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GENERAL PATHOLOGY INTRODUCTION

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RUDOLPH VIRCHOW (1821-1902) " FATHER OF MODERN PATHOLOGY "

- The second most profound thing ever said , in the 2nd millennium was by Rudolph Virchow.
- He said ' all diseases are the result of visible cell abnormalities'.
- i.e abnormal histology ' Histopathology'

Pathology : is the study of disease (pathos = suffering , logos = study)

The study divided into

General pathology:

It concerned with response of living tissues to injury i.e. what changes occur in the living cells and tissues when they are subjected to abnormal stimuli. The study of general pathology constitutes the backbone to understand systemic pathology.

Systemic (special) pathology:

It is the study of diseases affecting different body systems (cardiovascular system , respiratory system , alimentary tract ,urinary system , nervous system … etc.)

THE MAIN ASPECTS OF ANY DISEASE INCLUDE

DEFINITION and categorization of the disease

ETIOLOGY : This includes:

Predisposing factors e.g. low immunity in case of infective diseases.

Exciting cause e.g. tubercle bacilli in case of T.B.

PATHOGENESIS it means mechanisms of development of the disease.

"sequence of events from the initial stimulus to the ultimate expression of the disease"

Morphological And Anatomical Alterations Due to Pathological Processes can lead to the following Sequel:

- Gross
- Microscopic
- Radiologic
- Molecular

morphological changes (pathological features)

these are divided into

- **Gross features** :they are also called naked eye features or macroscopic features , they include all changes that can be detected by the naked eye e.g. change in size ,color and consistency of the disease organ. Gross features help in disease diagnosis and in differentiation between different lesion e.g. between abscess and tumor.
- **Microscopic features** (by ordinary light microscopy): these are cellular and/or extracellular changes that characterize each disease e.g. detection of malignant cells in case of cancer and detection of bilharzia ova in case of bilharziasis…..
- **Special microscopic studies** : electron microscopy and immunochemistry.

FATE , PROGNOSIS AND COMPLICATION:

- Fate is the course of disease . It may be

Good fate e.g. regressive disease course in mild inflammations

Bad fate : complication (including death)

- Prognosis is prediction of the disease course . It may be

Good prognosis as mild inflammation and benign tumor

Poor prognosis as in malignant tumor (cancer) and septicemia.

ROLE OF PATHOLOGY IN DIAGNOSIS OF DISEASE

TYPES OF SPECIMENS REFERRED FOR PATHOLOGICAL DIAGNOSIS

1- **Biopsy:** this means examination of a tissue specimen which may be:

Punch biopsy e.g. from GIT, lung & bladder lesions through endoscopy (endoscopic biopsy)

Core biopsy e.g. from liver ,kidney, lung, mediastinum …etc; usually guided by ultrasonography (US)or computerized tomography (CT) (guided biopsies)

Incisional biopsy: this is a surgically obtained part of a lesion e.g. part of a breast mass

Excisional biopsy: this is surgical excision of the whole lesion e.g. whole breast mass

Partial organ excision e.g. partial nephrectomy, or subtotal thyroidectomy, hysterectomy…etc


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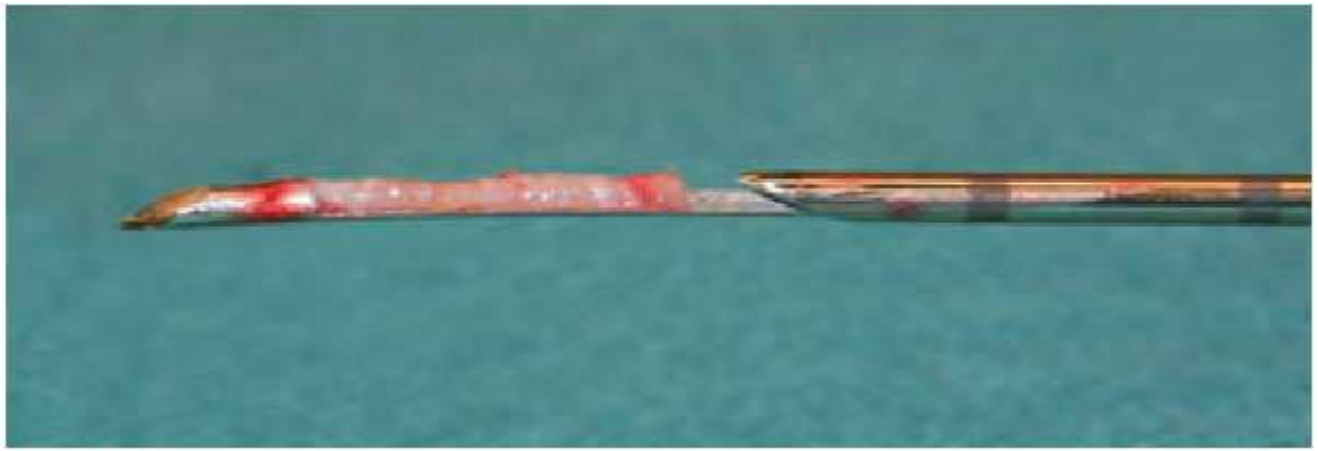

2- Autopsy: this is examination of tissue obtained from dead bodies it is important for:

Detection of the cause of death. By autopsy we may discover a disease which was not diagnosed or was wrongly diagnosed during life. Thus it has a teaching purpose.

Detection of the cause of death for medico legal purposes (forensic medicine)

Evaluation of organ state before using it for transplantation (cadaveric transplantation)

Research studies.

3- Frozen section examination:

In case of biopsy and autopsy, the target is to obtain paraffin sections which is time consuming slow technique ,starting with tissue fixation in 10% buffered formalin for at least 24 hours, followed by tissue processing (taking +_ extra 24 hours) though successive steps of dehydration (in ascending grades of alcohol), clearance (in xylene) and solidification (by embedding of the tissue in paraffin wax paraffin blocks). Paraffin blocks are then cut using a microtome to get thin paraffin sections (4-5 u thick), followed by staining with hematoxylin & eosin (H & E), special stains, or immunostains.

On the other hand frozen section (FS) examination is used for rapid diagnosis during surgery the biopsy is immediately transferred into a cryostat chamber, where it is frozen (within minutes) without fixation to < 30 c. this followed by cutting thin sections around 5-7 microns (through the microtome part of the cryostat), followed by staining & microscopic examination. Importance of FS examination is:

Rapid intra-operative diagnosis, e.g. a breast or thyroid mass needs to be evaluated whether benign or malignant to determine the type of surgery.

Some special stains (and immunostains) can not be performed on paraffin sections and need fresh frozen sections e.g. sudan III (fat stain)


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4- Cytology: Examination of body fluids or smears to detect any abnormal cells such as malignant cells & inflammatory cells. Example:

Body fluids as urine ,CSF, effusions (pleural , pericardial & synovial), ascites, synovial &cystic fluid e.g. ovarian cysts, mammary cysts

Sputum

Discharge e.g. nipple discharge, conjunctival discharge

Lavage fluid e.g. bronchial lavage , bladder and/or pelviureteric wash.

Brush cytology e.g. brush of common bile duct, bronchial and gastric brush.

Touch imprint cytology e.g. imprint of the cut surface of an excised lymph node or excised breast tumor , testicular imprint…

Fine needle aspiration cytology (FNAC) or fine needle aspiration biopsy (FNAB)

Cervicovaginal smears (PAP-smears): these smears are stained with papanicolau stain

Bone marrow aspirate

PREPARATION OF SPECIMENS FOR MICROSCOPIC EXAMINATION:

1- Preservation (fixation):

Tissue specimens (biopsy or autopsy):

a) For frozen sections: No fixation is required and has to be avoided.

b) To obtain paraffin sections, the tissue is pre-fixed in 10%buffered formalin. Some tissues need special fixatives e.g. Bouin's solution for testicular biopsies.

c) To obtain sections for electron microscopic examination ,the selected specimen is fixed in glutaraldehyde.

Cytology specimens may not need fixation or get fixed e.g. in ethyl alcohol.

2- Processing:

Tissue specimens

a) Frozen section examination: see above

b) Paraffin sections: see above

c) Bone biopsy should be decalcified (e.g. in diluted nitric acid),then processed to obtain paraffin sections as previously described

d) Electron microscopy specimens are processed in Epon to form solid blocks, then cut into ultra-thin sections by a special microtome, followed by contrast staining in lead acetate

Cytology specimens: some specimens as FNA and nipple discharge are directly smeared on glass slides, other specimens as effusions may need centrifugation (by centrifuge or cytospin) to precipitate and cells, followed by smearing of the precipitate. Many stains can be used, as H& E, papenicolau (PAP) & Geimsa. Immunostains can be also done.

RESPONSE OF LIVING TISSUES TO INJURY

CAUSES OF CELLULAR INJURY:

- 1- Infectious agents including viruses, rickettsiae, bacteria and their toxins, fungi and parasites.
- 2- Hypoxia (decrease of oxygen supply) due to:
- a) Ischemia: Reduction or loss of blood supply such as in cases of arterial thrombosis.
- b) Inadequate oxygenation e.g. in cases of cardio-respiratory failure.
- c) loss oxygen carrying capacity of the blood as in cases of anemia and carbon monoxide poisoning.
- 3- Physical agents including trauma, heat, cold, radiation and electric shock.
- 4- Chemical agents e.g. acids, alkalies, alcohol, metals as lead, some pigments & some drugs.
- 5- Immunologic reactions (hypersensitivity)
- 6- Nutritional imbalances.
- 7- Genetic derangements.

RESULTS OF INJUTY OF CELLS AND TISSUES:

- 1- **Reversible cell injury (degeneration):** this is disturbed cell metabolism & morphology
- 2- **Irreversible cell injury (cell death):**

  a) Necrosis: cell death caused by an irritant.

  b) Apoptosis: cell suicide.
- 3- Inflammation
- 4- Repair (healing of tissue injury)
- 5- Intracellular accumulations (as fat, proteins, carbohydrates and pigments). These accumulations may sometimes be the cause of cel injury, but in other instances they may result from cell injury.

– 6- Extracellular depositions as calcification and amyloidosis.

– 7-cellular adaptations of growth and differentiation:

a) Atrophy: shrinkage of cell size

b) Hypertrophy: increase of cell size

c) Hyperplasia: increase of cell number

d) Metaplasia: transformation of one cell type into another

– 8- Abnormalities of cell growth:

a) Dysplasia: abnormal cell shape.

b) Neoplasia: proliferation of abnormal cells mass (tumor)

– 9- Vascular disturbances as hemorrhage, thrombosis and edema

CELL INJURY

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REVERSIBLE AND IRREVERSIBLE CELL INJURY

CAUSES OF CELL INJURY:

- Infection: viruses, rickettsiae, bacteria and their toxins, fungi and parasites
- Hypoxia(decease of oxygen supply) due to:
  - Ischemia: reduction or loss of blood supply as in cases of arterial thrombosis.
  - Inadequate oxygenation e.g. in cases of cardio-respiratory failure.
  - Loss of oxygen carrying capacity of the blood as in cases of anemia.
- Physical agents including trauma, heat, cold, radiation and electric shock.
- Chemical agents as acids, alkalies, alcohol, some metals & pigments &some drugs.
- Immunologic reactions (hypersensitivity).
- Nutritional imbalances.
- Genetic derangements.

MECHANISM OF CELL INJURY:

- Four cellular systems are particularly vulnerable to cell injury:
  1. Cell membranes.
  2. Aerobic respiration and production of ATP.
  3. synthesis of enzymes and structural proteins.
  4. The genetic apparatus
- The main abnormalities occurring after cell injury are:
  1. ATP depletion (mainly in cases of hypoxia e.g. due to ischemia).
  2. Altered cell membrane permeability (due to reduced energy production).

3. Increase of intracellular calcium due to influx of calcium ions from extracellular spaces across damaged cell membrane, increase of intracellular calcium activates:

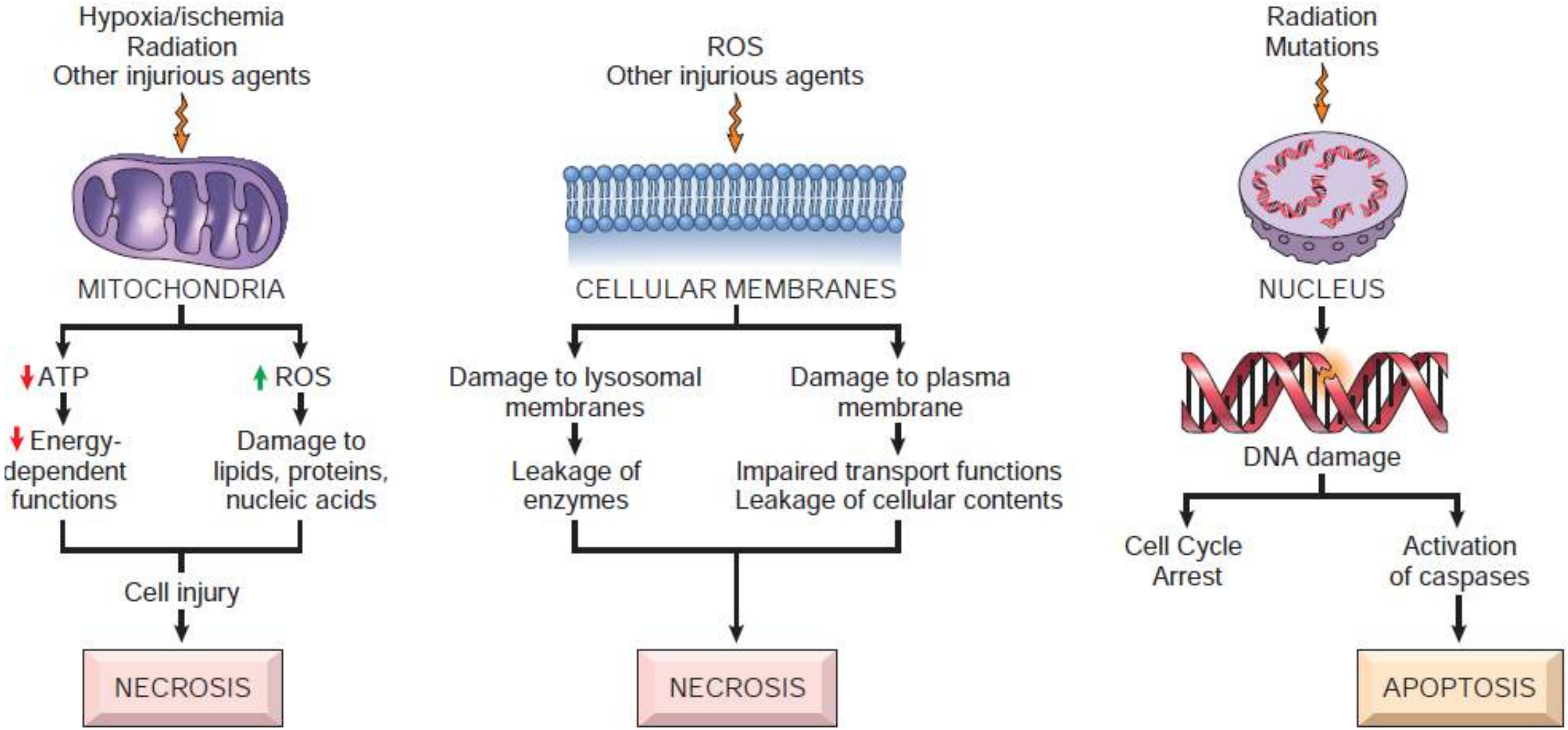
a) phospholipases that degrade membrane phospholipids,

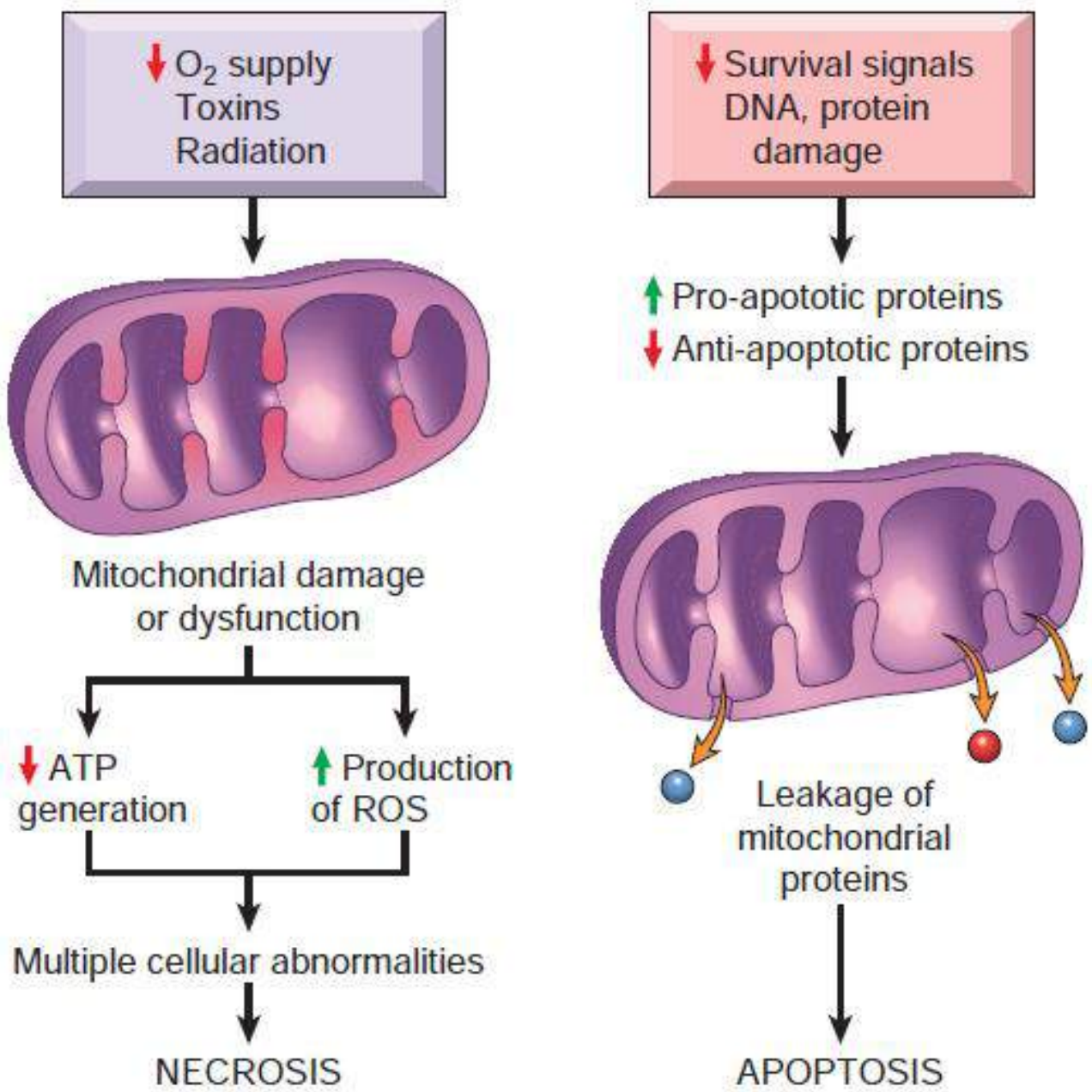
b) ATP-ase (cause ATP depletion)

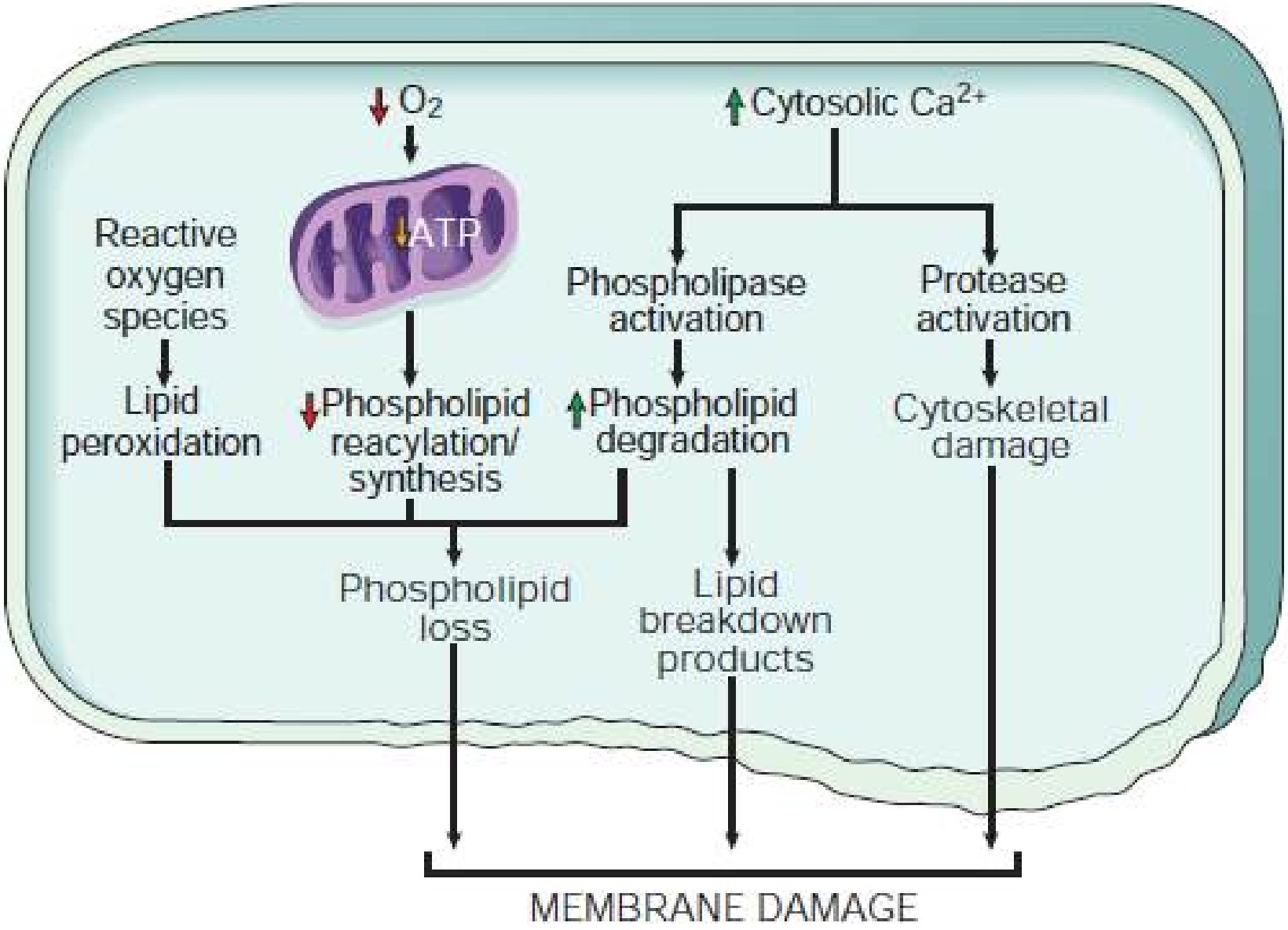
c) Endonucleases (cause DNA injury) &

d) Proteases that break cellular proteins.

4. development of intracellular toxic compounds as H202.


Hypoxia/ischemia
Radiation
Other injurious agents
MITOCHONDRIA
ATP
ROS
Energy-dependent functions
Damage to lipids, proteins, nucleic acids
Cell injury
NECROSIS
ROS
Other injurious agents
CELLULAR MEMBRANES
Damage to lysosomal membranes
Damage to plasma membrane
Leakage of enzymes
Impaired transport functions
Leakage of cellular contents
NECROSIS
Radiation
Mutations
NUCLEUS
DNA damage
Cell Cycle Arrest
Activation of caspases
APOPTOSIS


↓ O_2 supply
Toxins
Radiation
Mitochondrial damage
or dysfunction
↓ ATP
generation
↑ Production
of ROS
Multiple cellular abnormalities
NECROSIS
↓ Survival signals
DNA, protein
damage
↑ Pro-apototic proteins
↓ Anti-apoptotic proteins
Leakage of
mitochondrial
proteins
APOPTOSIS

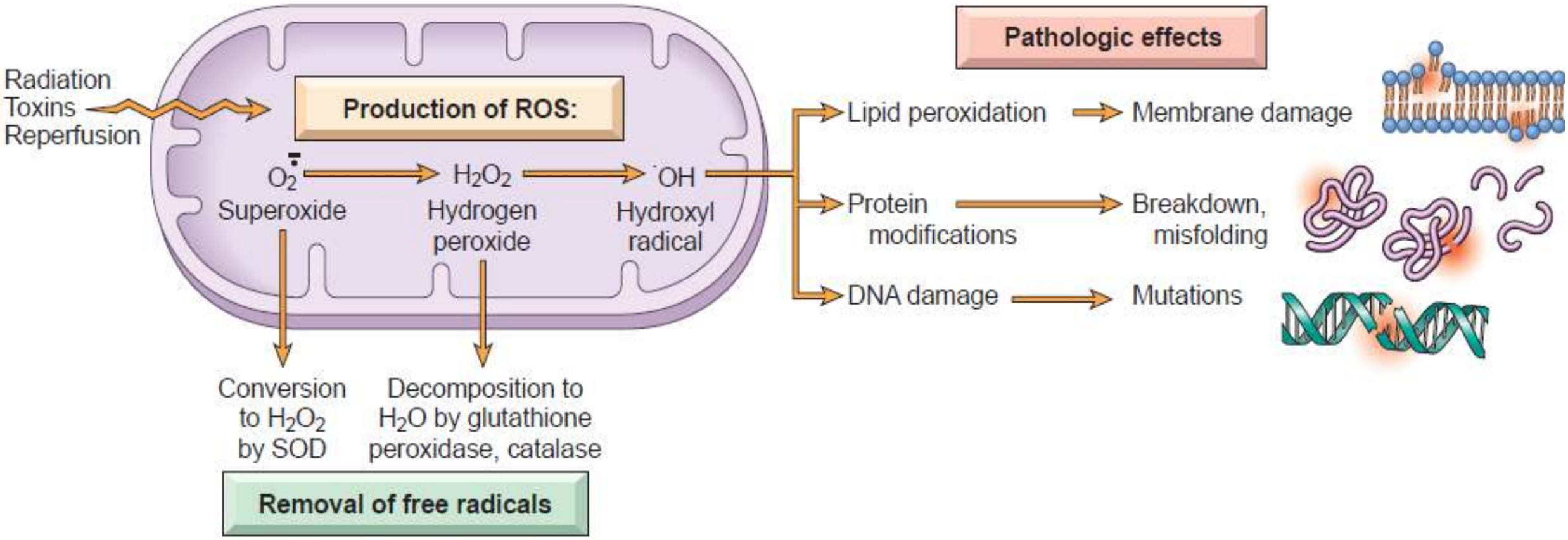

↓ O_2
↑ Cytosolic Ca^{2+}
↓ATP
Reactive oxygen species
Phospholipase activation
Protease activation
Lipid peroxidation
↓Phospholipid reacylation/ synthesis
↑Phospholipid degradation
Cytoskeletal damage
Phospholipid loss
Lipid breakdown products
MEMBRANE DAMAGE

Oxidative Stress: Accumulation of Oxygen-Derived Free Radicals

Free radicals are chemical species that have a single unpaired electron in an outer orbit. Unpaired electrons are highly reactive “attack” and modify adjacent molecules, such as inorganic or organic chemicals—proteins, lipids, carbohydrates, nucleic acids many of which are key components of cell membranes and nuclei.

Cell injury induced by free radicals, particularly ROS, is an important mechanism of cell damage in many pathologic conditions, such as chemical and radiation injury, ischemia reperfusion injury (induced by restoration of blood flow in ischemic tissue), cellular aging, and microbial killing by phagocytes.

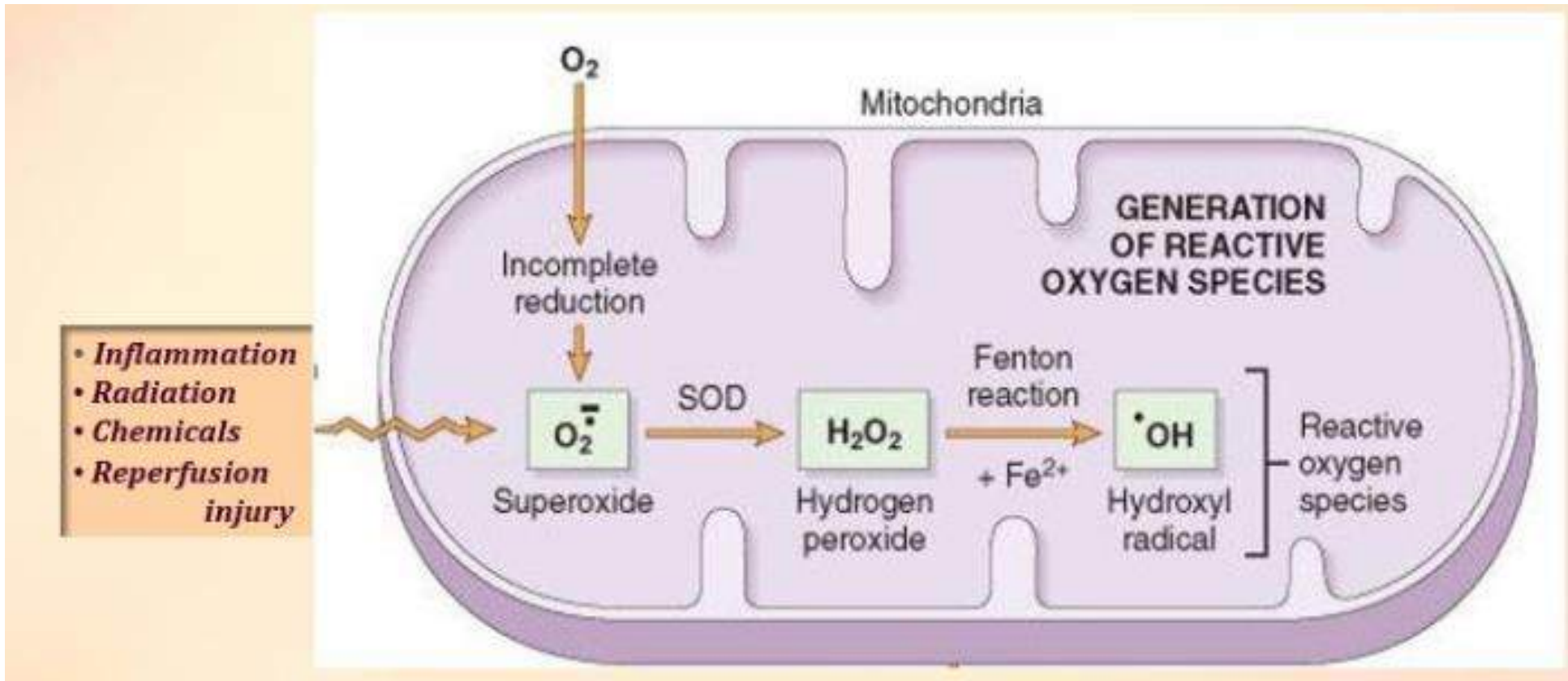
ROS are a type of oxygen-derived free radical whose role in cell injury is well established. ROS are produced normally in cells during mitochondrial respiration and energy generation, but they are degraded and removed by intracellular ROS scavengers. Increased production or decreased scavenging of ROS may lead to an excess of free radicals, a condition called *oxidative stress*.


Radiation
Toxins
Reperfusion
Production of ROS:
$O_2^{\cdot-}$
Superoxide
H_2O_2
Hydrogen peroxide
$^{\cdot}OH$
Hydroxyl radical
Conversion to H_2O_2 by SOD
Decomposition to H_2O by glutathione peroxidase, catalase
Removal of free radicals
Pathologic effects
Lipid peroxidation
Membrane damage
Protein modifications
Breakdown, misfolding
DNA damage
Mutations

FREE RADICALS AND CELL INJURY

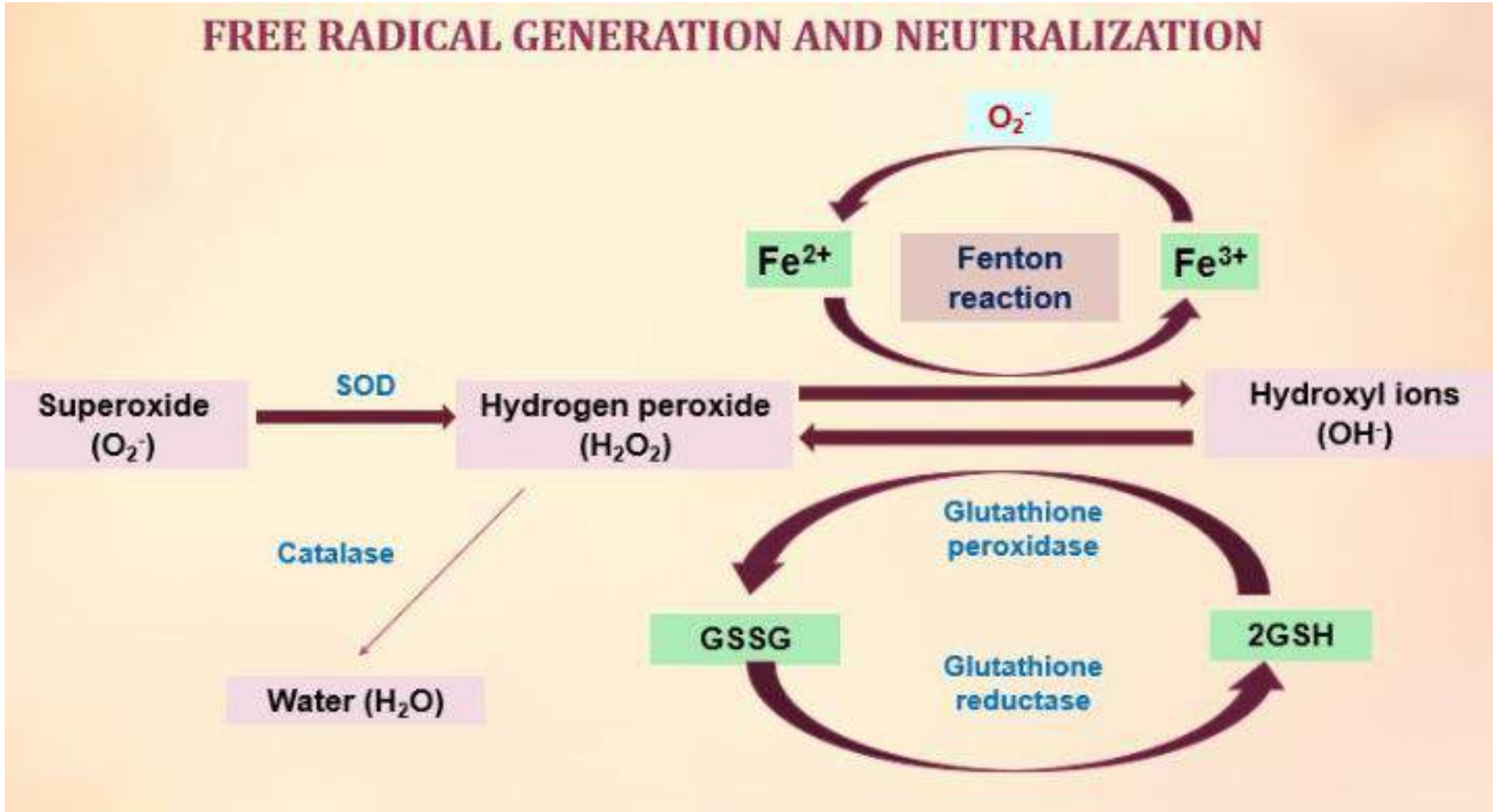
- **Free radicals are generated by**
  - **The reduction – oxidation reactions that occurs during normal metabolic process**
    - **Cells generate energy by reducing molecular oxygen to water**
    - **During this process, small amount of partially reduced reactive oxygen forms [i,e. Superoxide anion radical (O_2^-), Hydrogen peroxide (H_2O_2), and Hydroxyl ions (OH^-)] are produced in which different numbers of electrons have been transferred from O2**

- **Absorption of radiant energy** (UV rays , x-rays)- ionizing radiation can hydrolyze water into Hydroxyl (OH^-) and hydrogen (H) free radicals
- **Rapid bursts of Superoxide production** occurs in the activated polymorphonuclear leukocytes during inflammation
- **Nitric oxide** –
  - NO is produced by endothelial cells, macrophages, neurons and other cell types
  - NO can act as free radical and can also be converted into highly reactive peroxynitrite anion ($ONOO^-$), NO_2 and NO_3^-
- **Enzymatic metabolism of exogenous chemicals and drugs** generate free radicals that are not ROS but have similar effects e.g. – CCl3 from CCl4
- **Reperfusion injury**
- **Transition metals such as iron and copper** donate or accept free electrons during intracellular reactions and catalyze free radical formation (Fenton reaction)

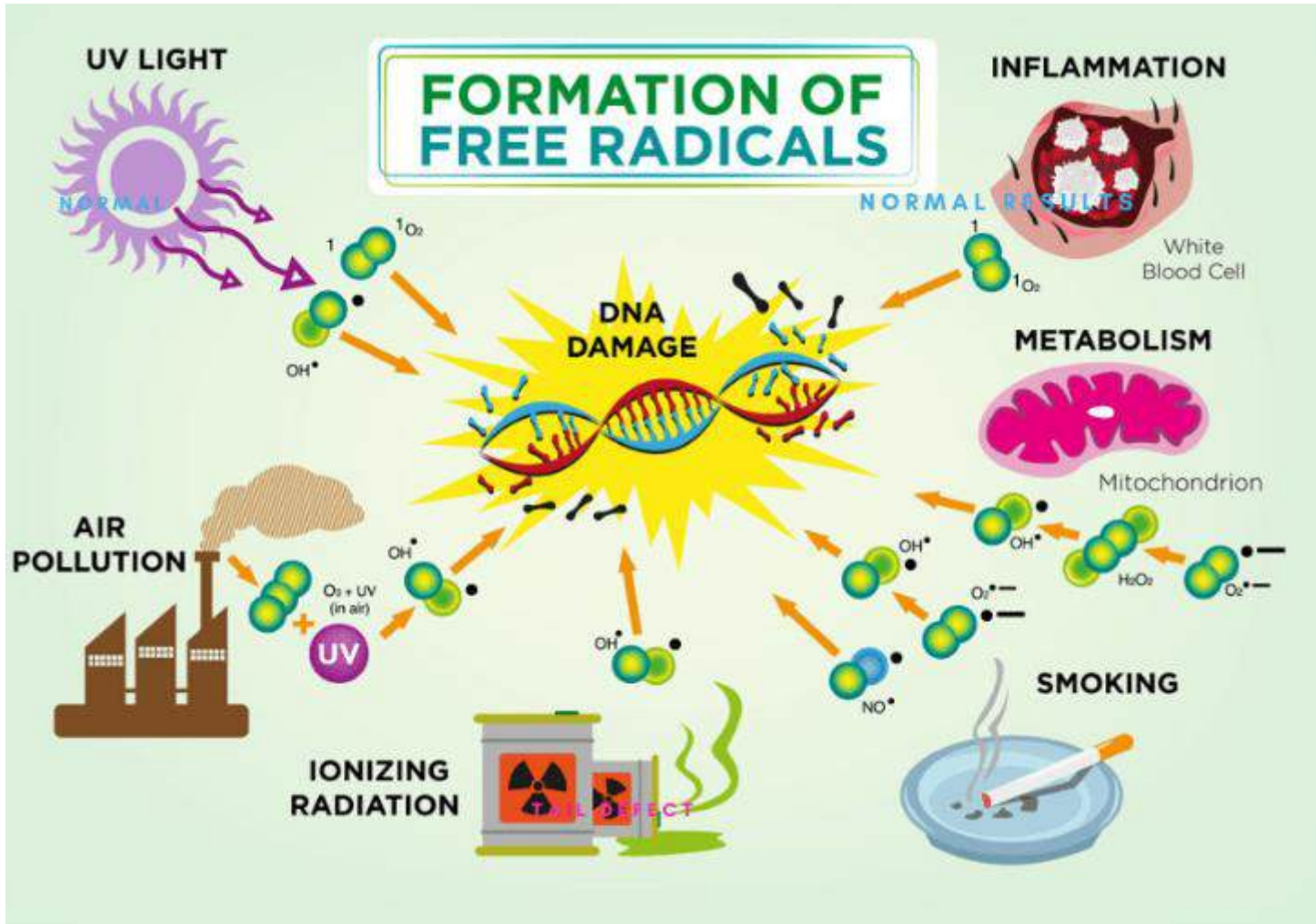

• Inflammation
• Radiation
• Chemicals
• Reperfusion injury
O_2
Mitochondria
GENERATION OF REACTIVE OXYGEN SPECIES
Incomplete reduction
$O_2^{\cdot-}$
Superoxide
SOD
H_2O_2
Hydrogen peroxide
Fenton reaction
+ Fe^{2+}
$^{\cdot}OH$
Hydroxyl radical
Reactive oxygen species

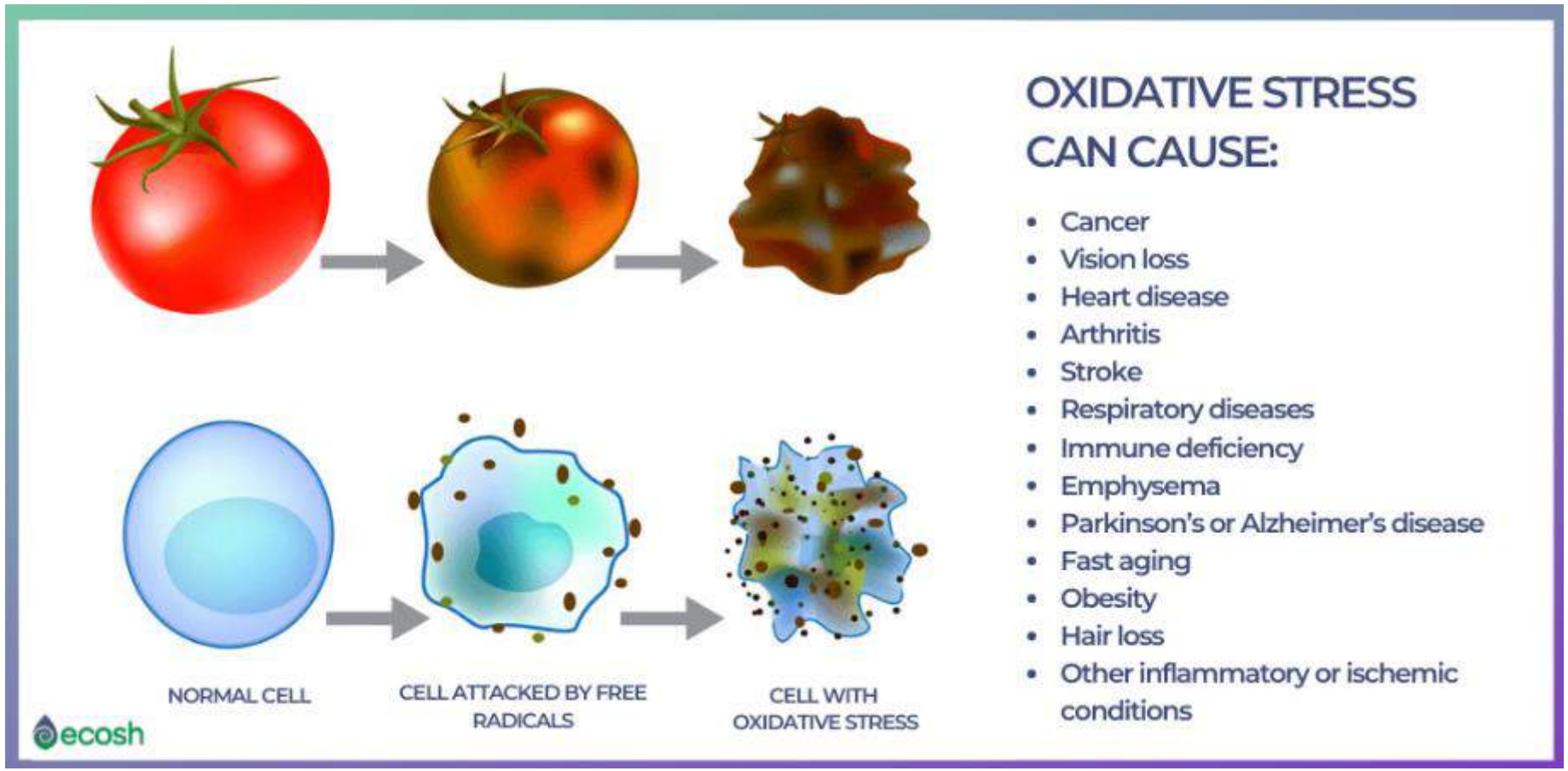
- **Cells have defense system to prevent free radical injury**
  - **Normally free radicals are neutralized by anti – oxidant enzymes and substances like**
    - **Superoxide dismutase – present in cytoplasm and produced by mitochondria**
    - **Catalase – produced by peroxisomes**
    - **Glutathione peroxidase – produced by mitochondria and present in cytoplasm**
    - **Vitamin C in cytoplasm**
    - **Ferritin and Ceruloplasmin present in cytoplasm – Levels of active forms of iron and copper are minimized by binding of ions to storage and transport proteins like transferrin, ferritin, ceruloplasmin there by minimizing the formation of hydroxyl ion**
    - **Vitamins E, A and β Carotene in the plasma membrane and cell membrane of organelles**

- **Fenton reaction**
  - **Oxygen is converted into superoxide (O_2^-) by oxidative enzymes in the endoplasmic reticulum, mitochondria, plasma membrane, peroxisomes and cytosol**
  - **Superoxide (O_2^-) is converted into Hydrogen peroxide by dismutation. Hydrogen peroxide is also derived from oxidases in peroxisomes**
  - **Hydrogen peroxide is converted into Hydroxyl by the Cu^{2+}/ Fe^{2+} catalyzed Fenton reaction. This reaction is reversible and hydroxyl can be converted into hydrogen peroxide in the presence of Glutathione peroxidase**
  - **Intracellular free iron is in the Ferric state (Fe^{3+}) and must be reduced to Ferrous form to participate in reaction**


FREE RADICAL GENERATION AND NEUTRALIZATION
O_2^-
Fe^{2+}
Fenton reaction
Fe^{3+}
Superoxide (O_2^-)
SOD
Hydrogen peroxide (H_2O_2)
Hydroxyl ions (OH^-)
Catalase
Glutathione peroxidase
GSSG
2GSH
Glutathione reductase
Water (H_2O)

- **Effects of Free radicals are-**
  -
    - **Lipid peroxidation of membrane**
    - **Oxidative modification of proteins**
    - **Lesions in DNA**
  - **Lipid peroxidation of membrane –**
    - **Double bonds in unsaturated fatty acids of membrane lipids are attacked by oxygen derived free radicals, particularly by OH**
    - **This produces peroxides which initiates the autocatalytic reaction**
  - **Oxidative modification of proteins**
    - **Free radicals promote oxidation of amino acid residue side chains, formation of protein-protein cross linkages (e.g. disulfide bonds) & oxidation of protein back bone protein fragmentation**
    - **Oxidative modification of proteins damage the active sites of enzymes, disrupt the conformation of structural proteins and enhance proteosomal degradation of unfolded and misfolded proteins**
  - **Lesions in DNA**
    - **Free radicals cause single and double stranded breaks in DNA, cross – linking of DNA strands and formation of adducts**
    - **Oxidative DNA damage has been implicated in cell ageing & in malignant transformation**


FORMATION OF FREE RADICALS
UV LIGHT
NORMAL
INFLAMMATION
NORMAL RESULTS
White Blood Cell
DNA DAMAGE
METABOLISM
Mitochondrion
AIR POLLUTION
O3 + UV (in air)
UV
IONIZING RADIATION
CELL DEFECT
SMOKING
OH•
NO•
H2O2
O2•—



OXIDATIVE STRESS CAN CAUSE:

- Cancer
- Vision loss
- Heart disease
- Arthritis
- Stroke
- Respiratory diseases
- Immune deficiency
- Emphysema
- Parkinson's or Alzheimer's disease
- Fast aging
- Obesity
- Hair loss
- Other inflammatory or ischemic conditions

EFFECTS OF CELL INJURY:

A) REVERSIBLE INJURY (DEGNERATION):

- Degenerations are morphological changes due to disturbance of cellular metabolism caused by mild (non-lethal) injury.
  Degenerations are reversible if the irritant is removed. If the irritant is prolonged or its intensity is increased, the cells may die (necrosis/ irreversible injury).

Parenchymal (metabolically active) cells, as liver cells, renal tubules & cardiac muscle are more vulnerable to degeneration.
Mesenchymal cells (e.g. fibroblasts) are more resistant.

- Degenerations are either due to intracellular accumulation of water or fat:

  1. cell swelling due to accumulation of water: it is a mild form of cell injury. Two subtypes:

  a) cloudy swelling: small amount of water → cell swelling with granular cytoplasm

  b) hydropic swelling (also called vacuolar degeneration, hydropic degeneration or ballooning degeneration). Accumulation of larger amounts of water → the swollen cells appear pale and show clear cytoplasmic vacuoles

  2. cell swelling due to accumulation of fat (fatty change)

B) **IRREVERSIBLE INJURY (CELL DEATH):** Two types:

- Necrosis: due to severe or prolonged cell injury (same causes of degeneration).
- Apoptosis: this is cell suicide (programmed cell death). It occurs in certain circumstances, frequently unrelated to tissue irritation

CELL SWELLING DUE TO ACCUMULATION OF WATER

PATHOGENESIS:

Mild injury (particularly mild hypoxia) inhibit oxidative phosphorylation suppression of ATP production . this leads to:

- Disturbance of membrane transport mechanisms → sodium enters the cell (accompanied by water) & potassium diffuses out of the cell → cell swelling
- Anaerobic cellular metabolism → accumulation of inorganic phosphates, lactate & purine nucleosides → increased intracellular osmotic load → cell swelling

PATHOLOGY:

Gross picture: the affected tissue or organ appears swollen and pale.

Microscopic picture:

- Cloudy swelling : cells are swollen showing pale eosinophilic granular cytoplasm
- Hydropic swelling: cells are swollen with a single large clear vacuole or multiple vacuoles

Examples:

- Cloudy swelling or hydropic degeneration (ballooning)of renal tubules in cases of nephritis & liver cells in viral hepatitis
- Ballooning of B cells of islets of Langerhans in cases of diabetes mellitus
- Ballooning of epidermal cells in cases of viral infections & mild burns
- Ballooning of tubule in cases of electrolyte imbalance (potassium deficiency)

FATTY CHANGE (STEATOSIS)

DEFINITION: Accumulation of lipids (neutral fat) inside parenchymal cells. It can affect the heart, kidney & other organs, but is by far most common in the liver (hepatic steatosis).

AETIOLOGY: CAUSES & PATHOGENESIS:

1- Fatty change of liver: causes (& pathogenesis) include:

a) Hypoxia or bacterial toxins → suppression of mitochondrial lipid metabolism enzymes → intracellular accumulation of fat

b) Hepatocellular specific causes: since the liver is the main organ responsible for fat metabolism, its cells may undergo fatty change in the following conditions:

- Excess fat carried to liver cells (more than their capacity to utilize these amounts) e.g.

- Obesity (excess dietary fat).
- Starvation & diabetes mellitus: → excessive mobilization of fat from fat stores to liver.

- Deficiency of lipotropic factors as choline & methionine → accumulation of neutral fat inside liver cells.
- Hepatotoxins as alcohol which → ↑ fatty acid synthesis, ↓ fatty acid oxidation & peripheral lipolysis. There are many other hepatotoxins as CCI4 & some drugs.
- Some liver cell diseases as viral hepatitis C.

2- fatty change of other organs (as kidney & heart) is mainly due to hypoxic or toxic depression of mitochondrial enzymes

PATHOLOGY:

Gross picture:

- The organ appears enlarged, with tense capsule. Consistency is soft greasy . cut surface is bulging are rounded. Color is yellow ; diffuse or patchy
- The most commonly affected organs are:

  1-liver : Affection may be extensive (diffuse) in severe toxic injury or spotty (patchy) due to milder injury as hypoxia. In such cases the liver appear mottled (nutmeg appearance).

  2-Heart : Affection may be also diffuse as in case of diphtheritis toxic myocarditis or patchy such as in hypoxia cases . patchy affection of myocardial fibers → yellow streaks alternating with the non-affected brownish muscle fibers → tigroid or tabby cat appearance .

  3-kidney: affection is mainly cortical (where tubules exist) & is spotty or rarely diffuse.

Microscopic picture :

- With ordinary stains fat appears as small clear fat vacuoles or a single large vacuoles that may flatten the nucleus and displace it eccentrically → signet ring appearance .
- With special stains fat can be stained orange (sudanIII) or black (osmic acid)

Clinical significance:

Fatty change is a severer form of cell injury that may progress to cell necrosis resulting in

- In case of diffuse heart affection it may → heart failure.
- In case of liver affection , it may → progress to liver cirrhosis

Necrosis

DIFINITION:

Necrosis means death of a group of cells within a living body caused by an irritant.

CAUSES & PATHOGENESIS :

Causes & pathogenesis of reversible and irreversible cell injury

GROSS FEATURES:

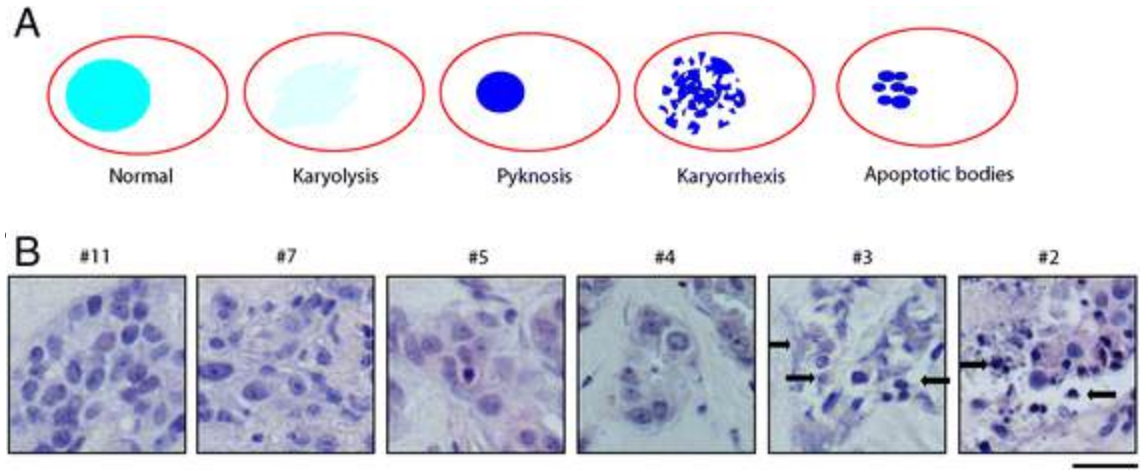
- The necrotic tissue appear opaque yellow and may be swollen.
- The surrounding tissues appear hyperemic due to inflammation.

MICROSCOPIC FEATURES:

1- Cellular changes:

a) nuclear changes: due to enzymatic digestion.

- Pyknosis:the nucleus becomes small and dark
- Karyorrhexis: nuclear fragmentation.
- Karyolysis: faint dissolved nucleus.



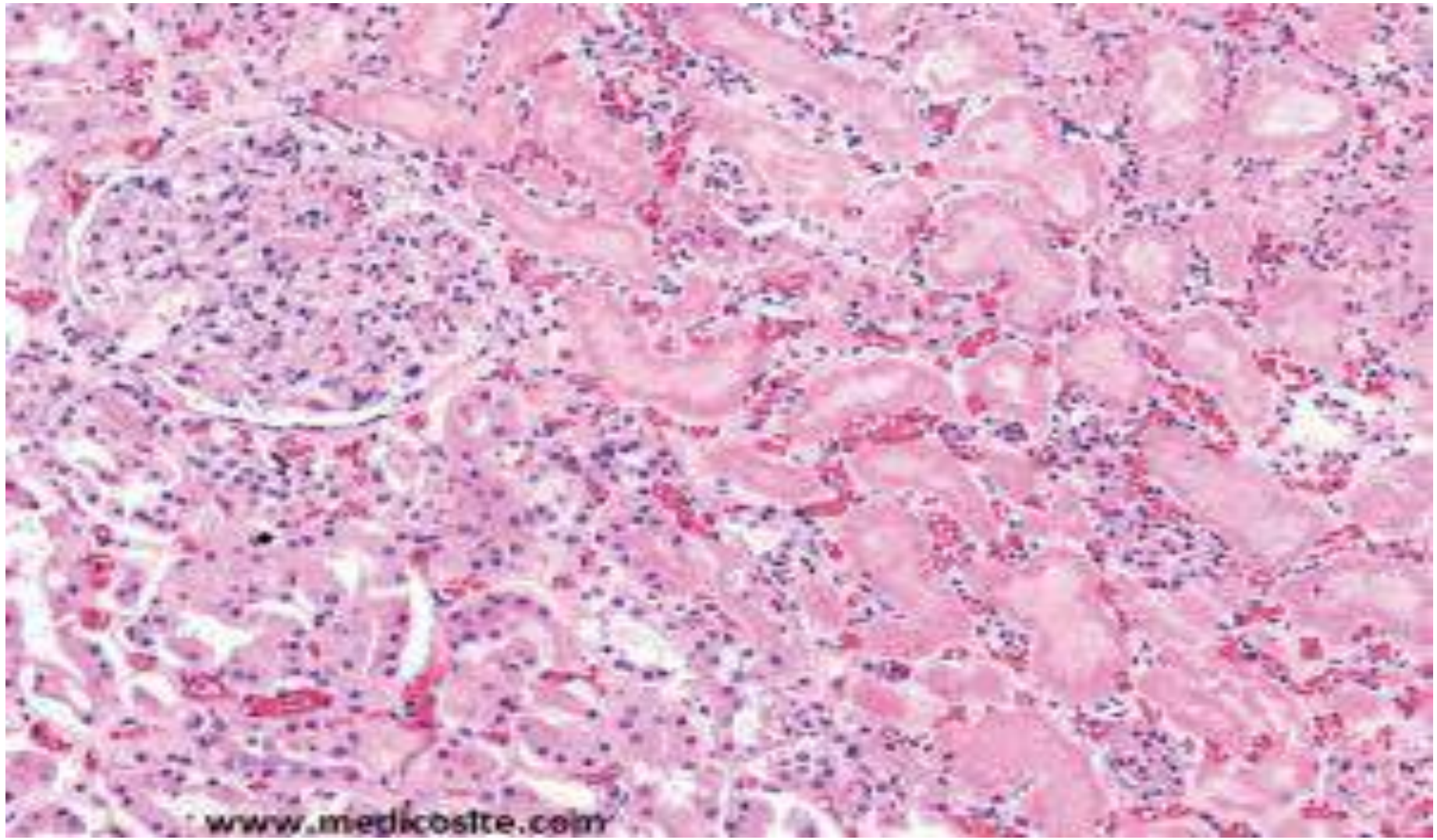
b) cytoplasmic changes:

- the cell may appear swollen (cytomegaly)
- cell membranes appear indistinct.
- Cytoplasm is eosinophilic (staining of denatured proteins)

2- architectural changes: two main possibilities:

a) necrotic tissue may rapidly appear structureless due to cell lysis (autolysis by lysosomal enzymes of the dead cells heterolysis by proteolytic enzymes derived from inflammatory cells in the area)

b) protein denaturation (coagulation) may precede cell lysis (mainly in cases of ischemia). In such cases the necrotic cells preserve the architectural outlines of the original tissue → structural ghosts. However, lysis occurs later and the necrotic tissue finally appears structureless.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FATE OF NECROTIC TISSUE :

1- inflammation surrounds the necrotic area due to release of chemical mediators.

2- healing : regeneration or fibrosis (depending on type of damaged cells)

3- dystrophic calcification may occur.

TYPES OF NECROSIS:

1-Coagulative necrosis:

It occurs in infarcts(ischemic necrosis) of all organs except CNS.

There is denaturation of cell proteins , which lasts for at least some days ; thus the basic outline of the necrotic cell is preserved deposite loss of the nuclei.

Finally lysis occurs and necrotic tissue becomes structureless

2- liquefactive necrosis :

Occurs in infarcts CNS (unknown reasons) and in pus.

It is due to prevalence of cell lysis over protein denaturation as in case of pus (by proteolytic enzymes liberated from pus cells)

3- Gangrenous necrosis:

this necrosis (usually coagulative or liquefactive) followed by putrefaction by saprophytes

4- Caseous necrosis:

This type of necrosis is typical of tuberculosis. The necrotic tissue appears yellowish white & (cheesy) resembling casein (caseous). The caseous appearance is explained by:

-necrosis starts as ischemic coagulative necrosis due to endarteritis obliterans

-coexisting hypersensitivity (allergic inflammation) due to tuberculous antigens tuberculoprotein) release of cytotoxins and proteolytic enzymes partial liquefaction of the coagulated necrotic cells cell fragmentation .

-tubercle bacilli are rich in fats. Liberation of these fats from dead bacteria adds to the cheesy character of this type of necrosis.

- Microscopically it appears granular eosinophilic structureless material (fragmented necrotic cells).

5-Fat Necrosis : two subtypes :

a) *enzymatic fat necrosis :*

- Cause :it occurs in cases of acute hemorrhagic pancreatitis
- Mechanism : ruptured pancreatic ducts escape of lipase and protease enzymes digestion (necrosis) of the surrounding peritoneal fat cells .
- Grossly : the affected areas may show chalky white hard calcific patches. this is because fatty acids liberated from necrotic fat cells have a high affinity to combine with calcium forming calcium soaps.
- Microscopically: swollen necrotic fat cells , surrounded by chronic inflammatory cells (including foreign body giant cells) and fibrosis , sometimes with calcification

b)Traumatic fat necrosis :

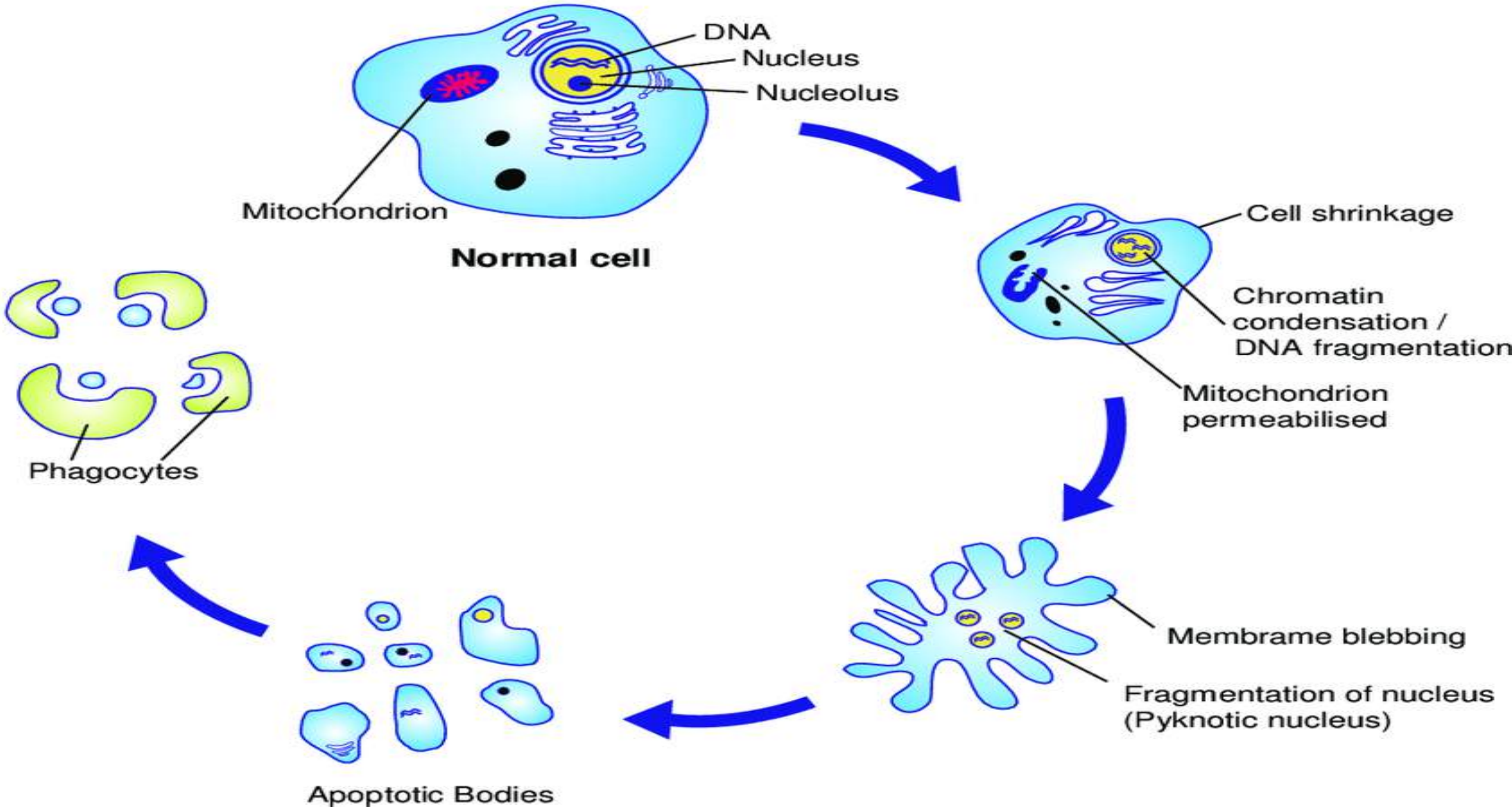
- Cause : it is common in the female breast and subcutaneous fat & is usually caused by trauma (which may be surgical)
- Mechanism: rupture of fat cells results in their auto –digestion and release of fatty acids , which combine with calcium.
- Grossly : hard , sometimes chalky white mass. It may be clinically mistaken for a tumor as in case of fat necrosis of the breast . biopsy will diagnose the condition .
- Microscopically resembles enzymatic fat necrosis .
- 6-Fibrinoid necrosis :it affects muscle fibers &collagen which become fragmented finer particles resembling fibrin . it develops in autoimmune collagen disease (as rheumatic fever , reheumatoid arthritis , lupus erythematosus …etc). .it is due to autoantibodies against collagen . it is not true necrosis since it does not affect living cells.

APOPTOSIS

DEFINITION: Apoptosis in Greek means “dropping off “. It is another form of cell death that usually involves few or single cells . this type of cell death seems to be programmed and is described as cell suicide or programmed cell death aiming at removal of un-necessary or diseased cells .it can occur in physiological & pathological conditions . it can occur without tissue injury (or with mild injury not causing necrosis). Apoptosis is not associated with release of chemical mediators &therefore does not excite inflammation.

MORPHOLOGICAL FEATURES OF APOPTOSIS:

- Shrinkage of cell size .
- Nuclear chromatin condensation , followed by fragmentation of DNA.
- Formation of membrance blebs , followed by their separation apoptotic bodies.
- The apoptotic bodies consist of a dark nuclear fragment surrounded by eosinophilic cytoplasm . they becomes engulfed by phagocytic cells .
- Apoptosis does not excite inflammation & is not accompanied by healing or calcification .


DNA
Nucleus
Nucleolus
Mitochondrion
Normal cell
Cell shrinkage
Chromatin condensation / DNA fragmentation
Mitochondrion permeabilised
Membrame blebbing
Fragmentation of nucleus (Pyknotic nucleus)
Apoptotic Bodies
Phagocytes

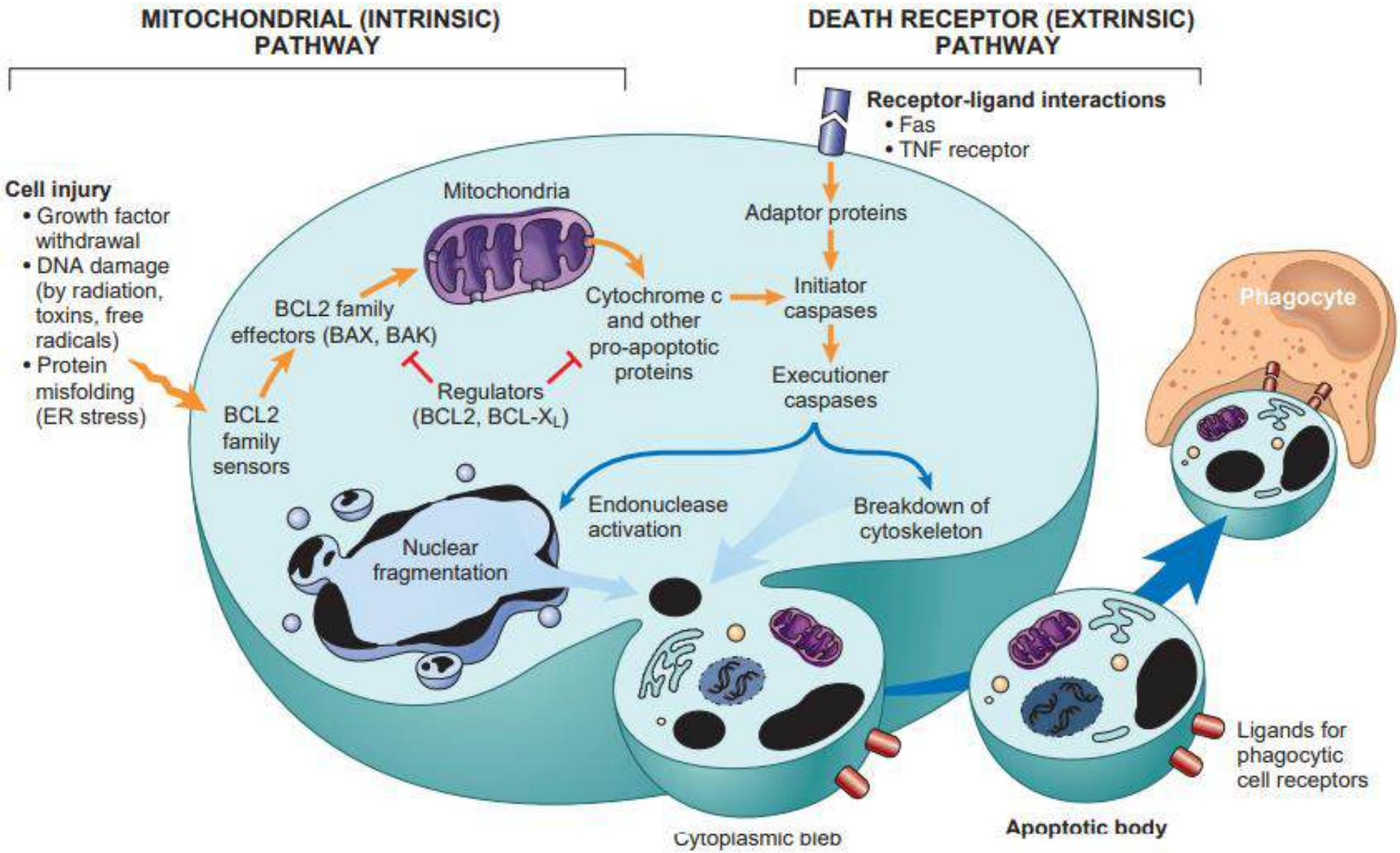
EXAMPLES OF APOPTPSIS :occurrence of apoptosis is known in several conditions:

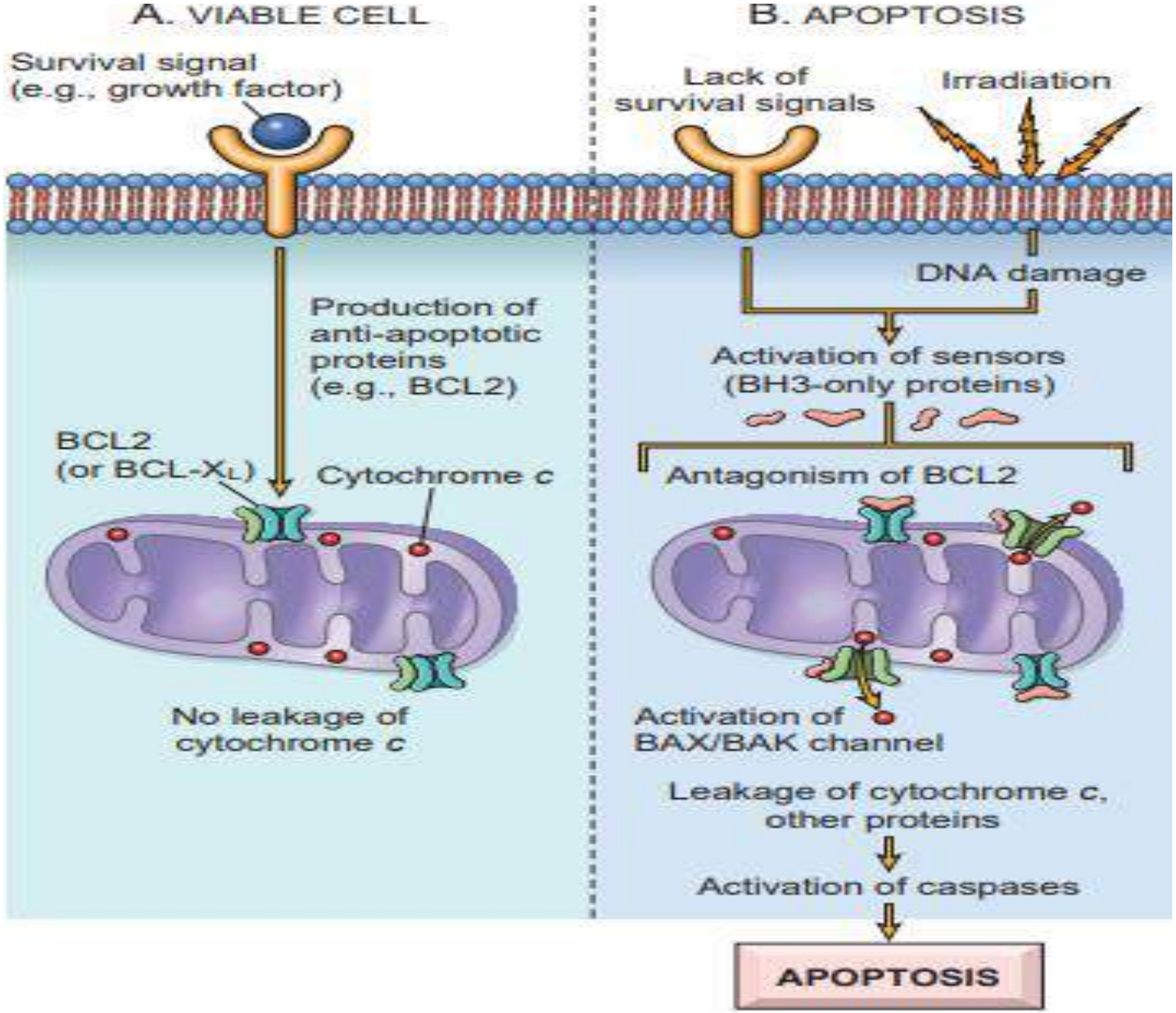
1-In physiological (normal)states such as :

- During embryogenesis .
- Hormone dependent involution of tissues e.g. endometrium during menstrual cycle
- Cells after achieving their purpose e.g. neutrophils in acute inflammation
- Normal turnover of cells (e.g. intestinal epithelium) to maintain a constant number of cells.

2-In pathological states such as :

- Liver cells in viral hepatitis (councilman bodies).
- Apoptosis of malignant tumor cells.
- In some cases of atrophy.
- In cases of mild radiation injury and mild thermal injury.
- Cytotoxicity induced by T lymphocytes as in organ rejection.


MITOCHONDRIAL (INTRINSIC) PATHWAY
DEATH RECEPTOR (EXTRINSIC) PATHWAY
Receptor-ligand interactions
• Fas
• TNF receptor
Cell injury
• Growth factor withdrawal
• DNA damage (by radiation, toxins, free radicals)
• Protein misfolding (ER stress)
Mitochondria
Adaptor proteins
BCL2 family effectors (BAX, BAK)
Cytochrome c and other pro-apoptotic proteins
Initiator caspases
Executioner caspases
Regulators (BCL2, BCL-XL)
BCL2 family sensors
Endonuclease activation
Breakdown of cytoskeleton
Nuclear fragmentation
Phagocyte
Ligands for phagocytic cell receptors
Cytoplasmic bleb
Apoptotic body


A. VIABLE CELL
B. APOPTOSIS
Survival signal
(e.g., growth factor)
Lack of
survival signals
Irradiation
DNA damage
Production of
anti-apoptotic
proteins
(e.g., BCL2)
Activation of sensors
(BH3-only proteins)
BCL2
(or BCL-XL)
Cytochrome c
Antagonism of BCL2
No leakage of
cytochrome c
Activation of
BAX/BAK channel
Leakage of cytochrome c,
other proteins
Activation of caspases
APOPTOSIS

Other Mechanisms of Cell Death

Necroptosis. As the name indicates, this form of cell death is a hybrid that shares aspects of both necrosis and apoptosis.
Morphologically, and to some extent biochemically, it resembles necrosis, as both are characterized by loss of ATP, swelling of the cell and organelles, generation of reactive oxygen species (ROS), release of lysosomal enzymes, and ultimately rupture of the plasma membrane.
Mechanistically, it is triggered by signal transduction pathways that culminate in cell death, a feature similar to apoptosis.
Because of these overlapping features, necroptosis is sometimes called *programmed necrosis*
“caspase-independent” programmed cell death.

Pyroptosis is a form of apoptosis that is accompanied by the release of the fever-inducing cytokine IL-1 (*pyro* refers to fever). Microbial products that enter infected cells are recognized by cytoplasmic innate immune receptors and can activate the multiprotein complex called the *inflammasome*. The function of the inflammasome is to activate caspase-1 (also known as interleukin-1β– converting enzyme), which cleaves a precursor form of interleukin-1 (IL-1) and releases its biologically active form.

Ferroptosis*.* Only discovered in 2012, ferroptosis is a distinct form of cell death that is triggered when excessive intracellular levels of iron or reactive oxygen species overwhelm the glutathione-dependent antioxidant defenses to cause unchecked membrane lipid peroxidation.

Cellular aging

It is the result of a progressive decline in the proliferative capacity and life span of cells and the effects of continuous exposure to exogenous factors that cause accumulation of cellular and molecular damage .

The mechanisms for cellular aging

1 DNA damage

2 decreased cellular replication

3 reduced regenerative capacity of tissue stem cells.

4 Accumulation of metabolic damage.

Cellular aging is **multifactorial**

1 an endogenous molecular program.

2 continuous exposure through out life to adverse exogenous influences.

It‘s called **wear and tear** process, in cell aging molecular injury to cells exceeds their repair capacity thus accelerating the aging process.

Favored theory for cell aging is **the progressive effects of free radicals through out life.**

Intracellular accumulation and Extracellular deposition

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Consultant of pathology

El shifa medical hospital

M.B.,B.CH.,

Egyptian board of pathology (Cairo university)

Palestinian board of pathology

INTRACELLULR ACCUMULATIONS AND EXTRACELLULAR DEPOSITIONS

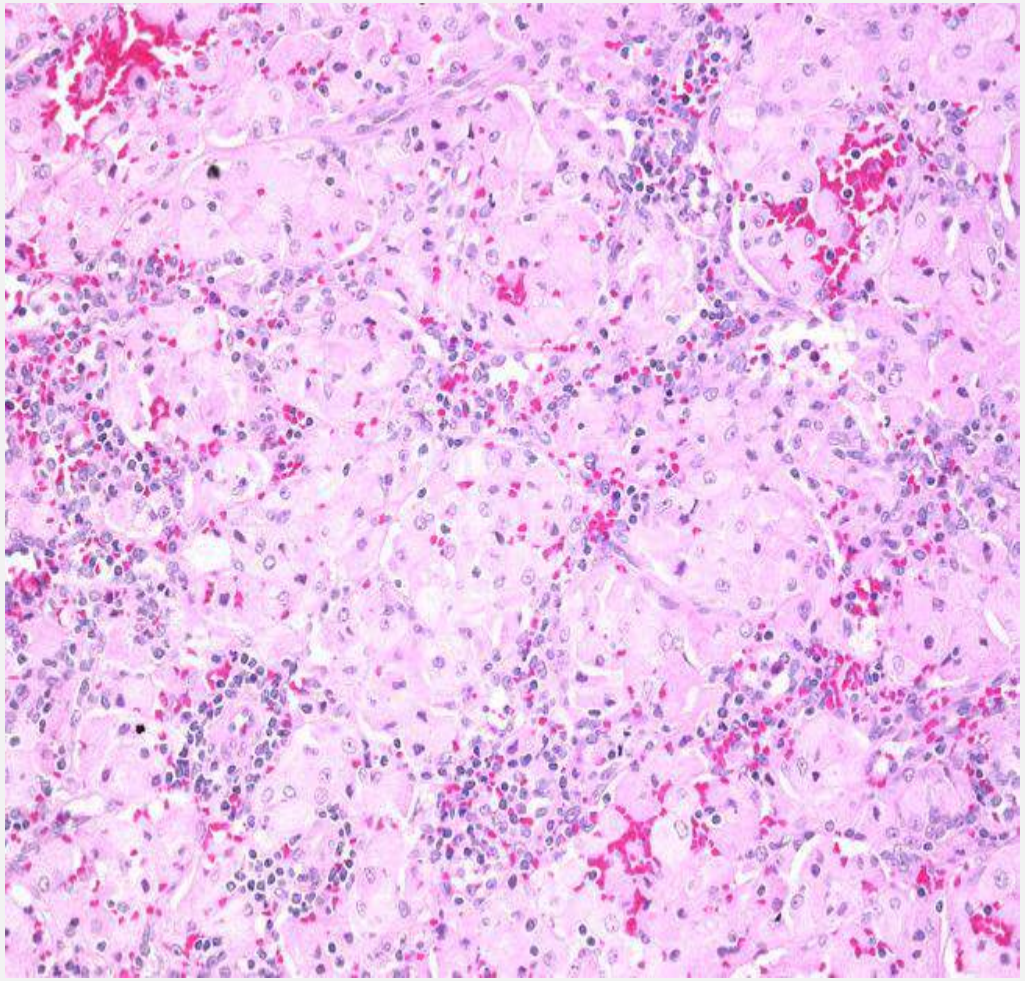
1- INTRACELLULR ACCUMULATIONS

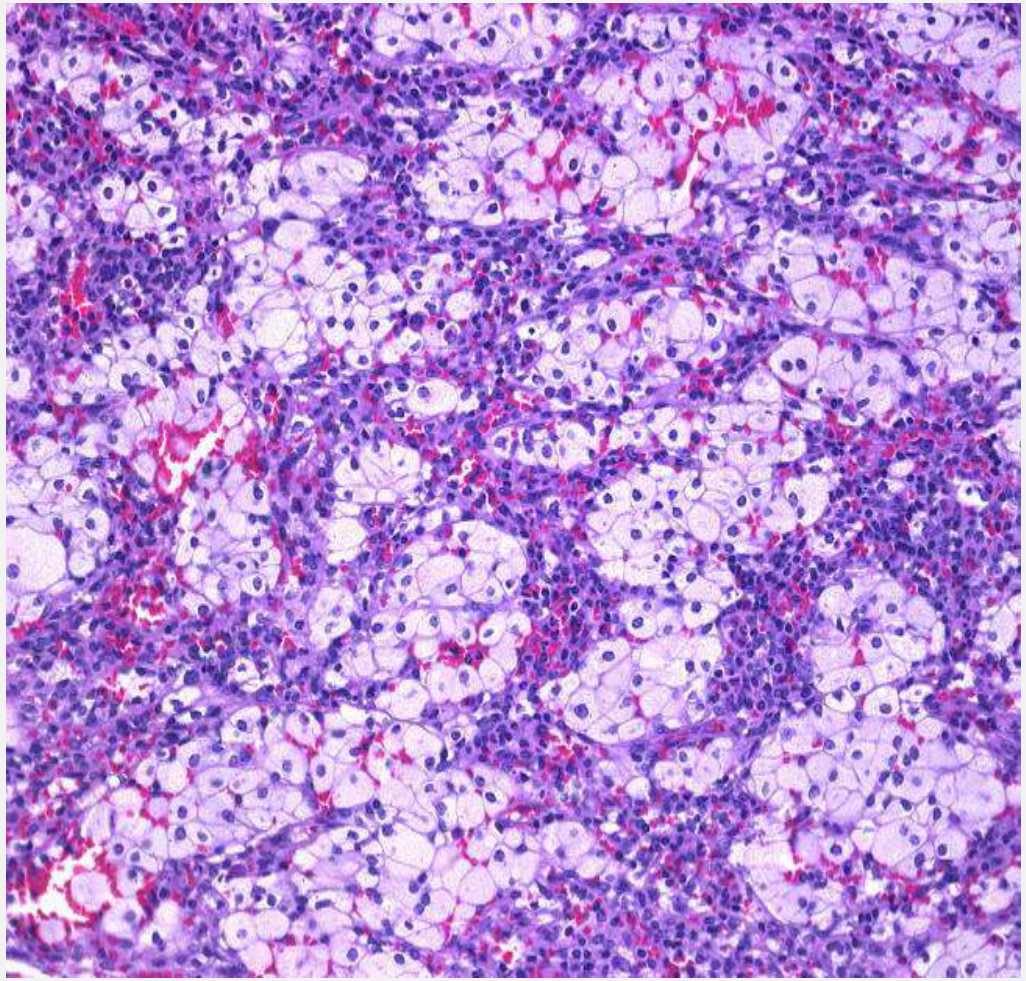
Water

See cloudy swelling & hydropic degeneration

FATS

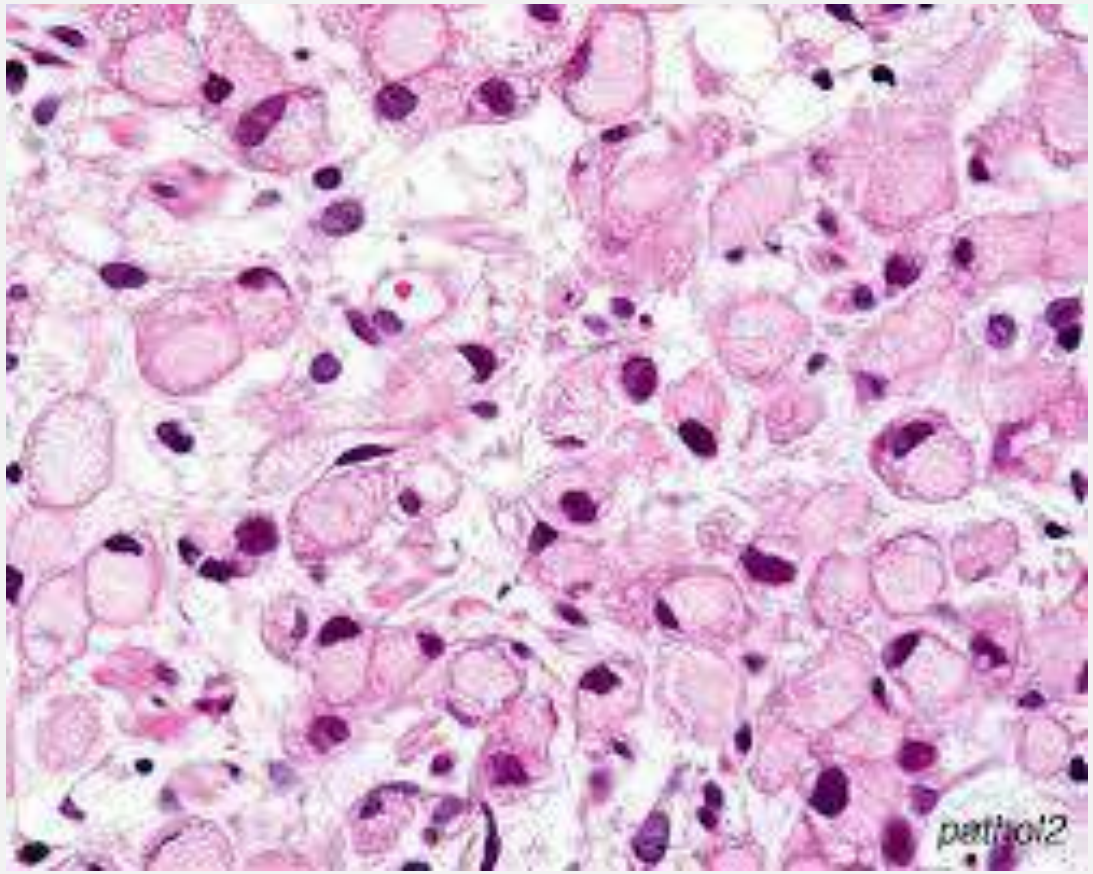
- Change: see before.
- Atherosclerosis: see systemic pathology.
- Xanthoma: deposition of fat in skin (engulfed by dermal macrophages).
- Gaucher's disease: accumulation of glucocerebrosides inside phagocytic cells.
- Neimann picks disease: accumulation of sphingomyelins inside phagocytic & parenchymal cells .





MUCIN
MUCOID DEGENERATION

- This is accumulation of mucin inside epithelial cells which swell & show vacuolated cytoplasm, may with eccentric nuclei (signet ring cells). Cells may rupture leading to extracellular pools of mucin.
- Occurs in a number of pathological conditions. Example
- In case of catarrhal inflammation (see before).
- In case of mucoid and signet ring cell carcinoma (see later).
- In case of mucinous cystadenoma of the ovary (see later).
- Remark: extracellular accumulation of mucin is called Myxomatous degeneration (see later).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PROTEINS

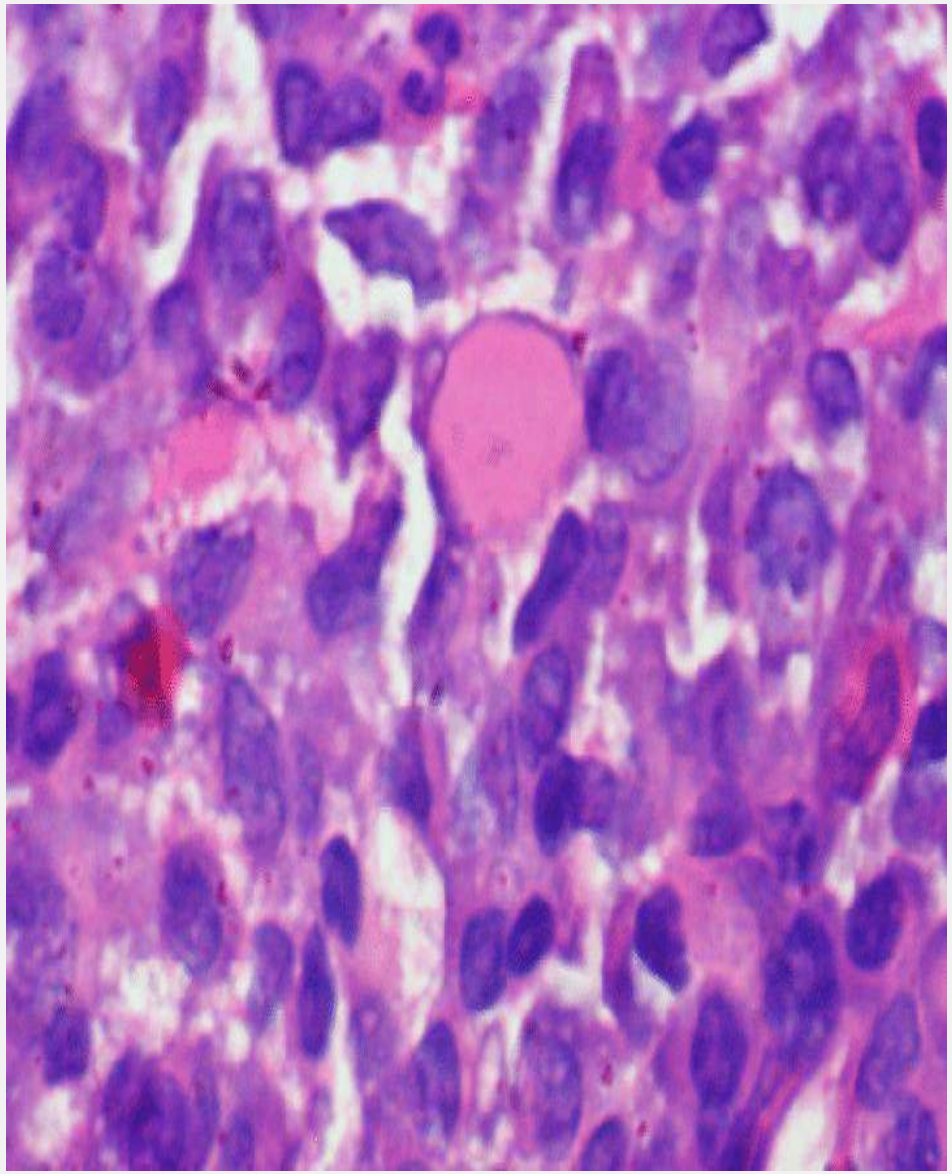
HYALINE CHANGE (HYALINOSIS)

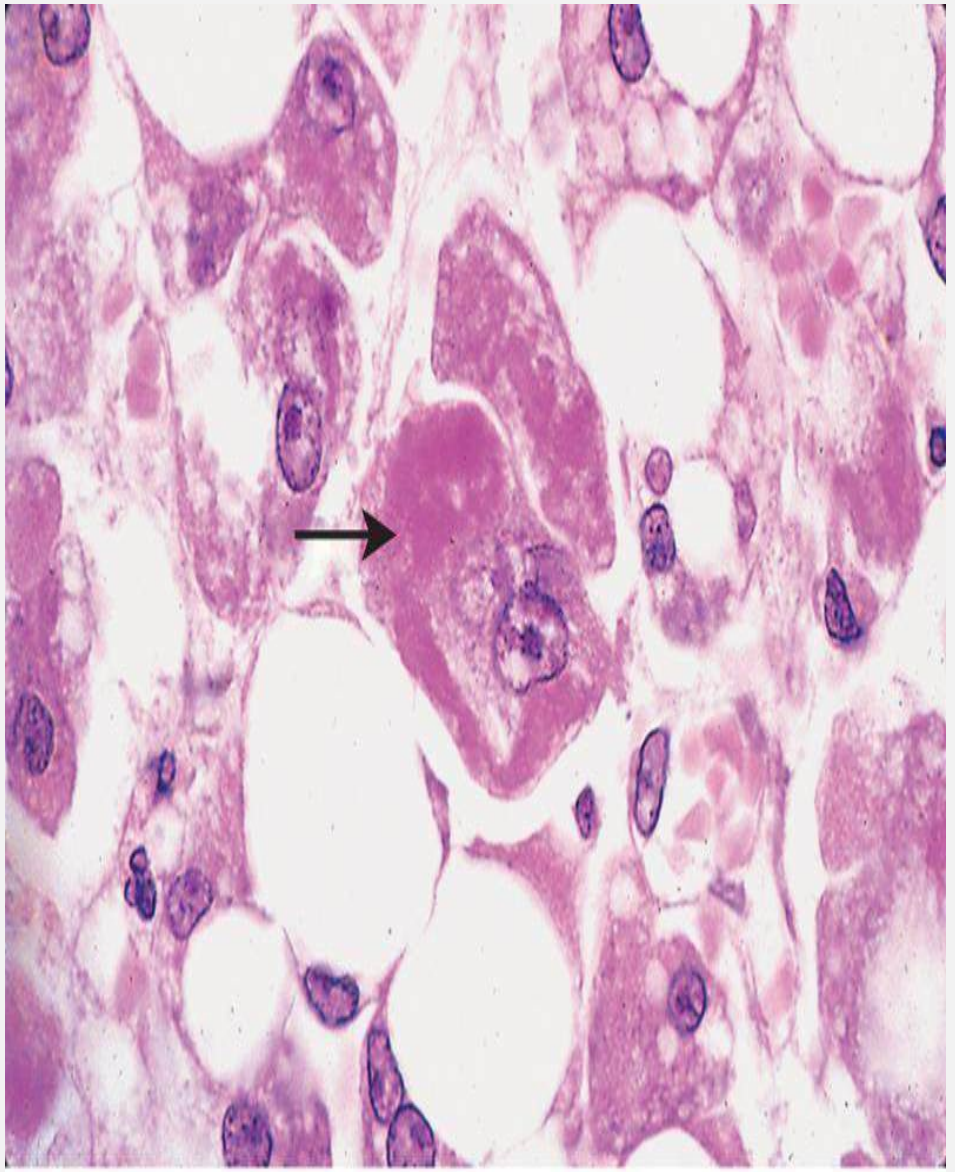
DEFINITION:

The term “hyaline” refers to any cellular or extracellular alteration manifested by homogenous, glassy-pink appearance in sections stained with hematoxylin & eosin. It is a microscopic change with no specific gross features. The mechanism of hyalinosis is excess protein, synthesized or deposited in the affected cell or matrix.

Examples of cellular hyalinosis:

- Russel bodies: hyaline change of plasma cells which appear as bright eosinophilic oval bodies . it is due to overproduction of immunoglobulins in some prolonged chronic inflammations as rhinoscleroma.
- Mallory alcoholic hyaline seen in liver cells in alcoholic hepatitis.
- Hyalinosis of islets of Langerhans in cases of diabetes mellitus.
- Corpora amylacea: laminated hyaline bodies in the lumen of prostatic acini in cases of prostatic hyperplasia.





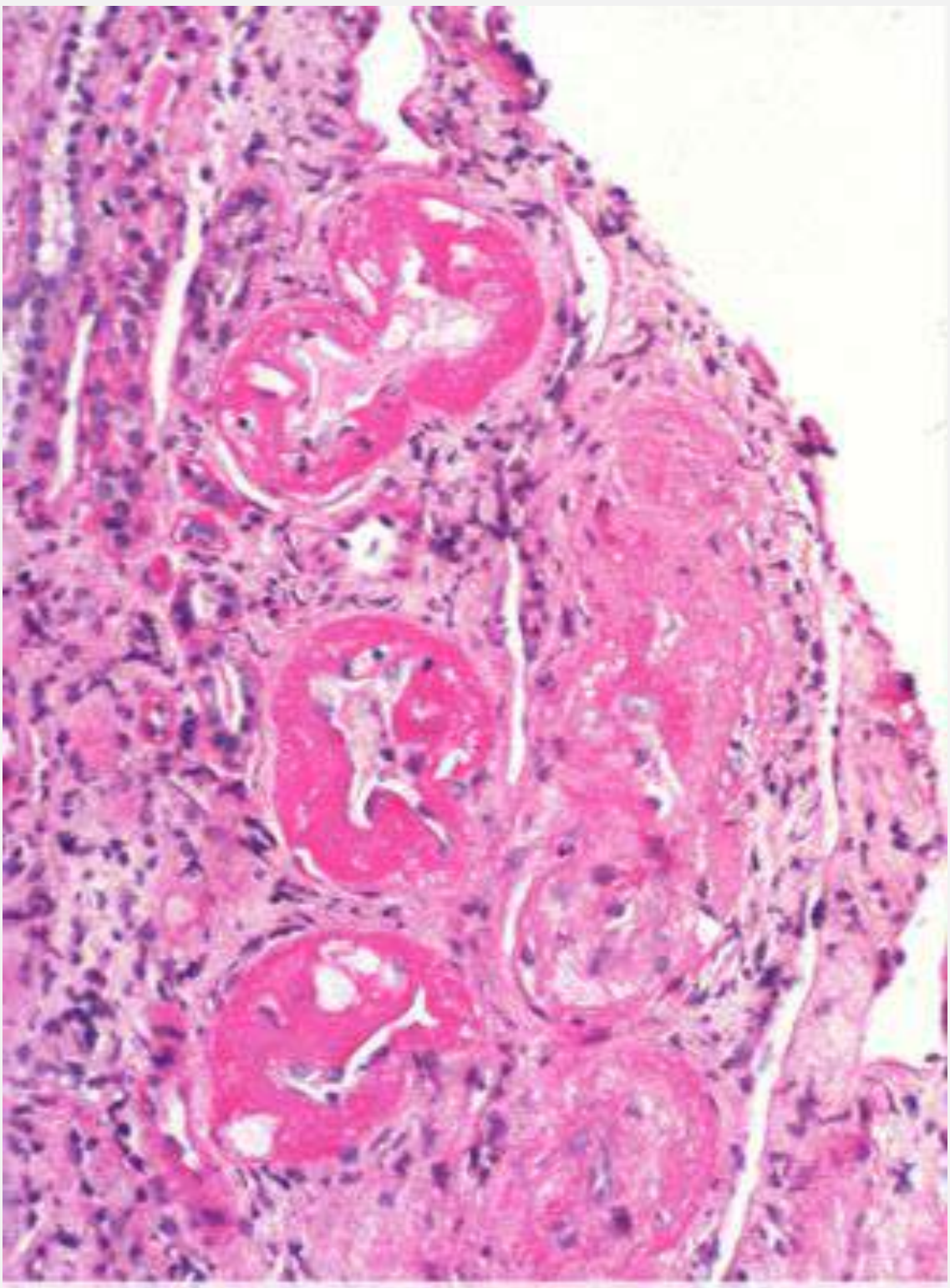
Examples of extracellular (connective tissue) hyalinosis:

- Hyalinosis of old scars and keloids.
- Hyalinosis of organized (fibrotic) thrombi.
- Hyalinosis of some mesenchymal tumors as leiomyoma.
- Vascular Hyalinosis : examples

- Hyalinosis of arteriolar walls in cases of hypertension diabetes mellitus & old age
- Hyalinosis of fibrosed glomeruli in cases of chronic glomerulonephritis.

GLYCOGEN

In case of glycogen storage diseases



PLGMENTS

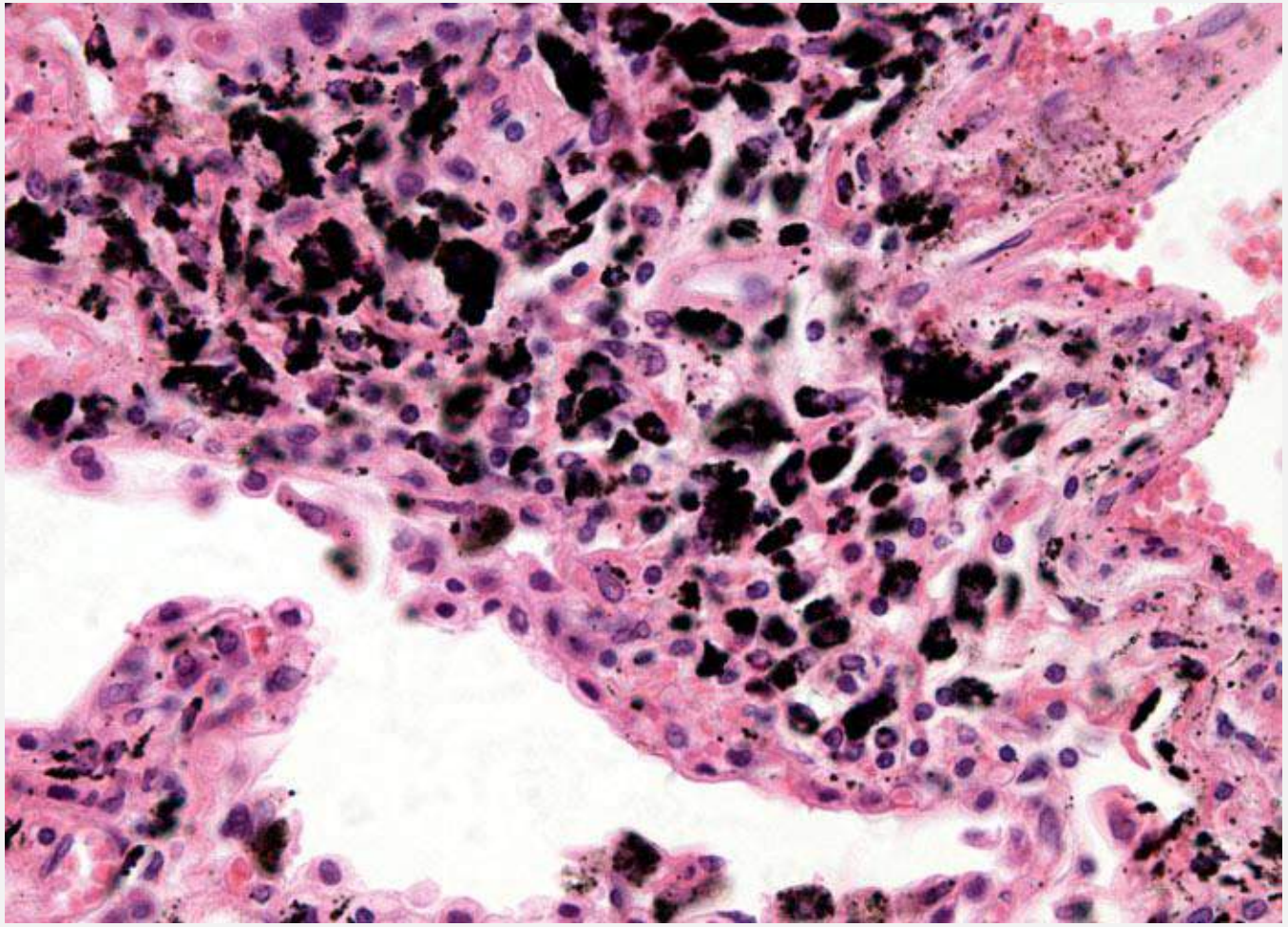
Intracellular accumulation of pigments includes two major forms:

A) EXOGENOUS PIGMENTATION

1- By inhalation: the most common example is anthracosis which is black pigmentation of lungs caused by inhalation of carbon due to smoking or air pollution. This carbon is engulfed by macrophages and is partly carried to the draining lymph nodes.

2- By skin inoculation (tattooing)

3- By ingestion: in cases of chronic lead poisoning (plumbism) there is blue black pigmentation of the gums due to combination of lead with hydrogen sulphide (from decomposed food particles between teeth) → lead sulphide.



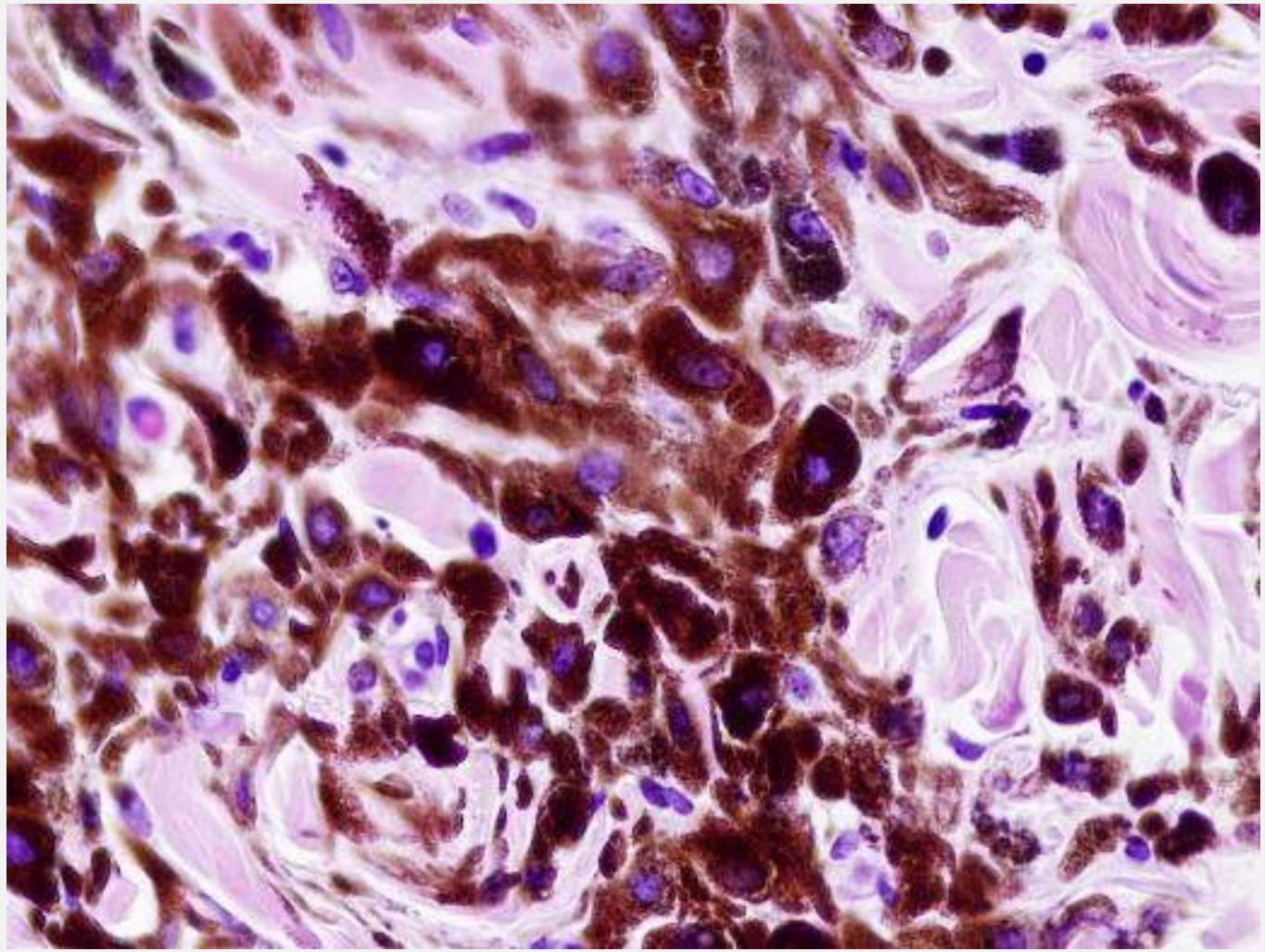
B) ENDOGENOUS PLGMENTATION

1- MELANIN

Melanin is formed melanocytes from tyrosine by action of tyrosinase. It normally exists in skin, hair, eyes, meninges and basal ganglia.

Causes of increased melanin pigmentation (hyperpigmentation):

- Prolonged exposure to sun.
- Addison's disease: chronic adrenocortical insufficiency → feed back rise of ACTH (which has a melanocyte hormone- like action) pigmentation of skin & mucus membranes.
- Pigmented tumors: benign melanoma (nevi) and malignant melanoma.
- Melisma (chloasma) : hyperpigmented melanotic patches affecting face of women during pregnancy (associated with pigmentation of nipples and genitalia).
- Café au lait skin patches in patients with multiple neurofibromatosis.



Causes of deficient melanin pigmentation(hypopigmentation):

- *Albinism:* this is generalized hypopigmentation due to tyrosinase deficiency. It an inherited autosomal recessive defect characterized by absence of melanin pigment in hair, skin & iris & choroid of eyes.
- *Leukoderma:* patchy skin hypopigmentation. May be congenital or acquired (as in leprosy)

2- LIPOFUSCIN (LIPOCHROME)

This yellowish brown lipid-derived pigment normally exists in small amounts in different cells of the body. Pigment is increased most commonly in cases of organ atrophy . example:

1) Brown atrophy of the heart:

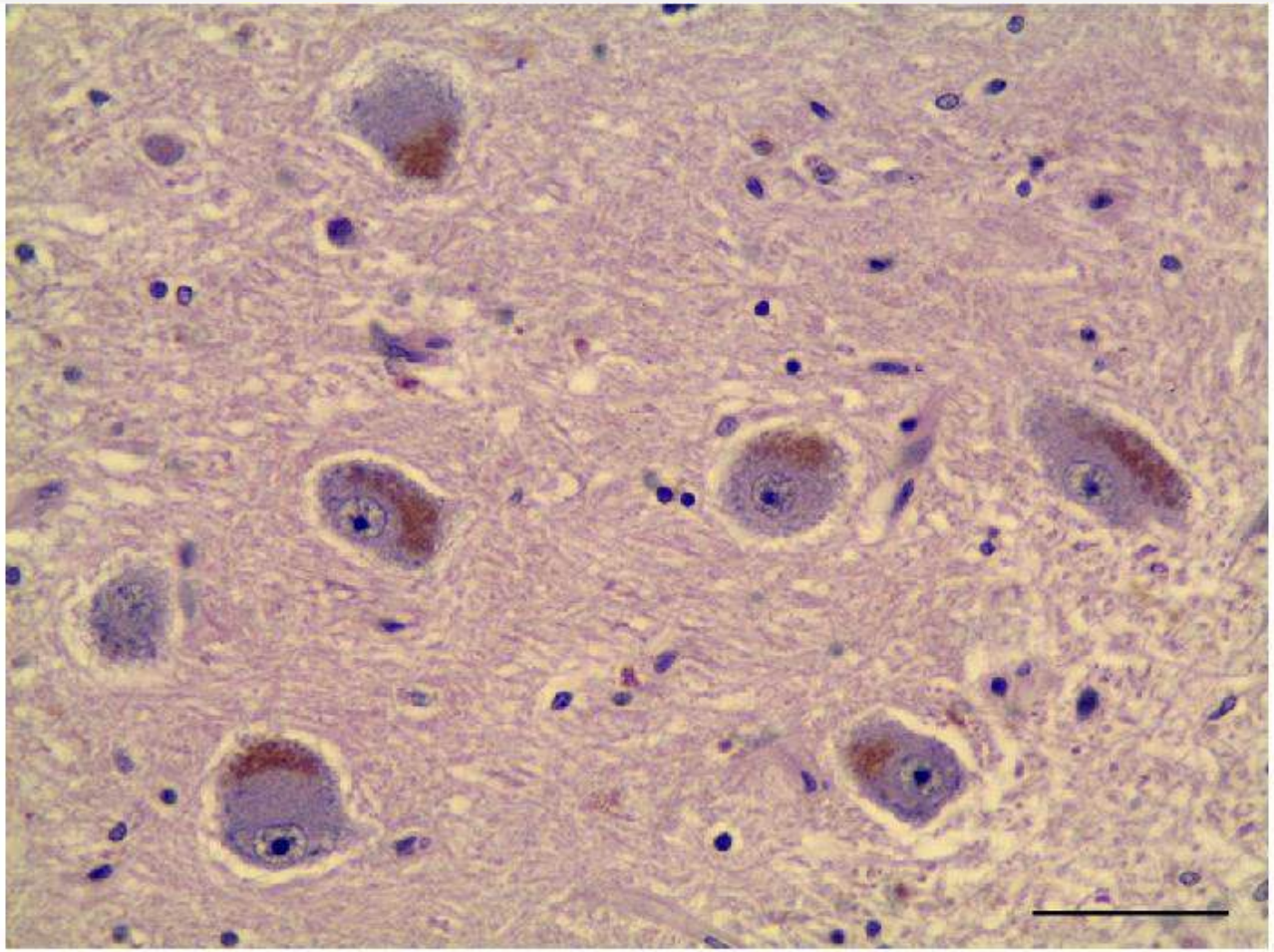
Cause: generalized atrophy in old age (senile atrophy) or wasting diseases.

Pathogenesis: lipofuscin is normally derives from peroxidation of polyunsaturated lipids of cellular membranes. This process is exaggerated in in atrophic cells. Since aging (senility) is the commonest cause of atrophy; lipofuscin is sometimes considered as a “wear-and-tear” or aging pigment. Therefore organ atrophy may be accompanied by dark brown coloration (brown atrophy).

Gross features: heart is reduced in size & has dark brown myocardium. Coronaries appear tortuous & pericardial fat disappears.

Microscopic features: Brownish lipofuscin granules are seen in atrophic muscle fibers.

2) melanosis coli: this is brown black lipofuscin pigmentation of colonic mucosa occurring in patients with habitual intake of anthraquinone purgatives → increased lysosomal activity of intestinal macrophages from which this pigment is derived.



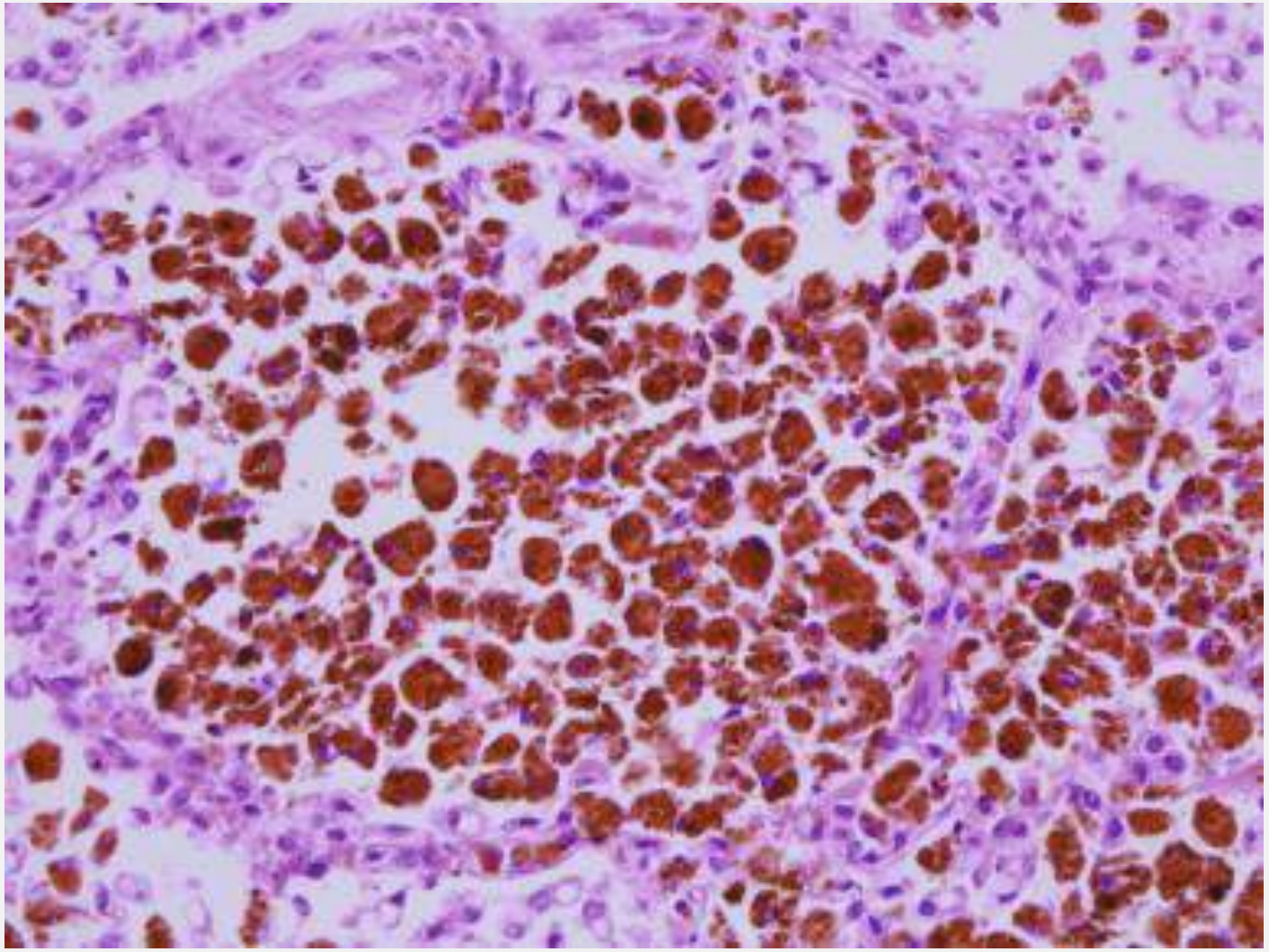
3- HAEMOGLAOBIN- DERIVED PIGMENTS

1)HAEMOSIDERIN

A brownish iron containing pigment. It gives positive Prussian blue reaction i.e. it gives a blue coloration when treated with potassium ferrocyanide & hydrochloric acid. The pigment occurs in localized or systemic forms:

LOCALIZED HAEMOSIDEROSIS

In areas of hemorrhage, haemosiderin appears inside & outside macrophages. The affected tissue appears brownish & firm due to fibrosis. Example: in cases of lung congestion and endometriosis



GENERALIZED HAEMOSIDEROSIS (HEMOCHROMATOSIS)

Pathogenesis of hemochromatosis: excess accumulation of body iron:

- Normally iron is absorbed from the intestine → blood → carried & stored inside the cells in association with a protein called apoferritin, forming together ferritin micelles
- If there is abnormal iron overload → excess ferritin micelles which aggregate → hemosiderin → abnormal brown pigmentation of the affected cells.
- Hemosiderin accumulates both in parenchymal cells and phagocytic cells (mononuclear phagocytes, reticuloendothelial cells).

- In primary hemochromatosis, there is a genetic error leading to excess absorption of dietary iron → prolonged iron overload (for years) → progressive damage of the affected parenchymal cells serious effects (see below).
- In secondary hemochromatosis , iron overload may be transient as in cases of repeated blood transfusions → mild transient parenchymal cell affection → less marked damage . however significant affection may occur in some of the secondary type such as iron overload due to chronic bone marrow hypofunction → impaired iron utilization → prolonged increase of blood iron.

Types of hemochromatosis:

a) Primary hemochromatosis (Bronzed Diabetes) :

Aetiology: iron overload due to an inborn error characterized by increased absorption of dietary iron. It is also called hereditary hemochromatosis (HHC). It mainly affects males and is rare in females (due to physiological loss of iron in menses and pregnancy). Iron accumulation is lifelong and around the 5^{th} decade, it will be severe enough to cause symptoms and complications.

Pathology & effects: plasma iron level is elevated. The parenchymal cells (and phagocytes) show hemosiderin deposits. Progressive parenchymal damage cell necrosis and fibrosis. The affected organ is enlarged, brown & firm. The main manifestations of primary haemochromatosis are:

1- skin: Bronzed coloration due to hemosiderin deposits & 2ry increase of melanin

2- diabetes mellitus due to pancreatic destruction. The pancreas is brownish & firm.

3-pigmentary cirrhosis due to liver destruction .liver is brown , firm and nodular.

Malignancy (hepatocellular carcinoma) complicates 10% of cases

4-heart is enlarged , pigmented and show fibrosis heart failure.

5- affection of other sites e,g. joint testis endocrine glands…….etc

b- Secondary hemochromatosis (secondary hemosiderosis)

Aetiology :iron overload due to

1-repeated blood transfusions.

2-hemolytic anemia.

3- impaired utilization of iron as in cases of bone marrow hypofunction.

Excess intake of iron e.g. with iron therapy.

Pathology : brown hemosiderin pigment appears in phagocytic cells & parenchymal cells e.g. of different body organs , but cellular damage is milder than in primary hemochromatosis.

2)OTHER HEMOGLOBIN DERIVED PIGMENTS

a)BILIRUBIN : An iron-free pigment. It is inceased in case of jaundice.

b) HAEMOZION: A brown iron containing pigment related to hematin. It is produced by parasites feeding on blood cells as in case of bilharziasis & malaria . the pigment is released in blood engulfed by macrophages of liver , spleen & other organs macrophage pigmentation called parasitic pigmentation.

II- EXTRACELLULAR DEPOSITIONS

CALCIUM

PATHOLOGICAL CALCIFICATION

Definition: deposition of calcium salts in sites other than bones and teeth

Grossly, the calcified tissue appears chalky white and hard.

Microscopically, calcification appears as blue granules (with hematoxylin & eosin)

Types of pathological calcification include:

DYSTROPHIC CALCIFICATION

Definition: this is calcification of dead or degenerated tissues in spite of a normal blood calcium level. It is the most common type of pathological calcification

Pathogenesis it is due to breakdown of organic phosphate → change of PH (alkalinity)of dead tissues and increase phosphatase activity → calcium deposition

Examples:

- Atherosclerosis
- Goitre
- Degenerated tumors as leiomyoma & necrotic tumors as breast cancer .
- Degenerated valves as in chronic Rheumatic valvulitis & in old age .
- Caseous tuberculous lesions
- Dead parasites and ova as bilharziasis
- Fat necrosis
- Thrombi , particularly venous thrombi (phlebolith) .
- Lithopedion (intrauterine dead calcified fetus).

2-METASTATIC CALCIFICATION

Definition this is calcification of normal tissues due to hypercalcaemia .

Pathogenesis : Causes of hypercalcemia include increased calcium absorption from intestine and / or increased calcium mobilization from bone as in cases of :

- Hyperparathyroidism including primary hyperparathyroidism (due parathyroid hyperplasia or functioning parathyroid tumors) & 2ry hyperparathyroidism in case of chronic renal failure .
- Bone destruction by malignant tumors (as myeloma &metastatic cancers).

- Hypervitaminosis D.
- Excessive intake of milk (rich in calcium) in patients with peptic ulcers .
- Systemic sarcoidosis .

  Sites : Any tissue , but principally tissues with relative alkalinity including :
- Tissues that secrete acidic products as stomach mucosa ,renal tubules (nephrocalcinosis)& lung alveolar walls
- Arterial walls (which are normally slightly alkaline) .

3- IDIOPATHIC CALCINOSIS

A rare type of calcification of unknown aetiology . it may be localized affection a focus of skin & soft tissue nodular masses of calcium (termed “tumoral calcinosis “) .It is rarely generalized (calcinosis universalis)affecting skin ,soft tissues & nerve .

4-Stones

Urinary stone ,biliary stones & salivary duct stones : See systemic pathology .

AMYLOIDOSIS

DEFINITION:

Amyloidosis (also called B fibrillosis) is extracellular deposition of amyloid substance . mainly in wall of blood vessels , basement membrane and along reticulin fibers.

Although protein in nature, it was termed amyloid i.e. starch-like because it reacts with iodine and sulphuric acid giving a blue color.

Staining of amyloid:

Gross staining is done on slices of the suspected organ e.g. on post mortem specimens.

1) lugols iodine stains amyloid dark brown and the rest of tissue pale yellow .

2) iodine and 1% sulphuric acid stain the amyloid blue.

Microscopic staining : can be done on paraffin or frozen sections:

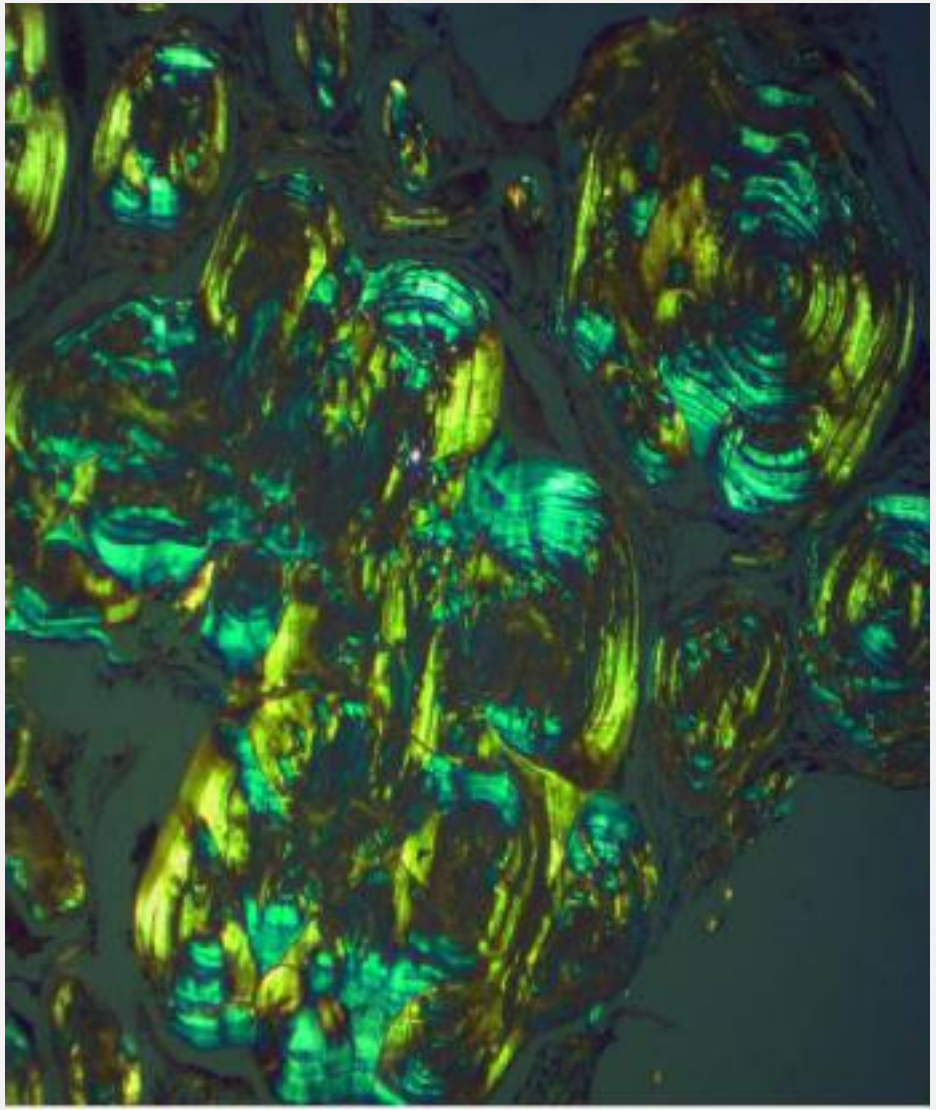
1)Hematoxylin & eosin stain : amyloid appears homogenous and eosinophilic (pale red)

2) Congo red stain : Amyloid is stained orange red. If the same section are examined under polarizing light , amyloid exhibits characteristic apple-green bipolar refringene.

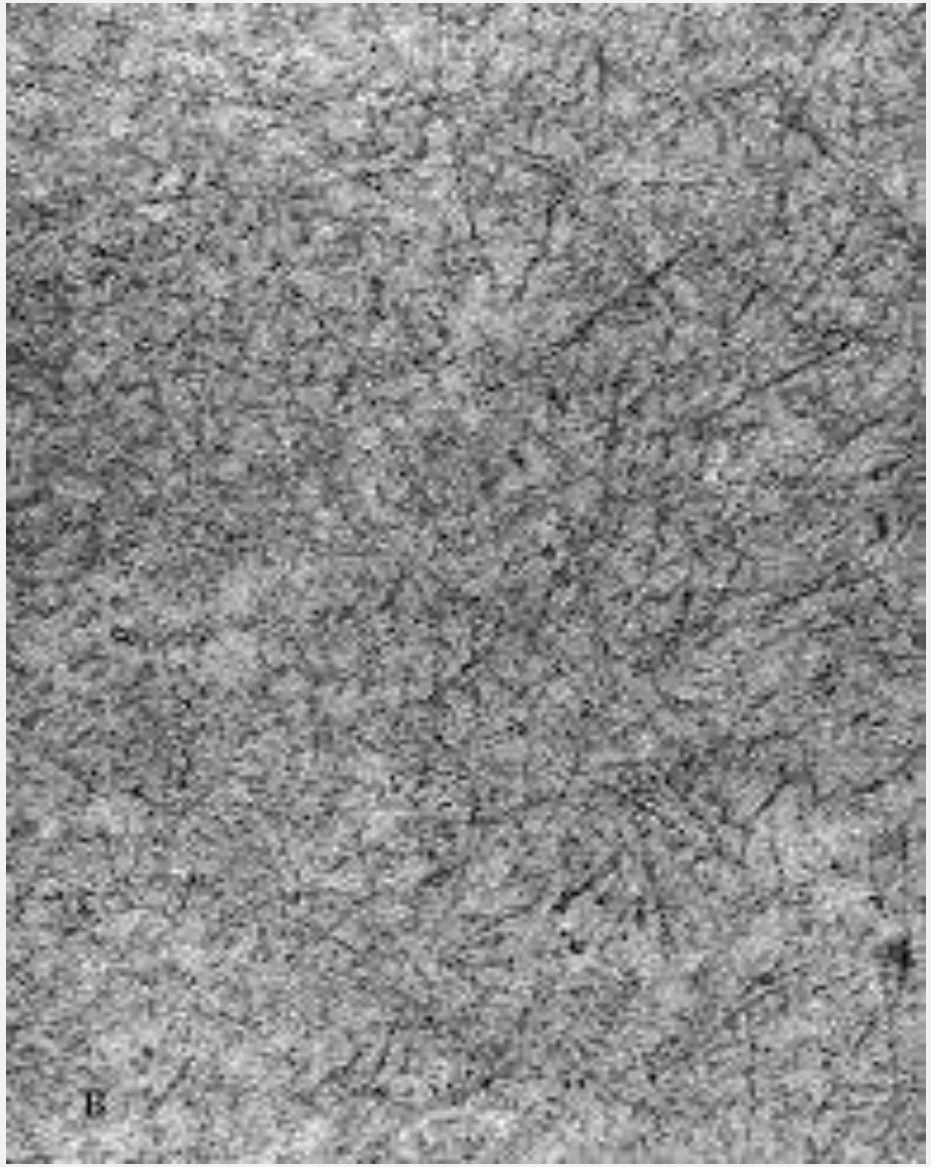
3) metachromatic stains as crystal violet or methyl violet stain the amyloid deposits rose red ,while the rest of tissue are stain violet.

DIAGNOSIS OF AMYLOIDOSIS DURING LIFE:

By biopsy from suspected sites as kidney. In case of suspected generalized amyloidosis biopsies are easiest from rectum and gingiva. Microscopic examination of biopsy specimens aided by special stains (as congo red)will diagnose the condition.



Congo red staining under polarizing light shows apple green birefringence



NATURE OF AMYLOID:

90% of the amyloid is a fibril protein & the remaining 10% is a glycoprotein called P component. Macrophages play an important role on amyloidosis by proteolytic cleavage of the precursor proteins → amyloid fibrils. Amyloid fibril proteins are of several types:

- *In case of systemic amyloidosis*, the amyloid fibril proteins may be:

  1) AL (amyloid light chain protein of immunoglobulins) . it is secreted by plasma cells in case of plasma cell neoplasms (known as plasmacytoma or myeloma)

2) AA (amyloid-associated protein). It is a non-immunoglobulin protein present as a precursor protein in serum called serum amyloid associated protein (SAA) secreted by the liver. Synthesis of SAA may be markedly increased in chronic destructive disease anywhere in the body as tuberculosis.

3) Less common proteins as B2 microglobulin & transthyretin (pre-albumin)

- *In case of localized amyloidosis*, amyloid is locally formed in the affected tissue e.g. procalcitonin in case of thyroid medullary (C cell) carcinoma ,AB2 protein in case of cerebral amyloidosis… etc (see below).

Types of amyloidosis

Systemic amyloidosis

- B cell dyscrasias (primary)
- Reactive systemic (secondary)
- Hereditary

hemodialysis associated amyloidosis

localized amyloidosis

- Senile amyloidosis
- Amyloid deposits within endocrine tumor
- Idiopathic localized amyloid deposits

TYPES OF AMYLOISOSIS:

1) Systemic (generalized) amyloidosis:

Many organs are affected. Most common causes of death are: renal failure, heart failure, malabsorption (when bowel is affected) &Addison's disease (when adrenal glands are involved). Types of generalized amyloidosis:

a)B Cell Dyscrasias (primary amyloidosis):

- AL is secreted due to abnormalities of B lymphocytes and plasma cells, as in cases of multiple myeloma (malignant neoplasm of plasma cells), where amyloidosis occurs in about 15% of these patients.
- It affects heart (causing heart failure), tongue, GIT , skeletal muscles as well as other organs as kidney.

b) Reactive systemic Amyloidosis (secondary Amyloidosis): AA Type:

- AA is increased causing generalized amyloidosis in the following chronic severe destructive conditions:
  - Chronic suppurations: e.g. chronic osteomyelitis, chronic lung abscess, chronic empyema & bronchiectasis
  - Granulomas as tuberculosis
  - Autoimmune diseases as ulcerative colitis and rheumatoid arthritis
  - Some malignant tumors as Hodgkin's disease &gastric carcinoma
- It most commonly affects kidneys, liver, spleen & adrenal glands.

c) Hereditary Amyloidosis: Several types. The amyloid protein is AA or transthyretin (prealbumin). It may be generalized (as in familial Mediterranean fever) or localized.

2) Hemodialysis-associated Amyloidosis : Affects up to 70% of patients with chronic renal failure subjected to chronic hemodialysis. It is due to deposition of the amyloid protein “B2 microglobulin” which is not filtered by normal dialysis membranes. These deposits are seen in joints, synovium and tendon sheaths.

3)Localized Amyloidosis:

a) Senile Amyloidosis: affects the vessels of the brain (gray matter) in cases if Alzheimer's disease (senile dementia). The amyloid protein is B2 amyloid deposits (AB2 protein)

b)Amyloid deposits within endocrine tumors: e.g. amyloid deposits within medullary carcinoma of thyroid. The amyloid protein is procalcitonin produced by the tumor cells.

c) Idiopathic localized amyloid deposits: may occur in any of several sites as larynx, tongue, urinary bladder, muscles, heart… etc. the amyloid protein is AL secreted by plasma cells which often exist around the amyloid deposits and therefore this from of amyloidosis is considered a localized form of B cell dyscrasias.

PATHOLOGY OF THE AFFECTED ORGANS:

1) THE KIDNEY:

Kidney amyloidosis is the most common and the most serious involvement in the disease.

Gross picture:

- Size: kidney is enlarged but in prolonged cases it may become small (contracted) due to ischemic changes.
- Cut section: pale gray waxy amyloid spots are seen. The cut surface is flat and the borders are sharp.
- Firm in consistency.
- Gross staining can be applied.

Microscopic Picture:

- Amyloid deposits are seen in:
  - Glomeruli: in the basement membranes of capillaries and in the mesangial matrix. In advanced cases the capillary lumens are obliterated.
  - Tubules: within their basement membranes and peritubular connective tissue.
  - Walls of vessels → vascular narrowing → ischemic contracture of the kidney.
- Amyloid appears homogenous. According to type of stain the appearance will be:
  - Hematoxylin and eosin stain pink and refractive.
  - Congo red stain → orange red amyloid → apple-green birefringence with polarizing light
  - Methyl violet stain → metachromatic rose red staining of amyloid, while other tissues are stained violet

Clinical effects:

- Nephrotic syndrome: this is proteinuria (due to glomerular affection) associated with hypoproteinaemia, and generalized oedema as well as hyperlipidemia and lipiduria.
- Polyuria (resembling diabetes insipidus) due to reduced water reabsorption.
- Hypertension and renal failure in advanced cases.

2) THE LIVER:

Gross picture: liver is enlarged and firm. Cut section shows pale gray waxy amyloid streaks. The cut surface is flat with sharp borders. Gross staining can be applied.

Microscopic picture: amyloid deposits (detected by hematoxylin and eosin stain and by special stains) are seen in the walls of arterioles and venules as well as in the perisinusoidal space (disse space), then progressively in the sinusoidal walls sinusoidal narrowing and pressure atrophy of the adjacent liver cells**.**

Clinical Effects:

Hepatic dysfunction is usually slight (due to great hepatic reserve). Liver failure is rare.

3) THE SPLEEN: Two patterns

a) Sago Spleen (focal or white pulp type): the splenic lymphoid follicles are affected where amyloid is deposited in the walls of central arterioles → moderate splenomegaly with mottled cut surface by pale gray waxy amyloid spots against the red pulp.

b) Diffuse Amyloid Spleen (diffuse or red pulp type): the red pulp is affected where amyloid is deposited in the walls of sinusoids → marked splenomegaly with uniformly pale gray waxy cut surface

4) HEART: May be a localized (usually in old age), or may be a part of generalized amyloidosis.

There is moderate cardiac enlargement. The typical pattern is subendocardial amyloid deposits, particularly in the atria. There are also amyloid deposits progressively occurring between the myocardial fibers, causing their pressure atrophy. Heart failure may complicate the condition.

5) THE ENDOCRINE GLANDS: in cases of generalized amyloidosis, many glands as the pituitary and adrenals may be affected. Clinical effects may not appear except in advanced cases, e.g. Addison's disease due to adrenal amyloidosis

6) THE GASTROOINTESTINAL TRACT: any part of the GIT can be affected.

- Tongue affection macroglossia.
- Intestinal affection mucosal atrophy, ulcerations, hemorrhages, malabsorption & diarrhea.

7) **ANY OTHER ORGAN: (**Skin. Respiratory passages, urinary bladder… etc)

MUCIN

Definition: pathological accumulation of mucopolysaccharides between connective tissue fibers.

Grossly: the affected tissue appears soft & gelatinous.

Microscopically: stellate shaped mesenchymal cells, embedded in pale mucinous matrix.

Examples:

1- myxedema.

2- mesenchymal tumors as leiomyoma, schwannoma, chondroma, chondrosarcoma & liposarcome.

URIC ACID & URATES

GOUT

Definition: disturbance in purine metabolism, leading to increase of serum uric acid &deposition of sodium urate crystals in tissues.

Aetiology:

1) Primary gout: A heterogeneous group with known enzyme defect.

Some cases have hereditary predisposition including a rare sex linked frim affecting males (Lesch-Nyhan syndrome)

2) Secondary gout due to excess nucleoprotein destruction as in chronic myeloid leukemia.

Pathology:

1) Increased serum uric acid (hyperuricemia) above 6 mg % (normal = 3-6 mg%)

2) Monosodium urate (MSU) crystal deposition leading to:

a) Acute arthritis. Joints (particularly the big toe) are severely inflamed microscopically there is dense exudation of neutrophils.

b) Chronic tophaceous arthritis: → excess deposition of MSU crystals in cartilage & synovium → chronic inflammation & fibrosis. Joint ankyloses may occur.

c) Tophi:

Grossly: these are small nodular lesions

Structurally they consist of aggregated urate crystals.

Microscopically there are deposits of amorphous material surrounded by chronic granulomatous inflammation rich in giant cells (foreign body granuloma).

Sites: these tophi appear in:

- Joint structures: synovium, tendons, ligaments & cartilage → (cartilage erosion)
- Cartilage of the nose and ear pinna → ulceration of the overlying skin
- Subcutaneous , particularly in eye lids → ulceration of the overlying skin
- Other sites as cardiac valves & interstitial tissue of kidney → gouty nephropathy

d) gouty nephropathy: it is characterized by

- Tophi in interstitial tissue of kidneys
- Uric acid/ urate stones in pelvis
- Renal failure may occur.

Growth disturbances

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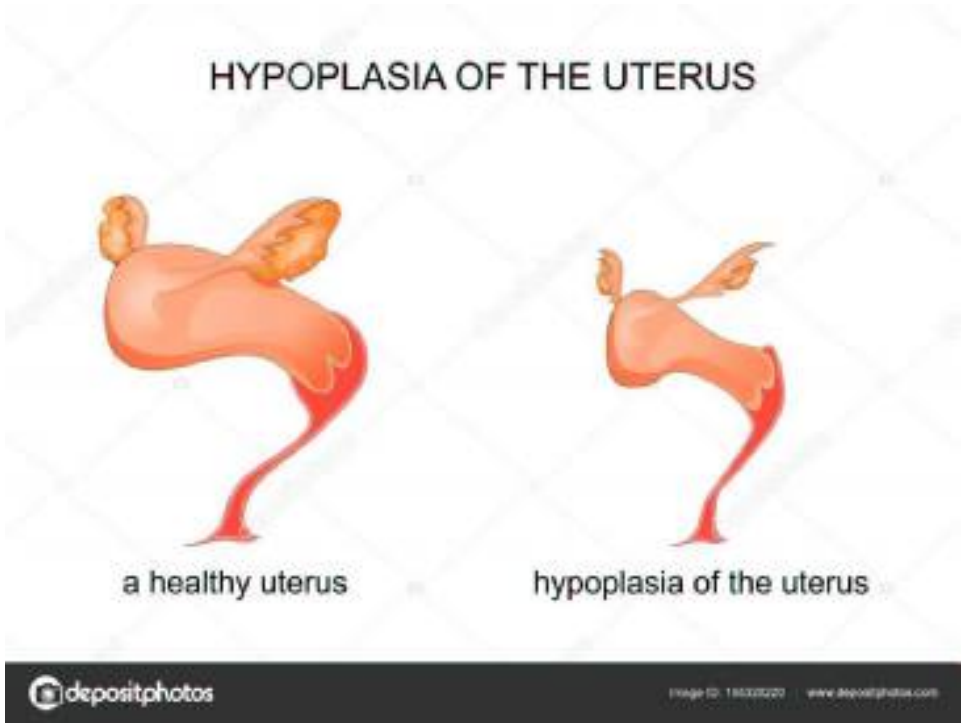
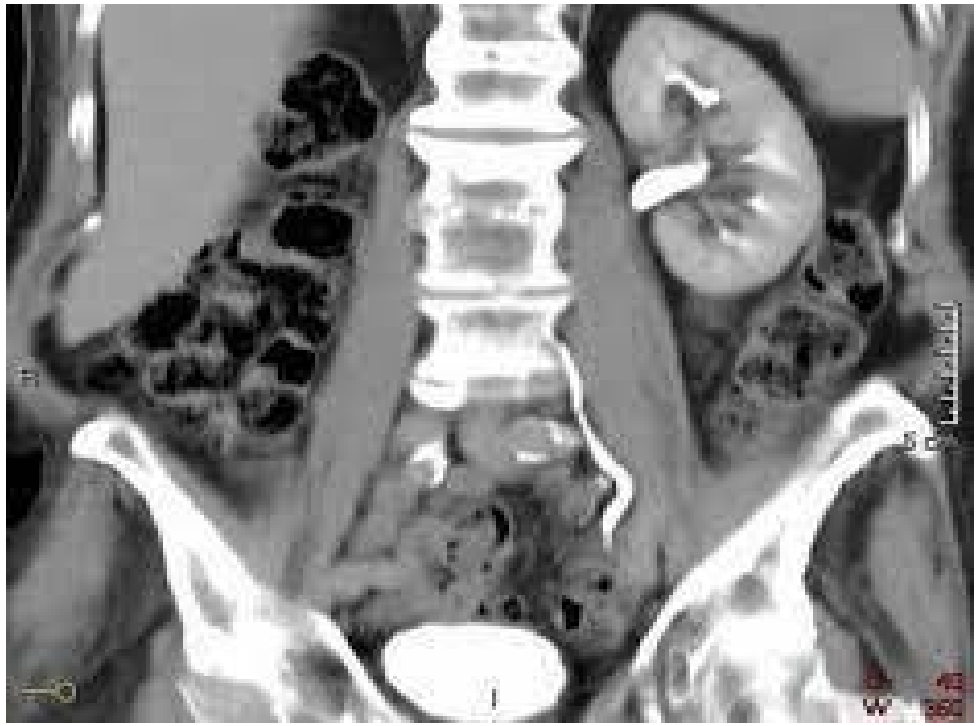
GROWTH DISTURBANCES

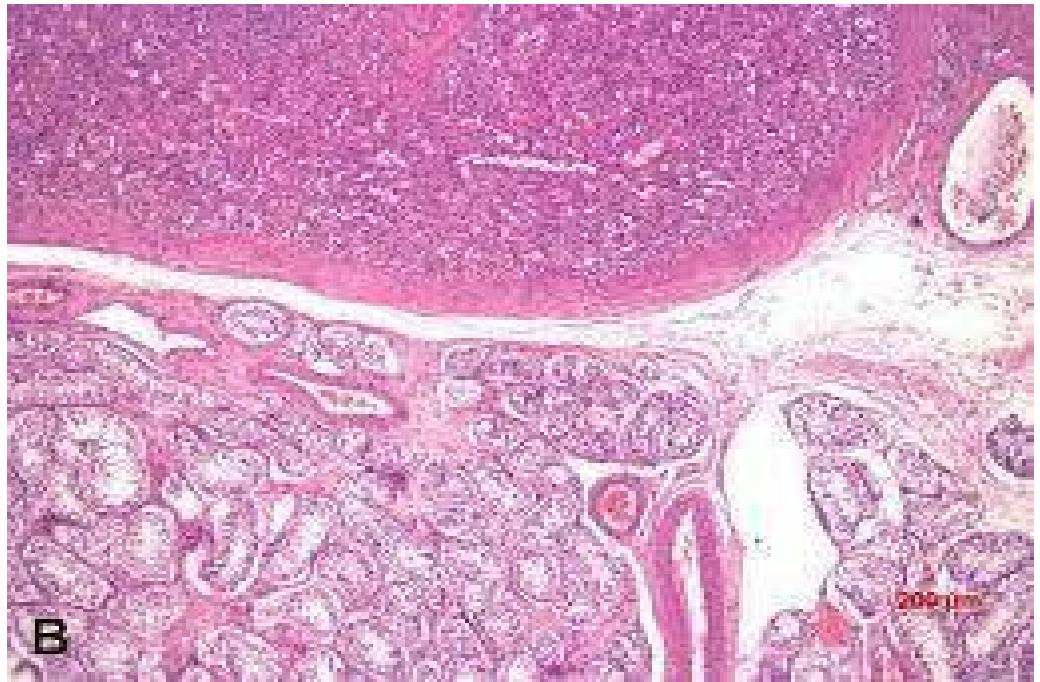
Disturbances or disorders of growth may be:

A) CONGENITAL: such as:

- Agenesis: failure of development of an organ (or part of it) e.g. absent kidney
- Hypoplasia: undersized organ e.g. hypoplastic kidney and infantile uterus.
- Aplasia: this is failure of cell growth .it may represent severe hypoplasia. The affected organ is rudimentary (e.g. rudimentary kidney, rudimentary tooth…)
- Other congenital anomalies as supernumerary organ (e.g. supernumerary kidney), organ duplication (as intestine), ectopic tissue (e.g. parathyroid within thymus), fused organs (as gonadosplenic fusion) …. etc.


HYPOPLASIA OF THE UTERUS
a healthy uterus
hypoplasia of the uterus
depositphotos




B

B) ACQUIRED: yhporta (1 (2Hypertrophy (3hyperplasia (4Metaplasia (5 Dysplasia 6) neoplasia

ATROPHY

Definition:

Cellular atrophy is acquired shrinkage of cell size due to decrease cell anabolism and/or increase cell catabolism .The cell remain alive with reduce organelles .

Tissue or organ atrophy is decrease in its size and weight after it reached its full development . This is either due to cell atrophy or cell loss. The atrophic part may be replaced by fibrous tissue or adipose tissue.

Aetiology and types:

1) physiological atrophy:

a) localized atrophy e.g. atrophy of thymus after puberty & atrophy of mammary glands and ovaries after menopause due to diminished hormone stimulation.

b) Generalized atrophy due to age may be physiological or pathological :

physiological aging of cells is an age related disorder (senile atrophy), believed do be due to decreased oxidative phosphorylation by the aged mitochondria → decreased energy and decrease capacity of uptake of nutrients

pathological premature aging (progeria): this early (premature) aging in young individuals due to error in DNA replication → reduce cell viability

pathological Atrophy:

a)Generalized atrophy ; it affects all tissues and organs (including the brain). Heart is small and shows brown atrophy, skin is wrinkled due to loss of elastic fibers , bones & muscle are week……..etc. cuases include:

- Decrease anabolism in case of chronic malnutrition and starvation.
- Increase catabolism as in advance stages of malignancy (cachexia) , T.B & thyrotoxicosis.
- Progeria.

b)localized atrophy:

- diffuse atrophy: it is due to decrease workload e.g. atrophy of limb muscles following prolonged immobilization after bone fracture and atrophy of non-functioning renal tubules in case of chronic glomerulonephritis.
- Neuropathic atrophy it is due to loss of innervation e.g. atrophy of muscles of affected limb in case of poliomyelitis.
- Hormonal atrophy: it is due to loss of endocrine stimulation e.g. breast atrophy following surgical resection of ovaries

- Atrophy due to diminished blood supply: it includes

1- pressure atrophy due to pressure on the cells and their feeding vessels from outside e.g. atrophy of liver cells in cases of amyloidosis & atrophy of the vertebrae (but not of the avascular intervertebral discs) due to pressure by aortic aneurysm.

2-vascular atrophy this is atrophy of a tissue or organ due to diminished blood supply caused by a vascular disease causing narrowing of the vessels e.g. kidney atrophy due to atherosclerosis of renal artery.

- Acquired aplasia (cell loss) which commonly idiopathic (unknown cause) as testicular germ cell aplasia (sertoli cell only syndrome) which is a common causes of male infertility and bone marrow aplasia → aplastic anemia

HYPERTROPHY

Definition:

Hypertrophy is increase in the size of the cell; consequently leading to increase in the size of the affected tissue or organ. Cell hypertrophy is due to increased protein synthesis & occurs to meet increased functional demands. Pure hypertrophy occurs in muscles, but in other tissues hypertrophy is usually associated with hyperplasia.

Aetiology and types :

1- physiological Hypertrophy: the best examples include:

a) Pregnant uterus due to hormonal stimulation.
b) Hypertrophy of striated muscles in muscle builders.

2- Pathological Hypertrophy:

a) Adaptive type: it affects the muscle coat of hollow organs due to increased entra-luminal pressure. Examples:

- Left ventricular hypertrophy due to hypertension or aortic valve stenosis
- Urinary bladder hypertrophy due to stricture of the bladder neck (caused by bilhariziasis, tumor or others).
- Hypertrophy of intestinal wall in cases if chronic intestinal obstruction.
- Hypertrophy of stomach in case of pyloric stenosis

b) Compensatory type: if one of a paired organ is out of function or surgically removed, the other organ undergoes compensatory Hypertrophy e.g. kidney enlargement when the other kidney is surgically removed.

HYPERPLASIA

Definition:

Hypertrophy is increase in the number of cells, leading to increase in the size of the affected tissue or organ. It is usually accompanied by some degree of Hypertrophy. It can occur only in cells capable of division i.e. all cells except nerve cells, skeletal and cardiac muscle cells

Aetiology and Types:

1- Physiological Hyperplasia: e.g. mammary glands &genitalia at puberty (physiological hormonal hyperplasia)

2- Pathological Hyperplasia: Hyperplasia in pathological states includes:

a) Hormonal hyperplasia e.g. endometrial &mammary hyperplasia due to excessive oestrogen stimulation

b) Irritation hyperplasia of lymphoid tissue in response to antigenic stimulation

c) Compensatory hyperplasia (considered physiological or pathological). Examples:

- Bone marrow hyperplasia following hemorrhage or hemolysis
- Hyperplasia of the liver after partial hepatectomy → progressive restoration of the normal liver weight in few weeks. Awareness of liver hyperplasia has encouraged partial liver transplantation, since hyperplasia of the remaining liver in the donor & of the transplanted part in the recipient will restore normal liver size in both. Hyperplasia is stimulated by growth factors (e.g. TGF-a) produced by liver cells . eventual cessation of cell growth is caused by growth inhibitors (e.g. TGF-B) produced by the non-parenchymal cells of the liver.

Differences between Hyperplasia and Neoplasia:

HYPERPLASIA	NEOPLASIA
• Excited by a stimulus • Reversible, i.e. cell proliferation stops if the stimulus abates. • Proliferated cells are normal-shaped • May be useful as compensatory hyperplasia.	• A stimulus may not be detected • Irreversible, i.e. cell proliferation is unlimited & progresses, even if any evoking stimulus has stopped. • Proliferated cells are abnormal shaped (in case of malignant neoplasia • harmful

Although hyperplasia is distinctly different from neoplasia, it may be precancerous i.e. pathological hyperplasia may lead to malignant neoplasia.

METAPLASIA

Definition:

Metaplasia is the transformation of one mature differentiated cell type into another of the same category. It is a reversible process that represents adaptive substitution of cells more sensitive to stress by other more resistant cell types that can better withstand the adverse environment . like hyperplasia, it is precancerous.

Aetiology and types:

1- Epithelial Metaplasia: the most common examples include:

a) Squamous metaplasia: this is the transformation of columnar or transitional cells into stratified squamous epithelium. This is some times followed by leukoplakia.

Examples of Squamous metaplasia:

- urinary bladder mucosa in case of bilharzial cystitis.
- Tracheal and bronchial mucosa in smokers or vitamin a deficiency.
- Bile duct epithelium at sites of impacted stones
- Endocervical mucosa in case of chronic cervicitis

Leukoplakia:

- These are thick irregular white mucosal patches usually related to chronic irritation. They are precancerous lesions that may → squamous cell carcinoma
- The most common sites are tongue, vulva and urinary bladder
- Microscopically, leukoplakia appears as hyperkeratotic thick stratified squamous epithelium. The underlying subepithelial layer shows chronic inflammation.
- Leukoplakia either represents squamous metaplasia with keratinization (e.g. in case of leukoplakia of the urinary bladder) or it may represent hyperplasia with keratin formation if it arises in mucous membranes already composed of stratified squamous epithelium (as tongue and vulva).

b) Intestinal Metaplasia: of the gastric mucosa at the edges of peptic ulcers.

2- Mesenchymal Metaplasia: Fibroblasts may become transformed into chondroblasts osteoblasts; thus producing bone or cartilage in abnormal sites. Theregore, soft tissue ossification can occur in foci of injury.

Localized Myositis Ossificans may represent an example of mesenchymal metaplasia:

- This condition is characterized by muscle necrosis(may be traumatic).
- The damaged muscle is infiltrated by granulation tissue.
- Fibroblasts of the granulation tissue may show osteoblastic metaplasia leading to ossification.

Old fibrotic tuberculous lesions may also show osseous metaplasia

3- **Serosal metaplasia:** mesothelial cells can change into glandular ,stratified or other epithelial types. Examples in females, the peritoneum may develop endometrial tissue (endometriosis) due to serosal metaplasia

4- **Tumor metaplasia:** it may be epithelial metaplasia e.g. glandular ,stratified carcinoma (adenocarcinoma) may show areas of squamous metaplasia (referred to as adenoacanthoma). Stromal metaplasia (e.g. cartilaginous and/ or osseous metaplasia) may occur in some tumors.

DYSPLASIA

Definition:

Dysplasia is a non-neoplastic disordered proliferation of cells; usually induced by prolonged cell irritation. Dysplasia literally means any abnormal growth. It is a microscopic change with no specific gross changes. It chiefly affects epithelial cells.

Microscopic Characteristics:

- It is characterized by loss of uniformity of the individual cells accompanied by loss of their architectural orientation (polarity). Dysplastic cells are atypical looking.

  They show pleomorphism (variation in size and shape), enlarged dark (hyperchromatic) nuclei and increased mitotic activity.
- Degree of dysplasia: According to degree of cell atypia and extent of involvement, dysplasia is graded

CARCINOMA IN SITU

(intraepithelial Neoplasia Intraepithelial Carcinoma, Pre-invasive Carcinoma)

Definition:

Carcinoma in situ (CIS) represents a preinvasive stage of cancer & is characterized by severe epithelial atypia (severe dysplasia) without invasion of the basement membrans CIS is essentially a microscopic change. Once the basement membrane is invaded the CIS phase ends and actual (invasive) malignant tumor starts.

Pathological Features

Gross features:

- CIS may be difficult to detect grossly.
- However it may cause a thick indurated patch (as CIS of cervix or bladder)
- Rarely CIS may cause a mass as in cases of mammary ducts.

Microscopic features: CIS is essentially a microscopic change characterized by:

- Diffuse cellular atypia involving the whole thickness of the affected epithelium. The cells are pleomorphic with dark nuclei and numerous mitoses i.e cytologically malignant. Their architectural orientation (polarity) is disturbed.
- No invasion of basement membrane.

Fats: progression into invasive carcinoma occurs after a variable tine (usually years).

Examples of common sites of CIS

1- Mammary gland 2- Bladder 3- Cervix & endometrium 4- GIT 5- Skin.

inflammation

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Inflammation

Definition:

Inflammation is a reaction of living vascularized tissue to injury.

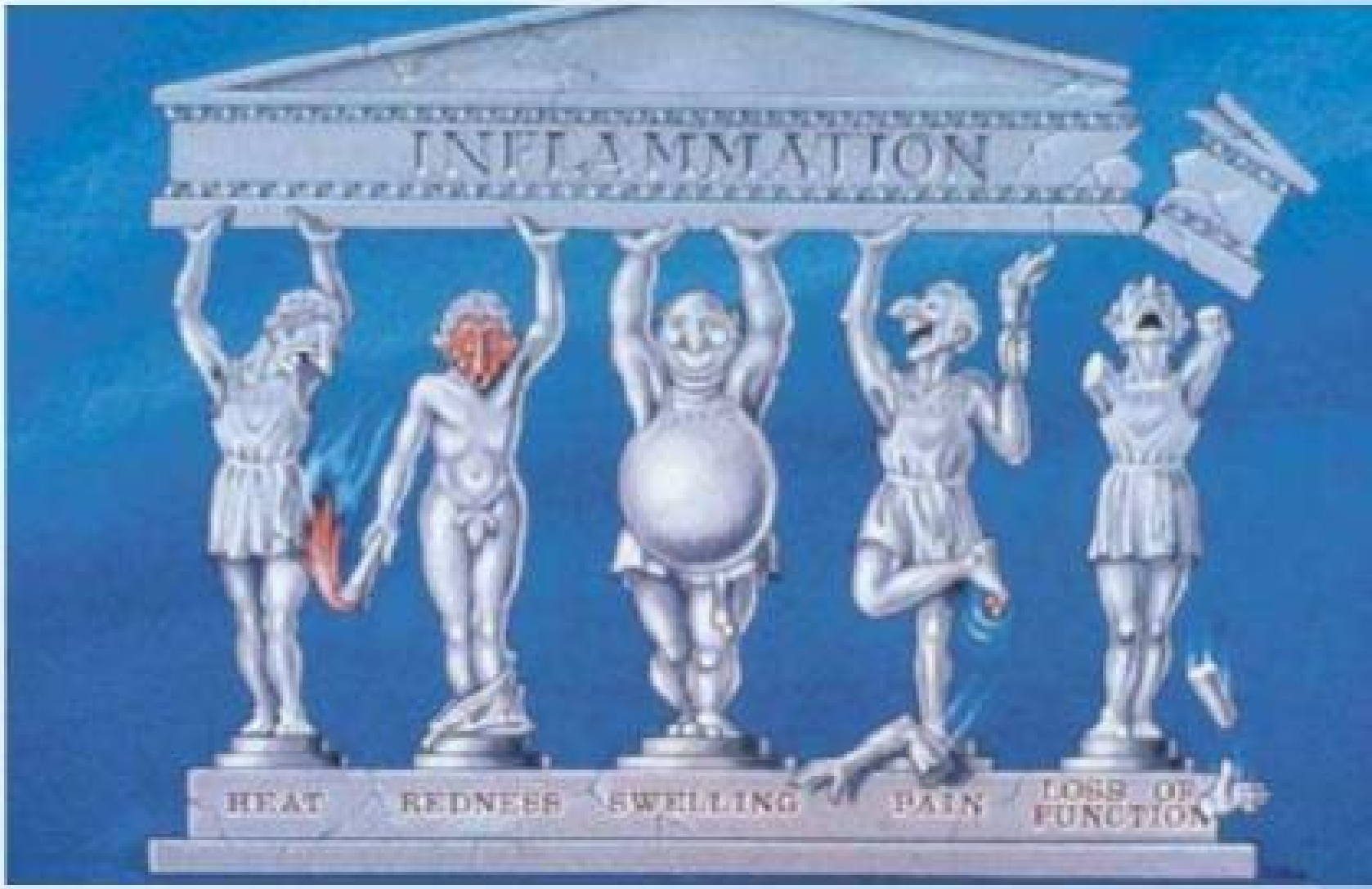
It is essentially characterized by local vascular change resulting in formation of fluid and cellular exudate , followed by lymphatic dilation (due to absorption of the exudates)& a local cellular reaction to tissue histiocytes(to phagocytize the inflammatory products

Thus inflammation partly represents a protective response aiming at disposal of the initial cause of injury (irritant as microbes or toxin) and also disposal of the consequences of such injury(e.g necrotic cells)

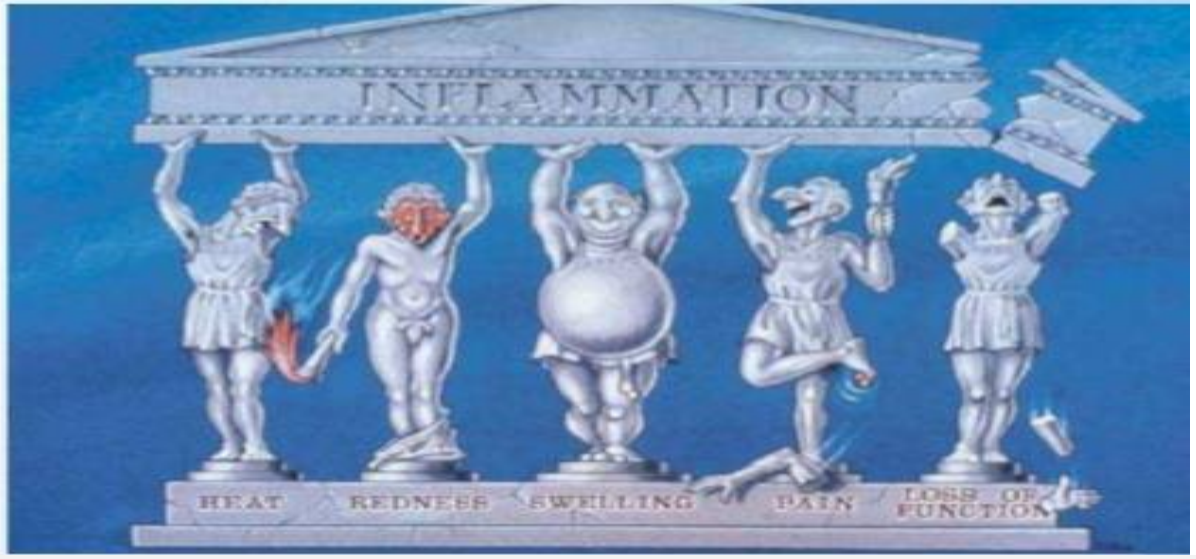
In spite of its protective nature, inflammation may have adverse effect(e.g pain, thrombosis ,perforation).

The suffix itis is added to the organ to denote its inflammation e.g tonsillitis , appendicitis, colitis ,hepatitis……

Inflammation



Inflammation



Historical Highlights

Although clinical features of inflammation were described in an Egyptian papyrus dated around 3000 BC, Celsus, a Roman writer of the first century AD, first listed the four cardinal signs of inflammation: *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). These signs are hallmarks of acute inflammation. A fifth clinical sign, loss of function *(functio laesa)*, was added by Rudolf Virchow in the 19th century. In 1793 the Scottish surgeon John Hunter noted

AETIOLOGY: injurious agents(irritants) including:

1-Infectious(living) irritant: bacteria & their toxins ,viruses , fungi & parasites

2-physical irritants as heat, cold and radiation

3_mechanical irritant as trauma

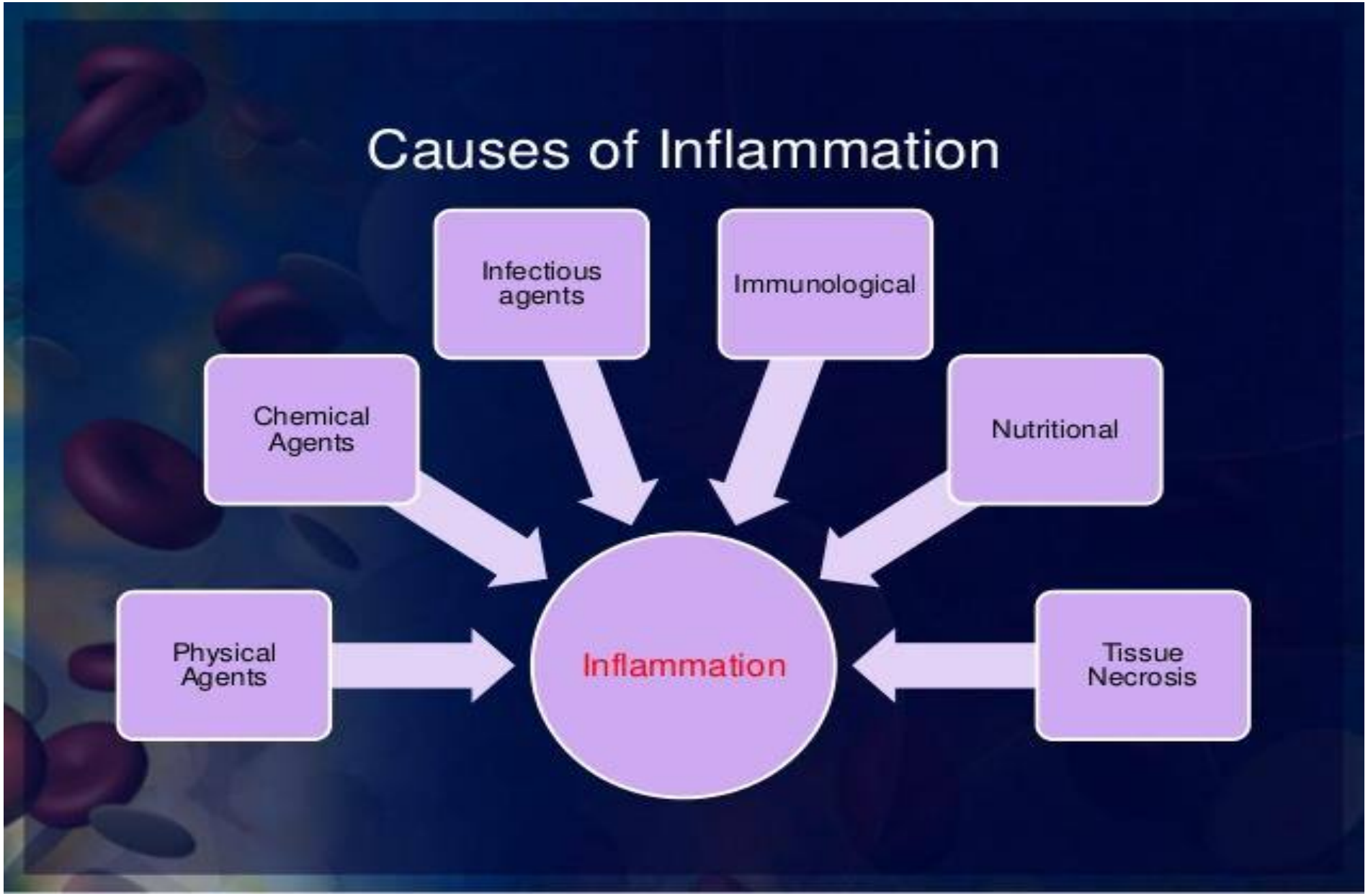
4_chemical irritant as acids , alkalies , inorganic and organic poisons

5-irritantion by exposure to antigen leading to hypersensitivity reaction

6-Nutritional imbalance.

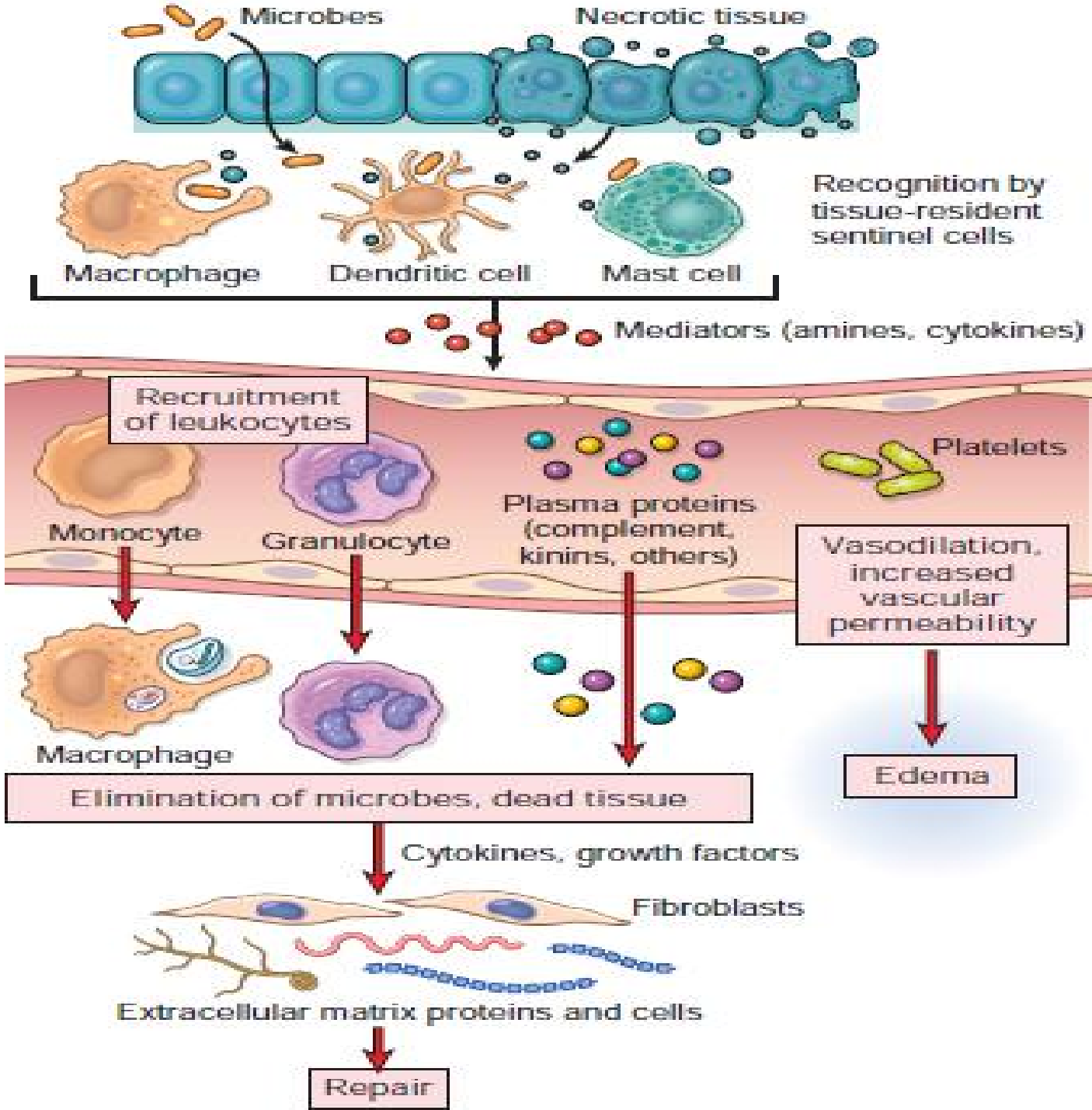
TYPES OF INFLAMMATION:

1-ACUTE 2-CHRONIC 3-SUBACUTE


Causes of Inflammation
Infectious agents
Immunological
Chemical Agents
Nutritional
Physical Agents
Inflammation
Tissue Necrosis

The steps of the inflammatory response can be remembered as the five Rs:

(1) Recognition of the injurious agent,
(2) Recruitment of leukocytes,
(3) Removal of the agent,
(4) Regulation (control) of the response,
(5) Resolution (repair).



Acute inflammation:

local changes in acute inflammation:

I) Local tissue damage & release of chemical mediators

II)LOCAL VASCULAR CHANGES

III)THE INFLAMMATORY CELLULAR EXUDATE

IV)ACTIVATION OF TISSUE HISTIOCYTES

Systemic (general)change in acute inflammation:

I) leukocytosis

II) fever

Local signs & symptoms of acute inflammation.

Fate of acute inflammation.

Types of acute inflammation.

l)Local tissue damage & release of chemical mediators:

At the site of injury ,there are some degenerated and necrotic cells. Accompanied by release of chemical substances(chemical mediators) that control the inflammatory response. These mediators may be derived from cells, plasma or bacteria.

Chemical mediators

Types of Chemical mediators:

I- cell derived chemical mediators:

1-vasoactive amines e.g histamine , serotonin

2-arachidonic acid metabolites e.g prostaglandin , leukotrienes

3-cytokines e.g lymphokines , monokines

4-lysosomal enzymes

5-platelet activating factors

II-plasma factors:

1-kinins as bradykinin

2-complement system

3-the clotting system

4-the fibrinolytic system

III- Bacterial products

Effects of chemical mediators:

1-Vasodilatation e,g by histamine & prostaglandins

2-Increase vascular permeability e.g by histamine & prostaglandins

3-Chemotaxis

4-Other effect as fever , leukocytosis and pain

II)Local vascular changes

THE VASCULAR phase of the inflammatory response

Including the following sequence:

1-transient vasoconstriction: due to irritation of the vessel wall stimulation of the vasoconstrictor nerves. It lasts for seconds or minutes followed by vasodilation

2-vasodilation:

Caused by action of chemical mediators as histamine on vessel wall

It affects arterioles , capillaries and venules and lead to opening of capillary bed

The increase blood flow (hyperemia) → redness & hotness of inflamed area (flare)

3-increase vascular permeability and formation of exudate:

Mechanism

Endothelial cells contraction & retraction (by chemical mediators) widening of the intercellular junction creating gaps between the endothelial cells

Endothelial injury

It lead to vascular leakage → fluid exudate

4-Vascular slowing(stasis):this is local slowing of the circulation in the area:
It is due to :
-Increase blood viscosity due to vascular leakage.it is most important cause.
Opening of capillary bed.-
It is an important step allowing for leukocyte excudation
It may have an adverse effect since vascular stasis can lead to thrombosis

The vascular changes lead to formation of exudate:

Formation of the inflammatory fluid excudate

Mechanism of formation & composition:

1. Increase in capillary hydrostatic pressure(due to increased blood flow)
2. Increased vascular permeability leakage of fluid rich in plasma proteins , particular fibrinogen , which has a protein content 3gm/dl and specific gravity 1015 . This protein rich fluid is called exudate .it differs from the normal tissue fluid or transudate which has protein 1g/dl & lower specific gravity 1015.
3. Reduced intravascular osmotic pressure (OP) & increased interstitial OP; both are due to loss of plasma proteins in the exudate

The amount of fluid exudate :is influenced by many factors such as :
Type of tissue Type of irritant

Functions of inflammatory fluid exudate:

1-dilutes bacterial toxins & chemical irritant

2-brings antibodies to the area as opsonine ,antitoxins , bacteriolysin and other……

3-brings chemical mediators derived from plasma e.g complement

4-contains fibrinogen → fibrin (by activation of the clotting system)

Function of fibrin :

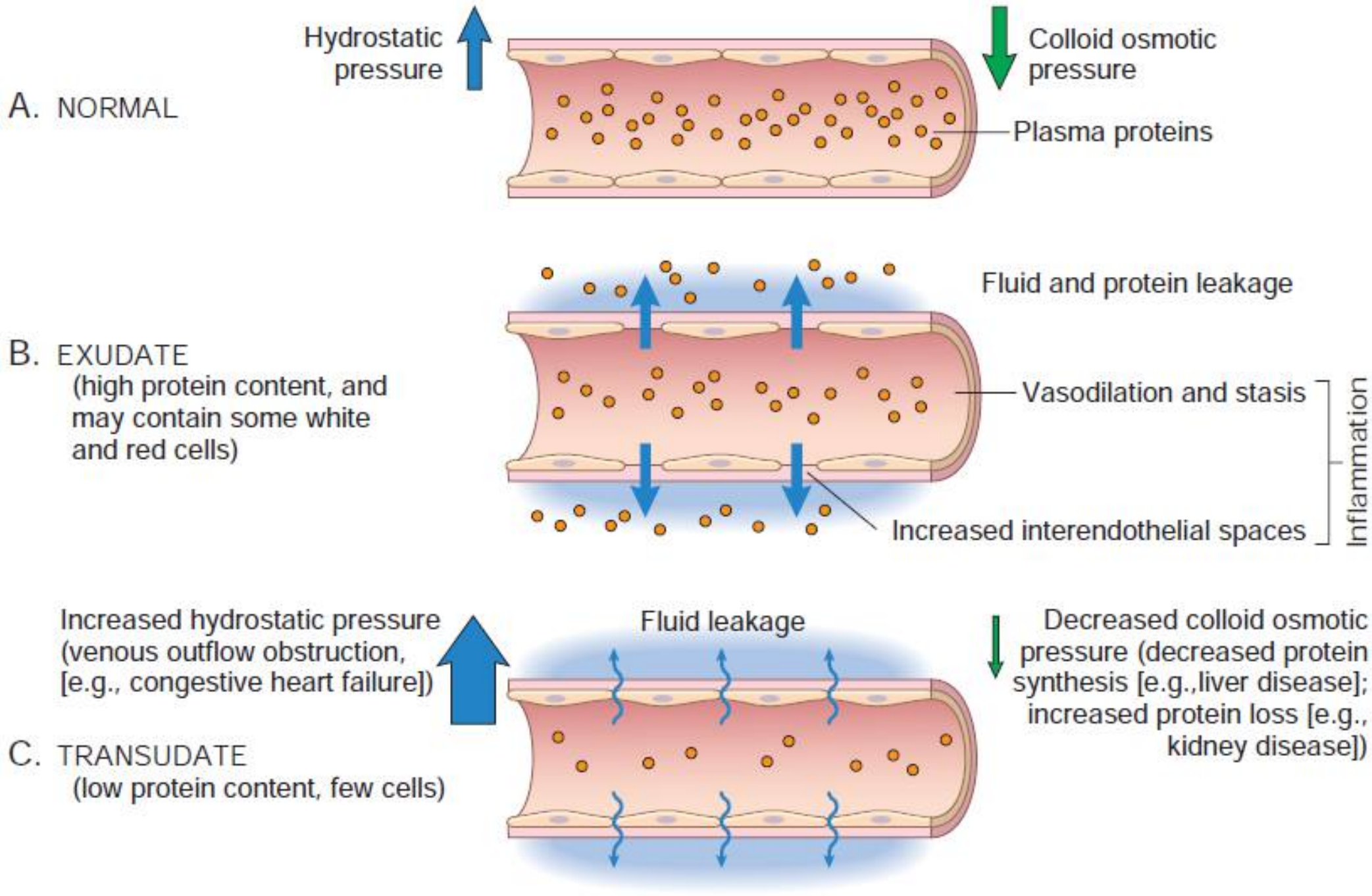
-helps localizing infection by surrounding the inflamed area and block some lymphatics

-forms a network upon which phagocytic cells can move towards their target

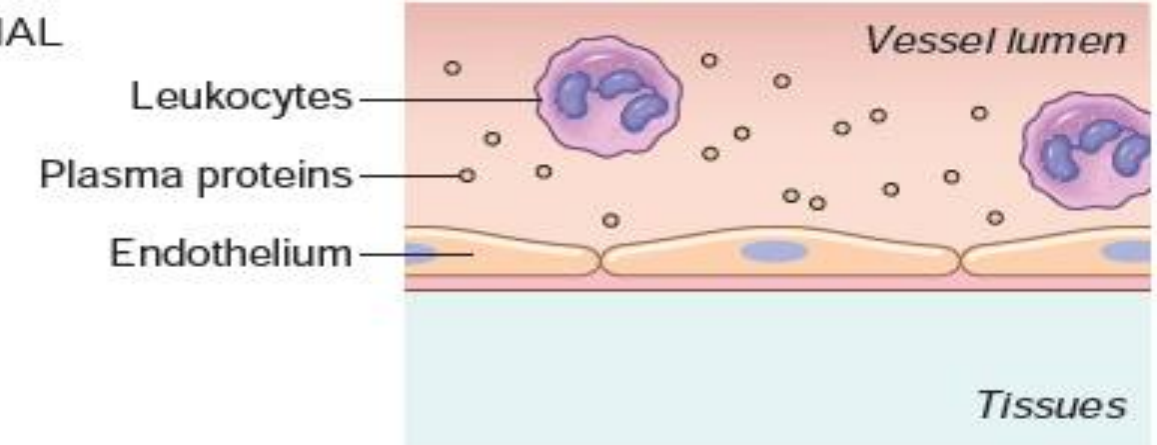
-fibrin also allows movement of proliferating fibroblast during the process of repair

5-supplies nutrients of inflammatory cells

6-if finally drains the products of inflammation

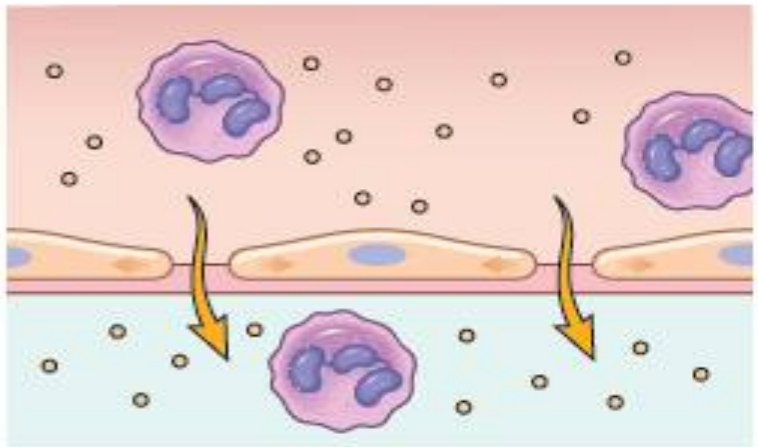

A. NORMAL
Hydrostatic pressure
Colloid osmotic pressure
Plasma proteins
B. EXUDATE
(high protein content, and may contain some white and red cells)
Fluid and protein leakage
Vasodilation and stasis
Increased interendothelial spaces
Inflammation
Increased hydrostatic pressure (venous outflow obstruction, [e.g., congestive heart failure])
C. TRANSUDATE
(low protein content, few cells)
Fluid leakage
Decreased colloid osmotic pressure (decreased protein synthesis [e.g.,liver disease]; increased protein loss [e.g., kidney disease])

A. NORMAL



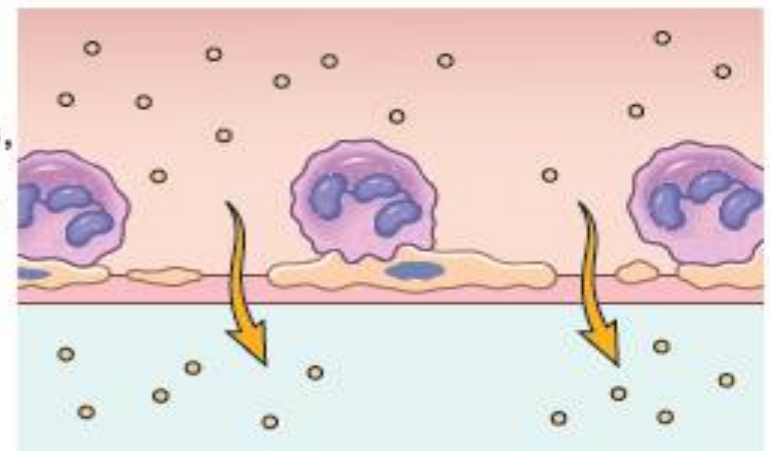
B. RETRACTION OF ENDOTHELIAL CELLS

- Induced by histamine, other mediators
- Rapid and short-lived (minutes)



C. ENDOTHELIAL INJURY

- Caused by thermal burns, some microbial toxins
- Rapid; may be long-lived (hours to days)



Fate:

Fluid exudate is absorbed by lymphatics . if viable bacteria exist in the exudate they may cause inflammation of lymphatic vessels(lymphangitis) and/or the draining lymph nodes (lymphadenitis).bacteria through lymphatics may reach the blood causing bacteremia , toxemia , pyaemia , or septicemia

inflammation

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The inflammatory cellular exudate
(THE CELLULAR PHASE OF THE IMFLAMMATORY RESPONSE)

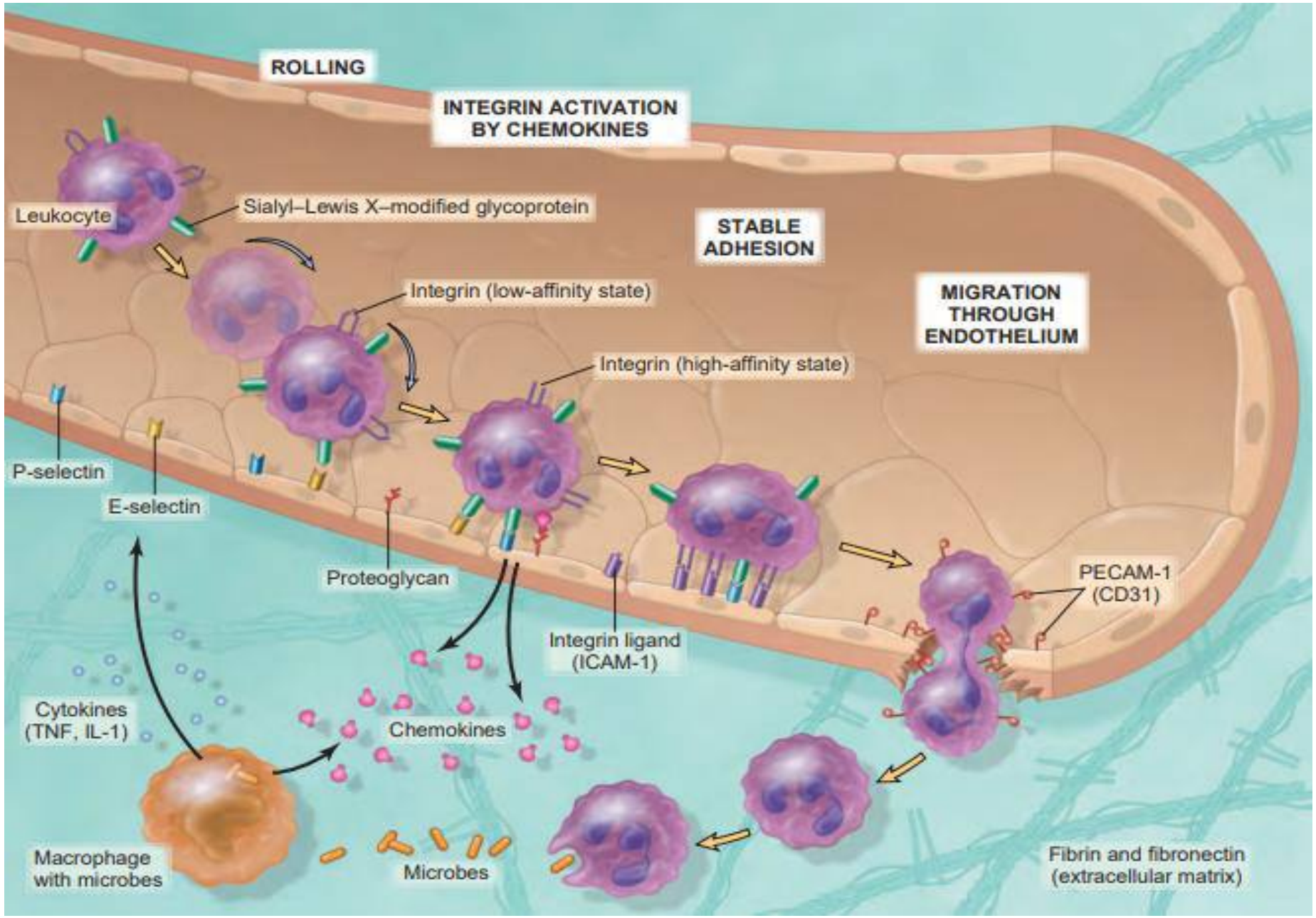
The cellular phase comprises the following steps:

1- Margination and pavementing of leucocytes:

•In normal flowing blood, erythrocytes and leucocytes are confined to the central (axial) column surrounded by plasma.

•When blood slowing occurs, some leukocytes (mainly neutrophils &monocytes fall out of the central column and begin to line the endothelium (margination)

•Adhesion (pavementing) of the marginating leukocytes to the endothelial surface occurs. Adhesion is achieved by complementary adhesive molecules (receptors) on the surfaces of leukocytes and endothelial cells in a way like a key and lock. These receptors include selectins, immunoglobulins and integrins. Adhesion is very important for leukocyte emigration


ROLLING
INTEGRIN ACTIVATION BY CHEMOKINES
STABLE ADHESION
MIGRATION THROUGH ENDOTHELIUM
Leukocyte
Sialyl–Lewis X–modified glycoprotein
Integrin (low-affinity state)
Integrin (high-affinity state)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
PECAM-1 (CD31)
Cytokines (TNF, IL-1)
Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)

Therefore defective adhesion → defective emigration → poor phagocytosis recurrent infections. There are genetic conditions characterizes by poor leukocyte adhesion such as type 1 leukocyte adhesion deficiency (integrin error) & type 2 leukocyte adhesion deficiency (selectin error)

2- Emigration of leucocytes (neutrophils &monocytes).

•Once the leukocytes adhere to the endothelium, they gain stability, allowing them to insert pseudopodia into the junction between the endothelial cells, eventually succeeding in traversing the basement membrane and escape into the extravascular space (emigration).

•In most types of acute inflammation, neutrophils (also called polymorphnuclear neutrophils, PMNs or microphages) emigrate first, followed 24 hours later by monocytes (these together with tissue histiocytes are called macrophages). It has to be noted that monocytes emigrate after neutrophils, partly because neutrophils release chemotactic (attracting) factors for monocytes.

3- Passive escape of red cells (diapedesis) :

Occasional passive emigration of red cells may occur, being mechanically pushed by the emigrating leukocytes (diapedesis). No significance is known for this process.

4-Chemotaxis:

•It is the directed movement of emigrating leukocytes to the site of injury. The aim of this movement is to reach the organisms or particles to be phagocytized by these leukocytes

•Both of emigration & chemotaxis are controlled by chemotactic factors:

a) chemotactic factors for neutrophils include bacterial products (mainly derived from cocci), complement components particularly C5a &C3a, neutrophil components , lymphokines & others.

b) chemotactic factors for monocytes include bacterial products (mainly derived from bacilli), complement components particularly C5a &C3a, neutrophil components , lymphokines & others.

•**Mechanism of attraction & movement of leukocytes towards their target includes:**

a) chemotactic agents bind to specific receptors on the cell membranes of the leukocytes → activation of the enzyme phospholipase C.

b) activation of phospholipase C → release of calcium from both the intracellular & extracellular stores. this calcium activates intracellular contractile proteins (tubulin and actin) leading to active cell movement as well as extracellular contractile proteins (laminin &fibronectin) leading to passive cell movement.

3- Phagocytosis:

•**Definition & mechanism of phagocytosis:** phagocytosis is the process by which the phagocytic cells recognize then engulf abnormal particles such as bacteria, dead cells, fibrin and foreign bodies, followed by their degradation:

a) recognition & attachment of bacteria (opsonisation): bacteria are coated by an opsonin which is an immunoglobulin or complement factor

b) Engulfment: phagocytic leukocytes surround the opsonised bacteria & send engulfed . fusion of pseudopodia phagocytic vacuole (phagosome).

Phagosome fusion with the limiting membrane of the lysosomal granules Discharge of granule content phagolysosome bacterial degradation.

C) degradation : killing bacteria may be done through :

I) oxygen dependent mechanism: formation of hydrogen peroxide or superoxide which bactericidal.

ii) oxygen independent mechanism: lysosome hydrolyzes bacterial wall glycoprotein a powerful bactericidal activity.

Types of phagocytic cell in acute inflammation:

a)Neutrophils (polymorphnuclear neutrophils ,PMNS or microphages)

these are mainly attracted to & engulf cocci.

Some neutrophils may die due to bacterial toxins (leukocidins). Dead neutrophils may be called pus cells. These dead cells release their proteolytic enzymes digestion (liquefaction) of necrotic tissue and fibrin facilitation of both of their phagocytosis by macrophages and their drainage by lymphatics

b)Macrophages:

-they include emigrating monocytes, as well as tissue histiocytes

-mainly attracted to & engulf bacilli, necrotic cells, fibrin, pigment & foreign bodies.

c)other cells of the mononuclear phagocyte system such as Kupffer cells of liver, littoral cells of spleen and lymph nodes, microglia cells of CNS…etc

• *The efficiency of phagocytosis*

a) it depends on many factors as patients immunity, dose & virulence of bacteria and nature of tissue (e.g phagocytosis is less efficient in serous sacs).

b) in adverse conditions, bacteria may resist phagocytosis. Examples:

- phagocytic cells may be killed by bacterial toxins (leukocidins).
- some bacteria may remain alive inside macrophages (as tubercle bacilli).

IV)ACTIVATION OF TISSUE HISTIOCYTES

Tissue histiocytes are activated and become macrophages similar to the emigrating monocytes. Macrophages can prepare the inflamed tissue for repair by:

- Phagocytosis (of necrotic cells, fibrin ,RBCs, foreign bodies ,pigments (in addition to bacteria…
- Release of growth factors which stimulate the process of repair
- Other functions (see later)

SYSTEMIC (GENERAL) CHANGES IN ACUTE INFLAMMATION

1- Leukocytosis:

Increased blood leukocytes above normal (> 10,000 per mm3) is due to bone marrow stimulation by leukocytosis promoting factors (cytokines), mainly IL-1 &TNF.

REMARK: some infections as typhoid may cause leucopoenia instead of leukocytosis.

2- fever (pyrexia):

Pyrogenic factors, principally IL-1 & TNF → disturbance of the thermoregulatory center in the hypothalamus → vasoconstriction of skin vessels → fever (reduced heat loss).

LOCAL SIGNS & SYMPTIOMS OF ACUTE INFAMMATION

1- *Redness* due to vasodilatation & opening of capillary bed increased blood flow.

2- *Hotness* due to increased blood flow. Redness & hotness are celled flare swelling (the wheal) due to accumulation of exudate (inflammatory edema).

3- *Pain*: due to:

- Nerve compression by exudate
- Irritation by mediators as bradykinin and prostaglandin E2

4- *Loss of function*: due to pain and tissue damage.

FATE OF ACUTE INFLAMMATION

1-Resolution: this is return of the tissue to its normal state. It occurs when inflammation is limited and tissue damage is minimal.in such cases, neutralization of toxins and mediators, phagocytosis and drainage of the exudate by lymphatics is not accompanied by healing. Example resolution of lobar pneumonia.

2- Regression and healing: inflammation subsides (as described above), but there is tissue damage which is gradually repaired .

3- Progression and spread: with weak immunity, bacteria may spread :

- Direct spread causing extension and widening of the inflammatory filed.
- Lymphatic spread causing lymphangitis and lymphangitis
- Blood spread which may lead to serious effects as septicemia.

4-Chronicity: this occur if the injurious agent could not be eliminated completely.

Types of acute inflammation

1- Suppurative (purulent , septic or pyogenic) inflammation : characterized by pus formation . suppurative inflammation be :

a) localized as abscess , boil and carbuncle

b) diffuse as cellulitis , suppurative appendicitis & diffuse septic peritonitis.

2-Non suppurative types:

a)serous

b)fibrinous

c)serofibrinous

d) catarrhal

e) pseudomembranous

f) hemorrhagic

g) necrotizing

h) allergic

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g) necrotizing

h) allergic

I- suppurative inflammation
purulent , septic or pyogenic

Definition: acute inflammation characterized by pus formation (liquefactive necrosis).

Caused by pyogenic organisms as staphylococcus aureus ,staphylococcus hemolyticus, gonococci, pneumococci and others .

Mechanism (pathogenesis) of pus formation:

•Pyogenic organisms cause:

a)Remarkable necrosis.

b)Attraction of a huge number of neutrophils.

c)Death of many neutrophils due to high virulence of the bacteria.

•Dead neutrophils (pus cells)release their proteolytic enzymes → liquefaction of necrotic tissue &fibrin. The liquefied material mixed with pus cells &fluid exudate form a turbid creamy fluid called pus.

Composition of pus:

- Fluid exudate without fibrin (liquefied).
- Cells: a large number of pus cells ,neutrophils , some macrophages & some RBCs
- Necrotic fragments (sloughs) and liquefied necrotic tissue.
- Bacteria and bacterial pigments which may be yellowish (as in staphylococcal infections) or greenish .

Characters of pus :

Pus caused by staphylococcus aureus infection _is an exudative fluid characterized by :

•Creamy thick (due to excess nucleic acids , liquefied fibrin & liquefied necrotic tissue)

•Non –coagulable (no fibrinogen)

•Odoless & alkaline (pH of necrotic cells is alkaline)

•Yellowish due to bacterial pigments &hemoglobin –derived pigments.

Pus of other types of bacteria differs a little e.g. it may be thin and sanguineous (rich in blood)in case of streptococcal infection or greenish

Types of suppurative inflammation:

1-localized : commonly caused by staphylococcus aureus which produce coagulase enzyme fibrin deposition localization .the most common forms of localized suppurative inflammation are : a) abscess. B) boil (furuncle). C)carbuncle.

2-diffuse : caused by streptococcus haemolyticus which produce hyaluronidase (spreading factor) & streptokinase (fibrinolysin) which dissolves fibrin . the most common examples are :

a)cellulitis b)suppurative appendicitis c)diffuse septic peritonitis.

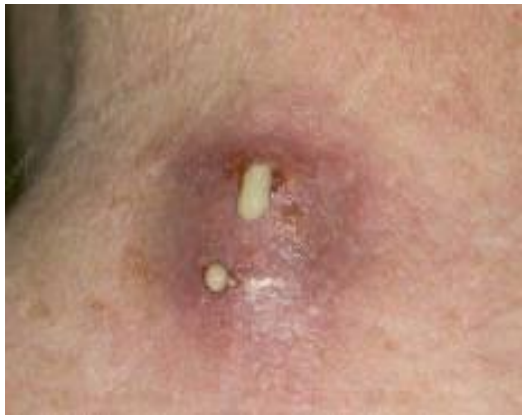
ABSCESS

Definition:

A type of localized suppurative inflammation characterized by a cavity containing pus.

Aetiology: it is commonly caused by staphylococcus aureus infection.

Sites: it is most common in the subcutaneous tissues, but can occur in any organ (lung, liver, brain, kidney, testis, ovary…etc)



Pathological features:

1- Early, two zones can be recognized:

a) A central zone of necrotic.

b) A peripheral zone of inflammation showing many neutrophils, pus cells, macrophages, dilated capillaries and fibrin.

2-later, progressive liquefaction starts at the margin of necrotic tissue three zones:

A)a center necrotic core.

b)A mid zone of pus.

c)The peripheral zone of inflammation (now called the pyogenic membrane).

3-further enlargement: the center necrotic core may disappear by further liquefaction and the abscess may enlarge if the bacteria cause further necrosis and liquefaction.

4- fate of abscess:

a)Small abscess: pus is may be absorbed, followed by healing.

b)Large abscess: since absorption of pus occurs at a very slow rate, a big abscess (if not surgically incised) pointing & rupture (spontaneous evacuation) healing.

Complications of abscess:

1- spread of infection:

a)Direct spread leads to abscess enlargement.

b)Lymphatic spread leads to lymphangitis and lymphadenitis.

c)Blood spread may lead to:

•Toxaemia: bacterial toxins circulating in the blood.

•Septicaemia: large numbers of virulent bacteria & their toxins circulating in blood. Commonly fatal.

•Pyaemia: septic venous thrombi (septic thrombophlebitis)may develop close to the abscess. If these thrombi become fragmented → circulating septic emboli → multiple small abscesses in distant organs. These small abscesses are called pyemic abscesses and the whole process is called pyemia

2- Complications of evacuation and healing :

a)Ulcer: it is a local defect within a surface (skin, mucosa…). It is due to separation of inflammatory necrotic tissue. If infection persists defective healing chronic ulcer

b)Sinus: it is a blind ended tract between a deep abscess and the surface, e.g. a peritoneal abscess may cause sinuses on the abdominal wall. if infection persists it remains as a chronic sinus

c)Fistula: evacuation of a deep abscess may result in a tract communicating between two surfaces or hollow organs. This double ended tract is called fistula. Ano-rectal fistula complicating a perianal abscess is an example. If infection persists ,it changes into a chronic fistula.

d)Keloid

e)Hemorrhage e.g. hemoptysis when a lunge abscess opens into a bronchus.

f)Rupture: e.g. brain abscess into ventricles & right hepatic lobe abscess into base of right lung

3-Chronicity: if the abscess is neither evacuated spontaneously nor surgically, it gets surrounded by fibrosis and becomes a chronic abscess. Pus dries and dystrophic calcification may occur.
Examples: a) chronic abscess: may be clinically mistaken for a tumor. b) chronic lung abscess.

4- Other complications:

a)Putrefaction → gangrene (e.g. putrefaction of a lung abscess by saprophytic bacteria)

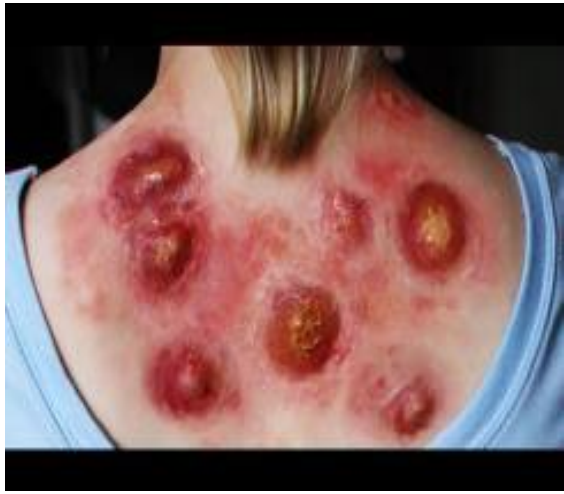
b)Compression effects : e.g. in case of brain abscess → increased intracranial tension & liver abscess → obstructive jaundice.

FURUNCLE (BOIL)

Staphylococcal infection of the hair follicles (folliculitis) is common in the face of males and axilla of females. Folliculitis may regress, or progress to suppuration → furuncle (boil) =small abscess related to the hair follicle. Furuncles may be multiple (furunculosis).

CARBUNCLE

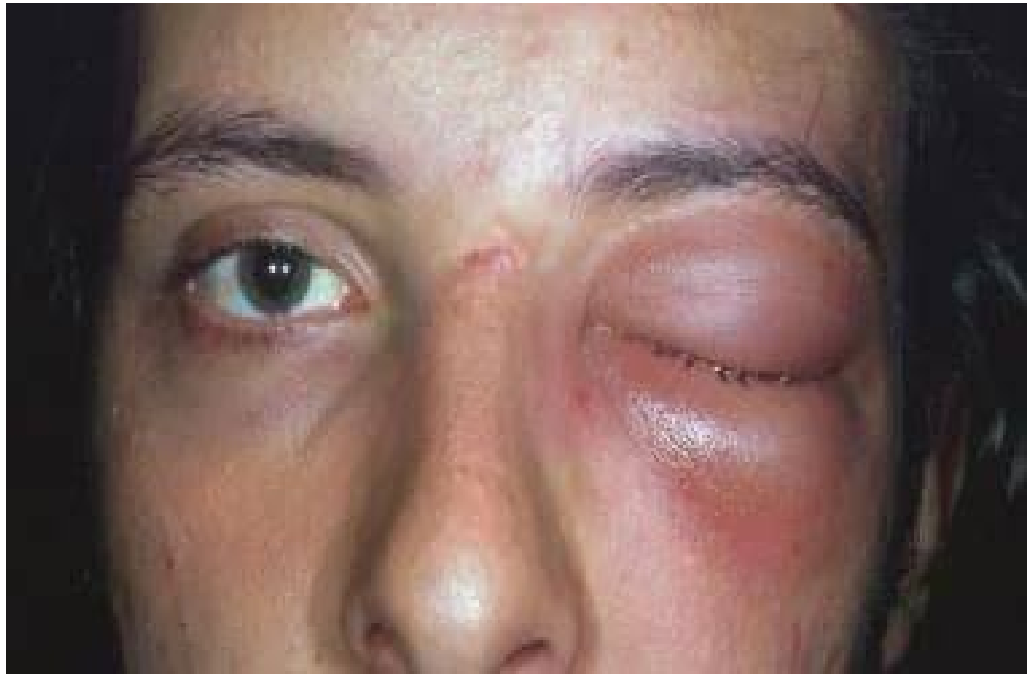
- A special type of localized suppurative inflammation characterized by multiple communicating deep subcutaneous abscesses, opening on skin by multiple sinuses.

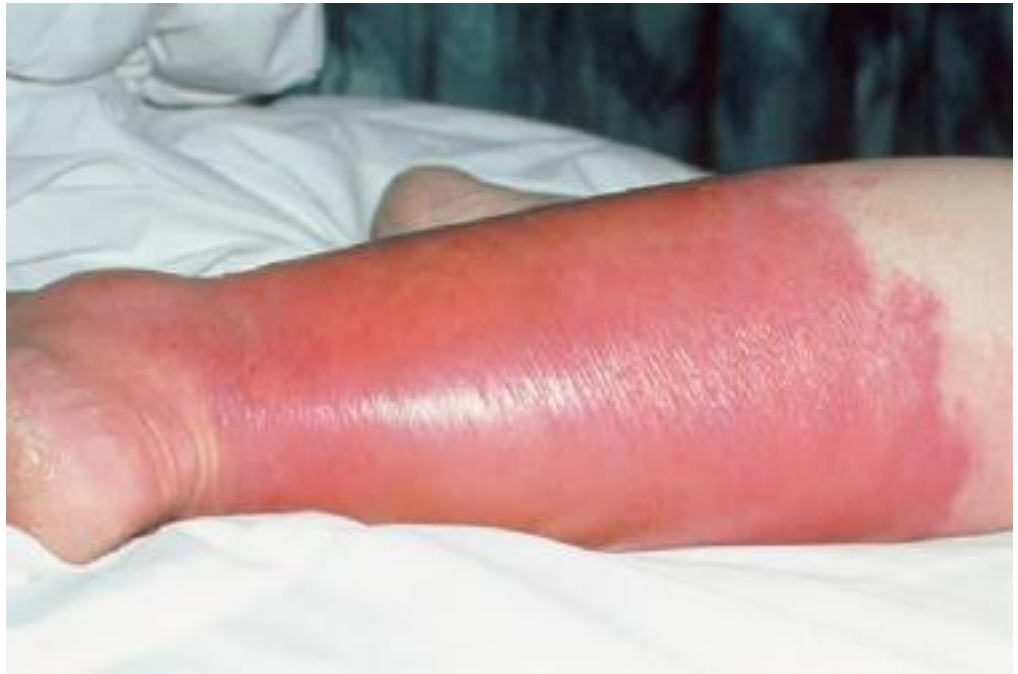


- It only occurs in special sites where the skin and subcutaneous tissues are thick and tough due to dense fibrous septa that extend between the deep fascia and the dermis; thus dividing the subcutaneous fat into compartments, therefore infection reaching these multiple compartments leads to multiple suppurative foci. Sites of carbuncle include back of neck, scalp & buttocks.
- More common in diabetics (low immunity). It starts as a boil → then progress → carbuncle.

CELLULITIS

Cellulitis is an acute diffuse suppurative inflammation, more common in diabetics. The differences between cellulitis and abscess are listed in the following table:





Abscess	Cellulitis
• Localized suppurative inflammation. • Caused by staphylococcus aureus. • Bacteria → coagulase → localization. • Occurs in any organ or tissue, but is most common in subcutaneous tissue. • Pus is characterized by: a) thick due to the presence of large amount of liquefied fibrin. b) contains few erythrocytes. c) contains few sloughs. • Spread of infection is less common.	• Diffuse suppurative inflammation. • Streptococcus haemolyticus. • Bacteria → fibrinolysin & hyaluronidase diffusion. • Occurs in loose connective tissues as subcutaneous tissue, areolar tissues of orbit, scrotum & pelvis. • Pus is characterized by: a)thin, due to less amount of liquefied fibrin (fibrinolysin antagonizes fibrin deposition). b) sanguineous (contains many RBCs) c)contains many sloughs due to extensive necrosis • Spread of infection is more common

II- NON SUPPURATIVE INFLAMMATION

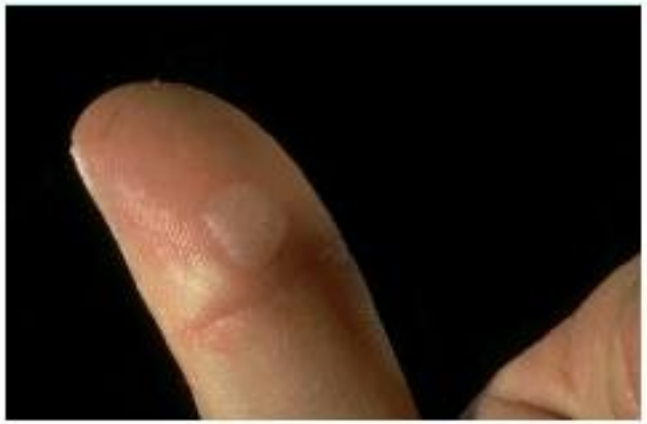
SEROUS INFLAMMAION

Characterized by excessive serous fluid poor in fibrin.

Examples:

- Skin blisters due to skin burns.
- Epidermal vesicles due to herpes simplex viral infection.
- Inflammation of serous membranes (pleura, pericardium and peritoneum)

Skin Blister-Serous Inflammation



FIBRINOUS INFLAMMATION

Characterized by an exudate rich in fibrin, with a little fluid component

Examples:

1)Lobar pneumonia : excess fibrin → consolidation of the affected lobes.

2)Adult hyaline membrane disease.

3)Inflammation of serous membranes.

SEROFIBRINOUS INFLAMMATION OF SEROUS MEMBERANES

DEFINITION: this is inflammation of serous membranes rich in both fluid exudate fibrinogen . the fluid component may predominate (wet or serous type) .

Remark : serous membranes may be affected by other types of inflammation e.g. suppurative inflammation.

Gross picture:

At the beginning , the visceral and parietal layers of the serous membrane appear hyperemic and edematous.

Then they become thickened , reticulated , opaque and grayish ,particularly in case of the dry (fibrinous) type

The serous sac cavity contains abundant serous fluid (effusion) particularly in case of the wet (serous) type.

Microscopic features:

Serosal cells undergo degeneration and shedding

The subserosa shows dilated capillaries , fibrin and acute inflammatory cells.

In case of dry (fibrinous) inflammation the , the serosal layer becomes covered by thick network of fibrin entangling acute inflammatory cells.

CATARRHAL INFLAMMATION

Characteristics : a mild form of acute inflammation of mucous membranes characterized by an exudate mixed with mucus secreted by the irritated mucous membrane

Examples: catarrhal rhinitis (common cold) and catarrhal appendicitis.

Gross picture: swollen hyperemic mucosa; first dry then pours a discharge of serous fluid mixed with mucin.

Microscopic picture: epithelial cells of the mucosa are swollen and vaculated de to excess mucin (mucoid degeneration). The submucosa shows dilated capillaries, PMNS, macrophages and fibrin.

Pseudomembranous (membranous) INFLAMMATION

Characteristics & pathogenesis:

•A severe form of acute inflammation of mucous membranes characterized by a false membrane composed of necrotic tissue & fibrin

•Virulent bacteria secreting exotoxins as mycobacterium diphtheria → mucosal necrosis and marked submucosal inflammation → false membrane composed of necrotic mucosal patches and excessive fibrin .

Examples : diphtheria &bacillary dysentery .

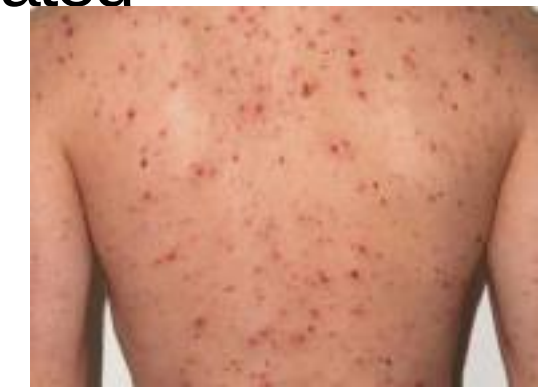
Gross picture: the original mucous membrane is replaced by another (false) membrane ,which appears yellowish gray , thick and adherent .if forcibly removed ,it leaves a bleeding surface and is reformed rabidly .

Microscopic picture : the false membrane consists of necrotic patches ,fibrin , bacteria and acute inflammatory cells . the underlying submucosa shows dilated capillaries , fibrin and acute inflammatory cells (PMNs and macrophages).

HAEMORRHAGIC INFLAMMATION

Characterized by excess RBCs within the exudate due to associated vascular damage .

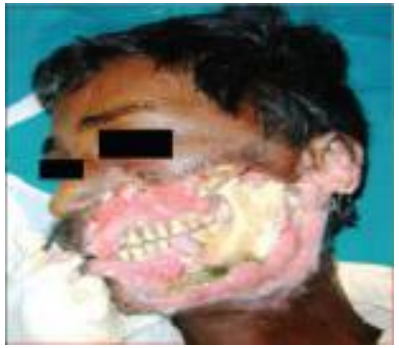
Example : small pox . & hemorrhagic cystitis



NECROTIZING INFLAMMATION

Characterized by: extensive necrosis in association with inflammation.

Example : cancrum oris .



ALLERGIC INFLAMMATION

The Underlying cause of inflammation in hypersensitivity.

Characterized by many eosinophils .

Example : urticaria , allergic rhinitis and bronchial asthma .

CHRONIC INFLAMMATION

PATHOLOGICAL FEATURES OF CHRONIC INFLAMMATION

- Chronic inflammation lasts for a long duration .
- It may follow acute inflammation due to failure of defense mechanisms .
- It may start chronic by gradual onset (not preceded by an acute phase) due to one or more of the following :

a)Infection with resistant organisms e.g. tuberculosis .

b)Non –living irritants as foreign bodies e.g. silicosis &asbestosis (inhalation of silica or asbestos particles into lungs)

c)Development of autoimmunity e.g. rheumatoid arthritis .

- The inflammatory response basically resembles that of acute inflammation .the main differences between acute & chronic inflammation are listed in the next table ;

ACUTE INFLAMMATION

- Rapid onset and short duration.
- Marked vasodilatation.
- More abundant fluid exudate.
- Main inflammatory cells.

Neutrophils & macrophages

- No fibrosis in acute inflammation.

Variations in acute inflammatory cells:

1. Eosinophils appear in allergic inflammation.
2. Neutrophils may be few or absent in cases of inflection with bacilli as typhoid.
3. Lymphocytes & plasma cells may be the predominant cells in viral inflammation.

CHRONIC INFLAMMATION

- Gradual onset & long duration
- Less marked vasodilatation . Endarteritis obliterans may occur (thickening & narrowing of small blood vessels)
- Usually scanty fluid exudate .
- Main inflammatory cells : Macrophages , lymphocytes ,plasma cells and giant cells
- Fibrosis occurs

TYPES OF CHRONIC INFLAMMATION

1.CHRONIC NONSPECIFIC INFLAMMATION :

- They usually follow acute inflammation , e.g. chronic abscess &chronic pyelonephritis .
- They are termed “nonspecific” since they all show the same microscopic features (chronic inflammatory cells , fibrosis , vascular thickening .etc.) irrespective of the cause .

2. CHRONIC SPECIFIC INFLAMMATIONS :

- They usually start chronic without a pre-existing acute phase .
- They exhibit the conventional microscopic features of chronic inflammation (chronic inflammatory cells , fibrosis , vascular thickening .etc.) but moreover there are additional features specific for each type as the presence of bilharzia ova in cases of bilharziasis and the presence of silica particles in cases of silicosis .
- The majority of chronic specific inflammations occur in the form of granulomas .

GRANULOMAS

DEFINITION & PATHOLOGICAL CHARACTERISTICS::

- A particular form of chronic inflammation characterized by nodular collections of macrophages with a variable mixture of lymphocytes , plasma cells , giant cells & sometimes neutrophils .
- The macrophages commonly change into large eosinophilic cells . these modified macrophages are called epithelioid cells
- Some granulomas may exhibit central necrosis .
- Granulomas often represent type IV hypersensitivity , where stimulated T lymphocytes release lymphokines that attract large numbers of macrophages

TYPES OF GRANULOMAS:

1- infectious granulomas : most of these granulomas are necrotizing .Examples:

- Bacterial as tuberculosis , brucellosis , syphilis , leprosy and cat –scratch disease .
- Parasitic as schistosomiasis (bilharziasis)
- Fungal as coccidiomycosis , crypococcosis and histoplasmosis .

2-foreign body granulomas : mostly non-necrotizing granulomas. Examples :

- Silicosis .
- Foreign body granulomas around surgical sutures , or other foreign bodies when trapped in a tissue as pieces of glass , metal , wood… etc.

3-granulomas of unsettled aetiology : mostly non-necrotizing granulomas . Examples: Sarcoidosis & Crohn's disease .

TYPES & FUNCTIONS OF INFLAMMATORY CELLS

According to type of inflammation:

1- Acute inflammatory cells

- Neutrophils (microphages, polymorphnuclear neutrophils). They are most numerous in pyogenic infections. Dead neutrophils are called pus cells.
- Macrophages. They are derived from blood monocytes & tissue histiocytes
- Possible variations e.g.
  - eosinophils in allergic inflammation
  - lymphocytes & plasma cells in viral infections
  - paucity of neutrophils in bacillary infections as typhoid

2- Chronic inflammatory cells :

- Lymphocytes. (T & B lymphocytes)
- Plasma calls (derived from stimulated B lymphocytes)
- Macrophages
- Giant cells. They are most commonly seen in granulomas.

According to function

1-phagocytic cells:

- Neutrophils mainly engulf cocci
- Macrophages have several functions:

Phagocytosis of :

a) bacterial, particularly bacilli.

b) necrotic cells, fibrin, debris. Foreign bodies, pigments.

c) phagocytosis of tumor cells (in case of malignancy)

secretion of :

a) chemical mediators (monokines) as IL-1 & TNF

b) growth factors which play vital function in repair

c) alpha interferon → blocks viral replication (antiviral effect)

d) enzymes as collagenase & elastase (have role in repair)

e) others as some coagulation factors & complement components

. activation of T lymphocytes: macrophages engulf the engulf the antigen & present it to T lymphocytes T lymphocyte sensitization lymphokines immune functions.

. formation of giant cells greater phagocytic activity

•Giant cells are large multinucleated cells

. They are derived from macrophages by fusion or by repeated nuclear divisions without cytoplasmic division.

. They have a greater phagocytic capacity and can engulf larger particles.

. There are several types of giant cells as foreign body giant cells (engulfing foreign bodies) and langhan giant cells (in case of tuberculosis)

•<u>Eosinophils:</u> weak phagocytic activity. Also have an antihistamine action

2- immunological cells (lymphocytes and plasma cells):

- **T lymphocytes:** when sensitized (by antigen presentation through macrophages) they secrete lymphokines several functions such as activation of macrophages to perform efficient phagocytosis (cell mediated immunity)
- **B lymphocytes:** when stimulated by antigen plasma cells immunoglobulin antibodies (humoral immunity).

Repair

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REPAIR (HEALING)

DEFINITION:

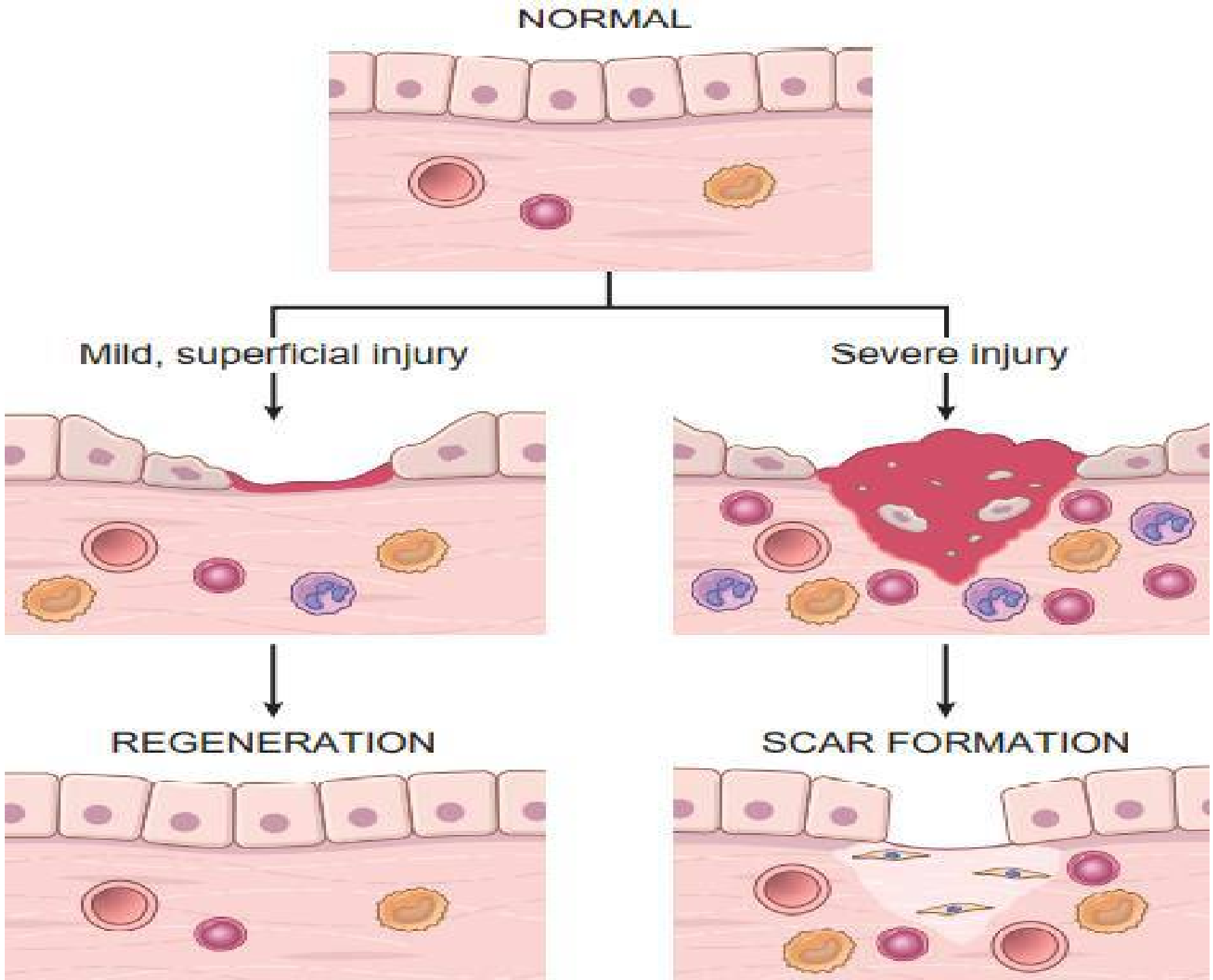
Repair is the replacement of a damaged tissue by a new healthy one .

TYPES OF REPAIR:

1-Regeneration : replacement of the damaged tissue by tissue of the same type .

2-Healing by connective tissue deposition :

- Fibrosis (scarring): in any part of the body except CNS
- Gliosis (in CNS) .


NORMAL
Mild, superficial injury
Severe injury
REGENERATION
SCAR FORMATION

WHAT DETERMINES THE TYPE OF REPAIR ?

The type of repair is mainly determined by the type of damaged cells , because the different cell types have different capacities to divide :

1- Labile cells :

These cells continuously divide actively through life to replace cell loss . they have short G0 phase . complete regeneration is possible following their injury . labile cells include :

Hematopoietic cells in the bone marrow and the majority of surface epithelia, such as the stratified squamous epithelia of the skin, oral cavity, vagina, and cervix; the cuboidal epithelia of the ducts draining exocrine organs (e.g., salivary glands, pancreas, biliary tract); the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; and the transitional epithelium of the urinary tract. These tissues can readily regenerate after injury as long as the pool of stem cells is preserved.

2-Stable cells (quiescent cells):

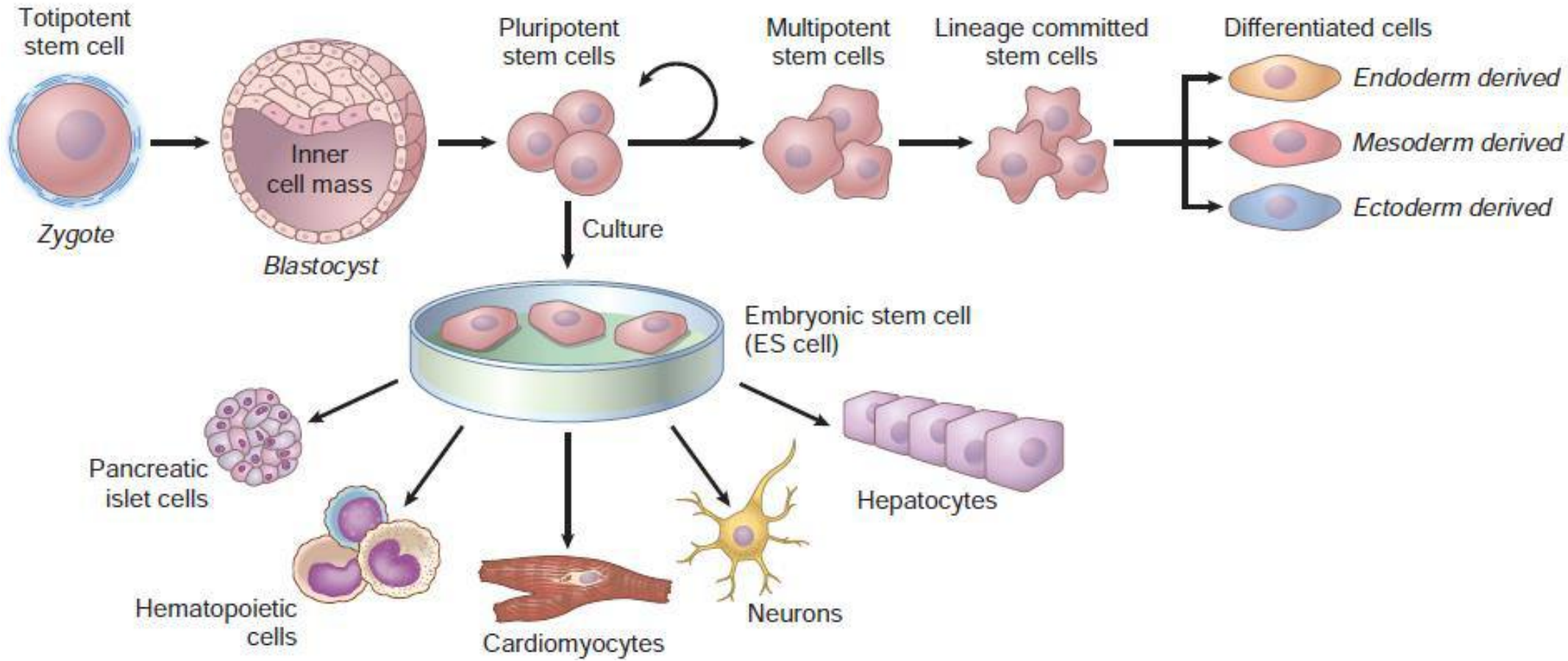
These cells have a limited capacity of division . they remain in the G0 phase for long periods but retain the capacity to enter the mitotic cell cycle if in need . following injury , repair may occur by regeneration or by fibrosis . stable cells include :

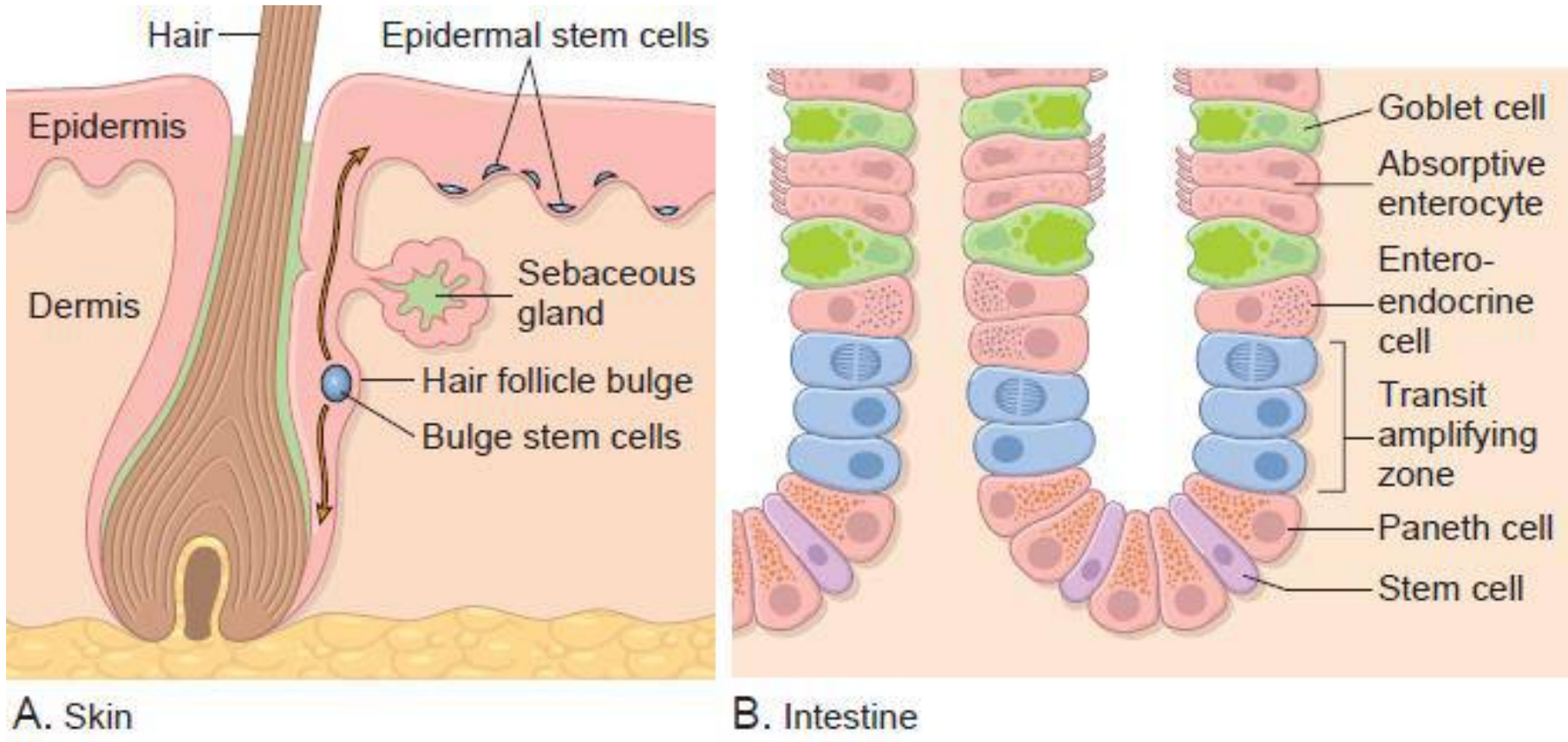
- Parenchymal cells of the glandular organs (liver , kidney , pancreas … etc)
- Mesenchymal cells as fibroblasts , astrocytes osteoblasts , chondroblasts , smooth muscle and endothelial cells .

3-Permanent (non-dividing)cells :

These cells have no capacity for division in postnatal life . injury to these cells is repaired by connective tissue deposition . permanent cells include:

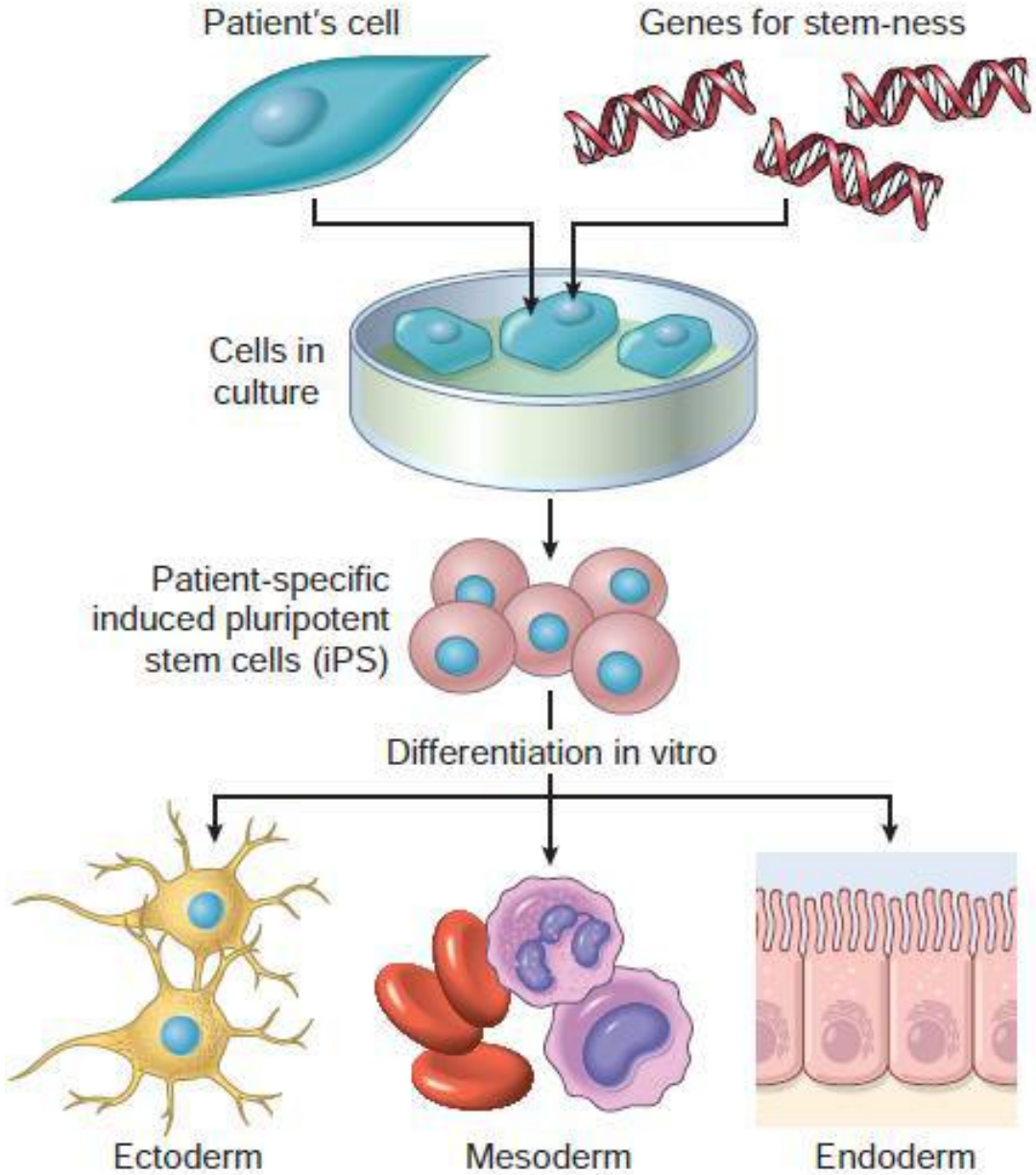
- Skeletal and cardiac muscle cells . damage is healed by fibrosis .
- Nerve cells . damage is healed by gliosis


Totipotent stem cell
Zygote
Inner cell mass
Blastocyst
Pluripotent stem cells
Culture
Multipotent stem cells
Lineage committed stem cells
Differentiated cells
Endoderm derived
Mesoderm derived
Ectoderm derived
Embryonic stem cell (ES cell)
Pancreatic islet cells
Hematopoietic cells
Cardiomyocytes
Neurons
Hepatocytes



A. Skin

B. Intestine


Patient's cell
Genes for stem-ness
Cells in culture
Patient-specific induced pluripotent stem cells (iPS)
Differentiation in vitro
Ectoderm
Mesoderm
Endoderm

1- FACTORS AFFECTING EFFICINCY & TYPE OF REPAIR :

a) LOCAL FACTORS :

- Type of damaged cells (labile , stable or permanent).
- Blood supply e.g. local ischemia → defective repair .
- Persistent infection or presence of foreign bodies → delays repair .
- Extent of tissue damage .

b)General (systemic)factors :

- Age :repair is better in younger ages .
- Nutritional deficiencies including proteins , vitamin C (&vitamin D in case of bone healing) & some minerals as zinc (zinc is important for collagen synthesis).
- Glucocorticoid and cytotoxic drug therapy delay repair
- Endocrine diseases as diabetes mellitus & Cushing syndrome → defective repair .

2-FACTORS CONTROLLING THE MECHANISM OF REPAIR:

a) Growth Factors : cell division is controlled by stimuli called growth factors which are mostly produced by macrophages . the cell cycle consists of G1 phase (pre-synthesis) → S phase (DNA synthesis) → G2 phase (premitotic) → M phase (mitotic).

The physiologic state of non- division of the quiescent cells is called G0 phase . the growth factors recruit G0 cells into the cell cycle . Growth factors include:

- **Epidermal growth factor (EGF)** : Mitogenic for epithelial cells and fibroblasts .
- **Platelet derived growth factor (PDGF):** produced by many cells (including macrophages) and stored in platelet granules . it is mitogenic for fibroblasts ,neuroglia cells and smooth muscle .
- **Fibroblast growth factors (FGFs):** stimulate fibroblast proliferation and formation of new blood vessels .
- **Transforming growth factor alpha (TGF-a):** stimulates fibroblast proliferation (stimulatory effect) and also enhances collagen degradation (inhibitory effect).
- **Transforming growth factor beta (TGF-B):** stimulates fibrogenesis (stimulatory effect) . it has also a growth inhibition action (inhibitory effect).
- **IL-1 ,TNF & other macrophage derived growth factors .**

b) Cell to cell interactions (contact inhibition):

- Cells of normal un-injured tissues are in intimate contact . this contact prevents their un-needed division . the mechanism of this growth inhibition is not clear , but it involves inhibitory signals , surface receptor interactions and growth inhibition factors (chalones) that suppress mitosis (as TGF-B).
- Tissue damage → cell loss → loss of contact inhibition → stimulation of the cells to divide until they establish contact again (by the end of repair) leading to contact inhibition once more .

c) Cell to matrix interactions :

- Extracellular matrix (ECM) proteins (glycoproteins) include fibronectin & laminin → important roles influencing cell migration ,proliferation , differentiation & adhesion .
- Abnormalities in these interactions → serious effects , e.g. chronic liver disease disturbing the extracellular framework → abnormal repair → cirrhosis (see later).

REPAIR BY REGENERATION

DEFINITION:

Replacement of the damaged tissue by tissue of the same type.

CELLS CAPABLE OF REGENERATION :

1- Labile cells : these cells regenerate easily .

2- Stable cells : regeneration occurs in optimal conditions

3- No regeneration of permanent cells

EXAMPLES OF REGENERATION :

1-REGENERATION OF EPIDERMIS:

a)Abrasion : superficial injury of epidermis complete regeneration .

b)Skin wound : it means injury of epidermis and dermis . the epidermis regenerates and the dermis undergoes healing by fibrosis (see wound healing)

2-REGENERATION OF MUCUS MEMBRANES of GIT and urinary tract

3-REGENERATION OF LIVER CELLS :

- Mild parenchymal liver injury not disturbing the extracellular hepatic framework (e.g. in acute viral hepatitis) → complete regeneration restoring the normal liver structure
- Chronic diffuse parenchymal liver disease disturbing the framework (as in chronic hepatitis & alcoholism) → fibrosis accompanied by irregular proliferation of hepatocytes → diffuse liver nodularity (regeneration nodules). This condition is known as liver cirrhosis
- Remark : injury to portal tract alone , not affecting the hepatic (as in bilharziasis) → portal fibrosis .

4-HEALING OF BONE FRACTURE :

Mechanism of healing : the events occur between the fracture ends of bone

- Stage 1 : hematoma
- Stage 2 : inflammatory exudate (traumatic inflammation)
- Stage 3 : phagocytosis (demolition) by macrophages and osteoclasts gradual removal of the damaged bone fragments , blood & inflammatory cells . this is associated with release of growth factors which control the subsequent steps of repair
- Stage 4 : granulation tissue formation (procallus) : granulation tissue invades the area within one week. It consists of capillary loops and mesenchymal cells derived from the periosteum and endosteum . this granulation tissue it is called procallus, since it precedes the formation of true hard bony callus (pro- means precedes).

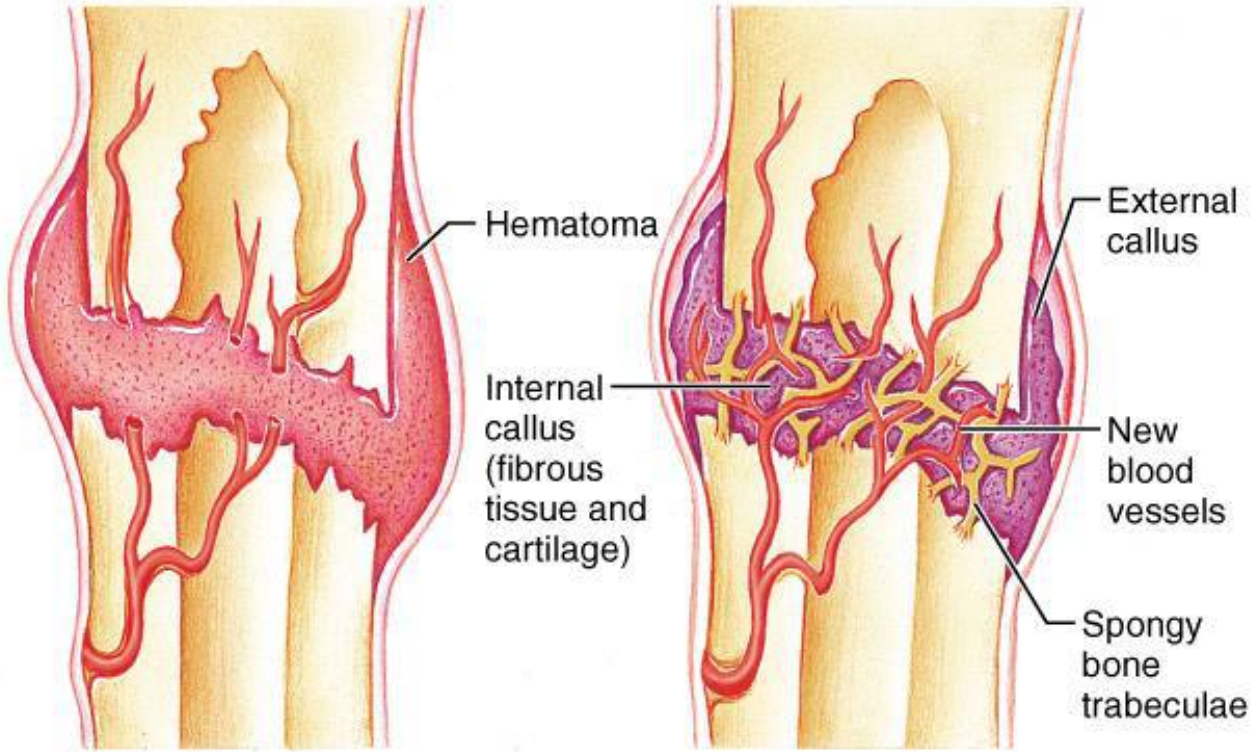
•Stage 5: woven bone & cartilage (provisional callus). During 3 weeks, some mesenchymal cells differentiate into chondroblasts → cartilage islands & other mesenchymal cells differentiate into osteoblasts → osteoid tissue which consists of bone matrix (osseomucin) & collagen and lacks calcification associated with gradual loss of capillaries. This osteoid tissue undergoes gradual calcification (by alkaline phosphatase activity) → osseous tissue which appears as non lamellar bone (woven bone.) thus the provisional callus consists of cartilage ,osteoid & woven is transformed into permanent mature lamellar bone

•Stage 6 : formation of lamellar bone (permanent callus) due to calcification (see stage 5) cartilage disintegrates and is invaded by osteoblasts. Meanwhile, the woven (nonlamellar) bone is gradually removed by osteoclasts and replaced by lamellar bone composed of osteoid tissue which undergoes calcification together with deposition of collagen bundles which are arranged in orderly lamellar fashion (concentrically around blood vessels → formation of Haversian system)

•Stage 7: remodeling. Callus remodeling (adjustment) occurs through:

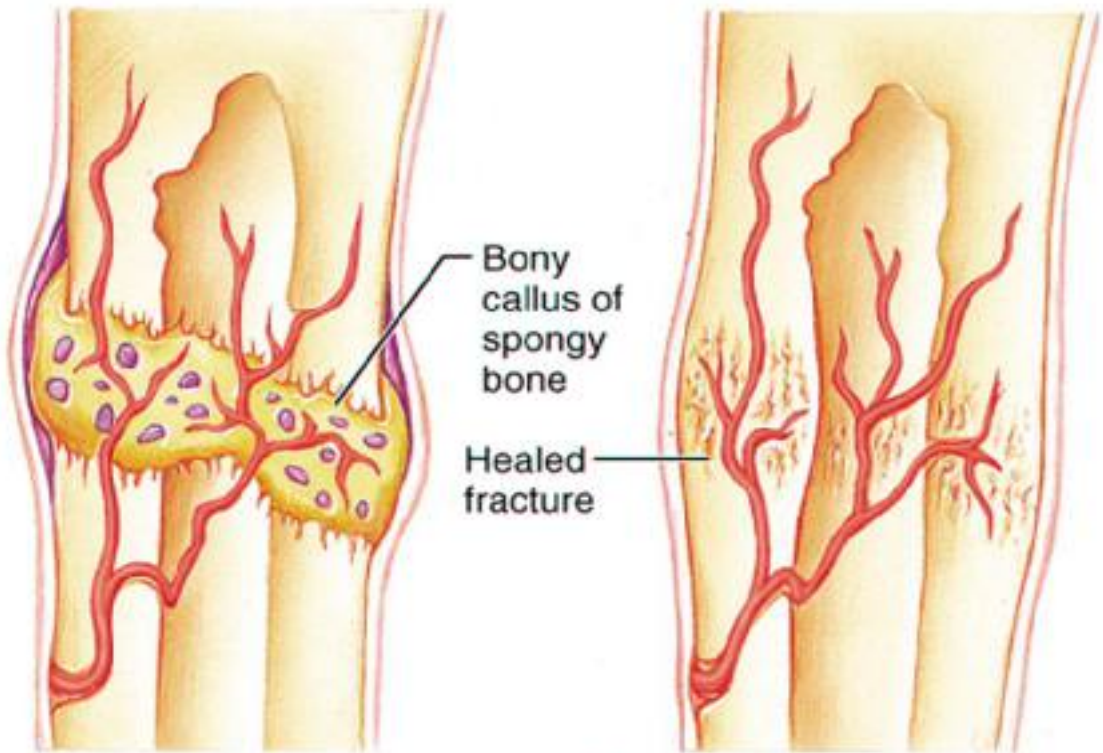
a) removal of the unnecessary internal & external callus (by osteoclastic activity)

b) further adjustment of the intermediate callus (to give it optimal size, strength and lamellar property) by further osteoblastic and osteoclastic activity, in response to mechanical stresses along lines of weight bearing.



① **Hematoma formation**

② **Fibrocartilaginous callus formation**



③ **Bony callus formation**

④ **Bone remodeling**

Remarks:

- Callus in Latin means hard. However, the term was used to describe tissue uniting fracture ends, regardless of its consistency . sometimes , the procallus is described as soft callus , while the provisional and permanent callus are described as hard callus.
- Healing of bone (> 4 weeks) may be so perfect that the fracture site may not be identified.
- Bone marrow regenerates inside the medullary canal.

Causes of defective (imperfect) bone healing & failure of bony union:

Some conditions may lead to nonunion, weak union or fibrous union (pseudoarthrosis):

A) Local factors:

a)Inadequate immobilization or malalignment.

b)Pathological fracture e.g. due to bone tumor or osteoporosis.

c)Soft tissue interposition between the fracture ends.

d)Ischemia.

e)Infection.

B) General factors: as

a) Old age.

b) Nutritional deficiencies.

c) Glucocorticoid therapy.

d) Diabetes mellitus.

5-HEALING OF DAMAGE TO NERVOUS SYSTEM:

a) Injury of a peripheral nerve may be regenerated since nerve cells are preserved:

Mechanism of regeneration of peripheral nerve cut:

- **Nerve injury leads to:**

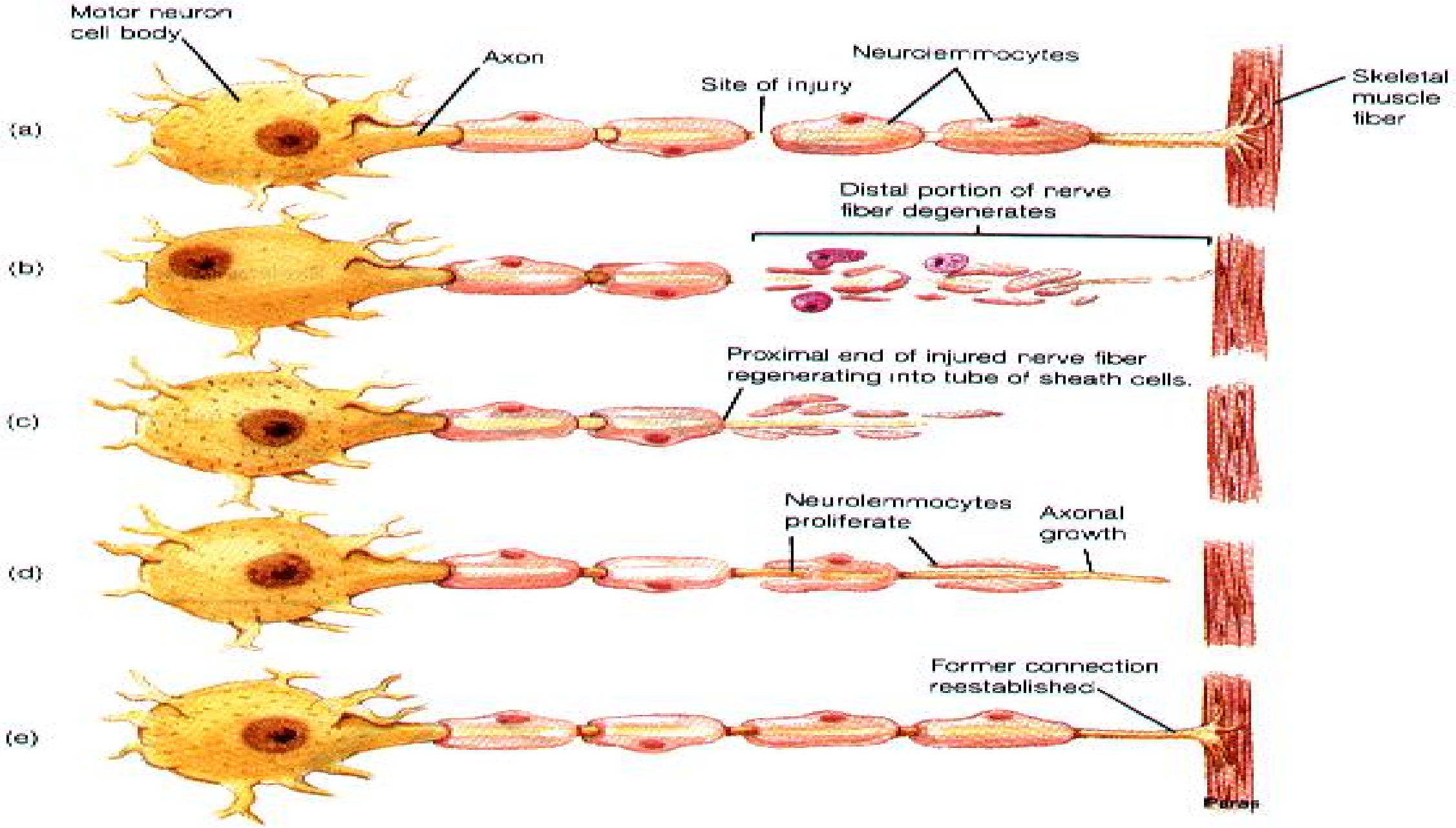
1- Axonal degeneration of the nerve cells, which appear swollen with eccentric nuclei & loss of nissel granules (chromatolysis). They recover within three weeks.

2- Wallerian degeneration: within 48 hours, the myelin and axis cylinder of the nerve become disintegrated. These changes affect the nerve fibers distal to the point of section & proximally up to the first node of ranvier.

- **Schwann cells** resist injury. Together with macrophages they act as phagocytic cells engulfing the products of wallerian degeneration. They also proliferate from both the distal segment and proximal stump → integrated neurilemmal tube.
- **Growth of axis cylinders:** they are secreted by the alive nerve cells. They grow inside the integrated neurilemmal tube at a rate of about 1 mm/day.
- **Myelin sheath formation** around the growing axons is the final stage

Traumatic Neuroma (Stump or Amputation Neuroma): It is a complication of nerve healing occurring if the two ends of the nerve are not opposite each other or if the nerve is severed (absent distal nerve segment as in case of amputation). In these cases the proliferating schwann cells and neurofilaments mix together forming a painful mass called traumatic neuroma, or amputation neuroma (stump neuroma).

b) damage of central nervous system: damage to nerve cells within the CNS (brain & spinal cord) can never be regenerated, since nerve cells cannot divide. Repair starts by phagocytosis of dead tissue (by macrophages & microglia cells) then laying down a special type of connective tissue formed by astrocytes called gliosis


Motor neuron cell body
Axon
Site of injury
Neurolemmocytes
Skeletal muscle fiber
(a)
Distal portion of nerve fiber degenerates
(b)
Proximal end of injured nerve fiber regenerating into tube of sheath cells.
(c)
Neurolemmocytes proliferate
Axonal growth
(d)
Former connection reestablished
(e)

HEALING BY FIBROSIS

DEFINITION

Replacement of damaged tissue by granulation tissue which matures into fibrous (scar) tissue.

MECHANISM OF FIBROSIS

- The process starts by formation of granulation tissue (fibroblasts & capillaries), which matures into fibrous tissue by deposition of collagens followed by remodeling.
- The process is controlled by growth factors.
- Granulation tissue appears moist, red (richly vascularized) and granular, while fibrous tissue is firm & grayish (hypovascular)

- The process of granulation tissue followed by fibrosis runs along the following steps:

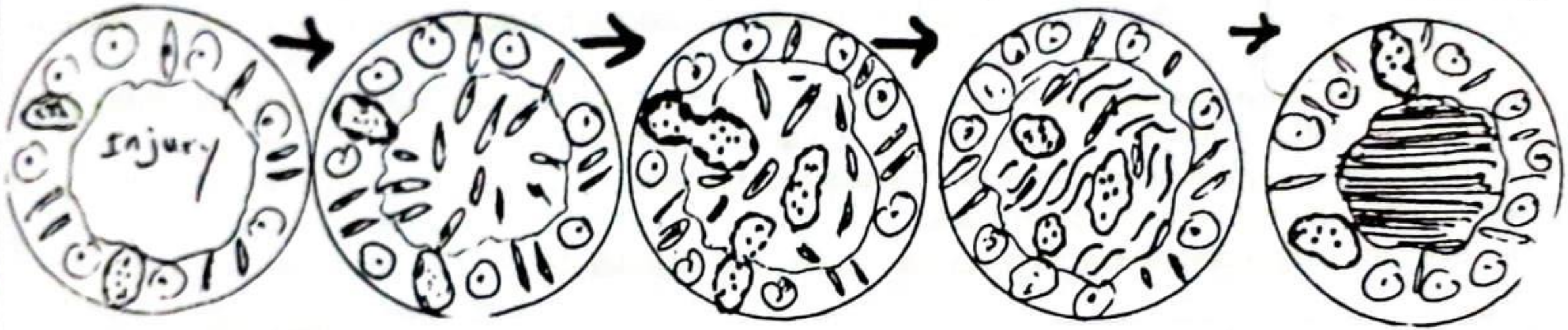
  1- *Angiogenesis (neovascularization):* formation of new capillaries occurs as follows :

  a) proteolytic degradation of the basement membrane of the parent vessel to allow for migration of endothelial cells, which proliferate forming solid endothelial buds.

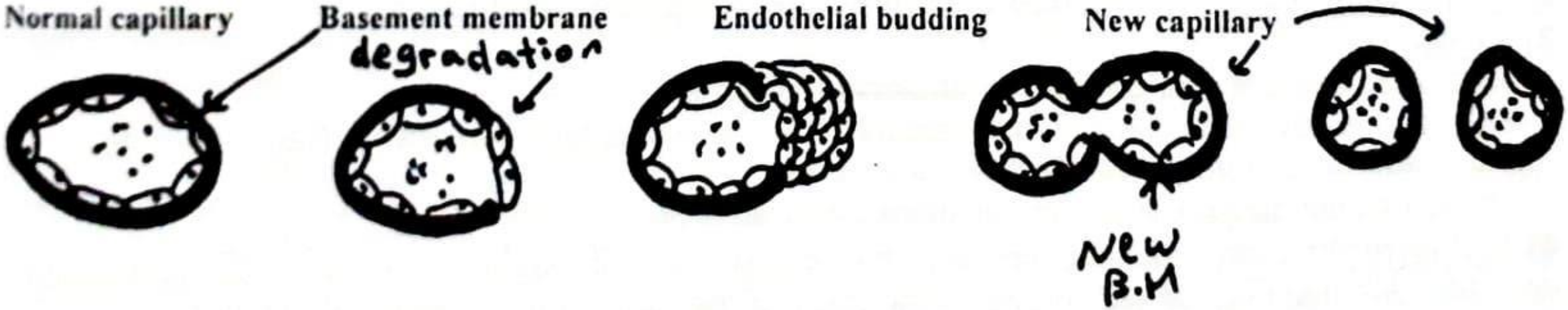
  b) canalization (maturation) of endothelial buds to form capillary tubes which anastomose with adjacent .

GRANULATION TISSUE

FIBROSIS



ANGIOGENESIS



2- Fibroblast migration , proliferation & secretion of collagen (fibrogenesis , fibrosis):

a) Migration of fibroblasts to the site of injury followed by fibroblast proliferation .

b) Fibroblasts secrete ECM proteins (fibronectin & proteoglycan) followed by type III collagen (thin fibrils) and later type I collagen (thick fibrils).

3-Progressive maturation & remodeling to form the permanent scar (fibrous tissue):

a) Progressive type I collagen synthesis is accompanied by resorption of many capillaries by macrophages .

b) When the scar is big (in case of secondary union), some fibroblasts acquire a smooth muscle contractile function to minimize the scar size . these cells are called myofibroblasts .

c) Collagenase secreted by macrophages also modify the scar size. The mature (final) scar consists of matrix ,dense collagen (type I), few or no capillaries and inactive looking fibroblasts (resting fibrocytes). The scar is nearly avascular.

EXAMPLE OF HEALING BY FIBROSIS

1- HEALING OF WOUNDS

Types Of Wound Healing

1)Healing by primary union (healing by first intention)

Wound characteristics: non-gaping , clear (not infected) wound with minimal tissue loss & close edges. Best example is stitched surgical wound.

Mechanism of healing:

- After injury, the wound contains clotted blood and products of traumatic inflammation (neutrophils and macrophages). The surface of the wound is covered by dried clot (scab), which separates within 2weeks.
- Phagocytosis of clot &products of injury & release of growth factors by macrophages.

- Epidermal cells (being labile) regenerate rapidly , starting from the basal layer at both sides of the wound , which meet at ease (since the wound is not gaping)& continue proliferation to restore the full epidermal thickness
- Granulation tissue from the wound edges fills the gap under the epidermis .
- Maturation of granulation tissue into fibrous (scar) tissue .
- Skin adenexa (hair follicles , sweat glands …) lost within the wound will not regenerate .

2) Healing by secondary union (healing by second intention)

Wound characteristics : Gaping & infected wounds (including abscess ulcer , fistula …etc).there is marked tissue loss & edges are widely separated .

Mechanism of healing :

Mechanism of healing is basically the same as primary union with the following differences :

- Longer healing time
- Larger amount of granulation tissue → bigger scar .
- Epidermal regeneration is delayed than in primary union (see below).
- Wound contraction occurs in secondary union & constitutes another major difference .

Healing steps include:

- The wound is filled with clotted blood , debris , neutrophils , pus cells & macrophages.
- Phagocytosis & release of growth factors is done by macrophages .
- Epidermal cells start proliferation from the basal layer on both sides , but fail to meet (since the wound is gaping)
- Granulation tissue (describe)grows from the wound edges & wound bottom & gradually fills the wound gap

- Epidermal regeneration can now successfully occur ,since the proliferating epidermal cells can move on the surface of granulation tissue until they meet .
- Maturation of granulation tissue into fibrous (scar) tissue.
- Wound contraction by myofibroblasts .
- Skin adenexa within the wound are lost and do not regenerate

Complications of Wound Healing : More common in secondary union

1) Cosmetic deformities due to extensive scarring .

2)Functional troubles e.g. due to contracture of scars around joints .

3)Keloid :

- it is a protuberant scar covered by stretched epidermis .

- it is due to overdone repair , which occurs , in some susceptible persons as negroes or due to presence of foreign bodies within the wound .

-it recurs after surgical excision but shrinks by irradiation .

4) Epidermoid cyst (implantation cyst): it is a cyst filled with keratin . it is due to proliferation of epithelial cells that may be trapped within the depth of the wound during epithelial regeneration .

5) Chronic ulcer , chronic fistula or chronic sinus

Definitions:

- Chronic ulcer: persistent surface discontinuity due to loss of epithelium.
- Chronic sinus: a persistent blind- ended tract, opening to a surface by a single orifice
- Chronic fistula: a persistent double ended tract with opening on 2 surfaces

Mechanism: chronic ulcer , sinus & fistula are due to defective repair:

- This may be due to persistent infection → destruction of granulation tissue
- It may be also due to excessive deposition of collagen at the edges of the wound without filling the whole wound with granulation tissue

6) Carcinoma may rarely develop from the epithelium related to a scar; particularly scars of burns. This type of squamous cell carcinoma is known as marjolin's ulcer.

A comparison between the types of wound healing

A) healing by primary union (first intention)	B) healing by secondary union(second intention)
• Type of wound: clean ,non-gaping e.g. surgical incision • Mechanism of healing: a)Day 1: the narrow wound gap os filled with clotted blood and covered by a scab of dry clotted blood. b)Day 2: Epidermal regeneration occurs at both edges starting from the basal layer(accompanied by laying down of new basement membrane). The process is complete within 1-2 days. Exudation of neutrophils appears on the wound gap. c)Day 3:macrophages replace neutrophils and start phagocytosis & secretion of growth factors. d)Day 4,5:granulation tissue arises from the wound edges & fills the gap. Collagen fibrils start to appear. e)second to fourth week: -The surface scab separates (by the end of the 2nd week) -maturation of granulation tissue into fibrous tissue (describe). Finally the wound consists of a small mature scar covered by regenerated epidermis. -Skin adenexa do not regenerate. • Complications: less common	• Type of wound:gaping, infected • Mechanism of healing: Healing is basically similar to first intention, but differs in: a)necrotic debris, clots & inflammatory cells (neutrophils &macrophages) are more extensive. Pus may also exist. Phagocytosis takes longer time & therefore the process of healing takes a longer period. b)epidermal proliferation starts early, but fails to reconstitute the epidermal covering, except after filling the gap with granulation tissue (which arises from edges & bottom & gradually fills the gap). By this time the epidermal cells can grow over the surface of granulation tissue to complete the process of epidermal regeneration. c)The amount of granulation tissue is much lager , and consequently the scar is big. d)Wound contraction is a major difference; an action done by myofibroblasts. The wound finally consists of a contracted scar covered by regenerated epidermis without adenexa which do not regenerate. • Complications: more common

Healing of serofibrinous inflammation

Mechanism: fibrous healing of inflamed serous membranes occurs along the following steps:

- The process starts by absorption of fluid exudate & phagocytosis of fibrin and debris
- This is followed by granulation tissue (descried) derived from the subserosal tissue
- Serosal cells regenerate
- Maturation of granulation tissue into fibrous tissue occurs

Complication: fibrosis may be extensive leading to fibrous extensions between visceral and parietal layers called adhesions. These adhesions may cause serious effects e.g. intestinal obstruction in case of peritoneal adhesions.

Neoplasia

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Palestinian board of pathology

DEFINITION

A neoplasm (tumor) is a new growth forming an abnormal mass, caused by autonomous self controlling proliferation of cells independent of stimuli.

GENERAL CHARACTERISTICS OF TUMORS

Tumor proliferation is uncontrolled (does not follow the rules of normal cell growth), e.g.:

- Tumors can be derived from any cells even from cells that do not normally divide (nerve cells and striated muscle cells).
- Tumors continue proliferation even if the patient is starved.
- Cell proliferation is irreversible and unlimited. Thus cell proliferation progresses ever after cessation of any evoking stimuli. Example lung carcinoma will continue growing even if the patient stops smoking.

Tumor proliferation has no useful function. Some tumor cells may function in a harmful way e.g. tumors of neuroendocrine origin may secrete hormones.

Any neoplasm has two basic components:

1. The transformed (neoplastic) cells:
   a) the vast majority of tumors arise from a single transformed cell i.e. monoclonal.
   b) Few tumors are polyclonal i.e. the neoplastic cells are descendants of many transformed cells.
2. The supporting stroma & vessels consist of non-transformed elements derived from the host in response to factors released from the tumor e.g. angiogenesis factor.

CLASSIFICATION OF TUMORS

A) ACCORDING TO THEIR BEHAVIOR (BILOLGOCAL CLASSIFICATION)

1)Benign neoplasms (generally have good prognosis). See table below

2)Malignant neoplasms (generally have poor prognosis). See table below

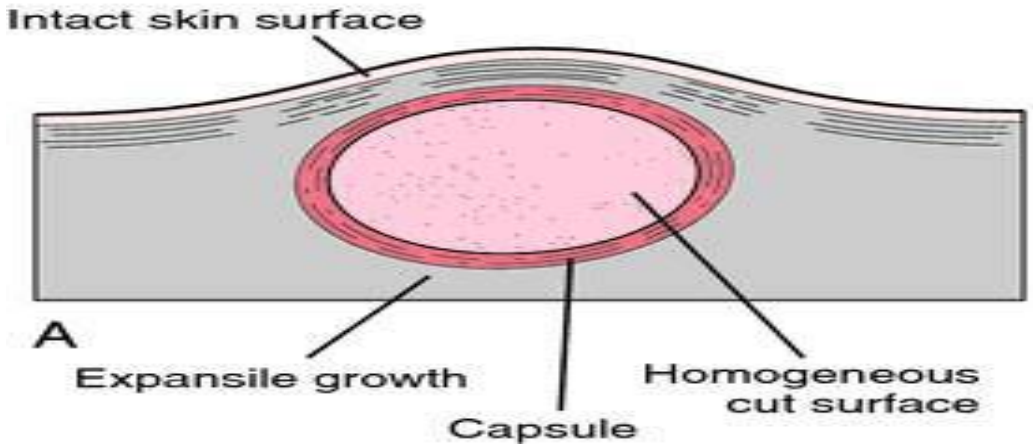
3)Intermediate tumors (locally malignant neoplasms locally aggressive tumors)

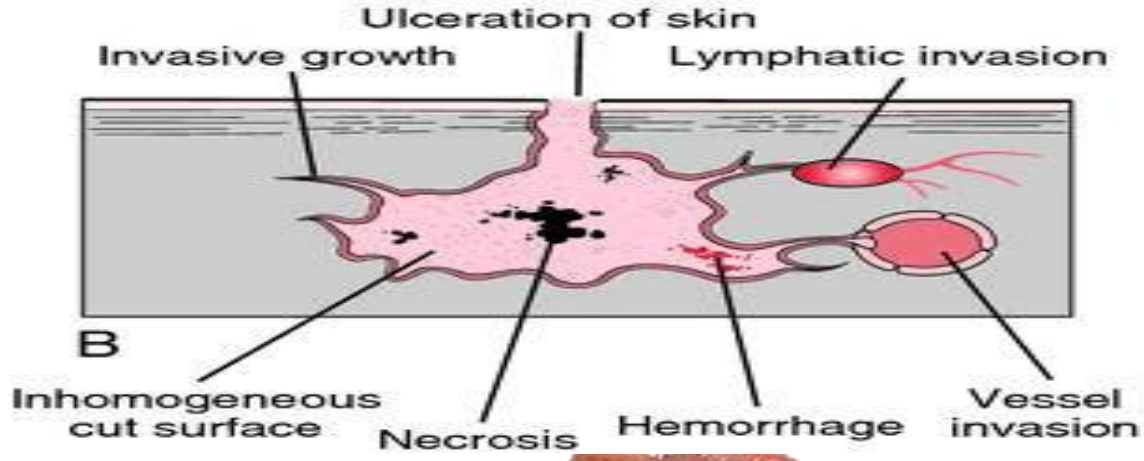
B) ACCORDING TO TISSUE OF ORIGIN (HISTOLOGICAL CLASSIFICATION)

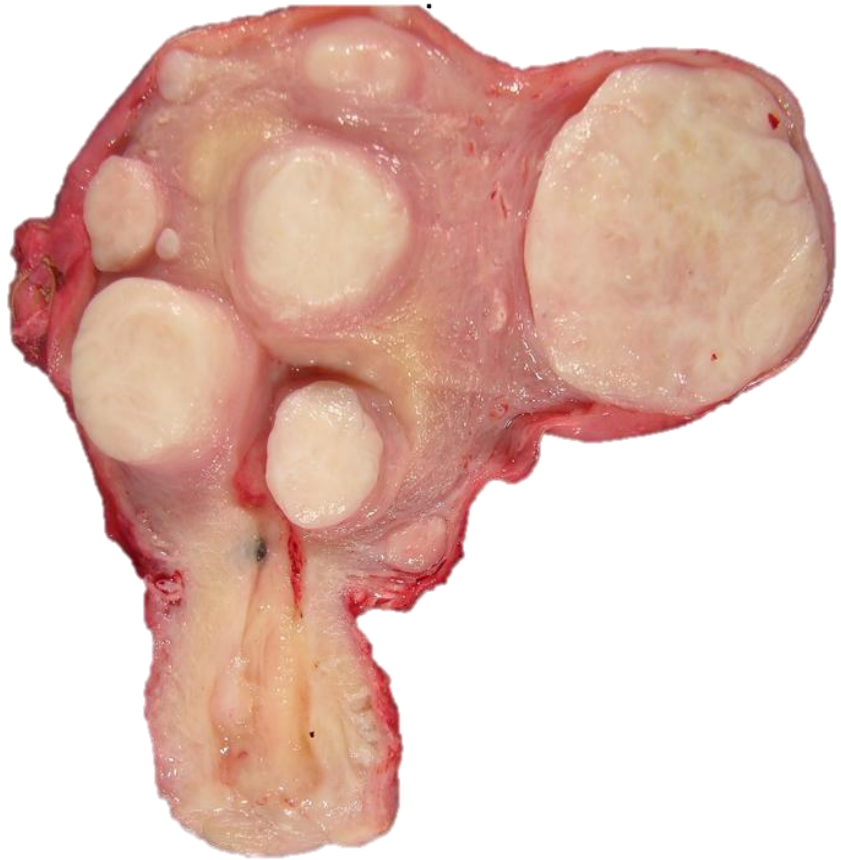
1) Epithelial tumors

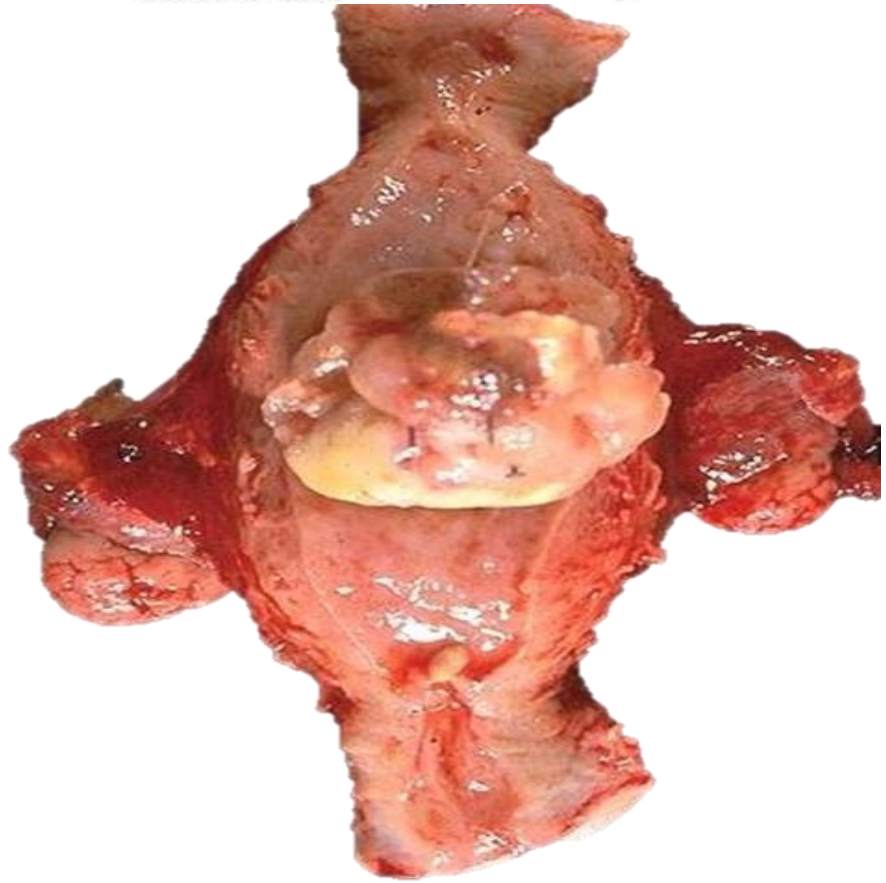
2)Mesenchymal tumors

3)Others


Intact skin surface
A
Expansile growth
Capsule
Homogeneous
cut surface


Ulceration of skin
Invasive growth
Lymphatic invasion
B
Inhomogeneous
cut surface
Necrosis
Hemorrhage
Vessel
invasion





CHARACTERISTICS OF BENIGN AND MALIGNANT NEOPLASMS:

Benign	Malignant
A) TUMOR BEHAVIOR 1 Rate of growth: often slow. 2 Mode of growth: Expansile, i.e. compressing the surrounding tissues without invasion. 3 prognosis: a) Benign tumors do not spread b) Benign tumors do not recur if well excised. c) Benign tumors do not dangerous unless:	**A) TUMOR BEHARIOR** 1 Rate of Growth: often rapid. 2 Mode of growth: Invasive, i.e. infiltrating and destroying the surrounding normal tissues. Some degree of expansion also exists. 3 Prognosis: a) Malignant tumors spread(see later) b) Recurrence after surgical excision is very common either from tumor cell remnants(not removed with excised tissue) or from a new neoplastic transformation. c) Malignant tumors are serious & cause death. Causes of death include:

- They arise in vital organs as brain.
- They arise in hollow organs (as intestine) causing obstruction.
- They produce hormones as in tumors of endocrine glands.
- Some benign tumors may change malignant. This may be clinically (becoming infiltrative, destructive and metastasizing) it is pathologically manifested by change of the gross pattern including capsular invasion necrosis &hemorrhage and change of microscopic pattern including loss of cellular &histological differentiation.

- Local organ destruction by direct spread.
- Distant organ destruction by metastases
- Destruction of vital centers (brain tumors)
- Obstruction of the lumen of hollow organs e.g. intestinal tumors
- Organ failure e.g.
- Renal failure due to urinary obstruction (or bilateral renal tumors)
- Liver failure & jaundice in case of primary or metastatic liver tumors

- Malnutrition due to:

➢ Loss of appetite.
➢ Interference with food intake (in cancer of GTI).
➢ Chronic toxemia due to secondary bacterial infection.

- Anemia is common due to:

✓ Recurrent hemorrhages from the tumor.
✓ Bone marrow destruction by metastases.
✓ High tumor cell metabolism may lead to folic acid deficiency.
✓ Iron deficiency may also occur.
✓ Autoimmune hemolysis in some cases.

- Cachexia:

-This is marked wasting & weakness (due to anemia, toxemia, malnutrition, organ failure).
-It is manifested by marked decrease of body weight accompanied by profound weakness, anorexia & anaemia. The body resistance is lowered & infections as pneumonia may terminate the patient's life.
-Recently it has been shown that TNF (released form activated macrophages) may play an important role in cachexia since it suppresses the patient's appetite & interferes with fat metabolism

- Para-neoplastic syndromes occur in 10% of cases. They are caused by abnormal products of the tumor e.g. ACTH causing Cushing's syndrome

B) TUMOR STRUCTURE
1-GROSS FEATURES:

- Tumor margins are well defined.
- Cut section of the tumor is commonly uniform with no hemorrhage or necrosis.
- A tumor arising inside a solid organ appears globular or ovoid & often becomes surrounded by a fibrous capsule composed of a rim of condensed connective tissue.

B) TUMOR STRUCTURE
1-GROSS FEATURES:

- Tumor margins are irregular or ill-defined.
- Cut section of the tumor often shows areas of hemorrhage and necrosis.
- A tumor inside a solid organ appears as an irregular noncapsulated mass. However vey rarely a malignant tumor may acquire a capsule (mostly incomplete & microscopically shows frequent foci of tumor invasion).

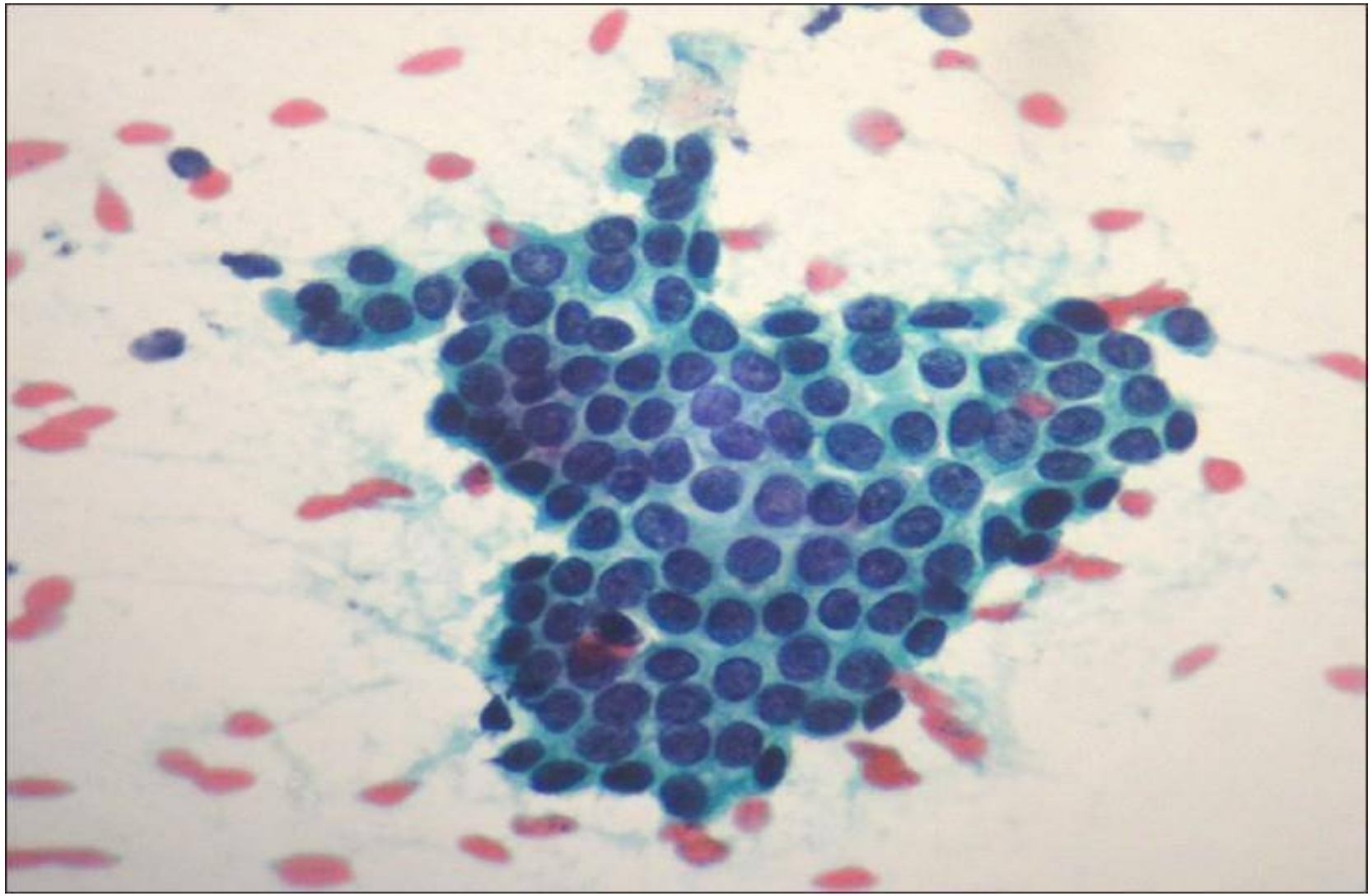
- A tumor arising from surface epithelia from a non-capsulated polyp (papilloma).

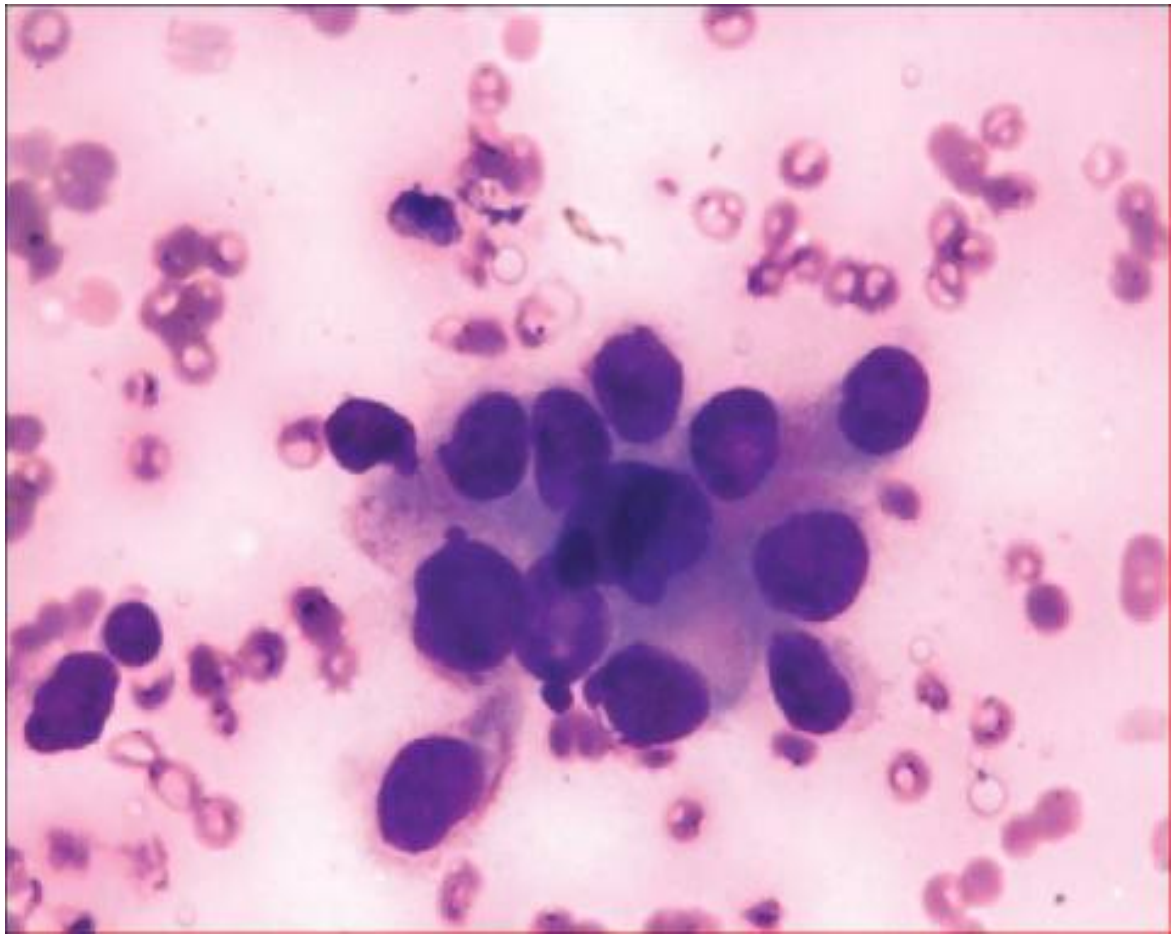
- A tumor arising from surface epithelia appears as noncapsulated masses assuming different patterns:

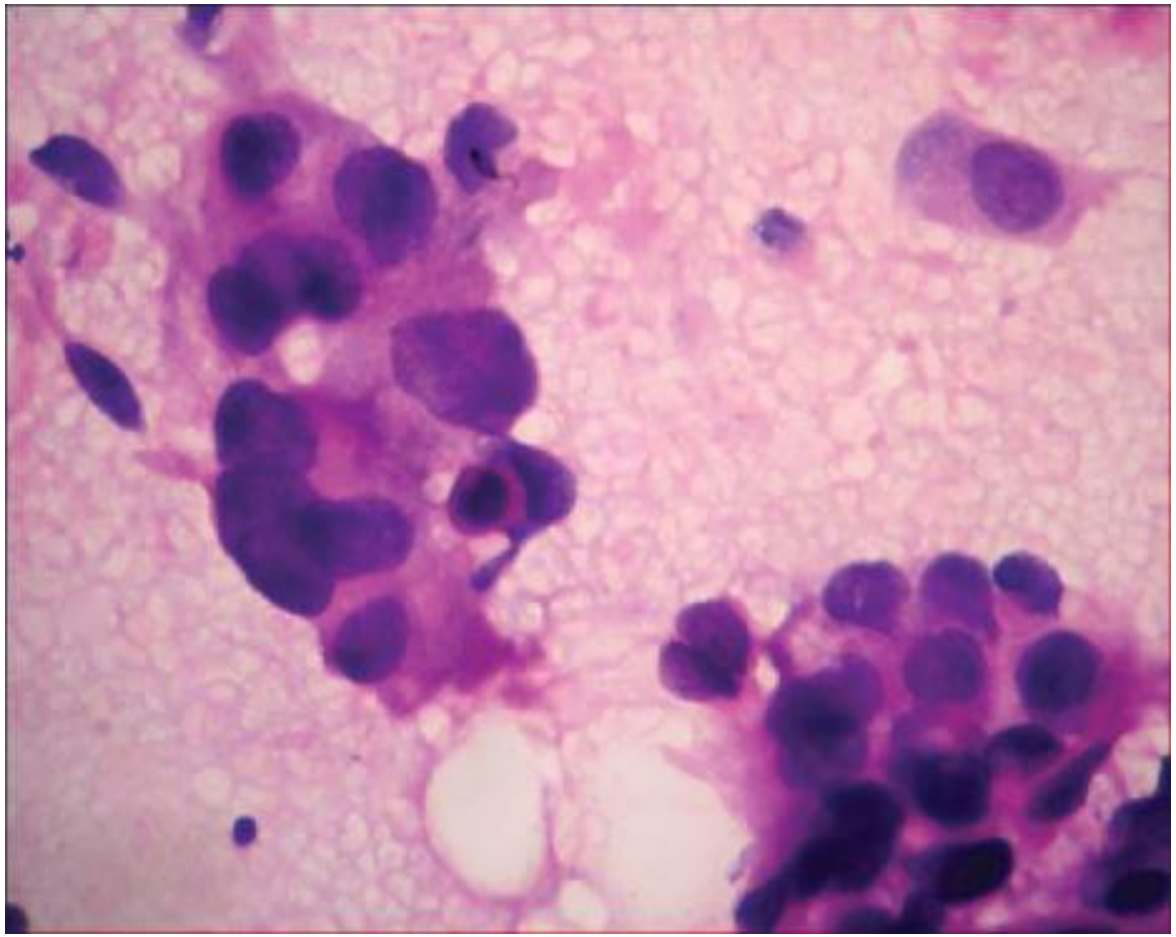
➢ Polypoid fungating cauliflower-like mass bulging over the surface. The base of the mass shows some infiltration under the surface.

➢ Ulcerating pattern: the malignant ulcer is irregular and has raised everted edges and rough necrotic floor.

➢ Infiltrating pattern: the growth infiltrates below the surface in tubular organs as intestine: this infiltrative pattern may be localized to a segment causing annular stricture.







2-MICTOSCOPIC FEATURES:

a)Cell differentiation:

cellular differentiation is the extent to which tumor cells resemble comparable normal cells. In benign tumors the cells are perfectly differentiated i.e. closely mimic the corresponding normal cells. Rare mitoses.

2-MICTOSCOPIC FEATURES:

a)Cellular anaplasia

this is abnormal differentiation: malignant cells show grades of cellular atypia referred to as anaplasia ranging between mild anaplasia & marked anaplasia characterized by:

- Cellular pleomorphism: nuclei may be irregular or bizarre shaped.
- Nuclear enlargement & hyperchromatism: due to increased synthesis of DNA, the nuclei appear dark (hyperchromatic) &the nucleo-cytoplasmic (N/C) ratio is increased approaching 1:1 normally N/C ratio is approximately 1:5.

- Nucleoli may be prominent.
- Abundant mitoses & frequently abnormal mitotic figures (e.g. tripolar spindles).
- Tumor giant cells containing a single large polypoid nucleus or multiple nuclei.

b) Histological Differentiation:

This is the degree of resemblance of the structural pattern of the tumor to the normal tissue.

b) Histological Differentiation:

in benign tumors the tumor cells exhibit structural patterns similar to the normal tissue. Thus adenoma of thyroid consists of acini almost similar to those of normal thyroid

Carcinoma may be graded as
well differentiated (grade I),
moderately differentiated (grade II),
poorly differentiated (grade III) &
undifferentiated (grade IV)
Better differentiated tumors tend to show less marked cellular anaplasia & grow slower. On the other hand undifferentiated tumor show great cellular anaplasia & grow faster. undifferentiated (grade IV) carcinoma is sometimes termed anaplastic carcinoma

c)Other features:

- The tumor has stroma containing few vessels.
- Secondary changes as myxoid or hyaline change may occur, but necrosis and hemorrhage are extremely exceptional.

c)Other features:

- The tumor stroma is rich in vessels, which may be sometimes thin- walled.
- Secondary changes may occur, and foci of hemorrhage and necrosis are common.

FACTORS INFLUENCING THE PROGNOSIS OF MALIGNANT TUMORS:

1 tumor type: e.g. melanoma & most sarcomas have poorer prognosis than most carcinomas.

2 tumor site: e.g. superficial tumors as those arising from skin are diagnosed earlies and treated earlier than deeply seated tumors and brain tumors.

3 differentiation: well differentiated tumors grow slower than the less differentiated ones.

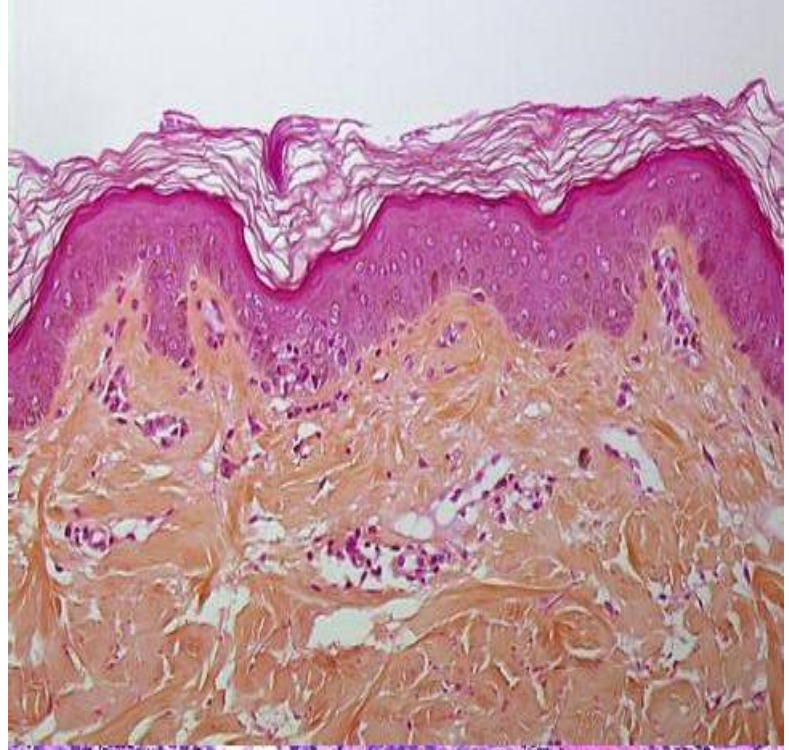
4 tumor stage the higher the stage the worst in the prognosis. TNM staging

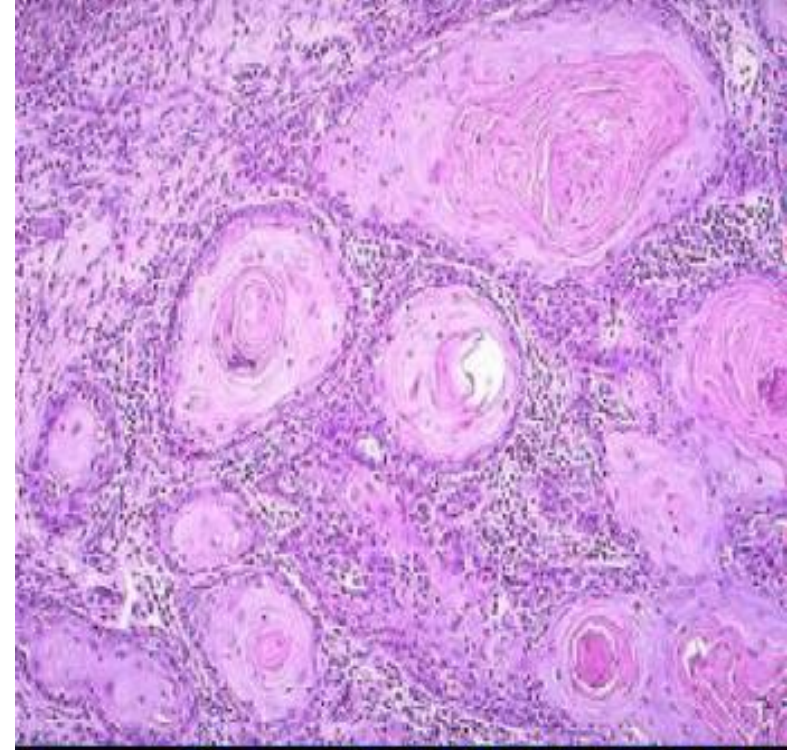
5 immune response against cancer

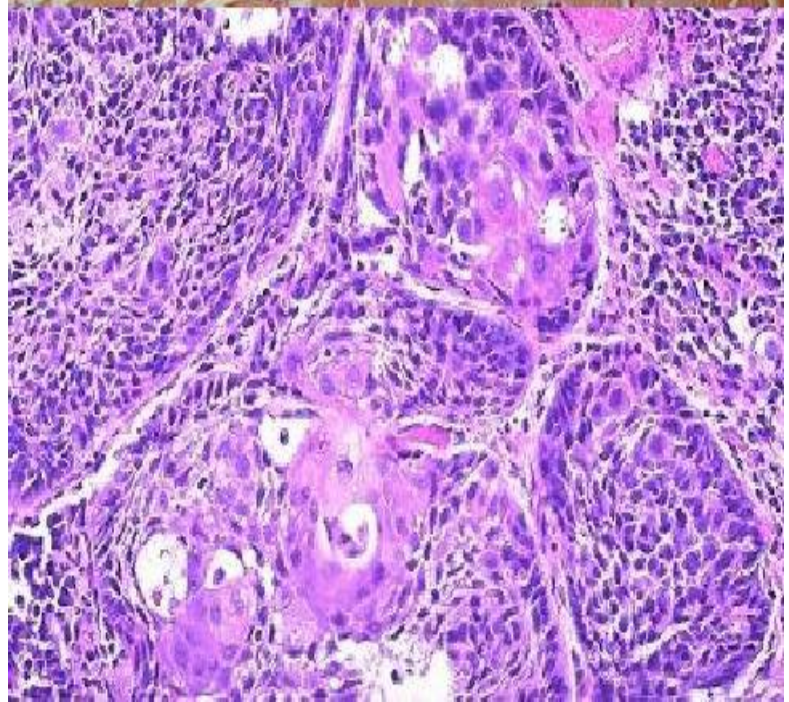
6 Growth Fraction (GF): this is the proportion of cells within neoplasm entering the cell cycle (i.e. out of G0 phase). The importance of GF is that most antineoplastic drugs act on dividing cells; thus tumors with high GF are most susceptible to anticancer agents & are also the most rapidly growing if left untreated

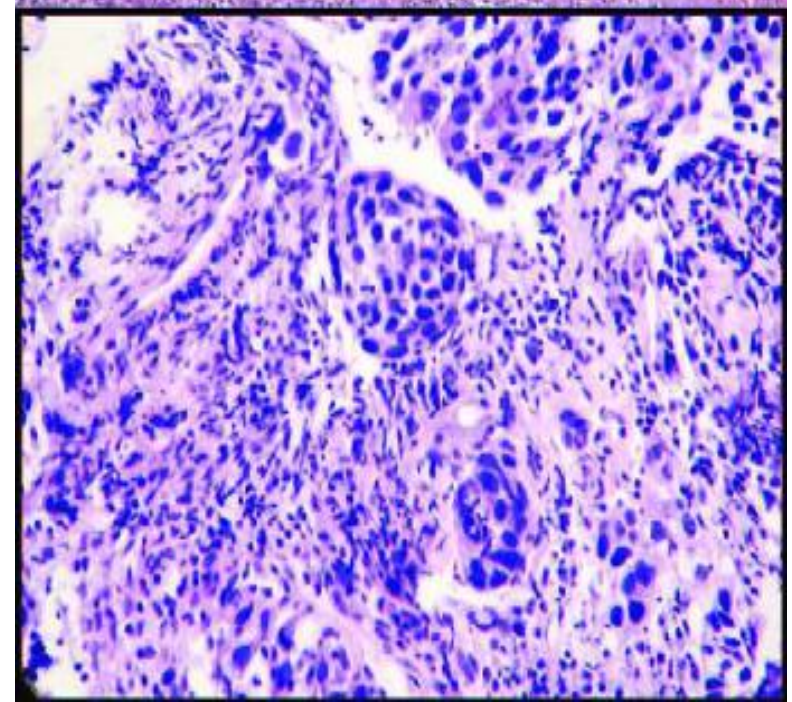
7 Efficiency of treatment : there are three main methods of treatment of malignant tumors (used separately or in various combinations) including surgery , chemotherapy (anti cancer drugs)and irradiation . the efficiency of treatment affect the prognosis.

8- Tumor hormonal receptors : the growth of some tumors depends partly on hormone stimulation . the cells of such tumors have hormone receptors. Examples include estrogen receptors positive in breast carcinoma and androgen receptors positive in prostatic carcinoma. Depriving these tumors from hormone stimulation helps in controlling their growth. Example anti- estrogen therapy (oophorectomy) for breast cancer and anti-androgen therapy (orchidectomy) for prostatic cancer . Thus a hormone receptors positive tumor is better than a hormone receptors negative tumor.









SPREAD OF MALIGNANT TUMORS

MECHANISM OF SPREAD

Malignant tumors spread locally to surrounding tissues and distantly to remote sites (metastases).

Mechanism of spread includes:

1) Invasion of Extracellular Matrix (ECM): The following steps are included:

- *Loss of cellular cohesion:* normal cells are glued together by molecules called cadherins.

  Tumor cells lose the normal cadherin expression, allowing them to detach (loosening up).
- *Attachment of tumor cells (through receptors) to matrix components:* mainly to laminin of basement membrane and fibronectin of the interstitial tissue. Attachment to ECM promotes the next steps.

- *Degradation of the ECM by proteolytic enzymes secreted by the tumor cells or by stimulated host cells (fibroblasts & macrophages).* Several enzymes are released as type IV collagenase (causing lysis of basement membranes of epithelia and of vessels) and cathepsin D (causing degradation of interstitum). Degradation of ECM is very is very important for the tumor cells to create passageways for their migration.
- *Migration(mobility) of tumor cells (by pseudopodia).* This is mediated by tumor-derived cytokines (mobility factors) such as “autocrine mobility factor”. The process may be helped by acquiring negative charges on surface of tumor cells causing their repulsion and loss of contact inhibition.

2- **Vascular Dissemination and Homing of Tumor Cells:**

- Tumor cell mobility → contact of tumor cells with blood vessels.
- Tumor cell penetrate lymphatics, capillaries & venules, but rarely arterioles (thick-walled)
- Once the tumor cells cross the vascular basement membranes, they reach circulation as tumor emboli. Fate of tumor emboli:

  a) Most tumor emboli are destroyed by immune mechanisms.

  b) The surviving tumor cells (single or in clumps) adhere to platelets. This affords them some protection from antitumor host immune cells.

  c) Finally the surviving tumor cell emboli get impacted in small vessels adherence to the endothelium → crossing the basement membrane (by mechanisms similar to those described above) → settlement in the new site (homing) → proliferation of tumor cells → metastatic deposits (metastasis, secondary tumors).

ROUTES OF SPREAD

1- LOCAL (DIRECT) SPREAD

- Malignant cells spread in all directions along lines of least resistance. Some structures as cartilage, periosteum & elastic tissue delay direct spread. Mechanism of direct spread (invasion of ECM): see above.
- Direct spread to a surface (skin or mucosa) leads to ulceration (malignant ulcer). Direct spread from one hollow organ to anther adjacent one causes a malignant fistula (e.g. between rectum and vagina)
- Some tumors may spread along the perineural space, e.g. prostatic carcinoma causing severe pain.

2- DISTANT SPREAD (METASTASIS)

metastasis (development of secondary malignant implants, discontinuous with the primary tumor) can occur by many routes; the most common of which is lymphatic & vascular spread.

A) LYMPHATIC SPREAD: Occurs more commonly with carcinomas that sarcomas:

1) Lymphatic Embolism:

- Malignant cells invade the wall of lymphatic vessels. Detached cells are carried as tumor emboli with lymph.
- Tumor emboli are arrested in the subcapsular sinus of the lymph node. The malignant cells proliferate & gradually destroy & replace the node.
- Spread from one node to another may occur by efferent lymphatics.
- Grossly: the affected nodes are enlarged & firm. Cut surface appears grayish white. If lymph node capsules are infiltrated, the nodes become fixed.
- Microscopically the metastatic deposit resembles the primary tumor from which it is derived.
- Progressive spread by the lymphatic route may ultimately lead to tumor emboli within the main lymphatic ducts (thoracic duct), from which tumor emboli reach the venous circulation causing hematogenous spread

2) Lymphatic permeation: sometimes, malignant cells grow inside the lumen of lymphatics as solid columns causing marked lymphatic obstruction and lymphatic oedema. Breast carcinoma is an example of tumors that commonly permeate the lymphatics.

B) HEMATOGENOUS (BLOOD) SPREAD:

Pattern of blood spread in sarcoma & carcinoma: see later

Ways & mechanism by which malignant cells reach the blood:

- Malignant cells may reach the venous circulation through thoracic duct (after lymphatic spread). This is the usual way in case of carcinoma.
- Malignant cells may reach the circulation by direct invasion of blood vessels within the tumor. This is the usual way in vase of sarcoma. It is worth moting that malignant tumors are richly vascularized due to release of a tumor derived angiogenesis factor that leads to formation of feeding vessels derived from the host. These vessels are more numerous and thin-walled in case of sarcomas.

Course of tumor emboli depends on anatomical factors:

- Emboli derived from primary tumors of organs drained by systemic veins (vena cava) e.g. Breast, skin and kidney, are carried through pulmonary arteries to lungs causing lung metastases.
- Emboli derived from tumors of lungs (whether primary or metastatic) are carried through pulmonary veins to left side of heart → systemic arterial circulation → metastases in different organs as liver, bones, brain…etc.

- Emboli derived from primary tumors of organs drained by the portal vein (tumors of gastrointestinal tract) are carried to liver causing liver metastases. Further spread from liver gives rise to emboli that reach the hepatic veins and consequently to the inferior vena cava to lung … etc.
- Emboli reaching the vertebral system of veins from tumors of pelvic, abdominal or thoracic organs leads to metastases in brain, spinal cord and vertebrae without causing lung metastases. This is because the vertebral veins have wide anastomotic channels connection them with the lumbosacral, abdominal and thoracic veins.

Pathology of organ metastases:

- The most common sites of metastases are the liver, lungs, bones &brain.
- Metastases are rare in muscles ,spleen, pancreas &intestine.
- Gross picture: Metastases appear as scattered round nodules of variable sizes.
- Microscopic picture: Metastases resemble the primary tumor from which they are derived.

- Bone metastases:
  - It is common in carcinomas of thyroid, breast, lung, prostate & kidney.
  - It develops in vascular bone sites (ends of long bones, vertebrae, ribs, sternum, pelvis & skull)
  - Bone metastases are commonly osteolytic
  - In case of cancer prostate it may be osteosclerotic (new bone formation is stimulated around the metastatic deposit, since malignant cells of prostatic origin secrete phosphatase).
  - Effects of bone metastases include
    ١) pathological fracture.
    ٢) severe pain
    ٣)bone marrow destruction leading to anemia, leucopenia & thrombocytopenia

C) SPREAD THROUGH BODY CABITIES (TRANSCOELOMIC SPREAD):

When the serosal covering of an organ is infiltrated by malignant cells of a tumor within this organ, some of these cells may detach and become implanted in other sites. This may be associated with hemorrhagic effusion. Transcoelomic spread includes:

- Trans-peritoneal spread from carcinoma of stomach, colon, pancreas …etc metastatic peritoneal/ omental nodules accompanied by hemorrhagic ascites.

Krukenberg tumors: in females, carcinoma of stomach (or colon) may be associated with bilateral ovarian metastases, termed “krukenberg tumors” which were thought to represent transcoelomic spread. They are now believed to be due to retrograde lymphatic or blood spread, since krukenberg tumors can also occur in case of cancers of breast, urinary bladder & biliary tract.

- Trans-pleural and trans-pericardial spread from lung or breast carcinoma causes metastases on the diaphragm accompanied by hemorrhagic pleural or pericardial effusion.
- Trans CSF spread may occur in malignant tumors of brain metastases within the walls of ventricles, base of skull and spinal cord.

D) OTHER METHODS OF SPREAD:

- Transluminal implantation: malignant cells detached from transitional carcinoma of the renal pelvis may become implanted in the mucosa of urinary bladder forming secondary deposits.
- Surgical implantation: instruments contaminated with malignant cells during surgical management of a tumor may transfer tumor cells into the surgical wound causing secondary tumor deposits.
- Implantation from carcinoma of lower lip may lead to a secondary tumor in the upper lip.

CHARACTERISTICS OF CARCINOMA AND SARCOMA

The characteristics of the most two common types of malignant tumors (carcinoma and sarcoma) are listed in the following table.

carcinoma	sarcoma
Definition: malignant tumor of epithelium - Most common form of malignancy. Age: usually (but not always) above 40 - years Growth rate: rapid but slower than - sarcoma. Mode of growth: tumor margins are often more infiltrative than sarcoma.	Definition: malignant tumor of mesenchyme. Much less common than carcinoma. Age: usually (but not always) below 20 years Growth rate: generally faster than carcinoma. Mode of growth: tumor margins appear less infiltrative &more expansile than carcinoma.

Gross features:

- Size is usually (but not always) less bulky than sarcoma.
- Haemorrhage &necrosis are usually less.
- Consistency: usually hard. May be soft as in mucoid & medullary carcinomas.
- Colour is usually grayish.
- Carcinoma in a solid organ forms an irregular growth.
- Carcinoma arising from a surface forms a fungating cauliflower mass, an ulcerative growth or an infiltrative pattern which may be diffuse or annular (see before).

Gross features:

- Most sarcomas form bulky masses.
- Haemorrhage &necrosis : usually prominent.
- Consistency: usually soft and fleshy.
- Colour is tinged pink due to richer vascularity.
- Sarcomas arising in a solid organ forms an expansile bulky growth.
- Sarcomas do not arise from surface epithelium therefore do not classically appear as ulcerating or cauliflower masses, but thy can arise from subepithelial mesenchyme, and appear as bulky expansile growth .

Microscopic features:

Cellular anaplasia: usually less marked than sarcoma

Histological differentiation: depends on arrangement of the tumor cells. When the tumor is anaplastic, it may be confused with undifferentiated sarcoma. It is worth nothing that, both in cases of carcinoma and sarcoma, poor grades of histological differentiation are associated with high grades of cellular anaplasia.

Cell cohesion: neoplastic cells exhibit variable grades of cohesion. This is however poor in anaplastic carcinomas

Blood vessels are less and better formed than in sarcoma

Hemorrhage, necrosis & secondary changes are usually less profound than in sarcoma.

Microscopic features:

Cellular anaplasia is generally greater than carcinoma. Than carcinoma.

Histological differentiation depends in most cases on cell products which may be intracellular (as fat in case of liposarcoma) or extracellular (matrix) as collagen in case of fibrosarcoma and osteoid in case of osteosarcoma. Thus if a sarcoma arising for example from osteoblasts, shows no osteoid, it is considered undifferentiated sarcoma.

Cell cohesion is often absent and the tumor cells occur singly

Blood vessels are more numerous and thin-walled

Hemorrhage, necrosis & secondary changes as hyaline and myxomatous changes are common

Distant spread

Usually slower than sarcoma

Occurs early by lymphatics then by blood.

However , some carcinomas spread relatively early by blood (carcinoma of thyroid, breast, lung, kidney, prostate & placenta).

Staging of carcinoma:

TNM system: This is the most popular system for cancer staging

T: represents tumor state & size, graded as Tis (tumor in situ), T1, T2, T3, T4.

N: represents the degree of spread to lymph nodes and is graded as N0,N1,N2 & N3 (N0 means absent)

M: represents metastases due to blood spread and is graded as 0 (absent) or 1(present).

Distant spread

Usually faster than carcinoma

Occurs early by blood &rarely (10%) by lymphatics.

Staging of sarcoma:

TNM system (modified):

T: usually graded as T1 or T2 according to size

N: usually graded as N0 &N1

M: usually graded as M0 &M1

CHARACTERISRICS OF INTERNEDIATE TUMORS

(LOCALLY MALIGNANR TUMORS, TUMORS OF ETTARIC BEHAVIOR)

- These tumors are characterized by:

  1 a slower rate of growth than frank malignant tumors.

  2 local invasion without distant spread (no metastases)

  3 proliferating tumor cells usually show low grade atypia

- Prognosis: much better than malignant tumors. However:

  1 local recurrence after surgical excision is common

  2 they may rarely change into frank malignant tumors that metastasize.

- Example of intermediate locally malignant tumors:
  1. Basal cell carcinoma.
  2. Giant cell tumors of bone (osteoclastoma).
  3. Adamantinoma.
  4. some neuroendocrine tumors as carcinoid tumors.
  5. Chordoma.
  6. Some tumors of CNS as craniopharyngioma.

HISTOLOGICAL CLASSIFICATION OF TUMOR

Tissue	Benign	Malignant
A) EPITHELIUM:		
1-SURFACE EPITHELUM:		
a)stratified squamous	Squamous cell papilloma	Squamous cell carcinoma
b) Transitional	Transitional cell papilloma	Transitional cell carcinoma
c) Ducts of glands	duct papilloma	Duct carcinoma
d) Mucosa of GIT	Adenomatous	Adenocarcinoma
2-GLANDULAR EPITHELIUM		
Endocrine & exocrine glands.	Adenoma	Adenocarcinoma

B)MESENCHYME:		
1-CONNECTIVE TISSUE		
a)fibrous	Fibroma	Fibrosarcoma
b)adipose	Lipoma	Liposarcoma
c)primitive mesenchyma	Myxoma	Myxosarcoma
d)bone	Osteoma & osteoblastoma	Osteosarcoma
e)cartilage	Chondroma, osteochondroma	Chondrosarcoma
2-SMOOTH MUSCLE:	Leiomyoma	Leiomyosarcoma
3-STRIATED MUSCLE:	Rhabdomyoma	Rabdomyosarcoma
4-ENDOTHELIUM	Angioma	Angiosarcoma
5-MESOTHELIUM	Rare	Mesothelioma
6-SYNOVIUM	Rare	Synovial sarcoma

C)OTHER e.g. :		
1- pigmented cells	Nevus (benign melanoma)	Malignant melanoma
2- totipotent cells	Teratoma, mature (benign)	Teratoma, immature & malignant
3- embryonic cells	……	Embryonic tumors.
4- lymphoid & hemopoeitic	…….....	Lymphoma & leukemia .
5- schwann cells	Schwannoma	Malignant schwannoma.
6- trophoblast	Vesicular mole	Choriocarcinoma.
7- neuroglia	Example astrocytoma grade I	Example: astrocytic tumors grade II.III &IV
8- mixed origin	Example: adenofibroma	carcinosarcoma

EMBRYONIC TUMORS

Definition & age: malignant tumors derived from embryonic cell remnants (ectodermal, endodermal or mesodermal). They mostly occur in infants and young children. Rare in adults.

Origin: in the embryo, each organ is derived from a group of embryonic cells (ectodermal, mesodermal or/and endodermal). After birth, remnants of these cells may exist & continue differentiation for few years. Embryonic tumors arise from these embryonic cell remnants which differ from teratomas in a) consist of structures derived from the embryonic cells from which the tumor arises (&not from all layers as in teratoma) b)almost always malignant.

Structure:

- Primitive embryonic (undifferentiated) malignant small round cells
- Some of these primitive cells may differentiate into mature tissues of the same class from mesodermal cells they are derived (e.g. smooth muscle in embryonic tumors derived from mesodermal cells)

Examples:

1. Neuroblastoma of adrenal medulla & sympathetic ganglia.
2. Retinoblastoma of eye.
3. Nephroblastoma of kidney.
4. Hepatoblastoma of liver.
5. Medulloblastoma of brain.

HAMARTOMA

This is tumor-like developmental malformation formed of noncapsulated mature tissues of the affected organ, arranged haphazardly. It usually stops growing after puberty. Some are precancerous.

Example of hamartomas:

- Lung hamartoma (a mixture of cartilage, smooth muscle and bronchial mucosal tissue).
- Kidney hamartoma
- Angiomas (hemangioma and lymphangioma)
- Navi
- Exostosis (osteochondroma)
- Neurofibromatosis

Epidemiology of cancer

Cancer incidence

Cancer is the second leading cause of death.

Most common cancers:

♂: prostate, lung, colorectal

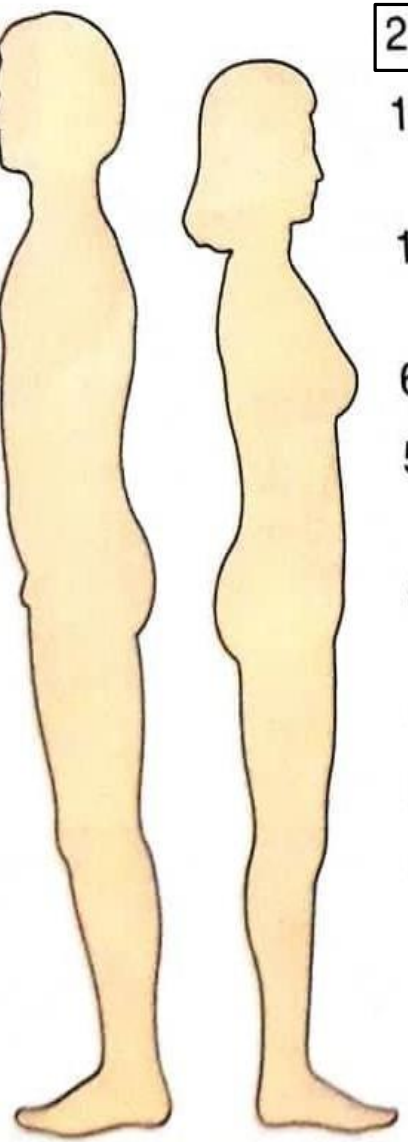
♀: Breast, lung, colorectal

Most common causes of CA deaths:

♂: lung, prostate, colorectal

♀: lung, Breast, colorectal

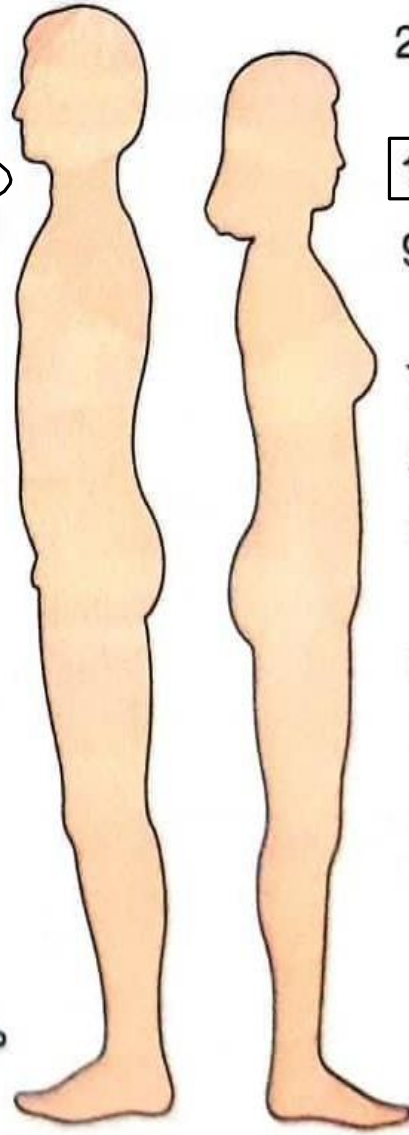
A. 2010 ESTIMATED CANCER INCIDENCE BY SITE AND SEX*



Prostate	28%	28%	Breast
Lung and bronchus	15%	14%	Lung and bronchus
Colon and rectum	9%	10%	Colon and rectum
Urinary bladder	7%	6%	Uterine corpus
Melanoma of the skin	5%	5%	Thyroid
Non-Hodgkin lymphoma	4%	4%	Non-Hodgkin lymphoma
Kidney	4%	4%	Melanoma
Oral cavity	3%	3%	Kidney
Leukemia	3%	3%	Ovary
Pancreas	3%	3%	Pancreas
All other sites	19%	20%	All other sites

* Excluding basal and squamous cell skin cancers and carcinoma in situ (except urinary bladder)

B. 2010 ESTIMATED CANCER DEATHS BY SITE AND SEX



Lung and bronchus	29%	26%	Lung and bronchus
Prostate	11%	15%	Breast
Colon and rectum	9%	9%	Colon and rectum
Pancreas	6%	7%	Pancreas
Liver	4%	5%	Ovary
Leukemia	4%	4%	Non-Hodgkin lymphoma
Esophagus	4%	3%	Leukemia
Non-Hodgkin lymphoma	4%	3%	Uterine corpus
Urinary bladder	3%	2%	Liver
Kidney	3%	2%	Brain
All other sites	20%	24%	All other sites

Factors that affect CA incidence

- Geographic location
- Environmental variables
- Age
- Heredity
- Acquired preneoplastic disorders

1. Geographic location

- **Geographic differences are environmental rather than genetic.**

  Gastric CA -- High in Japan

  Skin CA------ High in New Zealand

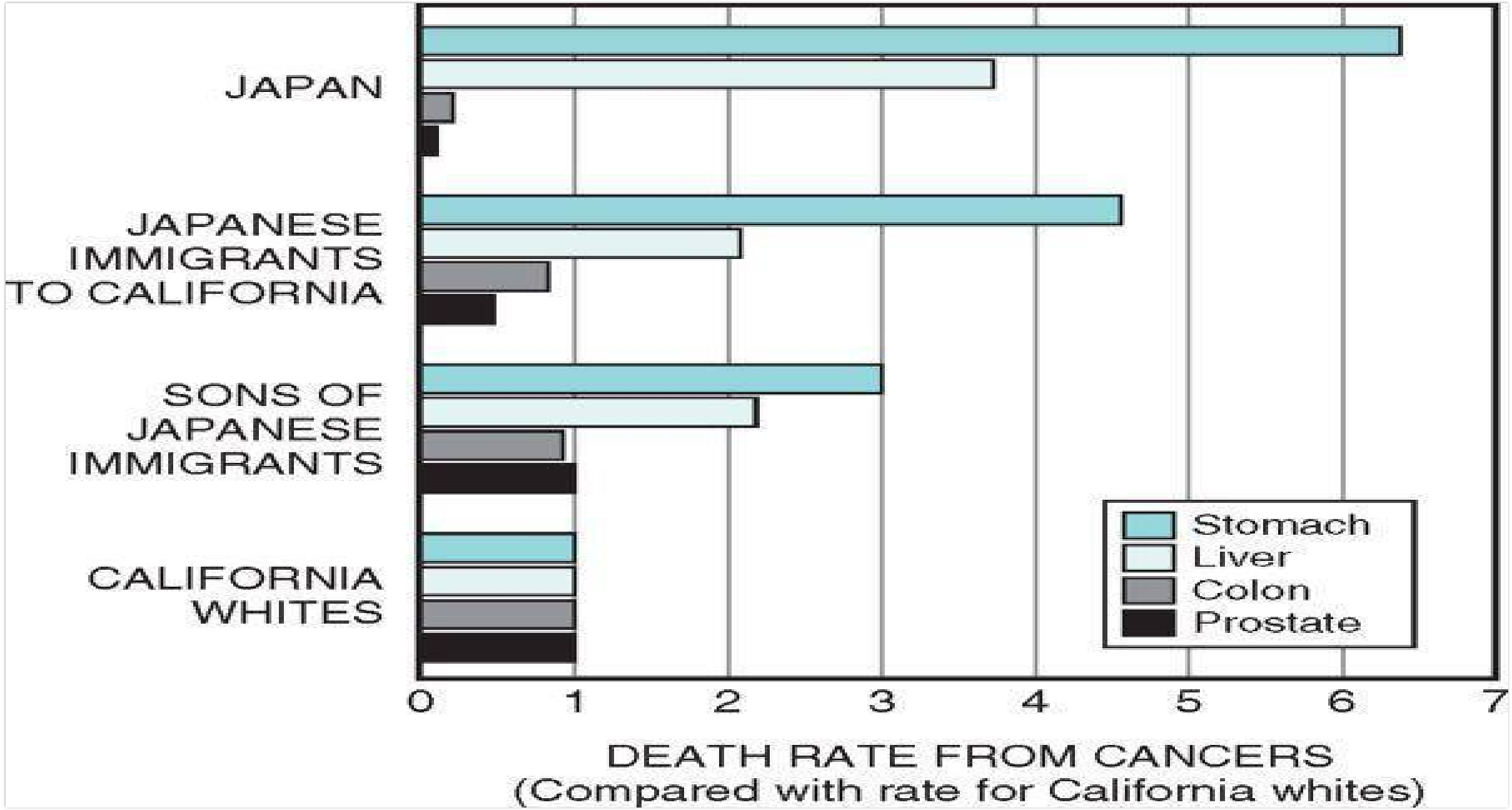
  Hepatocellular CA --- High in Africa,China

  Breast CA ---- High in USA

  Prostatic CA ---- High in USA

  Colorectal CA ----High in USA

- **Second generation Japanese living in US have intermediate mortality rates**


JAPAN
JAPANESE IMMIGRANTS TO CALIFORNIA
SONS OF JAPANESE IMMIGRANTS
CALIFORNIA WHITES
Stomach
Liver
Colon
Prostate
0
1
2
3
4
5
6
7
DEATH RATE FROM CANCERS
(Compared with rate for California whites)

2- Environmental factors

- Sunlight … skin cancer
- Diet… colon CA
- Personal habits
- Occupation

Personal habits

- **Smoking:**

  Oropharynx, larynx, lung, esophagus, pancreas, cervix, kidney & bladder.

- **Alcohol:**

  Oropharynx, larynx, esophagus & HCC (alcoholic cirrhosis)

- *Cervical CA is related to:*
  - *Age at first intercourse.*
  - *Number of sexual partners.*

  } STD (HPV)

3- Age

- In general , cancer incidence ↑ with AGE

Most cancer mortality (55y-75)

- However , certain cancers occur

more in children (<15 years)

Acute Leukemia

Some CNS Tumors (medulloblastoma)

Neuroblastoma

Wilms tumor (nephroblastoma)

4- Heredity

- 5-10% of tumors

- **Three categories:**
  - Autosomal dominant inherited cancer syndromes
  - Autosomal recessive syndromes of defective DNA repair.
  - Familial cancers

Aetiological aspect of neoplasia

Most tumors arise from a single clone of cells (monoclonal) and rarely polyclonal. It is now accepted that most changes in the genetic material of the cell is paramount importance in carcinogenesis factors that can produce such genetic damage are called cracinogens. Tumor development is a complex multistep process starting by tumor initiation i.e. changing normal cells into abnormal cells (latent tumor cells) through gene abnormalities caused by unknown or known stimuli , followed by tumor cell promotion (transformation of latent cells into tumor cells , that start unlimited division & tumor formation). The requirement of more than one factors for tumor production may explain why cancer develop in some smokers but not in all smokers.

I) the molecular basis of cancer

Genetic predisposition of cancer:

Genetic defect may be hereditary e.g. inheritance of RB gene → retinoblastoma , APC gene → colonic cancer & BRCA genes breast cancer.

More commonly genetic defects are acquired defects causing carcinogenesis involve four classes of normal cell regulatory genes where gene damage by carcinogens → carcinogenesis (tumorogenesis). The gene classes include growth promoting proto-oncogenes , growth inhibiting tumor suppressor genes (anti-oncogenes), genes that regulate apoptosis & gene that regulate DNA repair.

1 ONCOGENES AND PROTO-ONCOGENES:

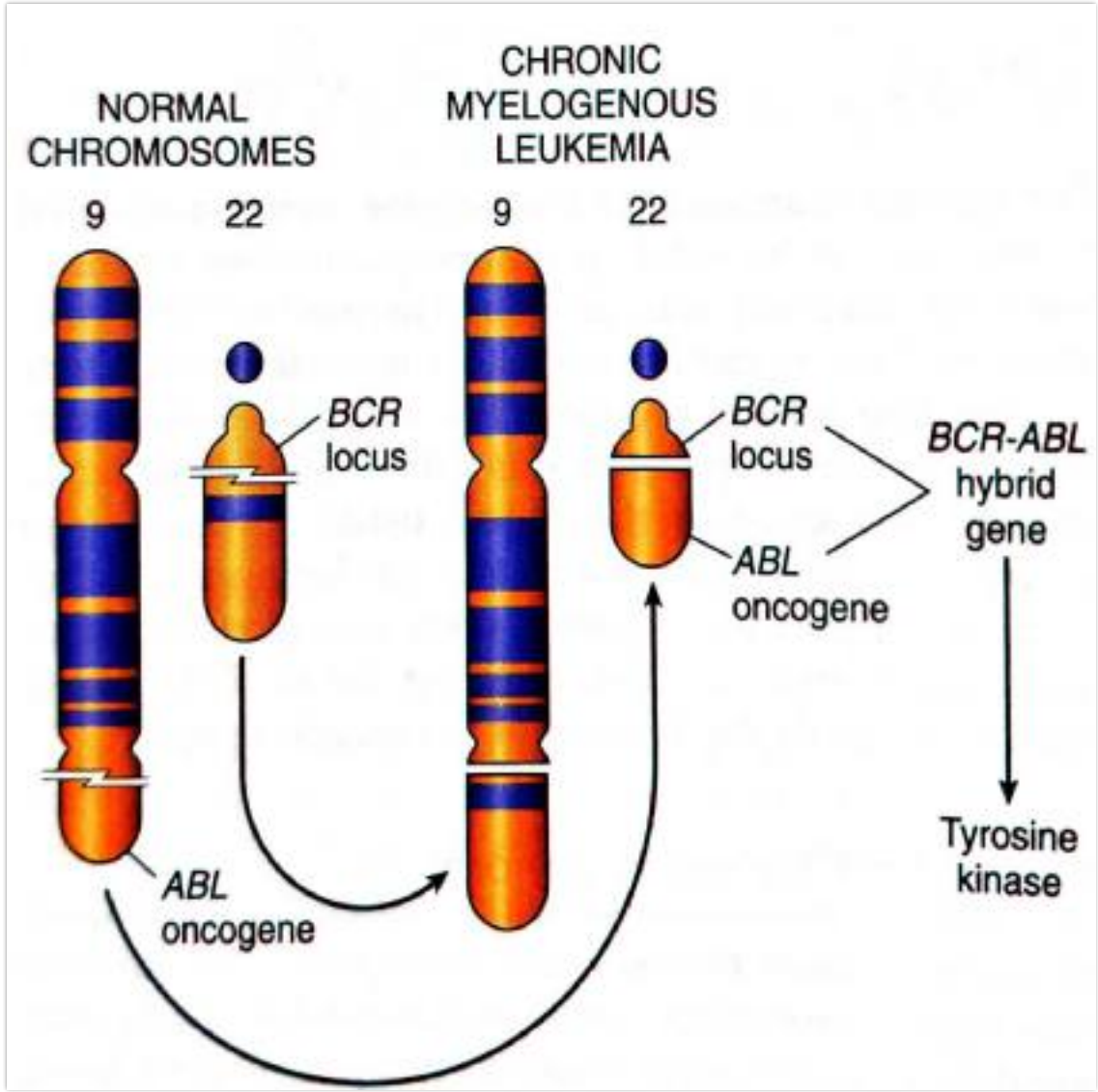
There are normal cellular genes called protooncognes having a potential to transform into cancer – causing oncogenes.

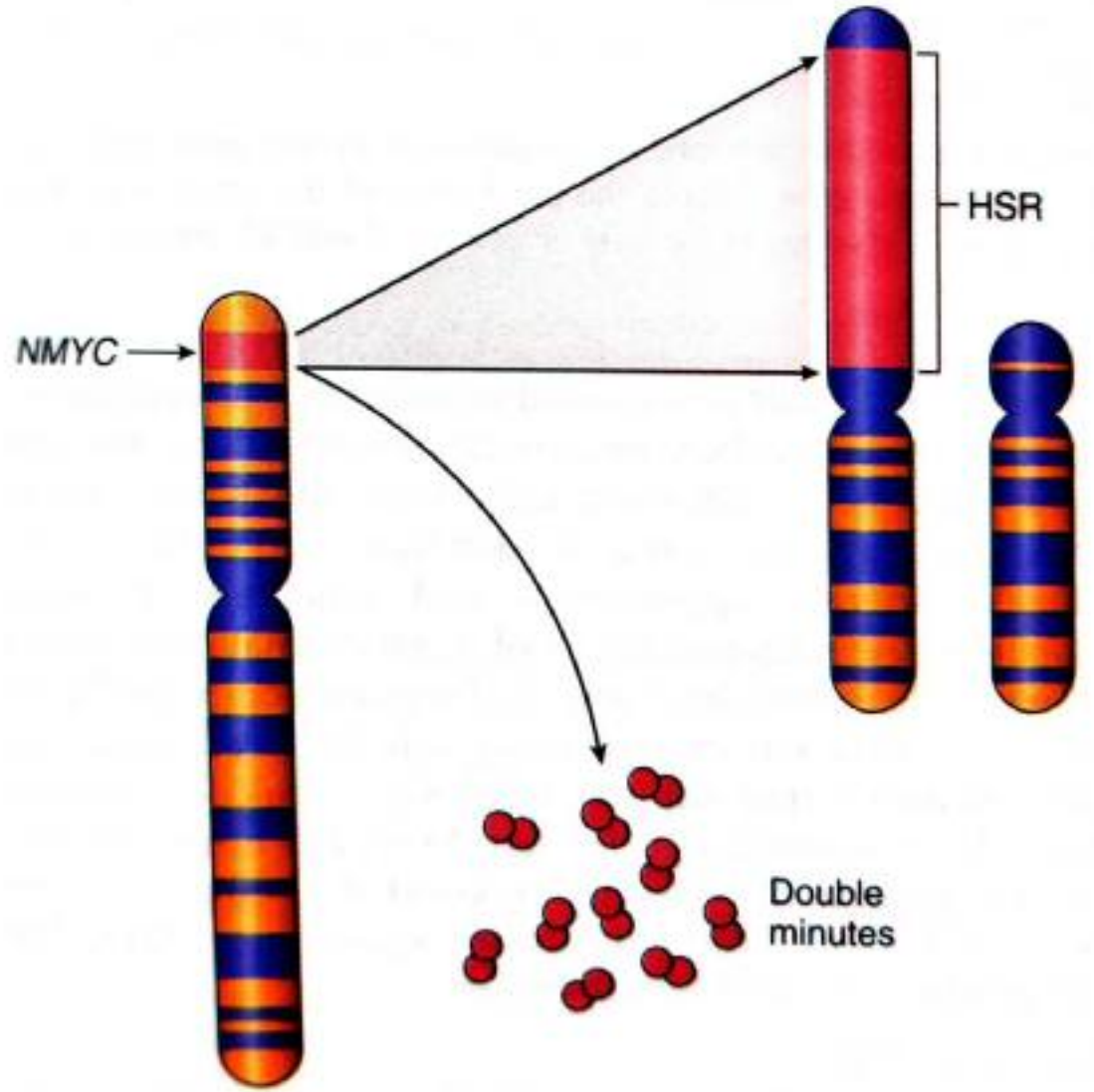
The transformation of proto-oncogenes into oncogenes occur by one of three mechanisms:

i. point mutations, possibly due to exposure to cancer – causing chemicals.

ii. chromosomal translocations where during cell divisions a part of a certain chromosome (with its genes) is relocated into another chromosome leading to gene fusion or change in the sequence of genes, finally resulting in activation and transformation of proto-oncogenes

iii. Gene amplification: this is reduplication of proto-oncogenes.


NORMAL CHROMOSOMES
CHRONIC MYELOGENOUS LEUKEMIA
9
22
9
22
BCR locus
BCR locus
ABL oncogene
BCR-ABL hybrid gene
ABL oncogene
Tyrosine kinase


NMYC
HSR
Double minutes

Oncogenes encode synthesis of proteins called oncoproteins. These oncoproteins differ from the normal products of proto-oncogenes in that they are devoid of important regulatory elements and that their production in the transformed (neoplastic) cells is not dependent on growth factors or other external signals.

2 TUMOR SUPPRESSOR GENES (ANTIONCOGENES)

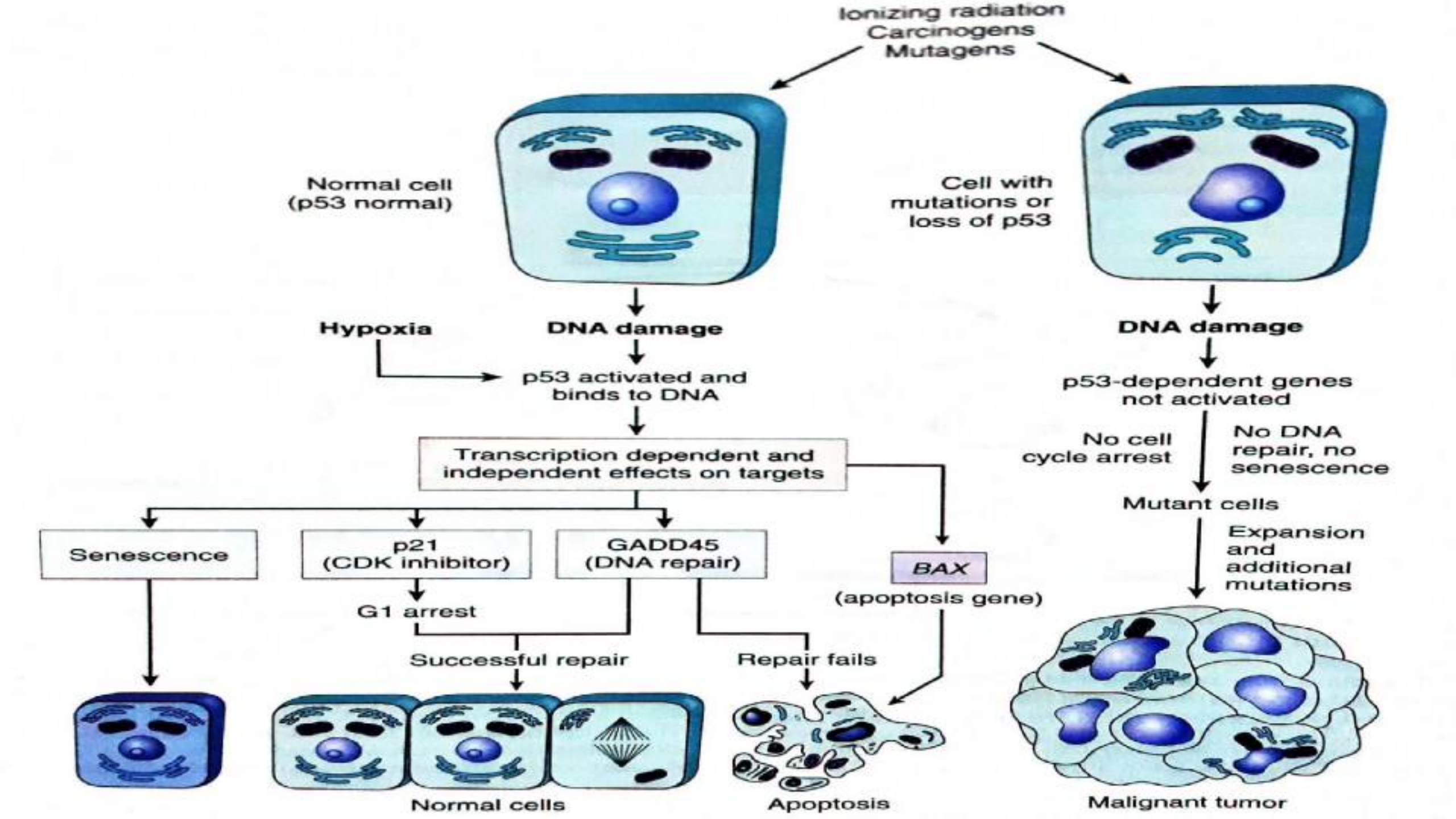
Cancer may arise not only by activation of growth promoting oncogenes, but also by inactivation of genes that normally suppress cell proliferation (cancer suppressor gene) such as P53 gene. Loss of P53 gene , inherited aberration or acquired mutation of the P53 gene are frequently detected in different types of cancer.

3 APOPTOSIS GENES:

Some gene as BCL2 prevent apoptosis thus extending cell survival and in combination with other factors may play an important role in tumorogenesis.

4 DNA REPAIR GENES:

These genes do not contribute directly to cell growth. however, they normally correct error of DNA that may occur during cell division. Inherited mutation of these genes ⟶ increased risk of cancer development (genomic instability syndromes).


Ionizing radiation
Carcinogens
Mutagens
Normal cell
(p53 normal)
Cell with
mutations or
loss of p53
Hypoxia
DNA damage
DNA damage
p53 activated and
binds to DNA
p53-dependent genes
not activated
No cell
cycle arrest
No DNA
repair, no
senescence
Transcription dependent and
independent effects on targets
Mutant cells
Expansion
and
additional
mutations
Senescence
p21
(CDK inhibitor)
GADD45
(DNA repair)
BAX
(apoptosis gene)
G1 arrest
Successful repair
Repair fails
Normal cells
Apoptosis
Malignant tumor

II) mechanism of neoplastic transformation

The multistep theory

Carcinogens –acting on cell genes –can lead to tumors through the following steps:

1 intiation: induction of certain irreversible changes on genome of the cells. These initiated cells are not transformed cells and do not have growth autonomy. They just have altered DNA (gene mutation) and are called latent tumor cells.

2 promotion: further irritation of latent tumor cells e.g. by some hormones or chemicals (tumor promoters) stimulate the latent cells to undergo autonomous proliferation which is reversible at the early phases.

3 neoplastic transformation: abnormal differentiation occur and the cell undergo continuous purposeless uncontrolled irreversible proliferation.

III) types of carcinogens

1 chemical carcinogens: Examples:

- Aromatic hydrocarbons as 3,4 benzpyrene (exist in cigarette smoking) cause cancer lung.
- Aromatic amines as B naphthylamine cause cancer bladder.
- Bacterial metabolites as nitrosamines cause cancer stomach.
- Azo dyes as scarlet red cause hepatic cancer.
- Asbestos cause mesothelioma.
- Aflatoxins (produced by aspergillus flavus fungus) cause hepatic carcinoma.
- Vinyl chloride cause hepatic angiosarcoma.
- Alkylating agents (as mustard gas) cause nasal , laryngeal and lung cancer.
- Arsenic (skin cancer) ,nickel and chromium (lung cancer).

2 physical carcinogens:

Prolonged exposure to ultraviolet rays (sun) can causes cancer skin.

Ionizing radiation causes leukemia , osteosarcoma ,skin malignancy and lung cancer.

3 irses:

Some viruses are carcinogenic. They are either DNA or RNA viruses. Infection of human cells with these viruses can alter the genetic materials.

Examples of DNA viruses include hepatitis c (liver cancer), epstein barr virus (nasopharyngeal carcinoma and Burkett's lymphoma), human papilloma virus (cancer cervix).

Example of RNA virus is human T cell leukemia virus (T cell lymphoma & leukemia).

4- hormones:

They cannot causes tumor initiation but act as promoters, examples include

Estrogen: high level of estrogen (as in non-ovulating adults & in case of granulosa cell tumor of ovary) can promote endometrial carcinoma and mammary carcinoma.

Androgen in high level can promote prostatic carcinoma.

Role of contraceptive pills in cancer breast is questionable. however, they can lead to benign tumor of liver (hepatic adenoma).

IV) chronic disease predisposition (precancerous lesions)

Some chronic diseases may lead to a precancerous lesion (a non- malignant lesion that is liable to undergo malignant transformation). Examples include:

Chronic inflammatory diseases as:

- Ulcerative colitis.
- Atrophic gastritis.
- Radiodermatitis.
- Tertiary syphilis of tongue
- Lupus vulgaris (cutaneous T.B)

Gall stones and urinary stones

Hyperplastic and metaplastic lesion as endometrial hyperplasia, mammary hyperplasia and leukoplakia.

Some benign tumors e.g. villous bladder papilloma & GIT adenomatous polyps

Others as liver cirrhosis, varicose ulcer, Paget's disease if bone and undescended testis.

SERUM TUMOR MARKERS DETECTED WITHIN THE BLOOD

- Assessment of the level of these markers helps in diagnosis & follow up of tumors e.g.

- Carcinoembryonic antigen (CEA) in cancer colon, stomach, pancreas & breast
- Alphafetoprotein (AFP) in hepatic cancer and germ cell tumors.
- prostatic specific antigen (PSA) & prostatic acid phosphatase in cancer prostate
- CA125 (adenocarcinoma particularly ovarian)
- CA 19-9 (adenocarcinoma particularly colonic)

SPONTANEOUS TUMOR REGRESSSION

- Rarely cancer may suddenly regress spontaneously (without treatment) & permanently (without recurrence). The mechanism is not know: may be immunological or hormonal.
- Examples of such tumors include malignant melanoma, neuroblastoma, choriocarcinoma & clear cell type of renal cell carcinoma.