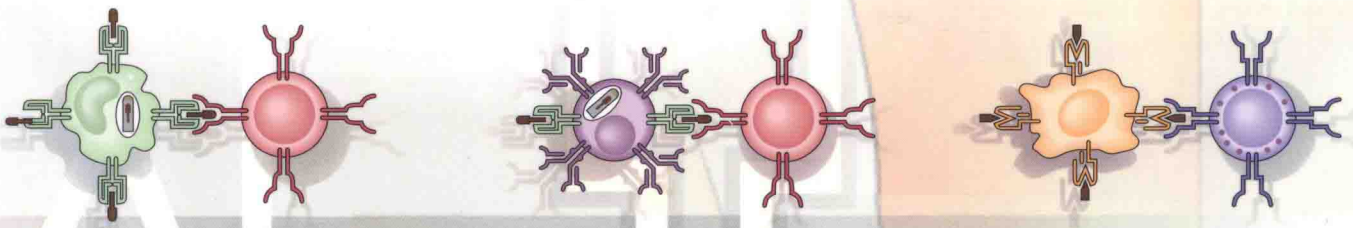
Cellular and Molecular Immunology

FOURTH EDITION



ABUL K. ABBAS

ANDREW H. LICHTMAN

JORDAN S. POBER

FOURTH EDITION

CELLULAR AND MOLECULAR IMMUNOLOGY

Abul K. Abbas, MBBS

Professor and Chair
Department of Pathology
University of California–San Francisco School of Medicine
San Francisco, California

Andrew H. Lichtman, MD, PhD

Associate Professor of Pathology
Harvard Medical School
Brigham and Women's Hospital
Boston, Massachusetts

Jordan S. Pober, MD, PhD

Professor of Pathology, Immunobiology, and Dermatology
Yale University School of Medicine
New Haven, Connecticut

W.B. SAUNDERS COMPANY

A Harcourt Health Sciences Company
Philadelphia London New York St. Louis Sydney Toronto

W.B. SAUNDERS COMPANY
A Harcourt Health Sciences Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Abbas, Abul K.
Cellular and molecular immunology / Abul K. Abbas, Andrew H. Lichtman, Jordan S. Pober.—4th ed.

p. cm.

Includes bibliographical references and index.

ISBN 0-7216-8233-2

I. Lichtman, Andrew H. II. Pober, Jordan S. III. Title.
[DNLM: 1. Cellular immunity. 2. Molecular immunology. 3. Immunity, Cellular. 4. Antigens—immunology. 5. Lymphocytes—immunology. QW 568 A122c 2000]

QR185.5.A23 2000 616.07'9—dc21

DNLM/DLC 99-33582

Acquisitions Editor: William Schmitt
Senior Developmental Editor: Hazel N. Hacker
Manuscript Editor: Jennifer Ehlers
Senior Production Manager: Linda R. Garber
Illustration Specialist: Rita Martello
Book Designer: Kevin O'Malley

CELLULAR AND MOLECULAR IMMUNOLOGY ISBN 0-7216-8233-2

Printed in the United States of America

Last digit is the print number: 9 8 7 6 5 4 3 2 1

CELLULAR AND MOLECULAR IMMUNOLOGY

TO
Ann, Jonathan, Rehana
Sheila, Eben, Ariella, Amos, Ezra
Barbara, Jeremy, Jonathan

Preface

The fourth edition of this book has been extensively rewritten to achieve several goals. The science of immunology continues to make remarkable advances, and with each passing year we understand more and more about the functioning of the normal immune system. In the 3 years since the last edition of this book, we have gained extensive new knowledge in several areas of the field, including the anatomic organization of the immune system, the mechanisms of antigen capture and transport to sites of immune responses, the molecular basis of antigen processing, and the mechanisms of immunologic tolerance. We have incorporated much of this new information in the context of normal immune responses. To accommodate these new insights without significantly increasing the size of the book, we have reduced discussions of historical debates that are now resolved by experiment.

Several other changes have been introduced to make the book easier to read and more useful as a study tool. All illustrations have been revised and are in color to enhance the ease of understanding the information content. The number of illustrations has been increased by almost 50%, with many new illustrations highlighting important principles and concepts. We have also used new illustrations to replace verbal descriptions of experiments and to summarize conclusions derived from these experiments. Within the text, important conclusions, or "take-home messages," are emphasized by an italicized, boldface font. Experimental results, which we often include to demonstrate how scientific facts are established, are presented in a format that makes them readily distinguishable from the body of the text. Some new chapters have been added, and some chapters from previous editions have been combined for ease of presenting information in a logical and concise way. Two new appendixes have been added, one containing a glossary of terms that are commonly used in immunology and the other summarizing the principles underlying commonly used techniques. Many features that have proved useful in previous editions have been retained, such as boxes to present details about selected experimental approaches, disease entities, and biologic processes. We hope the changes will make the book more readable and will help students assimilate the key principles of immunology.

Many individuals have made invaluable contributions to this fourth edition. The following colleagues (listed in alphabetical order) read one or more chapters and gave us insightful comments and suggestions: Fred Alt, Hugh Auchincloss, Jason Cyster, Shiv Pillai, Hidde Ploegh, Chris Rudd, and Robert Schreiber. Our illustrators, David and Alexandra Baker of DNA Illustrations, were remarkable in their ability to interpret our ideas and convert them into clear and appealing diagrams. Our editor, Bill Schmitt, was a constant source of support and encouragement. Many other members of the staff of W.B. Saunders played critical roles at various stages of this project; these include Hazel Hacker, Pat Morrison, Paul Fry, Linda R. Garber, and

Jennifer Ehlers. 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.

Finally, the patience and forbearance of our families have exceeded what we should reasonably ask of them; without them, none of this would have been possible.

Abul K. Abbas
Andrew H. Lichtman
Jordan S. Pober

NOTICE

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy become necessary or appropriate. Readers are advised to check the product information currently provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and the contraindications. It is the responsibility of the treating physician, relying on experience and knowledge of the patient, to determine dosages and the best treatment for the patient. Neither the publisher nor the editor assumes any responsibility for any injury and/or damage to persons or property.

THE PUBLISHER

Contents

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.

1

General Properties of Immune Responses

The term immunity is derived from the Latin word *immunitas,* which referred to the exemption from various civic duties and 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. Based on 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

Table 1–1 Effectiveness of Vaccination for Some Common Infectious Diseases

Disease	Maximum Number of Cases	Year of Maximum Number of Cases	Number of Cases in 1992	Percent Change
Diphtheria	206,939	1921	4	−99.99
Measles	894,134	1941	2,237	−99.75
Mumps	152,209	1968	2,572	−98.31
Pertussis	265,269	1934	4,083	−98.46
Polio (paralytic)	21,269	1952	4	−99.98
Rubella	57,686	1969	160	−99.72
Tetanus	1,560	1923	45	−97.12
Haemophilus influenzae type B infection	~20,000	1984	1,412	−92.94
Hepatitis B	26,611	1985	16,126	−39.40

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* GL Mandell, JE Bennett, and R Dolin (eds). Principles and Practices of Infectious Diseases, 4th ed. Churchill Livingstone, New York, 1995, p 2772.

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 mechanisms that exist before infection, are capable of rapid responses to microbes, and react 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 natural killer (NK) 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 stimulated by 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. The pathogenicity of microbes is, in part, related to their ability to resist the mechanisms of innate immunity.

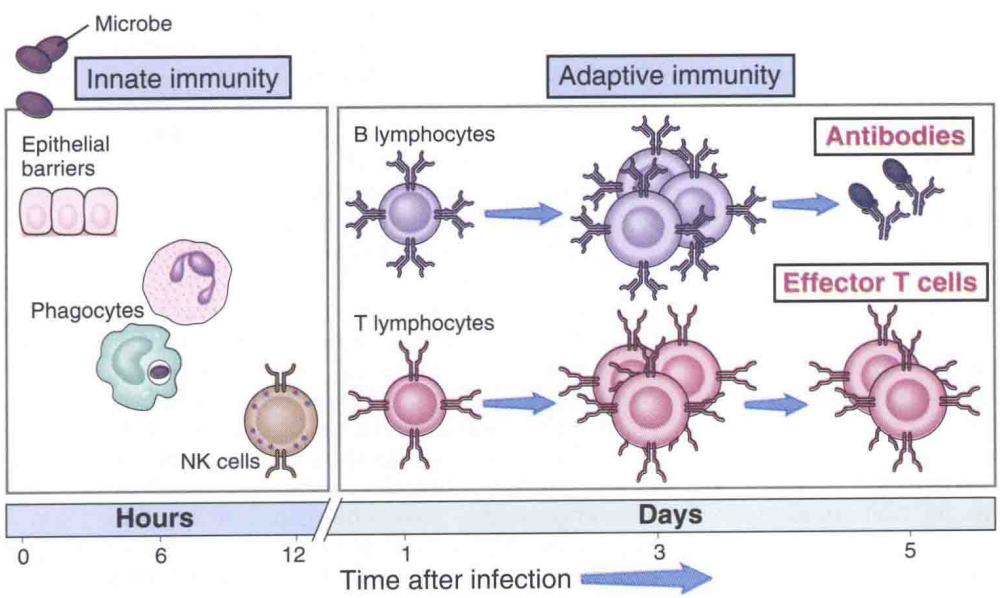


Figure 1–1 Innate and adaptive immunity.
The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. Only selected mechanisms are shown; for example, the complement system, an important component of innate immunity, is not included. The kinetics of the innate and adaptive immune responses are approximations, and may vary in different infections. NK, natural killer.

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	Very large
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

In contrast to innate immunity, more highly evolved defense mechanisms 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 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 macromolecules and an ability to "remember" and respond more vigorously to repeated exposures to the same microbe. Because of its extraordinary capacity to distinguish among different, even closely related, microbes and macromolecules, adaptive immunity 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 **lymphocytes** and their products. Foreign substances that induce specific immune responses or are the targets of such responses are called **antigens.**

Innate and adaptive immune responses are components of an integrated system of host defense in which numerous cells and molecules function cooperatively. Two important links exist 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.

The concept that adaptive immune responses enhance and "improve" innate immunity is also reflected in the phylogeny of defense mechanisms (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 antibodies, 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, which 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, called **antibodies,** that are produced by cells called **B lymphocytes.** Antibodies specifically 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 cells called **T lymphocytes.** 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 lysis of infected cells.

Protective immunity against a microbe may be in-

BOX 1–1 Evolution of the Immune System

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

Various cells in invertebrates respond to microbes by enclosing these infectious agents within aggregates 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 molecules or complement proteins. However, they contain a number of soluble molecules that bind to and lyse microbes. These molecules include lectinlike 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. 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 virtually 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 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 immunoglobulin M; this number increases to two types in anuran 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.

	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)	+	+

Abbreviations: IgM, immunoglobulin M; NK, natural killer.
Key: +, present; –, absent.

duced 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. Immunity can also be conferred upon 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 anti-