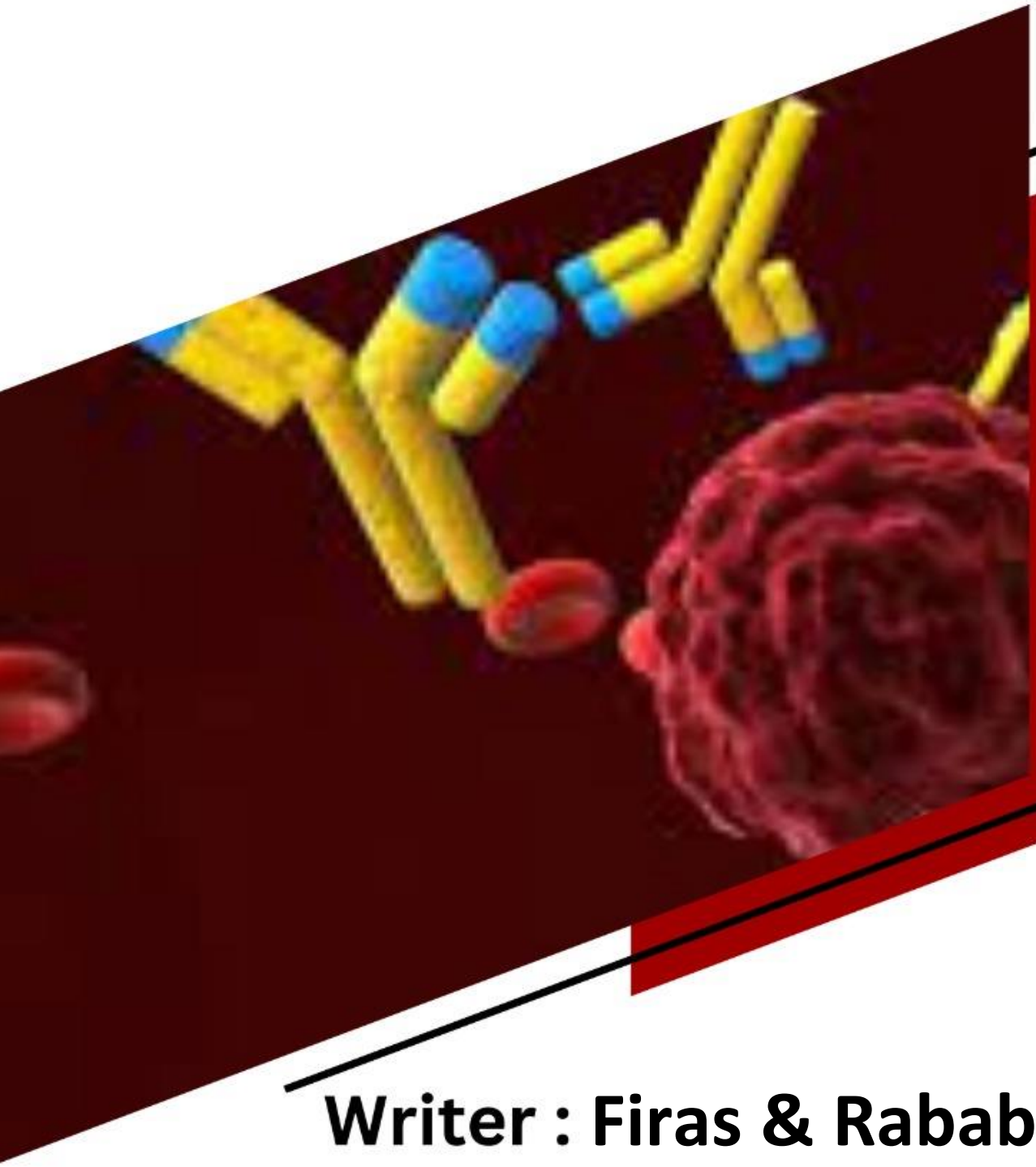
Doctor 021

IMMUNOLOGY

Sheet no. 2



Writer : Firas & Rababa’h

Corrector : Rababa’h & Firas

Doctor : Anas

OVERVIEW OF THE IMMUNE SYSTEM:

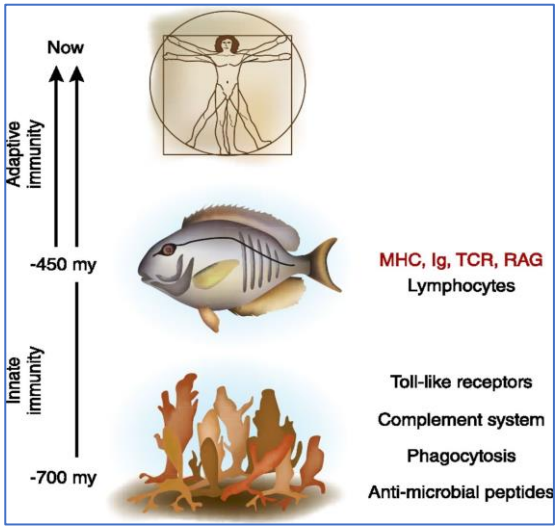
The immune system includes the role of physical, cellular, and chemical systems that are in place and work together **to respond to all aspects of foreignness.**

the immune system responds in a fashion that can be summarized by the 3 Rs:

- **The immune system targets any "foreign" object, so the first step is to recognize what is self and non- self** (to recognized what is foreign)
- **The second step is to restore homeostasis by eliminating the foreign object.**
- **The third step is to remember the invading pathogen to respond better the next time it is encountered.**
- **The immune system is not only active when danger arises but is constantly sensing danger and is important for normal physiology and homeostasis like the cardiovascular and renal systems.**
- **Mechanisms for discriminating "self" from "non-self" evolved to accomplish the task of fighting pathogens, launching a long history of host-pathogen co-evolution**
- **Virtually all organisms have at least one form of defense that helps repel disease-causing organisms.**

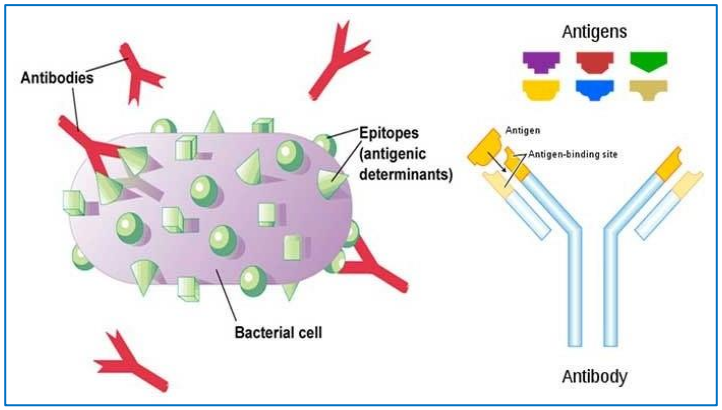
Transplantation of parts of sponge to other sponges is met by an immune response

- **Pathogens evolve new strategies to overcome immune mechanisms, and so the host defense becomes more complex to defend against invading pathogens.**



- **Jawed vertebrates have developed higher complexity of defense reflected in the adaptive immune response.**

Jawed vertebrates have small molecules that are related to adaptive immunity such as: MHC, Ig (in the following pic)

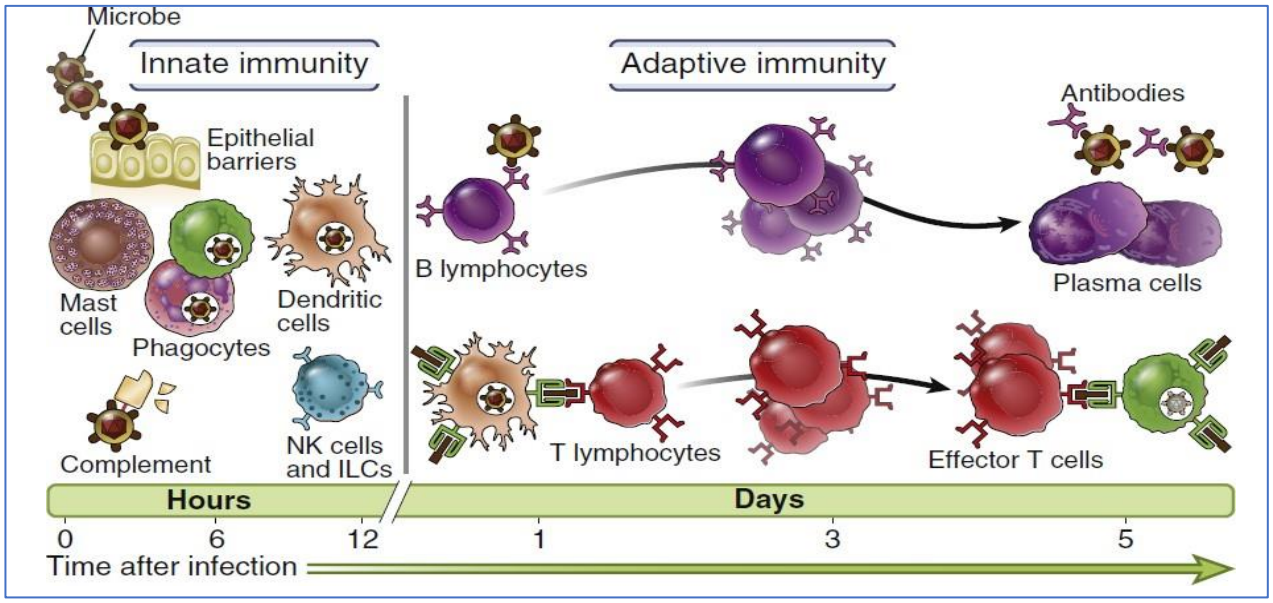


- **<u>Antigens</u> are any substance that stimulates the immune system to produce <u>antibodies</u>. <u>Antigens</u> can be bacteria, viruses, or fungi that cause infection and disease.**
- **<u>Antigens</u> may also originate from within the body ("self-antigen") but should not be attacked by the immune system in normal situations.** example: protiens

A video for the terms and definitions :(from the doctor)

https://www.immunopaedia.org.za/glossary/

INNATE AND ADAPTIVE IMMUNITY:



- **Host defenses are grouped under <u>innate</u> immunity, which provides <u>immediate</u> protection against microbial invasion** and it's not specific.
- **<u>adaptive</u> immunity, which develops <u>more slowly</u> and provides more specialized defense against infections**

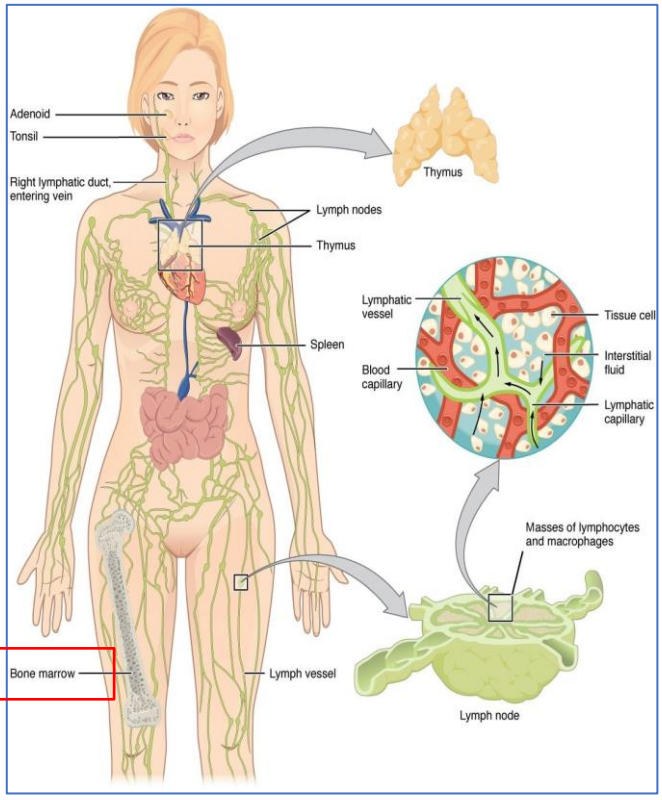
	Innate immunity	Adaptive Immunity
Components	 1. Physical and chemical barriers 2. Phagocytic leukocytes 3. Dendritic cells 4. Natural Killer cells 5. Plasma proteins (complement)	 1. Humoral immunity (B cells, which mature into antibody secreting plasma cells) 2. Cell-mediated immunity (T cells, which mature into effector helper and cytotoxic T cells)
Activity	Always present	Normally silent
Response and potency	Immediate response, but has a limited and lower potency	Slower response (over 1-2 weeks, but is much more potent
Specificity	General: can recognize general classes of pathogens (i.e. bacteria, viruses, fungi, parasites) but cannot make fine distinctions	Recognizes highly specific antigens
Course	Attempts to immediately destroy the pathogen, and if it can't, it contains the infection until the more powerful adaptive immune system acts.	Slower to respond; effector cells are generally produced in 1 week and the entire response occurs over 1-2 weeks. However, this course can vary somewhat during different responses in an individual.

LOCATION OF THE IMMUNE SYSTEM:

- **The immune system duty is to survey the whole body so it should be present <u>everywhere</u>. But there are sites where immune cells collect to fulfil their function (e.g., lymph nodes).**

→ B, T cells especially in lymph nodes, GI or thymus (but also can be found in all the body).

- **For example, in the small intestine there is lymphatic tissue that surveys intestinal pathogens called Peyer's patches.**
- **The bone marrow is an important place for generation of immune and non-immune blood cells.**

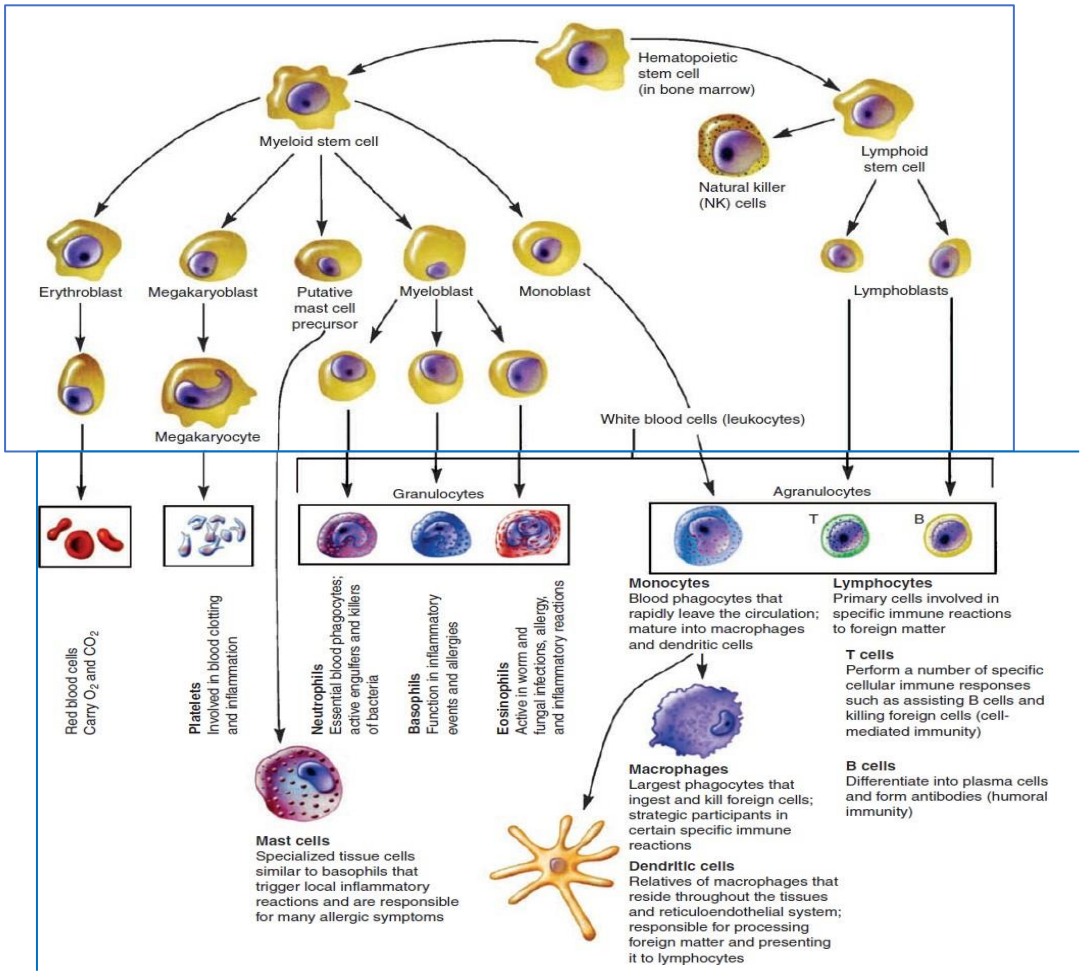


- **Immunology is a relatively <u>recent science</u> with <u>applications</u> that extend to other medical sciences, thus it is important for medical students.**
- **The immune system in an <u>ancient</u> defense mechanism composed of tissues, cells and molecules that interact with each other with <u>great complexity</u>.** (Adaptive immunity is more complex than innate immunity)

- **Parts of the immune system are continuously active and help in maintaining homeostasis.**
- **Specialized immune cells are mainly in the bone marrow and then circulate the blood or aggregate in lymph nodes.**
- **The immune system arms can be divided in general into innate and adaptive.**

CELLS OF THE IMMUNE SYSTEM:

- **The cells of the innate and adaptive immune system are normally present as circulating cells in the blood and lymph, as anatomically defined collections in lymphoid organs, and as scattered cells in virtually all tissues.**
- Cells that have immune function derived from the hematopoietic stem cells (they can divide several times to many states)
  →it derives to myeloid (that is also a stem cell that can derive to many states)
  *The same goes to lymphoid stem cells
  *The doctor mentioned the highlighted cells in the pic and their derivatives. K is part of the innate immunity



- **Phagocytes →Neutrophils and macrophages are the main phagocytes**
- **Mast Cells, Basophils, Eosinophils**
- **Antigen-Presenting Cells**
- **Lymphocytes**

Although most of these cells are found in the blood, their responses to microbes are usually <u>localized to tissues.</u>

Most of the immune cells leave the bone marrow to the circulation either remain there most of the time like (eg, neutrophils) or go tissues to serve their function (eg, mast cells).

TABLE 2–1 Normal Blood Cell Counts

		Mean Number per Microliter	Normal Range
	White blood cells (leukocytes)	7400	4500-11,000
1 ←	Neutrophils	4400	1800-7700
	Eosinophils	200	0-450
	Basophils	40	0-200
2 ←	Lymphocytes	2500	1000-4800
3 ←	Monocytes	300	0-800

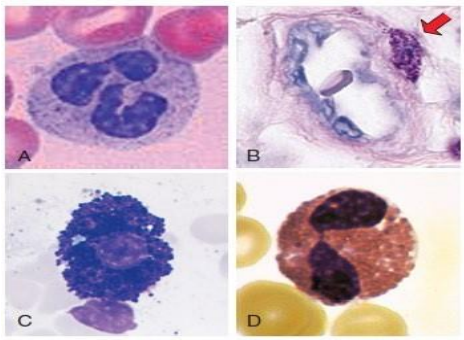
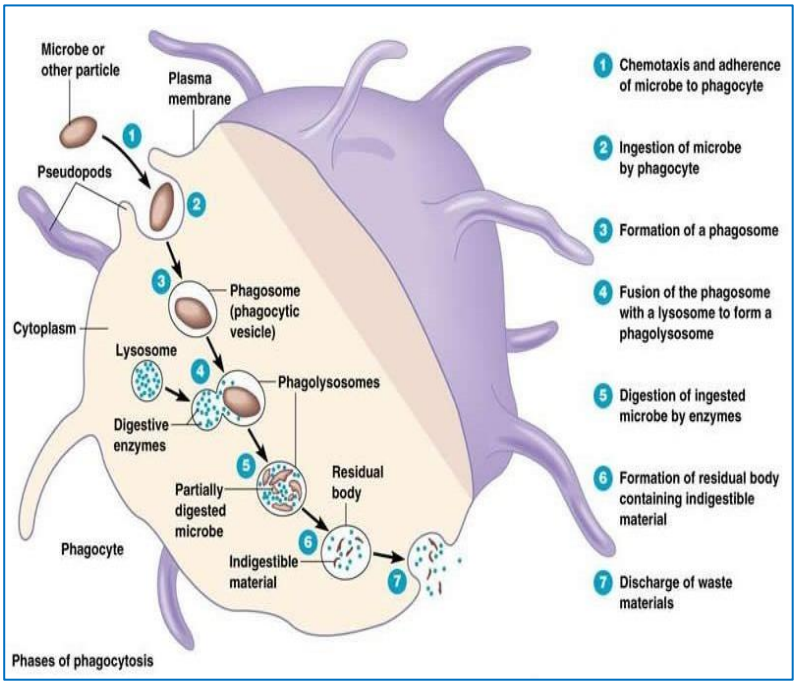


FIGURE 2–1 Morphology of neutrophils, mast cells, basophils, and eosinophils. A, The light micrograph of a Wright-Giemsa–stained blood neutrophil shows the multilobed nucleus, because of which these cells are also called polymorphonuclear leukocytes, and the faint cytoplasmic granules. **B,** The light micrograph of a Wright-Giemsa–stained section of skin shows a mast cell *(arrow)* adjacent to a small blood vessel, identifiable by the red blood cell in the lumen. The cytoplasmic granules in the mast cell, which are stained purple, are filled with histamine and other mediators that act on adjacent blood vessels to promote increased blood flow and delivery of plasma proteins and leukocytes into the tissue. *(Courtesy of Dr. George Murphy, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)* **C,** The light micrograph of a Wright-Giemsa–stained blood basophil shows the characteristic blue-staining cytoplasmic granules. *(Courtesy of Dr. Jonathan Hecht, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)* **D,** The light micrograph of a Wright-Giemsa–stained blood eosinophil shows the characteristic segmented nucleus and red staining of the cytoplasmic granules.

PHAGOCYTES:

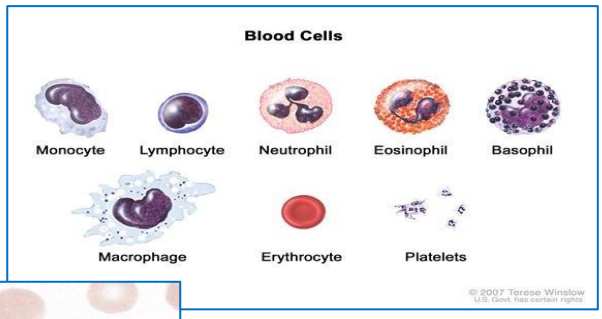
- **Phagocytes, including neutrophils and macrophages, are cells whose primary function is to identify, ingest, and destroy microbes.**



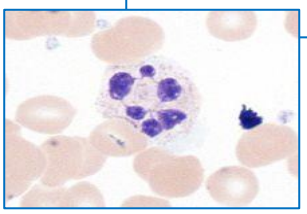
- **Phagocytes also communicate with other cells in ways that promote or regulate immune responses.**

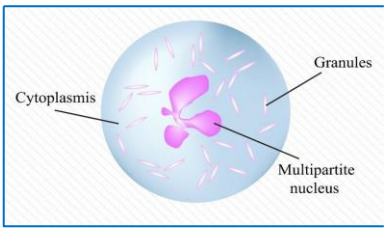
NEUTROPHILS:

- **Neutrophils, also called <u>polymorphonuclear leukocytes</u>, are the most abundant population of circulating white blood cells and mediate the earliest phases of inflammatory reactions.**



Polymorphonuclear means that their nucleus has several shapes (lobulation)





- **The nucleus of a neutrophil is <u>segmented</u> into 3-5 connected <u>lobules.</u>**

- **<u>Short lifespan</u>, they circulate for about 6 hours, Production of neutrophils** (from the bone marrow) **is <u>stimulated by granulocyte colony- stimulating factor</u> (G-CSF). An adult human produce more than 1×10^{11} neutrophils per day.** (If they are called to tissues, they may survive a few more hours)

  They are produced in large numbers but if there is no infection most of them circulate then die.

- **The cytoplasm contains granules of two types. The majority, called <u>specific granules</u>, are filled with enzymes such as lysozyme, collagenase, and elastase. The remainder are <u>azurophilic granules</u>, which are lysosomes containing enzymes and other microbicidal substances.** (Collagenases and elastases help the neutrophils to move by breaking the ECM to enter the tissue)
- **Neutrophils may migrate to sites of infection <u>within a few hours</u> after the entry of microbes.**
- **After entering tissues, neutrophils function for a few hours and then die.** (The key difference from macrophages)**.**

How do they work:

1. Identify the microbe as foreign. (Will be explained more later)
2. Bind through receptors.
3. Ingest it through phagosomes that combine with lysosome that contains digestive enzymes like lysozymes.

Called granulocytes then are named depending on the dye used. (Recall previous pics)

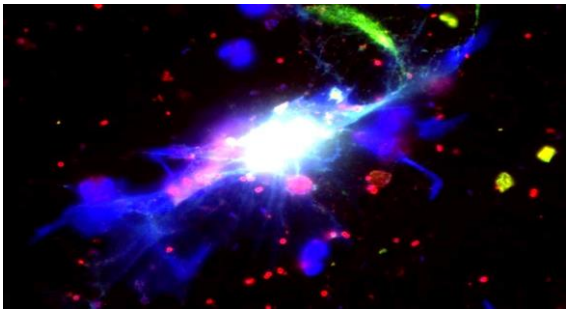
Called neutrophiles because they were seen using a neutral dye.

- functions of the neutrophils:

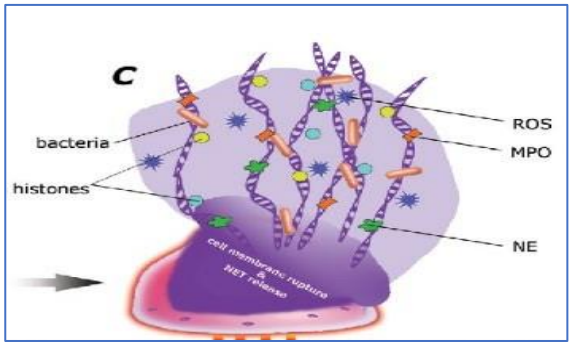
1- Engulf the microbe and destroy it.

2- Secrete granules outside the cell to help break the ECM and help in the cell maneuver.

3- Sometimes they have a programmed explosion, that extracts its DNA in the form of **Neutrophil extracellular traps (NETs) which are networks of extracellular fibers, primarily composed of DNA from neutrophils, which bind pathogens.**

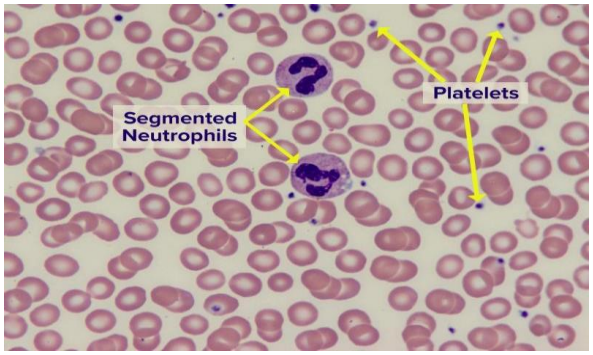


The DNA is squeezed inside the cell and when the cell explodes, the DNA is released and covers a wide area so it can bind pathogens. There are many research studies proved that NETs can also kill pathogens because they have an attached microbicidal substances such as ROS, MPO and NE.

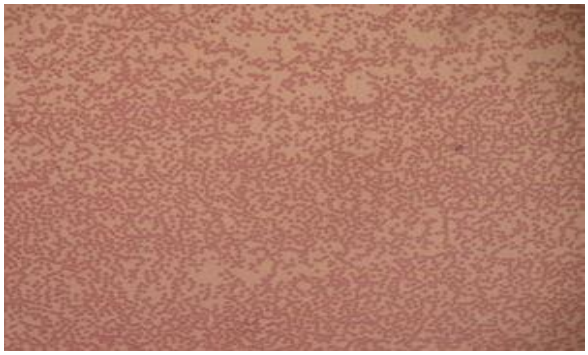


Neutropenia is an abnormally low concentration of neutrophils in the blood. Neutropenia has many causes and can be *congenital* and *acquired (e.g. cancer treatment, autoimmune diseases)*.

Neutropenia usually happens when a part of bone marrow is damaged which is commonly done by chemotherapy.



Normal



Blood film with a striking absence of neutrophils, leaving only red blood cells and platelets

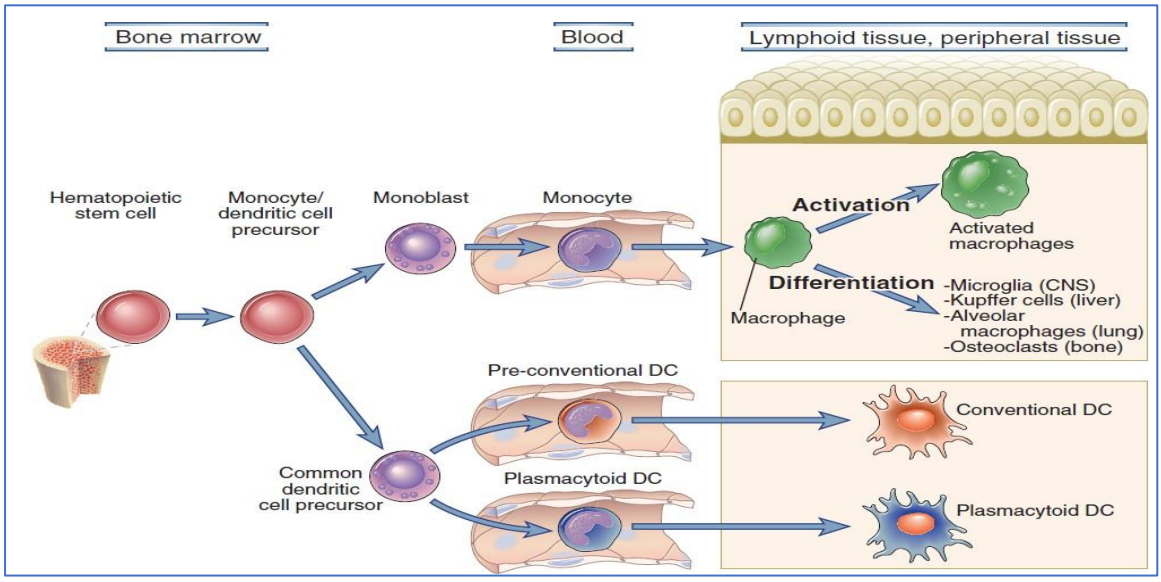
Febrile Neutropenia (case)

JP is a 34-year-old Caucasian male who is admitted to inpatient oncology service for induction chemotherapy for a recent diagnosis of acute myeloid leukemia (AML). His induction chemotherapy regimen consists of 7 + 3 induction chemotherapy with cytarabine and daunorubicin. He was placed on neutropenic precautions, started on appropriate antimicrobial prophylaxis, and a port was placed for chemotherapy administ rat ion. Ten days after the completion of his induction chemotherapy (day 17), he spiked a fever of 38.8°C (101.8°F) and complained of chills and nausea.

One of the treatments of Neutropenia is granulocyte colony-stimulating factor which we've discussed before.

PHAGOCYTES

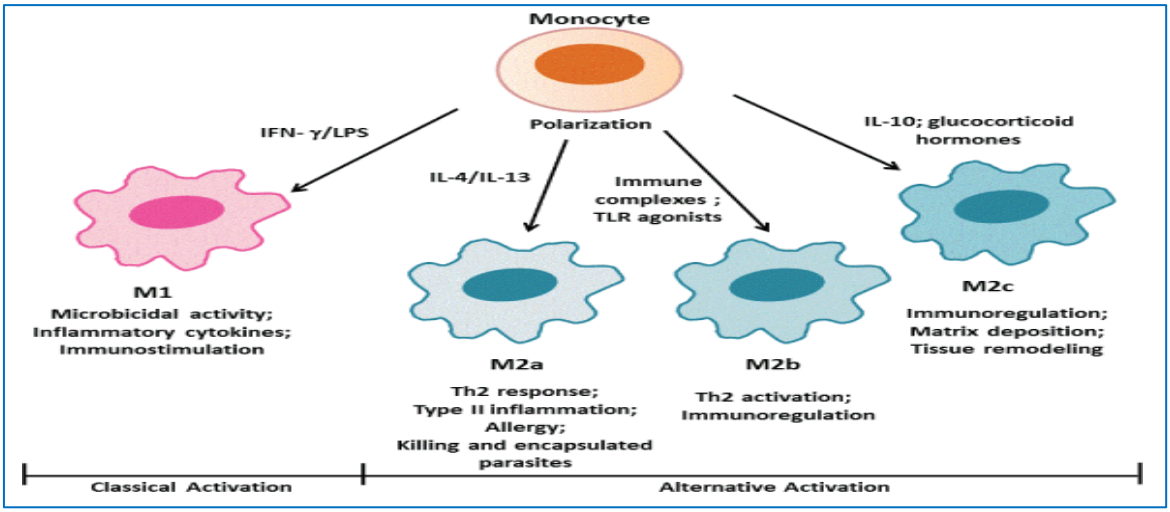
- **The cells of the mononuclear phagocyte system originate from a common precursor in the bone marrow, circulate in the blood as monocytes, and mature and become activated in various tissues.**
- **Once monocytes enter tissues, mature and become macrophages. Macrophages in different tissues have been given special names to designate specific locations.**



Cytokine: any mediator that is produced by a cell and recognized by the other.

So, when the monocyte enters a certain tissue and receive a certain cytokine it will be activated. Let's take the classical activation as an example. The monocyte received IFN-γ or LPS, so it's activated as a M1 microphage which does the three points in the following figure:

Macrophages can acquire distinct functional capabilities, depending on the types of activating stimuli



- **In addition to ingesting microbes, macrophages also ingest dead host cells as part of the cleaning up process after infection or sterile tissue injury.**

After the infection is reduced, the conc. of IFN-γ and LPS cytokines will be decreased, and the conc. of the anti-inflammatory cytokines will be increased such as IL-10 which leads to the alternative activation that calm down the inflammation.

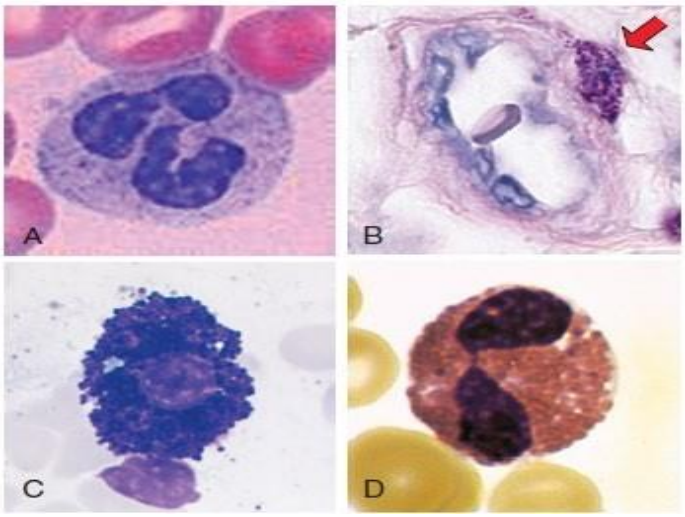
- **Activated macrophages secrete proteins, called cytokines, that bind to signalling receptors on other cells and thereby instruct those cells to respond in ways that contribute to host defence.**
- **Macrophages serve as APCs that display antigens to and activate T lymphocytes.** As the function of dendritic cells.
- **Another important function of macrophages is to promote repair of damaged tissues by stimulating new blood vessel growth (angiogenesis) and synthesis of collagen-rich extracellular matrix (fibrosis).**
- **Macrophage-like cells are phylogenetically the oldest mediators of innate immunity. Drosophila** (fruit fly) **responds to infection by surrounding microbes with "hemocytes," which are similar to macrophages, and these cells phagocytose the microbes and wall off the infection.**

MAST CELLS, BASOPHILS, ESINOPHILS

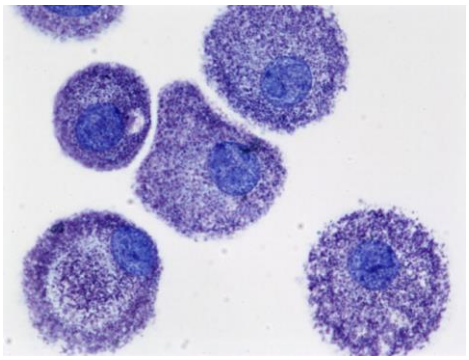
Basophils and eosinophils are not that common in blood, so they approximately make up less than 5% in the circulation. Thus, they don't have an important role in the immune response like neutrophils.

All three cell types share the common feature of having cytoplasmic granules filled with various inflammatory and antimicrobial mediators.

Another common feature of these cells is their involvement in immune responses that protect against helminths and immune responses that cause allergic diseases. An example: a person with asthma will have a lot of basophils and eosinophils in his lungs tissue and the mast cells that are residing in the tissue (B figure).



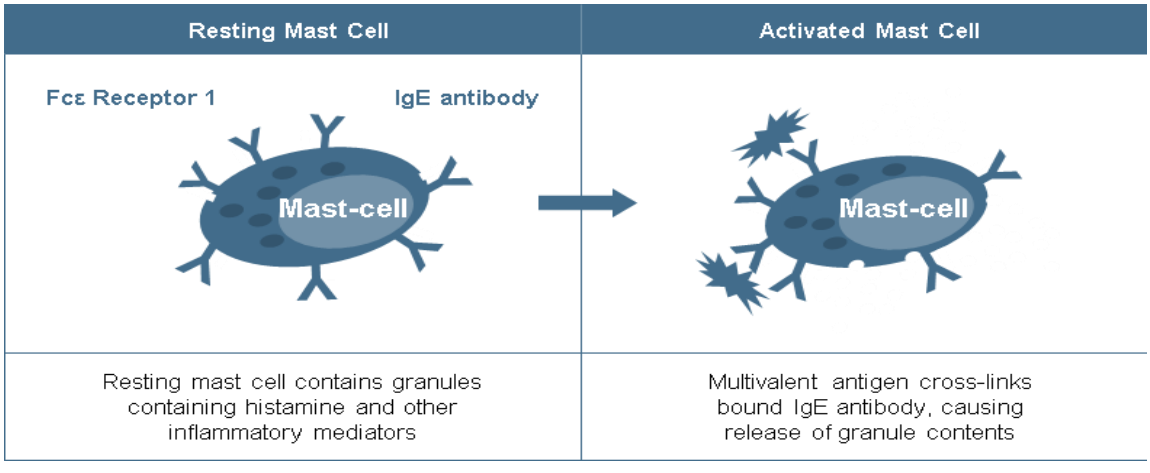
MAST CELLS



Mast cells are bone marrow–derived cells that are present in the skin and mucosal epithelium and contain abundant cytoplasmic granules filled with cytokines histamine, and other mediators.

Mature mast cells are not found in the circulation but are constitutively present in healthy tissues, usually adjacent to small blood vessels and nerves.

Mast cells express plasma membrane receptors for IgE and IgG antibodies and are usually coated with these antibodies

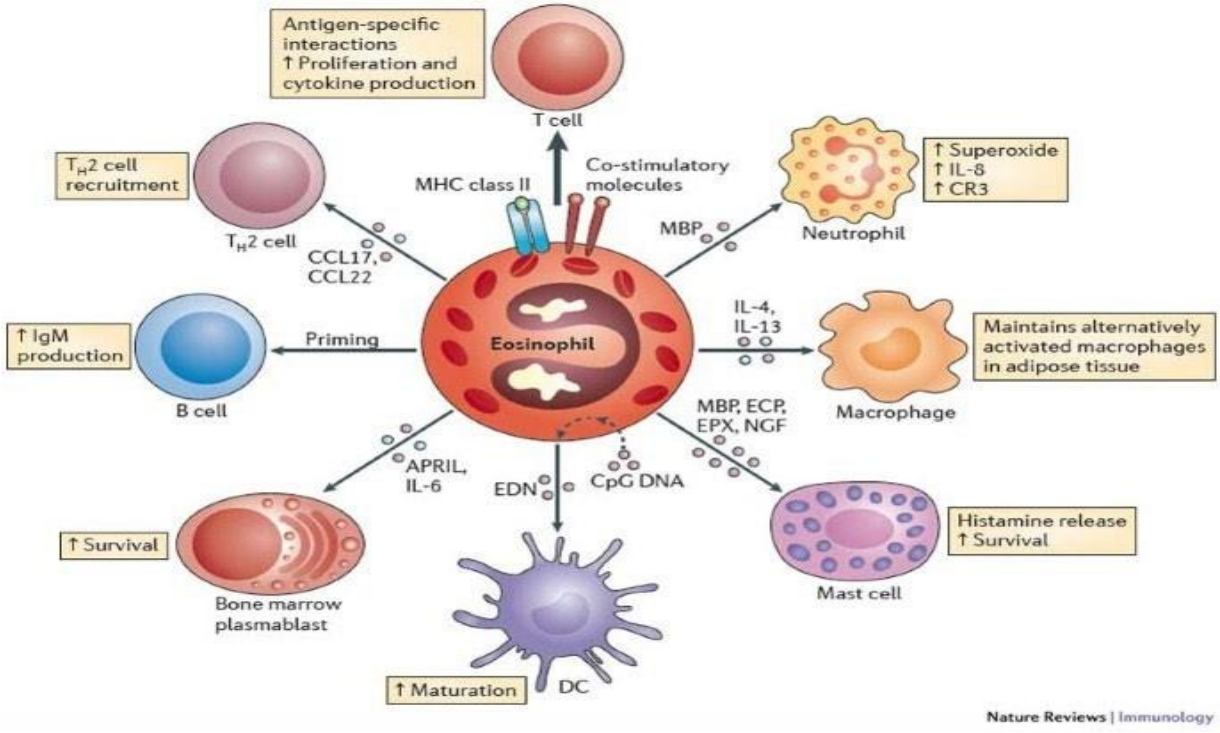


BASOPHILS

- Basophils are blood granulocytes with many structural and functional similarities to mast cells.
- Like mast cells, basophils express IgG and IgE receptors, bind IgE, and can be triggered by antigen binding to the IgE.
- Basophils constitute less than 1% of blood leukocytes, normally not present in and their importance is uncertain.
- When they participate in allergic reactions or responses to parasites, basophils release histamine and many other biologically active molecules that can contribute to inflammation.

EOSINOPHILS

- Eosinophils are blood granulocytes that express cytoplasmic granules containing enzymes that are harmful to the cell walls of parasites but can also damage host tissues.
- Several lines of evidence suggest that deficiency of eosinophils is not associated with any characteristic abnormality.



For more information:

Eosinophils: changing perspectives in health and disease
https://www.nature.com/articles/nri3341