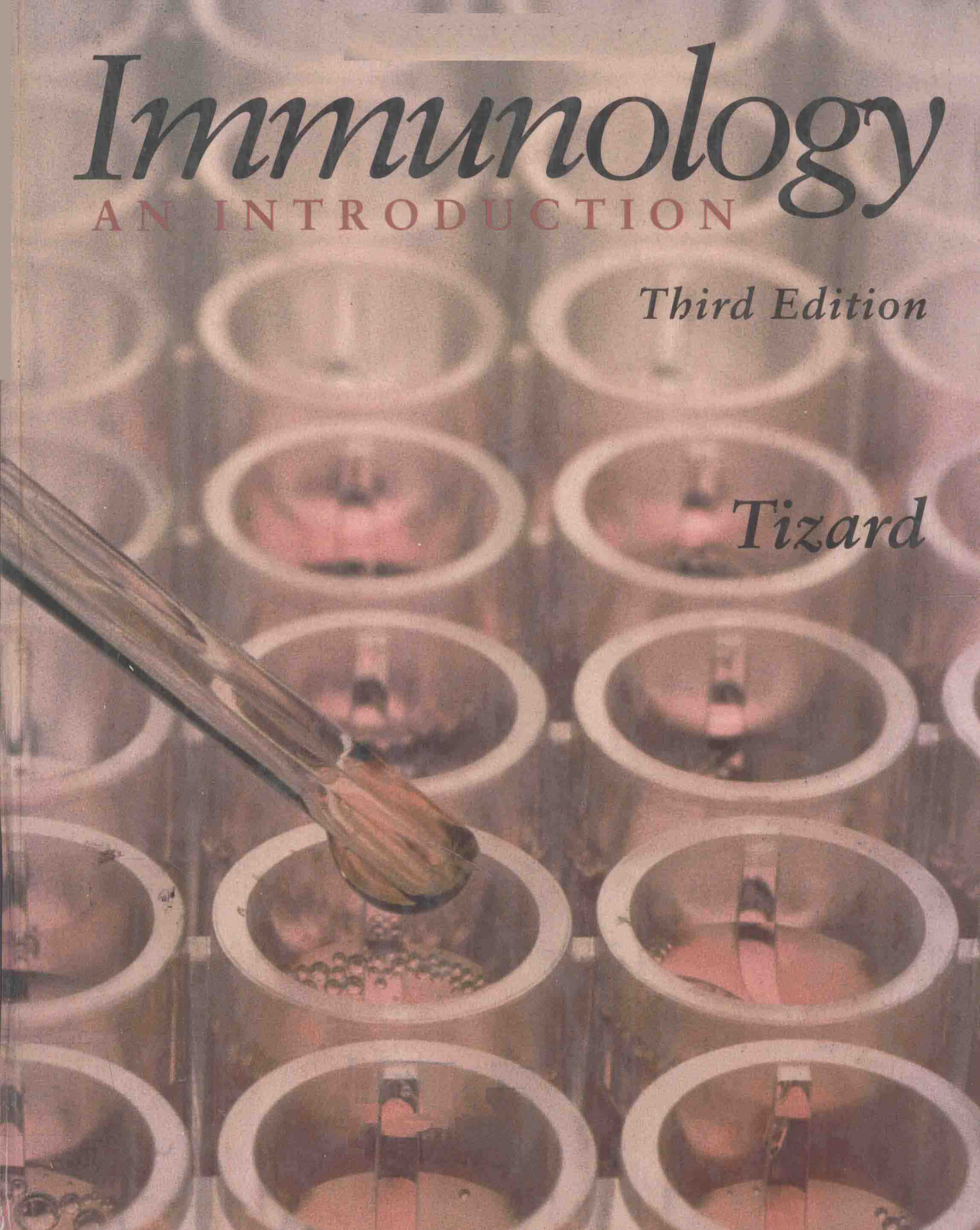
Immunology

AN INTRODUCTION

Third Edition



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Third Edition

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To Claire, Robert, and Fiona

Preface

The decade of the eighties was an extraordinarily exciting time for immunology. Intensive and productive research led to a steady stream of important discoveries and a remarkable evolution in our understanding of the immune system. This evolution of our concepts of the defense of the body and the ways in which the body differentiates self from non-self has ensured that immunology continues to grow and diversify.

Not only has immunology grown more complex as immunological phenomena are dissected in increasing detail, but it has expanded to invade broader areas of cell biology. The boundaries between immunology and other disciplines such as genetics and biochemistry have become increasingly blurred. As a result, nowhere is the unity of life processes better exemplified than in modern immunology.

This book provides an overview of current immunology while assisting students through many of the complexities intrinsic to the subject in a readable narrative. My intent has been to cause minimal confusion or intimidation while not evading or distorting the issues involved. This has therefore required careful identification of those aspects of immunology that must be omitted as well as those that must be described in detail.

The text has been written primarily for students studying immunology for the first time. I have assumed that the student will have some basic knowledge of the key life science disciplines—biochemistry, genetics, microbiology, and cell biology. In order to refresh faded memories, the book contains short reviews in these disciplines at strategic points. Because of the obvious medical applications of immunology, the text necessarily uses a wide variety of medical terms. However, a glossary has been provided to help students in this area. Immunology, although largely focused on humans and laboratory rodents, is a discipline that applies to all mammals and indeed to all vertebrates. For this reason, I have taken a comparative approach to the subject. Many of my examples have been drawn from outside the usual human or mouse area. This will benefit those students whose careers may extend to areas of the life sciences other than medicine.

Distinctive Features

This is not a reference book but a textbook, and I have attempted to keep that distinction clear. To avoid disrupting the conceptual flow, I have bypassed excessive experimental or technical detail. I believe strongly that the overall view of the subject should be clear before the student returns to examine the experimental evidence in detail. This is especially important in immunology, where some aspects of the subject may appear unduly complex to the beginner and where the student can easily become overwhelmed and intimidated by the vast amount of information available. For this reason, I have again kept references out of the body of the text and confined reading lists to recent reviews and key papers.

Instructional Features

Key Concepts. Each chapter has its key concepts summarized at the beginning. These are designed to ensure that the student recognizes the main thrust of each chapter and is not distracted by detail. Students will not go far wrong if they review these first.

Illustrations. Many new illustrations have been provided and color added in order to enhance student comprehension. The illustrations are carefully designed to provide a visual complement to the text.

Methods. Immunology is an experimental science. It is essential that the student realize that the material presented has been obtained only from the results of large numbers of carefully controlled experiments. To provide insight into this process without interfering with the flow of the text, key experimental procedures have been outlined in blocks throughout the book.

"A Closer Look." Immunology, like so much of science, has many fascinating ramifications. Most of these cannot be fully explored in a textbook that seeks to encompass the entire discipline within a limited space. Nevertheless, many interesting highlights are described in boxes throughout the text.

Questions. Each chapter is followed by a number of thought-provoking questions. While some of these require the student to correlate factual data, others are of a philosophical or speculative nature. Thus there may be no "correct" answer for this type of question. In answering these questions, the student will gain additional understanding of the subject.

References. The references at the end of each chapter have been carefully selected to provide key papers and reviews that will enable interested students to expand their reading in an area if they so desire.

Glossary. Immunology, like all the new growth areas in biology, has developed a complex terminology. This is compounded by the need to use a variety of terms from medicine. This can be very confusing to the beginning student. For this reason, the glossary has been greatly expanded and precise definitions are provided for key terms.

Organization

In this new edition, I have tried to convey the excitement of current immunology while retaining my goals of brevity, simplicity, and clarity. I have sought to provide a readable narrative that will guide students through this complex subject with a minimum of confusion. Recent discoveries have provided a wealth of new information that expands, and in many cases clarifies, earlier knowledge. As a result, this revision has been very extensive. Most of the chapters have been completely rewritten and several new ones have been added.

The order of chapters has also been changed to provide a more logical flow of information. I fully acknowledge that there is no correct way to proceed through immunology, and each instructor and student will have their own ideas on how to proceed. One of the advantages of a single-author text is that each chapter is carefully integrated so that extensive cross-referencing is possible. This also should make it easy for an instructor to alter the order of instruction, should they so wish.

The chapters in this book have been organized in such a way that the student should be able to follow the sequence of events beginning with the administration of a foreign antigen and following the subsequent host response until the foreign antigen is eventually destroyed. This simple linear plan has been complicated by the division of the immune responses into those mediated by T cells and those mediated by B cells.

Several chapters have been merged and eight completely new chapters have been added to the text. The most important of these new chapters is Chapter 24, which describes the immunological basis of AIDS. Since the previous edition was published, AIDS has assumed a growing importance as the number of cases continues to increase and has become a major disaster in many less-developed countries, especially in Africa. This terrible disease has made the public much more aware of immunology as a discipline, and it is no longer unusual to see well-known immunologists interviewed or quoted in the media.

Recent developments in our understanding of antigen processing have required a new chapter on this topic. This is described in Chapter 4 on macrophages and antigen presentation. A related subject, the role of the major histocompatibility complex in antigen presentation, is described in Chapter 5. The physiologic functions of histocompatibility antigens as antigen-presenting molecules are now well defined and have enabled the chapter on these antigens to be rewritten from a functional, rather than a descriptive, viewpoint.

The T-cell antigen receptors have now been characterized in detail. This, together with greatly increased information on the heterogeneity of helper T cells, has necessitated a new chapter, Chapter 8, on helper T-cell function. A related growth area has been the study of cytokines. New proteins derived from the cells of the immune system are being described almost daily. These recent developments are described in Chapter 9.

Chapter 14 deals with the genetics of both the immunoglobulins and the T-cell antigen receptors. The genetic basis of T-cell receptor diversity has now been analyzed to almost the same extent as that of the immunoglobulins. It is instructive to compare the genetics of these two forms of cellular antigen receptors.

Another new chapter is Chapter 15, which describes the effector function of T cells. This chapter includes not only T-cell-mediated cytotoxicity but also macrophage activation and delayed hypersensitivity.

Finally, the phenomenon of tolerance has received renewed attention over the past few years and a stimulating controversy has arisen between the proponents of clonal deletion and those of suppression. The history of immunology suggests that both schools will be proven correct—*in part*. For this reason, the chapter on regulation of the immune system in the previous edition has been split so that tolerance is considered separately from other aspects of immune regulation, now found in Chapters 18 and 19.

The reader will find the information in the text to be up to date as of January 1991.

Acknowledgments

It is a pleasure to acknowledge my debt to those colleagues who gave me valuable support by discussing many of the key features of the text as well as critically evaluating its contents. Four individuals who reviewed the entire manuscript and provided many very useful and insightful comments were Drs. Cynthia Somer, Patricia Mancini, Constantine Tsdukas, and Brian Buske. I would especially like to thank Dr. John Williams, who kept my computer functioning when on several occasions it showed signs of delinquency—a sign of the times. I would also like to thank Betty Suehs and Francis Hicks for typing significant portions of the text.

I am particularly grateful to Julie Levin Alexander, Biology Editor, and to Nancy Lubars, Project Editor at Saunders College Publishing, for their patience, professionalism, and support.

As always, I must mention my deep appreciation of my wife Claire's tolerance for the inevitable disruption that writing a textbook brings to a home.

Ian Tizard
College Station
November 1991

Contents

CHAPTER ONE

General Principles of Immunology

Louis Pasteur working in his laboratory. (Courtesy of the Bettmann Archive)

CHAPTER OUTLINE

CHAPTER CONCEPTS

1. The idea that individuals could become resistant to an infectious disease is recent, and the mechanisms of this immunity have been clarified only over the past hundred years.
2. The immune system has two major tasks. It must protect individuals against infectious agents invading the body from outside, and it must prevent the development of abnormal cells within the body.
3. Molecules that induce an immune response are called antigens.
4. There are two types of immune response. One, mediated by antibodies, is responsible for resistance to infectious agents. The other, mediated by cells called lymphocytes, is responsible for the destruction of abnormal cells. Such abnormal cells include cancer cells and virus-infected cells.
5. The immune system does not usually react against normal body components. It is therefore said to be "tolerant" of self-components.

All animals must protect themselves against disease and death caused by microorganisms such as bacteria, fungi, viruses, and parasites. If an animal is to survive and function effectively, it must be able to defend itself against invasion by these organisms. Failure to do so will result in death from overwhelming infection. Invading microorganisms from the external environment are, however, not the only threats to the body. An animal must also protect itself against the development of abnormal cells within the body, such as cancer cells or virus-infected cells.

Immunology is the science that studies the body's defense mechanisms and the ways in which we can stimulate these defenses in order to protect against disease.

The defenses of the body are not always completely effective in excluding invaders. For example, most readers of this book will have suffered from the common cold within the past year or so. You will probably recollect having suffered from many such infections. It is therefore not surprising that until recently most people did not readily accept that recovery from some infections confers resistance to subsequent attacks of the same disease. Nevertheless, even the ancient Greeks suspected that those persons who survived one attack of the plague would not suffer the disease a second time. It would have required an act of great courage to test such a radical idea, and it is unlikely to have been widely accepted.

HISTORICAL BACKGROUND

Of the great diseases of humankind, smallpox was one of the most feared. Not only did it kill huge numbers of people, but survivors were scarred for life with disfiguring pockmarks. The Chinese determined, about the beginning of the eleventh century, that persons who survived an attack of smallpox would not get the disease a second time. It therefore became accepted practice in ancient China to infect young children with smallpox. Scabs from the pocks on the skin of an infected person were either put up the nose of an infant or rubbed into a scratch. Children who survived the resulting disease became resistant to smallpox; those who died saved their parents the trouble and expense of raising them only to have them die from the disease later. As the Chinese gained experience with this procedure, they found that the mildest disease occurred when the smallpox scabs used were selected from mildly affected donors. As a result, they eventually succeeded in reducing the hazards of the procedure to fairly low levels.

News of this method of protecting children against smallpox gradually spread westward along the caravan routes of Central Asia and eventually reached Turkey. In 1718, Lady Mary Wortley Montagu, the wife of the English ambassador in Constantinople, decided that the technique should be used on her children. (Her own face had been scarred by smallpox so she had a special interest in the disease.) (Fig. 1-1) Her chaplain attempted to dissuade her on the grounds that the technique would be ineffective in Christians. Nevertheless, Lady Montagu persisted, and her children were protected.

News of the technique, by now called **variolation** ("variola" is the Latin word for smallpox), spread rapidly to England where Queen Anne's son and heir had recently died from smallpox. The British ruling classes were thus acutely aware of the disease and adopted variolation with enthusiasm. It did not

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