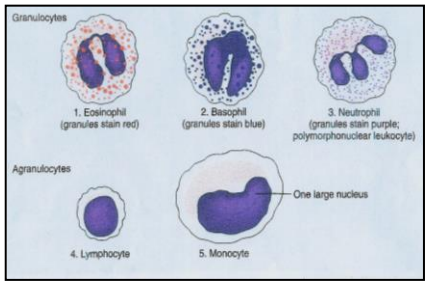
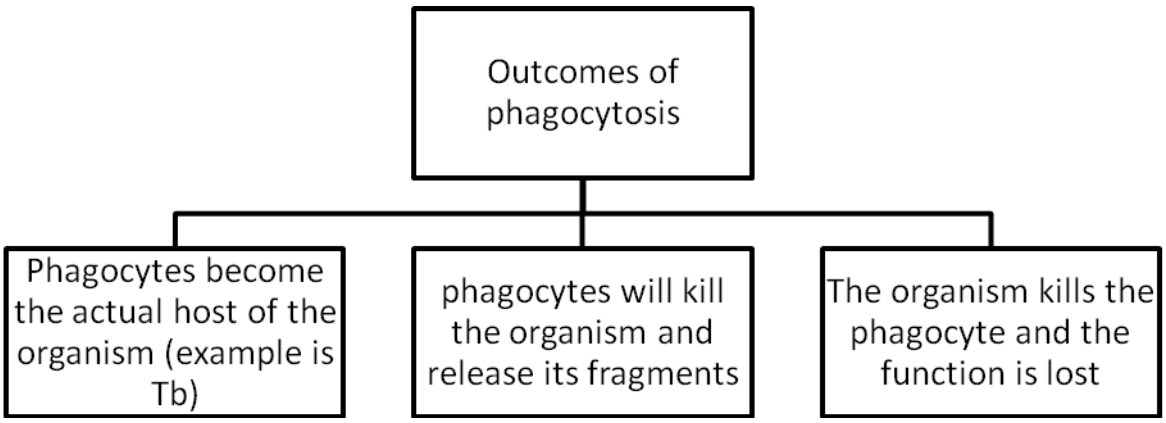
- **Leukocytes are classified to:**
  - **Granulocytes (presence of granules in the cytoplasm)**: eosinophils (with red staining granules) – basophils (with blue staining granules) – neutrophils (with multilobated nuclei and purple staining granules).
  - **Agranulocytes (no presence of granules in the cytoplasm)**: lymphocytes and monocytes.



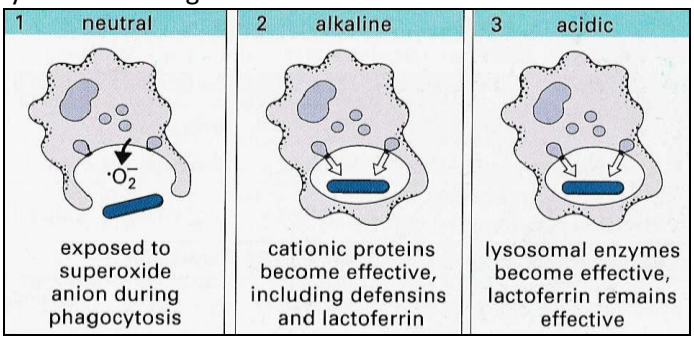
- The activity of neutrophils is exclusively directed against bacterial infection. Macrophages come in the second place but in addition their activity can be directed against viruses & fungi in addition to bacteria.
- **Phagocytes function:**
  - **Recruitment (التجنيد والتطويع):**
    - ✓ When there is tissue injury (for example: bacterial infection) → macrophages will be activated leading to the release of cytokines (such as TNF, IL-1) & chemokines (such as IL-8) → also, complement system will be activated (leading to the release of C5a which is considered as chemotaxic fragment) → in addition, mast cells will be activated (leading to the production of P-selectin & PAF)→ all of these aactions will lead to the expression of adhesion molecules on the surface of endothelial cells in blood vessels aiding in the recruitment of phagocytes.
    - ✓ Endothelial cells will express adhesion molecules. The receptors for these adhesion molecules are expressed or found on the surface of phagocytes. Each receptor will attach to its adhesion molecule leading to the adhesion of phagocytes to the blood vessel wall and finally their transmigration.

Receptor on PMN	Adhesion molecule on the surface of endothelial cells
Mucin-like	P-selectin & E-selectin… when these adhesion molecules bind to their receptor this will lead to the rolling phase of phagocytes.
β_1-integrins & β_2-integrins	For VCAM-1 & ICAM-1 respectively… when attached, this will lead to firm adhesion of phagocytes
L-selectin	GlyCAM

  - **Phagocytosis:**
    - ✓ Microorganism will adhere to the phagocyte → the membrane of the phagocyte will be activated and the microorganism will be taken by endocytosis → inside the phagocyte a phagosome will be formed → this phagosome will fuse with lysosomes containing hydrolytic enzymes → killing and digestion of the microorganism will occur → and degradation products will be released.
      Note: PMNs also express Fc-receptors & complement-receptor which aid in the formation of a phagosome (opsonization).



- **Killing:**
  - ✓ Inside the phagosome which will be formed after the phagocyte takes up the microorganism by endocytosis, pH will be changed and according to that different lysosomal enzymes and killing mechanisms will be activated:



  - ✓ *Oxygen-dependent killing pathways: they are classified to:*

    * Peroxidase-independent: in which an oxygen molecule will be converted to superoxide radical, hydroxyl radical and hydrogen peroxide. These are going to kill the bacterium.

    * Peroxidase-dependent: in which hydrogen peroxide (by the aid of: endocytosed peroxidase, myeloperoxidase from lysosomes & catalase from peroxisomes) will be converted to toxic oxidant which will kill the bacterium.
  - ✓ *The nitric oxide (NO) pathway*: in which IFN-γ and TNF will bind to their receptors on phagocytes and induce the expression of NOS enzyme which will act on L-arginine to convert it to NO and citrulline.

- **Pathogenesis of septic shock:**
  - LPS from the cell wall of gram (-) bacteria will activate macrophages and lead to the release of cytokines such as (TNF & IL-1). These cytokines will lead to the activation of endothelial cells of the blood vessels resulting in expression of adhesion molecules, a procoagulant phenotype and secondary waves of cytokine production.
  - LPS will also activate the complement cascade releasing C5a (which is a chemotaxic fragment).
  - A procoagulant state will be favored by increasing tissue factor (TF) production and decreasing anticoagulant factors such as (tissue factor pathway inhibitor, thrombomodulin & protein C). Also, there will be anti-fibrinolytic state by increasing the levels of PAI. All of these actions will lead to microvascular thrombosis (DIC) which will result is tissue ischemia.
  - Inflammatory mediators such as IL-6, IL-8, NO, PAF & ROS will lead to relaxation of vascular smooth muscle cells (vasodilation) resulting in hypotension. They will also cause the adhesion molecule VE-cadherin to be displaced from the tight junctions of endothelial cells resulting in increased vascular permeability and therefore tissue edema.
  - There will also be metabolic abnormalities such as insulin resistance & hyperglycemia (which will decrease the bactericidal activity of neutrophils), in addition to adrenal insufficiency caused by frank adrenal necrosis due to DIC.
  - In initial response to sepsis there will be inflammation and a hyperimmune state which will last 1-2 days. Then, there will immune suppression and hypoimmune state. This immune suppression will be caused by:
    - ✓ A shift from Th1 to Th2 response.
    - ✓ Anergy (absence of the normal immune response to a particular antigen or allergen)
    - ✓ Apoptosis of CD4 T-cells, B-cells & dendritic cells.
    - ✓ Loss of macrophage expression of MHC class II and costimulatory molecules.
    - ✓ Immunosuppressive effects of apoptotic cells.