# INTRODUCTION TO THE IMMUNE SYSTEM

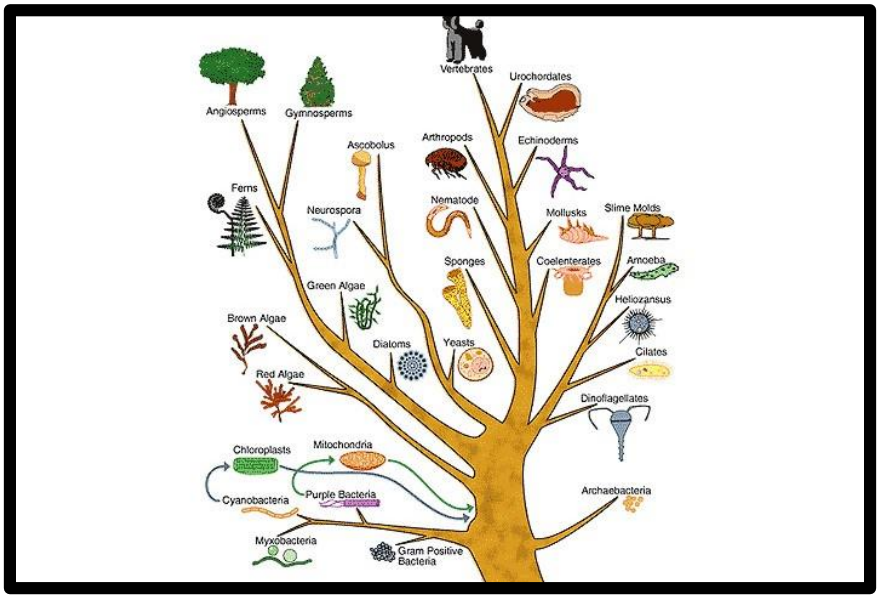
# Evolution and why the immune system is so fragmented and complicated

- The first **eukaryotes** with a DNA nucleus appeared on earth about **2.7 billion years** ago. DNA regulates all functions of the cell. There are **20,000 to 25,000** genes in the human genome with about 3,200,000,000 nucleotides of DNA.
- **1.5 billion years ago** mitochondria that contain DNA and process energy entered eukaryotes to create the starting point for all complex life.
- **1 billion** years ago evolution gave rise to chloroplasts which triggered the evolution of photosynthesis and plant life.

# Evolution

- Over the millenniums as new threats to living organisms came from viruses, bacteria, environmental catastrophes and other species new immune defenses based on gene **mutations** emerged to support 'survival of the fittest' and evolution.
- And as evolution produced new and more advanced species, so did the immune system with retention and modification of the old immune factors and additions to meet new antigen threats. (like building a drip sand castle).

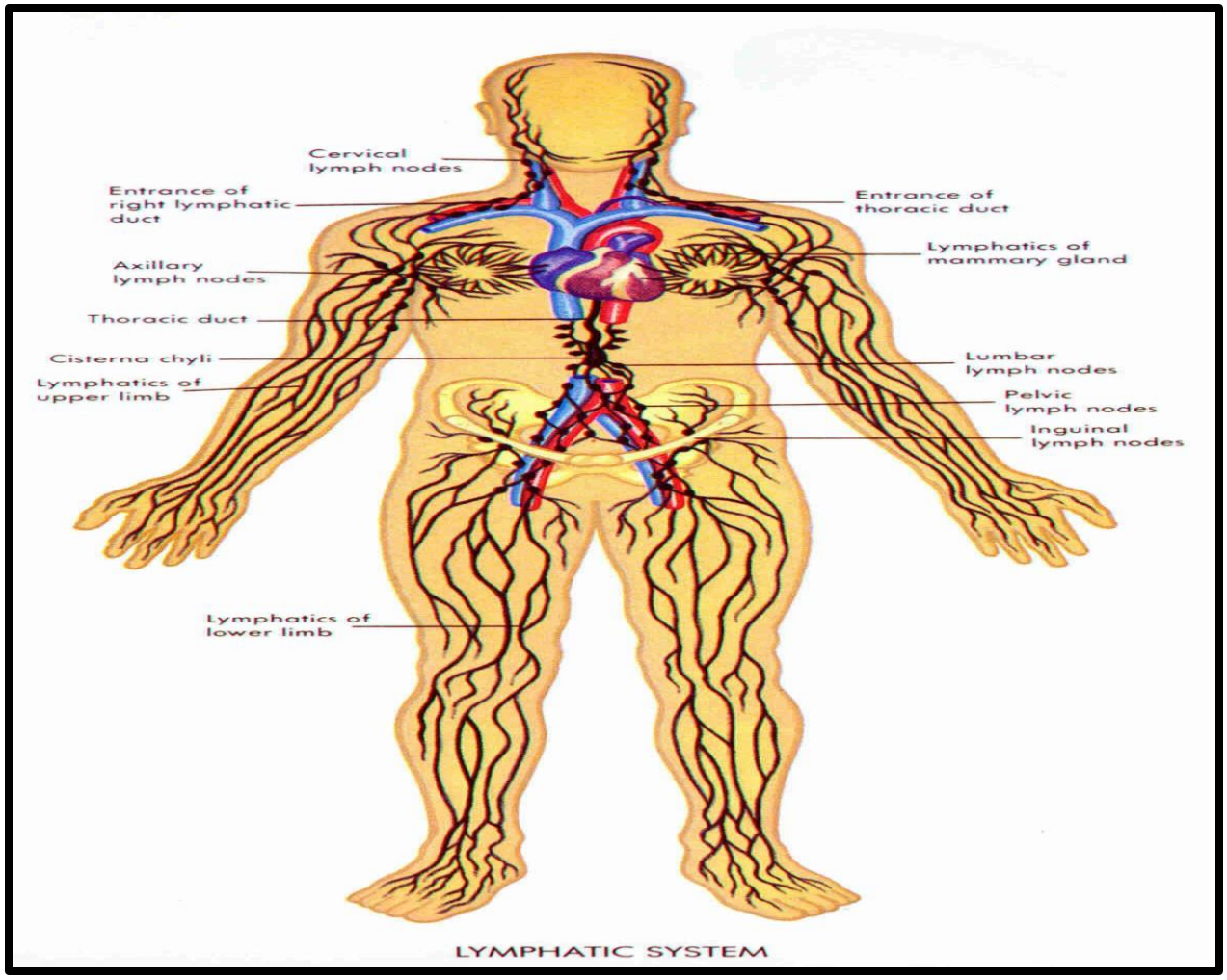
In the beginning, there was no master plan or blueprint but humans evolution climbed the Tree of Life



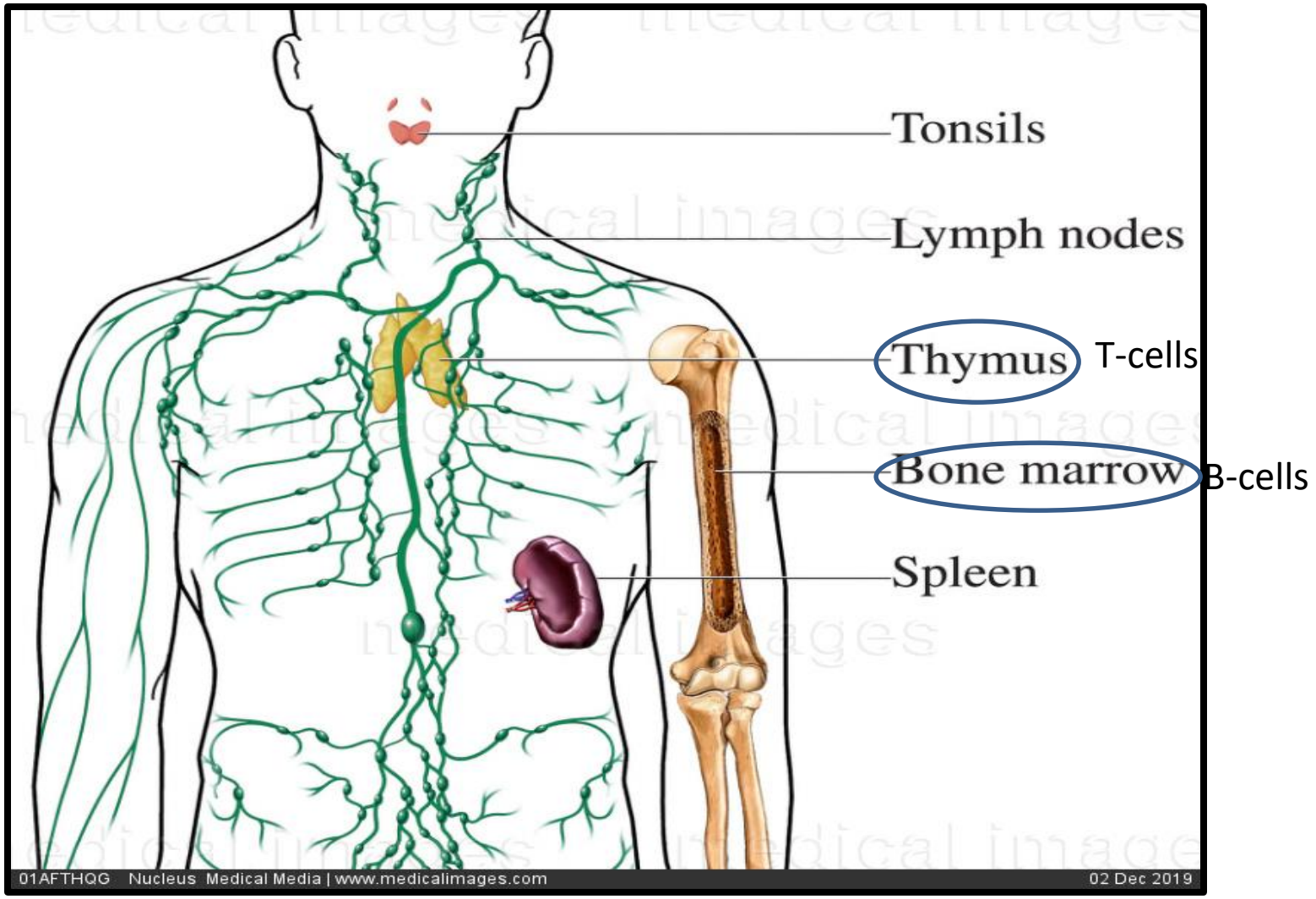

- Chimpanzees are our closest relative as a species and we share at least 98% of our genome with them.
- Earthworms 70%
- Fruit flies 60%
- Bananas 60%

# The Lymphoid and Myeloid Systems—Macro and micro anatomy

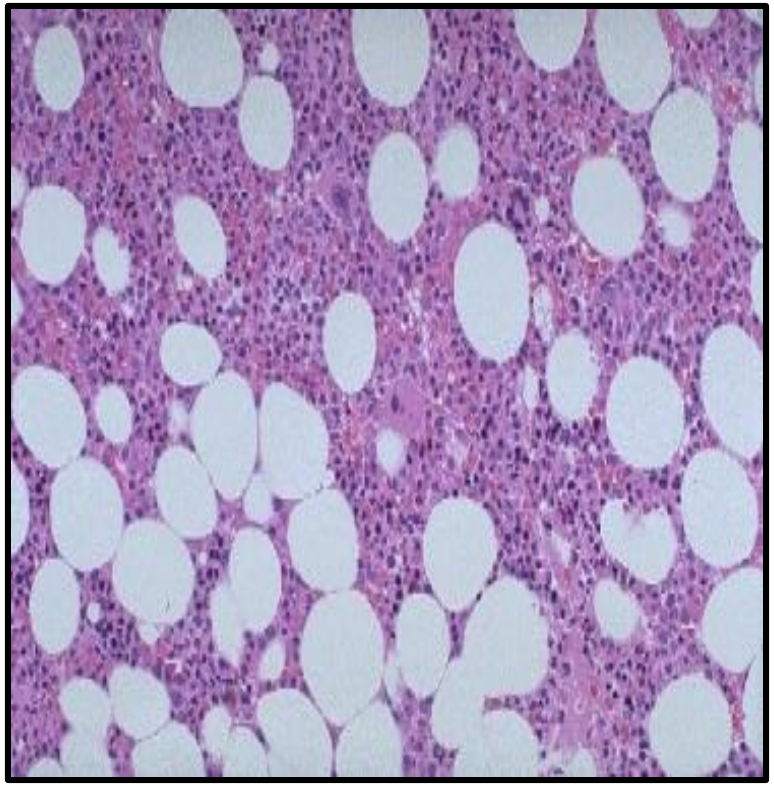
The Lymphatic System: a parallel system to the cardio-vascular system that drains into **lymph nodes**. It is where **lymphocytes of the immune system hang out.**

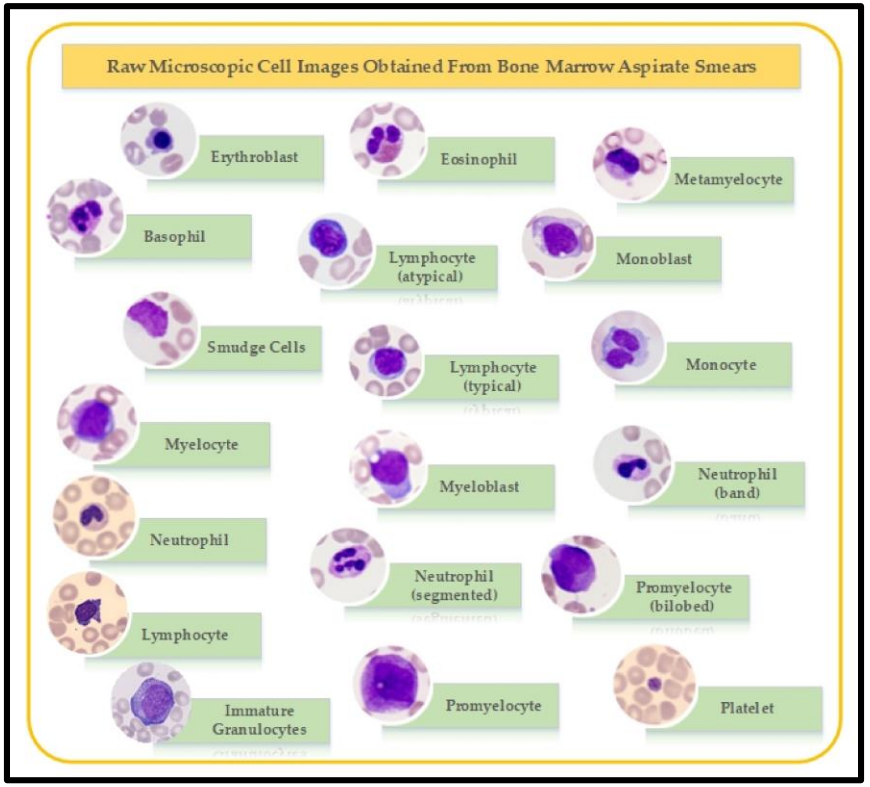


# Lymphatic System/lymphoid tissue/**lymphocytes**

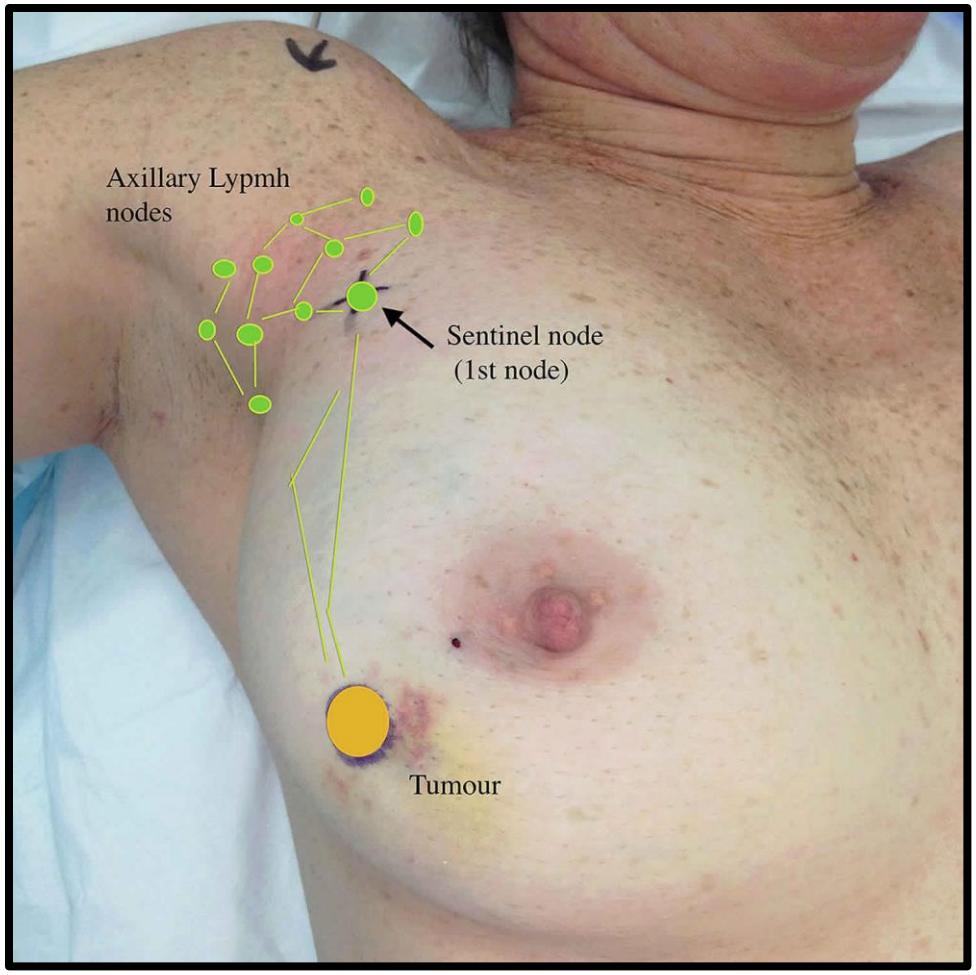


# Bone Marrow Biopsy



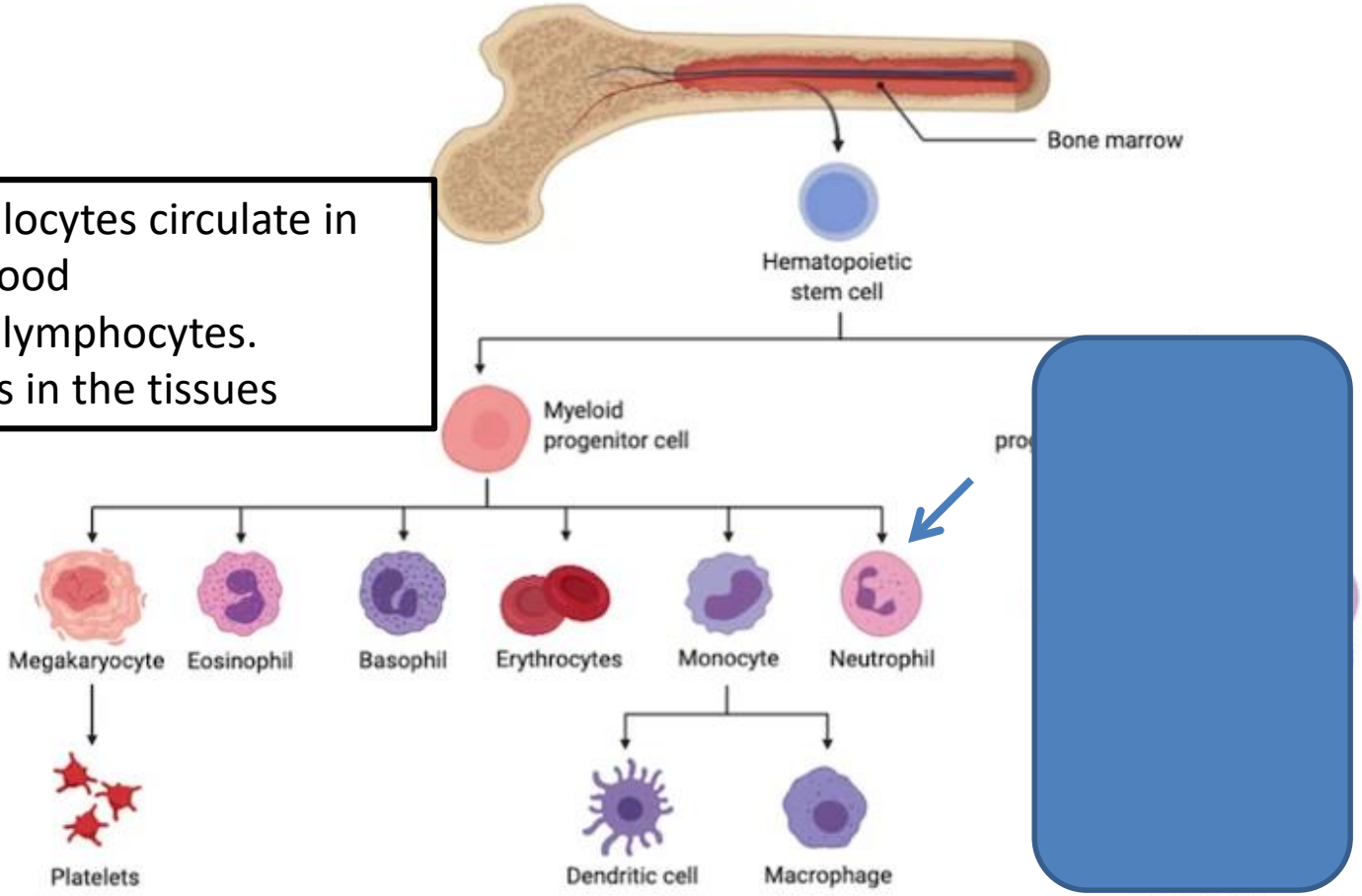


# Standard approach for early stage breast cancer.

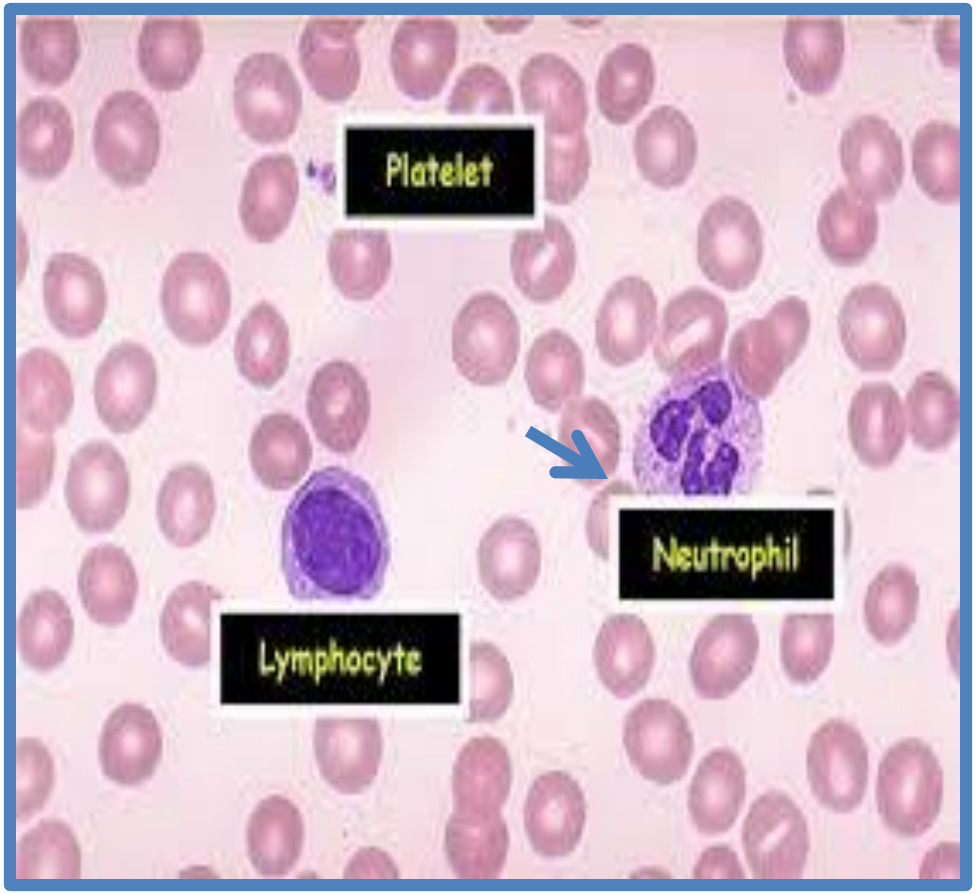


# Myeloid Cells

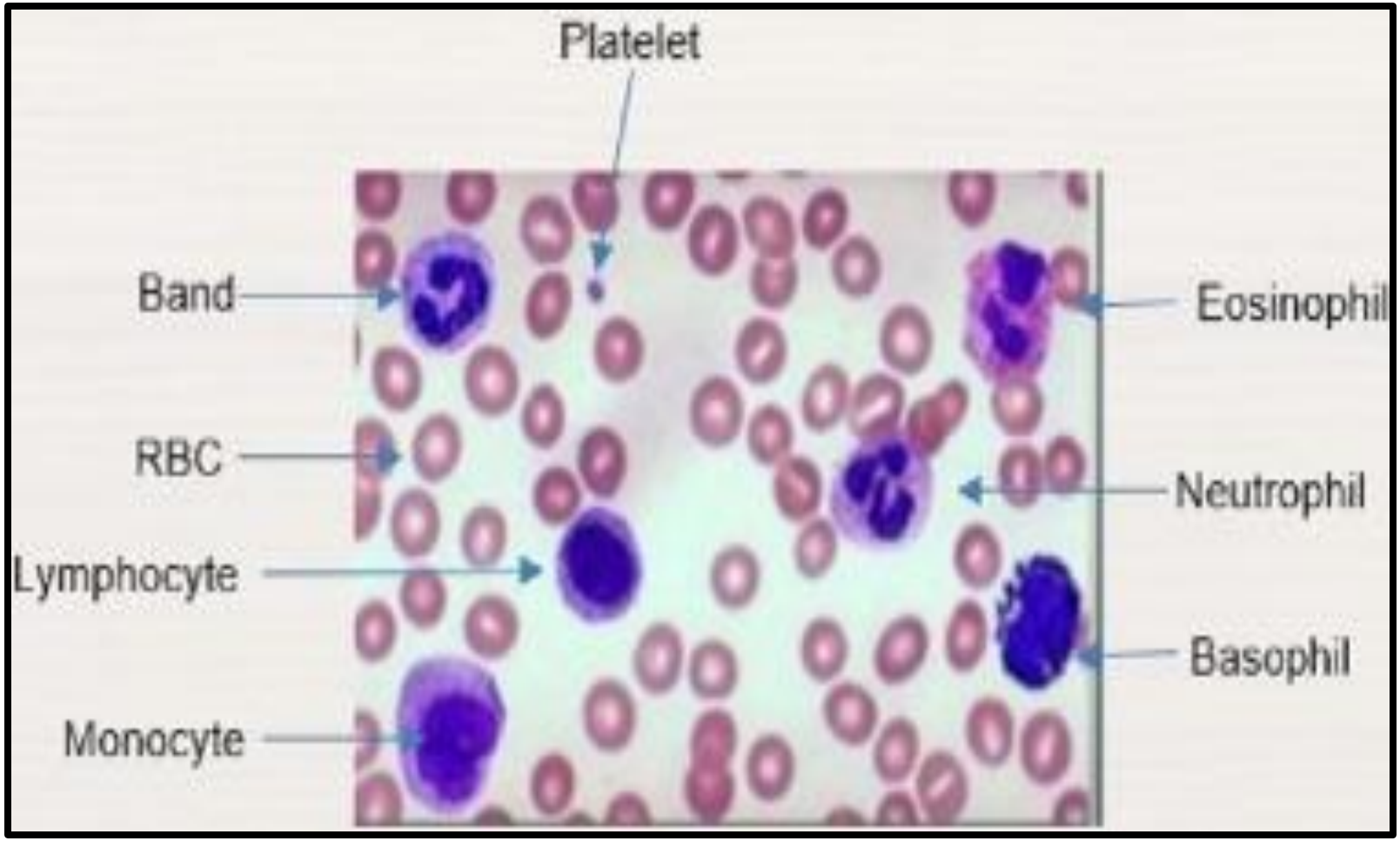
Granulocytes circulate in the blood
As do lymphocytes.
Others in the tissues



Peripheral Blood Smear: **Neutrophils or polys or polymorphic nuclear leukocytes** from the bone marrow circulate in the blood stream and are professional **phagocytes** as they destroy bacteria



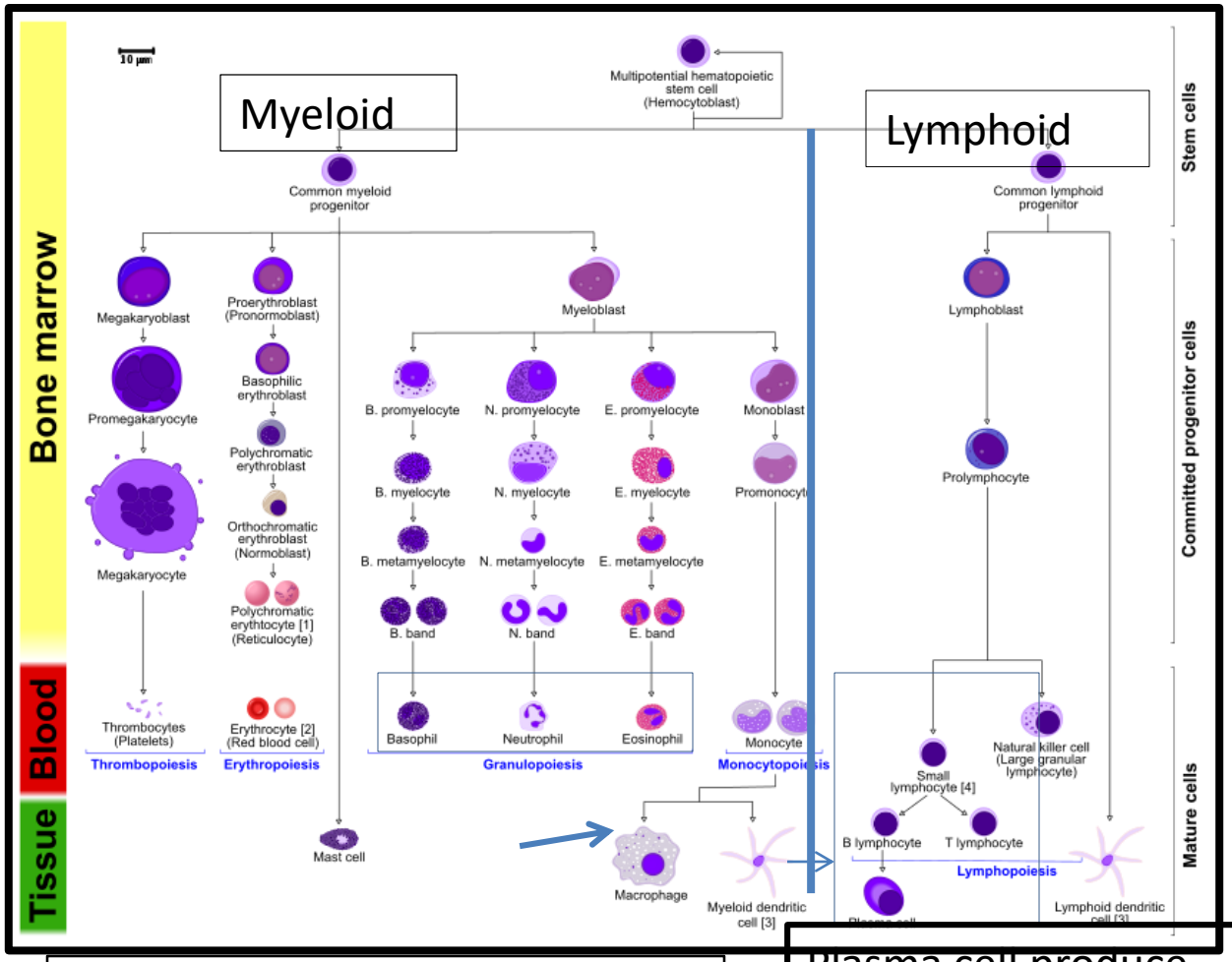
# Blood Smear (H&E stain)



# CBC and Differential Blood Cell Count (**WBC-5-10,000 normal**)

| | | |
|---|---|---|
| **Neutrophils Relative** | **37.0** % | *bacterial infections* |
| **Lymphocytes Relative** | **53.0** % | *immune system, leukemia* |
| **Monocytes Relative** | **7.0** % | *immune system, mature into macrophages* |
| **Eosinophils Relative** | **2.0** % | *Allergic reactions, parasitic diseases* |
| **Basophils Relative** | **1.0** % | *inflammation* |
| **Neutrophils Absolute** | **3.3** 10*3/uL | *1.5 - 7.8 10*3/uL* |
| **Lymphocytes Absolute** | **4.7** 10*3/uL | *0.8 - 3.9 10*3/uL* |
| **Monocytes Absolute** | **0.6** 10*3/uL | *0.2 - 0.9 10*3/uL* |
| **Eosinophils Absolute** | **0.2** 10*3/uL | *0.0 - 0.5 10*3/uL* |
| **Basophils Absolute** | **0.1** 10*3/uL | *0.0 - 0.2 10*3/uL* |

# Blood Cell Formation (Myeloid and Lymphoid Cells)

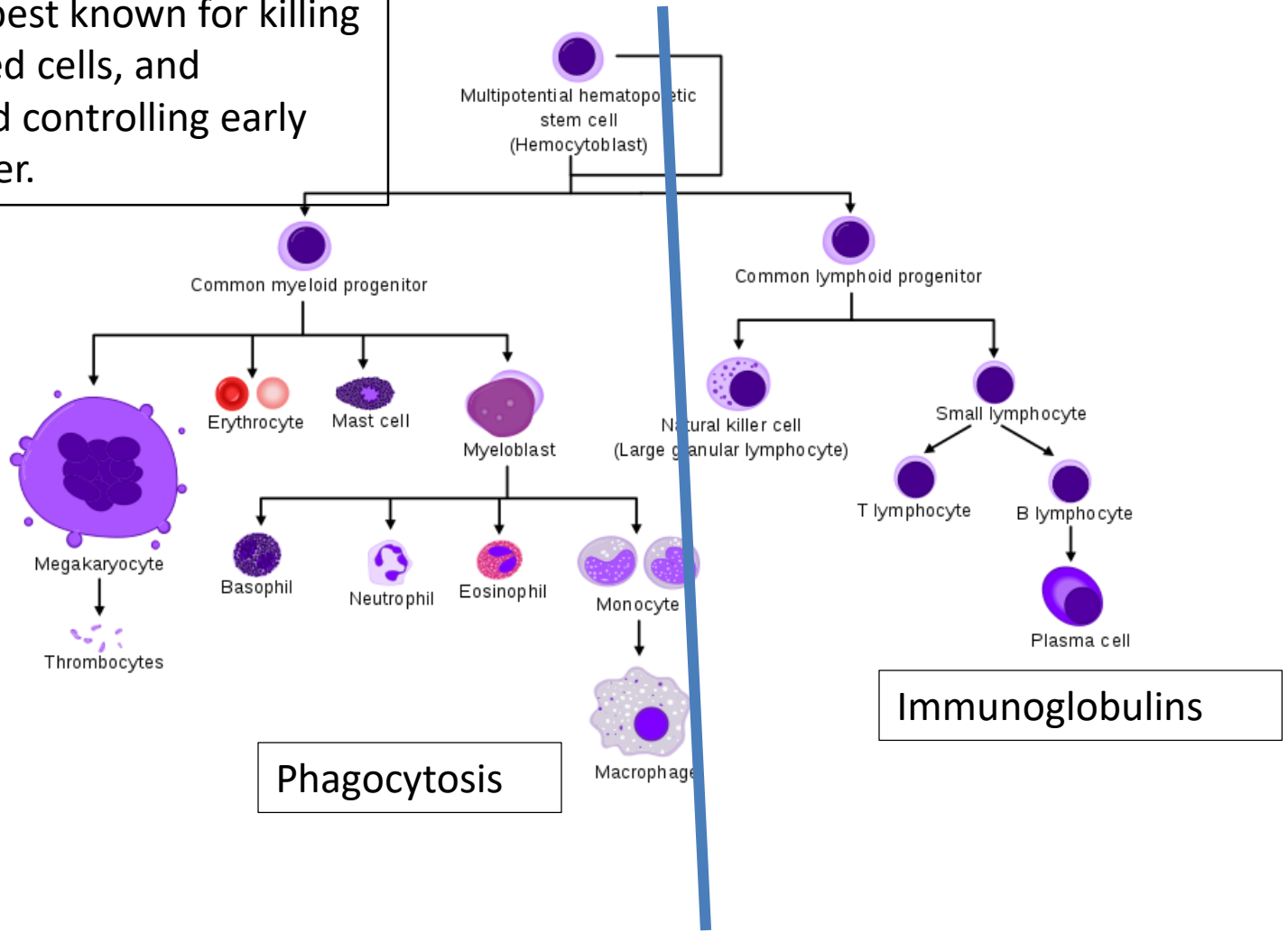



Macrophages & Monocytes
Are main producers of cytokines

Plasma cell produce immunoglobulins

# Another Diagram of Immune Cells

NK cells are best known for killing virally infected cells, and detecting and controlling early signs of cancer.



# Immunoglobulins: Humoral Immunity; B lymphocytes that form plasma cells

- **Immunoglobulins**, also known as **antibodies,** are glycoprotein molecules produced mainly by **plasma cells** and initiate the immune response by specifically recognizing and binding to particular antigens, such as bacteria or viruses, and aiding in their destruction.
- These immunoglobulins are produced by B cells that produce plasma cells of the immune system in response to exposure to antigen.

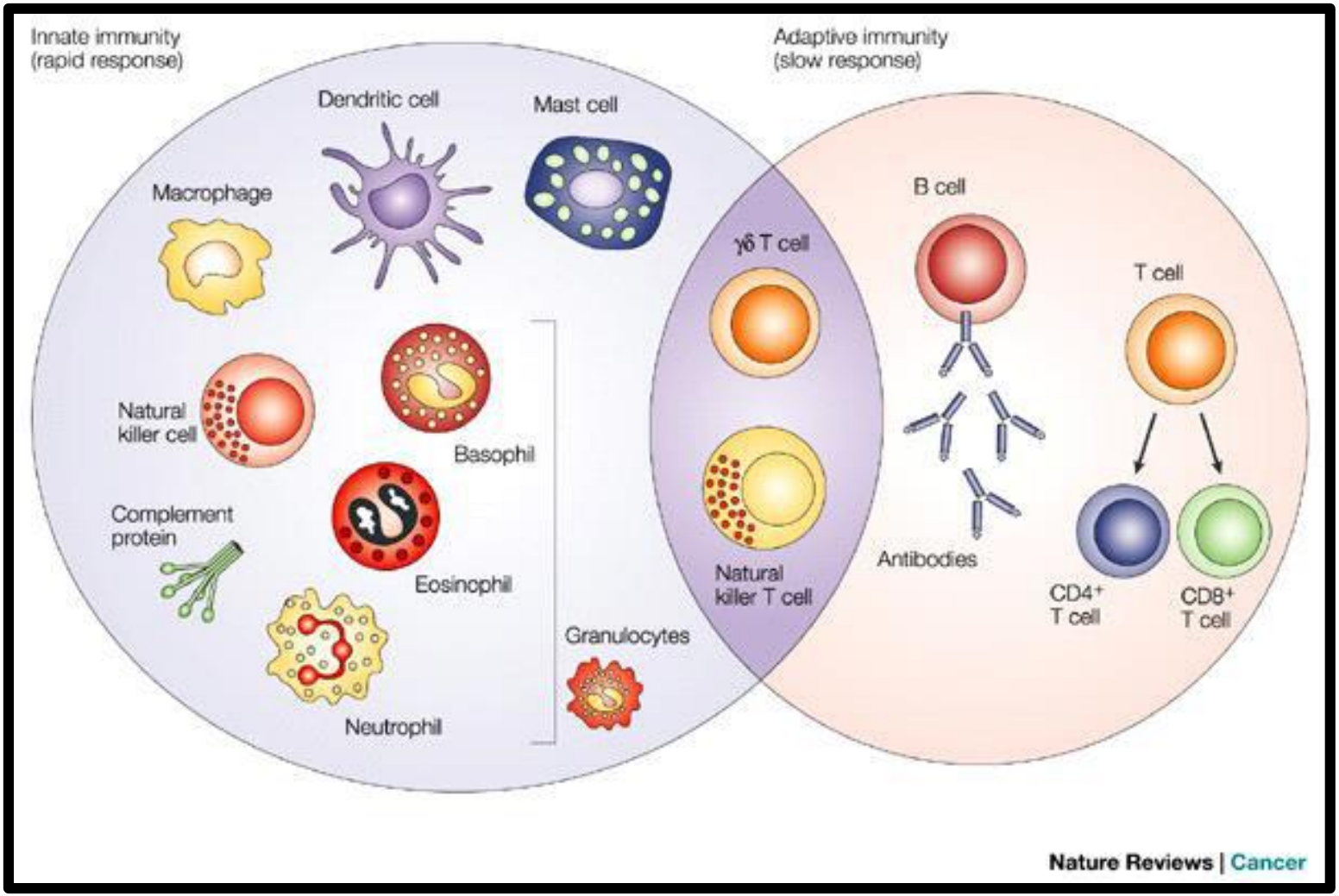
# Classes of Immunoglobulins (Standard Blood Test)

The five major antibody classes are:

- **Immunoglobulin G (IgG)**, 80%, is found in all body fluids and protects against bacterial and viral infections.
- **Immunoglobulin M (IgM)**, is the first antibody to be released by B cells during primary response
- Immunoglobulin D (IgD), important in B cell activation
- **Immunoglobulin A (IgA)**, which is found in high concentrations in the mucous membranes, particularly those lining the respiratory passages and gastrointestinal tract, and **prevent attachment** of pathogens to epithelial surfaces.
- **Immunoglobulin E (IgE)**, found on mast cells and basophils and triggers release of histamine which is associated mainly with **allergic reactions** like hay fever, asthma and atopic dermatitis. Omalizumab (Xolair®) is an anti-IgE medicine approved for asthma & hives.

# The Operating System of Immunity: Innate versus Adaptive Immunity

# Innate versus Adaptive Immunity



# Barriers of the Innate System

- Skin/hair/sweat
- Mucous Membrane (prevent adhesion)
- Lungs etc.
- Saliva

# **Complement--**chemical innate immune system primarily made in the liver

- The complement system of which there are nine major components (**bind to antigen–antibody complexes) that facilitate the uptake and destruction of pathogens by phagocytic cells (**Monocytes, macrophages, and neutrophils)
- The membrane-bound antibody activates the first complement component, which activates eight additional complement proteins (C1 through C9) and forms what is known as the **membrane attack complex**, a series of proteins that forms a pore in the membrane, resulting in the lysis of target cells.

# **Macrophages** come from Monocytes

- When activated these cells secrete **cytokines** including **TNF, IL-1, IL-6**, IL-8 and IL-12 and so on. They are phagocytes also.
- Macrophages, and monocytes are the main sources of **inflammatory and anti inflammatory cytokines**
- They also release chemokines, leukotrienes, prostaglandins and complement.

# **Dendritic Cells** (myeloid and lymphoid)

- Dendritic cells (DCs) are antigen-presenting cells that capture, process, and present antigens to lymphocytes (both B & T) to initiate and regulate the adaptive immune response. **They are the only antigen-presenting cell capable of stimulating naive T cells**, and hence they are pivotal in the generation of adaptive immunity. **Act as a bridge between innate and adaptive immunity**
- Because dendritic cells express both **class I and class II MHC** proteins, they can activate both cytotoxic and helper T cells.

# Natural Killer Cells and Mast Cells Innate Immunity

- **A Natural Killer Cell** is an innate lymphocyte able to bind to certain tumor cells and virus-infected cells **without the stimulation of antigens**, and kill them when signals that prevent them from attacking (like MHC class I molecules) are absent or downgraded on a target cell.
- **Mast Cells** are ubiquitous (skin & gut) and release **histamine** as well as other vasoactive molecules, which cause urticaria. Increasing evidence implicates the important role of mast cells in allergy (atopic dermatitis. asthma) and autoimmune disease like rheumatoid arthritis and multiple sclerosis.

# Eosinophils and Basophils

- **Eosinophils**--involved in host defense against parasites and promoting **allergic reactions**. IL-4 and 5 being key cytokines for eosinophil proliferation, survival and priming. Eosinophil are attracted by specific chemokines.
- **Basophils**-- A type of immune cell that has granules (heparin and **histamine**) that are released during allergic reactions.

# Cytokines

# The acute immune response (**first responders**) to antigens (like bacteria or viruses) and injury

**Cytokines** are first responders **secreted by immune cells** and act as signaling proteins reacting to injury, infections, foreign antigens or insult.

**Metaphorically, Cytokines can be described as the software that runs the immune system** and when that software malfunctions, dysregulation of the immune system can result in debilitating autoimmune diseases such as lupus, rheumatoid arthritis, diabetes. ulcerative colitis and cancers.

# Principal Cytokines

- **Interleukins** of which there are 33 (but **IL1** has 11 members all of which are **pro-inflammatory**
- **Tumor Necrosis Factor**. (TNF) two receptors for TNF, namely TNF receptor 1 (TNFR-1, p55 receptor) and TNFR-2 (p75 receptor) **Major pro-inflammatory cytokines**
- **Interferons** three types of interferons (IFN), alpha, beta and gamma

# More Principal Cytokines

- **Growth factors** (vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and platelet-derived growth factor (PDGF**))** **and many more**.
- **Chemokines**

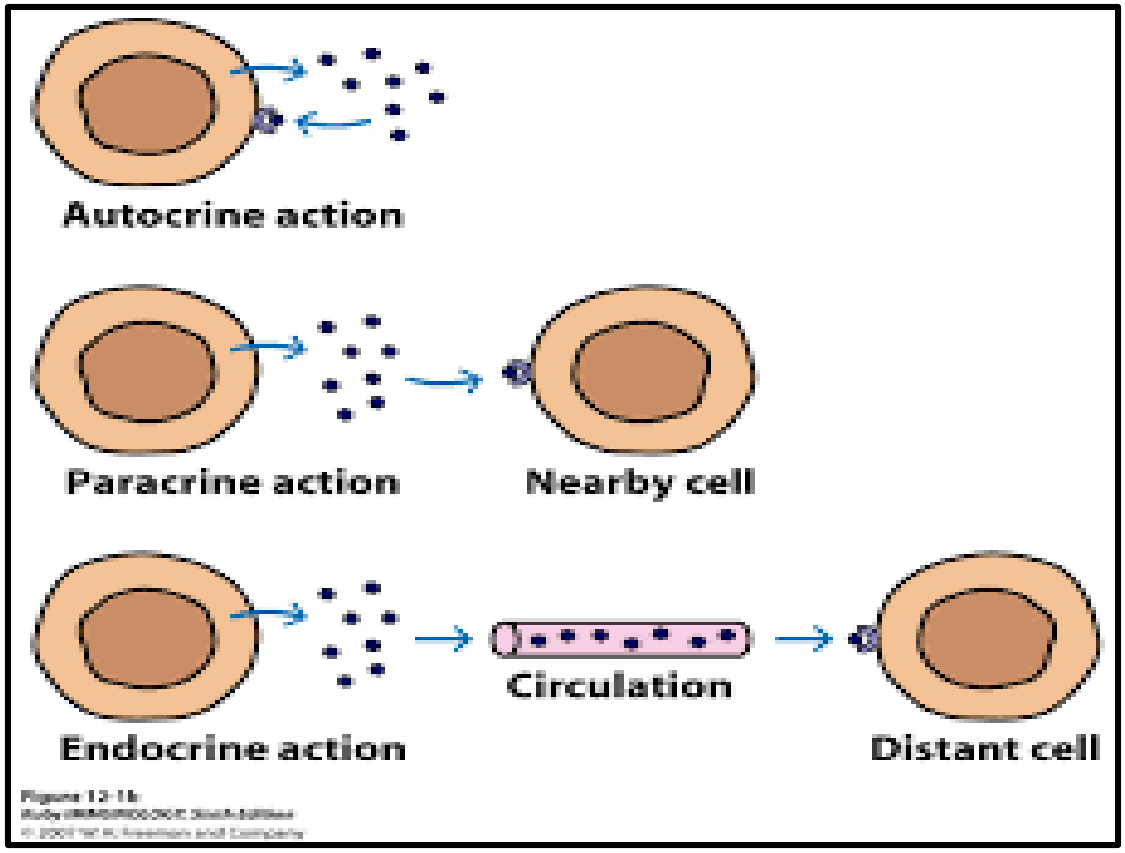
# More on Cytokines

Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, and mast cells as well as endothelial cells, fibroblasts, and various stromal cells: a given cytokine may be produced by more than one type of cell.

Cells that aren't considered immune cells also release cytokines and include:

- Endothelial cells (cells that line the inside of your blood vessels and internal organs.
- Epithelial cells of the skin.
- Fibroblasts (cells in connective tissue).
- Stromal cells (cells in connective tissue).
- Schwann cells (cells that surround neurons).

# Cytokines act in several ways



# Symptoms associated with cytokines

- The key **pro-inflammatory cytokines are IL-1, IL-6, IL-23 and TNF-α**. These cytokines signal via type I cytokine receptors (CCR1) that are structurally divergent from other cytokine receptor types.
- Pyrogenic cytokines such as **tumor necrosis factor (TNF), interleukin (IL)-1, IL-6, and interferons** act on the brain endothelial cells of the hypothalamus to evoke fever elicited by prostaglandin $E_2$ synthesis in these cells.
- These three cytokines likewise cause the flu-like syndrome of myalgia, chills etc.

# Some cytokines are pro-inflammatory, others anti-inflammatory

**TNF inhibitors** are the most commonly used type of biologic medication to combat autoimmune disorders.

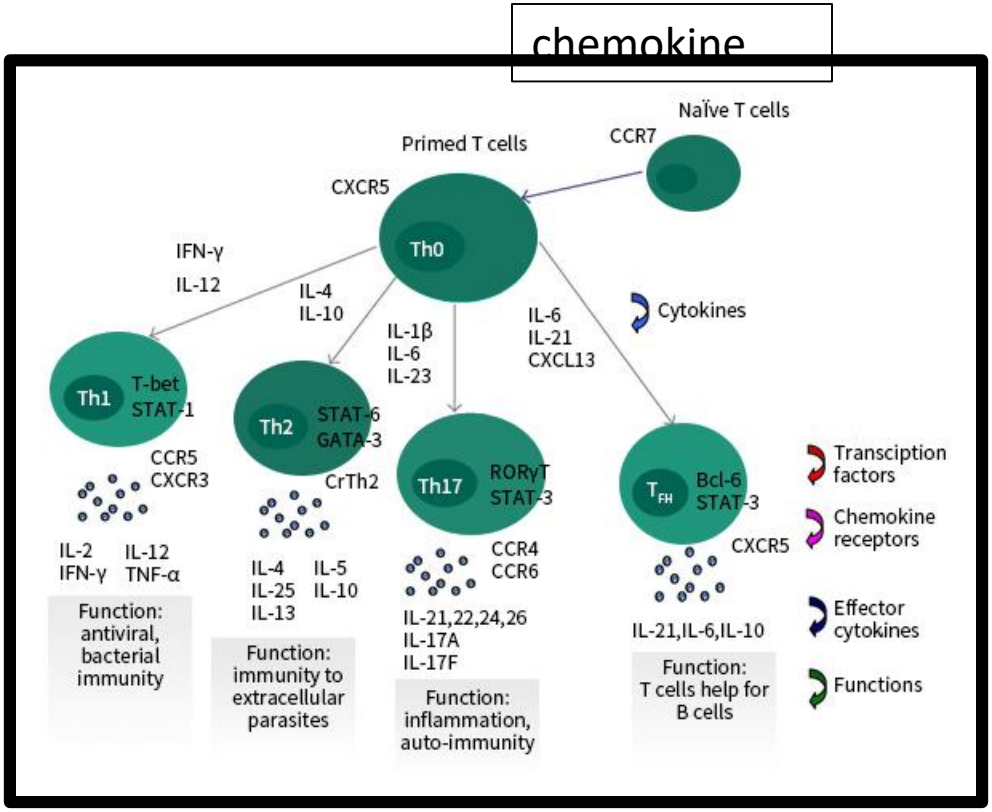
**Anti-inflammatory Biologic Drugs**

Etanercept **(Enbrel),** Golimumab **(Simponi**), Infliximab **(Remicade),**Adalimumab **(Humira),**Cimzia, Inflectra, Reniflexis, Avsola, Amjevita, Hyrimoz, Hulio, Erelzi, Yusimry, Yuflyma, Idacio, Hadlima, Eticovo, Cyltezo, Abrilada.

# How do OTC flu meds work (decrease inflammation)

- One of the main stimuli for COX-2 (cyclooxygenase-2) induction is cytokines (such as interleukin-1,( IL-1) and tumor necrosis factor-α, (TNF-α) that lead to the production of prostaglandins in the hypothalamus
- Acetaminophen decreases intracellular glutathione levels and modulates cytokine production in human macrophages
- Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and indomethacin work by inhibiting enzyme and cytokines that produces prostaglandins
- Tumeric (Curcumin) has an antioxidant and anti-inflamatory effect on leukotremes, prostaglandins, cytokines, chemokines, and growth factors,

# How Inflammatory Cytokines work



# In a nutshell?

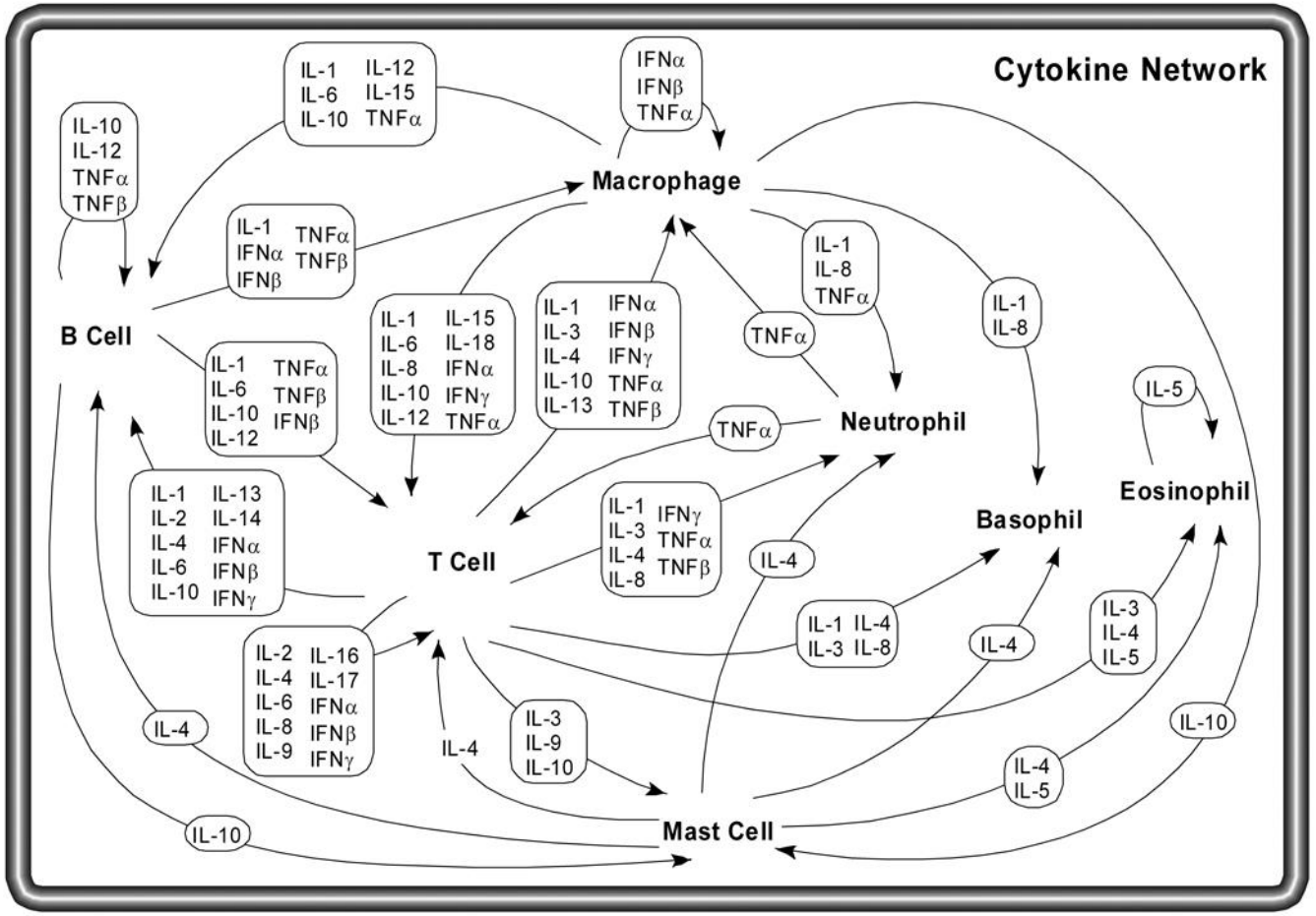
| Family | Functions | Examples |
|---|---|---|
| Cytokines | Pro-inflammatory; ↑ inflammatory mediators; ↑ innate immune responses | IL-1α, IL-1β, TNF-α, IL-12, IL-18, IL-23 |
| | Anti-inflammatory; ↓ inflammatory genes; ↓ cytokine-mediated lethality | IL-10, IL-13, TGF-β, IL-22, IL-1Ra, IFNα/β |
| | Angiogenic; neovascularization; pro-metastatic | VEGF, IL-1, IL-6, IL-8 |
| | Osteoclast activation | RANKL |
| Chemokines | ↑ Cellular emigration; ↑ cell activation | IL-8, MCP-1, MIP-1α, CC and CXC chemokines |
| Interferons (IFNs) | Type I: anti-viral immunity; ↑ class I MHC; anti-inflammatory; anti-angiogenic | IFNα, IFNβ, IFNω |
| | Type II: macrophage activation; increase class II MHC IFNγ also ↑ class I MHC and is responsible for anti-viral immunity (stimulates $CD8^+$ T cells/Th1 responses). | IFNγ |
| Adipokines | Pro-inflammatory; ↓ autoimmune disease pro-atherogenic | IL-1α, TNF-α, IL-6, leptin, adiponectin, resistin |
| Tumor necrosis factors | Pro-inflammatory pyrogenic; non-specific immunity; apoptosis | TNF-α, TNF-β |
| Mesenchymal growth factors | Fibrosis; pro-metastatic | FGF, HGF, TGF-β, BMP |
| Colony stimulating factors | Hematopoiesis; pro and anti-inflammatory | IL-3, IL-7, G-CSF, GM-CSF, M-CSF |
| Nerve growth factors | ↑ nerve/Schwann cells; B-cell activation | BNDF, NGF |

MHC: major histocompatibility complex.

# **Interleukins**: a large group of proteins that can elicit many reactions in cells

- Interleukins (IL) play essential roles in the activation and differentiation of the **entire** immune system.
- There are presently 33 interleukins, the IL-1 family has 11 members and include IL-1α, IL-1β, IL-18 and IL-33. Although each member of the IL-1 family is a **separate gene**, their products overlap in functions as pro-inflammatory cytokines.

# Interleukins (IL)




Notice how often Interleukin 1, 10, and 6 plus TNF appear on this chart