Once a foreign particle has been phagocytized, lysosomes and other cytoplasmic granules immediately come in contact with the phagocytic vesicle and their membranes fuse with those of the vesicle, thereby dumping their contents of:

[1] Proteolytic enzymes (hydrolases).

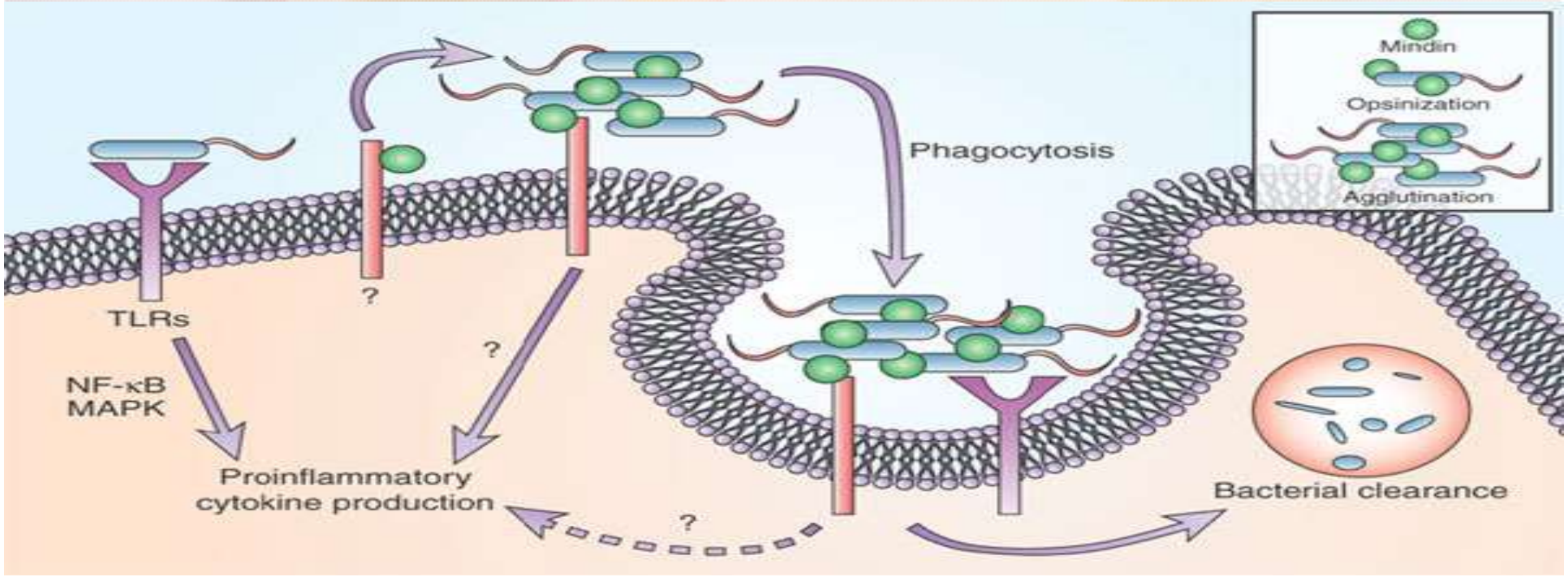
[2] Bactericidal agents (e.g. defensins).

[3] Lipases: The lysosomes of macrophages (but not of neutrophils) contain large amounts of lipases

which digest the thick lipid membranes possessed by some bacteria.

[4] Oxidizing agents: Also, one of the lysosomal enzymes, *myeloperoxidase* catalyzes the reaction between H2O2 and chloride ions to form hypochlorite (HOCL), which is exceedingly bactericidal. In addition, powerful oxidizing agents are formed by enzymes (*NADPH oxidase*) in the membrane of the phagosome or by the peroxisome. These oxidizing agents include superoxide (O2-), hydrogen peroxide (H2O2), and hydroxyl ions (- OH-). They are bactericidal agents and can kill most bacteria even in small quantities.

The phagocytic vesicle now becomes a digestive vesicle and digestion of the phagocytized particle begins immediately. So neutrophils and macrophages can kill most bacteria by the bactericidal agents even when lysosomal enzymes fail to digest them. Some bacteria have protective coats or other factors that prevent their destruction by the digestive enzymes and at the same time also secrete substances that resist the killing effects of neutrophils and macrophages. These bacteria are often responsible for many of the chronic diseases such as tuberculosis.



Macrophage and Neutrophil Response During Inflammation: When tissue injury occurs (due to trauma, bacteria, chemicals, heat...etc) different substances which cause dramatic secondary changes in the tissues are released by the injured tissues. The entire complex of tissue changes following tissue injury is called inflammation. It is characterized by:

- Vasodilatation of local blood vessels with consequent excess local blood flow.
- Increased permeability of the capillaries with leakage of large quantities of fluid into the interstitial spaces.
- Often clotting of the fluid in the interstitial spaces because of excessive amounts of fibrinogen and other proteins leaking from the capillaries.
- Migration of large numbers of granulocytes and monocytes into the tissue.
- Swelling of the tissue cells.

Some of the many tissue products that cause these reactions are histamine, bradykinin, secrotonin, prostaglandins, and multiple proteins released by T-lymphocytes.

The followings summarize the macrophage and neutrophil response during inflammation:

[1] Within the first hour or so after inflammation begins large numbers of neutrophils begin to invade the inflamed area from the blood. This is caused by products from the inflamed tissues that initiate the following reactions:

a. They alter the inside surface of the capillary endothelium causing neutrophlis to stick to the capillary walls in the inflamed area (margination).

b. They cause the endothelial cells of the capillaries and small venules to separate easily, allowing openings large enough for neutrophils to pass by diapedesis into the tissue spaces.

c. Other products of the inflammation cause chemotaxis of neutrophils toward the injured tissue. Chemotactic agents include products of the complement system (explained later), leukotrienes, and polypeptides from lymphocytes, basophils and mast cells.

Thus, within several hours after tissue damage begins, the area becomes well supplied with neutrophils. Because the neutrophils are already mature cells, they are ready to begin immediately their phagocytic actions. Neutrophils also release thromboxanes that are vasoconstrictors and platelet-aggregating agents, and leukotrienes that increase vascular permeability and attract other neutrophils to the site.

[2] Also within a few hours after the onset of acute severe inflammation, the number of neutrophils in the blood increases this is called neutrophilia. This is caused by products of inflammation that enter the blood stream then are transported to the bone marrow and there act on the marrow capillaries and on stored neutrophils to mobilize these immediately into the circulating blood. This makes more neutrophils available to the inflamed tissue area.

[3] Along with the invasion of neutrophils, monocytes leave the blood, by margination, diapedesis and chemotaxis, and enter the inflamed tissue and enlarge to become macrophages. Because the number of monocytes in the blood is low, also the storage pool of monocytes in the bone marrow is much less than that of neutrophils, the buildup of macrophages in the inflamed tissue area is much slower than that of neutrophils, requiring several days to become effective. Furthermore, even after invading the inflamed tissue, monocytes are still immature cells requiring 8 hours or more to swell to much larger sizes and develop large quantities of lysosomes, only then acquiring the full capacity for phagocytosis.

Activated T-lymphocytes (explained later) at the site of inflammation release GM-CSF, y-interferon and other factors which affect macrophages. They cause monocytes from the blood to accumulate at the site of inflammation and become macrophages; they inhibit macrophage migration from the site; and they activate the macrophage, enhancing its microbicidal properties, its ability to secrete proteolytic enzymes and generate toxic oxygen metabolites.

[4] As a response to inflammation, there is also greatly increased production of both granulocytes and monocytes by the bone marrow. This is controlled by multiple growth factors as explained earlier, including mainly ILs and CSFs. These factors are formed in the inflamed tissue by macrophages, activated T-lymphocytes, endothelial cells, and fibroblasts.

The ILs and CSFs stimulate the production of the relevant committed stem cells by stimulating the early divisions of the precursor cells in the bone marrow and the conversion of the committed stem cells into granulocytes and monocytes by causing proliferation & maturation of the cells in the granulocytic and monocytic committed cell lines.

When neutrophils and macrophages engulf large numbers of bacteria and necrotic tissue, all neutrophils and many or most of macrophages eventually die. After several days a cavity is formed in the inflamed tissue containing dead neutrophils, dead macrophages, necrotic tissue and tissue fluid. Such a mixture is known as "pus". After the infection has been suppressed, dead cells and necrotic tissue in the pus gradually autolyze over a period of days, and the end products are usually absorbed into the surrounding tissues until most of the evidence of tissue damage is gone.

Immunity

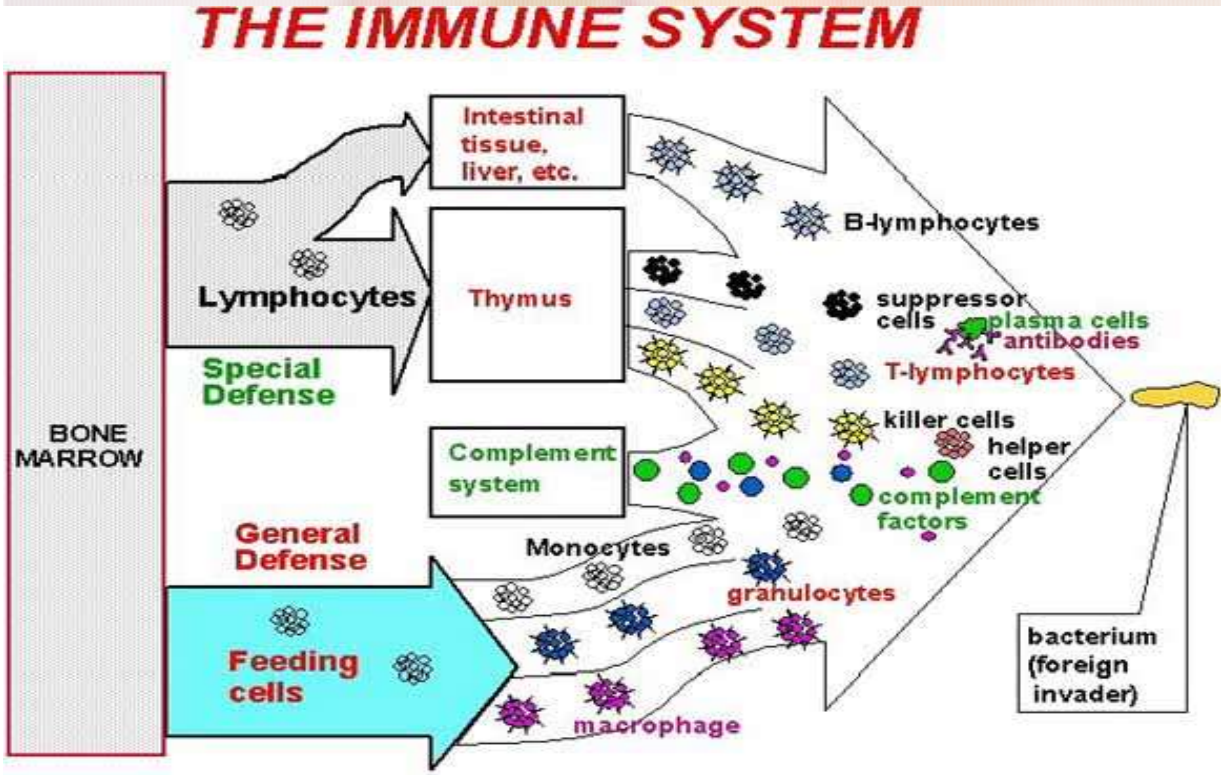
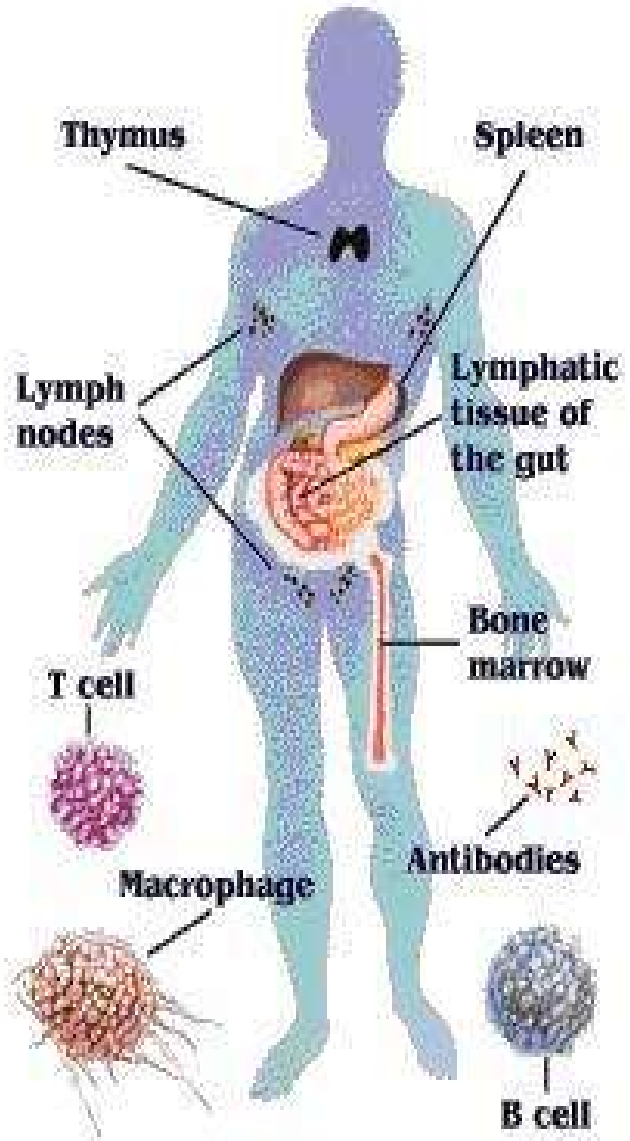


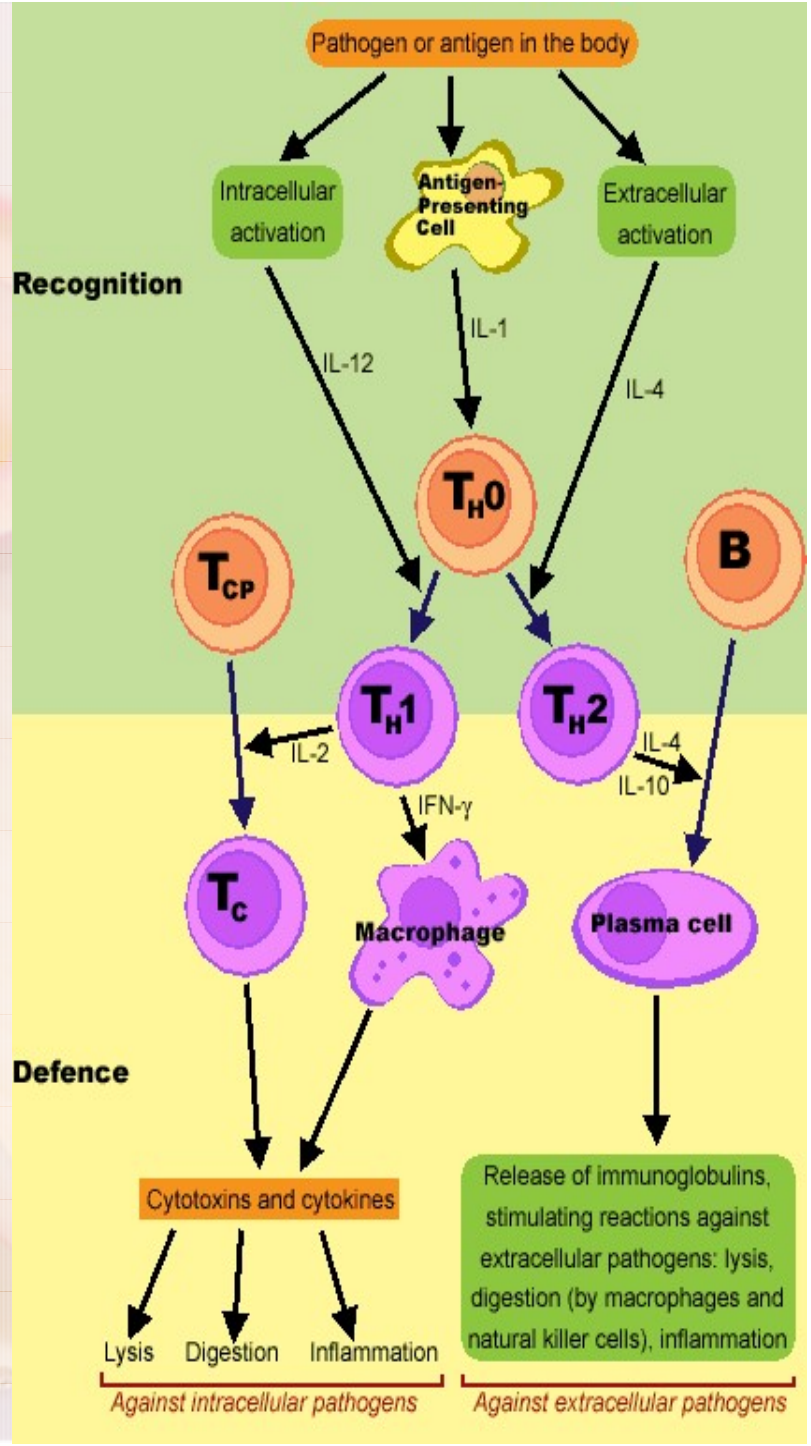
Figure 20. Immune system block diagram.



Immune Mechanisms (Function of Lymphocytes):

White blood cells protect the body by two defense mechanisms:

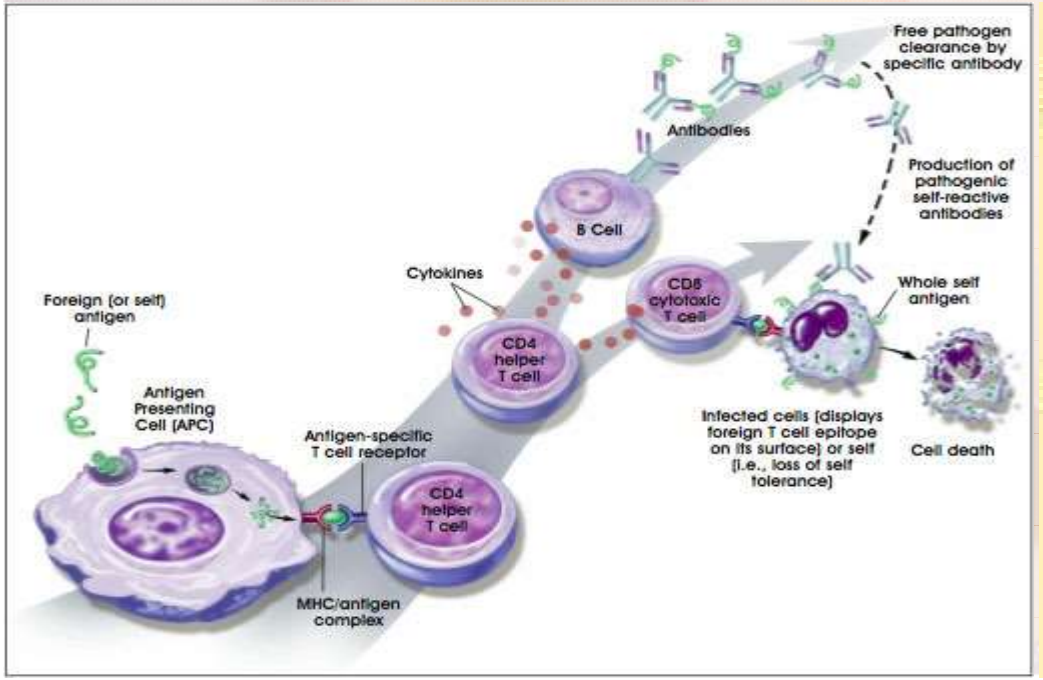
1. Non specific defense mechanism-by phagocytosis.
2. Specific defense mechanism-by immune system, which is a *specific system* acts *against specific organisms or particles*, and *becomes effective* only *after the initial interactions with the specific organism or particle* i.e. immunity against a foreign invading agent does not occur until after first invasion by the foreign agent. Lymphocytes are the key constituents of the immune system. The substance or particle that is capable of stimulating the immune system is called "antigen", most antigens are proteins or large polysaccharides.

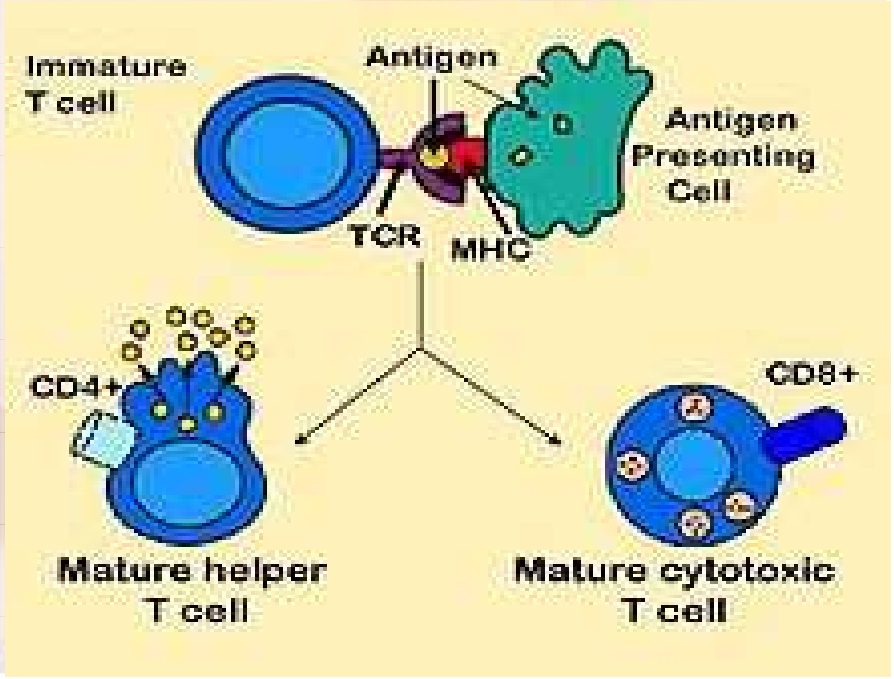


The body has two types of immune defense systems; humoral and cellular. Both react to antigens.

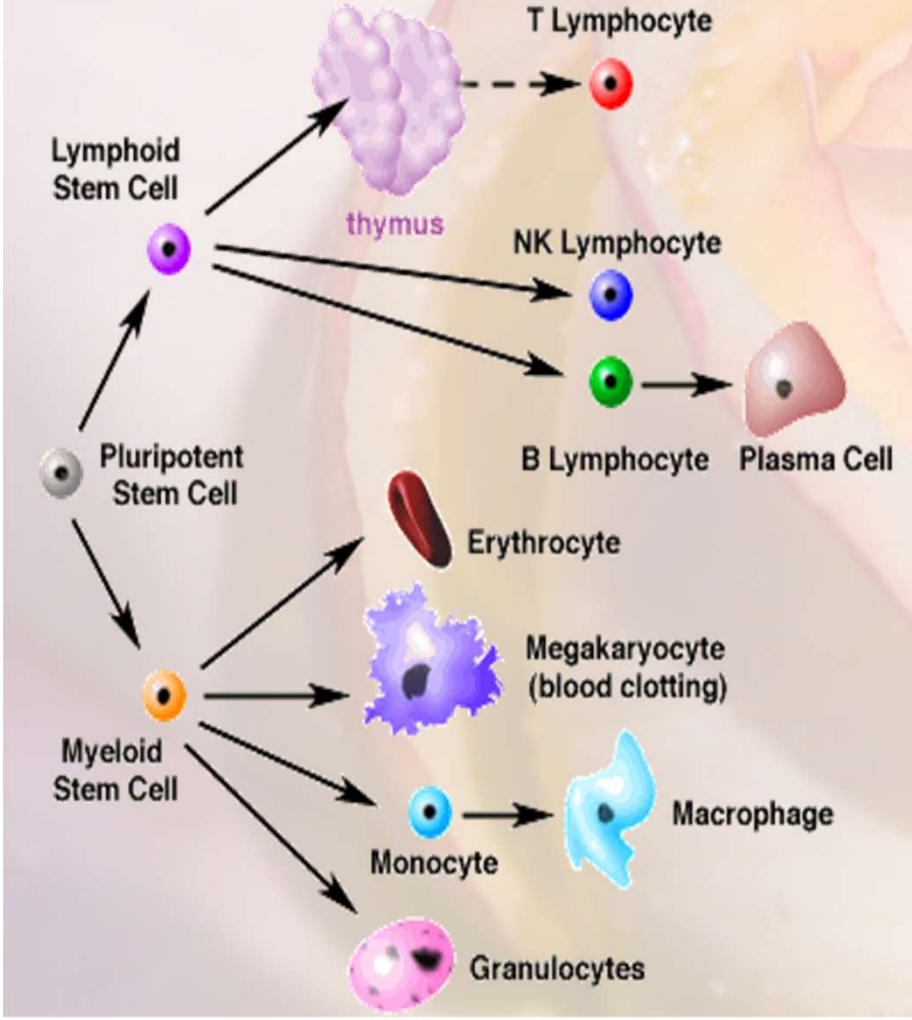
[1] Humoral immunity (B-cell immunity) is immunity due to circulating antibodies (Abs) which are globulins. It is a major defense against bacterial infections.

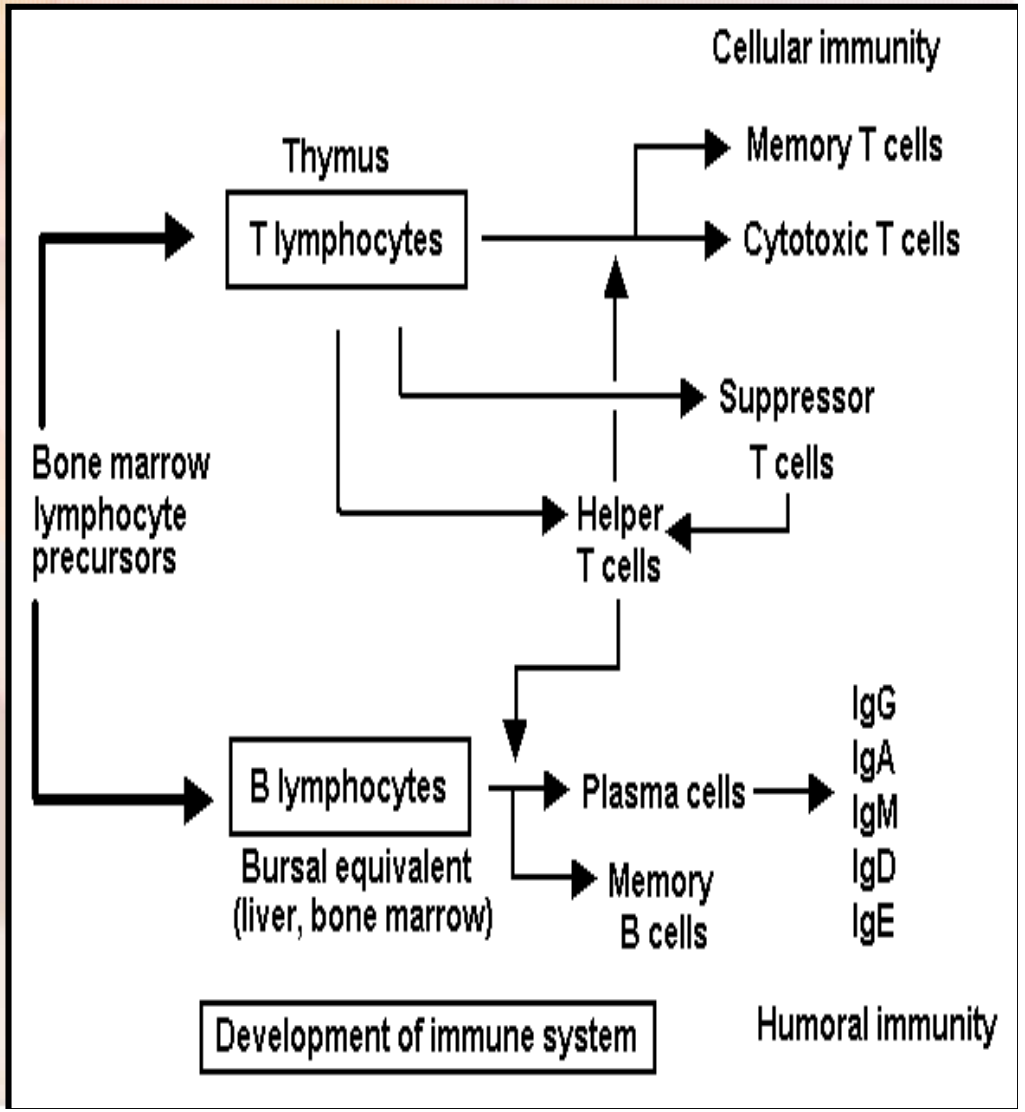
[2] Cellular of cell-mediated immunity (T-cell immunity) is achieved by formation of large numbers of activated lymphocytes that are specially designed to destroy the foreign agent. It constitutes a major defense against infections due to viruses, fungi and a few bacteria such as the tubercle bacillus. It is responsible for rejection of transplants of foreign tissue, and for delayed allergic reactions. It also helps defend against tumors.





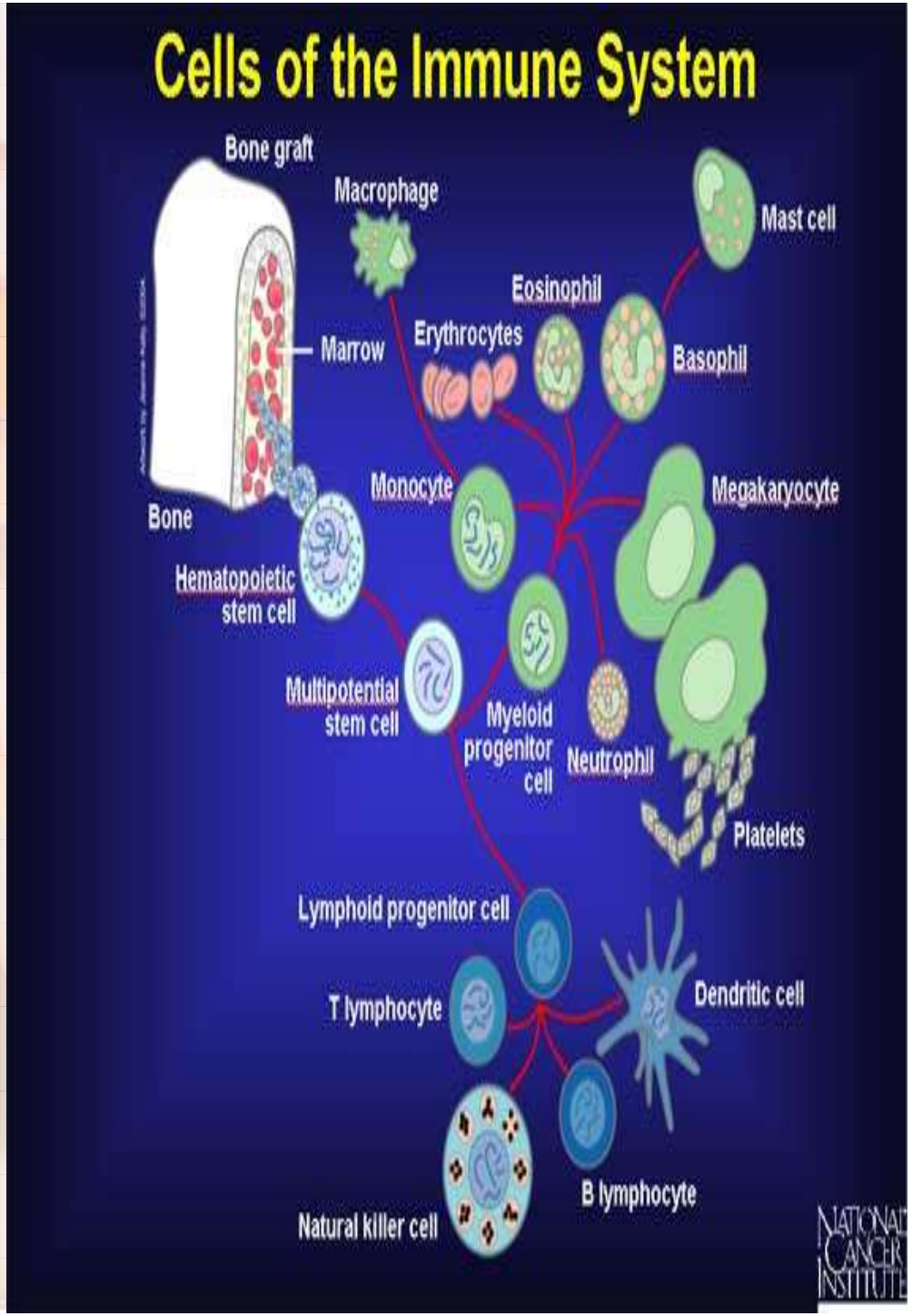
Development of the Immune System: During fetal development bone marrow lymphocyte precursors that have migrated to the thymus differentiate into lymphocytes responsible for cellular immunity (T lymphocytes).



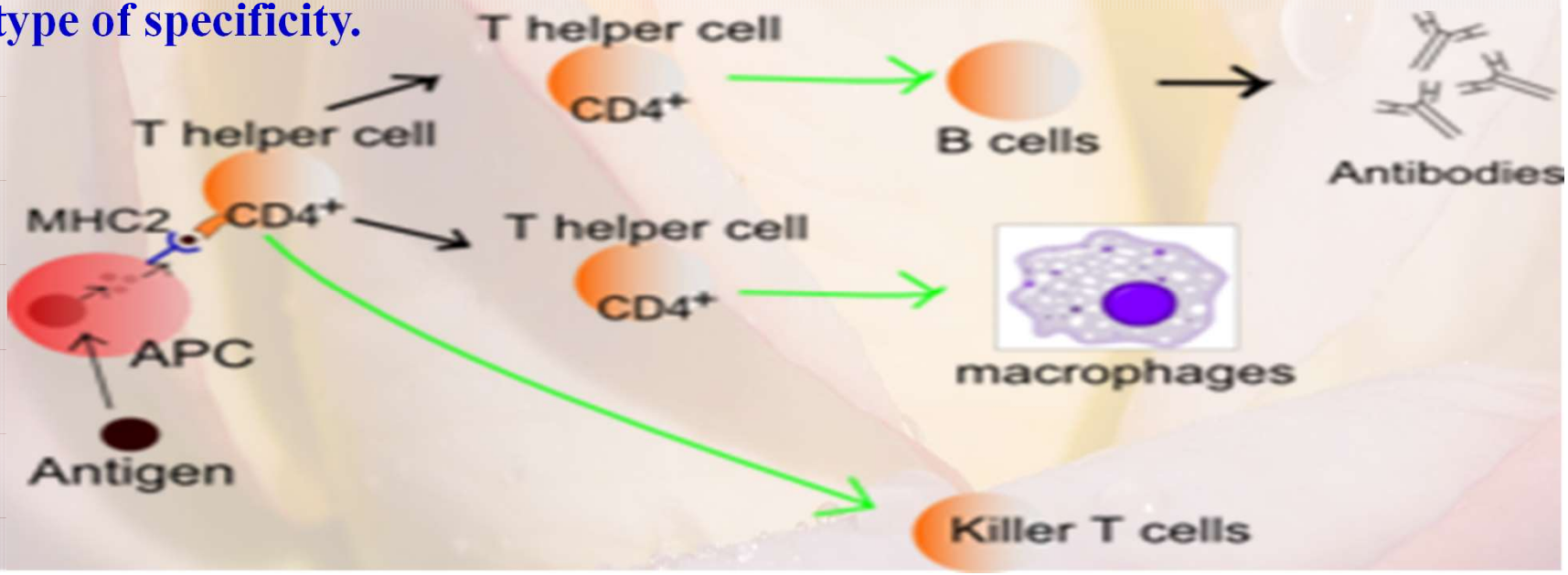


In birds, the precursors that migrate to the bursa of Fabricius (a lymphoid structure at end of gut) becomes transformed into lymphocytes responsible for humoral immunity (B lymphocytes). There is no bursa in human beings and transformation to B lymphocytes occurs in the liver during fetal life and after birth in the bone marrow.

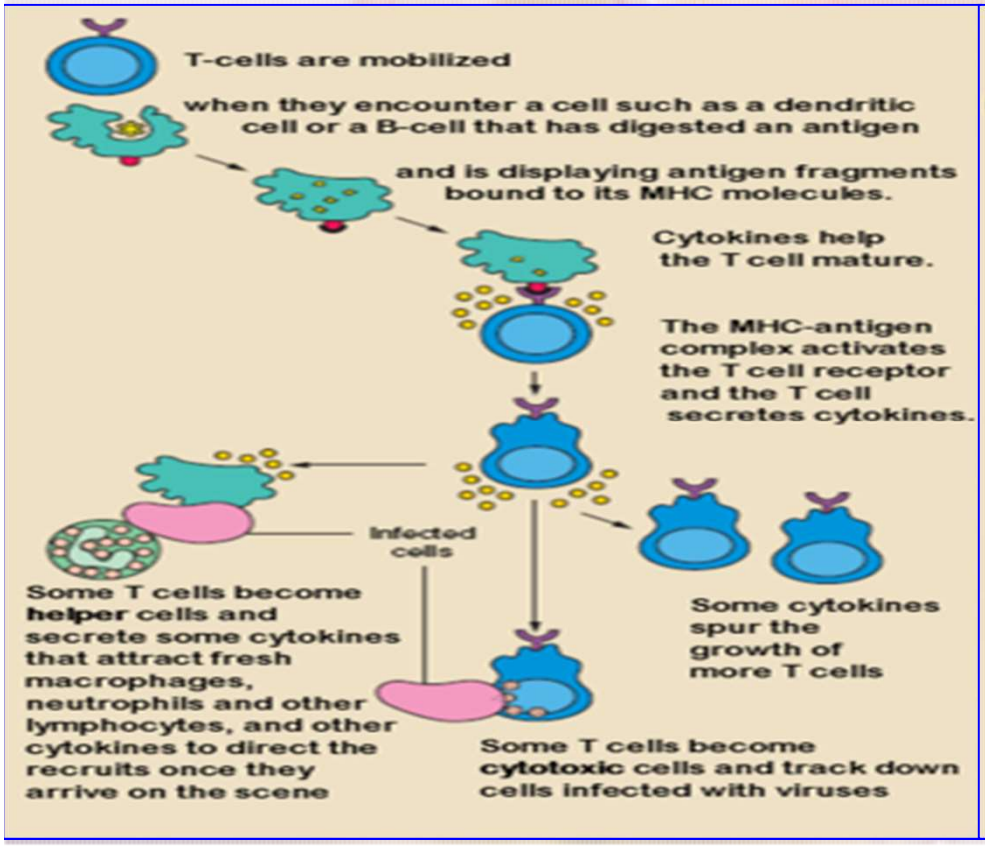
After residence in the thymus or liver, many of the T and B lymphocytes migrate to the lymph nodes and bone marrow. T and B lymphocytes are morphologically indistinguishable, but can be identified by special techniques.

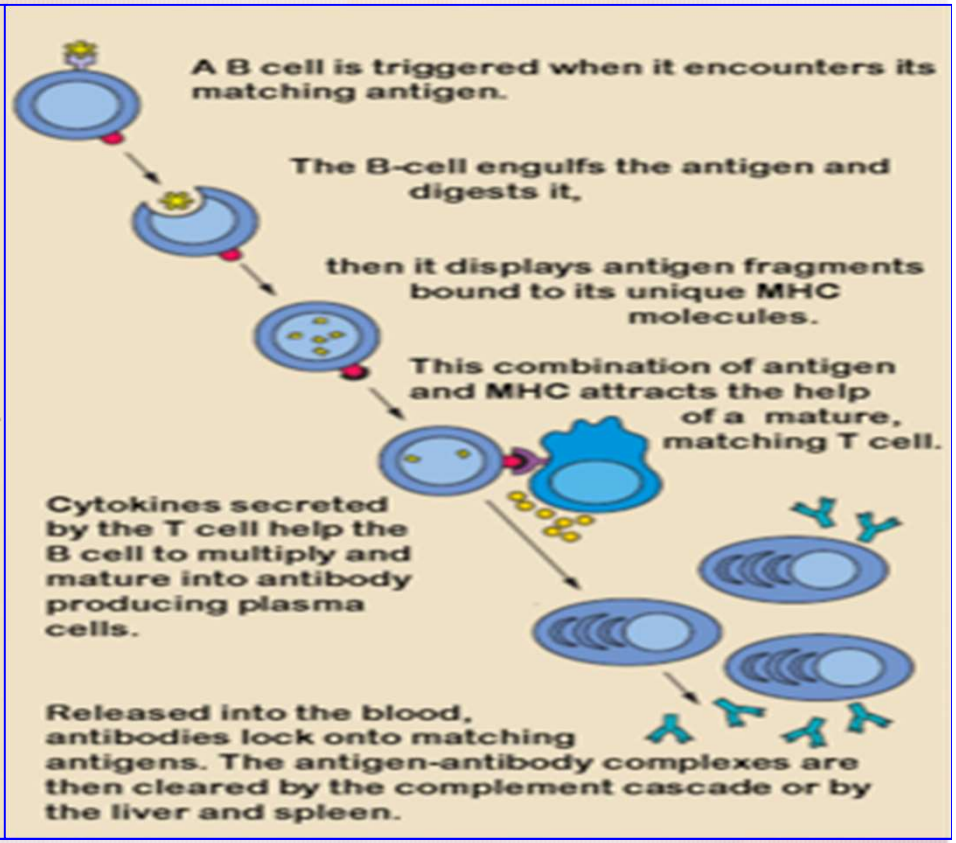


The number of different antigens (Ags) recognized by lymphocytes in the body is extremely large. It is now clear that the recognition ability is innate and develops without exposure to the Ag. Stem cells differentiate into many million different T and B lymphocytes, each with the ability to respond to a particular Ag. The reason for this is the following: In the case of B lymphocytes, each one has on the surface of its cell membrane Ab molecules which act as Ag binding receptors, that will attaches to the cell membrane and this leads to the activation process. In the case of the T lymphocytes, molecules called surface receptor proteins (or T-cell markers), are on the surface of the T-cell membrane, and these too, are highly specific for the one specified activating Ag. Each B or T lymphocyte when stimulated by the appropriate Ag, is capable of forming highly specific Abs or T cells i.e. Abs or T cells which have single type of specificity.



Cytokines: They are hormonelike chemical messengers that affect the immune response secreted by lymphocytes, macrophages, endothelial cells and in some instances fibroblast. Some of the principal cytokines include: Interleukins (1, 2, 3, 4, 5, 6, 7, 12 and 13), tumor necrosis factor, , and interferons, and colony-stimulating factors. As this field of research is growing very rapidly, new factors are found and named.

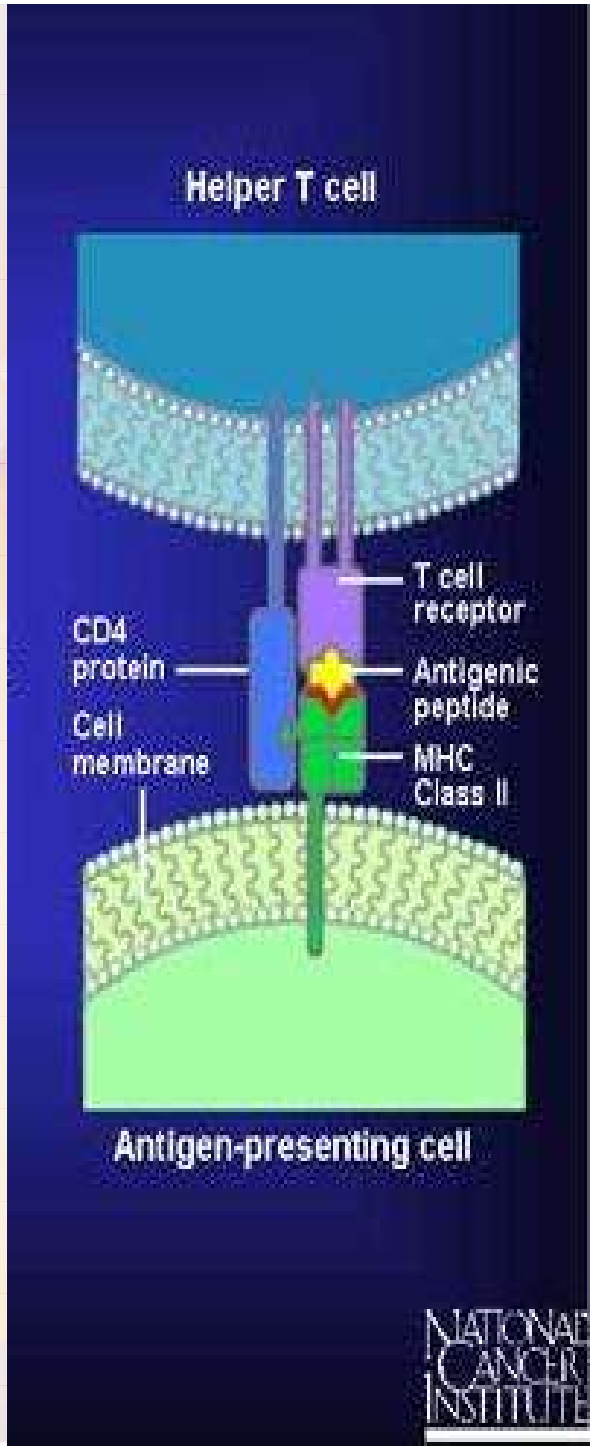




The B cells differentiate into plasma cells and memory B cells

The T cells are of 4 varieties:

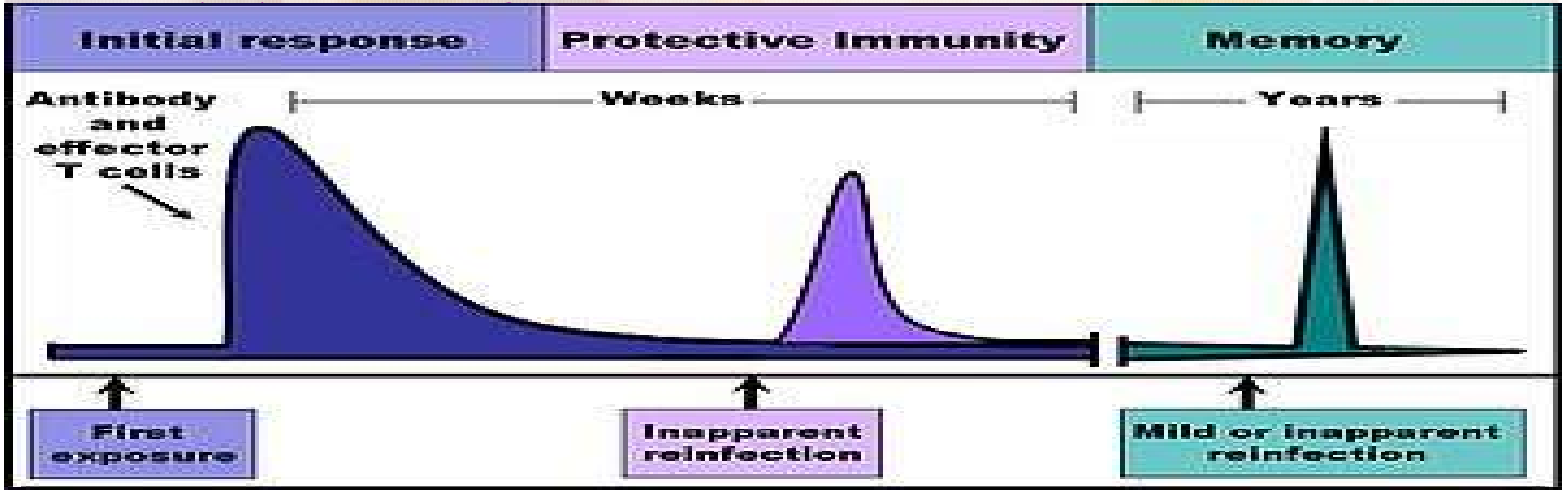
***1.Helper T cells*, which are the most numerous of the T-cells, "help" in the functions of the immune system. They do this by forming cytokines that act on other cells of the immune system as well as on bone marrow cells. Among the important cytokines secreted by the helper T cells are the following: Interleukins, granulocyte-monocyte colony stimulating factor (GM-CSF), and interferon. There are 2 subtypes of helper T cells: T helper 1 cells which are concerned primarily with cellular immunity and T helper 2 cells which interact primarily with B-cells in relation to humoral immunity. It is the helper T cells that are inactivated or destroyed by the acquired immunodeficiency syndrome (AIDS) virus, with eventual loss of immune function and death from a variety of infections or cancer.**



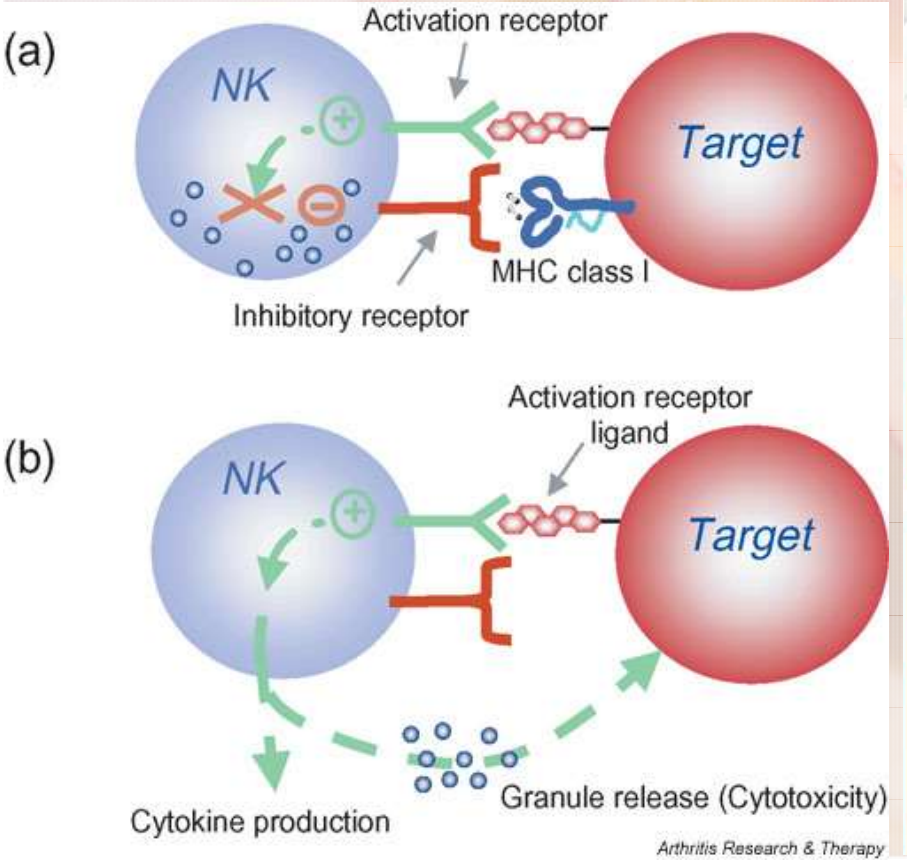
2.Suppressor T cells **are also involved in regulation of humoral and cellular immunity. They are capable of suppressing the functions of both cytotoxic and helper T cells, keeping them from causing excessive immune reactions that might be severely damaging to the body.**

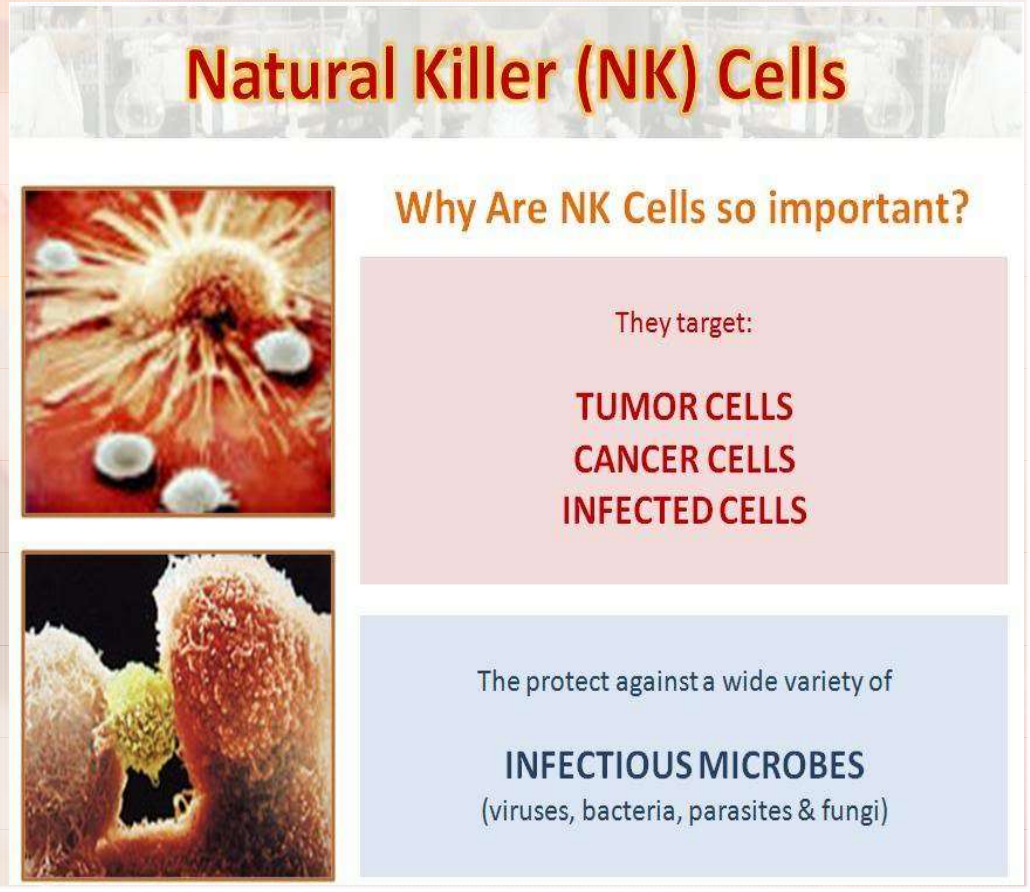
3.Cytotoxic T cells**, also called *killer cells*, are direct attack cells capable of killing microorganisms and destroying transplanted and other foreign cells.**

4.Memory T cells**: Memory B and T cells are cells that have been exposed to an Ag and are readily converted to effector cells when later encounter with the same Ag. Unlike other lymphocytes, they**



Natural Killer Cells (NK cells): They constitute a small fraction of the lymphocytes and are sometimes called non-T and non-B lymphocytes. They are large lymphocytes and kill cells without any apparent prior antigenic stimulation or exposure and without the involvement of major histocompatibility antigens. Their activity is increased by IL-2. They have a significant role in elimination of malignant or virally infected target cells.





The Complement System:

Complement consists of a series of about 20 proteins, mainly enzymes, present in plasma as inactive precursors. The principal actors in this system are 11 proteins designated C1 through C9, B, and D. C1 is made up of 3 subunits C1q, C1r, and C1s. the complement system can be activated by the classical pathway and the alternate pathway.

As a consequence of activation, multiple end products are formed which cause important effects that help to prevent damage by the invading organism or toxin.