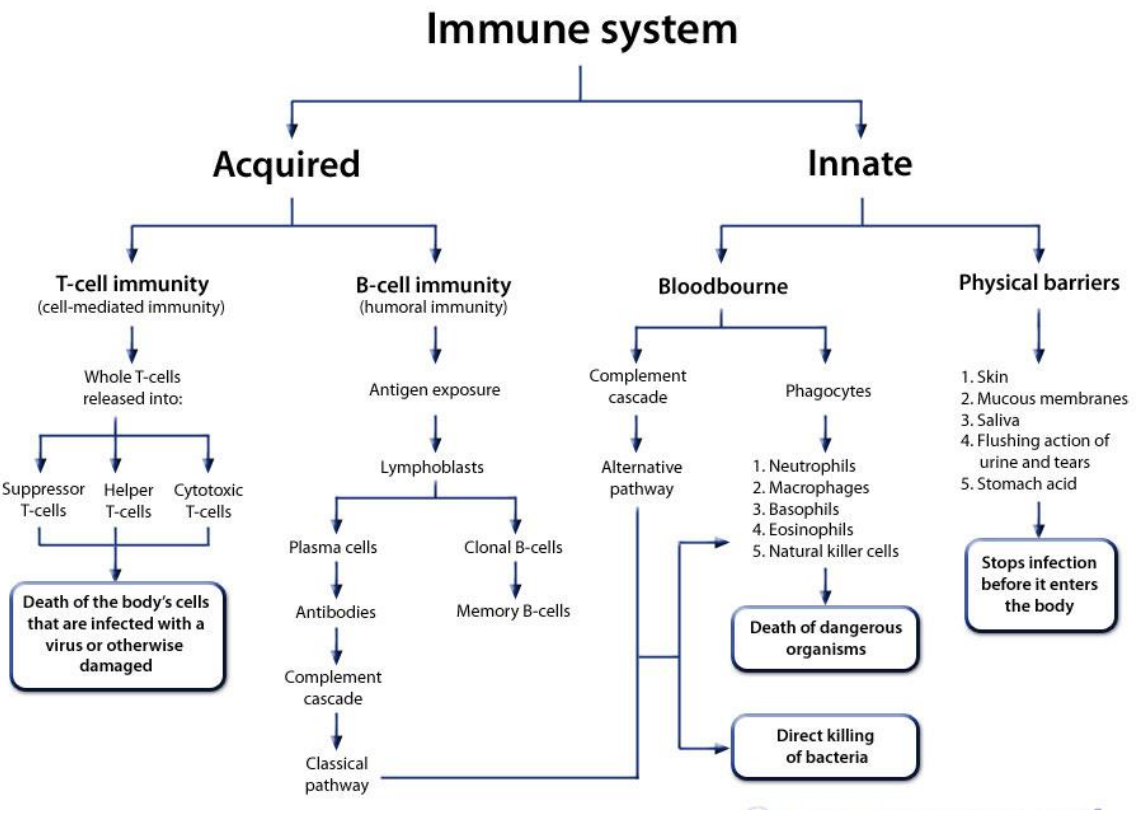
Immunology is a branch of biomedical science that covers the study of all aspects of the immune system in all organisms.It deals with the physiological functioning of the immune system in states of both health and diseases; malfunctions of the immune system in immunological disorders (autoimmune diseases, hypersensitivities, immune deficiency, transplant rejection); the physical, chemical and physiological characteristics of the components of the immune system *in vitro*, *in situ* and *in vivo*. Immunology has applications in several disciplines of science, and as such is further divided.

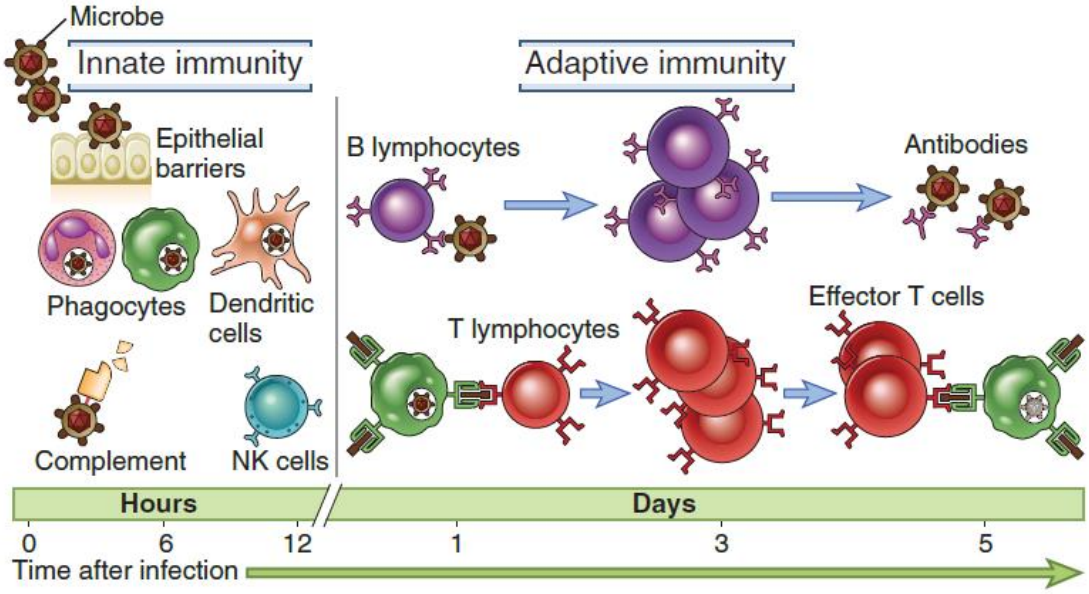
Importance of immune system in health and disease.

Role of the immune system	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
Defense against tumors	Potential for immunotherapy of cancer
The immune system recognizes and responds to tissue grafts and newly introduced molecules	Immune responses are barriers to transplantation and gene therapy
The immune system can injure cells and induce pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases



Innate and adaptive immunity

Innate immunity provides the early line of defense against microbes. It consists of cellular and biochemical defense mechanisms that are in place even before infection and are poised to respond rapidly to infections. These mechanisms react to products of microbes and injured cells, and they respond in essentially the same way to repeated exposures. The mechanisms of innate immunity are specific for structures that are common to groups of related microbes and may not distinguish fine differences between microbes. The principal components of innate immunity are (1) physical and chemical barriers, such as epithelia and antimicrobial chemicals produced at epithelial surfaces; (2) phagocytic cells (neutrophils, macrophages), dendritic cells, and natural killer (NK) cells and other innate lymphoid cells; and (3) blood proteins, including members of the complement system and other mediators of inflammation.



Adaptive immunity

Adaptive immunity, also called specific immunity or acquired immunity, requires expansion and differentiation of lymphocytes in response to microbes before it can provide effective defense; that is, it adapts to the presence of microbial invaders. Innate immunity is phylogenetically older, and the more specialized and powerful adaptive immune system evolved later.

Humoral immunity is mediated by molecules in the blood and mucosal secretions, called **antibodies**, which are produced by cells called **B lymphocytes** (**B cells**). Antibodies recognize microbial antigens,
neutralize the infectivity of the microbes, and target microbes for elimination by various effector mechanisms. Humoral immunity is the principal defense mechanism against extracellular microbes and their toxins because secreted antibodies can bind to these microbes and toxins and assist in their elimination. Antibodies themselves are specialized and may activate different mechanisms to combat microbes (**effector mechanisms**).For example, different types of antibodies promote the ingestion of microbes by host cells (phagocytosis), bind to and trigger the release of inflammatory mediators from cells, and are actively transported into the lumens of mucosal organs and through the placenta to provide defense against ingested and inhaled microbes and against infections of the newborn, respectively.

TABLE 1-2 Features of Innate and Adaptive Immunity

	Innate	Adaptive
Characteristics		
Specificity	For molecules shared by groups of related microbes and molecules produced by damaged host cells	For microbial and nonmicrobial antigens
Diversity	Limited; germline encoded	Very large; receptors are produced by somatic recombination of gene segments
Memory	None	Yes
Nonreactivity to self	Yes	Yes
Components		
Cellular and chemical barriers	Skin, mucosal epithelia; antimicrobial molecules	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells, innate lymphoid cells	Lymphocytes

TABLE 1-3 Cardinal Features of Adaptive Immune Responses

Feature	Functional Significance
Specificity	Ensures that the immune response to a microbe (or nonmicrobial antigen) is targeted to that microbe (or antigen)
Diversity	Enables the immune system to respond to a large variety of antigens
Memory	Increases the ability to combat repeat infections by the same microbe
Clonal expansion	Increases the number of antigen-specific lymphocytes to keep pace with microbes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows the immune system to recover from one response so that it can effectively respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

Specificity and diversity. Immune responses are specific for distinct antigens and, in fact, for different portions of a single complex protein, polysaccharide, The parts of such antigens that are specifically recognized by individual lymphocytes are called **determinants** or **epitopes.** This fine specificity exists because individual lymphocytes express membrane receptors that can distinguish subtle differences in structure between distinct epitopes. Clones of lymphocytes with different specificities are present in unimmunized individuals and are able to recognize and respond to foreign antigens. This concept is the basic tenet of the clonal selection hypothesis. The total number of antigenic specificities of the lymphocytes in an individual, called the lymphocyte repertoire, is extremely large.

Diversity .Ability of the lymphocyte repertoire to recognize a very large number of antigens is the result of variability in the structures of the antigen-binding sites of lymphocyte receptors for antigens. In other words, there are many different clones of lymphocytes that differ in the structures of their antigen receptors and therefore in their specificity for antigens, contributing to a total store that is extremely diverse. The expression of different antigen receptors in different clones of T and B cells is the reason that these receptors are said to be clonally distributed.

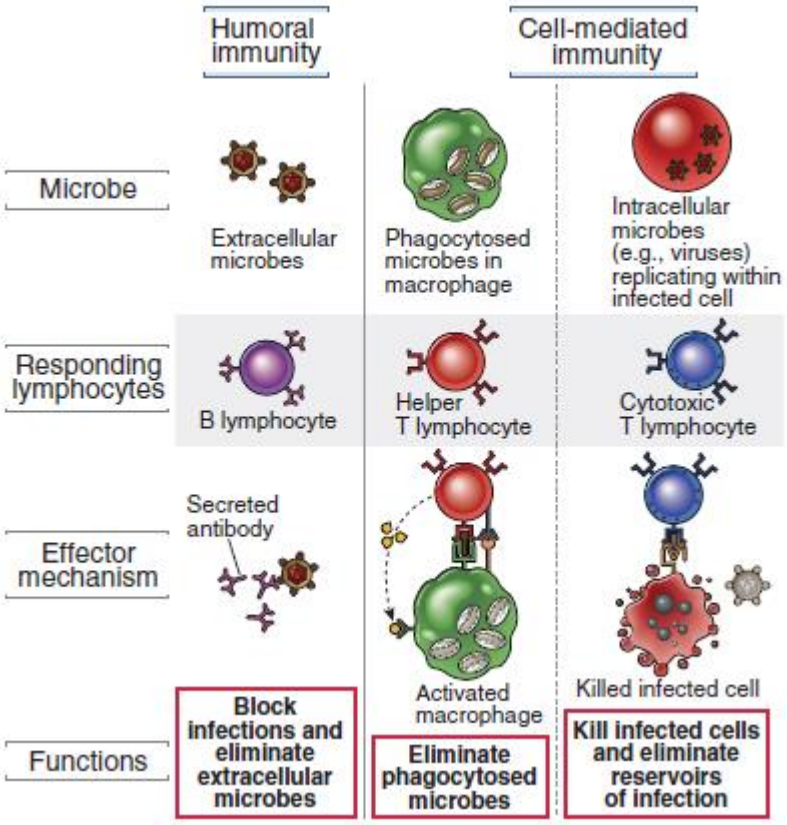
Memory. Exposure of the immune system to a foreign antigen enhances its ability to respond again to that antigen. Responses to second and subsequent exposures to the same antigen, called secondary immune responses, are usually more rapid, larger, and often qualitatively different from the first, or primary, immune response to that antigen. Immunologic memory occurs because each exposure to an antigen generates long-lived memory cells specific for the antigen, which are more numerous than the naive lymphocytes specific for the antigen that exist before antigen exposure. In addition, memory cells have special characteristics that make them more efficient at responding to and eliminating the antigen than are naive lymphocytes that have not previously been exposed to the antigen. For instance, memory B lymphocytes produce antibodies that bind antigens with higher affinities than do antibodies produced in primary immune responses, and memory T cells react much more rapidly and vigorously to antigen challenge than do naive T cells.

Clonal expansion. Lymphocytes specific for an antigen undergo considerable proliferation after exposure to that antigen. The term *clonal expansion* refers to an increase in the number of cells that express identical receptors for the antigen and thus belong to a clone. This increase in antigen- specific cells enables the adaptive immune response to keep with rapidly dividing infectious pathogens.

Specialization.The immune system responds in distinct and special ways to different microbes, maximizing the effectiveness of antimicrobial defense mechanisms. Thus, humoral immunity and cell-mediated immunity are elicited by different classes of microbes or by the same microbe at different stages of infection (extracellular and intracellular), and each type of immune response protects the host against that class of microbe. Even within humoral or cell-mediated immune responses, the nature of the antibodies or T lymphocytes that are generated may vary from one class of microbe to another.

Contraction and homeostasis. All normal immune responses wane with time after antigen stimulation, thus returning the immune system to its resting basal state, a state called **homeostasis .**

Nonreactivity to self. One of the most remarkable properties of every normal individual′s immune system is its ability to recognize, respond to, and eliminate many foreign (non-self) antigens while not reacting harmfully to that individual′s own (self) antigenic substances. Immunologic unresponsiveness is also called **tolerance.**



Cell-mediated immunity, also called **cellular immunity**, is mediated by **T lymphocytes** (**T cells**). Intracellular microbes, such as viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inaccessible to circulating antibodies. Defense against such infections is a function of cell-mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection. Some T lymphocytes also contribute to eradication of extracellular microbes by recruiting leukocytes that destroy these pathogens and by helping B cells make effective antibodies.

Cell-Mediated Immunity: Activation of T Lymphocytes and Elimination of Cell-Associated Microbes

When activated by antigen and costimulators in lymphoid organs, naive T cells secrete cytokines that function as growth factors and respond to other cytokines secreted by APCs. The combination of signals (antigen, costimulation, and cytokines) stimulates the proliferation of the T cells and

their differentiation into effector T cells. The effector T cells generated in the lymphoid organ may migrate back into the blood and then into any site where the antigen (or microbe) is present. These effector cells are reactivated by antigen at sites of infection and perform the functions responsible for elimination of the microbes. Different classes of T cells differentiate into effector cells with distinct functional properties. Helper T cells secrete cytokines and express surface molecules that mediate their functions. Some of these activated helper T cells function to recruit neutrophils and other leukocytes to sites of infection; other helper cells activate macrophages to kill ingested microbes; and still other helper T cells stay in the lymphoid organs and help B lymphocytes. CTLs directly kill cells harboring microbes in the cytoplasm. These microbes may be viruses that infect many cell types or bacteria that are ingested by macrophages but have learned to escape from phagocytic vesicles into the cytoplasm (where they are inaccessible to the killing machinery of phagocytes, which is largely confined to vesicles). By destroying the infected cells, CTLs eliminate the reservoirs of infection.

Humoral Immunity: Activation of B Lymphocytes and Elimination of Extracellular Microbes

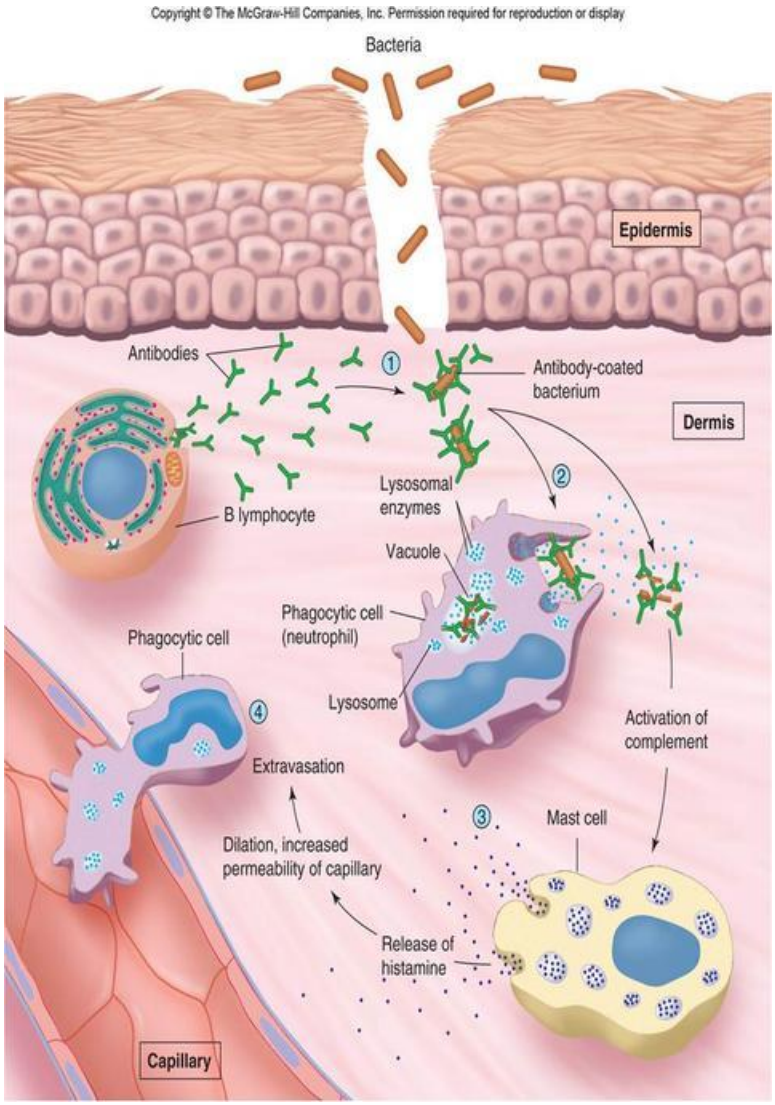
On activation, B lymphocytes proliferate and then differentiate into plasma cells that secrete different classes of antibodies with distinct functions. Many polysaccharide and lipid antigens have multiple identical antigenic determinants (epitopes) that are able to engage many antigen receptor molecules on each B cell and initiate the process of B cell activation. Typical globular protein antigens are not able to bind to many antigen receptors, and the full response of B cells to protein antigens requires help from CD4+ T lymphocytes.

Inflammation

Inflammation is a protective response involving host cells, blood vessels, and proteins and other mediators that is intended to eliminate the initial cause of cell injury, as well as the necrotic cells and tissues resulting from the original insult, and to initiate the process of repair.

Components of both the innate and adaptive immune systems may respond to certain antigens to initiate a process known as inflammation. The cardinal signs of inflammation are pain , heat , redness , swelling (tumor) , and loss of function. Enlarged capillaries that result from vasodilation cause redness (erythema) and an increase in tissue temperature. Increased capillary permeability allows for an influx of fluid and cells, contributing to swelling (edema) . Phagocytic cells attracted to the site release lytic enzymes, damaging healthy cells. An accumulation of dead cells and fluid forms pus,

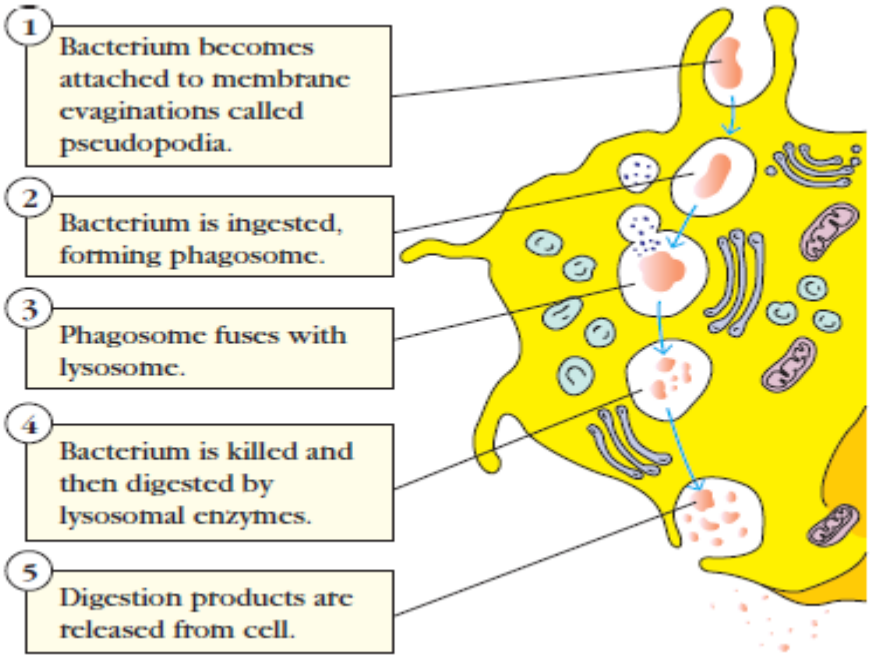
whereas mediators released by phagocytic cells stimulate nerves and cause pain . The innate immune system contributes to inflammation by activating the alternative and lectin-binding complement pathways, attracting and activating phagocytic cells that secrete cytokines and chemokines, activating NK cells, altering vascular permeability, and increasing body temperature



Phagocytosis

Despite the strong defenses of our protective epithelial layers, some pathogens have evolved strategies to penetrate these defenses, and epithelia may be disrupted by wounds, abrasions, and insect bites that may transmit pathogens. Once pathogens penetrate through the epithelial barrier layers into the tissue spaces of the body, an array of cellular membrane receptors and soluble

proteins that recognize microbial components play the essential roles of detecting the pathogen and triggering effective defenses against it. Phagocytic cells make up the next line of defense against pathogens that have penetrated the epithelial cell barriers. Macrophages, neutrophils, and dendritic cells in tissues and monocytes in the blood are the main cell types that carry out phagocytosis the cellular uptake (eating) of particulate materials such as bacteria a key mechanism for eliminating pathogens. This major role of the cells attracted to the site of invading organisms is evolutionarily ancient, present in invertebrates as well as vertebrates. Elie Metchnikoff initially described the process of phagocytosis in the 1880s using cells from starfish (echinoderm invertebrates) similar to vertebrate white blood cells and ascribed to phagocytosis a major role in immunity. He was correct in this conclusion; we now know that defects in phagocytosis lead to severe immunodeficiency.Most tissues contain resident populations of macrophages that function as guards for the innate immune system. Through various cell surface receptors they recognize microbes such as bacteria, extend their plasma membrane to engulf them, and internalize them in phagosomes . Lysosomes then fuse with the phagosomes, delivering agents that kill and degrade the microbes. Neutrophils are a second major type of phagocyte, usually recruited to sites of infection. Finally, dendritic cells also can bind and phagocytose microbes. Uptake and degradation of microbes by dendritic cells play key roles in the initiation of adaptive immune responses. In addition to triggering phagocytosis, various receptors on phagocytes recognize microbes and activate the production of a variety of molecules that contribute in other ways to eliminating infection.


1
Bacterium becomes attached to membrane evaginations called pseudopodia.
2
Bacterium is ingested, forming phagosome.
3
Phagosome fuses with lysosome.
4
Bacterium is killed and then digested by lysosomal enzymes.
5
Digestion products are released from cell.