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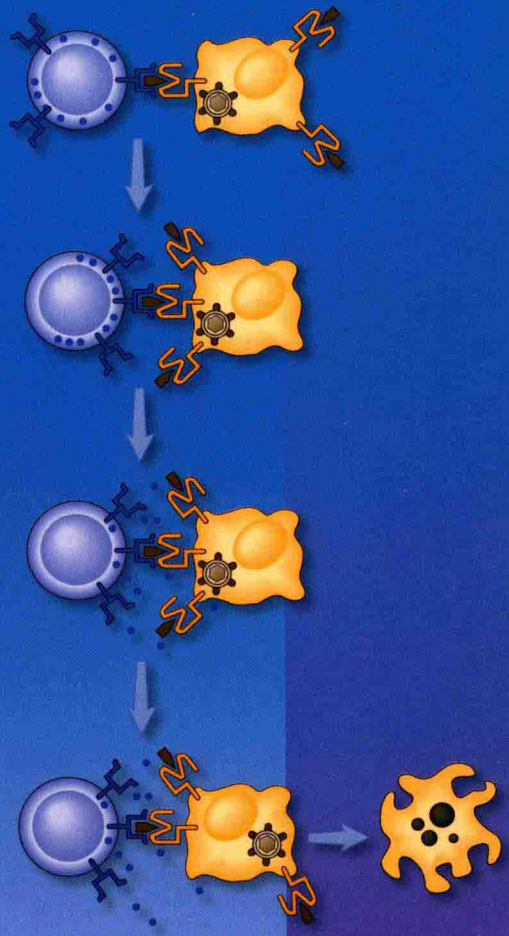

SECOND EDITION

Basic Immunology

Functions and Disorders of the Immune System

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BASIC IMMUNOLOGY

Functions and Disorders of the Immune System

Second Edition

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BASIC IMMUNOLOGY

To
Ann, Jonathan, Rehana
Sheila, Eben, Ariella, Amos, Ezra

Preface

The second edition of *Basic Immunology* has been revised to reflect new advances in our understanding of the immune system and to improve on the presentation of information in ways most useful to students and teachers. We have been extremely gratified by how well the first edition of *Basic Immunology* has been received by students in the courses that we teach, and the guiding principles on which the book is based have not changed from the first edition. As teachers of immunology, we are becoming increasingly aware that assimilating detailed information and experimental approaches is difficult in many medical school and undergraduate courses. The problem of how much detail is appropriate has become a pressing one because of the continuous and rapid increase in the amount of information in all the biomedical sciences. This problem is compounded by the development of integrated curricula in many medical schools, with reduced time for didactic teaching and an increasing emphasis on social and behavioral sciences and primary health care. For all these reasons, we have realized the value for many medical students of presenting the principles of immunology in a concise and clear manner.

It is our view that several developments have come together to make the goal of a concise and modern consideration of immunology a realistic one. Most important, immunology has matured as a discipline, so that it has now reached the stage when the essential components of the immune system, and how they interact in immune responses, are understood quite well. There are, of course, many details to be filled in, and the longstanding challenge of applying basic principles to human diseases remains a difficult task. Nevertheless, we can now teach our students, with reasonable confidence, how the immune system works. The second important development has been an increasing emphasis on the roots of immunology, which lie in its role in defense against infections. As a result, 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.

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. Our fundamental objective has been to synthesize the key concepts from the vast amount of experimental data that emerge in the rapidly advancing field of immunology. The choice of what is most important is based largely on what is most clearly established by experimentation, what our students find puzzling, and what explains the wonderful efficiency and economy of the immune system. Inevitably, however, such a choice will have an element of bias, and our bias is toward emphasizing the cellular interactions in immune responses and limiting the description of many of the underlying biochemical and molecular mechanisms to the essential facts. Second, we have focused on immune responses against infectious microbes, and all our discussions of the immune system are in this context. Third, we have emphasized immune responses in humans (rather than experimental animals), drawing on parallels with experimental situations whenever

necessary. Fourth, we have made liberal use of illustrations to highlight important principles but have reduced factual details that may be found in more comprehensive textbooks. Fifth, we have discussed immunologic diseases also from the perspective of principles, emphasizing their relation to normal immune responses and avoiding details of clinical syndromes and treatments. We have added selected clinical cases in the Appendix, to illustrate how the concepts of immunology may be applied to common human diseases. Finally, we have realized that in any concise discussion of complex phenomena, it is inevitable that exceptions and caveats will fall by the wayside. We have avoided exceptions and caveats without hesitation, but with a willingness to modify our conclusions as new information continues to emerge.

It is our hope that students will find this book clear, cogent, and manageable. Most important, 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 be relevant 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 more widely 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.

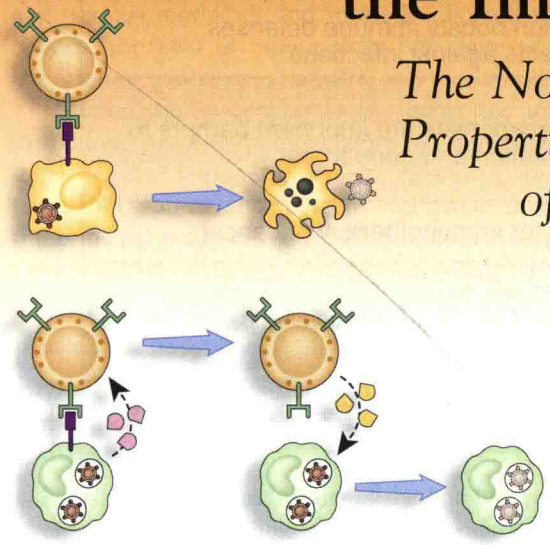
Several individuals played key roles in the writing of this book. Our editor, Jason Malley, has been a skilled and helpful colleague throughout. We have been fortunate to again work with David and Alexandra Baker of DNA Illustrations, who have translated ideas into pictures that are informative and aesthetically pleasing. Our project manager, Linda Grigg, kept the project organized and on track despite pressures of time and logistics. To all of them we owe our many thanks.

Abul K. Abbas
Andrew H. Lichtman

Contents

1 Introduction to the Immune System

The Nomenclature, General Properties, and Components of the Immune System



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 is the *immune response*. Immunology is the study of the immune system and its responses to invading pathogens. **The physiologic function of the immune system is to prevent infections and to eradicate established infections,** 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 (Fig. 1-1). Conversely, stimulating immune responses against microbes by the process of vaccination is the most effective method for protecting individuals against infections and is, for example, the approach that has led to the worldwide eradication of smallpox (Fig. 1-2). The emergence of the acquired immunodeficiency syndrome (AIDS) since the 1980s has tragically emphasized the importance of the immune system for defending individuals against infections. But the impact of immunology goes beyond infectious disease (see Fig. 1-1). The immune response is the major barrier to successful organ transplantation, an increasingly used therapy for organ

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
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are important barriers to transplantation and gene therapy
Defense against tumors	Potential for immunotherapy of cancer
Antibodies are highly specific reagents for detecting any class of molecules	Immunologic approaches for laboratory testing are widely used in clinical medicine and research

Figure 1–1 The importance of the immune system. Some of the functions and features of the immune system, and their importance in health and disease, are summarized.

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
Haemophilus influenzae type B	~20,000 (1984)	1,212	-93.14
Hepatitis B	26,611 (1985)	6,646	-75.03

Figure 1–2 The effectiveness of vaccination for some common infectious diseases. There is a 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 and the incidence of the disease is continuing to decrease. (Adapted from Orenstein WA, AR Hinman, KJ Bart, and SC Hadler. Immunization. *In* GL Mandell, JE Bennett, and R Dolin [eds]. Principles and Practices of Infectious Diseases, 4th ed. Churchill Livingstone, New York, 1995, and Morbidity and Mortality Weekly Reports, Centers for Disease Control 49:1159-1201, 2001.)

failure. Attempts to treat cancers by stimulating immune responses against cancer cells are being tried for many human malignancies. Furthermore, abnormal immune responses are the causes of many diseases with serious morbidity and mortality. For all these reasons, the field of immunology has captured the attention of clinicians, scientists, and the lay public.

In this opening chapter of the book, the topics introduced are the nomenclature of immunology, some of the 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 so they are able to find microbes and respond to them in ways that lead to their elimination?

Basic principles are introduced in this chapter that set the stage for much more detailed discussions of immune responses in the remainder of this book.

Innate and Adaptive Immunity

Host defense mechanisms consist of innate immunity, which mediates the initial protection against infections, and adaptive immunity, which develops more slowly and mediates the later, even more effective, defense against infections (Fig. 1-3). The term *innate immunity* (also called natural or native immunity) refers to the fact that this type of host defense is always present in healthy individuals, prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues. *Adaptive immunity* (also called specific or acquired immunity) is the type of host defense that is stimulated by microbes that invade tissues, that is, it adapts to the presence of microbial invaders.

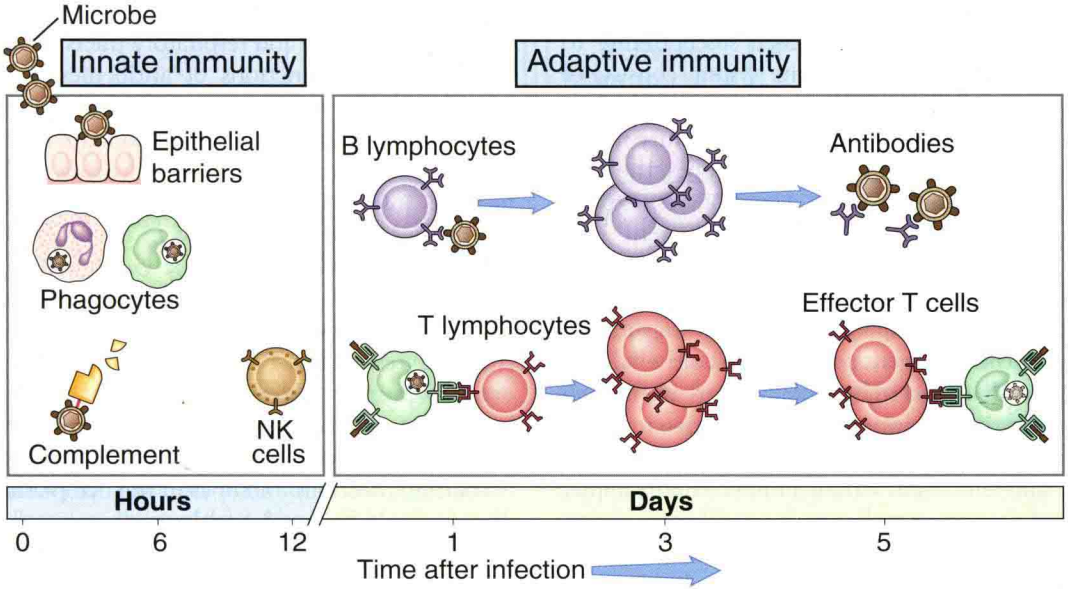


Figure 1–3 The principal mechanisms of innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Some of the mechanisms prevent infections (e.g., epithelial barriers) and others eliminate microbes (e.g., phagocytes, NK cells, and the complement system). 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.

The first line of defense in innate immunity is provided by epithelial barriers and by specialized 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 natural killer (NK) cells, and several plasma proteins, including the proteins of the complement system. All these mechanisms of innate immunity specifically recognize and react against microbes but do not react against noninfectious foreign substances. Different mechanisms of innate immunity may be specific for molecules produced by different classes of 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.

Although innate immunity can effectively combat many infections, microbes that are pathogenic for humans (i.e., capable of causing disease) have evolved to resist innate immunity. Defense against these infectious agents is the task of the adaptive immune response, and this is why defects in the adaptive immune system result in increased susceptibility to infections. The adaptive immune system consists of lymphocytes and their products, such as antibodies. Whereas the mechanisms of innate immunity recognize structures shared by classes of microbes, the cells of adaptive immunity, namely, lymphocytes, express receptors that specifically recognize different substances produced by microbes as well as noninfectious molecules. These substances are called **antigens.** Adaptive immune responses are only triggered if microbes or their antigens pass through epithelial barriers and are delivered to lymphoid organs where they can be recognized by lymphocytes. Adaptive immune responses generate mechanisms that are specialized to combat different types of infections. For example, antibodies function to eliminate microbes in extracellular fluids, and activated T lymphocytes eliminate microbes living inside cells. These specialized mechanisms of adaptive immunity are described throughout the book. 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 instance, 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. There are many similar examples of the cooperation between innate and adaptive immunity that are referred to in later chapters. By convention the terms *immune system* and *immune response* refer to adaptive immunity, unless stated otherwise.

Types of Adaptive Immunity

There are two types of adaptive immunity, called *humoral immunity* and *cell-mediated immunity*, that are mediated by different cells and molecules and are designed to 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.** Antibodies are secreted into the circulation and mucosal fluids, and they neutralize and eliminate microbes and microbial toxins that are present in the blood 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 getting established. Antibodies do not have 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 called **T lymphocytes.** Some T lymphocytes activate phagocytes to destroy microbes that have been ingested by the phagocytes into phagocytic vesicles. Other T lymphocytes kill any type of host cells that are harboring infectious microbes in the cytoplasm. As is discussed in Chapter 3 and later chapters, the antibodies produced by B lymphocytes are designed to specifically recognize extracellular microbial antigens, whereas T lymphocytes recognize antigens produced by intracellular microbes. Another important difference between B and T lymphocytes is that most T cells recognize only microbial protein antigens, whereas antibodies are able to recognize many different types of

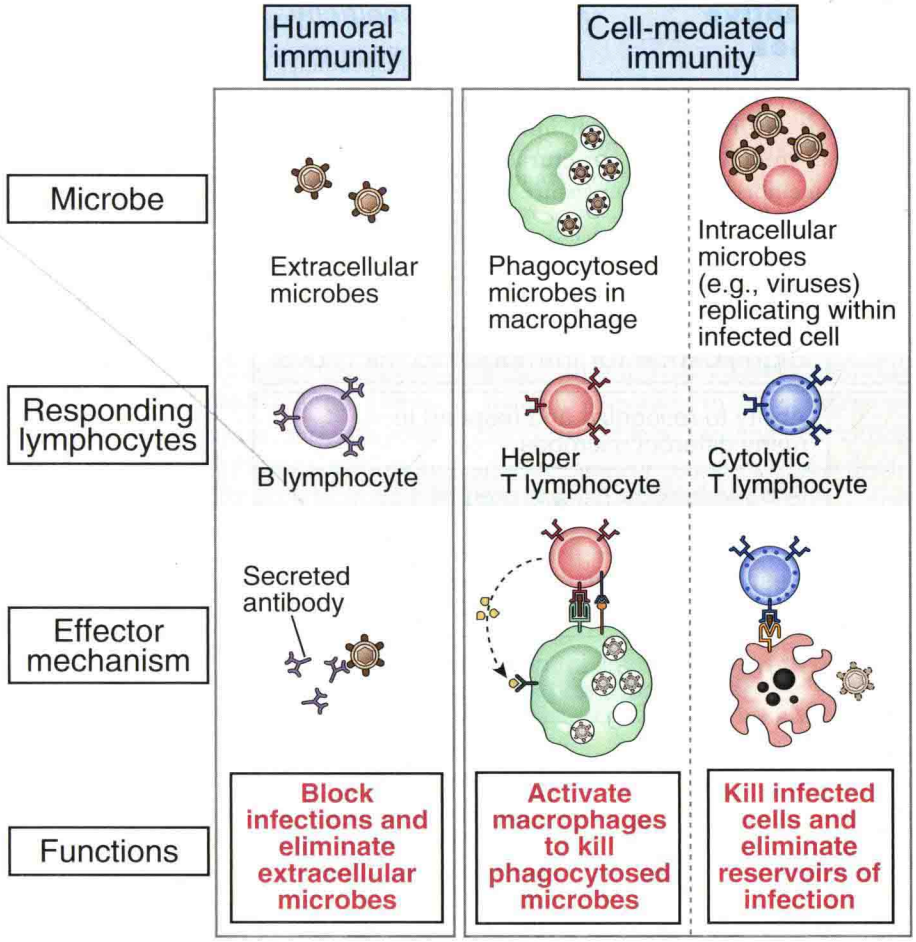


Figure 1–4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected cells.

microbial molecules, including proteins, carbohydrates, and lipids.

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). An individual who is 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 to a "naive" individual who has not previously encountered that microbe's antigens. We will be concerned mainly with the mechanisms of active immunity. In passive immunity, a naive individual receives cells (e.g., lymphocytes) or molecules (e.g., antibodies) from another individual who is immune to an infection; for the limited lifetime of the transferred antibodies or cells, the recipient is able to combat the infection. 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. An excellent 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 milk.

Properties of Adaptive Immune Responses

The most important properties of adaptive immunity, and the ones that distinguish it from innate immunity, are a fine specificity for structurally distinct antigens and memory of prior exposure to antigen (Fig. 1-5).

Specificity

The specificity of immune responses is illustrated by the observation that prior exposure to an antigen results in heightened responses to subsequent challenge with that antigen but not to challenge with other, even quite similar antigens (Fig. 1-6). The immune system has the potential for distinguishing

Property	Significance for immunity to microbes
Specificity	Ability to recognize and respond to many different microbes
Memory	Enhanced responses to recurrent or persistent infections
Specialization	Responses to distinct microbes are optimized for defense against these microbes
Nonreactivity to self antigens	Prevents injurious immune responses against host cells and tissues

Figure 1–5 Properties of adaptive immune responses. The important properties of adaptive immune responses, and how each feature contributes to host defense against microbes, are summarized.

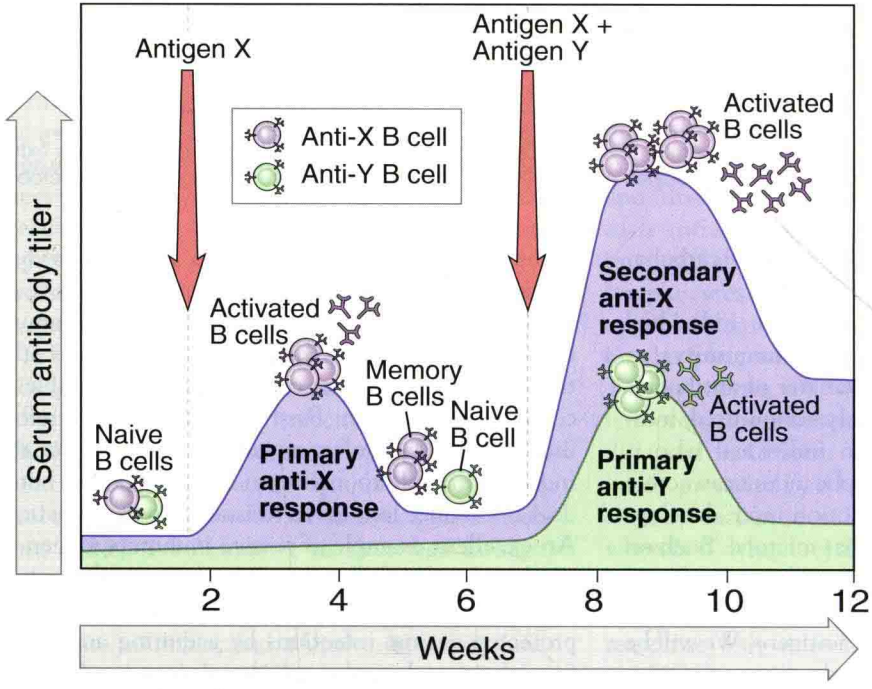


Figure 1–6 Specificity and memory in adaptive immunity, illustrated by primary and secondary immune responses. Antigens X and Y induce the production of different antibodies (specificity). The secondary response to antigen X is more rapid and larger than the primary response (memory) and is different from the primary response to antigen Y (again reflecting specificity). Antibody levels decline with time after each immunization.

among at least a billion different antigens or portions of antigens. Specificity for many different antigens implies that the total collection of lymphocyte specificities, sometimes called the lymphocyte repertoire, is extremely diverse. The basis of 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 of which is 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 arise before encounter with these antigens, and each antigen elicits an immune response by selecting and activating the lymphocytes of a specific clone (Fig. 1-7). We now know how the specificity and diversity of lymphocytes are generated (see Chapter 4).

Memory

The immune system mounts larger and more effective responses to repeated exposures to the same antigen. The response to the first exposure to antigen, called the **primary immune response,** is mediated by lymphocytes, called **naive lymphocytes,** that are seeing antigen for the first time. The term *naive lymphocyte* refers to the fact that these cells are immunologically inexperienced, not having previously recognized and responded to antigens. Subsequent encounters with the same antigen lead to responses, called **secondary immune responses,** that are usually more rapid, larger, and better able to eliminate the antigen than are the primary responses (see Fig. 1-6). Secondary responses are the result of the activation of **memory lymphocytes,** which are long-lived cells that were induced during the primary immune response. Immunologic memory optimizes the ability of the immune system to

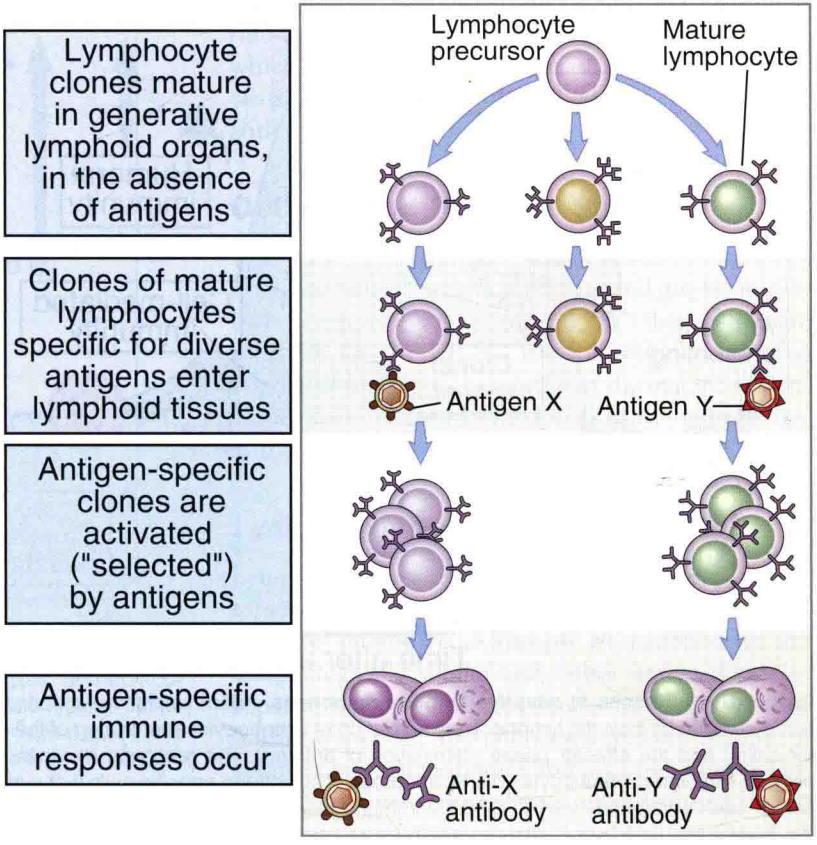


Figure 1–7 The clonal selection hypothesis. Mature lymphocytes with receptors for many antigens develop before encounter with these antigens. Each antigen (e.g., the examples X and Y) selects a preexisting clone of specific lymphocytes and stimulates the proliferation and differentiation of that clone. The diagram shows only B lymphocytes giving rise to antibody-secreting effector cells, but the same principle applies to T lymphocytes. The antigens shown are surface molecules of microbes, but the clonal selection hypothesis is also true for soluble antigens.

combat persistent and recurrent infections, because each encounter with a microbe generates more memory cells and activates previously generated memory cells. Memory is also one of the reasons why vaccines confer long-lasting protection against infections.

Immune responses have other characteristics that are important for their functions (see Fig. 1-5). Immune responses are specialized, and different responses are designed to best defend against different classes of microbes. The immune system is able to react against an enormous number and variety of microbes and other foreign antigens, but it normally does not react against the host's own potentially antigenic substances, so-called self antigens. All immune responses are self-limited and decline as the infection is eliminated, allowing the system to return to a resting state, prepared to respond to another infection. Much of the science of immunology is devoted to understanding the mechanisms underlying these characteristics of adaptive immune responses.

Phases of Immune Responses

Immune responses consist of sequential phases: antigen recognition, activation of lymphocytes, elimination of antigen, decline, and memory (Fig. 1-8). Each phase corresponds to particular reactions

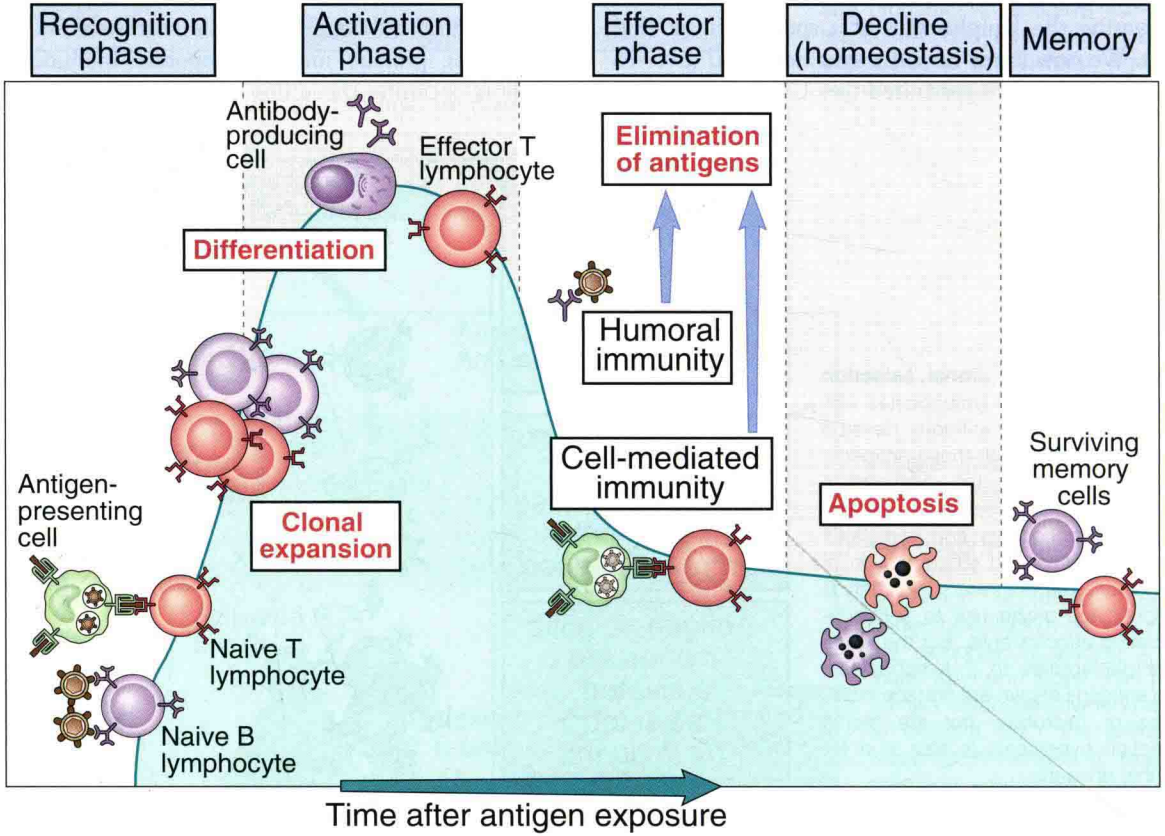


Figure 1–8 Phases of adaptive immune responses. Adaptive immune responses consist of sequential phases: recognition of antigen by specific lymphocytes, activation of lymphocytes (consisting of their proliferation and differentiation into effector cells), and the effector phase (elimination of antigen). The response declines as antigen is eliminated and most of the antigen-stimulated lymphocytes die by apoptosis. The antigen-specific cells that survive are responsible for memory. The duration of each phase may vary in different immune responses. The y-axis represents an arbitrary measure of the magnitude of the response. These principles apply to humoral immunity (mediated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes).