

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

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 gives rise to an immune response, that is, which can immunize. For example, an isolated antigenic determinant or epitope is not usually an immunogen; it can be recognized by antibody, but is too small to trigger an immune response. Competing pandemic (H1N1)2009 vaccines, all nicely antigenic, were tested to see which was 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 has the same epitopes—to be discussed later. You can imagine how useful a tolerogen might be. We don't have any clinical tolerogens at present, though, except our whole bodies, to which we do not usually respond (but other people would, so we know that our tissues are antigenic and therefore potentially immunogenic.)

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

THE CELLS OF THE BLOOD.

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

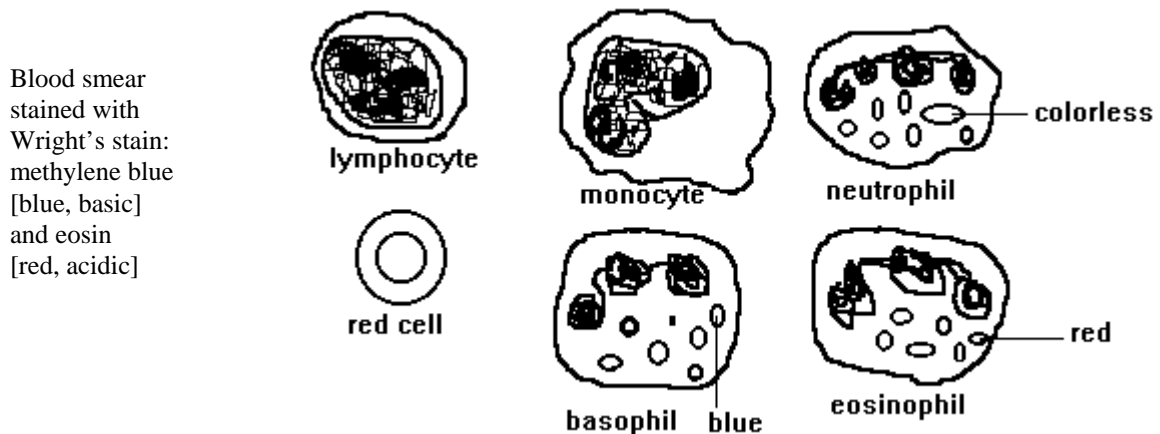
Platelets: Fragments derived from megakaryocytes, involved in clotting. 150-400,000/ μL .

Leukocytes: Nucleated cells of the blood; white blood cells.

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.

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**.



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, about 70% are T cells, 20% B cells, and the rest something else. We'll get into how we know this, and what 'something else' means, later.

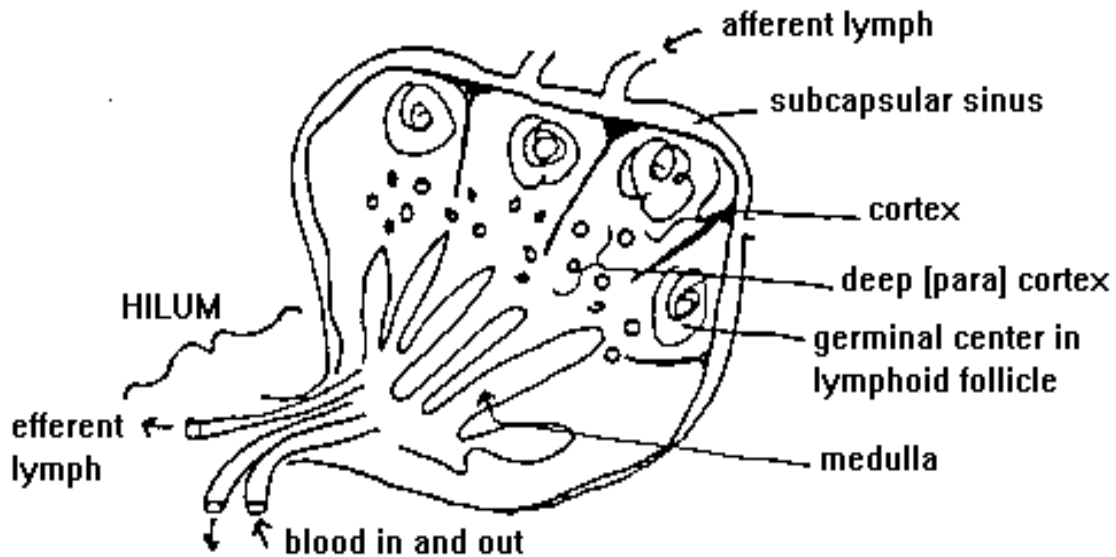
**Consistently higher in developing countries.

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

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.

LYMPHOID ANATOMY. The lymphoid system can be divided into **central** and **peripheral** lymphoid organs. Central organs are ones in which lymphocytes develop: the bone marrow and the thymus. (In mammalian embryos, hematopoietic function begins in the aorta.) We'll discuss lymphoid ontogeny in more detail in a later Unit.

In the peripheral organs, cells are organized to trap and respond to foreign invaders: these organs include lymph nodes, spleen, Peyer's patches and mesenteric lymph nodes of the gut, tonsils and adenoids. At any moment a large number of lymphocytes are found in the blood and lymph, too, but most are in the peripheral lymphoid organs.

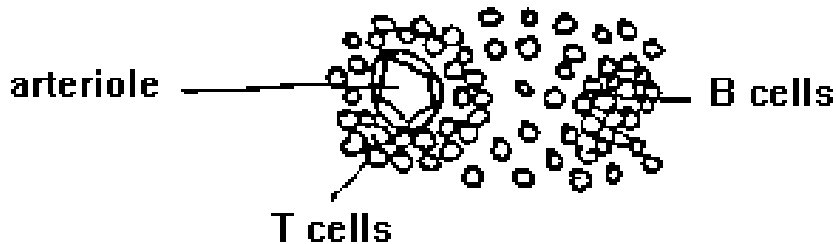
LYMPH NODE ANATOMY:

Arterioles enter at the hilum (stalk), and split up into capillaries which drain into venules (the ones with the high cuboidal endothelium); veins exit at the hilum. Lymph channels 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 lighter areas with many dividing cells can be seen inside follicles; these are called **germinal centers** and represent the visible aspect 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).

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 not. Can you imagine experiments or observations that would test this (quite true) hypothesis, specifically that the paracortical cells come from the thymus?

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's patches underlie the mucosa, especially in the small intestine. The functional structure of the Peyer's patches includes specialized mucosal M cells, which are gatekeepers, taking up proteins and particles as big as viruses and transporting them to the abluminal 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's patch. The patches themselves drain to a large collection of mesenteric lymph nodes. Peyer's patches are important sentinels for the immune system and we'll return to them when we know more about T cells.

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. Red pulp makes the spleen the body's most important filter of particulates, such as bacteria or damaged platelets. The white pulp consists of islands of cells. 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 the body's great filter, and the most important store of monocytes.



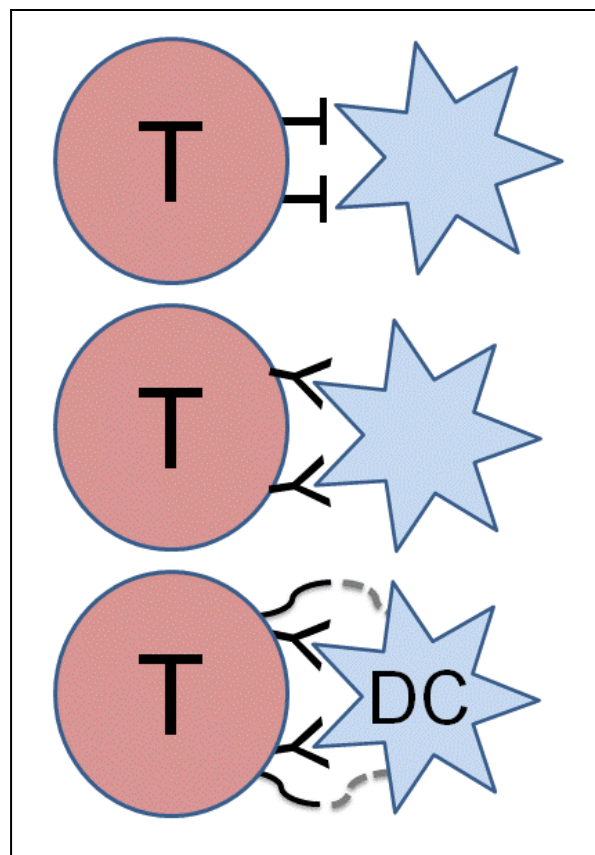
LYMPHOCYTE ACTIVATION. Each lymphocyte has **receptors**; there are many copies on each cell, but all are identical so that the cell has just a single specificity. T cell receptors are composed of alpha and beta chains. B cell receptors are samples of the antibodies that the cell will eventually secrete. 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 enough, several nearby receptors must be simultaneously bound by antigen, and other cell surface molecules must be involved too (accessory interactions or costimulation). The **activated** cell begins to proliferate and differentiate. Lymphocytes can divide as fast as every 6 hours.

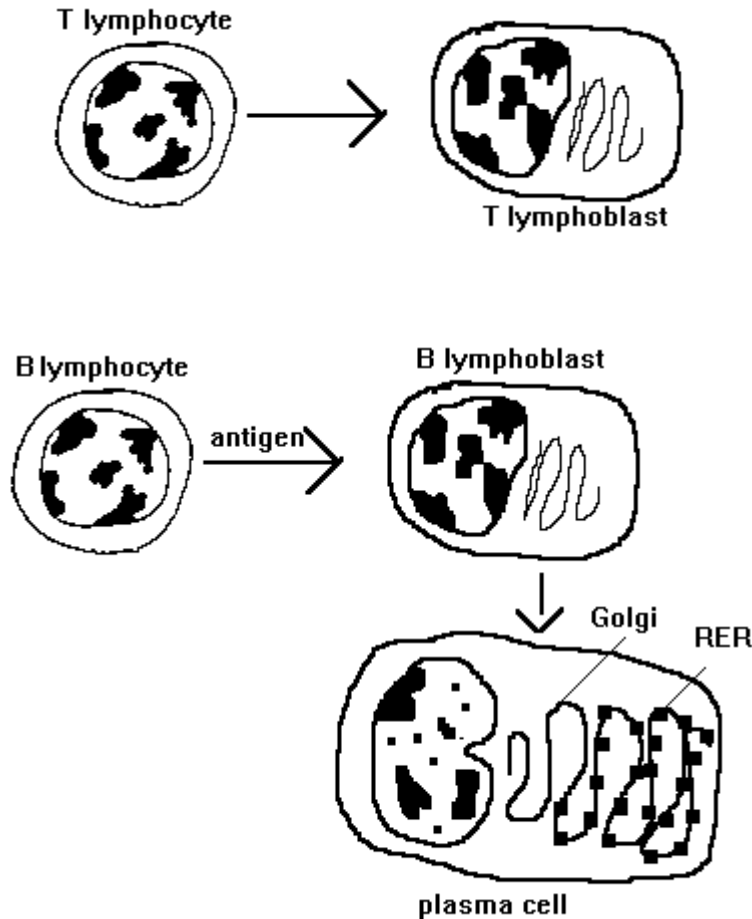
Figure:

The receptor isn't the right fit for that antigenic determinant. No T cell activation.

The receptor is a good fit for the presented antigenic determinant, but there are no appropriate accessory interactions between the presenting cell and the T cell. The T cell might actually be inactivated. In that case, for that T cell, the antigen would be a *tolerogen*.

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.



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 precursors¹ (*-blasts*), not differentiated descendents. 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?

¹ *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 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 by serum.