Medical Immunology

Fifth Edition
Revised and Expanded

edited by
Gabriel Virella

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Preface

In 1986, Marcel Dekker, Inc., published the first edition of *Introduction to Medical Immunology*. It is remarkable that in 2001 the same publisher continues to enthusiastically back the publication of the fifth edition, now with the shorter title of *Medical Immunology*. This is a book that goes against the grain. Notes in the margins, boxes with correlations, or learning objectives will not challenge the reader. What we try to provide is a classic text with updated information, written with a solid medical perspective. We believe that this approach is the most appropriate one for the education of physicians of the 21st century. Whether used by a medical student or by a resident, intern, or young specialist, the book will provide a good balance between basic and clinical science. Of course, it is as true now as it was years ago that the field of immunology continues to grow at a brisk pace, and that many concepts are victims of constant revision. It is very true of immunology that the more we know the greater is our ignorance. But all of us involved in the fifth edition have enthusiastically undertaken the task of providing a general introductory book that should remain viable for half a decade. If we use past editions as a yardstick, we have achieved this goal.

This new edition has been thoroughly revised and reorganized. We have, obviously, maintained its emphasis on the clinical application of immunology. We also remain faithful to our strong conviction that this textbook is written not to impress our peers with extraordinary insights or revolutionary knowledge, but rather to be helpful to medical students and young professionals who need an introduction to the field. This means that the scientific basis of immunology needs to be clearly conveyed without allowing the detail to obscure the concept. The application to medicine needs to be transparently obvious, but without unnecessary exaggeration. The text must present a reasonably general and succinct overview, but needs to cover areas that appear likely to have a strong impact in the foreseeable future. The book should stimulate students to seek more information and to develop his or her own "thinking" but cannot be a castle of theoretical dreams (and nightmares).

With these goals in mind, one major change that we made in this edition was the redistribution of topics and rearrangement of chapters, to ensure a more logical and cohesive presentation. The first part, "Basic Immunology," includes a new chapter on phagocytic cells preceding "Infections and Immunity," thus bringing to a close a logical sequence that starts with the discussion of the cells and tissues involved in the immune response. The sec-

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ond part, "Diagnostic Immunology," consists of a single, new chapter in which the most modern aspects of diagnostic immunology are presented in a simple and effective fashion. The chapters in Part III ("Clinical Immunology") have been thoroughly revised, and are peppered with cases in order to provide a solid anchor between the discussion of concrete problems presented by patients with diseases of immunological basis and the relevant scientific principles. A new part—"Immunodeficiency Diseases"—has been added to reflect the extraordinary significance of immunodeficiency diseases in clinical immunology, from providing experiments of nature that allow us to understand how the immune system is organized in humans to secondary immunodeficiencies (including those caused iatrogenically as well as the acquired immunodeficiency syndrome) encountered by physicians of all specialties with increasing frequency. Part IV contains three important chapters: one dealing with the diagnosis of immunodeficiencies, the second dedicated to primary immunoeficiencies, and the last dedicated to secondary immunodeficiencies.

In preparing this new edition, I have been lucky in securing the continuing participation of many of the collaborators responsible for previous editions, and I was also able to recruit new blood, bringing new perspectives to some key chapters. I also express our gratitude to Marcel Dekker for his continuing support, and to Ms. Kerry Doyle for her editorial efforts. We applied our best efforts to produce a concise textbook that should bring to the attention of our readers the intrinsic fascination of a discipline that seeks understanding of fundamental biological knowledge, with the goal of applying that knowledge to the diagnosis and treatment of human diseases. We hope that this new edition will be a worthy successor to the previous four.

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1
Introduction

Gabriel Virella

I. 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 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, measles, mumps, poliomyelitis, and smallpox, to name just a few examples, can be grasped when we reflect on the fact that these diseases, which were at one time 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 become 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-nonself discrimination, control of cell and tissue differentiation, transplantation, cancer immunotherapy, etc. The focus of in-

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terest 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.

II. GENERAL CONCEPTS

A. 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:

Mechanical barriers such as the integrity of the epidermis and mucosal membranes
Physicochemical barriers, such as the acidity of the stomach fluid
The 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
Ingestion and elimination of bacteria and particulate matter by granulocytes, which is independent of the immune response

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:

1. *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 can be accomodated 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.
2. *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.

B. Stages of the 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

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Table 1.1 A 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; opsonization and phagocytosis; cytotoxicity
Consequences	Activation of T and B lymphocytes	Proliferation and differentiation of T and B lymphocytes	Elimination of nonself; neutralization of toxins and viruses

lymphocyte population with specific receptors able to recognize an antigen or antigen fragments generated by specialized cells known as antigen-presenting cells (APCs). The proliferation and differentiation of APCs is usually enhanced by amplification systems involving the APCs themselves and specialized T-cell subpopulations (T helper cells, defined below). 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 reactions triggered by mediators released by the immune system.

III. CELLS OF THE IMMUNE SYSTEM

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 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 immune response. Several subpopulations of lymphocytes have been defined:

1. B lymphocytes, which are the precursors of antibody-producing cells, known as plasma cells.
2. T lymphocytes, which can be divided into several subpopulations:
   a. Helper T lymphocytes (T_H), which play a very significant amplification role in the immune responses. Two functionally distinct subpopulations of T helper lymphocytes emerging from a precursor population (T_H0) have been defined: 1) T_H1 lymphocytes, which assist the differentiation of cytotoxic cells and also activate macrophages (activated macrophages, in turn, play a role as effectors of the immune response), and 2) T_H2 lymphocytes,

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which are mainly involved in the amplification of B-lymphocyte responses.

These 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.

b. Cytotoxic T lymphocytes, which are the main immunological effector mechanism involved in the elimination of nonself or infected cells.
c. Immunoregulatory T lymphocytes, which lack unique membrane markers but have the ability to downregulate the immune response through the release of cytokines such as interleukin-10 (IL-10).

3. Antigen-presenting cells, such as macrophages and macrophage-related cells and dendritic 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 the recognition by lymphocytes. In addition, these cells also 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.
4. Phagocytic cells, such as monocytes, macrophages, and granulocytes, 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. This is achieved by means of antibodies and complement, as discussed below. However, if the antigen is located on the surface of a cell, antibody induces the attachment of cytotoxic cells that cause the death of the antibody-coated cell (antibody-dependent cellular cytotoxicity, ADCC).
5. Natural killer (NK) cells play a dual role in the elimination of infected and malignant cells. These cells are unique in that they have two different mechanisms of recognition: they can identify malignant or viral-infected cells by their decreased expression of histocompatibility antigens, and they can recognize antibody-coated cells and mediate ADCC.

IV. ANTIGENS AND ANTIBODIES

Antigens are usually exogenous substances (cells, proteins, and polysaccharides) which are recognized by receptors on lymphocytes, thereby eliciting the immune response. The receptor molecules located on the membrane of lymphocytes interact with small portions of those foreign cells or proteins, designated as antigenic determinants or epitopes. An adult human being has the capability to recognize millions of different antigens, some of microbial origin, others present in the environment, and even some artificially synthesized.

Antibodies are proteins that appear in circulation after infection or immunization and that have the ability to react specifically with epitopes of the antigen introduced in the organism. Because antibodies are soluble and are present in virtually all body fluids ("humors"), the term humoral immunity was introduced to designate the immune responses in which antibodies play the principal roles as effector mechanism. Antibodies are also generically designated as immunoglobulins. This term derives from the fact that antibody molecules structurally belong to the family of proteins known as globulins (globular proteins) and from their involvement in immunity.

The knowledge that the serum of an immunized animal contained protein molecules able to bind specifically to the antigen led to exhaustive investigations of the characteris-

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tics and consequences of the antigen-antibody reactions. At a morphological level, two types of reactions were defined:

1. If the antigen is soluble, the reaction with specific antibody under appropriate conditions results in precipitation of large antigen-antibody aggregates.
2. If the antigen is expressed on a cell membrane, the cell will be cross-linked by antibody and form visible clumps (agglutination).

Functionally, antigen-antibody reactions can be classified by their biological consequences:

Viruses and soluble toxins released by bacteria lose their infectivity or pathogenic properties after reaction with the corresponding antibodies (neutralization).

Antibodies complexed with antigens can activate the complement system. Nine major proteins or components that are sequentially activated constitute this system. Some of the complement components are able to promote ingestion of microorganisms by phagocytic cells, while others are inserted into cytoplasmic membranes and cause their disruption, leading to lysis of the offending microbial cell.

Antibodies can cause the destruction of microorganisms by promoting their ingestion by phagocytic cells or their destruction by cells mediating ADCC. Phagocytosis is particularly important for the elimination of bacteria and involves the binding of antibodies and complement components to the outer surface of the infectious agent (opsonization) and recognition of the bound antibody and/or complement components as a signal for ingestion by the phagocytic cell.

Antigen-antibody reactions are the basis of certain pathological conditions, such as allergic reactions. Antibody-mediated allergic reactions have a very rapid onset—a matter of minutes—and are known as immediate hypersensitivity reactions.

V. LYMPHOCYTES AND CELL-MEDIATED IMMUNITY

Lymphocytes play a significant role as effector cells in three main types of situations, all of them considered as expression of cell-mediated immunity, i.e., immune reactions in which T lymphocytes are the predominant effector cells.

A. Immune Elimination of Intracellular Infectious Agents

Viruses, bacteria, parasites, and fungi have developed strategies that allow them to survive inside phagocytic cells or cells of other types. Infected cells are generally not amenable to destruction by phagocytosis or complement-mediated lysis. The study of how the immune system recognizes and eliminates infected cells resulted in the definition of the biological role of the histocompatibility antigens (HLA) that had been described as responsible for graft rejection (see below). Those membrane molecules have a peptide-binding pouch that needs to be occupied with peptides derived from either endogenous or exogenous proteins. The immune system does not recognize self-peptides associated with self-HLA molecules. In the case of infected cells, peptides split from microbial proteins synthesized by the infected cell as part of the microbial replication cycle become associated with HLA

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molecules. The HLA-peptide complexes are presented to the immune system and activate specific cytotoxic T lymphocytes as well as specific T_H1 lymphocytes. Both cytotoxic T cells and T_H1 lymphocytes can mediate killing of the infected cells against which they became sensitized. Cytotoxic T cells kill the infected cells directly, stopping the replication of the intracellular organism, while activated T_H1 cells release cytokines, such as interferon-γ, which activate macrophages and increase their ability to destroy the intracellular infectious agents.

B. Transplant (Graft) Rejection

As stated above, the immune system does not respond (i.e., is tolerant) to self-antigens, including antigens of the major histocompatibility complex (MHC), which includes the HLA molecules. However, transplantation of tissues among genetically different individuals of the same species or across species is followed by rejection of the grafted organs or tissues. The rejection reaction is triggered by the presentation of peptides generated from nonself MHC molecules. The MHC system is highly polymorphic (hundreds of alleles have been defined and new ones are added on a regular basis to the known repertoire), and this leads to the generation of millions of peptides, which differ in structure from individual to individual.

C. Delayed Hypersensitivity

While the elimination of intracellular infectious agents can be considered as the main physiological role of cell-mediated immunity and graft rejection is an unexpected and undesirable consequence of a medical procedure, other lymphocyte-mediated immune reactions can be considered as pathological conditions arising spontaneously in predisposed individuals. The most common example involves skin reactions, or cutaneous hypersensitivity, induced by direct skin contact or by intradermal injection of antigenic substances. These reactions express themselves 24–48 hours after exposure to an antigen to which the patient had been previously sensitized, and because of this timing factor received the designation of delayed hypersensitivity reactions.

VI. SELF VERSUS NONSELF DISCRIMINATION

The immune response is triggered by the interaction of an antigenic determinant with specific receptors on lymphocytes. It is calculated that there are several millions of different receptors in lymphocytes—10^{15}–10^{18} on T cells and 10^{11} on B cells—sufficient to respond to a wide diversity of epitopes presented by microbial agents and potentially noxious exogenous compounds. At the same time, the immune system has the capacity to generate lymphocytes with receptors able to interact with epitopes expressed by self antigens. During embryonic differentiation and adult life the organism uses a variety of mechanisms to ensure that potentially autoreactive lymphocytes are eliminated or turned off. This lack of response to self antigens is known as tolerance to self.

When the immune system is exposed to exogenous compounds, it tends to develop a vigorous immune response. The discrimination between self and nonself is based the fact that the immune system has the ability to recognize a wide variety of structural differences on exogenous compounds. For example, infectious agents have marked differences in their

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chemical structure, easily recognizable by the immune system. Cells, proteins, and polysaccharides from animals of different species have differences in chemical constitution, which as a rule are directly related to the degree of phylogenetic divergence between species. Those also elicit potent immune responses. Finally, many polysaccharides and proteins from individuals of any given species show antigenic heterogeneity, reflecting the genetic diversity of individuals within a species. Those differences are usually minor (relative to differences between species) but can still be recognized by the immune system. Transfusion reactions, graft rejection, and hypersensitivity reactions to exogenous human proteins are clinical expressions of the recognition of this type of differences between individuals.

VII. GENERAL OVERVIEW

One of the most difficult intellectual exercises in immunology is to try to understand the global organization and control of the immune system. Its extreme complexity and the wide array of regulatory circuits involved in fine-tuning the immune response pose a formidable obstacle to our understanding. A concept map depicting a simplified view of the immune system is reproduced in Figure 1.1.

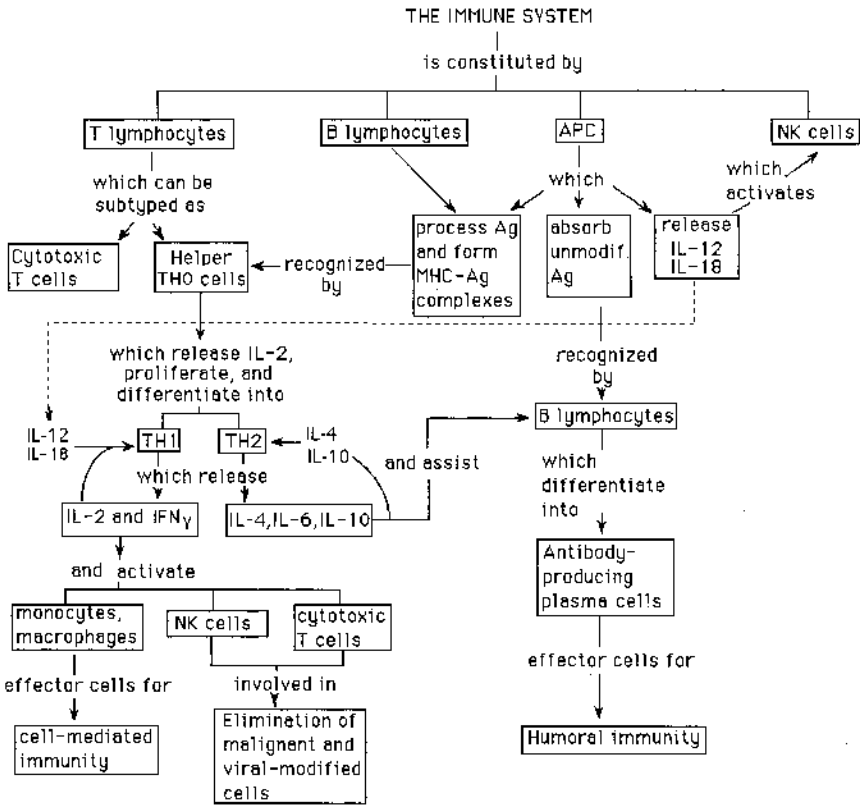

Fig. 1.1 A concept map representing the main components of the immune system and their interactions.

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If we use as an example the activation of the immune system by an infectious agent that has managed to overcome the innate anti-infectious defenses, the first step must be the uptake of the infectious agent by a cell capable of presenting it to the immune system in favorable conditions for the induction of an immune response. In the case of T lymphocytes, APCs expressing MHC-II molecules play this role. A variety of cells can function as APCs, including tissue macrophages, B cells, and dendritic cells. Those cells adsorb the infectious agent to their surface, ingest some of the absorbed microorganism, and process it into small antigenic subunits. These subunits become intracellularly associated with histocompatibility antigens, and the resulting complex is transported to the cytoplasmic membrane, allowing stimulation of helper T lymphocytes. The interaction between surface proteins expressed by antigen-presenting cells and T lymphocytes as well as cytokines released by the antigen-presenting cells act as costimulants of the helper T cells. How antigen is presented to B cells is not very clear, but it is well established that the activation of an immune response takes place in a lymphoid organ (lymph node, peri-intestinal lymphoid tissues, spleen). All cellular elements necessary for the inductive and effector stages of an immune response are present on the lymphoid tissues, where there is ample opportunity for interactions and cooperation between those different cells.

Once stimulated to proliferate and differentiate, helper T cells become able to assist the differentiation of effector cells. However, not all helper T cells seem to assist all types of effector cells that require their help. Activated T_H1 helper lymphocytes secrete cytokines that act on a variety of cells, including macrophages (further increasing their level of activation and enhancing their ability to eliminate infectious agents that may be surviving intracellularly), and cytotoxic T cells, which are very efficient in the elimination of virus-infected cells. In contrast, activated T_H2 helper lymphocytes secrete a different set of cytokines that will assit the proliferation and differentiation of antigen-stimulated B lymphocytes, which then differentiate into plasma cells. The plasma cells are engaged in the synthesis of large amounts of antibody.

As stated earlier, antibodies are the main effector molecules of the humoral immune response. As specific antibodies bind to a microorganism and the complement system is activated, the microorganisms will either be ingested and destroyed by phagocytic cells or be killed by complement-mediated lysis or by leukocytes able to mediate ADCC.

Once the microorganism is removed, negative feedback mechanisms become predominant, turning off the immune response. The downregulation of the immune response appears to result from the combination of several factors, such as the elimination of the positive stimulus that the microorganism represented and the activation of lymphocytes with immunoregulatory activity that secrete cytokines that deliver inactivating signals to other lymphocytes.

At the end of the immune response, a residual population of long-lived lymphocytes specific for the offending antigen will remain. This is the population of memory cells that is responsible for protection after natural exposure or immunization. It is also the same generic cell subpopulation that may cause accelerated graft rejections in recipients of multiple grafts. As discussed in greater detail below, the same immune system that protects us can be responsible for a variety of pathological conditions.

VIII. IMMUNOLOGY AND MEDICINE

Immunological concepts have found ample applications in medicine in areas related to diagnosis, treatment, prevention, and pathogenesis.

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1. The exquisite specificity of the antigen-antibody reaction has been extensively applied to the development of diagnostic assays for a variety of substances. Such applications received a strong boost when experiments with malignant plasma cell lines and normal antibody-producing cells resulted serendipitously in the discovery of the technique of hybridoma production, the basis for the production of monoclonal antibodies, which have had an enormous impact in the fields of diagnosis and immunotherapy.
2. Immunotherapy is a field with enormous possibilities, although the results of many attempts at the therapeutic application of immune strategies have been disappointing. Nevertheless, stimulation of the immune system with cytokines (particularly IL-2), downregulation of inflammatory reactions with anticytokine antibodies or recombinant soluble receptors, treatment of leukemia with monoclonal antibodies and immunotoxins, and prevention of graft rejection with monoclonal antibodies are but a few examples of successful medial applications of immunotherapy protocols.
3. The study of children with deficient immune system development (immunodeficiency disease) has provided the best tools for the study of the immune system in humans, while at the same time giving us ample opportunity to devise corrective therapies. The acquired immunodeficiency syndrome (AIDS) underscored the delicate balance that is maintained between the immune system and infectious agents in the healthy individual and has stimulated a considerable amount of basic research into the regulation of the immune system that may have enormous implications not only in the treatment of HIV/AIDS, but in many other areas of medicine.
4. The importance of maintaining self-tolerance in adult life is obvious when we consider the consequences of the loss of tolerance. Several diseases, some affecting single organs, others of a systemic nature, have been classified as autoimmune diseases. In such diseases the immune system reacts against cells and tissues; this reactivity can either be the primary insult leading to the disease or represent a factor contributing to the evolution and increasing severity of the disease. New knowledge of how to induce a state of unresponsiveness in adult life through oral ingestion of antigens has raised hopes for the rational treatment of autoimmune conditions.
5. Not all reactions against nonself are beneficial. If and when the delicate balance that keeps the immune system from overreacting is broken, hypersensitivity diseases may become manifest. Common allergies, such as asthma and hay fever, are prominent examples of diseases caused by hypersensitivity reactions. Manipulation of the immune response to induce a protective rather than harmful immunity was first attempted with success in this type of disease.
6. Research into the mechanisms underlying the normal state of tolerance against nonself attained during normal pregnancy continues to be intensive, since this knowledge could be the basis for more effective manipulations of the immune response in patients needing organ transplants and for the treatment or prevention of infertility.
7 The concept that malignant mutant cells are constantly being eliminated by the immune system (immune surveillance) and that malignancies develop when the mutant cells escape the protective effects of the immune system has been extensively debated, but not quite proven. However, anticancer therapies directed at

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