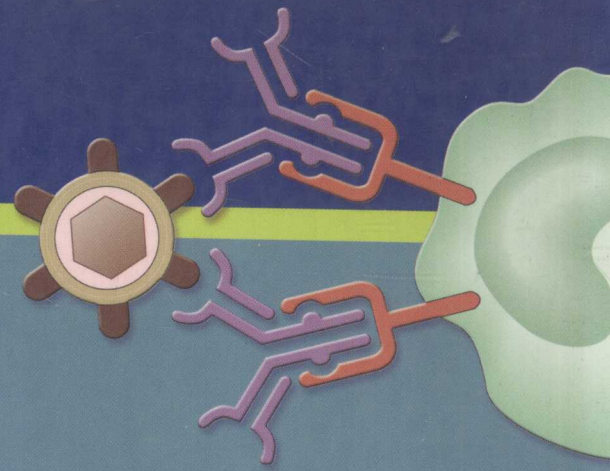


Fifth Edition



Abul K. Abbas
Andrew H. Lichtman

Cellular and Molecular Immunology

SAUNDERS

Cellular and Molecular Immunology

Fifth Edition

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CELLULAR AND MOLECULAR IMMUNOLOGY

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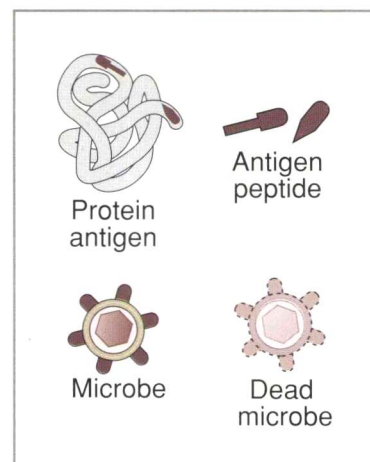
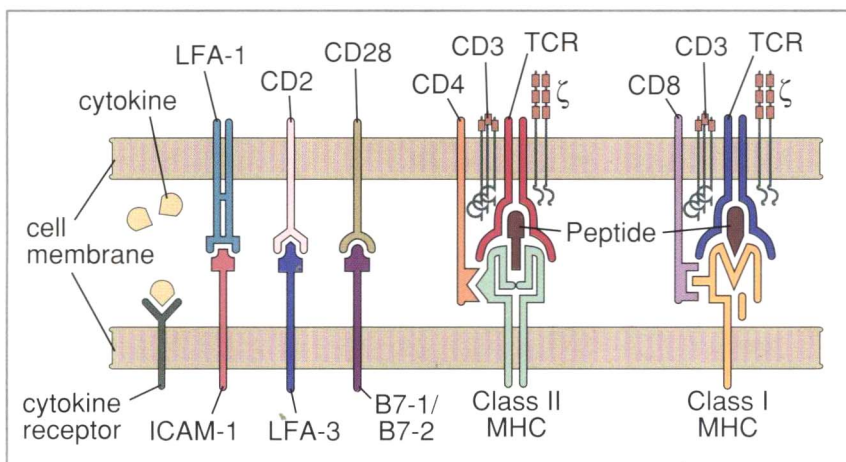
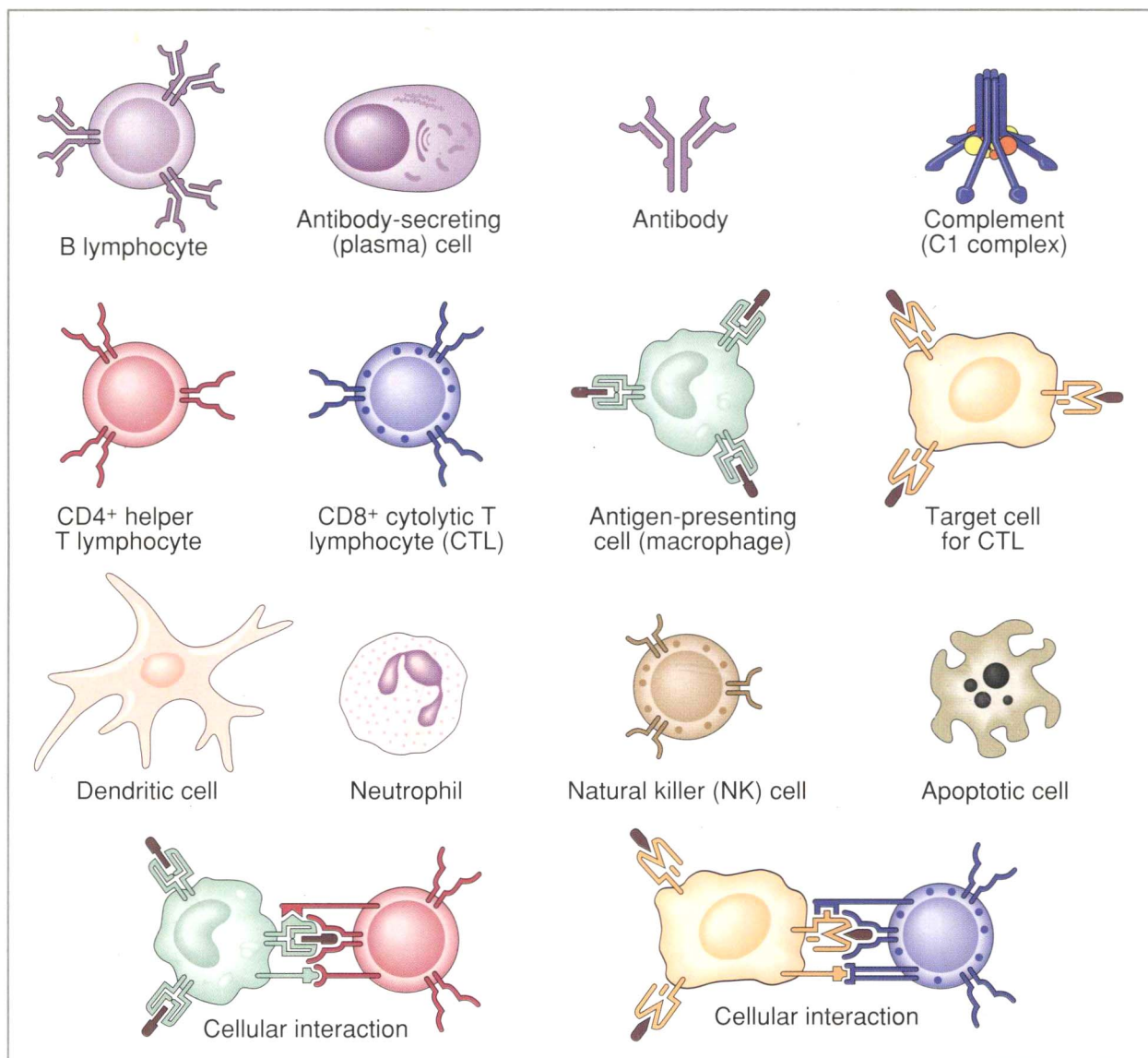
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Cellular and Molecular Immunology

TO

Ann, Jonathan, Rehana

Sheila, Eben, Ariella, Amos, Ezra

Preface

The fifth edition of this book has been extensively revised to incorporate new discoveries in immunology and the constantly growing body of knowledge. It is remarkable to us that new paradigms continue to be established in the field and unifying principles continue to emerge from analysis of complex molecular systems. Examples of areas in which our understanding has grown impressively since the last edition of this book include innate immunity and the functions of Toll-like receptors, the role of chemokines and their receptors in maintaining the functional architecture of lymphoid tissues, the functions of adapter proteins and kinase pathways in immune cell signal transduction pathways, and the basis of natural killer cell recognition of ligands. We have added new information while striving to emphasize important principles and not increase the size of the book. We have also completely reviewed the book and updated sections and changed them when necessary for increased clarity, accuracy, and completeness.

The changes in format that have evolved through the previous editions to make the book easier to read have been retained. These include the use of bold italic text to highlight “take-home messages,” presentation of experimental results in bulleted lists distinguishable

from the main text, and the use of boxes (including several new ones) to present detailed information about experimental approaches, disease entities, and selected molecular or biological processes. We have also strived to further improve the clarity of illustrations by simplifying the iconography. The table format has been completely reworked to improve readability.

Many individuals have made invaluable contributions to this fifth edition. Among the colleagues who have helped us, we would like to convey special thanks to Shiv Pillai for his generous willingness to review chapter drafts. Our illustrators, David and Alexandra Baker of DNA Illustrations, remain full partners in the book and provide invaluable suggestions for clarity and accuracy. Our editors, Jason Malley and Bill Schmitt, have been a source of support and encouragement. Our Developmental Editor, Hazel Hacker, shepherded the book through its preparation and production. Many other members of the staff of Elsevier Science played critical roles at various stages of this project; these include Gene Harris, Linda Grigg, and Heather Krehling. We are also grateful to our students, from whom we continue to learn how to present the science of immunology in the clearest and most enjoyable way.

Abul K. Abbas
Andrew H. Lichtman

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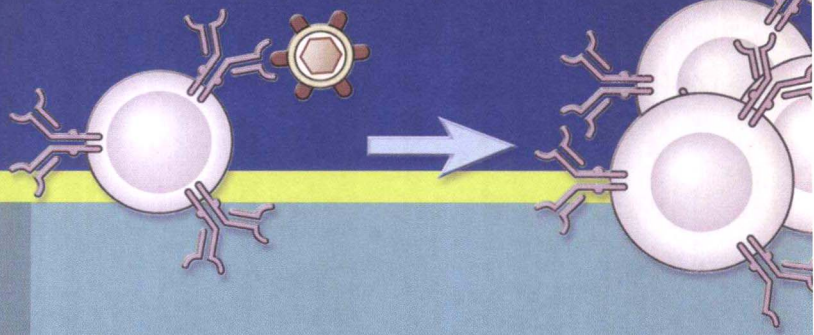
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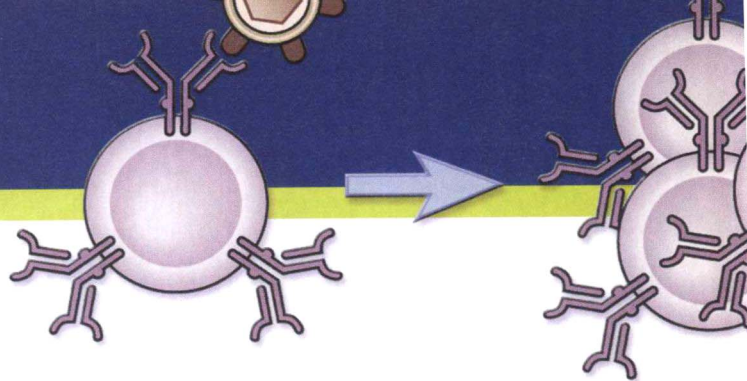
Section I



Introduction to Immunology

The first two chapters of this book introduce the nomenclature of immunology and the components of the immune system. In Chapter 1, we describe the types of immune responses and their general properties and introduce the fundamental principles that govern all immune responses. Chapter 2 is devoted to a description of the cells and tissues of the immune system, with an emphasis on their anatomic organization and structure-function relationships. This sets the stage for more thorough discussion of how the immune system recognizes and responds to antigens.

Chapter 1



General Properties of Immune Responses

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The term *immunity* is derived from the Latin word *immunitas*, which referred to the protection from legal prosecution offered to Roman senators during their tenures in office. Historically, immunity meant protection from disease and, more specifically, infectious disease. The cells and molecules responsible for immunity constitute the **immune system**, and their collective and coordinated response to the introduction of foreign substances is called the **immune response**.

The physiologic function of the immune system is defense against infectious microbes. However, even noninfectious foreign substances can elicit immune responses. Furthermore, mechanisms that normally protect individuals from infection and eliminate foreign substances are themselves capable of causing tissue injury and disease in some situations. Therefore, a more inclusive definition of immunity is a reaction to foreign substances, including microbes, as well as to macromolecules such as proteins and polysaccharides, regardless of the physiologic or pathologic consequence of such a reaction. Immunology is the study of immunity in this broader sense and of the cellular and molecular events that occur after an organism encounters microbes and other foreign macromolecules.

Historians often credit Thucydides, in Athens during the fifth century BC, as having first mentioned immunity to an infection that he called “plague” (but that was probably not the bubonic plague we recognize today). The concept of immunity may have existed long before, as suggested by the ancient Chinese custom of making children resistant to smallpox by having them inhale powders made from the skin lesions of patients recovering from the disease. Immunology, in its modern form, is an experimental science, in which explanations of immunologic phenomena are based on experimental observations and the conclusions drawn from them. The evolution of immunology as an experimental discipline has depended on our ability to manipulate the function of the immune system under controlled conditions. Historically, the first clear example of this manipulation, and one that remains among the most dramatic ever recorded, was Edward Jenner’s successful

vaccination against smallpox. Jenner, an English physician, noticed that milkmaids who had recovered from cowpox never contracted the more serious smallpox. On the basis of this observation, he injected the material from a cowpox pustule into the arm of an 8-year-old boy. When this boy was later intentionally inoculated with smallpox, the disease did not develop. Jenner's landmark treatise on **vaccination** (Latin *vaccinus*, of or from cows) was published in 1798. It led to the widespread acceptance of this method for inducing immunity to infectious diseases, and vaccination remains the most effective method for preventing infections (Table 1-1). An eloquent testament to the importance of immunology was the announcement by the World Health Organization in 1980 that smallpox was the first disease that had been eradicated worldwide by a program of vaccination.

Since the 1960s, there has been a remarkable transformation in our understanding of the immune system and its functions. Advances in cell culture techniques (including monoclonal antibody production), immunochemistry, recombinant DNA methodology, x-ray crystallography, and creation of genetically altered animals (especially transgenic and knockout mice) have changed immunology from a largely descriptive science into one in which diverse immune phenomena can be explained in structural and biochemical terms. In this chapter, we outline the general features of immune responses and introduce the concepts that form the cornerstones of modern immunology and that recur throughout this book.

Innate and Adaptive Immunity

Defense against microbes is mediated by the early reactions of innate immunity and the later responses of adaptive immunity (Fig. 1-1 and Table 1-2). **Innate immunity** (also called natural or native immunity) consists of cellular and biochemical defense mechanisms that are in place even before infection and poised to respond rapidly to infections. These mechanisms react only to microbes and not to noninfectious substances, and they respond in essentially the same way to repeated infections. The principal components of innate immunity are (1) physical and chemical barriers, such as epithelia and antimicrobial substances produced at epithelial surfaces; (2) phagocytic cells (neutrophils, macrophages) and NK (natural killer) cells; (3) blood proteins, including members of the complement system and other mediators of inflammation; and (4) proteins called cytokines that regulate and coordinate many of the activities of the cells of innate immunity. The mechanisms of innate immunity are specific for structures that are common to groups of related microbes and may not distinguish fine differences between foreign substances. Innate immunity provides the early lines of defense against microbes.

In contrast to innate immunity, there are other immune responses that are stimulated by exposure to infectious agents and increase in magnitude and defensive capabilities with each successive exposure to a particular microbe. Because this form of immunity

Table 1-1. Effectiveness of Vaccines for Some Common Infectious Diseases

Disease	Max. number of cases	Number of cases in 2000	Percent change
Diphtheria	206,939 (1921)	2	-99.99
Measles	894,134 (1941)	63	-99.99
Mumps	152,209 (1968)	315	-99.80
Pertussis	265,269 (1934)	6,755	-97.73
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	152	-99.84
Tetanus	1,560 (1923)	26	-98.44
<i>Haemophilus influenzae</i> type B	~20,000 (1984)	1,212	-93.14
Hepatitis B	26,611 (1985)	6,646	-75.03

This table illustrates the striking decrease in the incidence of selected infectious diseases for which effective vaccines have been developed. In some cases, such as with hepatitis B, a vaccine has become available recently, and the incidence of the disease is continuing to decrease.

Adapted from Orenstein WA, AR Hinman, KJ Bart, and SC Hadler. Immunization. In Mandell GL, JE Bennett, and R Dolin (eds). Principles and Practices of Infectious Diseases, 4th ed. Churchill Livingstone, New York, 1995, and Morbidity and Mortality Weekly Report 49:1159-1201, 2001.

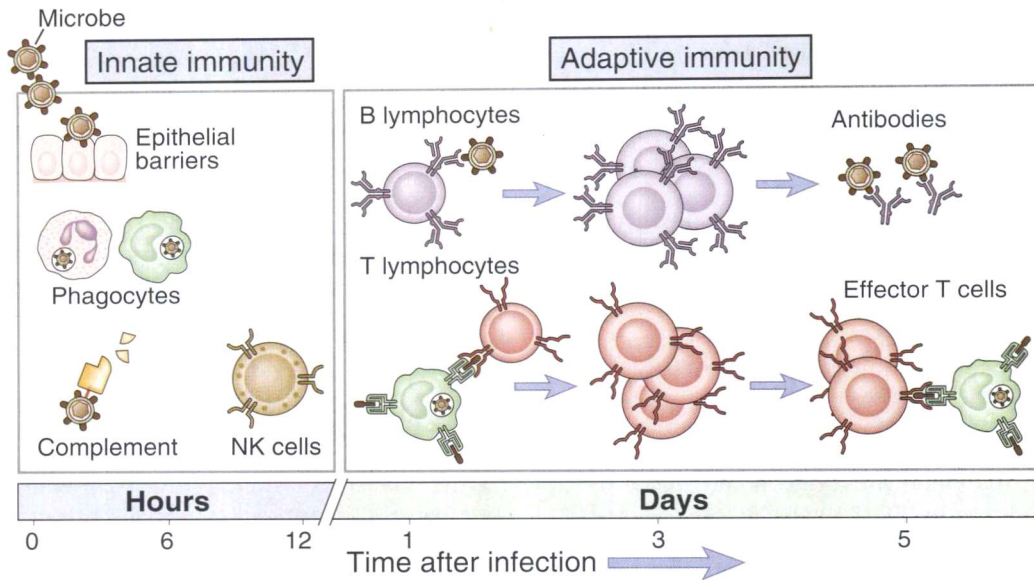


Figure 1-1 Innate and adaptive immunity.

The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

develops as a response to infection and adapts to the infection, it is called **adaptive immunity**. The defining characteristics of adaptive immunity are exquisite specificity for distinct molecules and an ability to “remember” and respond more vigorously to repeated exposures to the same microbe. The adaptive immune system is able to recognize and react to a large number

of microbial and nonmicrobial substances. In addition, it has an extraordinary capacity to distinguish among different, even closely related, microbes and molecules, and for this reason it is also called **specific immunity**. It is also sometimes called acquired immunity, to emphasize that potent protective responses are “acquired” by experience. The components of adaptive immunity are

Table 1-2. Features of Innate and Adaptive Immunity

	Innate	Adaptive
Characteristics		
Specificity	For structures shared by groups of related microbes	For antigens of microbes and for 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		
Physical and chemical barriers	Skin, mucosal epithelia; antimicrobial chemicals	Lymphocytes in epithelia; antibodies secreted at epithelial surfaces
Blood proteins	Complement	Antibodies
Cells	Phagocytes (macrophages, neutrophils), natural killer cells	Lymphocytes

This table lists the major characteristics and components of innate and adaptive immune responses. Innate immunity is discussed in much more detail in Chapter 12.

lymphocytes and their products. Foreign substances that induce specific immune responses or are the targets of such responses are called **antigens**. By convention, the terms *immune responses* and *immune system* refer to adaptive immunity, unless stated otherwise.

Innate and adaptive immune responses are components of an integrated system of host defense in which numerous cells and molecules function cooperatively. The mechanisms of innate immunity provide effective defense against infections. However, many pathogenic microbes have evolved to resist innate immunity, and their elimination requires the powerful mechanisms of adaptive immunity. There are two important links between innate immunity and adaptive immunity. First, the innate immune response to microbes stimulates adaptive immune responses and influences the nature of the adaptive responses. Second, adaptive immune responses use many of the effector mechanisms of innate immunity to eliminate microbes, and they often function by enhancing the antimicrobial activities of the defense mechanisms of innate immunity. We will return to a more detailed discussion of the mechanisms and physiologic functions of innate immunity in Chapter 12.

Innate immunity is phylogenetically the oldest system of host defense, and the adaptive immune system evolved later (Box 1-1). In invertebrates, host defense against foreign invaders is mediated largely by the mechanisms of innate immunity, including phagocytes and circulating molecules that resemble the plasma proteins of innate immunity in vertebrates. Adaptive immunity, consisting of lymphocytes and anti-

bodies, first appeared in jawed vertebrates and became increasingly specialized with further evolution.

Types of Adaptive Immune Responses

*There are two types of adaptive immune responses, called **humoral immunity** and **cell-mediated immunity**, that are mediated by different components of the immune system and function to eliminate different types of microbes* (Fig. 1-2). **Humoral immunity** is mediated by molecules in the blood and mucosal secretions, called **antibodies**, that are produced by cells called **B lymphocytes** (also called 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 different types of antibodies may activate different effector mechanisms. For example, some types of antibodies promote phagocytosis, and others trigger the release of inflammatory mediators from leukocytes such as mast cells. **Cell-mediated immunity**, also called cellular immunity, is mediated by **T lymphocytes** (also called T cells). Intracellular microbes, such as viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inac-

BOX 1-1

Evolution of the Immune System

Mechanisms for defending the host against microbes are present in some form in all multicellular organisms. These mechanisms constitute innate immunity. The more specialized defense mechanisms that constitute adaptive immunity are found in vertebrates only.

Various cells in invertebrates respond to microbes by surrounding these infectious agents and destroying them. These responding cells resemble phagocytes and have been called phagocytic amebocytes in acelomates, hemocytes in molluscs and arthropods, coelomocytes in annelids, and blood leukocytes in tunicates. Invertebrates do not contain antigen-specific lymphocytes and do not produce immunoglobulin (Ig) molecules or complement proteins. However, they contain a number of soluble molecules that bind to and lyse microbes. These molecules include lectin-like proteins, which bind to carbohydrates on microbial cell walls and agglutinate the microbes, and numerous lytic and antimicrobial factors such as lysozyme, which is also produced by neutrophils in higher organisms. Phagocytes in some invertebrates may be capable of secreting cytokines that resemble macrophage-derived cytokines in the vertebrates. Thus, host defense in invertebrates is mediated by the cells and molecules that resemble the effector mechanisms of innate immunity in higher organisms.

Many studies have shown that invertebrates are capable of rejecting foreign tissue transplants, or allografts. (In vertebrates, this process of graft rejection is dependent on adaptive immune responses.) If sponges (Porifera) from two different colonies are parabiosed by being mechanically held together, they become necrotic in 1 to 2 weeks, whereas sponges from the same colony become fused and continue to grow. Earthworms (annelids) and starfish (echinoderms) also reject tissue grafts from other species of the phyla. These rejection reactions are mediated mainly by phagocyte-like cells. They differ from graft rejection in vertebrates in that specific memory for the grafted tissue either is not generated or is difficult to demonstrate. Nevertheless, such results indicate that even invertebrates must express cell surface molecules that distinguish self from nonself, and such molecules may be the precursors of histocompatibility molecules in vertebrates.

The various components of the mammalian immune system appear to have arisen together in phylogeny and have become increasingly specialized with evolution (see Table). Thus, of the cardinal features of adaptive immune responses, specificity, memory, self/nonself discrimination, and a capacity for self-limitation are present in the lowest vertebrates, and diversity of antigen recognition

Continued on following page

	Innate immunity			Adaptive immunity	
	Phagocytes	NK cells	Antibodies	T and B lymphocytes	Lymph nodes
Invertebrates					
Protozoa	+	—	—	—	—
Sponges	+	—	—	—	—
Annelids	+	+	—	—	—
Arthropods	+	—	—	—	—
Vertebrates					
Elasmobranchs (sharks, skates, rays)	+	+	+ (IgM only)	+	—
Teleosts (common fish)	+	+	+ (IgM, others?)	+	—
Amphibians	+	+	+ (2 or 3 classes)	+	—
Reptiles	+	+	+ (3 classes)	+	—
Birds	+	+	+ (3 classes)	+	+ (some species)
Mammals	+	+	+ (7 or 8 classes)	+	+

Key: +, present; —, absent.

increases progressively in the higher species. All jawed vertebrates contain antibody molecules. The appearance of antibodies coincides with the development of specialized genetic mechanisms for generating a diverse repertoire. Fishes have only one type of antibody, called IgM; this number increases to two types in amphibians such as *Xenopus* and to seven or eight types in mammals. The diversity of antibodies is much lower in *Xenopus* than in mammals, even though the genes coding for antibodies are structurally similar. Lymphocytes that have some characteristics of both B and T cells are probably present in the

earliest vertebrates, such as lampreys, and become specialized into functionally and phenotypically distinct subsets in amphibians and most clearly in birds and mammals. The major histocompatibility complex, which is the genetic locus that controls T lymphocyte antigen recognition, is present in some of the more advanced species of amphibians and fishes and in all birds and mammals. The earliest organized lymphoid tissues detected during evolution are the gut-associated lymphoid tissues; spleen, thymus, and lymph nodes are found in higher vertebrates.

cessible 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.

Protective immunity against a microbe may be induced by the host's response to the microbe or by the transfer of antibodies or lymphocytes specific for the microbe (Fig. 1–3). The form of immunity that is induced by exposure to a foreign antigen is called **active immunity** because the immunized individual plays an active role in responding to the antigen. Individuals and lymphocytes that have not encountered a particular antigen are said to be **naïve**. Individuals who have responded to a microbial antigen and are protected from subsequent exposures to that microbe are said to be **immune**.

Immunity can also be conferred on an individual by transferring serum or lymphocytes from a specifically immunized individual, a process known as adoptive

transfer in experimental situations. The recipient of such a transfer becomes immune to the particular antigen without ever having been exposed to or having responded to that antigen. Therefore, this form of immunity is called **passive immunity**. Passive immunization is a useful method for conferring resistance rapidly, without having to wait for an active immune response to develop. An example of passive immunity is the transfer of maternal antibodies to the fetus, which enables newborns to combat infections before they acquire the ability to produce antibodies themselves. Passive immunization against bacterial toxins by the administration of antibodies from immunized animals is a lifesaving treatment of potentially lethal infections, such as tetanus. The technique of adoptive transfer has also made it possible to define the various cells and molecules that are responsible for mediating specific immunity. In fact, humoral immunity was originally defined as the type of immunity that could be transferred to unimmunized, or naïve, individuals by antibody-

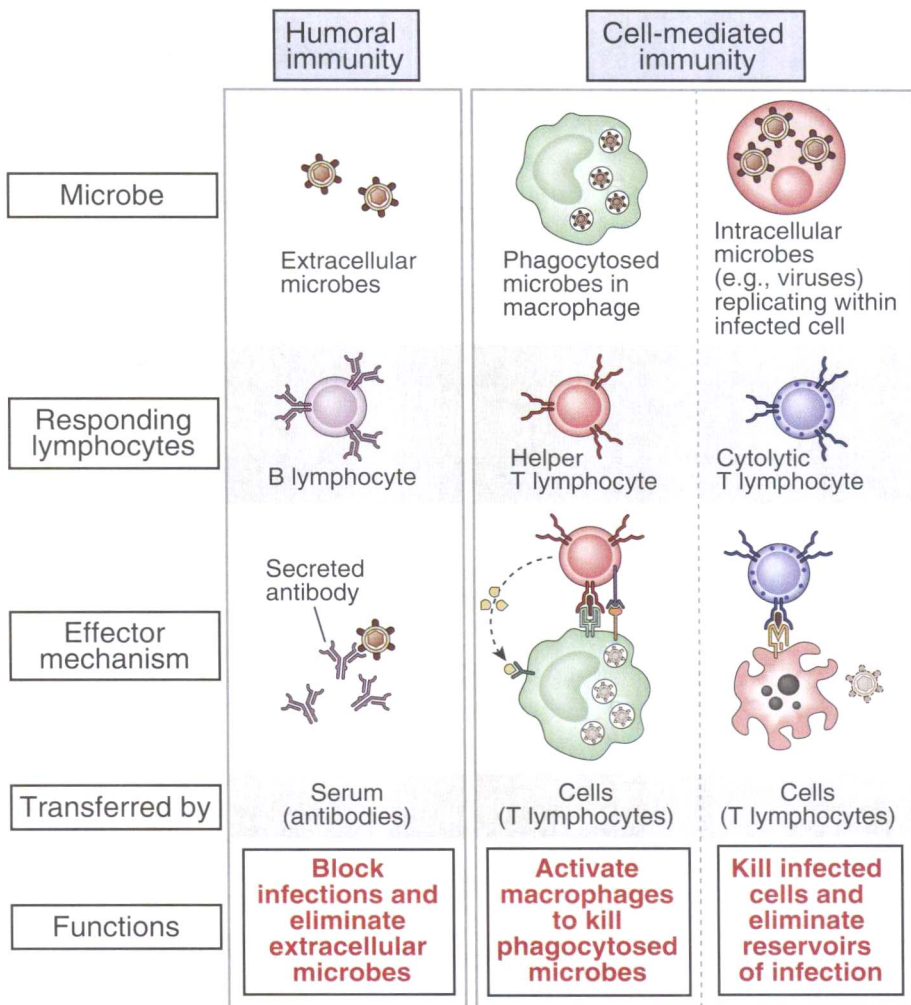


Figure 1-2 Types of adaptive immunity.

In humoral immunity, B lymphocytes secrete antibodies that prevent infections by and eliminate extracellular microbes. In cell-mediated immunity, T lymphocytes either activate macrophages to kill phagocytosed microbes or cytolytic T lymphocytes directly destroy infected cells.

containing cell-free portions of the blood (i.e., plasma or serum [once called humors]) obtained from previously immunized individuals. Similarly, cell-mediated immunity was defined as the form of immunity that can be transferred to naive individuals with cells (T lymphocytes) from immunized individuals but not with plasma or serum.

The first experimental demonstration of humoral immunity was provided by Emil von Behring and Shibasaburo Kitasato in 1890. They showed that if serum from animals who had recovered from diphtheria infection was transferred to naive animals, the recipients became specifically resistant to diphtheria infection. The active components of the serum were called antitoxins because they neutralized the pathologic effects of the diphtheria toxin. In the early 1900s, Karl Landsteiner and other investigators showed that not only toxins but also nonmicrobial substances could induce humoral immune responses. From such studies arose the more general term **antibodies** for the serum proteins that mediate humoral immunity. Substances that bound antibodies and generated the production of antibodies were then called **antigens**. (The properties

of antibodies and antigens are described in Chapter 3.) In 1900, Paul Ehrlich provided a theoretical framework for the specificity of antigen-antibody reactions, the experimental proof for which came during the next 50 years from the work of Landsteiner and others using simple chemicals as antigens. Ehrlich's theories of the physicochemical complementarity of antigens and antibodies are remarkable for their prescience. This early emphasis on antibodies led to the general acceptance of the humoral theory of immunity, according to which immunity is mediated by substances present in body fluids.

The cellular theory of immunity, which stated that host cells were the principal mediators of immunity, was championed initially by Elie Metchnikoff. His demonstration of phagocytes surrounding a thorn stuck into a translucent starfish larva, published in 1893, was perhaps the first experimental evidence that cells respond to foreign invaders. Sir Almroth Wright's observation in the early 1900s that factors in immune serum enhanced the phagocytosis of bacteria by coating the bacteria, a process known as opsonization, lent support to the belief that antibodies prepared microbes

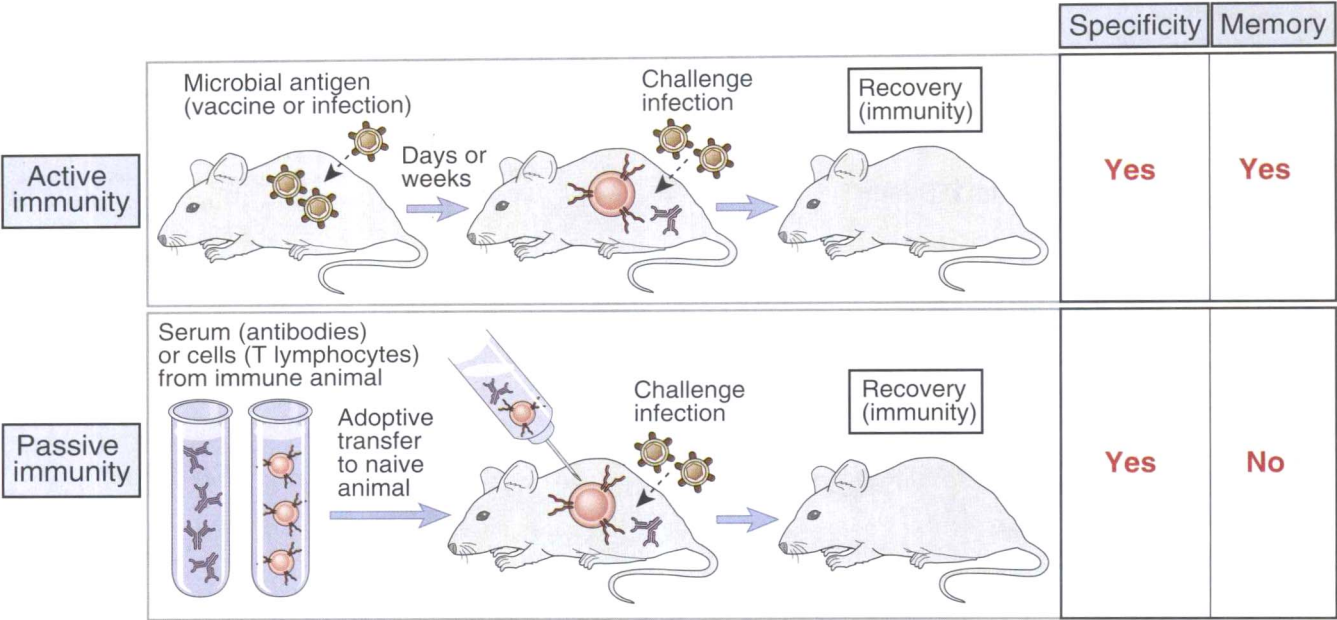


Figure 1-3 Active and passive immunity. Active immunity is conferred by a host response to a microbe or microbial antigen, whereas passive immunity is conferred by adoptive transfer of antibodies or T lymphocytes specific for the microbe. Both forms of immunity provide resistance to infection (immunity) and are specific for microbial antigens, but only active immune responses generate immunologic memory.

for ingestion by phagocytes. These early “cellularists” were unable to prove that specific immunity to microbes could be mediated by cells. The cellular theory of immunity became firmly established in the 1950s, when George Mackaness showed that resistance to an intracellular bacterium, *Listeria monocytogenes*, could be adoptively transferred with cells but not with serum. We now know that the specificity of cell-mediated immunity is due to lymphocytes, which often function in concert with other cells, such as phagocytes, to eliminate microbes.

In the clinical setting, immunity to a previously encountered microbe is measured indirectly, either by assaying for the presence of products of immune responses (such as serum antibodies specific for microbial antigens) or by administering substances purified from the microbe and measuring reactions to these substances. A reaction to a microbial antigen is detectable only in individuals who have previously encountered the antigen; these individuals are said to be “sensitized” to the antigen, and the reaction is an indication of “sensitivity.” Although the reaction to the purified antigen has no protective function, it implies that the sensitized individual is capable of mounting a protective immune response to the microbe.

Cardinal Features of Adaptive Immune Responses

All humoral and cell-mediated immune responses to foreign antigens have a number of fundamental prop-

erties that reflect the properties of the lymphocytes that mediate these responses (Table 1-3).

■ **Specificity and diversity.** Immune responses are specific for distinct antigens and, in fact, for different portions of a single complex protein, polysaccharide, or other macromolecule (Fig. 1-4). The

Table 1-3. Cardinal Features of Adaptive Immune Responses

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens
Specialization	Generates responses that are optimal for defense against different types of microbes
Self-limitation	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

The features of adaptive immune responses are essential for the functions of the immune system.