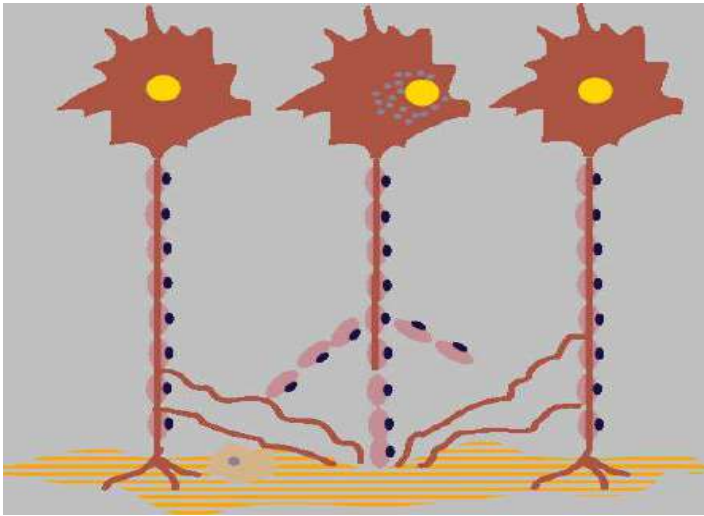
Axon sprouts with a fingerlike
growth cone advance using the
Schwann cells as guides

Newly connected axon matures and
the pre-injury cytoarchitecture and
function are restored

Steps of Regeneration:



Steps of Regeneration:



What is a Neuroma?

If the gap between the 2 ends of a crushed nerve fibre is more than 3 mm, the nerve fibres tend to intermesh and form a tumor like swelling called Neuroma. This is very painful in the case of sensory nerves.

NO REGENERATION IN CNS:

- Regeneration **DOES NOT** take place in optic nerve and in the CNS due to the following reasons:
 1. The endoneural tubes are absent in the CNS as there are no schwann cells are present; so the regenerating axons cannot be guided.
 2. The oligodendrocytes cannot aid in regeneration as the schwann cells.
 3. The activity of the astrocytes results in the formation of scar tissue.

Criteria used for cytopathological diagnosis of cancer

Cytoplasmic features

- Relative amount
- Quality and Content

Relative amount

- Rather than the absolute amount, the relative amount or N/C ratio is important.

Relative amount

- The reduction of cytoplasm due to the expansion of the nucleus is usually an important feature of malignancy and, if observed, is significant.

Relative amount

- Cytoplasmic boundaries are sometimes not sharp enough to allow judgment of the N/C ratio.
- In this case, other features have to be considered in order to make the diagnosis.

Quality and content

- The quality of the cytoplasm reflects cell differentiation.
 - keratinised cells
 - mucin-producing cells

- Keratinization, also termed as cornification, is a process of cytodifferentiation which the keratinocytes undergo
- when proceeding from their post-germinative state (stratum basale) to finally differentiated, hardened cell filled with protein
- constituting a structurally and functionally distinct keratin- containing surface layer known as stratum corneum. DEFINITION

Quality and content

- Sometimes this is visible with routine staining and sometimes it needs special stains.
 - amyloid-producing cells of medullary carcinoma
 - melanin-producing cells of a melanoma
 - c-kit positive cells from a GIST

Diagnostic pitfalls

- Poor collection technique
- Poor fixation
- Inflammatory changes
- Cellular changes related to radiation and/or chemotherapy
- Atypical cellular changes related to hemorrhage, infarction, or necrosis

False negative diagnoses

- Desmoplasia
- Well-differentiated tumor cells
- Sampling problems
- The presence of inflammation, radiation, and chemotherapy changes sometime can be over interpreted

False positive diagnoses

- Pregnancy
- Contamination
- Inflammation and inflammatory changes, radiation and chemotherapy effects
- The presence of hemorrhage and infarction sometimes induce atypical changes in the cells
- Inexperience by the pathologist may induce false positive diagnosis

Take home message

- No single feature diagnostic of malignancy
- Each organ has its own diagnostic limitation by cytology
- Simple clear communication between pathologists and clinicians is very important
- All the information about the patient should be given to the pathologist in order to decrease the frequency of pitfalls
- Sources of error are avoidable, to a certain extent, by experience and by knowledge of the clinical history

Conventional Diagnosis of Tumor

- Signs and symptoms
 - Palpable lump, pain
 - Fever, Fatigue, Weight gain or loss
 - Altered metabolism
- Medical imaging: X-ray, CT, ECT, MRI
- Gold standard : Surgical biopsy/ pathological diagnosis
 - direct microscopic examination

Pathological Diagnosis of Neoplasia

- Recognize: roles of pathological diagnosis applied in clinical oncology
- Understand: definition, morphology, nomenclature, differentiation, differences between benign and malignant neoplasm, Grading and staging, Precancerous lesions
- Familiar with: principles and technologies of diagnostic pathology

Methodologies of Diagnostic Pathology

- Classical Methodologies
 - Histological diagnosis: Biopsy, Intraoperative consultation
 - Cytological diagnosis: Fine-needle aspiration; Abrasive cytology; Exfoliative cytology
 - Autopsy
- Modern Technologies
 - Histochemistry
 - Immunohistochemistry
 - Molecular biological methods
 - Electronic microscopy
 - Digital pathology and telepathology

Histopathological Diagnosis

- Biopsy: paraffin-embedded tissue section
 - Incisional biopsy
 - Excisional biopsy
- Surgical excision: paraffin-embedded tissue section
 - Organs or tissues with the tumors
 - Regional lymph nodes
- Intraoperative consultation
 - Frozen section

Parameters used in histological diagnosis of neoplasm

- Gross appearance
- Microscopic appearance
 - histological pattern
 - tumor cell cytology
- Immunohistochemistry
- Histochemistry
- Cytogenetics /molecular pathology
- Electron microscopy

Gross appearance

- Observe, describe and record gross appearance of tissues or organs by excision, especially lesions or tumors in the specimen



Immunohistochemistry (IHC) in Tumor Diagnosis

- Diagnosis confirmed in 40%
- Important diagnostic information gained in 50%: narrowing of possibilities, or special diagnosis
- Tumor phenotypes identified
- IHC needed in 10-25% malignant tumors for reclassification, e.g., lymphoma
- New entities and classifications established

Molecular Pathology in Tumor Diagnosis

- Genetic abnormalities of Tumors
 - Changes in chromosome number and structure
 - Changes in genes (proto-oncogenes, tumor suppressive genes, DNA repair genes)
- Diagnosis
 - Cytogenetic investigations
 - Molecular genetic investigations

- Cytopathology refers to diagnostic techniques that are used to examine **cells** from various body sites to determine the **cause or nature of disease**

Advantages vs Disadvantages

-Advantages

- Samples can be collected quickly and easily
- Inexpensive
- Little or no risk to the patient
- Examine the cause or nature of disease
 - Specific vs nonspecific inflammation
 - Inflammation vs neoplasia
- Direct therapy
- Determine next diagnostic procedures

Advantages vs Disadvantages

-Disadvantages

It is not always possible to

- Localize neoplastic lesion
- Distinguish preinvasive of invasive cancer
- Distinguish reactive of dysplastic and neoplastic changes
- Determine tumor type

Cytopathology Methods

- Exfoliative cytology
 - spontaneously shed cells in body fluids
- Abrasive cytology
 - dislodge cells from body surfaces
- Fine needle aspiration cytology (FNA)
 - Superficial nodules and organs – easily targeted
 - Deep organs – guidance of CT, US

Cytopathology Methods

- Exfoliative cytology
 - spontaneously shed cells in body fluids
 - Urine
 - CSF (cerebrospinal fluid)
 - Sputum
 - Effusion in body cavities (pleura, pericardium, peritoneum)
- Cytopathology Methods

Cytopathology Methods

- Abrasive cytology
 - — dislodge cells from body surfaces
- Imprint
- Scraping and swabbing
- Endoscopic brushing of mucosal surfaces
- Washing of mucosal or serosal surfaces



CHANGES OF NUCLEUS AND CYTOPLASM IN MALIGNANCY

A) Nuclear Changes:

1-**Nuclear hypertrophy**: nuclear enlargement that leads to increased N/C ratio.

2-**Nuclear size variation**

3-**Nuclear shape variation**



4- **Hyperchromatism and chromatin irregularity:** refers to increased chromatin materials. It is distributed as coarse, clumps. This is different from normal cells, which have evenly distributed chromatin.



5- **Multinucleation:** Malignant cells may contain more than one nucleus. However, some normal cells such as hepatocytes and histiocytes may contain more than one nucleus. Multinucleated malignant cells differ from nonmalignant multinucleated cells by the fact that the nuclei of malignant cells are unequal in size (in contrast to that of normal cells).

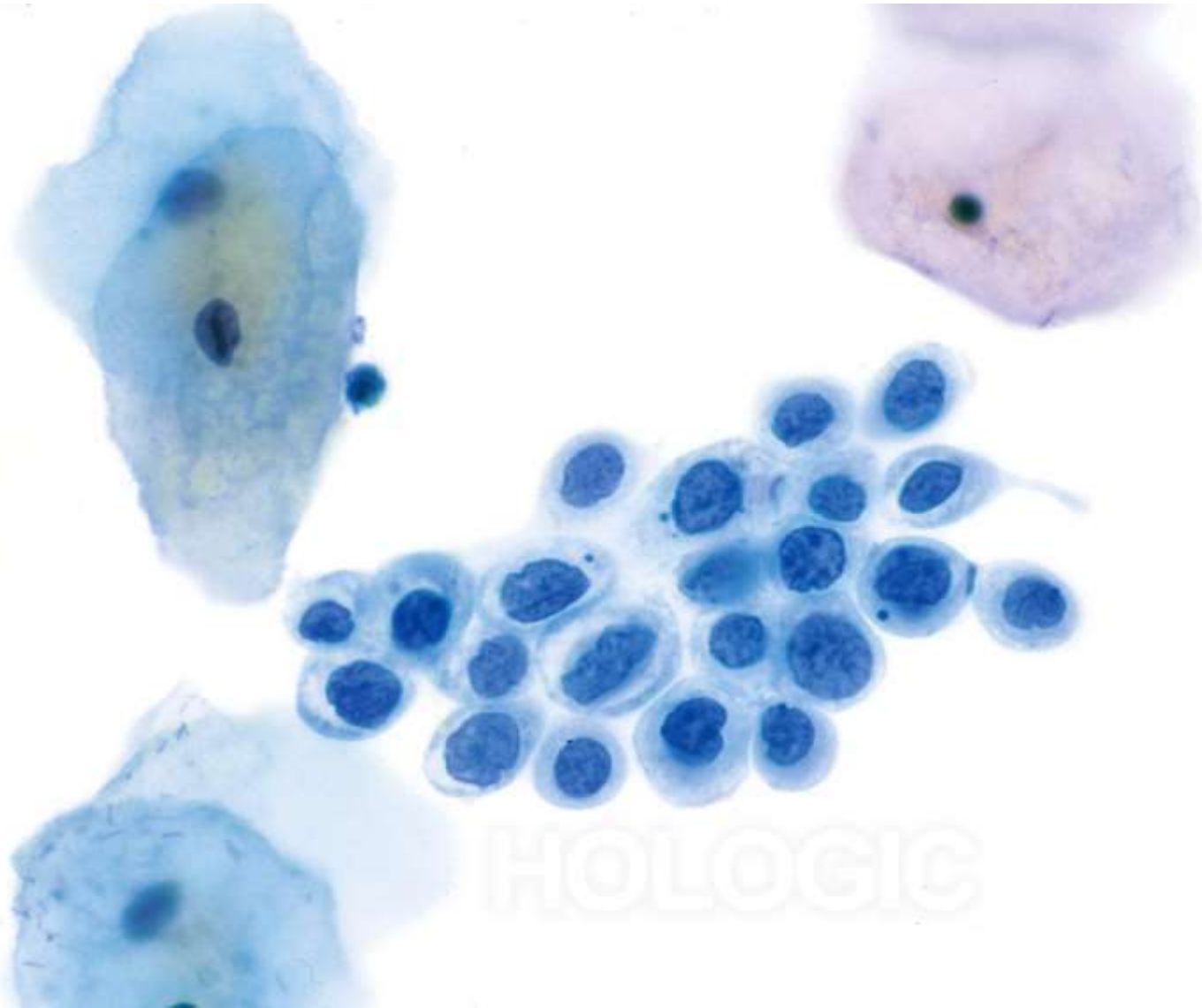


6-Irregularity of the nuclear membrane.

7-Irregular and prominent nucleoli: giant nucleoli or multiple nucleoli may be present that differ in their sizes and shapes. It should be remembered, however, that normal columnar and goblet cells may contain 2 nucleoli.



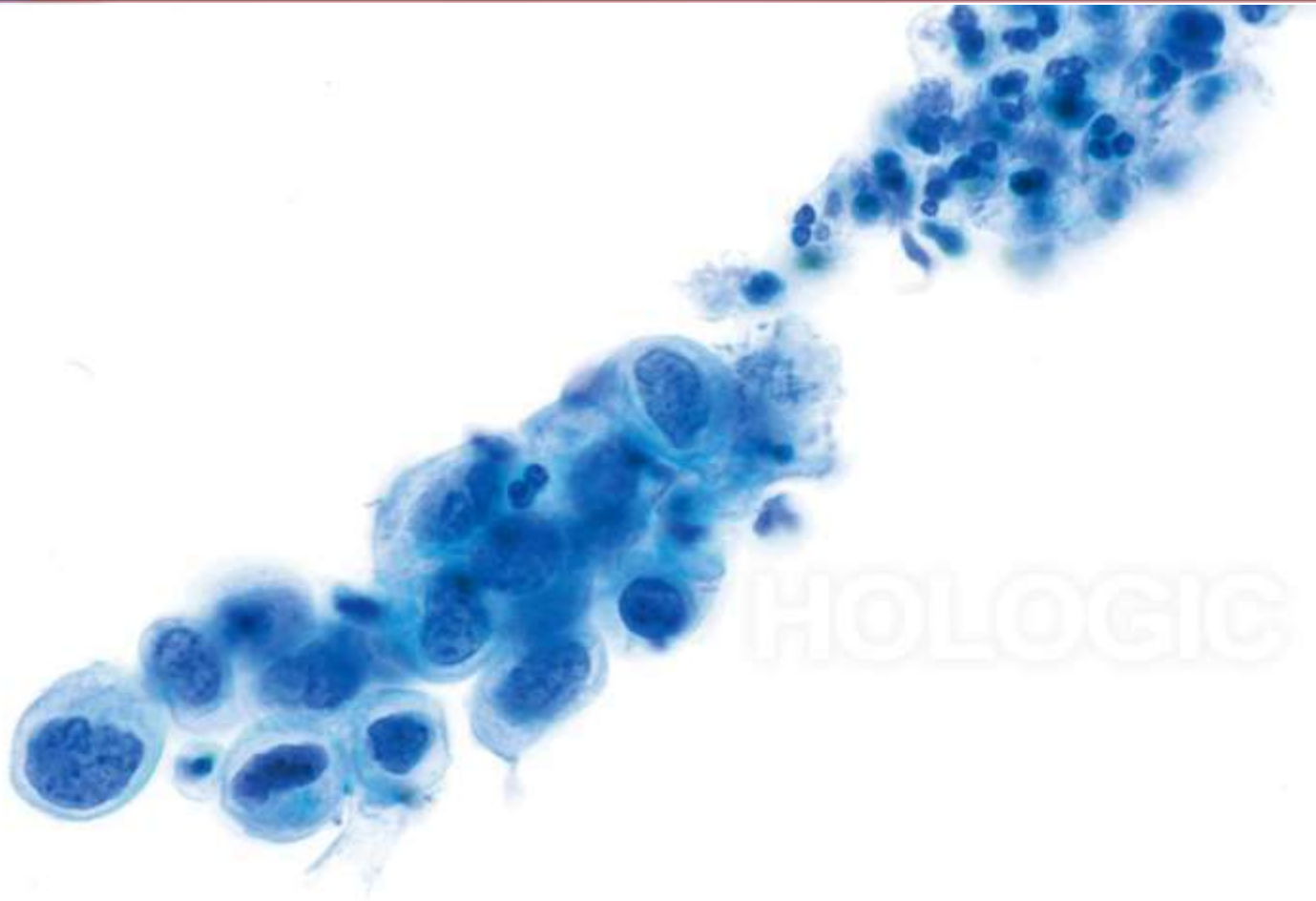
N/C ratio is markedly increased



HOLOGIC

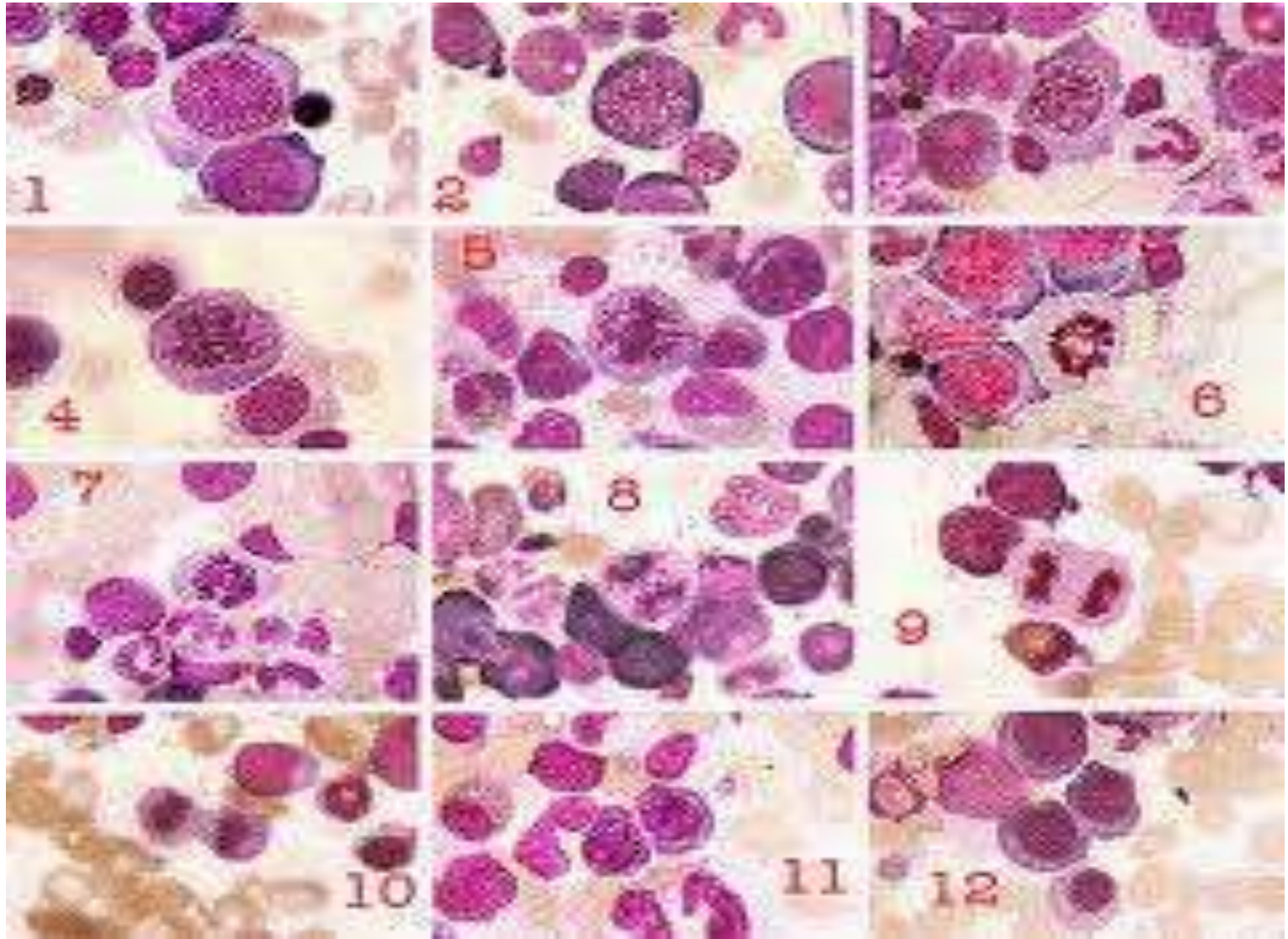


Nuclear size variation



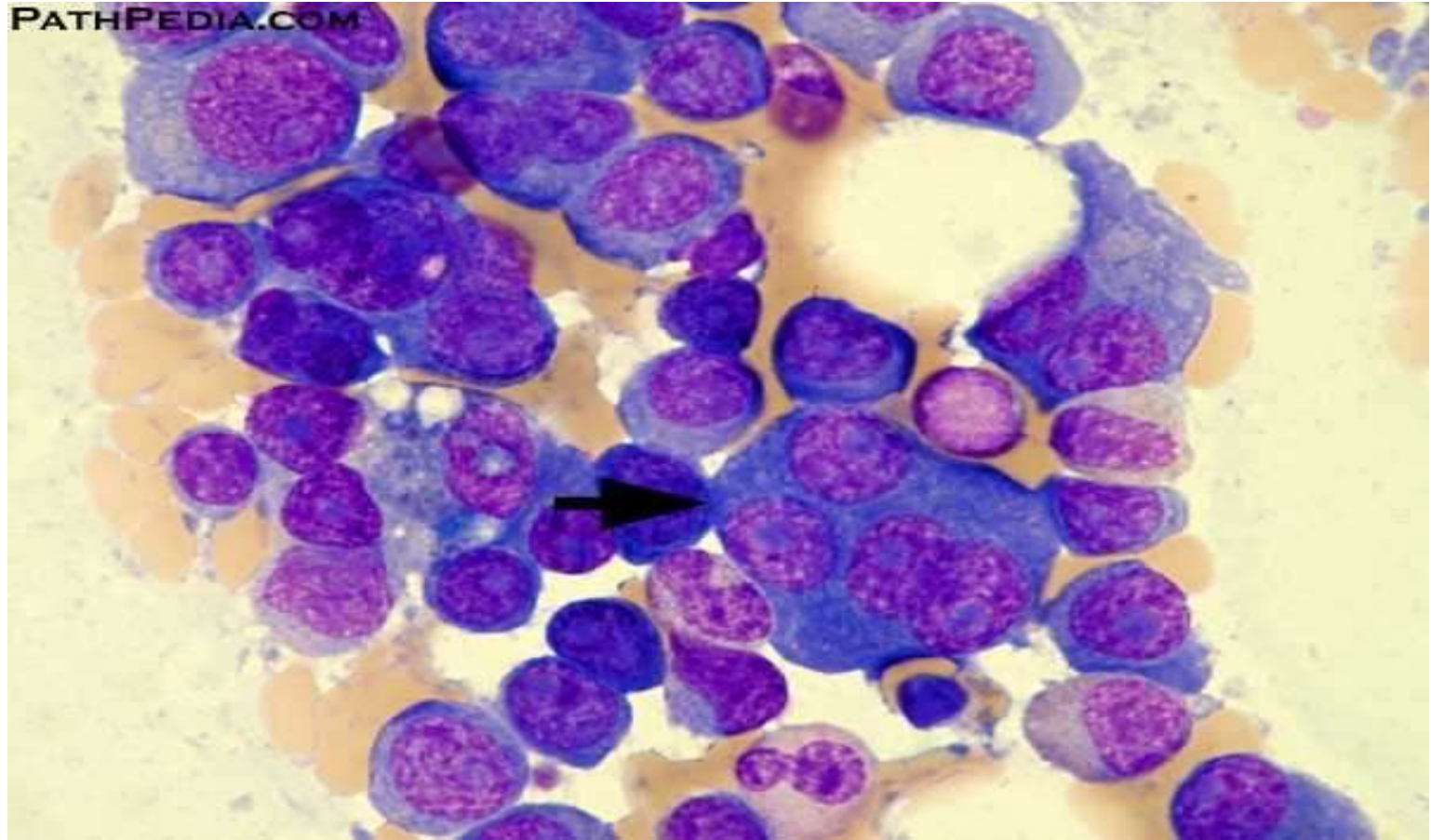


Hyperchromatism





PATHPEDIA.COM



Multi-nucleation with two, three, four, or more nuclei is a common finding in many cells

- Dysplasia :
 - Definition : a loss in the uniformity of the individual cells and a loss in their architectural orientation.
 - Non-neoplastic.
 - Occurs mainly in the epithelia.
 - Dysplastic cells shows a degree of :
pleomorphism, hyperchromasia, increased mitosis and loss of polarity.

Dysplasia

- Clinical significance:
 - It is a premalignant condition.
 - The risk of invasive cancer varies with:
 - ✓ Grade of dysplasia (mild, moderate, sever).
 - ✓ Duration of dysplasia.
 - ✓ Site of dysplasia.

Neoplasia

- Dysplasia does not mean cancer.
- Dysplasia does not necessarily progress to cancer.
- Dysplasia may be reversible.
- If dysplastic changes involve the entire thickness of the epithelium it is called:

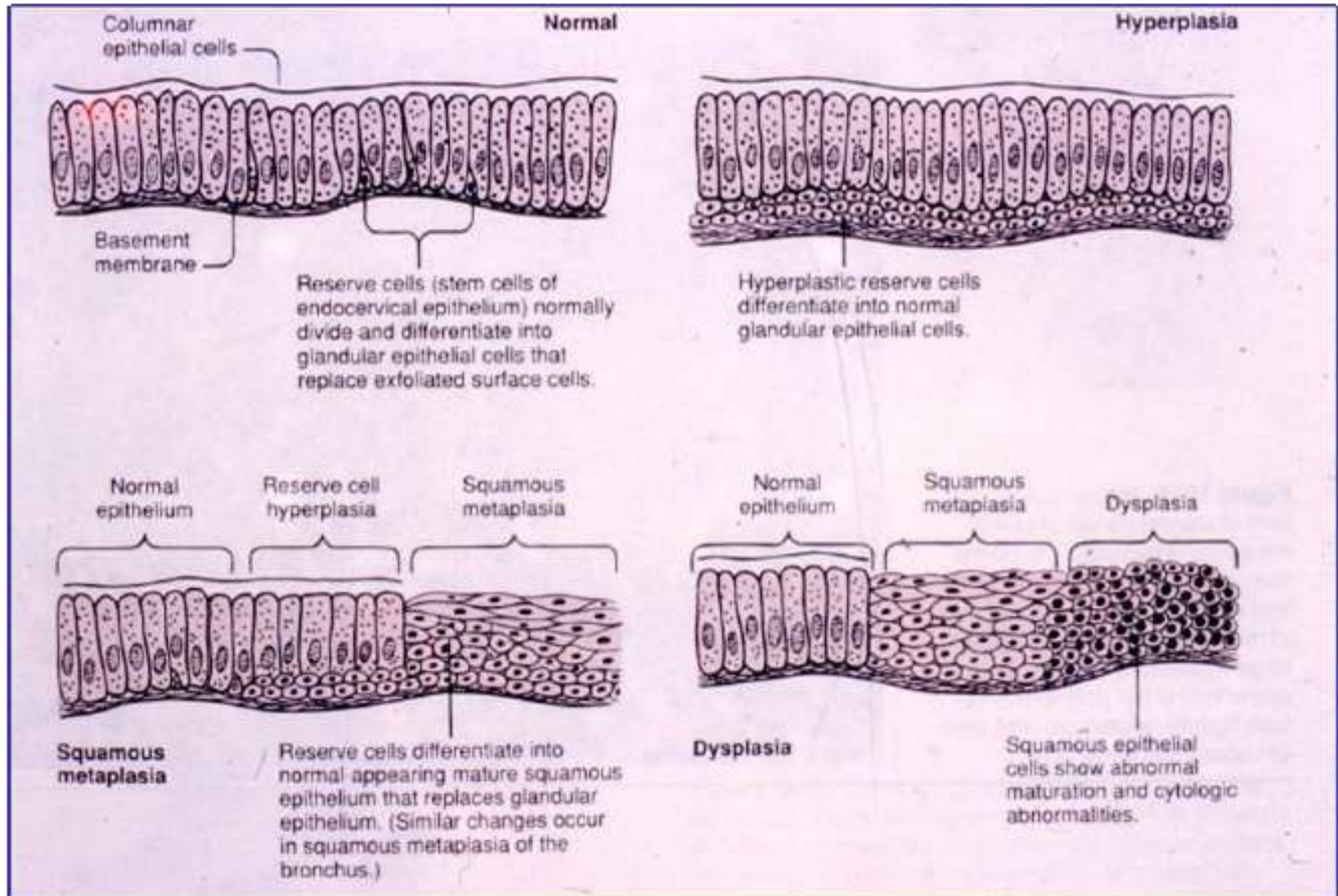
CARCINOMA IN- SITU

Dysplasia Features

- Increased rate of multiplication.
- Disordered maturation.

- **Nuclear abnormality**
 - Increased N/C ratio
 - Irregular nuclear membrane
 - Increased chromatin content
- **Cytoplasmic abnormalities**
due to failure of normal

CHANGES IN UTERINE CERVIX



Neoplasia

- Carcinoma in situ
 - Definition: an intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration of the basement membrans.
 - Application only to epithelial neoplasms.

Metastases

- A primary neoplasm is more likely to appear within an organ as a solitary mass.
- The presence of metastases are the best indication that a neoplasm is malignant. The original clone of cells that developed into a neoplasm may not have had the ability to metastasize, but continued proliferation of the neoplastic cells and acquisition of more genetic mutations within the neoplastic cells can give them the ability to metastasize

Spread of Tumors

- Direct invasion- infiltration & destruction of surrounding tissue.
- Metastasis – noncontiguous spread to other organ/body locations.
 - Lymphatics – carcinomas, lymphatic drainage.
 - Veins & arteries – sarcomas, renal cell carcinoma, hepatocellular carcinoma.
 - implantation – “open field”, ovarian carcinomas, appendix = **pseudomyxoma peritonei**.

Neoplasia

- Adenoma : benign epithelial neoplasms producing gland pattern ...OR... derived from glands but not necessarily exhibiting gland pattern.
- Papilloma : benign epithelial neoplasms growing on any surface that produce microscopic or macroscopic finger – like pattern.

TERATOMA

- Teratoma
 - Teratoma contains recognizable mature or immature cells or tissues representative of more than one germ-cell layer and some times all three.
 - Teratomas originate from totipotential cells such as those normally present in the ovary and testis.

If all the components parts are well differentiated, it is a benign (mature) teratoma.

If less well differentiated, it is an immature (malignant) teratoma.

TERATOMA

- Such cells have the capacity to differentiate into any of the cell types found in the adult body. So they may give rise to neoplasms that mimic bone, epithelium, muscle, fat, nerve and other tissues.
- Most common sites are: ovary & testis

TERATOMA

- If all the components parts are well differentiated, it is a benign (mature) teratoma.
- If less well differentiated, it is an immature (malignant) teratoma.

What are hamartomas and choristoma?

- Hamartoma : a mass composed of cells native to the organ.

e.G. pulmonary hamartoma.

- Choristoma : a mass composed of normal cells in a wrong location.

e.G. pancreatic choristoma in liver or stomach.

- Malformation and not neoplasm.

Hamartomas and Choristoma

- They are distinguished from neoplasms by the fact that they do not exhibit continued growth. They are group of tumor-like tissue masses which may be confused with neoplasms.

Staging and Grading

Staging and Grading

- Devised for malignant neoplasms.
- The stage and/or grade generally determine the treatment and the prognosis
- In general, the higher the stage, the larger a neoplasm is and the farther it has likely spread.
- In general, the higher the grade, the more likely it is that the tumor is rapidly growing and will invade and metastasize.

Staging and Grading

- Devised for malignant neoplasms.
- The stage and/or grade generally determine the treatment and the prognosis
- In general, the higher the stage, the larger a neoplasm is and the farther it has likely spread.
- In general, the higher the grade, the more likely it is that the tumor is rapidly growing and will invade and metastasize.

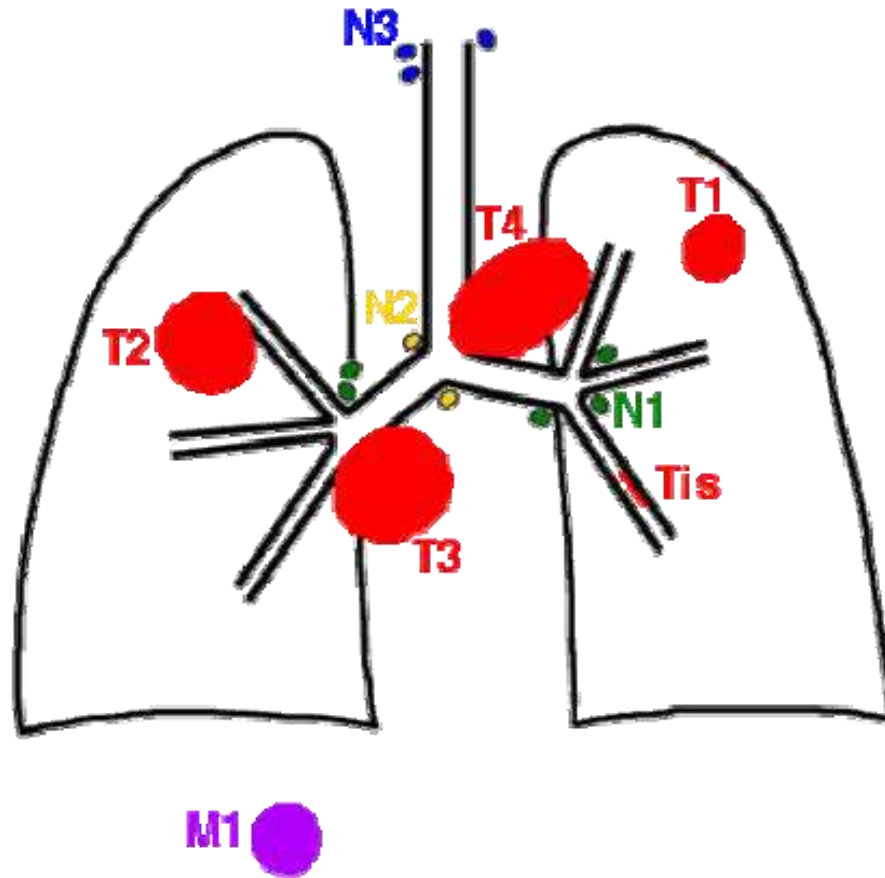
Staging Tumors:

Extent of Spread

- Generally correlates better with prognosis than histopathologic grading.
- Used in therapy selection.
- Union International Centre Cancer (UICC).
 - **TNM system**
- American Joint Committee (AJC) on Cancer Staging
 - Stages 0-IV

Staging of Malignant Neoplasms

Stage	Definition
Tis/T0	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present



In the diagram above utilizing a lung carcinoma as example, the principles of staging are illustrated

Grading

= degree of differentiation

- Grading schema are based upon the microscopic appearance of a neoplasm with H&E staining.
- In general, a higher grade means that there is a lesser degree of differentiation and the worse the biologic behavior of a malignant neoplasm will be.
- A well-differentiated neoplasm is composed of cells that closely resemble the cell of origin.
- A poorly differentiated neoplasms have cells that are difficult to recognize as to their cell of origin.
- Grading schema have been devised for many types of neoplasms, mainly carcinomas.
- Most grading systems have three or four grades (designated with numbers or roman numerals).

Grading of Malignant Neoplasms

Grade	Definition
I	Well differentiated
II	Moderately differentiated
III	Poorly differentiated
IV	Nearly anaplastic

Dysplasia

- Disordered growth
- Loss in uniformity of the individual cells.
- Loss of architectural orientation.
- Pleomorphism.
- Hyperchromatic.
- Increased mitoses (normal).

Carcinoma in situ

- Dysplastic changes involve entire thickness of epithelium.
- If left untreated, will progress to invasive cancer.

Neoplasia

- Dysplasia :
 - Definition : a loss in the uniformity of the individual cells and a loss in their architectural orientation.
 - Non-neoplastic.
 - Occurs mainly in the epithelia.
 - Dysplastic cells shows a degree of :
pleomorphism, hyperchromasia, increased mitosis and loss of polarity.

Dysplasia

- Clinical significance:
 - It is a premalignant condition.
 - The risk of invasive cancer varies with:
 - ✓ Grade of dysplasia (mild, moderate, sever).
 - ✓ Duration of dysplasia.
 - ✓ Site of dysplasia.

Neoplasia

- Dysplasia does not mean cancer.
- Dysplasia does not necessarily progress to cancer.
- Dysplasia may be reversible.
- If dysplastic changes involve the entire thickness of the epithelium it is called:

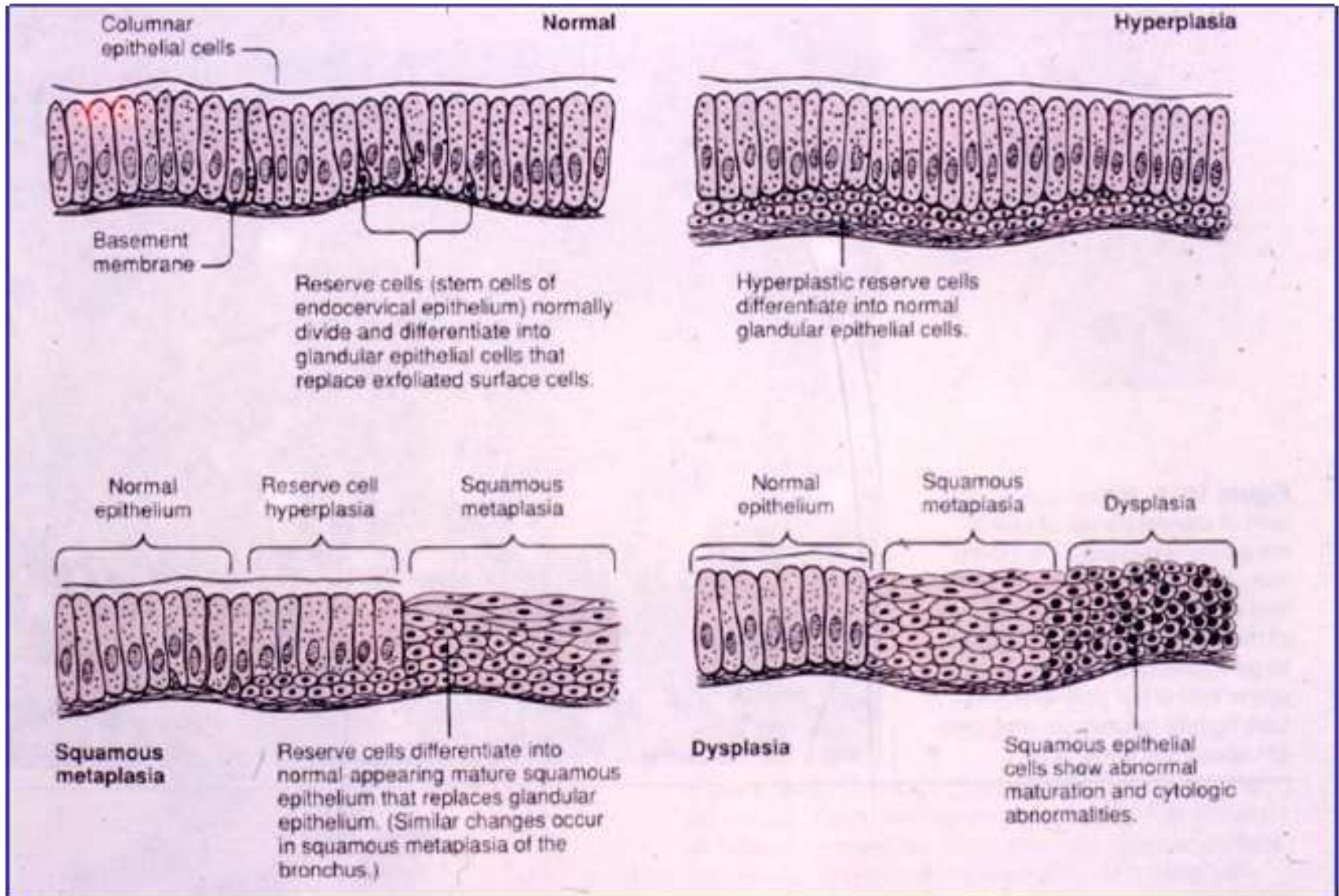
CARCINOMA IN- SITU

Dysplasia Features

- Increased rate of multiplication.
- Disordered maturation.

- **Nuclear abnormality**
 - Increased N/C ratio
 - Irregular nuclear membrane
 - Increased chromatin content
- **Cytoplasmic abnormalities**
due to failure of normal

CHANGES IN UTERINE CERVIX



Neoplasia

- Carcinoma in situ
 - Definition: an intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration of the basement membrans.
 - Application only to epithelial neoplasms.

Metastases

- A primary neoplasm is more likely to appear within an organ as a solitary mass.
- The presence of metastases are the best indication that a neoplasm is malignant. The original clone of cells that developed into a neoplasm may not have had the ability to metastasize, but continued proliferation of the neoplastic cells and acquisition of more genetic mutations within the neoplastic cells can give them the ability to metastasize

Spread of Tumors

- Direct invasion- infiltration & destruction of surrounding tissue.
- Metastasis – noncontiguous spread to other organ/body locations.
 - Lymphatics – carcinomas, lymphatic drainage.
 - Veins & arteries – sarcomas, renal cell carcinoma, hepatocellular carcinoma.
 - implantation – “open field”, ovarian carcinomas, appendix = **pseudomyxoma peritonei**.

Neoplasia

- Adenoma : benign epithelial neoplasms producing gland pattern ...OR... derived from glands but not necessarily exhibiting gland pattern.
- Papilloma : benign epithelial neoplasms growing on any surface that produce microscopic or macroscopic finger – like pattern.

TERATOMA

- Teratoma
 - Teratoma contains recognizable mature or immature cells or tissues representative of more than one germ-cell layer and some times all three.
 - Teratomas originate from totipotential cells such as those normally present in the ovary and testis.

If all the components parts are well differentiated, it is a benign (mature) teratoma.

If less well differentiated, it is an immature (malignant) teratoma.

TERATOMA

- Such cells have the capacity to differentiate into any of the cell types found in the adult body. So they may give rise to neoplasms that mimic bone, epithelium, muscle, fat, nerve and other tissues.
- Most common sites are: ovary & testis

TERATOMA

- If all the components parts are well differentiated, it is a benign (mature) teratoma.
- If less well differentiated, it is an immature (malignant) teratoma.

What are hamartomas and choristoma?

- Hamartoma : a mass composed of cells native to the organ.

e.G. pulmonary hamartoma.

- Choristoma : a mass composed of normal cells in a wrong location.

e.G. pancreatic choristoma in liver or stomach.

- Malformation and not neoplasm.

Hamartomas and Choristoma

- They are distinguished from neoplasms by the fact that they do not exhibit continued growth. They are group of tumor-like tissue masses which may be confused with neoplasms.

Staging and Grading

Staging and Grading

- Devised for malignant neoplasms.
- The stage and/or grade generally determine the treatment and the prognosis
- In general, the higher the stage, the larger a neoplasm is and the farther it has likely spread.
- In general, the higher the grade, the more likely it is that the tumor is rapidly growing and will invade and metastasize.

Staging and Grading

- Devised for malignant neoplasms.
- The stage and/or grade generally determine the treatment and the prognosis
- In general, the higher the stage, the larger a neoplasm is and the farther it has likely spread.
- In general, the higher the grade, the more likely it is that the tumor is rapidly growing and will invade and metastasize.

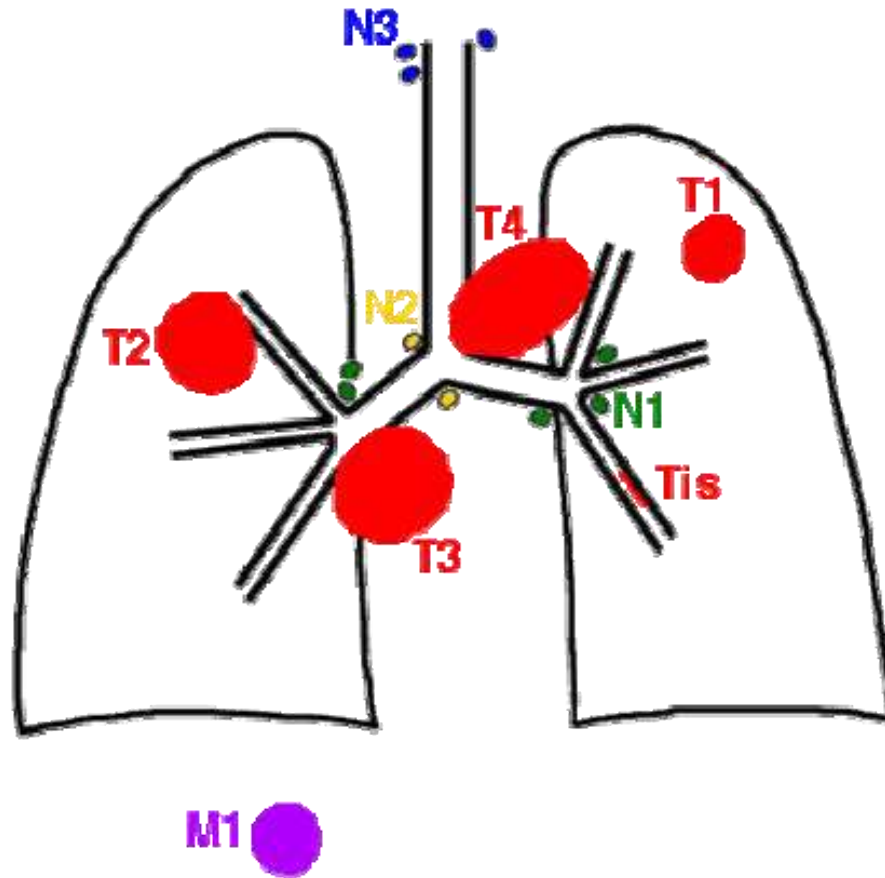
Staging Tumors:

Extent of Spread

- Generally correlates better with prognosis than histopathologic grading.
- Used in therapy selection.
- Union International Centre Cancer (UICC).
 - **TNM system**
- American Joint Committee (AJC) on Cancer Staging
 - Stages 0-IV

Staging of Malignant Neoplasms

Stage	Definition
Tis/T0	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present



In the diagram above utilizing a lung carcinoma as example, the principles of staging are illustrated

Grading

= degree of differentiation

- Grading schema are based upon the microscopic appearance of a neoplasm with H&E staining.
- In general, a higher grade means that there is a lesser degree of differentiation and the worse the biologic behavior of a malignant neoplasm will be.
- A well-differentiated neoplasm is composed of cells that closely resemble the cell of origin.
- A poorly differentiated neoplasms have cells that are difficult to recognize as to their cell of origin.
- Grading schema have been devised for many types of neoplasms, mainly carcinomas.
- Most grading systems have three or four grades (designated with numbers or roman numerals).

Grading of Malignant Neoplasms

Grade	Definition
I	Well differentiated
II	Moderately differentiated
III	Poorly differentiated
IV	Nearly anaplastic

Artefacts in histopathology

- **Histopathology** is a science completely dependent upon microscopic examination and interpretation. Basic requirements for arriving at a conclusive diagnosis include correct biopsy procedure, proper fixation and processing techniques, adequate sectioning and staining. Identification of structural and morphological details of tissue components is very important for arriving at a conclusive diagnosis.
- An **artefact** can be defined as an artificial structure or tissue alteration on a prepared microscopic slide as a result of an extraneous factor.

CAUSES OF ARTEFACTS

1. Clinical application of chemicals
2. Local injection of anesthetics
3. Surgical suctioning
4. Excessive heat
5. Freezing
6. Surgical mishandling of specimen
7. Inadequate tissue fixation
8. Improper fixation medium
9. Faulty tissue processing
10. Embedded sponges
11. Improper staining.

CLASSIFICATION OF ARTEFACTS

1. During surgery
 1. Injection artefacts
 2. Forceps artefacts
 3. Fulguration artefacts.
2. During fixation and transport
 1. Fixation artefacts
 2. Freezing artefacts
 3. Artefacts during transportation.
3. Tissue processing artefacts
4. Other artefacts
 - I. During Surgery.

A. Injection Artefacts

- Injection of large amounts of anesthetic solution into the area
 1. Needle insertion may produce hemorrhage with extravasation that masks the cellular architecture
 2. Separation of connective tissue bands with vacuolization can occur.

- **REMEDY**

Local anesthetic infiltration is acceptable if the field is wide enough in relation to the lesion. Direct injection into the lesion is best avoided.

B. Forceps Artefacts: When the teeth of the instrument penetrate the specimen, it results in voids or tears

Crush artefact: Crush artefact occurs due to tissue distortion resulting from even the most minimal compression of the tissue.

- **REMEDY**

1. Use small atraumatic forceps or Adson's forceps without teeth
2. A suture should be placed in one edge of the specimen (substitute for forceps for tissue immobilization).

- **C. Fulguration Artefacts:** These artefacts are produced as a result of electrocautery.

- **REMEDY**

1. The use of electrocautery is contra-indicated as biopsy
2. Care must be exercised to use the cutting and not the coagulation electrode when obtaining a biopsy specimen
3. The incision margin should be adequately away from the interface of the lesion
4. One should avoid accidental contact of cutting tip
5. Scalpel should be used for initial incision around or into the lesion.

- **II. Fixation Artefacts:** During fixation, tissues commonly change in volume.
 1. Artefacts related to diffusion of unfixed material
 2. Diffusion of materials out of tissue
 3. False fixation of extraneous material to tissue
 4. Improper Fixation: Delay in fixation or inadequate fixation produces changes
 1. Altered staining quality of cells
 2. Cells appear shrunken and show cytoplasmic clumping
 3. Indistinct nuclear chromatin
 4. Vascular structures, nerves and glands exhibit loss of detail
 5. Impression of scar formation or loss of cellularity
 6. Use of improper fixative: Fixation in alcohol results in poor staining of the epithelium

Artefacts introduced during specimen transport

I. Freezing Artefacts: These are characterized by formation of interstitial and intracytoplasmic vacuoles

- **Remedy**

Use of Lillie's acetic acid, alcohol, formalin (AAF): Afixative containing 40% formaldehyde

II. Improper specimen transport, processing and sectioning

- During transport, proper measures should be taken for preventing curling of tissue.

III. Processing artefacts

- A. Processing floaters or cutting board metastasis: These are extraneous pieces of tissue contaminating small biopsies.
 1. When a biopsy is handled in the laboratory
 2. When the tissue sections are being floated
 1. A tissue fragment looks different from others
 2. A tissue fragment is on a slightly different plane from others
 3. A tissue fragment showing pathologic changes totally different from others
- **Remedy:** Use clean cassettes, cutting boards, instruments etc

- **B. Sponge artefacts:** These are seen in tissues placed in cassettes sandwiched between sponges.
- **Remedy:** Tissue or lens paper is recommended as a substitute.

- **C. Artefacts of Chemical Treatment:**
 - a. Most common artefact of this type is “shrinkage”
 - b. Loss of fat: Fat containing cells appear “empty”.