IMMUNOLOGY III

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Preface

Immunology is the study of those processes used by the host to maintain constancy in his internal environment when confronted 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

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

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Section One

THE PRINCIPLES OF IMMUNOLOGY

Chapter 1

Introduction to Immunology

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

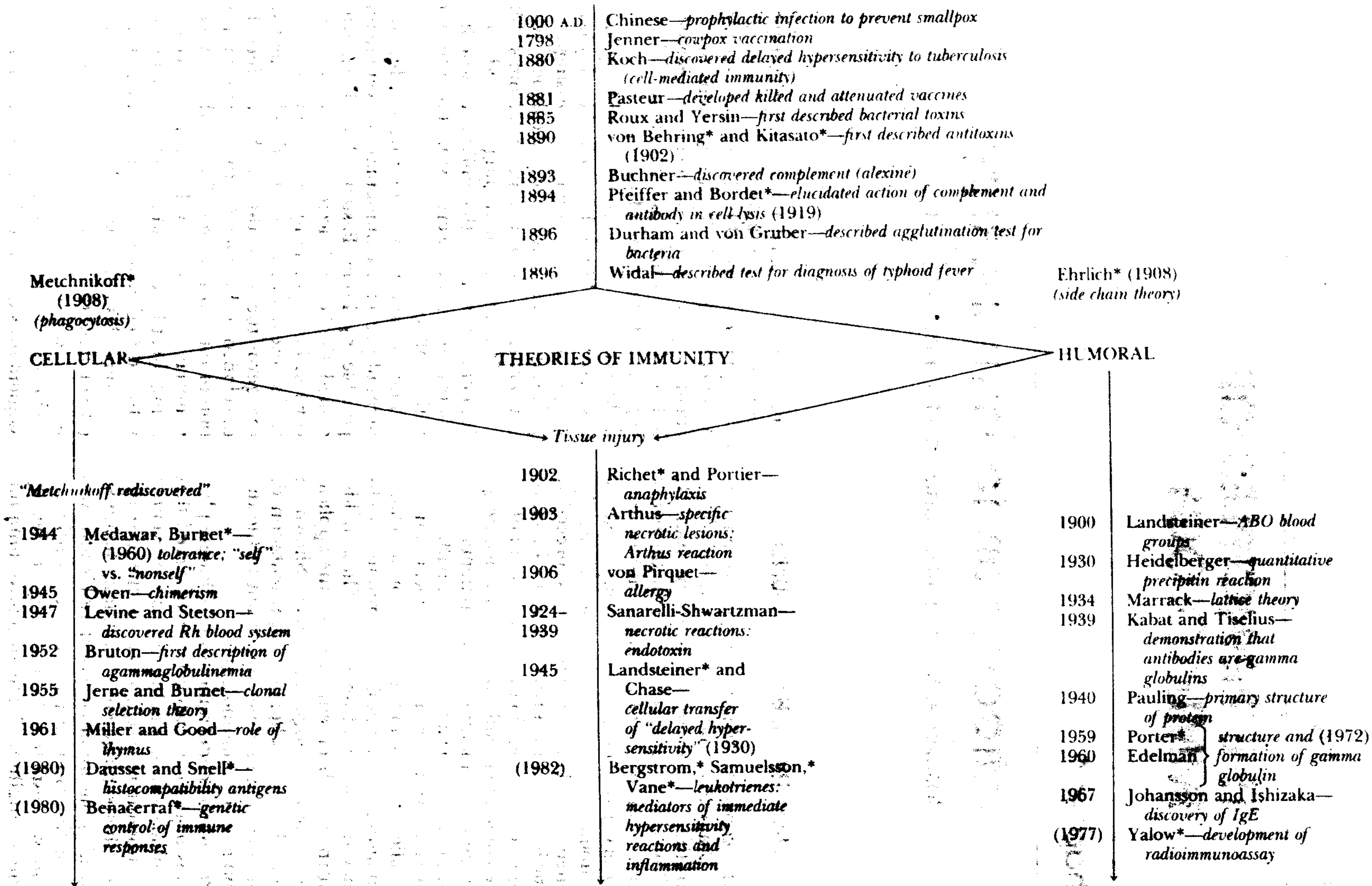
HISTORICAL BACKGROUND

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 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* (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

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-