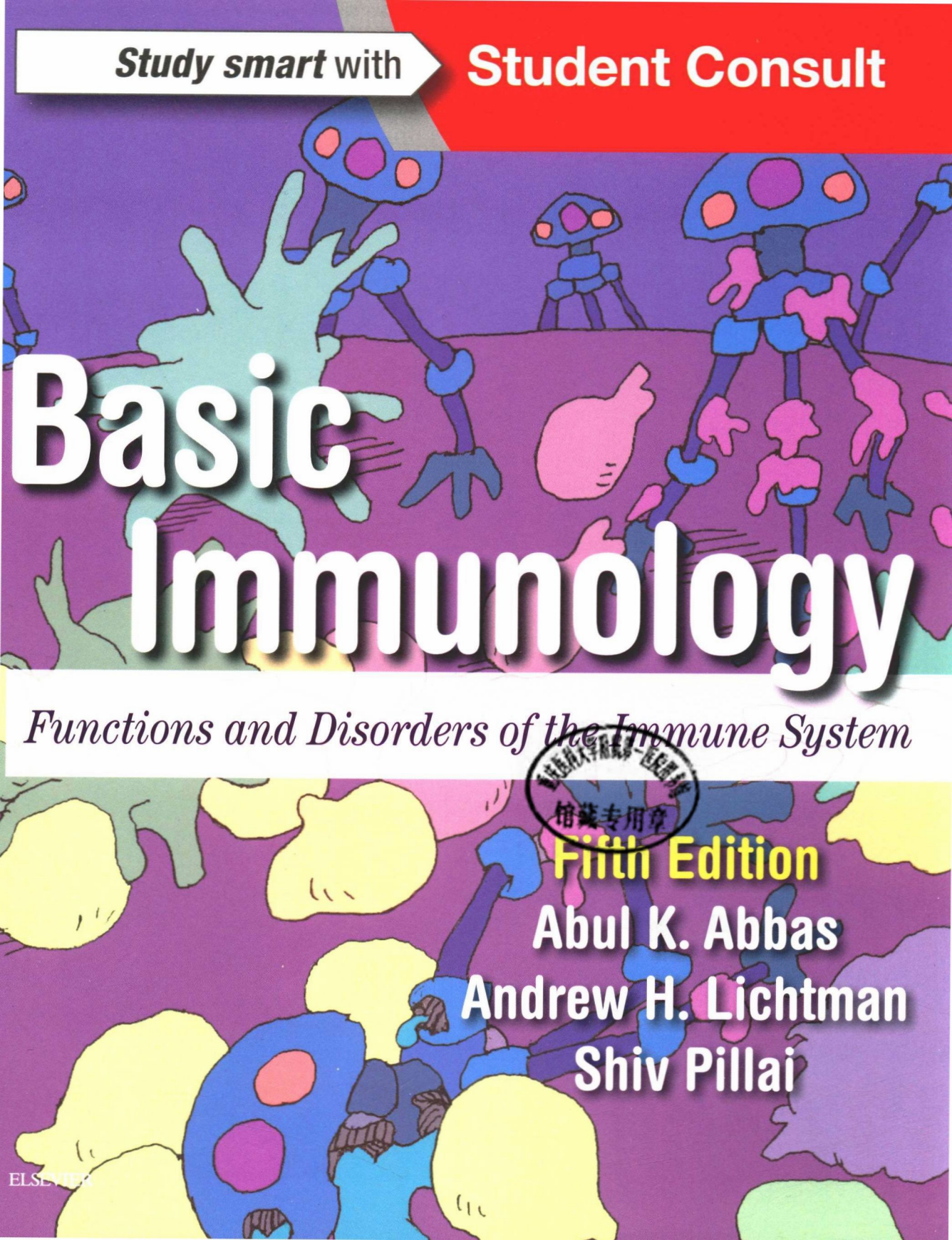
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Fifth Edition
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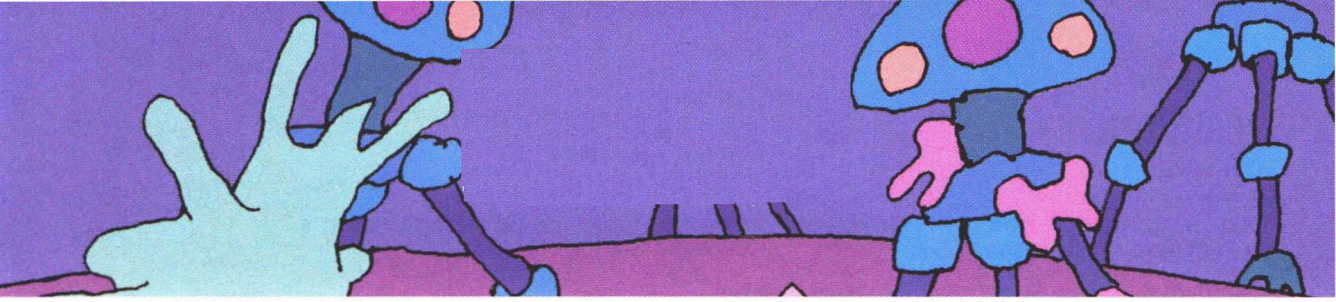

BASIC IMMUNOLOGY

Functions and Disorders of the Immune System

FIFTH EDITION

Abul K. Abbas, MBBS
Distinguished Professor in Pathology
Chair, Department of Pathology
University of California San Francisco
San Francisco, California

Andrew H. Lichtman, MD, PhD
Professor of Pathology
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Shiv Pillai, MBBS, PhD
Professor of Medicine and Health Sciences and Technology
Harvard Medical School
Ragon Institute of Massachusetts General Hospital, MIT and Harvard
Boston, Massachusetts

Illustrations by David L. Baker, MA
Alexandra Baker, MS, CMI
DNA Illustrations, Inc.

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St. Louis, Missouri 63043
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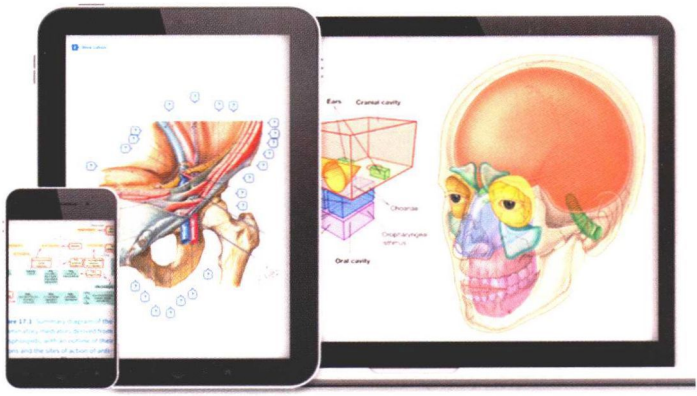

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BASIC IMMUNOLOGY

To our students

PREFACE

The fifth edition of *Basic Immunology* has been revised to include recent important advances in our understanding of the immune system and to organize and present information in order to maximize its usefulness to students and teachers. The previous editions have been enthusiastically received by students in the many courses that we and our colleagues teach, and we have not wavered from the guiding principles on which the book has been based through all the past editions. Our experience as immunology teachers and course directors has helped us to judge the amount of detailed information that can be usefully included in introductory medical school and undergraduate courses and the value of presenting the principles of immunology in a succinct and clear manner. We believe a concise and modern consideration of immunology is now a realistic goal, largely because immunology has matured as a discipline and has now reached the stage when the essential components of the immune system and how they interact in immune responses are understood quite well. As a result, we can now teach our students, with reasonable confidence, how the immune system works. In addition, we are better able to relate experimental results, using simple models, to the more complex but physiologically relevant issue of host defense against infectious pathogens. There has also been exciting progress in applying basic principles to understanding and treating human diseases.

This book has been written to address the perceived needs of both medical school and undergraduate curricula and to take advantage of the new understanding of immunology. We have tried to achieve several goals. First, we have presented the most important principles governing the function of the immune system by synthesizing key concepts from the vast amount of experimental data that emerge in the field of immunology. The choice of what is most important is based largely on what is most clearly established by scientific investigation and what has the most relevance to human health and disease. We also have realized that in any concise discussion of complex phenomena it is inevitable that exceptions and caveats cannot be discussed in any detail. Second, we have focused on immune responses against infectious microbes, and most of our discussions of the immune system are in this context. Third, we have made liberal use of illustrations to highlight important principles, but we have reduced factual details that may be found in more comprehensive textbooks. Fourth, we have also discussed immunologic diseases from the perspective of principles, emphasizing their relation to normal immune responses and avoiding details of clinical syndromes and treatments. We have included selected clinical cases in an appendix to illustrate how the principles of immunology may be applied to common human diseases. Finally, in order to make each chapter readable on its own, we have repeated key ideas in different places in the book. We feel such repetition will help students to grasp the most important concepts.

We hope that students will find this new edition of *Basic Immunology* clear, cogent, manageable, and enjoyable to read. We hope the book will convey our sense of wonder about the immune system and excitement about how the field has evolved and how it continues to grow in relevance to human health and disease. Finally, although we were spurred to tackle this project because of our associations with medical school courses, we hope the book will be valued by students of allied health and biology as well. We will have succeeded if the book can answer many of the questions these students have about the immune system and, at the same time, encourage them to delve even more deeply into immunology.

Several individuals played key roles in the writing of this book. Our new editor, James Merritt,

has been an enthusiastic source of encouragement and advice. Our talented illustrators, David and Alexandra Baker of DNA Illustrations, have revamped all of the artwork for this new edition and have transformed our ideas into pictures that are informative and aesthetically pleasing. Clay Broeker has moved the book through the production process in an efficient and professional manner. Our development editor, Rebecca Gruliow, has kept the project organized and on track despite pressures of time and logistics. To all of them we owe our many thanks. Finally, we owe an enormous debt of gratitude to our families, whose support and encouragement have been unwavering.

Abul K. Abbas
Andrew H. Lichtman
Shiv Pillai

BASIC IMMUNOLOGY

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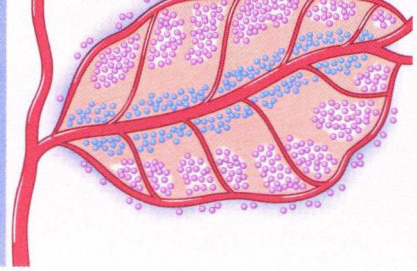

CHAPTER 1

Introduction to the Immune System

Nomenclature, General Properties, and Components

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Immunity is defined as resistance to disease, specifically infectious disease. The collection of cells, tissues, and molecules that mediate resistance to infections is called the **immune system,** and the coordinated reaction of these cells and molecules to infectious microbes comprises an **immune response. Immunology** is the study of the immune system, including its responses to microbial pathogens and damaged tissues and its role in disease.

The most important physiologic function of the immune system is to prevent or eradicate infections (Fig. 1-1), and this is the principal context in which immune responses are discussed throughout this book. The importance of the immune system for health is dramatically illustrated by the frequent observation that individuals with defective immune responses are susceptible to serious, often life-threatening infections. Conversely, stimulating immune responses against microbes through vaccination is the most effective method for protecting individuals against infections; this approach has led to the worldwide eradication of smallpox, the only disease that has been eliminated from civilization by human intervention (Fig. 1-2). Unfortunately, interruptions of vaccination programs in developing countries and in regions of social conflict have led to local reemergence of some infectious diseases, such as polio, that have been largely eliminated from other parts of the world. The appearance of acquired immunodeficiency syndrome (AIDS) in the 1980s tragically emphasized the importance of the immune system for defending individuals against infection. The immune system does more than provide

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 can injure cells and induce pathologic inflammation	Immune responses are the cause of allergic, autoimmune, and other inflammatory diseases
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy

FIGURE 1-1 Importance of the immune system in health and disease. This table summarizes some of the physiologic functions of the immune system and its role in disease. *AIDS*, Acquired immunodeficiency syndrome.

protection against infections (see Fig. 1-1). It prevents the growth of some tumors, and some cancers can be treated by stimulating immune responses against tumor cells. Immune responses also participate in the clearance of dead cells and in initiating tissue repair.

In contrast to these beneficial roles, abnormal immune responses cause many inflammatory diseases with serious morbidity and mortality. The immune response is the major barrier to the success of organ transplantation, which is often used to treat organ failure. The products of immune cells can also be of great practical use. For example, antibodies, which are proteins made by certain cells of the immune system, are used in clinical laboratory testing and in research as highly specific reagents for detecting a wide variety of molecules in the circulation and in cells and tissues. Antibodies designed to block or eliminate potentially harmful molecules and cells are used widely for the treatment of immunologic diseases, cancers, and other types of disorders. For all these reasons, the field of immunology has captured the attention of clinicians, scientists, and the lay public.

This chapter introduces the nomenclature of immunology, important general properties of all immune responses, and the cells and tissues that are the principal components of the immune system. In particular, the following questions are addressed:

- What types of immune responses protect individuals from infections?
- What are the important characteristics of immunity, and what mechanisms are responsible for these characteristics?
- How are the cells and tissues of the immune system organized to find and respond to microbes in ways that lead to their elimination?

We conclude the chapter with a brief overview of immune responses against microbes. The basic principles introduced here set the stage for more detailed discussions of immune responses in later chapters. A glossary of the important terms used in this book is provided in Appendix I.

Disease	Maximum number of cases (year)	Number of cases in 2014	Percent change
Diphtheria	206,939 (1921)	0	–100
Measles	894,134 (1941)	669	–99.93
Mumps	152,209 (1968)	737	–99.51
Pertussis	265,269 (1934)	10,631	–95.99
Polio (paralytic)	21,269 (1952)	0	–100
Rubella	57,686 (1969)	2	–99.99
Tetanus	1560 (1923)	8	–99.48
Hemophilus influenza type B	~20,000 (1984)	34	–99.83
Hepatitis B	26,611 (1985)	1,098	–95.87

FIGURE 1-2 Effectiveness of vaccination for some common infectious diseases. The striking decrease in the incidence of selected infectious diseases in the United States for which effective vaccines have been developed. (Modified from Orenstein WA, Hinman AR, Bart KJ, Hadler SC: Immunization. In Mandell GL, Bennett JE, Dolin R, editors: *Principles and practices of infectious diseases,* 4th edition, New York, 1995, Churchill Livingstone; and *MMWR* 64, No. 20, 2015.)

INNATE AND ADAPTIVE IMMUNITY

Host defenses are grouped under innate immunity, which provides immediate protection against microbial invasion, and adaptive immunity, which develops more slowly and provides more specialized defense against infections (Fig. 1-3). Innate immunity, also called natural immunity or native immunity, is always present in healthy individuals (hence the term *innate*), prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues. 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 response evolved later.

In innate immunity, the first line of defense is provided by epithelial barriers of the skin and mucosal tissues and by cells and natural antibiotics present in epithelia, all of which function to block the entry of microbes. If microbes do breach epithelia and enter the tissues or circulation, they are attacked by phagocytes, specialized lymphocytes called innate lymphoid cells, which include natural killer cells, and several plasma proteins, including the proteins of the complement system. All these mechanisms of innate immunity specifically recognize and react against microbes. In addition to providing early defense against infections, innate immune responses enhance adaptive immune responses against the infectious agents. The components and mechanisms of innate immunity are discussed in detail in Chapter 2.

The adaptive immune system consists of lymphocytes and their products, such as antibodies. Adaptive immune responses are especially important for defense against

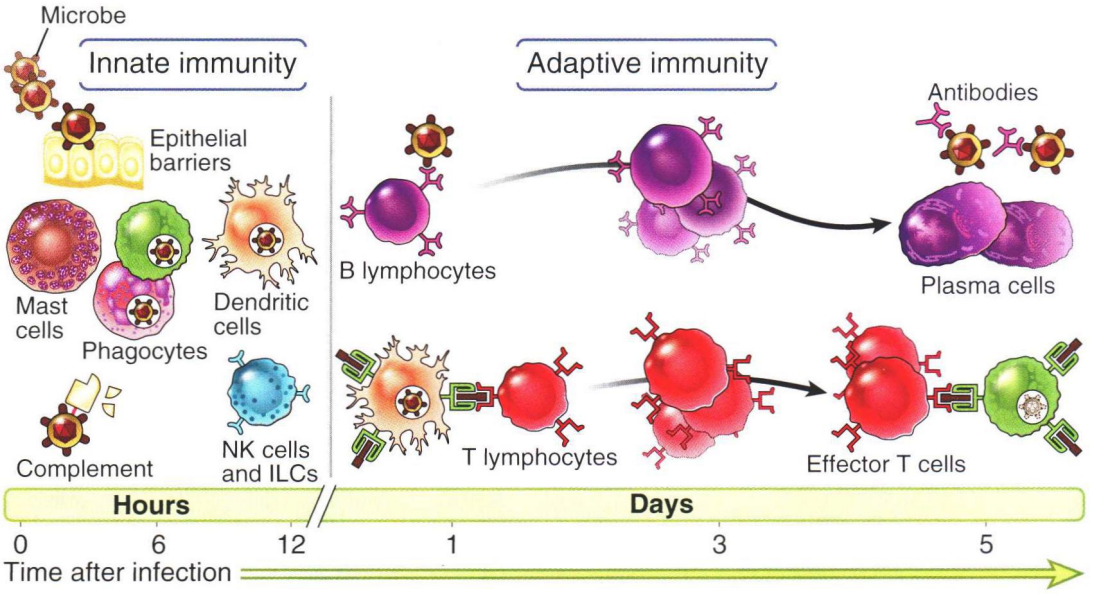

FIGURE 1-3 Principal mechanisms of innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Some mechanisms (e.g., epithelial barriers) prevent infections, and other mechanisms (e.g., phagocytes, natural killer [NK] cells and other innate lymphoid cells [ILCs], the complement system) eliminate microbes. Adaptive immune responses develop later and are mediated by lymphocytes and their products. Antibodies block infections and eliminate microbes, and T lymphocytes eradicate intracellular microbes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

infectious microbes that are pathogenic for humans (i.e., capable of causing disease) and may have evolved to resist innate immunity. Whereas the mechanisms of innate immunity recognize structures shared by classes of microbes, the cells of adaptive immunity (lymphocytes) express receptors that specifically recognize a much wider variety of molecules produced by microbes as well as noninfectious substances. Any substance that is specifically recognized by lymphocytes or antibodies is called an **antigen.** Adaptive immune responses often use the cells and molecules of the innate immune system to eliminate microbes, and adaptive immunity functions to greatly enhance these antimicrobial mechanisms of innate immunity. For example, antibodies (a component of adaptive immunity) bind to microbes, and these coated microbes avidly bind to and activate phagocytes (a component of innate immunity), which ingest and destroy the microbes. Examples of the cooperation between innate and adaptive immunity are discussed in later chapters.

By convention, the terms *immune response* and *immune system* generally refer to adaptive immunity, and that is the focus of most of this chapter.

TYPES OF ADAPTIVE IMMUNITY

The two types of adaptive immunity, called humoral immunity and cell-mediated immunity, are mediated by different cells and molecules and provide defense against extracellular microbes and intracellular microbes, respectively (Fig. 1-4).

- **Humoral immunity** is mediated by proteins called **antibodies,** which are produced by cells called **B lymphocytes**. Secreted antibodies enter the circulation and mucosal fluids, and they neutralize and eliminate microbes and microbial toxins that are present outside host cells, in the blood, extracellular fluid derived

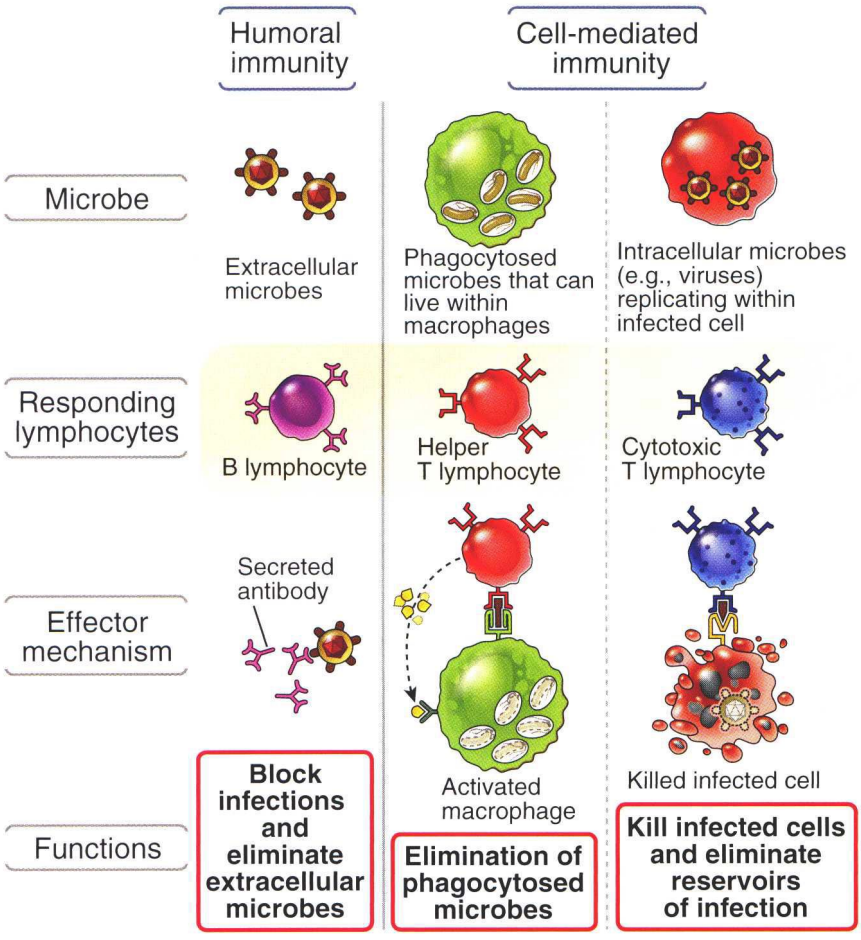

FIGURE 1-4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, different types of T lymphocytes recruit and activate phagocytes to destroy ingested microbes and kill infected cells.

from plasma, and in the lumens of mucosal organs such as the gastrointestinal and respiratory tracts. One of the most important functions of antibodies is to stop microbes that are present at mucosal surfaces and in the blood from gaining access to and colonizing host cells and connective tissues. In this way, antibodies prevent infections from ever being established. Antibodies cannot gain access to microbes that live and divide inside infected cells.

- Defense against such intracellular microbes is called **cell-mediated immunity** because it is mediated by cells, which are called **T lymphocytes**. Some T lymphocytes activate phagocytes to destroy microbes that have been ingested by the phagocytes into intracellular vesicles. Other T lymphocytes kill any type of host cells that are harboring infectious microbes in the cytoplasm. In both cases, the T cells recognize microbial antigens that are displayed on host cell surfaces, which indicates there is a microbe inside the cell.

The specificities of B and T lymphocytes differ in important respects. Most T cells recognize only protein antigens, whereas B cells and antibodies are able to recognize many different types of molecules, including proteins, carbohydrates, nucleic acids, and lipids. These and other differences are discussed in more detail later.

Immunity may be induced in an individual by infection or vaccination (active immunity) or conferred on an individual by transfer of antibodies or lymphocytes from an actively immunized individual (passive immunity).

- In **active immunity,** an individual exposed to the antigens of a microbe mounts an active response to eradicate the infection and develops resistance to later infection by that microbe. Such an individual is said to be immune to that microbe, in contrast with a naive individual, not previously exposed to that microbe's antigens.
- In **passive immunity,** a naive individual receives antibodies or cells (e.g., lymphocytes, feasible only in animal experiments) from another individual already immune to an infection. The recipient acquires the ability to combat the infection for as long as the transferred antibodies or cells last. Passive immunity is therefore useful for rapidly conferring immunity even before the individual is able to mount an active response, but it does not induce long-lived resistance to the infection. The only physiologic example of passive immunity is seen in newborns, whose immune systems are not mature enough to respond to many pathogens but who are protected against infections by acquiring antibodies from their mothers through the placenta and breast milk. Clinically, passive immunity is limited to treatment of some immunodeficiency diseases with antibodies pooled from multiple donors, and for emergency treatment of some viral infections and snakebites using serum from immunized donors.

PROPERTIES OF ADAPTIVE IMMUNE RESPONSES

Several properties of adaptive immune responses are crucial for the effectiveness of these responses in combating infections (Fig. 1-5).

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
Clonal expansion	Increases number of antigen-specific lymphocytes from a small number of naive lymphocytes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

FIGURE 1-5 Properties of adaptive immune responses. This table summarizes the important properties of adaptive immune responses and how each feature contributes to host defense against microbes.

Specificity and Diversity

The adaptive immune system is capable of distinguishing among millions of different antigens or portions of antigens. Specificity is the ability to distinguish between many different antigens. It implies that the total collection of lymphocyte specificities, sometimes called the **lymphocyte repertoire,** is extremely **diverse.** The basis for this remarkable specificity and diversity is that lymphocytes express clonally distributed receptors for antigens, meaning that the total population of lymphocytes consists of many different clones (each made up of one cell and its progeny), and each clone expresses an antigen receptor that is different from the receptors of all other clones. The **clonal selection hypothesis,** formulated in the 1950s, correctly predicted that clones of lymphocytes specific for different antigens develop before an encounter with these antigens, and each antigen elicits an immune response by selecting and activating the lymphocytes of a specific clone (Fig. 1-6). We now