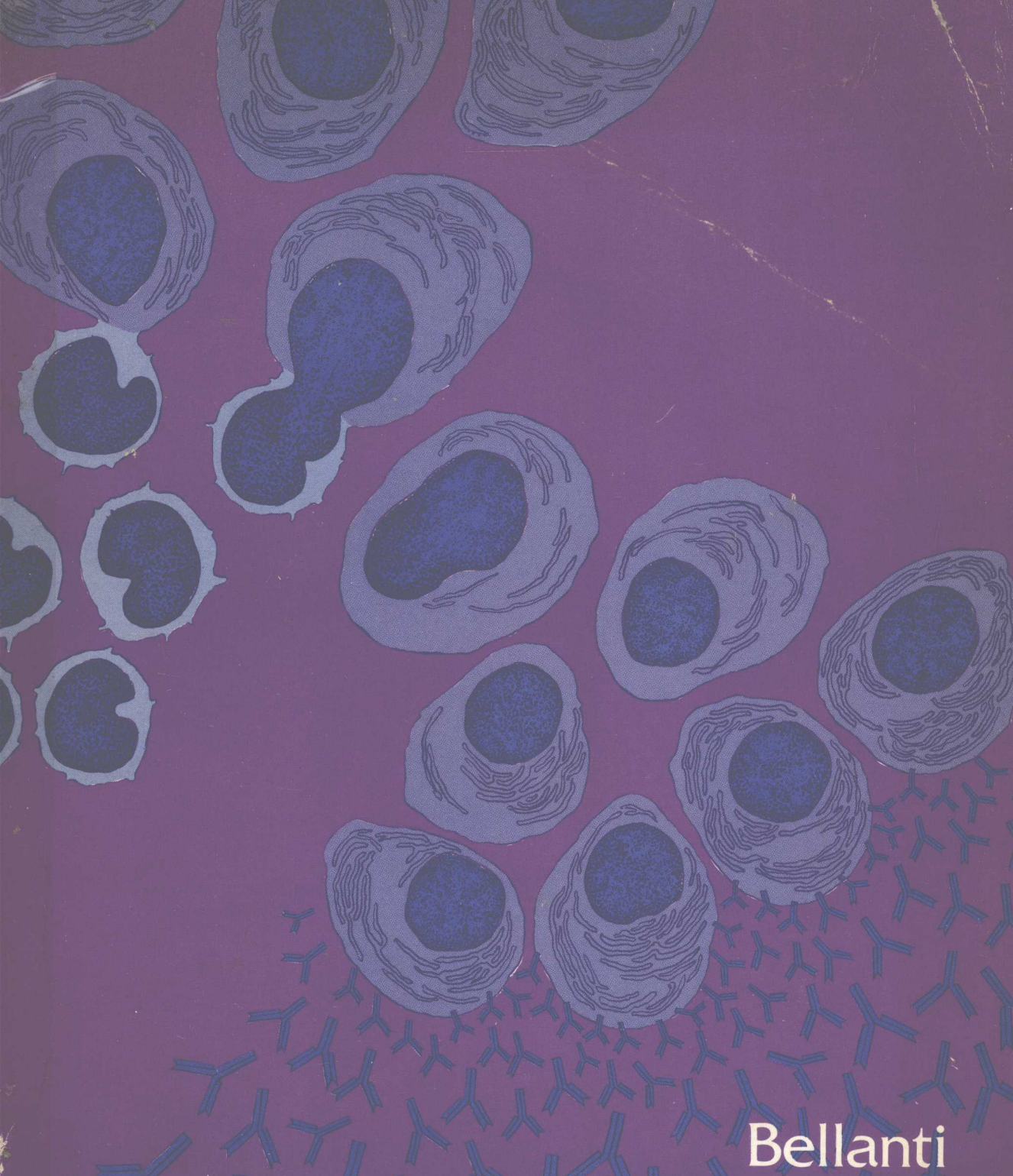


Bellanti

IMMUNOLOGY

Basic Processes

W.B. Saunders Company 1985
Philadelphia London Toronto Mexico City Rio de Janeiro Sydney Tokyo

SECOND EDITION

IMMUNOLOGY

Basic Processes

Joseph A. Bellanti, M.D.

Professor of Pediatrics and Microbiology
Director, International Center for
Interdisciplinary Studies of Immunology
Georgetown University School of Medicine
Washington, D.C.

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

Apartado 26370—Cedro 512
Mexico 4, D.F., Mexico

Rua Coronel Cabrita, 8
Sao Cristovao Caixa Postal 21176
Rio de Janeiro, Brazil

9 Waltham Street
Artarmon, N.S.W. 2064, Australia

Ichibancho, Central Bldg., 22-1 Ichibancho
Chiyoda-Ku, Tokyo 102, Japan

Library of Congress Cataloging in Publication Data

Bellanti, Joseph A., 1934–

Immunology: Basic Processes

Rev. ed. of: Immunology, basic processes. 1979.

1. Immunology. I. Bellanti, Joseph A., 1934– Immunology, basic processes. II. Title. [DNLM: 1. Immunity. QW 504 B3115]

QR181.B388 1985 616.07'9 84–3121

ISBN 0–7216–1244–X

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

Portuguese (*1st Edition*)—Editora Interamericana Ltda., Rio de Janeiro, Brazil

Cover illustration by Margaret Siner and Jane Hurd

Immunology: Basic Processes ISBN 0-7216-1244-X

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

This edition is dedicated with affection to my parents, my wife Jacqueline, and my children Dawn, Lisa, Jeannine, Loretta, Maria, Joseph (who was born during the First Edition), and little Tony (who was born during the Second Edition) and to my grandchildren Jeannine, Shannan, Mark, and Kristen (who were born during the preparation of the Third Edition).

Contributors

Joseph A. Bellanti, M.D.
Professor of Pediatrics and Microbiology, and Director, International Center for Interdisciplinary Studies of Immunology, Georgetown University School of Medicine, Washington, D.C.
Introduction to Immunology; General Immunobiology; Immunogenetics; Antigen-Antibody Interactions; Cell-Mediated Immune Reactions; A Unifying Model for Immunologic Processes

George M. Bernier, M.D.
Joseph M. Huber Professor and Chairman of Medicine, Dartmouth Medical School; Chairman of Medicine, Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire.
Antibody and Immunoglobulins: Structure and Function

Lynn H. Caporale, Ph.D.
Assistant Professor of Biochemistry, Georgetown University Medical Center, Washington, D.C.
The Complement System

Herbert B. Herscowitz, Ph.D.
Professor of Microbiology, Georgetown University Schools of Medicine and Dentistry, Washington, D.C.
Immunophysiology: Cell Function and Cellular Interactions in Antibody Formation

Anne L. Jackson, Ph.D.
Becton-Dickinson Monoclonal Center, Mountain View, California.
Antigens and Immunogenicity

Josef V. Kadlec, S.J., M.D.
Assistant Professor of Pediatrics and Microbiology, Georgetown University Medical School; Member, International Center for Interdisciplinary Studies of Immunology, Georgetown University Hospital, Washington, D.C.
Introduction to Immunology; General Immunobiology

Paul Katz, M.D.
Associate Professor of Medicine, and Director, Division of Rheumatology, Immunology, and Allergy, Georgetown University School of Medicine; Attending Physician, Georgetown University Hospital, Washington, D.C.
Immunomodulation: Immunopotentiation, Tolerance, and Immunosuppression

Steven L. Kunkel, Ph.D.

Assistant Professor, Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan.
The Complement System

Ross E. Rocklin, M.D.

Professor of Medicine, Tufts University School of Medicine; Chief, Allergy Division, New England Medical Center, Boston, Massachusetts.
Cell-Mediated Immune Reactions

Kenneth W. Sell, M.D., Ph.D.

Clinical Professor of Pediatrics, Georgetown University School of Medicine, Washington, D.C.; Scientific Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.
Immunogenetics

Carl-Wilhelm Vogel, M.D.

Assistant Professor of Biochemistry and Medicine; Member, International Center for Interdisciplinary Studies of Immunology, and Vincent T. Lombardi Cancer Center, Georgetown University Schools of Medicine and Dentistry, Washington, D.C.
The Complement System

Peter A. Ward, M.D.

Professor and Chairman, Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan.
The Complement System

James N. Woody, Capt., MC., U.S.N., M.D., Ph.D.

Professor of Pediatrics and Microbiology, Georgetown University School of Medicine, Washington, D.C.; Director, Transplantation Research Program Center, Naval Medical Research Institute, Bethesda, Maryland.
Immunogenetics

Chester M. Zmijewski, Ph.D.

Associate Professor, Department of Pathology and Laboratory Medicine; Associate Director, Department of Pathology and Laboratory Medicine; Director, Immunology, University of Pennsylvania, Philadelphia, Pennsylvania.
Antigen-Antibody Interactions

Preface

The Second Edition of *Immunology: Basic Processes* comprises the first of three sections of a larger book entitled *Immunology III,* which, in addition to the fundamental principles, discusses mechanisms and clinical applications. *Immunology: Basic Processes* is directed to undergraduate, predoctoral, nursing, and medical technology students as well as to any readers wishing a contemporary overview of the elementary concepts of immunology.

All chapters have been completely updated and revised. New sections have been added to Chapters 3 (Immunogenetics), 6 (Complement Activity), 7 (Immunophysiology: Cell Function and Cellular Interactions), and 10 (Immunomodulation: Immunopotentiation, Tolerance, and Immunosuppression). These changes reflect our increasing awareness of the genetic diversity of antibody and immunoglobulins as well as the use of monoclonal antibodies to identify new antigenic and cell surface receptors.

Many persons have contributed to the preparation of the Second 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 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 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 owing to a special friend who stayed at my side throughout the revision of the book 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 my 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 by the student and the teacher, and it is in this spirit that the book is written. It 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, in the laboratory, in 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 revision.

JOSEPH A. BELLANTI

Contents

Chapter 1

Introduction to Immunology

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

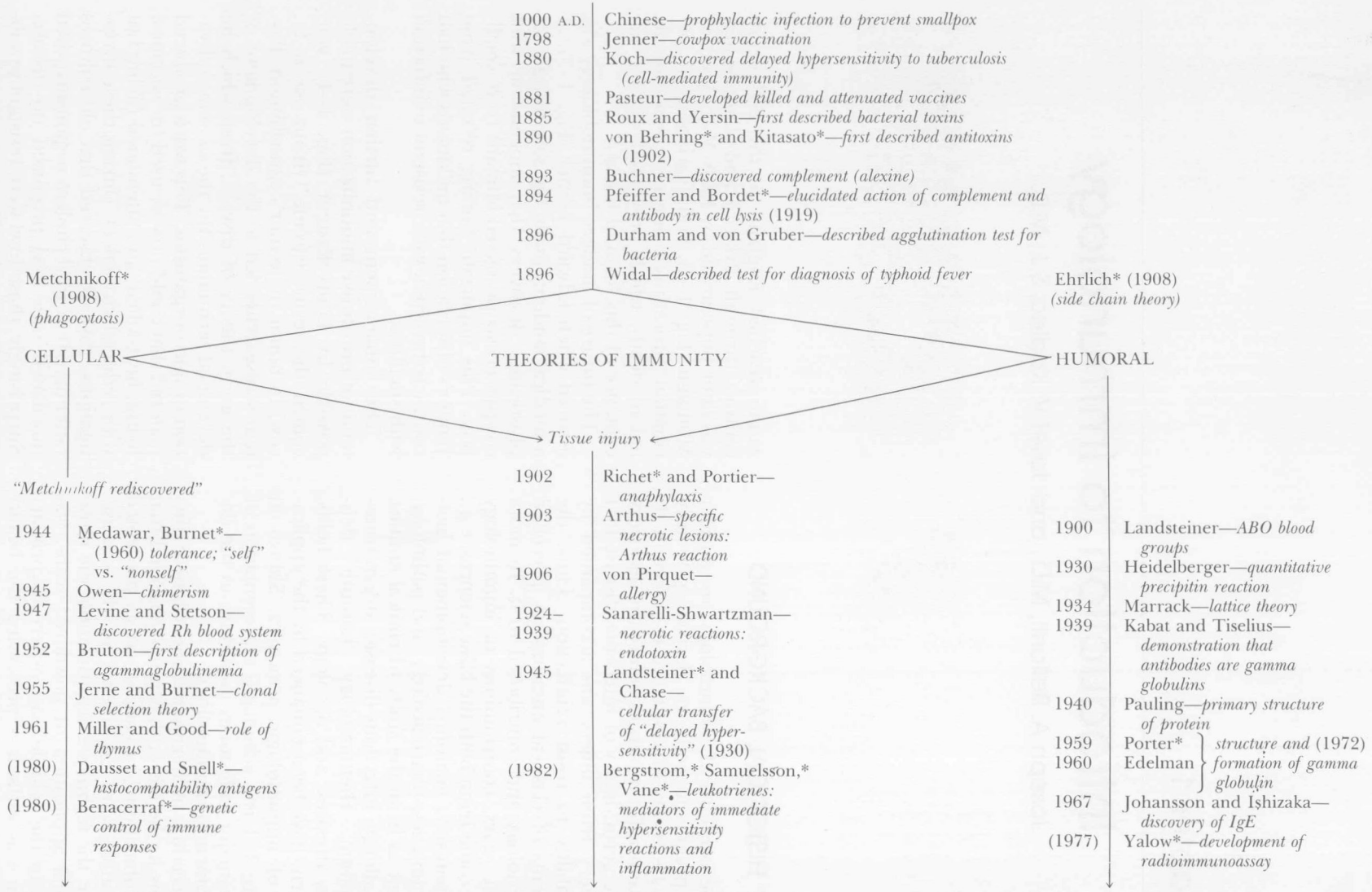
HISTORICAL BACKGROUND

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 immunization 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



Nobel Prize winners in immunology are indicated by an asterisk,* and the date of award is shown in parentheses.

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*.

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

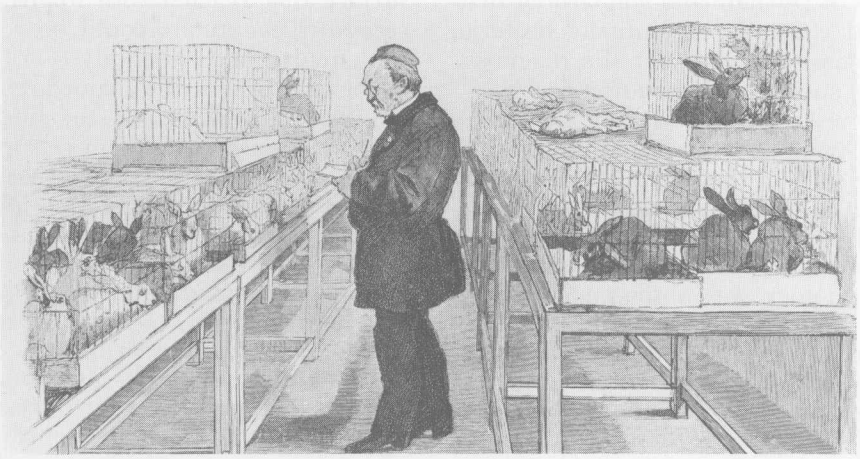


Figure 1–4. Louis Pasteur (1822–1895). (Courtesy of National Library of Medicine.)

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-

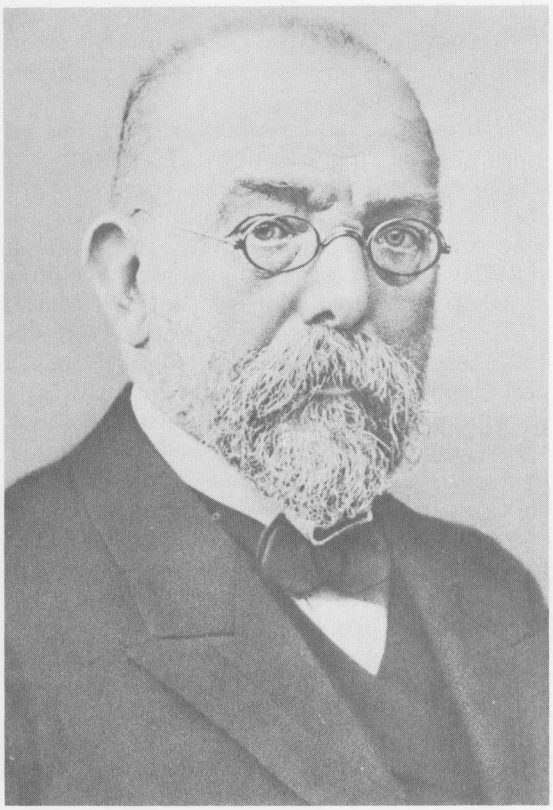


Figure 1–6. Robert Koch (1843–1910). (Courtesy of National Library of Medicine.)

Figure 1–7. Pierre Paul Emile Roux (1853–1933). (Courtesy of National Library of Medicine.)

Figure 1–8. Emil Adolf von Behring (1854–1917). (Courtesy of National Library of Medicine.)

Figure 1–9. Paul Ehrlich (1854–1915). (Courtesy of National Library of Medicine.)

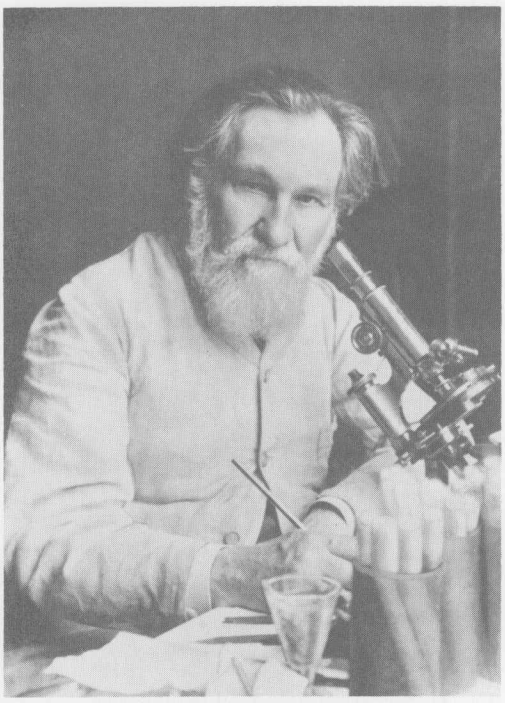
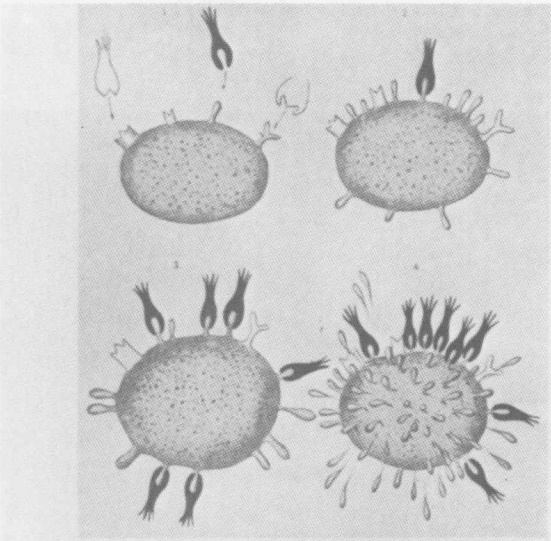


Figure 1–10. Elie Metchnikoff (1845–1916). (Courtesy of National Library of Medicine.)

lular and humoral factors are involved in understanding the principles underlying the immunologic processes that result in protection or tissue injury.

Today, there still remain two schools of immunologic investigation. The humoral school reached its peak with the discovery and characterization of the protein molecules that contain antibody activity, the *immunoglobulins* (Chapter 5). This work has culminated in the elucidation of the total amino acid sequence of almost all antibody molecules. At the same time, the cellular area is now being actively investigated from the standpoint of protection against infectious agents and graft rejection as well as immunity to tumors in man. The cellular-humoral dichotomy is also illustrated by the clinical observations of increased susceptibility to infection seen in individuals with congenital defects of the immunologic system. Some lack the humoral protective function but retain the cellular; others are deficient in cellular but have normal humoral activity; still others are defective in both humoral and cellular functions. Clearly, both areas are of pro-



DIAGRAMMATIC REPRESENTATION OF THE SIDE-CHAIN THEORY
(PLATES I AND II)

Fig. 1 "The groups [the haptophore group of the side-chain of the cell and that of the food-stuff or the toxin] must be adapted to one another, *e.g.*, as male and female screw (PASTEUR), or as lock and key (E. FISCHER)."

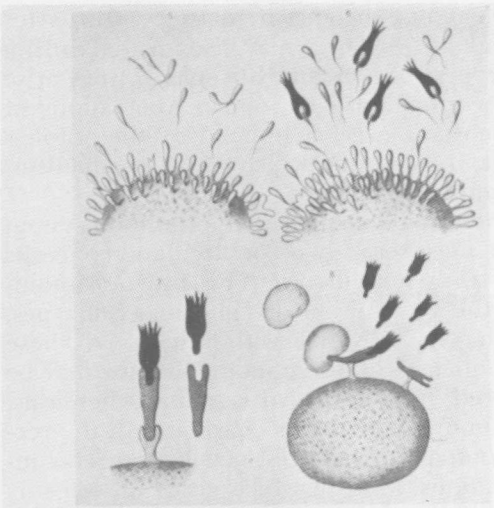
Fig. 2 ". . . the first stage in the toxic action must be regarded as being the union of the toxin by means of its haptophore group to a special side-chain of the cell protoplasm."

Fig. 3 "The side-chain involved, so long as the union lasts, cannot exercise its normal, physiological, nutritive function . . ."

Fig. 4 "We are therefore now concerned with a defect which, according to the principles so ably worked out by . . . Weigert, is . . . [overcorrected] by regeneration."

Figure 1–11. Diagrammatic representation of the side-chain theory, showing the presence of pre-existing receptors on the cell surface *(A)*, which when produced in excess *(B)* could be released as antibody. (From Croonian Lecture, "On Immunity with Special Reference to Cell Life," Proc. R. Soc. Lond. (Biol.), *66*:424, 1906; courtesy of National Library of Medicine.)

Illustration continues on opposite page



DIAGRAMMATIC REPRESENTATION OF THE SIDE-CHAIN THEORY

(cont.)

Fig. 5 ". . . the antitoxins represent nothing more than the side-chains, reproduced in excess during regeneration and therefore pushed off from the protoplasm—thus coming to exist in a free state."

Fig. 6 [The free side-chains (circulating antitoxins) unite with the toxins and thus protect the cell.]

Fig. 7 ". . . two haptophore groups must be ascribed to the 'immune-body' [haemolytic amboceptor], one having a strong affinity for a corresponding haptophore group of the red blood corpuscles, . . . and another . . . which . . . becomes united with the 'complement' . . ."

Fig. 8 "If a cell . . . has, with the assistance of an appropriate side-chain, fixed to itself a giant [protein] molecule . . . there is provided [only] one of the conditions essential for the cell nourishment. Such . . . molecules . . . are not available until . . . they have been split into smaller fragments. This will be . . . attained if . . . the 'tentacle' . . . possesses . . . a second haptophore group adapted to take to itself ferment-like material . . ."

Figure 1–11. *Continued.*

found importance to man. Although one or the other aspect will be stressed at times throughout this book, cellular and humoral factors of immunity are interrelated and interdependent.

Immunity and Hypersensitivity

The term *immune* is derived from the Latin *immunis* (free from taxes or free from burden). In classical usage, immunity referred to the relative resistance of the host to reinfection by a given microbe. It is now evident that immune responses are not always beneficial, nor are they associated solely with resistance to infection. On the contrary, they can even confer unpleasant and harmful effects on the host. The noxious effect has been called *hypersensitivity* or *allergy*. Listed in Figure 1–1 are some of the pioneers who contributed to this field of tissue injury. The immunologic system is equipped not only to perform a *defense* function against infectious agents but also to concern itself with the more diverse biologic functions of *homeostasis* and *surveillance* (Table 1–1).

At the turn of the century, von Pirquet put forward a hypothesis to explain the multifaceted aspects of the immune response. He coined the term "allergy" to mean "altered reactivity" of the host; one change was recognized as immunity, and the other as hypersensitivity. Von Pirquet made no distinction between beneficial and harmful responses and suggested that they were all manifestations of a common biologic process of sensitization, which he encompassed by the term "allergy". He restricted the use of the term "immunity" to mean protection from infectious agents and the term "allergy" for a more generalized reactivity of the host to foreign substances. Over the years, allergy and immunity have become reversed in their meanings; immunity has come to mean that which von Pirquet defined originally as allergy, and allergy has come to mean hypersensitivity. Nevertheless, von Pirquet's concepts of the broad scope of the immune response are now accepted in immunology.

IMMUNOLOGY IN THE MODERN SENSE

A contemporary definition of immunity would include "all those physiologic mecha-

Table 1–1. Functions of the Immune System

Function	Nature of Immunologic Stimulus	Example	Aberrations	
			Hyper-	Hypo-
Defense	Exogenous	Microorganisms	Allergy	Immunologic deficiency disorders
Homeostasis	Endogenous or exogenous	Removal of effete and damaged cells	Autoimmune disease	—
Surveillance	Endogenous or exogenous	Removal of cell mutants	—	Malignant disease