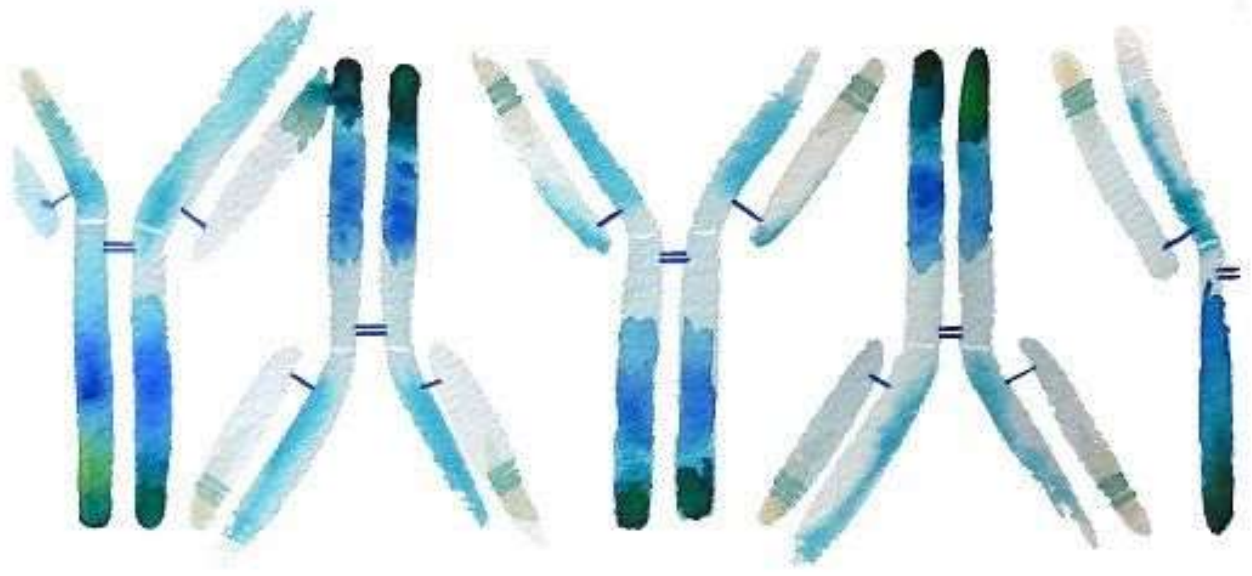
Medical Immunology



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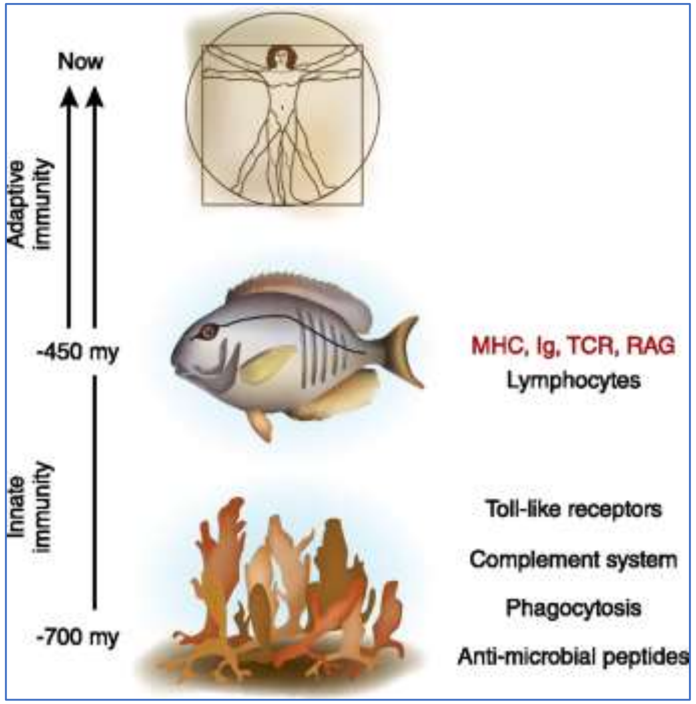
Lecture 2

- The immune system includes the role of **physical**, **cellular**, and **chemical systems** that are in place and that respond to all aspects of **foreignness**.
- The immune system targets any “foreign” object, so the first step is to **recognize** what is self and non- self.
- 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** similar to the cardiovascular and renal systems.

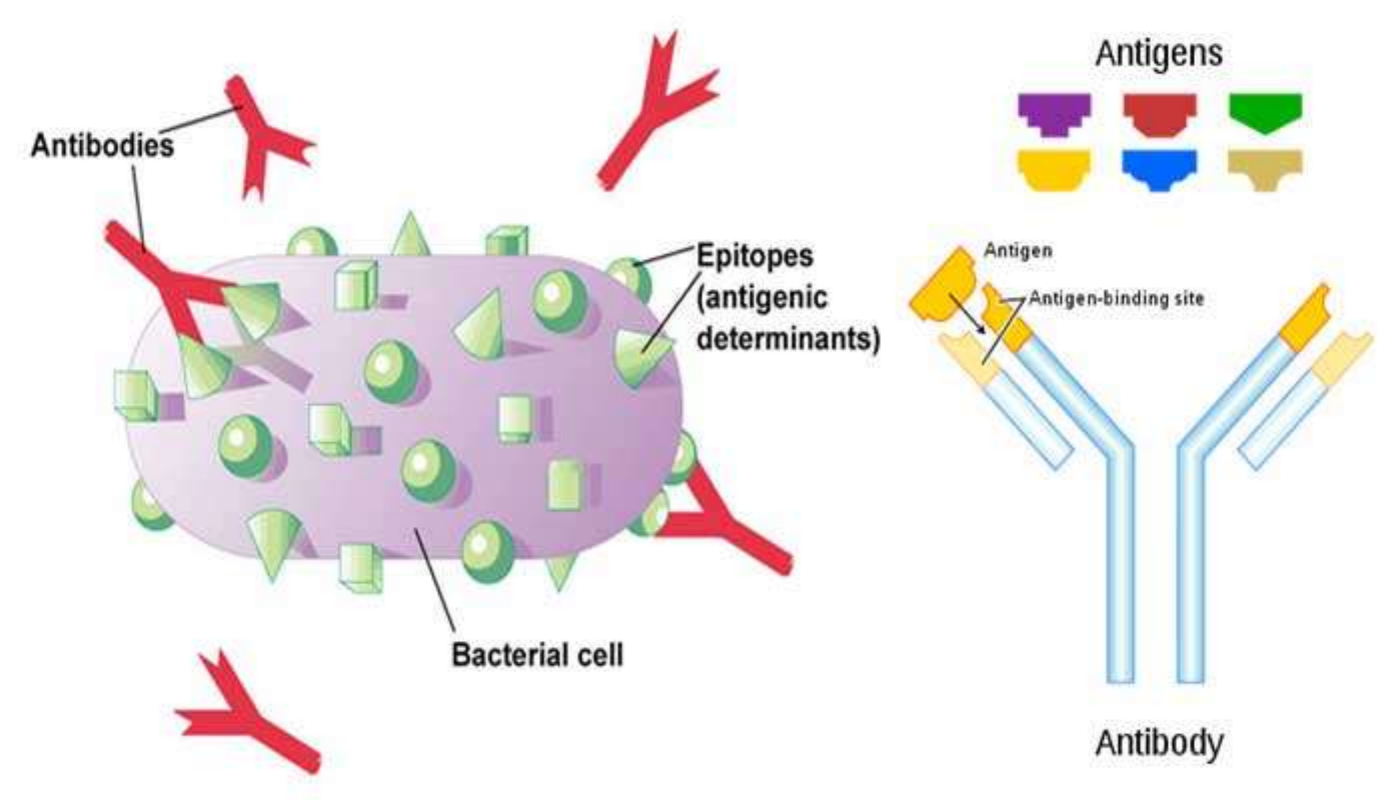
- Mechanisms for discriminating "**self" from "non-self"** evolved to accomplish the task of fighting pathogens, launching a long history of **host-pathogen co-evolution.**
- Virtually all organisms have at least one form of defence that helps repel disease-causing organisms.
- Pathogens evolve new strategies to over come immune mechanisms, and so the host defence becomes more complex to defend against invading pathogens.
- **Jawed vertebrates** have developed higher complexity of defence reflected in the **adaptive immune response**.

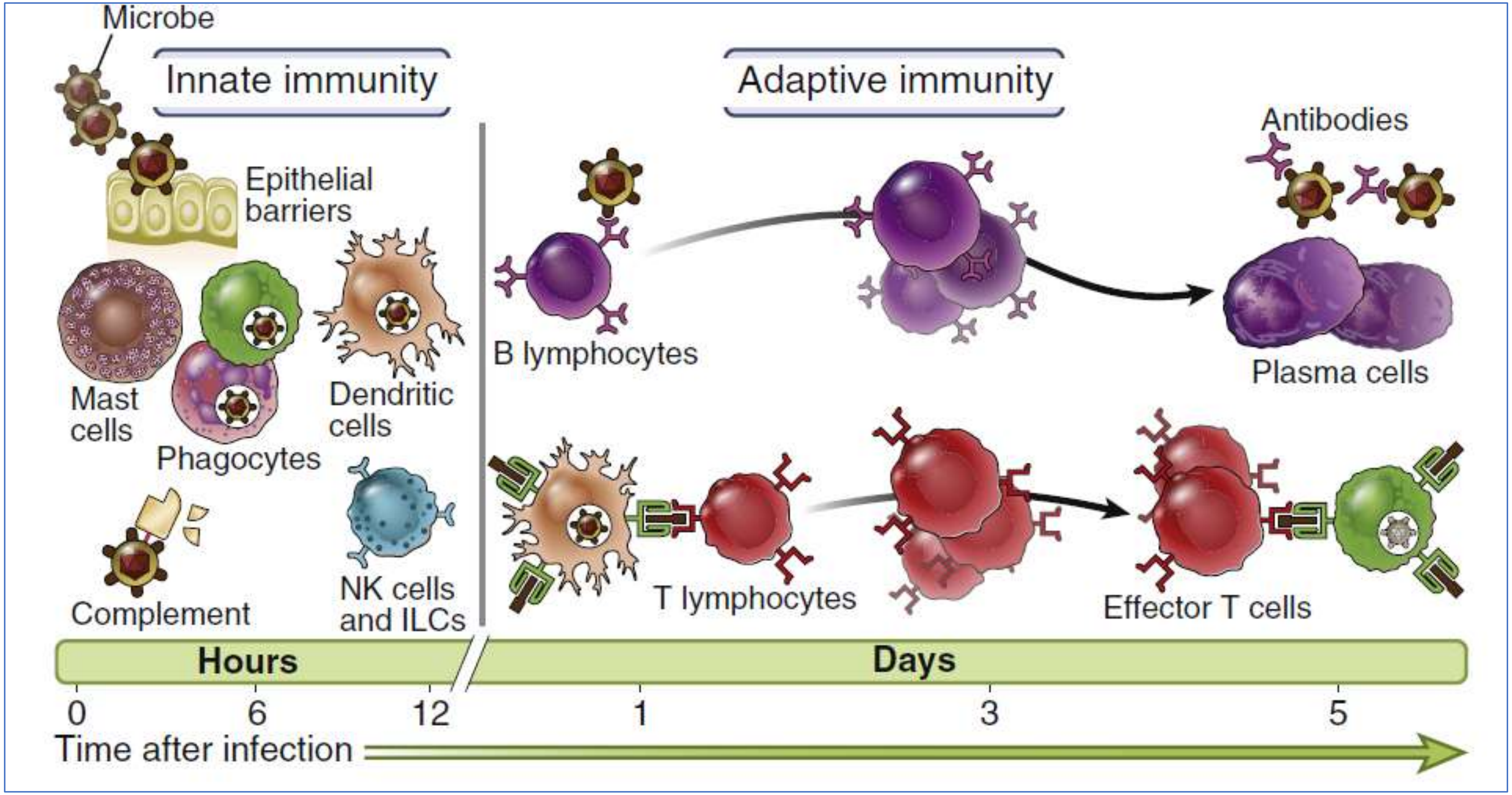
Transplantation of parts of sponge to other sponges is met by an immune response



- **Antigens** are any substance that stimulates the immune system to produce **antibodies**. **Antigens** can be bacteria, viruses, or fungi that cause infection and disease.

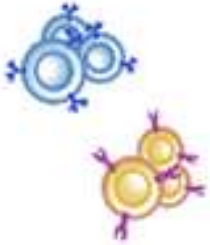
- **Antigens** may also originate from within the body ("self-antigen"), but should not be attacked by the immune system in normal situations.





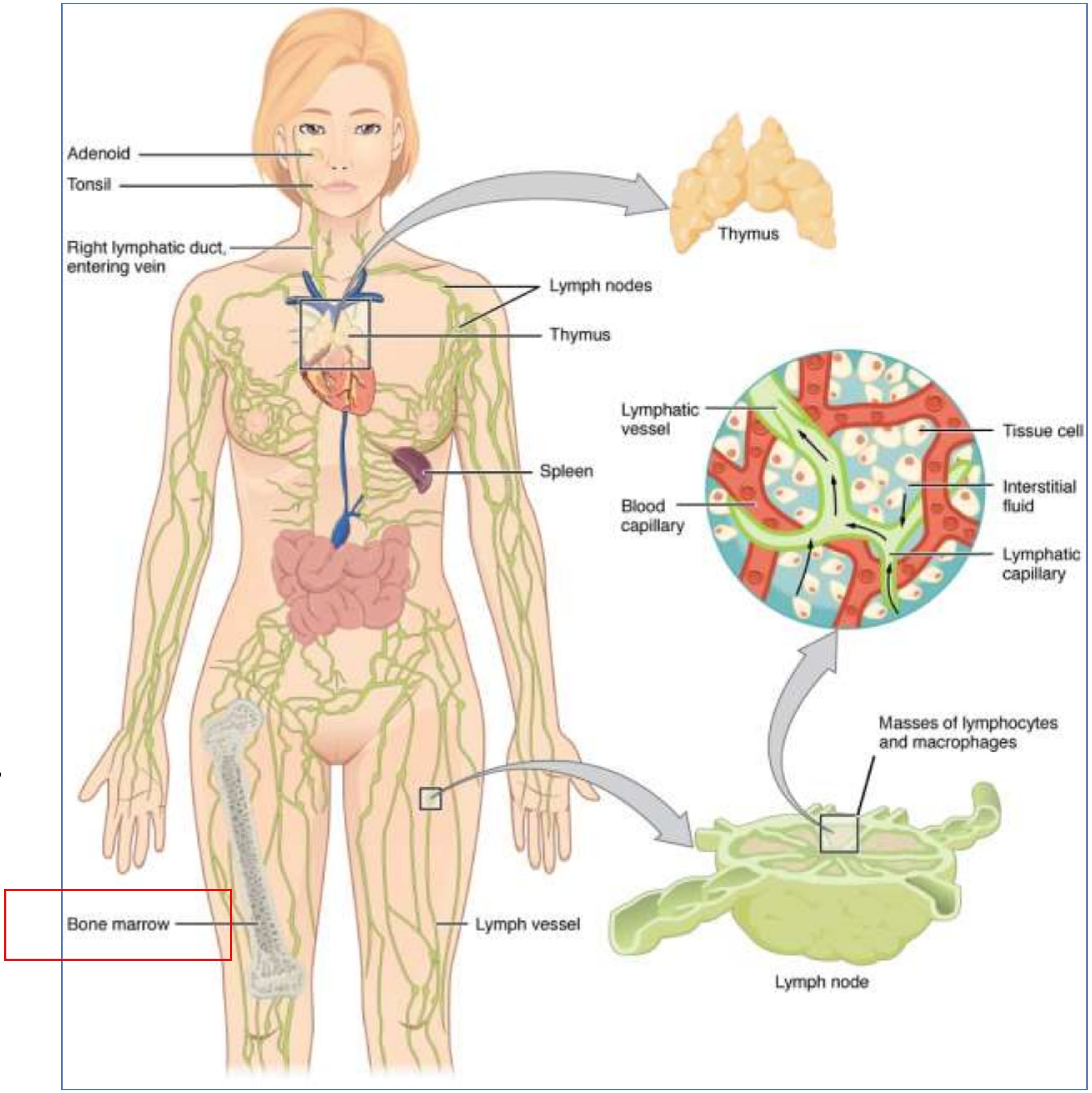
- Host defenses are grouped under **innate** immunity, which provides **immediate** protection against microbial invasion, and **adaptive** immunity, which develops **more slowly** and provides more specialized defense against infections

Immunology introduction / INNATE AND ADAPTIVE IMMUNITY

	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.

Immunology introduction / Location of the immune system

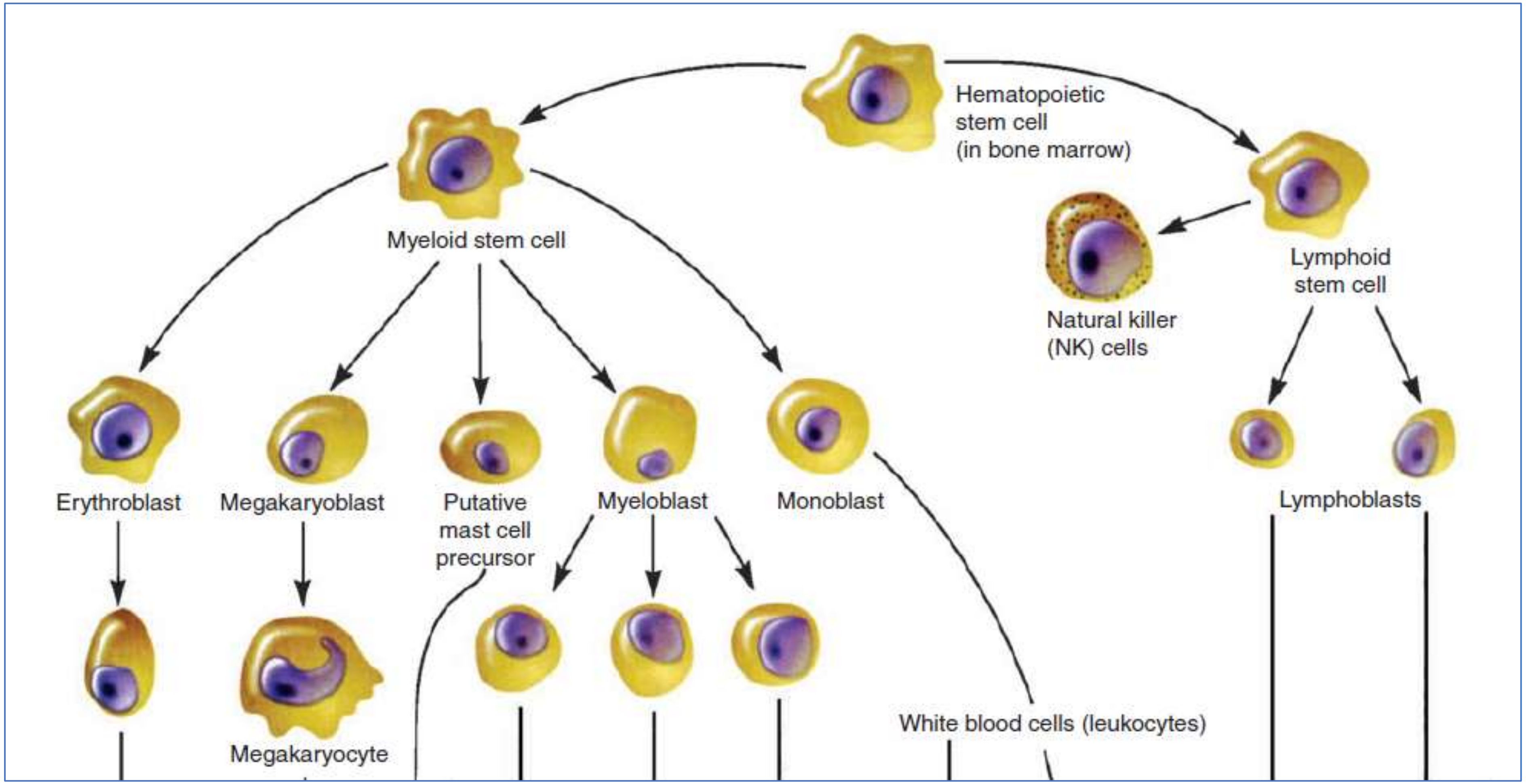
- The immune system duty is to survey the whole body so it should be present **everywhere**. But there are sites where immune cells collect to fulfil their function (e.g. lymph nodes).
- For example, in the small intestine there is lymphatic tissue that surveys intestinal pathogens called Peyer's patches.
- The bone marrow is an important place for generation of immune and non-immune blood cells.



- Immunology is a relatively **recent science** with **applications** that extend to other medical sciences, thus it is important for medical students.
- The immune system in an **ancient** defence mechanism composed of tissues, cells and molecules that interact with each other with **great complexity**.
- 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**.

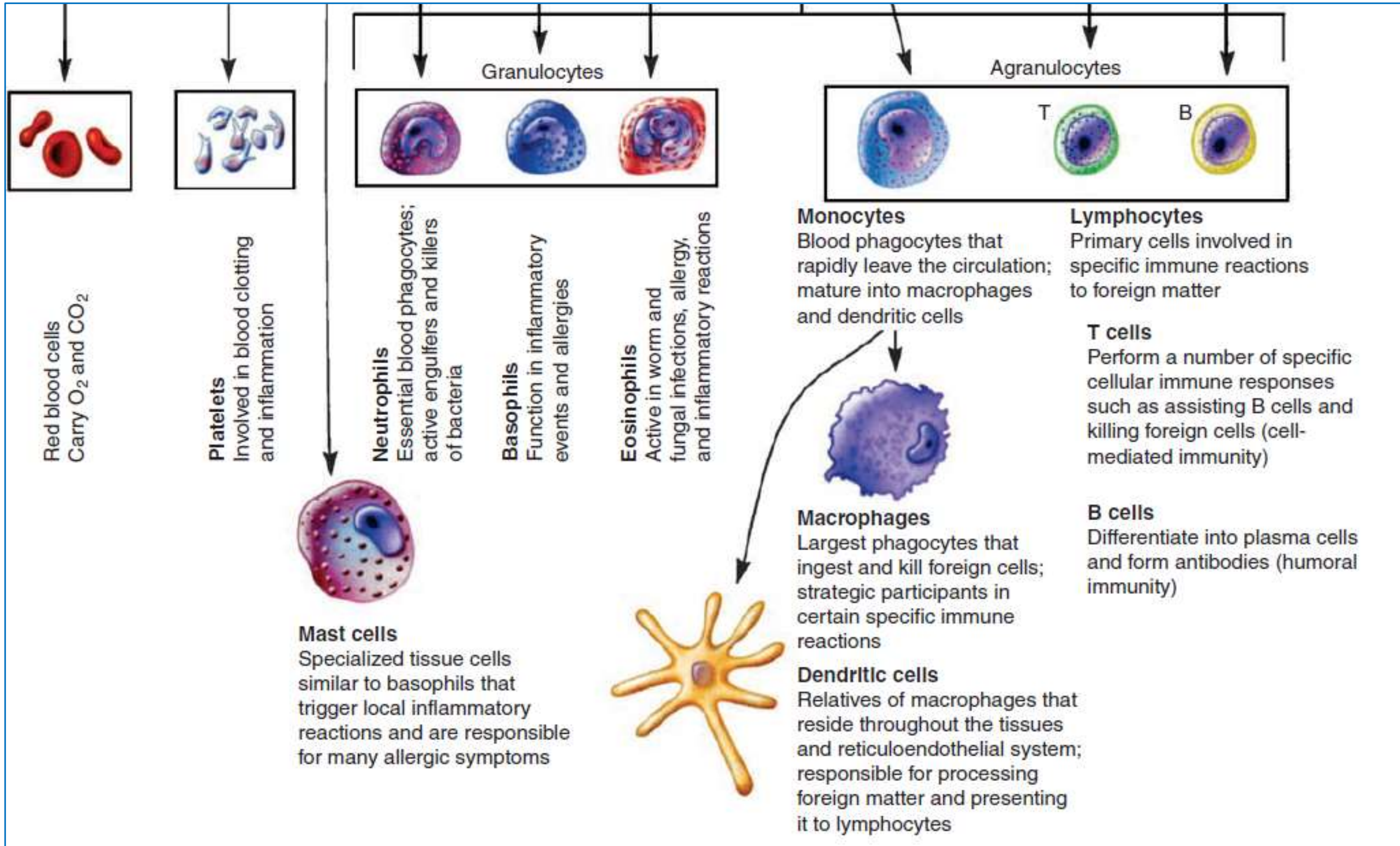
Cells of the immune system

- 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 of the immune system

- **Phagocytes**
- **Mast Cells, Basophils, Eosinophils**
- **Antigen-Presenting Cells**
- **Lymphocytes**



Cells of the immune system

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

- Although most of these cells are found in the blood, their responses to microbes are usually **localized to tissues.**

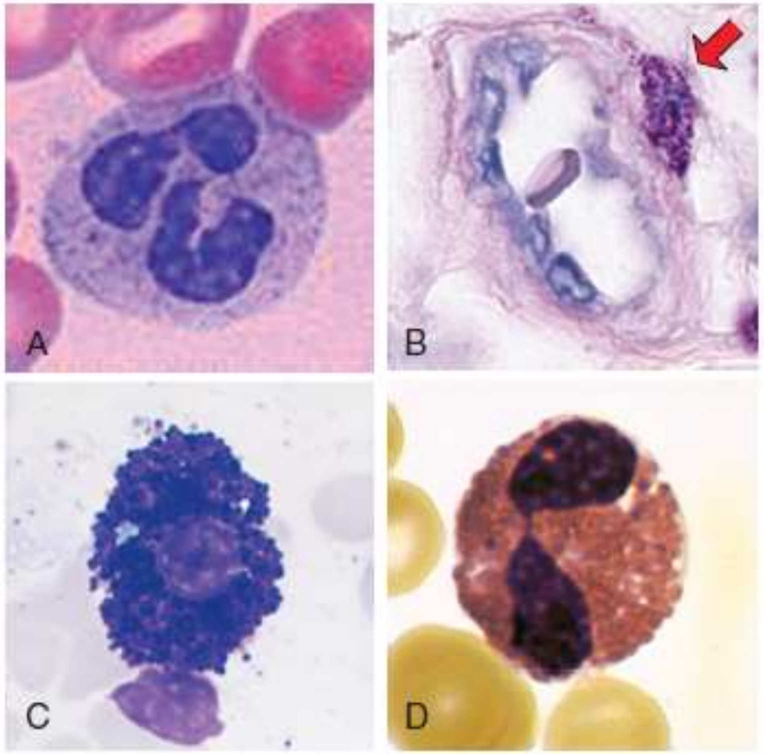
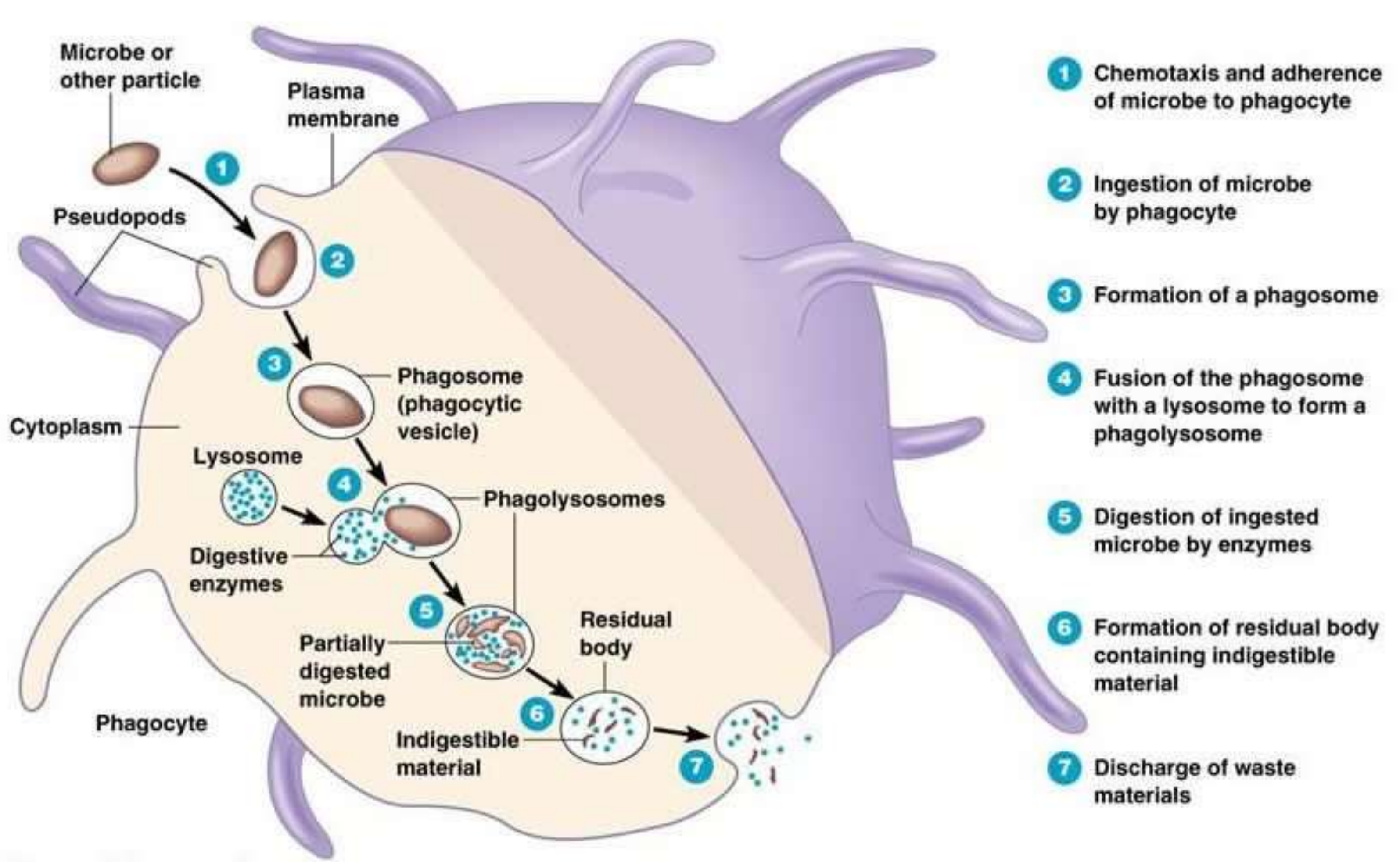


FIGURE 2–1 Morphology of neutrophils, mast cells, basophils, and eosinophils. A, The light micrograph of a Wright-Giemsa–stained blood neutrophil shows the multilobed nucleus, because of which these cells are also called polymorphonuclear leukocytes, and the faint cytoplasmic granules. **B,** The light 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.

Cells of the immune system / 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.



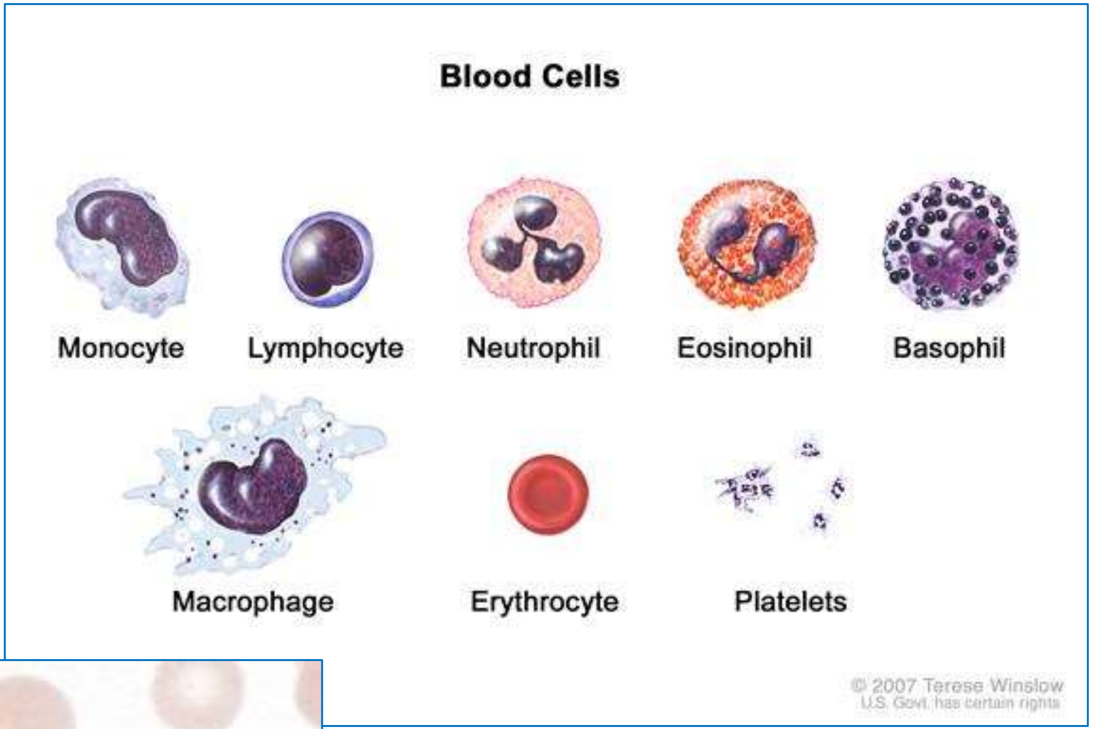
Phases of phagocytosis

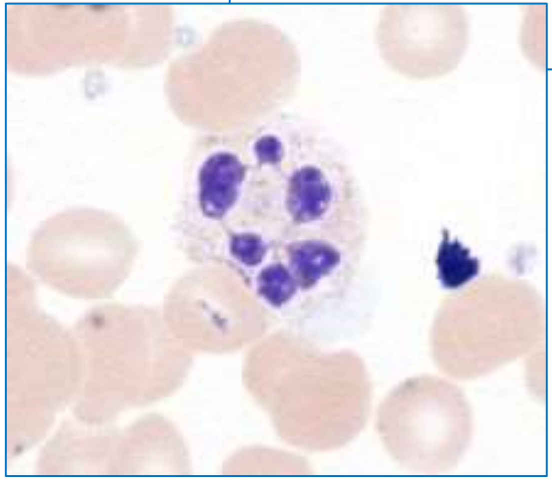
Cells of the immune system / Phagocytes/ Neutrophils

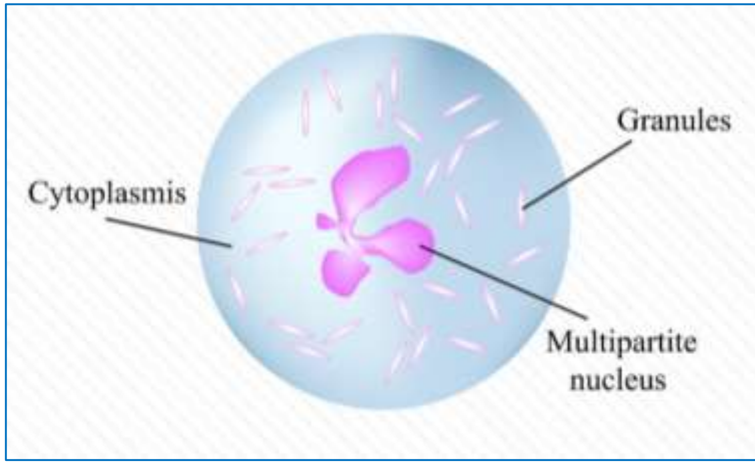
- Neutrophils, also called **polymorphonuclear leukocytes**, are the most abundant population of circulating white blood cells and mediate the earliest phases of inflammatory reactions.

- The nucleus of a neutrophil is **segmented** into 3-5 connected **lobules**

- **Short lifespan**, they circulate for about 6 hours, Production of neutrophils is **stimulated by granulocyte colony-stimulating factor** (G-CSF). An adult human produces more than 1×10^{11} neutrophils per day





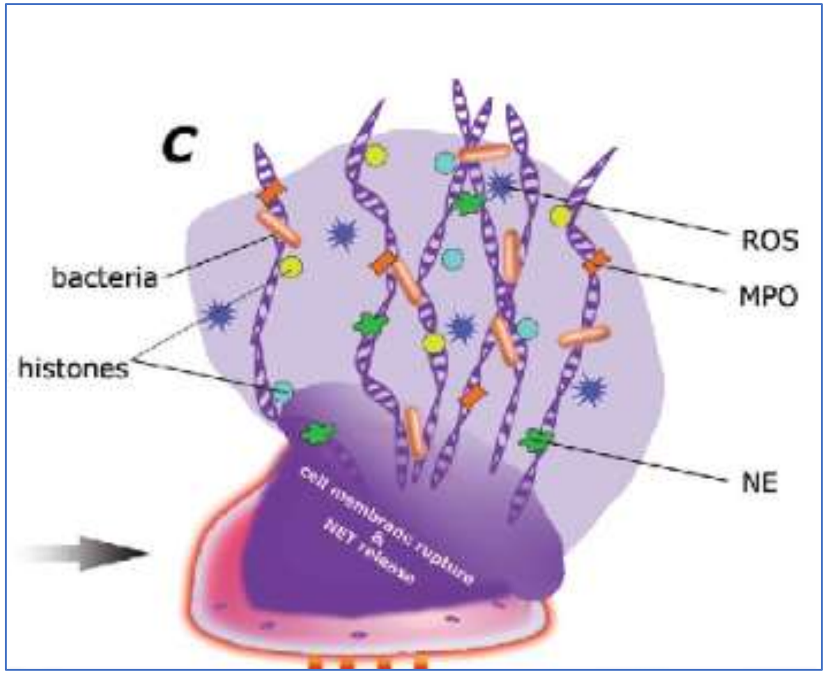


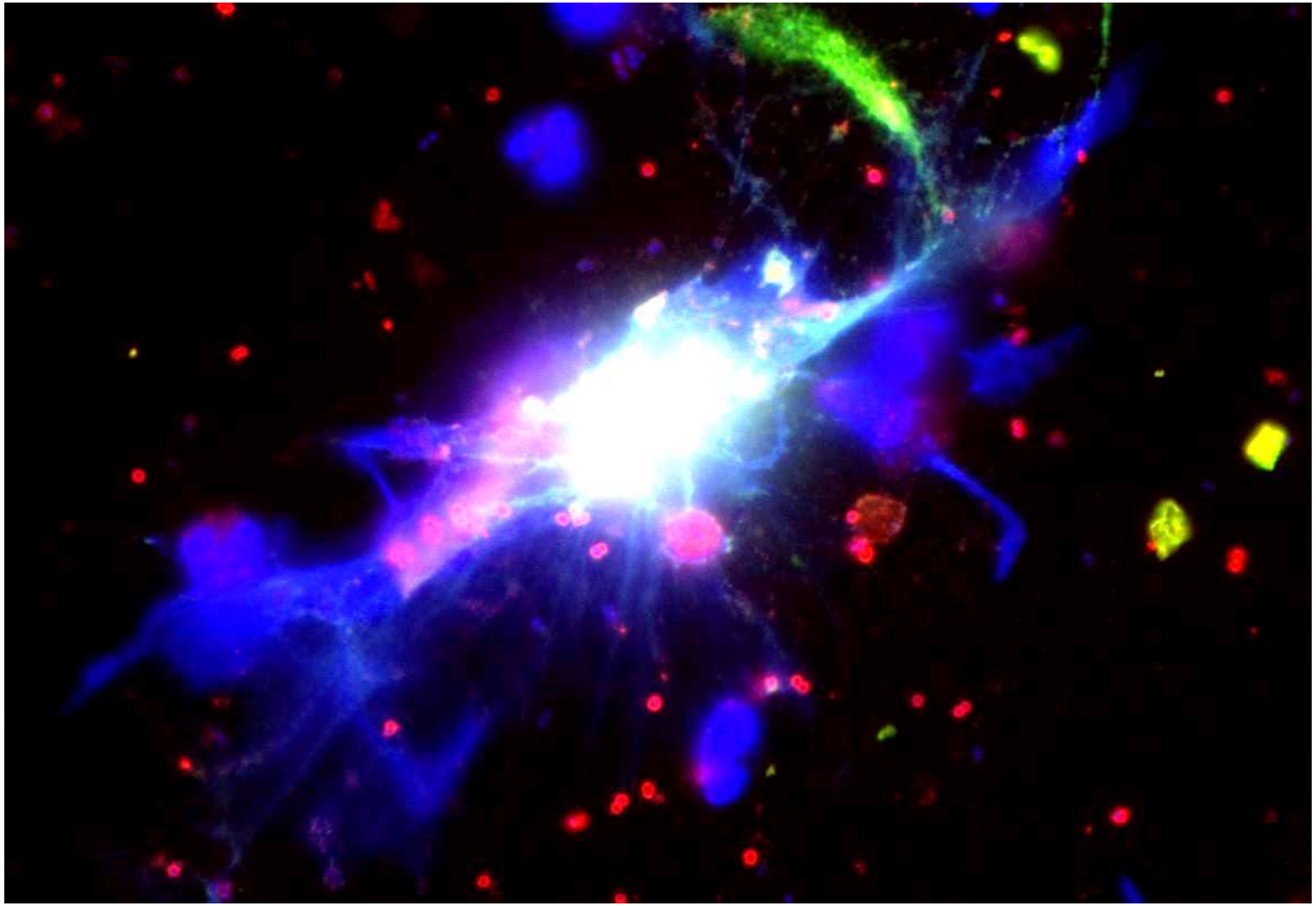
- The cytoplasm contains granules of two types. The majority, called **specific granules**, are filled with enzymes such as lysozyme, collagenase, and elastase. The remainder are **azurophilic granules**, which are lysosomes containing enzymes and other microbicidal substances.

- Neutrophils may migrate to sites of infection **within a few hours** after the entry of microbes.

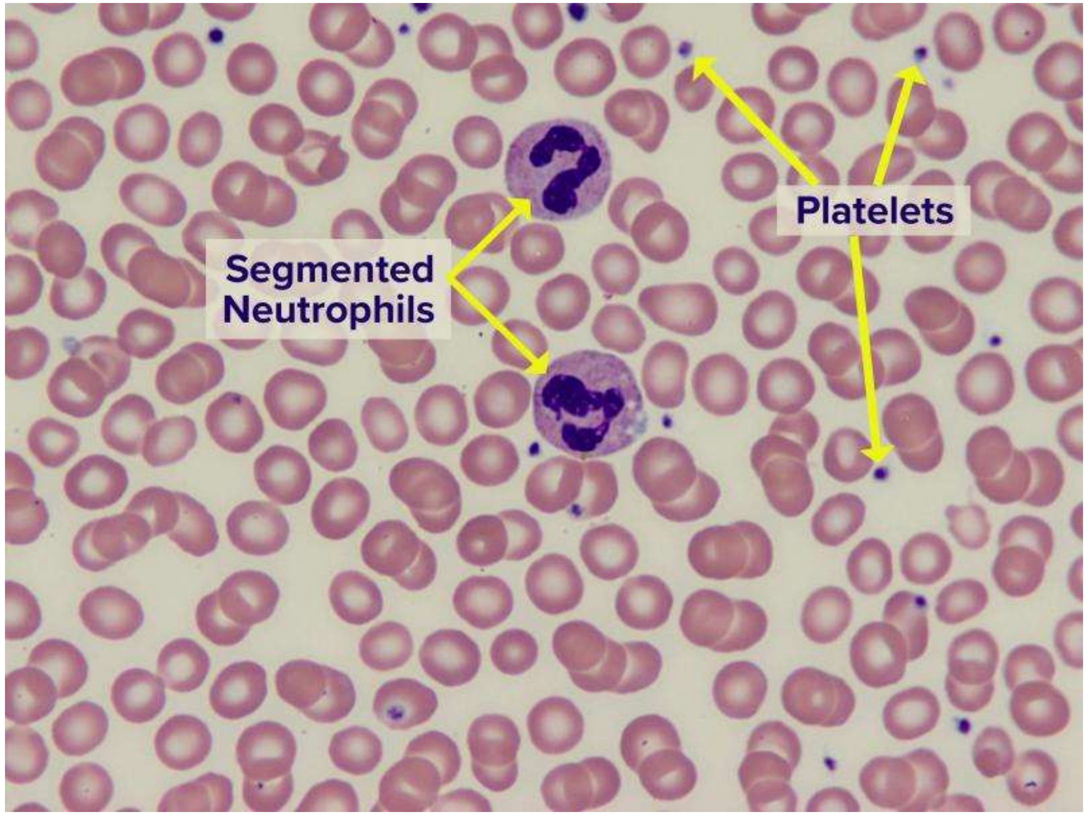
- After entering tissues, neutrophils function for a few hours and then die.

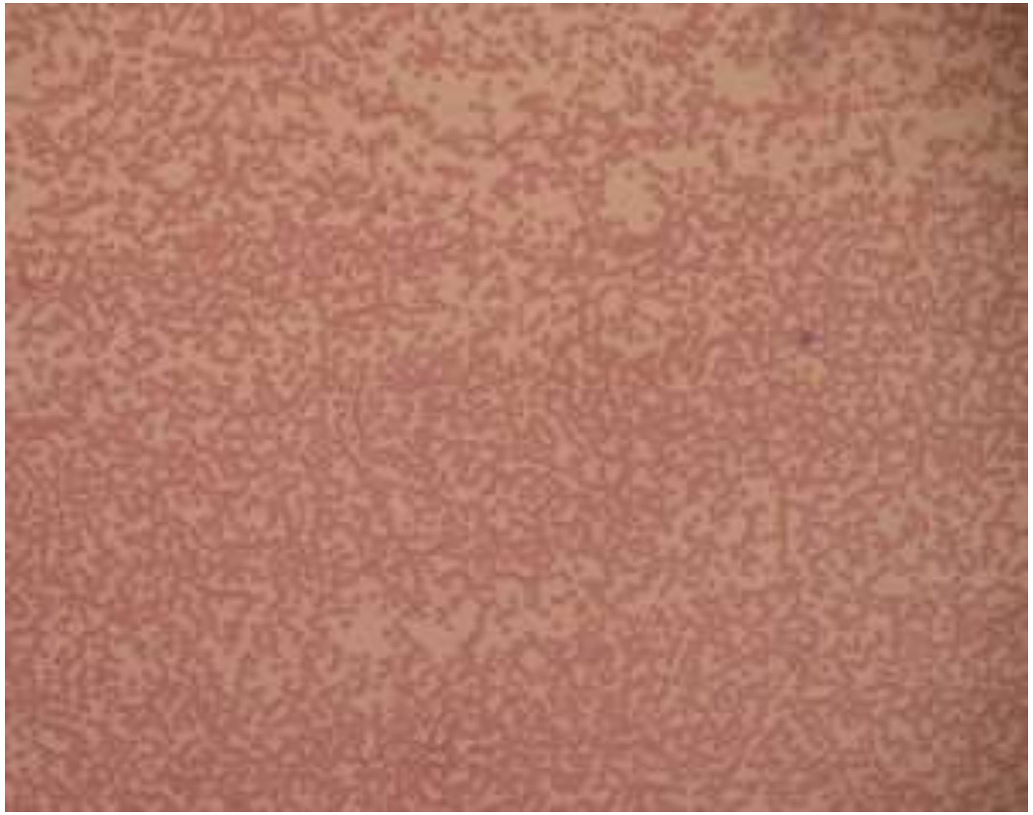
Cells of the immune system / Phagocytes/ Neutrophils





- Neutrophil extracellular traps (NETs) are networks of extracellular fibers, primarily composed of DNA from neutrophils, which bind pathogens.





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

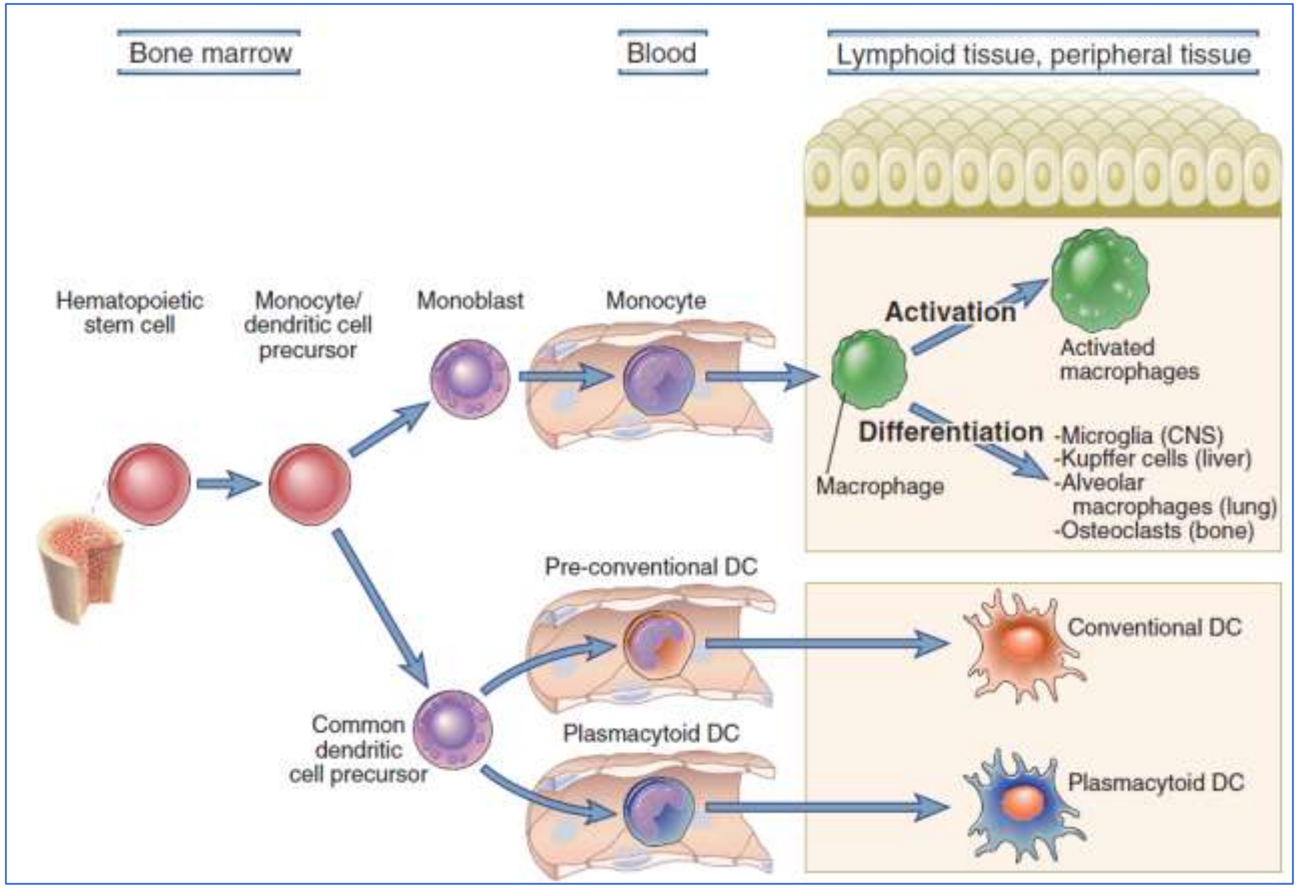
Neutropenia is an abnormally low concentration of neutrophils in the blood. Neutropenia has many causes and can be *congenital* and *acquired (e.g. cancer treatment, autoimmune diseases)*.

Febrile Neutropenia

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 administration**. 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.

- 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.



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

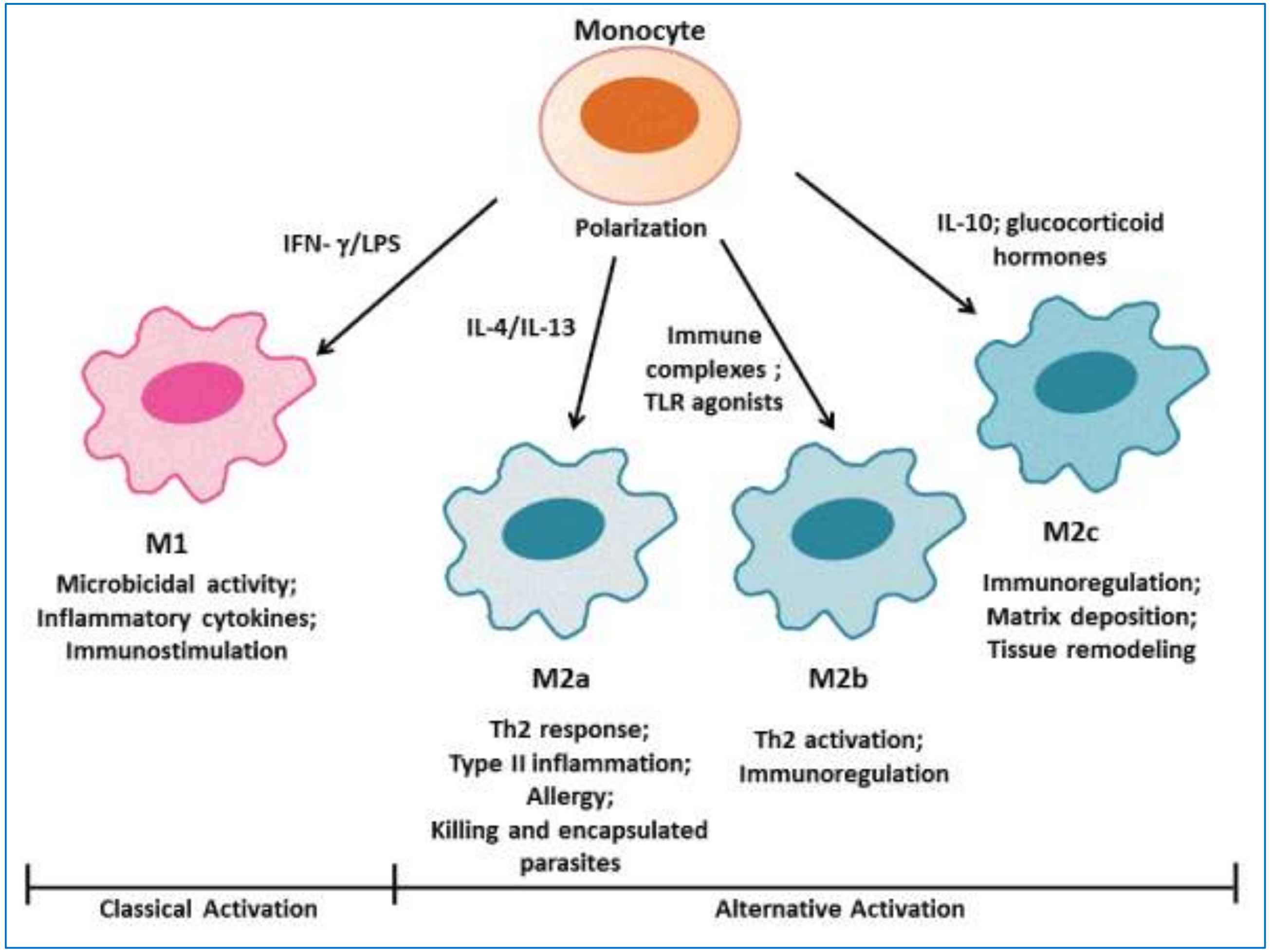
- Activated macrophages secrete proteins, called **cytokines**, that bind to signalling receptors on other cells and thereby **instruct** those cells to respond in ways that contribute to host defence.

- Macrophages serve as APCs that **display antigens** to and activate T lymphocytes.

- 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).

Cells of the immune system / Phagocytes/ *Macrophages*

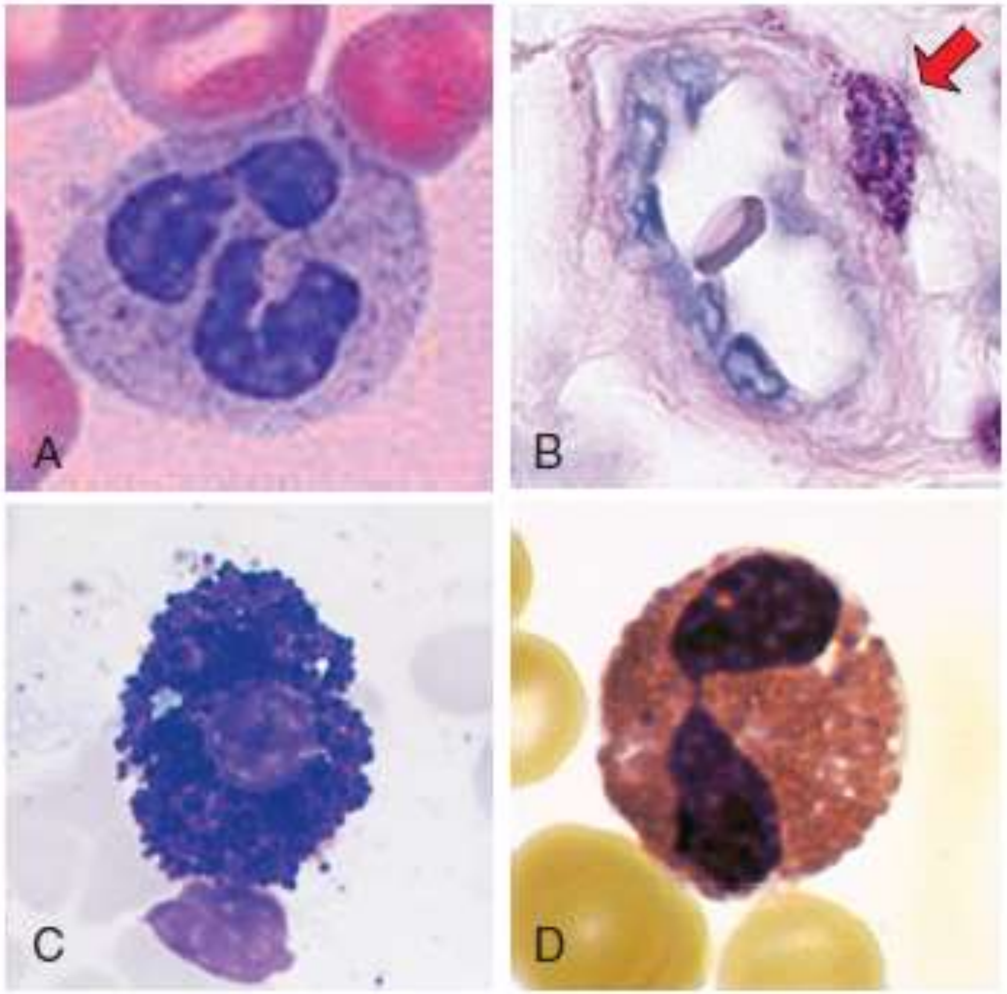
Macrophage-like cells are phylogenetically the **oldest mediators of innate immunity**. ***Drosophila*** responds to infection by surrounding microbes with "hemocytes,"
which are similar to macrophages, and these cells phagocytose the microbes and wall off the infection.



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

- 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**

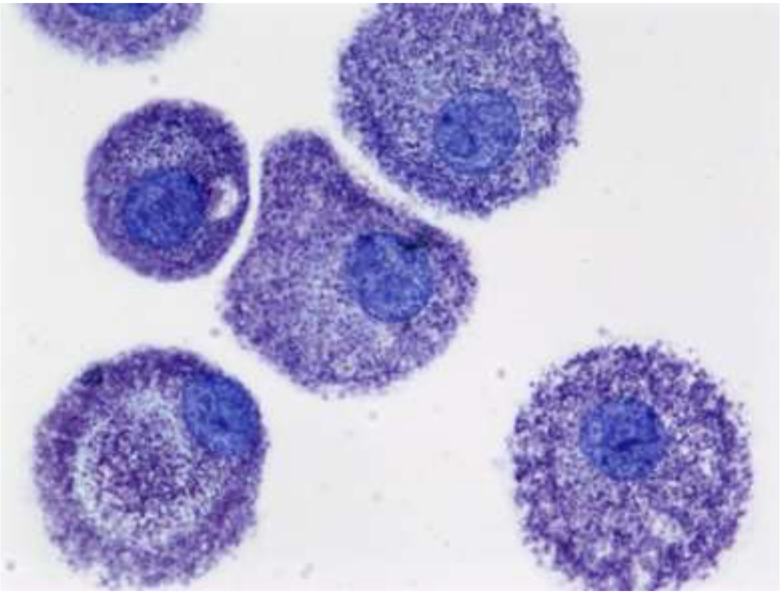


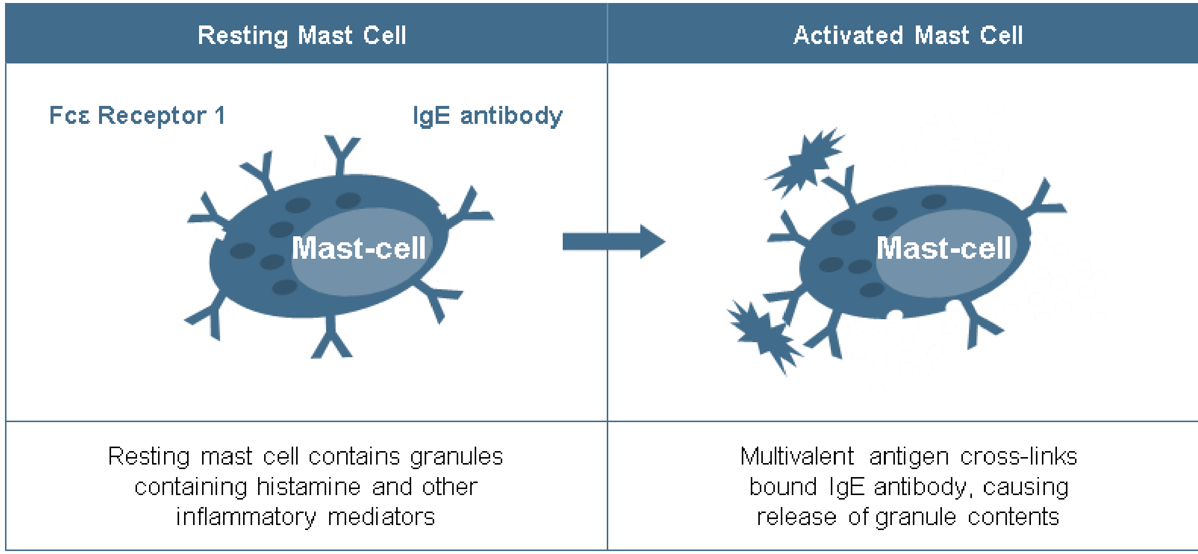
Cells of the immune system / Mast Cells

- 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





Cells of the immune system / Basophils

- Basophils are blood granulocytes with many structural and functional similarities to mast cells.

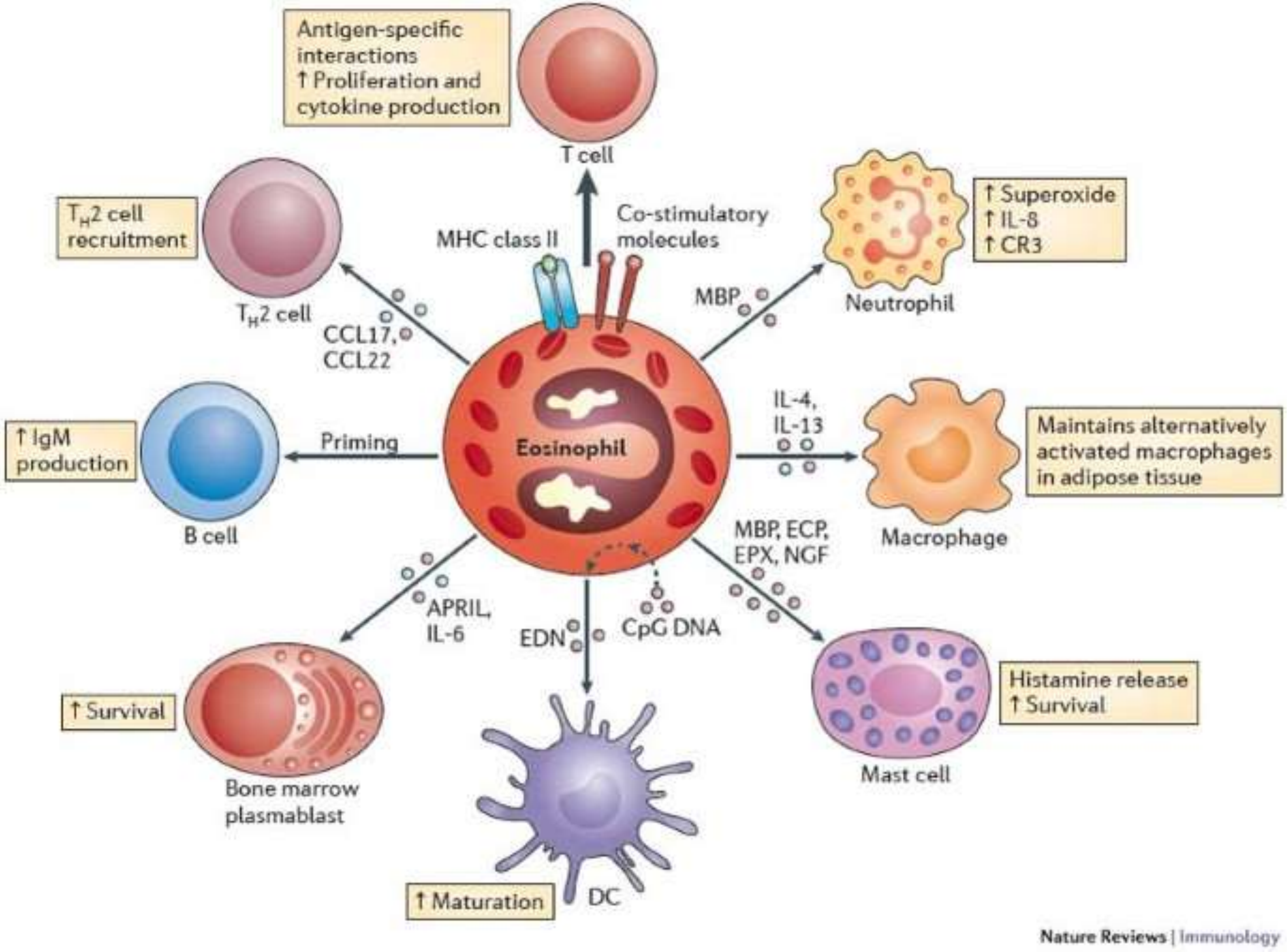
- Like mast cells, basophils express IgG and IgE receptors, bind IgE, and can be triggered by antigen binding to the IgE.

- Basophils constitute **less than 1%** of blood leukocytes, normally **not present** in tissues 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 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.



Eosinophils: changing perspectives in health and disease

https://www.nature.com/articles/nri3341

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 2. Cells and tissues of the immune system