RETICULOENDOTHELIAL SYSTEM AND FUNCTIONS OF THE SPLEEN

Nonspecific Host Defenses

DR SYED SHAHID HABIB
MBBS DSDM PGDCR FCPS
Professor & Consultant Clinical Physiology
Dept. of Physiology
College of Medicine & KKUH

OBJECTIVES

At the end of this lecture you should be able to:

- Describe Monocyte macrophage system (RES)
- Functions of monocytes/macrophages in different tissues
- Mechanism of chemotaxis, phagocytosis and microbial killing
- Explain functions of spleen
- Understand the basic concept of the indications and risks of spleenectomy.

IMMUNITY

Innate immunity
(non specific)
Examples:
- Phagocytes (Neut, Mono, NK)
- Complement
- Barriers

Acquired immunity
(specific, adaptive)

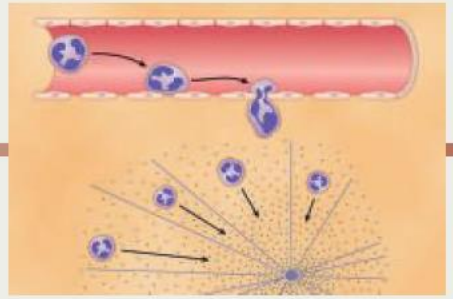
Cell mediated
T lymphocytes

Humoral
Antibody mediated
B lymphocytes

Note: Macrophages are key components of the innate immunity and activate adaptive immunity by transforming into Antigen Presenting Cells

Innate immunity
(non specific)
Examples:

- **Phagocytes**
- **Complement**
- **Barriers**

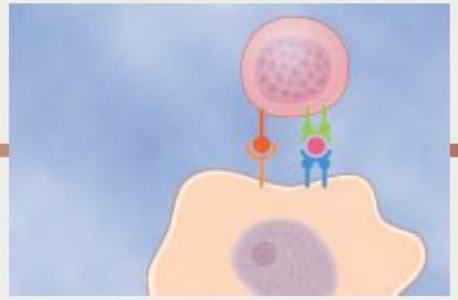


UNIT VI

CHAPTER 34

Resistance of the Body to Infection: I. Leukocytes, Granulocytes, the Monocyte-Macrophage System, and Inflammation

Acquired immunity
(specific, adaptive)



UNIT VI

CHAPTER 35

Resistance of the Body to Infection: II. Immunity and Allergy

RETICULOENDOTHELIAL SYSTEM

It is a network of connective tissue fibers inhabited by phagocytic cells such as macrophages ready to attack and ingest microbes.

- **Monocytes transform themselves into macrophages in tissue & this system of phagocytes is called as Monocye-Macrophage Cell System**
- **RES term is old although they are neither reticular in appearance nor they have endothelial origin just these phagocytic cells are located in reticular connective tissue**
- **Therefore, the term reticuloendothelial system is is not used nowadays.**

Reticuloendothelial System
Monocyte/Macrophage System

TISSUE MACROPHAGE SYSTEM COMPONANTS

3

- Monocytes in **Blood**
- Mobile & Fixed Macrophages in **Tissue**
- **Specialized endothelial cells** in bone marrow, spleen and lymph nodes

German pathologist Karl Albert Ludwig Aschoff introduced the term reticuloendothelial system in 1924,

General Functions of RES

1. **Phagocytosis**: Bacterial, dead cells, foreign particles **(direct).**
2. **Immune function**: processing antigen and antibodies production **(indirect).**
3. **Breakdown** of aging RBC.
4. **Storage** of RBC and and recycling **iron.**

WBCs Concentration (Normal Counts)

Cells	Approximate Normal range (/µL)	Percentage of Total WBC	Life Span
Total WBC	4000-11000	- - -	
Granulocytes •Neutrophils • Eosinophils • Basophils	 3000-6000 150-300 0-100	 50-70% 1-4% 0.4	4-8 hours in blood and 4-5 days in tissues
Lymphocytes	1500-4000	20-40%	Weeks-months
Monocytes (macrophages)	300-600	2-8%	10-20 hours (months)

Polymorphonuclear neutrophils	62.0%
Polymorphonuclear eosinophils	2.3%
Polymorphonuclear basophils	0.4%
Monocytes	5.3%
Lymphocytes	30.0%

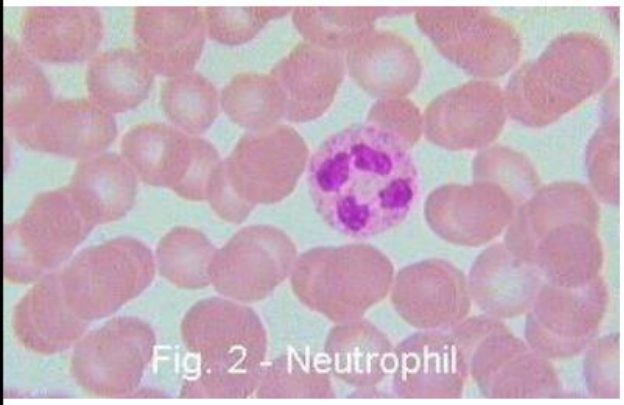


Fig. 2 - Neutrophil

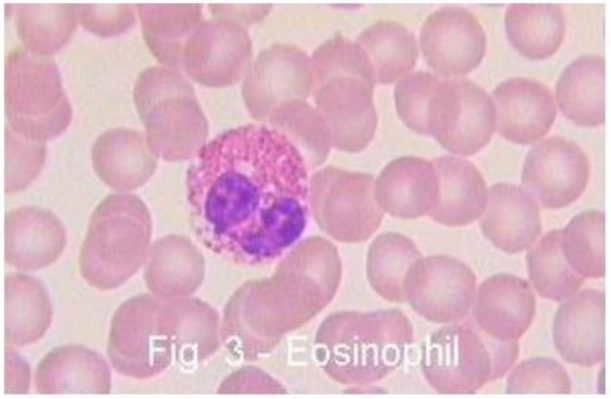


Fig. 3 - Eosinophil

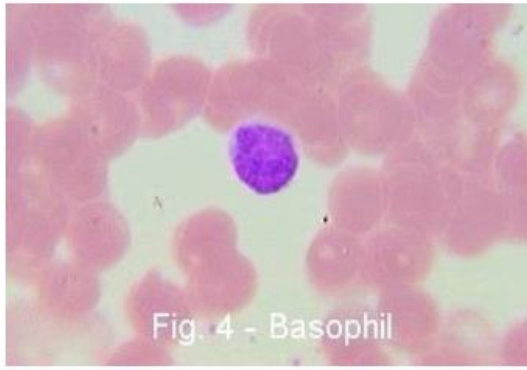


Fig. 4 - Basophil

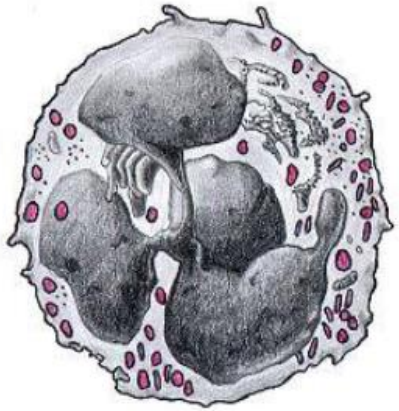


Fig. 8 - Neutrophil

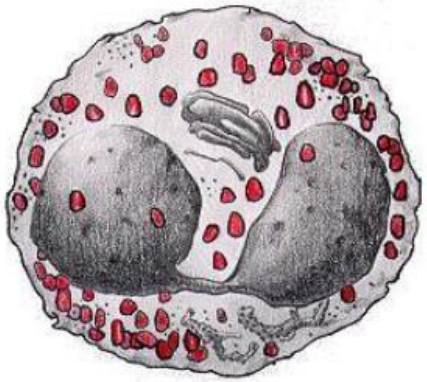


Fig. 9 - Eosinophil

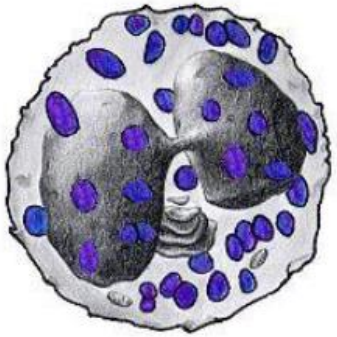


fig. 10 - Basophil

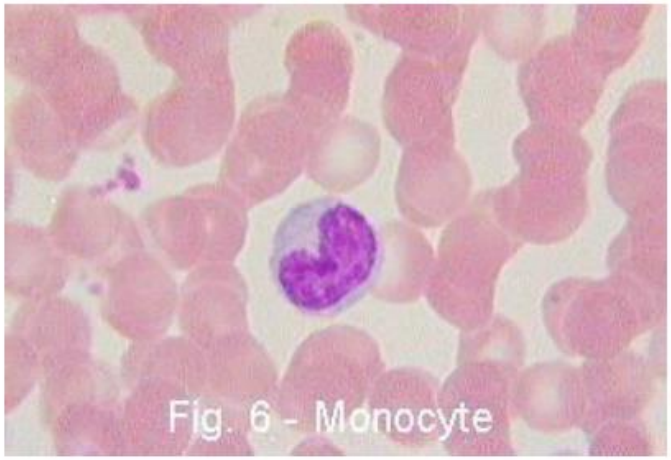


Fig. 6 - Monocyte

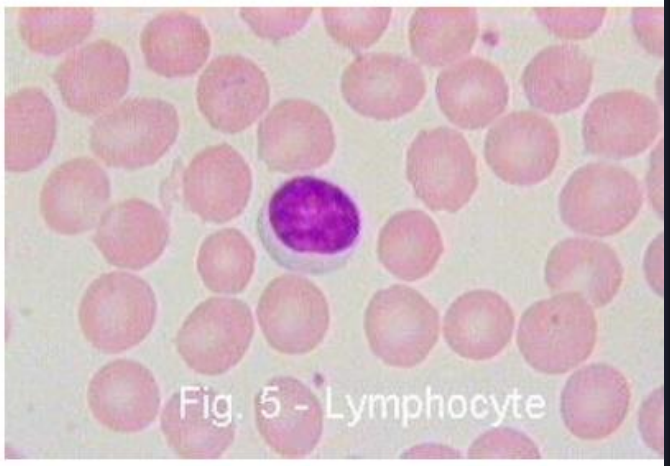


Fig. 5 - Lymphocyte

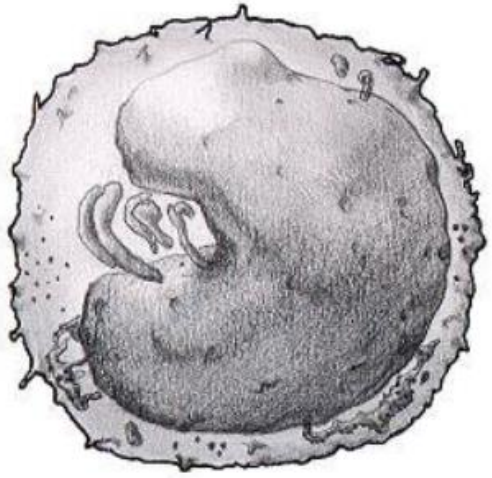


Fig. 12 - Monocyte

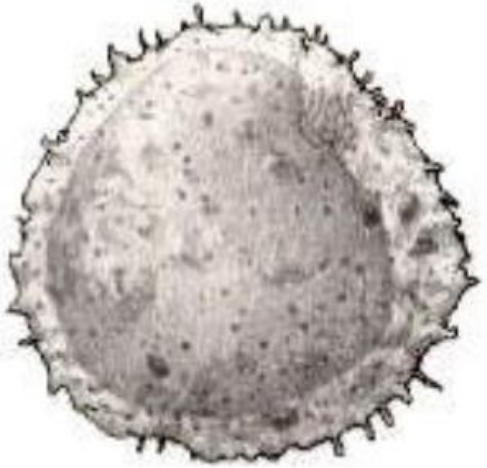


Fig. 11 - Lymphocyte

Responses During Inflammation Macrophage and Neutrophil

- 1st line of defense – Tissue macrophages & Physical Barriers
- 2nd line of defense – Neutrophil Invasion of the inflamed area
- 3rd line of defense – Monocytes –macrophage invasion of inflamed area
- 4th line of defense – Increased production of granulocytes and Monocytes by Bone marrow

DEFENSIVE PROPERTIES OF
MACROPHAGES & NEUTROPHILS

- **Margination:** WBC Roll, Bind and then stick along the walls of blood capillaries
- **Diapedesis:** WBC squeezes itself through endothelial holes leaving blood capillaries
- **Chemotaxis:** WBC move by amoeboid motion towards inflammation area following chemotactic substances (Bacterial toxins, Complement [C5a], LKB4) are released from site of infection
- **Phagocytosis:** Upon reaching the site of infection neutrophils start to engulf infecting organism

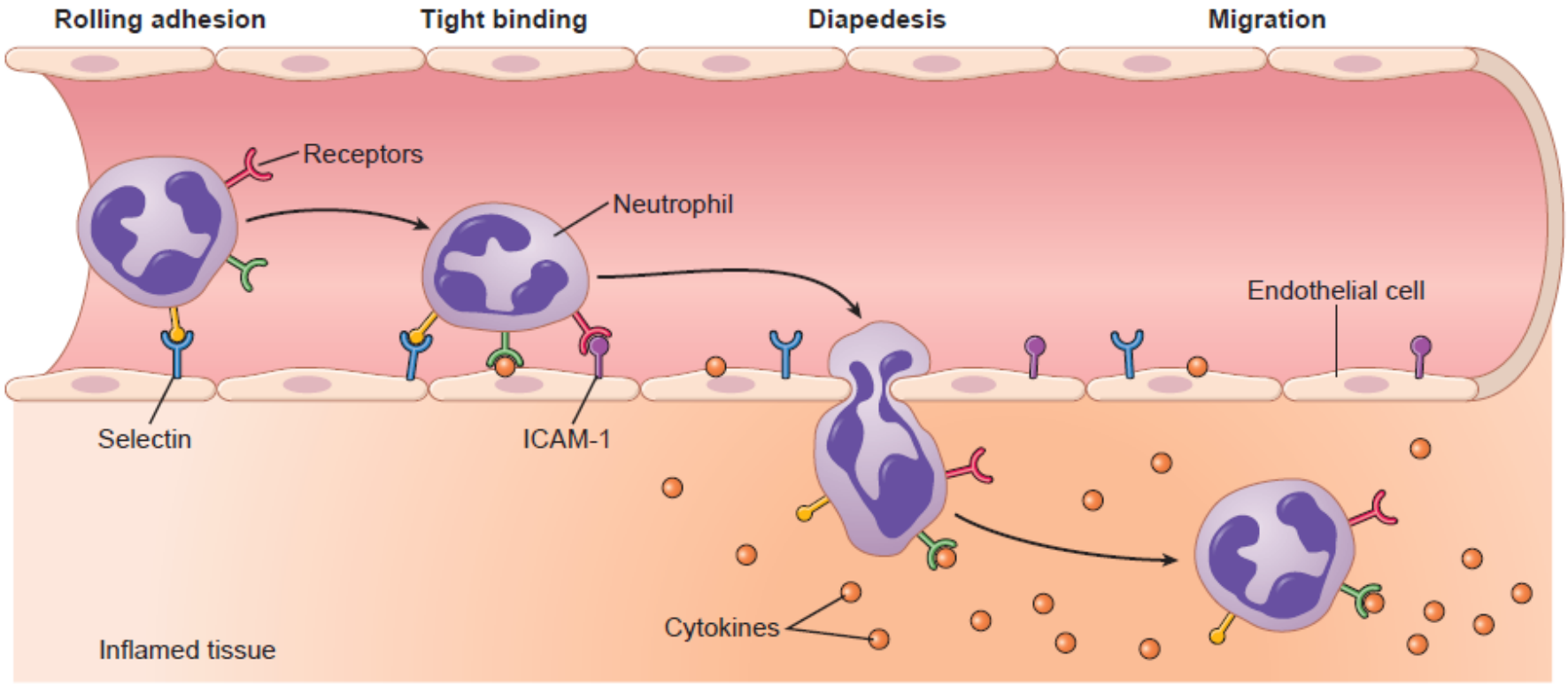


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 *(ICAM-1)* in the surface of endothelial cells. These adhesion molecules bind to complementary molecules/receptors on the neutrophil, causing it to adhere to the wall of the capillary or venule. The neutrophil then migrates through the vessel wall by diapedesis toward the site of tissue injury.

MONOCYTES

- **Size:** 15-20 µm (active cells 60-80 µm)
- **Small Granules (Prim) & Vacoules**
- More Efficient **Phagocytosis** than Neutrophils (100 bacteria vs 3-20 by Neutr, larger particles like RBCs & malarial parasites)
- Life span: 10-20 hours in blood…& in tissues?
- **Two types:** Mobile & Fixed
- Lysosomes contain **lipases** unlike Neutrophils.
- Acts as **Antigen Presenting Cells**

Quick Review: Cells of the RES or Tissue Macrophage System	
Descriptions	Locations
Fixed macrophages: (reticulum cells) large cells, small nucleus	Spleen, lymph nodes, bone marrow, liver, skin (histiocytes), lungs (macrophages), etc.
Free macrophages: large wandering cells	Spleen, lymph nodes, lungs, many other tissues
Circulating monocytes: large, motile cells with indented nuclei	Blood

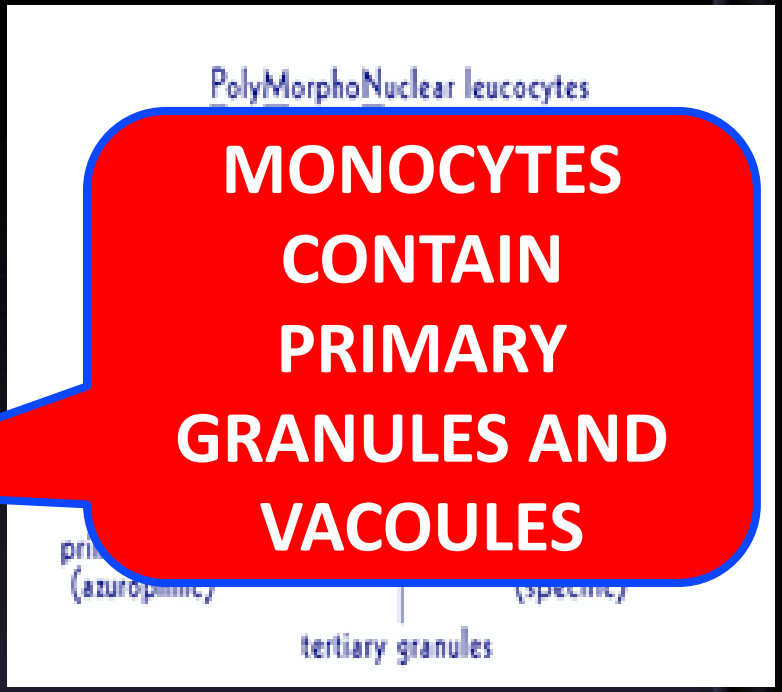
NEUTROPHILS

- Most Abundant WBCs 60-70 %
- Size: 15-20 µm
- Nucleus: Multilobed 2-5 lobes
- Life span: 6-8 hours

POOLS:
Bone Marrow, Circulating and Marginated Pool

NEUTROPHIL GRANULES

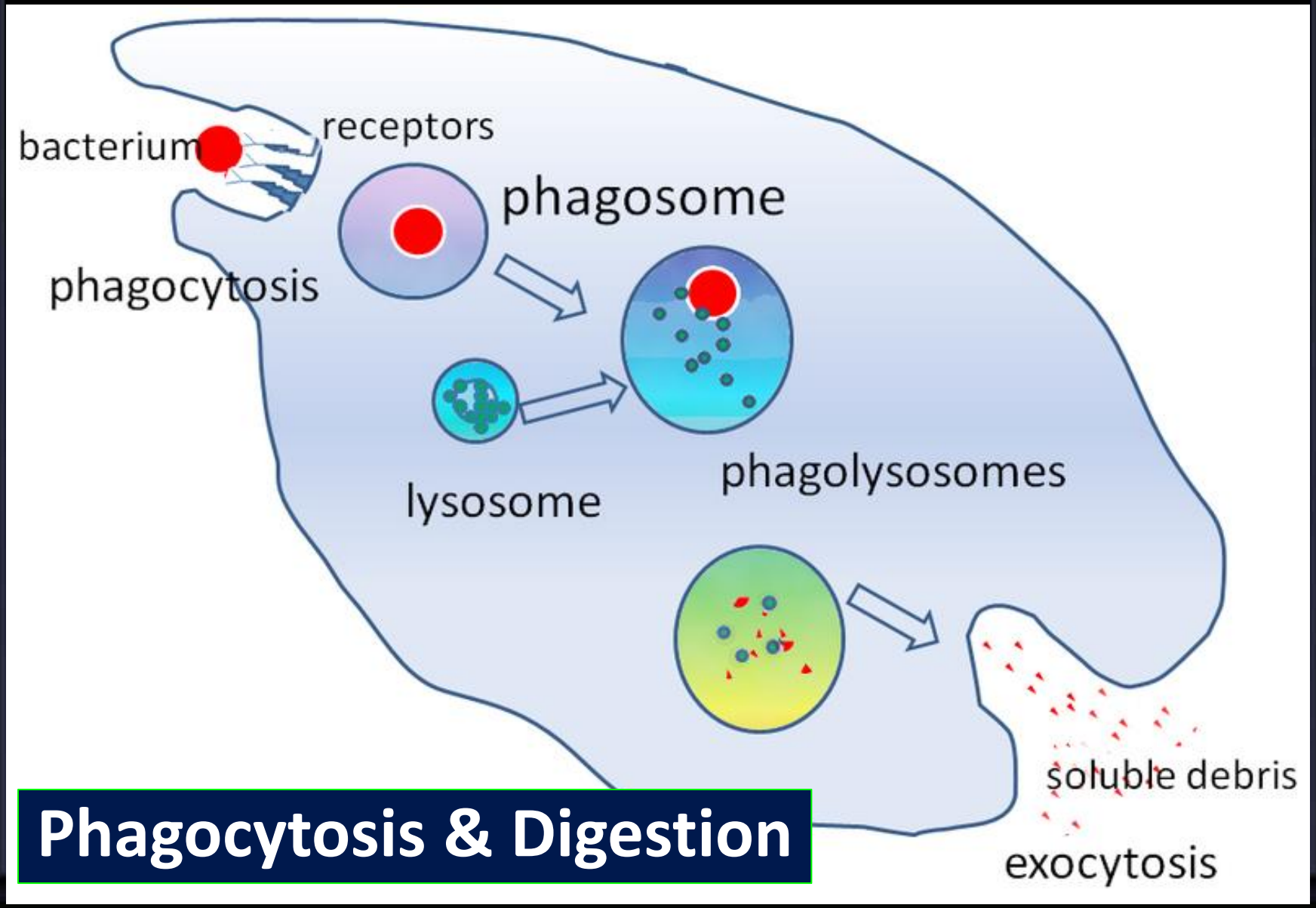
- **Primary Granules (Non Specific, Azurophilic, lysosomes) [33%]:**
  Acid hydrolases, MPO, HOCl, Defensins
- **Secondary Granules (Specific) [67%]:**
  Lysozyme, Lactoferrin, Alkaline Phaphatase, Gelatinase, Bacteriostatic & Bacericidal products.
- **Tertiary Granules :** (help to digest tissues)
  Collagenase, Hyaluronidase and Gelatinase.



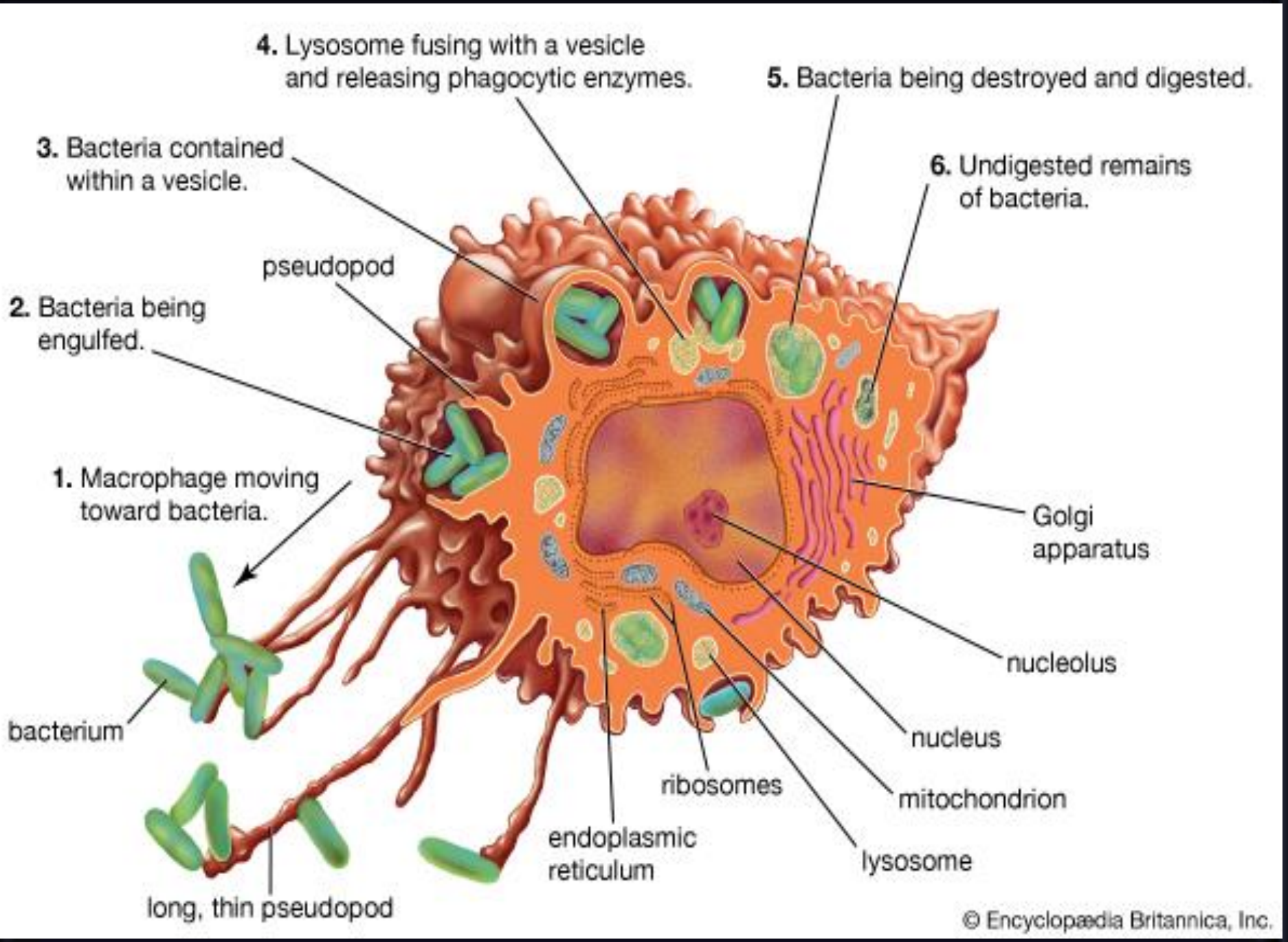
MONOCYTES CONTAIN PRIMARY GRANULES AND VACOULES

Glycogen granules: for anaerobic glycolysis.

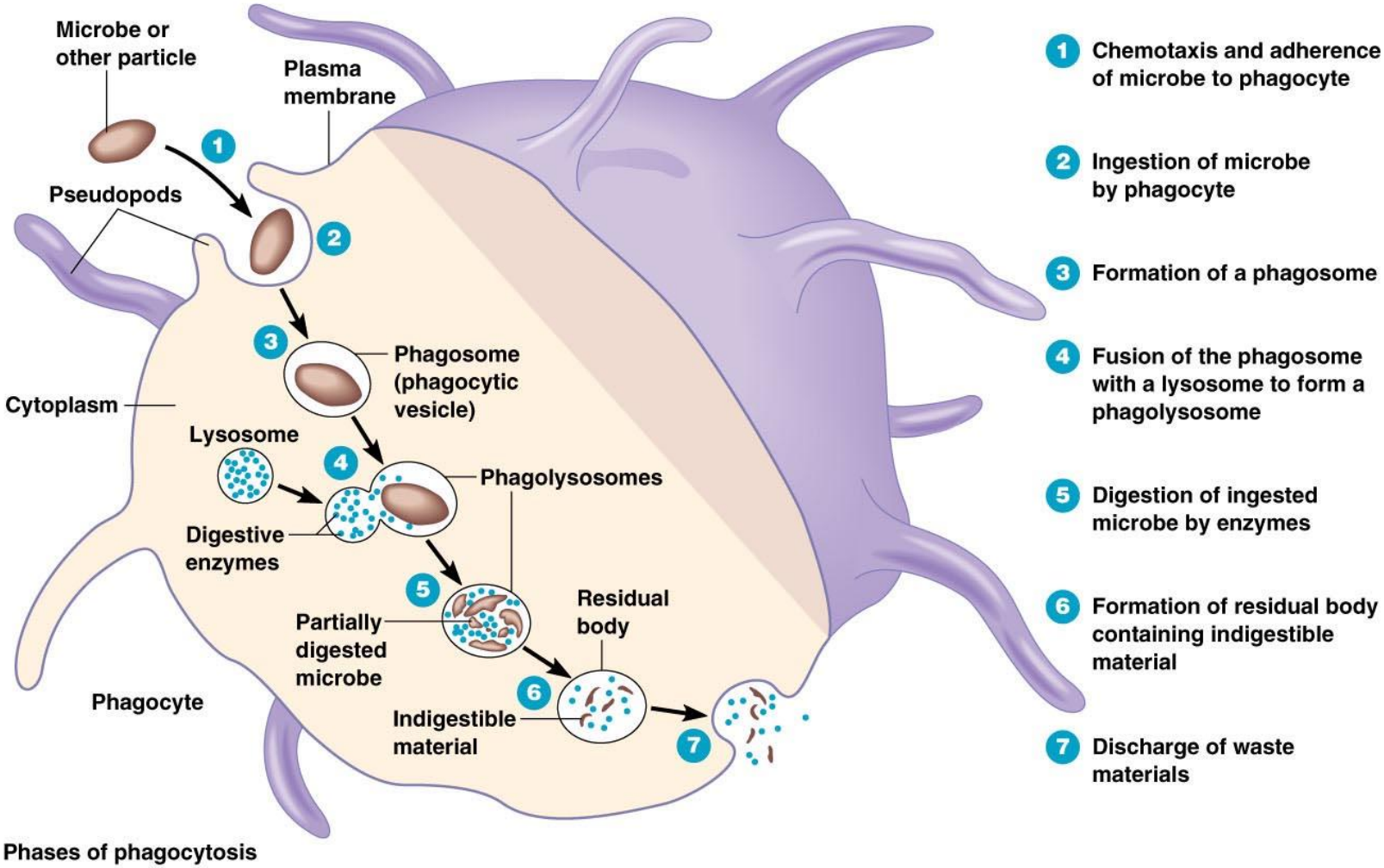
Direct funtion of RES



Phagocytosis & Digestion



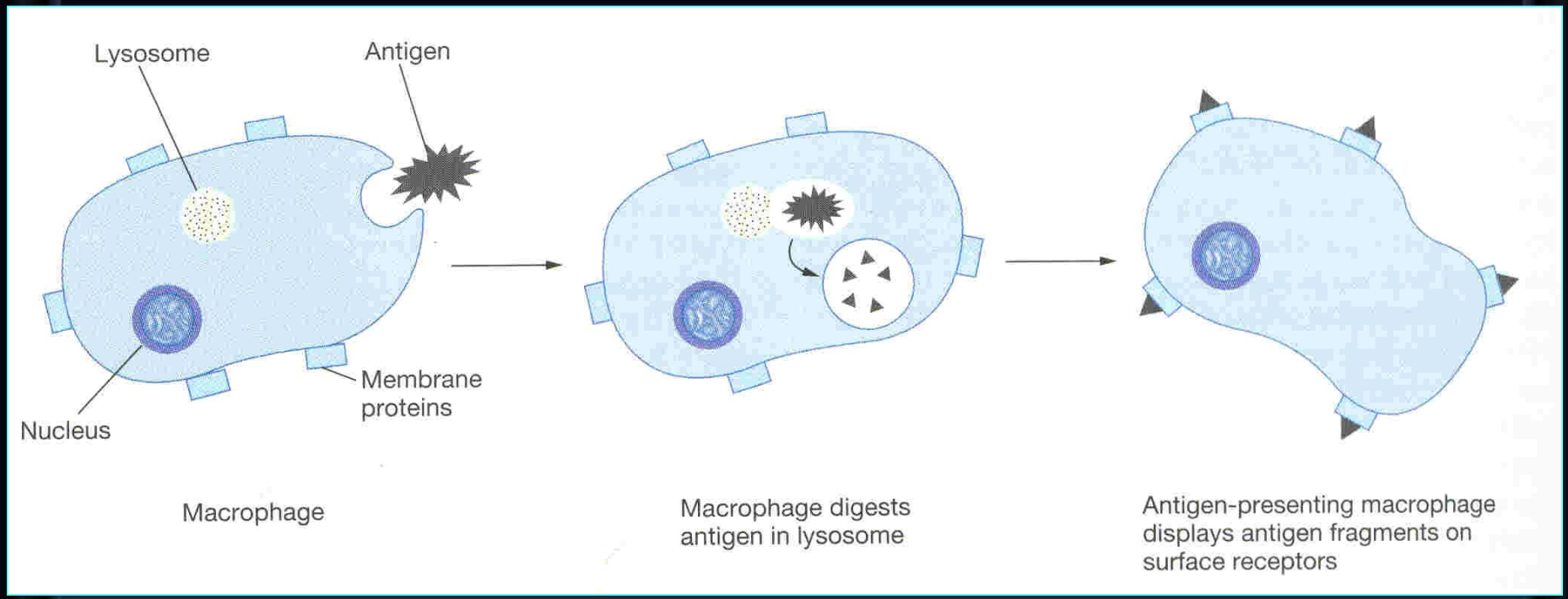
Macrophage: a wandering, walking cell. "Big eater" capable of phagocytosis. Is a modified monocyte in tissues



Phases of phagocytosis

Indirect Immune function Of RES

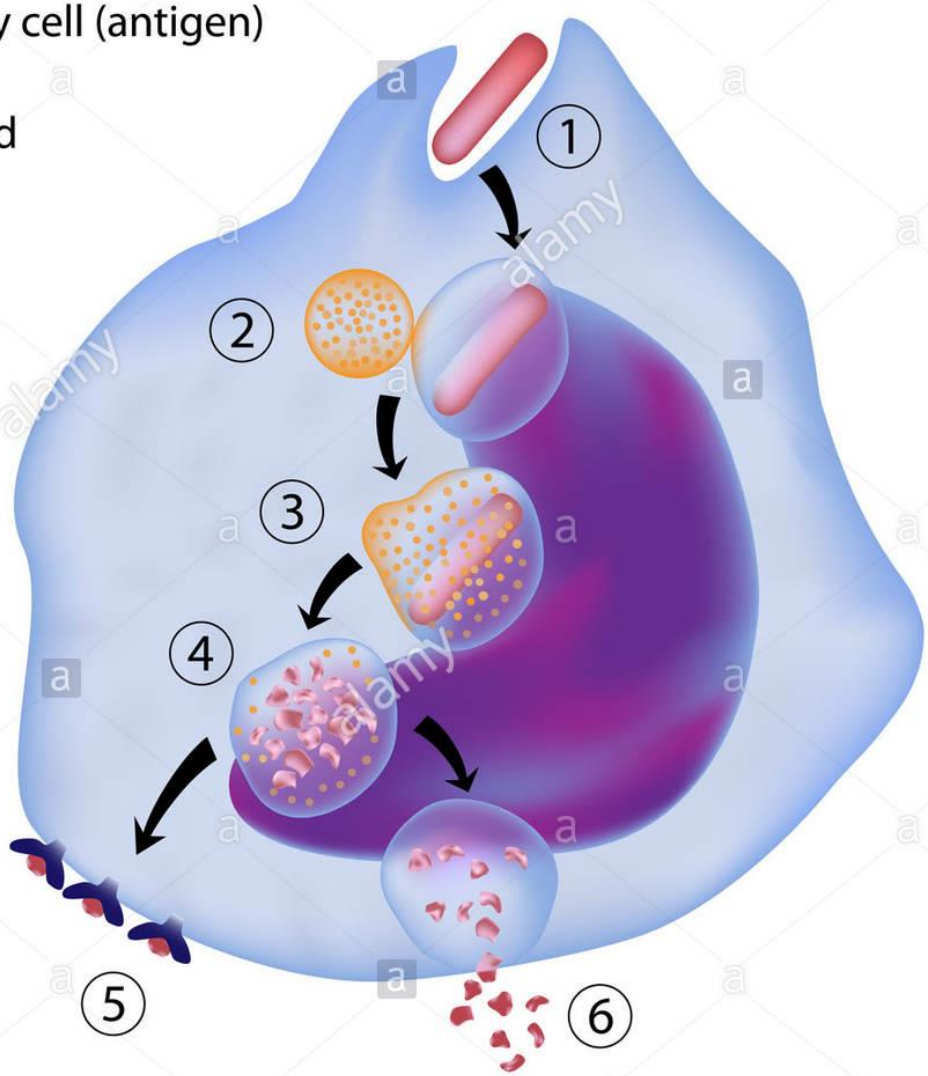
Antigen Presenting Cells

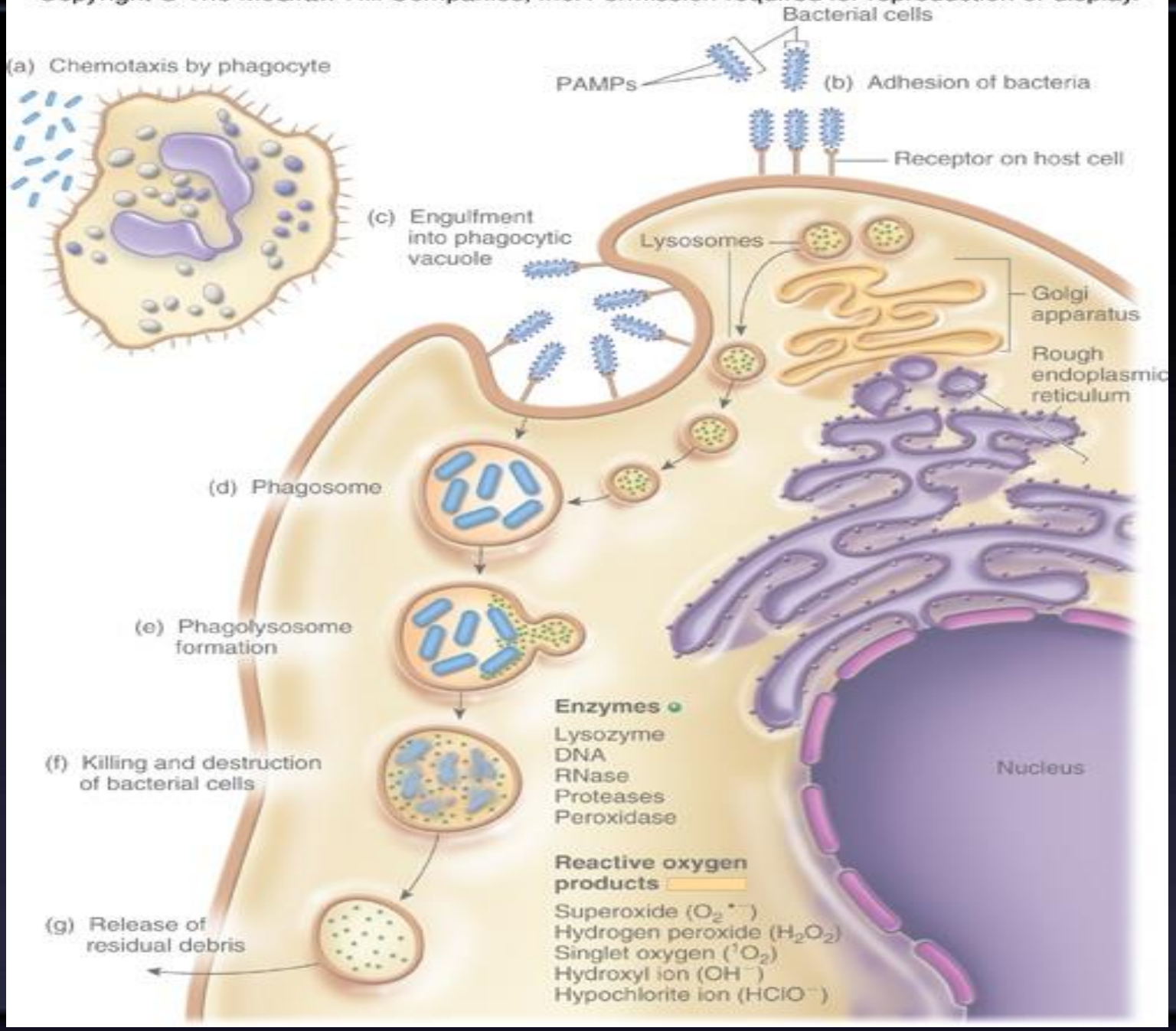


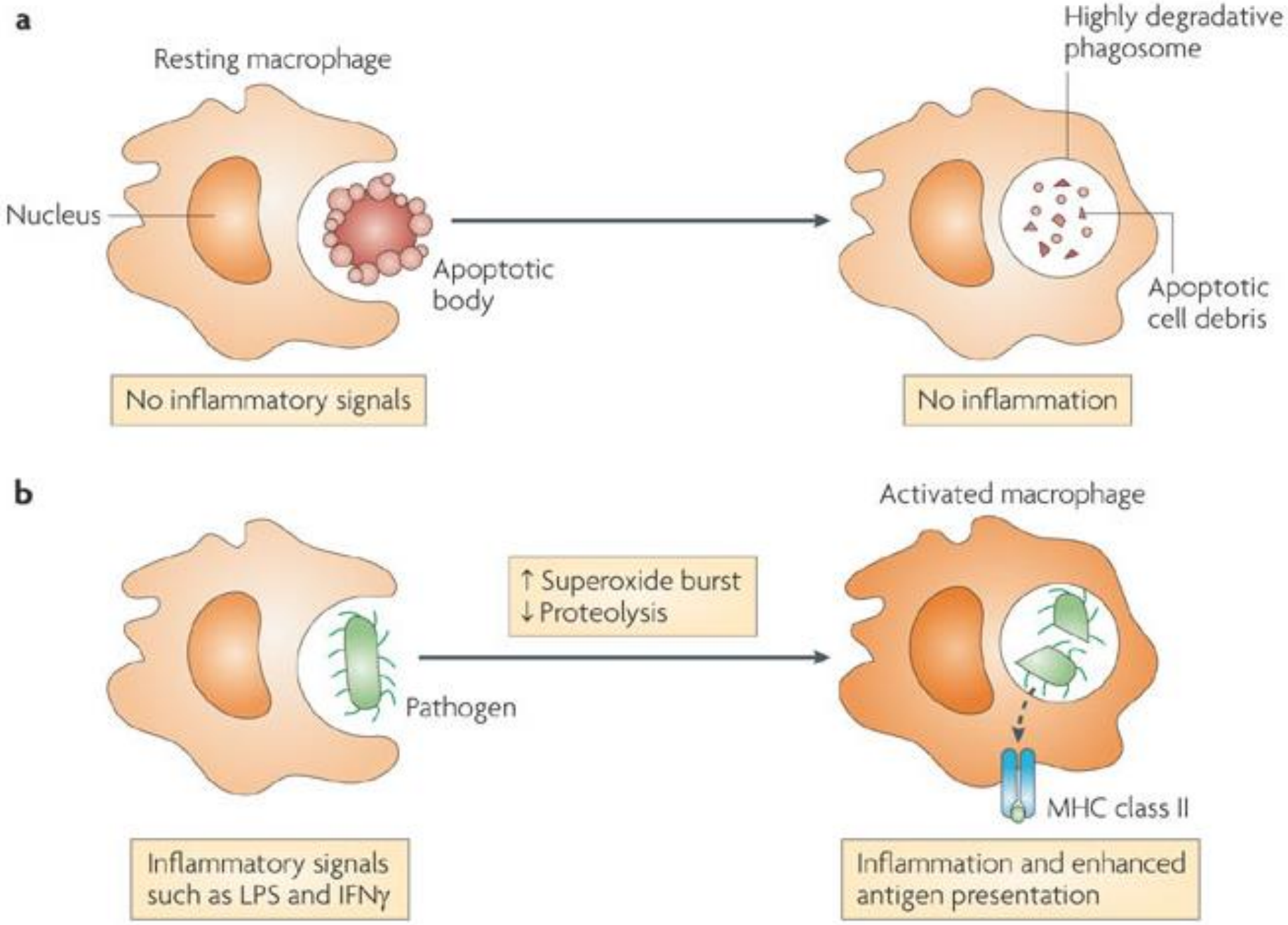
Displaying it attached to an MHC class II molecule

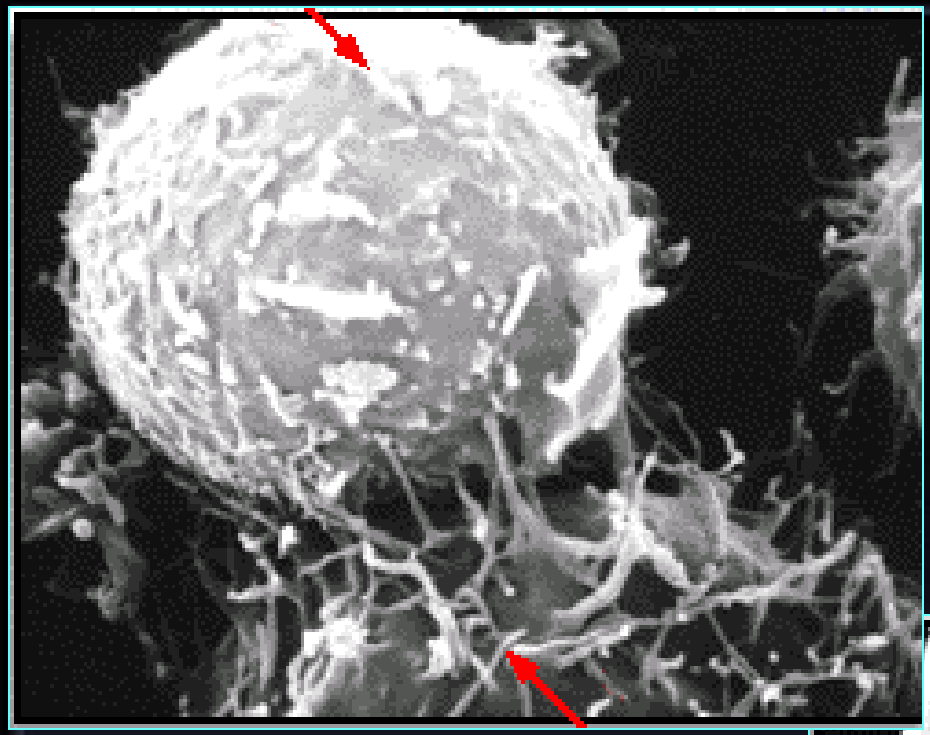
Role of an Antigen-Presenting Cell

1. Phagocytosis of enemy cell (antigen)
2. Fusion of lysosome and phagosome
3. Enzymes start to degrade enemy cell
4. Enemy cell broken into small fragments
5. Fragments of antigen presented on APC surface
6. Leftover fragments released by exocytosis



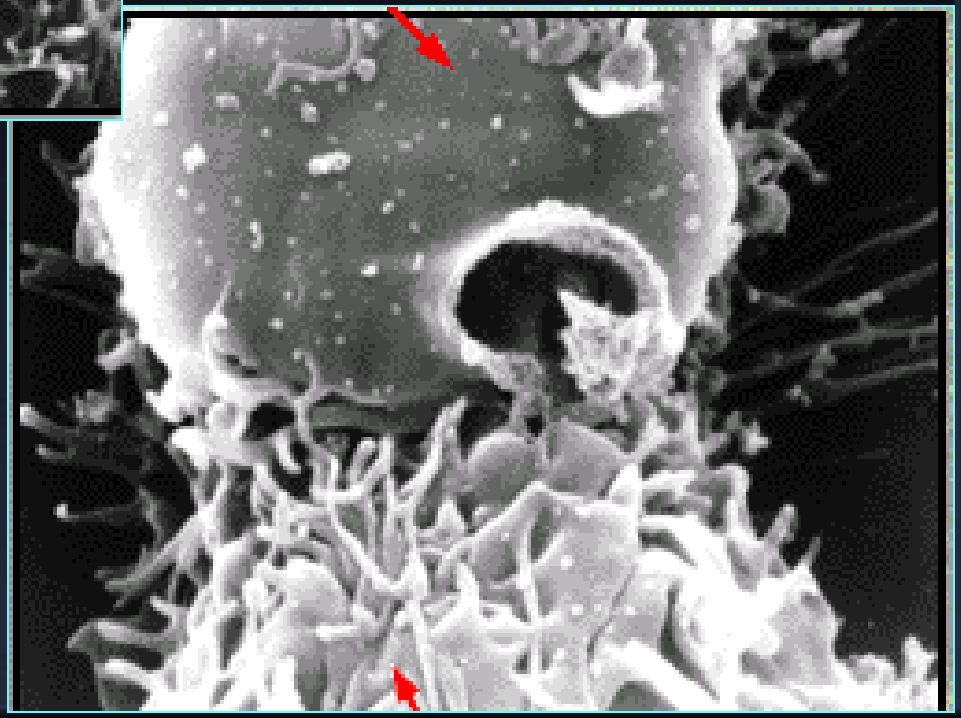


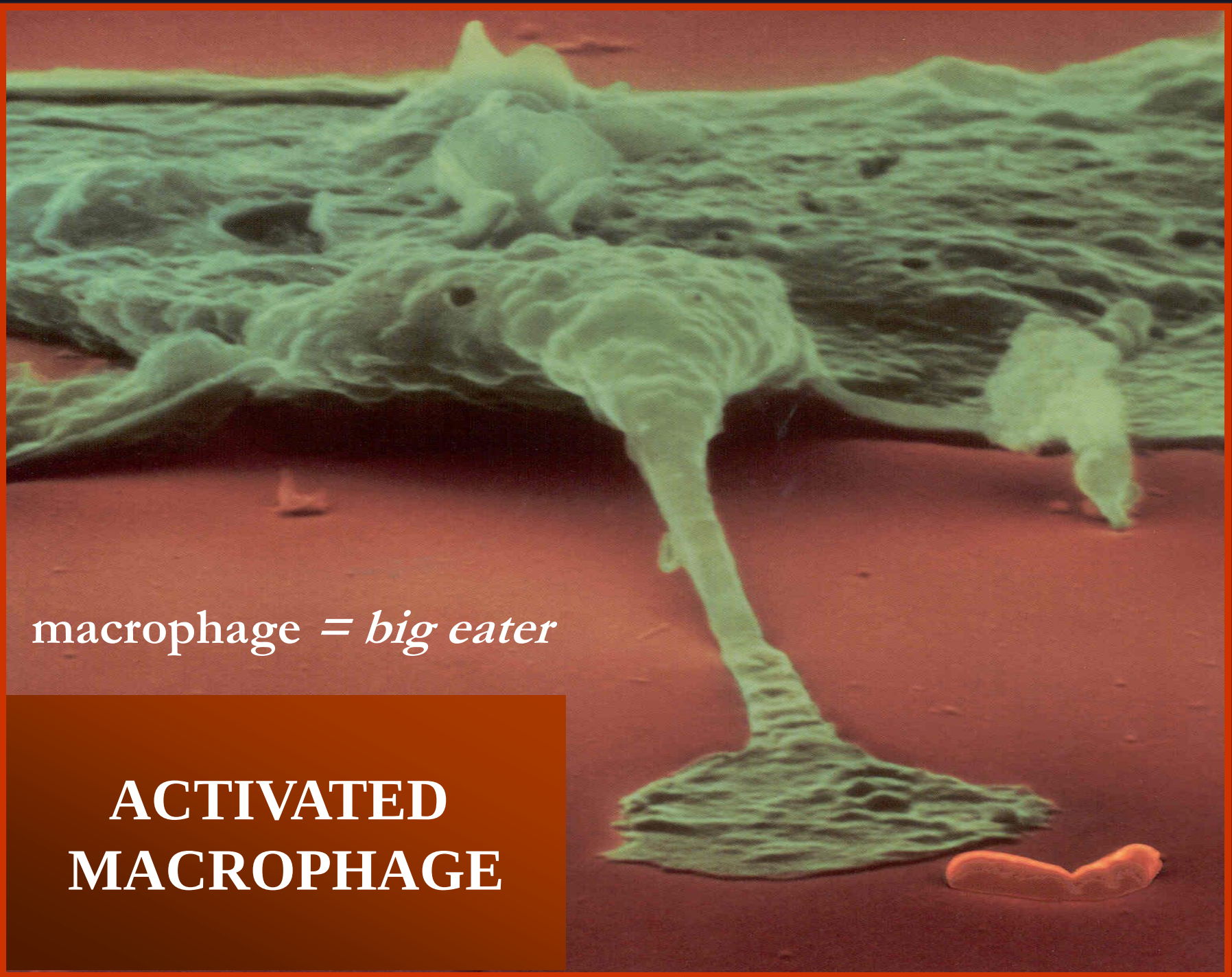

a
Resting macrophage
Nucleus
Apoptotic body
No inflammatory signals
Highly degradative phagosome
Apoptotic cell debris
No inflammation
b
Activated macrophage
↑ Superoxide burst
↓ Proteolysis
Pathogen
MHC class II
Inflammatory signals such as LPS and IFNγ
Inflammation and enhanced antigen presentation



RESTING MACROPHAGE

ACTIVATED MACROPHAGE




macrophage = *big eater*
ACTIVATED MACROPHAGE

Reticuloendothelial System
Monocytes/Macrophage System

- Monocytes when enter the tissues they transform themselves into macrophages this system of phagocytes is called as **Monocye-Macrophage Cell System**

Examples are: -

1. Skin, mucosa and Subc tissues (Langerhans cell)
2. Lymph Nodes (Sinus histiocytes)
3. Alveolar macrophages
4. Liver sinuses (Kupffer Cells)
5. Spleen & Bone marrow
6. Microglia in Brain
7. Kidneys (Mesangial Cells)
8. Bone (Osteoclasts)

Hofbauer cells in Placenta

Epithelioid cells in Granulomas

Tissue macrophages

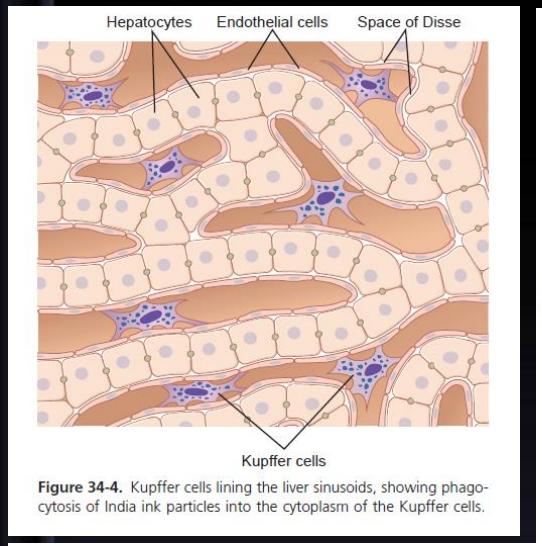


Figure 34-4. Kupffer cells lining the liver sinusoids, showing phagocytosis of India ink particles into the cytoplasm of the Kupffer cells.

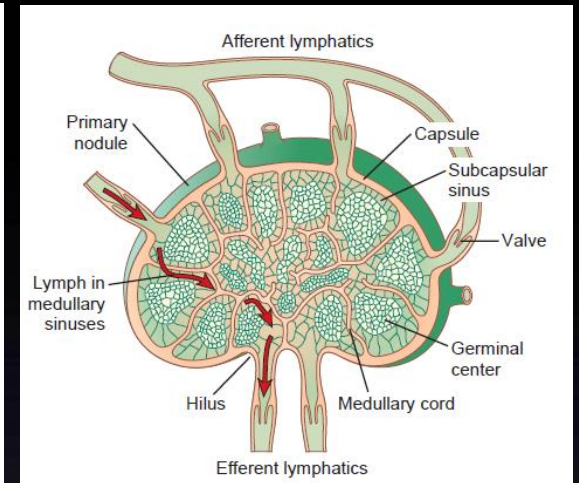
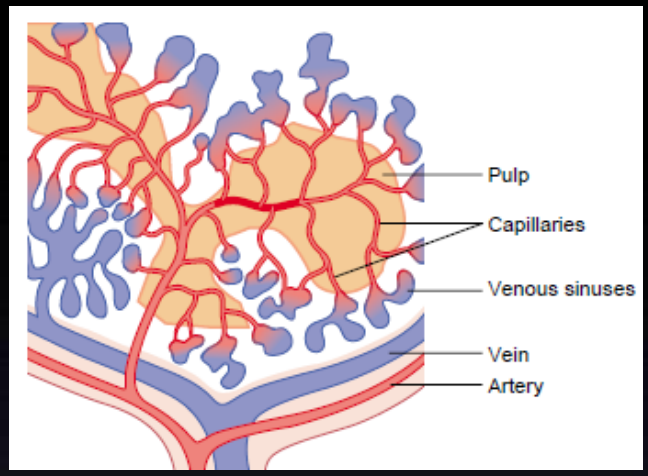
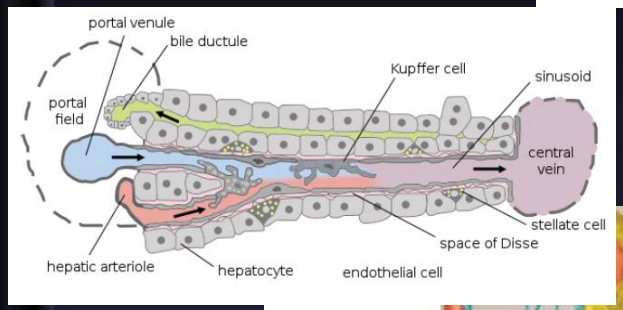
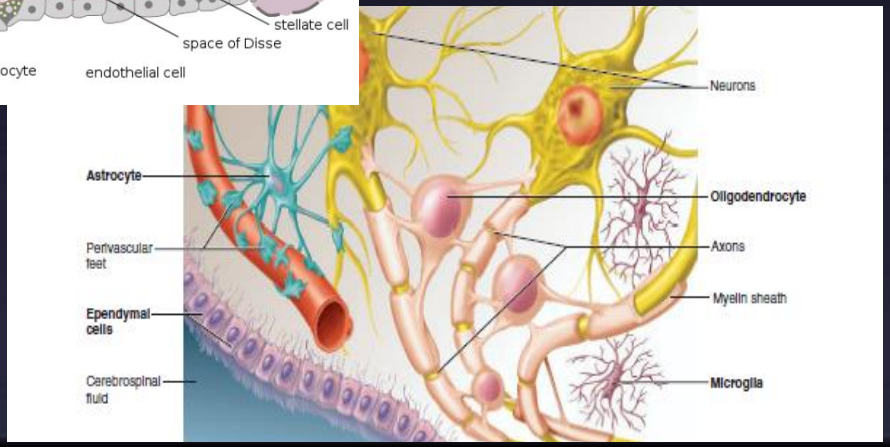
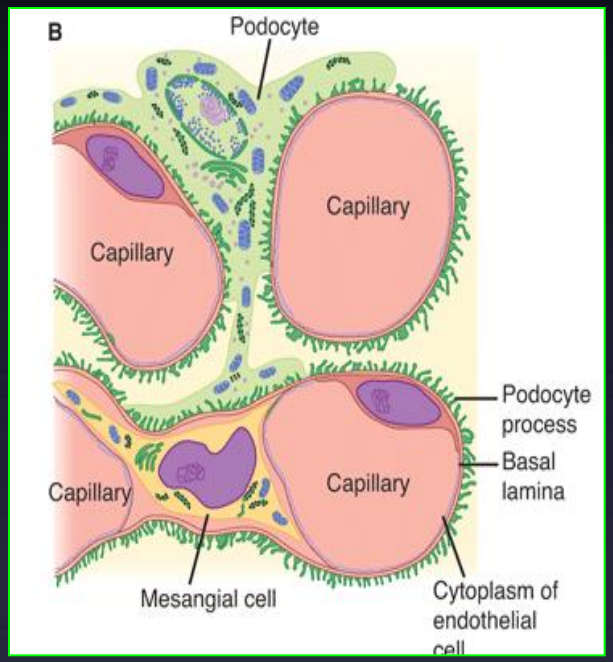


Figure 34-3. Functional diagram of a lymph node.

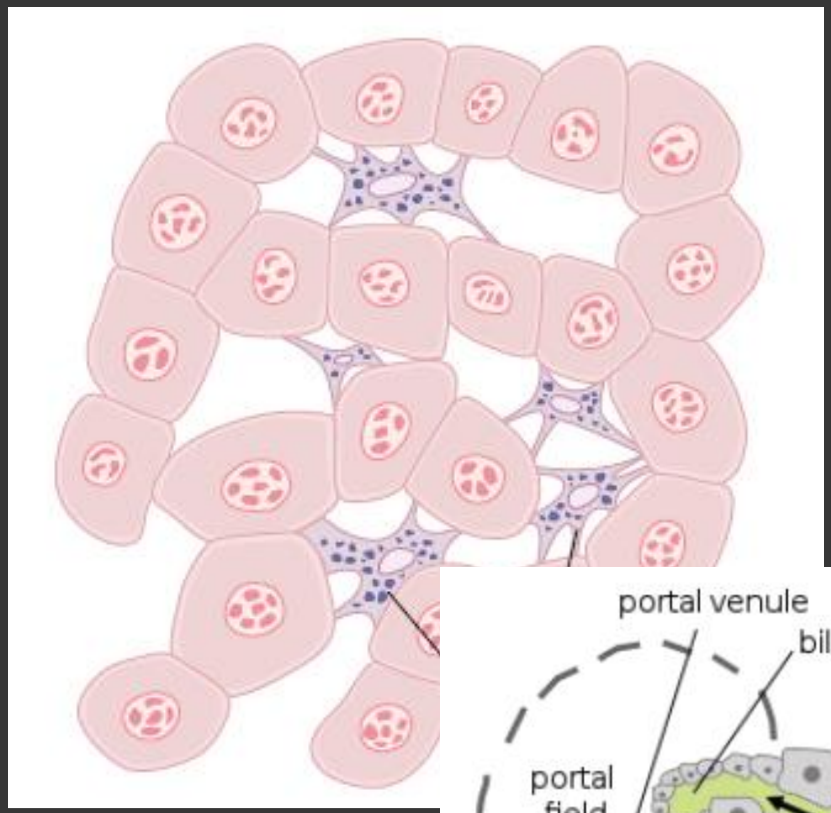


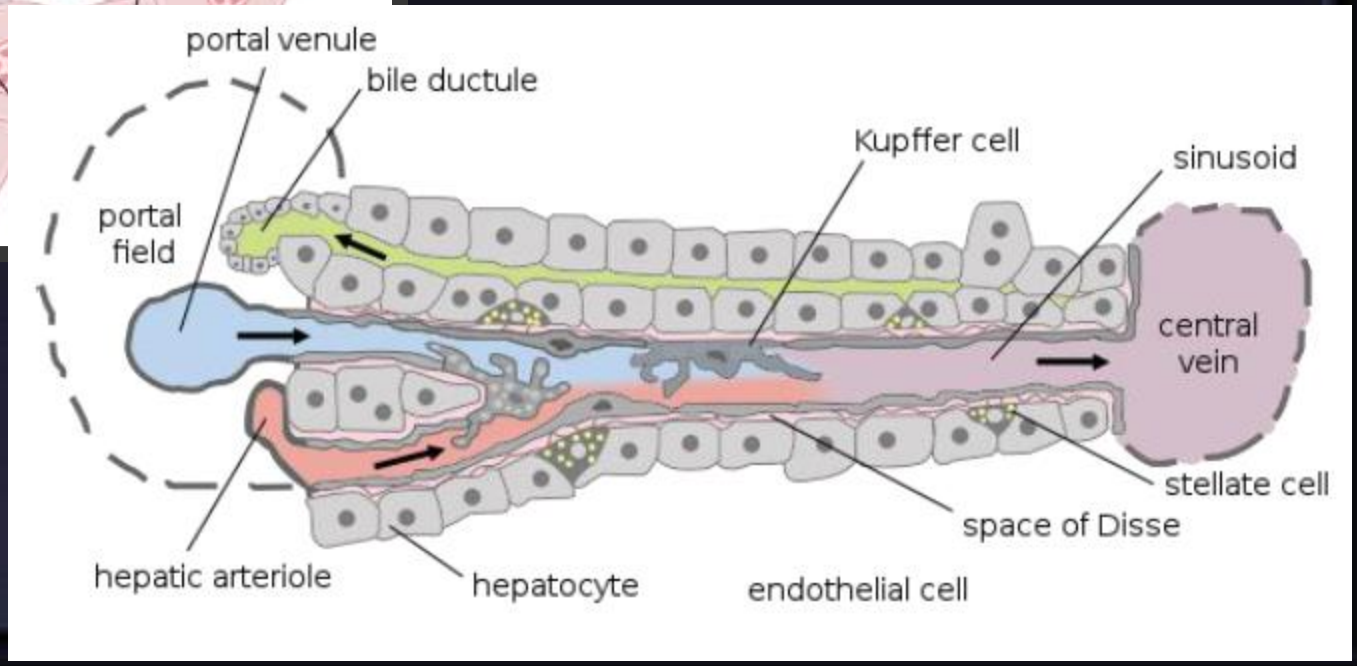






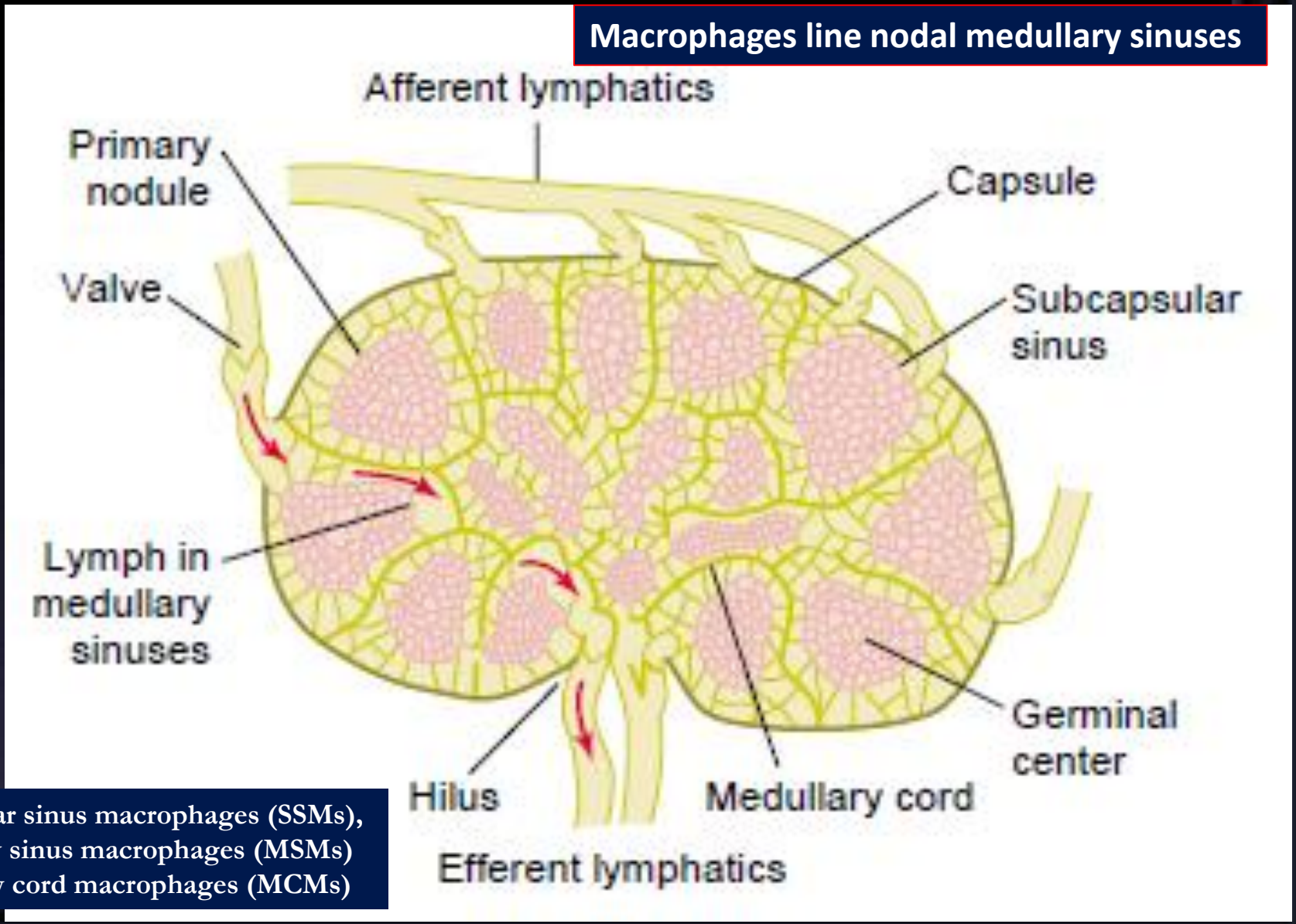
Tissue macrophages in Liver sinuses





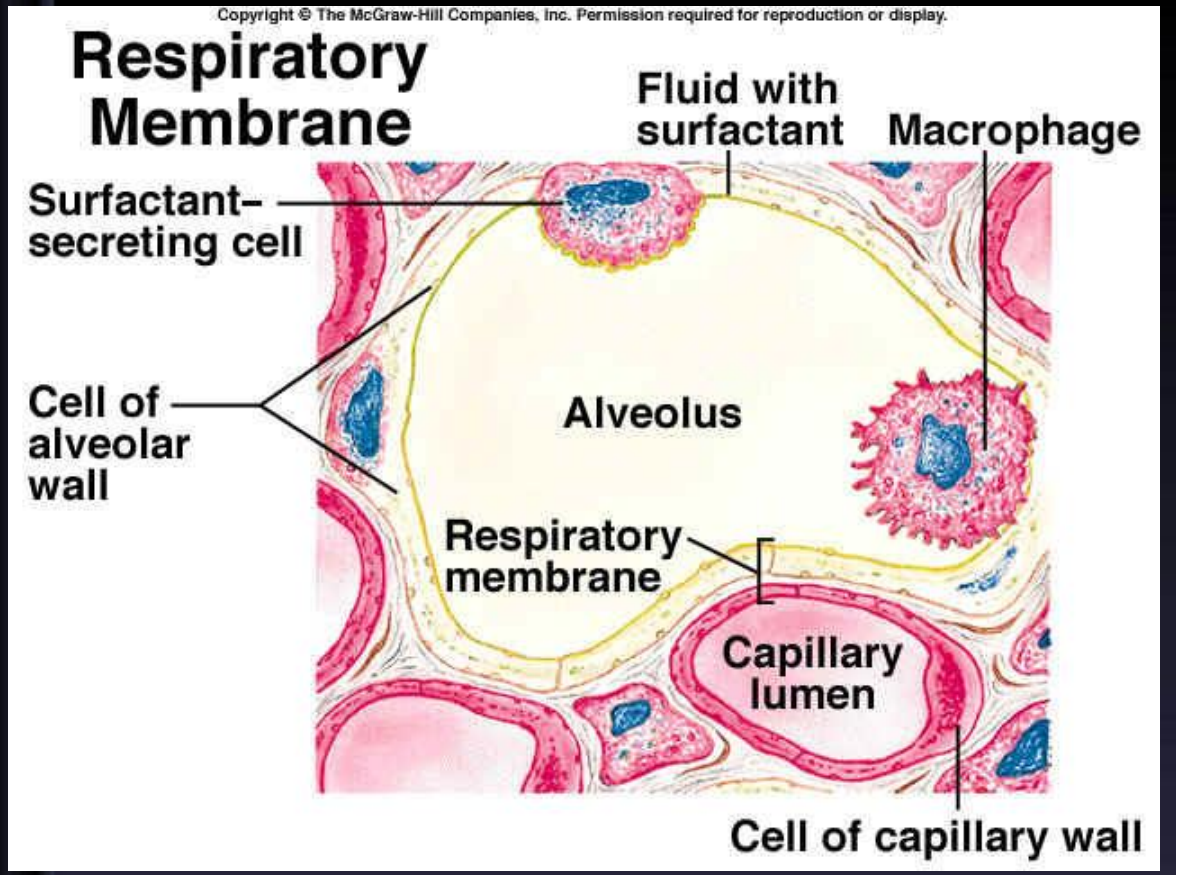
Tissue macrophages in Lymph Nodes

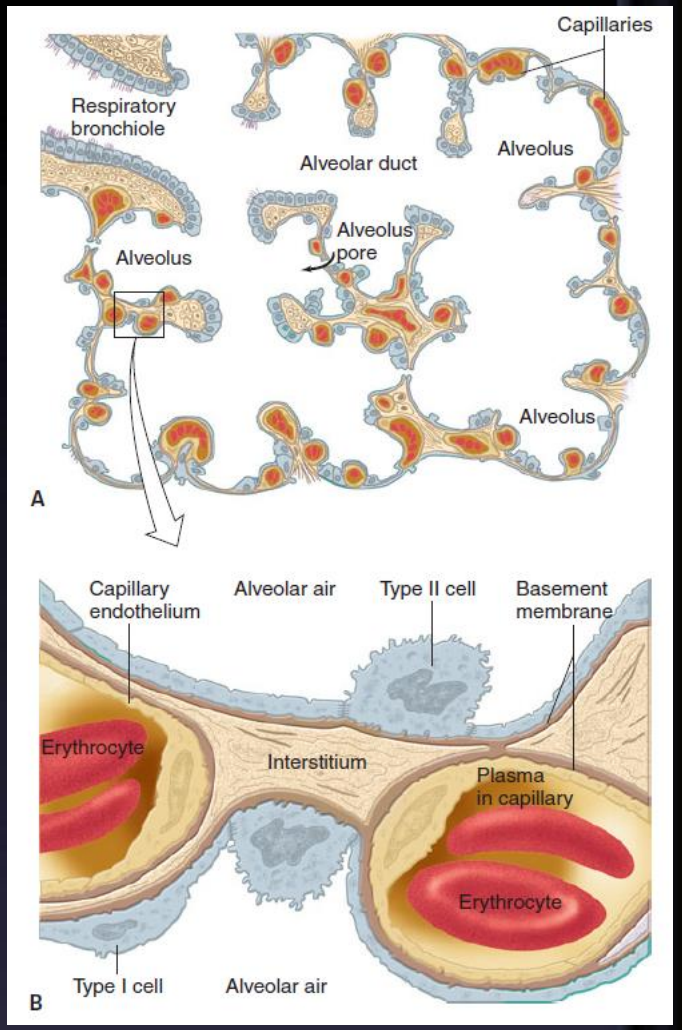
Macrophages line nodal medullary sinuses



subcapsular sinus macrophages (SSMs),
medullary sinus macrophages (MSMs)
medullary cord macrophages (MCMs)

Tissue macrophages in Lungs

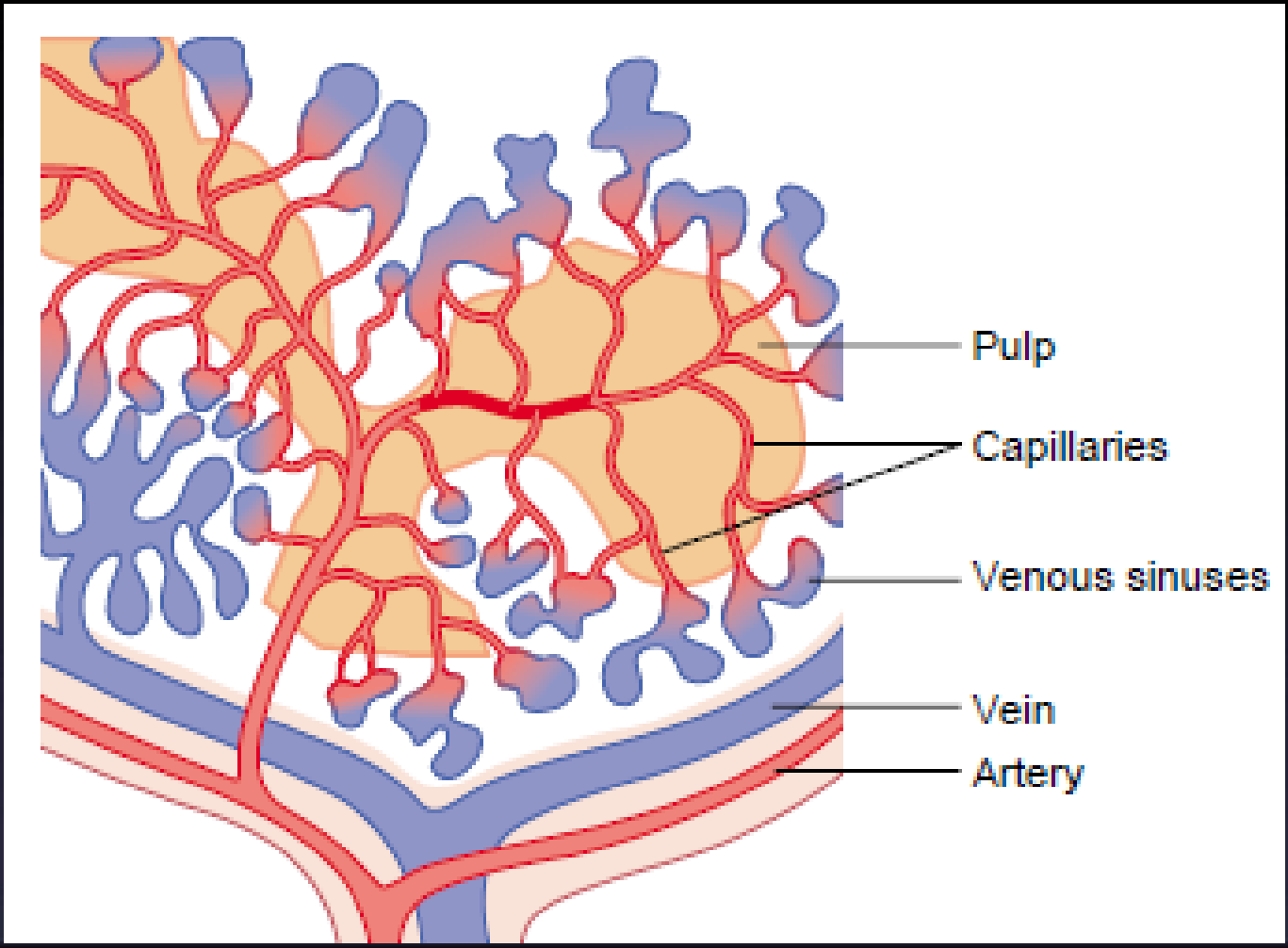




"dust cells" because of their content of intracellular carbon particles

Tissue macrophages in Spleen

The blood squeezes through the trabecular cords meshwork of red pulp.



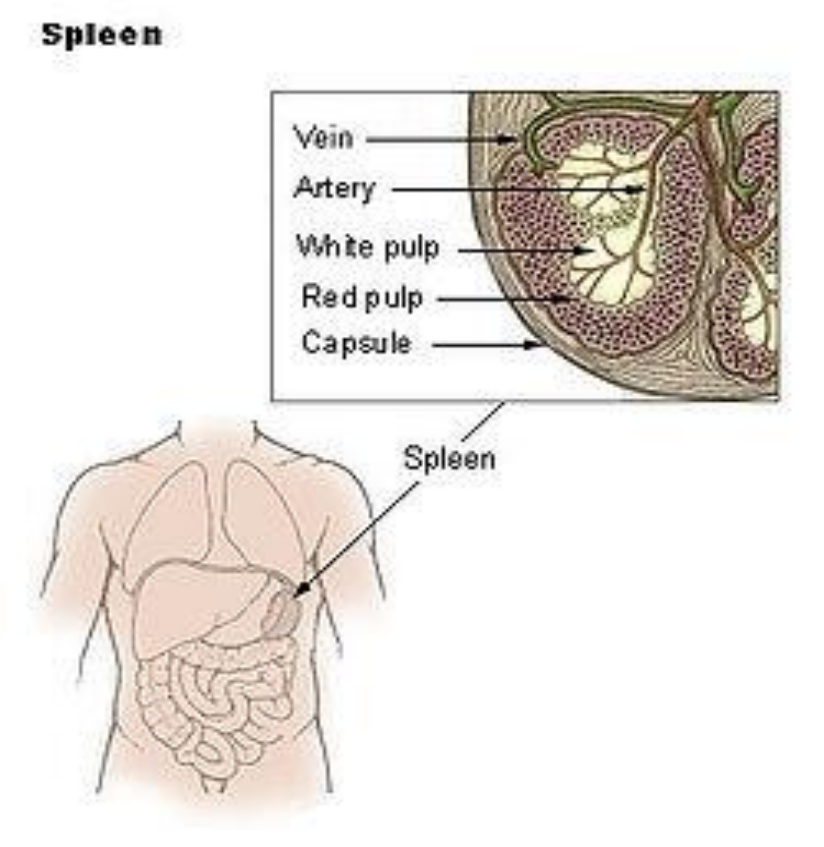
SPLEEN

- Is soft purple gray in color located in the left upper quadrant of the abdomen.
- It is a highly vascular lymphoid organ.
- It plays an important roles in: red blood cells integrity and has immune function.
- It holds a reserve of blood in case of hemorrhagic shock.
- It is one of the centers of activity of the RES and its absence leads to a predisposition toward certain infections.
- Despite its importance, there are no tests specific to splenic function.

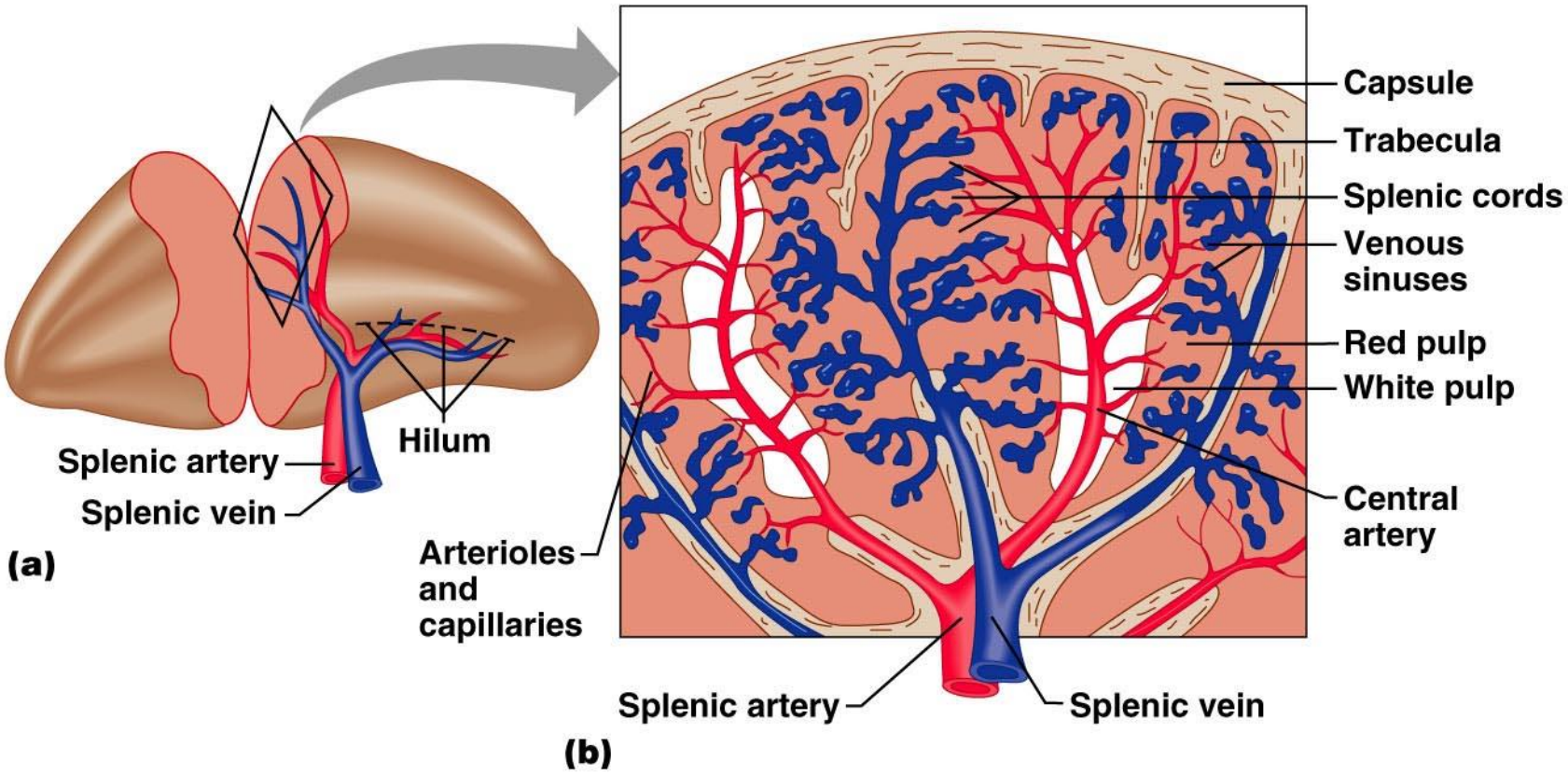
STRUCTURE OF SPLEEN

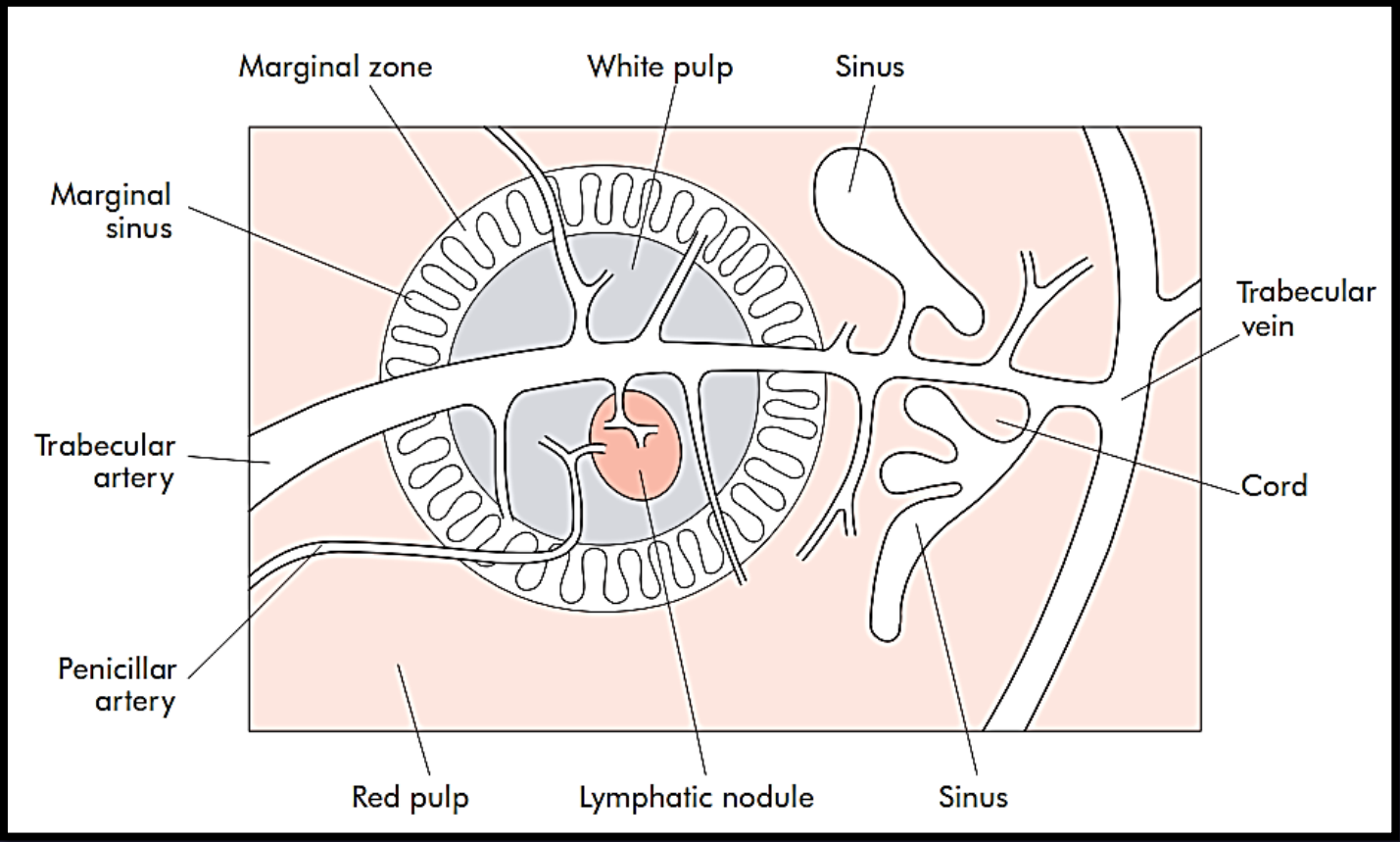
- **White pulp: Thick sleeves of lymphoid tissue, that provides the immune function of the spleen.**

- **Red pulp: surrounds white pulp, composed of Venous sinuses filled with whole blood and Splenic cords of reticular connective tissue rich in macrophages.**



Spleen




Marginal zone
White pulp
Sinus
Marginal sinus
Trabecular vein
Trabecular artery
Cord
Penicillar artery
Red pulp
Lymphatic nodule
Sinus

FUNCTIONS OF SPLEEN

Red Pulp- Red Pulp- filtering function

- **RBC's able to deform through sinusoidal wall and endothelium Culling**
- **Macrophage activation - macrophages filter and destroy foreign material in blood Macrophage activation**

White pulp - immunologic functions

– trapping and processing of antigens

– the major site of antibody synthesis

– key role in removal of encapsulated bacteria (Strep pneumo)

Cytopoiesis:

- From the fourth month of intrauterine life, some degree of hemopoiesis occurs in the fetal spleen.
- Stimulation of the white pulp may occur following antigenic challenge, resulting in the proliferation of T and B cells and macrophages.
- This may also occur in myeloproliferative disorders, thalassaemias and chronic haemolytic anaemias.

FUNCTIONS OF SPLEEN

- **Formation of blood cells**

–play in important role in the hemopoieticfunction in embryo

–during the hepatic stage, spleen produces the blood cells along with liver

- **Destruction of blood cells**

–the older RBCs, lymphocytes & thrombocytes are destroyed in spleen and recycles iron. Increased in hereditary spherocytosis

- **Reservoir function**

–A large number of RBCs and platelets are stored in spleen and recycles iron

–RBCs are released form spleen into circulation during the emergency conditions like hypoxia & hemorrhage

- **Role in defense of body**

–spleen filters the blood by removing the microorganism

–macrophages in splenic pulp phagocytose microorganisms & foreign bodies

–spleen contains about 25% of T lymphocytes & 15% of B lymphocytes & form the site of antibody production mainly IgM

FUNCTIONS OF SPLEEN

•Role in defense of body

—Immune function:spleen filters the blood by removing the microorganism. Macrophages in splenic pulp phagocytose microorganisms & foreign bodies

- **spleen contains about 25% of T lymphocytes & 15% of B lymphocytes**
- **The spleen processes foreign antigens and is the major site of specific immunoglobulin M (IgM) production.**
- **The non-specific opsonins, properdin and tuftsin, are synthesized.**
- **These antibodies are of B- and T-cell origin and bind to the specific receptors on the surface of macrophages and leukocytes, stimulating their phagocytic, bactericidal and tumoricidal activity.**

Immune Functions of Spleen

1. Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to blood-borne antigens.
2. Destruction and processing of antigens.
3. Reservoir of lymphocytes in white pulp.
4. Site for Phagocytosis of bacteria and worn-out blood cells (Slow blood flow in the red pulp cords allows foreign particles to be phagocytosed)

Immune Functions of Spleen cont.

5. Site of B cell maturation into plasma cells, which synthesize antibodies in its white pulp and initiates humoral response.
6. Removes antibody-coated bacteria along with antibody-coated blood cells.
7. It contains (in its blood reserve) half of the body monocytes within the red pulp, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages that promoting tissue healing.

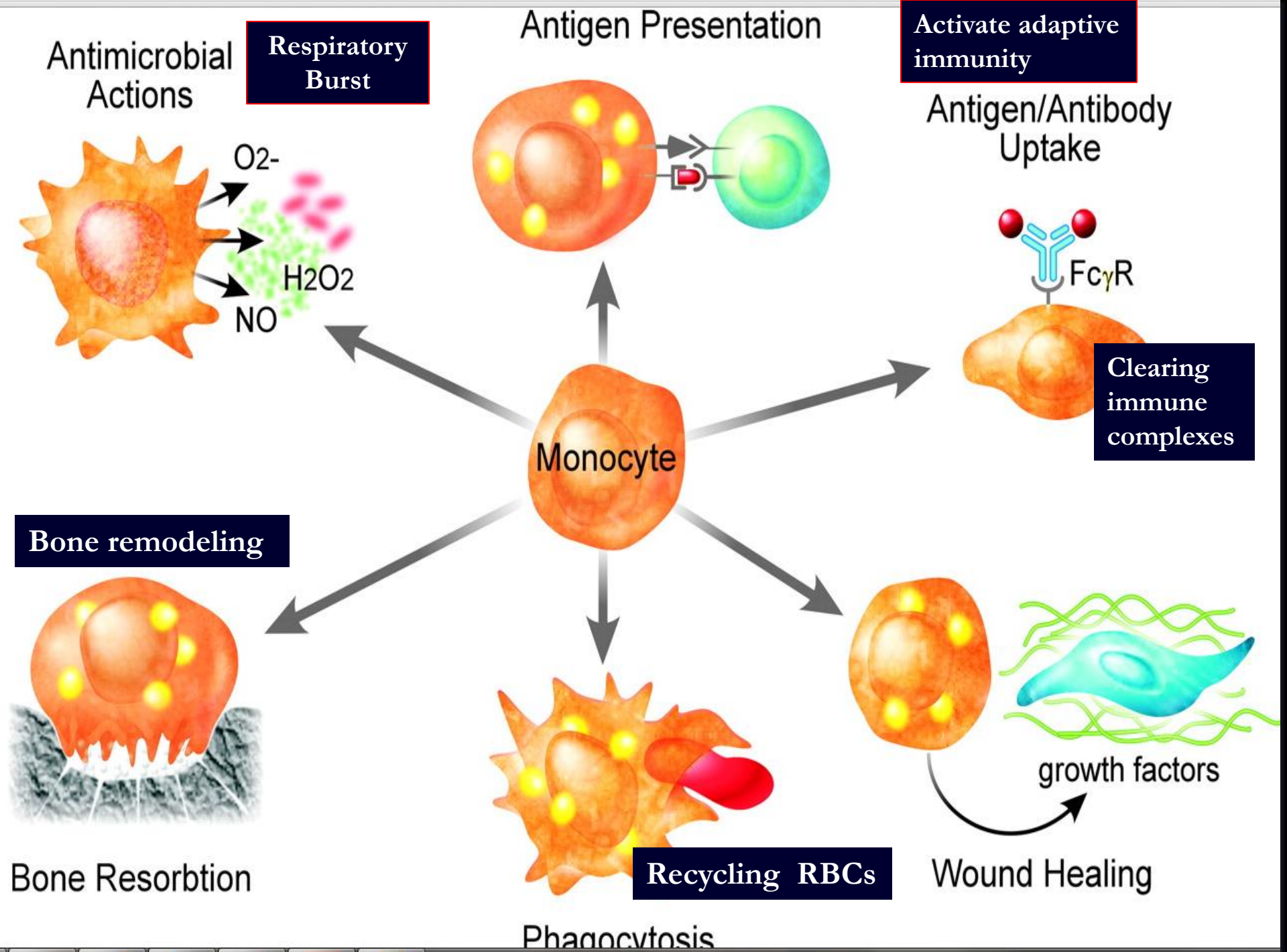
Spleenectomy

Indications:

1. **Hypersplenism**: enlargement of the spleen (splenomegaly) with defects in the blood cells count.
2. Primary spleen **cancers.**
3. **Haemolytic anaemias**: Sickle cell anaemia, Thalassemia, hereditary spherocytosis (HS) and elliptocytosis
4. Idiopathic thrombocytopenic purpura **(ITP).**
5. Trauma.
6. Hodgkin's disease.
7. Autoimmune hemolytic disorders.

Risks & complications of Spleenectomy

- Overwhelming bacterial infection or post splenectomy sepsis.
- Patient is prone to malaria.
- Inflammation of the pancreas and collapse of the lungs.
- Excessive post-operative bleeding (surgical).
- Post-operative thrombocytosis and thrombosis.


Antimicrobial Actions
Respiratory Burst
O2-
H2O2
NO
Antigen Presentation
Activate adaptive immunity
Antigen/Antibody Uptake
FcγR
Clearing immune complexes
Monocyte
Bone remodeling
Bone Resorbtion
Recycling RBCs
Phagocytosis
growth factors
Wound Healing

	Macrophage/Monocyte	Neutrophil
Morphology	Large mononuclear cells with granular cytoplasm	Smaller cells with multi-lobed nucleus and neutral cytoplasmic granules
Location	Often resident in tissues (remove routine cell debris)	Blood – requires recruitment to site of infection
Killing ability	Require activation by bacterial molecules ± IFNγ	Activated during recruitment, then able to kill internalised bacteria automatically
After killing	Migrate to local lymph nodes	Die at site by apoptosis (then taken up by macrophages)
Antigen presentation	Can present antigen (Class II up-regulated by IFNγ)	Cannot present antigen (don't normally express Class II)


THANKS