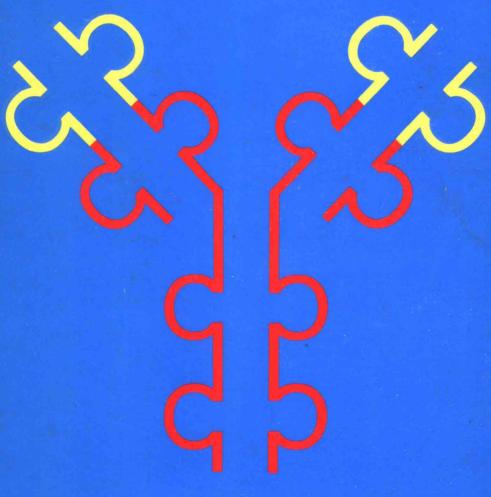
IMMUNOLOGY A Short Course

SECOND EDITION

Eli Benjamini Sidney Leskowitz



WILEY-LISS

IMMUNOLOGY A Short Course

SECOND EDITION

Eli Benjamini

Department of Medical Microbiology and Immunology School of Medicine University of California Davis, California

Sidney Leskowitz

Department of Pathology
Tufts University School of Medicine



Address all Inquiries to the Publisher Wiley-Liss, Inc., 605 Third Avenue, New York, NY 10158-0012

Copyright © 1991 Wiley-Liss, Inc.

Printed in United States of America

Under the conditions stated below the owner of copyright for this book hereby grants permission to users to make photocopy reproductions of any part or all of its contents for personal or internal organizational use, or for personal or internal use of specific clients. This consent is given on the condition that the copier pay the stated per-copy fee through the Copyright Clearance Center, Incorporated, 27 Congress Street, Salem, MA 01970, as listed in the most current issue of "Permissions to Photocopy" (Publisher's Fee List, distributed by CCC, Inc.), for copying beyond that permitted by sections 107 or 108 of the US Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

While the authors, editors, and publisher believe that drug selection and dosage and the specifications and usage of equipment and devices, as set forth in this book, are in accord with current recommendations and practice at the time of publication, they accept no legal responsibility for any errors or omissions, and make no warranty, express or implied, with respect to material contained herein. In view of ongoing research, equipment modifications, changes in governmental regulations and the constant flow of information relating to drug therapy, drug reactions and the use of equipment and devices, the reader is urged to review and evaluate the information provided in the package insert or instructions for each drug, piece of equipment or device for, among other things, any changes in the instructions or indications of dosage or usage and for added warnings and precautions.

Recognizing the importance of preserving what has been written, it is a policy of John Wiley & Sons; Inc. to have books of enduring value published in the United States printed on acid-free paper, and we exert our best efforts to that end.

Library of Congress Cataloging-in-Publication Data

```
Benjamini, Eli.
Immunology: a short course / Eli Benjamini, Sidney Leskowitz.
2nd ed.
p. cm.
Includes bibliographical references.
Includes index.
ISBN 0-471-56751-5
1. Immunology. I. Leskowitz, Sidney. II. Title.
[DNLM: 1. Allergy and Immunology. 2. Immunity. QW 50 B4681]
QR181.B395 1991
616.07'9—dc20
DNLM/DLC
for Library of Congress
```

PREFACE TO THE SECOND EDITION

An anxiety common to authors of text books in rapidly developing fields is the necessity of relatively frequent revisions to include material which, in the previous edition, was in the "twilight zone," between fact and fancy but which since has gained the status of important fact. Indeed, the rapidly developing field of immunology requires continuous revisions, hence, the present edition.

In this second edition, various concepts and findings have been updated and expanded; new information has been added on such diverse topics as the molecular biology and genes controlling antibody synthesis and isotype switch, T-cell differentiation and the T-cell receptor, antigen processing and presentation, cytokines and lymphokines, new therapeutic approaches for immunodeficiency disorders and tumors, and new aspects of prophylaxis and immunotherapy of infectious diseases. In addition, we have added a section on AIDS and several techniques such as Western blots and fluorescence-activated cell sorting. We have also expanded the glossary and added review questions as well as several clinical correlates.

Although we have deleted and shortened some sections, the expanded and added material increased somewhat the size of the book. We can, however, assure the readers that with this second edition, as with the first edition, we remain committed to the motto "less is more" and have attempted to present the principles of immunology in a concise, palatable, and easily digestible form.

Revision and change is the constant burden that authors writing about a dynamically changing field have to carry. Students, too, have to partake of that burden and must prepare themselves with the realization that science is not static and they must continually move on to new levels of understanding. Good luck to us both.

PREFACE TO THE FIRST EDITION

Why was this book written? At a time when so many excellent, extensive, and beautifully illustrated texts flood the bookstores, why offer another one? The reasons are fairly simple and rather unsophisticated. In our collective 40 some-odd years of teaching all kinds of students, we have become convinced that most texts fail their purpose because they overshoot the mark.

Anyone coming into contact with these students year after year cannot fail to appreciate the burden under which they operate. If they are to graduate, they must learn an enormous amount of material on an exceptionally diverse series of subjects, each increasing in scope yearly. As any student can tell you, every faculty lecturer considers his/her particular topic absolutely essential for future graduates, and so the pile of required "essentials" grows and grows. This is a manifestly untenable approach to curriculum.

A second cruel observation arises from long years of questioning students: many of them are not really that interested in immunology! As exciting, dynamic, and all-encompassing in its passion that we practitioners of immunology find it to be, the students have many other interests and concerns, one of which is to pass the five or six other subjects usually taken simultaneously with immunology.

This book was therefore conceived along the lines of the noted architect Mies van der Rohe's dictum, "less is more." We have devised this text to present the bare essentials of immunology in a palatable form that will enable most students to grasp the essential principles of immunology sufficiently to pass their course. For those developing a deeper interest in the field, numerous advanced and more complete texts exist to further their interests.

The book follows the outlines of most immunology courses and is divided into chapters that mostly approximate the length of an average lecture reading assignment. A short introduction setting the stage precedes each chapter, the end of each chapter contains a summary, and a series of study questions appears at the very end. The questions are designed to enable students to evaluate their own progress and comprehension; the appended answers are meant as a further learning experience. As new terms or concepts are introduced, they are italicized and defined for easy recognition and recall.

It is our hope that students using this text will avoid that choking sensation so common in a course in immunology and even conceive a curiosity about the subject that will lead to further study.

ACKNOWLEDGMENTS

The authors are deeply indebted to a number of colleagues and students for valuable contributions to the first and/or second edition of the book.

Dr. Demosthenes Pappagianis of the University of California School of Medicine at Davis contributed the chapter on immunoprophylaxis and immunotherapy, which provides useful, practical insights into the application of immunology to the prevention and therapy of infectious diseases.

Dr. Geoffrey Sunshine of Tufts University Veterinary School was deeply involved in the revision of many chapters of the second edition. His valuable and major contributions to the second edition are grate-

fully acknowledged.

Drs. Linda Werner and Jacqueline Maisonnave of the University of California School of Medicine at Davis and Drs. Peter Brodeur, Arthur Rabson, and Lanny Rosenwasser of Tufts University School of Medicine were most helpful in reading and contributing valuable suggestions to portions of the first edition. Many other colleagues reviewed portions of the text, and we are grateful for their criticisms and comments. These colleagues include Drs. James R. Carlson, Robert S. Chang, Allan C. Enders, Kent L. Erickson, Paul Luciw, Claramae H. Miller,

and Robert J. Scibienski of the University of California School of Medicine, Davis; Drs. Dov Michaeli and Patricia R. Salber of the University of California School of Medicine, San Francisco; Dr. Shoshana Levy, Stanford University School of Medicine; Dr. Henry N. Claman, University of Colorado School of Medicine; Dr. Patricia Kongshavn, McGill University School of Medicine; and Dr. Karen M. Yamaga, University of Hawaii School of Medicine. Our apologies to other colleagues whose names have been unintentionally omitted.

Finally, we applaud the forbearance of our wives, Joy and Thelma, who continued to tolerate our irritability and whining during the writing of this book.

CONTENTS

PREFACE TO THE SECOND EDITION	xxi
PREFACE TO THE FIRST EDITION	xxiii
ACKNOWLEDGMENTS	xxv
CHAPTER 1: INTRODUCTION AND OVERVIEW	
Introduction	1
Overview	2
Innate and Acquired Immunity	2
Innate Immunity	3
Acquired Immunity	3
Active, Passive, and Adoptive Immunization	4
Characteristics of the Immune Response	4
Cells Involved in the Immune Response	5
Clonal Selection Theory	6
Humoral and Cellular Immunity	8
Humoral Immunity	8
Cell-Mediated Immunity	9
Molecular Biology of the Immune Response	10
Benefits of Immunology	11
Damaging Effects of the Immune Response	12

Regulation of the Immune Response							13
The Future of Immunology							14
CHAPTER 2: ELEMENTS OF INNATE							
AND ACQUIRED IMMUNITY							
Introduction							17
Innate or Natural Immunity							18
Physiological Barriers (Skin and Mucous Membranes)							18
Phagocytosis					•		19
Inflammation							21
Fever							23
Biologically Active Substances							23
Acquired Immunity	•	·			·		23
Lymphatic Organs							24
Primary Lymphoid Organs	•	•	•		•	•	24
The Thymus Gland	•	•	•		•	•	25
Bursa of Fabricius and the Bone Marrow							26
Secondary Lymphoid Organs	•	•	•		•	•	27
The Spleen	•	•	•	•	•	•	27
Lymph Nodes							28
Circulation of Lymphocytes							30
The Fate of Antigen After Penetration	•	•	•		•	•	31
Summary							33
References							34
Review Questions							34
Answers to Review Questions							35
Allsweis to Review Questions	•	•	•		•	•	33
CHAPTER 3: IMMUNOGENS AND ANTIGENS							
Introduction							37
Requirements for Immunogenicity							38
Foreignness							38
High Molecular Weight							38
Chemical Complexity							39
Haptens							39
							40
Antigenicity							40
Major Classes of Antigens		•	•	• •	•	•	40
Binding of Antigen With Antibodies or Immunologically							42
Competent Cells							42
Cross-reactivity							42 44
imminological Adilivanis							44

CONTENTS	vii
	V !!

Summary	45
References	45
Review Questions	46
Answers to Review Questions	47
CHAPTER 4: ANTIBODY STRUCTURE	
Introduction	49
Isolation and Characterization	50
Structure of Light and Heavy Chains	51
Domains	54
Hinge Region	55
Variable Region	55
Immunoglobulin Variants	58
Classes of Immunoglobulins	58
Structural Features of IgG	58
Structural Features of IgM	59
Structural Features of IgA	60
Structural Features of IgD	61
Structural Features of IgE	62
Allotypes	62
Idiotypes	63
Summary	64
References	65
Review Questions	66
Answers to Review Questions	67
The word to Movie in Quadrate 11 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	0,
CHAPTER 5: BIOLOGICAL PROPERTIES	
OF IMMUNOGLOBULINS	
Introduction	69
Biological Properties of IgG	70
Agglutination and Formation of Precipitate	72
Passage Through the Placenta	72
Opsonization	73
Antibody-Dependent, Cell-Mediated Cytotoxicity (ADCC)	73
Activation of Complement	74
Neutralization of Toxin	74
Immobilization of Bacteria	74
Neutralization of Viruses	75
Summary	75
Riological Properties of IgA	75

Role in Mucosal Infections	76
Bactericidal Activity	76
Antiviral Activity	76
Biological Properties of IgM	77
Agglutination	77
Isohemagglutinins	77
Activation of Complement	78
Biological Properties of IgD	78
Biological Properties of IgE	79
Importance of IgE in Parasitic Infections and in Hypersensitivity	
Reactions	79
Summary	79
References	80
Review Questions	81
Answers to Review Questions	82
CHAPTER 6: THE GENETIC BASIS	
OF ANTIBODY STRUCTURE	
Introduction	83
Genetic Events in the Synthesis of Immunoglobulin Chains	84
A Brief Review of Nonimmunoglobulin Gene Structure	84
Organization and Rearrangement of Light Chain Genes	86
Organization and Rearrangement of Heavy Chain Genes	89
Regulation of Immunoglobulin Gene Expression	90
Class or Isotype Switching	91
Generation of Antibody Diversity	93
Presence of Multiple V Genes in the Germ Line	93
Combinatorial Association	93
Random Assortment of H and L Chains	93
Junctional and Insertional Diversity	94
Somatic Cell Mutation	94
Summary	95
References	95
Review Questions	96
Answers to Review Questions	98
ANTIDODY INTERACTIONS	
CHAPTER 7: ANTIGEN-ANTIBODY INTERACTIONS	10
Introduction	
Primary Interactions Between Antibody and Antigen	104
Association Constant	104

CONTENTS ix

Affinity and Avidity	105
Secondary Interactions Between Antibody and Antigen	105
Agglutination Reactions	105
Titer	106
Prozone	107
Zeta Potential	108
The Coombs' Test	108
Passive Agglutination	111
Precipitation Reaction	111
The Reaction in Solutions	111
Precipitation Reactions in Gels	113
Patterns of Identity	114
Patterns of Non-identity	114
Patterns of Partial Identity	115
Radial Immunodiffusion	115
Immunoelectrophoresis	116
Western Blots (Immunoblots)	116
Immunoassays	117
Direct Binding Immunoassays	117
Solid-Phase Immunoassays	120
Immunofluorescence	122
Direct Immunofluorescence	122
Indirect Immunofluorescence	122
Fluorescence-Activated Cell-Sorting Analysis	123
Immunoabsorption and Immunoadsorption	125
Monoclonal Antibodies	125
Summary	127
References	129
Review Questions	130
Answers to Review Questions	132
OLIADTED O. COMPLEMENT	
CHAPTER 8: COMPLEMENT	135
Introduction	136
The Complement System	
The Classical Complement Pathway	136
Activation of C1	136
Activation of C4	138
Activation of C2	138
Activation of C3	138
The Membrane Attack Complex	139

Activation of C5, C6, and C7	139
Activation of C8 and C9	139
The Alternative Complement Pathway	139
Biological Activity of Complement Components	141
Anaphylatoxins	141
Chemotaxins	142
Immune Adherence	142
Opsonization	142
Regulation of Complement Activation	143
Complement Deficiency	143
The Complement Fixation Test	144
Summary	146
References	146
Review Questions	147
Answers to Review Questions	148
CHAPTER 9: THE ONTOGENY (DEVELOPMENT)	
OF CELLS INVOLVED IN THE IMMUNE RESPONSE	151
Introduction	151
Cells Involved in the Immune Response	152
Identification and Characterization of Cells	154 154
Ontogeny of the B Lymphocyte	154
B-Cell Markers	157
Surface Immunoglobulin (sIg)	157
Fc Receptors (FcR) (CD16)	157
EBV Receptors (CD21)	158
MHC Class II Gene Products	158
Ontogeny of the T Lymphocyte	160
Selection of T Cells in the Thymus	160
Acquisition of T-Cell Markers	161
Antigen-Specific T-Cell Receptor (TcR)	161
Ti	161
CD3	
Genes Coding for Ti	162 163
γδ T Cells	
Other T-Cell Accessory Molecules	164
CD4 and CD8	164
Adhesion Molecules	165
CD2	165
TEA 1	165

Lymphocyte Homing Molecules	165
Functional Markers of T and B Cells	166
Mitogens and Lectins	166
Cells That Process and Present Antigen	166
Summary	167
References	168
Review Questions	169
Answers to Review Questions	171
CHAPTER 10: TRIGGERING THE IMMUNE RESPONSE	
Introduction	173
Kinetics of the Immune Response	174
Secondary Response	175
Cellular Cooperation in the Immune Response	176
Cell Cooperation Model for Triggering T and B Cells	176
Processing and Presentation of Protein Antigens	177
Polypeptide Degradation	177
Association With Major Histocompatibility Complex (MHC)	
Molecules	178
Activation of T Cells by Antigen	179
Engagement of Receptors	179
Second Signals	181
Lymphokine Production	181
Activation of B Cells	182
Hapten-Carrier Effect	183
T-Independent Responses	185
Cytokines	186
Summary	188
References	189
Review Questions	189
Answers to Review Questions	191
CHAPTER 11: THE ROLE OF THE MAJOR	
HISTOCOMPATIBILITY COMPLEX	
IN THE IMMUNE RESPONSE	
Introduction	193
Organization and Structure of MHC Genes and Products	194
MHC Class I Molecules	194
MHC Class II Molecules	197
MHC Class III Molecules	198

Role of the MHC in Controlling the T-Cell Response	198
MHC Restriction	199
Activation of CD8 ⁺ Cytotoxic T Cells	201
What Determines Whether an Antigen Elicits a Class I or Class II	
Restricted Response?	202
Association of Disease With MHC Type	204
Summary	205
References	206
Review Questions	207
Answers to Review Questions	208
CHAPTER 12: DISORDERS OF THE	
IMMUNE RESPONSE	
Introduction	211
Immune Deficiency Disorders	212
Primary Immunodeficiency Disorders	213
Immunodeficiency Diseases Associated With B Cells or	
Antibody	214
X-Linked Infantile Agammaglobulinemia	214
Transient Hypogammaglobulinemia	215
Common Variable Hypogammaglobulinemia	215
Selective Immunoglobulin Deficiencies	216
Immunodeficiency Disorders Associated With T Cells and	
Cell-Mediated Immunity	217
Congenital Thymic Aplasia (DiGeorge Syndrome)	217
Chronic Mucocutaneous Candidiasis	218
Severe Combined Immunodeficiency Disease (SCID)	218
Phagocytic Dysfunctions	220
Leukocyte Adhesion Deficiency (LAD)	221
Diseases Due to Abnormalities in the Complement System	221
Secondary Immunodeficiency Diseases	222
Acquired Immunodeficiency Syndrome (AIDS)	223
The Disease and Its Epidemiology	223
Human Immunodeficiency Virus (HIV)	224
Immunopathogenic Mechanisms of HIV Infection	226
Diagnosis of HIV Infection	229
Therapy and Vaccination	230
Immune Diseases Due to Abnormal Production of Immune	
Components	231
Gammopathies	231