The Immune System is adapted from Janeway’s Immunobiology, also published by Garland Science.
This book is aimed at students of all types who are coming to immunology for the first time. The guiding principle of the book is a focus on human immune systems—how they work and how their successes, compromises, and failures affect the daily life of every one of us. In providing the beginning student with a coherent, concise, and contemporary narrative of the mechanisms used by the immune system to control invading microbes, the emphasis has had to be on what we know, rather than how we know it. In other words, our emphasis here is more on the work of nature than on the work of immunologists.

Nevertheless, since the third edition of *The Immune System* was published in 2009 the work of immunologists has dramatically advanced the boundaries of knowledge. Following close behind the discovery of immunological mechanisms has been the rational design of new drugs and therapies based on this knowledge. Other important developments have been an increasing understanding of the numerous idiosyncrasies of human immune systems and the importance of studying immune-system cells in the tissues where they function. While working on this fourth revision of *The Immune System* I was not infrequently struck and excited by the extent to which phenomena that were loose ends in 2009 are now connected and making sense in ways that were unpredictable. As a result, substantial changes have been made in this fourth edition. For readers and instructors familiar with the third edition, what follows is a guide to the major changes. For those who are new to the book it will provide an overview of its contents.

Chapter 1 provides a focused introduction to the cells and tissues of the immune system, and to their place and purpose within the human body. The two following chapters describe the innate immune response to infection. These replace the single chapter in the previous edition, reflecting how innate immunity continues to be a rich area for new discovery. Particularly relevant is the now widespread appreciation that the vast majority of microorganisms inhabiting human bodies are essential for human health, for the development of the immune system, and for preventing the growth and invasion of pathogenic microorganisms. These concepts are introduced in Chapter 2, along with the immediate, front-line defenses of complement, defensins, and other secreted proteins. The induced cellular defenses of innate immunity—macrophages, neutrophils, and natural killer cells—are the topic of Chapter 3. In the previous edition of the book, there was an introductory chapter on adaptive immunity at this point. This has been dropped in the fourth edition, partly because of overlap with Chapter 1 and partly on the advice of the book’s users.

The next six chapters cover the fundamental biology of the adaptive immune response. Chapters 4 and 5 describe how B lymphocytes and T lymphocytes
detect the presence of infection. These chapters introduce antibodies, the variable antigen-binding receptors of B cells and T cells, and the polymorphic major histocompatibility complex (MHC) class I and II molecules that present peptide antigens to T-cell receptors.

Chapters 6 and 7 describe and compare the development of B cells and T cells, including the gene rearrangements that generate the antigen receptors and the selective processes that eliminate cells with potential for causing autoimmunity. At the end of these two chapters, mature but naive B cells and T cells enter the circulation of the blood and the lymph in the quest for their specific antigens. Chapters 8 and 9 describe how these naive lymphocytes respond to infections and use diverse effector mechanisms to get rid of them. Here we look in detail at the dendritic cells that activate naive T cells, how immune responses are generated in secondary lymphoid organs, the differentiation of activated T cells into various effector subsets, and the generation of antibodies by B cells. The order and scope of these six chapters are the same as in previous editions of the book, but they have undergone significant revision, particularly to account for the increased knowledge and understanding of the functional diversity of both CD4 T cells and the classes and subclasses of human antibodies.

In the previous edition, Chapter 10 was divided into three parts that dealt with mucosal immunity, immunological memory, and the connection between innate and adaptive immunity. These three important areas have been given a chapter each in this edition. Chapter 10 now describes the nature of the immune response in mucosal tissue, where most immune activity takes place, and the ways in which it differs from the systemic immune response, with emphasis on the gut and the mucosal immune system's interactions with commensal microorganisms.

Chapter 11 is a new chapter that combines two related topics—immunological memory and vaccination—that were in different chapters in the previous edition. Users of the book have for some years suggested bringing these two topics together. Now is an opportune time to do so, because vaccine research and development is undergoing a renaissance after a period of considerable decline.

The more we learn about the immune system, the more blurred the distinction between innate and adaptive immunity becomes. On reflection this should not be surprising, because the two systems have been coevolving in vertebrate bodies for the past 400 million years. The largely new content of Chapter 12, entitled ‘Coevolution of Innate and Adaptive Immunity’, concentrates on several populations of lymphocyte that combine characteristics of innate and adaptive immunity. These include natural killer cells, γδ cells, natural killer T cells, and mucosa-associated invariant T cells. After years of being a cipher, the ligands that bind to the variable antigen receptors of γδ are now being discovered and defined.

The first part of Chapter 13, ‘Failures of the Body’s Defenses,’ describes the ways in which some pathogens change and avoid the immunological memories gained by their human hosts during previous infections. The second part of the chapter describes the inherited genetic defects that segregate in human populations and cause a wide range of immunodeficiency diseases. An invaluable by-product of identifying such patients and treating their diseases has been the ability to define the physiological functions of the component of the human immune system that is missing or nonfunctional in each different immunodeficiency disease. The third part of the chapter is devoted to the human immunodeficiency virus (HIV). At this time there is renewal of hope for HIV vaccines and immunotherapies based upon the results of studying the successful immune responses in exceptional individuals who maintain health despite having been infected with HIV.
Chapter 14 in this edition, ‘IgE-mediated Immunity and Allergy,’ has evolved from Chapter 12 in the previous edition, ‘Over-reactions of the Immune System.’ After introducing the four types of hypersensitivity reaction, the chapter focuses on the immunology of IgE and how it provides protection against parasitic worms in the people of developing countries and causes type I hypersensitivity reactions (allergies) in the people of industrialized countries. Much of this chapter is new and explains how IgE and its powerful receptor on mast cells, eosinophils, and basophils constitute an entire arm of the immune system that evolved specifically to control multicellular parasites, notably helminth worms. In-depth consideration of the type II, III, and IV hypersensitivity reactions is now given in Chapter 15, ‘Transplantation of Tissues and Organs,’ and Chapter 16, ‘Disruption of Healthy Tissue by the Adaptive Immune Response,’ which cover transplantation and autoimmunity, respectively. As users of the book have pointed out, different forms of transplant rejection and different types of autoimmune disease provide good examples of the type II, III, and IV hypersensitivity reactions. In these two chapters and also Chapter 17, on ‘Cancer and its Interactions with the Immune System,’ the amount of clinical description has been reduced so as to accommodate examples of promising new immunotherapies that are being used to treat transplant rejection, graft-versus-host disease, autoimmune disease, and various types of cancer. Although the order of the chapters on transplantation and autoimmunity has been changed in the fourth edition, the scope of these chapters has not changed.

In addition to these major changes, all chapters have been subject to revision aimed at bringing the content up to date and improving its clarity. Exemplifying the extent of these changes, about 20% of the figures are new and they include new images generously donated by colleagues.

I thank and acknowledge the authors of *Janeway’s Immunobiology* and of *Case Studies in Immunology* for giving me license with the text and figures of their books. I have been fortunate to work with a collegial team of experts on this fourth edition. Sheryl L. Fuller-Espie (Cabrini College, Radnor, Pennsylvania) superbly composed the questions and answers for the end-of-chapter questions. Eleanor Lawrence expertly edited the text and the figures as well as the end-of-chapter questions. Nigel Orme created all the new illustrations for this edition, and Yasodha Natkunam provided some superb new micrographs. Emma Jeffcock did wonders with the layout. I am indebted to Janet Foltin for her valuable contributions to this revision and to Denise Schanck, who has led the team and orchestrated the entire operation. Frances Brodsky has not only been a loyal user of the book but has generously given of her advice, suggestions, and much else to this Fourth Edition of *The Immune System.*
The author and publisher would like to thank the following reviewers for their thoughtful comments and guidance:

Carla Aldrich, Indiana University School of Medicine-Evansville; Igor C. Almeida, University of Texas at El Paso; Ivica Arsoy, C.U.N.Y. York College; Roberta Attanasio, University of Georgia; Susanne Brix Pedersen, Technical University of Denmark; Eunice Carlson, Michigan Technological University; Peter Chinkupete, De Montfort University; Michael Chumley, Texas Christian University; My Lien Dao, University of South Florida; Karen Duus, Albany Medical Center; Michael Edidin, The Johns Hopkins University; Randle Gallucci, The University of Oklahom; Michael Gleeson, Loughborough University; Gail Goodman Snitkoff, Albany College-Pharmacy & Health Sciences; Elaine Green, Coventry University; Neil Greenspan, Case Western Reserve University; Robin Herlands, Nevada State College; Cheryl Hertz, Loyola Marymount University; Allen L. Honeyman, Baylor College of Dentistry; Susan H. Jackman, Marshall University School of Medicine; Deborah Lebman, Virginia Commonwealth University; Lisa Lee-Jones, Manchester Metropolitan University; Lindsay Marshall, Aston University; Mehrdad Matloubian, University of California, San Francisco; Mark Miller, University of Tennessee; Debasish Mitra, Pune University India; Ashley Moffett, University of Cambridge; Carolyn Mold, University of New Mexico School of Medicine; Marc Monestier, Temple University; Kimberly J. Payne, Loma Linda University; Edward Roy, University of Illinois Urbana-Champaign; Ulrich Sack, Universitat Leipzig; Paul K. Small, Eureka College; Brian Sutton, King’s College London; Richard Tapping, University of Illinois; John Taylor, Newcastle University; Ruurd Torensma, The Radboud University Nijmegen Medical Centre; Alan Trudgett, Queen’s University Belfast; Alexander Tsygankov, Temple University; Bart Vandekerckhove, Universiteit Gent; Paul Whitley, University of Bath; Laurence Wood, Texas Tech University Health Center.
Resources for Instructors and Students

Case Studies in Immunology
by Raif Geha and Luigi Notarangelo

The companion book, *Case Studies in Immunology*, provides an additional, integrated discussion of clinical topics to reinforce and extend the basic science. Diseases covered in *Case Studies* are indicated by a clipboard symbol in the margin of *The Immune System*. *Case Studies in Immunology* is sold separately.

INSTRUCTOR RESOURCES

Instructor resources are available on the Garland Science Instructor’s Resource Site, located at http://www.garlandscience.com/instructors. The password-protected website provides access to the teaching resources for both this book and all other Garland Science textbooks. Qualified instructors can obtain access to the site from their sales representative or by emailing science@garland.com.

Art of *The Immune System*, Fourth Edition

The images from the book are available in two convenient formats: PowerPoint® and JPEG. They have been optimized for display on a computer. Figures are searchable by figure number, by figure name, or by keywords used in the figure legend from the book.

Figure-integrated Lecture Outlines

The section headings, concept headings, and figures from the text have been integrated into PowerPoint presentations. These will be useful for instructors who would like a head start in creating lectures for their course. Like all of our PowerPoint presentations, the lecture outlines can be customized. For example, the content of these presentations can be combined with videos and questions from the book or ‘Question Bank,’ to create unique lectures that facilitate interactive learning.

Question Bank

Written by Sheryl L. Fuller-Espie, PhD, DIC, Cabrini College, the revised and expanded question bank includes a variety of question formats: multiple-choice, true-false, matching, essay, and challenging ‘thought’ questions.
USMLE-style questions help prepare students for medical licensing examinations. There are more than 900 questions, and a large number of the multiple-choice questions are suitable for use with personal response systems (that is, clickers). The questions are organized by book chapter and provide a comprehensive sampling of concepts that can be used either directly or as inspiration for instructors to write their own test questions.

Diploma® Test Generator Software

The questions from the question bank have been loaded into the Diploma test generator software. The software is easy to use and can scramble questions to create multiple tests. Questions are organized by chapter and type, and can be additionally categorized by the instructor according to difficulty or subject. Existing questions can be edited and new ones added. It is compatible with several course management systems, including Blackboard®.

STUDENT RESOURCES

The resources for students are available on The Immune System Student Website, located at http://www.garlandscience.com/IS4-students.

Flashcards

Each chapter contains a set of flashcards, built into the website, that allow students to review key terms from the text.

Glossary

The complete glossary from the book is available on the website and can be searched or browsed.
Contents

Chapter 1  Elements of the Immune System and their Roles in Defense 1
Chapter 2  Innate Immunity: the Immediate Response to Infection 29
Chapter 3  Innate Immunity: the Induced Response to Infection 47
Chapter 4  Antibody Structure and the Generation of B-Cell Diversity 81
Chapter 5  Antigen Recognition by T Lymphocytes 113
Chapter 6  The Development of B Lymphocytes 149
Chapter 7  The Development of T Lymphocytes 177
Chapter 8  T Cell-Mediated Immunity 199
Chapter 9  Immunity Mediated by B Cells and Antibodies 231
Chapter 10  Preventing Infection at Mucosal Surfaces 267
Chapter 11  Immunological Memory and Vaccination 295
Chapter 12  Coevolution of Innate and Adaptive Immunity 329
Chapter 13  Failures of the Body’s Defenses 365
Chapter 14  IgE-Mediated Immunity and Allergy 401
Chapter 15  Transplantation of Tissues and Organs 433
Chapter 16  Disruption of Healthy Tissue by the Adaptive Immune Response 473
Chapter 17  Cancer and Its Interactions with the Immune System 509

Answers to Questions A:1
Glossary G:1
Figure Acknowledgments F:1
Index I:1
## Detailed Contents

### Chapter 1

**Elements of the Immune System and their Roles in Defense**

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-1</td>
<td>Numerous commensal microorganisms inhabit healthy human bodies</td>
<td>2</td>
</tr>
<tr>
<td>1-2</td>
<td>Pathogens are infectious organisms that cause disease</td>
<td>3</td>
</tr>
<tr>
<td>1-3</td>
<td>The skin and mucosal surfaces form barriers against infection</td>
<td>4</td>
</tr>
<tr>
<td>1-4</td>
<td>The innate immune response causes inflammation at sites of infection</td>
<td>8</td>
</tr>
<tr>
<td>1-5</td>
<td>The adaptive immune response adds to an ongoing innate immune response</td>
<td>10</td>
</tr>
<tr>
<td>1-6</td>
<td>Adaptive immunity is better understood than innate immunity</td>
<td>12</td>
</tr>
<tr>
<td>1-7</td>
<td>Immune system cells with different functions all derive from hematopoietic stem cells</td>
<td>12</td>
</tr>
<tr>
<td>1-8</td>
<td>Immunoglobulins and T-cell receptors are the diverse lymphocyte receptors of adaptive immunity</td>
<td>16</td>
</tr>
<tr>
<td>1-9</td>
<td>On encountering their specific antigen, B cells and T cells differentiate into effector cells</td>
<td>17</td>
</tr>
<tr>
<td>1-10</td>
<td>Antibodies bind to pathogens and cause their inactivation or destruction</td>
<td>18</td>
</tr>
<tr>
<td>1-11</td>
<td>Most lymphocytes are present in specialized lymphoid tissues</td>
<td>19</td>
</tr>
<tr>
<td>1-12</td>
<td>Adaptive immunity is initiated in secondary lymphoid tissues</td>
<td>20</td>
</tr>
<tr>
<td>1-13</td>
<td>The spleen provides adaptive immunity to blood infections</td>
<td>23</td>
</tr>
<tr>
<td>1-14</td>
<td>Most secondary lymphoid tissue is associated with the gut</td>
<td>25</td>
</tr>
</tbody>
</table>

**Summary to Chapter 1**

Questions

Page 26

### Chapter 2

**Innate Immunity: the Immediate Response to Infection**

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>Physical barriers colonized by commensal microorganisms protect against infection by pathogens</td>
<td>29</td>
</tr>
<tr>
<td>2-2</td>
<td>Intracellular and extracellular pathogens require different types of immune response</td>
<td>30</td>
</tr>
<tr>
<td>2-3</td>
<td>Complement is a system of plasma proteins that mark pathogens for destruction</td>
<td>31</td>
</tr>
<tr>
<td>2-4</td>
<td>At the start of an infection, complement activation proceeds by the alternative pathway</td>
<td>32</td>
</tr>
<tr>
<td>2-5</td>
<td>Regulatory proteins determine the extent and site of C3b deposition</td>
<td>34</td>
</tr>
<tr>
<td>2-6</td>
<td>Phagocytosis by macrophages provides a first line of cellular defense against invading microorganisms</td>
<td>36</td>
</tr>
<tr>
<td>2-7</td>
<td>The terminal complement proteins lyse pathogens by forming membrane pores</td>
<td>37</td>
</tr>
<tr>
<td>2-8</td>
<td>Small peptides released during complement activation induce local inflammation</td>
<td>39</td>
</tr>
<tr>
<td>2-9</td>
<td>Several classes of plasma protein limit the spread of infection</td>
<td>39</td>
</tr>
<tr>
<td>2-10</td>
<td>Antimicrobial peptides kill pathogens by perturbing their membranes</td>
<td>41</td>
</tr>
<tr>
<td>2-11</td>
<td>Pentraxins are plasma proteins of innate immunity that bind microorganisms and target them to phagocytes</td>
<td>43</td>
</tr>
</tbody>
</table>

**Summary to Chapter 2**

Questions

Page 43

Page 44
Chapter 3

Innate Immunity: the Induced Response to Infection 47

3-1 Cellular receptors of innate immunity distinguish ‘non-self’ from ‘self’ 47
3-2 Tissue macrophages carry a battery of phagocytic and signaling receptors 49
3-3 Recognition of LPS by TLR4 induces changes in macrophage gene expression 51
3-4 Activation of resident macrophages induces a state of inflammation at sites of infection 53
3-5 NOD-like receptors recognize bacterial degradation products in the cytoplasm 54
3-6 Inflammasomes amplify the innate immune response by increasing the production of IL-1β 55
3-7 Neutrophils are dedicated phagocytes and the first effector cells recruited to sites of infection 56
3-8 Inflammatory cytokines recruit neutrophils from the blood to the infected tissue 57
3-9 Neutrophils are potent killers of pathogens and are themselves programmed to die 59
3-10 Inflammatory cytokines raise body temperature and activate the liver to make the acute-phase response 62
3-11 The lectin pathway of complement activation is initiated by the mannose-binding lectin 63
3-12 C-reactive protein triggers the classical pathway of complement activation 66
3-13 Toll-like receptors sense the presence of the four main groups of pathogenic microorganisms 66
3-14 Genetic variation in Toll-like receptors is associated with resistance and susceptibility to disease 67
3-15 Internal detection of viral infection induces cells to make an interferon response 68
3-16 Plasmacytoid dendritic cells are factories for making large quantities of type I interferons 71
3-17 Natural killer cells are the main circulating lymphocytes that contribute to the innate immune response 71
3-18 Two subpopulations of NK cells are differentially distributed in blood and tissues 72
3-19 NK-cell cytotoxicity is activated at sites of virus infection 73
3-20 NK cells and macrophages activate each other at sites of infection 75

3-21 Interactions between dendritic cells and NK cells influence the immune response 76

Summary to Chapter 3 78

Questions 78

Chapter 4

Antibody Structure and the Generation of B-Cell Diversity 81

The structural basis of antibody diversity 82

4-1 Antibodies are composed of polypeptides with variable and constant regions 82
4-2 Immunoglobulin chains are folded into compact and stable protein domains 83
4-3 An antigen-binding site is formed from the hypervariable regions of a heavy-chain V domain and a light-chain V domain 85
4-4 Antigen-binding sites vary in shape and physical properties 86
4-5 Monoclonal antibodies are produced from a clone of antibody-producing cells 88
4-6 Monoclonal antibodies are used as treatments for a variety of diseases 90

Summary 91

Generation of immunoglobulin diversity in B cells before encounter with antigen 91

4-8 Random recombination of gene segments produces diversity in the antigen-binding sites of immunoglobulins 92
4-9 Recombination enzymes produce additional diversity in the antigen-binding site 95
4-10 Developing and naive B cells use alternative mRNA splicing to make both IgM and IgD 96
4-11 Each B cell produces immunoglobulin of a single antigen specificity 96
4-12 Immunoglobulin is first made in a membrane-bound form that is present on the B-cell surface 97

Summary 98

Diversification of antibodies after B cells encounter antigen 98

4-13 Secreted antibodies are produced by an alternative pattern of heavy-chain RNA processing 98
4-14 Rearranged V-region sequences are further diversified by somatic hypermutation 100
4-15 Isotype switching produces immunoglobulins with different C regions but identical antigen specificities 101
4-16 Antibodies with different C regions have different effector functions 103
4-17 The four subclasses of IgG have different and complementary functions  
Summary 105  
Summary to Chapter 4 107  
Questions 110

Chapter 5  
*Antigen Recognition by T Lymphocytes* 113  
T-cell receptor diversity 114  
5-1 The T-cell receptor resembles a membrane-associated Fab fragment of immunoglobulin 114  
5-2 T-cell receptor diversity is generated by gene rearrangement 115  
5-3 The RAG genes were key elements in the origin of adaptive immunity 117  
5-4 Expression of the T-cell receptor on the cell surface requires association with additional proteins 117  
5-5 A distinct population of T cells expresses a second class of T-cell receptor with \( \gamma \) and \( \delta \) chains 118

Summary 119  
Antigen processing and presentation 120  
5-6 T-cell receptors recognize peptide antigens bound to MHC molecules 121  
5-7 Two classes of MHC molecule present peptide antigens to two types of T cell 122  
5-8 The two classes of MHC molecule have similar three-dimensional structures 123  
5-9 MHC molecules bind a variety of peptides 124  
5-10 MHC class I and MHC class II molecules function in different intracellular compartments 125  
5-11 Peptides generated in the cytosol are transported to the endoplasmic reticulum for binding to MHC class I molecules 126  
5-12 MHC class I molecules bind peptides as part of a peptide-loading complex 127  
5-13 Peptides presented by MHC class II molecules are generated in acidified intracellular vesicles 129  
5-14 Invariant chain prevents MHC class II molecules from binding peptides in the endoplasmic reticulum 130  
5-15 Cross-presentation enables extracellular antigens to be presented by MHC class I 131  
5-16 MHC class I molecules are expressed by most cell types, MHC class II molecules are expressed by few cell types 132  
5-17 The T-cell receptor specifically recognizes both peptide and MHC molecule 132

Summary 133  
Antigen processing and presentation 120  
5-18 The diversity of MHC molecules in the human population is due to multigene families and genetic polymorphism 135  
5-19 The HLA class I and class II genes occupy different regions of the HLA complex 137  
5-20 Other proteins involved in antigen processing and presentation are encoded in the HLA class II region 138  
5-21 MHC polymorphism affects the binding of peptide antigens and their presentation to T cells 138  
5-22 MHC diversity results from selection by infectious disease 140  
5-23 MHC polymorphism triggers T-cell reactions that can reject transplanted organs 143

Summary 144  
Summary to Chapter 5 144  
Questions 144

Chapter 6  
The Development of B Lymphocytes 149  
The development of B cells in the bone marrow proceeds through several stages 150  
6-1 B-cell development in the bone marrow 150  
6-2 B-cell development is stimulated by bone marrow stromal cells 151  
6-3 Pro-B-cell rearrangement of the heavy-chain locus is an inefficient process 152  
6-4 The pre-B-cell receptor monitors the quality of immunoglobulin heavy chains 153  
6-5 The pre-B-cell receptor causes allelic exclusion at the immunoglobulin heavy-chain locus 154  
6-6 Rearrangement of the light-chain loci by pre-B cells is relatively efficient 155  
6-7 Developing B cells pass two checkpoints in the bone marrow 157  
6-8 A program of protein expression underlies the stages of B-cell development 157  
6-9 Many B-cell tumors carry chromosomal translocations that join immunoglobulin genes to genes that regulate cell growth 160  
6-10 B cells expressing the glycoprotein CD5 express a distinctive repertoire of receptors 161

Summary 162  
Selection and further development of the B-cell repertoire 163  
6-11 The population of immature B cells is purged of cells bearing self-reactive B-cell receptors 164
Chapter 6
The Development of B Lymphocytes

6-12 The antigen receptors of autoreactive immature B cells can be modified by receptor editing 165
6-13 Immature B cells specific for monovalent self antigens are made nonresponsive to antigen 166
6-14 Maturation and survival of B cells requires access to lymphoid follicles 167
6-15 Encounter with antigen leads to the differentiation of activated B cells into plasma cells and memory B cells 168
6-16 Different types of B-cell tumor reflect B cells at different stages of development 170

Summary to Chapter 6 172
Questions 173

Chapter 7
The Development of T Lymphocytes 177

7-1 T cells develop in the thymus 178
7-2 Thymocytes commit to the T-cell lineage before rearranging their T-cell receptor genes 180
7-3 The two lineages of T cells arise from a common thymocyte progenitor 181
7-4 Gene rearrangement in double-negative thymocytes leads to assembly of either a γ:δ receptor or a pre-T-cell receptor 183
7-5 Thymocytes can make four attempts to rearrange a β-chain gene 184
7-6 Rearrangement of the α-chain gene occurs only in pre-T cells 185
7-7 Stages in T-cell development are marked by changes in gene expression 186

Summary to Chapter 7 174
Questions 173

Chapter 8
T Cell-Mediated Immunity 199

8-1 Dendritic cells carry antigens from sites of infection to secondary lymphoid tissues 200
8-2 Dendritic cells are adept and versatile at processing pathogen antigens 202
8-3 Naive T cells first encounter antigen presented by dendritic cells in secondary lymphoid tissues 203
8-4 Homing of naive T cells to secondary lymphoid tissues is determined by chemokines and cell-adhesion molecules 204

Activation of naive T cells by antigen 199

8-5 Activation of naive T cells requires signals from the antigen receptor and a co-stimulatory receptor 206
8-6 Signals from T-cell receptors, co-receptors, and co-stimulatory receptors activate naive T cells 207
8-7 Proliferation and differentiation of activated naive T cells are driven by the cytokine interleukin-2 209
8-8 Antigen recognition in the absence of co-stimulation leads to a state of T-cell anergy 210
8-9 Activation of naive CD4 T cells gives rise to effector CD4 T cells with distinctive helper functions 211
8-10 The cytokine environment determines which differentiation pathway a naive T cell takes 213
8-11 Positive feedback in the cytokine environment can polarize the effector CD4 T-cell response 214
8-12 Naive CD8 T cells require stronger activation than naive CD4 T cells 215

Summary to Chapter 8 194
Questions 196

Chapter 9
Immune Response and Tolerance 217

9-1 T cells undergo further differentiation in secondary lymphoid tissues after encounter with antigen 193
Summary 194

Questions 196

Summary to Chapter 9 217
Questions 218
8-16 Cytotoxic CD8 T cells are selective and serial killers of target cells at sites of infection 222
8-17 Cytotoxic T cells kill their target cells by inducing apoptosis 223
8-18 Effector T_{H1} CD4 cells induce macrophage activation 224
8-19 T_{FH} cells, and the naive B cells that they help, recognize different epitopes of the same antigen 225
8-20 Regulatory CD4 T cells limit the activities of effector CD4 and CD8 T cells 226
Summary 227

Summary to Chapter 8 227
Questions 228

Chapter 9 Immunity Mediated by B Cells and Antibodies 231

Antibody production by B lymphocytes 231
9-1 B-cell activation requires cross-linking of surface immunoglobulin 232
9-2 B-cell activation requires signals from the B-cell co-receptor 232
9-3 Effective B cell-mediated immunity depends on help from CD4 T cells 234
9-4 Follicular dendritic cells in the B-cell area store and display intact antigens to B cells 235
9-5 Antigen-activated B cells move close to the T-cell area to find a helper T_{FH} cell 236
9-6 The primary focus of clonal expansion in the medullary cords produces plasma cells secreting IgM 238
9-7 Activated B cells undergo somatic hypermutation and isotype switching in the specialized microenvironment of the primary follicle 239
9-8 Antigen-mediated selection of centrocytes drives affinity maturation of the B-cell response in the germinal center 241
9-9 The cytokines made by helper T cells determine how B cells switch their immunoglobulin isotype 243
9-10 Cytokines made by helper T cells determine the differentiation of antigen-activated B cells into plasma cells or memory cells 244
Summary 245

Antibody effector functions 245
9-11 IgM, IgG, and monomeric IgA protect the internal tissues of the body 246
9-12 Dimeric IgA protects the mucosal surfaces of the body 246
9-13 IgE provides a mechanism for the rapid ejection of parasites and other pathogens from the body 247
9-14 Mothers provide protective antibodies to their young, both before and after birth 250
9-15 High-affinity neutralizing antibodies prevent viruses and bacteria from infecting cells 251
9-16 High-affinity IgG and IgA antibodies are used to neutralize microbial toxins and animal venoms 253
9-17 Binding of IgM to antigen on a pathogen’s surface activates complement by the classical pathway 255
9-18 Two forms of C4 tend to be fixed at different sites on pathogen surfaces 256
9-19 Complement activation by IgG requires the participation of two or more IgG molecules 257
9-20 Erythrocytes facilitate the removal of immune complexes from the circulation 258
9-21 Fcγ receptors enable effector cells to bind and be activated by IgG bound to pathogens 258
9-22 A variety of low-affinity Fc receptors are IgG-specific 260
9-23 An Fc receptor acts as an antigen receptor for NK cells 261
9-24 The Fc receptor for monomeric IgA belongs to a different family than the Fc receptors for IgG and IgE 262
Summary 263

Summary to Chapter 9 263
Questions 264

Chapter 10 Preventing Infection at Mucosal Surfaces 267

The communication functions of mucosal surfaces render them vulnerable to infection 267
10-2 Mucins are gigantic glycoproteins that endow the mucus with the properties to protect epithelial surfaces 269
10-3 Commensal microorganisms assist the gut in digesting food and maintaining health 269
10-4 The gastrointestinal tract is invested with distinctive secondary lymphoid tissues 272
10-5 Inflammation of mucosal tissues is associated with causation not cure of disease 273
10-6 Intestinal epithelial cells contribute to innate immune responses in the gut 275
10-7 Intestinal macrophages eliminate pathogens without creating a state of inflammation 276
10-8 M cells constantly transport microbes and antigens from the gut lumen to gut-associated lymphoid tissue 277
10-9 Gut dendritic cells respond differently to food, commensal microorganisms, and pathogens 278
10-10 Activation of B cells and T cells in one mucosal tissue commits them to defending all mucosal tissues 279
10-11 A variety of effector lymphocytes guard healthy mucosal tissue in the absence of infection 281
10-12 B cells activated in mucosal tissues give rise to plasma cells secreting IgM and IgA at mucosal surfaces 282
10-13 Secretory IgM and IgA protect mucosal surfaces from microbial invasion 283
10-14 Two subclasses of IgA have complementary properties for controlling microbial populations 285
10-15 People lacking IgA are able to survive, reproduce, and generally remain healthy 286
10-16 T_{H}2-mediated immunity protects against helminth infections 288
Summary to Chapter 10 290
Questions 292

Chapter 11
Immunological Memory and Vaccination 295

11-1 Antibodies made in a primary immune response persist for several months and provide protection 296
11-2 Low levels of pathogen-specific antibodies are maintained by long-lived plasma cells 297
11-3 Long-lived clones of memory B cells and T cells are produced in the primary immune response 297
11-4 Memory B cells and T cells provide protection against pathogens for decades and even for life 299
11-5 Maintaining populations of memory cells does not depend upon the persistence of antigen 299
11-6 Changes to the antigen receptor distinguish naive, effector, and memory B cells 300
11-7 In the secondary immune response, memory B cells are activated whereas naive B cells are inhibited 300
11-8 Activation of the primary and secondary immune responses have common features 301
11-9 Combinations of cell-surface markers distinguish memory T cells from naive and effector T cells 302
11-10 Central and effector memory T cells recognize pathogens in different tissues of the body 304
11-11 In viral infections, numerous effector CD8 T cells give rise to relatively few memory T cells 305
11-12 Immune-complex-mediated inhibition of naive B cells is used to prevent hemolytic anemia of the newborn 306
11-13 In the response to influenza virus, immunological memory is gradually eroded 307
Summary 308

Vaccination to prevent infectious disease 308
11-14 Protection against smallpox is achieved by immunization with the less dangerous cowpox virus 308
11-15 Smallpox is the only infectious disease of humans that has been eradicated worldwide by vaccination 309
11-16 Most viral vaccines are made from killed or inactivated viruses 310
11-17 Both inactivated and live-attenuated vaccines protect against poliovirus 311
11-18 Vaccination can inadvertently cause disease 312
11-19 Subunit vaccines are made from the most antigenic components of a pathogen 313
11-20 Invention of rotavirus vaccines took at least 30 years of research and development 313
11-21 Bacterial vaccines are made from whole bacteria, secreted toxins, or capsular polysaccharides 314
11-22 Conjugate vaccines enable high-affinity antibodies to be made against carbohydrate antigens 315
11-23 Adjuvants are added to vaccines to activate and enhance the response to antigen 316
11-24 Genome sequences of human pathogens have opened up new avenues for making vaccines 316
11-25 The ever-changing influenza virus requires a new vaccine every year 318
11-26 The need for a vaccine and the demands placed upon it change with the prevalence of disease 319
11-27 Vaccines have yet to be made against pathogens that establish chronic infections 322
11-28 Vaccine development faces greater public scrutiny than drug development 323

Summary 324
Summary to Chapter 11 325
Questions 326

Chapter 12

Coevolution of Innate and Adaptive Immunity 329

Regulation of NK-cell function by MHC class I and related molecules 330
12-1 NK cells express a range of activating and inhibitory receptors 330
12-2 The strongest receptor that activates NK cells is an Fc receptor 332
12-3 Many NK-cell receptors recognize MHC class I and related molecules 333
12-4 Immunoglobulin-like NK-cell receptors recognize polymorphic epitopes of HLA-A, HLA-B, and HLA-C 335
12-5 NK cells are educated to detect pathological change in MHC class I expression 336
12-6 Different genomic complexes encode lectin-like and immunoglobulin-like NK-cell receptors 339
12-7 Human KIR haplotypes uniquely come in two distinctive forms 340
12-8 Cytomegalovirus infection induces proliferation of NK cells expressing the activating HLA-E receptor 341
12-9 Interactions of uterine NK cells with fetal MHC class I molecules affect reproductive success 342

Summary 345

Maintenance of tissue integrity by γδ T cells 347
12-10 γδ T cells are not governed by the same rules as αβ T cells 347
12-11 γδ T cells in blood and tissues express different γδ receptors 348
12-12 Vγ9Vδ2 T cells recognize phosphoantigens presented on cell surfaces 350
12-13 Vγ4Vδ5 T cells detect both virus-infected cells and tumor cells 351

12-14 VγVδ1 T-cell receptors recognize lipid antigens presented by CD1d 352

Summary 354
Restriction of αβ T cells by non-polymorphic MHC class I-like molecules 354
12-15 CD1-restricted αβ T cells recognize lipid antigens of mycobacterial pathogens 354
12-16 NKT cells are innate lymphocytes that detect lipid antigens by using αβ T-cell receptors 356
12-17 Mucosa-associated invariant T cells detect bacteria and fungi that make riboflavin 357

Summary 359
Summary to Chapter 12 360
Questions 361

Chapter 13

Failures of the Body's Defenses 365

Evasion and subversion of the immune system by pathogens 365
13-1 Genetic variation within some species of pathogens prevents effective long-term immunity 366
13-2 Mutation and recombination allow influenza virus to escape from immunity 366
13-3 Trypanosomes use gene conversion to change their surface antigens 368
13-4 Herpesviruses persist in human hosts by hiding from the immune response 369
13-5 Some pathogens sabotage or subvert immune defense mechanisms 371
13-6 Bacterial superantigens stimulate a massive but ineffective CD4 T-cell response 373
13-7 Subversion of IgA action by bacterial IgA-binding proteins 374

Summary 375

Inherited immunodeficiency diseases 375
13-8 Rare primary immunodeficiency diseases reveal how the human immune system works 375
13-9 Inherited immunodeficiency diseases are caused by dominant, recessive, or X-linked gene defects 377
13-10 Recessive and dominant mutations in the IFN-γ receptor cause diseases of differing severity 378
13-11 Antibody deficiency leads to poor clearing of extracellular bacteria 379
<table>
<thead>
<tr>
<th>Section</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>13-12</td>
<td>Diminished production of antibodies also results from inherited defects in T-cell help</td>
</tr>
<tr>
<td>13-13</td>
<td>Complement defects impair antibody-mediated immunity and cause immune-complex disease</td>
</tr>
<tr>
<td>13-14</td>
<td>Defects in phagocytes result in enhanced susceptibility to bacterial infection</td>
</tr>
<tr>
<td>13-15</td>
<td>Defects in T-cell function result in severe combined immune deficiencies</td>
</tr>
<tr>
<td>13-16</td>
<td>Some inherited immunodeficiencies lead to specific disease susceptibilities</td>
</tr>
<tr>
<td>13-17</td>
<td>Acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>13-18</td>
<td>HIV is a retrovirus that causes a slowly progressing chronic disease</td>
</tr>
<tr>
<td>13-19</td>
<td>In the twentieth century, most HIV-infected people progressed in time to get AIDS</td>
</tr>
<tr>
<td>13-20</td>
<td>Genetic deficiency of the CCR5 co-receptor for HIV confers resistance to infection</td>
</tr>
<tr>
<td>13-21</td>
<td>HLA and KIR polymorphisms influence the progression to AIDS</td>
</tr>
<tr>
<td>13-22</td>
<td>HIV escapes the immune response and develops resistance to antiviral drugs by rapid mutation</td>
</tr>
<tr>
<td>13-23</td>
<td>Clinical latency is a period of active infection and renewal of CD4 T cells</td>
</tr>
<tr>
<td>13-24</td>
<td>HIV infection leads to immunodeficiency and death from opportunistic infections</td>
</tr>
<tr>
<td>13-25</td>
<td>A minority of HIV-infected individuals make antibodies that neutralize many strains of HIV</td>
</tr>
<tr>
<td></td>
<td>Summary</td>
</tr>
<tr>
<td></td>
<td>Questions</td>
</tr>
<tr>
<td>Chapter 14</td>
<td>IgE-Mediated Immunity and Allergy</td>
</tr>
<tr>
<td>14-1</td>
<td>Different effector mechanisms cause four distinctive types of hypersensitivity reaction</td>
</tr>
<tr>
<td>14-2</td>
<td>IgE-mediated immune responses defend the body against multicellular parasites</td>
</tr>
<tr>
<td>14-3</td>
<td>IgE antibodies emerge at early and late times in the primary immune response</td>
</tr>
<tr>
<td>14-4</td>
<td>Allergy is prevalent in countries where parasite infections have been eliminated</td>
</tr>
<tr>
<td></td>
<td>Summary</td>
</tr>
<tr>
<td></td>
<td>Questions</td>
</tr>
<tr>
<td>Chapter 15</td>
<td>Transplantation of Tissues and Organs</td>
</tr>
<tr>
<td></td>
<td>Allogeneic transplantation can trigger hypersensitivity reactions</td>
</tr>
</tbody>
</table>
Blood is the most common transplanted tissue. Before blood transfusion, donors and recipients are matched for ABO and the Rhesus D antigens. Incompatibility of blood group antigens causes type II hypersensitivity reactions. Hyperacute rejection of transplanted organs is a type II hypersensitivity reaction. Anti-HLA antibodies can arise from pregnancy, blood transfusion, or previous transplants. Transplant rejection and graft-versus-host disease are type IV hypersensitivity reactions. Summary

Transplantation of solid organs

Organ transplantation involves procedures that inflame the donated organ and the transplant recipient. Acute rejection is a type IV hypersensitivity caused by effector T cells responding to HLA differences between donor and recipient. HLA differences between transplant donor and recipient activate numerous alloreactive T cells. Chronic rejection of organ transplants is caused by a type III hypersensitivity reaction. Matching donor and recipient HLA class I and II allotypes improves the success of transplantation. Immunosuppressive drugs make allogeneic transplantation possible as routine therapy. Some treatments induce immunosuppression before transplantation. T-cell activation can be targeted by immunosuppressive drugs. Alloreactive T-cell co-stimulation can be blocked with a soluble form of CTLA4. Blocking cytokine signaling can prevent alloreactive T-cell activation. Cytotoxic drugs target the replication and proliferation of alloantigen-activated T cells. Patients needing a transplant outnumber the available organs. The need for HLA matching and immunosuppressive therapy varies with the organ transplanted. Summary

Hematopoietic cell transplantation

Hematopoietic cell transplantation is a treatment for genetic diseases of blood cells. Allogeneic hematopoietic cell transplantation is the preferred treatment for many cancers. After hematopoietic cell transplantation, the patient is attacked by alloreactive T cells in the graft. HLA matching of donor and recipient is most important for hematopoietic cell transplantation. Minor histocompatibility antigens trigger alloreactive T cells in recipients of HLA-identical transplants. Some GVHD helps engraftment and prevents relapse of malignant disease. NK cells also mediate graft-versus-leukemia effects. Hematopoietic cell transplantation can induce tolerance of a solid organ transplant. Summary

Summary to Chapter 15

Questions

Chapter 16

Disruption of Healthy Tissue by the Adaptive Immune Response

Every autoimmune disease resembles a type II, III, or IV hypersensitivity reaction. Autoimmune diseases arise when tolerance to self antigens is lost. HLA is the dominant genetic factor affecting susceptibility to autoimmune disease. HLA associations reflect the importance of T-cell tolerance in preventing autoimmunity. Binding of antibodies to cell-surface receptors causes several autoimmune diseases. Organized lymphoid tissue sometimes forms at sites inflamed by autoimmune disease. The antibody response to an autoantigen can broaden and strengthen by epitope spreading. Intermolecular epitope spreading occurs in systemic autoimmune disease. Intravenous immunoglobulin is a therapy for autoimmune diseases.
<table>
<thead>
<tr>
<th>Chapter 16</th>
<th>Summary to Chapter 16</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monoclonal antibodies that target TNF-α and B cells are used to treat rheumatoid arthritis</td>
<td>490</td>
<td>503</td>
</tr>
<tr>
<td>Rheumatoid arthritis is influenced by genetic and environmental factors</td>
<td>491</td>
<td>503</td>
</tr>
<tr>
<td>Autoimmune disease can be an adverse side-effect of an immune response to infection</td>
<td>492</td>
<td>503</td>
</tr>
<tr>
<td>Noninfectious environmental factors affect the development of autoimmune disease</td>
<td>494</td>
<td>503</td>
</tr>
<tr>
<td>Type 1 diabetes is caused by the selective destruction of insulin-producing cells in the pancreas</td>
<td>495</td>
<td>503</td>
</tr>
<tr>
<td>Combinations of HLA class II allotypes confer susceptibility and resistance to type 1 diabetes</td>
<td>496</td>
<td>503</td>
</tr>
<tr>
<td>Celiac disease is a hypersensitivity to food that has much in common with autoimmune disease</td>
<td>498</td>
<td>503</td>
</tr>
<tr>
<td>Celiac disease is caused by the selective destruction of intestinal epithelial cells</td>
<td>498</td>
<td>503</td>
</tr>
<tr>
<td>Senescence of the thymus and the T-cell population contributes to autoimmunity</td>
<td>501</td>
<td>503</td>
</tr>
<tr>
<td>Autoinflammatory diseases of innate immunity</td>
<td>502</td>
<td>503</td>
</tr>
</tbody>
</table>

Chapter 17

Cancer and Its Interactions With the Immune System

<table>
<thead>
<tr>
<th>Chapter 17</th>
<th>Summary to Chapter 17</th>
<th>Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer results from mutations that cause uncontrolled cell growth</td>
<td>510</td>
<td>529</td>
</tr>
<tr>
<td>A cancer arises from a single cell that has accumulated multiple mutations</td>
<td>510</td>
<td>530</td>
</tr>
<tr>
<td>Exposure to chemicals, radiation, and viruses facilitates progression to cancer</td>
<td>512</td>
<td>530</td>
</tr>
<tr>
<td>Certain common features distinguish cancer cells from normal cells</td>
<td>513</td>
<td>530</td>
</tr>
<tr>
<td>Immune responses to cancer have similarities with those to virus-infected cells</td>
<td>514</td>
<td>530</td>
</tr>
<tr>
<td>Allogeneic differences in MHC class I molecules enable cytotoxic T cells to eliminate tumor cells</td>
<td>515</td>
<td>530</td>
</tr>
<tr>
<td>Mutations acquired by somatic cells during oncogenesis can give rise to tumor-specific antigens</td>
<td>516</td>
<td>530</td>
</tr>
<tr>
<td>Cancer/testis antigens are a prominent type of tumor-associated antigen</td>
<td>517</td>
<td>530</td>
</tr>
<tr>
<td>Successful tumors evade and manipulate the immune response</td>
<td>518</td>
<td>530</td>
</tr>
</tbody>
</table>
The small intestine is the major site in the human body that interacts with microorganisms.