

**CELLS, ORGANS, AND MOLECULES:
ANATOMY AND PHYSIOLOGY OF THE IMMUNE SYSTEM**

THE CELLS OF THE BLOOD FROM AN IMMUNOLOGICAL PERSPECTIVE.

Erythrocytes: Red blood cells ($\sim 5 \times 10^6/\mu\text{L}$) ($\sim 5 \times 10^{12}/\text{L}$) of blood.

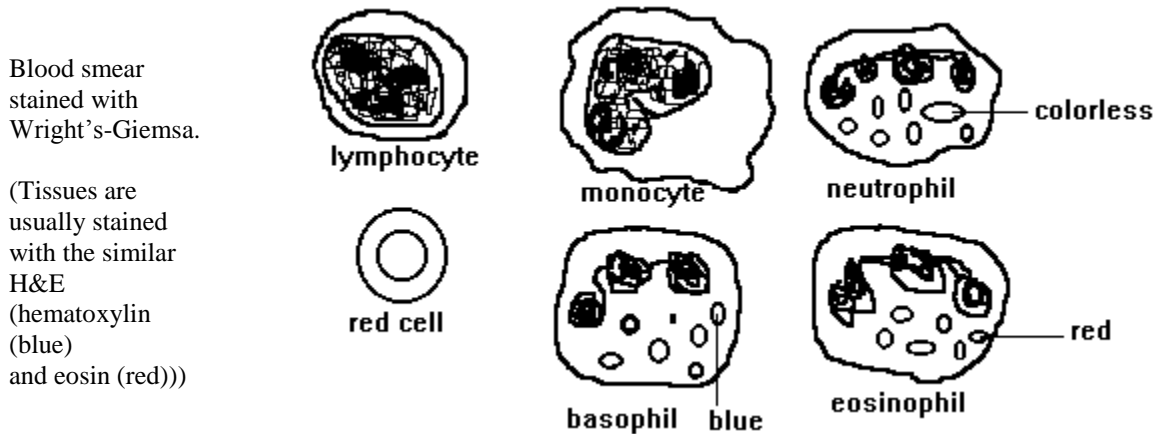
Platelets: Fragments derived from bone marrow megakaryocytes, involved in clotting. 150-400,000/ μL .

Leukocytes: Nucleated cells of the blood; white blood cells. When you centrifuge anticoagulated blood, they sediment on top of the packed red cells, forming the “buffy¹ coat.”

Mononuclear cells: Leukocytes whose nucleus has a smooth outline; **monocytes** (immature, becoming mature **macrophages** or **dendritic cells** in the tissues), and **lymphocytes**. In tissue sections it's sometimes hard to tell the difference between macrophages and lymphocytes. Pathologists sidestep that problem by referring to “a mononuclear cell infiltrate,” meaning both T cells and macrophages.

Polymorphonuclear cells: Cells whose nucleus is lobulated, also called granulocytes because they have (usually) rather prominent cytoplasmic granules. They are:

Eosinophils; Basophils (closely related to tissue **mast cells**); and **Neutrophils**.



¹ Buffy means “kind of buff-colored” and has nothing to do with slaying vampires. *Nothing*.

NUMBERS.

Adults: Total white blood cells (WBC): 4,500-10,500 per μL of blood ($4.5\text{-}10.5 \times 10^9/\text{L}$).

Differential

Neutrophils	40-60%*
Eosinophils	1-4% **
Basophils	0-2%
Monocytes	2-8%
Lymphocytes	20-40% *

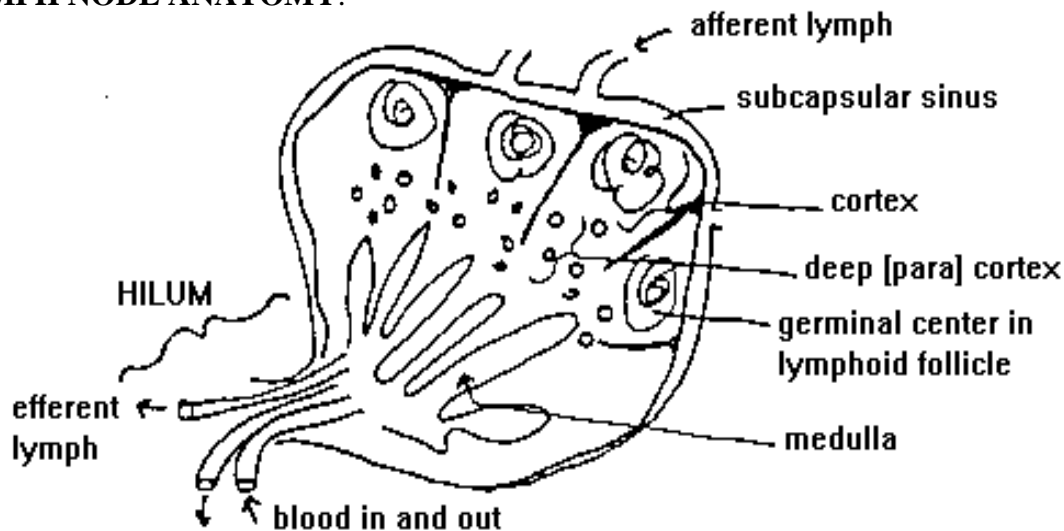
*Young children (up to at least 2 years) have more lymphocytes than neutrophils; the percentages are reversed compared to adults. Of lymphocytes in blood, about 70% are T cells, 20% B cells, and the rest something else. We'll get into what 'something else' means, later.

**Consistently higher in developing and tropical countries.

ASK YOURSELF: Can you calculate how many lymphocytes you have in your 5 or 6 liters of blood?

ASK YOURSELF: Why do you think people in tropical countries have a higher eosinophil count?

LYMPHOID ORGANIZATION. Immunologists divide the lymphoid system into **central** and **peripheral** lymphoid organs. Central organs are ones in which lymphocytes *develop*: the bone marrow and the thymus. (In mammalian embryos, bone marrow function is first found in the yolk sac and then in the liver.) We'll discuss lymphoid ontogeny² in more detail in a later Unit. In the peripheral organs, mature cells are organized to trap and respond to foreign invaders that usually arrive from body surfaces via the lymphatics. Peripheral organs include lymph nodes, spleen, Peyer patches and mesenteric lymph nodes of the gut, tonsils, and adenoids. At any moment many lymphocytes are found in the blood and lymph, too, but most are in the peripheral lymphoid organs.

LYMPH NODE ANATOMY:

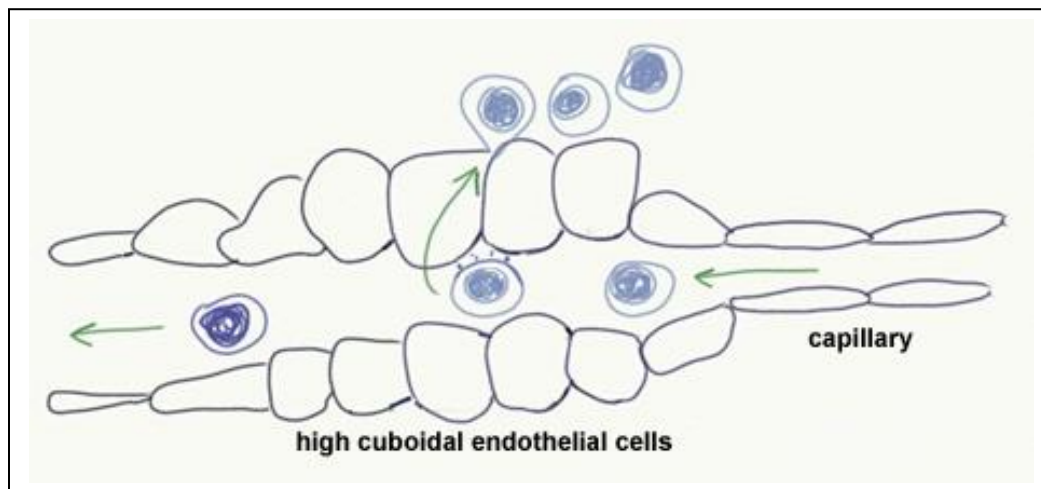
² Ontogeny, development from earliest stages. Greek *on*, *ontos* = being; *-geny* = way of becoming. The "Ontogenic Argument" is: *Which came first, the chicken or the egg?*

Arterioles enter at the hilum (the stalk), and split up into capillaries which drain into venules (the ones with the high cuboidal endothelium, discussed in next paragraph); veins exit at the hilum. Lymph channels (afferent) enter at the periphery. Lymph flows into the subcapsular sinus, percolates through the substance of the node and leaves in efferent lymphatics via the hilum.

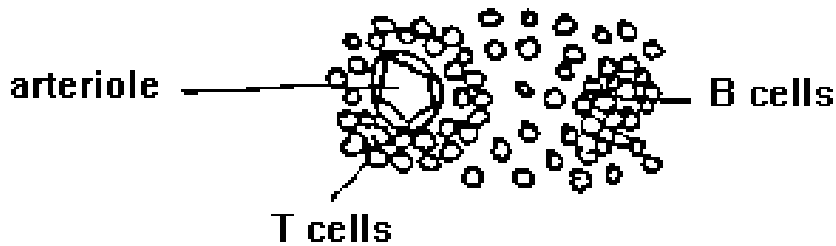
► The node's outer region is called the *cortex*, and it is full of tightly packed (but highly motile) lymphocytes arranged in **follicles**. Frequent very crowded areas with many dividing cells can be seen in the cortex; ► these are called **germinal centers** and represent visible evidence of an immune response. The *deep or paracortex* is a little less dense, but still has huge numbers of lymphocytes. Dendritic cells that arrive in the afferent lymph tend to gather at the interface between the cortex (mostly B cells, arising from the bone marrow) and the paracortex (mostly T cells, arising from the thymus). ► Follicular helper T cells (T_{fh}) migrate from the deep cortex into the follicles where they help B cells get activated.

ASK YOURSELF: I've just suggested to you that the lymphocytes in the paracortex of a lymph node are derived from the thymus, while the ones in the germinal centers are mostly not. Can you come up with experiments, procedures, or observations that would test this (true) hypothesis, specifically that the paracortical cells come from the thymus?

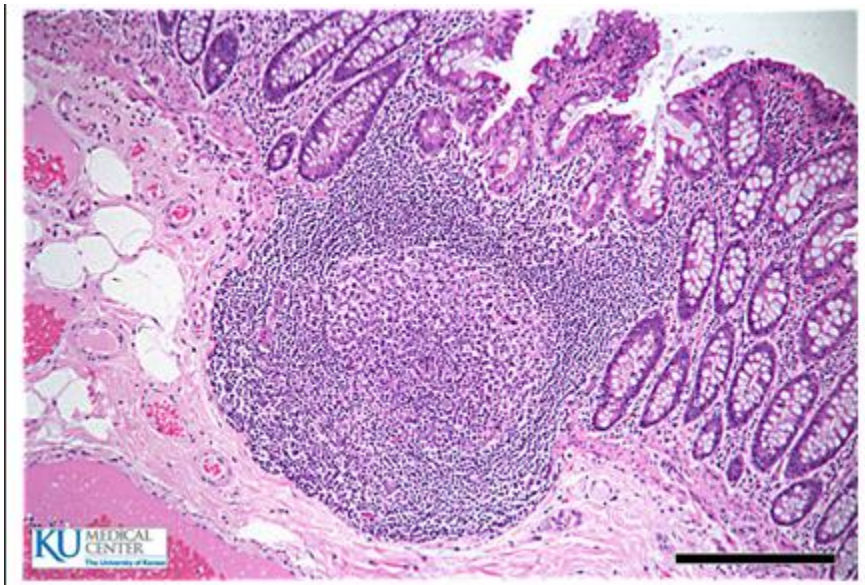
LYMPHOCYTE RECIRCULATION. It makes sense for some lymphocytes to be out in the circulation, to increase their chances of interacting as soon as possible with foreign substances that may be in the body, and to spread protection around evenly. ► The pattern of **recirculation** is this: a lymphocyte in the blood encounters the cells lining certain **postcapillary venules** in the lymphoid tissues, especially lymph nodes. These *endothelial* cells are unusual—not flat as is the usual case, but high and cuboidal. Recirculating lymphocytes bind to and pass between these specialized endothelial cells into the lymph node, where they may stay, or pass eventually into the lymph which drains from that lymph node to the next one in the chain. Lymph works its way into the largest lymph channels such as the thoracic duct near the heart; from there it is emptied into the venous blood and the circulatory loop can start over again. Thus there are two circulations, blood and lymphatic, in which lymphocytes cross from blood to lymph at the nodes, and from lymph back to blood at the heart.



SPLEEN ANATOMY. Spleen has red and white pulp; the red pulp roughly corresponds to the medulla in lymph node, containing lots of phagocytic cells and capable of making red cells when necessary. Because of the red pulp, the spleen is the body's most important filter of particulates, such as bacteria or damaged platelets. The white pulp consists of islands of lymphocytes. The sheath of cells which surrounds the central arteriole is mostly T cells; the more diffuse collection of cells further from the arteriole is mostly B cells. The spleen is also the most important store of monocytes.



GUT-ASSOCIATED LYMPHOID TISSUE. The gut, with its large and, of necessity, permeable surface, has the largest collection of secondary lymphoid tissue in the body, sometimes called GALT or MALT (gut- or mucosa-associated lymphoid tissue.) Lymph node-like structures called **Peyer patches** underlie the mucosa, especially in the small intestine. The functional structure of the Peyer patches includes ► specialized mucosal M cells, which are gatekeepers, ingesting proteins and particles as big as a virus and transporting them to the abluminal³ side. There a rich content of dendritic cells acquire antigens and carry them to the adjacent B cell follicles and T cells zones of the Peyer patch. The patches themselves drain to a large collection of mesenteric lymph nodes. It is here where the body has to solve its most difficult problem: *Is this foreign stuff (food, normal gut bacteria) harmless, or is it dangerous?*



Peyer Patch

³ The side away from the lumen of the gut.

ANTIGEN, IMMUNOGEN, TOLEROGEN. **Antigen** refers to a substance which can be recognized by the immune system. ► An antigen frequently is also an **immunogen**, which is an antigen in a form which can give rise to an immune response, that is, which can immunize. For example, an isolated antigenic determinant (see below) is not usually an immunogen; it can be recognized by antibody, but is too small to trigger an immune response. Competing Ebola (EBOV) vaccines, all nicely antigenic, are being tested to see which is the best *immunogen*. A **tolerogen** is antigen delivered in a form, or by a route, which does not give rise to an immune response, and which furthermore *prevents* an immune response to subsequently administered immunogen which is antigenically similar or identical. You can imagine how useful a tolerogen might be. We don't have any clinical tolerogens at present...or do we? We'll discuss this under Type 1 immunopathology.

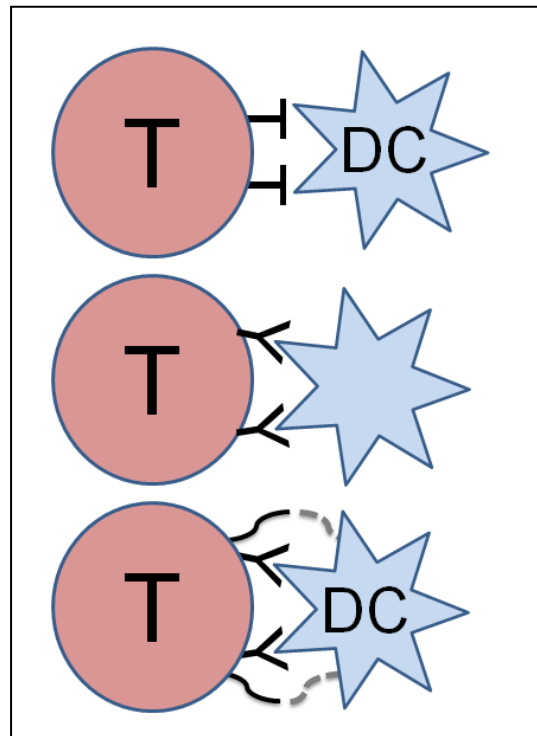
ASK YOURSELF: If you could turn any antigen into a tolerogen, which would you choose?

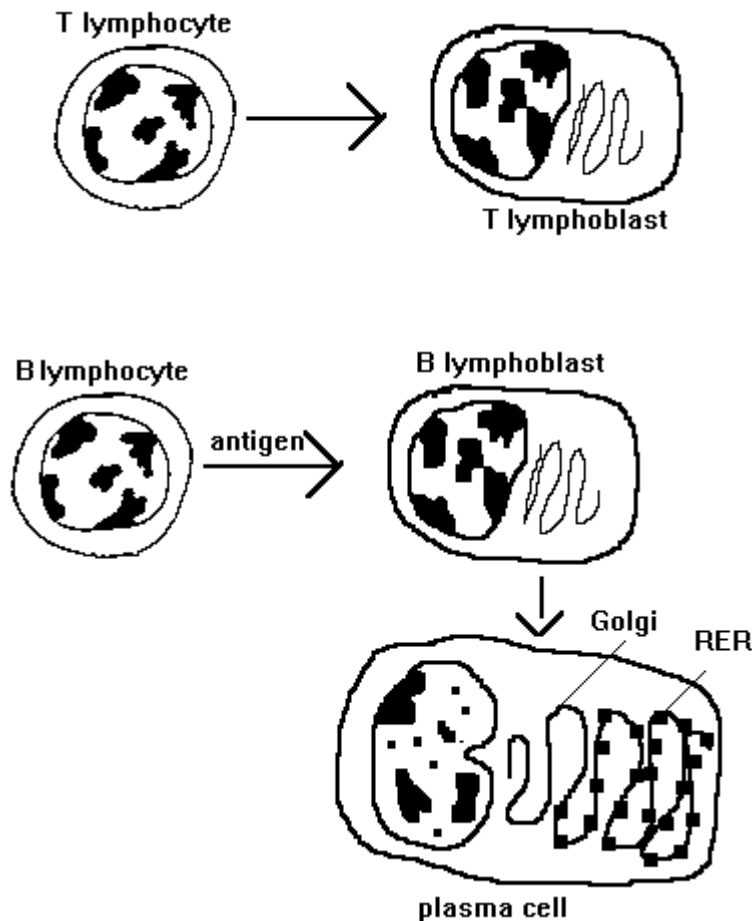
INTRODUCTION TO LYMPHOCYTE SPECIFICITY AND ACTIVATION. Each lymphocyte has **receptors**; there are thousands on each cell, but all are identical so that each cell has just a single specificity, different from nearly all the others. T cell receptors are composed of alpha and beta chains. B cell receptors are samples of the antibodies that the cell will eventually secrete. ► The part of an antigen that fits into the receptor is the **antigenic determinant** or **epitope**. To activate the T or B cell several conditions must be met: the fit between receptor and the antigen it sees must be good (specific) enough, several nearby receptors must be simultaneously bound by antigen, and other cell surface molecules must be involved as well (accessory interactions or costimulation). Once the cell is correctly **activated** it begins to **proliferate**. Lymphocytes can divide as fast as every 6 hours, so in just a few days you have thousands of cells specific for the antigen that got the process started. These cells also **differentiate**: into **effectors** that do the job (B cell blasts and plasma cells that release antibodies into the blood; helper T cells that pour out cytokines; killer T cells that induce their targets to die) and into **memory cells** that recirculate efficiently (some stay put in a specific tissue) and are very easily triggered by another exposure to antigen.

Top: A dendritic cell is showing antigenic fragments to a T cell in the lymph node. The T cell's receptors aren't the right fit for that antigenic determinant. No T cell activation.

Middle: The T cell receptors are a good fit for the antigenic determinant, but there are no appropriate accessory interactions between the body cell and the T cell, because, unlike a dendritic cell, this is not a "professional" antigen-presenting cell. It's a normal body cell. The T cell will not get activated unless something has *really* gone wrong.

Bottom: There are the ► right accessory interactions between the T cell and a dendritic cell (DC), as well as good fit between T cell receptors and the presented antigenic determinant. The T cell is sure to get activated, because all the signals are right.



LYMPHOCYTE DIFFERENTIATION.

When a stimulated T cell becomes large and differentiated, it is called a **lymphoblast**. This is a confusing name, and I'm sorry, but I didn't name it. The misnomer comes from the pioneering pathologists who thought these cells were early lymphocyte precursors⁴ (*-blasts*), not differentiated descendants. A B cell also becomes a (B) lymphoblast and then goes beyond that to the incredibly specialized **plasma cell**, with an enormous protein-making rough endoplasmic reticulum (RER). They work so hard to pump out antibody that many of them will die in a few days; others back off a few notches and remain as long-term memory cells.

ASK YOURSELF: Something to start thinking about: The cells of your immune system are kept out of your brain by a blood-brain barrier. If this barrier were to break down accidentally, would your brain then be foreign to your immune system? (Another way of thinking about this is: do you think your brain is a tolerogen to your immune system, or a potential immunogen which your immune system has not yet had a chance to 'see'?) Do you think you would make an (auto)immune response? Would that be harmful?

⁴ *Blast* in Greek means sprout or germ.

Learning Objectives for Anatomy & Physiology of the Immune System

1. Define:
 - leukocytes
 - mononuclear cells
 - polymorphonuclear cells
 - granulocytes
 - mast cells
 - plasma and serum
2. Sketch schematically a neutrophil; eosinophil; basophil; small lymphocyte; lymphoblast; plasma cell; monocyte. Indicate the characteristic features which are used to distinguish each cell type.
3. List the normal adult white cell count and differential percentages. From these, calculate absolute counts for the different cell types (as cells of that type / μ L).
4. Name the major central and peripheral lymphoid organs.
5. Describe the recirculation of lymphocytes from blood to lymph and back; include in your discussion the specialized features of lymph node blood vessel endothelium that permit recirculation.
6. Define antigen, and compare it to immunogen and tolerogen. Define antigenic determinant and epitope.
7. Discuss lymphocyte activation by antigen with respect to: receptor binding, proliferation, differentiation. Draw a graph showing relative time on one axis and relative lymphocyte numbers on the other, in response to antigen administration.
8. Distinguish between 'humoral' (antibody-mediated) and 'cell-mediated' (T cells) immunity in terms of: the types of lymphocytes involved, the nature of the molecules they release when activated, the types of inflammatory cells they preferentially involve. State which of these immunities can be transferred from one animal or person to another by plasma.