RETICULOENDOTHELIAL SYSTEM AND FUNCTIONS OF THE SPLEEN

Nonspecific Host Defenses

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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

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: Reticulo refers to the propensity of these large phagocytic cells in various organs to form a network or a reticulum by cytoplasmic extensions; endothelial refers to their proximity to the vascular endothelium
- Therefore, the term reticuloendothelial system is not used nowadays since they are neither reticular nor of endothelial origin.

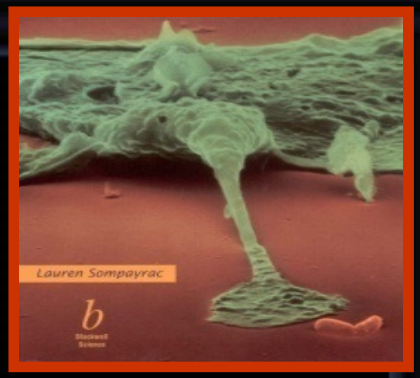
Monocyte/Macrophage System

TISSUE MACROPHAGE SYSTEM COMPONANTS

- Monocytes in **Blood** circulate for about 72 hours after leaving the Bone Marrow
- Mobile & Fixed Macrophages in **Tissue** (Life Span 3 months)
- **Specialized endothelial cells** in bone marrow, spleen and lymph nodes

Some may end up as the **multinucleated giant cells** seen in chronic inflammatory diseases such as tuberculosis.

MONOCYTES



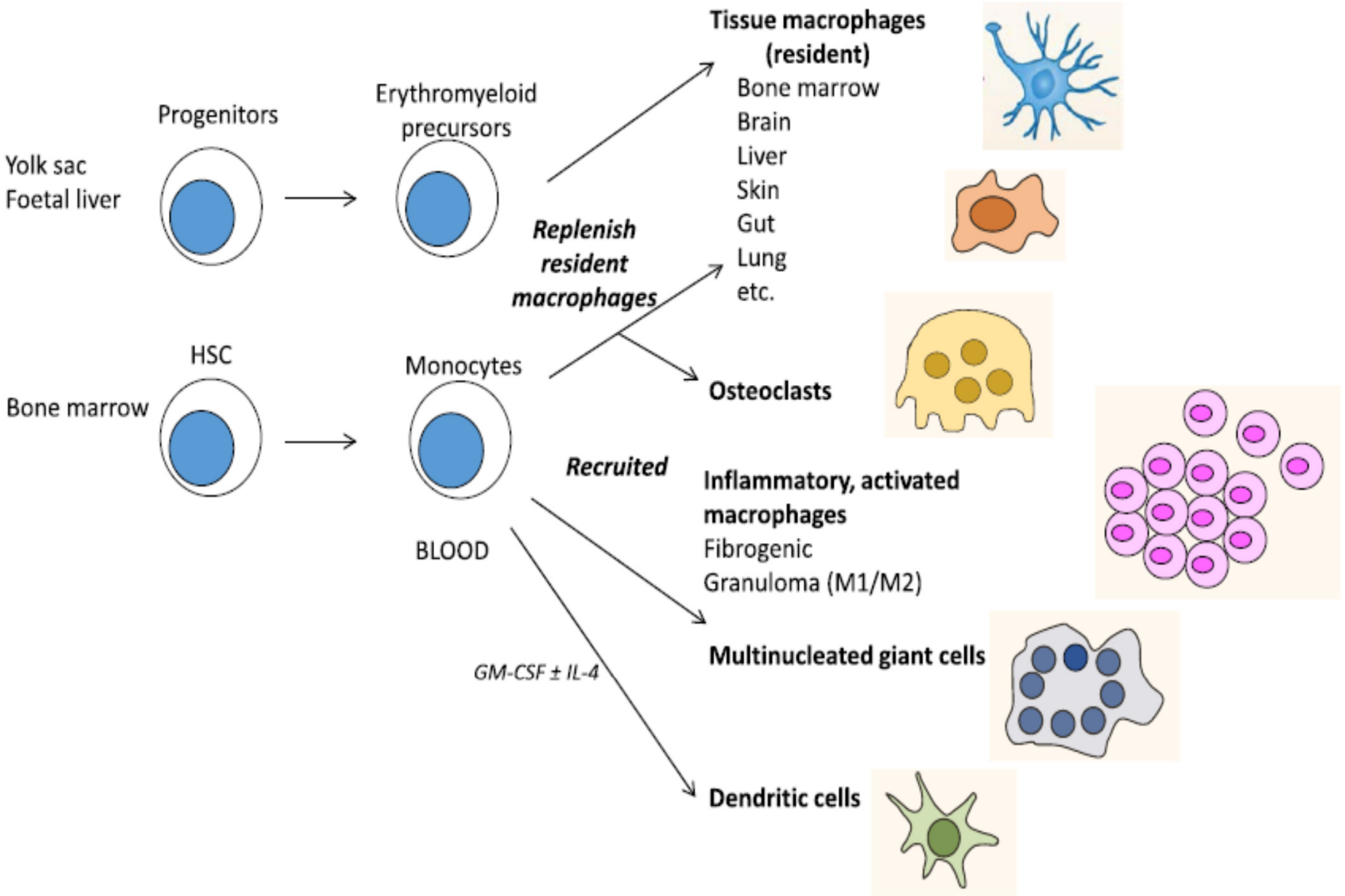
- **Size:** 15-20 µm (active cells 60-80 µm)
- **Small Granules (azurophilic) & Vacoules**
- More Efficient **Phagocytosis** than Neutrophils

(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**

Azurophilic granules of monocuytes are primary lysosomes or storage granules. Lysosomes contain Acid hydrolases, MPO, HOCl, Defensins

Origins and distribution of Tissue Macrophages



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

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.**

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

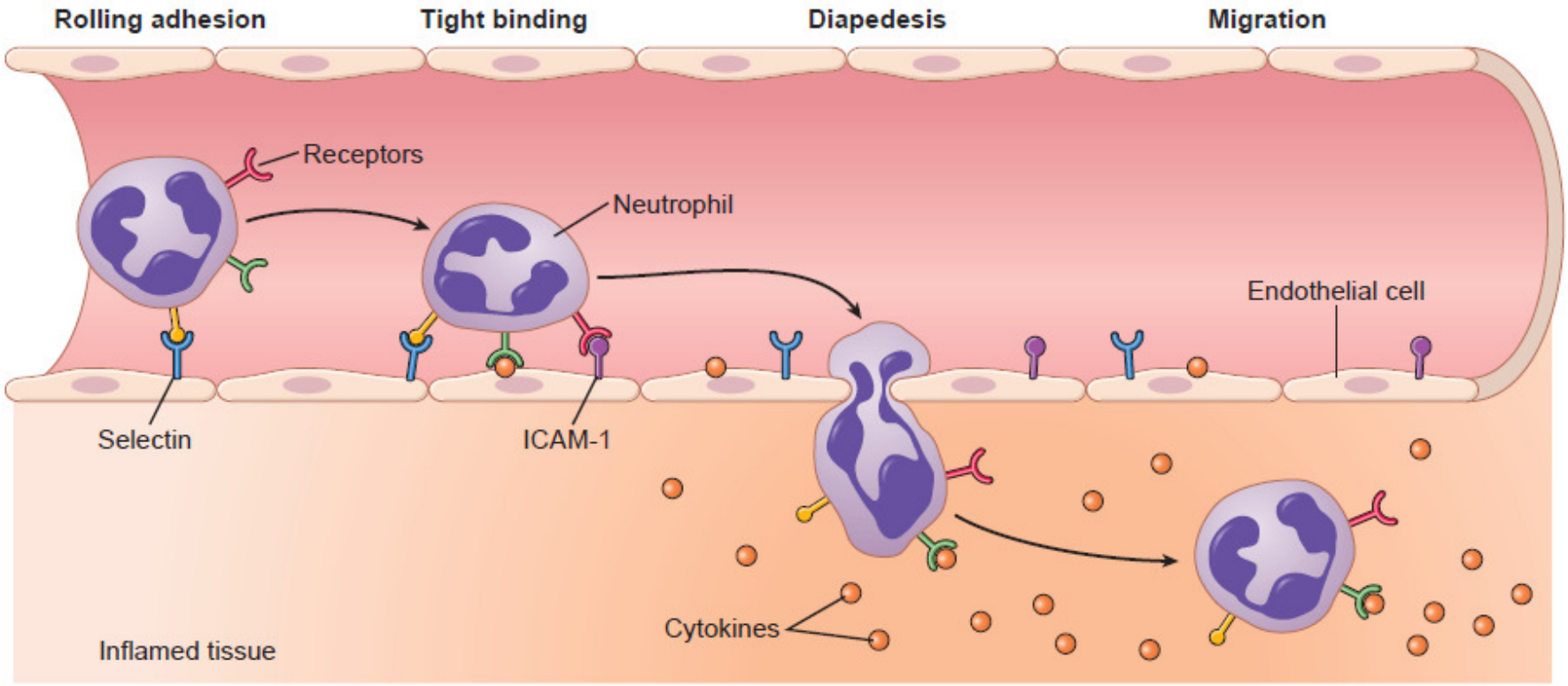
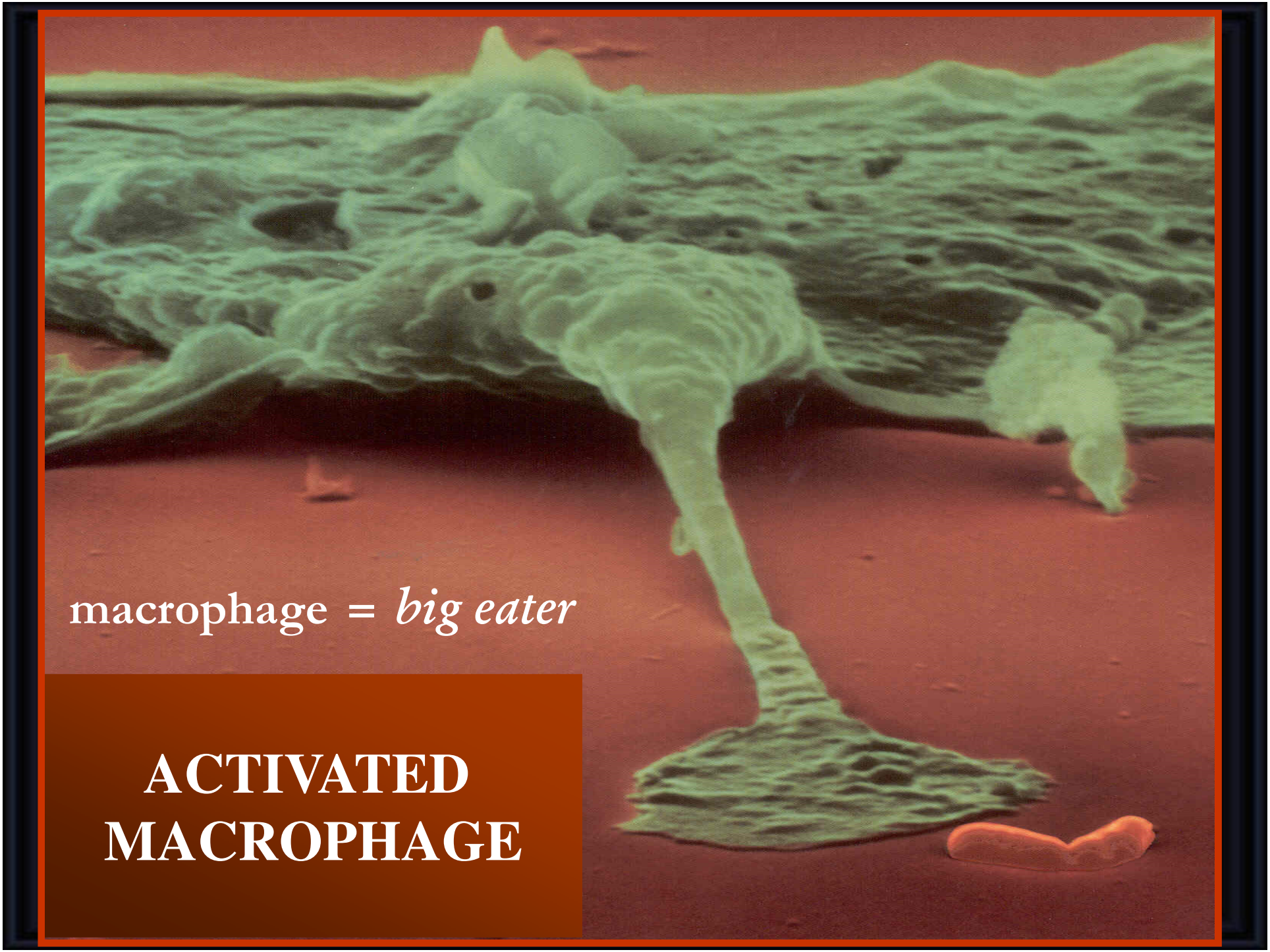
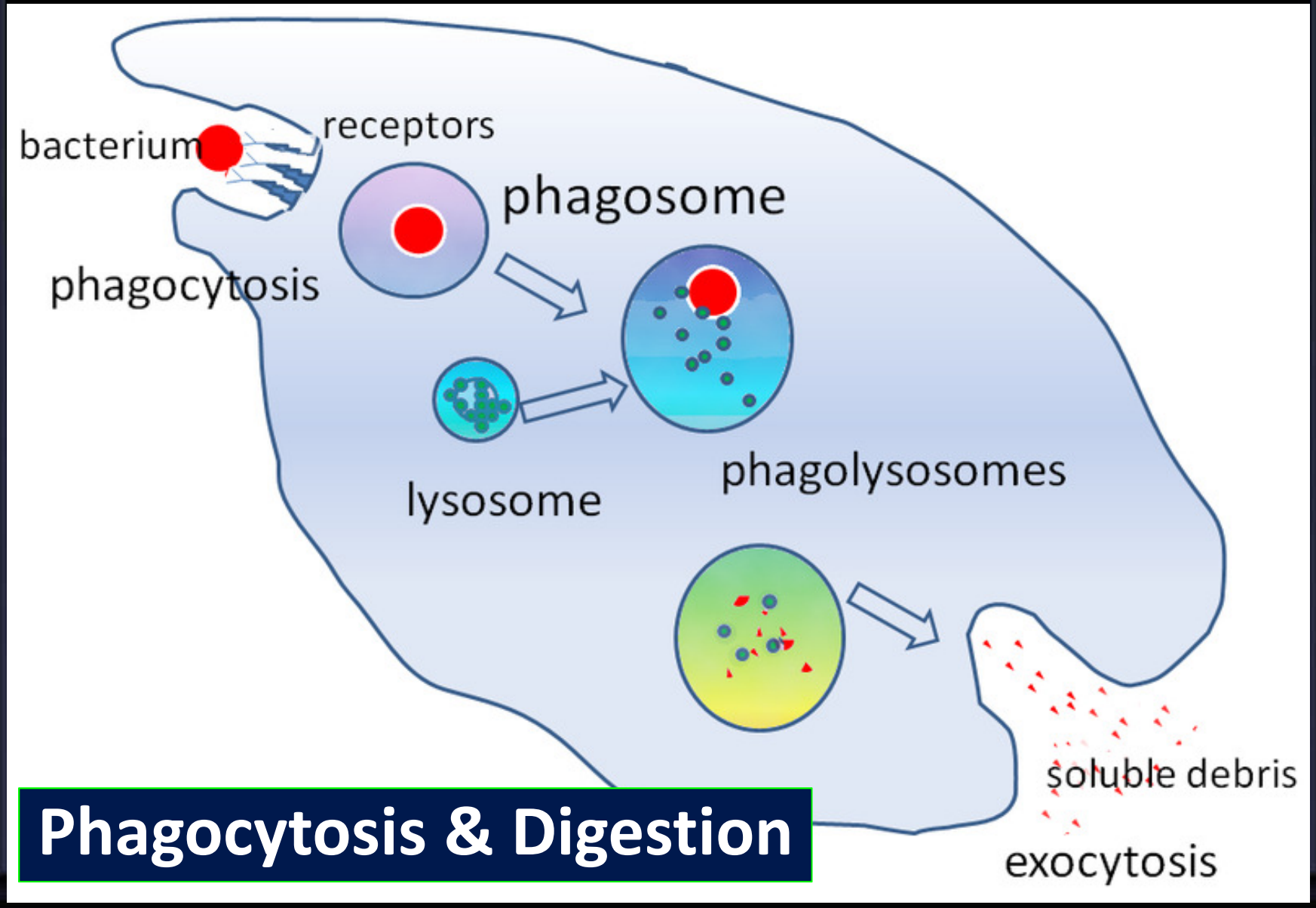


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 *(ICAM-1)* in the surface of endothelial cells. These adhesion molecules bind to complementary 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.

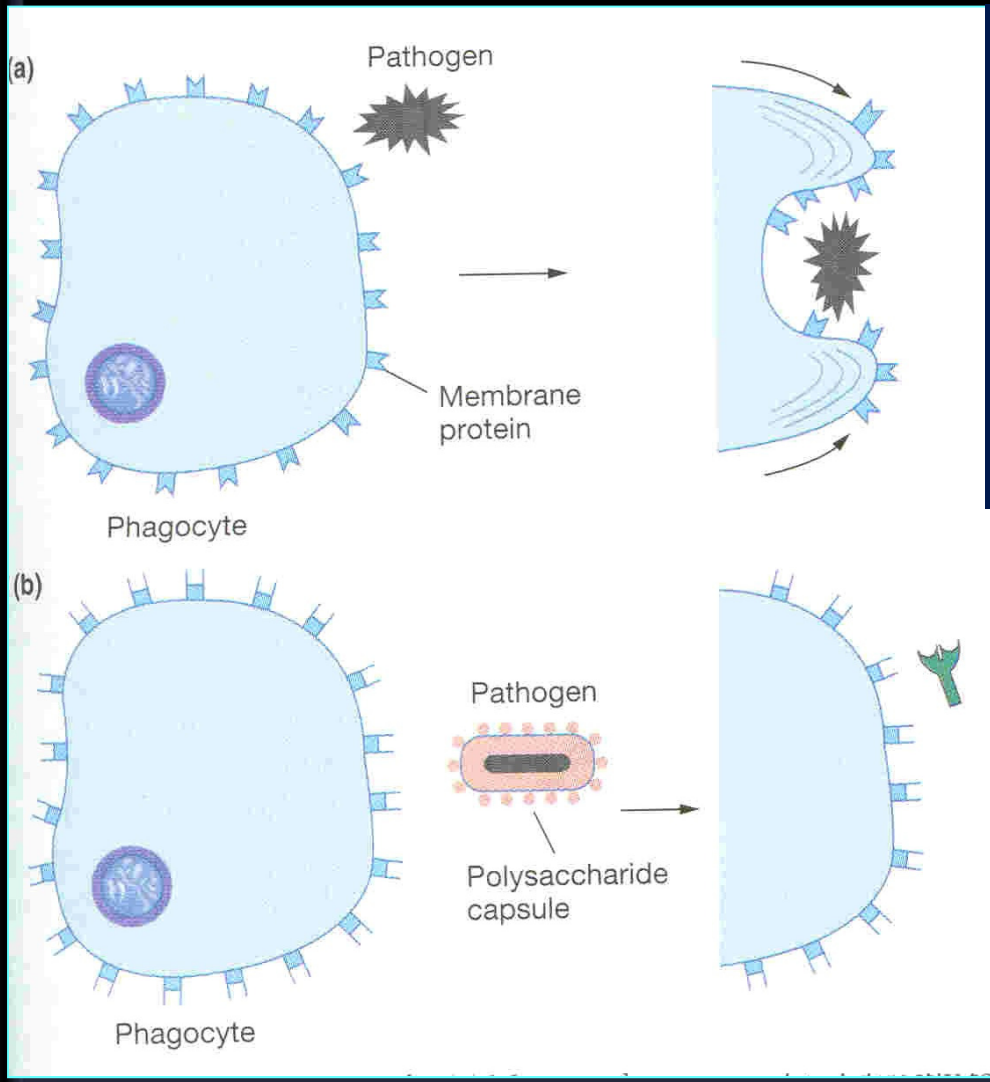

macrophage = *big eater*
ACTIVATED MACROPHAGE

Direct funtion of RES



Phagocytosis & Digestion

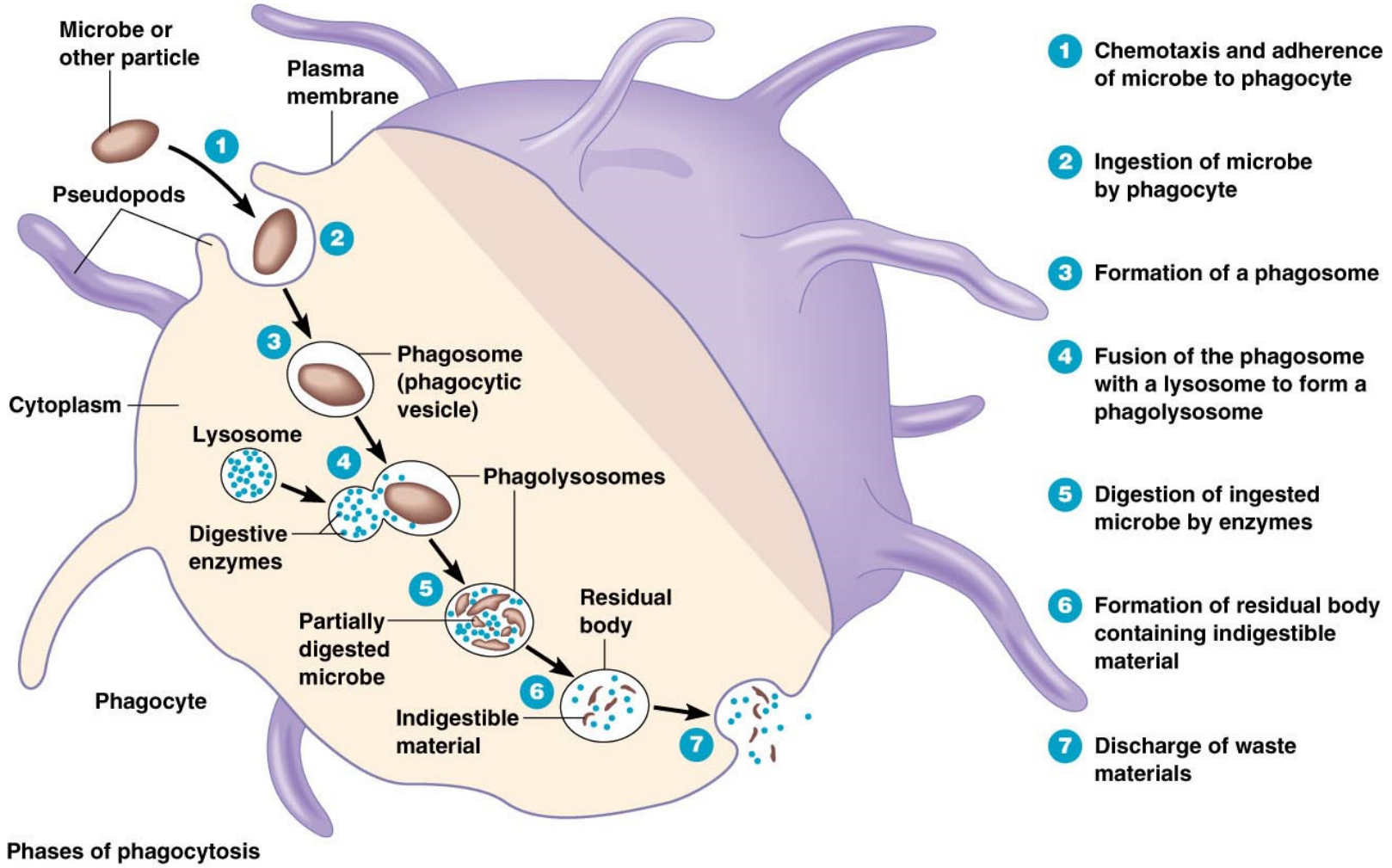
Opsonization & Phagocytosis



Phagocytosis is increased by certain substance a process called OPSONIZATION

Complement 3b or antibodies like IgG make them ready for killing a process known as opsonization.

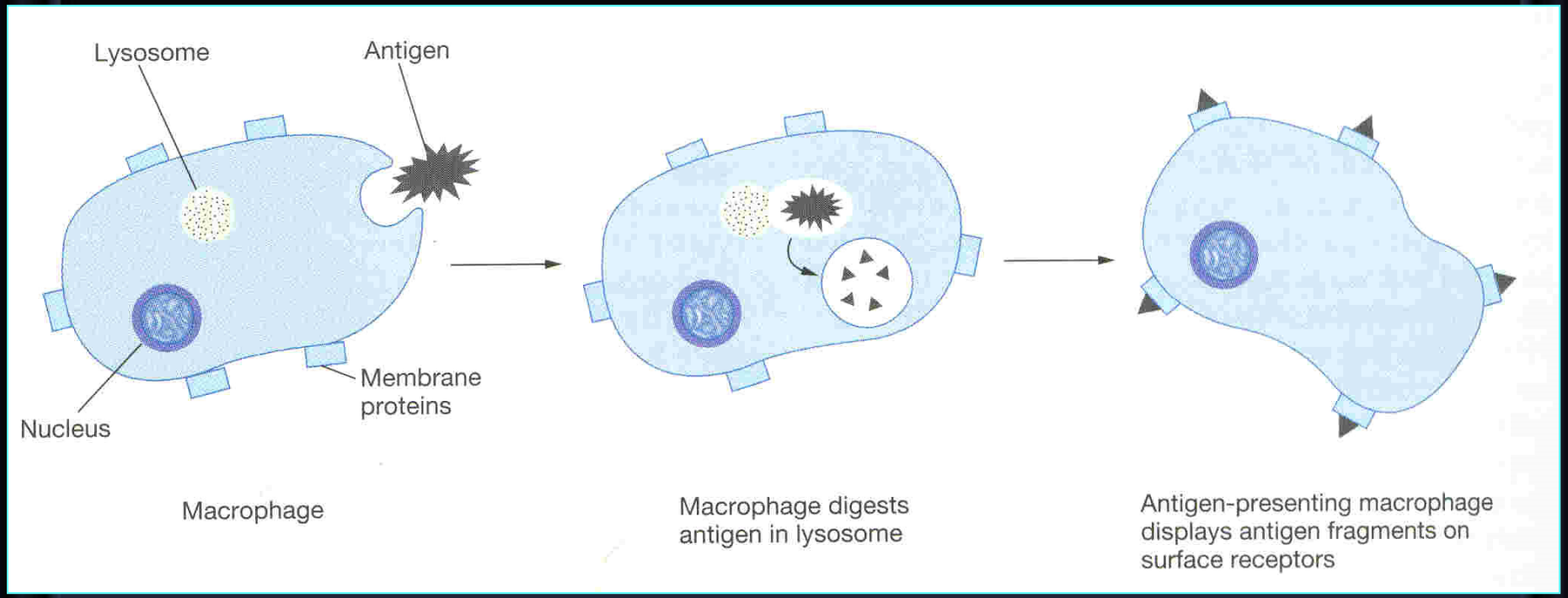
Macrophage: a wandering, walking cell. "Big eater" capable of phagocytosis. Is a modified monocyte in tissues



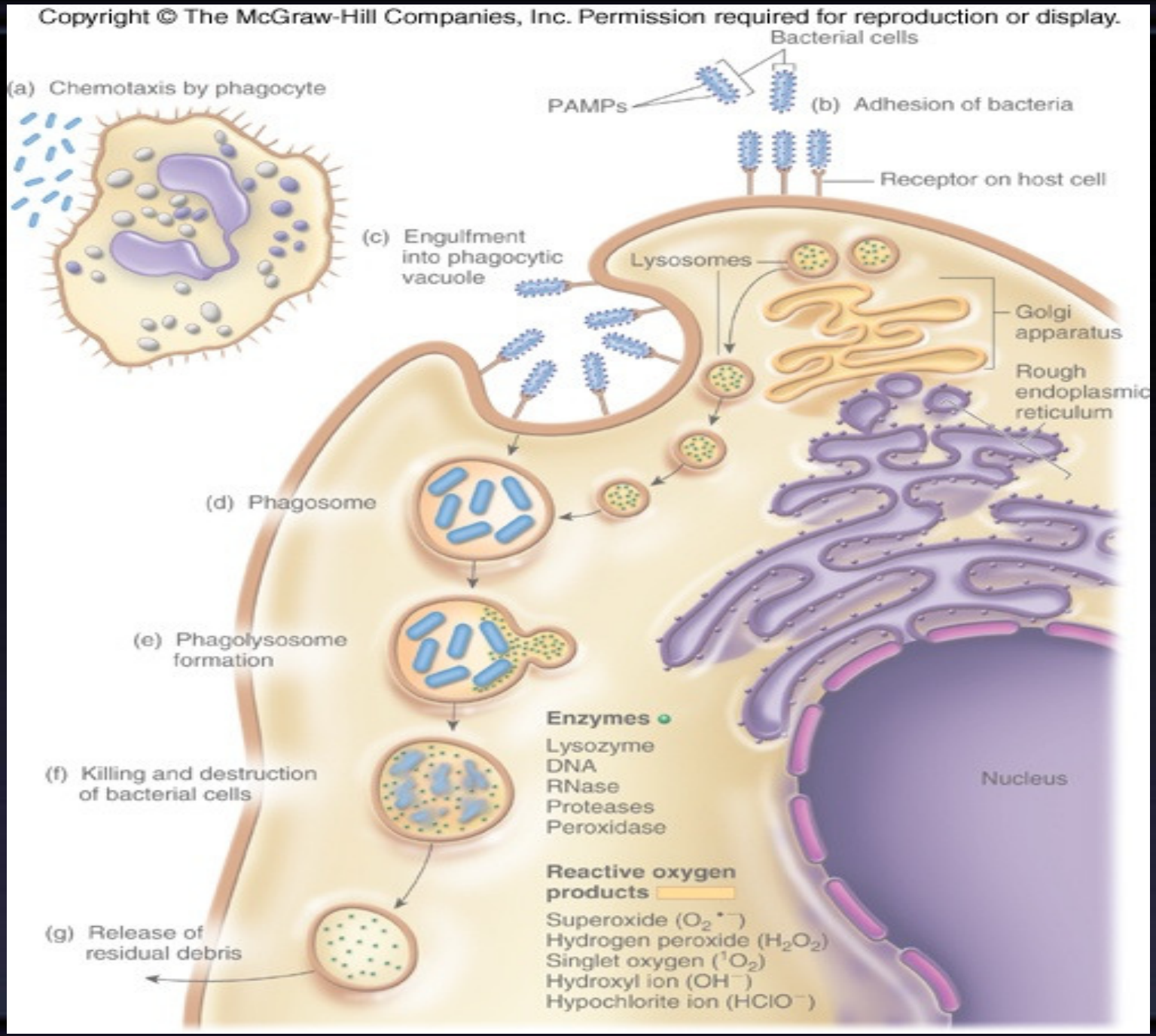
Indirect Immune function Of RES

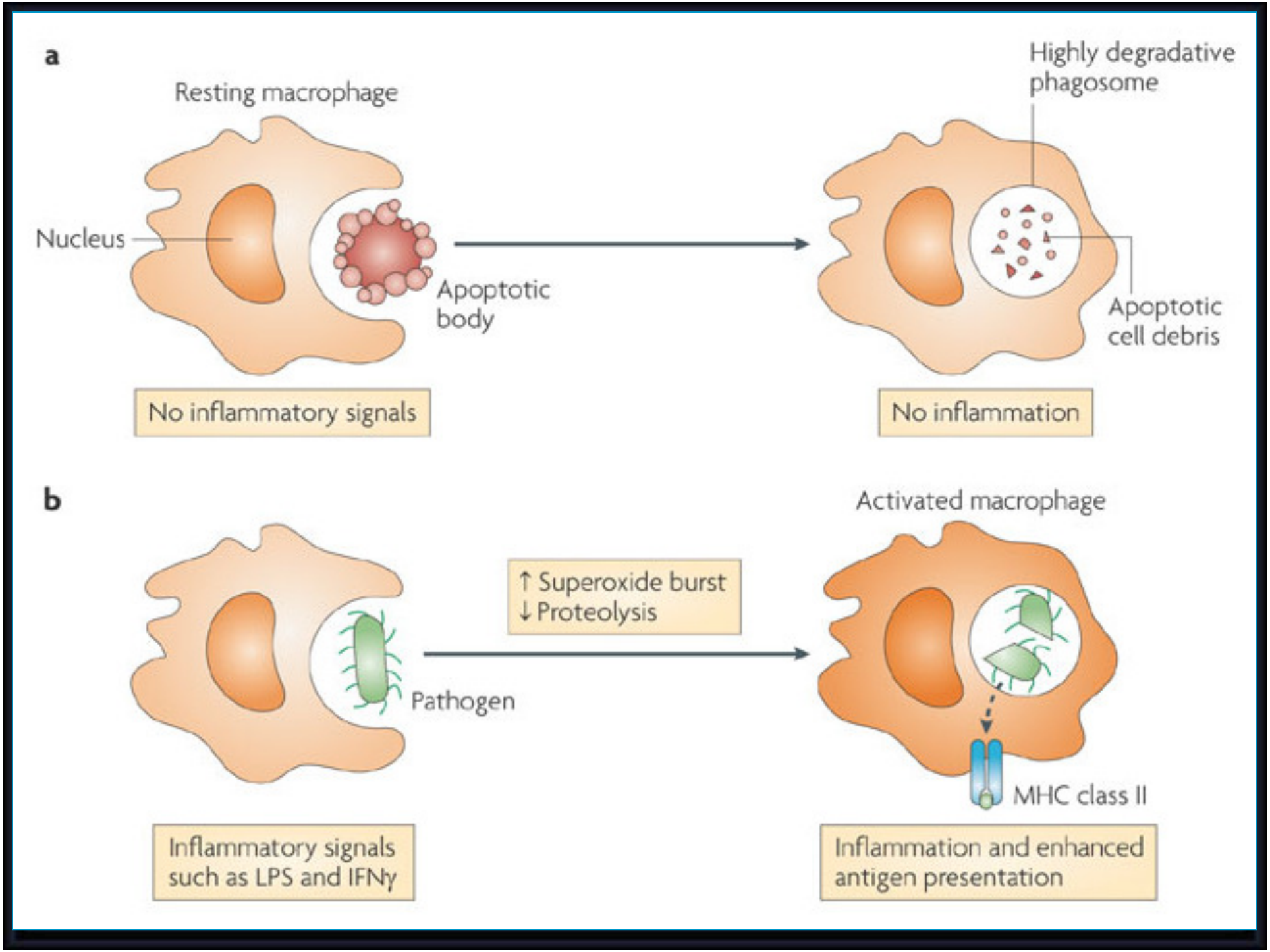
Antigen Presenting Cells

Displaying it attached to an MHC class II molecule



Classical APCs include macrophages, dendritic cells, Langerhans cells and B cells




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

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 (Sinus histiocytes)
6. Bone marrow
7. Microglia in Brain
8. Kidneys (Mesangial Cells)
9. Bone (Osteoclasts)

Hofbauer cells in Placenta

Epithelioid cells in Granulomas

Tissue macrophages

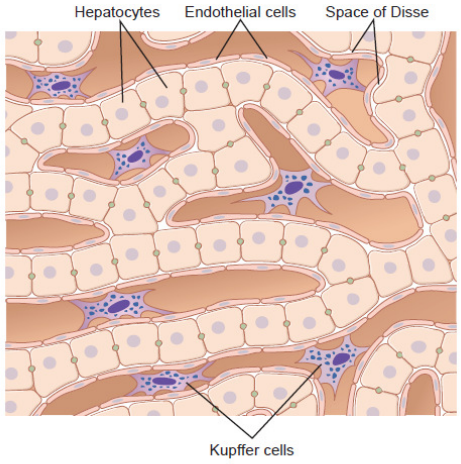


Figure 34-4. Kupffer cells lining the liver sinusoids, showing phagocytosis of India ink particles into the cytoplasm of the Kupffer cells.

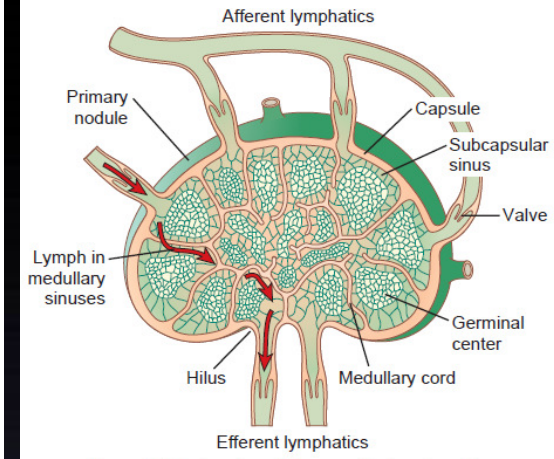
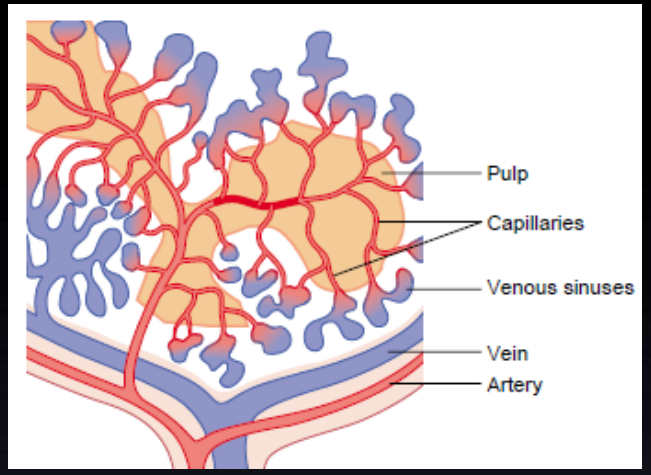
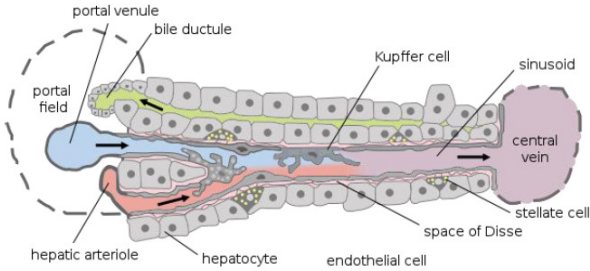
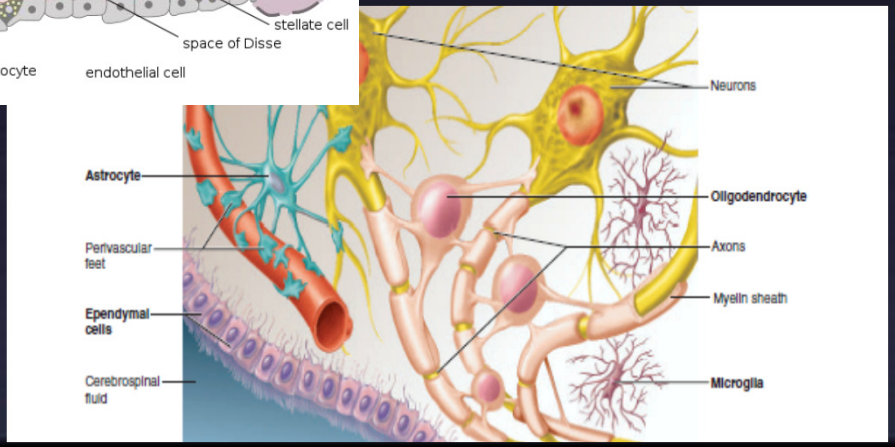
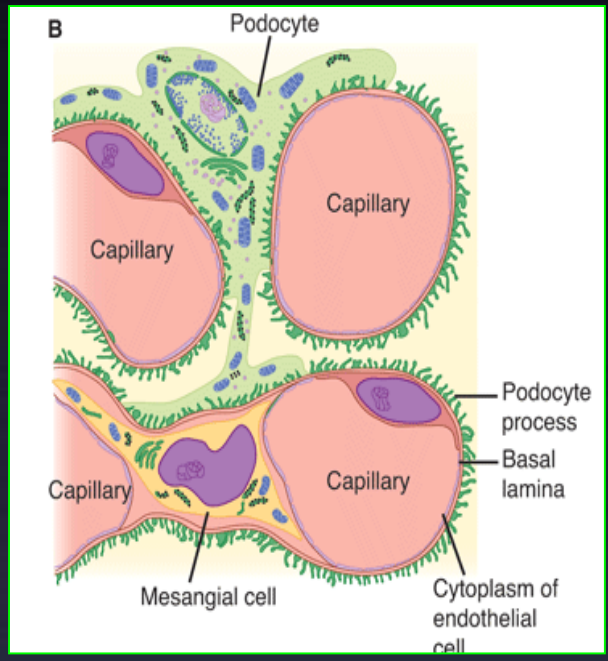


Figure 34-3. Functional diagram of a lymph node.

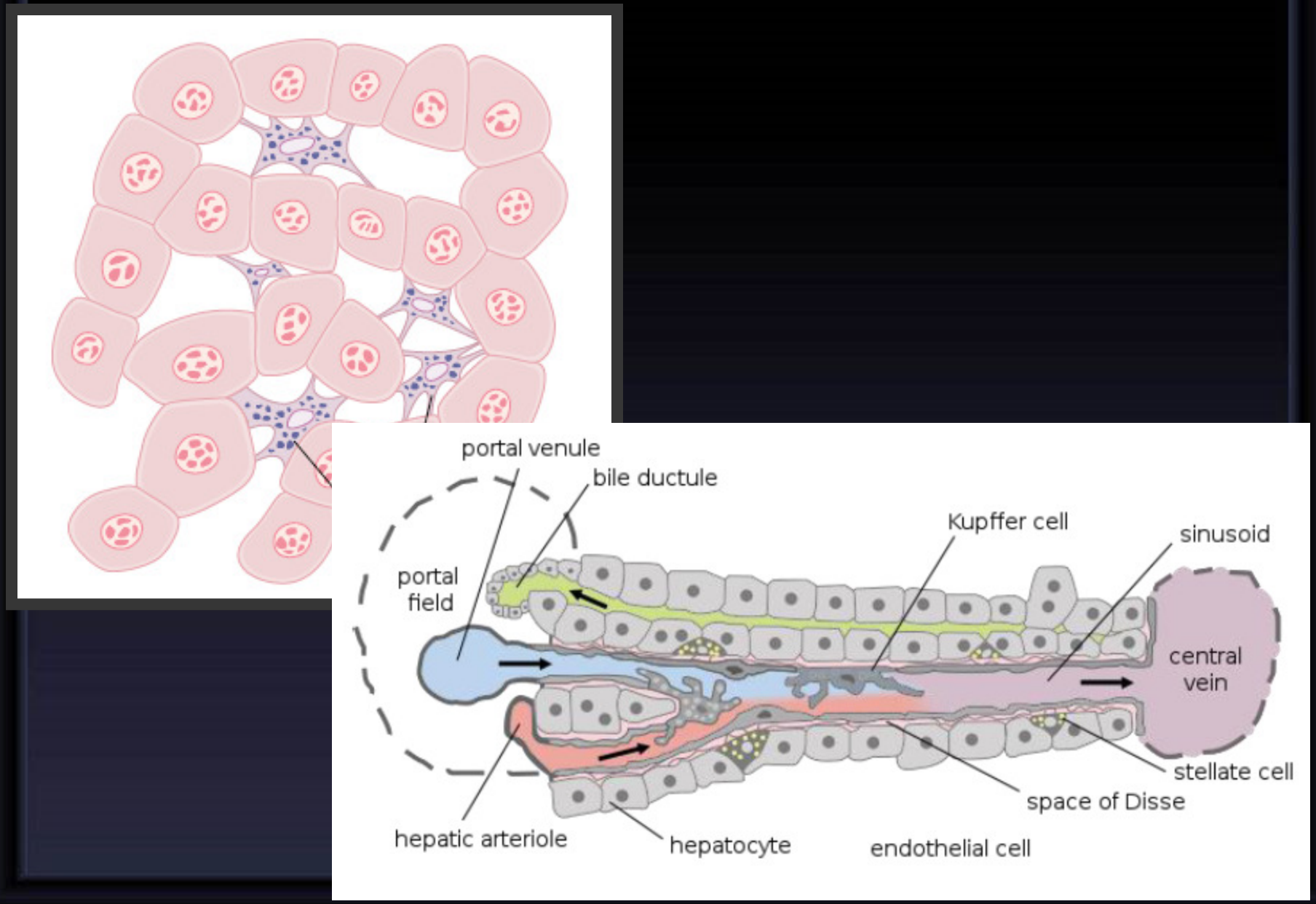






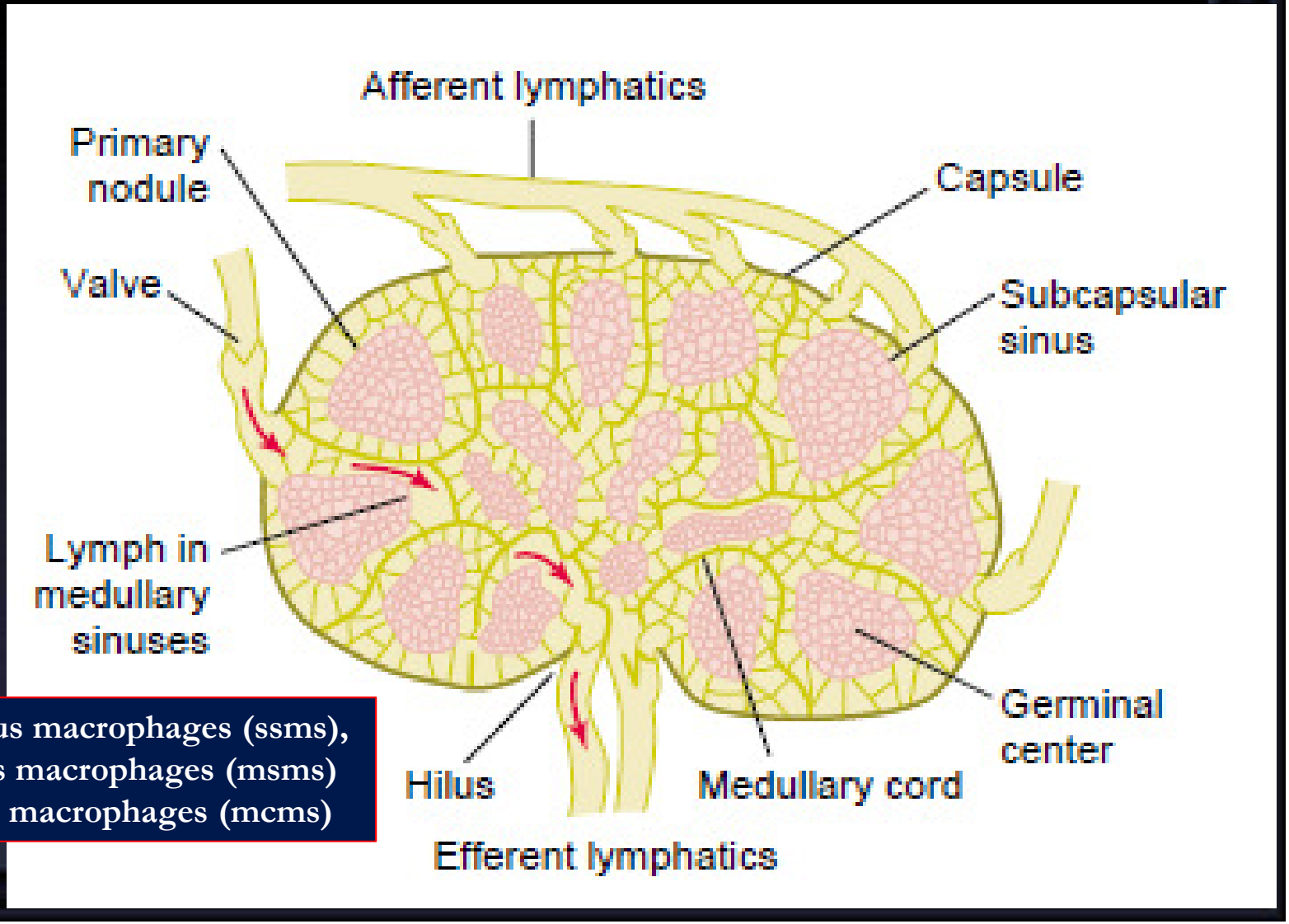


Tissue macrophages in Liver sinuses



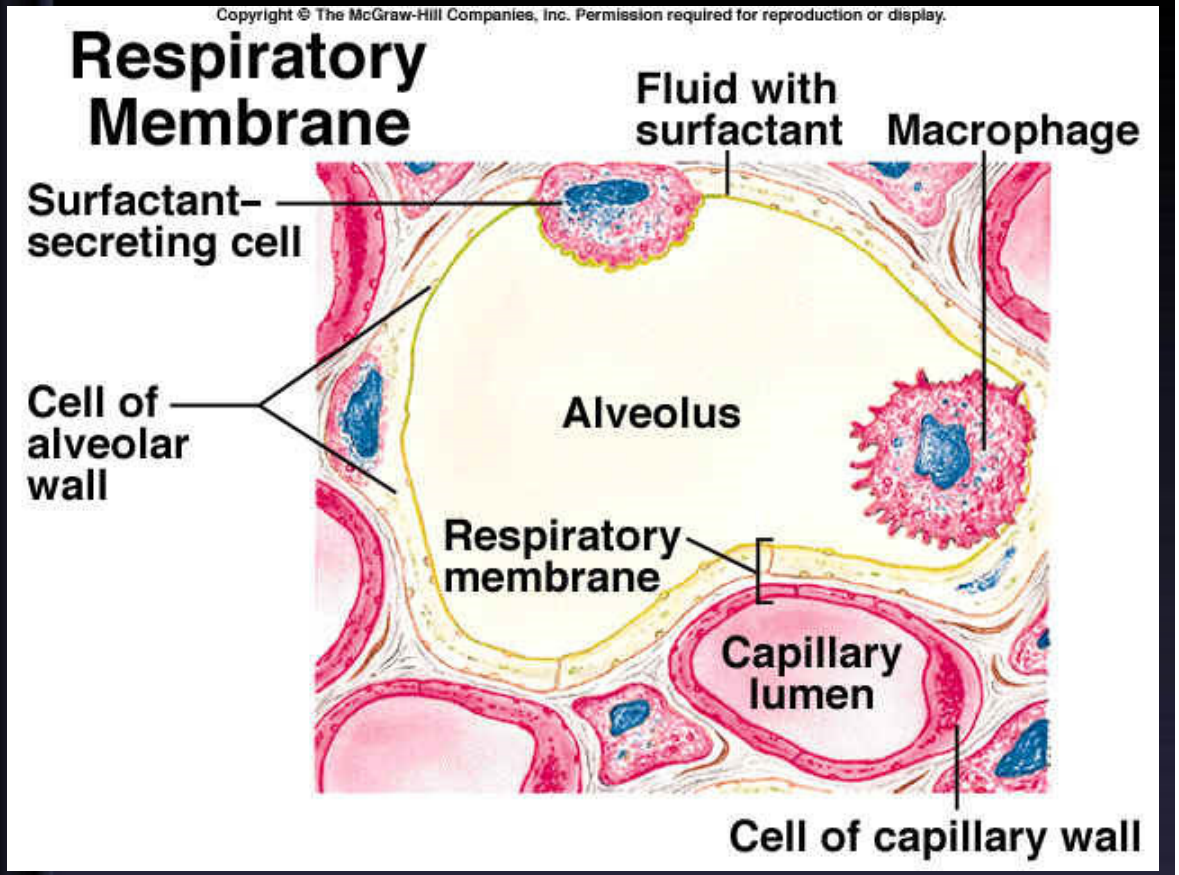
Tissue macrophages in Lymph Nodes

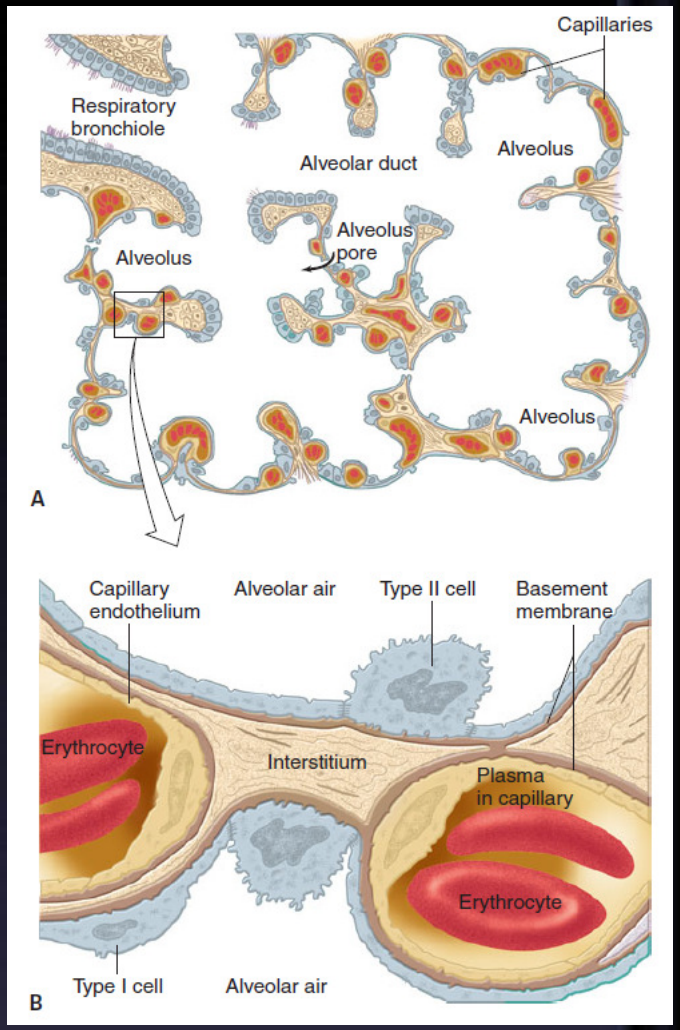
Macrophages line nodal medullary sinuses



Subcapsular sinus macrophages (ssms),
Medullary sinus macrophages (msms)
Medullary cord macrophages (mcms)

Tissue macrophages in Lungs

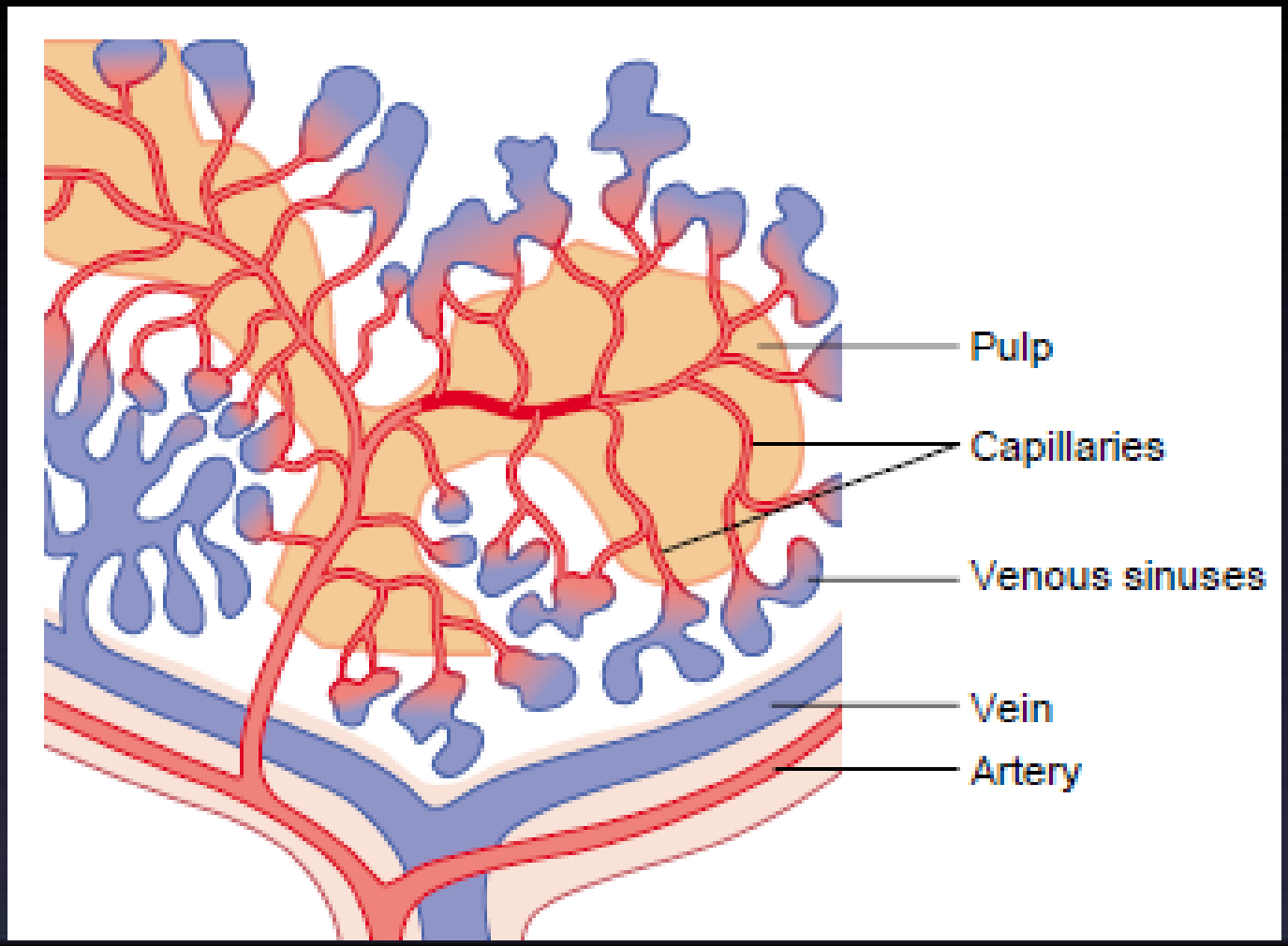




"dust cells" because of their content of intracellular carbon particles

Tissue macrophages in Spleen

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



Lymphoid Organs

Primary lymphatic organs

Primary lymphatic organs are where lymphocytes are formed and mature. They provide an environment for stem cells to divide and mature into B- and T- cells:

These include: red bone marrow and the thymus gland.

Both T-cell and B-cells are 'born' in the bone marrow.
However, whereas B cells also mature in the bone marrow, T-cells have to migrate to the thymus, which is where they mature in the thymus.

Secondary lymphatic organs

Secondary lymphoid tissues are arranged as a series of filters monitoring the contents of the extracellular fluids, i.e. lymph, tissue fluid and blood.

Secondary lymphoid tissues are also where lymphocytes are activated.

These include: lymph nodes, tonsils, spleen, Peyer's patches and mucosa associated lymphoid tissue (MALT).

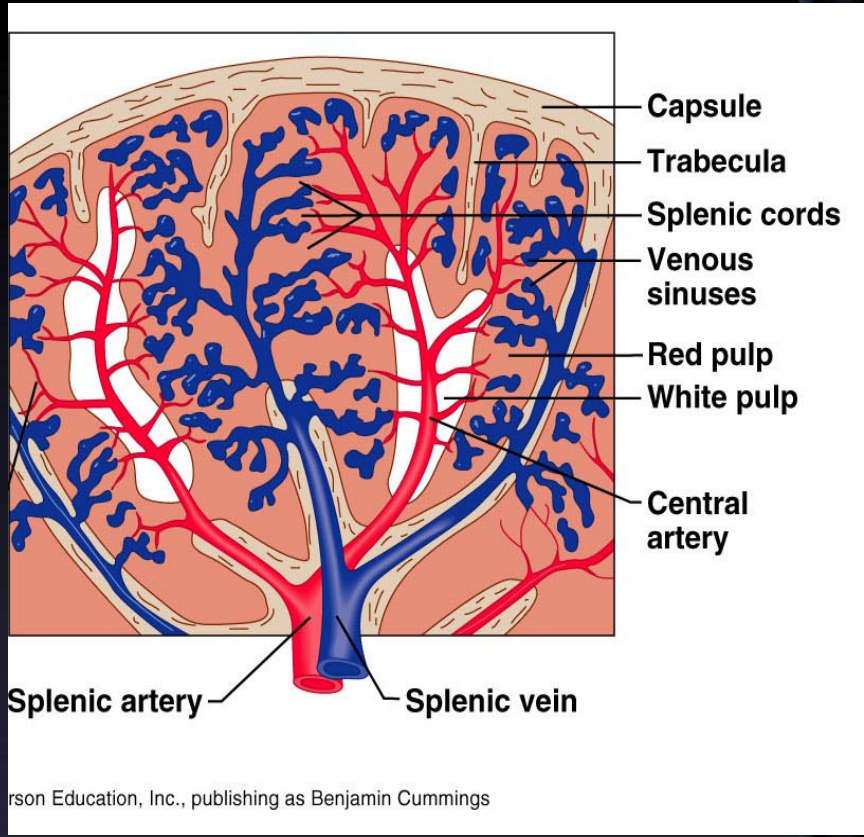
SPLEEN

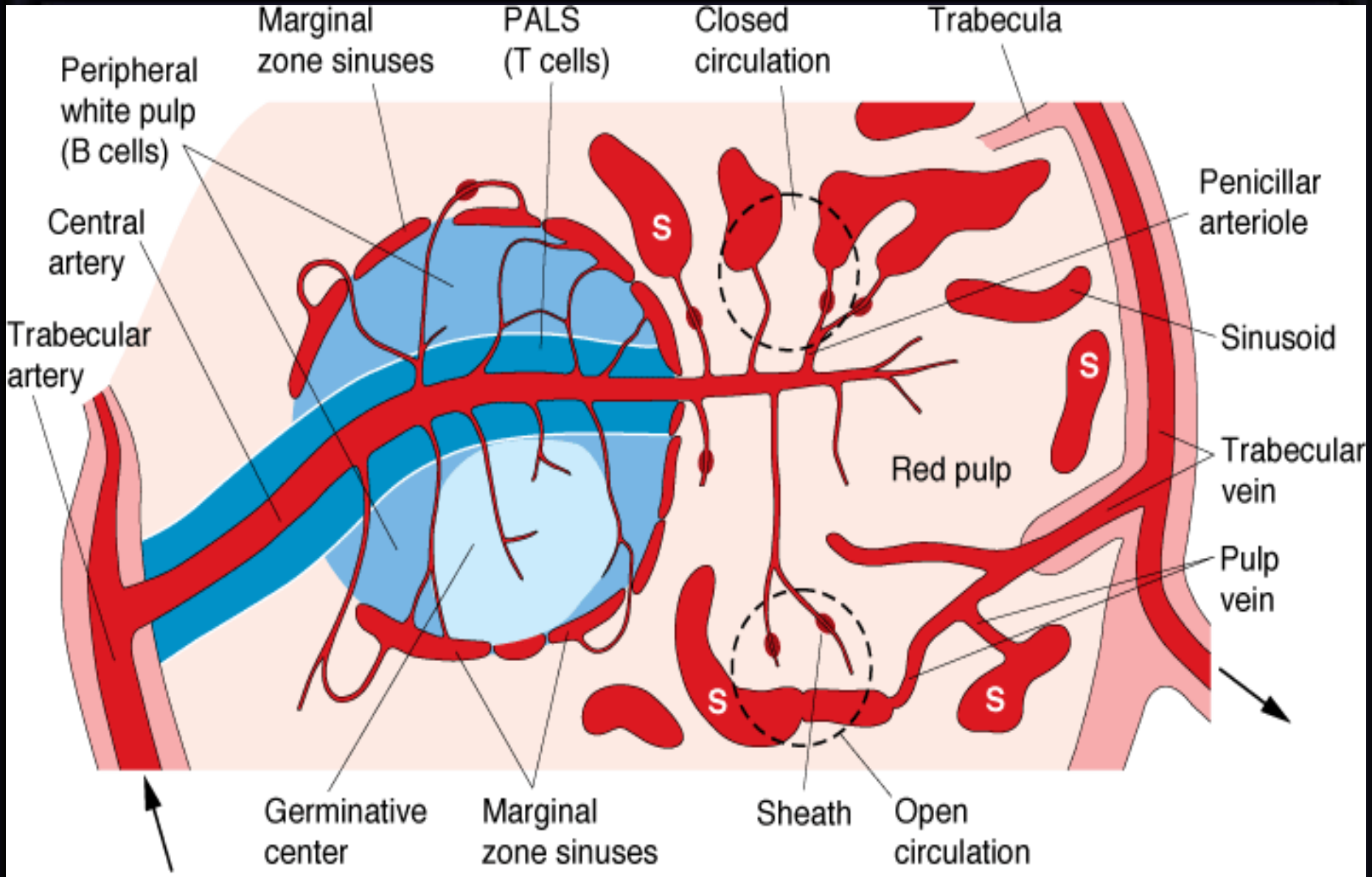
- Is soft purple gray in color located in the left upper quadrant of the abdomen.
- It is a highly vascular lymphoid organ.
- It plays an important roles in: red blood cells integrity and has immune function.
- It holds a reserve of blood in case of hemorrhagic shock.
- It is one of the centers of activity 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

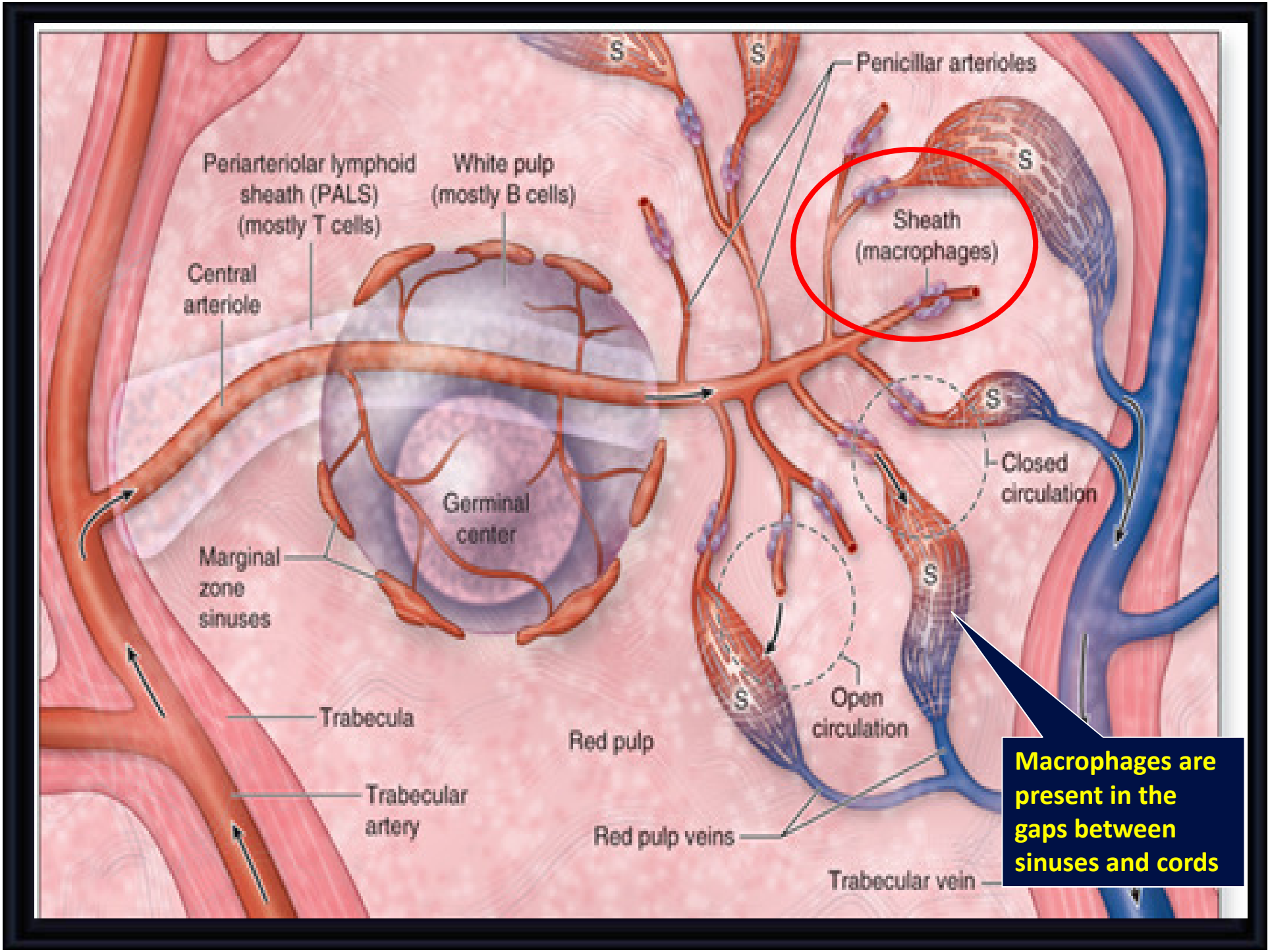
White pulp: Thick sleeves of lymphoid tissue, that provides the immune function of the spleen.

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





Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com


S
S
Penicillar arterioles
Periarteriolar lymphoid sheath (PALS) (mostly T cells)
White pulp (mostly B cells)
Central arteriole
Sheath (macrophages)
S
S
Closed circulation
Germinal center
Marginal zone sinuses
S
S
Open circulation
Trabecula
Red pulp
Trabecular artery
Red pulp veins
Trabecular vein
Macrophages are present in the gaps between sinuses and cords

FUNCTIONS OF SPLEEN

Red Pulp- Red Pulp- **Hematological functions (filtering function)**

- RBC's able to deform through sinusoidal wall and endothelium Culling (Increased in hereditary spherocytosis).
- Retrieve iron for the body

White pulp - Immunologic functions

– trapping and processing of antigens

– initiates immunologic response (APC)

– the major site of antibody synthesis

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

- Macrophage activation
- Site of **B cell maturation** into plasma cells, which synthesize antibodies in its white pulp and initiates **humoral response.**

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

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

Immune functions: Spleen filters the blood by removing the microorganism. Macrophages in splenic pulp phagocytose microorganisms & foreign bodies

- Spleen acts as reservoir of lymphocytes (contains about 25% of T cells & 15% B Cells)
- 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 that bind to the specific receptors on the surface of macrophages and other leukocytes, stimulating their phagocytic, bactericidal and tumoricidal activity.

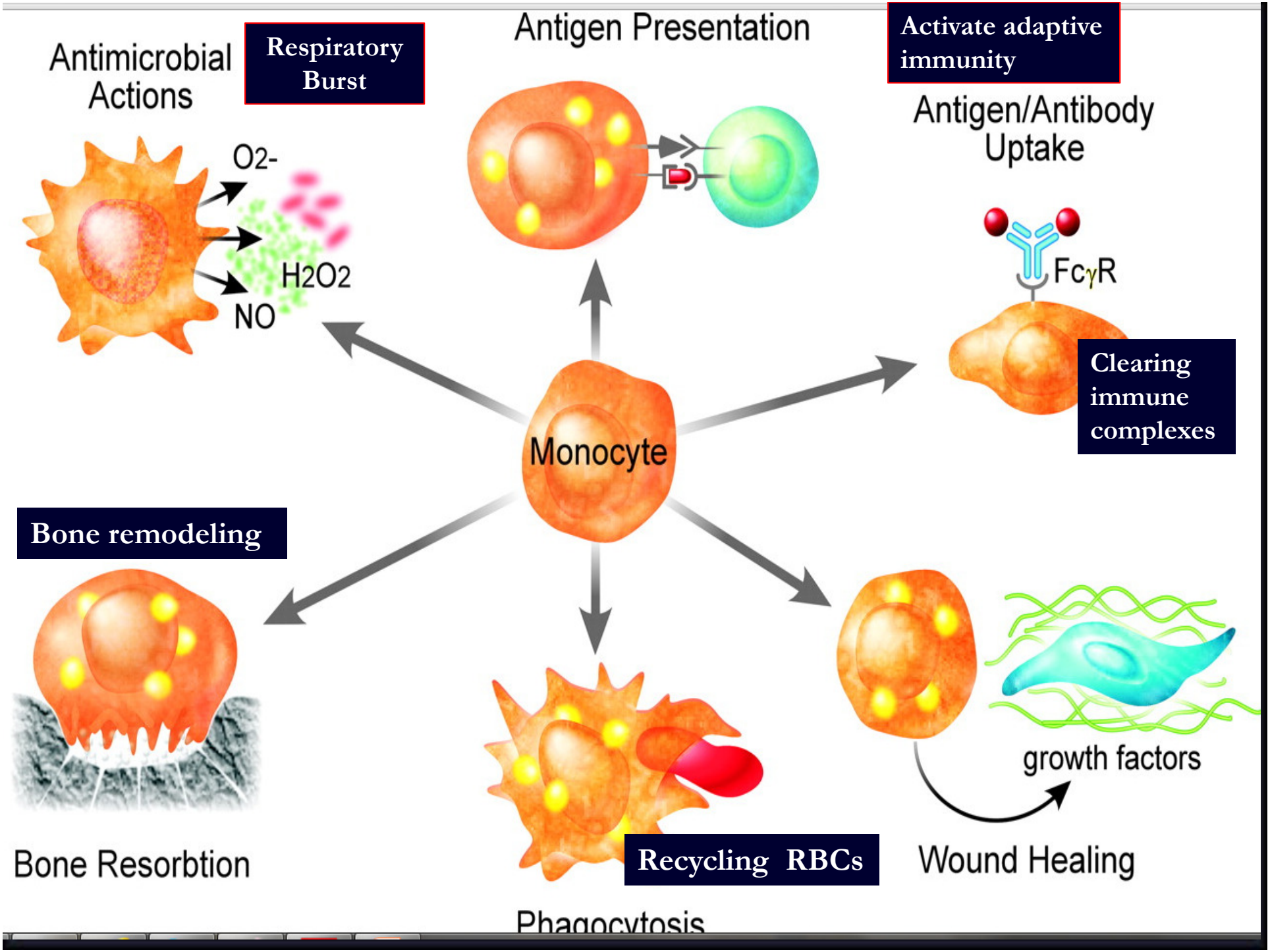
Spleenectomy

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