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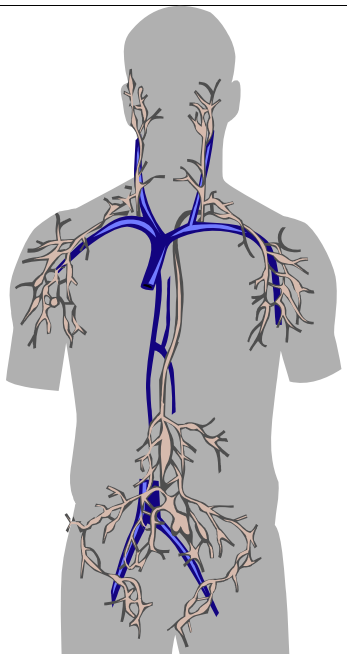
The Lymphatic System



REVISED
9:43 pm, Jun 20, 2006

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Functions of the Lymph System

1) Maintains volume and pressure of extracellular fluid by returning excess water and dissolved substances from the interstitial fluid to the circulation.

2) Lymph nodes and other lymphoid tissues are the site of clonal production of immunocompetent lymphocytes and macrophages in the specific immune response.

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The first function relates to our discussion of the filtration which occurs from the arterial end of capillaries (Starling's Law of the capillaries).

Drainage into the Lymph System

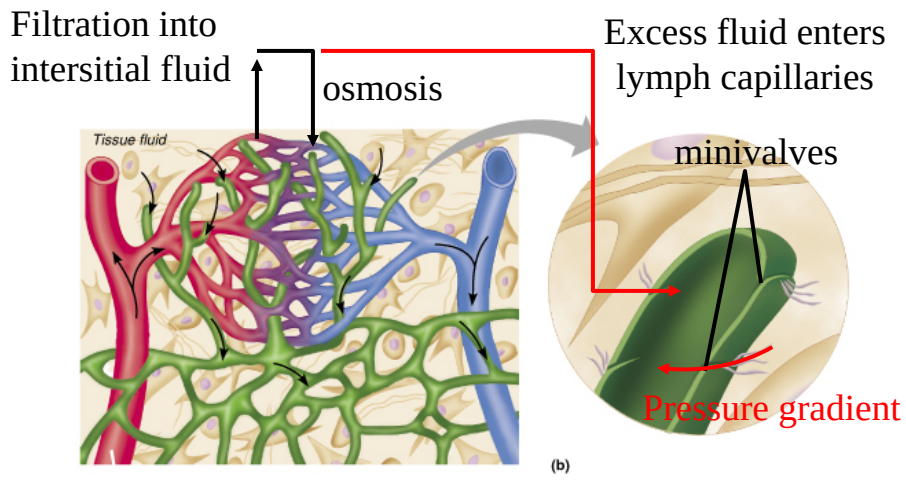
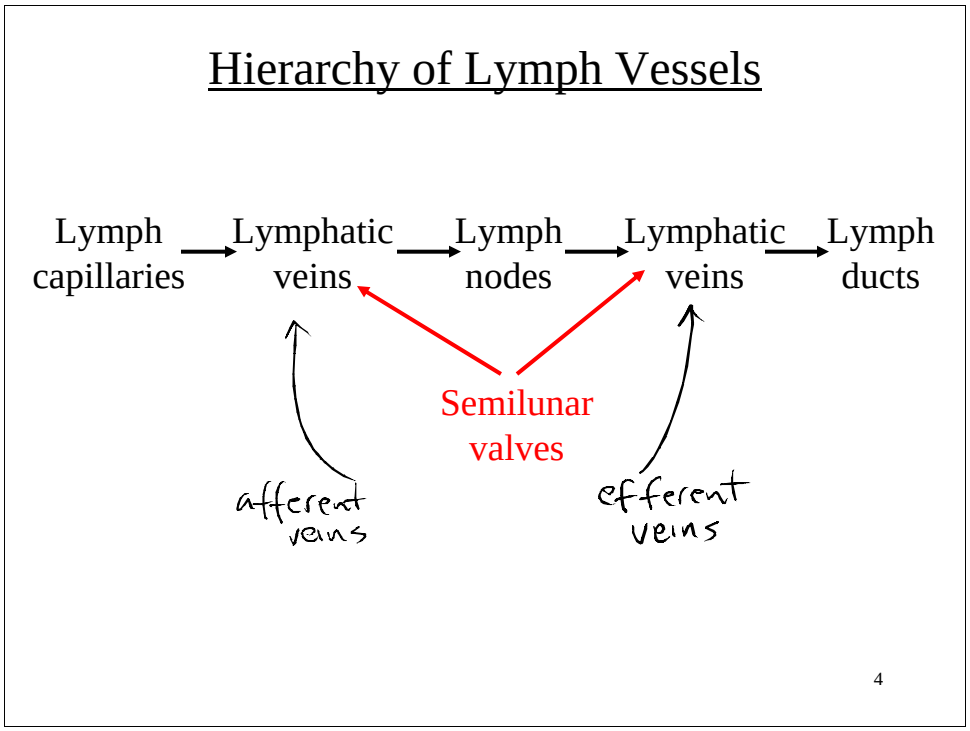
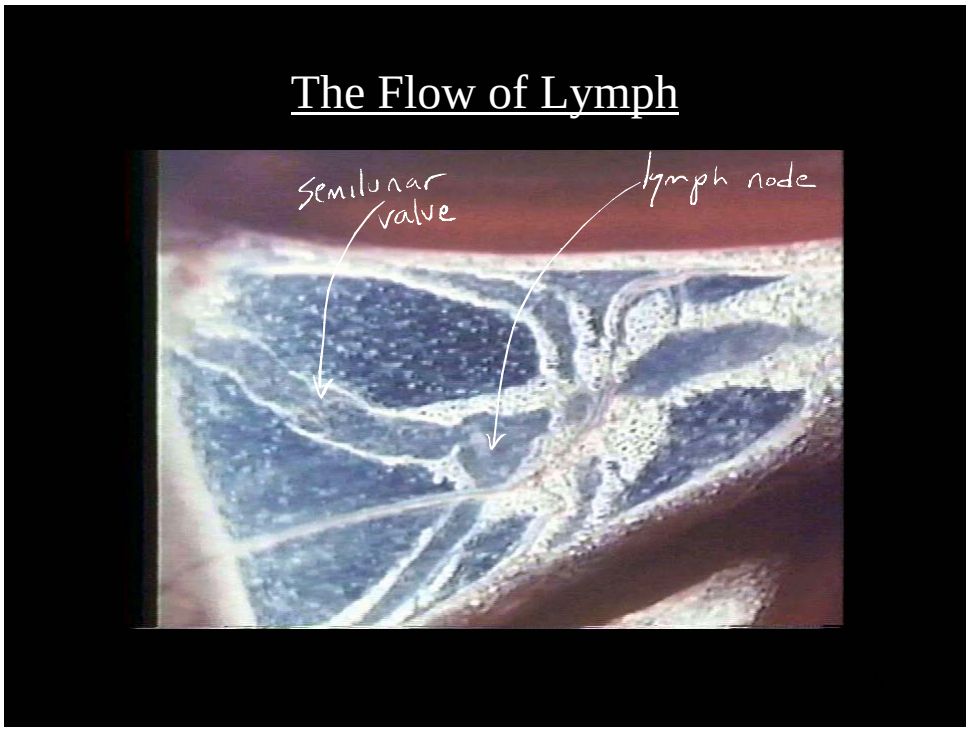


Figure 20.1

Filtration forces water and dissolved substances from the capillaries into the interstitial fluid. Not all of this water is returned to the blood by osmosis, and excess fluid is picked up by lymph capillaries to become lymph. From lymph capillaries fluid flows into lymph veins (lymphatic vessels) which virtually parallel the circulatory veins and are structurally very similar to them, including the presence of semilunar valves. Lymph capillaries have flap-like minivalves which allow fluid to enter when pressure gradient is normal, but close to prevent backflow when pressure is higher in the lymph capillary.



Lymph veins (also known as lymphatic vessels) both enter and leave the lymph nodes as they pass from one node to another before eventually reaching the lymph duct.



See the video clip on the Lymph System in Realmedia format.

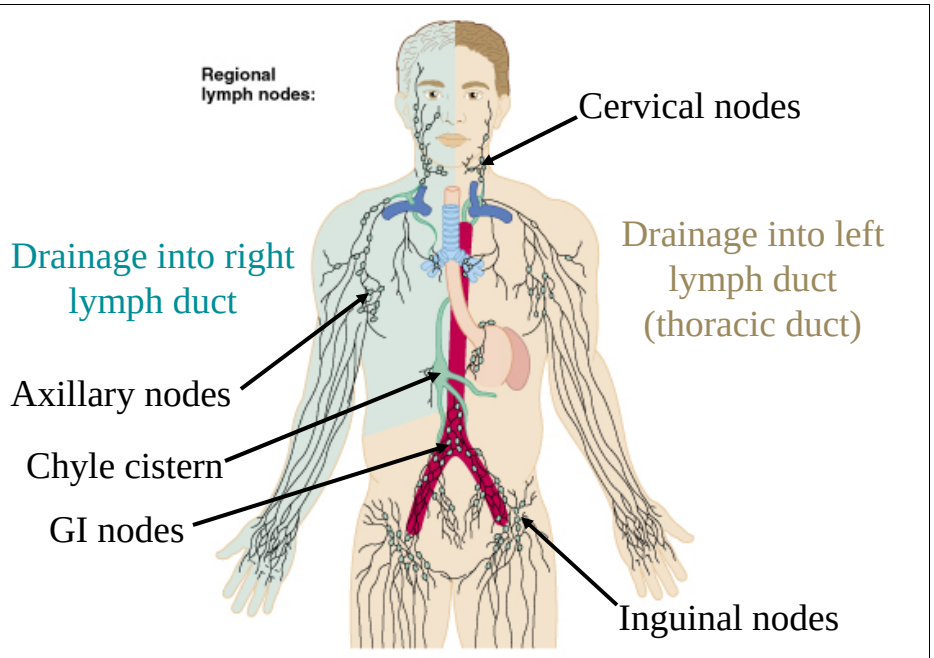
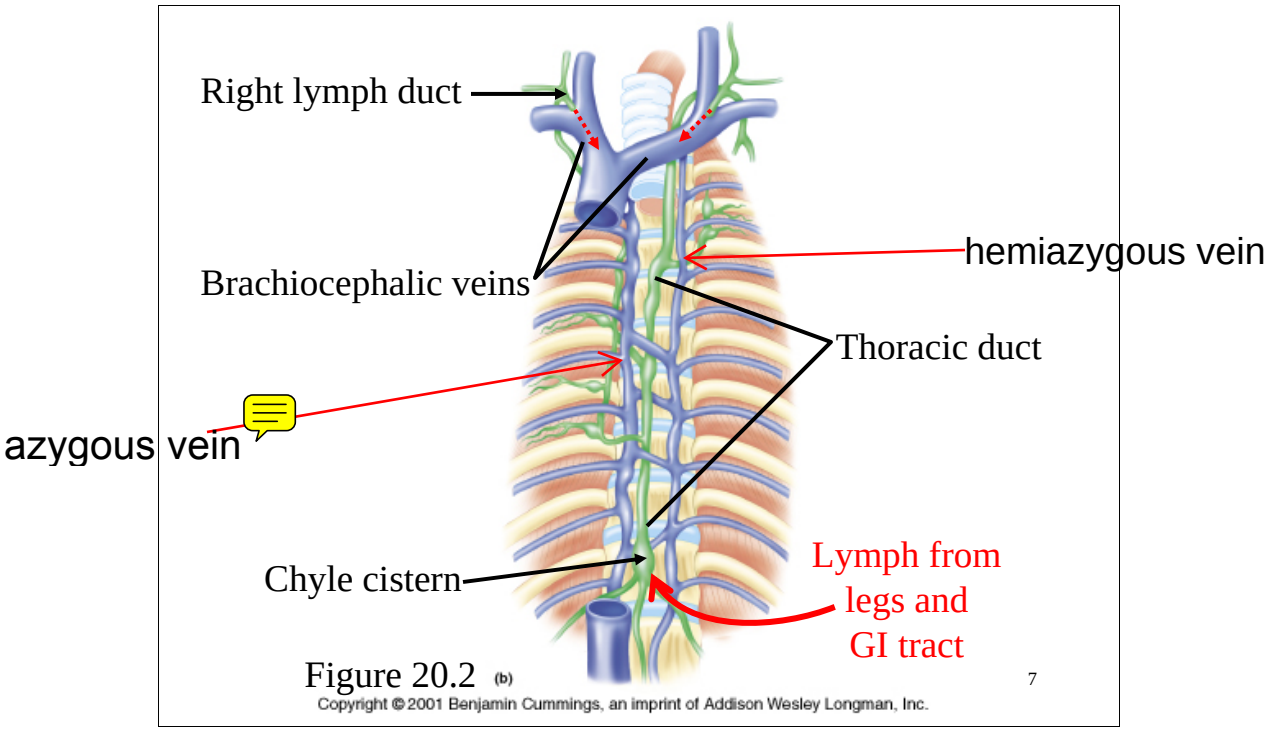


Figure 20.2

Note the unequal drainage of the lymph system into the two ducts. The nodes shown are the high concentration areas only, which occur at the convergence of lymph vessels from the body regions. It has been estimated that lymph cannot pass more than a few centimeters without passing through at least one node.



The lymphatic veins flow into one of two lymph ducts. The right lymph duct drains the right arm, shoulder area, and the right side of the head and neck. The left lymph duct, or thoracic duct, drains everything else, including the legs, GI tract and other abdominal organs, thoracic organs, and the left side of the head and neck and left arm and shoulder. These ducts then drain into the subclavian veins on each side where they join the internal jugular veins to form the brachiocephalic veins.

Lymphokinetic Motion

- the flow of the lymph.

1) Lymph flows down the pressure gradient.

2) Muscular and respiratory pumps push lymph forward due to function of the semilunar valves.

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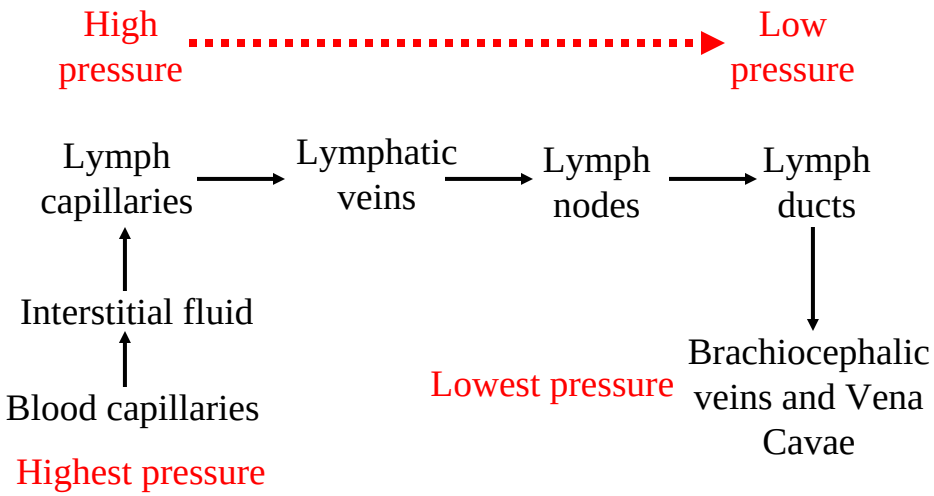
Some other mammals utilize muscular contractions to move the lymph, but humans rely entirely on the “pumps” and pressure gradient.

Pressure in Lymphokinetic Motion



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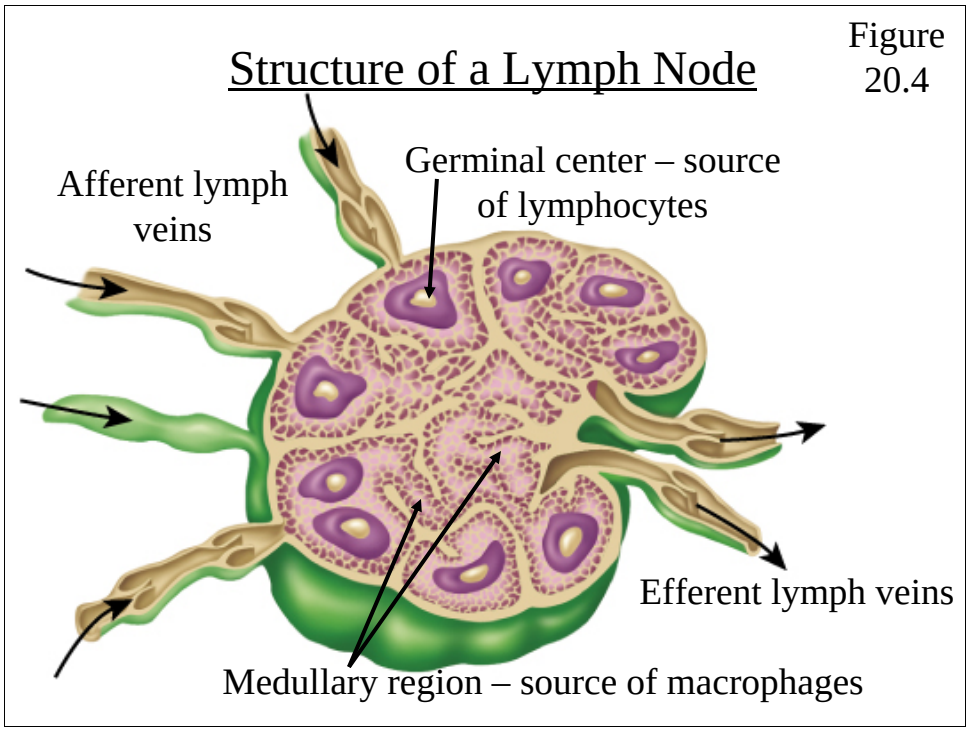
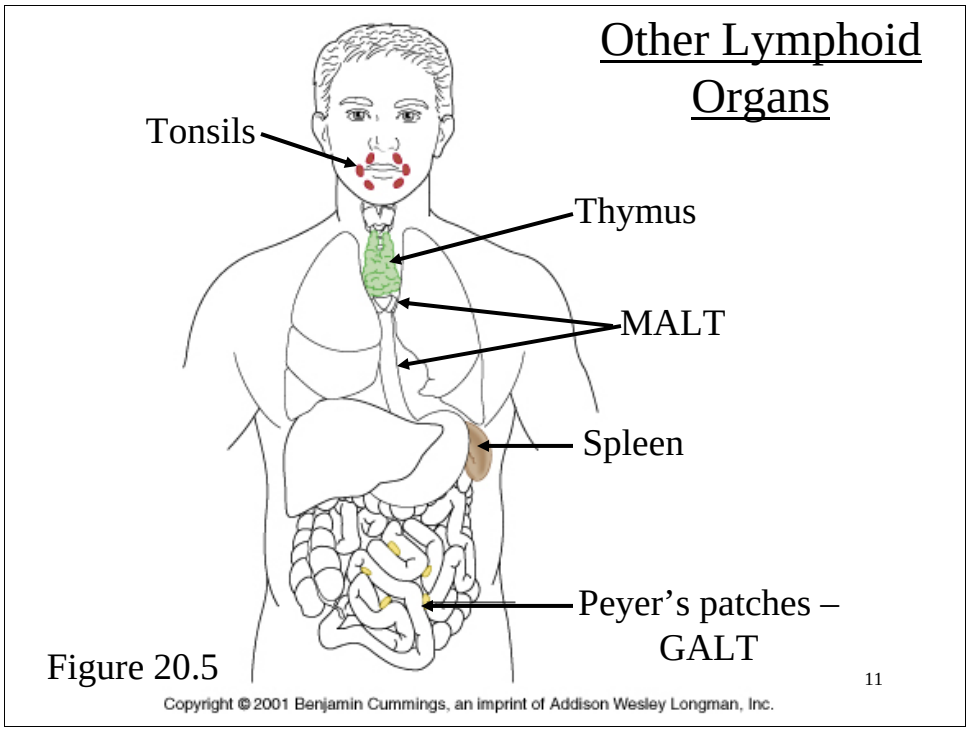


Lymph nodes: Lymph nodes are small encapsulated organs located along the pathway of lymphatic vessels. They vary from about 1 mm to 1 to 2 cm in diameter and are widely distributed throughout the body, with large concentrations occurring in the areas of convergence of lymph vessels. They serve as filters through which lymph percolates on its way to the blood. Antigen-activated lymphocytes differentiate and proliferate by cloning in the lymph nodes.



Diffuse Lymphatic Tissue and Lymphatic nodules: The alimentary canal, respiratory passages, and genitourinary tract are guarded by accumulations of lymphatic tissue that are not enclosed by a capsule (i.e. they are *diffuse*) and are found in connective tissue beneath the epithelial mucosa. These cells intercept foreign antigens and then travel to lymph nodes to undergo differentiation and proliferation. Local concentrations of lymphocytes in these systems and other areas are called *lymphatic nodules*. In general these are single and random but are more concentrated in the GI tract in the ileum, appendix, cecum, and tonsils. These are collectively called the Gut Associated Lymphatic Tissue (**GALT**). **MALT** (Mucosa Associated Lymphatic Tissue) includes these plus the diffuse lymph tissue in the respiratory tract.

The spleen: The spleen filters the blood and reacts immunologically to blood-borne antigens. This is both a morphologic (physical) and physiologic process. In addition to large numbers of lymphocytes the spleen contains specialized vascular spaces, a meshwork of reticular cells and fibers, and a rich supply of macrophages which monitor the blood. Connective tissue forms a capsule and trabeculae which contain myofibroblasts, which are contractile. The human spleen holds relatively little blood compared to other mammals, but it has the capacity for contraction to release this blood into the circulation during anoxic stress. White pulp in the spleen contains lymphocytes and is equivalent to other lymph tissue, while red pulp contains large numbers of red blood cells that it filters and degrades.

Immunocompetence - the ability to recognize self vs. non-self antigens.

Antigen – a protein or other substance which stimulates recognition by immunocompetent lymphocytes.

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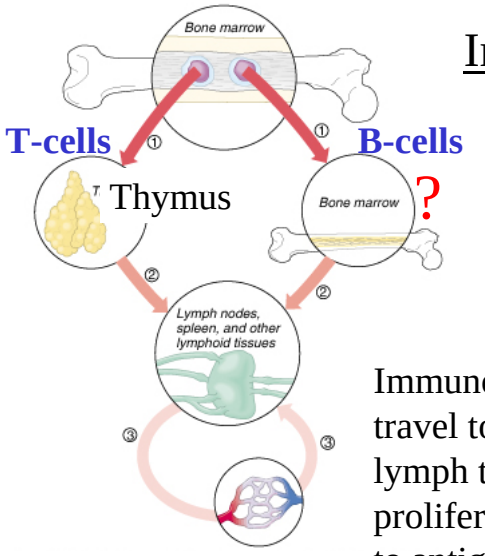

Sites of Immunocompetence

Bursa of fabricus in chickens; bursa equivalent in humans: bone marrow, possibly the distal bowel.

Immunocompetent lymphocytes travel to lymph nodes and other lymph tissue where they proliferate and mature in response to antigenic stimulation and then enter the circulation.

Figure 20.8

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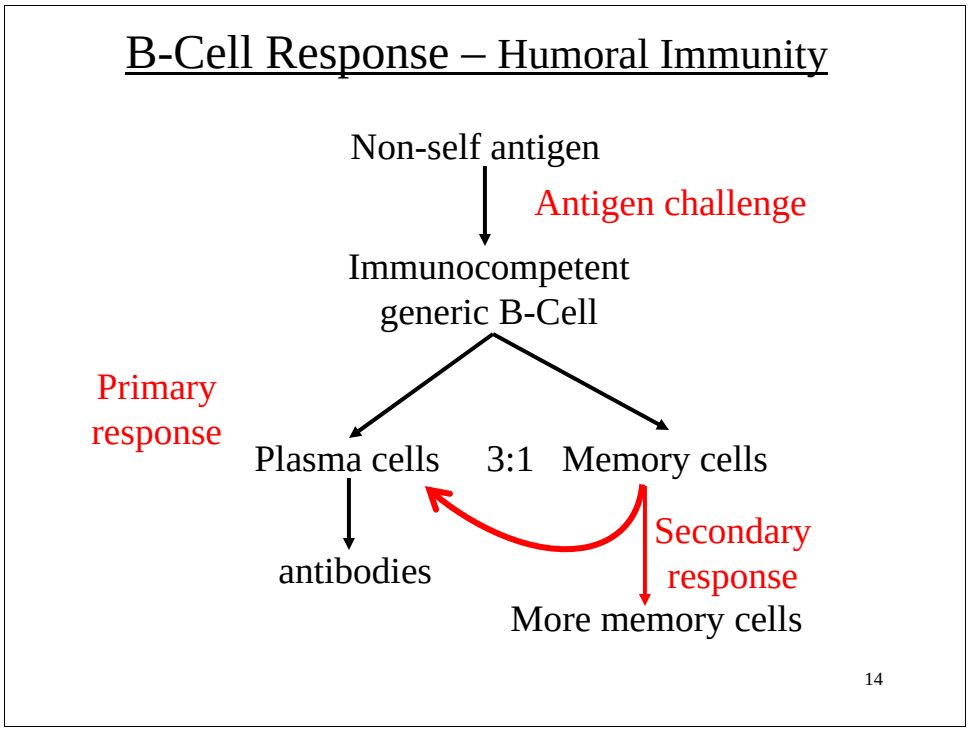
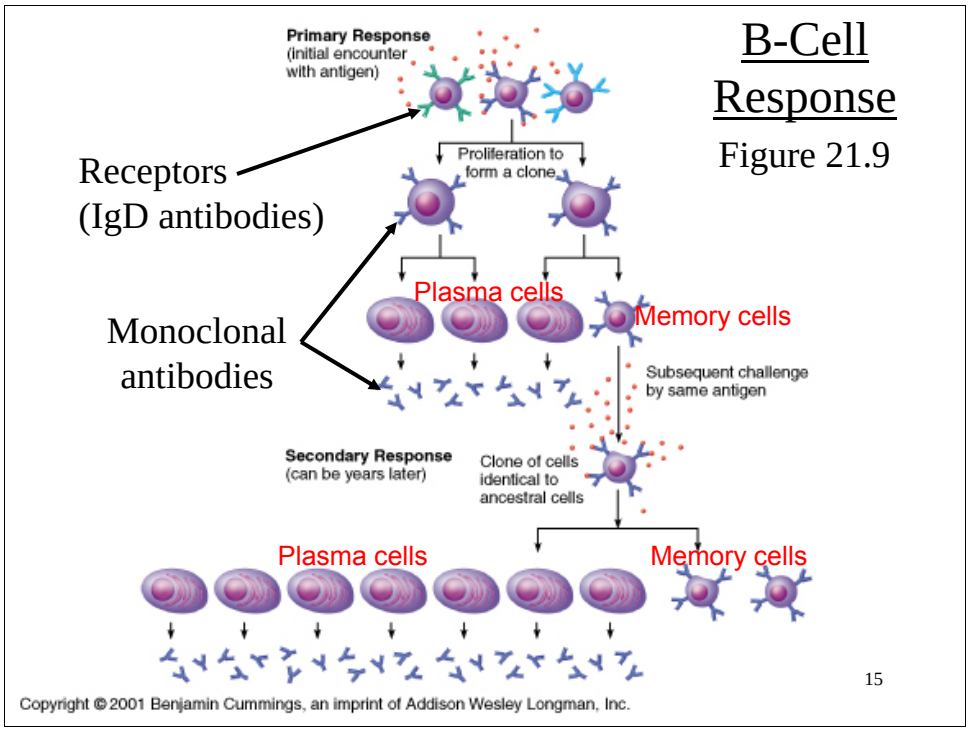
The B in B-cells comes from the **Bursa of Fabricus**, a structure in birds where the cloaca and gut join. This is where B-cells were first identified.

In humans, which have no bursa, immuncocompetence is believed to occur in the bone marrow, and in other areas which act as bursa equivalents. The bulk of immunocompetence occurs by the end of puberty and slowly decreases with age. The thymus eventually atrophies and disappears.



Immunocompetent B-cells in the lymph nodes and elsewhere are capable of responding to bacterial and some viral antigens. This is called "**antigen challenge**" and causes the activated B-cell to clone producing **plasma cells** and **memory cells**. The plasma cells secrete antibodies against the antigen, called **monoclonal antibodies**. (See "Antibody Actions" in slides 16 and 17.) This is called the **primary response** and takes about 7 to 10 days to reach its peak. The memory cells retain the ability to quickly produce large numbers of plasma cells and more memory cells should a subsequent exposure to the antigen occur, called the **secondary response**. Secondary responses peak in about 1 day. Your ability to produce a secondary response to a disease due to the presence of memory cells is called **active immunity**, and can last for many years.



Note that several immunocompetent B-cell lymphocytes are shown with different receptors (IgD antibodies) on their surface. A large variety of B-cells with different receptors helps to ensure that most bacterial and many viral antigens of the appropriate types will find a receptor which matches them.

Antibody Actions:

Agglutination – exemplified by blood typing reactions.

Opsonization – labeling, promotes phagocytosis.

Neutralization – binds to active sites of toxins.

Precipitation – makes soluble antigens insoluble.

Fixes and activates **complement** – causes opsonization, inflammation, and cell lysis.

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See the next slide.

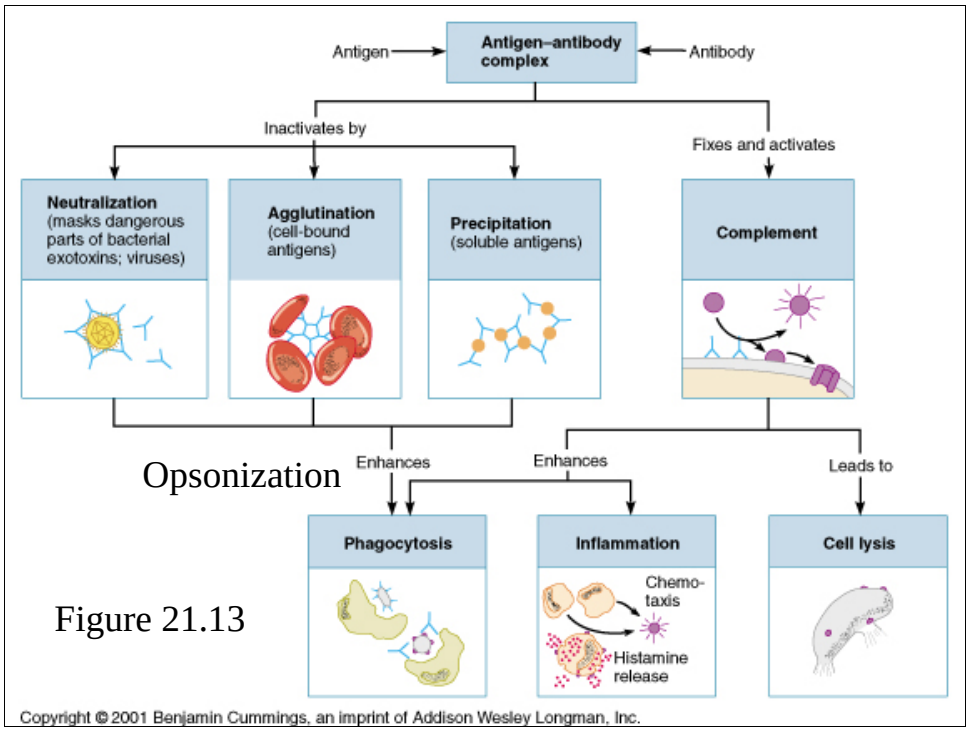
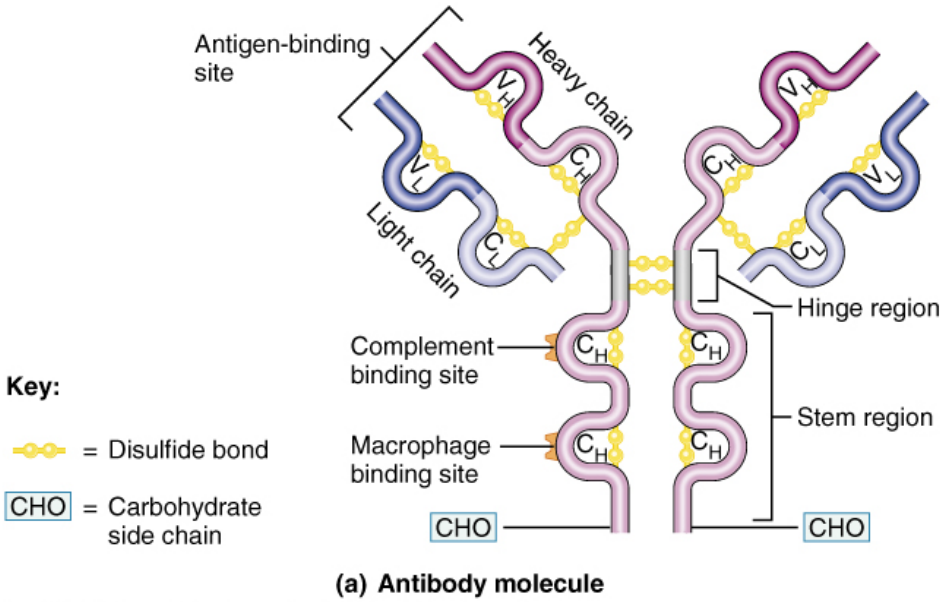


Figure 21.13

Monomer antibodies have the shape of a “Y” (See next slide) with two antigen attachment points. The pentamer antibody can attach to five times as many antigens.

Antibody Structure



(a) Antibody molecule

Note the **constant regions** (**C**) which are always present, the **variable regions** (**V**) which determine the specific binding characteristics, the **complement binding site** which activates complement (See slide 21), and the **macrophage binding site** which stimulates **opsonization.**

Table 22.3

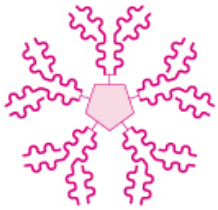
B-Cell receptors

Early release during primary response

TABLE 22.3 Immunoglobulin Classes

IgD (monomer)

IgD is virtually always attached to the external surface of a B cell, where it functions as the antigen receptor of the B cell; important in B cell activation.



IgM (pentamer)

IgM exists in monomer and pentamer (five united monomers) forms. The monomer, which is attached to the B cell surface, serves as an antigen receptor. The pentamer (illustrated) circulates in blood plasma and is the first Ig class released by plasma cells during the primary response. (This fact is diagnostically useful because presence of IgM in plasma usually indicates current infection by the pathogen eliciting IgM's formation.) Because of its numerous antigen binding sites, IgM is a potent agglutinating agent and readily fixes and activates complement.

Table 22.3

Becomes most important and prevalent antibody

Present in secretions

Stimulates mast cells and basophils to produce inflammation

TABLE 22.3 Immunoglobulin Classes

IgG (monomer)

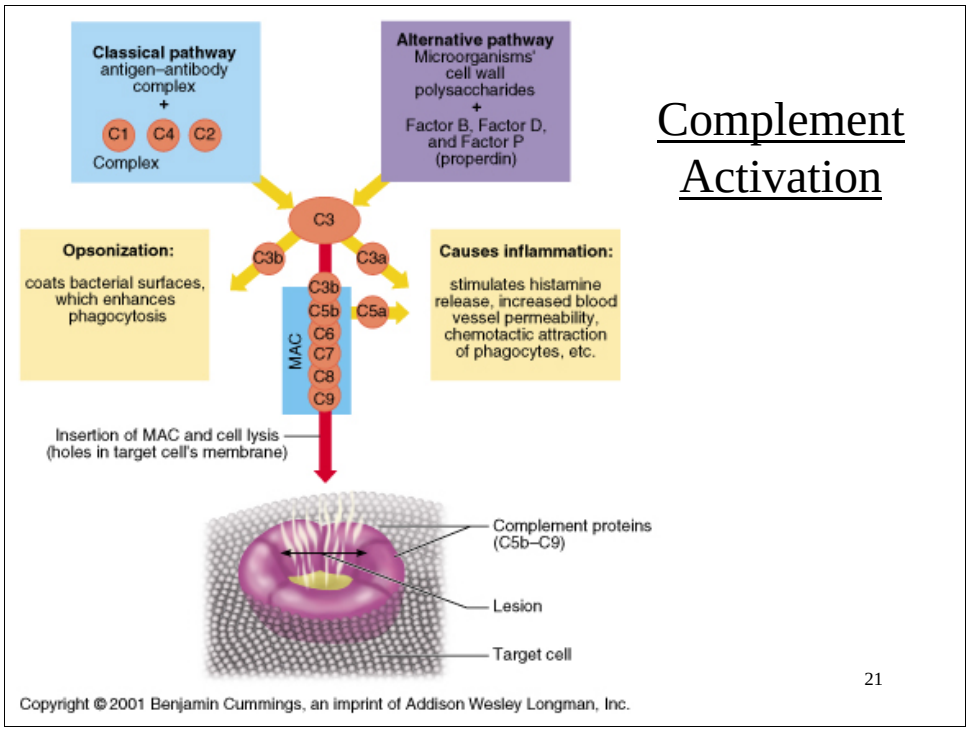
IgG is the most abundant and diverse antibody in plasma, accounting for 75–85% of circulating antibodies. It protects against bacteria, viruses, and toxins circulating in blood and lymph, readily fixes complement, and is the main antibody of both primary and secondary responses. It crosses the placenta and confers passive immunity from the mother to the fetus.

IgA (dimer)

IgA monomer exists in limited amounts in plasma. The dimer (illustrated), referred to as secretory IgA, is found in body secretions such as saliva, sweat, intestinal juice, and milk, and helps prevent attachment of pathogens to epithelial cell surfaces (including mucous membranes and the epidermis).

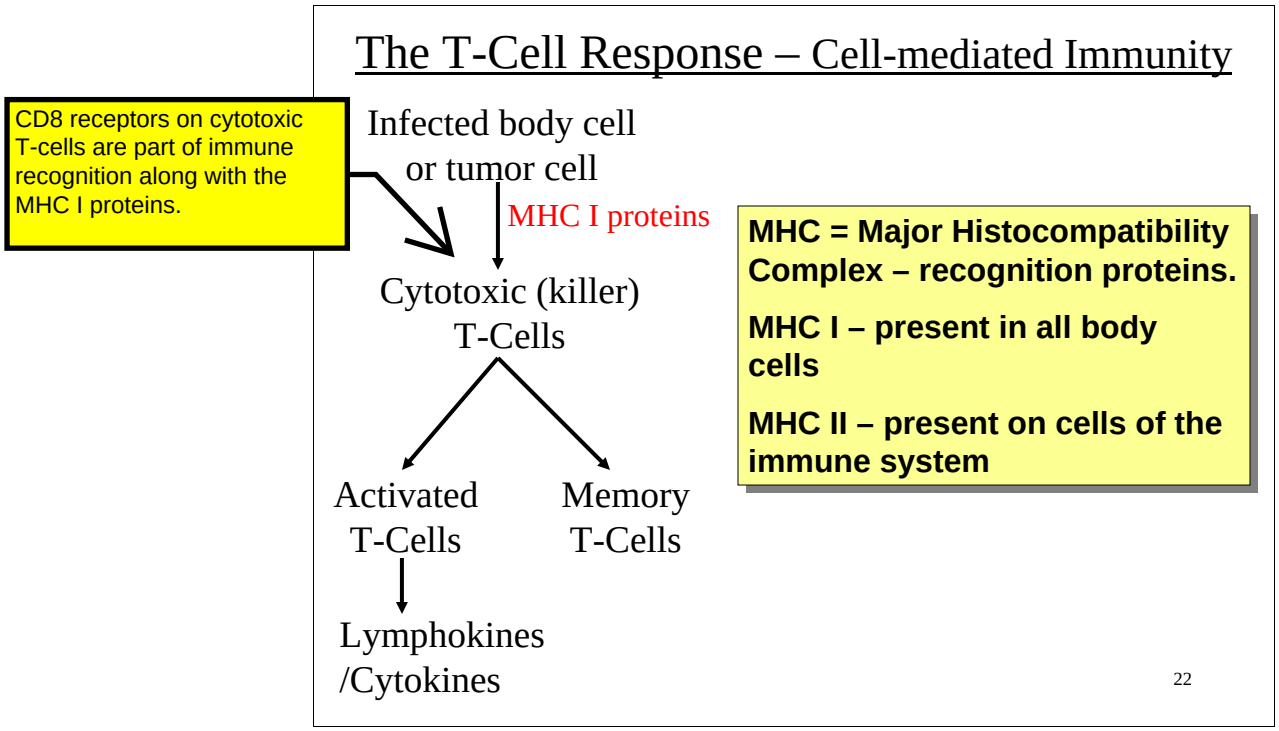
IgE (monomer)

IgE is slightly larger than the IgG antibody. It is secreted by plasma cells in skin, mucosae of the gastrointestinal and respiratory tracts, and tonsils. Its stem region becomes bound to mast cells and basophils, and when its receptor ends are triggered by an antigen, it causes the cells to release histamine and other chemicals that mediate inflammation and an allergic reaction. Typical only traces of IgE are found in plasma, but levels rise during severe allergic attacks or chronic parasitic infections of the gastrointestinal tract.

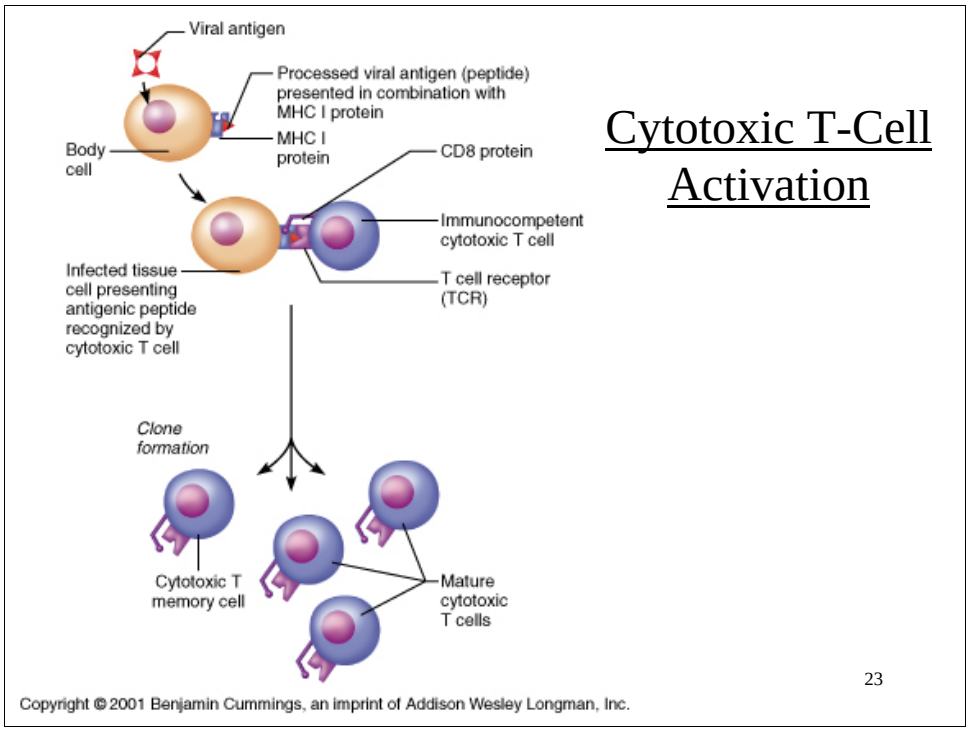


Complement Activation

Complement can be activated by contact with antibodies (see slide 18) or by contact with certain bacteria.



MHC (**Major Histocompatibility Complex**) are proteins used for recognition by immune system cells. **MHC I** proteins are displayed by all cells of the body (important for non-immune cell recognition) and **MHC II** proteins are displayed by cells of the immune system (important for immune cell recognition).
These are then displayed along with proteins from an infectious organism or tumor cell and trigger the T-cell response.



Cytotoxic (killer) T-cells are activated by coming into contact with an infected body cell or tumor cell. They recognize the **MHC I** proteins possessed by the body cells in combination with the processed viral antigen. **CD8 proteins** are antigens that are part of the recognition process of the cytotoxic T-cells. In response to activation the T-cells clone to produce mature (activated) cytotoxic T-cells and memory cells.

Lymphokines/Cytokines:

a. interleukin I - costimulator for activated T-cells

b. interleukin II - stimulates both B and T-cell proliferation

c. MAF - macrophage activating factor

d. MIF - macrophage migration inhibiting factor

e. perforin - causes cell lysis

f. lymphotoxin - kills cells by fragmenting their DNA

g. tumor necrosis factor -

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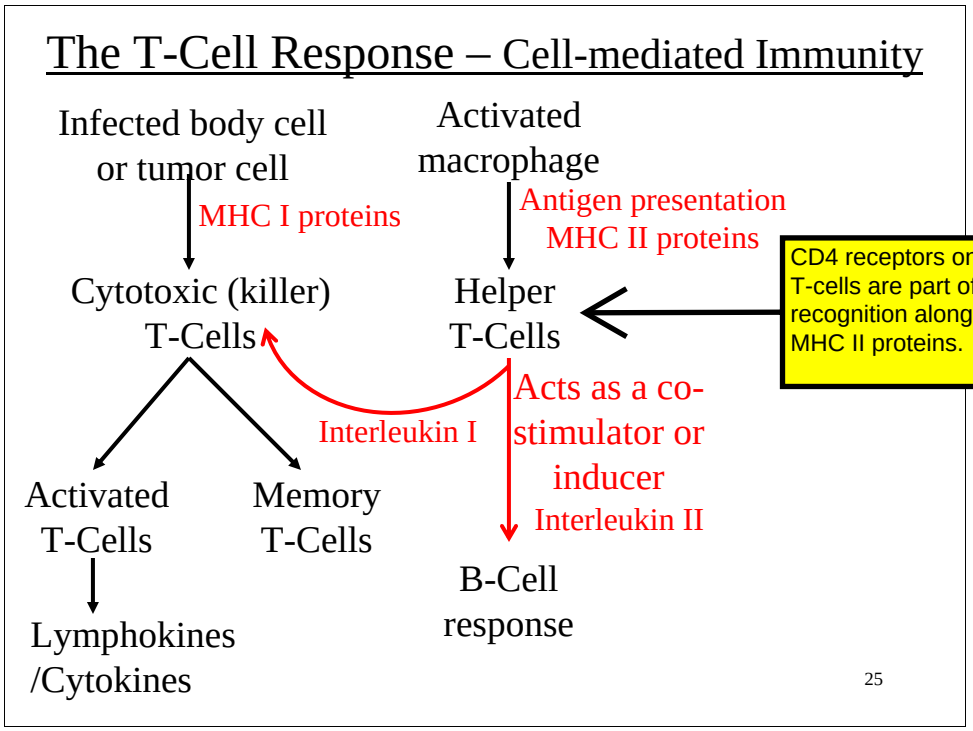
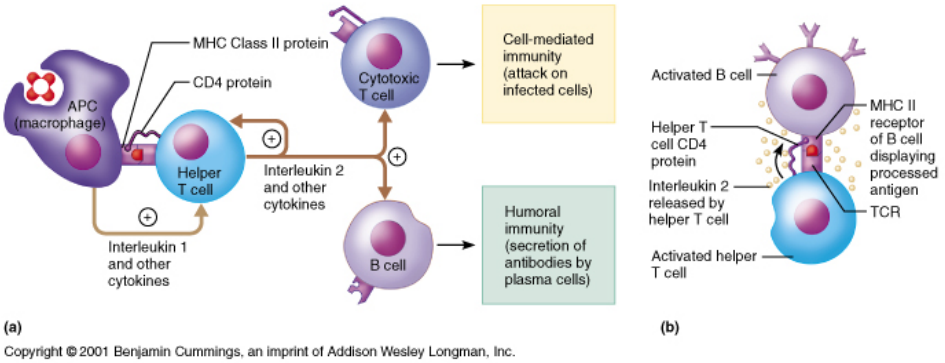
Cytotoxic T-cells secrete **lymphokines** and **cytokines**. Here are some of them.



MHC II proteins are displayed by cells of the immune system. These are then displayed along with proteins from an infectious organism or tumor cell and presented to the **Helper T-cells** to activate them.

Role of Helper-Inducer T-Cells



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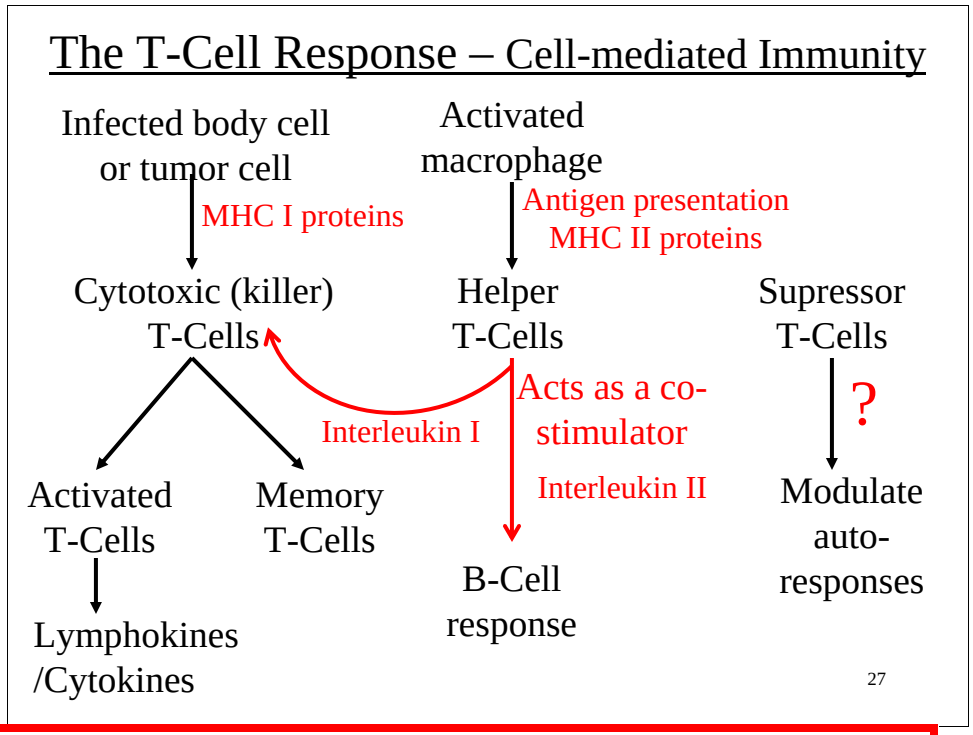
Helper T-cells express **CD4 proteins** and are activated by **macrophages** (**APCs**) using **MHC II** recognition proteins. Helper T-cells then stimulate both cell-mediated and humoral immune responses. The **human immunodeficiency virus** (**HIV**) uses the CD4 receptor to infect Helper T-cells, macrophages, and other immunologic cells.



Regulatory T cells (also known as suppressor T cells) are a specialized subpopulation of T cells that act to suppress activation of the immune system and thereby maintain immune system homeostasis and tolerance to self. The existence of a dedicated population of "suppressor" T cells was the subject of significant controversy among immunologists for many years. However, recent advances in the molecular characterization of this cell population have firmly established their existence and their critical role in the vertebrate immune system. Interest in regulatory T cells has been heightened by evidence from experimental mouse models demonstrating that the immunosuppressive potential of these cells can be harnessed therapeutically to treat autoimmune diseases and facilitate transplantation tolerance or specifically eliminated to potentiate cancer immunotherapy.

Hypersensitivity

1. Type I Hypersensitivity - allergic reactions. Memory cells to non-pathogenic antigens release IgE antibodies which bind to basophils and mast cells. Produces allergy and anaphylaxis.
2. Type II Hypersensitivity - autoimmunity.
Examples: multiple sclerosis, myasthenia gravis, Graves disease, and some forms of Type 1 diabetes mellitus.
3. Type III Hypersensitivity (a.k.a. immune complex disease) antigen-antibody complexes lodge in endothelial cells inducing inflammation by triggering the complement pathway with resulting cell lysis, hemorrhage, and tissue destruction. Examples include: systemic lupus erythematosus (SLE), rheumatoid arthritis and acute glomerulonephritis.

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