Introduction to pathology -1

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Pathology is The science that studies diseases in four main concepts:

1. *pathophysiology*: the mechanism by which the disease happens or alters the normal physiology
2. *The characteristic morphological changes* of the disease in organs including:
   a- Macroscopical changes seen by naked eye
   b- Microscopical changes seen under the microscope
3. *The causes of disease* (etiology)
4. *Brief descriptions of the main clinical features* of the disease

Disease : any derangement of the normal physiology &/or anatomy of the body whether accompanied by histopathological changes or not (which can be specific or non-specific) causing symptoms and signs

a disease usually affects one system of the body

syndrome is a multi-system disease (affecting more than one body system)

Main branches of pathology

Histopathology: that deals with all the body systems except blood diseases

Hematology: that deals with blood diseases only (anemia, leukemia…etc)

Etiology of diseases

The causes of diseases are classified mainly into

A-Congenital diseases : these diseases that are transmitted from parents during fetal life and are present since birth.

B- Acquired diseases : These diseases happens during life, they are not present since birth, they are caused by an acquired cause affecting the body after birth.

A-congenital diseases

They can be:

1-congenital hereditary: these are congenital diseases occurring due to specific genetic changes (DNA abnormalities or mutations) like Down's syndrome and Turner Syndrome

- ***2- congenital non-hereditary*** : these are congenital diseases most of them are due to non genetic cause transmitted from parents during fetal life.

B- Acquired Diseases

1- ***inflammatory diseases*** : these occur due to tissue inflammation by various causes:

- Infections (by microorganisms): viral,bacterial,parasitic, fungal.
- Chemical : like acids,bases,benzene ingestion,and variouspoisons like cyanide,carbon monoxide…etc
- Physical : cold, heat, UV light, X-ray induced inflammation . Traumatic causes as well like physical damage to the tissues.

immune diseases -2

These are either diseases of excess immune response (like autoimmune diseases : rheumatoid arthritis) or diseases of low immune response (like various immunodeficiencies : AIDS)

3- Degenerative diseases

These diseases occur due to tissue or complete organ degeneration like (Alzheimer disease, Parkinson disease and osteoarthritis)

diseases of body stores and deposits: **-4**

these occur due to deficiency or excess deposit or a normal or abnormal materials, like :

iron deficiency anemia

billiary stones

heart valve calcification

vitamins and nutritional deficiencies

5-metabolic diseases: diabetes mellitus,hyperlipidemia, and hypercholestrolemian

6- neoplastic diseases : all tumors (benign or malignant). Tumors may occur in any age

7-hypoxia diseases : caused by low tissue oxygenation or low blood supply (myocardial infraction)

8-psychogenic diseases : like schizophrenia, depression

some diseases have more than one etiology (ex. Diabetes mellitus can be considered as infectious: viral , autoimmune or genetic)

Requirements for pathological diagnosis

Pathological diagnosis depends on:

1-Clinical information : (age, sex, duration of the disease, main symptoms, origin of biopsy)

2-Pathological examination: which include many levels (gross examination, microscopic examination, and special techniques)

Never examine a biopsy without full clinical information

Types of biopsies

biopsies are of 2 types

- 1-excisional biopsy: when the entire lesion is removed surgically and sent for histopathological examination; usually for small lesions
- 2-incisitional biopsies : when only part of the lesion is removed surgically ; such biopsy is done for large lesions or large masses

rules to take a gross sample (biopsy)

- 1- the larger the lesion the more the number of biopsies to be taken, as one biopsy from a big lesion may not be representative
- 2-for any necrotic or ulcerative lesion the biopsy is preferably to be taken from the periphery of the lesion not the centre which may contain only necrotic material.
- 3- gross samples must be handled very carefully avoiding squeezing and crushing of tissue

- 4- when more than one biopsy are submitted for the same lesion all must be taken for pathological examination; as the smallest less impressive biopsy may be the only one that contains the diagnostic pathological features
- 5- after taking the biopsy it must be fixed properly immediately to avoid tissue necrosis; it must be put in a suitable container with 5-10 times amount of fixative.

: Fixation

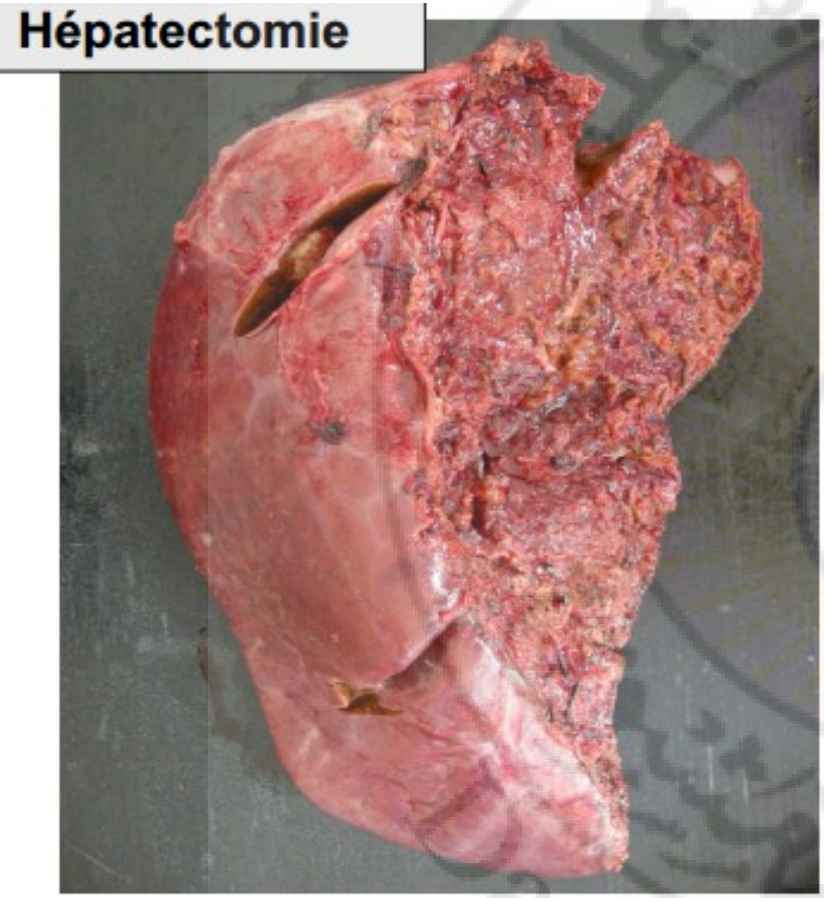
- Formol 10%
- Formol et alcool
- AFA
- Bouin

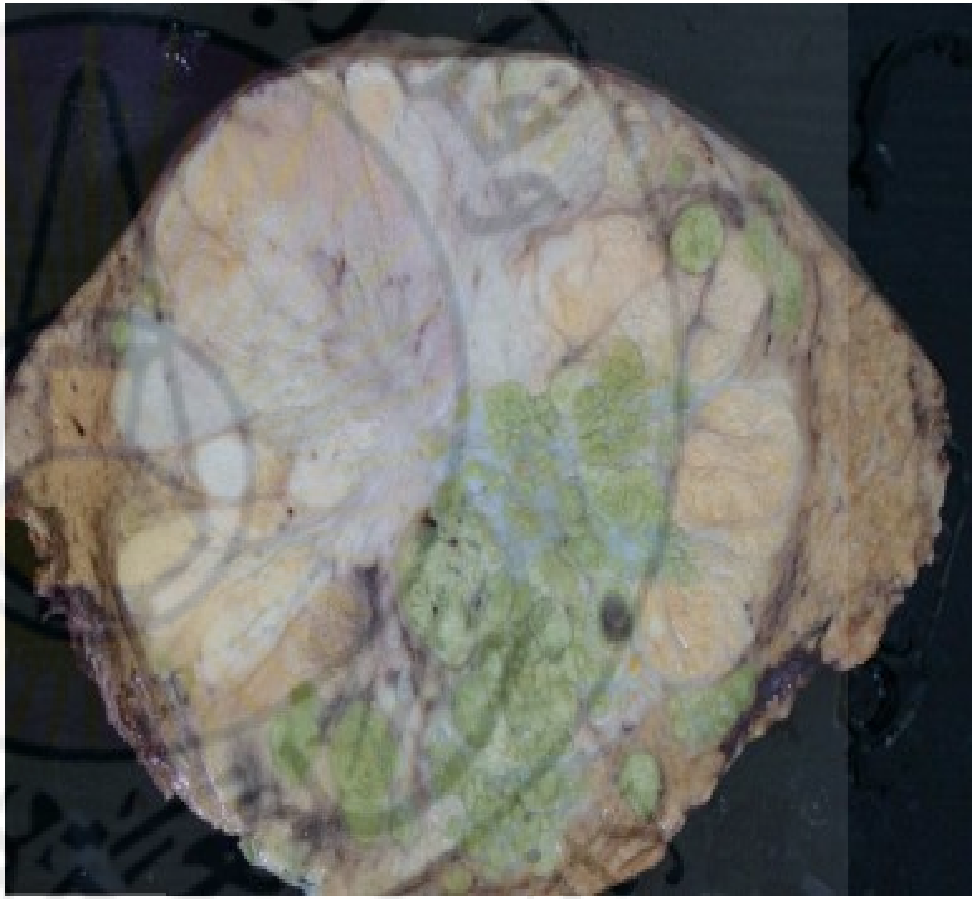
Levels of pathological examination

A- Gross examination:

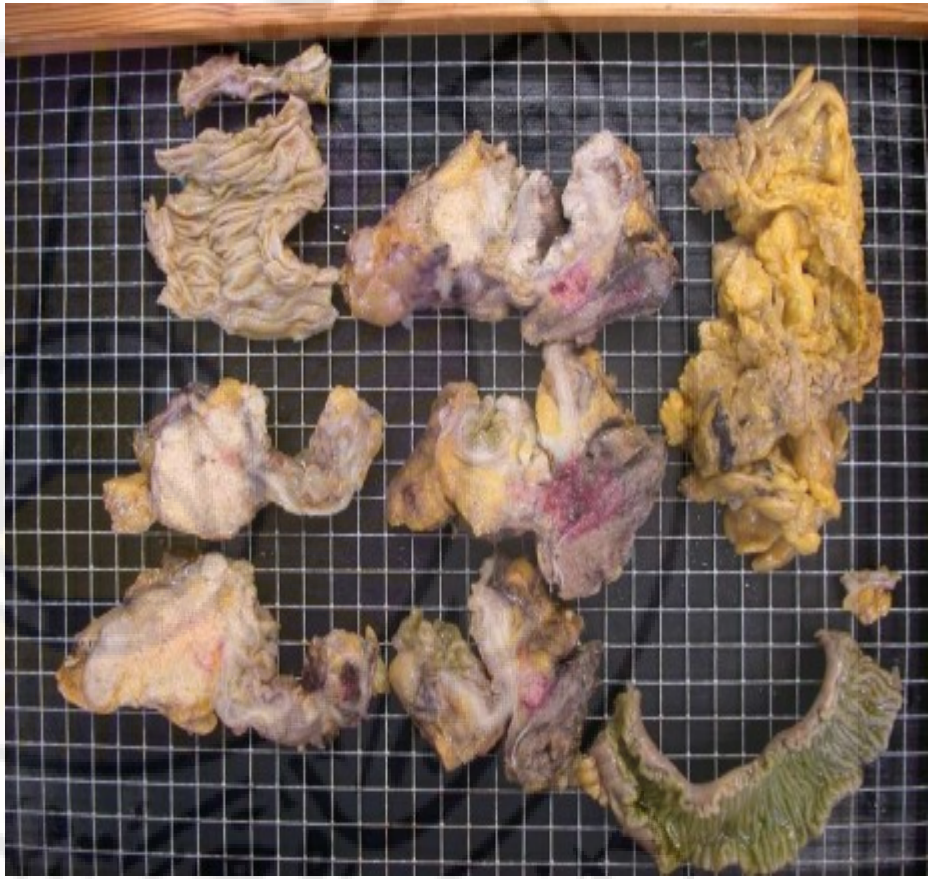
done through direct eye examination; gross examination of the biopsy includes taking notes on origin of the biopsy, shape, dimensions, color, consistency (soft or hard), and weigh. Biopsy must then be cut into standard pieces of (1-1.5 x 1-1.5) cm ,(2-3) mm thickness to be submitted to processing for histopathological examination

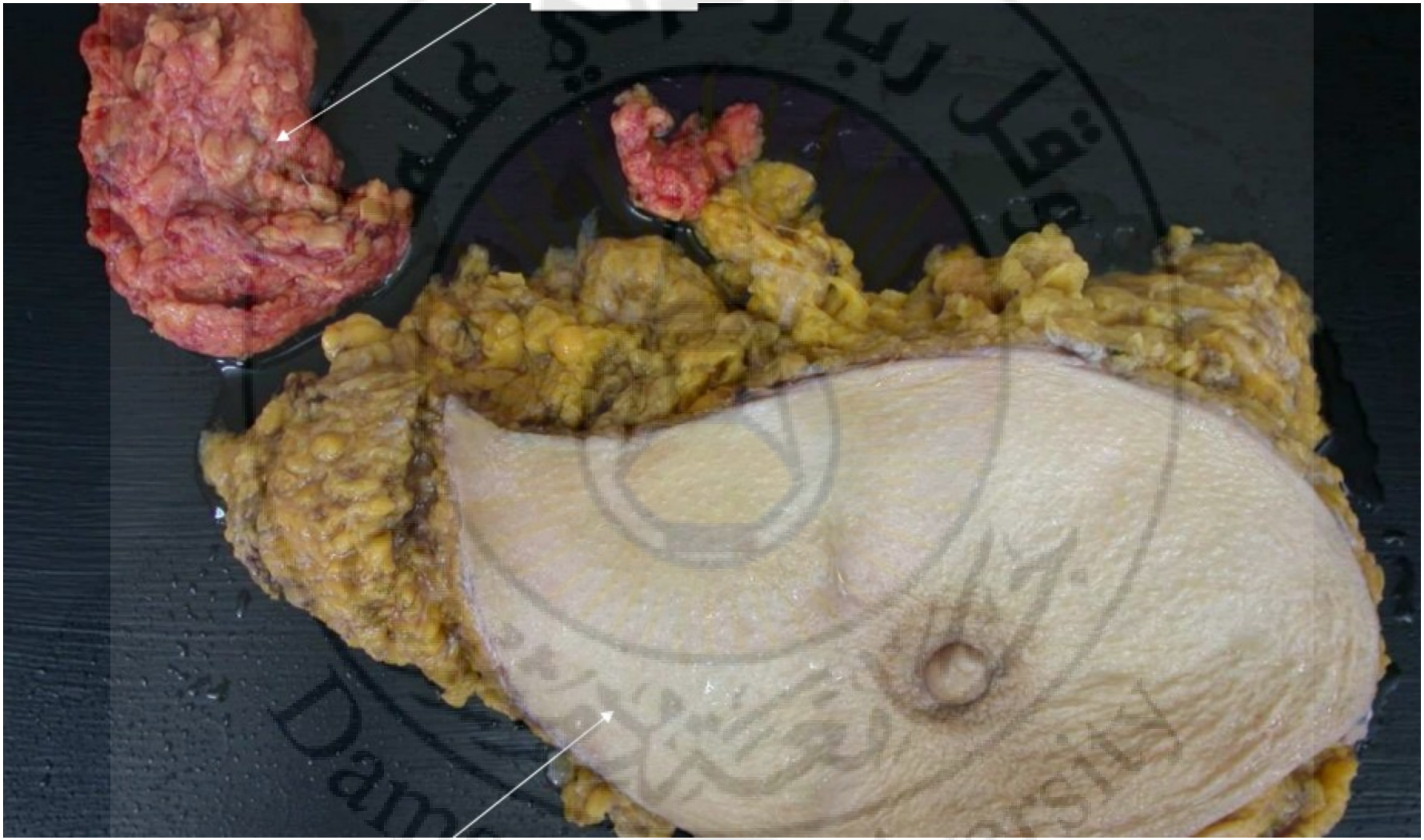
Gross examination

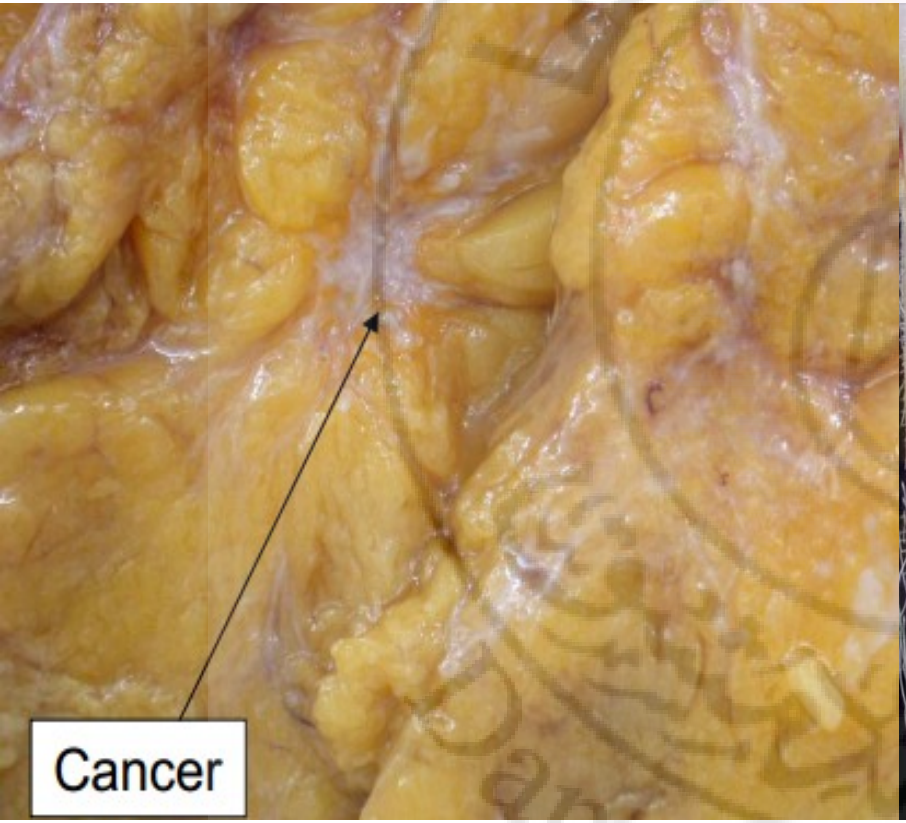


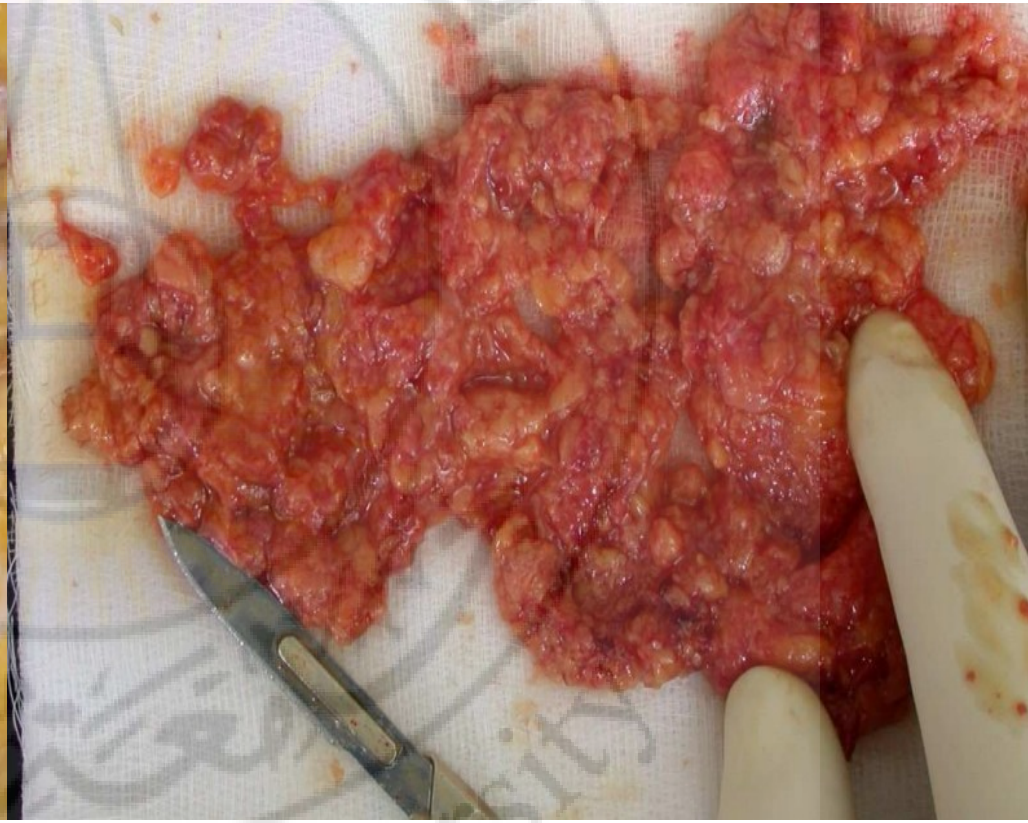


Section of specimens

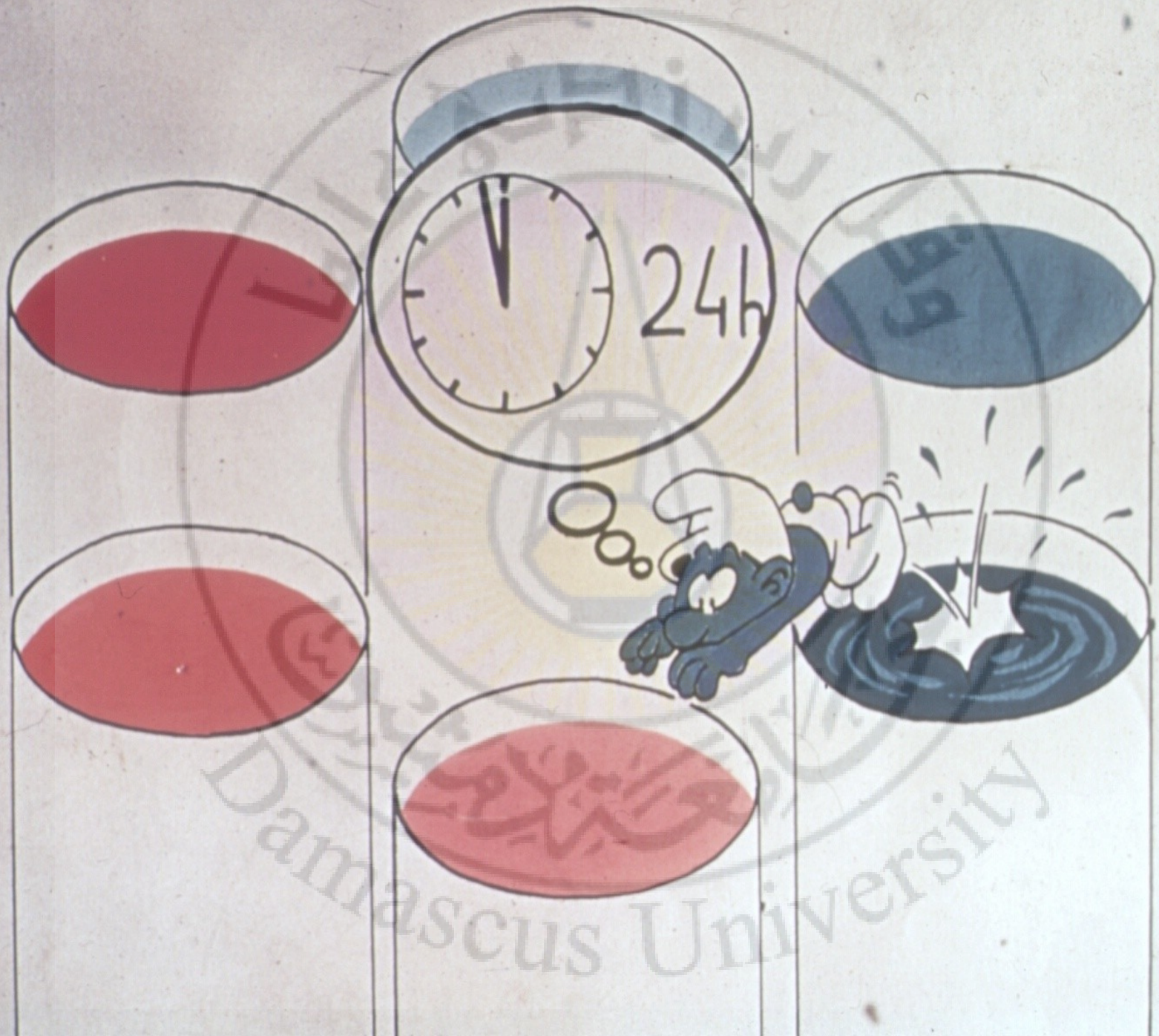




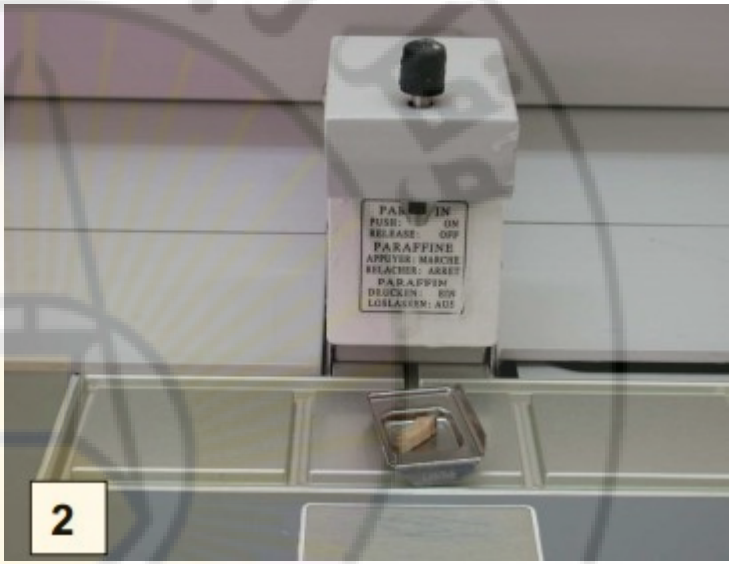

Cancer




Mamelon
Prélèvements systématiques au niveau des différents quadrants
Zone de mastopathie
Ganglions disséqués dans le curage

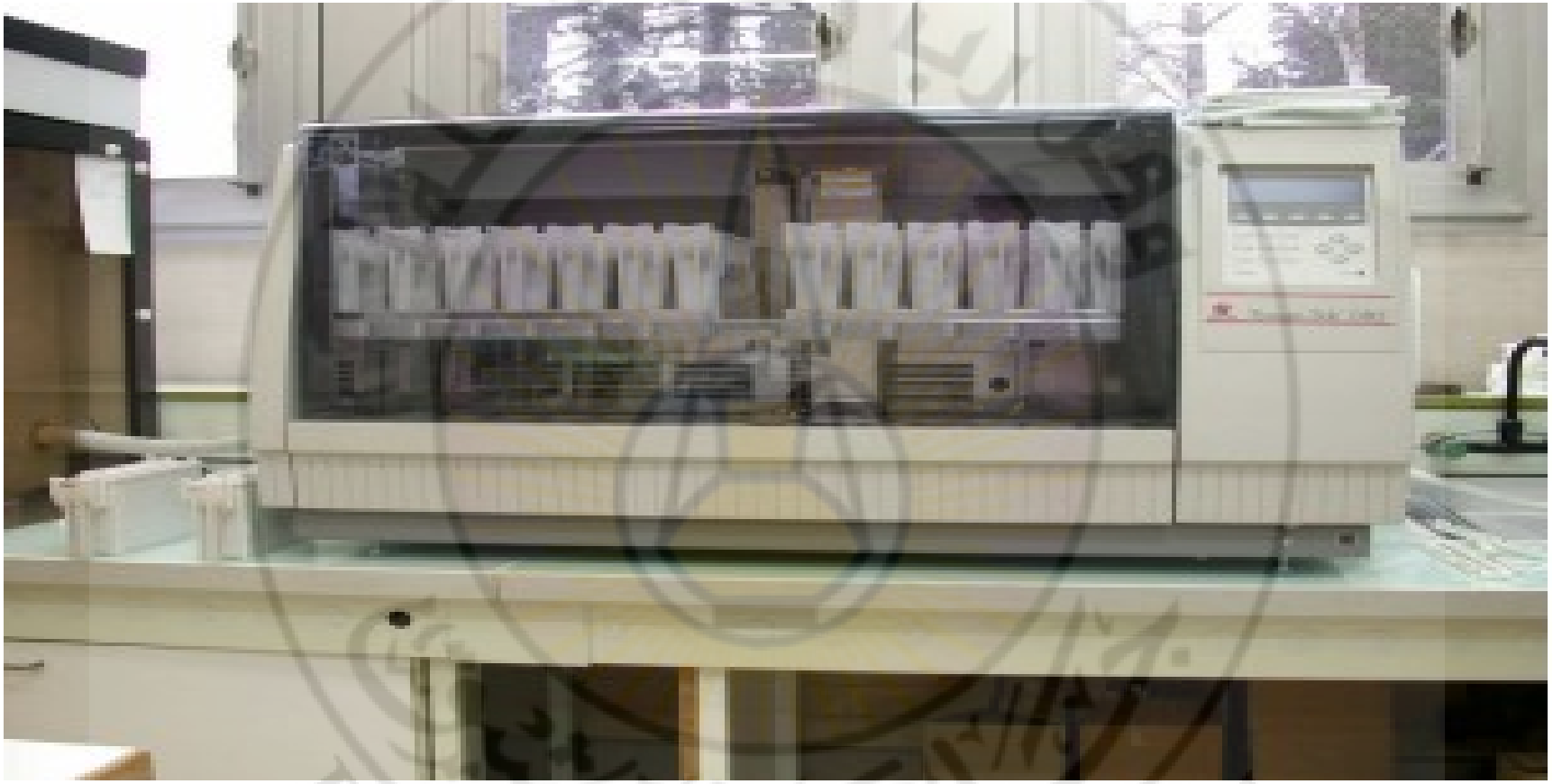


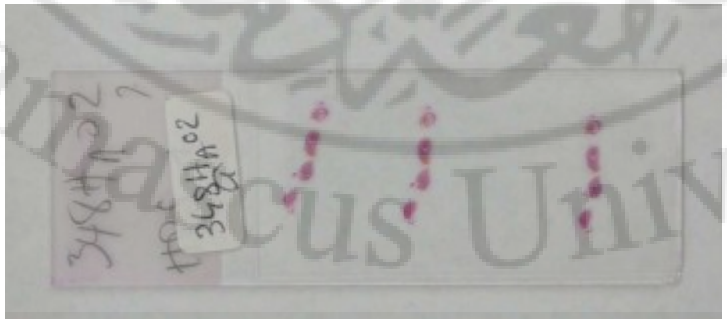
Inclusion in paraffine



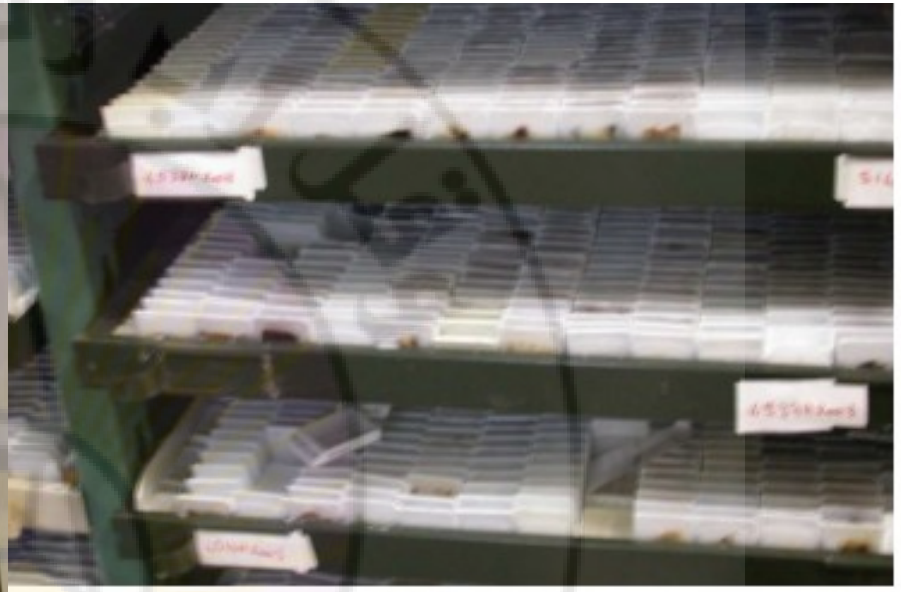
Section by microtome

Automate for routine staining





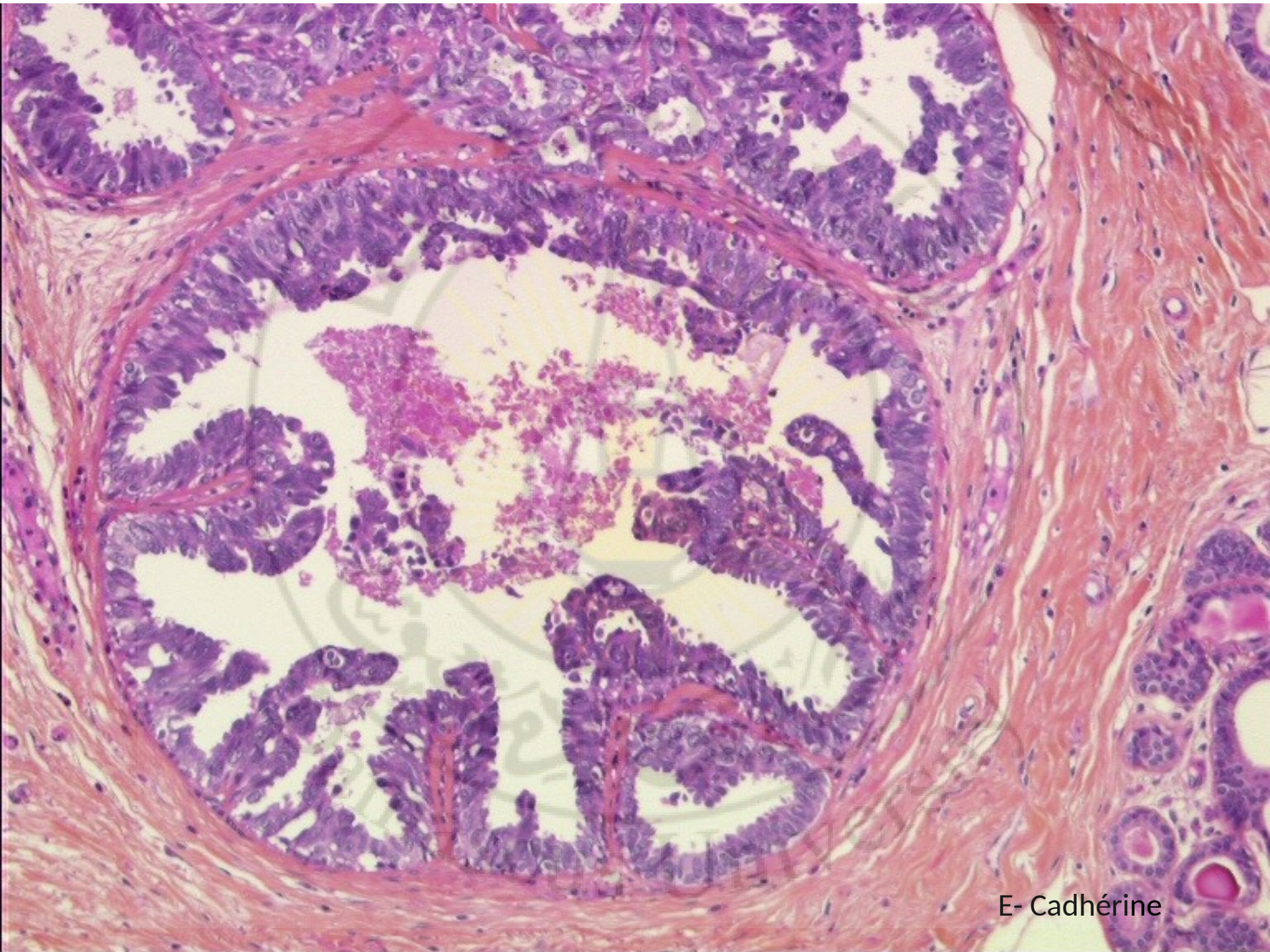
storage



B- Routine microscopical examination

The routine stain by which histopathological sections are examined is the (Hematoxylin and Eosin stain H&E). The main aim for this examination is to look for abnormal histological changes in the tissue .

A complete Knowledge of the normal histology is a must for the interpretation of the biopsy.

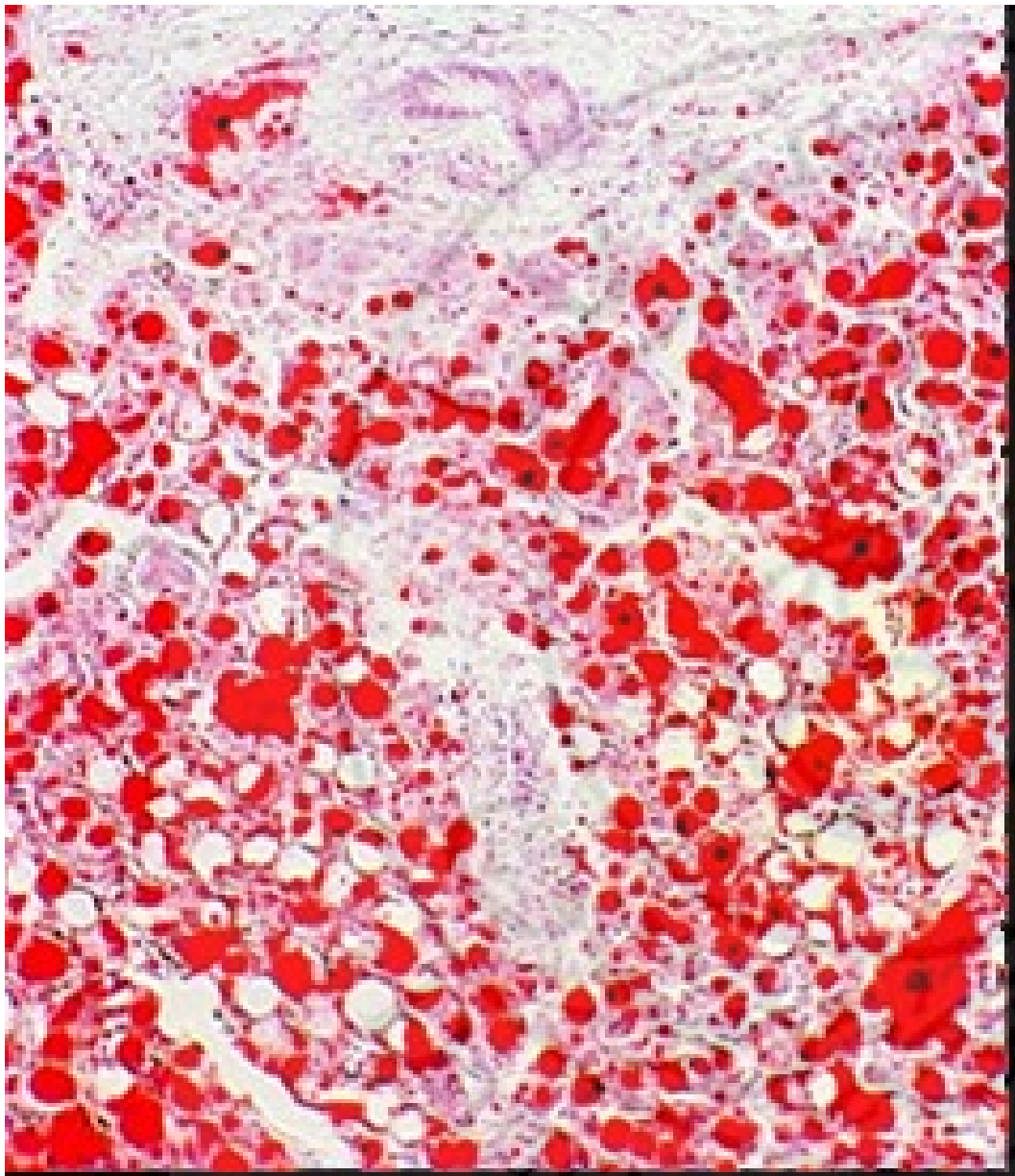

E- Cadhérine

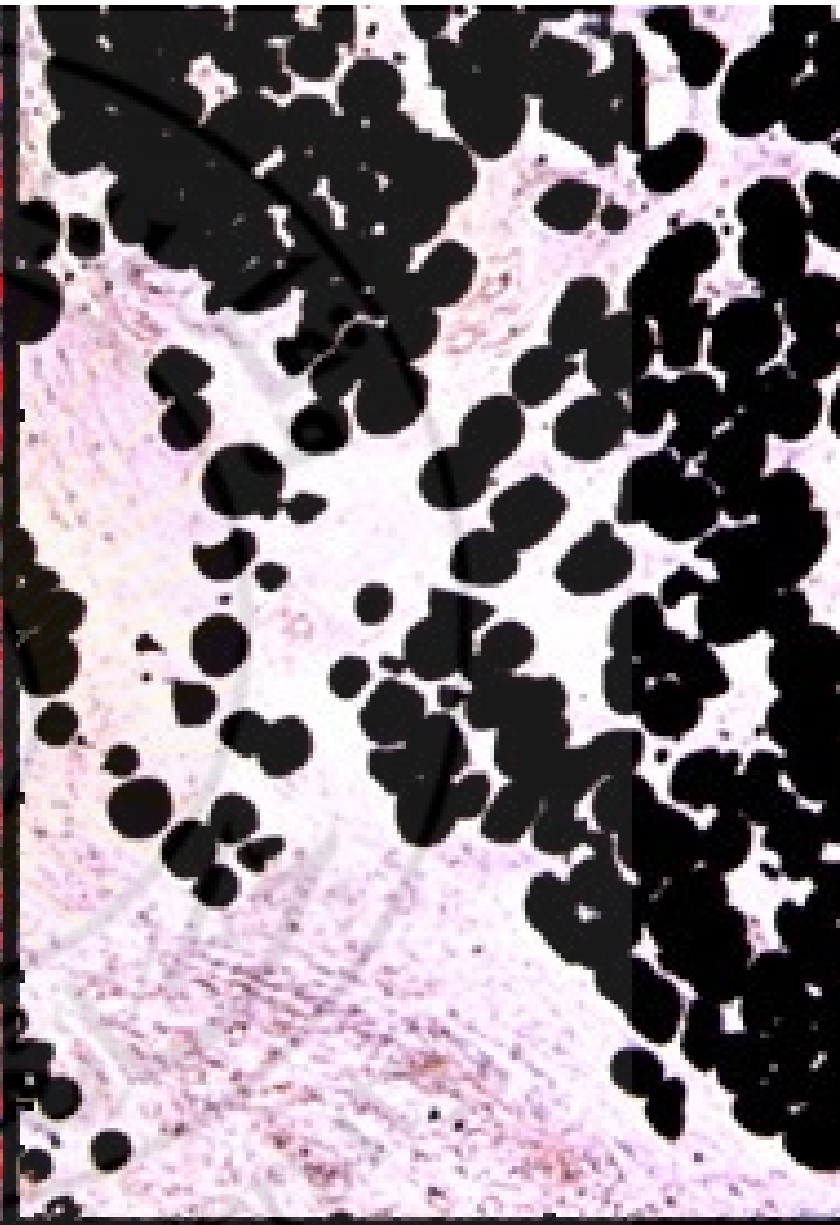
Pathological report

C- Special techniques

***1- special stains*:**

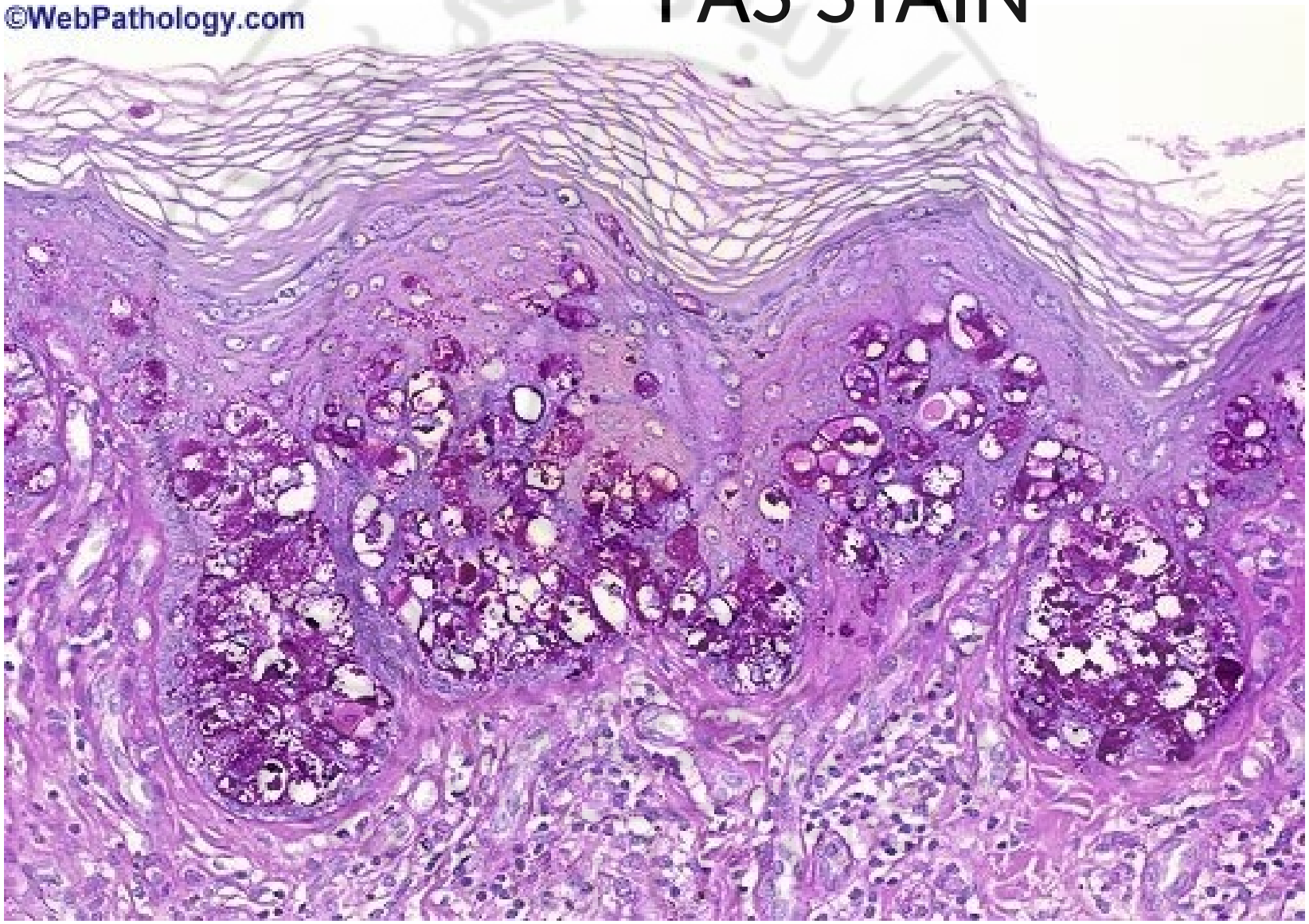
- PAS for carbohydrates and mucin
- Soudan stain and Oil Red O for fatty tissue
- Silver stain for parasites, fungi, and basement membrane
- Congo Red stain for the amyloidal proteins



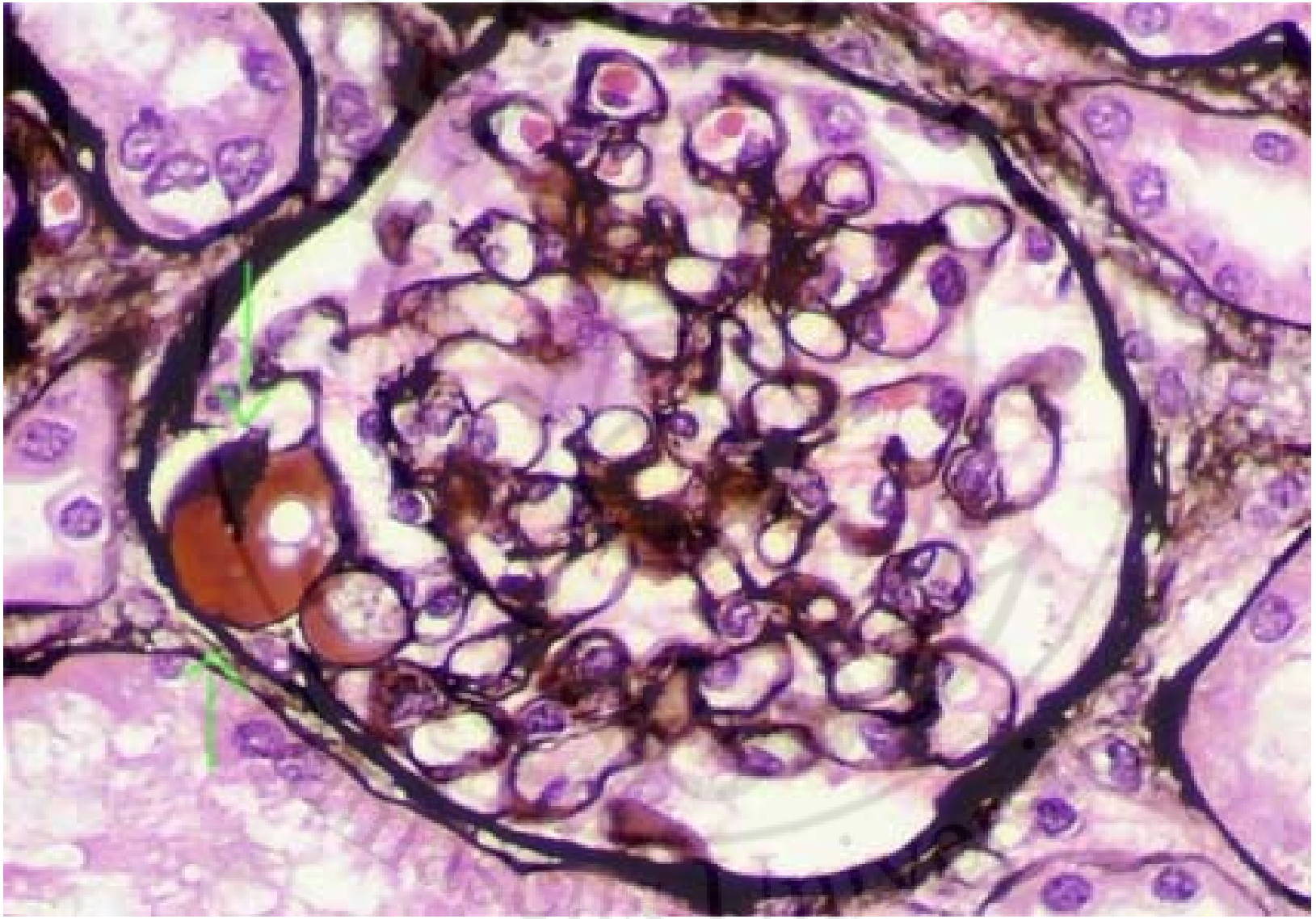


Appearance of lipids in light microscopy: left, Oil Red O; right, Sudan Black IV. These are stained frozen sections.

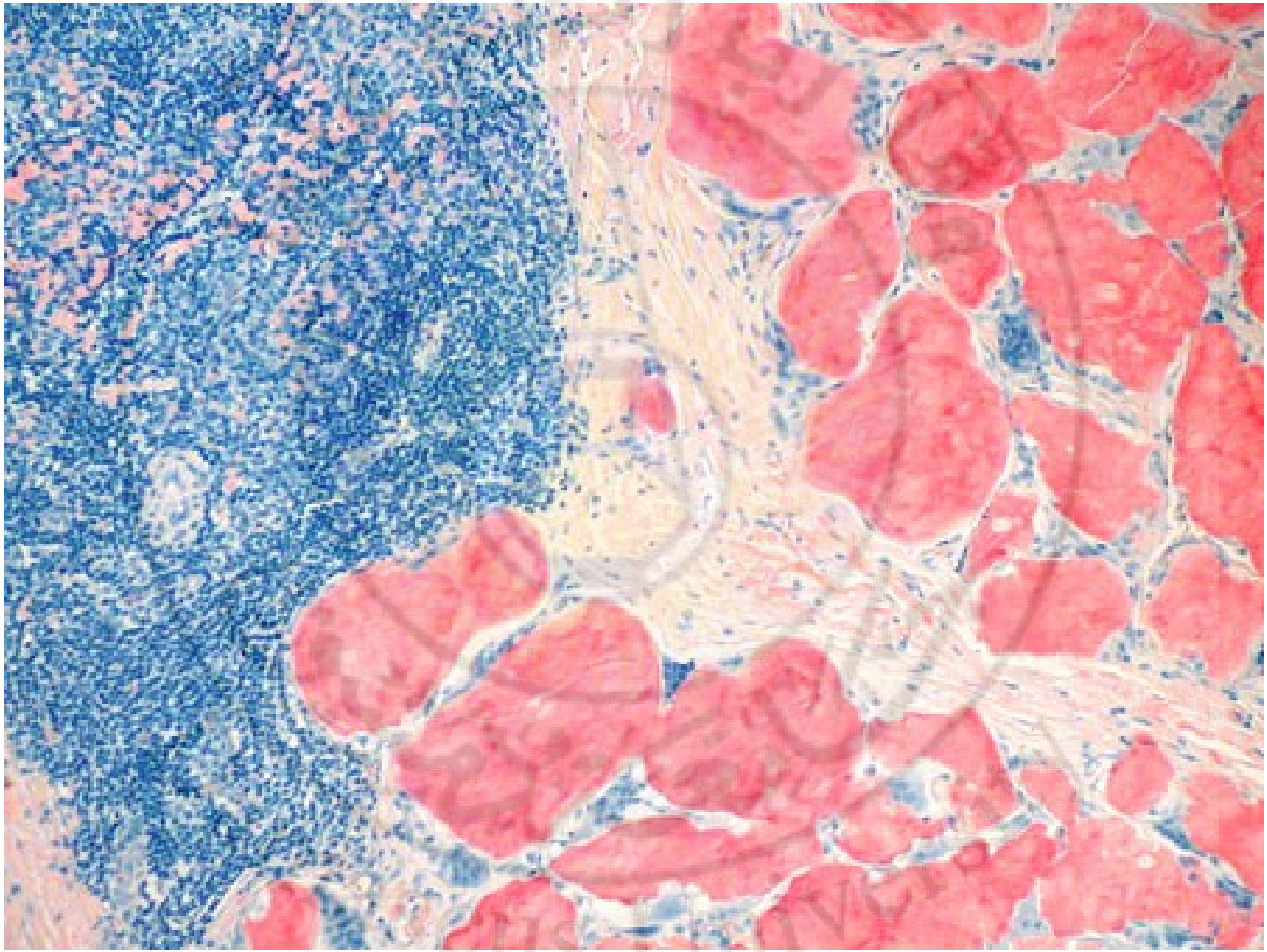
PAS STAIN



SILVER STAIN



RED CONGO

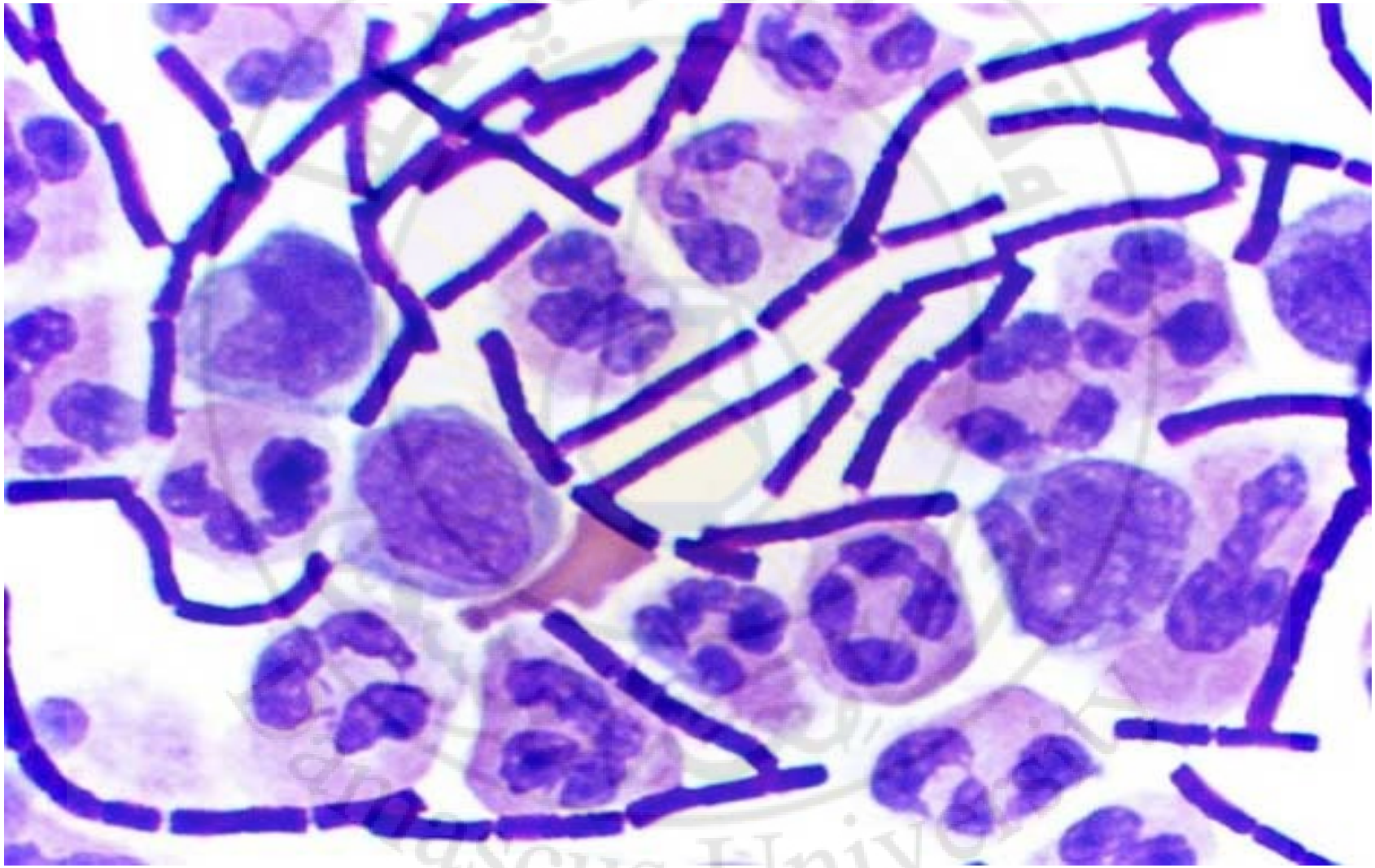


C- Special techniques

2- Microbiology methods :

- Gram stain : to look for certain bacteria
- Zeihl-Nelson stain: for bacilli of tuberculosis
- Grocott: for fungi

GRAM



C- Special techniques

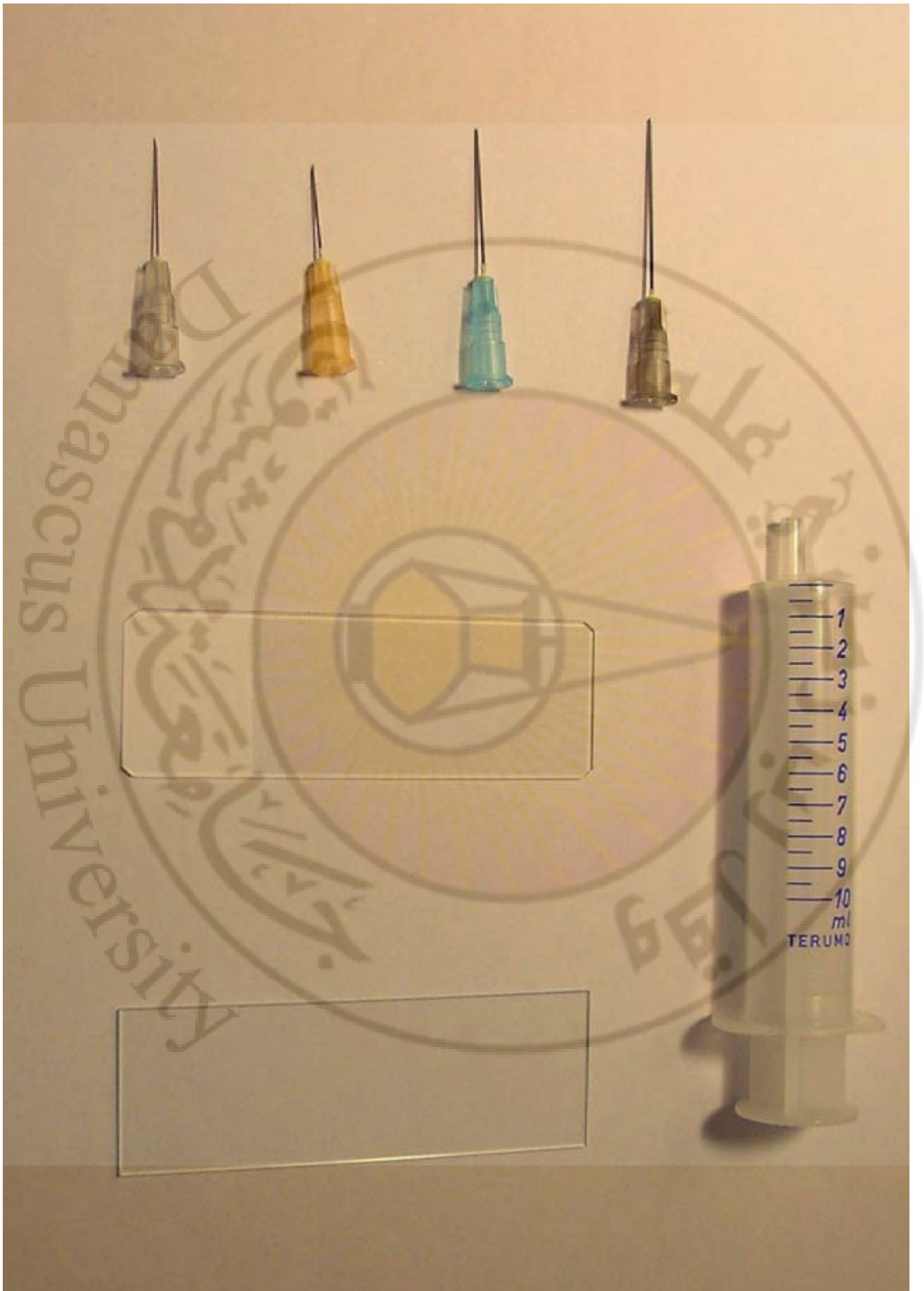
3-Radiological examination

Sometimes it is beneficial to perform radiological examination to the biopsy itself after excision ; specially in (bone, dental, and breast lesions). The main aim here is to look for the pattern of bone formation whether radiolucent or radio opaque or the pattern of calcification

C- Special techniques

4- Fine Needle Aspiration(FNA) & Cytology

These methods can be used before a biopsy is taken to give an idea of the lesion before the histological examination the best example is bone marrow aspiration in hematological conditions like leukemia. However this method can be used in any other lesion in any organ like breast, thyroid, or cervical masses and lymph nodes.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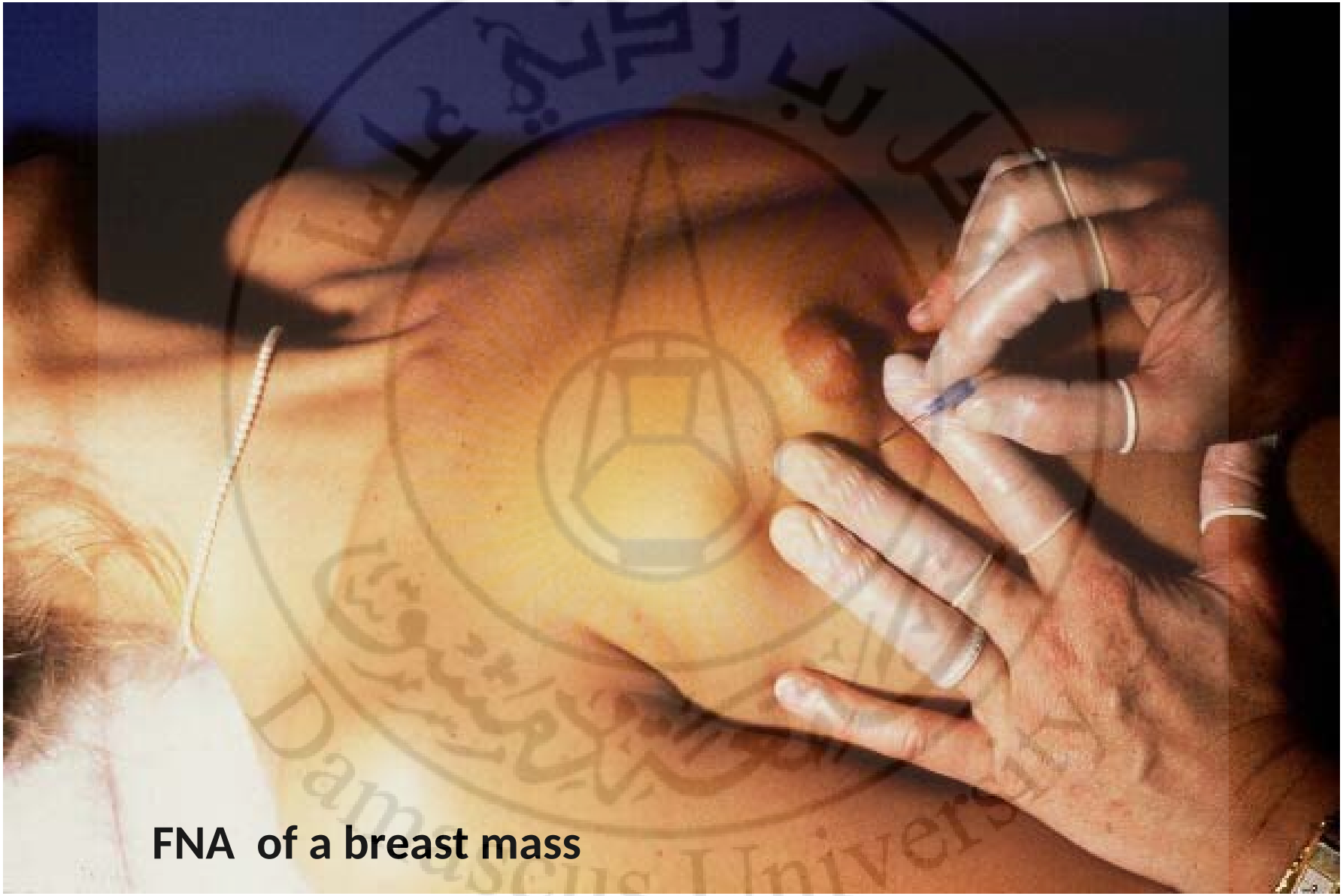
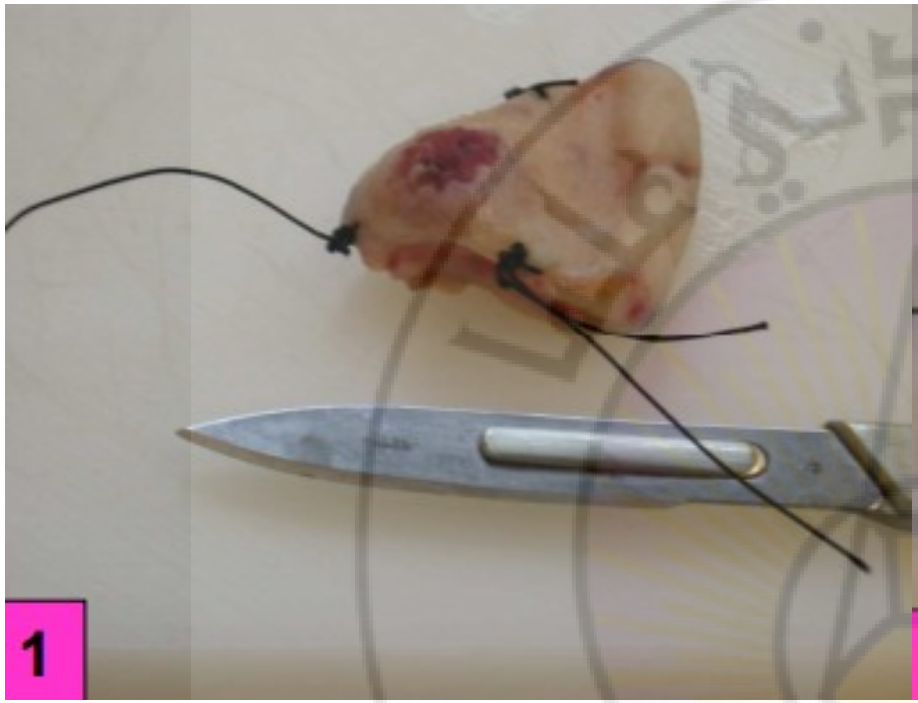


FNA of a breast mass

C- Special techniques

5-Frozen Section

In this method the biopsy is sent during operation, We examine, freeze, cut, stain it and give the response to the surgeon immediately; this method is used when an urgent intra-operative diagnosis is needed such as a tumor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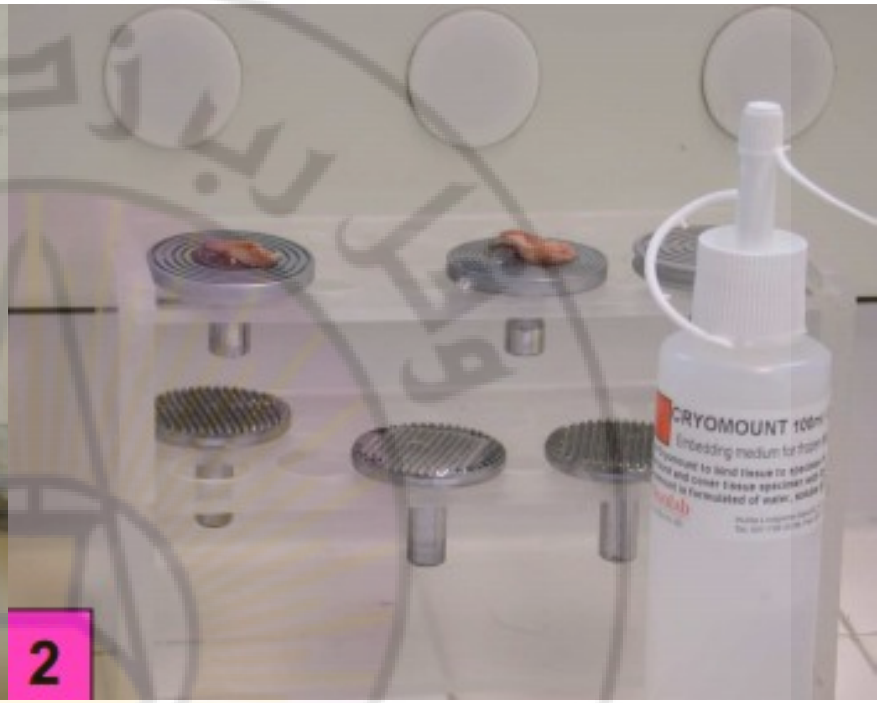
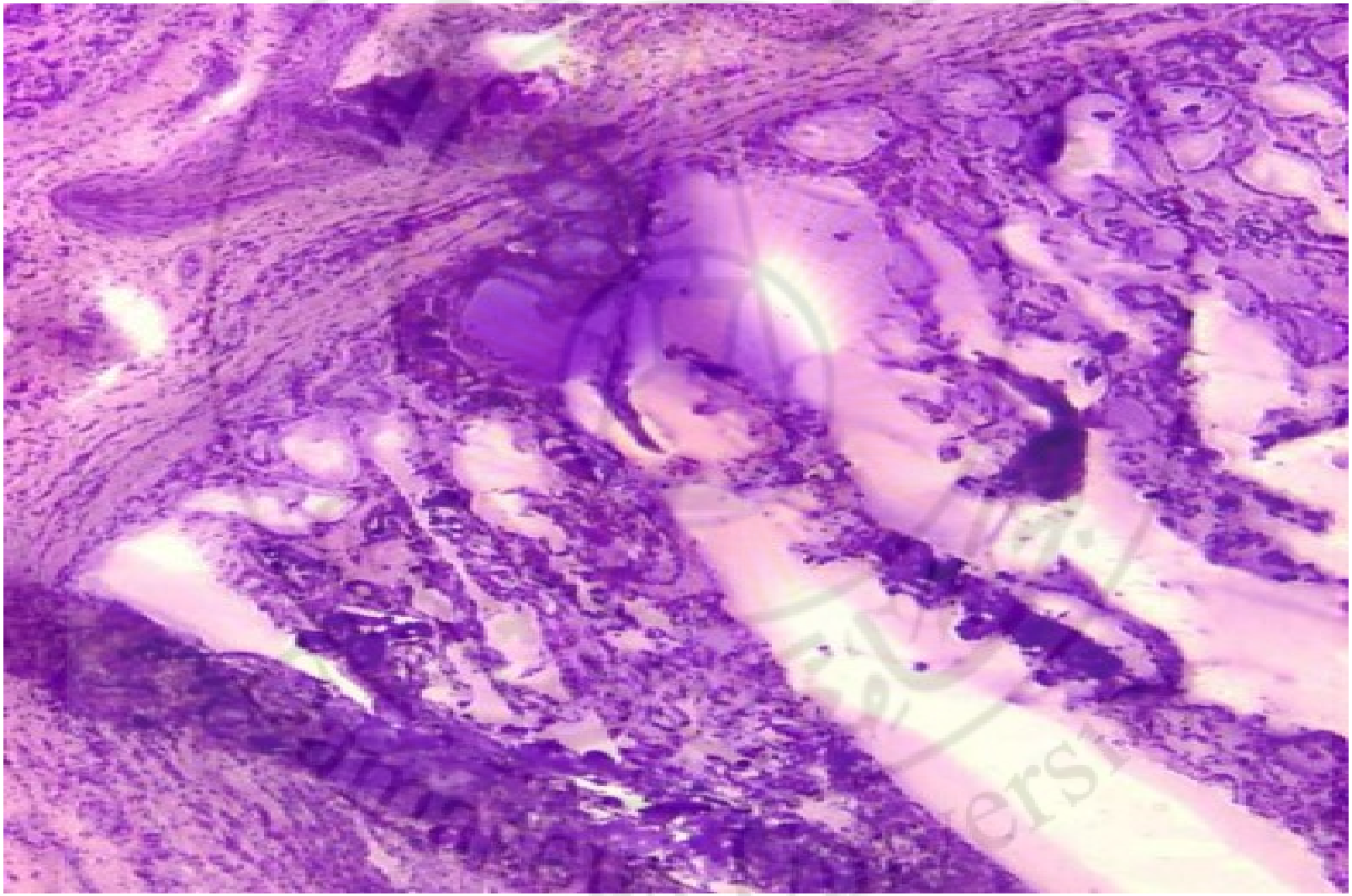

CRYOMOUNT
2


3


MICROM
4

frozen section



C- Special techniques

6-Enzyme histochemistry

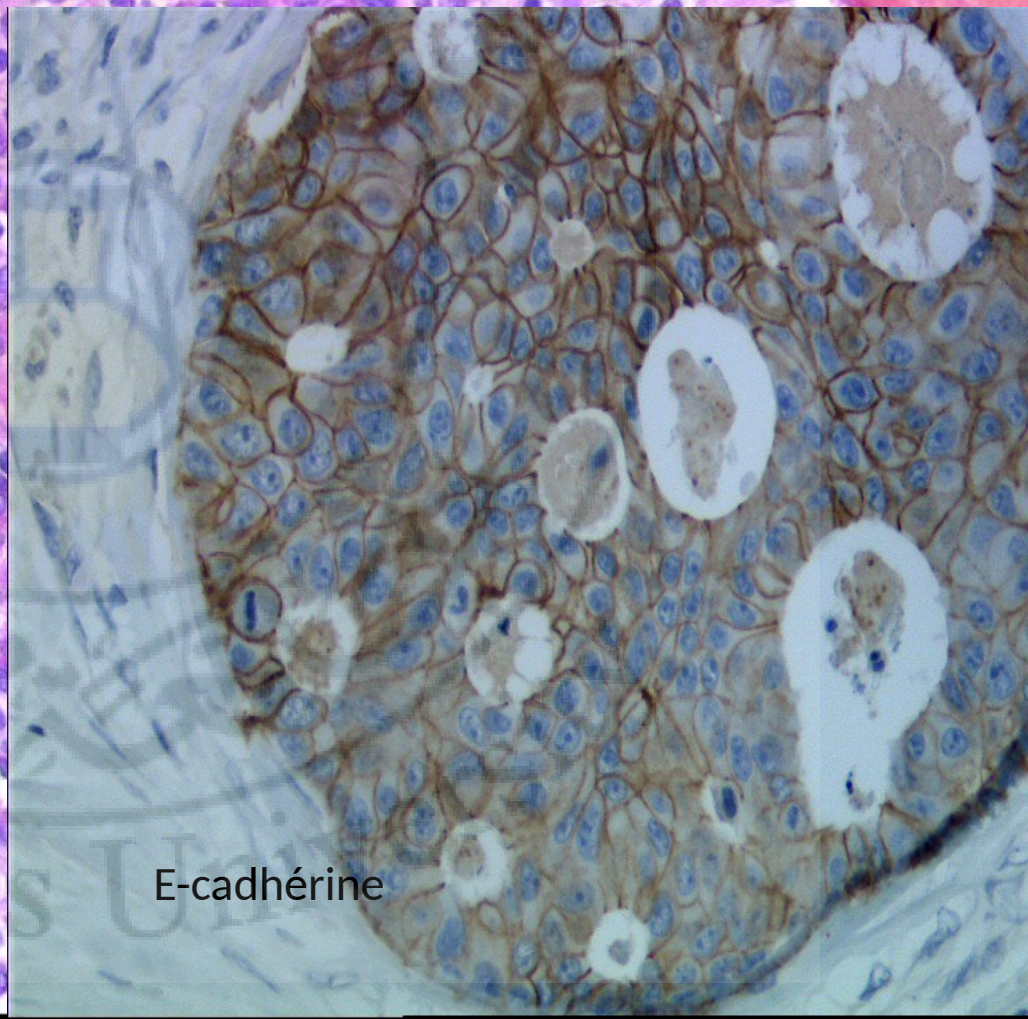
This method detects certain enzymatic reactions in the tissue, the main use is in muscular disorders and muscular dystrophy.

C- Special techniques

7- immunohistochemistry (IHC)

This method combines histological, chemical, and immunological reactions together. The main aim is to look for tumor markers , as sometimes tumors of different origin may have very similar histopathological picture example : we use E- cadherin for recognize ductal carcinoma from lobular carcinoma.

Ductal carcinoma



C- Special techniques

8- Cytogenetics

The main aim in this method is to look for certain chromosomal abnormalities (mutations) associated with many tumors especially tumors of lymph nodes (lymphoma) and tumors of blood (leukemia . And the diagnosis of syndromes

C- Special techniques

9- molecular pathology

This involves many methods like (PCR polymerase chain reaction,FC flow cytometry,ISH in situ hybridisation …) all of these aim at looking for a specific nucleic acid sequence in a tissue biopsy to compare it with a known sequence of a known agent like virus for example

C- Special techniques

10- Electron Microscopy EM examination

The main aim of electron microscopy In pathology is to look for the histogenesis of the biopsy especially in cases of unknown origin

Ex. It can differentiate between malignant tumors of epithelial and neural origin with a very similar histopathological picture on the routine stain level

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2021

Cellular adaptation

- Cellular adaptation is a new functional and/or morphological state of the cell in response to certain stimuli to adapt with it, it is usually a reversible process prior to cell injury

1- hyperplasia

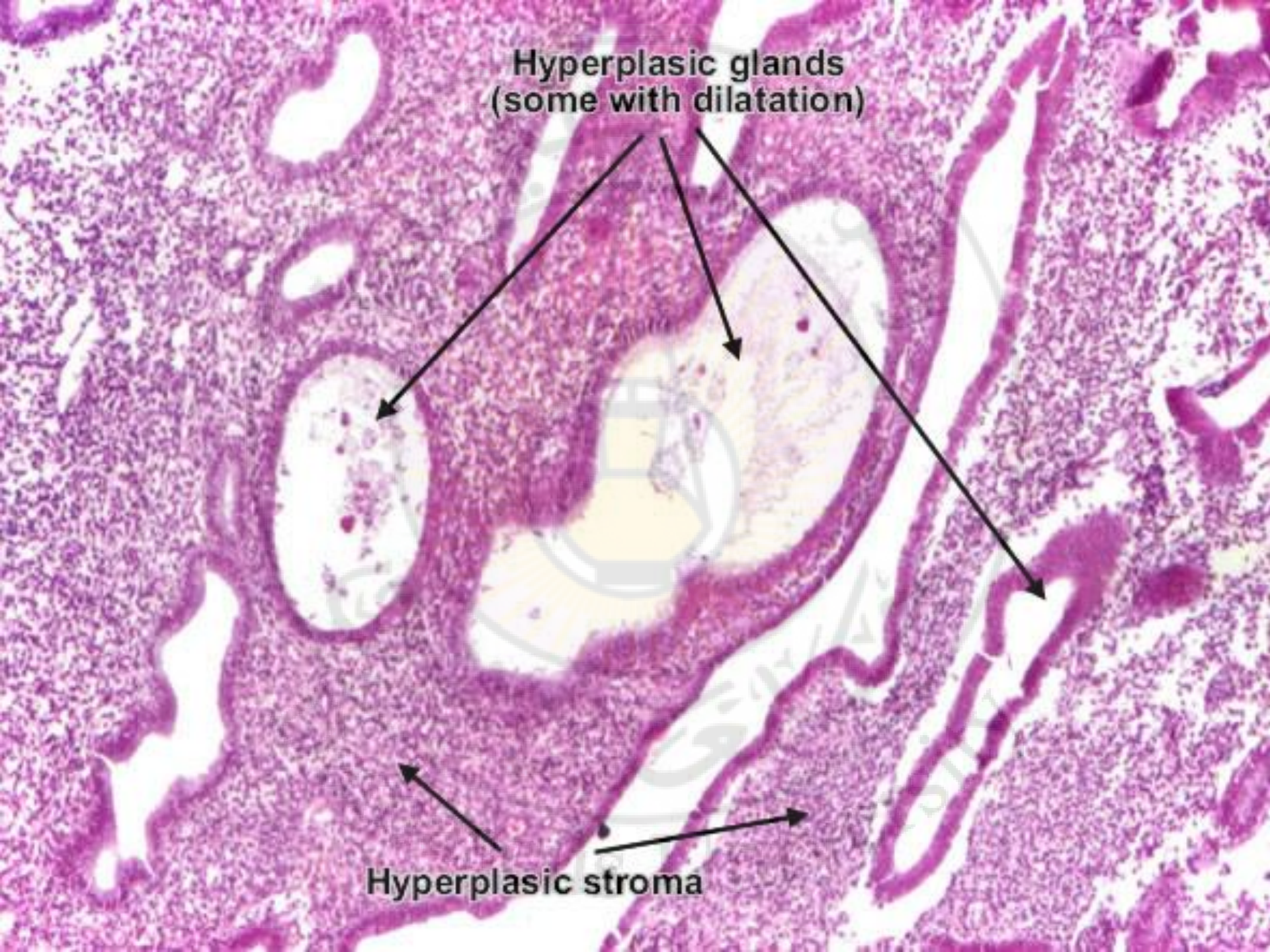
- It is an increase in the number of cells in the organ, with subsequent increase in organ volume, it occurs only in cells capable of DNA synthesis and division (ex. The cardiac muscle fibers can't undergo hyperplasia).
- ***It can be :***

1-Physiological: like mammary and endometrial hyperplasia during pregnancy (hormone dependent ,or hepatic compensatory hyperplasia after partial hepatectomy.

1-Hyperplasia

2- pathological: mostly occurs due to abnormal increase in hormonal action on the target organ:

- High estrogen level with pathological endometrial hyperplasia and increased risk of carcinoma
- During the process of healing, where the hyperplastic fibrous tissue may form a scar
- With certain viral infections that cause epithelial hyperplasia


Hyperplasic glands
(some with dilatation)
Hyperplasic stroma

2- hypertrophy

- It is an increase in the size of cells in an organ, with subsequent increase in organ volume , it occurs due to synthesis of new structural components (but there is no cell division nor DNA synthesis).it occurs in tissue capable of cell division or not
- ***It can be physiological like:***

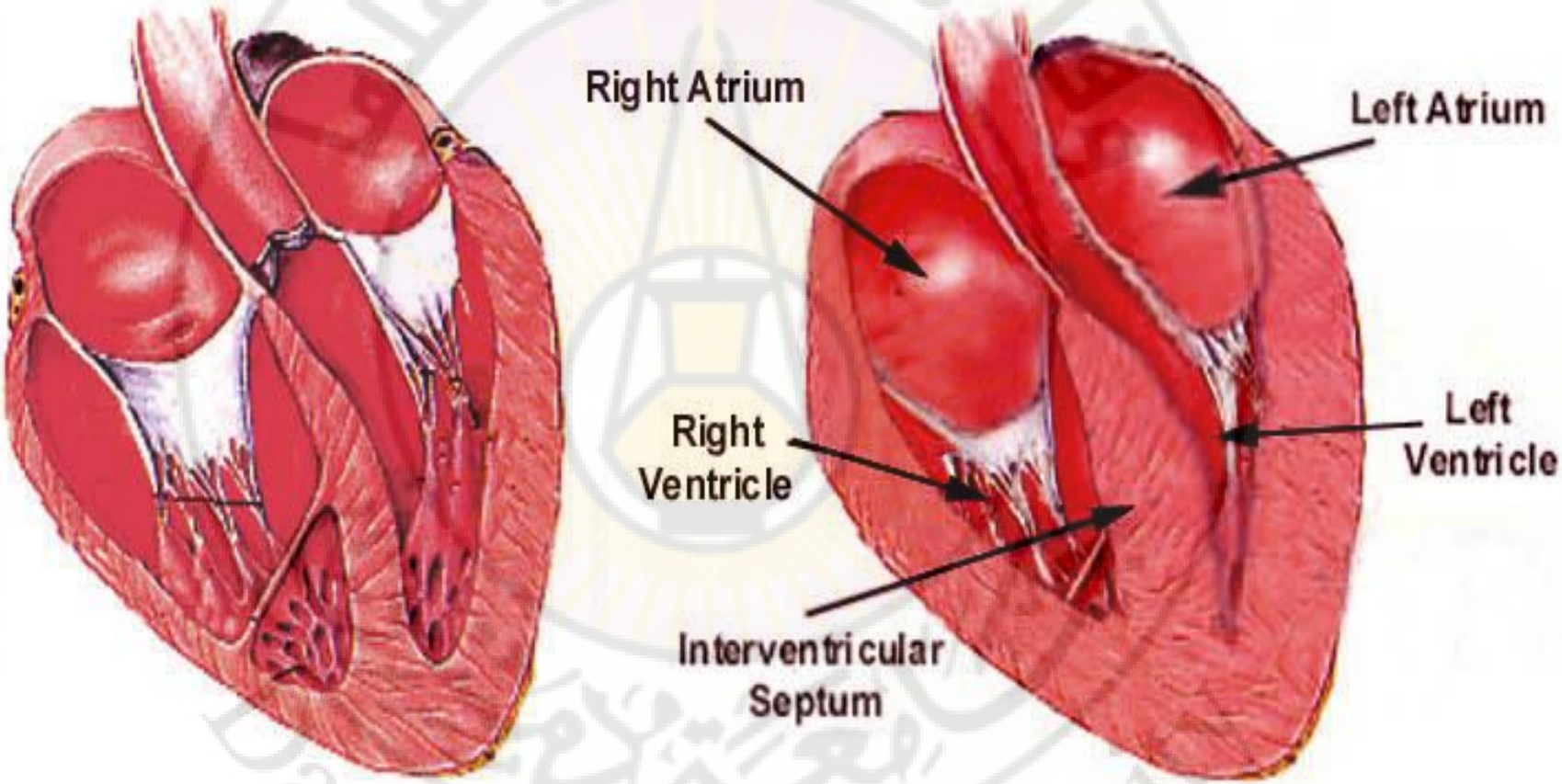
1-Mammary and endometrial hypertrophy during **pregnancy**(hormone dependent)

2-Skeletal muscle hypertrophy in **sport** and bodybuilding.

2-hypertrophy

- ***Or pathological*** like: Cardiac hypertrophy in patients with **increased workload** of the heart and heart failure .
- If pathological hypertrophy continues it will reach a limit beyond which no more cell enlargement is possible and the cell cardiac can't cope with the new metabolic demands,
- if the stimulus of hypertrophy continues after there will be cellular degeneration or atrophy or even cell death.

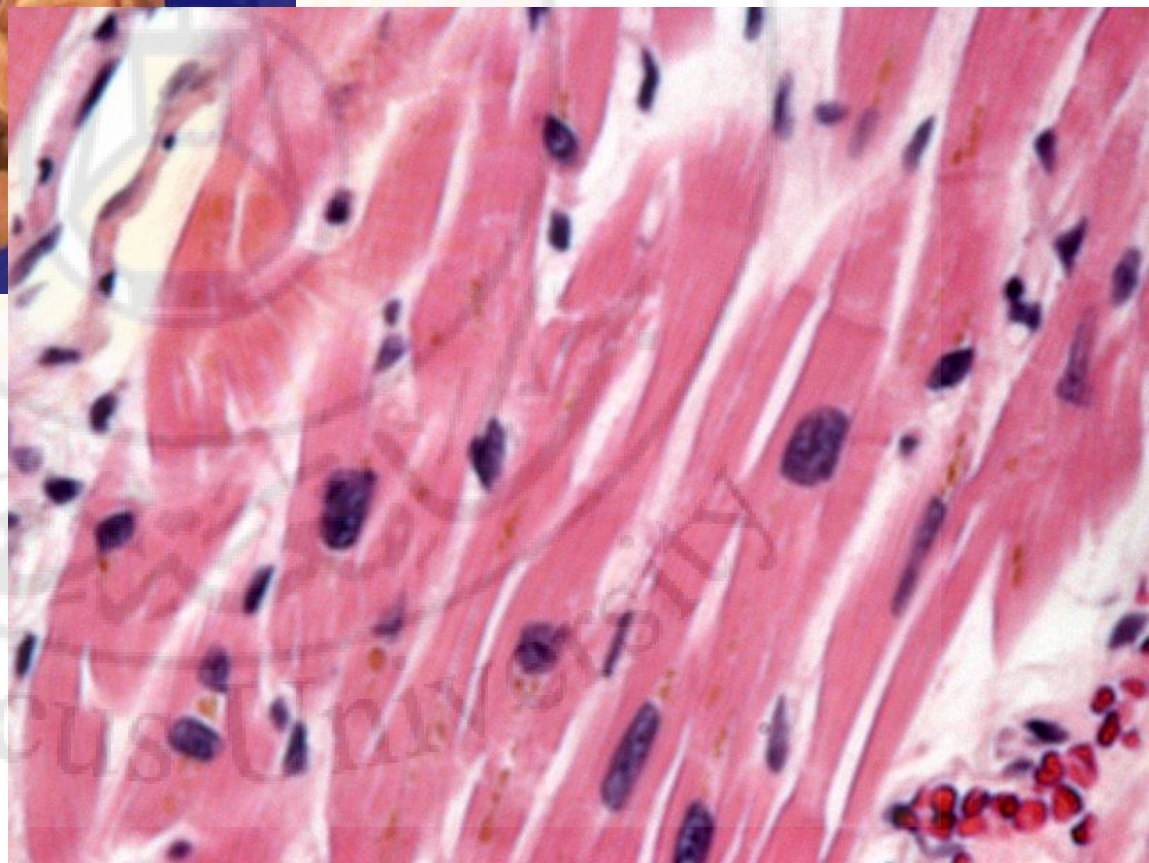
Hypertrophic Cardiomyopathy



Normal Heart

Hypertrophied Heart


METRIC 1
2



3- atrophy

- It is a shrinkage of the cell due to loss of cellular structural components, with subsequent decrease in organ volume.
- ***It can be physiological:***

1-During embryogenesis like notochord and thyroglossal duct

2-Uterine atrophy after delivery

3- atrophy

- ***Or pathological :***

1-decrease workload (disuse atrophy)like muscular atrophy in **bed ridden patients** for a broken limb .

2-loss of innervations(denervation atrophy)like muscular atrophy in **paralyzed limb**.

3-diminshed blood supply(ischemic atrophy) as brain atrophy in **elderly people**.

4- inadequate nutrition(**starvation atrophy**): in which the body starts to use muscular tissue for energy production after depletion of all the fatty tissue.

3-atrophy

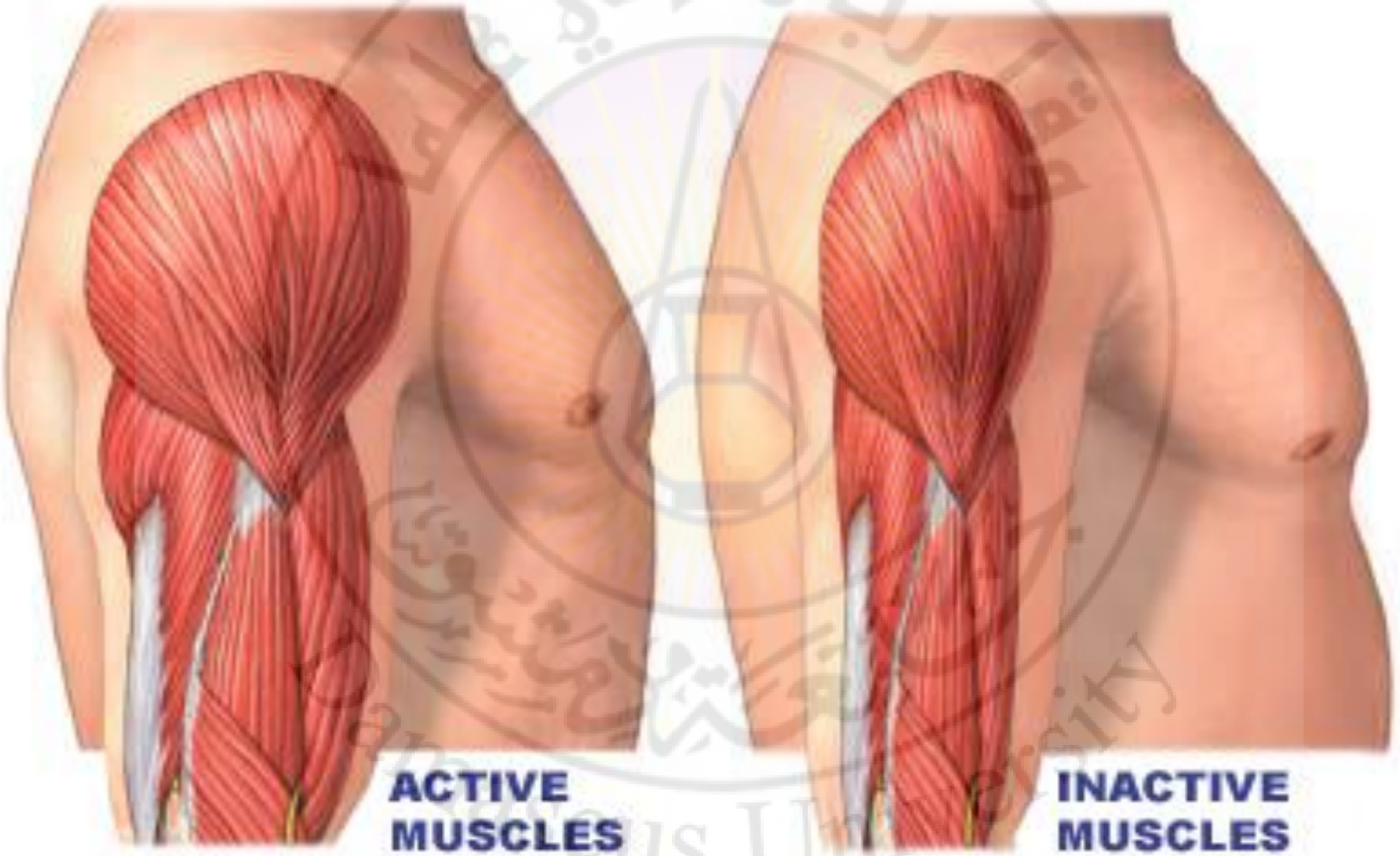
- ***pathological :***

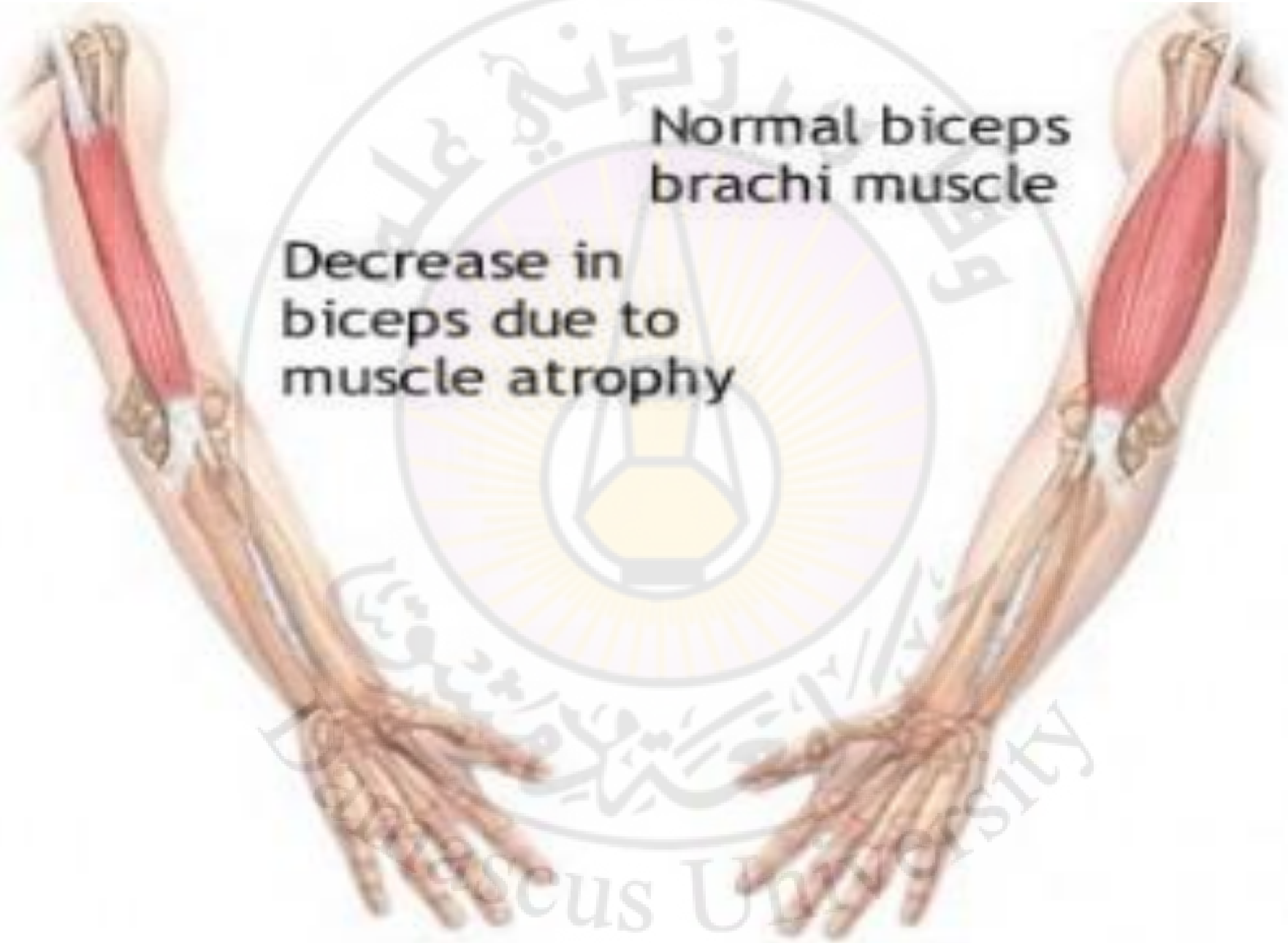
5- loss of endocrine stimulation like female organs atrophy (breast, vagina and uterus) after the **menopause** due to loss of estrogenic stimulation to these tissues.

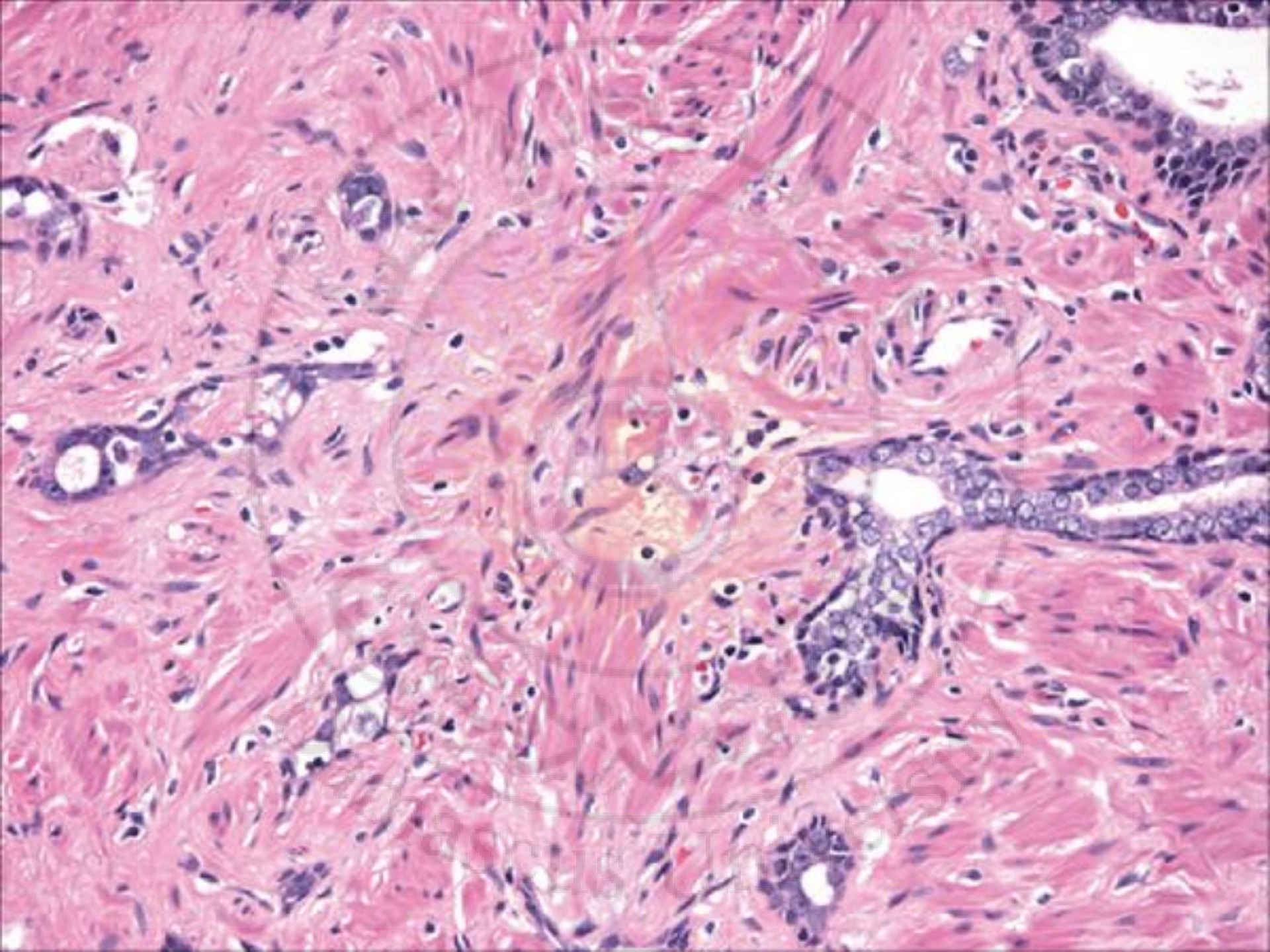
6- aging (**senile atrophy**) : due to the process of cell aging that occurs in some tissues like the brain, heart, and bone

7- pressure atrophy : like atrophy of tissues surrounding a mass like tumors.

8- cancer atrophy: (cachexia)due to overall altered metabolic pathway caused by some cancers


ACTIVE
MUSCLES
INACTIVE
MUSCLES


Normal biceps
brachi muscle
Decrease in
biceps due to
muscle atrophy



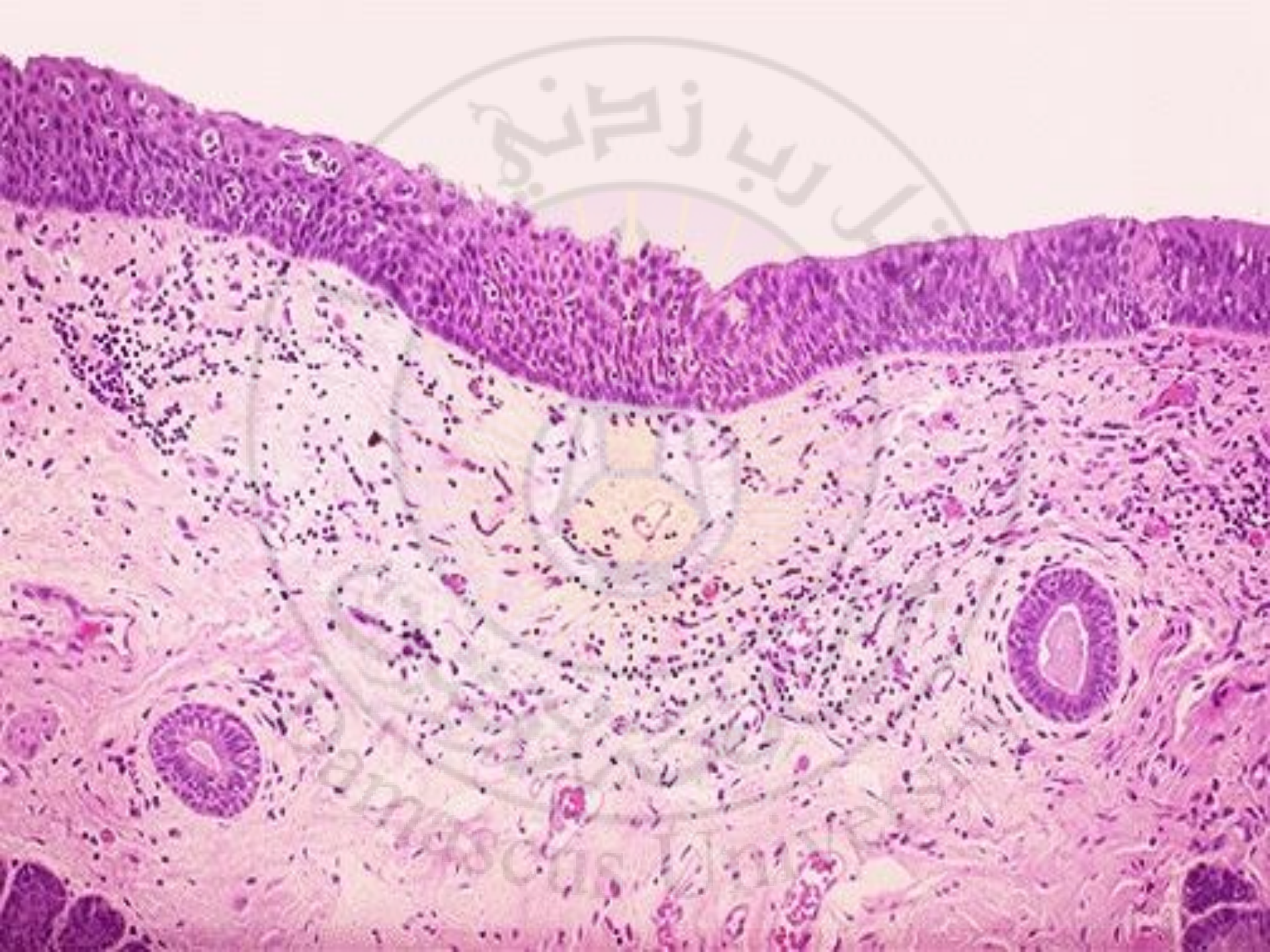
4- metaplasia

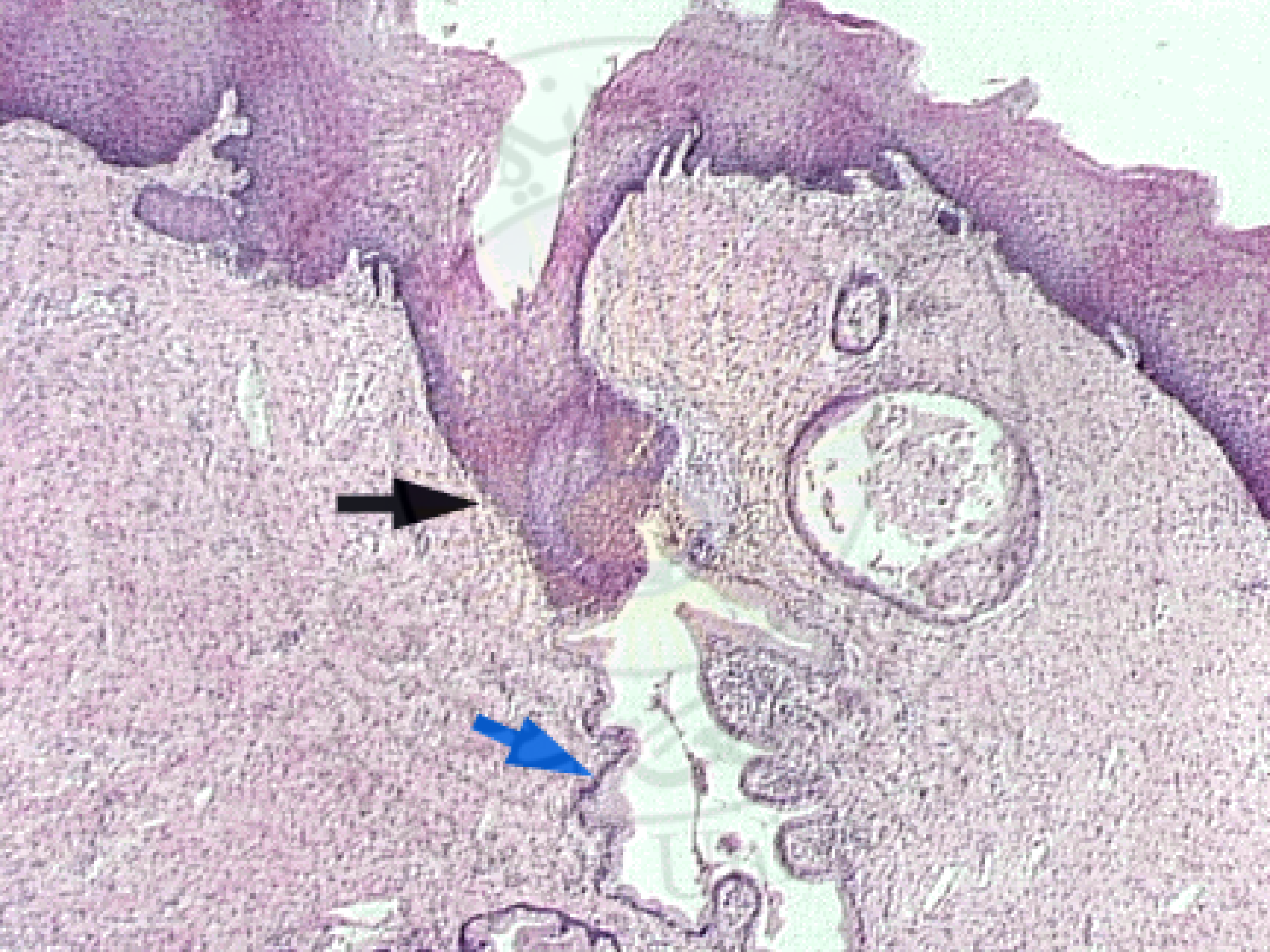
- It is the transformation of one mature cell type (epithelial or mesenchymal) into another mature adult cell type not physiologically present in that tissue.
- There is no physiological metaplasia which is almost always pathological as in these examples:

4-metaplasia

1-squamous metaplasia of columnar epithelium:

- squamous metaplasia of the respiratory epithelium due to chronic irritation (smokers)
- squamous metaplasia of (biliry, salivary, pancreatic) ducts epithelium due to chronic irritation caused by stones in these organs.





4-metaplasia

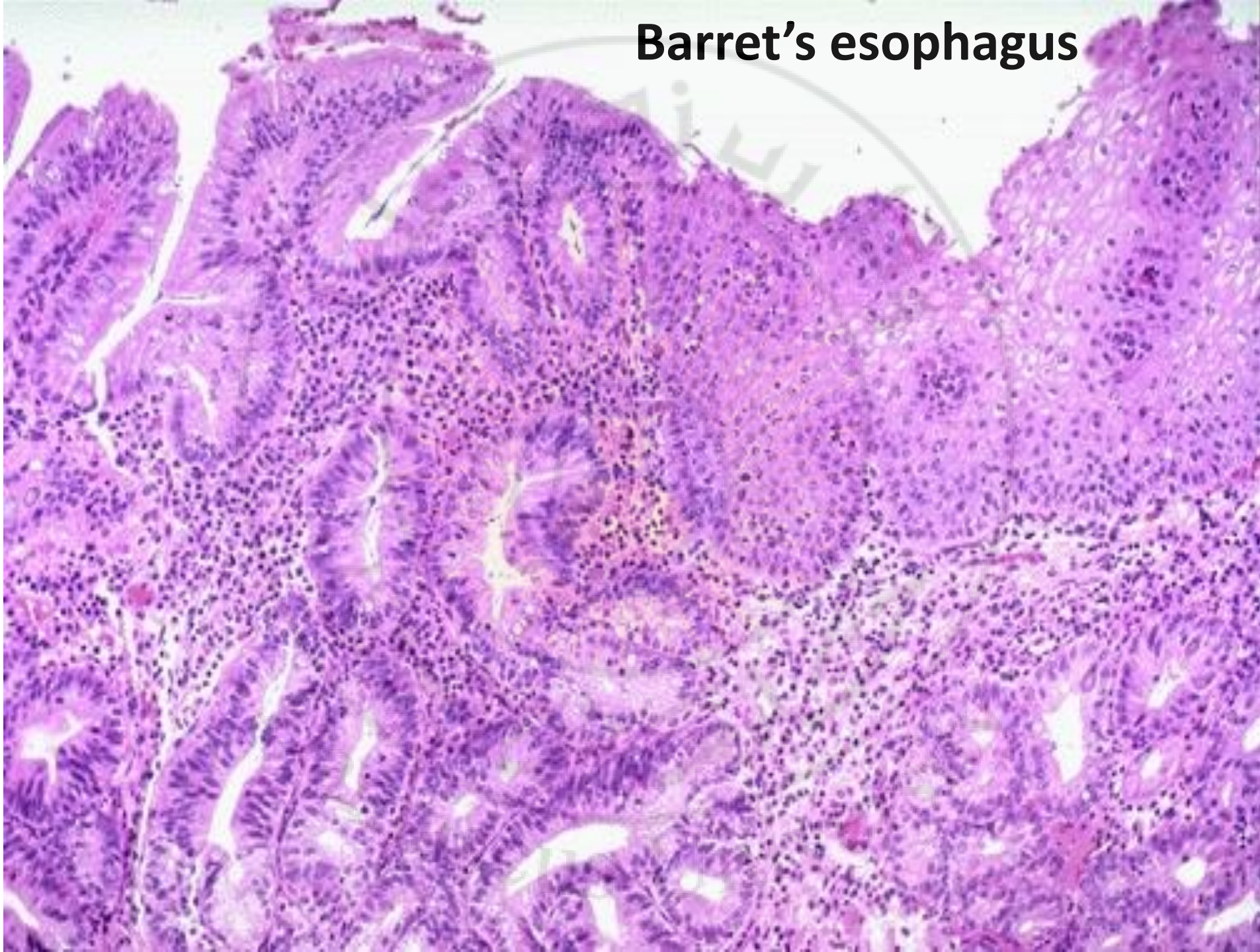
2-columnar metaplasia of squamous epithelium:

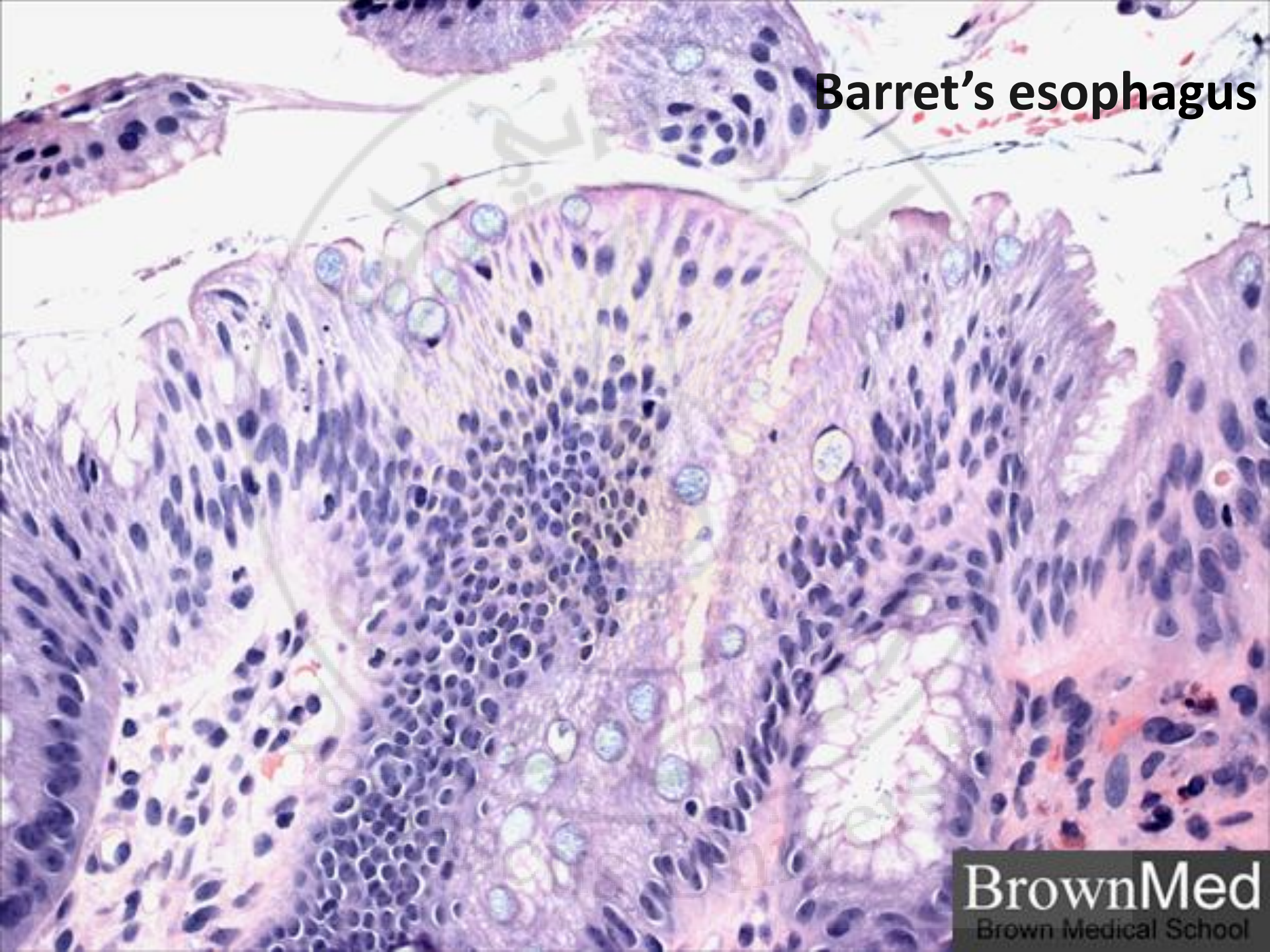
Columnar metaplasia of esophageal epithelium; a condition called (Barret's esophagus) in which the normal stratified squamous epithelium is replaced by intestinal type columnar

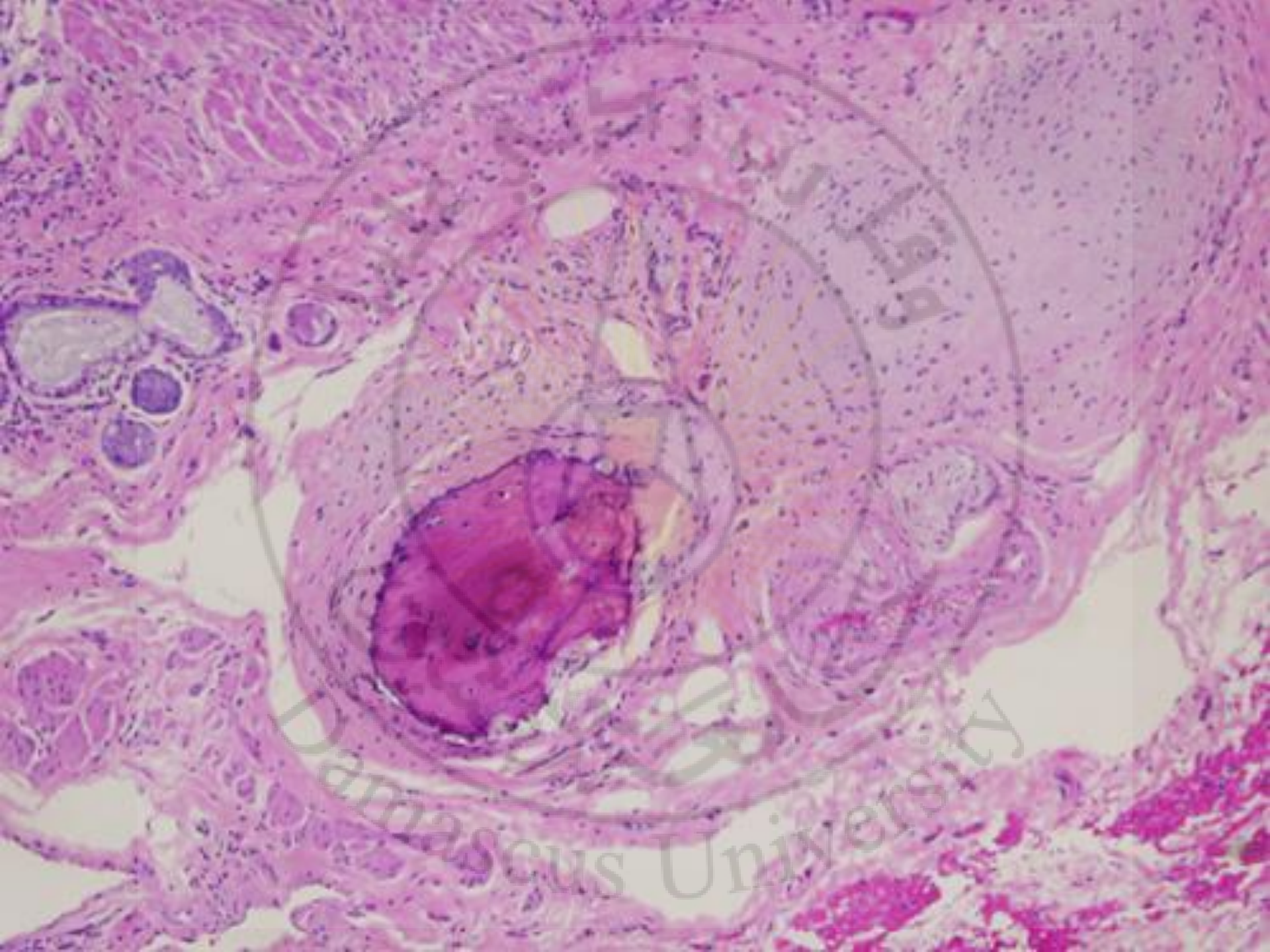
3- connective tissue metaplasia :

Formation of bone, cartilage, or fatty tissue not containing them originally, like in the condition of (myositis ossifcans) in which metaplastic bone is formed in skeletal muscles after a trauma.

Barret's esophagus




Barret’s esophagus
BrownMed
Brown Medical School



Pathogenesis of metaplasia

Metaplasia result from reprogramming of stem cells known to exist in most tissues, also called (reserve cells, undifferentiated mesenchymal cell) so a certain stimulus (smoking, Infections) makes these cells to re-differentiate to a new cell line.

metplasia is usually an undesired pathological process although it may protect the tissue from the stimulus; because on the long term if the stimulus that causes it persists, there will be a cancerous transformation of the metaplastic epithelium, thus it can be considered sometimes as a premalignant condition.

last nights of paris

an era of atrophy

5- acute inflammation

2018

Inflammation

Inflammation is the response or reaction of any living tissue to all forms of injury, it is usually a useful harmless pathophysiological process to overcome the injury, and to localize and eliminate the injurious agent and restore the tissue to normal or as close to normal as possible.

- Without inflammation, infections will spread in the body and wounds will never heal. However it can induce tissue damage if it is exaggerated.

Types of inflammation

1- Acute inflammation: it is the immediate and early inflammation that lasts hours-days

2-chronic inflammation: is a slow process, marked by formation of new connective tissue

Repair : the process by which the lost or destroyed tissue is replaced by new tissue, sometimes by the same tissue type but mostly by fibroblast and scar formation

Causes of inflammation in general

1- Infections : viral bacterial parasitic and fungal are among the most common and medically important causes of inflammation

2- Tissue necrosis: like myocardial infraction

3- Chemical : like chemical, acid injury…

4- Physical: like cold or heat injury, UV and X ray induced inflammation

5- Foreign bodies: like sutures, dirt

6- Immune reactions: also called hypersensitivity reactions which can be against environmental agents or against self tissues.

Pathophysiology of acute inflammation

There are a set of changes that occur in typical reactions of acute inflammation:

A- vascular changes (vasodilatation, congestion, &increased permeability)

B- cellular changes:

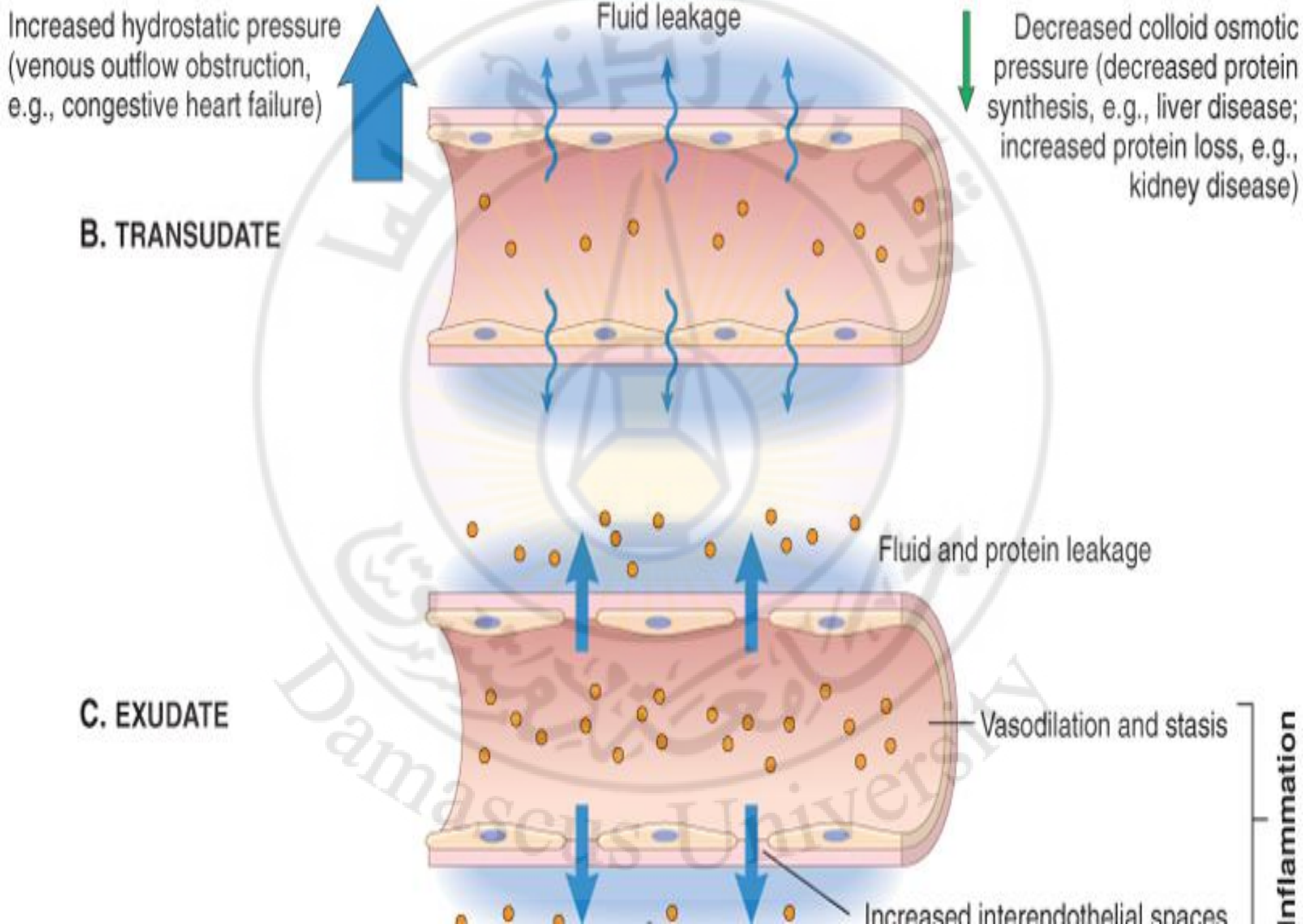
- Intravascular **WBC** events(pavementing, margination , emigration)
- Extravasular **WBC** events (chemotaxis, aggregation,phagocytosis)

All these steps are mediated by biochemical substances called ***inflammatory mediators***

Inflammatory fluid : in any inflammation there is a formation of certain amount of extravascular fluid in the tissue, this fluid is either of 2 types:

Transudate:is a clear serous fluid, that has a low protein content, low specific gravity less than 1020 and a low cellular content. It accumulate in tissue spaces due to increased hydrostatic pressure as in serous inflammation+ heat failure

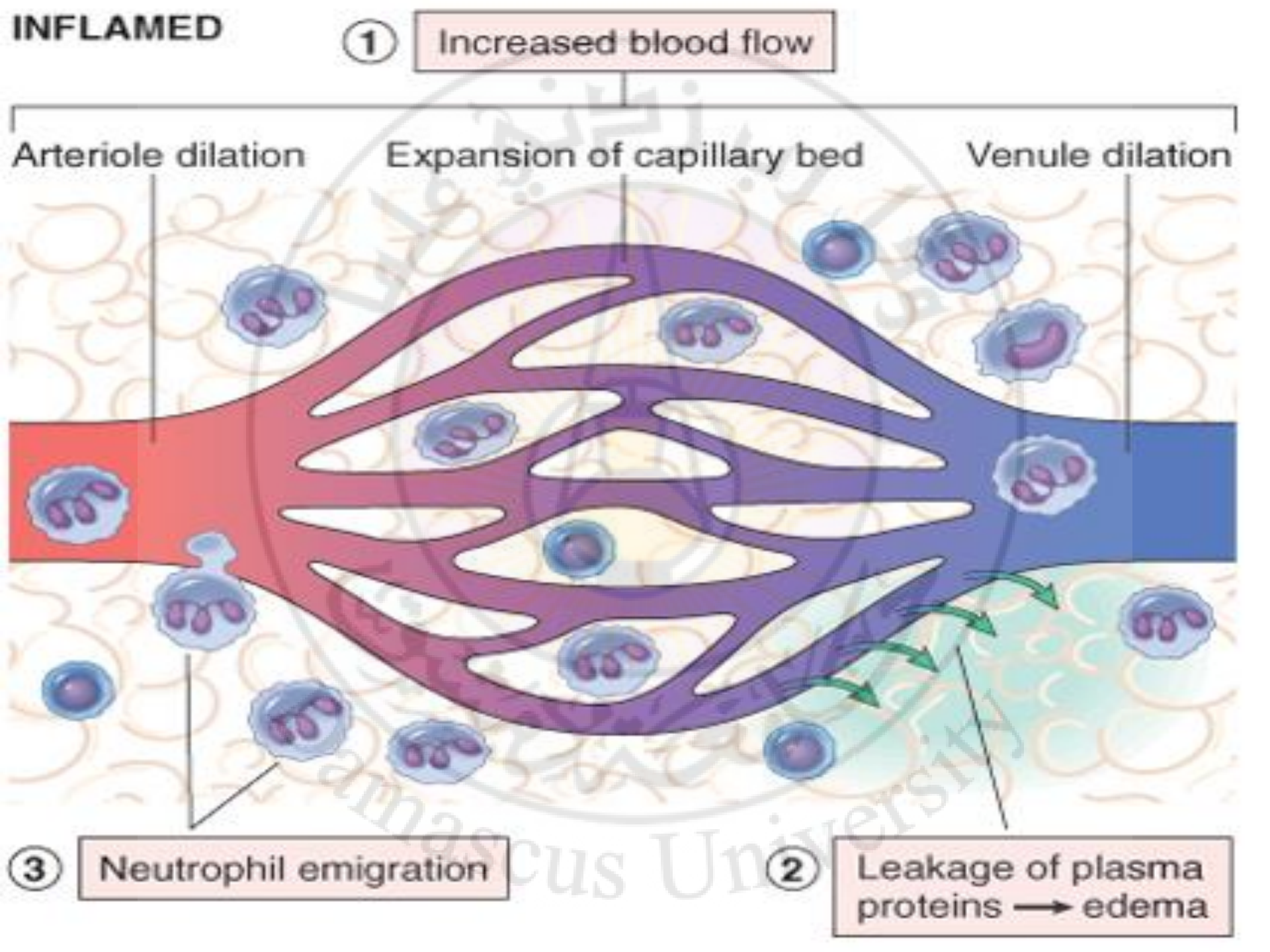
Exudate: a thick fluid of high protein content, high specific gravity more than 1020 and high cellular content mainly neutrophils ,accumulates in tissue spaces due to escape of plasma proteins and leukocytes due to increased vascular permeability as in acute suppurative inflammation


Increased hydrostatic pressure (venous outflow obstruction, e.g., congestive heart failure)
Fluid leakage
Decreased colloid osmotic pressure (decreased protein synthesis, e.g., liver disease; increased protein loss, e.g., kidney disease)
B. TRANSUDATE
Fluid and protein leakage
C. EXUDATE
Vasodilation and stasis
Increased interendothelial spaces
Inflammation

Vascular changes

1- change in blood vessel caliber

- Immediately at the beginning of any inflammation there is **vasoconstriction** lasting for 1-2 minutes. Its mechanism is not known , may be due to neurogenic axonal reflex.
- Then there will be **vasodilatation** (arterioles,capillaries,and postcapillary venules). This occur within few minutes of inflammation which will lead to locally increased blood flow and engorgement of capillary beds this is called **active hyperemia**


INFLAMED
1
Increased blood flow
Arteriole dilation
Expansion of capillary bed
Venule dilation
3
Neutrophil emigration
2
Leakage of plasma proteins → edema

- The increased volume of blood flow due to vasodilatation will lead to rise in intravascular hydrostatic pressure, resulting in movement of fluid from capillaries into the tissues. This fluid is called transudate which is filtered blood plasma and contains little protein. However, increasing vascular permeability will allow the movement of protein rich fluid and even cells into the intestinal space. This protein rich fluid is called exudate. This state of increased blood flow will last 10-15 minutes and is caused by chemical mediators like Histamine which is librated by tissue damage .

- Slowing of the blood flow in the venules (stagnation),with continuous blood flow from the arterioles there will be congestion (decreased outflow, increased inflow).this occurs within 10-30 minutes of inflammation.
- exudation will lead to concentration of red blood cells thus leading to increase in blood viscosity.
- RBCs Will be positioned centrally, while WBCs will be positioned peripherally near the vessel wall in a process called **margination**.

2-change in vascular permeability

this occurs by several mechanisms:

1-endothelial cell contraction leading to intercellular gaps:

the usual endothelium of venules is continuous layer (without gaps), in inflammation this will change, and some gaps between the endothelial cells will be formed so that WBCs can pass through the vessel wall to the extravascular compartment. This process occurs rapidly after binding of certain chemical mediators to specific receptors on the endothelial cell.

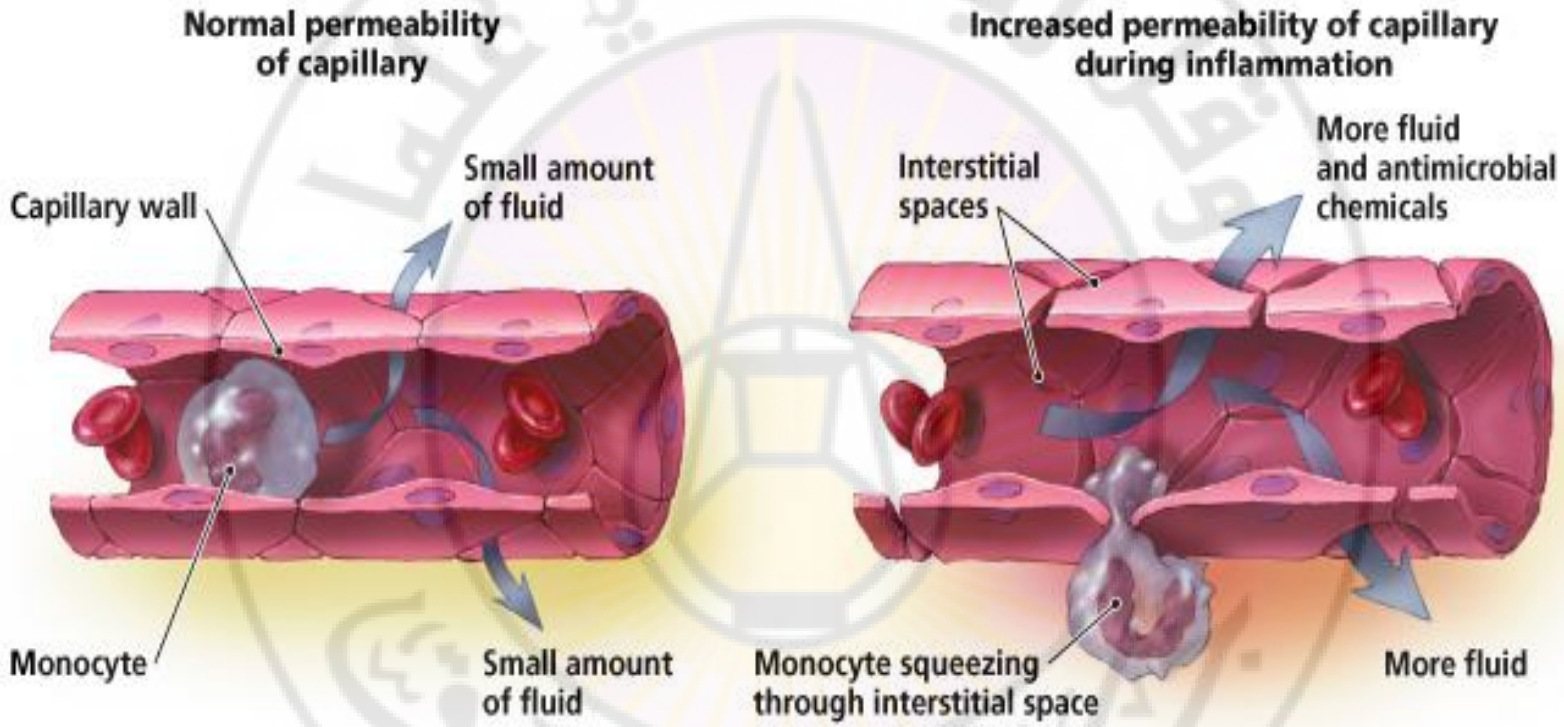
2-change in vascular permeability

2-endothelial injury: detachment

Which occurs in trauma, burns and infections; this results in vascular leakage by causing endothelial cell necrosis and detchment

3-leukocyte-dependant injury:

This refers to endothelial cell injury that results from accumulation of leukocytes during inflammation, which become activated and release toxic oxygen metabolites and proteolytic enzymes.



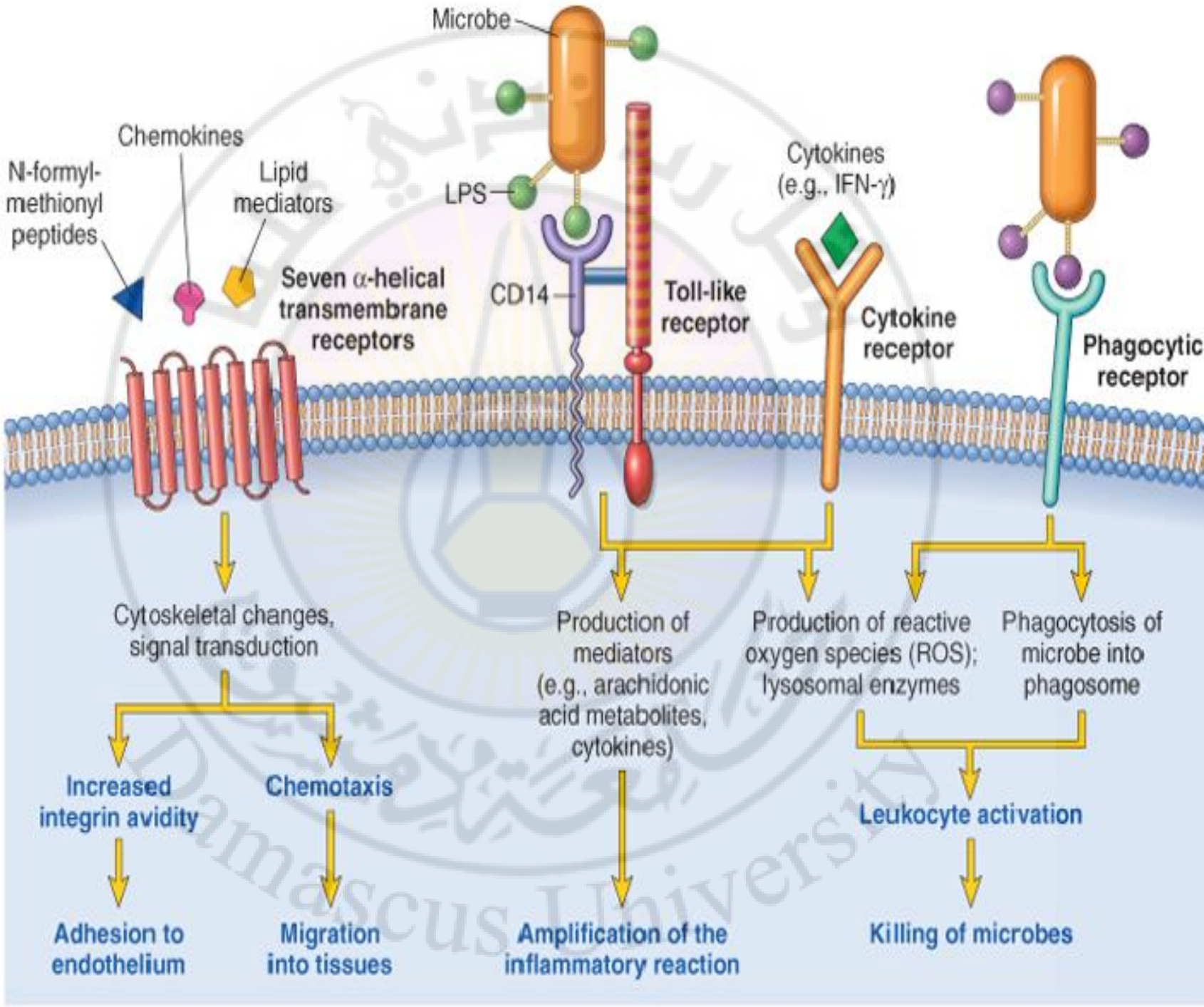
Cellular events

An important function of inflammatory response is to deliver leukocytes to the site of injury and to activate them. Leukocytes ingest offending agents, kill bacteria and remove necrotic tissue and foreign substances, however, once they are activated they produce products that can also harm host tissues

I-intravascular WBCs events

1-Margination : at the end of congestion phase the WBCs will be positioned at the periphery of the blood vessel near its internal wall, while the RBCs well take a central position.

2-Rolling &adhesion : the WBCs roll on the endothelial surface, then become activated by the effect of chemical mediators, finally they begin to stick firmly to the endothelial surface which will become pavemented by WBC. The adhesion is due to presence of adhesion molecules on the surface of the endothelial cells and the WBC that are complementary to each other (lock and key). They become expressed on the surface of these cells under the influence of the chemical mediators of inflammation.

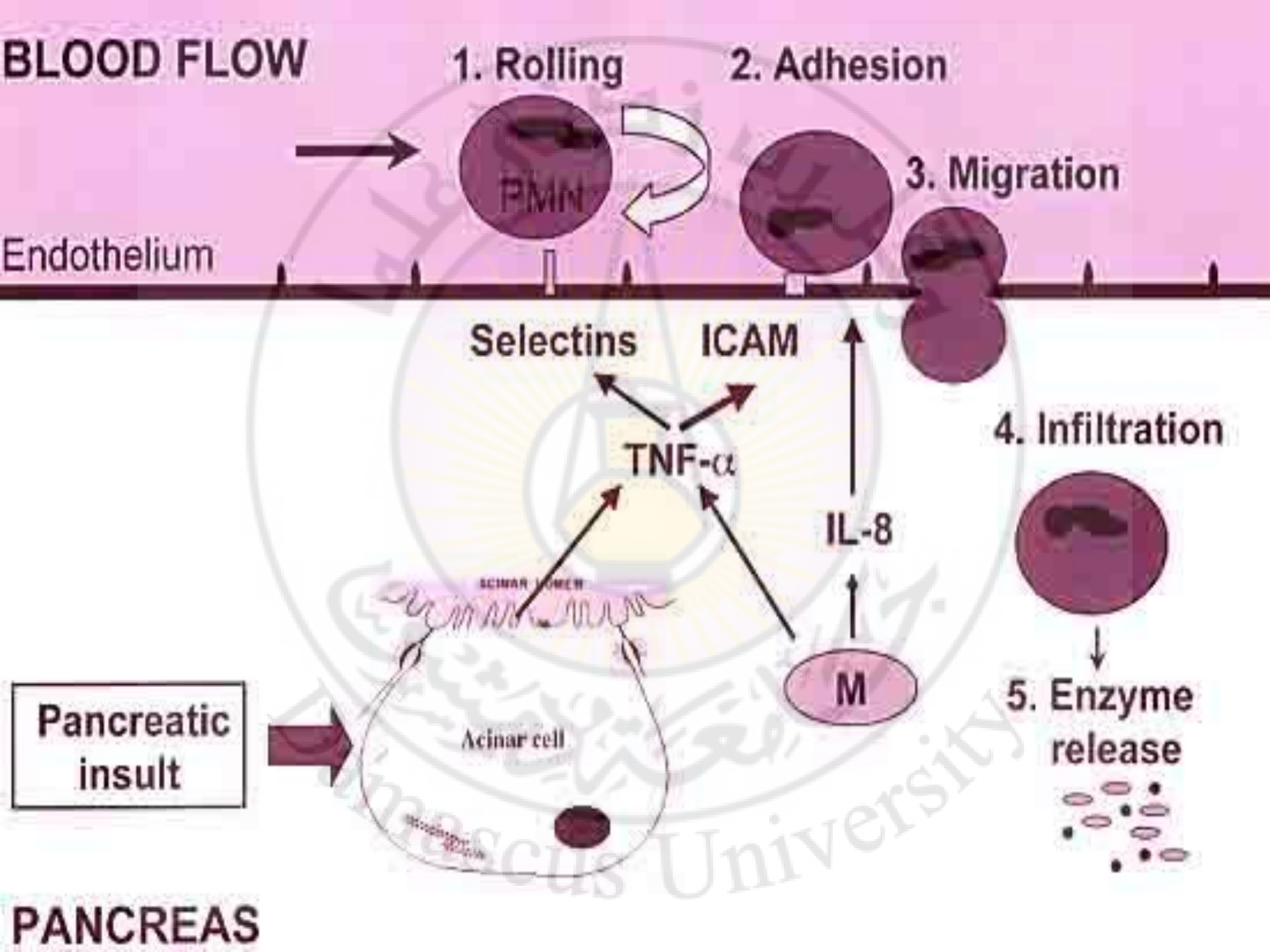

Recognition of microbes, mediators
Cellular response
Functional outcomes
Microbe
Chemokines
N-formyl-methionyl peptides
Lipid mediators
LPS
Seven α-helical transmembrane receptors
CD14
Toll-like receptor
Cytokines (e.g., IFN-γ)
Cytokine receptor
Phagocytic receptor
Cytoskeletal changes, signal transduction
Production of mediators (e.g., arachidonic acid metabolites, cytokines)
Production of reactive oxygen species (ROS); lysosomal enzymes
Phagocytosis of microbe into phagosome
Increased integrin avidity
Chemotaxis
Leukocyte activation
Adhesion to endothelium
Migration into tissues
Amplification of the inflammatory reaction
Killing of microbes

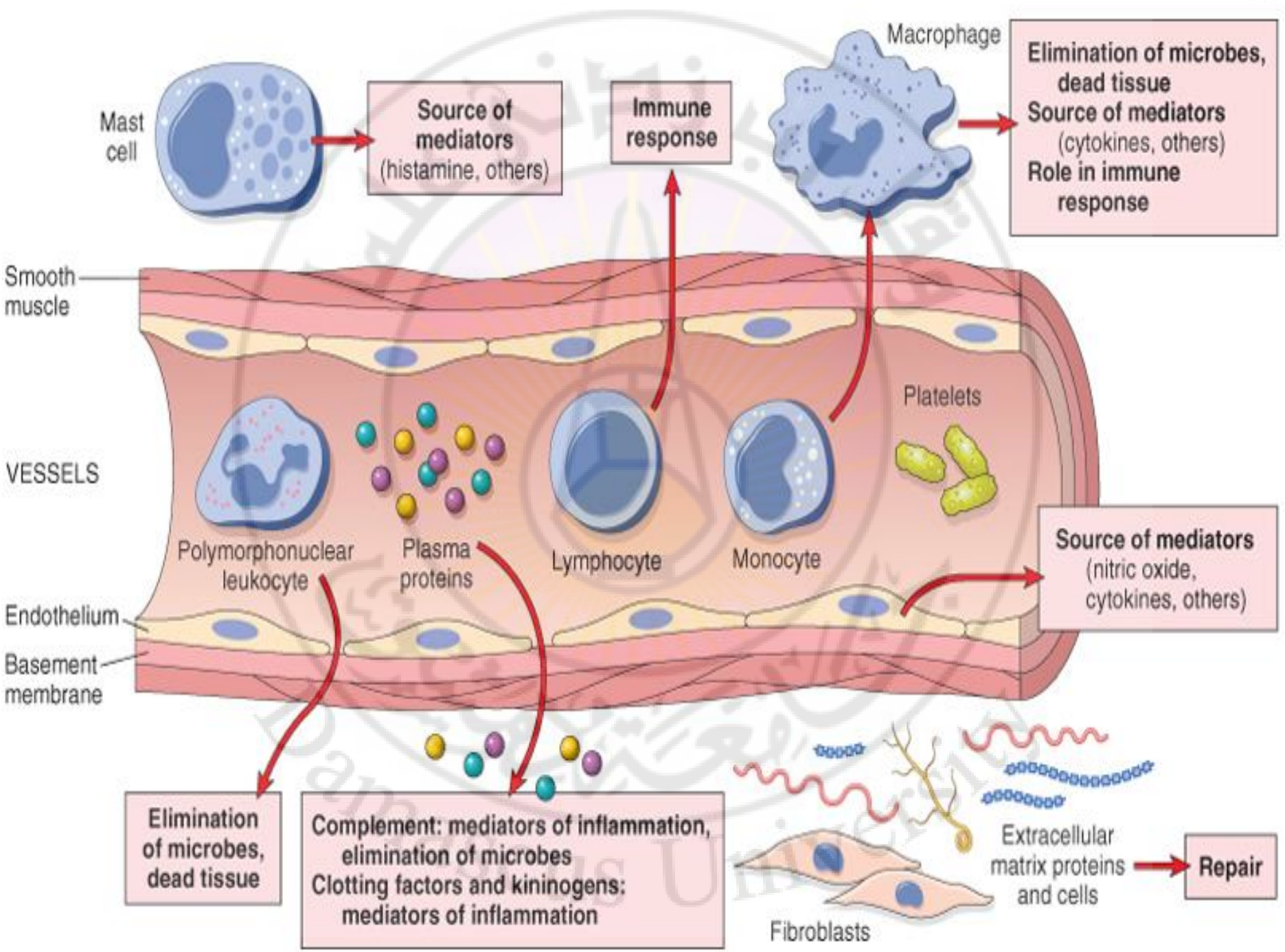
I-intravascular WBCs events

- the adhesion molecules belong to four families:

the selections,immunoglobulins ,integrins and mucin-like glycoproteins .

3-Emigration: The WBCs will then emigrate out of the vessel wall by their amoeboid movement by inserting pseudopods into junctions between the endothelial cells. The main types of emigrated WBCs in acute inflammation are neutrophils in the first 6-24 hrs and monocyte within 24-48hrs (once monocyte enters the extravascular tissue it will be called macrophage or histiocyte).


BLOOD FLOW
1. Rolling
2. Adhesion
3. Migration
PMN
Endothelium
Selectins
ICAM
TNF-α
IL-8
4. Infiltration
5. Enzyme release
M
Pancreatic insult
Acinar cell
PANCREAS


Mast cell
Source of mediators (histamine, others)
Immune response
Macrophage
Elimination of microbes, dead tissue
Source of mediators (cytokines, others)
Role in immune response
Smooth muscle
VESSELS
Platelets
Polymorphonuclear leukocyte
Plasma proteins
Lymphocyte
Monocyte
Source of mediators (nitric oxide, cytokines, others)
Endothelium
Basement membrane
Elimination of microbes, dead tissue
Complement: mediators of inflammation, elimination of microbes
Clotting factors and kininogens: mediators of inflammation
Extracellular matrix proteins and cells
Repair
Fibroblasts

II- Extravascular WBCs events

1-Chemotaxis: it is the attraction or directional movement of the emigrated extravascular WBCs towards an attractant, it is an active process mediated by chemical inflammatory mediators, called chemotactic agents. these mediators bind to the surface of WBC and enhance it to move in an amoeboid movement to the source of inflammation.

chemotactic agents: include

1- soluble bacterial products

2- complement system components like C5a

3- products of arachidonic acid metabolism especially leukotrein B4

4- cytokines like interleukin-8

II- Extravascular wbcs events

2-Aggregation: by the continuous effect of chemotaxis the WBCs will reach to the site of inflammation and aggregate in that tissue area

3- phagocytosis: and the release of lysosomal enzymes are the two major benefits occuring from the accumulation of leukocytes at the site of inflammation.

There are three distinct steps in phagocytosis:

steps of phagocytosis

1- recognition:

Neutrophils and monocytes recognize most injurious agents only when coated by serum factors called opsonin, these include immunoglobulines Fc portion as IGg and complement components such as C3b. These join specific receptors on leukocyte surface. Opsonization: is coating of the foreign particle by immunoglobulins or complement component which will make them recognizable by WBC as foreign

steps of phagocytosis

2- engulfment :

Cytoplasmic extensions from leukocytes form peudopods around the object to be engulfed to become a membrane-bound phagocytic vacuole that contains the particle called phagosome. This will fuse with membrane-bound lysosome to form phagolysosome. Lysosomes then release their enzymes which will lead to killing and degradation of ingested material. Some of these lysosomal enzymes leak to the extracellular space causing further tissue damage.

steps of phagocytosis

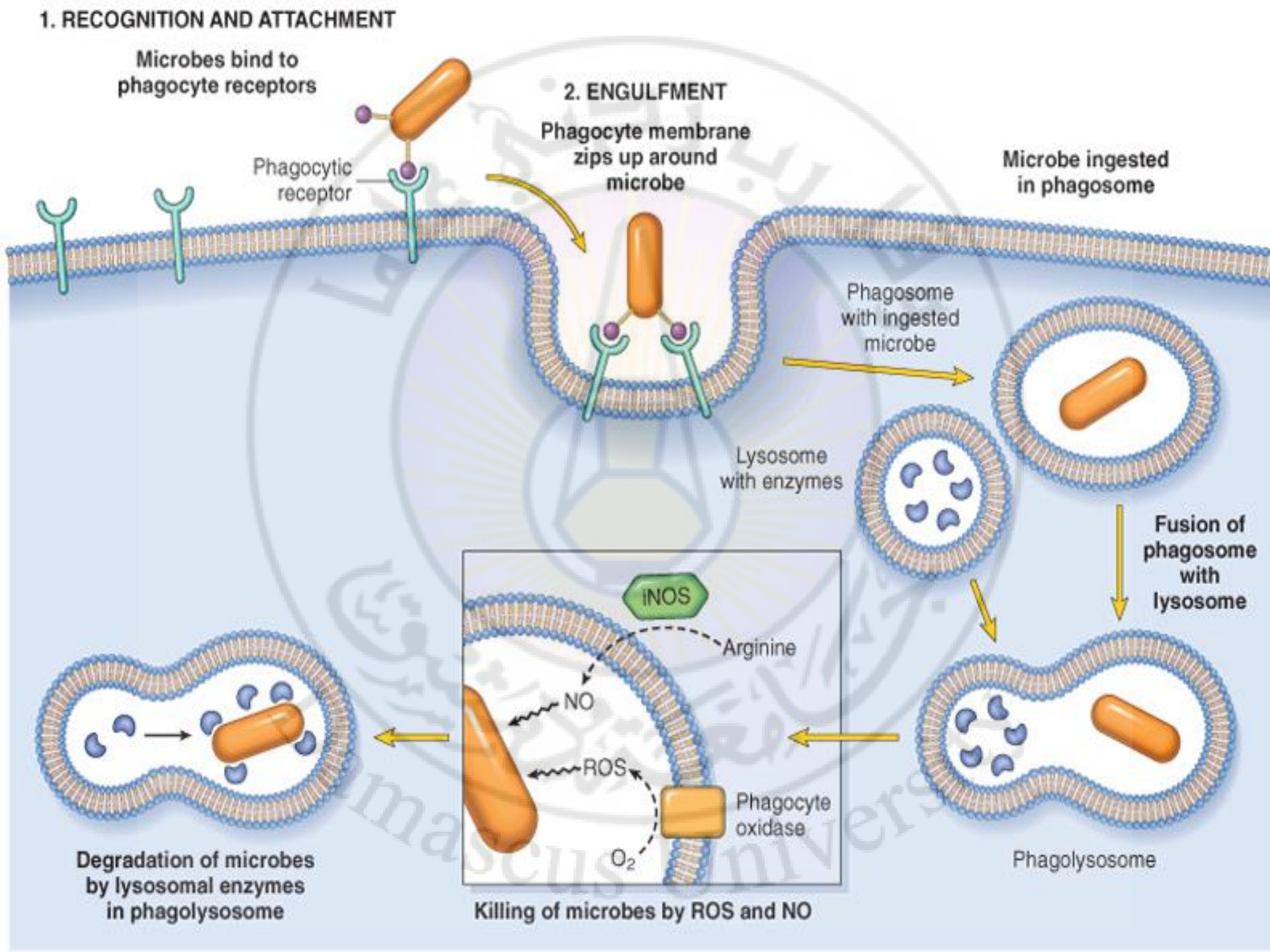
3-killing and degradation of ingested material;

The WBCs can kill the phagocytosized bacteria by the release of :

1-the enzymes in the granules of WBCs (acid hydrolase, myeloperoxidase,lactoferrin), a process called degranulation.

2-active oxygen compounds O_2^- H_2O_2 (FTR)

3-hypochlorite CL : which is the most powerful substance that kills bacteria


1. RECOGNITION AND ATTACHMENT
Microbes bind to phagocyte receptors
Phagocytic receptor
2. ENGULFMENT
Phagocyte membrane zips up around microbe
Microbe ingested in phagosome
Phagosome with ingested microbe
Lysosome with enzymes
Fusion of phagosome with lysosome
iNOS
Arginine
NO
ROS
Phagocyte oxidase
O_2
Degradation of microbes by lysosomal enzymes in phagolysosome
Killing of microbes by ROS and NO
Phagolysosome

The inflammatory mediators

These are the active biochemical compounds that play a role in all the steps of acute inflammation,

Mediators may be produced by cells at the site of inflammaion , or they may be circulating in the plasma (typically synthesized by the liver) as inactive precursors that are activated at the site of inflammation by proteolytic cleavage.

inflammatory mediators

1-mediators that are derived from plasma:

- The Kinin system
- The complement system
- The coagulation and fibrinolytic systems

2- mediators released from cells : either:

A- Peformed mediators in secretory granules:

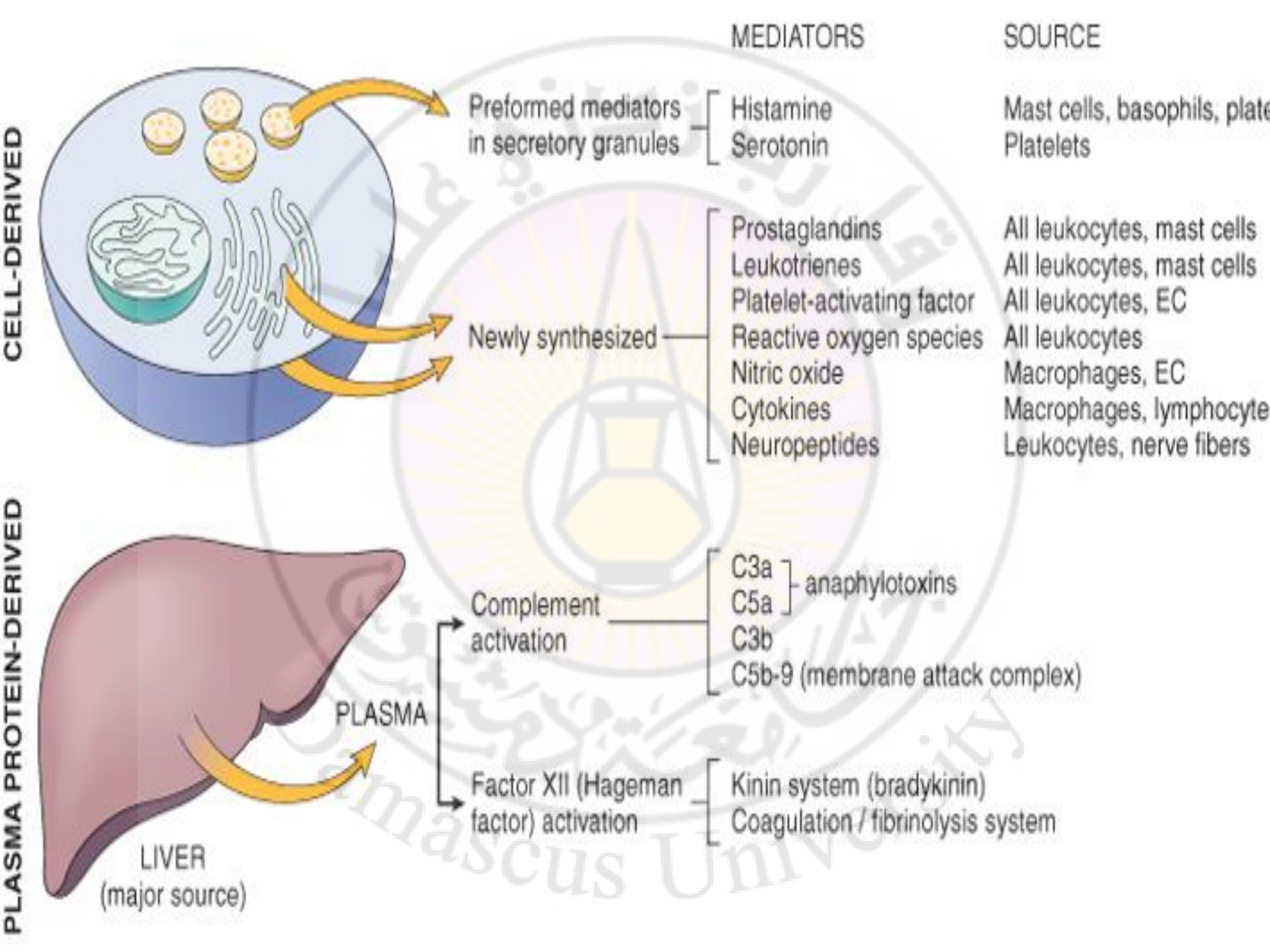
- **Histamine** secreted by mast cells, basophils and platelets
- **Serotonin** secreted by platelets, lysosomal enzymes secreted by neutrophils and macrophages

inflammatory mediators

2- mediators released from cells :

B- Newly synthesized mediators :

- **Prostaglandins** (PG) secreted by all leukocytes, platelets and endothelial cells
- **Leukotriens** (LT) secreted by all leukocytes.
- **Platelet activating factor**(PAF) secreted by all leukocytes and endothelial cells
- **Nitric oxide** secreted by macrophages


MEDIATORS
SOURCE
CELL-DERIVED
Preformed mediators in secretory granules
Histamine
Serotonin
Mast cells, basophils, plate
Platelets
Newly synthesized
Prostaglandins
Leukotrienes
Platelet-activating factor
Reactive oxygen species
Nitric oxide
Cytokines
Neuropeptides
All leukocytes, mast cells
All leukocytes, mast cells
All leukocytes, EC
All leukocytes
Macrophages, EC
Macrophages, lymphocyte
Leukocytes, nerve fibers
PLASMA PROTEIN-DERIVED
LIVER
(major source)
PLASMA
Complement activation
C3a
C5a
anaphylotoxins
C3b
C5b-9 (membrane attack complex)
Factor XII (Hageman factor) activation
Kinin system (bradykinin)
Coagulation / fibrinolysis system

Effects of chemical mediators

1- vascular dilatation: caused by histamine,prostaglandins (PGE2), complement component C3a & C5a

2-increased vasular permeability: histamine, leukotriens C4, D4 & E4,Prostaglandins

3-emigration of leukocytes: C5a, leukotrien B4,bacterial products

4- tissue damage : neutrophils and macrophage lysosomal enzymes, oxygen metabolites & nitric oxides

5-pain : prostaglandins and bradykinin

6-fever: interleukin 1 & Tumor necrosis factorTNF, Prostaglandins

Table 2-6. Role of Mediators in Different Reactions of Inflammation

Vasodilation	Prostaglandins
	Nitric oxide[R]
	Histamine
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Bradykinin Leukotrienes C_4, D_4, E_4 PAF Substance P
Leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4 (Bacterial products, e.g., *N*-formyl methyl peptides)
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
	Neuropeptides
Tissue damage	Lysosomal enzymes of leukocytes
	Reactive oxygen species
	Nitric oxide[R]

IL-1, Interleukin-1; PAF, platelet-activating factor; TNF, tumor necrosis factor.

Fate of inflammatory mediators

The action of most mediators are tightly regulated . Once activated or released from the cell,

mediators may:

- ***quickly decay*** (arachidonic acid metabolites)
- ***be inactivated*** by enzymes (e.g., kininase inactivates bradykinin)
- ***be eliminated*** (e.g., antioxidants scavenge toxic oxygen metabolites)
- ***be inhibited*** (complement inhibitory proteins)

Clinical features of acute inflammation

- The cardinal signs of acute inflammation are:

1-redness } due to the increased blood flow
2-heat } and congestion.

3-swelling due to the escape of the inflammatory fluid to the area of inflammation.

4-pain due to pressure on nerve ending by swelling and to chemical mediators (prostaglandins).

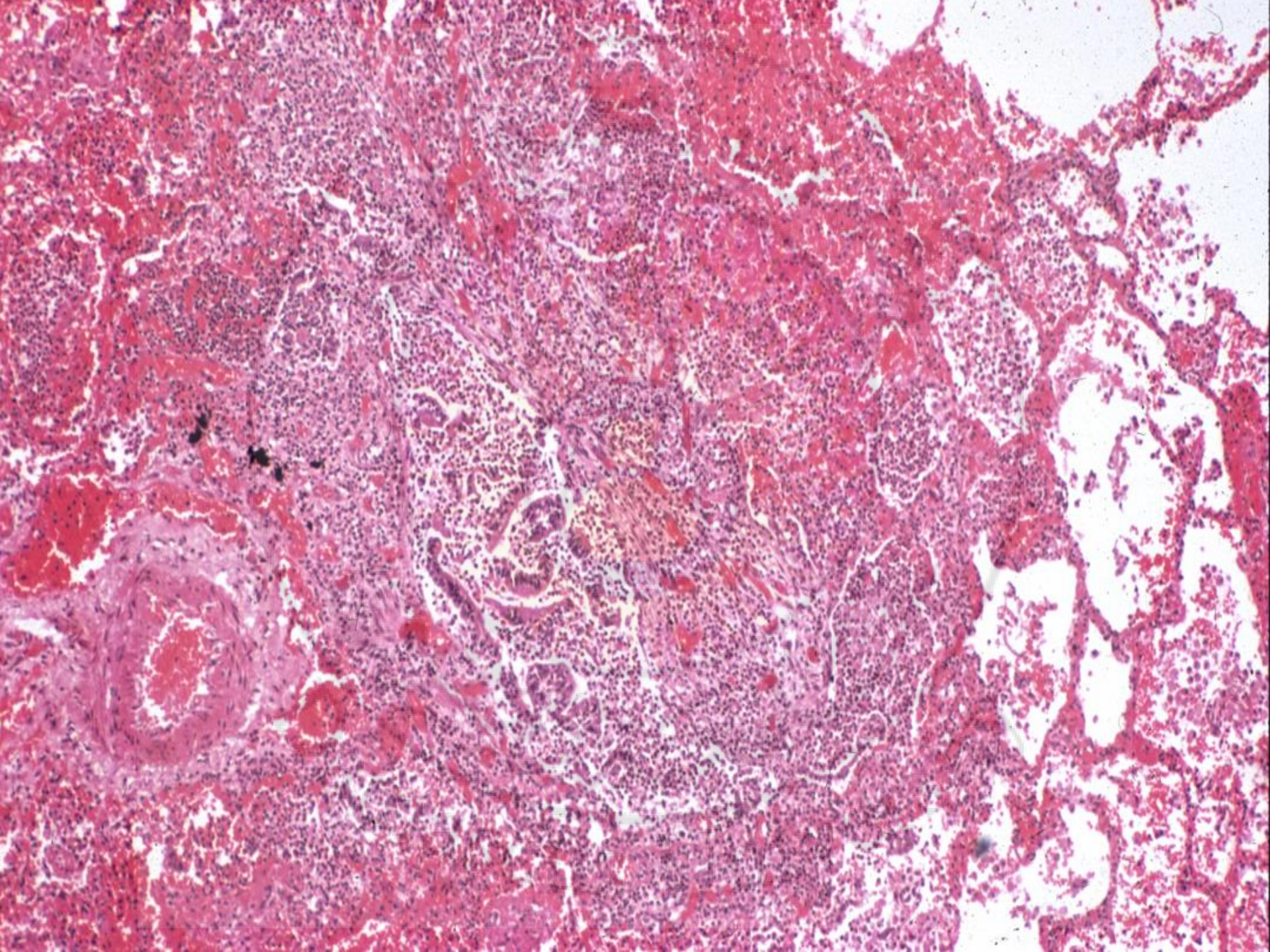
5-loss of function due to the pain and swelling.

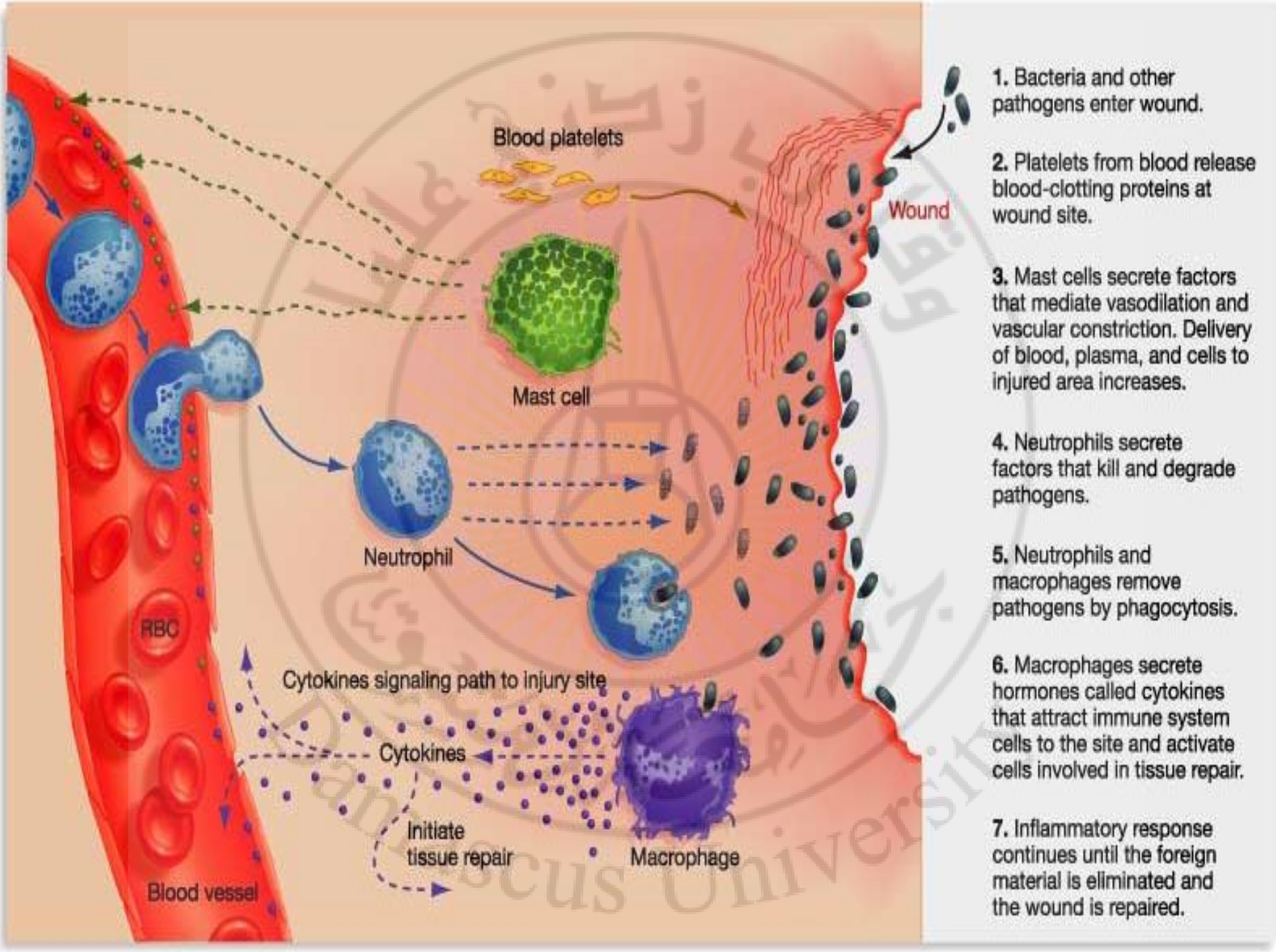
In Cure Process: The First to cure are (redness & heat), while (swelling, pain, & loss of function) may last longer.

Morphology (histopathological picture)

- **Inflammatory fluid** (exudate or transudate)
- **Infiltration of acute inflammatory cells** to the area (mainly neutrophils and macrophages)
- **Congestion and dilatation of blood vessels**

❖However in cases of (viral infection and tuberculosis), the main inflammatory cells will be lymphocytes, whereas in cases of(allergic reaction, parasitic infection, worm infestation), the main inflammtory cells will be eosinophils

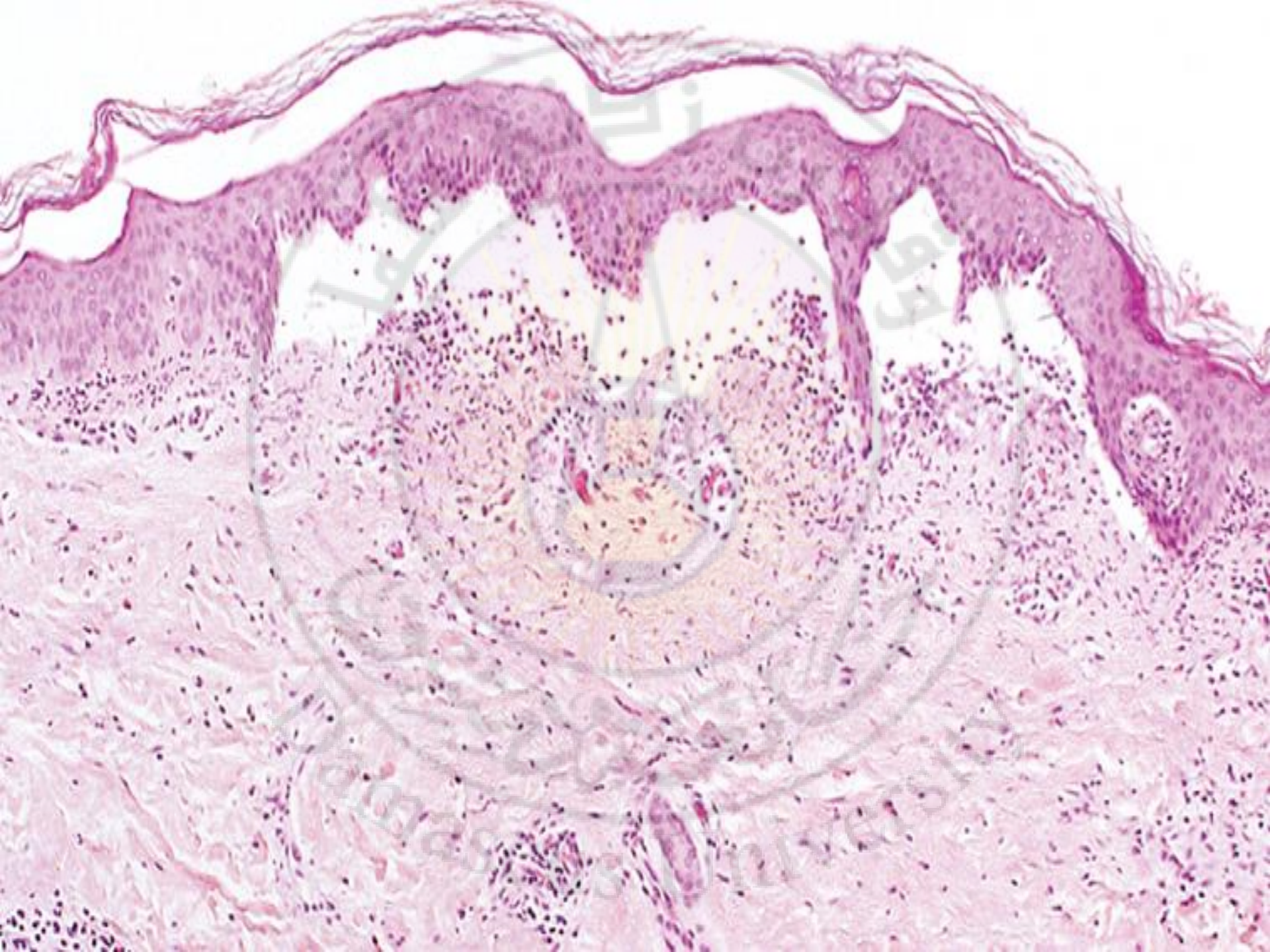


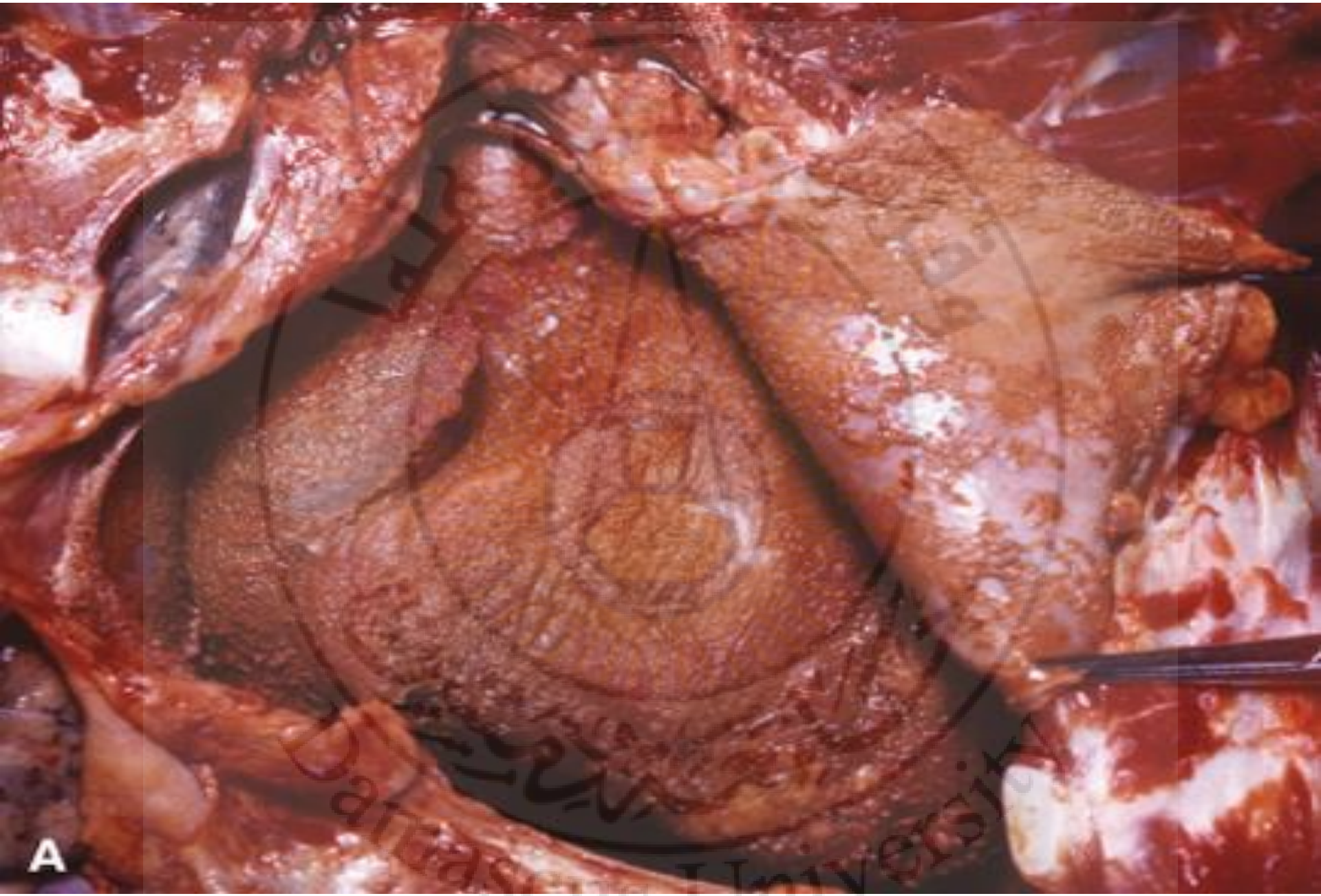

Blood platelets
Wound
Mast cell
Neutrophil
RBC
Cytokines signaling path to injury site
Cytokines
Initiate
tissue repair
Macrophage
Blood vessel
1. Bacteria and other pathogens enter wound.
2. Platelets from blood release blood-clotting proteins at wound site.
3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases.
4. Neutrophils secrete factors that kill and degrade pathogens.
5. Neutrophils and macrophages remove pathogens by phagocytosis.
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair.
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired.

Patterns of inflammation

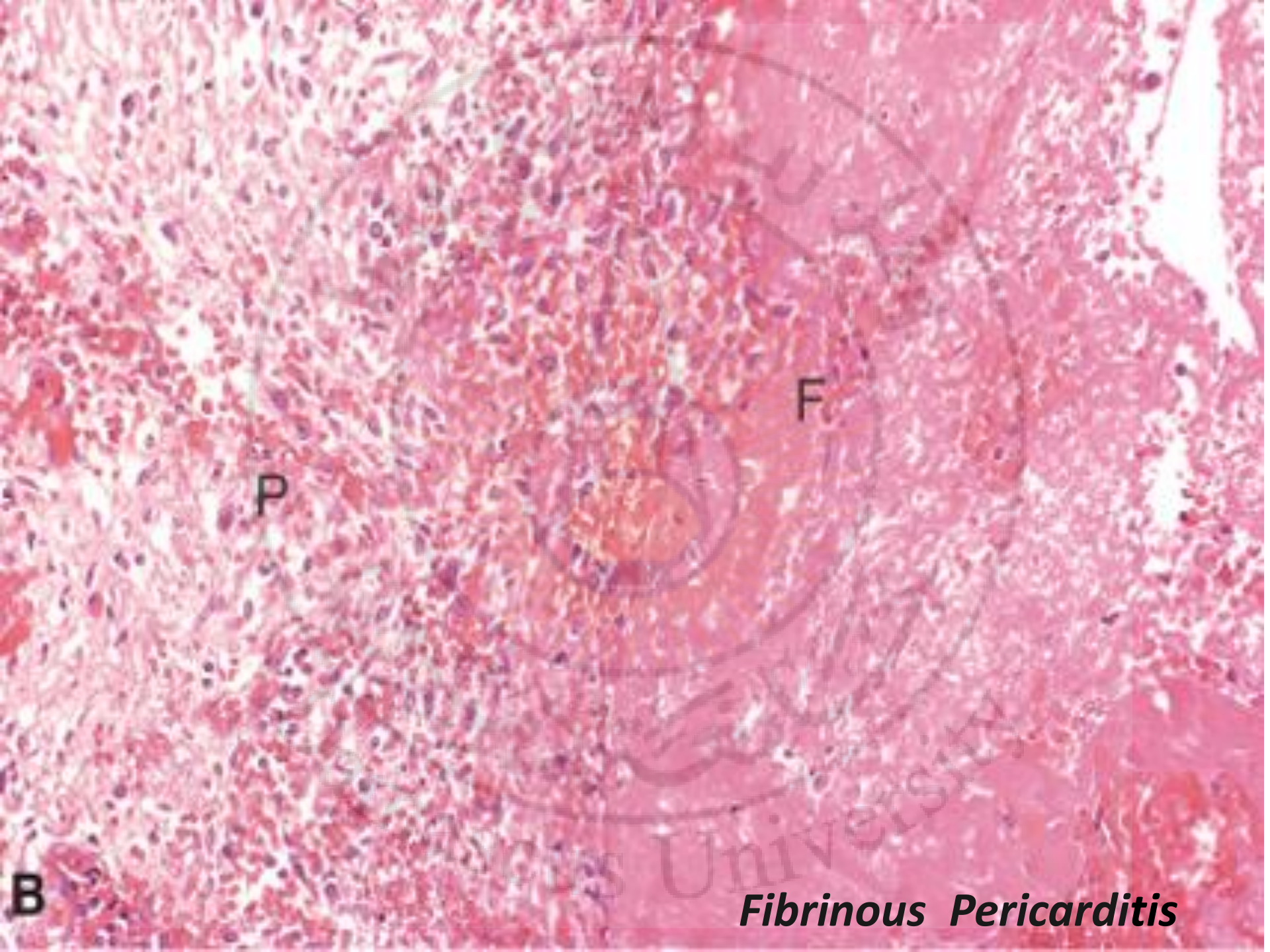
1- serous inflammation: in mild acute inflammation where only transudate is formed, the inflammatory focus is usually grossly colorless. Example: burn blister.

2-fibrinous inflammation: in more severe acute inflammation where exudate is formed (plasma, plasma proteins ‘‘fibrinogen’’,WBCs),with consequent deposition of masses of fibrin that is either organized into fibrous tissue or resolved by fibrinolysis. example: rheumatic pericarditis of the heart.





Fibrinous Pericarditis



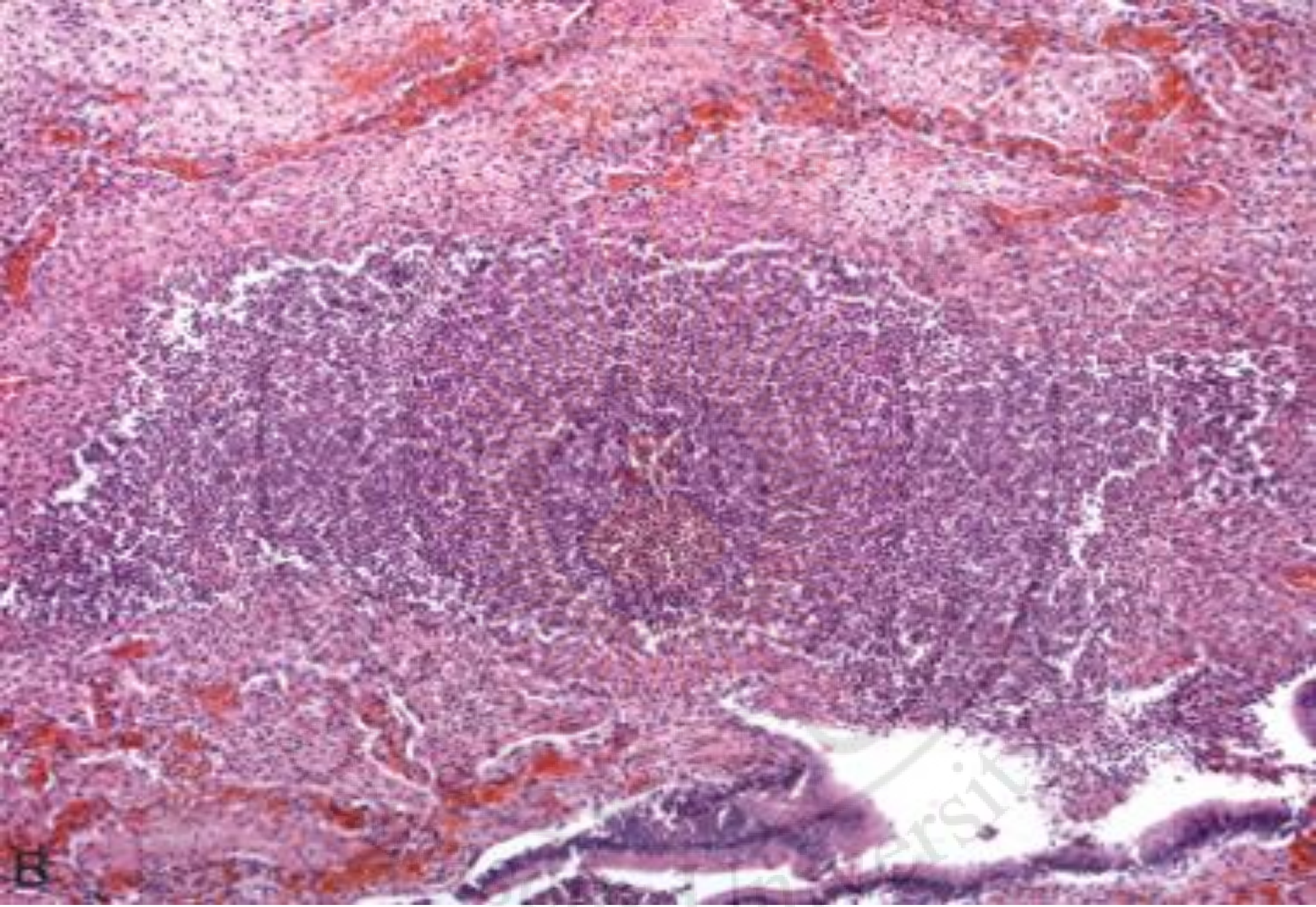
Fibrinous Pericarditis

Patterns of inflammation

3-purulent or suppurative inflammation : in very severe acute inflammation where pus is formed (exudate rich in cell debris and dead WBCs) example: abscess, infected wounds

Pus: a thick creamy yellowish,greenish or blood stained fluid of high protein content. Il accumulates in severe acute suppurative inflammation and abscesses

suppurative inflammation



supurative inflammation

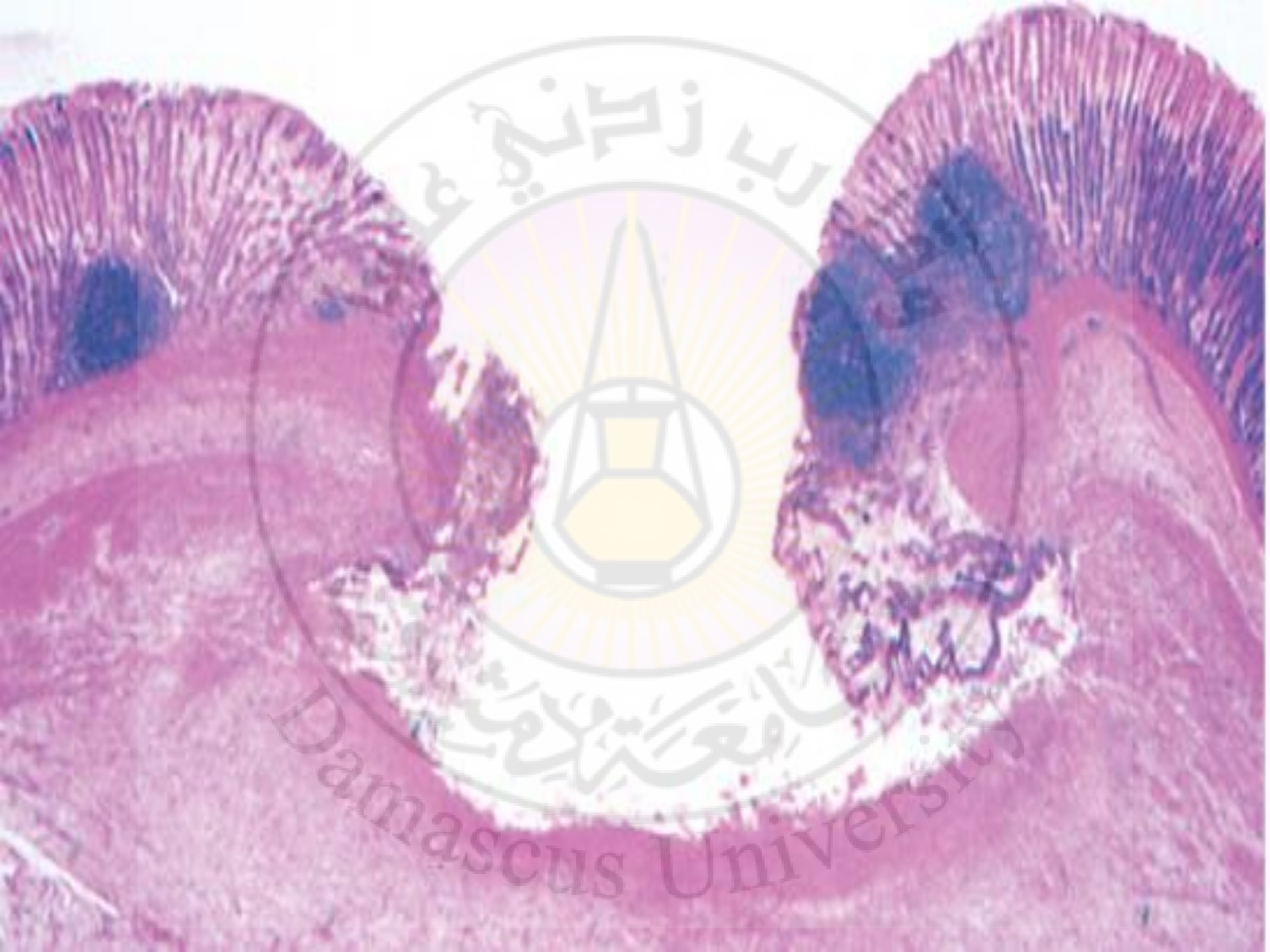
Patterns of inflammation

Abscess: a localized collection of pus caused by suppurative inflammation. The central part consist of collection of acidophilic amorphous debris composed of dead tissue cells, dead WBCs and bacteria . This is surrounded by a zone of viable neutrophils, which is surrounded by highly vascularized granulation tissue and fibrous tissue.

Patterns of inflammation

Ulcer: is a local defect or excavation of the surface of the skin or the lining of an organ (as GIT, respiratory tract or urinary tract lining epithelium) it is produced by sloughing of inflamed necrotic epithelium

4-membranous inflammation: in specific inflammation like diphtheria infection, there is a formation of dirty thick gray pseudomembrane on the inflammation focus



Fate of acute inflammation

Acute inflammation generally has one of three outcomes:

1-resolution : in which restoration to normal tissue occurring:

- When the injury is limited or of short duration and so there has been minimal tissue damage

- And in tissues that are capable of replacing necrotic cells.

Fate of acute inflammation

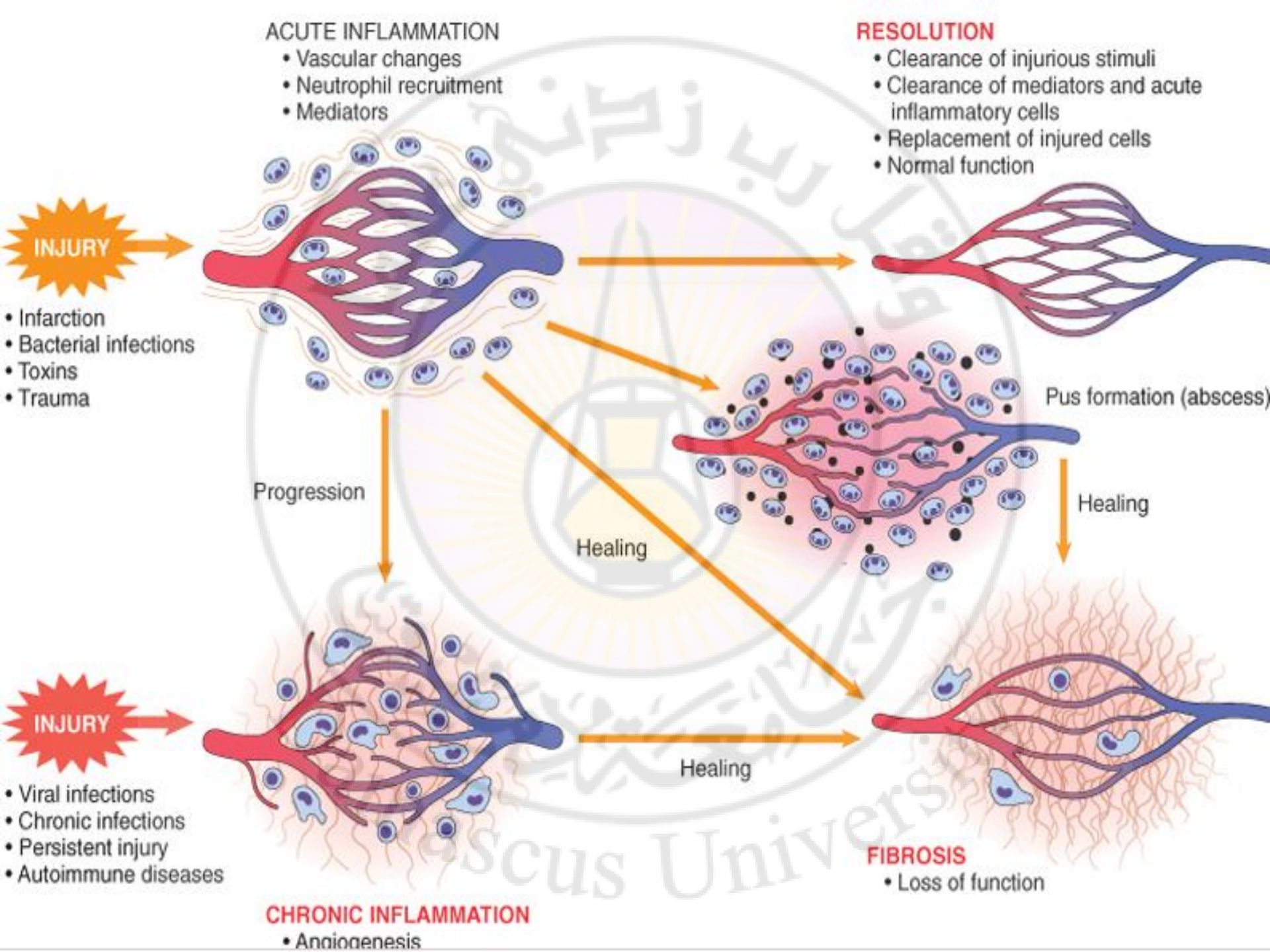
2- healing by fibrosis:

fibrosis and scar formation result from:

- Heavy fibrin deposition where extensive fibrinous exudates may not be completely absorbed and if not removed by fibrinolysis, they will be transformed into connective tissue by a process of organization.
- Dead of large amount of tissue : when the amount of necrotic tissue is large, it will be replaced by fibrous scar.

Fate of acute inflammation

3-progression to chronic inflammation :may follow acute inflammation if the offending agent is not removed.


ACUTE INFLAMMATION
• Vascular changes
• Neutrophil recruitment
• Mediators
RESOLUTION
• Clearance of injurious stimuli
• Clearance of mediators and acute inflammatory cells
• Replacement of injured cells
• Normal function
INJURY
• Infarction
• Bacterial infections
• Toxins
• Trauma
Pus formation (abscess)
Progression
Healing
Healing
INJURY
• Viral infections
• Chronic infections
• Persistent injury
• Autoimmune diseases
Healing
FIBROSIS
• Loss of function
CHRONIC INFLAMMATION
• Angiogenesis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Damascus University

Dr. Fariz AHMAD

6- chronic inflammation

2018

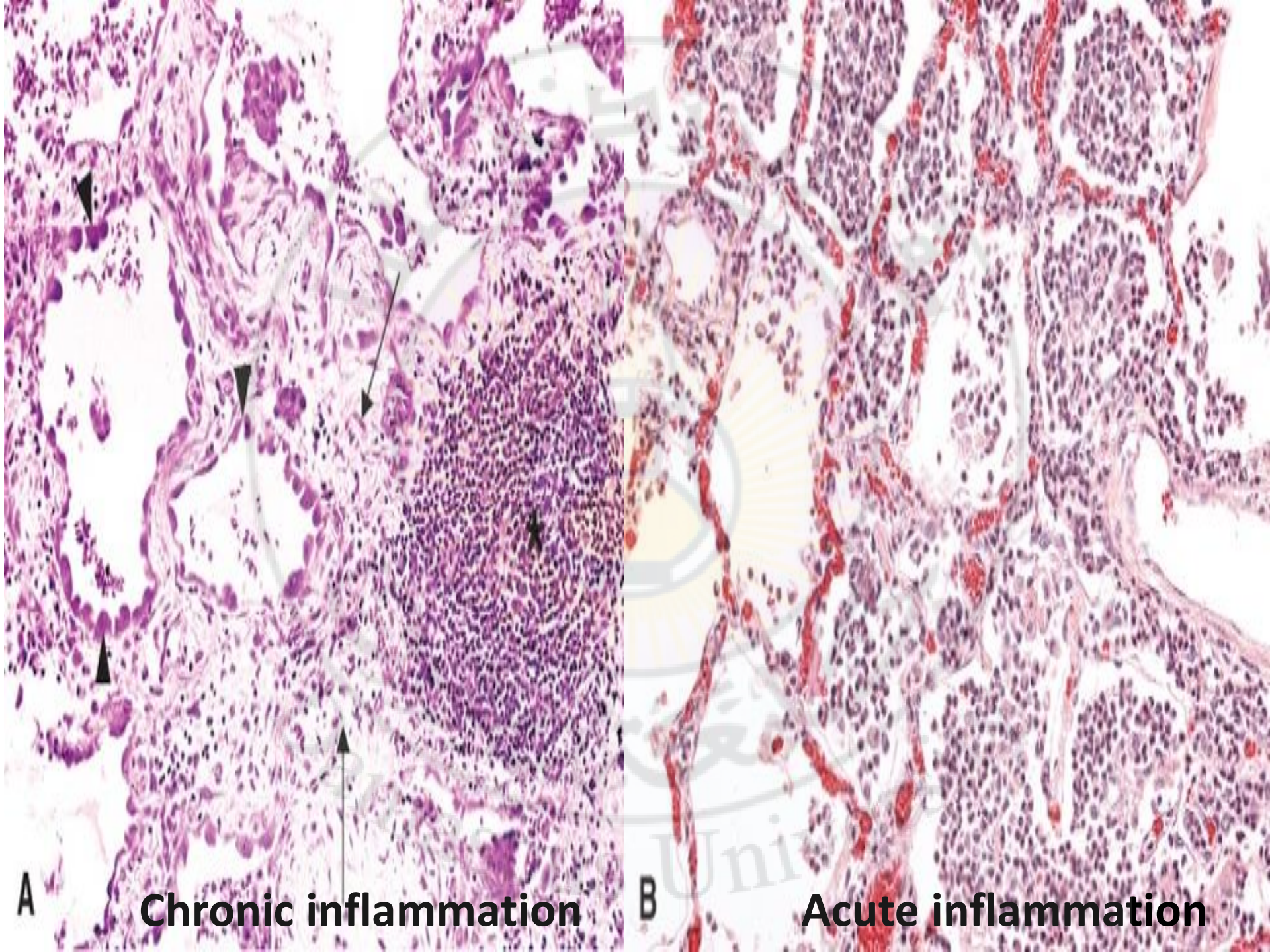
Chronic inflammation

Chronic inflammation is inflammation of prolonged duration (weeks to years) characterized by

***Infiltration** with mononuclear cells,* including macrophages, lymphocytes, and plasma cells

***Tissue destruction**,* largely induced by the products of the inflammatory cells

***Repair**, involving new vessel proliferation (angiogenesis) and fibrosis*


A
Chronic inflammation
B
Acute inflammation

Acute inflammation may progress to chronic inflammation due to either :

1- persistence of the injurious agent

2- interference with the normal process of healing

e.g. peptic ulcer of the duodenum initially shows acute inflammation, however recurrent duodenal epithelial injury by gastric acid interrupt this process and result in progression to chronic inflammation.

Chronic inflammation arises in the following settings:

1- ***Persistent infections*** by microbes that are difficult to eradicate: (mycobacteria, *Treponema pallidum,* and certain viruses and fungi

2- ***Immune-mediated inflammatory diseases****:* *(*rheumatoid arthritis and inflammatory bowel disease

3- ***allergic diseases*** such as bronchial asthma

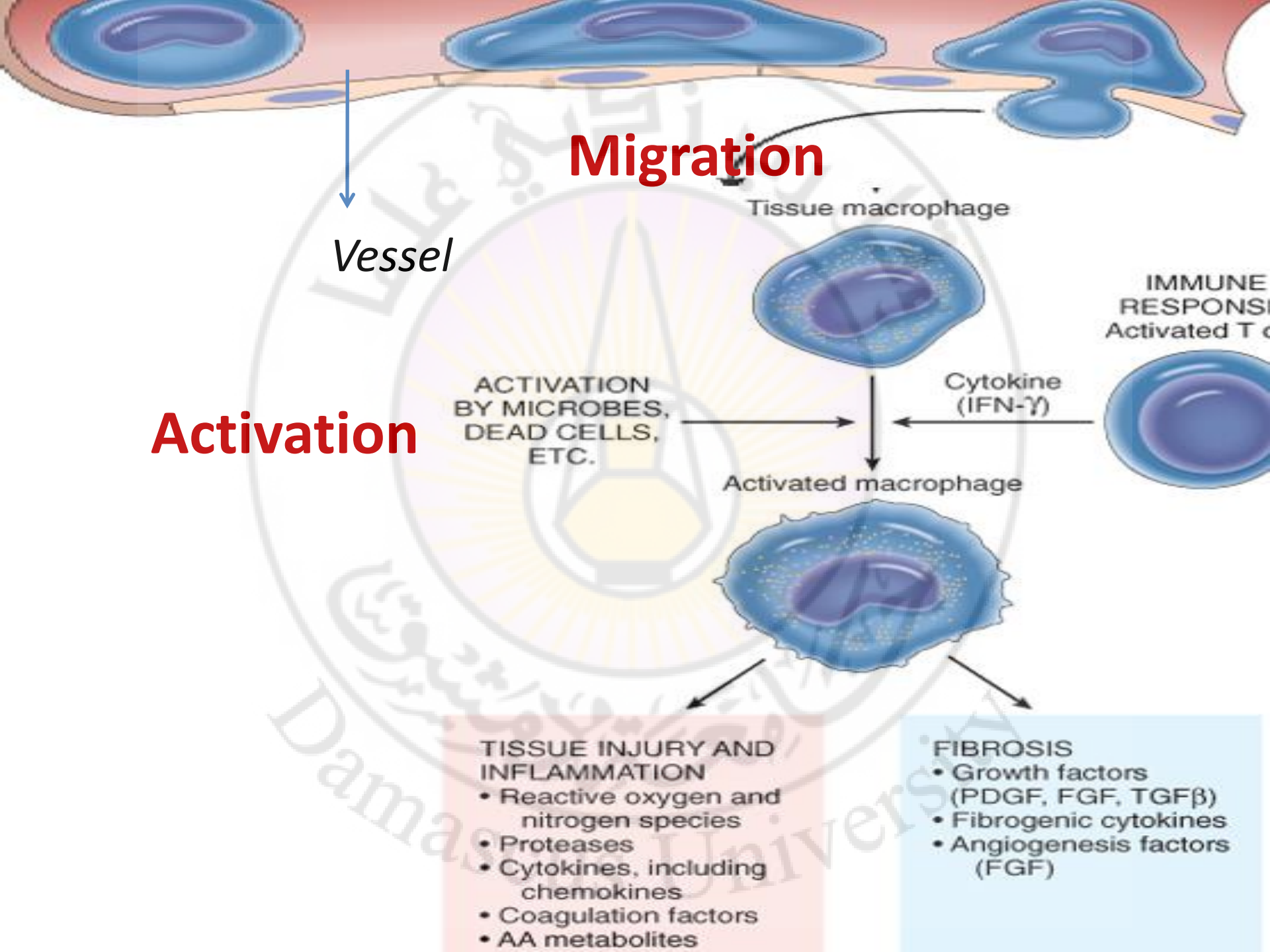
4- ***Prolonged exposure to potentially toxic agents****:* such as inhaled particulate silica (*silicosis),* chronically elevated plasma lipid components *(atherosclerosis)*

Chronic Inflammatory Cells

1-Macrophages, the dominant cells of chronic inflammation, are tissue cells derived from circulating blood *monocytes* after their emigration from the bloodstream. Macrophages are normally diffusely scattered in most connective tissues, and are also found in organs such as the *liver (**Kupffer cells**),* spleen and lymph nodes (***sinus histiocytes***), central nervous system (***microglial cells***), and lungs (***alveolar macrophages***). In all tissues, macrophages act as filters for particulate matter, microbes, and senescent cells, as well as acting as sentinels to alert the specific components of the adaptive immune system (T and B lymphocytes) to injurious stimuli.

1-Macrophages

- Under influence of chemotactic factors they begin to migrate to the site of injury within 24-48 hrs after the onset of acute inflammation.
- When monocytes reach the extravasular tissue, they undergo transformation into larger macrophages which have greater capacity for phagocytosis than blood monocytes.
- Macrophages will then be activated resulting in increased cell size, increased content of lysosomal enzymes and greater ability to kill ingested organisms. These activated macrophages appear large, flat pink. Such appearance may be similar to that of squamous epithelial cell and so they are called ***epithelioid cells***.


Migration
Vessel
Tissue macrophage
IMMUNE
RESPONSE
Activated T
Activation
ACTIVATION
BY MICROBES,
DEAD CELLS,
ETC.
Cytokine
(IFN-γ)
Activated macrophage
TISSUE INJURY AND
INFLAMMATION
• Reactive oxygen and
nitrogen species
• Proteases
• Cytokines, including
chemokines
• Coagulation factors
• AA metabolites
FIBROSIS
• Growth factors
(PDGF, FGF, TGFβ)
• Fibrogenic cytokines
• Angiogenesis factors
(FGF)

Macrophage are activated by:

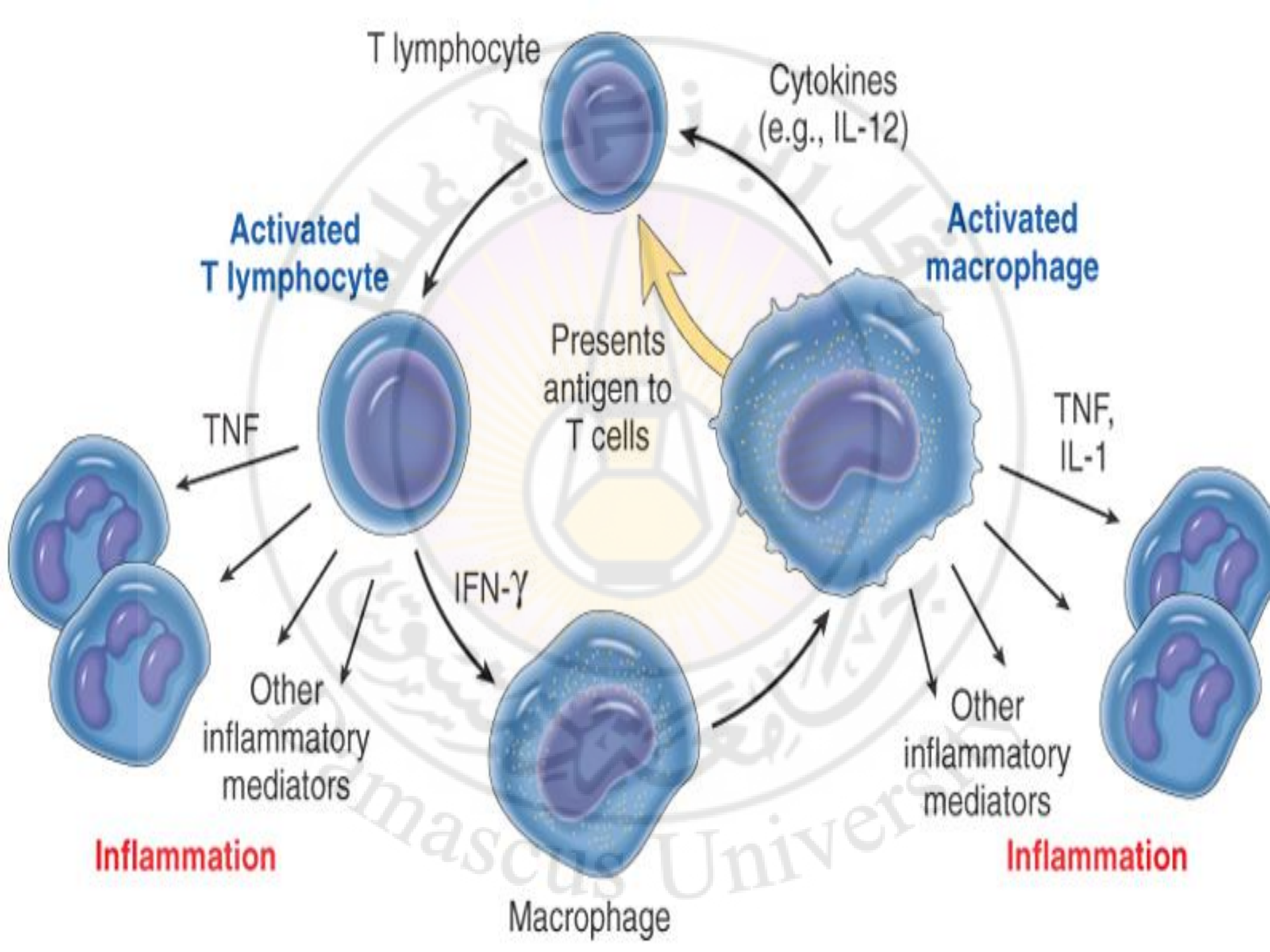
- Bacterial endotoxin
- Cytokins secreted by sensitized T-lymphocytes like interferone Y (INF-Y)
- Various mediators produced during acute inflammation
- Extracellular matrix proteins e.g. fibronectin

Activated macrophages secrete:

- Acid and neutral proteases
- Nitric oxide NO
- Arachidonic acid metabolites, causing tissue injury
- Cytokines like interleukin-1 and tumor necrosis factor (TNF)
- Growth Factors Like Fibroblast growth factor (FGF) that influence the proliferation of smooth muscles, fibroblasts and production of extracellular matrix

2-lymphocytes

- Both T & B lymphocytes migrate to the inflammatory site by the same mechanism used by other leukocytes. Lymphocytes and macrophages interact together in the process of chronic inflammation in the following way:
- Macrophages display antigens to lymphocytes in a process called antigen presentation and produce cytokine (IL1) that stimulate T-lymphocytes.
- Activated T- lymohocytes produce cytokines like INF Y which is a powerful activator of macrophages.
- And so there is a cycle of cell reactions that will sustain the chronic inflammation


T lymphocyte
Cytokines
(e.g., IL-12)
Activated
T lymphocyte
Activated
macrophage
Presents
antigen to
T cells
TNF
TNF,
IL-1
IFN-γ
Other
inflammatory
mediators
Other
inflammatory
mediators
Inflammation
Inflammation
Macrophage

3-Plasma cells : develop from activated B lymphocytes and produce antibodies directed either against persistent antigens in the inflammatory site or against altered tissue components.

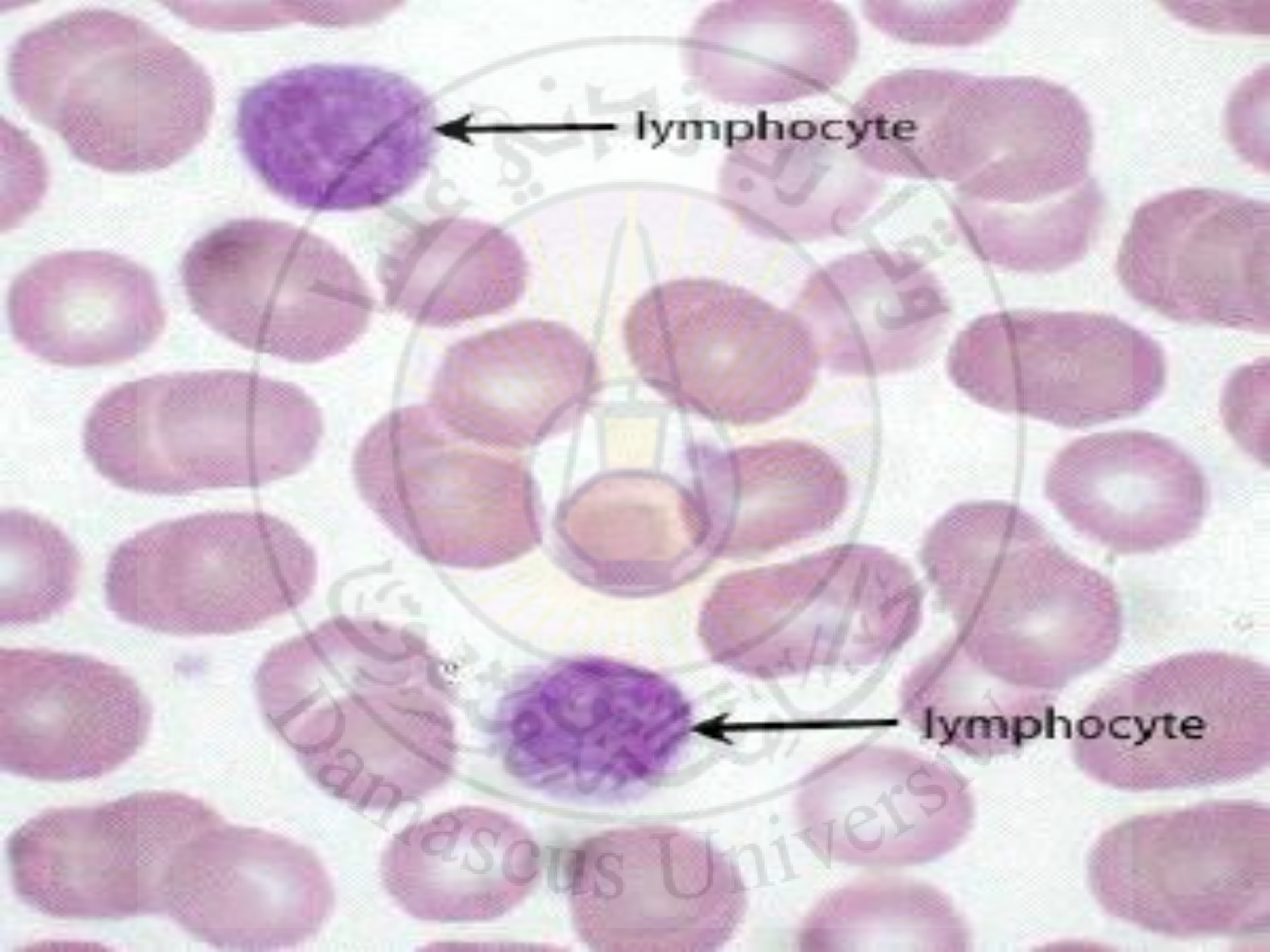
4-Eosinophils: are characteristically found in inflammatory sites around parasitic infections or as part of immune reactions mediated by IgE, typically associated with *allergies.*

5-Mast cells : are sentinel cells widely distributed in connective tissues throughout the body, and they can participate in both acute and chronic inflammatory responses

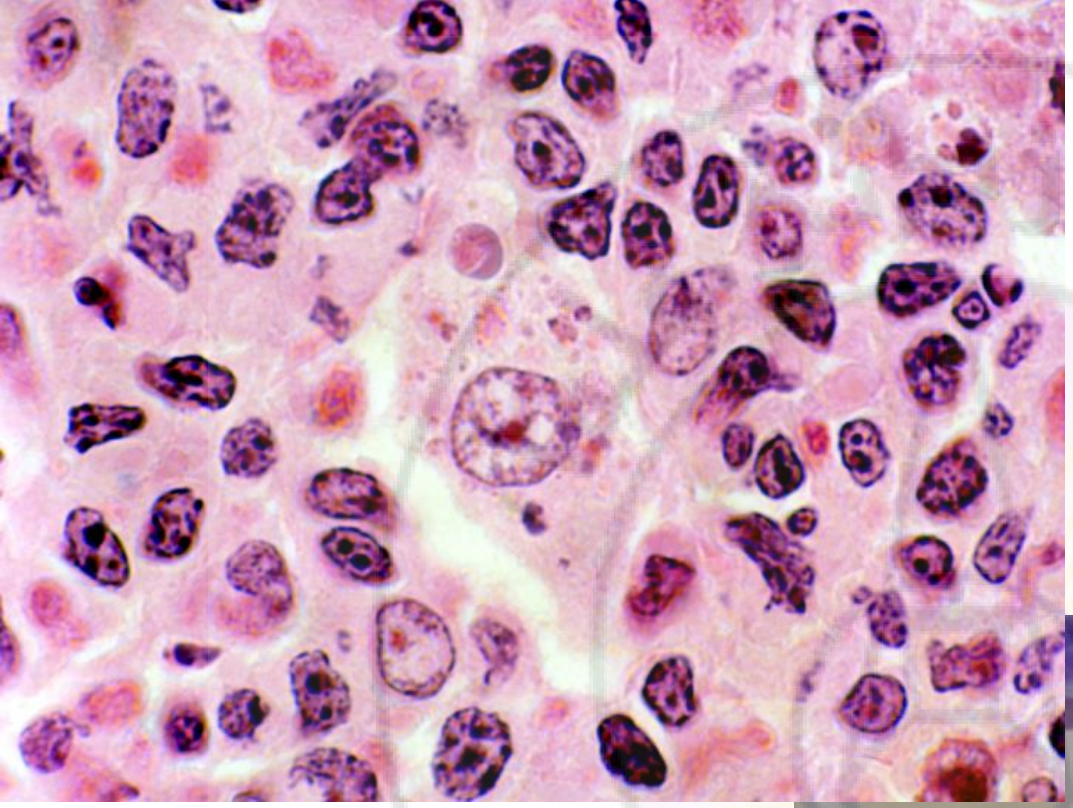
morphology of chronic inflammation

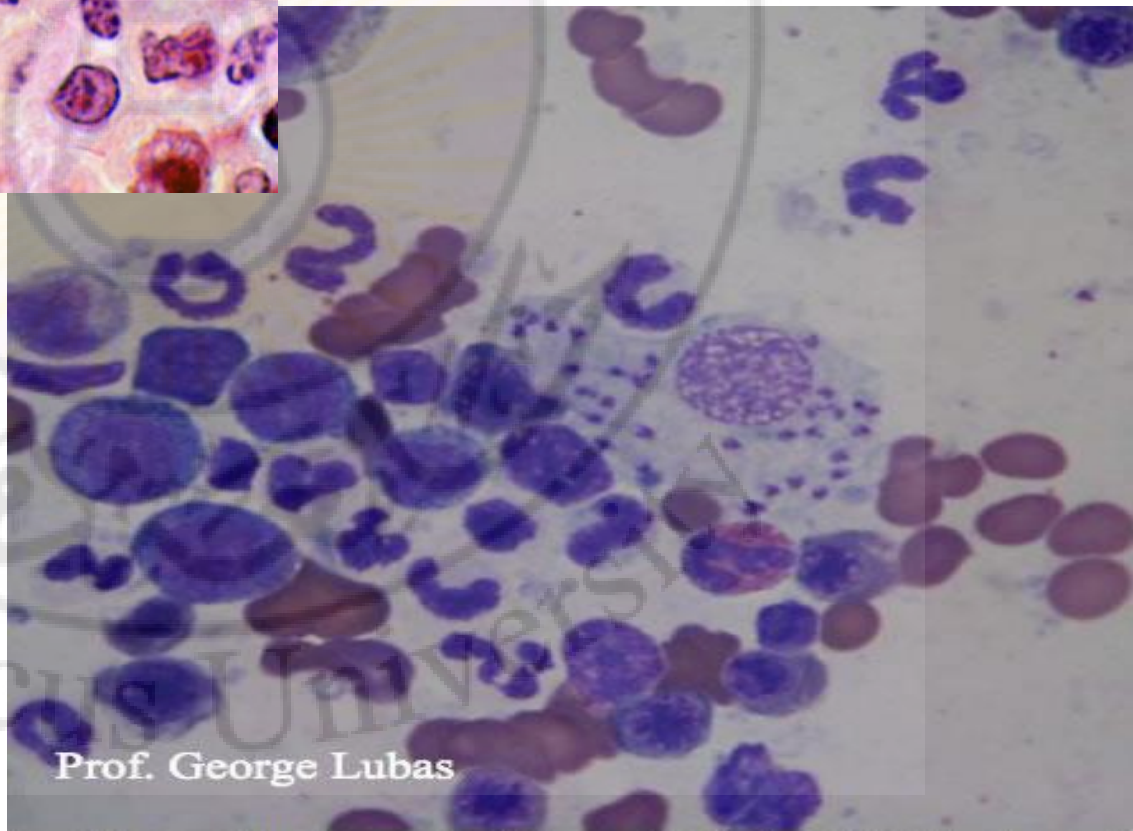
1-Infiltration of the tissue by mononuclear chronic inflammatory cells :

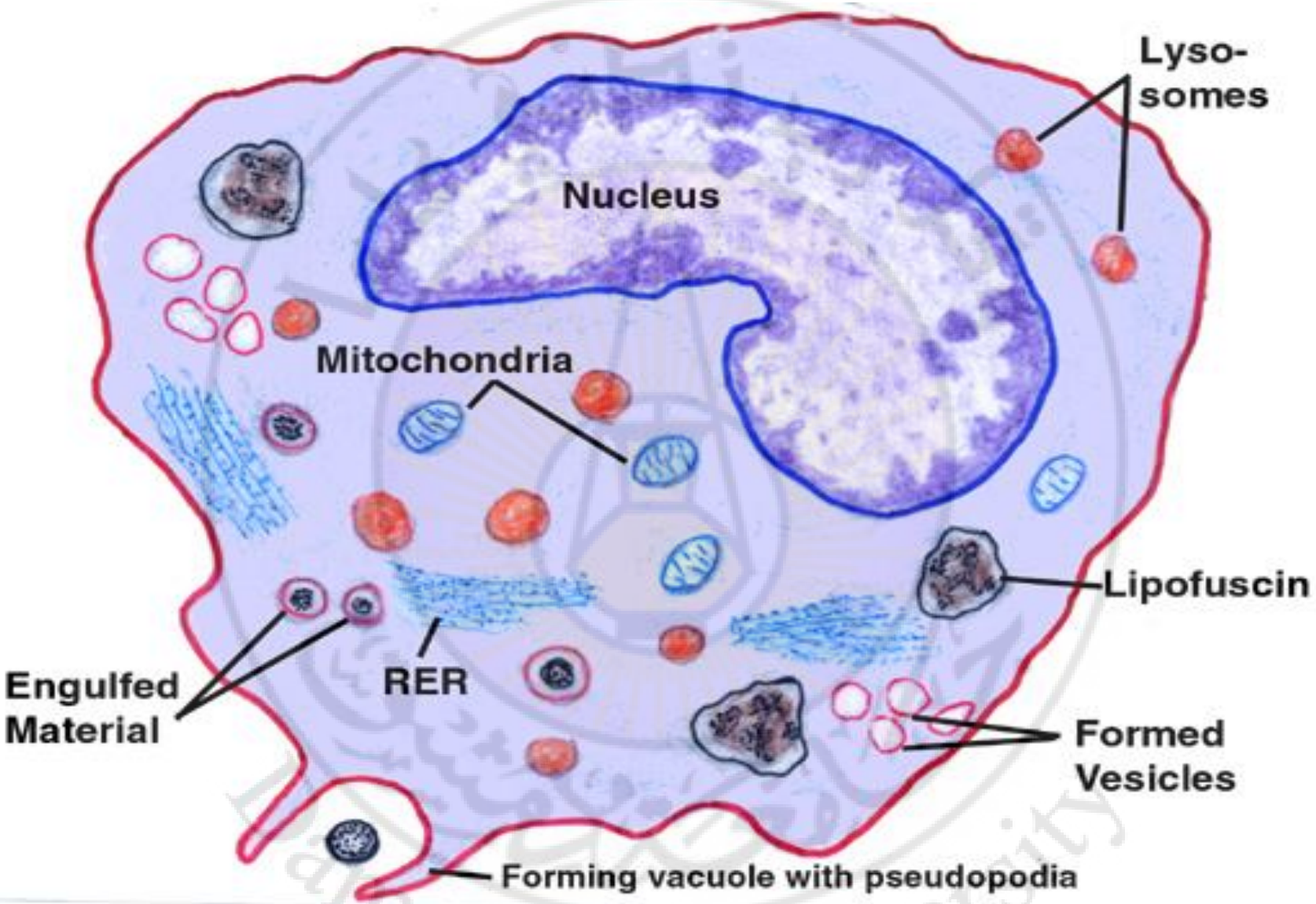
- ***lymphocytes***: small cells with a round darkly staining nucleus that fills the whole cell leaving a very thin rim of cytoplasm.
- ***Macrophages*** : large cells with a vesicular eccentric nucleus and large amount of cytoplasm that is filled with vacules.


lymphocyte
lymphocyte

Macrophages






Lyso-
somes
Nucleus
Mitochondria
Lipofuscin
Engulfed
Material
RER
Formed
Vesicles
Forming vacuole with pseudopodia

Macrophage

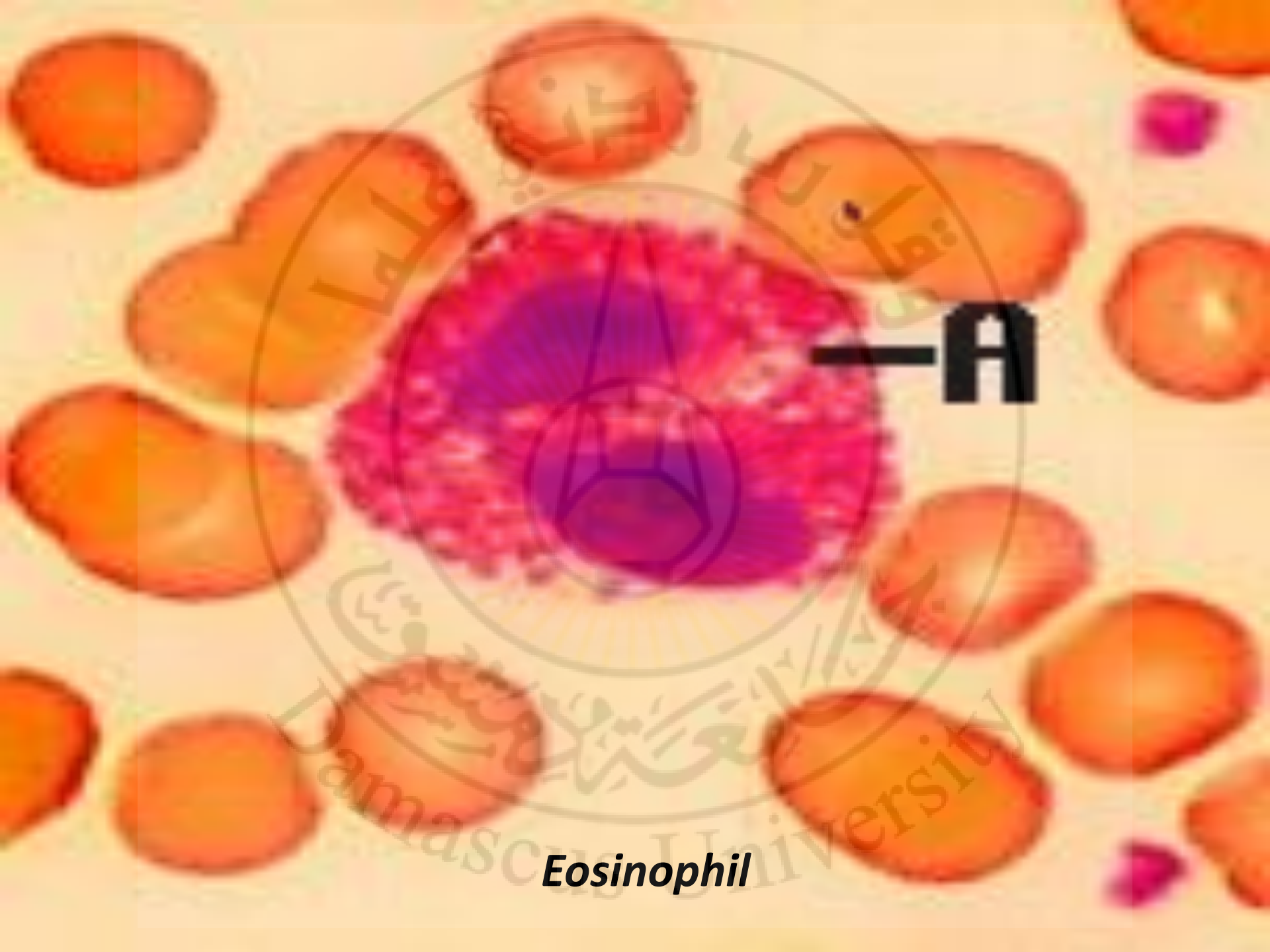
Morphology of chronic inflammation

- ***Plasma cells***: oval cells with an eccentrically placed nucleus that has a distinctive "cartwheel" distribution of chromatin . They have an abundant deeply basophilic cytoplasm.
- ***Eosinophils*** : they have bright pink granules that fill the cytoplasm, the nucleus is typically bilobed.

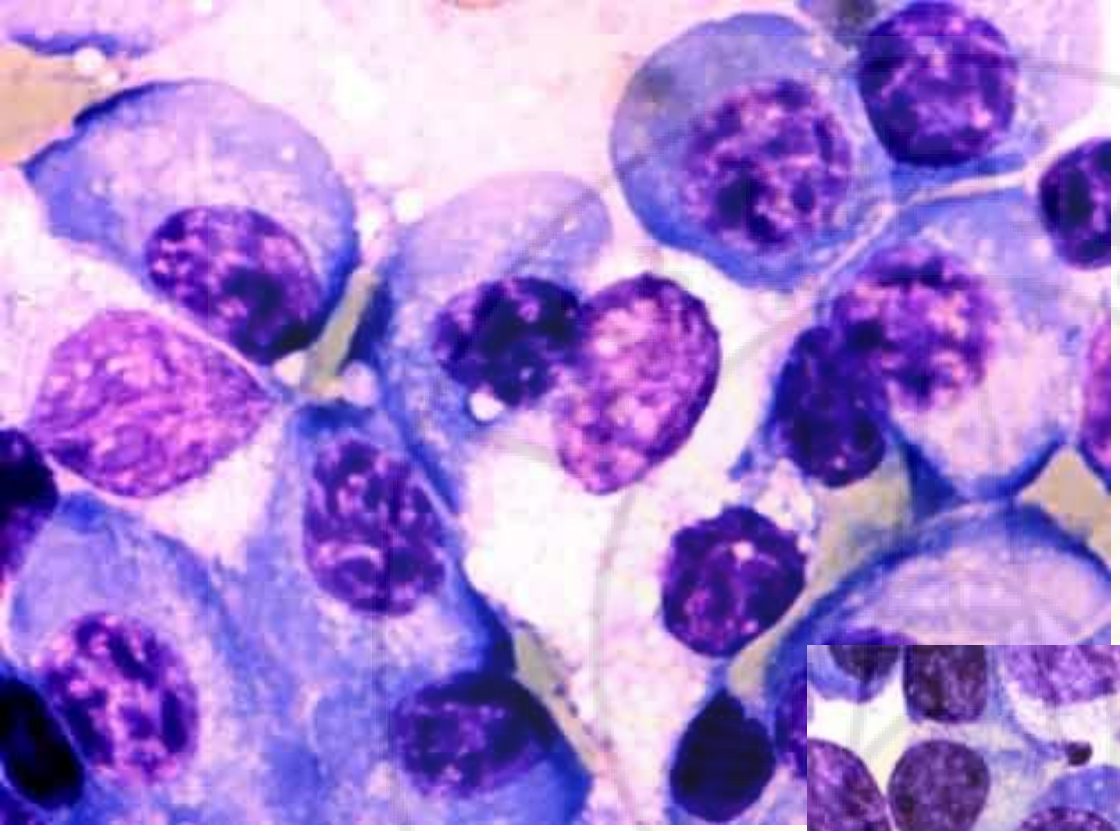
2- tissue destruction

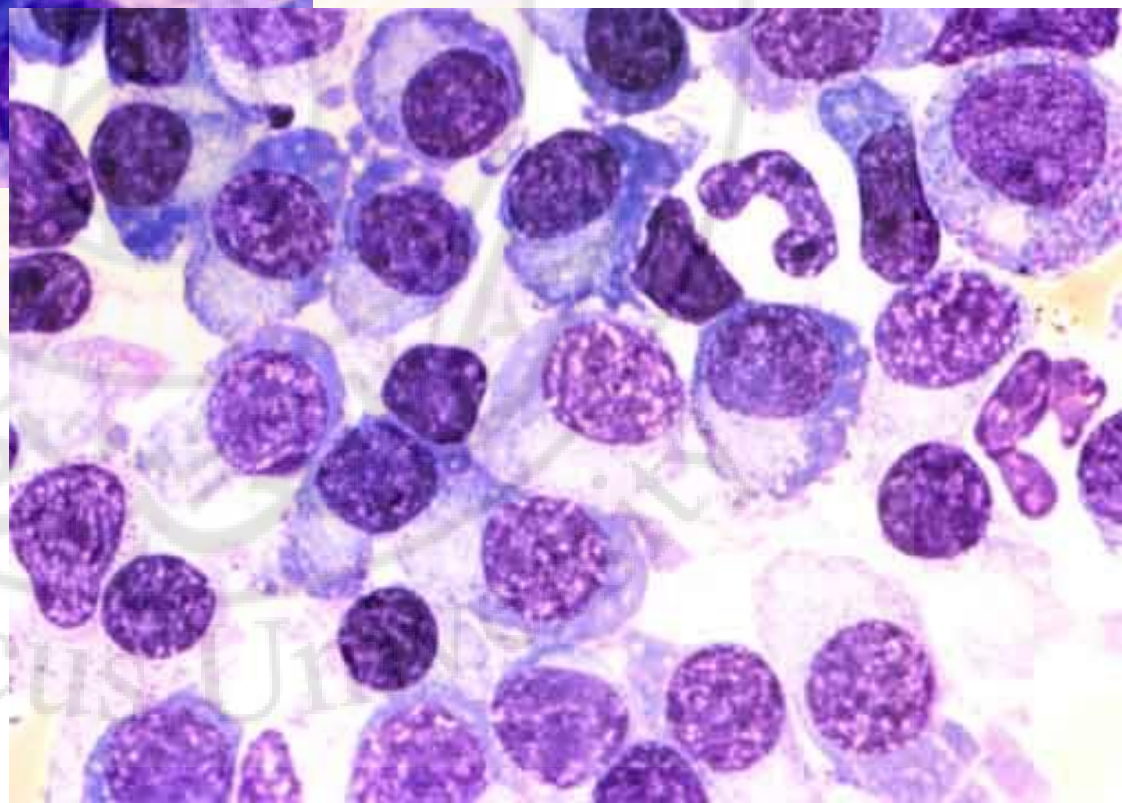
3- Proliferation of granulation tissue (fibroblasts, new blood vessels)

4-fibrosis : deposition of collagen fibers.

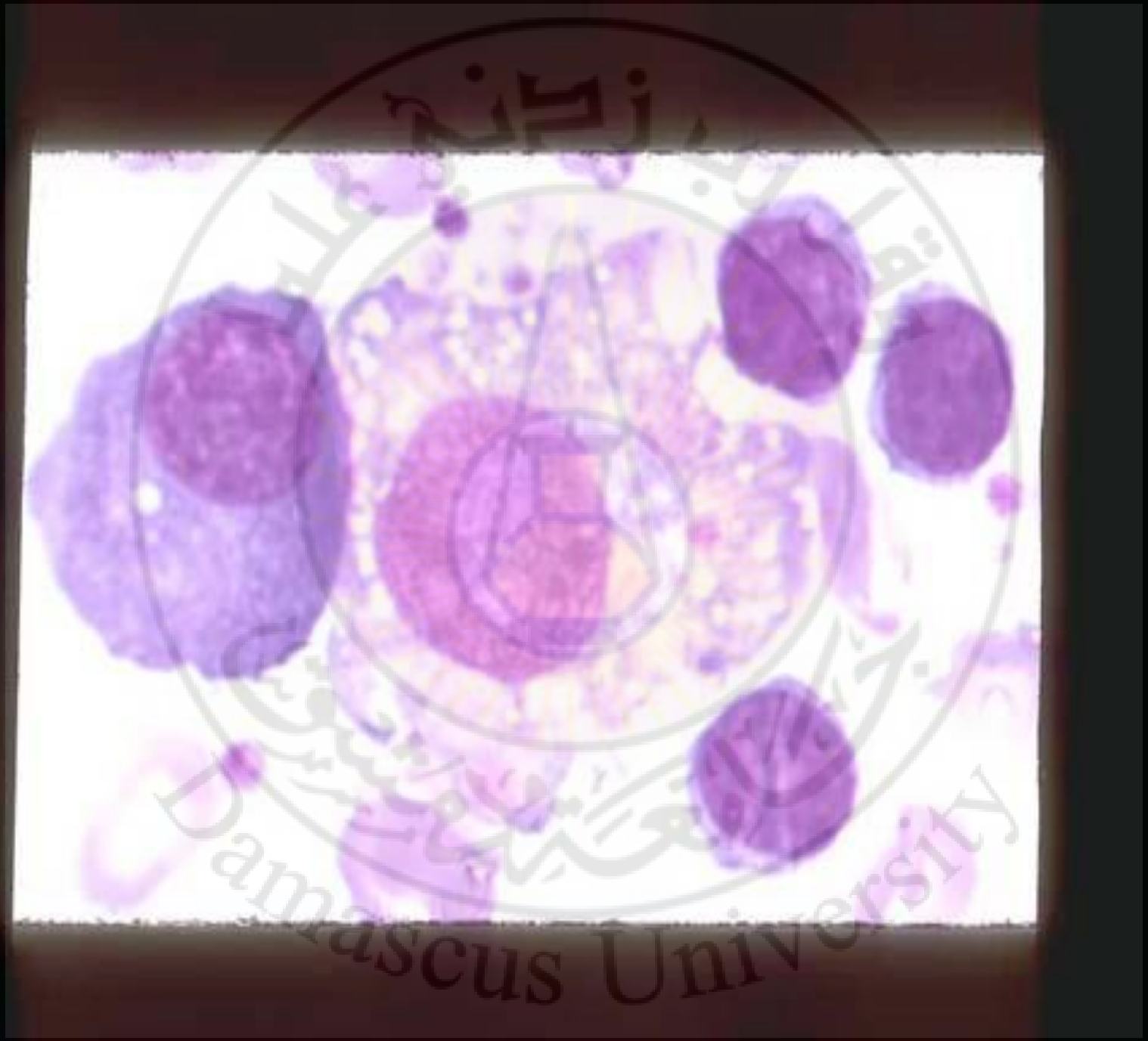


Eosinophil





Plasma cells



Granulomatous inflammation

- A distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages that have an epithelioid appearance forming a granuloma
- The formation of a granuloma “wall off “ the offending agent and should therefore be a useful defense mechanism, however, the causative agent is usually resistant to killing and degradation and the continuous inflammation in the granuloma will end with fibrosis and may cause organ dysfunction

Granulomas are seen in certain specific pathological states:

1- They can arise when there is persistent T cell response to certain microbes such as:

- *Mycobacterium tuberculosis*, the causative agent for **tuberculosis**
- *Treponema pallidum*, the causative agent for **syphilis**.

2-they can develop in response to a relatively insert **foreign body** that stays unremoved in the tissue e.g. suture or splinter and so they are called **foreign body granuloma.**

Morphology of granuloma

1- ***epithelioid cells:*** these are activated macrophages, they appear as large flat cells with a pink granular cytoplasm and indistinct cell boundaries, the aggregates of epithelioid cells are surrounded by a rim of lymphocytes which secret lymphokins responsible for continuous macrophage activation.

2- older granulomas have a rim of ***fibroblasts and connective tissue***

Morphology of granuloma

3-multinucleated giant cells : are frequently found in granulomas, they result from fusion of epithelioid cells and consist of a large mass of cytoplasm and many nuclei reaching as many as 50 nuclei, **there are two morphological types**:

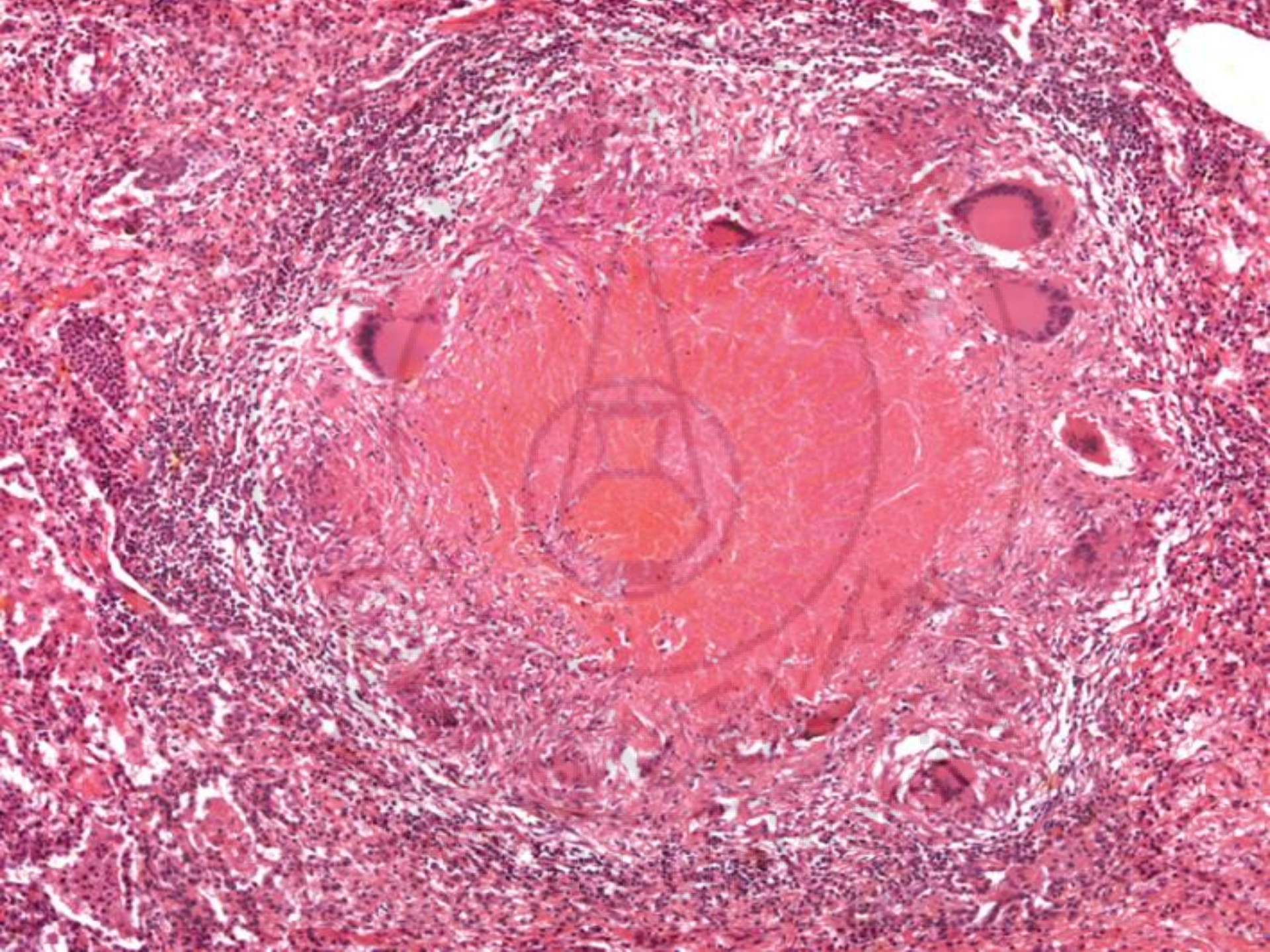
1-langhan's type: these giant cells have nuclei that are arranged around the periphery creating a horse shoe pattern.

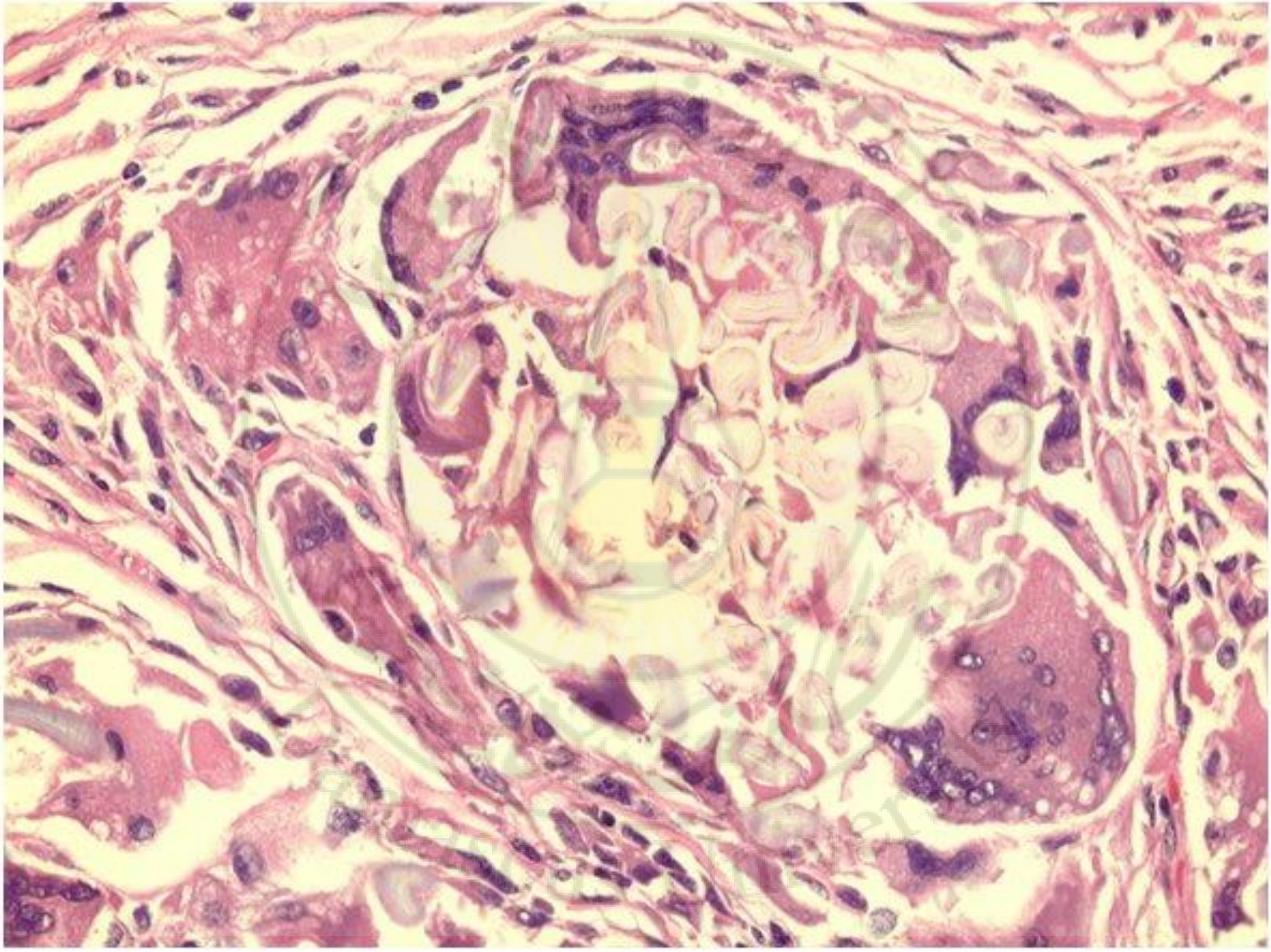
2-foreign body type: here the nuclei are scattered haphazardly, they are named so because they are found in the presence of large amount of indigestible material(foreign bodies)

Morphology of granuloma

4- granulomas that are associated with T.B. have a central zone of **caseous necrosis**, grossly this necrosis has a cheesy appearance and microscopically it appears as amorphous granular debris with complete loss of cellular details.

5- healing of granuloma is accompanied by **fibrosis** that may be very extensive .





Systemic effects of inflammation

- The systemic effects of inflammation are called the acute phase reaction or the systemic inflammatory response syndrome.
- The cytokines TNF, IL-1, IL-6 and prostaglandins are the most important mediators of acute phase reaction, they are produced by leukocytes and macrophages in response to infection and are released systemically.

The acute phase response consist of several clinical changes:

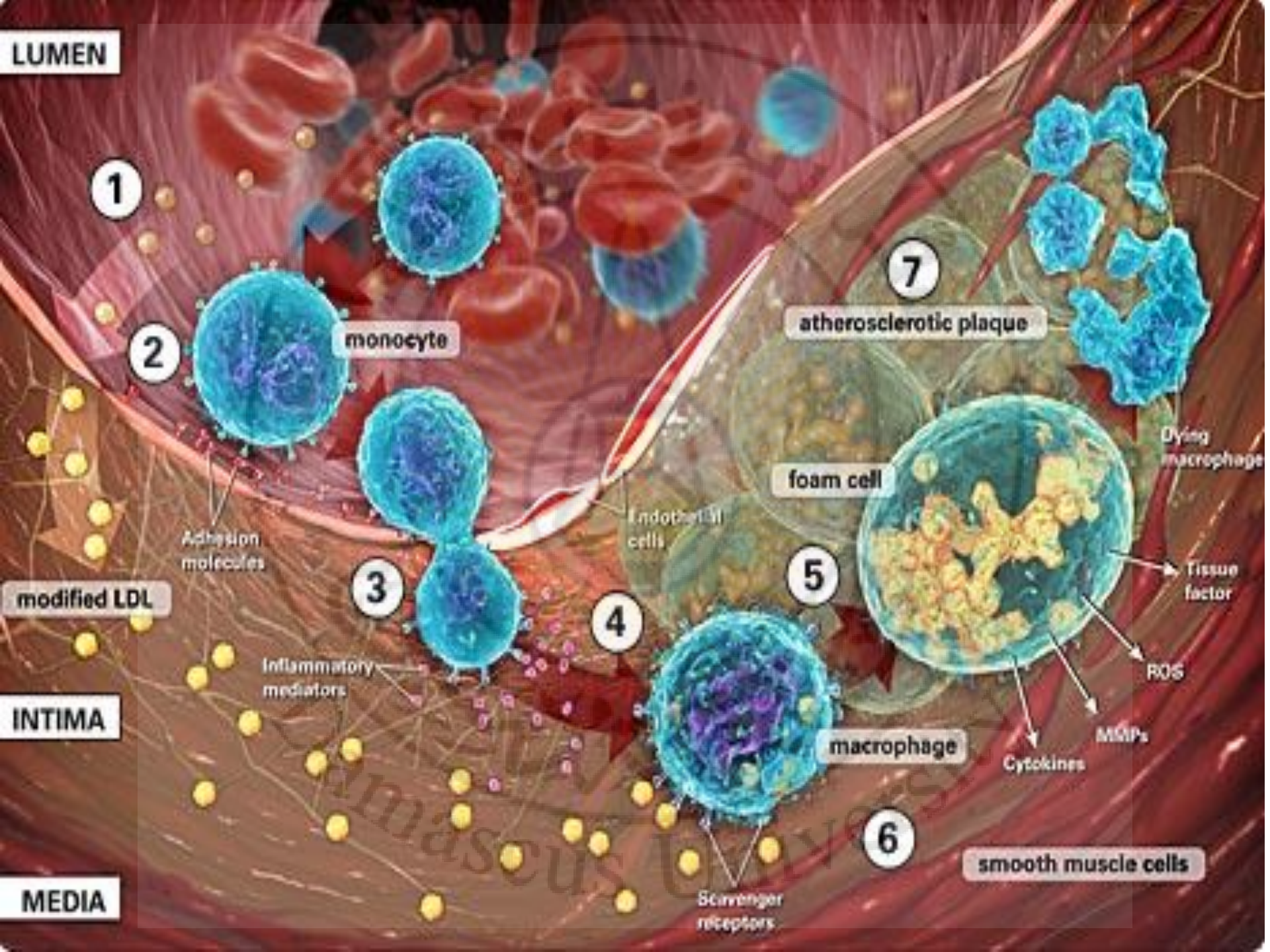
1- fever: this is elevation of body temperature above $37\ ^0C$ reaching in sever inflammation to $40\ ^0C$ and this is the most important feature of the acute phase response especially when the inflammation is caused by infection. Fever is produced in response to substances called purogens such as bacterial products that stimulate prostaglandin synthesis which will cause elevation of body temperature.

clinical changes

2-Elevated plasma levels of acute phase proteins : these are plasma proteins synthesized in the liver, their concentration rises as part of response to inflammatory stimuli . Example of these proteins are fibrinogen and C- reactive protein. These proteins act in the process of opsonisation to promote elimination of microbes.

3- Leukocytosis : is an increase in WBCs count in the blood and is a common feature in inflammation especially that caused by bacterial infections

Other features are increase in the heart rate and blood pressure,shivering, loss of appetite and malaise.


LUMEN
1
2
monocyte
Adhesion molecules
modified LDL
3
Inflammatory mediators
INTIMA
MEDIA
4
Endothelial cells
5
foam cell
Dying macrophage
Tissue factor
ROS
MMPs
Cytokines
macrophage
6
Scavenger receptors
smooth muscle cells
7
atherosclerotic plaque

Department of pathology
third year/General pathology

Neoplasia

2022

Neoplasia

Neoplasia is defined as purposeless uncontrolled and excessive proliferation of cells in the absence of physical stimuli.

Neoplasm(tumor): an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissue.

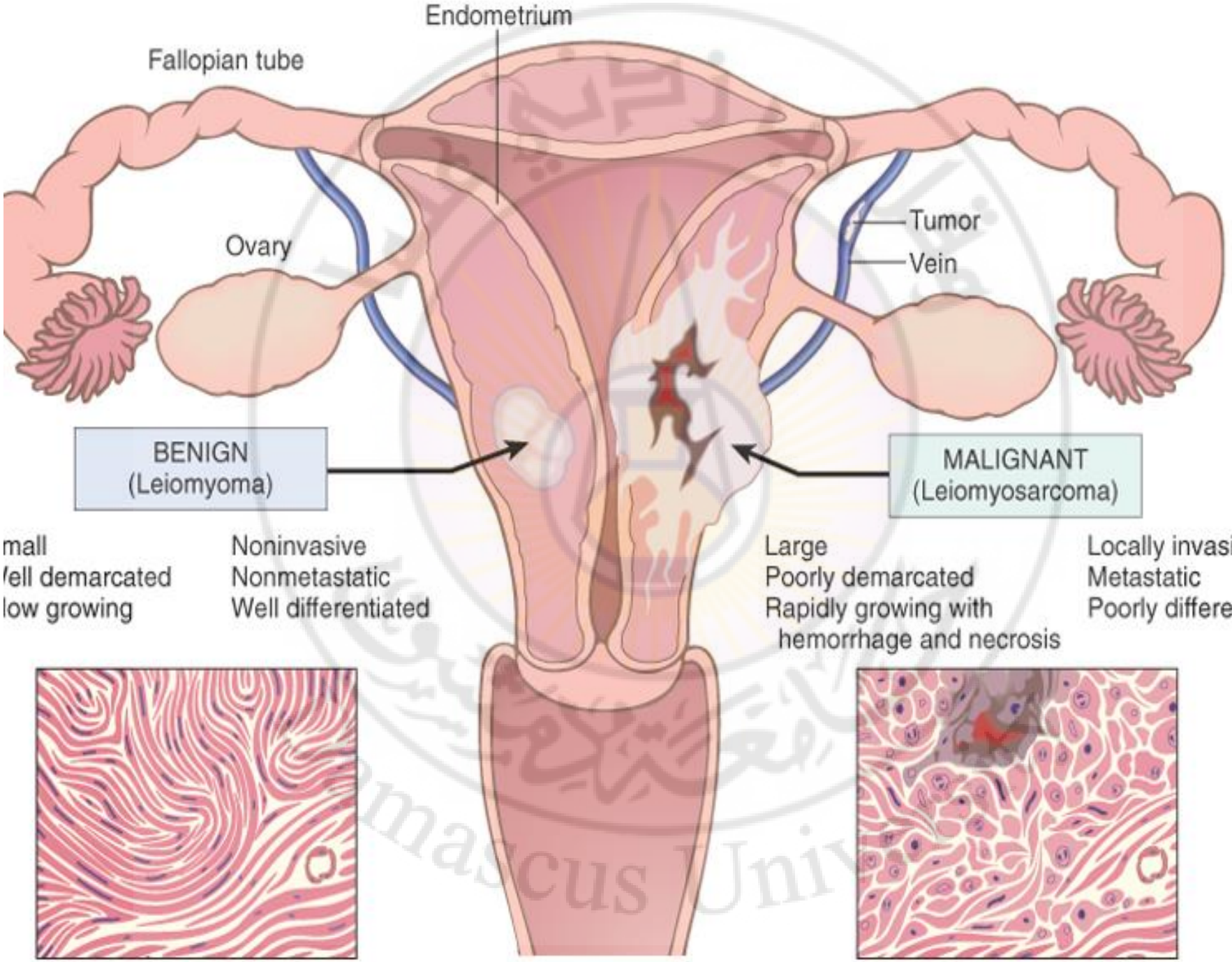
Tumors are divided into :

1- benign tumors:

Are tumors with cells that are uniform, grow slowly and remain localized neither invading the adjacent tissue nor giving metastasis elsewhere in the body

2-malignant tumors:

Are tumors with cells that are less well differentiate showing differences in size and shape and growing rapidly with invasion of the local tissue and metastasis to distant sites.

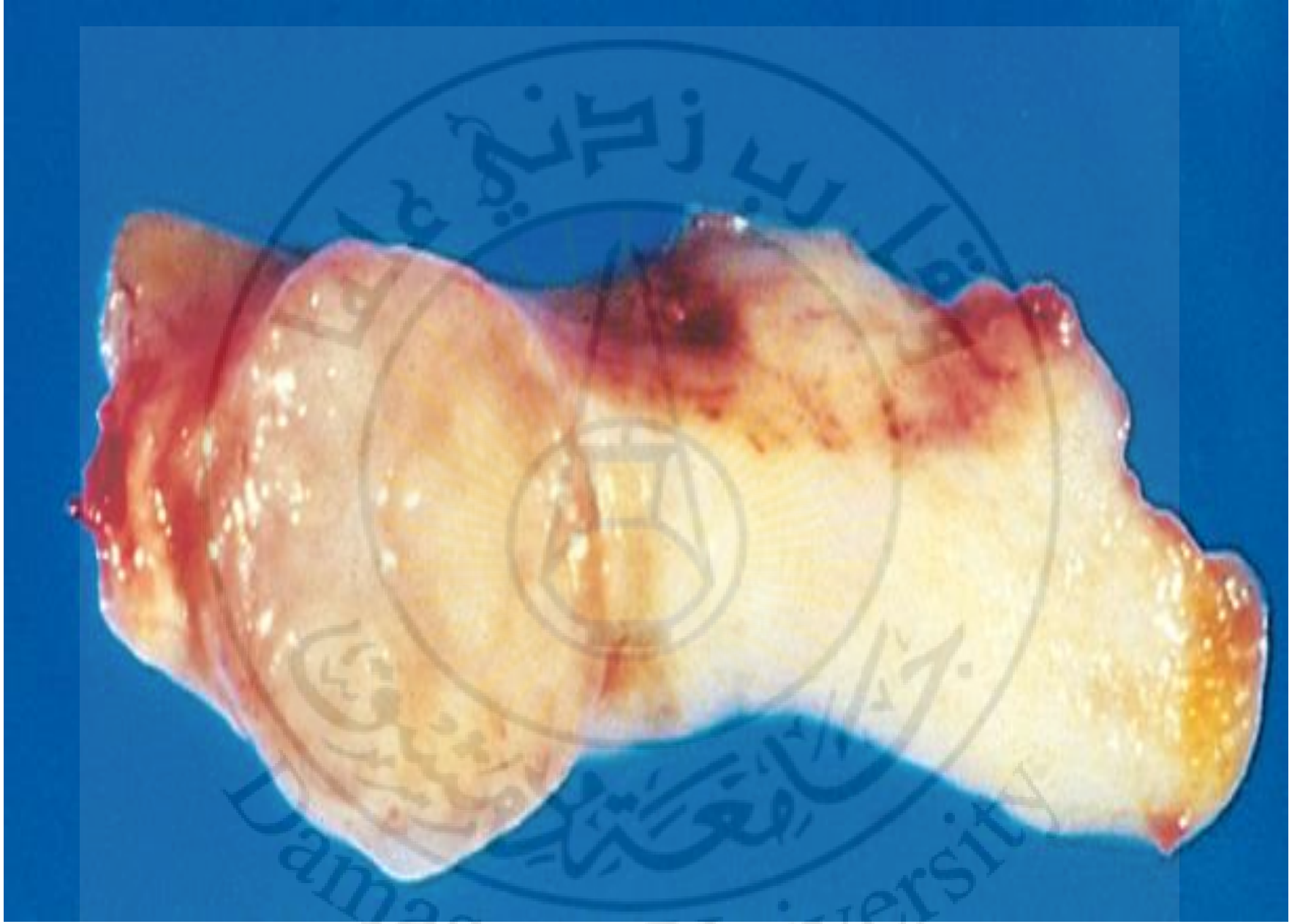

Endometrium
Fallopian tube
Ovary
Tumor
Vein
BENIGN
(Leiomyoma)
MALIGNANT
(Leiomyosarcoma)
mall
ell demarcated
low growing
Noninvasive
Nonmetastatic
Well differentiated
Large
Poorly demarcated
Rapidly growing with
hemorrhage and necrosis
Locally invasive
Metastatic
Poorly differentiate

Differentiation of neoplasms

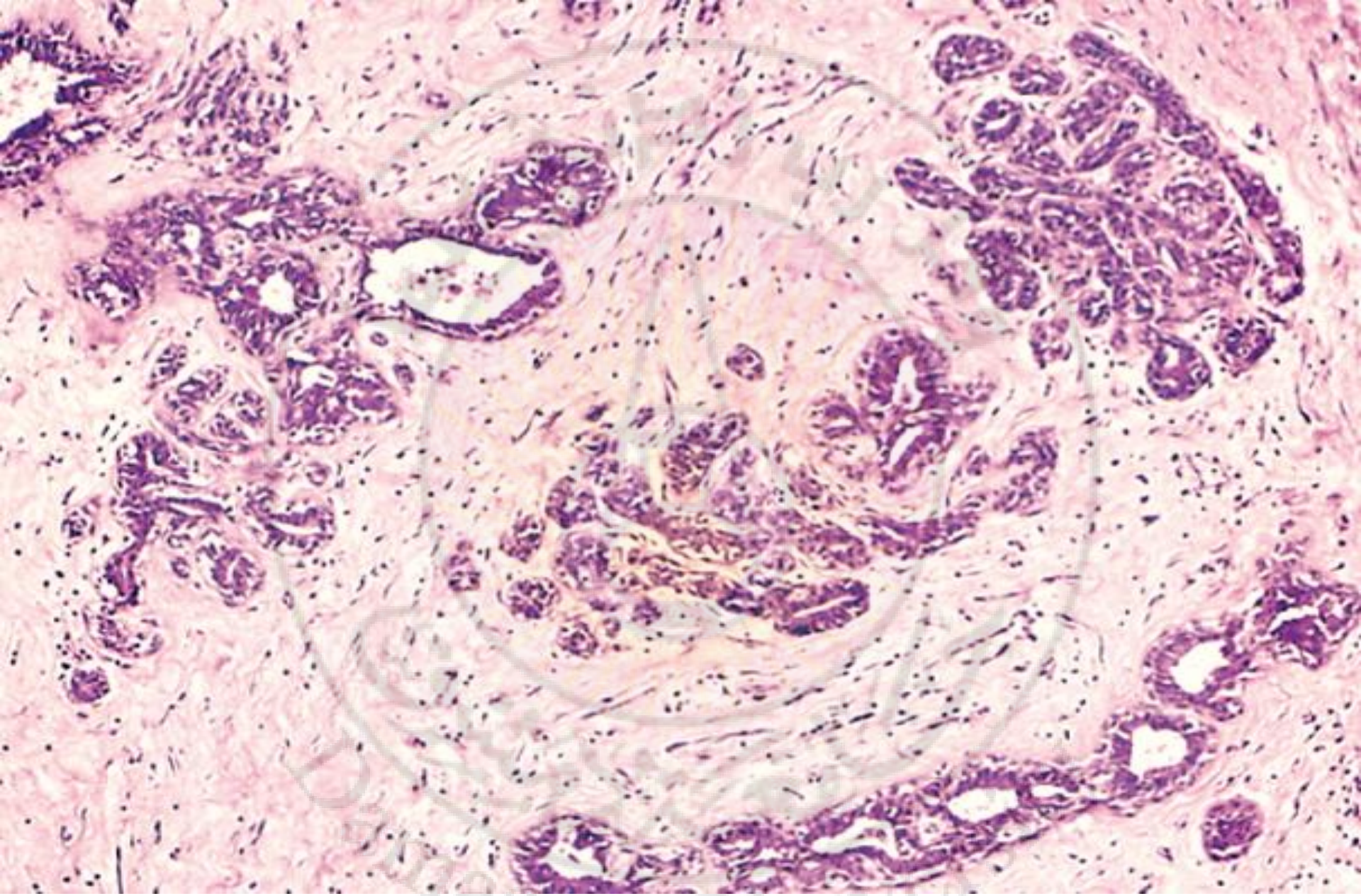
The differentiation of parenchymal cells refers to the extent to which they resemble their normal forebears morphologically and functionally.

Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts

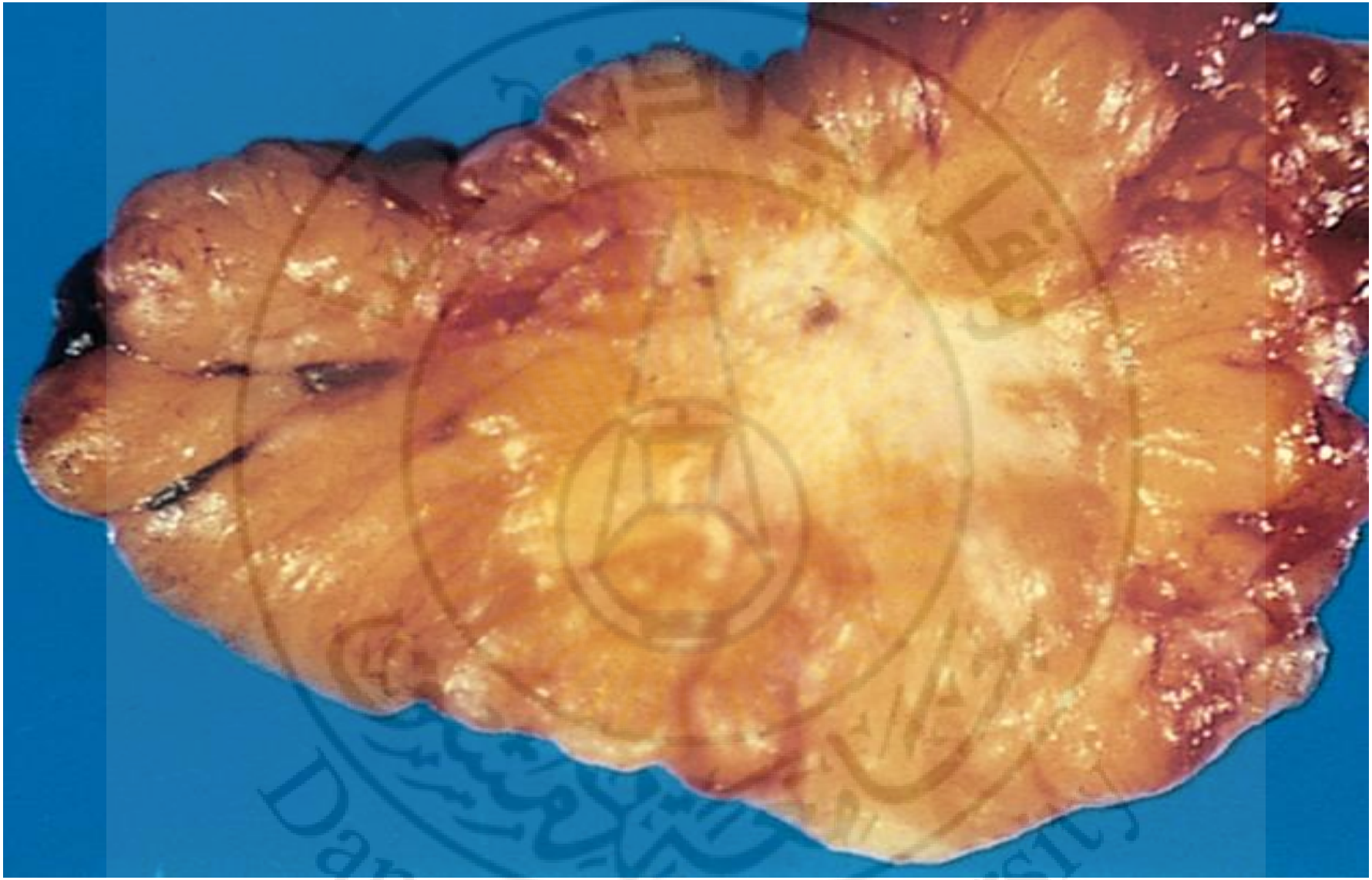
Malignant tumors display a range of differentiation from (well differentiated, moderately differentiated, poorly differentiated carcinomas and tumors showing extreme degree of dedifferentiation which is referred to anaplastic malignant tumors)



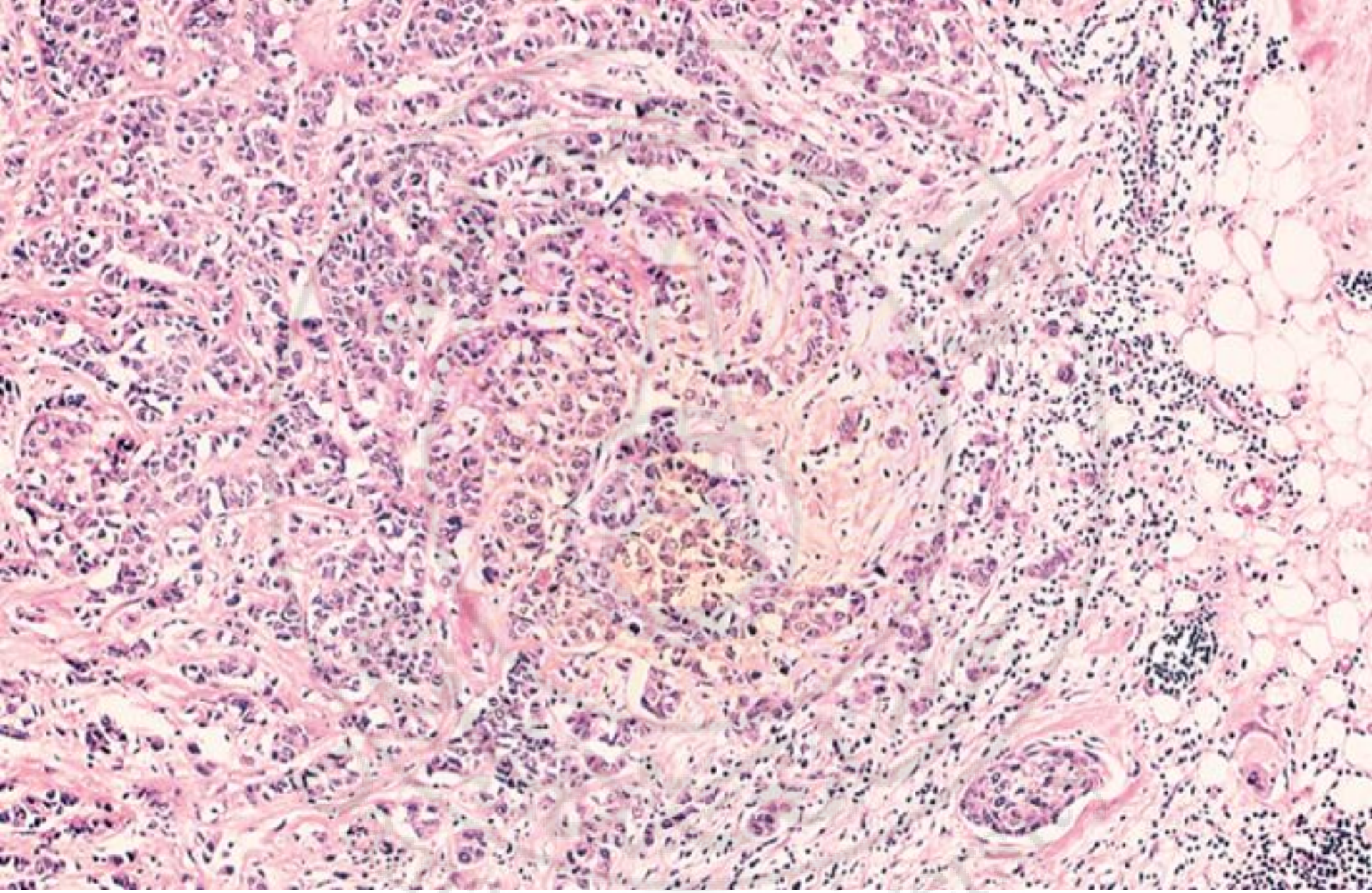
Fibroadenoma (breast)



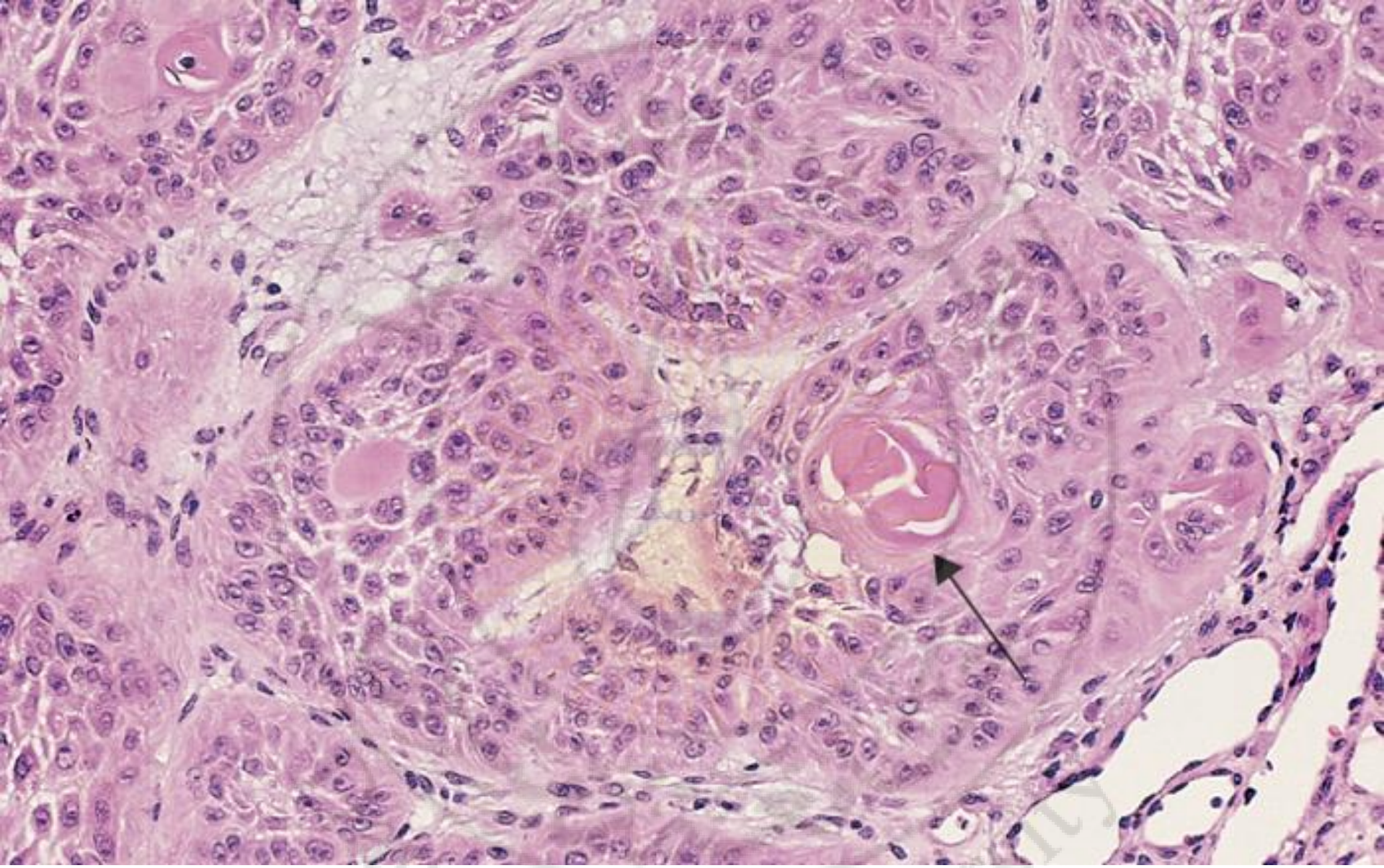
Fibroadenoma (breast)



Adenocarcinoma (breast)



Adenocarcinoma (breast)



Well defferentiated Squamouc cell carcinoma

Histopathological features of malignancy

1- ***cellular and nuclear pleomorphism*** : variation in size and shape of cells and their nuclei.

2- ***hyperchromatism*** : dark staining of nuclei due to abnormally increased chromatin.

3- ***increased nuclear cytoplasmic ratio*** (N/C ratio)i.e. that many reach 1/1 instead of normal 1/4 - 1/6

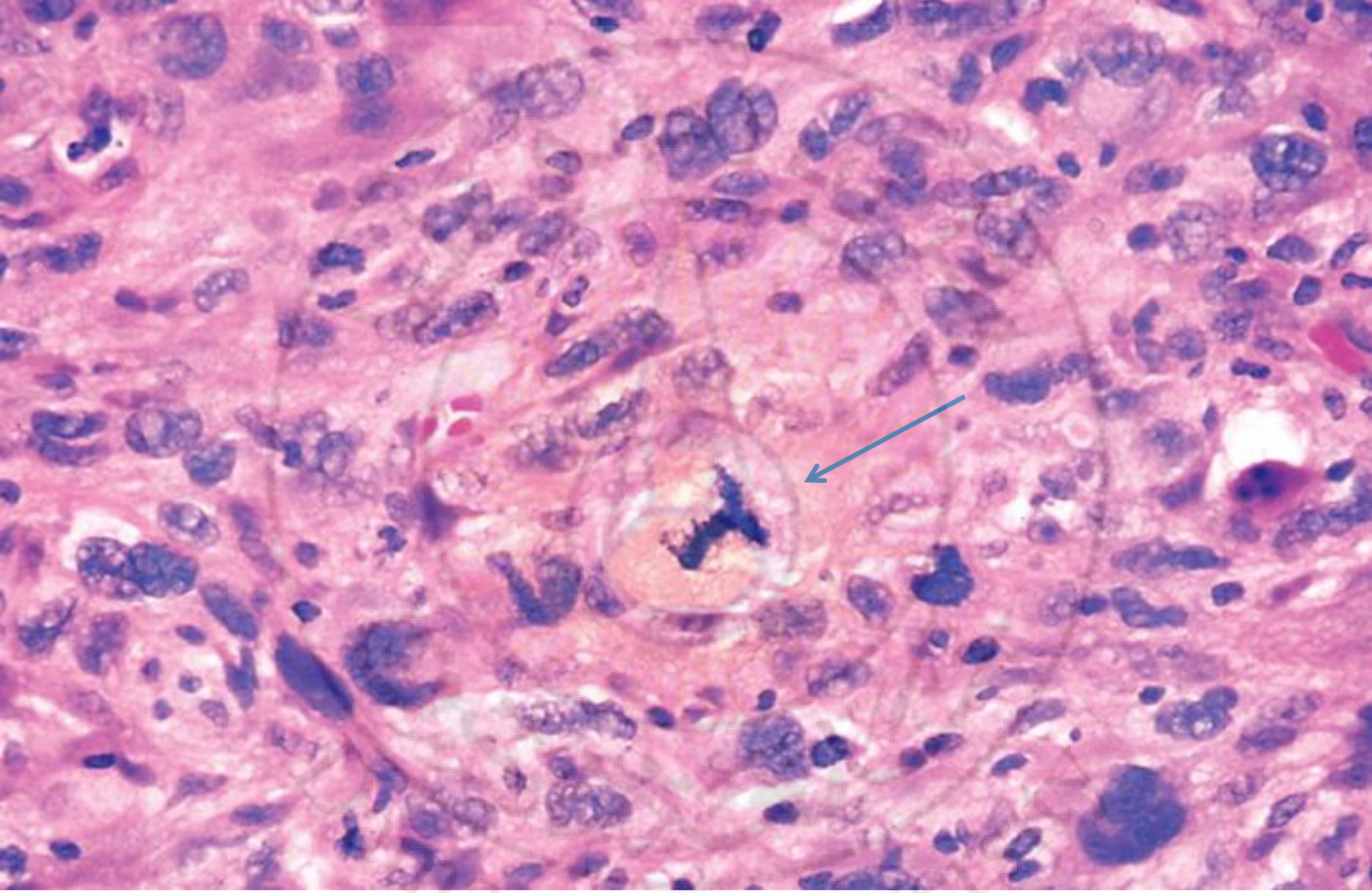
4- ***abundant mitosis***, reflecting increased proliferating activity.

5- ***abnormal mitoses*** (tripolar spindles)

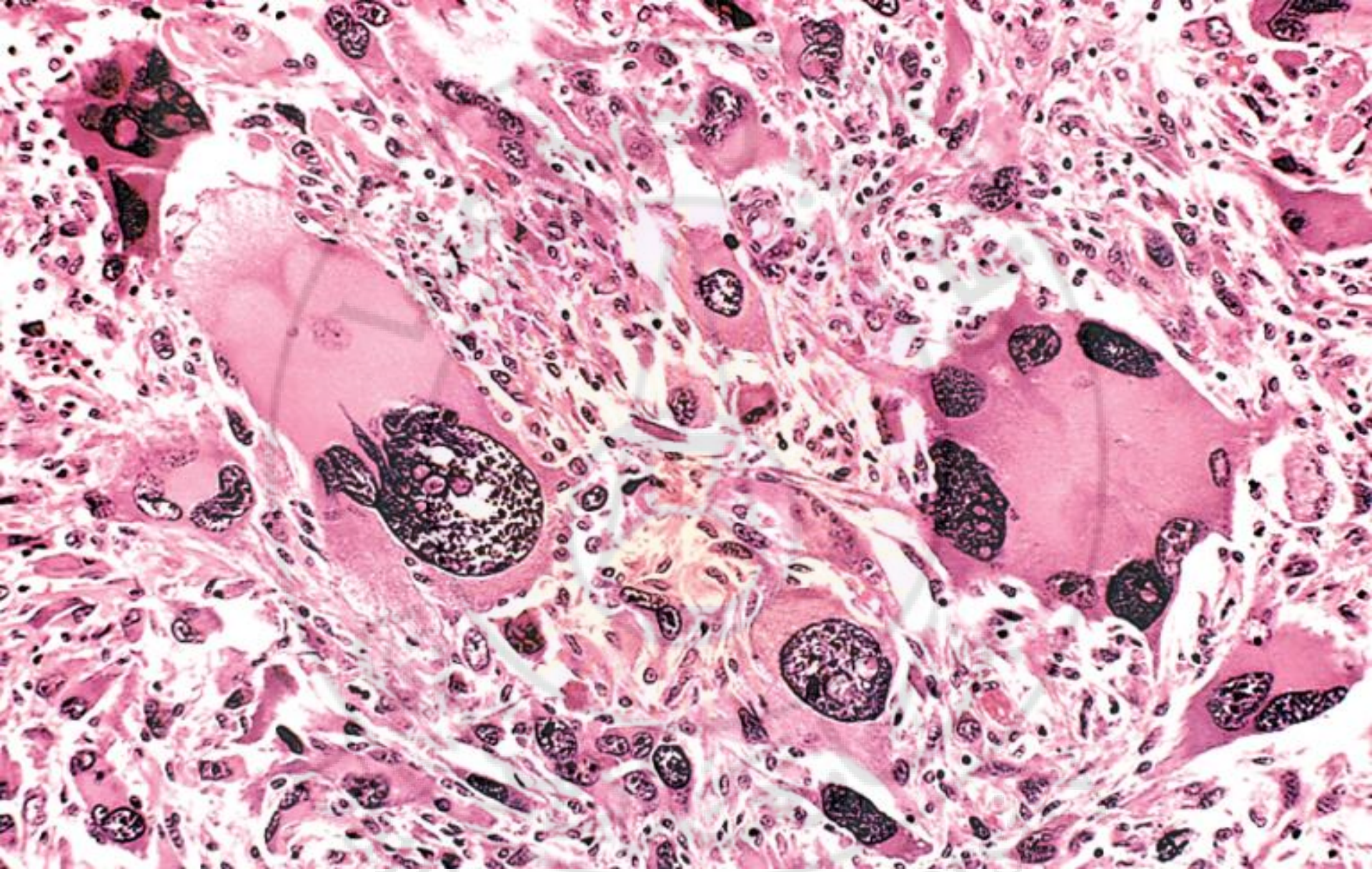
6- ***tumor giant cells*** containing a single polypoid nucleus or multiple nuclei

7- ***prominent nucleoli***

8- ***cytoplasmic basophilia***.



Mitose with Tripolar spindles



Rhabdomyosarcoma

	Benign tumors	Malignant tumors
Growth & meastasis	Expanding, remain localized Don't metastasize	Infiltrate locally and metastasize
Rate of growth	Slow	Faster
Histological features	•Similar to tissue of origin, •cells are uniform in size and shape	•Many differ from tissue of origin •Cellular and nuclear pleomorphism • enlarged hyperchromatic Nuclei •Prominent nucleoli & mitoses
Clinical effects	•Local pressure effects •Hormone secretion •Cured by adequate excision	•Local pressure •Tissue destruction •Inappropriate hormon secretion •Not cured by local excision

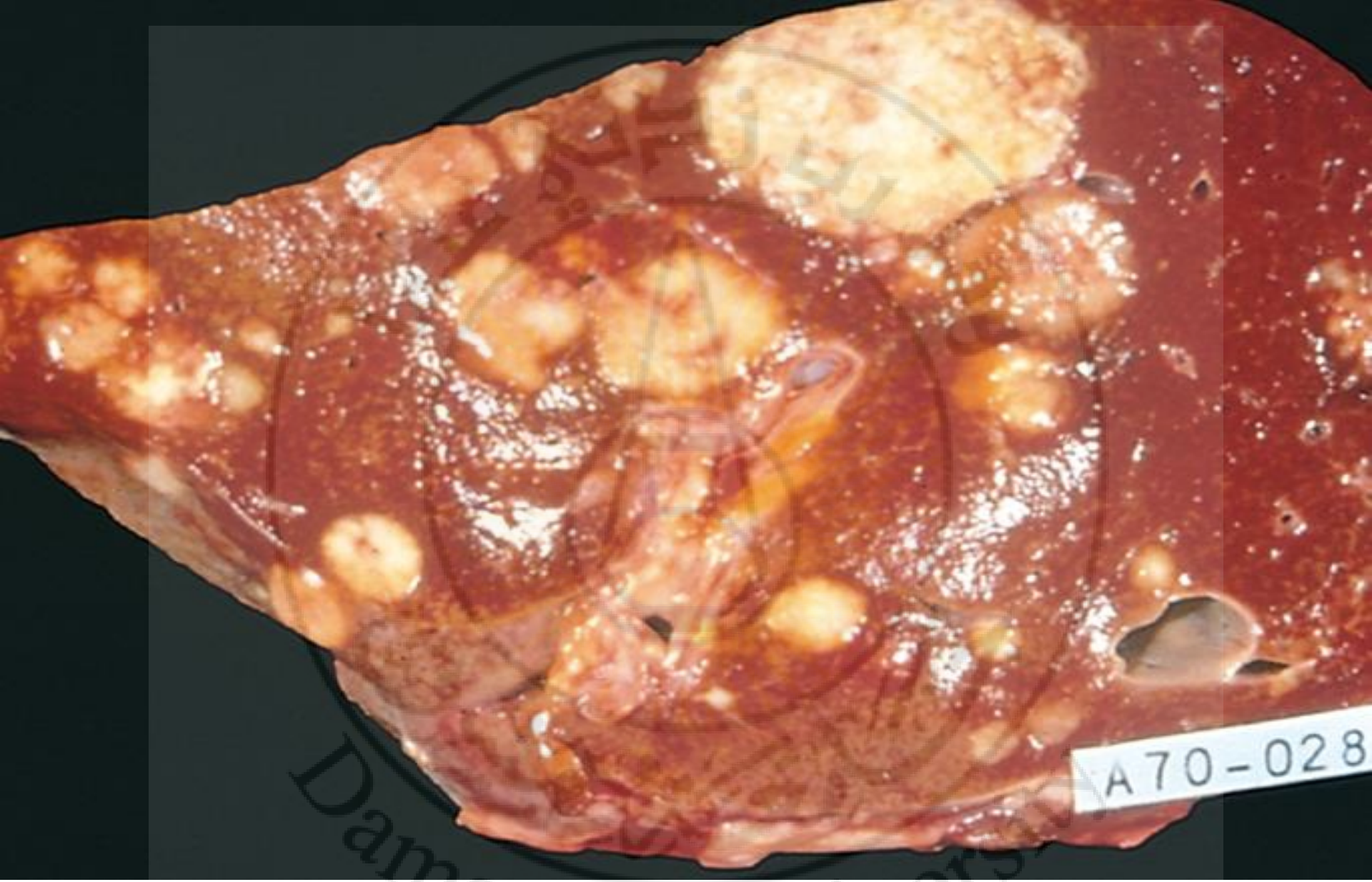
Routes of tumor spread and metastasis

1-Local spread: invasion to the adjacent tissues & organs, this is called direct extension of the tumor.

2-Lymphatic spread: invasion of lymphatic vessels, followed by spread to the regional lymph nodes and finally to other sites in the body, (common in the initial spread of carcinoma)

Routes of tumor spread and metastasis

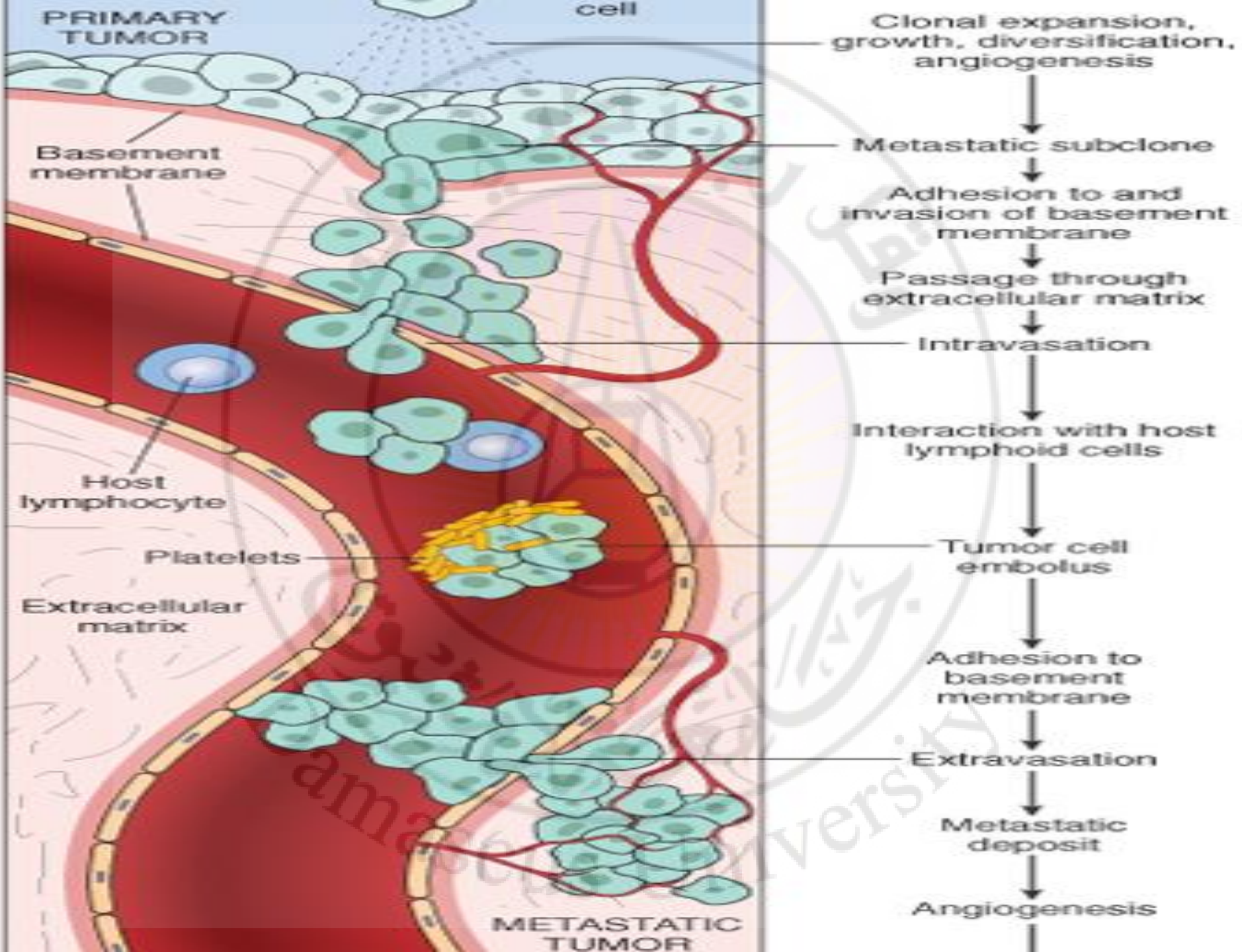
- ***3-Hematogenous spread:*** invasion of blood vessels (this is typical of all sarcoma) but it is also a favored route for certain carcinomas as in renal cell carcinoma. Veins are more readily invaded than arteries because of their thinner walls. The lung & liver are the commonest sites of hemaogenous ; other major sites are the bones and brain.



Metastases of breast cancer to liver

Routes of tumor spread and metastasis

4-Transcelomic spread: spread into body cavities, this occurs by seeding of malignant cells into peritoneal, pleural, pericardial & subarachidonic cavities, e.g. carcinoma of the stomach spreads trans-peritonealy to the ovaries (Krukenberg's tumor)


PRIMARY TUMOR
cell
Clonal expansion, growth, diversification, angiogenesis
Basement membrane
Metastatic subclone
Adhesion to and invasion of basement membrane
Passage through extracellular matrix
Intravasation
Interaction with host lymphoid cells
Host lymphocyte
Platelets
Tumor cell embolus
Extracellular matrix
Adhesion to basement membrane
Extravasation
Metastatic deposit
Angiogenesis
METASTATIC TUMOR

Nomenclature

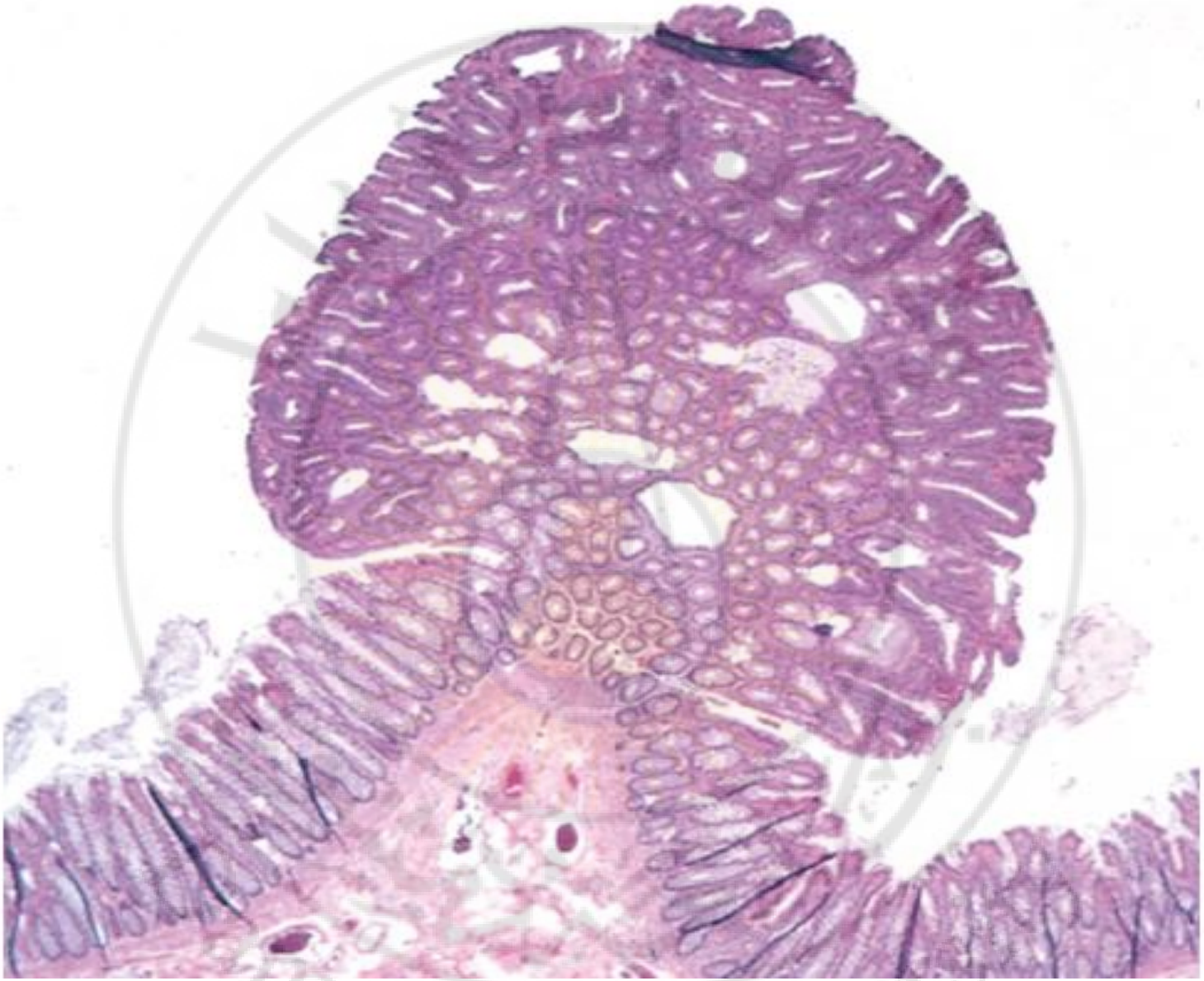
1-Benign Tumors:

In general, benign tumors are designated by attaching the **suffix *-oma*** to the cell type from which the tumor arises.

fibrous tissue	→	*fibr**oma***
cartilage	→	*chondr**oma***
Smooth muscles	→	*leiomy**oma***
Adipose tissue	→	*lip**oma***
Bone	→	*oste**oma***

Benign epithelial tumors are named either after their tissue of origin or in combination with their architecture.

- **Papilloma** : benign tumor of epithelial cells with formation of finger like projections.
- **Adenoma**: are tumors arising from glands or differentiating into glands.



Adenoma in the colon

2-malignant tumors

1-Carcinomas : Malignant neoplasms of epithelial cell origin :

-Squamous cell carcinoma

-Transitional cell carcinoma

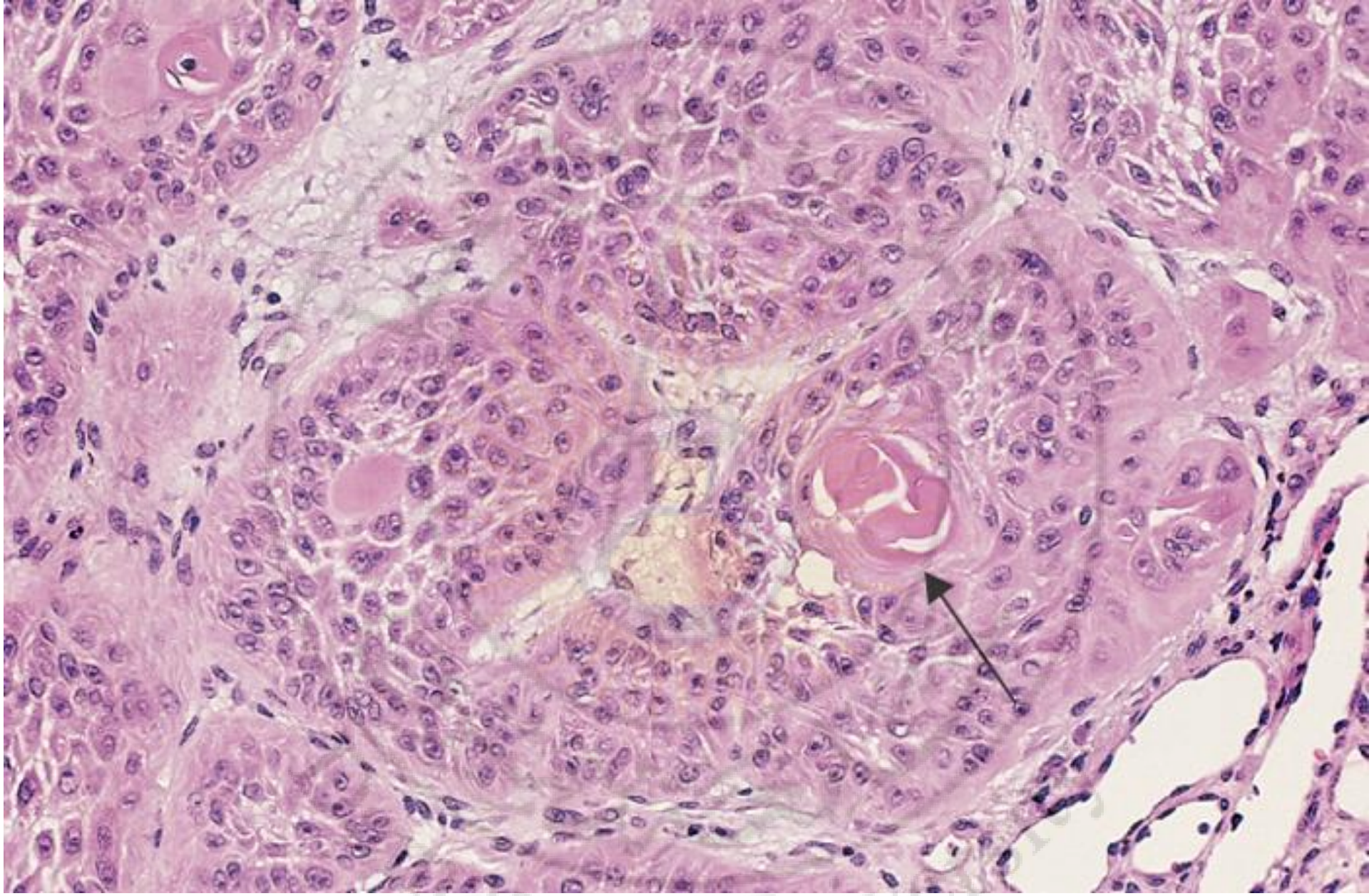
-Adenocarcinoma

2- Sarcomas : Malignant neoplasms arising in mesenchymal tissue :

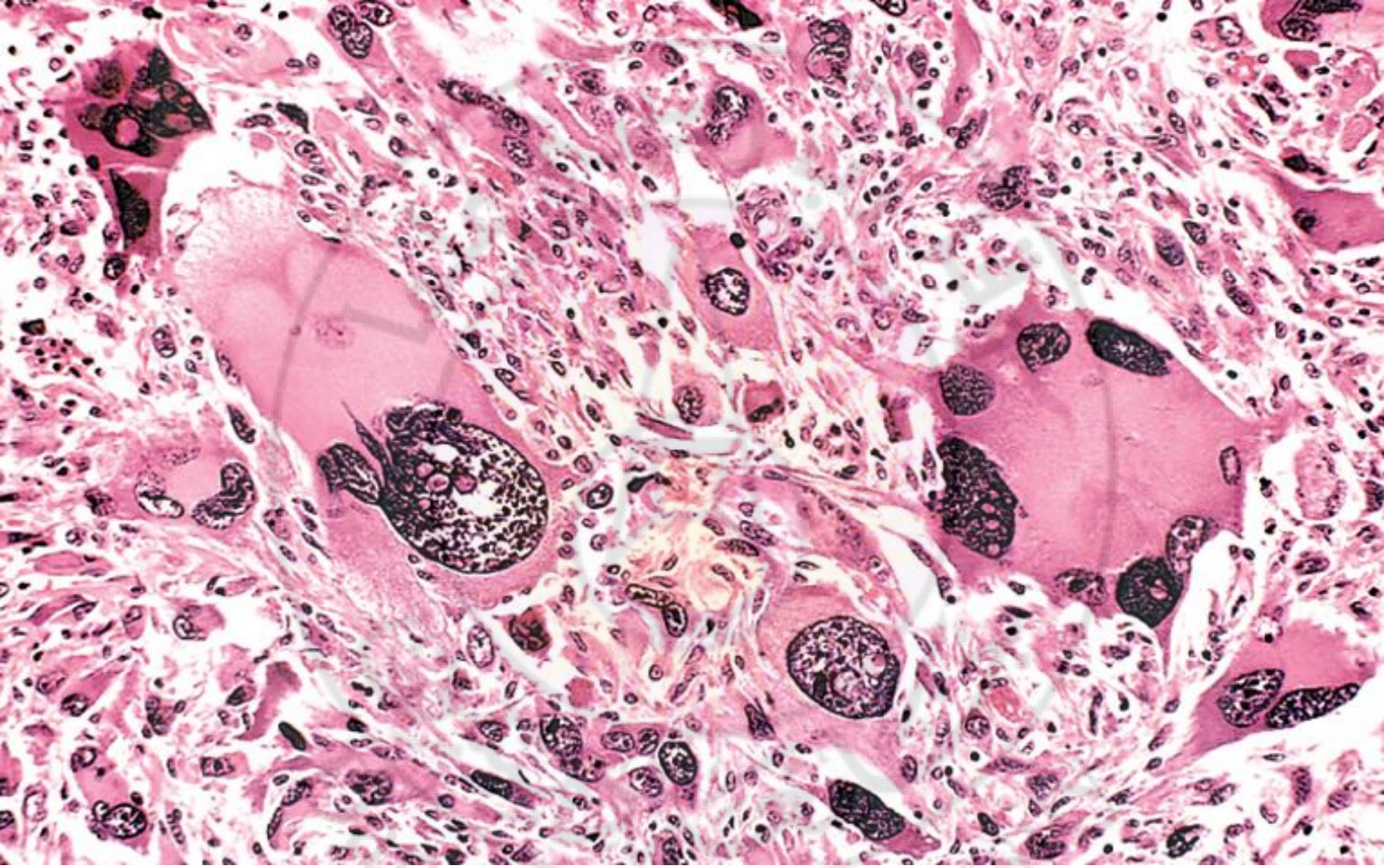
-Osteosarcoma (bone)

-Chondrosarcoma (cartilage)

-Leiomyosarcoma (smooth muscles)



Squamous cell carcinoma



Rhabdomyosarcoma

Clinical features of tumors

1- ***local effects*** due to pressure or destruction by direct infiltration of the tumor

2-hormonal effects by endocrine tumors which is more common in benign than malignant tumors e.g. adrenocortical adenoma causing Cushing's syndrome.

Clinical features of tumors

3-cancer cachexia which is loss of body fat , wasting and profound weakness associated with cancer.

The causes for cachexia are multifactorial :

A. Loss of appetite
B. Metabolic changes leading to reduced synthesis and storage of fat and increased mobilisation of fatty acids from adipocytes.
C. Production of cachectin (TNF-a) by macrophages and some tumor cells

Grading of cancer

- Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread in the individual patient are necessary for making accurate prognosis and for comparing end results of various treatment protocols.
- The cancer may be classified as grade ***I, II, III, or IV***, in order of increasing anaplasia.
- Difficulties in establishing clear-cut criteria have led in some instances to descriptive characterizations (e.g., "well-differentiated adenocarcinoma with no evidence of vascular or lymphatic invasion" or "highly anaplastic sarcoma with extensive vascular invasion").

Staging of cancer

Staging of cancers is based on:

- The size of the primary lesion
- The extent of spread to regional lymph nodes
- The presence or absence of metastases

This assessment is usually based on clinical, radiographic examination and surgical exploration.

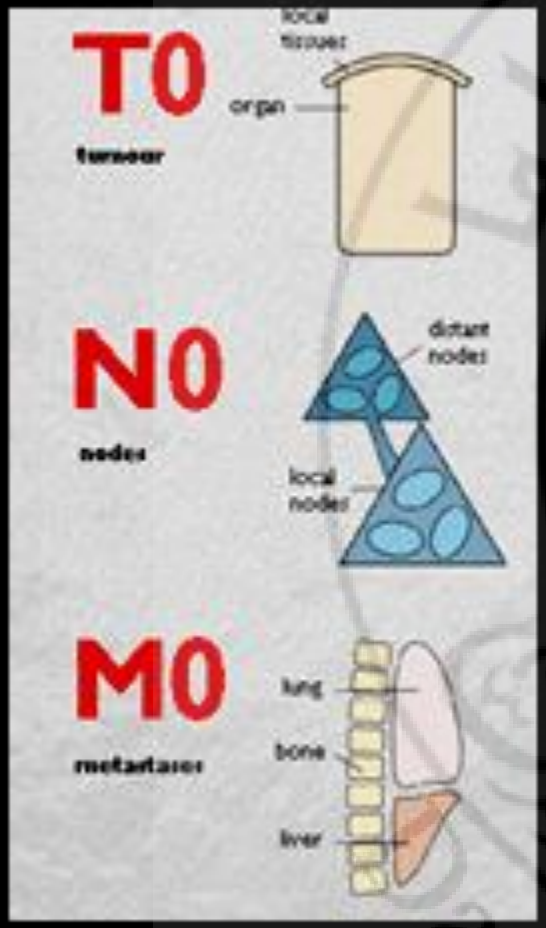
Two methodes of staging are currently in use:

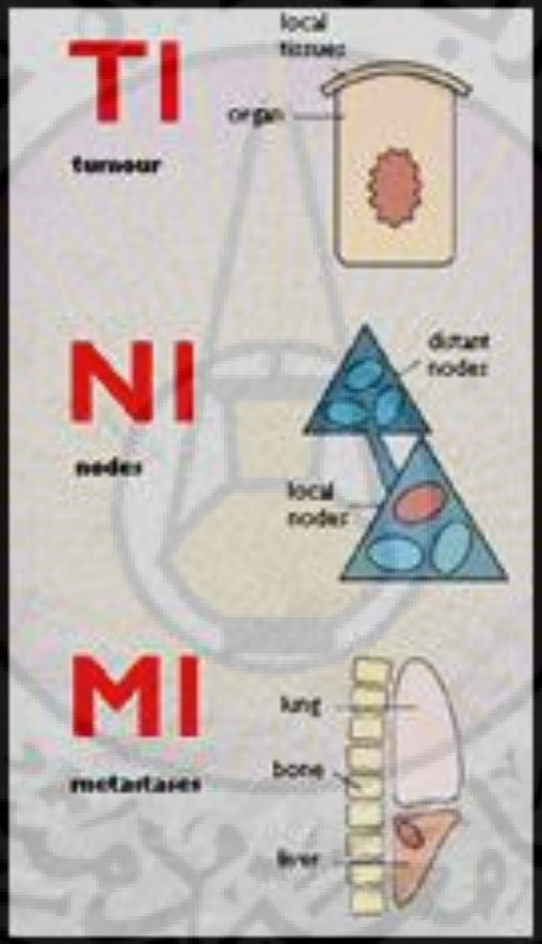
TNM system (**T**=primary tumor, **N**=regional lymph nodesinvolvement, **M**= metastases).

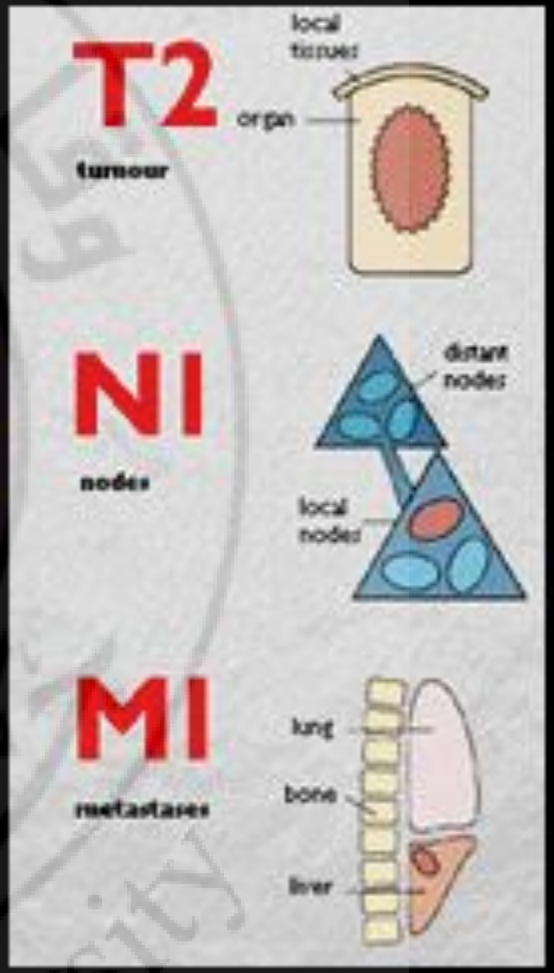
AJC (American Joint Comitee) system: the cancers are divided into stages 0 to IV, incorporating the size of primary lesions and the presence of nodal spread and of distant metastases

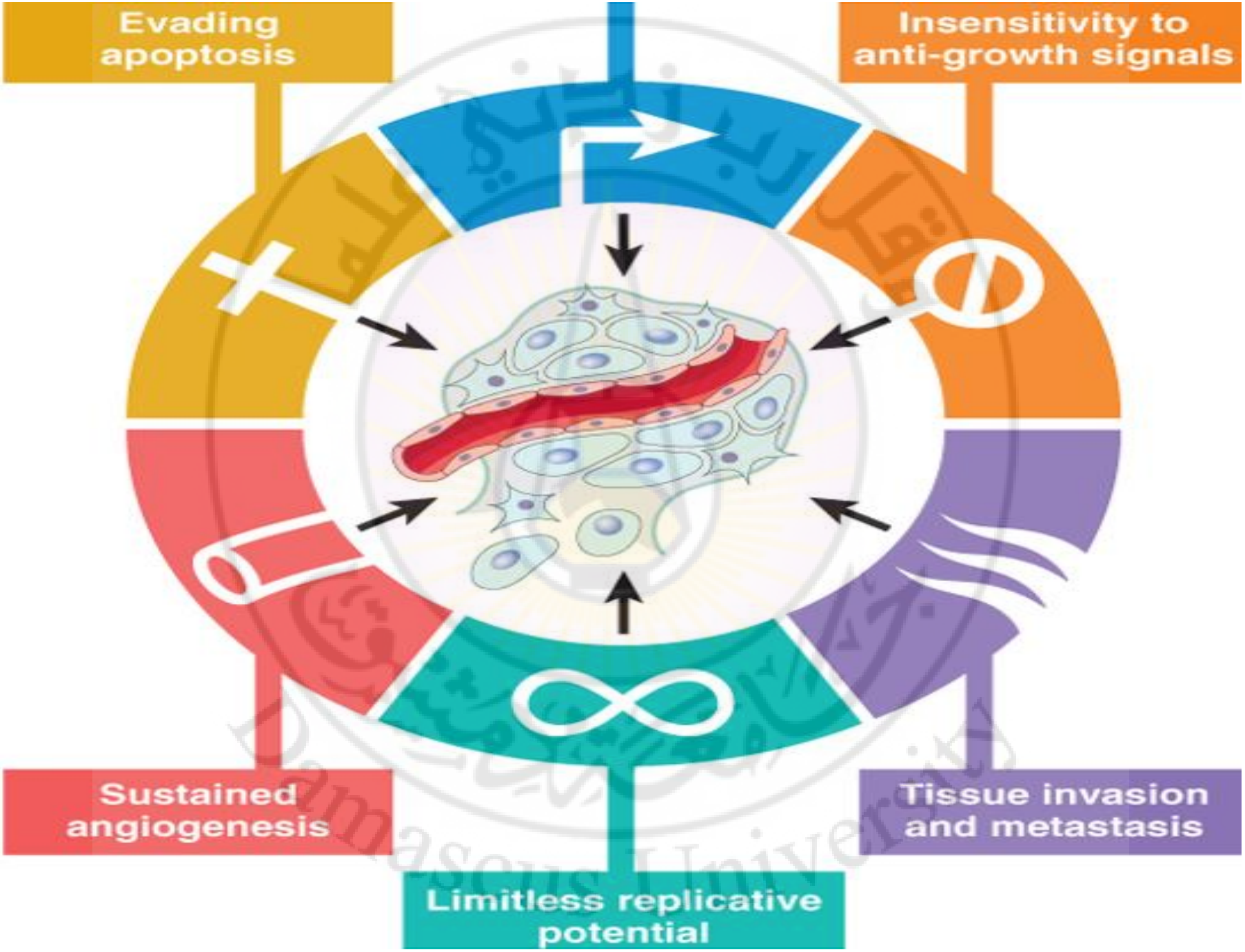
Staging has proved to be of greater value than grading because in grading different parts in the same tumors shows different grade of differentiation and may change as the tumor grows i.e. cancer progression

TNM staging for ca breast








Evading apoptosis
Insensitivity to anti-growth signals
Sustained angiogenesis
Tissue invasion and metastasis
Limitless replicative potential