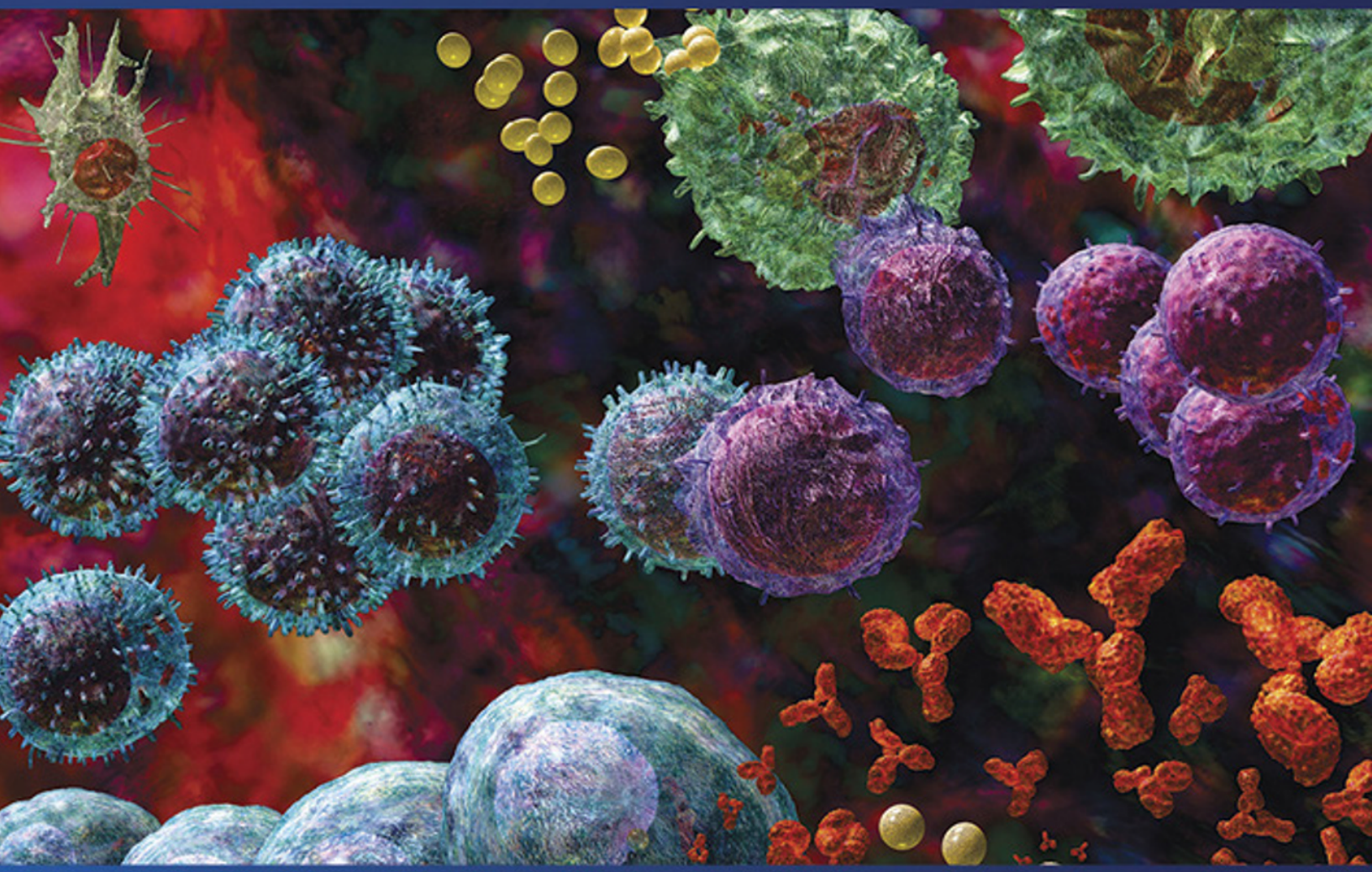
Richard Coico • Geoffrey Sunshine

SEVENTH EDITION

Immunology

A SHORT COURSE



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IMMUNOLOGY

A Short Course

To
Lisa, Jonathan, and Jennifer
R.C.

To
Ilene, Caroline, Alex, and Pearl
G.S.

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IMMUNOLOGY
A Short Course

SEVENTH EDITION

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WILEY Blackwell

This edition first published 2015 © 2015 by John Wiley & Sons Ltd

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
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Library of Congress Cataloging-in-Publication Data

Coico, Richard, author.
Immunology : a short course / Richard Coico, Geoffrey Sunshine. – Seventh edition.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-118-39691-9 (pbk.)
I. Sunshine, Geoffrey, author. II. Title.
[DNLM: 1. Allergy and Immunology. 2. Immune System Diseases. 3. Immune System Processes. 4. Immunity. QW 504]
QR181
616.07′9–dc23

2014023101

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover image: Russell Kightley

Set in 10/12 pt Times by Toppan Best-set Premedia Limited

1 2015

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ABOUT THE AUTHORS

Richard Coico is Professor of Cell Biology and Medicine and Vice Dean for Scientific Affairs at SUNY Downstate College of Medicine in New York. His major research interest concerns the study of the physiologic role of IgD—a B-cell membrane immunoglobulin co-expressed with IgM. Another area of research concerns computational approaches to the identification of candidate vaccines for several hemorrhagic viruses, including Ebola and Lassa Fever viruses. He serves on several editorial boards including *Current Protocols in Immunology*.

Geoffrey Sunshine is a Senior Scientist at the Health Effects Institute in Boston, Massachusetts, which funds research worldwide on the health effects of air pollution. He is also a lecturer in the Tufts School of Medicine immunology course. For several years, he has directed a course in immunology for graduate dental students at Tufts University School of Dental Medicine and previously directed a course for veterinary students at Tufts University School of Veterinary Medicine. He was also a member of the Sackler School of Graduate Biomedical Sciences at Tufts University, doing research on antigen presentation and teaching immunology to medical graduate and undergraduate students.

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PREFACE AND ACKNOWLEDGMENTS

As with our previous editions, the seventh edition of *Immunology: A Short Course* is intended to provide the reader with a clear and concise overview of our current understanding of the physiology of the immune system as well as the pathophysiology associated with various immune-mediated diseases. Although our knowledge of how the immune system develops and functions and the ways in which these physiological phenomena can fail or be compromised and thereby cause disease has significantly expanded since the previous edition, we have preserved our commitment to the motto *less is more*, the guiding light of this series. We are still committed to teaching our students and presenting to our readers only the information that we consider absolutely essential. To reflect this new knowledge, we have updated and rewritten every chapter in the sixth edition to incorporate new findings or to remove information that no longer reflects current thinking. We have also provided new multiple choice questions and answers at the end of each chapter so that the reader can evaluate his or her understanding. We have also made one other pivotal change as compared with earlier editions: At its most basic level, and since the first edition of the book, we have introduced the subject of immune response by highlighting the fact that it can be split into two arms: the innate response and the adaptive immune response. The past decade has witnessed the delineation of innate immunity in ways that have revolutionized our understanding of host–pathogen interactions and their impact on defense mechanisms in infectious diseases. Because of this growth in knowledge, we have added a new chapter on the subject of innate immunity (Chapter 2).

Other advances since the sixth edition include an explosion of targeted therapies for diseases ranging from cancer to Crohn's disease. For many years the path toward this goal was principally pharmacologic in nature. Now, with the advent of hybridoma technology to generate monoclonal antibodies and their use in translational studies in humans, we have entered an era in which we are witnessing the potential for these antibodies to treat many different diseases including inflammatory and autoinflammatory disorders and cancer. Indeed, many antibody therapies are now approved for clinical use by the U.S. Food and Drug Administration. Similarly, the growth in our knowledge of cytokines, together with the successful development of soluble cytokine receptors (antagonists), cytokine analogs, and anti-cytokine or anti-cytokine receptor antibodies has yielded many opportunities for therapeutic exploitation of this knowledge. The seventh edition highlights some of these important therapeutic successes and possibilities for success. We have also woven discussion of these therapies into chapters that deal with basic immune mechanisms. Our goal is to inspire the reader to consider how advances in the field of immunology have generated clinical and translational fruits that have improved health both through the prevention of infectious diseases using vaccines and by treating diseases with a variety of immune-based biological *magic bullets*, a term first coined by Paul Ehrlich more than 100 years ago.

Our goal is to provide a basic understanding of the immune system. For the reader who would like a more in-depth knowledge of clinical conditions, we refer in the text at several places to clinical cases in a companion book *Immunology: Clinical Case Studies and Disease Pathophysiology*, edited by Warren Strober (NIAID/NIH) and Susan Gottesman (SUNY-Downstate) (ISBN: 9780471326595, see http://bit.ly/ICCSDPsg). We are confident that the synergy created by the material in the seventh edition of *Immunology: A Short Course* and the linked clinical cases will be a true asset to students of medicine and other health professions.

We are very grateful to Dr. Philip Cohen (Temple University School of Medicine), who updated Chapter 13 on the subject of "Tolerance and Autoimmunity." We would also like to thank Dr. Susan Gottesman (SUNY-Downstate), who updated Chapter 18, "Immunodeficiency Disorders and Neoplasias of the Lymphoid System." We also offer our profuse thanks to Dr. Gottesman for reviewing and providing comments on drafts of every chapter, as well as writing many of the multiple choice questions and answers that are found on the accompanying website.

Richard Coico would like acknowledge the loving, enduring support of his wife, Lisa, during the writing of this book. "Her encouragement and inspiration is second to none with two possible exceptions, namely, our children, Jonathan and Jennifer. Jonathan, a talented writer himself, and Jennifer, an emerging public health advocate, are each blessed with patience and bright inquisitive minds"—the ideal mix of attributes for children and students alike. Finally, once

again, he would like to thank his mentor, Dr. G. Jeanette Thorbecke, who greatly influenced his commitment and passion to the field of immunology. Special thanks also go to co-workers, including secretaries, office assistants, and other staff members who helped with the preparation of the manuscript.

Geoffrey Sunshine would like to thank his companion lecturers in the Tufts University School of Medicine immunology course, Peter Brodeur and Arthur Rabson. They provided enormous help in addressing the key questions of what is important to teach students who know little or no immunology and how best to present this information. Peter also gave many constructive suggestions during the preparation of the current edition. In addition, Geoffrey would like to thank his wife, Ilene, for her continued support and understanding during the writing, and his daughter, Caroline, for her help in revising the Glossary.

The authors also wish to express their appreciation to our copyeditor, William Krol; Stephanie Sakson, at Toppan Best-set Premedia; and to Martin Davies, Karen Moore, Elizabeth Norton, and Sam French of John Wiley and Sons, who helped to publish the seventh edition.

Richard Coico
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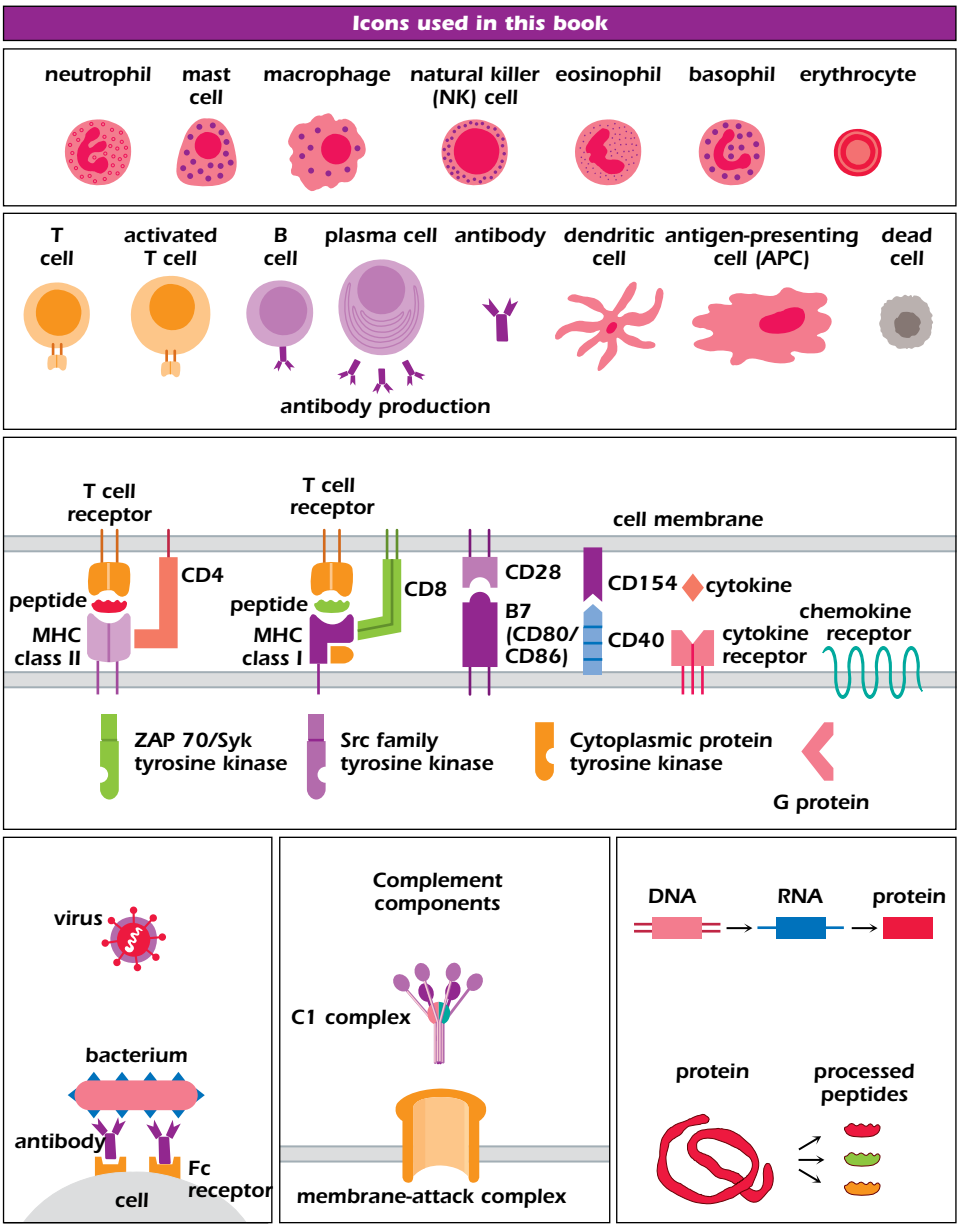
Standard **icons** are used throughout this book to denote different immunological molecules



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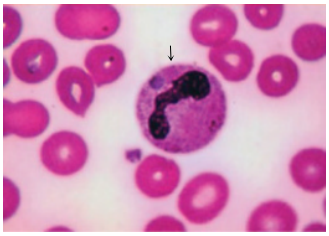

Figure 2.2. A PMN (surrounded by erythrocytes) with trilobed nucleus and cytoplasmic granules (×950). (Reproduced with permission from Olana and Walker, *Infect Med* 19: 318 [2007].)

arms of the immune system beginning with elements of the innate immune system followed by the adaptive immune system. But it is important to underscore the interrelationship of these two arms of our immune system. Clearly, they are interrelated developmentally due to their common hematopoietic precursor, the pluripotential stem cell. A classic example of their functional interrelationship is illustrated by the roles played by innate immune cells involved in ***antigen presentation***. These so-called ***antigen-presenting cells*** (APCs) do just what their name implies: they present antigens (e.g., pieces of phagocytized bacteria) to T cells within the adaptive immune system. As will be discussed in great detail in subsequent chapters, T cells must interact with APCs that display antigens for which they are specific in order for the T cells to be activated to generate antigen-specific responses. Thus, while the title of this section implies that the cells described below are principally involved in innate immune responses, it is important to recognize their important role in adaptive immune responses (Chapter 3) at this early stage of study of the immune system.

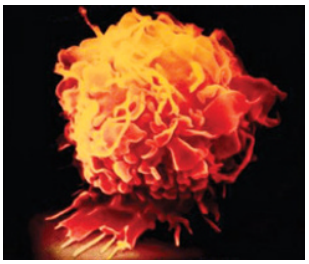

Figure 2.3. Scanning electron micrograph of macrophage with ruffled membrane and surface covered with microvilli (×5200). (Reproduced with permission from *J Clin Invest* 117 [2007].)

TABLE 2.2. Acute Phase Proteins

Protein	Immune System Function
C-reactive protein	• Binds to phosphocholine expressed on the surface of dead or dying cells and some types of bacteria • Opsonin
Serum amyloid P component	Opsonin
Serum amyloid A	• Recruitment of immune cells to inflammatory sites • Induction of enzymes that degrade extracellular matrix
Complement factors	• Opsonization, lysis, and clumping of target cells • Chemotaxis
Mannan-binding lectin	Mannan-binding lectin pathway of complement activation
Fibrinogen (α β globulin), prothrombin, factor VIII, von Willebrand factor	• Coagulation factors • Trapping invading microbes in blood clots. • Some cause chemotaxis
Plasminogen	Degradation of blood clots
Alpha 2-macroglobulin	• Inhibitor of coagulation by inhibiting thrombin. • Inhibitor of fibrinolysis by inhibiting plasmin
Ferritin	Binding iron, inhibiting microbe iron uptake
Hepcidin	Stimulates the internalization of ferroportin, preventing release of iron bound by ferritin within intestinal enterocytes and macrophages
Ceruloplasmin	Oxidizes iron, facilitating for ferritin, inhibiting microbe iron uptake
Haptoglobin	Binds hemoglobin, inhibiting microbe iron uptake
Orosomucoid (Alpha-1-acid glycoprotein, AGP)	Steroid carrier
Alpha 1-antitrypsin, Alpha alpha 1-antichymotrypsin	Serpin, downregulates inflammation

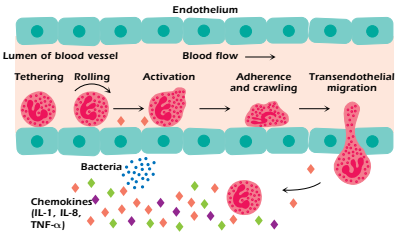

Figure 2.11. Leukocyte adhesion to endothelium leads to their adhesion, activation, and extravasation from the blood to tissue where they are needed to help destroy (e.g., phagocytize) pathogens such as bacteria that initiate this response.

Self-assessment review questions help you test yourself after each chapter.

REVIEW QUESTIONS

For each question, choose the ONE BEST answer or completion.

1. Which of the following applies uniquely with respect to B cells found in secondary lymphoid organs?
A) present as precursor B cells
B) express only IgM
C) terminally differentiate into plasma cells
D) undergo proliferation

2. The germinal centers found in the cortical region of lymph nodes and the peripheral region of splenic periarteriolar lymphatic tissue
A) support the development of immature B and T cells
B) function in the removal of damaged erythrocytes from the circulation
C) act as the major source of stem cells and thus help maintain hematopoiesis
D) provide an infrastructure that on antigenic stimulation contains large populations of B lymphocytes and plasma cells
E) are the sites of natural killer T (NKT)-cell differentiation

3. Which of the following sequence correctly describes lymphocyte migration from lymph nodes to blood?
A) postcapillary venules, efferent lymphatic vessels, thoracic duct, vena cava, heart
B) postcapillary venules, afferent lymphatic vessels, thoracic duct, vena cava, heart
C) postcapillary venules, efferent lymphatic vessels, vena cava, thoracic duct, heart
D) postcapillary venules, afferent lymphatic vessels, vena cava, thoracic duct, heart

4. Clonal expansion of which of the following cells occurs following their direct interaction with the antigen for which they are specific?
A) macrophages
B) basophils
C) Bcells
D) T cells
E) mast cells

The case icon indicates that you can find a correlated clinical case in *Immunology: Clinical Case Studies and Disease Pathophysiology*, edited by Warren Strober (NIAID/NIH) and Susan Gottesman (SUNY-Downstate) (ISBN: 9780471326595; see http://bit.ly/ICCSDPsg).

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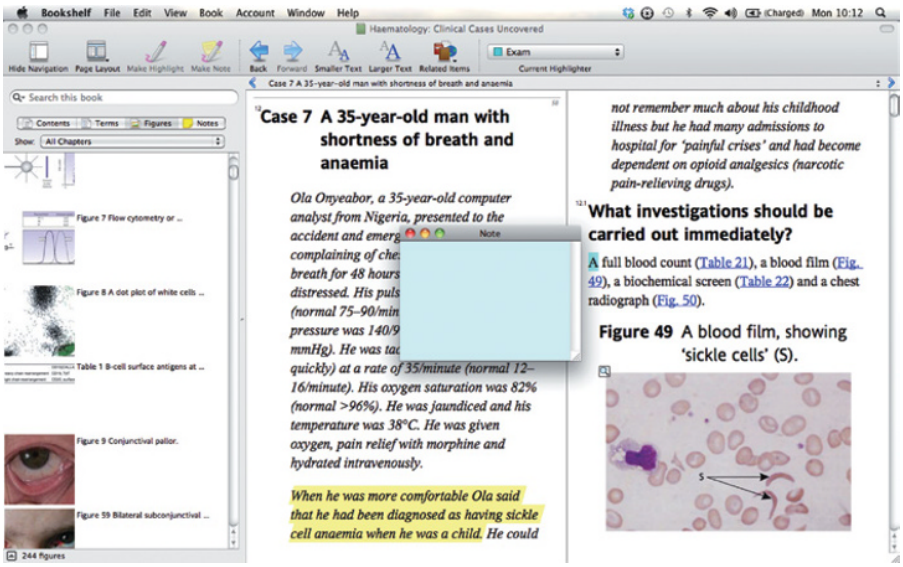

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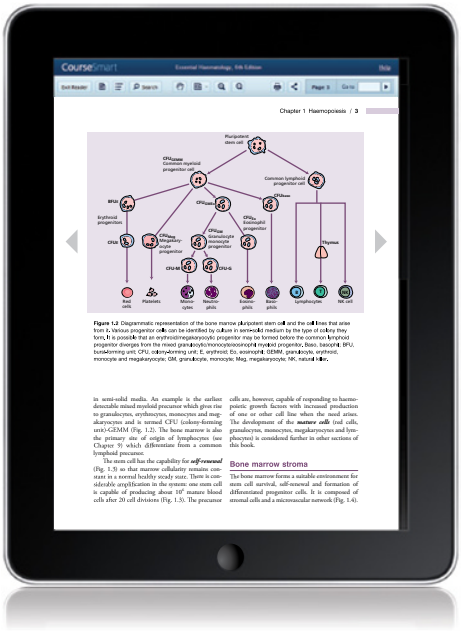

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1

OVERVIEW OF THE IMMUNE SYSTEM

INTRODUCTION

Anyone who has had the good fortune to hear an orchestra brilliantly perform a symphony composed by one of the great masters knows that each of the carefully tuned musical instruments contributes to the collective, harmonious sound produced by the musicians. In many ways, the normally tuned immune system continuously plays an orchestrated symphony to maintain homeostasis in the context of host defenses. However, as William Shakespeare noted, "Untune that string, and, hark, what discord follows!" (*Troilus and Cressida*). Similarly, an untuned immune system can cause discord, which manifests as autoimmunity, cancer, or chronic inflammation. Fortunately for most of us, our immune system is steadfastly vigilant in regard to tuning (regulating) itself to ensure that its cellular components behave and interact symbiotically to generate protective immune responses that ensure good health. In many ways the immune system can be described in anthropomorphic terms: Its memory allows it to remember and recognize pathogens years or decades after initial exposure; it can distinguish between the body's own cells and those of another organism; and it makes decisions about how to respond to particular pathogens—including whether or not to respond at all, as will be discussed in Chapters 2 and 3.

In his penetrating essays, scientist–author Lewis Thomas, discussing symbiosis and parasitism, described the forces that would drive all living matter into one huge ball of protoplasm were it not for regulatory and recognition mechanisms that allow us to distinguish self from nonself. The origins of these mechanisms go far back in evolutionary history, and many, in fact, originated as markers for allowing cells to recognize and interact with each other to set up symbiotic households. Genetically related sponge colonies that are placed close to each other, for example, will tend to grow toward each other and fuse into one large colony. Unrelated colonies, however, will react in a different way, destroying cells that come in contact with each other and leaving a zone of rejection between the colonies.

In the plant kingdom, similar types of recognition occur. In self-pollinating species, a pollen grain landing on the stigma of a genetically related flower will send a pollen tubule down the style to the ovary for fertilization. A pollen grain from a genetically distinct plant either will not germinate or the pollen tubule, once formed, will disintegrate in the style. The opposite occurs in cross-pollinating species: self-marked pollen grains disintegrate, whereas nonself grains germinate and fertilize.

The nature of these primitive recognition mechanisms has not been completely worked out, but almost certainly it involves cell-surface molecules that are able to specifically bind and adhere to other molecules on opposing cell surfaces. This simple method of molecular recognition has evolved over time into the very complex immune system that retains, as its essential feature, the ability of a protein molecule to recognize and bind specifically to a particular shaped structure on another molecule. Such molecular recognition is the underlying principle involved in the discrimination between self and nonself during an immune response. It is the purpose of this book to describe how the fully

Immunology: A Short Course, Seventh Edition. Richard Coico and Geoffrey Sunshine.

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mature immune system—which has evolved from this simple beginning—makes use of this principle of recognition in increasingly complex and sophisticated ways.

Perhaps the greatest catalyst for progress in this and many other biomedical areas has been the advent of molecular biologic techniques. It is important to acknowledge, however, that certain technological advances in the field of molecular biology were made possible by earlier progress in the field of immunology. For example, the importance of immunologic methods (Chapter 6) used to purify proteins as well as identify specific cDNA clones cannot be understated. These advances were greatly facilitated by the pioneering studies of Köhler and Milstein (1975), who developed a method for producing monoclonal antibodies. Their achievement was rewarded with the Nobel Prize in Medicine. It revolutionized research efforts in virtually all areas of biomedical science. Some monoclonal antibodies produced against so-called tumor-specific antigens have now been approved by the US Food and Drug Administration for use in patients to treat certain malignancies. Monoclonal antibody technology is, perhaps, an excellent example of how the science of immunology has transformed not only the field of medicine but also fields ranging from agriculture to the food science industry.

Given the rapid advances occurring in immunology and the many other biomedical sciences and, perhaps most important, the sequencing of the human genome, every contemporary biomedical science textbook runs a considerable risk of being outdated before it appears in print. Nevertheless, we take solace from the observation that new formulations generally build on and expand the old rather than replacing or negating them completely. Let's begin, therefore, with an overview of innate and adaptive immunity (also called ***acquired immunity***) which continue to serve as a conceptual compass that orients our fundamental understanding of host defense mechanisms.

INNATE AND ADAPTIVE IMMUNITY

The Latin term ***immunis***, meaning "exempt," gave rise to the English word ***immunity***, which refers to all the mechanisms used by the body as protection against environmental agents that are foreign to the body. These agents may be microorganisms or their products, foods, chemicals, drugs, pollen, or animal hair and dander.

Innate Immunity

Innate immunity is conferred by all those elements with which an individual is born and that are always present and available at very short notice to protect the individual from challenges by foreign invaders. The major properties of the innate immune system are discussed in Chapter 2. Table 1.1 summarizes and compares some of the features of the innate and adaptive immune systems. Elements of the innate system include body surfaces and internal components, such as the skin, the mucous membranes, and the cough reflex, which present effective barriers to environmental agents. Chemical influences, such as pH and secreted fatty acids, constitute effective barriers against invasion by many microorganisms. Another noncellular element of the innate immune system is the complement system. As in the previous editions of this book, we cover the subject of complement in Chapter 14.

TABLE 1.1. Major Properties of the Innate and Adaptive Immune Systems

Property	Innate	Adaptive
Characteristics	Antigen nonspecific	Antigen specific
	Rapid response (minutes to hours)	Slow response (days)
	No memory	Memory
Immune components	Natural barriers (e.g., skin, mucous membranes)	Lymphocytes
	Phagocytes and natural killer cells	Antigen recognition molecules (B and T cell receptors)
	Soluble mediators (e.g., complement)	Secreted molecules (e.g., antibody)
	Pattern recognition molecules	

Numerous other components are also features of innate immunity: fever, interferons (Chapter 12), other substances released by leukocytes, and pattern-recognition molecules (***innate receptors***), which can bind to various microorganisms (e.g., Toll-like receptors or TLRs; Chapter 2), as well as serum proteins such as β-lysin, the enzyme lysozyme, polyamines, and the kinins, among others. All of these elements either affect pathogenic invaders directly or enhance the effectiveness of host reactions to them. Other internal elements of innate immunity include phagocytic cells such as granulocytes, macrophages, and microglial cells of the central nervous system, which participate in the destruction and elimination of foreign material that has penetrated the physical and chemical barriers.

Adaptive Immunity

We introduce the subject of adaptive immunity in Chapter 3. Later chapters provide more details about the cellular and molecular features of this arm of the immune system. Adaptive immunity came into play relatively late, in evolutionary terms, and is present only in vertebrates. Although an individual is born with the capacity to mount immune responses to foreign substances, the number of B and T cells available for mounting such responses must be expanded before one is said to be immune to that substance. This is achieved by activation of lymphocytes bearing antigen-specific receptors

following their contact with the antigen. Antigenic stimulation of B cells and T cells together with antigen-presenting cells (APCs) initiates a chain of events that leads to proliferation of activated cells together with a program of differentiation events that generate the B- or T-effector cells responsible for the humoral or cell-mediated responses, respectively. These events take time to unfold (days to weeks). Fortunately, the cellular and noncellular components of the innate system are rapidly mobilized (minutes to hours) to eliminate or neutralize the foreign substance. One way to think about this host defense strategy is to consider this as a one-two punch launched initially by innate cells and noncellular elements of the immune system that are always available to quickly remove or cordon off the invader, followed by a round of defense that calls into play cells of the adaptive immune system (B and T cells) that are programmed to react with the foreign substance by virtue of their antigen-specific receptors. Moreover, the clonal expansion of these cells—a process first explained by the clonal selection theory discussed in the section below—gives rise to an arsenal of antigen-specific cells available for rapid responses to the same antigen in the future, a phenomenon referred to as ***memory responses***. By this process, the individual acquires the immunity to withstand and resist a subsequent attack by, or exposure to, the same offending agent.

The discovery of adaptive immunity predates many of the concepts of modern medicine. It has been recognized for centuries that people who did not die from such life-threatening diseases as bubonic plague and smallpox were subsequently more resistant to the disease than were people who had never been exposed to it. The rediscovery of adaptive immunity is credited to the English physician Edward Jenner, who, in the late eighteenth century, experimentally induced immunity to smallpox. If Jenner performed his experiment today, his medical license would be revoked, and he would be the defendant in a sensational malpractice lawsuit: He inoculated a young boy with pus from a lesion of a dairy maid who had cowpox, a relatively benign disease that is related to smallpox. He then deliberately exposed the boy to smallpox. This exposure failed to cause disease! Because of the protective effect of inoculation with cowpox (vaccinia, from the Latin word *vacca*, meaning "cow"), the process of inducing adaptive immunity has been termed ***vaccination***.

The concept of vaccination or immunization was expanded by Louis Pasteur and Paul Ehrlich almost 100 years after Jenner's experiment. By 1900, it had become apparent that immunity could be induced against not only microorganisms but also their products. We now know that immunity can be induced against innumerable natural and synthetic compounds, including metals, chemicals of relatively low molecular weight, carbohydrates, proteins, and nucleotides.

The compound to which the adaptive immune response is induced is termed an ***antigen***, a term initially coined due to the ability of these compounds to cause antibody responses to be generated. Of course, we now know that antigens can generate antibody-mediated and T-cell–mediated responses.

CLONAL SELECTION THEORY

A turning point in immunology came in the 1950s with the introduction of a Darwinian view of the cellular basis of specificity in the immune response. This was the now universally accepted clonal selection theory proposed and developed by Jerne and Burnet (both Nobel Prize winners) and by Talmage. The clonal selection theory had a truly revolutionary effect on the field of immunology. It dramatically changed our approach to studying the immune system and stimulated research carried out during the last half of the twentieth century. This work ultimately provided us with knowledge regarding the molecular machinery associated with activation and regulation of cellular elements of the immune system. The essential postulates of this theory are summarized below.

As we have discussed earlier, the specificity of the immune response is based on the ability of B and T lymphocytes to recognize particular foreign molecules (antigens) and respond to them in order to eliminate them. The process of clonal expansion of these cells is highly efficient, but there is always the rare chance that errors or mutations will occur, resulting in the generation of cells bearing receptors that bind poorly or not at all to the antigen, or, in a worse-case scenario, cells that have autoreactivity. Under normal conditions, nonfunctional cells may survive or be aborted with no deleterious consequences to the individual. In contrast, the rare self-reactive cells are clonally deleted or suppressed by other regulatory cells of the immune system charged with this role among others. If such a mechanism were absent, autoimmune responses might occur routinely. It is noteworthy that during the early stages of development, lymphocytes with receptors that bind to self-antigens are also produced, but fortunately they are also eliminated or functionally inactivated. This process gives rise to the initial repertoire of mature lymphocytes that are programmed to generate antigen-specific responses with a relatively minute population functionally benign, albeit potentially autoreactive cells (Figure 1.1). The circumstances and predisposing genetic conditions that may lead to the latter phenomenon are discussed in Chapter 13.

As we have already stated, the immune system is capable of recognizing innumerable foreign substance serving as antigens. How is a response to any one antigen accomplished? In addition to the now-proven postulate that self-reactive clones of lymphocytes are functionally inactivated or aborted, the clonal selection theory proposed the following:

- T and B lymphocytes of a myriad of specificities exist before there is any contact with the foreign antigen.
- Lymphocytes participating in an immune response express antigen-specific receptors on their surface membranes. As a consequence of antigen binding to the lymphocyte, the cell is activated and releases various products. In the case of B lymphocytes, these receptors, so-called ***B-cell receptors*** (BCRs), are the

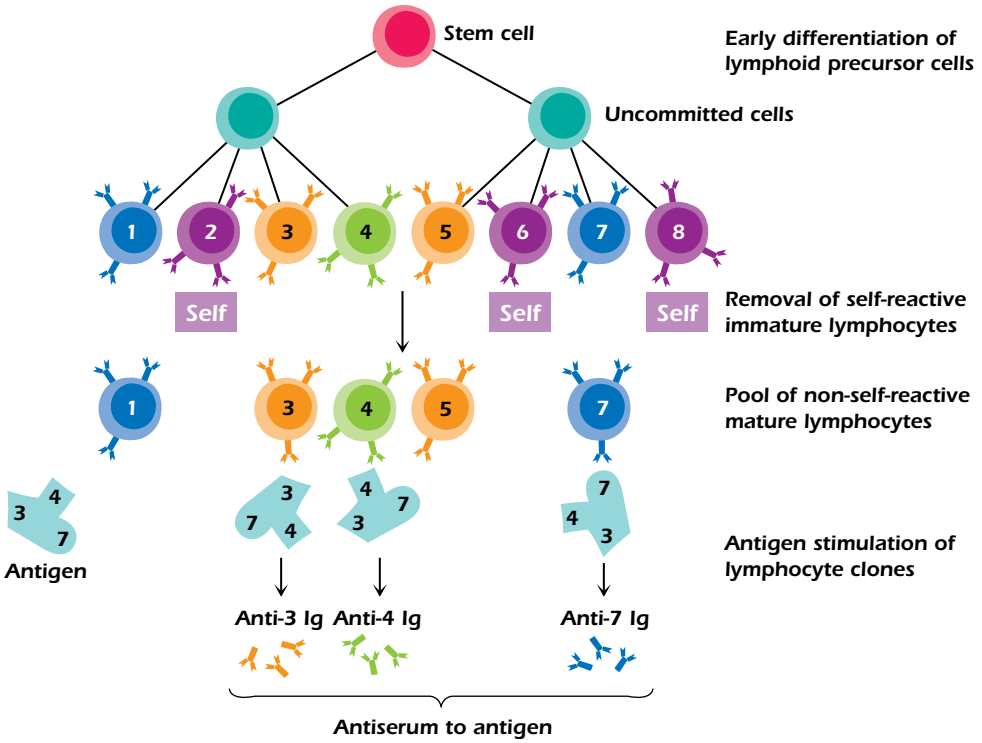

Figure 1.1. Clonal selection theory of B cells leading to antibody formation.

very molecules that subsequently get secreted as antibodies following B-cell activation.

- T cells have receptors denoted as T-cell receptors (TCRs). Unlike the B-cell products, the T-cell products are not the same as their surface receptors but are other protein molecules, called ***cytokines***, that participate in elimination of the antigen by regulating the many cells needed to mount an effective immune response.
- Each lymphocyte carries on its surface receptor molecules of only a single specificity as demonstrated in Figure 1.1 for B cells and also holds true for T cells.

These postulates describe the existence of a large repertoire of possible specificities formed by cellular multiplication and differentiation before there is any contact with the foreign substance to which the response is to be made. The introduction of the foreign antigen then selects from among all the available specificities those with specificity for the antigen, enabling binding to occur. The scheme shown in Figure 1.1 for B cells also applies to T cells; however, T cells have receptors that are not antibodies and secrete molecules other than antibodies.

The remaining postulates of the clonal selection theory account for this process of selection by the antigen from among all the available cells in the repertoire.

- Immunocompetent lymphocytes combine with the foreign antigen, or a portion of it termed the epitope or antigenic determinant, by virtue of their surface receptors. They are stimulated under appropriate conditions to proliferate and differentiate into clones of cells with the corresponding epitope-specific receptors.
- With B-cell clones, this will lead to the synthesis of antibodies having the same specificity. In most cases, the antigen stimulating the response is complex and contains many different epitopes, each capable of activating a clone of epitope-specific B cells. Hence, collectively, the clonally secreted antibodies constitute what is often referred to as polyclonal antiserum, which is capable of interacting with the multiple epitopes expressed by the antigen.
- T cells are similarly selected by appropriate epitopes or portions thereof. Each selected T cell will be activated to divide and produce clones of the same specificity. Thus the clonal response to the antigen will be amplified, the cells will release various cytokines, and subsequent exposure to the same antigen will now result in the activation of many cells or clones of that specificity. Instead of synthesizing and releasing antibodies like the B cells, the T cells synthesize and release cytokines. These cytokines, which are soluble mediators, exert their effect on other cells to grow or become activated facilitating elimination of the antigen. Several distinct regions of an antigen (epitopes) can be recognized: Several different clones of B cells will be stimulated to produce antibody, whose sum total is an antigen-specific antiserum that is made up of antibodies of differing specificity (Figure 1.1); all the T-cell clones that recog-