



GIT PHYSIOLOGY

- Text
- Only in Females' slide
- Only in Males' slides
- Important
- Numbers
- Doctor notes
- Notes and explanation

Lecture
No.7

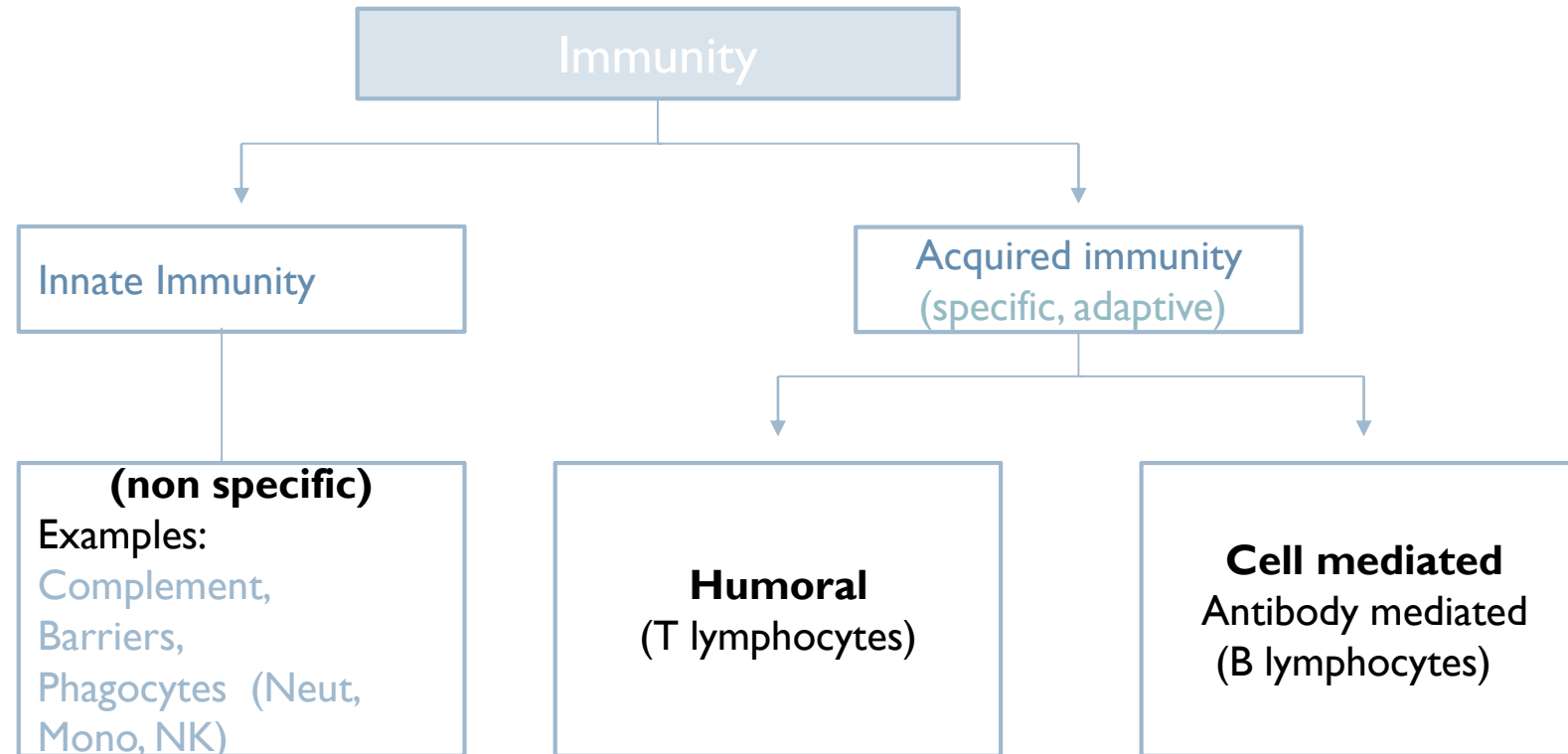
"Stay Focused And Extra Sparkly"

Reticuloendothelial System (RES) & Function of the Spleen

Objectives:

1. Define the term Reticuloendothelial system (RES).
2. Describe the cellular components of RES.
3. Describe the functions of the RES.
4. Define the structural function of the spleen.
5. Describe the functions of the spleen.
6. Understand the basic concept of the indication and risks of splenectomy.
7. Mechanism of chemotaxis, phagocytosis and microbial killing
8. Functions of monocytes/macrophages in different tissues

Overview of the immune system



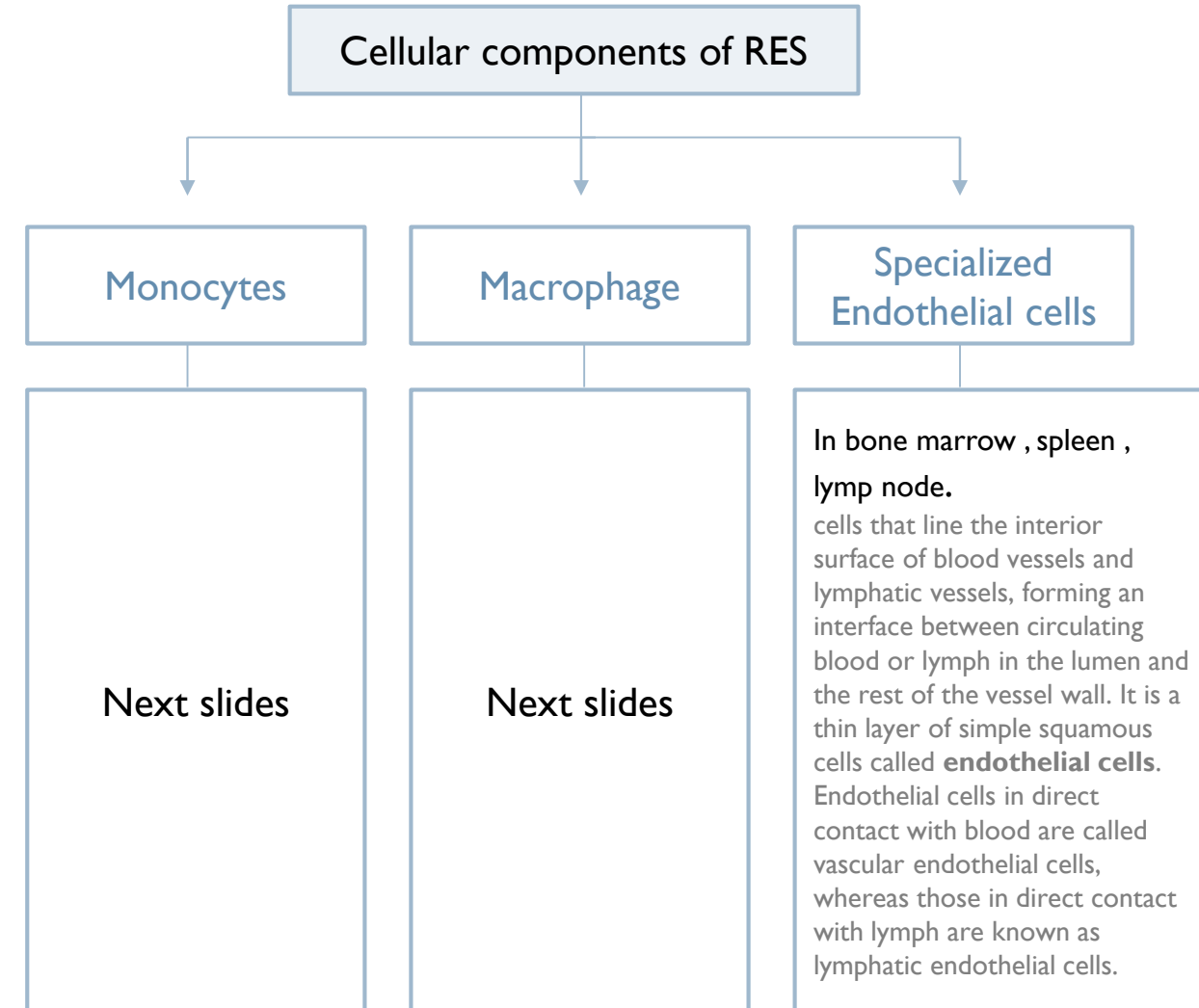
Note: Macrophages are key components of the innate immunity and activate adaptive immunity by transforming into Antigen Presenting Cells.

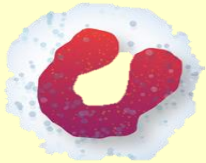
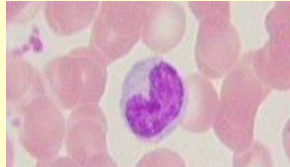

Reticuloendothelial system (RES)

- ▶ Reticuloendothelial System is an older term for the Mononuclear Phagocyte System.
- ▶ although they are neither reticular (mesh or network) in appearance nor they have endothelial origin just these phagocytic cells are located in reticular connective tissue.
- ▶ Therefore, the term reticuloendothelial system is not used nowadays.
- ▶ It is a network of connective tissue fibers inhabited (occupied) By **phagocytic cells** such as **macrophages** ready to attack and ingest microbes.
- ▶ RES is an essential component of the immune system.
- ▶ Most endothelial cells are not macrophages.

- The total combination of monocytes, mobile macrophages, fixed tissue macrophages, and a few specialized endothelial cells in the bone marrow, spleen, and lymph nodes is called the reticuloendothelial system.
- However, all or almost all these cells originate from monocytic stem cells; therefore, the reticuloendothelial system is almost synonymous with the monocyte-macrophage system. Because the term reticuloendothelial system is much better known in medical literature than the term monocyte-macrophage system, it should be remembered as a generalized phagocytic system located in all tissues, especially in the tissue areas where large quantities of particles, toxins, and other unwanted substances must be destroyed.

Cellular components of RES



Definition	<ul style="list-style-type: none"> Are a type of white blood cell "leukocyte." They are the largest type of leukocyte and can differentiate into macrophages.
Location	In the blood
Size	15-20 μm (active cells 60-80 μm)
Small granules	Prim & Vacoules
Efficient	<ul style="list-style-type: none"> More Efficient Phagocytosis than Neutrophils. 100 bacteria vs 3-20 by Neutrophils, larger particles like RBCs & malarial parasites.
Life span	10-20 hours in blood & in tissues.
Types	<ol style="list-style-type: none"> Mobile (to ingest large particle) Fixed (often in tissue)
N.B	<ul style="list-style-type: none"> Lysosomes contain lipases unlike Neutrophils. Acts as Antigen Presenting Cells.
Picture	   <div data-bbox="1992 1031 2254 1096" style="border: 1px dashed black; padding: 5px; display: inline-block;">زي حدوة الحصان</div>

✓ Monocytes transform themselves into macrophages in tissue & this system of phagocytes is called as Monocyte-Macrophage Cell.

✓ Characterized by an increase in:

- Cell size.
- Number and complexity of intracellular organelles Golgi, mitochondria, lysosomes.
- Intracellular digestive enzymes.

Neutrophils is the fastest & most potent chemotactic cell, while the monocyte is slower but stronger in response to the inflammatory process.

2nd Macrophages

Tissue macrophages provide a first line defense against infection

Definition	A large phagocytic cell found in stationary form in the tissues or as a mobile form white blood cell, especially at sites of infection.
Function	<ul style="list-style-type: none"> - They filter and destroy objects which are foreign to the body, such as bacteria, viruses. - Some macrophages are mobile, and they can group together to become one big phagocytic cell in order to ingest larger foreign particles.
Location	<ul style="list-style-type: none"> - In <u>all tissues</u>. - often remain fixed to their organs.
Formation of Macrophages	<div style="display: flex; flex-direction: column; align-items: center;"> <div style="display: flex; justify-content: space-between; width: 100%;"> <div style="border: 1px solid black; padding: 5px; width: 45%;">Begin by Stem cell in Bone Marrow</div> <div style="width: 10%; text-align: center;">→</div> <div style="border: 1px solid black; padding: 5px; width: 45%;">Monoblast maturing to promonocyte</div> </div> <div style="margin: 5px 0;">↓</div> <div style="display: flex; justify-content: space-between; width: 100%;"> <div style="border: 1px solid black; padding: 5px; width: 45%;">mature monocytes released into blood</div> <div style="width: 10%; text-align: center;">→</div> <div style="border: 1px solid black; padding: 5px; width: 45%;">Stay for 10-20 hours in circulation</div> </div> <div style="margin: 5px 0;">↓</div> <div style="display: flex; justify-content: space-between; width: 100%;"> <div style="border: 1px solid black; padding: 5px; width: 45%;">Then leave blood to tissues transforming into larger cells macrophage</div> <div style="width: 10%; text-align: center;">→</div> <div style="border: 1px solid black; padding: 5px; width: 45%;">Macrophage life span is longer up to few months in tissues</div> </div> </div>
Life spine	10-20 hours - months

Types of Macrophages

Macrophage differ depending on the **organs** in which they reside.

Types	Kupffer cells <i>Picture</i>	Alveolar cells (Duct cells) <i>Picture, another picture</i>	Tissue histiocytes (langerhans cell) (fixed macrophages)	Microglia	Reticular cells	Sinus histiocytes	Mesangial cells <i>Picture</i>	Osteoclasts	Hofbauer	Epithelioid
Location	Liver <i>Picture</i> <i>Picture</i>	Lung "Dust cells" because of their content of intracellular carbon particles.	- Skin. - Mucosa. - Subcutaneous tissues.	Brain	- Lymph nodes. <i>Picture</i> - Bone marrow. - Spleen. <i>Picture</i>	Lymph nodes. <i>Picture</i> <i>Picture</i>	Kidneys	Bone	Placenta	Granulomas

Macrophages Line Nodal Medullary sinuses:

- 1) subcapsular sinus macrophages (SSMs).
- 2) medullary sinus macrophages (MSMs).
- 3) medullary cord macrophages (MCMs).

Picture



Definition	<ul style="list-style-type: none"> Neutrophils are a type of white blood cell. In fact, most of the white blood cells that lead the immune system's response are neutrophils. Most Abundant WBCs 60-70 %.
Size	15-20 μm
Nucleus	Multilobed, 2-5 lobes
Life span	6-8 hours

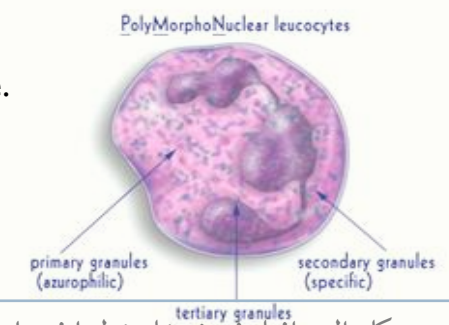
POOLS: "three populations of neutrophils"

Bone Marrow pool	Circulating pool	Marginating Pool
Neutrophils within bone marrow.	Neutrophils within blood.	Neutrophils adherent to endothelium in low flow exchange vessels.

Neutrophil granules

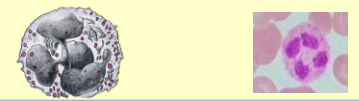
Monocytes contain primary granules and vacoules only, neutrophils Contain glycogen granules.
 Why it contain glycogen granules? for anaerobic glycolysis.

Primary Granules	Secondary Granules	Tertiary Granules
<ul style="list-style-type: none"> ✓ Non Specific. ✓ 33% ✓ Azurophilic. <p>Lysosomes contain:</p> <ul style="list-style-type: none"> - Acid hydrolases. - MPO. - HOCl. - Defensins 	<ul style="list-style-type: none"> ✓ Specific ✓ 67% <p>Granules contain:</p> <ul style="list-style-type: none"> - Lysozyme NOT Lysosomes. - Lactoferrin. - Alkaline Phaphatase. - Gelatinase. - Bacteriostatic & Bacericidal products. 	<ul style="list-style-type: none"> ✓ Help to digest tissues <p>Granules contain:</p> <ul style="list-style-type: none"> - Collagenase. - Hyaluronidase & Gelatinase.



كل الجرانيلوز يشغلون لما نحتاجهم فقط، فلنفترض جانا التهاب، البرايميري راح يصير له activated، اذا ما كان كافي للسيطرة على الالتهاب راح يشغل الثاني، بينما لو كان كفاية ما راح نحتاج الباقي وهكذا ☺

Picture



Neutrophils is the fastest & most potent chemotactic cell, while the monocyte is slower but stronger in response to the inflammatory process.

General Functions of RES

1. **Phagocytosis**: Bacterial, dead cells, foreign particles (**direct**).

- ✓ **Phagocytosis** is the processes of engulfing and ingestion of bacteria or other foreign bodies.
 - It is part of the natural or innate immune process.
- ✓ **Macrophages** are a powerful phagocytic cells:
 - Macrophages also means “Big eater”, they are capable of phagocytosis.
 - They are **modified monocyte** in tissues.
 - Ingest up to **100 bacteria**.
 - Ingest **larger particles** such as old RBC.
 - Get rid of **waste products**.

2. **Immune function**: processing antigen and antibodies production (**indirect**).

3. **Breakdown** of aging RBC.

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

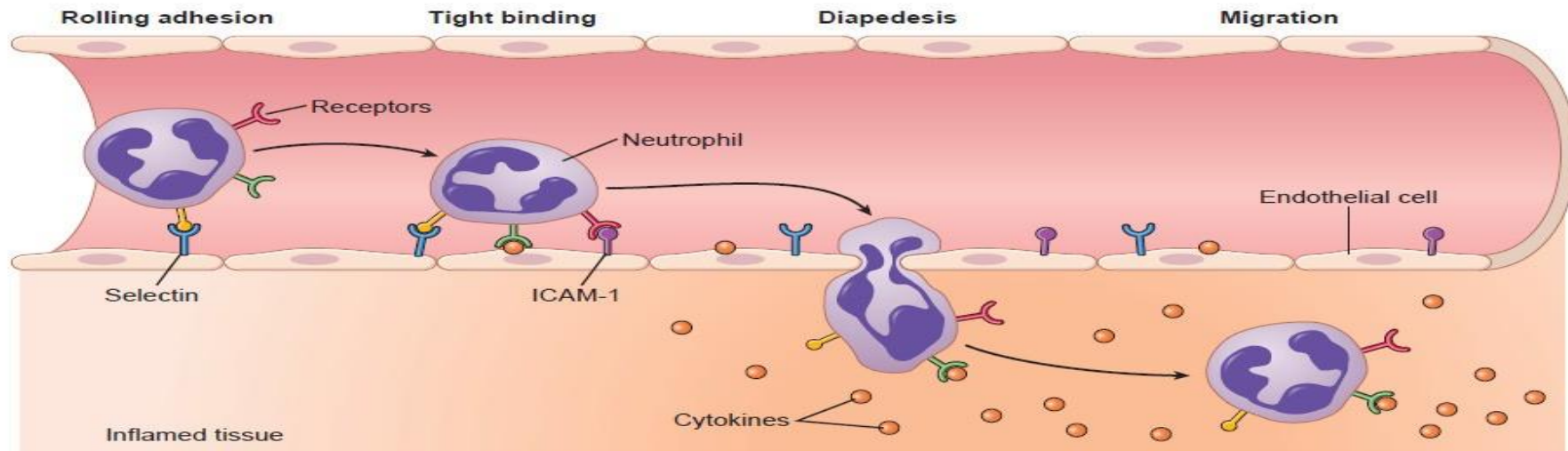


Figure 34-6. Migration of neutrophils from the blood into inflamed tissue. Cytokines and other biochemical products of the inflamed tissue cause increased expression of selectins and intercellular adhesion molecule-1 (*ICAM-1*) in the surface of endothelial cells. These adhesion molecules bind to complementary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

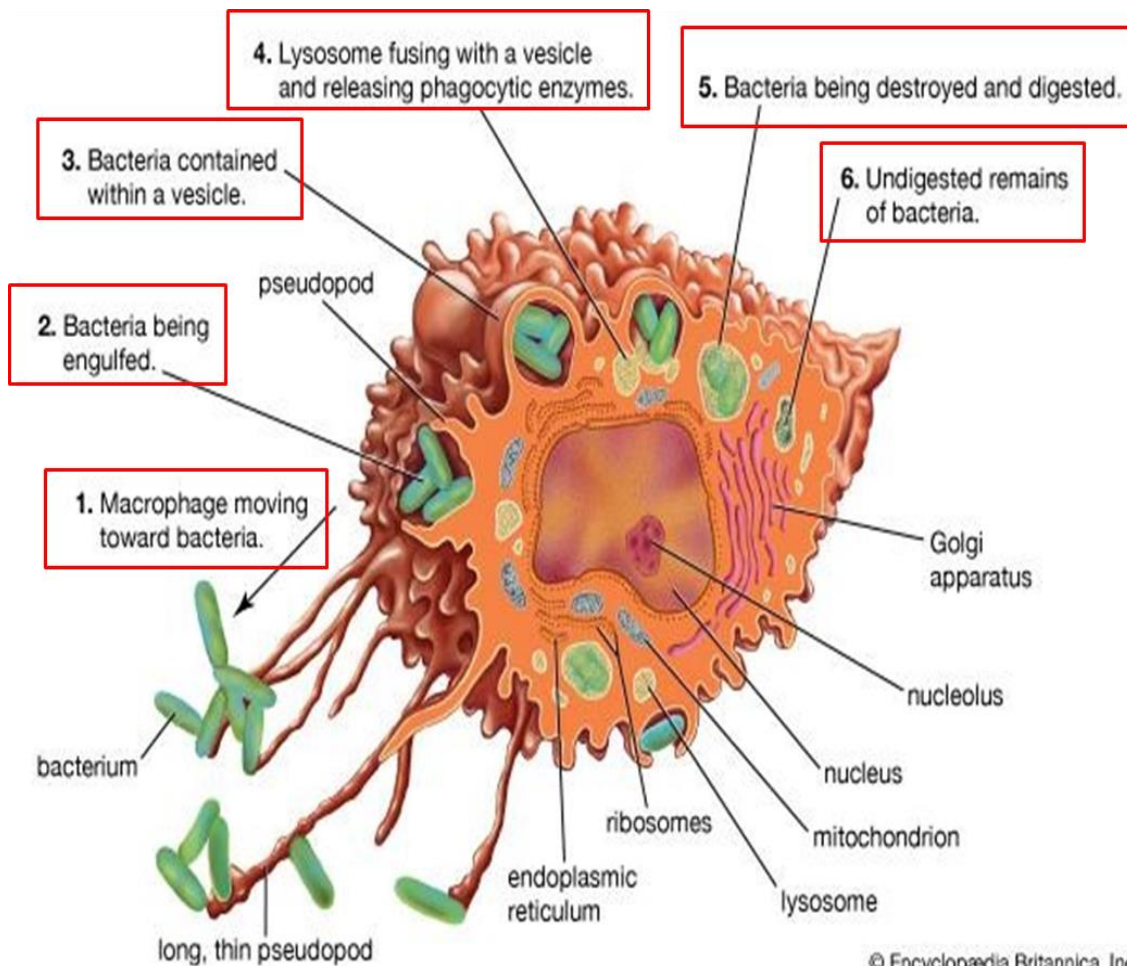
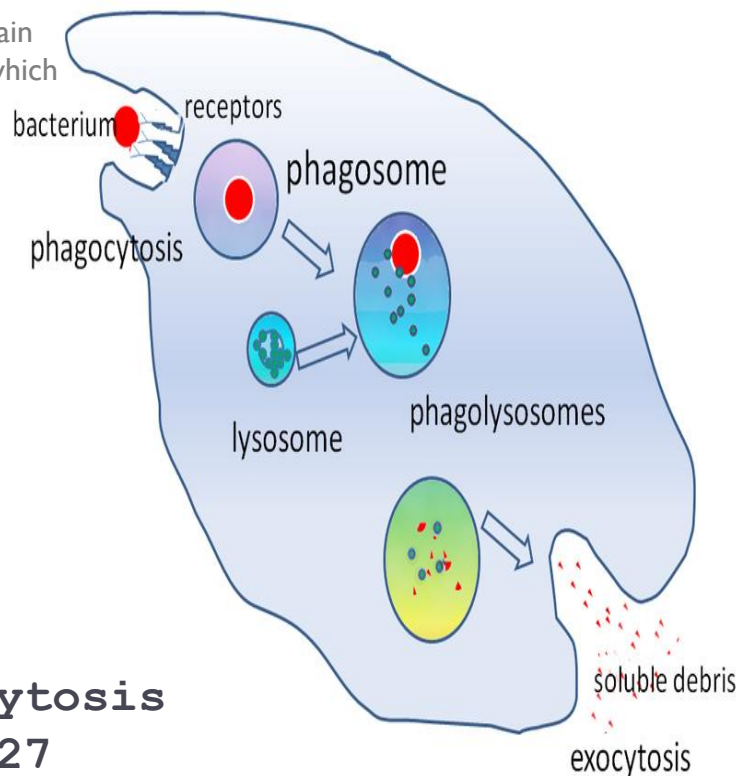
Direct anti-inflammatory function (Phagocytosis)



Bacteria vs. Macrophage
3:14

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- Macrophage moves toward the pathogen which will be engulfed in a phagosome.
- The lysosome will bind to the phagosome & release its substances.
- Now it becomes a phagolysosome which will digest the pathogen.
- The residual part of the digested pathogen will be released out of the cell by exocytosis.
- The residual part contain indigestible material which will be cleared from the tissue gradually through the blood circulation.



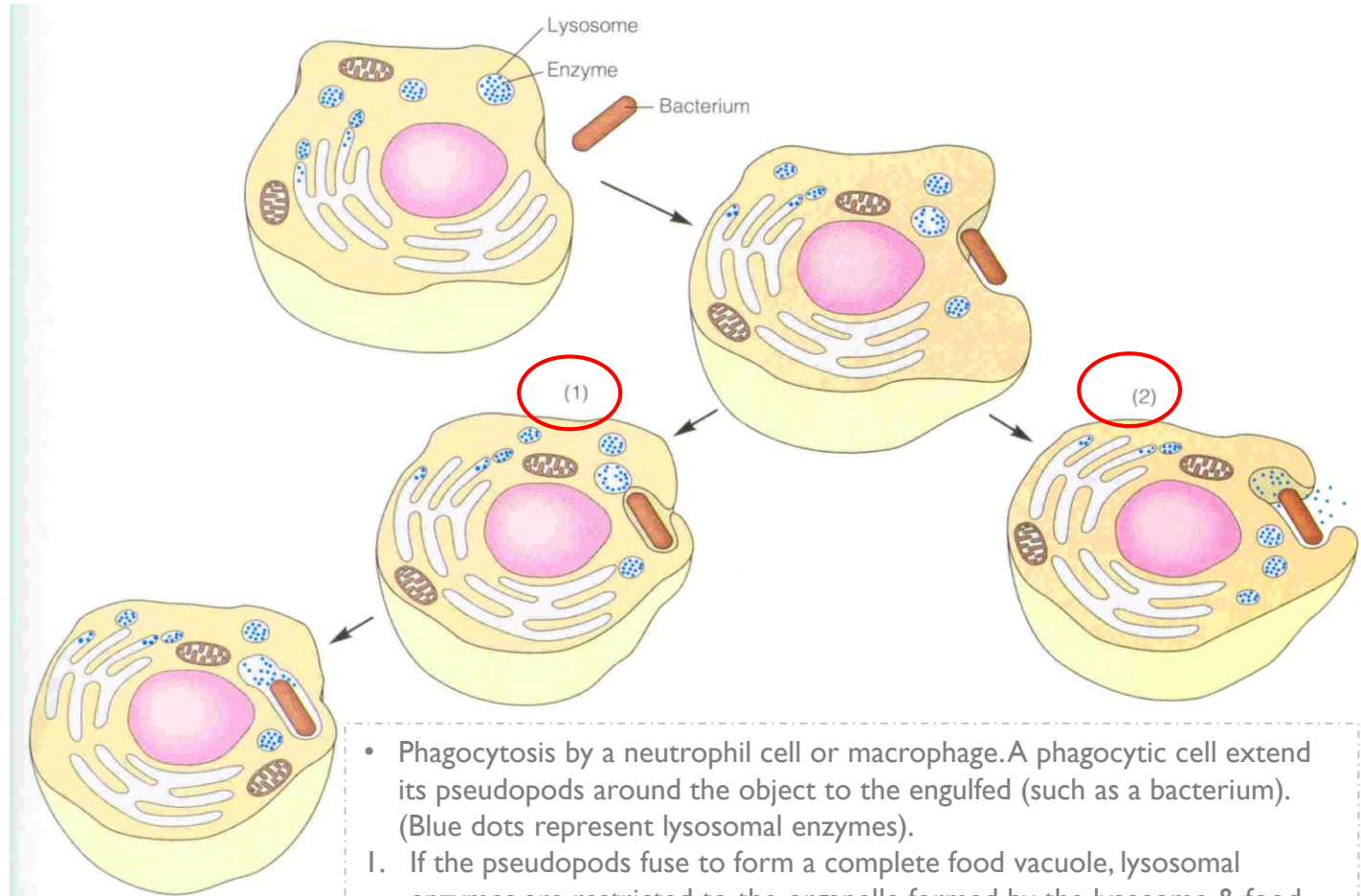
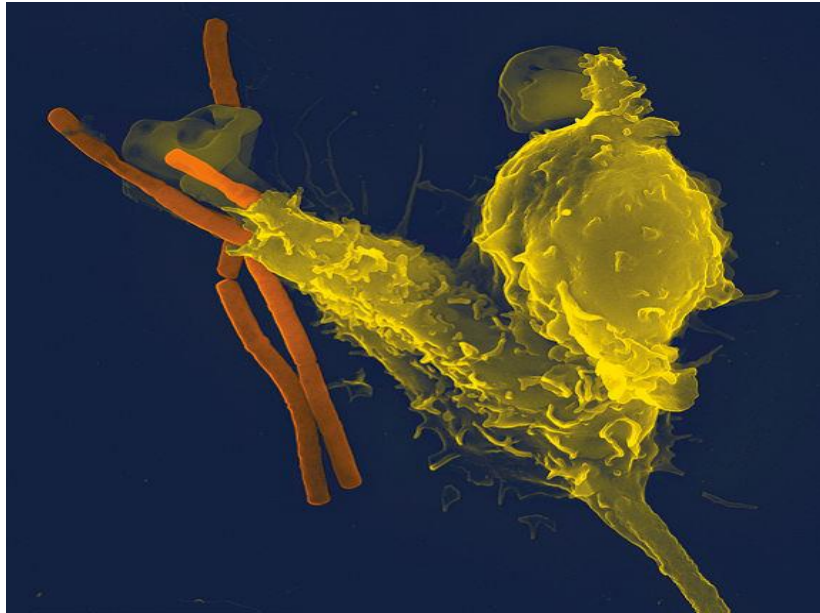
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Phagocytosis
2:27

Cont.

A scanning electron microscope: image of a single neutrophil yellow engulfing anthrax orange



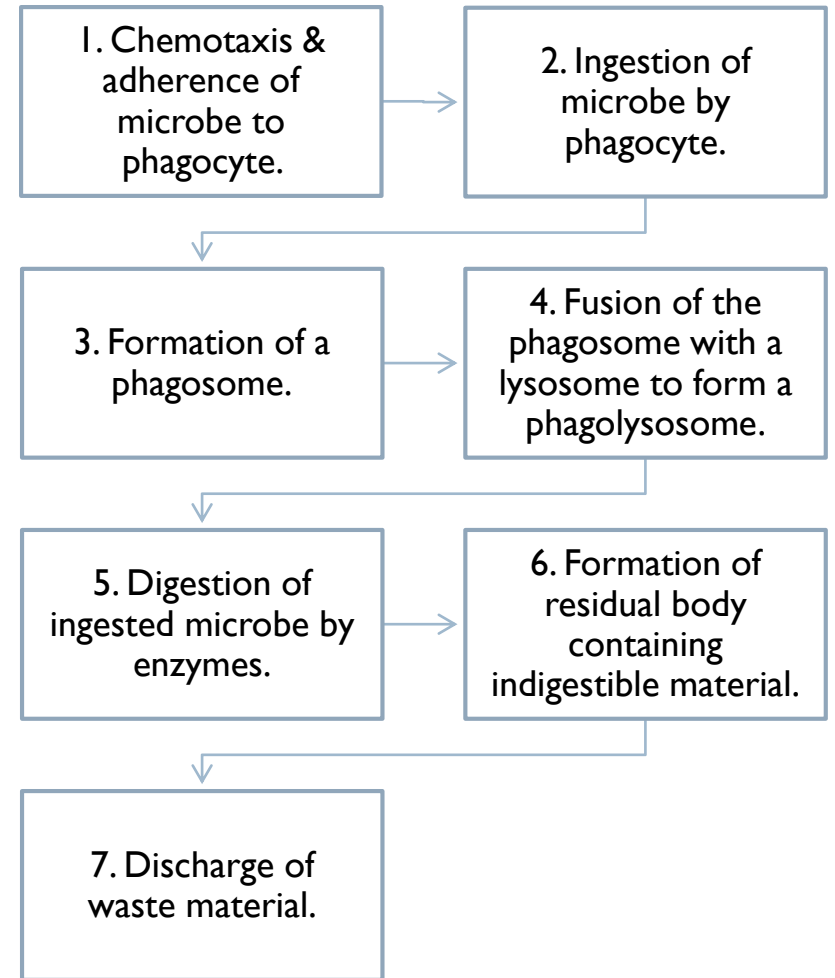
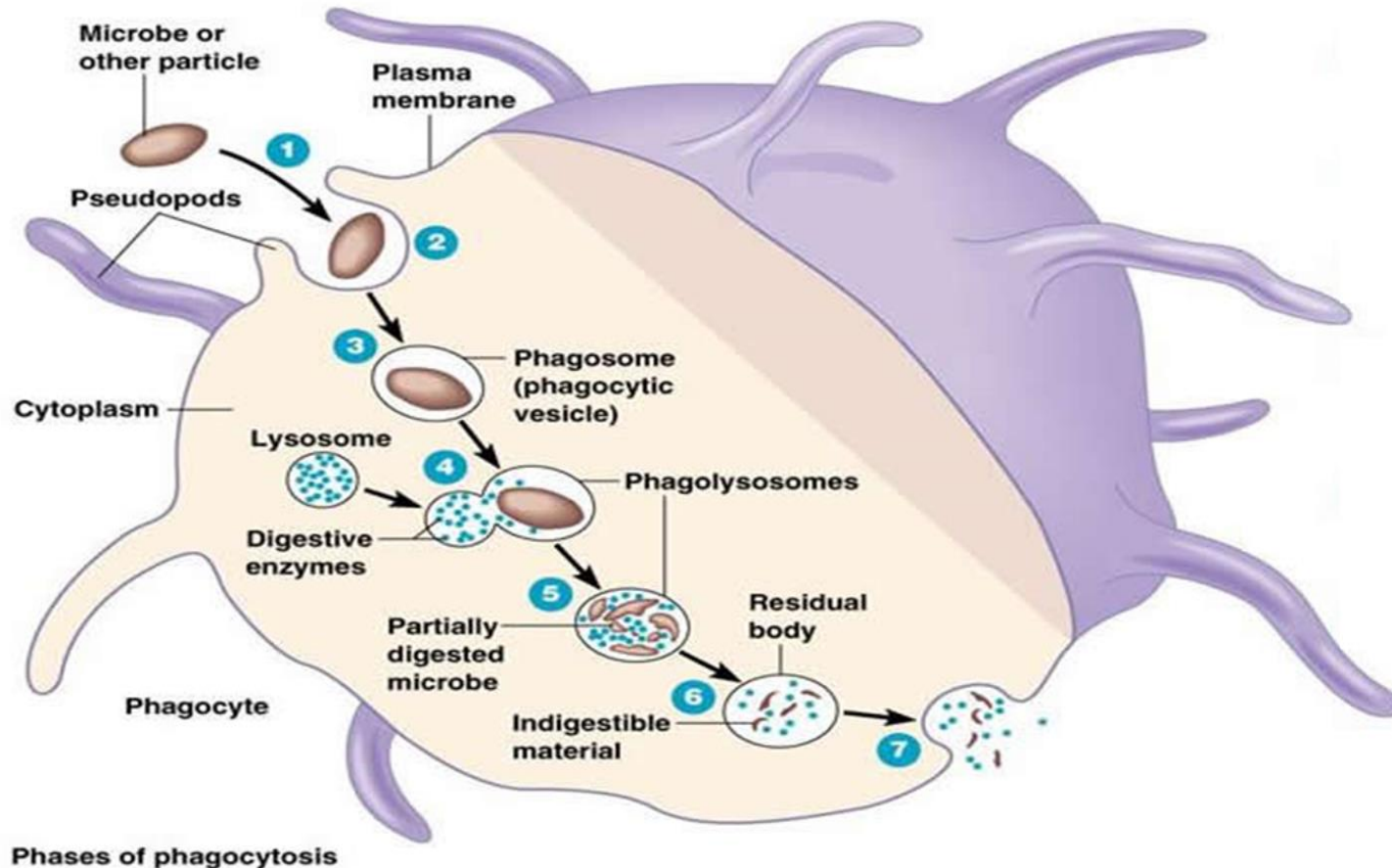
- Phagocytosis by a neutrophil cell or macrophage. A phagocytic cell extend its pseudopods around the object to be engulfed (such as a bacterium). (Blue dots represent lysosomal enzymes).
- 1. If the pseudopods fuse to form a complete food vacuole, lysosomal enzymes are restricted to the organelle formed by the lysosome & food vacuole.
- 2. If the lysosome fuses with the vacuole before fusion of the pseudopods is complete, lysosomal enzymes are released into the infected area of tissue.



Neutrophil Phagocytosis

1:00

Microbial killing



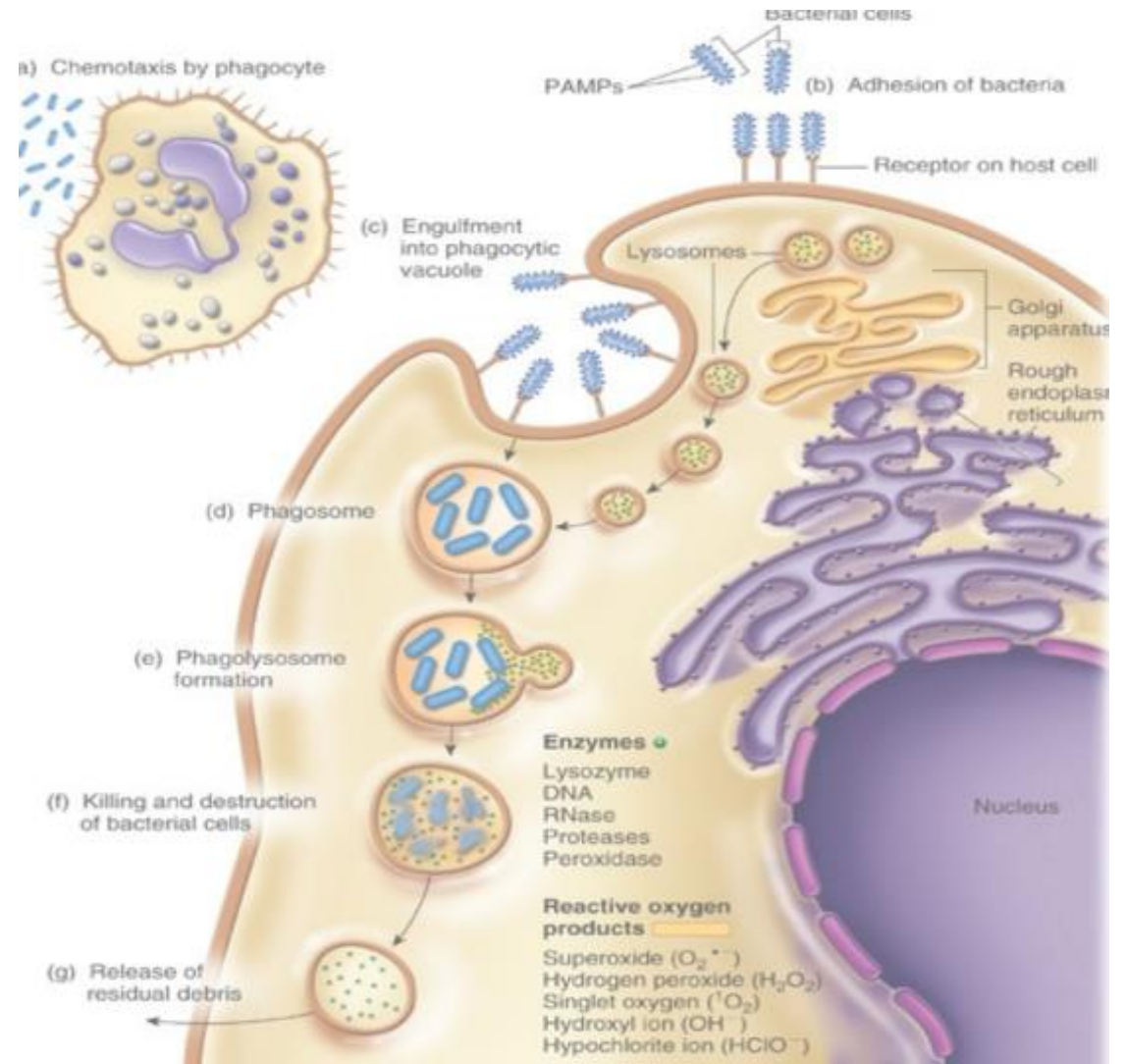
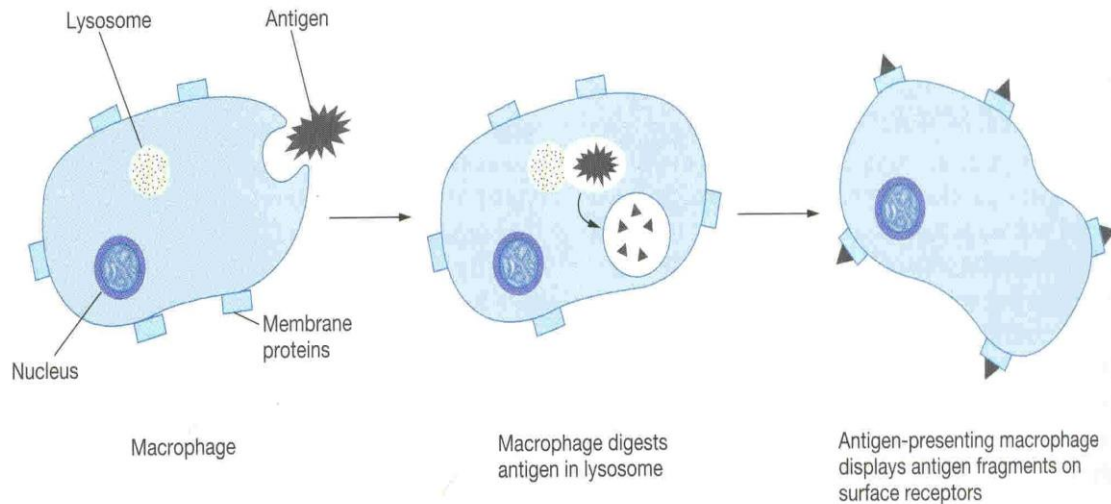
Macrophage: a wandering, walking cell. “Big eater” capable of phagocytosis. Is a modified monocyte in tissues.

Indirect Immune function Of RES

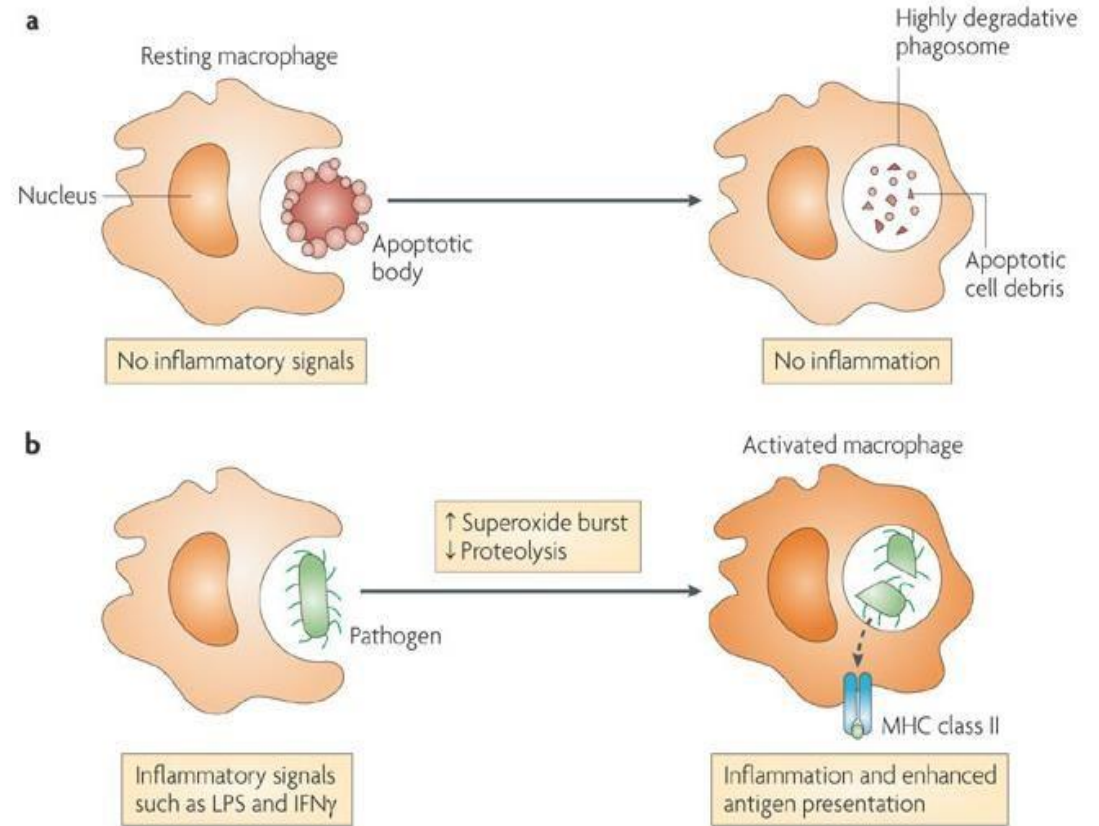
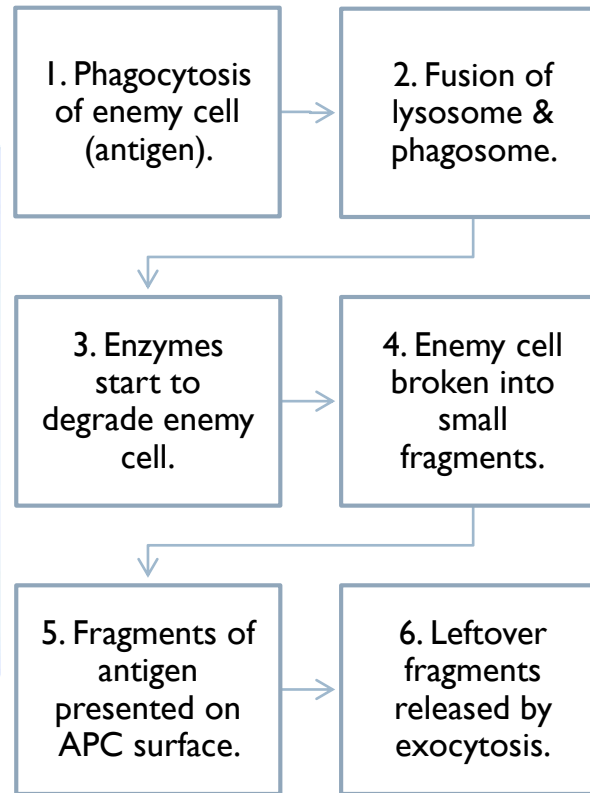
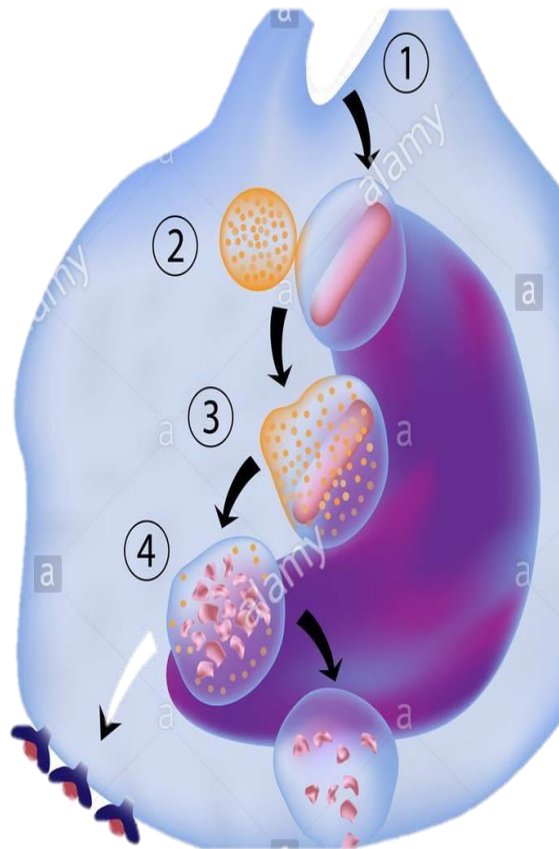
- ▶ Indirect immune function of RES:
 - ▶ As Antigen Presenting Cells.
 - ▶ Displaying it attached to an MHC class II molecule.
 - ▶ Ingest foreign body, process it and present it to lymphocytes.

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- Same as further steps in Direct function. But here after the pathogen get digested, a copy of the protein structure of antigen is taken and exposed on the surface of the surface of the cells and this is what we call it antigen presenting cell (APC).
- Finally this expressed by MHC class II



Role of an antigen-presenting cell



What I have to know from this picture?
 That phagocytosis is either due to inflammatory response or apoptotic bodies that get ingested from macrophage and degraded to be cleared from the body.

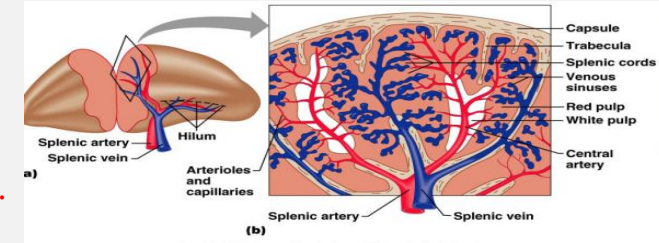
Lymphoid Organs

Lymphoid Organs		
Thymus	Lymph nodes	Spleen
<ul style="list-style-type: none">• High rate of growth and activity until puberty, then begins to shrink.• Site of t-cell maturation.	Small, encapsulated, bean-shaped organs stationed along lymphatic channels and large blood vessels of the thoracic and abdominal cavities.	Structurally similar to lymph node, it filters circulating blood to remove worn out rbc's and pathogens.

spleen

Main characteristic

- ✓ 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.



White pulp

Red pulp

Structural Function

- ✓ Thick sleeves of lymphoid tissue.
- ✓ provides the immune function of the spleen.
- ✓ trapping and processing of antigens.
- ✓ the major site of antibody synthesis.
- ✓ key role in removal of encapsulated bacteria (Strep pneumo).

- ✓ Surrounds white pulp, composed of **venous sinuses** filled with whole blood and splenic cords of reticular connective tissue rich in **macrophages**.
- ✓ provides the filtrate function of the spleen.
- ✓ RBC's able to deform through sinusoidal wall and endothelium Culling.
- ✓ Macrophage activation macrophages filter and destroy foreign material in blood
Macrophage activation.

Immune function

1. **Reservoir of lymphocytes**
2. Site of **B cell maturation** into plasma cells, which synthesize antibodies and initiates **humoral response**.

1. Site for **Phagocytosis** of bacteria and worn-out blood cells (Slow blood flow in the red pulp cords allows foreign particles to be phagocytosed)
2. 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**.

1. **Destruction and processing** of antigens. Because the organ is directly connected to blood circulation, it responds faster than other lymph nodes to **blood-borne antigens**.
2. Removes antibody-coated bacteria along with **antibody-coated blood cells**.

General function

1. **Hematopoiesis: fetal life. Formation of blood cells**, - it plays an important role in the hemopoietic function in embryo, - during the hepatic stage, spleen produces the blood cells along with liver.
2. **Destruction:** Spleen is a main site for **destruction of lymphocytes & thrombocytes and RBCs** specially old and abnormal e.g. spherocytosis.
3. **Filtered (defense of body):** Blood is **filtered** through the spleen. by removing the microorganism & foreign bodies.
4. **Reservoir:** **Reservoir** of **thrombocytes** and immature erythrocytes.
A large number of RBCs and platelets are stored in spleen.
RBCs are released form spleen into circulation during the emergency conditions like hypoxia & hemorrhage.
5. **Iron:** Recycles of **iron**.
- 6: **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, thalassemias and chronic hemolytic anemias.

Role in defense of body

1. Spleen **filters** the **blood** by removing the microorganism.
2. Macrophages in splenic pulp **phagocytose microorganisms** & foreign bodies.
3. Spleen contains about **25%** of **T lymphocytes** & **15%** of **B lymphocytes**.
4. The spleen processes foreign antigens and it is the site of antibody **production mainly IgM**.
5. The non-specific opsonins, properdin and tuftsin, are synthesized.
6. 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.

Splenectomy

Indications

1. **Hypersplenism**: enlargement of the spleen (splenomegaly) with defects in the blood cells count.
2. Primary spleen **cancers**.
3. **Haemolytic anaemias**: Sickle cell anemia, Thalassemia, hereditary spherocytosis (HS) and **elliptocytosis** (Hereditary elliptocytosis, also known as ovalocytosis, is an inherited blood disorder in which an abnormally large number of the patient's RBCs are elliptical rather than the typical biconcave disc shape).
4. Idiopathic thrombocytopenic purpura (**ITP**) (a bleeding disorder in which the immune system destroys platelets).
5. Trauma.
6. Hodgkin's disease (type of lymphoma).
7. Autoimmune hemolytic disorders.

Risks & complications

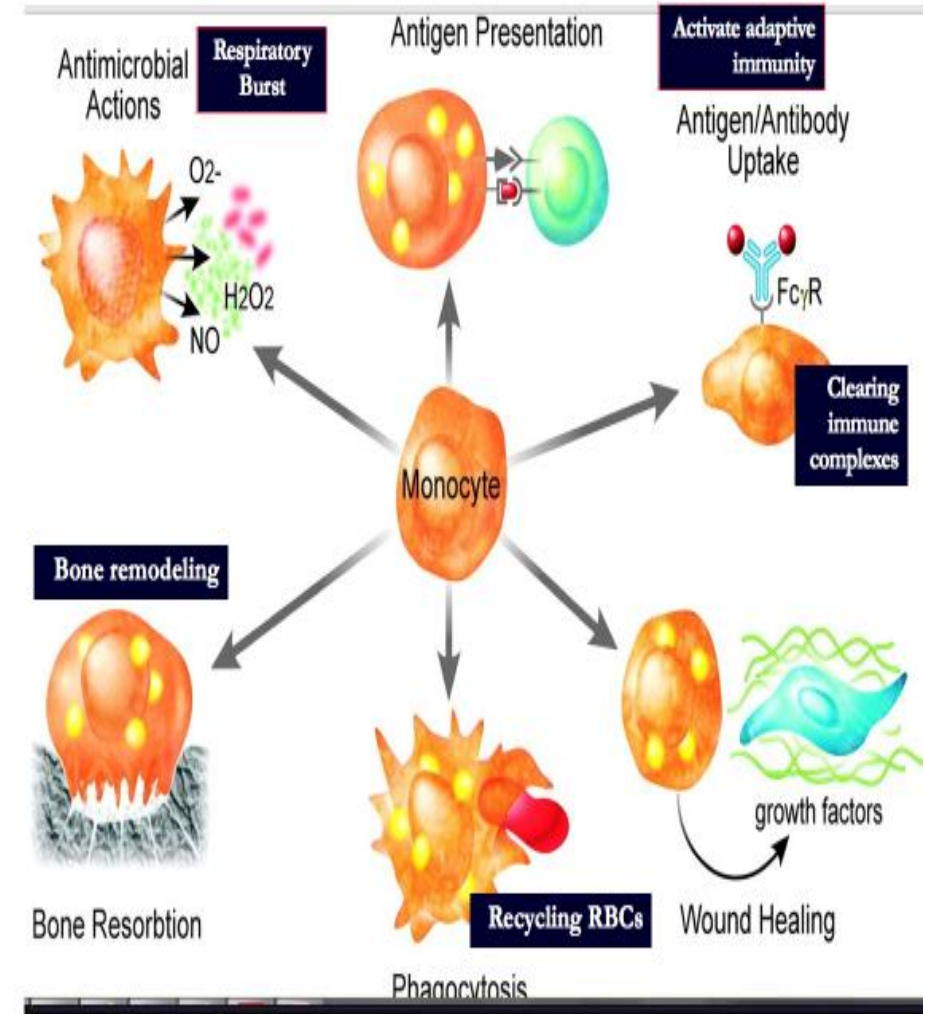
- Overwhelming **bacterial infection** or post splenectomy **sepsis**.
- Patient prone to **malaria**.
- Inflammation of the **pancreas** and collapse of the **lungs**.
- Excessive post-operative **bleeding** (surgical).
- Post-operative **thrombocytosis** and **thrombosis**.

WBCs Concentration

WBCs Concentration (Normal Counts)			
Cells	Approximate Normal range (/μL)	Percentage of TotalWBC	Life Span
Granulocytes	Neutrophils	50-70%	4-8 hours in blood. 4-5 days in tissues
	Eosinophils	1-4%	
	Basophils	0.4	
	Lymphocytes	20-40%	Weeks-months
	Monocytes (macrophages)	2-8%	10-20 hours (months)
TotalWBC: 4000-11000 μL			

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

Summary (from slides)



Summary (from slides)

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

	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 \pm IFN γ	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 IFN γ)	Cannot present antigen (don't normally express Class II)

Thank you!

اعمل لترسم بسمة، اعمل لتمسح دموعه، اعمل و أنت تعلم أن الله لا يضيع أجر من أحسن عملا.

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QUIZ



اقتراحات وشكاوي

References:

- 2017-2018 Dr. Nervana Bayoumi's Lecture.
- 2017-2018 Prof. Shahid Habib's Lecture.
- Guyton and Hall Textbook of Medical Physiology (Thirteenth Edition.)