# IMMUNOLOGY III

Joseph A. Bellanti, M.D.

#### W.B. Saunders Company 1985

Philadelphia London Toronto Mexico City Rio de Janeiro Sydney Tokyo

# IMMUNOLOGY III

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Chiyoda-Ku, Tokyo 102, Japan

#### Library of Congress Cataloging in Publication Data

Bellanti, Joseph A., 1934-

Immunology III

Rev. ed. of: Basic immunology. 2nd ed. c1984. Includes index.

1. Immunologic diseases. 2. Immunology. [DNLM: 1. Immunity. QW 504 I33]

I. Title.

RC582.B45 1985

616.07'9

84-1253

ISBN 0-7216-1668-2

Listed here is the latest translated edition of this book together with the language of the translation and the publisher.

Italian (1st Edition)-Piccin Editore, Padova, Italy

Portuguese (2nd Edition)-Editora Interamericana Ltda., Rio de Janeiro, Brazil

Spanish (1st Edition) -- Nueva Editorial Interamericana S.A. de C.V., Mexico 4 D.F., Mexico

Spanish (2nd Edition).--Nueva Editorial Interamericana S.A. de C.V., Mexico 4 D.F., Mexico

Cover illustration by Margaret Siner and Jane Hurd

Immunology III

ISBN 0-7216-1668-2

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Last digit is the print number:

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#### **Preface**

Immunology is the study of those processes used by the host to maintain constancy in his internal environment when contronted with foreign substances. Implicit in this definition is the fact that immunology embraces and discusses contributions made by both basic and clinical research observations. Thus, in the current text, contributions have come from collaborators in both the basic and the clinical sciences. *Immunology III* continues to emanate from an interdisciplinary center whose mission of research, education, and patient care is based upon the symbiotic relationship among individuals engaged in a multitude of scholarly disciplines. Moreover, since the source of the book is an international center, there is also the influence of the perspectives of the large number of visiting scientists, physicians, and students from various parts of the globe, who have greatly added to the scope and depth of the knowledge therein.

The book is directed to students at many levels: the undergraduate, the graduate, and the postgraduate. The first and second editions have been useful not only for teachers of a variety of subspecialty areas of medicine, including allergy, immunology, rheumatology, nephrology, infectious diseases, hematology-oncology, otolaryngology, and dermatology, but also for practicing physicians in need of a current overview of the state of the art in immunology to assist in the clinical management of patients. The text has also been applied to the teaching of dentistry, nursing, medical technology, and undergraduate biology. Certainly, it has been the intent of the author and his collaborators in all three editions to provide a comprehensive introductory text in immunology while maintaining a fidelity to a clinical theme.

Immunology III is organized like the previous editions—Principles, Mechanisms, and Clinical Applications. However, all chapters have been completely updated and revised to incorporate the most current information. In addition, several chapters have been expanded and new sections have been added in some, including Chapters 3 (Immunogenetics), 6 (The Complement System), 7 (Immunophysiology: Cell Function and Cellular Interactions in Antibody Formation), 10 (Immunomodulation: Immunopotentiation, Tolerance and Immunosuppression), 19 (Immune Defense Mechanisms in Tumor Immunity), and 21 (Neoplasms of the Immune System: Monoclonal Gammopathies and Lymphomas and Leukemias). Considerable basic knowledge has been stressed throughout the text, including the genetic diversity of antibody and immunoglobulins as well as the exciting applications of hybridoma technology. Also included in the present text is the most current knowledge of cells and subsets of cells based upon identification through monoclonal antibodies that identify new antigenic and cell surface receptors.

Many persons have contributed to the preparation of the third edition, and I wish to express my indebtedness to them. First, I would like to thank Dr. Philip L. Calcagno, who has been most generous and gracious in his support

xii Preface

and encouragement of this endeavor. I would like to express my sincere appreciation to Miss Jane Hurd and Miss Margaret Siner for the continued development of the imaginative figures that illustrate the concepts of the chapters of this book so vividly. Others who have read sections of the manuscript or who have made helpful suggestions include the following: Mrs. Barbara Zeligs, Dr. Lata Nerurkar, Dr. Anne Morris Hooke, Dr. Daniel Sordelli, Dr. Cristina Cerquetti, Dr. Robert M. Chanock, Dr. Robert H. Purcell, Dr. John Gerin, Dr. Anthony Fauci, Dr. Lawrence D. Frenkel, Dr. John Dwyer, and Dr. David M. Asher.

Particular appreciation is owed to a special friend who stayed at my side throughout the revision of *Immunology III* and who made this oftentimes tedious task a joy with his uplifting spirit and steadfast and gentle determination as the book progressed through its many drafts, illustrations, and galley and page proofs. Father Josef Kadlec, priest, physician, ethicist, microbiologist, immunologist, and friend: Thank you for persevering with me in this endeavor.

My appreciation is also extended to other colleagues at Georgetown and to my clinical and research fellows and house staff who have contributed to my intellectual life and to the life of the Immunology Center. I owe a special debt of gratitude to students of all ages for whom the book is written. Learning represents a joy of discovery shared between the student and the teacher, and it is in this spirit that *Immunology III* was written. The book is a product of conversations that I have had with every student I have met. It is the questions they ask in the lecture hall, the laboratory, and the clinic and at the bedside that have provided me with the incentive to write. Although many individuals have contributed information to this text, I alone assume responsibility for any errors found within these pages.

I wish also to thank Diane Hargrave Goldstein for her diligent typing of the entire manuscript.

Finally, I wish to express my thanks and appreciation to Mr. Albert Meier, to Ms. Constance Burton, and to Mr. Frank Polizzano and other colleagues at W. B. Saunders Company for their patience, support, suggestions, and inspiration during the lengthy preparation of this third revision.

JOSEPH A. BELLANTI

## Contents

Section One THE PRINCIPLES OF IMMUNOLOGY	1
Chapter 1 Introduction to Immunology  Joseph A. Bellanti, M.D., and Josef V. Kadlec, S.J., M.D.	1
Chapter 2 General Immunobiology  Joseph A. Bellanti, M.D., and Josef V. Kadlec, S.J., M.D.	- 16
Chapter 3 Immunogenetics	54
Chapter 4 Antigens and Immunogenicity	79
Chapter 5 Antibody and Immunoglobulins: Structure and Function  George M. Bernier, M.D.	89
Chapter 6 The Complement System	106
Chapter 7 Immunophysiology: Cell Function and Cellular Interactions in Antibody Formation	117
Chapter 8 Antigen-Antibody Interactions	160
Chapter 9 Cell-Mediated Immune Reactions  Joseph A. Bellanti, M.D., and Ross E. Rocklin, M.D.	176
	xlii

Chapter 10	
Immunomodulation: Immunopotentiation, Tolerance, and Immunosuppression	. 189
A Unifying Model for Immunologic Processes	
Section Two MECHANISMS OF RESPONSE	. 208
Part I	
Mechanisms of Tissue Injury	208
Chapter 12	
Inflammation Peter A. Ward, M.D.	208
Chapter 13	
Mechanisms of Tissue Injury Produced by Immunologic Reactions  Peter M. Henson, Ph.D., B.V.M.&S., M.R.C.V.S	218
Part II  Protective Mechanisms Involved in the Immune Response to Infectious Agents	261
Chapter 14	
Host-Parasite Relationships  Joseph A. Bellanti, M.D.	261
Chapter 15	
Mechanisms of Immunity to Bacterial Diseases	272
Chapter 16	
Mechanisms of Immunity to Viral Diseases  Joseph A. Bellanti, M.D.	283
Chapter 17	
Mechanisms of Immunity to Parasitic Diseases  Raymond H. Cypess, D.V.M., Ph.D.	306
Chapter 18	
Mechanisms of Immunity to Fungal Diseases.  Joseph A. Bellanti, M.D., and John P. Utz, M.D.	323
Chapter 19	
Immune Defense Mechanisms in Tumor Immunity	330

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Contents XV

Section Three	
CLINICAL APPLICATIONS OF IMMUNOLOGY	346
Chapter 20	
Immunologically Mediated Diseases	346
A. Immunologically Mediated Disease Involving Exogenous Antigens (Allergy)	349
B. Immunologically Mediated Disease Involving Allogeneic Antigens  Chester M. Zmijewski, Ph.D.	390
Organ Transplantation	396
C. Immunologically Mediated Disease Involving Autologous Antigens	409
Chapter 21	
Neoplasms of the Immune System	447
A. Monoclonal Gammopathies  George M. Bernier, M.D.	
B. Lymphomas and Leukemias  Jeffrey Cossman, M.D.	460
Chapter 22	
Immune Deficiency Disorders  Joseph A. Church, M.D., and Robert J. Schlegel, M.D.	471
Chapter 23	
Immunoprophylaxis: The Use of Vaccines  Joseph A. Bellanti, M.D., and John B. Robbins, M.D.	508
Chapter 24	
Immunotherapy: The Use of Passive Immunization.  Joseph A. Bellanti, M.D., and John B. Robbins, M.D.	533
Chapter 25	
Clinical Aspects of Immunosuppression: Use of Cytotoxic Agents	
and Corticosteroids	546
Chapter 26	
Diagnostic Applications of Immunology	558
Approach to the Patient with Immunologic Disease	571
Appendix 1 Problem: Repeated Infections in the Young Infant	571
Appendix 2 Problem: Repeated Infections in the Adult Patient	
Appendix 3 Problem: Approach to Patient with "Allergic" (Hypersensitivity) Disease	576

#### XVI

#### Content

Appendix 4 Problem: Approach to Immunologic Disease in the Newborn (Isoimmunization and Immunologic Problems in the Mother Affecting the Infant)	578
Appendix 5	
Problem: Approach to Patient with Musculoskeletal ("Autoimmune") Disorders	580
Appendix 6	
Problem: Use of Immunology in Diagnosis of Infectious Diseases	582
Index	585

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## THE PRINCIPLES OF IMMUNOLOGY

#### Chapter 1

### Introduction to Immunology

Joseph A. Bellanti, M.D., and Josef V. Kadlec, S.J., M.D.

#### HISTORICAL BACKGROUND

The concepts of immunology are ancient and pragmatic and are derived primarily from the study of resistance to infection. It was known for centuries before the discovery of the germ theory of infectious disease that recovery from illness was accompanied by the ability to resist reinfection. Thus, the elements of classical immunology preceded bacteriology and contributed to it. In more recent years, contributions to immunology have come from both the basic sciences, e.g., biochemistry, anatomy, developmental biology, genetics, pharmacology, and pathology, as well as from the study of clinical entities, e.g., allergy, infectious diseases, organ transplantation, rheumatology, immune deficiency diseases, and oncology. These fields, in turn, have been enhanced by the application of immunologic principles. Shown in Figure 1-1 is a schematic representation of some major milestones important in the development of immunology.

Preceding modern medicine, Chinese physicians in the eleventh century observed that the inhalation of smallpox crusts prevented the subsequent occurrence of the disease. Later, the technique of variolation, the intradermal application of powdered scabs, was used in the Middle East, where its primary intent was esthetic—"preserving the beauty of their daughters." This primitive immuni-

zation reached England in the eighteenth century through Pylarini and Timoni and was later popularized by Lady Mary Wortley Montagu (Fig. 1–2). Wide variations in vaccination procedures, however, occasionally led to death, which prevented the full acceptance of this form of therapy.

The future of modern immunobiology was assured when Edward Jenner (Fig. 1-3), as a medical student, made the surprisingly sophisticated discovery that inoculation with cowpox crusts protected humans from smallpox. This important finding resulted from Jenner's observation that milkmaids who had contracted cowpox were resistant to infection

with smallpox.

The enhancement and further development of preventive immunization were made possible by Louis Pasteur (Fig. 1-4), who coined the term "vaccine" (from vacca: L., cow) in honor of Jenner's contribution. Pasteur's researches led to the development of the germ theory of disease, from which he developed techniques for the in vitro cultivation of microorganisms. This work produced material that could now be used for vaccines: living, heat-killed, and attenuated (living but with reduced virulence). During these investigations, Pasteur observed that old cultures (attenuated) of fowl cholera organisms when inoculated into fowl produced no disease. Surprisingly, these fowl were resistant to subsequent infection with the organism and were

	Ehrlich* (1908) (side cham theory)	HCMORAL	Landariner—180 blood groups Heidelberger quantitative precipital reaction	Kabat and Tischus— demonstration that antibodies aregamma globulins Pauling—primary structure	Porters structure and (1972) Edelman   formation of gamma   globulin   Johansson and Ishizaka—discovery of IgE   Yalow*—development of radioimmunoassay
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Chinese—prophylactic infection to prevent smallbox Jenner—carpox raccination Koch—discoursed delayed hypersensitivity to tuberculosis (cell-mediated immunity) Pasteur—derieluped killed and attenuated vaccines Roux and Yersin—first described bacterial toxins von Behring* and Kitasato*—first described autitoxins (1902) Buchner—discovered complement (alexine) Pletifer and Bordet*—elucidated action of complement and antibody in self-hiss (1919)	bacteria Widal-described test for diagnosis of typhoid fever	THEORIES OF IMMUNITY  That injury	Richet* and Portier— anaphylaxus Arthus—specific necrotic lesions; Arthus reaction voa Pirquet— allergy	Sanarelli-Shwartzman— necrotic reactions: endotoxin Landsteiner* and Chase— cellular transfer	of "delayed hyper- sensitivity" (1930)  Bergstrom.* Samuelsson.* Vane*—Leutotrienes:  1962)  Parediators of immediate hyper-eactions did inflammation withners in immunology are indicated by an asterisk.* and the date of award is shown in parentheses
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Figure 1-1. Major milestones in immunology.



Figure 1–2. Lady Mary Wortley Montagu. (Courtesy of National Library of Medicine.)



Figure 1–3. Edward Jenner (1749–1823). (Courtesy of National Library of Medicine.)

solidly immune. This use of living, attenuated, or heat-killed cultures is still our therapy of choice in the prophylaxis of many infectious diseases (Fig. 1–5), a process referred to as active immunization (Chapter 23).

Later, Robert Koch (Fig. 1-6) discovered the tubercle bacillus during his studies of the bacterial etiology of infectious diseases. While attempting to develop a vaccine for tuberculosis, he observed the phenomenon known today as delayed hypersensitivity or cell-mediated immunity (Chapter 9).

Following the isolation of the diphtheria bacillus, Roux and Yersin demonstrated the existence of a potent soluble exotoxin elaborated by this organism (Fig. 1–7). This toxin was used by von Behring (Fig. 1–8) and Kitasato to inoculate animals that produced in their serum a toxin-neutralizing substance called *antitoxin*. This neutralizing capability

to foreignme



Figure 1-4. Louis Pasteur (1822-1895). (Courtesy of National Library of Medicine.)



Figure 1-5. Louis Pasteur, to left, watches as an assistant inoculates a boy for "hydrophobia" (rabies). (Wood engraving in "L'Illustration" from Harper's Weekly 29:836, 1885; courtesy of National Library of Medicine.)

could be transferred by the serum to uninoculated animals, a process called passive immunization. Their work formed a model for the modern techniques of preventing disease through passive immunization (immunotherapy). Pfeiffer and Bordet's work differentiated a substance in serum, distinct from antibody, called complement that also participates in the destruction of bacteria. The observations of Durham and von Gruber that serum could clump or agglutinate bacteria formed the basis for tests for the diagnosis of infectious specific agglutination reactions, such as the test described by Widal for the diagnosis of typhoid fever (Widal test).

Up to the turn of the century, the French and German schools dominated these areas of immunologic research. At that time there emerged two divergent vantage points from which immunology was observed and later developed: (1) the humoral, whose emphasis was the study of chemical products (i.e., antibodies) elaborated by cells, and (2) the cellular, whose emphasis was the biologic effects of intact cells involved in the host's response to foreignness (see Fig. 1-1). Paul Ehrlich (Fig. 1-9) proposed the humoral theory of antibody formation, and Elie Metchnikoff (Fig. 1-10) almost simultaneously developed the cellular theory of immunity. Both were correct, since in the individual both cellular and humoral factors are intimately interwoven and interdependent.

Ehrlich's side-chain theory proposed the pre-existence of receptors on the living cell surface that reacted with toxins; the excess receptors eventually could be released into the circulation as antibody (Fig. 1-11). It is ironic that one of the major areas of immunologic research today is the study of receptors on immunocompetent cells (Chapter 7). Subsequently, the major emphasis in immunology was directed at the identification, characterization, and biologic function of humoral factors (see Fig. 1-1).

Metchnikoff's theories of cellular immunity held that the body's scavenger cells, the phagocytes, were the prime detectors of foreign material as well as its primary defense system. His concepts went unrecognized for several decades but today represent an area of intensive immunologic research. Both cel-