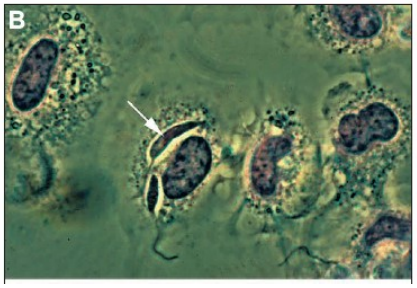
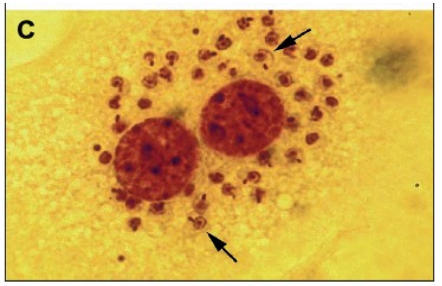
Overview of the Immune System





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Overview of the Immune System

Immune system is a defense system that has evolved to protect animals from invading pathogenic microorganisms

Historical Perspective

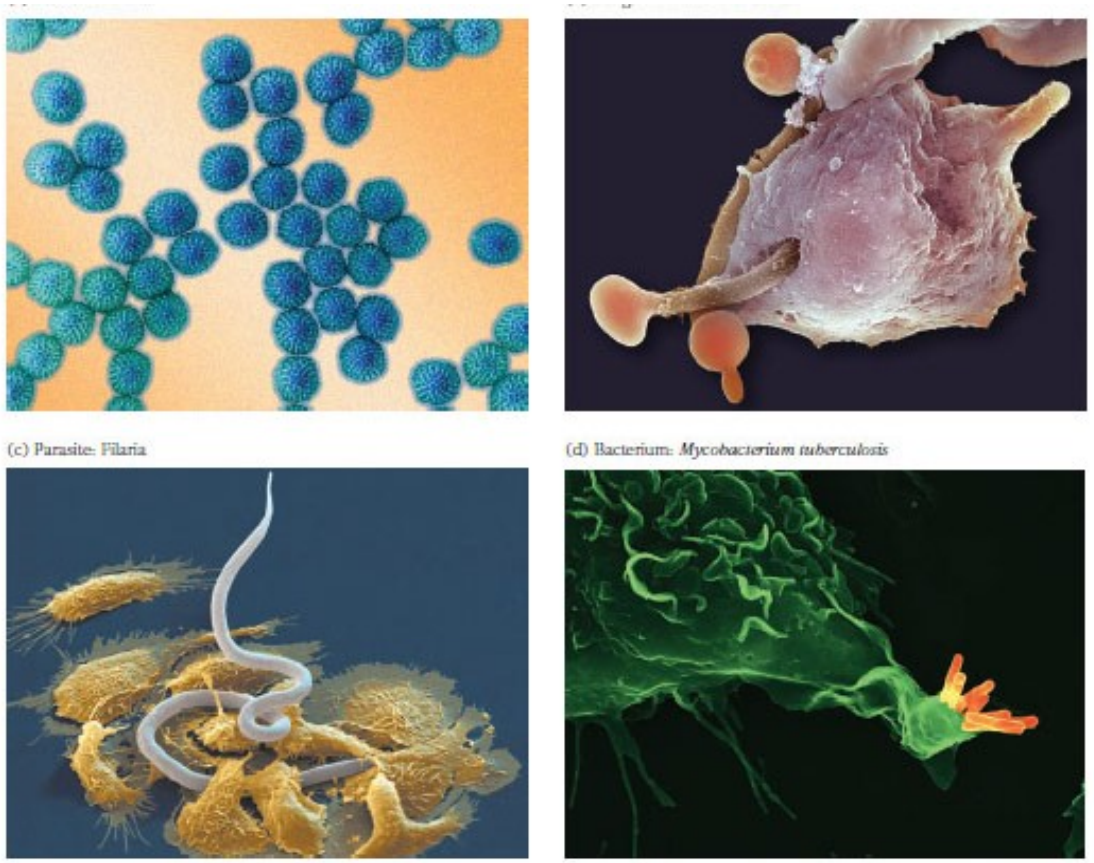
- **The discipline of immunology grew out of the observation that individuals who had recovered from certain infectious diseases were thereafter protected from the disease. The Latin term *immunis,* meaning “exempt,” is the source of the English word immunity, meaning the state of protection from infectious disease.**
- **Edward Jenner (17 May 1749 – 26 January 1823) was an English physician and scientist who was the pioneer of smallpox vaccine, the world's first vaccine. He is often called "the father of immunology", and his work is said to have "saved more lives than the work of any other human."**

Pathogen

Organisms causing disease are termed pathogens, and the process by which they induce illness in the host is called pathogenesis. The human pathogens can be grouped into four major categories : viruses, fungi, parasites, and bacteria.

TABLE Major categories of human pathogens

Major groups of human pathogens	Specific examples	Disease
Viruses	*Poliovirus*	Poliomyelitis (Polio)
	Variola Virus	Smallpox
	Human immunodeficiency Virus	AIDS
	Rubeola Virus	Measles
Fungi	*Candida albicans*	Candidiasis (Thrush)
	Tinea corporis	Ringworm
	Cryptococcus neoformans	Cryptococcal meningitis
Parasites	*Plasmodium species*	Malaria
	Leishmania major	Leishmaniasis
	Entamoeba histolytica	Amoebic colitis
Bacteria	*Mycobacterium tuberculosis*	Tuberculosis
	Bordetella pertussis	Whooping cough (pertussis)
	Vibrio cholerae	Cholera
	Borrelia burgdorferi	Lyme disease



Pathogens representing the major categories of microorganisms causing human disease.

(a) Viruses: Transmission electron micrograph of rotavirus, a major cause of infant diarrhea. (b) Fungi: *Candida albicans,* a yeast inhabiting human mouth, throat, intestines, and genitourinary tract; *C. albicans* commonly causes an oral rash (thrush) or vaginitis in immunosuppressed individuals or in those taking antibiotics that kill normal bacterial flora. (c) Parasites: The larval form of filaria, a parasitic worm, being attacked by macrophages. (d) Bacteria: *Mycobacterium tuberculosis,* the bacterium that causes tuberculosis, being ingested by a human macrophage.

The Immune System Includes Innate and Adaptive Components

- **Immunity—the state of protection from infectious disease —has both a less specific and more specific component.**
- **The less specific component, innate immunity, provides the first line of defense against infection**
- **Innate immunity can be seen to comprise four types of defensive barriers: anatomic, physiologic, phagocytic, and inflammatory.**

TABLE Summary of nonspecific host defenses

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

Innate Immunity

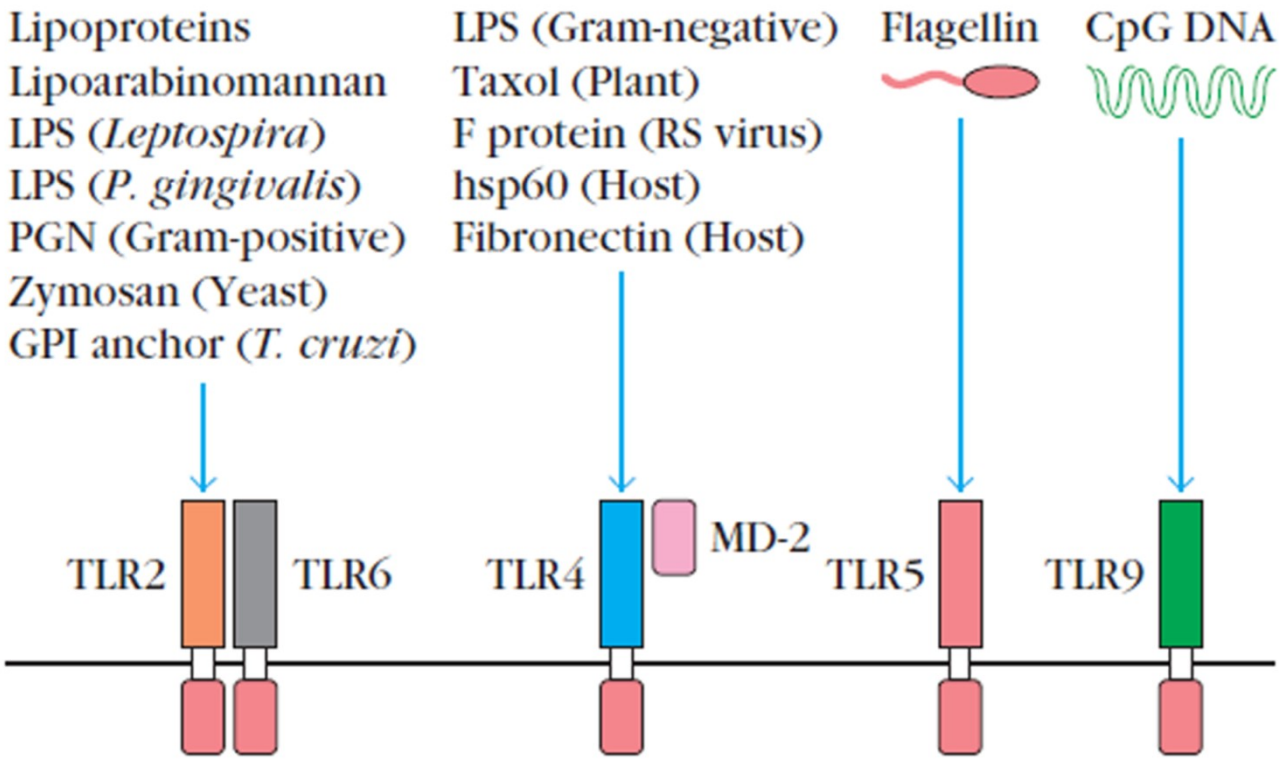
- **A variety of soluble factors contribute to innate immunity, among them the soluble proteins lysozyme, interferon, and complement. Lysozyme, a hydrolytic enzyme found in mucous secretions and in tears, is able to cleave the peptidoglycan layer of the bacterial cell wall.**

- **Interferon comprises a group of proteins produced by virus-infected cells. Among the many functions of the interferons is the ability to bind to nearby cells and induce a generalized antiviral state.**

- **Complement, is a group of serum proteins that circulate in an inactive state. A variety of specific and nonspecific immunologic mechanisms can convert the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either destroying the pathogens or facilitating their clearance.**

Innate Immunity

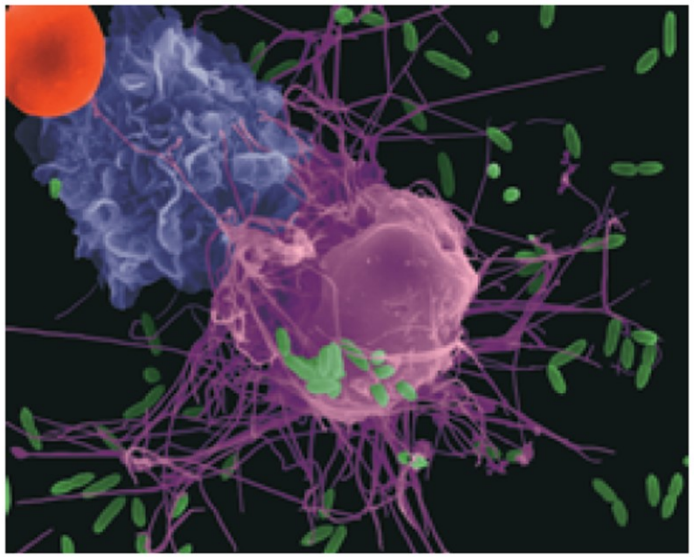
- **Many of the molecules involved in innate immunity have the property of pattern recognition, the ability to recognize a given class of molecules.Because there are certain types of molecules that are unique to microbes and never found in multicellular organisms, the ability to immediately recognize and combat invaders displaying such molecules is a strong feature of innate immunity.Molecules with pattern recognition ability may be soluble, like lysozyme and the complement components described above, or they may be cell-associated receptors. Among the class of receptors designated the toll-like receptors on Gram-negative bacteria.**

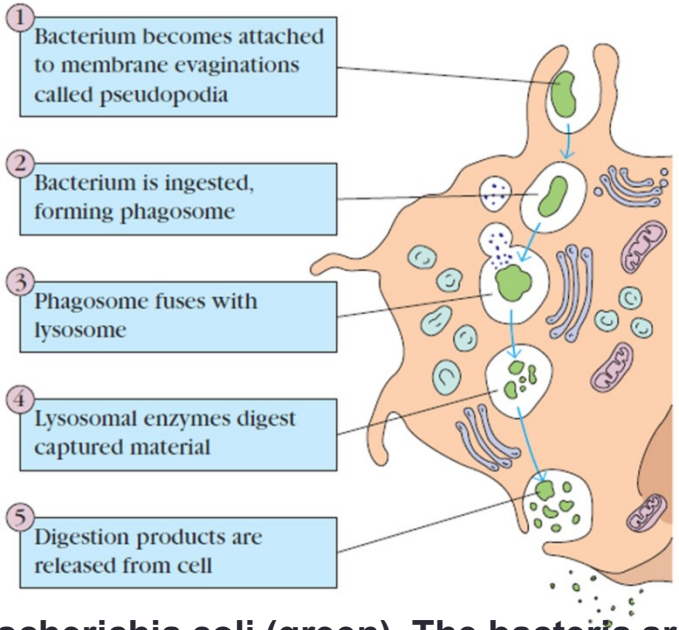


Location and targets of some pattern-recognition receptors. Many pattern-recognition receptors are extracellular and target microbes or microbial components in the bloodstream and tissue fluids, causing their lysis or marking them for removal by phagocytes. Other pattern-recognition receptors are present on the cell membrane and bind to a broad variety of microbes or microbial products. Engagement of these receptors triggers signaling pathways that promote inflammation or, in the case of the scavenger receptors, phagocytosis or endocytosis.

Innate Immunity

- **Another important innate defense mechanism is the ingestion of extracellular particulate material by phagocytosis. Phagocytosis is one type of endocytosis, the general term for the uptake by a cell of material from its environment. In phagocytosis, a cell's plasma membrane expands around the particulate material, which may include whole pathogenic microorganisms, to form large vesicles called phagosomes. Most phagocytosis is conducted by specialized cells, such as blood monocytes, neutrophils, and tissue macrophages. Most cell types are capable of other forms of endocytosis, such as *receptor-mediated endocytosis,* in which extracellular molecules are internalized after binding by specific cellular receptors, and *pinocytosis,* the process by which cells take up fluid from the surrounding medium along with any molecules contained in it.**

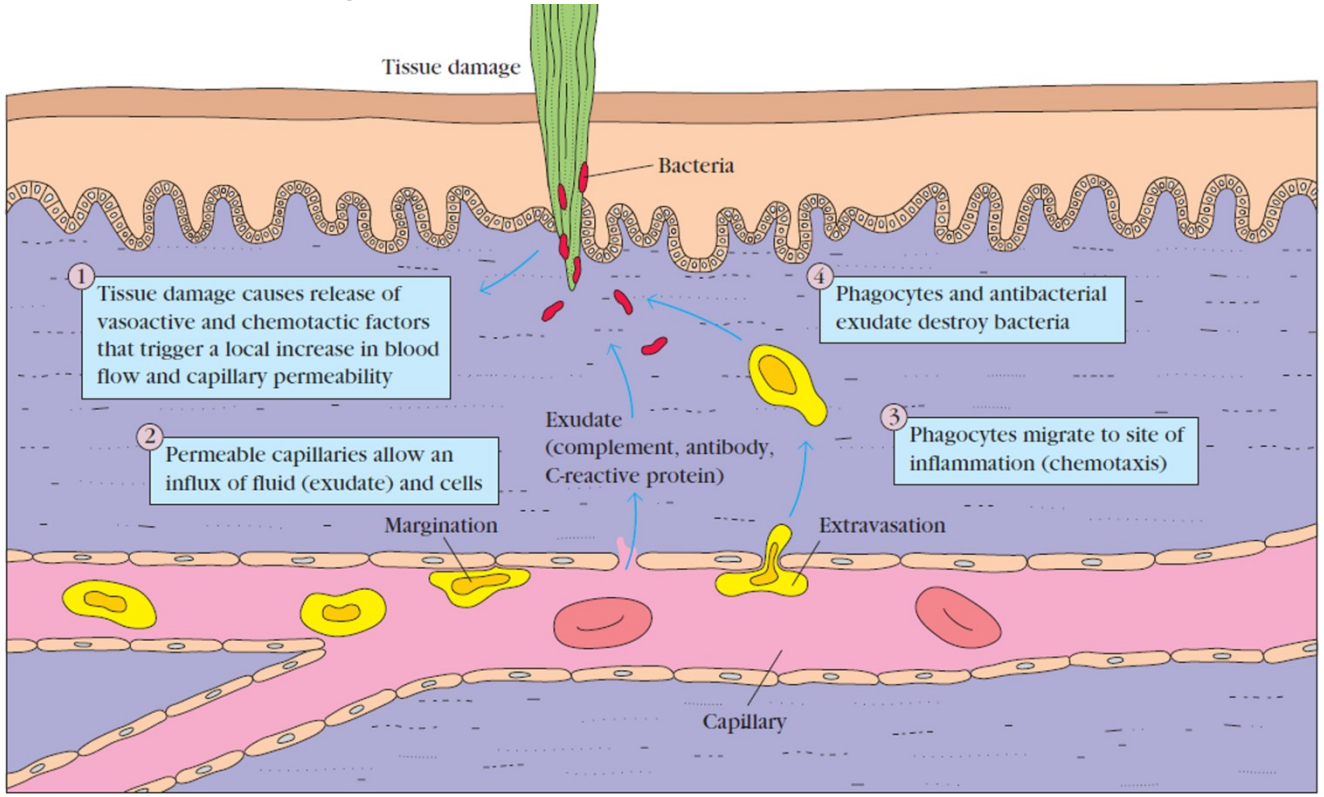




(a) Electronmicrograph of macrophage (pink) attacking Escherichia coli (green). The bacteria are phagocytized as described in part b and breakdown products secreted. The monocyte (purple) has been recruited to the vicinity of the encounter by soluble factors secreted by the macrophage. The red sphere is an erythrocyte.
(b) Schematic diagram of the steps in phagocytosis of a bacterium.

Innate Immunity

- **Tissue damage caused by a wound or by an invading pathogenic microorganism induces a complex sequence of events collectively known as the inflammatory response.**
- **In the first century AD, the Roman physician Celsus described the "four cardinal signs of inflammation" as *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain).**



Major events in the inflammatory response. A bacterial infection causes tissue damage with release of various vasoactive and chemotactic factors. These factors induce increased blood flow to the area, increased capillary permeability, and an influx of white blood cells, including phagocytes and lymphocytes, from the blood into the tissues. The serum proteins contained in the exudate have antibacterial properties, and the phagocytes begin to engulf the bacteria.

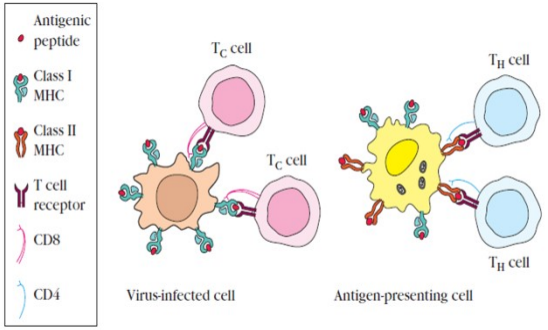
Adaptive Immunity

- **Adaptive immunity is capable of recognizing and selectively eliminating specific foreign microorganisms and molecules (i.e., foreign antigens).**
- **Adaptive immunity displays four characteristic attributes:**
- **Antigenic specificity**
- **Diversity**
- **Immunologic memory**
- **Self/nonself recognition**

Adaptive Immunity

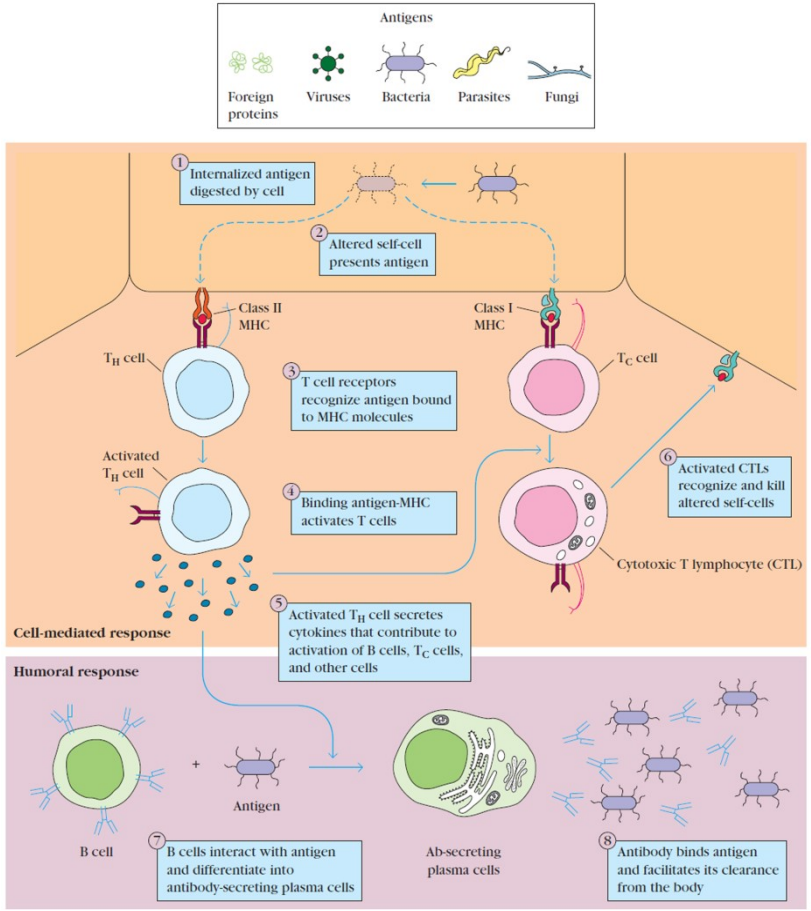
- **An effective immune response involves *T lymphocytes, antigen-presenting cells and B lymphocytes.* Lymphocytes are one of many types of white blood cells produced in the bone marrow by the process of hematopoiesis . Lymphocytes leave the bone marrow, circulate in the blood and lymphatic systems, and reside in various lymphoid organs.**
- **Activation of both the humoral and cell-mediated branches of the immune system requires cytokines produced by TH cells. To ensure carefully regulated activation of TH cells, they can recognize only antigen that is displayed together with class MHC II molecules on the surface of antigen-presenting cells (APCs). These specialized cells, which include macrophages, B lymphocytes, and dendritic cells, are distinguished by two properties: (1) they express class II MHC molecules on their membranes, and (2) they are able to deliver a co-stimulatory signal that is necessary for TH-cell activation.**
- **B cell matures in the bone marrow. Mature B cell possesses a single functional gene encoding the antibody displays antibody with one specificity on its membrane.**
- **Antibody functions as the effector of the humoral response by binding to antigen and neutralizing it or facilitating its elimination. When an antigen is coated with antibody, it can be eliminated in several ways. For example, antibody can cross-link several antigens, forming clusters that are more readily ingested by phagocytic cells. Binding of antibody to antigen on a microorganism can also activate the complement system, resulting in lysis of the foreign organism. Antibody can also neutralize toxins or viral particles by coating them,which prevents them from binding to host cells.**
- **Effector T cells generated in response to antigen are responsible for cell-mediated immunity. Bothactivated TH cells and cytotoxic T lymphocytes (CTLs) serve as effector cells in cell-mediated immune reactions. Cytokines secreted by TH cells can activate various phagocytic cells, enabling them to phagocytose and kill microorganisms more effectively. This type of cell-mediated immune response is especially important in ridding the host of bacteria and protozoa contained by infected host cells. CTLs participate in cell-mediated immune reactions by killing altered self-cells; they play an important role in the killing of virusinfected cells and tumor cells.**

Adaptive Immunity



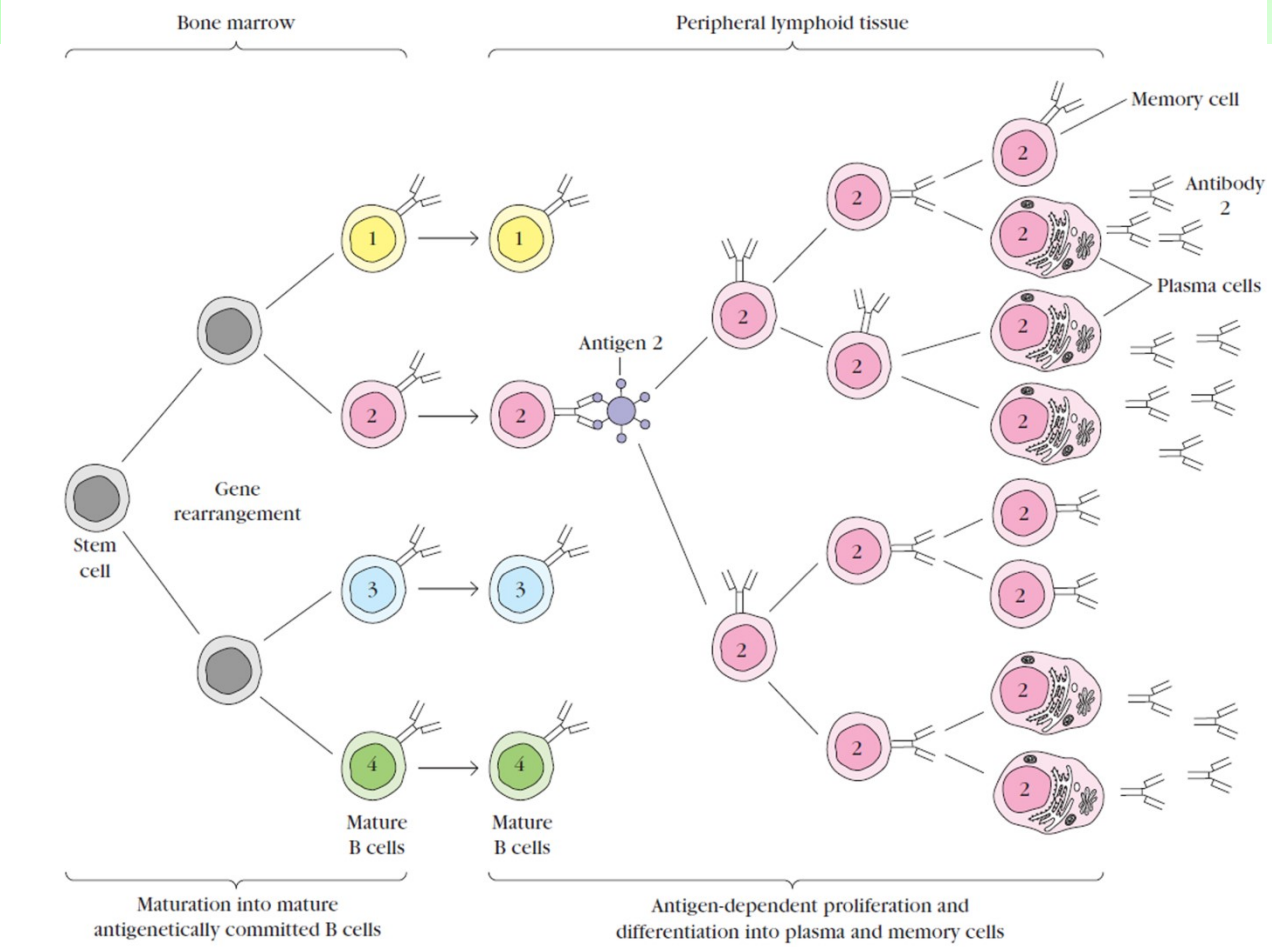
The role of MHC molecules in antigen recognition by T cells. (a) Class I MHC molecules are expressed on nearly all nucleated cells. Class II MHC molecules are expressed only on antigenpresenting .cells. T cells that recognize only antigenic peptides displayed with a class II MHC molecule generally function as T helper (T_H) cells. T cells that recognize only antigenic peptides displayed with a class I MHC molecule generally function as T cytotoxic (T_C) cells.

Adaptive Immunity



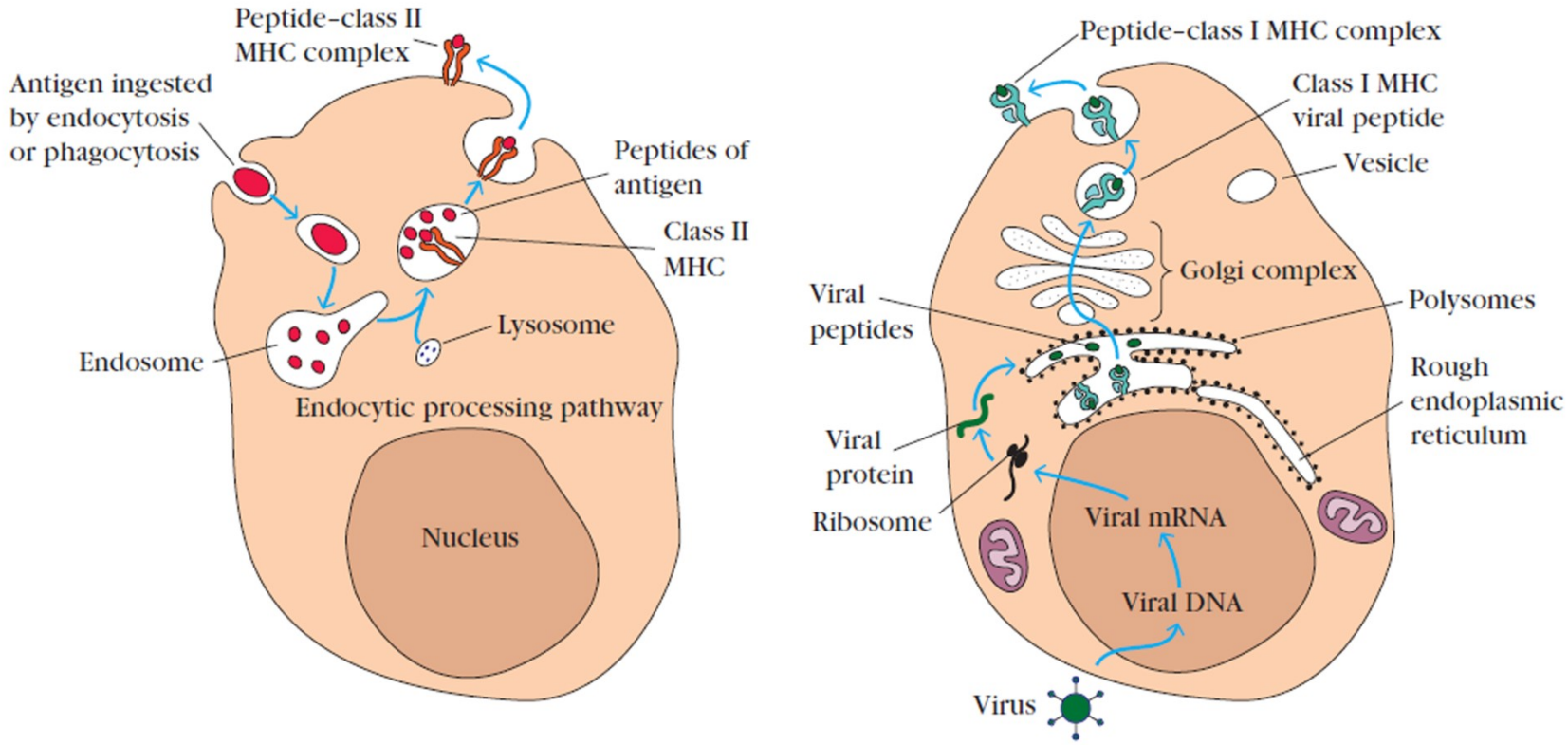
Overview of the humoral and cell-mediated branches of the immune system. In the humoral response, B cells interact with antigen and then differentiate into antibody-secreting plasma cells. The secreted antibody binds to the antigen and facilitates its clearance from the body. In the cell-mediated response, various subpopulations of T cells recognize antigen presented on self-cells. TH cells respond to antigen by producing cytokines. TC cells respond to antigen by developing into cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).

Adaptive Immunity



Maturation and clonal selection of B lymphocytes. Maturation, which occurs in the absence of antigen, produces antigenically committed B cells, each of which expresses antibody with a single antigenic specificity (indicated by 1, 2, 3, and 4). Clonal selection occurs when an antigen binds to a B cell whose membranebound antibody molecules are specific for epitopes on that antigen. Clonal expansion of an antigen-activated B cell (number 2 in this example) leads to a clone of memory B cells and effector B cells, called plasma cells; all cells in the expanded clone are specific for the original antigen. The plasma cells secrete antibody reactive with the activating antigen. Similar processes take place in the T-lymphocyte

Adaptive Immunity



Processing and presentation of exogenous and endogenous antigens. (a) Exogenous antigen is ingested by endocytosis
or phagocytosis and then enters the endocytic processing pathway. Here, within an acidic environment, the antigen is degraded into small peptides, which then are presented with class II MHC molecules on the membrane of the antigen-presenting cell. (b) Endogenous antigen, which is produced within the cell itself (e.g., in a virusinfected cell), is degraded within the cytoplasm into peptides, which move into the endoplasmic reticulum, where they bind to class I MHC molecules. The peptide–class I MHC complexes then move through the Golgi complex to the cell surface.

Comparison of Innate and Adaptive Immunity

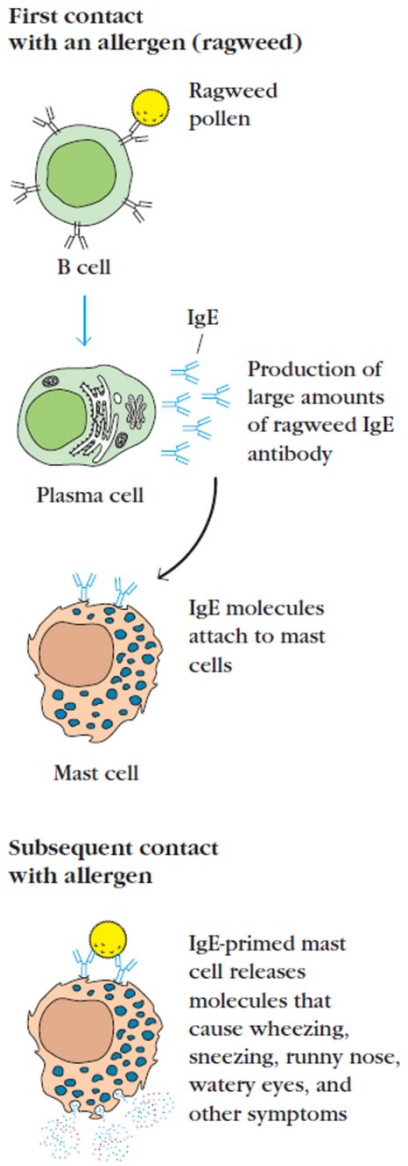
TABLE 1-3 Comparison of adaptive and innate immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

Immune Dysfunction

- **This overview would not be complete without mentioning that the immu system can function improperly. Sometimes the immune system fails to protect the host adequately or misdirects its activities to cause discomfort, debilitating disease, or even death. There are several comm manifestations of immune dysfunction:**
- **Allergy and asthma**
- **Graft rejection and graft-versus-host disease**
- **Autoimmune disease**
- **Immunodeficiency**

- **Allergy and asthma are results of inappropriate immune responses, oft to common antigens such as plant pollen, food, or animal dander.**



Immune Dysfunction

- In certain individuals, the immune system malfunctions by losing its sense of self and nonself, which permits an immune attack upon the host. This condition, autoimmunity, can cause a number of chronic debilitating diseases. The symptoms of autoimmunity differ depending on which tissues and organs are under attack. For example, multiple sclerosis is due to an autoimmune attack on the brain and central nervous system, Crohn's disease is an attack on the tissues in the gut, and rheumatoid arthritis is an attack on joints of the arms and legs.

- If any of the many components of innate or specific immunity is defective because of genetic abnormality, or if any immune function is lost because of damage by chemical, physical, or biological agents, the host suffers from immunodeficiency. Since the 1980s, the most common form of immunodeficiency has been acquired immune deficiency syndrome, or AIDS, which results from infection with the retrovirus human immunodeficiency virus, or HIV. In AIDS, T helper cells are infected and destroyed by HIV, causing a collapse of the immune system. It is estimated that 35 million persons worldwide suffer from this disease, which is usually fatal within 8 to 10 years after infection. Although certain treatments can prolong the life of AIDS patients, there is no known cure for this disease.

Cells of the Immune System

- All functionally specialized, mature blood cells (red blood cells, granulocytes, macrophages, dendritic cells, and lymphocytes) arise from a single cell type, the hematopoietic stem cell (HSC) . The process by which HSCs differentiate into mature blood cells is called hematopoiesis. Two primary lymphoid organs are responsible for the development of stem cells into mature immune cells: the bone marrow, where HSCs reside and give rise to all cell types; and the thymus, where T cells complete their maturation.
- HSC can become a common myeloid-erythroid progenitor (CMP), which gives rise to all red blood cells (the erythroid lineage), granulocytes, monocytes, and macrophages (the myeloid lineage), or it can become a common lymphoid progenitor (CLP), which gives rise to B lymphocytes, T lymphocytes, and NK cells.

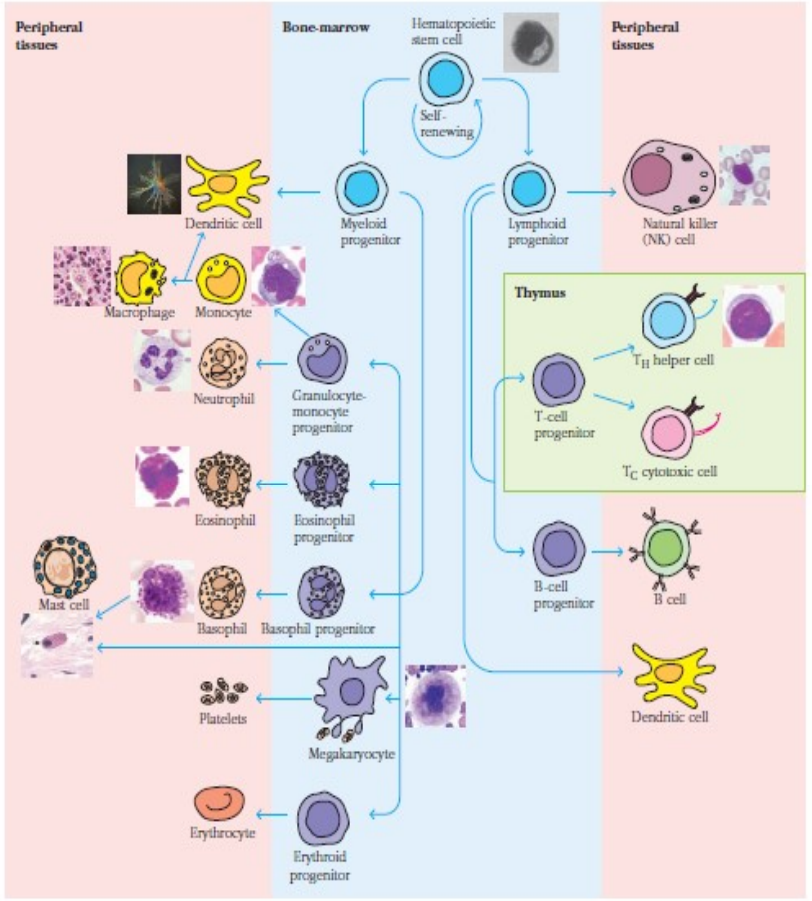
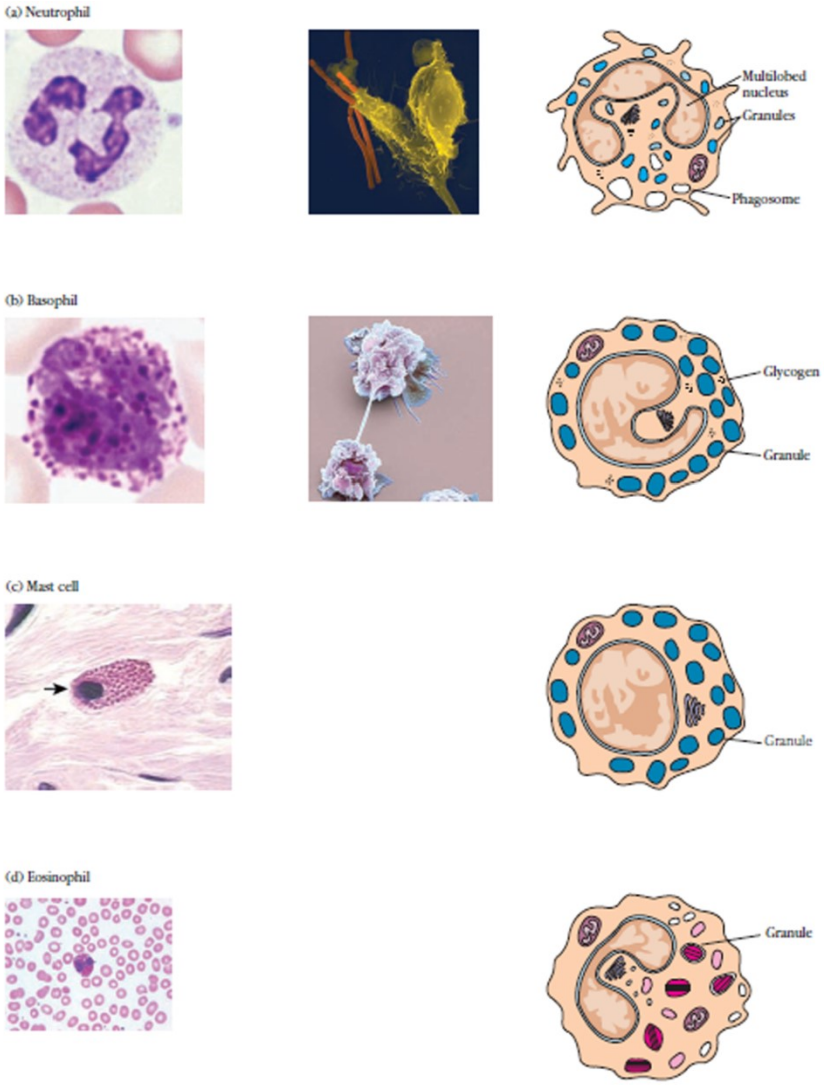


TABLE Concentration and frequency of cells in human blood

Cell type	Cells/mm^3	Total leukocytes (%)
Red blood cells	5.0×10^6	
Platelets	2.5×10^5	
Leukocytes	7.3×10^3	
Neutrophil	$3.7–5.1 \times 10^3$	50–70
Lymphocyte	$1.5–3.0 \times 10^3$	20–40
Monocyte	$1–4.4 \times 10^2$	1–6
Eosinophil	$1–2.2 \times 10^2$	1–3
Basophil	$<1.3 \times 10^2$	<1

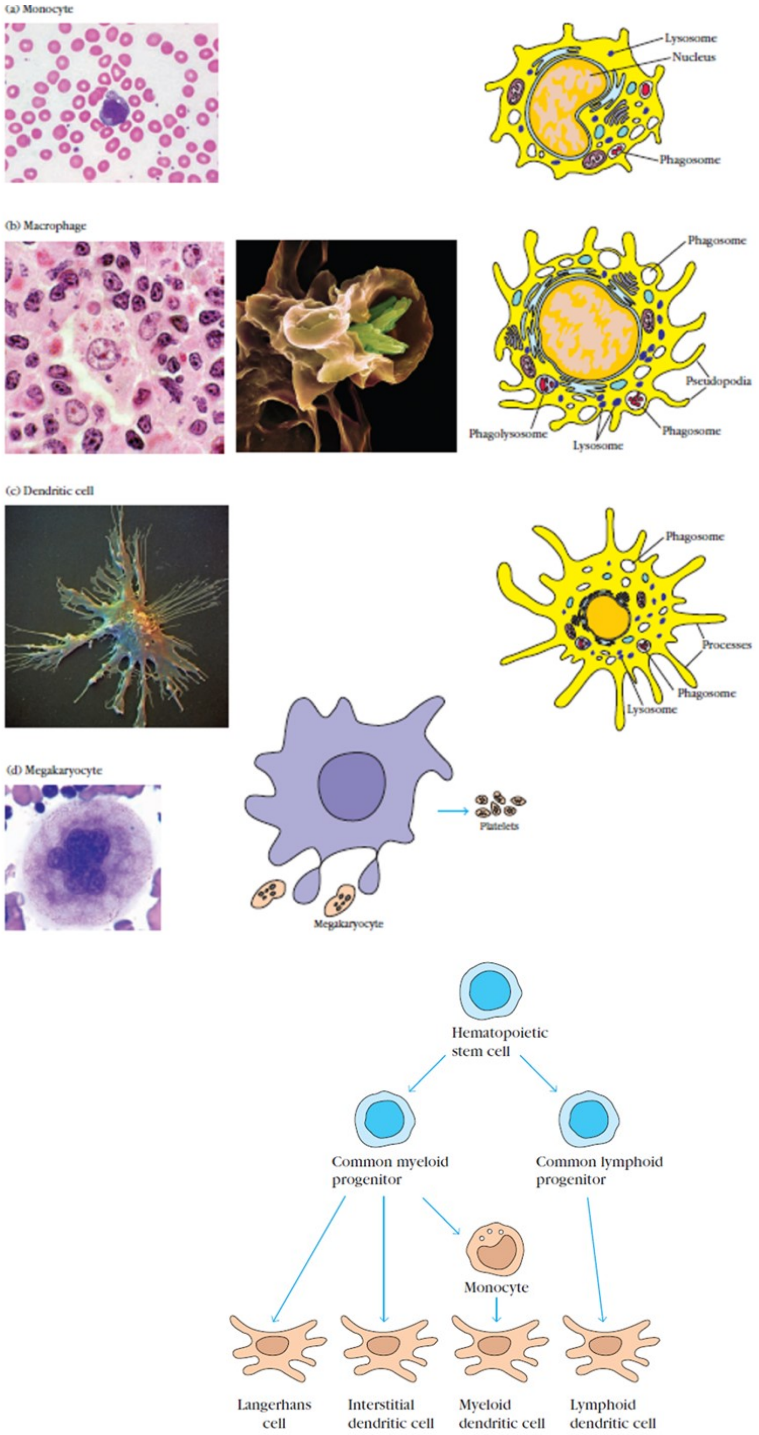
Granulocytes

- The cytoplasm of all granulocytes is replete with granules that are released in response to contact with pathogens. Neutrophils phagocytose (engulf) bacteria very effectively, and also secrete a range of proteins that have antimicrobial effects and tissue remodeling potential.
- Basophils are nonphagocytic granulocytes that contain large granules fi lled with basophilic proteins (i.e., they stain blue in standard H&E staining protocols).
- Histamine, one of the best known proteins in basophilic granules, increases blood vessel permeability and smooth muscle activity.
- Mast cells are released from the bone marrow into the blood as undifferentiated cells; they mature only after they leave the blood. Mast cells can be found in a wide variety of tissues, including the skin, connective tissues of various organs, and mucosal epithelial tissue of the respiratory, genitourinary, and digestive tracts. Like circulating basophils, these cells have large numbers of cytoplasmic granules that contain histamine and other pharmacologically active substances. Mast cells also play an important role in the development of allergies.
- Eosinophils, like neutrophils, are motile phagocytic cells that can migrate from the blood into the tissue spaces. Th eir phagocytic role is significantly less important than that of neutrophils, and it is thought that they play their most important role in the defense against multicellular parasitic organisms, including worms.



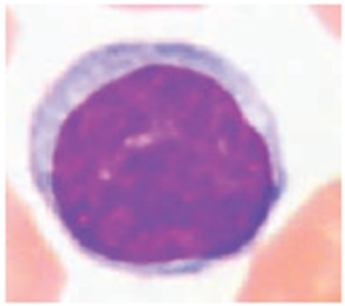
Myeloid Cells

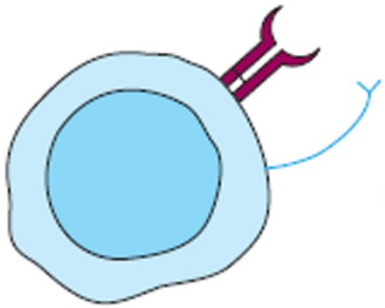
- Myeloid progenitors also give rise to a group of phagocytic cells (monocytes, macrophages, and dendritic cells) that have professional antigen-presenting cell (APC) function.
- Monocytes are a heterogeneous group of cells that migrate into tissues and differentiate into a diverse array of tissue-resident phagocytic cells, including macrophages and dendritic cells.
- Monocytes that migrate into tissues in response to infection can differentiate into specific tissue macrophages.
- Inflammatory macrophages and play a dual role in the immune system as effective phagocytes that can contribute to the clearance of pathogens from a tissue, as well as antigen-presenting cells that can activate T lymphocytes. Osteoclasts in the bone, microglial cells in the central nervous system, and alveolar macrophages in the lung are tissue-specific examples of macrophages with these properties.
- Dendritic cells are critical for the initiation of the immune response and acquired their name because they are covered with long membranous extensions that resemble the dendrites of nerve cells and extend and retract dynamically. DC arise from both the myeloid and lymphoid lineages of hematopoietic cells.
- Cells of the erythroid lineage—erythrocytes, or red blood contain high concentrations of hemoglobin, and circulate through blood vessels and capillaries delivering oxygen to surrounding cells and tissues.
- Megakaryocytes are large myeloid cells that reside in the bone marrow and give rise to thousands of platelets, very small cells (or cell fragments) that circulate in the blood and participate in the formation of blood clots.



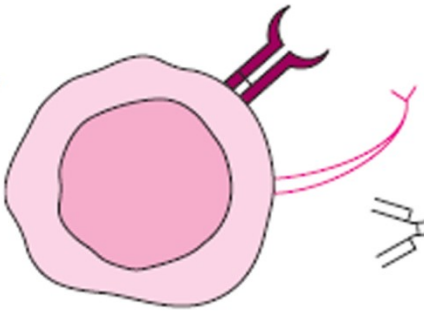
Common Lymphoid Progenitor

(a) Lymphocyte

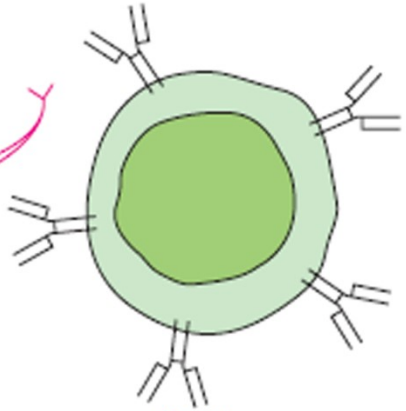




T_H helper cell

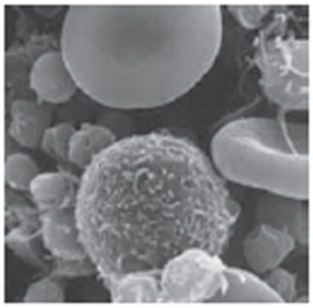


T_C cytotoxic T cell

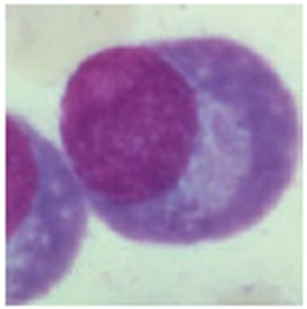


B cell

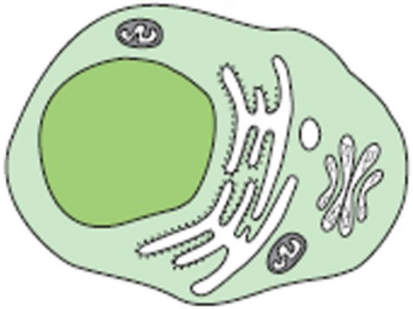
(b) Lymphocyte with red blood cells



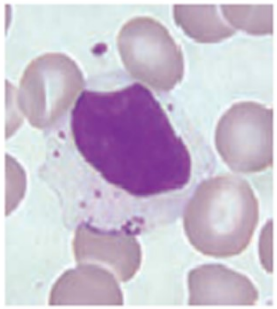
(c) Plasma cell

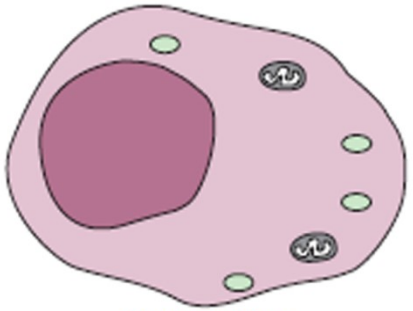


Plasma cell



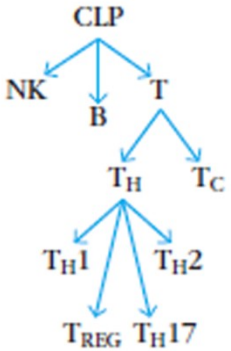
(d) NK cell





Natural killer (NK) cell

(e)



Common Lymphoid Progenitor

Lymphocytes are the principal cell players in the adaptive immune response. They represent 20% to 40% of circulating white blood cells and 99% f cells in the lymph. Lymphocytes can be broadly subdivided into three major populations on the basis of functional and phenotypic diff erences: B lymphocytes (B cells), T lymphocytes (T cells), and natural killer (NK) cells. In humans, approximately a trillion (1012) lymphocytes circulate continuously through the blood and lymph and migrate into the tissue spaces and lymphoid organs.

Surface proteins expressed by immune cells are oft en referred to by the cluster of diff erentiation (CD or cluster of designation) nomenclature.

- **T lymphocytes (T cells) derive their letter designation from their site of maturation in the thymus. The T cell expresses a unique antigen-binding receptor called the T-cell receptor. T lymphocytes are divided into two major cell types—T helper (TH) cells and T cytotoxic (TC) cells—that can be distinguished from one another by the presence of either CD4 or CD8 membrane glycoproteins on their surfaces. T cells displaying CD4 generally function as TH cells and recognize antigen in complex with MHC class II, whereas those displaying CD8 generally function as TC cells and recognize antigen in complex with MHC class I. The ratio of CD4 to CD8 T cells is approximately 2:1 in normal mouse and human peripheral blood.**

- **T helper type 1 (TH1) cells regulate the immune response to intracellular pathogens, and T helper type 2 (TH2) cells regulate the response to many extracellular pathogens. Two additional TH cell subsets have been recently identifi ed. T helper type 17 cells (TH17), so named because they secrete IL-17, play an important role in cell-mediated immunity and may help the defense against fungi.**

- **Another type of CD4 T cell, the regulatory T cell (TREG), has the unique capacity to inhibit an immune response.**

Common Lymphoid Progenitor

- **The B lymphocyte (B cell) derived its letter designation from its site of aturation, in the *b*ursa of Fabricius in birds; the name turned out to be apt, as *b*one marrow is its major site of maturation in humans, mice, and many other mammals.**

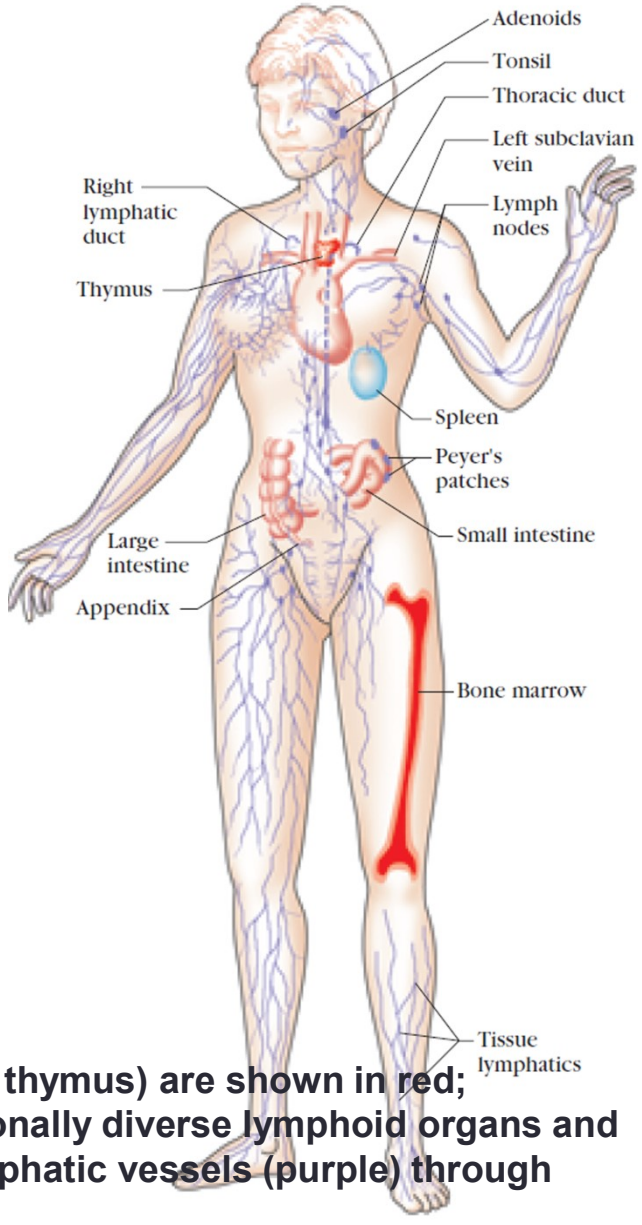
- **B cell display of the B-cell receptor (BCR), a membrane-bound immunoglobulin (antibody) molecule that binds to antigen.**

- **Activated B cells diff erentiate into effector cells known as plasma cells . Plasma cells lose expression of surface immunoglobulin and become highly specialized for secretion of antibody.**

- **Natural killer (NK) cells are lymphoid cells that are closely related to B and T cells. However, they do not express antigenspecific receptors and are considered part of the innate immune system. They are distinguished by the expression of a surface marker known as NK1.1, as well as the presence of cytotoxic granules. They are effi cient cell killers and attack a variety of abnormal cells, including some tumor cells and some cells infected with virus.**

Lymphoid Organs

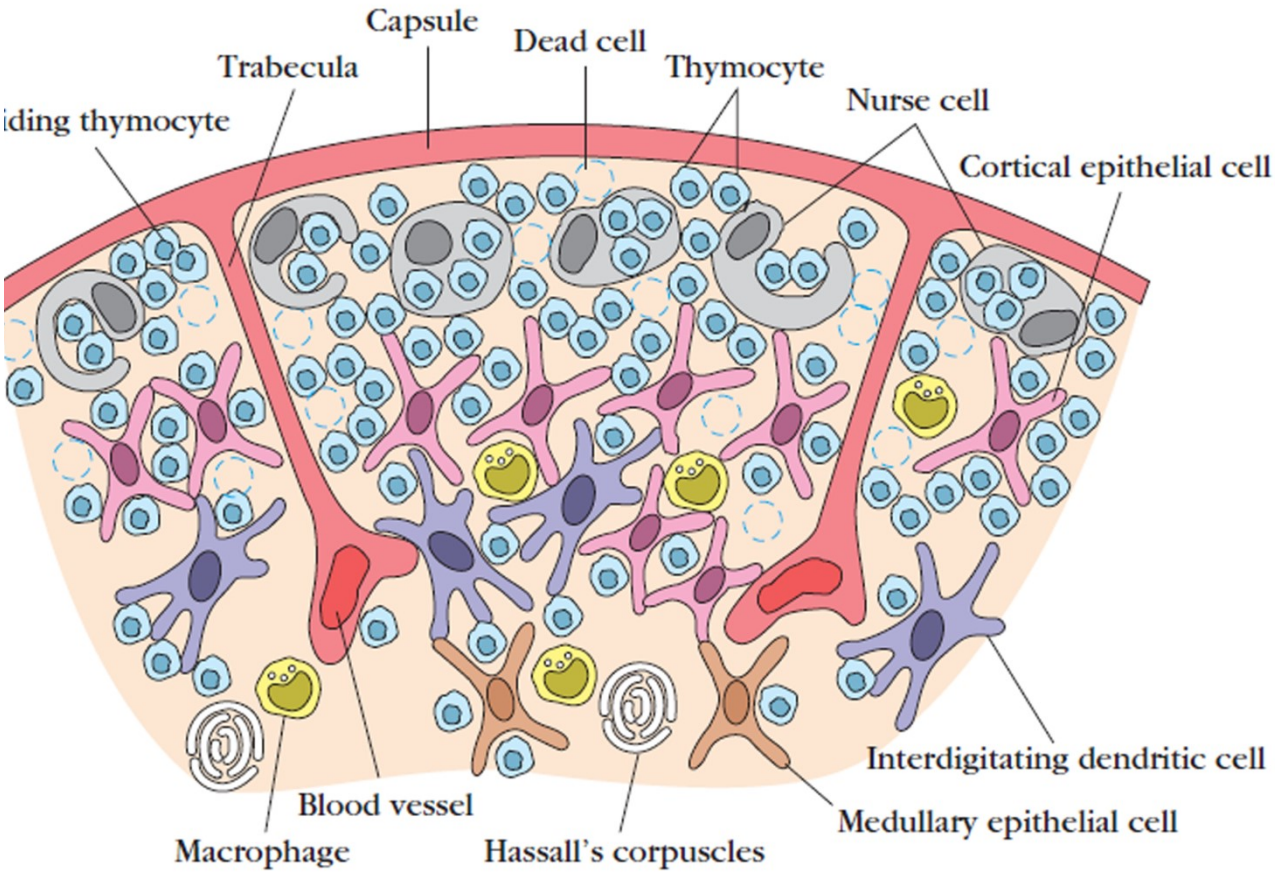
A number of morphologically and functionally diverse organs and tissues have various functions in the development of immune responses. These can be distinguished by function as the primary and secondary lymphoid organs. The thymus and bone marrow are the primary (or central) lymphoid organs, where maturation of lymphocytes takes place. The lymph nodes, spleen, and various mucosalassociated lymphoid tissues (MALT) such as gut-associated lymphoid tissue (GALT) are the secondary (or peripheral) lymphoid organs, which trap antigen and provide sites for mature lymphocytes to interact with that antigen.



The human lymphoid system. The primary organs (bone marrow and thymus) are shown in red; secondary organs and tissues, in blue. These structurally and functionally diverse lymphoid organs and tissues are interconnected by the blood vessels (not shown) and lymphatic vessels (purple) through which lymphocytes
circulate. Only one bone is shown, but all major bones contain marrow and thus are part of the

Lymphoid Organs

The thymus is the site of T-cell development and maturation. It is a flat, bilobed organ situated above the heart. Each lobe is surrounded by a capsule and is divided into lobules, which are separated from each other by strands of connective tissue called trabeculae. Each lobule is organized into two compartments:the outer compartment, or *cortex,* is densely packed with immature T cells, called thymocytes, whereas the inner compartment, or *medulla,* is sparsely populated with thymocytes.

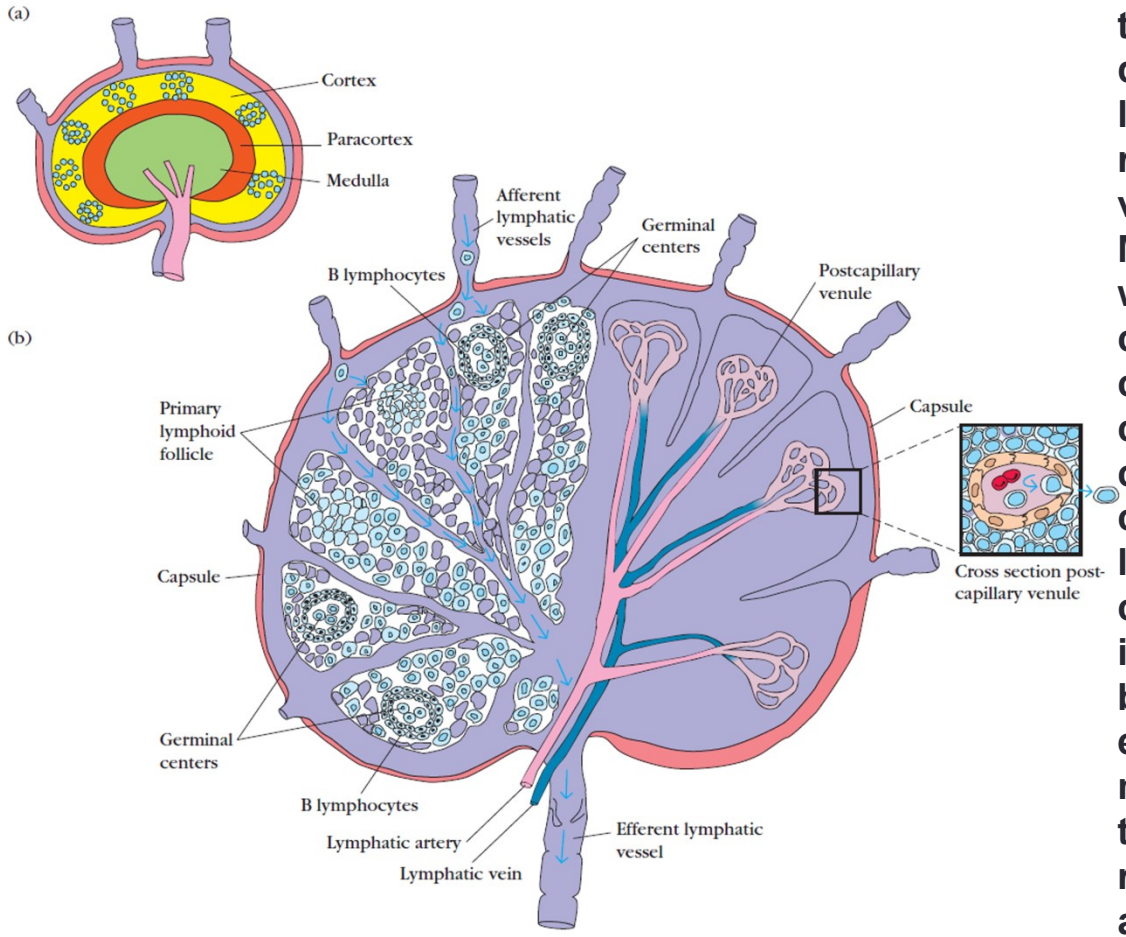


Diagrammatic cross section of a portion of the thymus, showing several lobules separated by connective tissue strands (trabeculae). The densely populated outer cortex is thought to contain many immature thymocytes (blue), which undergo rapid proliferation coupled with an enormous rate of cell death. Also present in the outer cortex are thymic nurse cells (gray), which are specialized epithelial cells with long membrane extensions that surround as many as 50 thymocytes. The medulla is sparsely populated and is thought to contain thymocytes that are more mature. During their stay within the thymus, thymocytes interact with various stromal cells, including cortical epithelial cells (light red), medullary epithelial cells (tan), interdigitating dendritic cells (purple), and macrophages (yellow). These cells produce thymic hormones and express high levels of class I and class II MHC molecules. Hassalls corpuscles, found in the medulla, contain concentric layers of degenerating epithelial cells.

Lymphoid Organs

In humans and mice, bone marrow is the site of B-cell origin and development. Arising from lymphoid progenitors, immature B cells proliferate and differentiate within the bone marrow, and stromal cells within the bone marrow interact directly with the B cells and secrete various cytokines that are required for development.

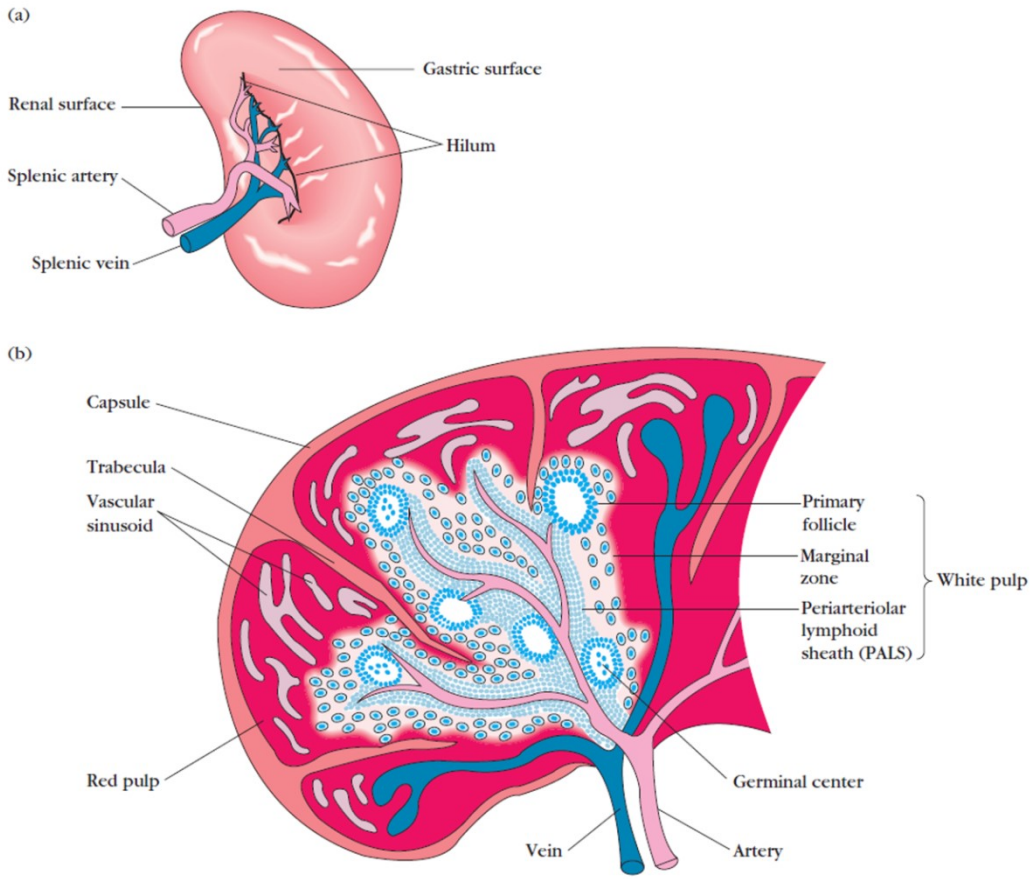
Lymph nodes are the sites where immune responses are mounted to antigens in lymph. They are encapsulated beanshaped structures containing a reticular network packed with lymphocytes, macrophages, and dendritic cells.



Structure of a lymph node. (a) The three layers of a lymph node support distinct microenvironments. (b) The left side depicts the arrangement of reticulum and lymphocytes within the various regions of a lymph node. Macrophages and dendritic cells, which trap antigen, are present in the cortex and paracortex. TH cells are concentrated in the paracortex; B cells are located primarily in the cortex, within follicles and germinal centers. The medulla is populated largely by antibody-producing plasma cells. Lymphocytes circulating in the lymph are carried into the node by afferent lymphatic vessels; they either enter the reticular matrix of the node or pass through it and leave by the efferent lymphatic vessel. The right side of (b) depicts the lymphatic artery and vein and the postcapillary venules. Lymphocytes in the circulation can pass into the node

Lymphoid Organs

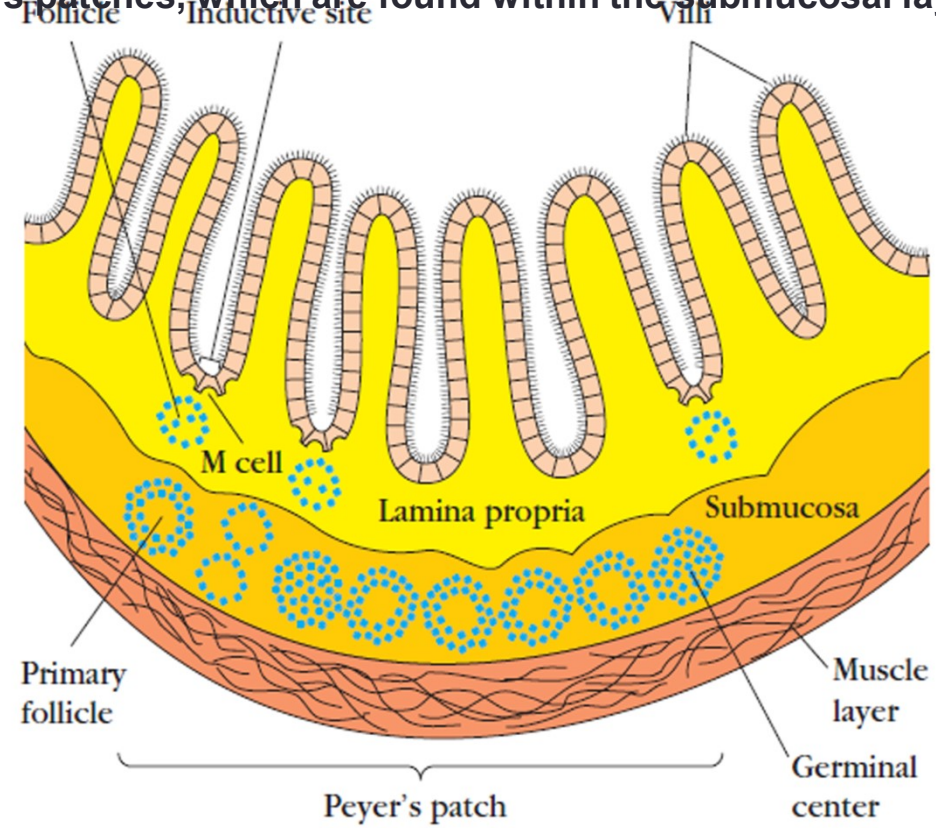
The spleen plays a major role in mounting immune responses to antigens in the blood stream. It is a large, ovoid secondary lymphoid organ situated high in the left abdominal cavity. While lymph nodes are specialized for trapping antigen from local tissues, the spleen specializes in filtering blood and trapping blood-borne antigens; thus, it can respond to systemic infections.



Structure of the spleen. (a) The spleen, which is about 5 inches long in adults, is the largest secondary lymphoid organ. It is specialized for trapping blood-borne antigens. (b) Diagrammatic cross section of the spleen. The splenic artery pierces the capsule and divides into progressively smaller arterioles, ending in vascular sinusoids that drain back into the splenic vein. The erythrocyte-filled red pulp surrounds the sinusoids. The white pulp forms a sleeve, the periarteriolar lymphoid sheath (PALS), around the arterioles; this sheath contains numerous T cells. Closely associated with the PALS is the marginal zone, an area rich in B cells that contains lymphoid follicles that can develop into secondary follicles containing germinal centers.

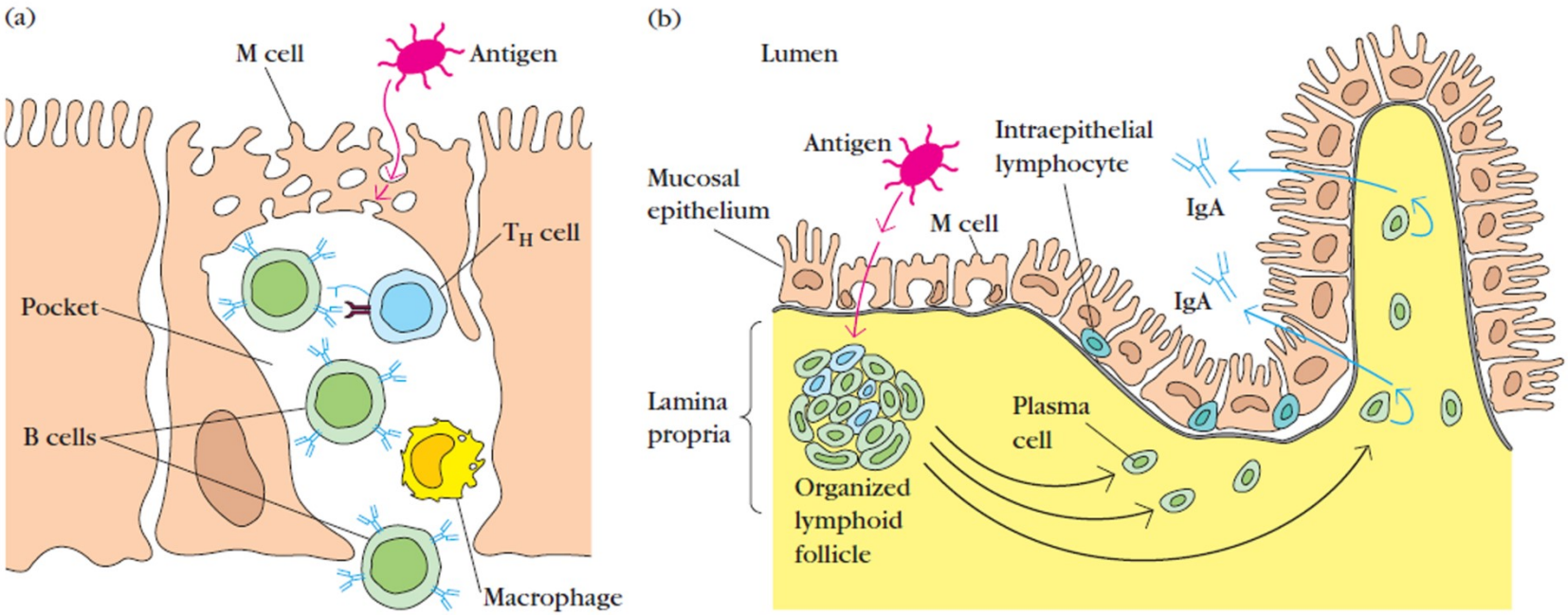
Lymphoid Organs

The mucous membranes lining the digestive, respiratory, and urogenital systems have a combined surface area of about 400 m2 (nearly the size of a basketball court) and are the major sites of entry for most pathogens. These vulnerable membrane surfaces are defended by a group of organized lymphoid tissues mentioned earlier and known collectively as mucosal-associated lymphoid tissue (MALT). Structurally, these tissues range from loose, barely organized clusters of lymphoid cells in the lamina propria of intestinal villi to well-organized structures such as the familiar tonsils and appendix, as well as Peyer's patches, which are found within the submucosal layer of the intestinal lining.



Cross-sectional diagram of the mucous membrane lining the intestine showing a nodule of lymphoid follicles that constitutes a Peyer's patch in the submucosa. The intestinal lamina propria contains loose clusters of lymphoid cells and diffuse follicles.

Lymphoid Organs



Structure of M cells and production of IgA at inductive sites. (a) M cells, located in mucous membranes, endocytose antigen from the lumen of the digestive, respiratory, and urogenital tracts. The antigen is transported across the cell and released into the large basolateral pocket. (b) Antigen transported across the epithelial layer by M cells at an inductive site activates B cells in the underlyinglymphoid follicles. The activated B cells differentiate into IgA-producing plasma cells, which migrate along the submucosa. The outer mucosal epithelial layer contains intraepithelial lymphocytes, of which many are CD8 T cells that express TCRs with limited receptor diversity for

Antigen

Substances that can be recognized by the immunoglobulin receptor of B cells, or by the Tcell receptor when complexed with MHC, are called antigens.

Immunogenicity Versus Antigenicity

- **Immunogenicity and antigenicity are related but distinct immunologic properties that sometimes are confused. Immunogenicity is the ability to induce a humoral and/or cellmediated immune response:**
- **Although a substance that induces a specific immune response is usually called an antigen, it is more appropriately called an immunogen.**
- **Antigenicity is the ability to combine specifically with the final products of the above responses (i.e., antibodies and/or cell-surface receptors). Although all molecules that have the property of immunogenicity also have the property of antigenicity, the reverse is not true. Some small molecules, called *haptens,* are antigenic but incapable, by themselves, of inducing a specific immune response. In other words, they lack immunogenicity.**

Antigen

Immunogenicity is determined, in part, by four properties of the immunogen: its foreignness, molecular size, chemical composition and complexity, and ability to be processed and presented with an MHC molecule on the surface of an antigen-presenting cell or altered self-cell.

- **FOREIGNNESS**

In order to elicit an immune response, a molecule must be recognized as nonself by the biological system. The capacity to recognize nonself is accompanied by tolerance of self, a specific unresponsiveness to self antigens For example, the common experimental antigen bovine serum albumin (BSA) is not immunogenic when injected into a cow but is strongly immunogenic when injected into a rabbit.

- **MOLECULAR SIZE**

There is a correlation between the size of a macromolecule and its immunogenicity. The most active immunogens tend to have a molecular mass of 100,000 daltons (Da).

- **CHEMICAL COMPOSITION AND HETEROGENEITY**

Size and foreignness are not, by themselves, sufficient to make a molecule immunogenic; other properties are needed as well. For example, synthetic homopolymers (polymers composed of a single amino acid or sugar) tend to lack immunogenicity regardless of their size. Studies have shown that copolymers composed of different amino acids or sugars are usually more immunogenic than homopolymers of their constituents. These studies show that chemical complexity contributes to immunogenicity. In this regard it is notable that all four levels of protein organization—primary, secondary, tertiary, and quaternary—contribute to the structural complexity of a protein and hence affect its immunogenicity.

Antigen

- **LIPIDS AS ANTIGENS**

Appropriately presented lipoidal antigens can induce B- and T-cell responses. For the stimulation of B-cell responses, lipids are used as haptens and attached to suitable carrier molecules such as the proteins keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA).

- **SUSCEPTIBILITY TO ANTIGEN PROCESSING AND PRESENTATION**

The development of both humoral and cell-mediated immune responses requires interaction of T cells with antigen that has been processed and presented together with MHC molecules. Large, insoluble macromolecules generally are more immunogenic than small, soluble ones because the larger molecules are more readily phagocytosed and processed. Macromolecules that cannot be degraded and presented with MHC molecules are poor immunogens.

Antigen

- **ADJUVANTS**
- **Adjuvants (from Latin *adjuvare,* to help) are substances that, when mixed with an antigen and injected with it, enhance the immunogenicity of that antigen. Adjuvants are often used to boost the immune response when an antigen has low immunogenicity or when only small amounts of an antigen are available. For example, the antibody response of mice to immunization with BSA can be increased fivefold or more if the BSA is administered with an adjuvant.**

TABLE Postulated mode of action of some commonly used adjuvants

	POSTULATED MODE OF ACTION			
Adjuvant	Prolongs antigen persistence	Enhances co-stimulatory signal	Induces granuloma formation	Stimulates lymphocytes nonspecifically
Freund's incomplete adjuvant	+	+	+	−
Freund's complete adjuvant	+	++	++	−
Aluminum potassium sulfate (alum)	+	?	+	−
Mycobacterium tuberculosis	−	?	+	−
Bordetella pertussis	−	?	−	+
Bacterial lipopolysaccharide (LPS)	−	+	−	+
Synthetic polynucleotides (poly IC/poly AU)	−	?	−	+

Antigen

Epitopes

Immune cells do not interact with, or recognize, an entire immunogen molecule; instead, lymphocytes recognize discrete sites on the macromolecule called epitopes, or antigenic determinants. Epitopes are the immunologically active regions of an immunogen that bind to antigen-specific membrane receptors on lymphocytes or to secreted antibodies. Studies with small antigens have revealed that B and T cells recognize different epitopes on the same antigenic

TABLE Comparison of antigen recognition by T cells and B cells

Characteristic	B cells	T cells
Interaction with antigen	Involves binary complex of membrane Ig and Ag	Involves ternary complex of T-cell receptor, Ag, and MHC molecule
Binding of soluble antigen	Yes	No
Involvement of MHC molecules	None required	Required to display processed antigen
Chemical nature of antigens	Protein, polysaccharide, lipid	Mostly proteins, but some lipids and glycolipids presented on MHC-like molecules
Epitope properties	Accessible, hydrophilic, mobile peptides containing sequential or nonsequential amino acids	Internal linear peptides produced by processing of antigen and bound to MHC molecules

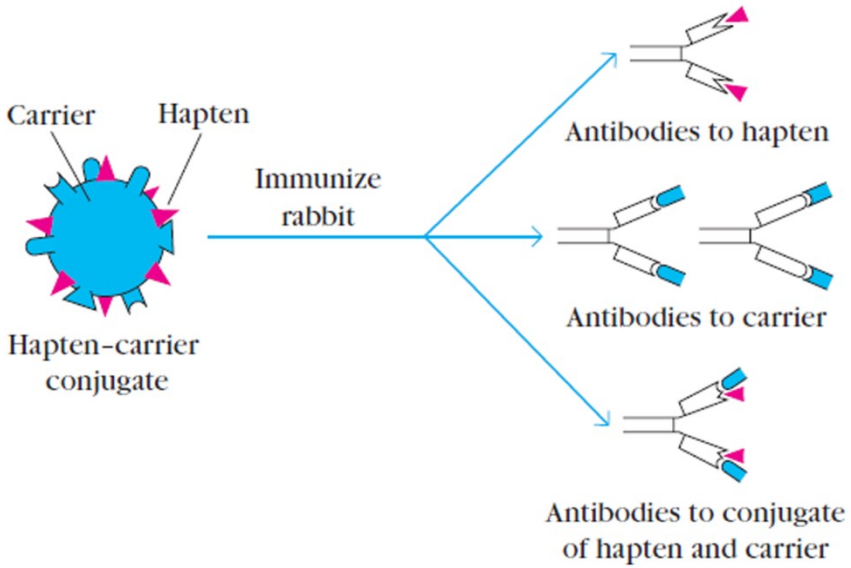
Antigen

Haptens and the Study of Antigenicity

- **The pioneering work of Karl Landsteiner in the 1920s and 1930s created a simple, chemically defined system for studying the binding of an individual antibody to a unique epitope on a complex protein antigen. Landsteiner employed various haptens, small organic molecules that are antigenic but not immunogenic. Chemical coupling of a hapten to a large protein, called a carrier, yields an immunogenic hapten-carrier conjugate. Animals immunized with such a conjugate produce antibodies specific for (1) the hapten determinant, (2) unaltered epitopes on the carrier protein, and (3) new epitopes formed by combined parts of both the hapten and carrier. By itself, a hapten cannot function as an immunogenic epitope.But when multiple molecules of a single hapten are coupled to a carrier protein (or nonimmunogenic homopolymer), the hapten becomes accessible to the immune system and can function as an immunogen.**

- **Many biologically important substances, including drugs, peptide hormones, and steroid hormones, can function as haptens. Conjugates of these haptens with large protein carriers can be used to produce hapten-specific antibodies. These antibodies are useful for measuring the presence of various substances in the body. For instance, the original home pregnancy test kit employed antihapten antibodies to determine whether a woman's urine contained human chorionic gonadotropin (HCG), which is a sign of pregnancy. However, as shown in the Clinical Focus, the formation of drug-protein conjugates in the body can produce drug allergies that may be life-threatening.**

Antigen



Injection with:	Antibodies formed:
Hapten (DNP)	None
Protein carrier (BSA)	Anti-BSA
Hapten–carrier conjugate (DNP-BSA)	Anti-DNP (major) Anti-BSA (minor) Anti-DNP/BSA (minor)

A hapten-carrier conjugate contains multiple copies of the hapten—a small nonimmunogenic organic compound such as dinitrophenol (DNP)—chemically linked to a large protein carrier such as bovine serum albumin (BSA). Immunization with DNP alone elicits no anti-DNP antibodies, but immunization with DNPBSA elicits three types of antibodies. Of these, anti-DNP antibody is predominant, indicating that in this case the hapten is the mmunodominant epitope in a hapten-carrier conjugate, as it often is in such conjugates.

Antibody

Antibodies are antigen binding proteins present on the B-cell membrane and secreted by plasma cells. Membrane-bound antibody confers antigenic specificity on B cells; antigen-specific proliferation of B-cell clones is elicted by the interaction of membrane antibody with antigen. Secreted antibodies circulate in the blood, where they serve as the effectors of humoral immunity by searching out and neutralizing antigens or marking them for elimination. All antibodies share structural features, bind to antigen, and participate in a limited number of effector functions.

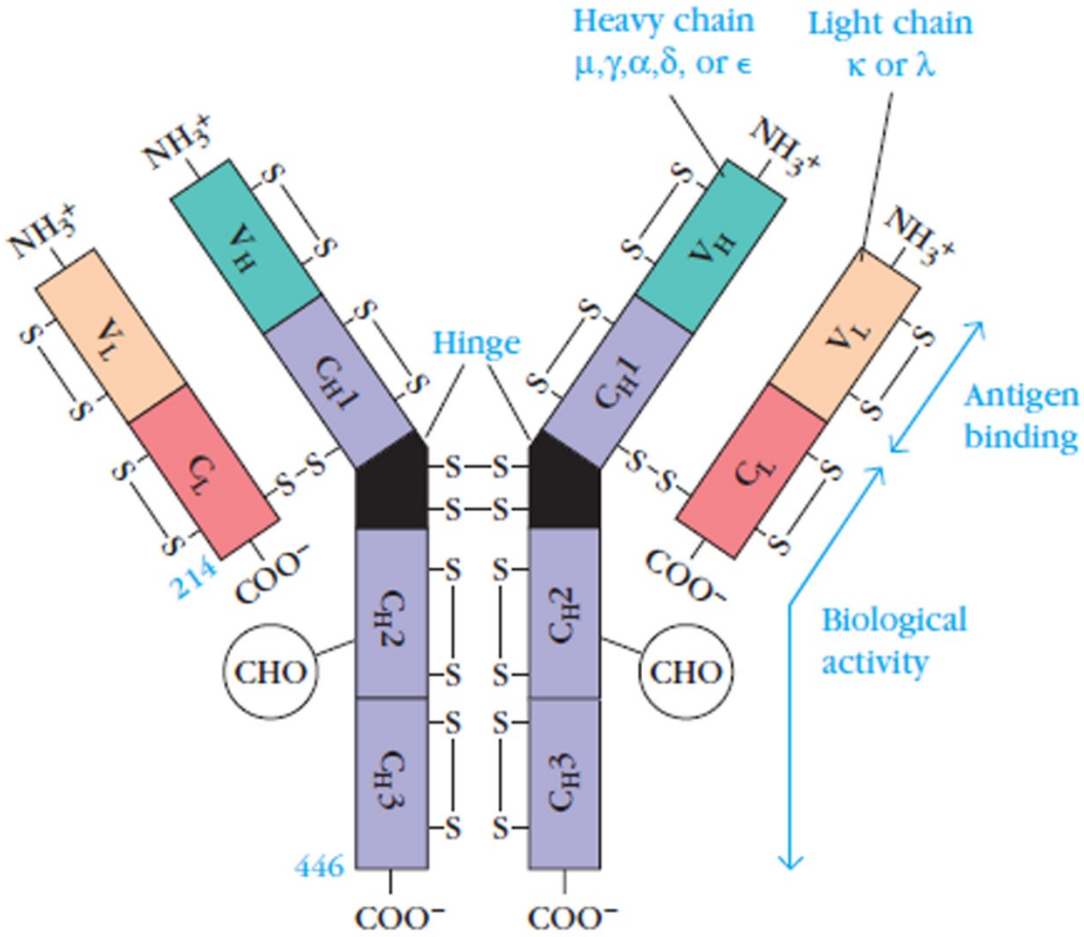
- **Antibody molecules have a common structure of four peptide chains. This structure consists of two identical light (L) chains, polypeptides of about 25,000 molecular weight, and two identical heavy (H) chains, larger polypeptides of molecular weight 50,000 or more. Like the antibody molecules they constitute, H and L chains are also called immunoglobulins. Each light chain is bound to a heavy chain by a disulfide bond, and by such noncovalent interactions as salt linkages, hydrogen bonds, and hydrophobic bonds, to form a heterodimer (H-L). Similar noncovalent interactions and disulfide bridges link the two identical heavy and light (H-L) chain combinations to each other to form the basic four-chain (H-L)2 antibody structure, a dimer of dimers.**

Antibody

- **The first 110 or so amino acids of the amino-terminal region of a light or heavy chain varies greatly among antibodies of different specificity. These segments of highly variable sequence are called *V regions:*VL in light chains and VH in heavy. All of the differences in specificity displayed by different antibodies can be traced to differences in the amino acid sequences of V regions. In fact, most of the differences among antibodies fall within areas of the V regions called *complementarity-determining regions (CDRs),* and it is these CDRs, on both light and heavy chains, that constitute the antigenbinding site of the antibody molecule. By contrast, within the same antibody class, far fewer differences are seen when one compares sequences throughout the rest of the molecule.**

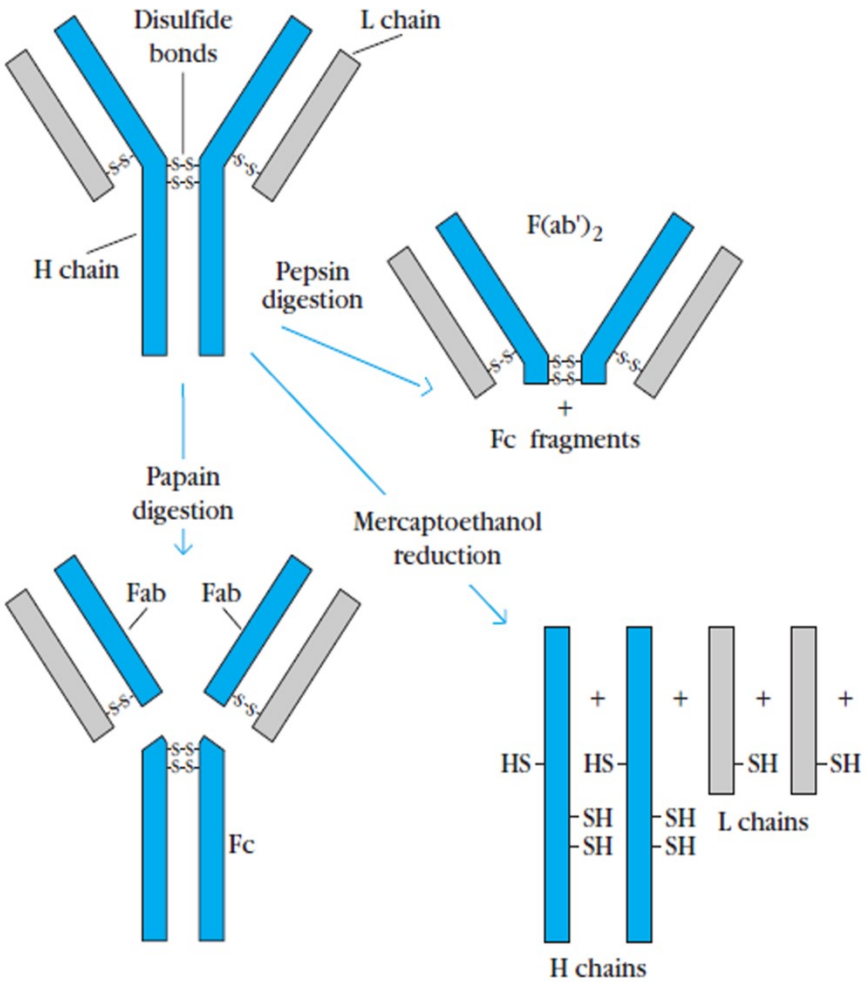
- **The regions of relatively constant sequence beyond the variable regions have been dubbed C regions, CL on the light chain and CH on the heavy chain. Antibodies are glycoproteins; with few exceptions, the sites of attachment for carbohydrates are restricted to the constant region. We do not completely understand the role played by glycosylation of antibodies, but it probably increases the solubility of the molecules. Inappropriate glycosylation, or its absence, affects the rate at which antibodies are cleared from the serum, and decreases the efficiency of interaction between antibody and the complement system and between antibodies and Fc receptors.**

Antibody



Schematic diagram of structure of Imunoglobulins derived from amino acid sequencing studies. Each heavy and light chain in an immunoglobulin molecule contains an amino-terminal variable (V) region (aqua and tan, respectively) that consists of 100–110 amino acids. The remainder of each chain in the molecule—the constant (C) regions (purple and red)—exhibits limited variation that defines the two light-chain subtypes and the five heavy-chain subclasses. The amino-terminal portions, corresponding to the V regions, bind to antigen; effector functions are mediated by the other domains.

Antibody



Brief digestion of immunoglobulin with the enzyme papain produced three fragments, two of which were identical fragments and a third that was quite different. The two identical fragments (each with a MW of 45,000), had antigen-binding activity and were called Fab fragments ("fragment, antigen binding"). The other fragment (MW of 50,000) had no antigenbinding activity at all. Because it was found to crystallize during cold storage, it was called the Fc fragment ("fragment, crystallizable").Digestion with pepsin, a different proteolytic enzyme, also demonstrated that the antigen-binding properties of an antibody can be separated from the rest of the molecule. Pepsin digestion generated a single 100,000- MW fragment composed of two Fab-like fragments designated th F(ab)2 fragment, which binds antigen. The Fc fragment was not recovered from pepsin digestion because it had been digested into multiple fragments.

A key observation in deducing the multichain structure of immunoglobulin was made when the molecule was subjected to mercaptoethanol reduction and alkylation, a chemical treatment that irreversibly cleaves disulfide bonds.

Antibody

TABLE Chain composition of the five immunoglobulin classes in humans

Class	Heavy chain	Subclasses	Light chain	Molecular formula
IgG	γ	$\gamma 1$, $\gamma 2$, $\gamma 3$, $\gamma 4$	κ or λ	$\gamma_2\kappa_2$ $\gamma_2\lambda_2$
IgM	μ	None	κ or λ	$(\mu_2\kappa_2)_n$ $(\mu_2\lambda_2)_n$ $n = 1$ or 5
IgA	α	$\alpha 1$, $\alpha 2$	κ or λ	$(\alpha_2\kappa_2)_n$ $(\alpha_2\lambda_2)_n$ $n = 1, 2, 3$, or 4
IgE	ϵ	None	κ or λ	$\epsilon_2\kappa_2$ $\epsilon_2\lambda_2$
IgD	δ	None	κ or λ	$\delta_2\kappa_2$ $\delta_2\lambda_2$

Antibody

- **Immunoglobulin E (IgE)**
- **The potent biological activity of IgE allowed it to be identified in serum despite its extremely low average serum concentration (0.3 g/ml). IgE antibodies mediate the immediate hypersensitivity reactions that are responsible for the symptoms of hay fever, asthma, hives, and anaphylactic shock.**

- **Immunoglobulin D (IgD)**
- **IgD was first discovered when a patient developed a multiple myeloma whose myeloma protein failed to react with antiisotype antisera against the then-known isotypes: IgA, IgM, and IgG.When rabbits were immunized with this myeloma protein, the resulting antisera were used to identify the same class of antibody at low levels in normal human serum. No biological effector function has been identified for IgD.**

Antibody

TABLE Properties and biological activities* of classes and subclasses of human serum immunoglobulins

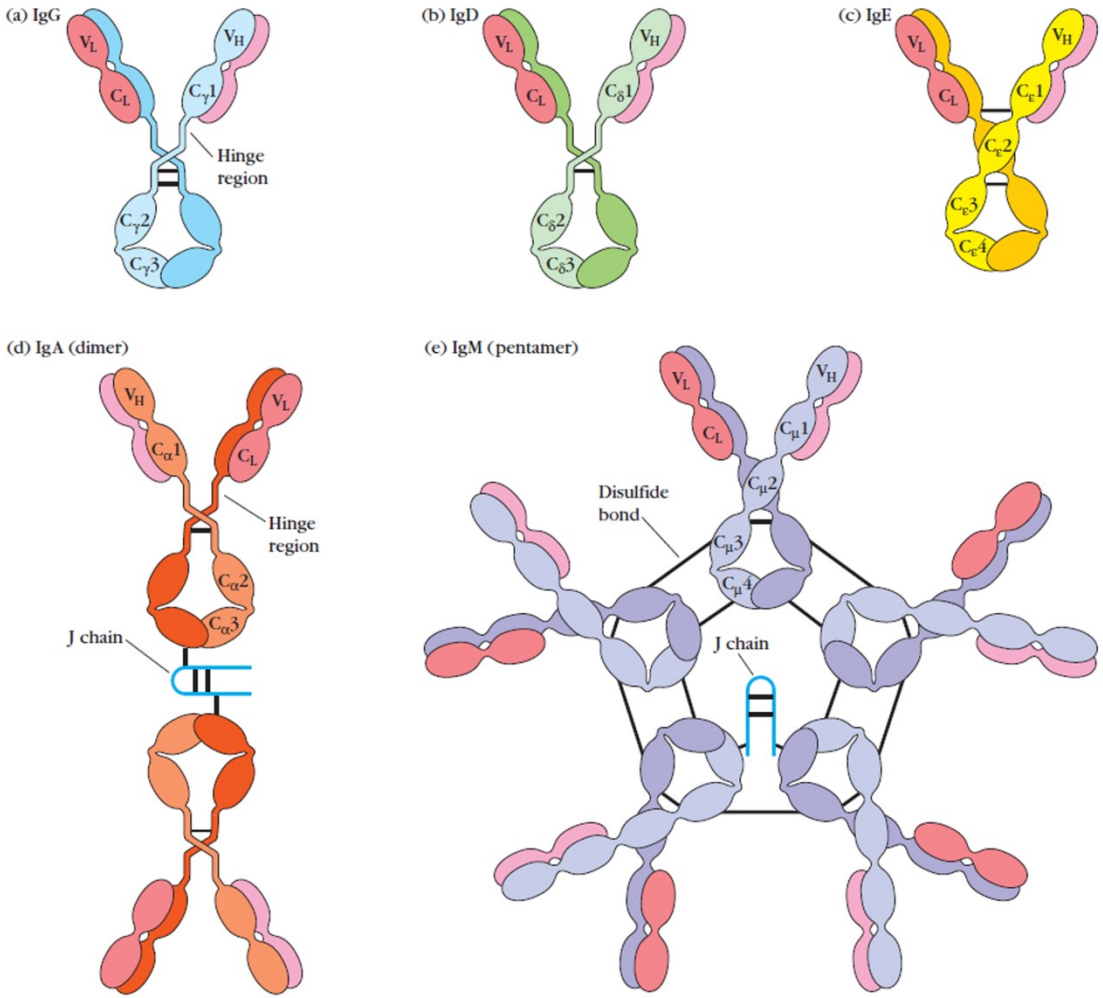
Property/Activity	IgG1	IgG2	IgG3	IgG4	IgA1	IgA2	IgM‡	IgE	IgD
Molecular weight†	150,000	150,000	150,000	150,000	150,000–600,000	150,000–600,000	900,000	190,000	150,000
Heavy-chain component	γ1	γ2	γ3	γ4	α1	α2	μ	ε	δ
Normal serum level (mg/ml)	9	3	1	0.5	3.0	0.5	1.5	0.0003	0.03
In vivo serum half life (days)	23	23	8	23	6	6	5	2.5	3
Activates classical complement pathway	+	+/−	++	−	−	−	+++	−	−
Crosses placenta	+	+/−	+	+	−	−	−	−	−
Present on membrane of mature B cells	−	−	−	−	−	−	+	−	+
Binds to Fc receptors of phagocytes	++	+/−	++	+	−	−	?	−	−
Mucosal transport	−	−	−	−	++	++	+	−	−
Induces mast-cell degranulation	−	−	−	−	−	−	−	+	−

*Activity levels indicated as follows: ++ = high; + = moderate; +/− = minimal; − = none; ? = questionable.

†IgG, IgE, and IgD always exist as monomers; IgA can exist as a monomer, dimer, trimer, or tetramer. Membrane-bound IgM is a monomer, but secreted IgM in serum is a pentamer.

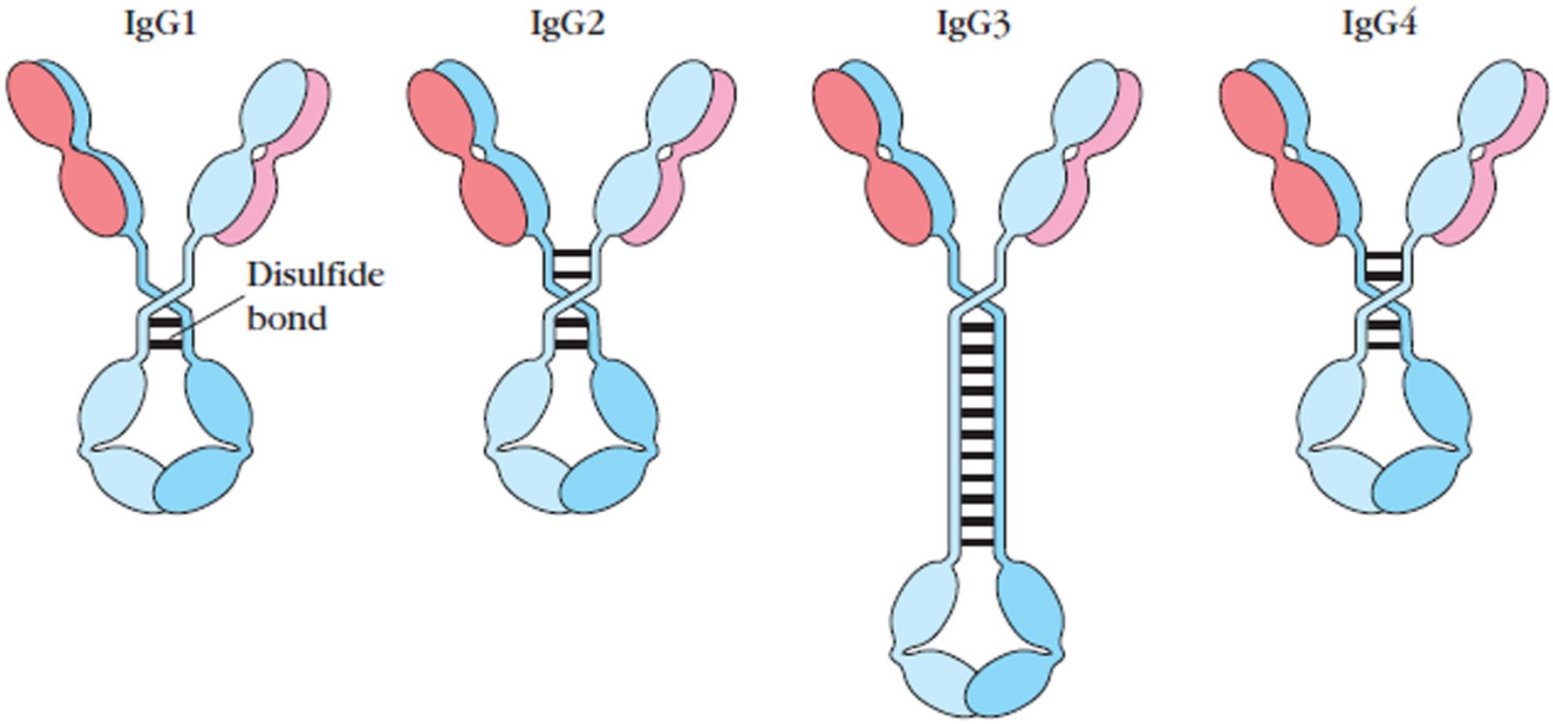
‡IgM is the first isotype produced by the neonate and during a primary immune response.

Antibody



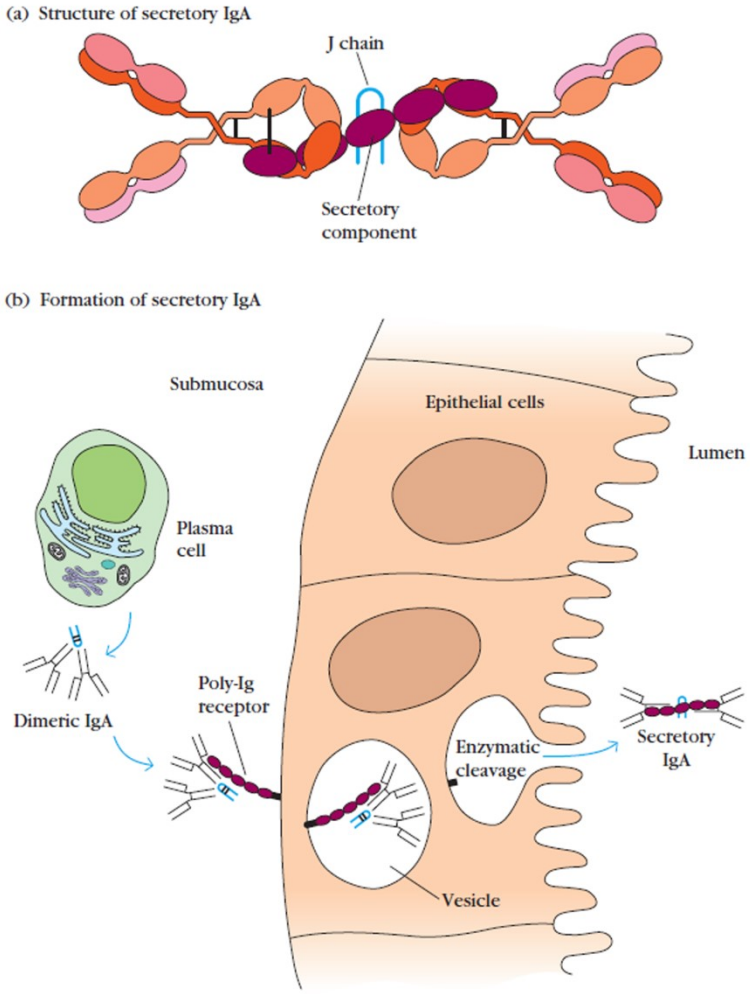
General structures of the five major classes of secreted antibody.

Antibody



General structure of the four subclasses of human IgG, which differ in the number and arrangement of the interchain disulfide bonds (thick black lines) linking the heavy chains.

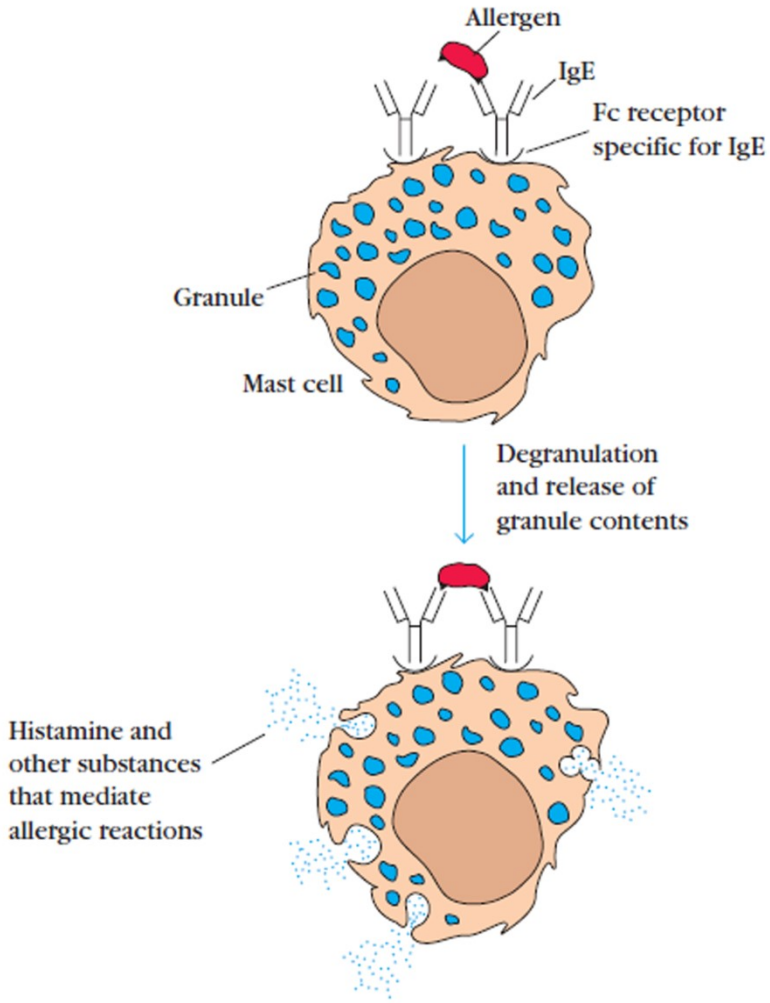
Antibody



Structure and formation of secretory IgA. (a) Secretory IgA consists of at least two IgA molecules, which are covalently linked to each other through a J chain and are also covalently linked with the secretory component. The secretory component contains five Ig-like domains and is linked to dimeric IgA by a disulfide bond between its fifth domain and one of the IgA heavy chains.

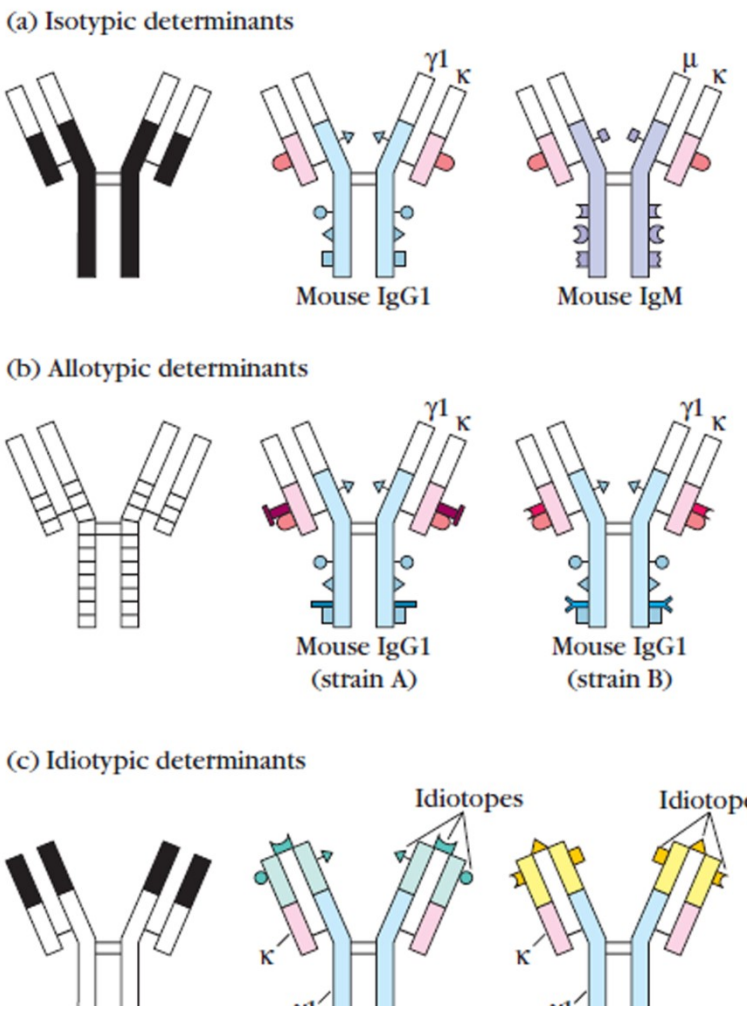
(b) Secretory IgA is formed during transport through mucous membrane epithelial cells. Dimeric IgA binds to a poly-Ig receptor on the basolateral membrane of an epithelial cell and is internalized by receptormediated endocytosis. After transport of the receptor-IgA complex to the luminal surface, the poly-Ig receptor is enzymatically cleaved, releasing the secretory component bound to the dimeric IgA.

Antibody



Allergen cross-linkage of receptor-bound IgE on mast cells induces degranulation, causing release of substances (blue dots) that mediate allergic manifestations.

Antibody



Antigenic determinants of immunoglobulins. For each type of determinant, the general location of determinants within the antibody molecule is shown (*left*) and two examples are illustrated (*center* and *right*).

(a) Isotypic determinants are constantregion determinants that distinguish each Ig class and subclass within a species.

(b) Allotypic determinants are subtle amino acid differences encoded by different alleles of isotype genes. Allotypic differences can be detected by comparing the same antibody class among different inbred strains.

(c) Idiotypic determinants are generated by the conformation of the amino acid sequences of the heavy- and light-chain variable regions specific for each antigen. Each individual determinant is called an idiotope, and the sum of the individual idiotopes is the idiotype.