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Preface

Thirty-three years ago, in 1986, the first edition of *Introduction to Medical Immunology* was published. I could not have imagined then that 33 years later I would be editing the seventh edition of *Medical Immunology*. This is a classic text in a traditional format, ideal for presenting clinically relevant and updated content from the overwhelming flow of information in the literature. Purposely, we emphasize knowledge for which there is a clear clinical application (or at the very least a clear experimental proof of concept). I believe that this approach is best suited for a general introductory book that provides a good balance between basic and clinical science.

This new edition of *Medical Immunology* has been thoroughly revised and reorganized following the described general guidelines.

The scientific basis of immunology is clearly conveyed in a general and succinct overview, including coverage of important emerging topics in terms that should be accessible to nonimmunologists, with emphasis on the application to medicine. The book should stimulate readers to seek more information and further develop their own education. Lists of recommended readings are included in each chapter.

The book starts with basic immunology followed by diagnostic immunology. We give special attention to diagnostic immunology because this area has fertile applications and has been the basis for important new knowledge. The last 15 chapters of this book are dedicated to clinical immunology, and the chapters have been thoroughly revised and updated. The final section on immunodeficiency diseases reflects the extraordinary significance of immunodeficiency diseases in clinical immunology. The study of primary immune deficiencies gives the best perspective about the intimate works of the human immune system, and secondary immunodeficiencies (including those caused iatrogenically as well as HIV induced) are encountered in virtually all fields of medicine.

The result is a concise book that conveys our collective intrinsic fascination with a discipline that seeks understanding of fundamental biological knowledge, with the goal of applying that knowledge to the diagnosis and treatment of human diseases.

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Introduction

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HISTORICAL OVERVIEW

The fundamental observation that led to the development of immunology as a scientific discipline was that an individual might become resistant for life to a certain disease after having contracted it only once. The term *immunity*, derived from the Latin "immunis" (exempt), was adopted to designate this naturally acquired protection against diseases such as measles or smallpox.

The emergence of immunology as a discipline was closely tied to the development of microbiology. The work of Pasteur, Koch, Metchnikoff, and of many other pioneers of the golden age of microbiology resulted in the rapid identification of new infectious agents. This was closely followed by the discovery that infectious diseases could be prevented by exposure to killed or attenuated organisms, or to compounds extracted from the infectious agents. The impact of immunization against infectious diseases such as tetanus, mumps, diphtheria, poliomyelitis, and smallpox, to name just a few examples, can be grasped when we reflect on the fact that these diseases, which were significant causes of mortality and morbidity, are now either extinct or very rarely seen. Indeed, it is fair to state that the impact of vaccination and sanitation on the welfare and life expectancy of humans has had no parallel in any other developments of medical science.

In the second part of this century, immunology started to transcend its early boundaries and became a more general biomedical discipline. Today, the study of immunological defense mechanisms is still an important area of research, but

immunologists are involved in a much wider array of problems, such as self and non-self discrimination, control of cell and tissue differentiation, transplantation, immunomodulation of autoimmune diseases, cancer immunotherapy, etc. The focus of interest has shifted toward the basic understanding of how the immune system works in the hope that this insight will allow novel approaches to its manipulation.

GENERAL CONCEPTS

Specific and nonspecific defenses

The protection of our organism against infectious agents involves many different mechanisms, some nonspecific (i.e., generically applicable to many different pathogenic organisms) and others specific (i.e., their protective effect is directed to one single organism).

Nonspecific defenses, which as a rule are innate (i.e., all normal individuals are born with them), include the following:

- Mechanical barriers such as the integrity of the epidermis and mucosal membranes
- Physicochemical barriers, such as the acidity of the stomach fluid
- Antibacterial substances (e.g., lysozyme, defensins) present in external secretions
- Normal intestinal transit and normal flow of bronchial secretions and urine, which eliminate infectious agents from the respective systems
- Nonimmune mechanisms for ingestion of bacteria and particulate matter by a variety of cells, but particularly well developed in **granulocytes**

Specific defenses, as a rule, are induced during the life of the individual as part of the complex sequence of events designated as the immune response. The immune response has two unique characteristics:

- **Specificity for the eliciting antigen**, for example, immunization with inactivated poliovirus only protects against poliomyelitis, not against viral influenza. The specificity of the immune response is due to the existence of exquisitely discriminative antigen receptors on lymphocytes. Only a single or a very limited number of similar structures (epitopes) can be accommodated by the receptors of any given lymphocyte. When those receptors are occupied, an activating signal is delivered to the lymphocytes. Therefore, only those lymphocytes with specific receptors for the antigen in question will be activated. A significant caveat, however, is that epitopes may be unexpectedly shared by microbial organisms and human tissues, and this may result in the emergence of antibodies reacting with totally unrelated entities. One classical example is antibodies elicited by intestinal bacteria that react with the AB antigens of human red cells, as discussed in detail in Chapter 14.

- **Memory**, meaning that repeated exposure to a given antigen elicits progressively more intense specific responses. Most immunizations involve repeated administration of the immunizing compound, with the goal of establishing a long-lasting, protective response. The increase in the magnitude and duration of the immune response with repeated exposure to the same antigen is due to the proliferation of antigen-specific lymphocytes after each exposure. The numbers of responding cells will remain increased even after the immune response subsides. Therefore, whenever the organism is exposed again to that particular antigen, there is an expanded population of specific lymphocytes available for activation, and as a consequence, the time needed to mount a response is shorter and the magnitude of the response is higher. This immunological memory is more effectively induced by protein antigens.

Stages of immune response

To better understand how the immune response is generated, it is useful to consider it as divided into separate sequential stages (Table 1.1). The first stage (**induction**) involves a small lymphocyte population with specific receptors able to recognize an antigen or antigen fragments generated by specialized cells known as antigen-presenting cells (APCs). The second stage (amplification) is mediated by activated APCs and by specialized T cell subpopulations (T-helper cells, defined later) that enhance each other's proliferation and differentiation. This is followed by the production of effector molecules (antibodies) or by the differentiation of effector cells (cells that directly or indirectly mediate the elimination of undesirable elements). The final outcome, therefore, is the elimination of the organism or compound that triggered the reaction by means of activated immune cells or by defensive reactions triggered by mediators released by the immune system.

Table 1.1 Simplified overview of the three main stages of the immune response

Stage of the immune response	Induction	Amplification	Effector
Cells/molecules involved	Antigen-presenting cells; lymphocytes	Antigen-presenting cells; helper T lymphocytes	Antibodies (+ complement or cytotoxic cells); cytotoxic T lymphocytes; macrophages
Mechanisms	Processing and/or presentation of antigen; recognition by specific receptors on lymphocytes	Release of cytokines; signals mediated by interaction between membrane molecules	Complement-mediated lysis; phagocytosis; cytotoxicity
Consequences	Activation of T and B lymphocytes	Proliferation and differentiation of T and B lymphocytes	Elimination of non-self; neutralization of toxins and viruses

CELLS OF IMMUNE SYSTEM

Lymphocytes and lymphocyte subpopulations

The peripheral blood contains two large populations of cells: the red cells, whose main physiological role is to carry oxygen to tissues, and the white blood cells, which have as their main physiological role the elimination of potentially harmful organisms or compounds. Among the white blood cells, lymphocytes are particularly important because of their central role in the adaptive immune response. Several subpopulations of lymphocytes have been defined:

- **B lymphocytes**, which are the precursors of antibody-producing cells, known as plasma cells.
- **T lymphocytes**, which can be divided into several subpopulations:
  - **Helper T lymphocytes (Th)**, which play a significant amplification role in the immune response. Two functionally distinct subpopulations of T-helper lymphocytes emerging from a precursor population (Th0) have been defined. In broad strokes, the Th1 population assists the differentiation of cytotoxic cells and also activates macrophages. Activated macrophages, in turn, play a role as effectors of the immune response. The Th2 lymphocytes, in turn, are mainly involved in the amplification of B-lymphocyte responses.

    The amplifying effects of helper T lymphocytes are mediated in part by soluble mediators—(cytokines)—and in part by signals delivered as a consequence of cell-cell interactions.
  - **Cytotoxic T lymphocytes**, which are the main immunologic effector mechanism involved in the elimination of non-self or infected cells.
  - **Immunoregulatory T lymphocytes**, which have the ability to downregulate the immune response through the release of cytokines such as interleukin-10 (IL-10) and through the expression of membrane molecules, such as CTLA-4, whose interaction with the corresponding receptors delivers a downregulatory signal.

Antigen-presenting cells (APC)

Antigen-presenting cells (APCs), such as the dendritic cells and the macrophages and macrophage-related cells, play a significant role in the induction stages of the immune response by trapping and presenting both native antigens and antigen fragments in a most favorable way for recognition by lymphocytes. In addition, these cells deliver activating signals to lymphocytes engaged in antigen recognition, both in the form of soluble mediators (interleukins such as IL-1, IL-12, and IL-18) and in the form of signals delivered by cell-cell contact.

The monocytes and macrophages also play significant roles as effectors of the immune response. One of their main functions is to eliminate antigens that have elicited an immune response. Antigens coated by antibodies and complement are