CLINICAL IMMUNOLOGY

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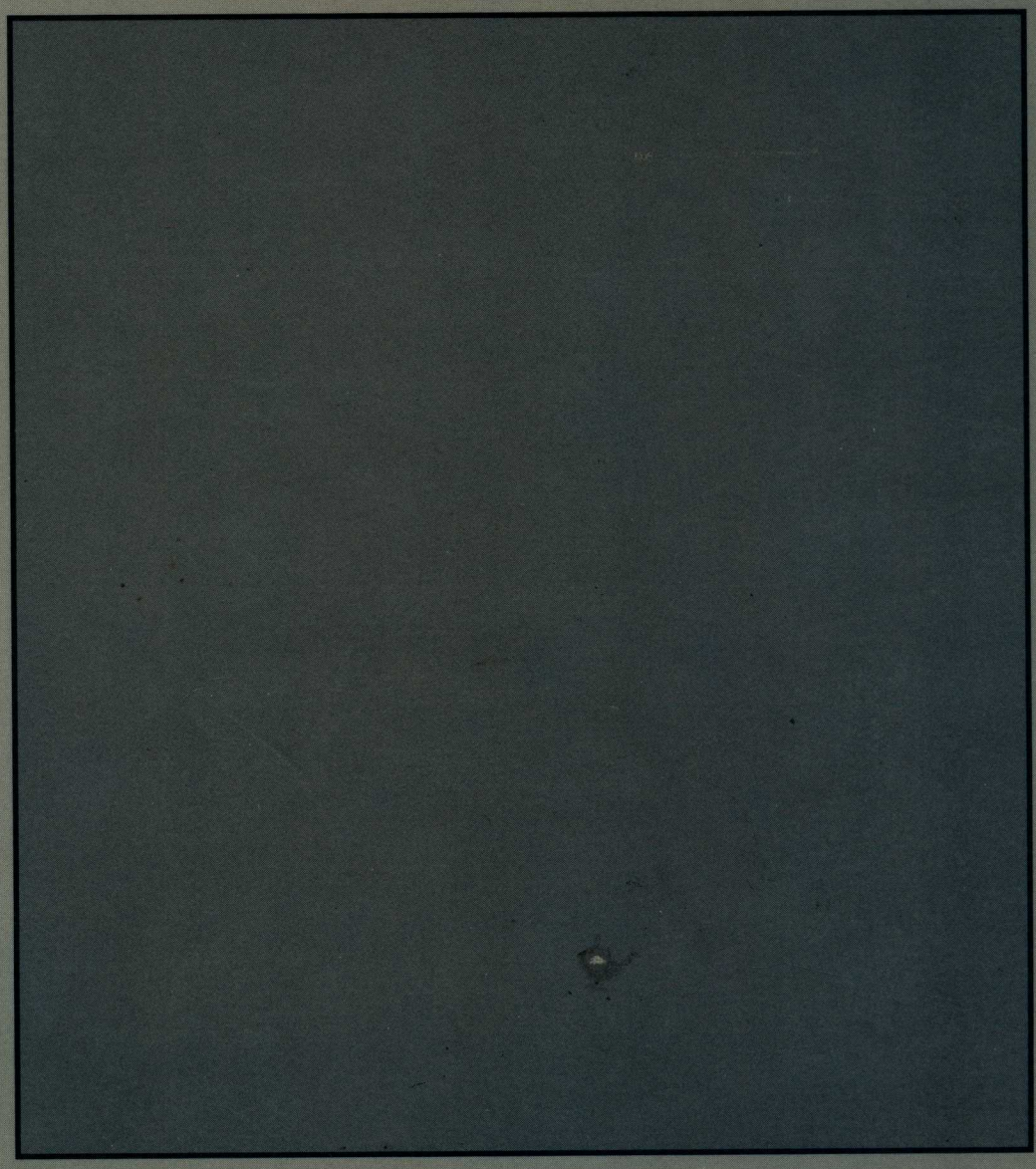

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CLINICAL IMMUNOLOGY

To
Our Students Who Inspire Us
and
Our Families Who (We Hope) Still Love Us

Preface

Immunology is a vital and flourishing discipline that in recent years has generated (really exploded) a formidable body of scientific observations. The growth of this field and the generation of scientific data have at times been so rapid that even research scientists in immunology find it difficult to keep pace with new developments. Clinical immunology is the application of the basic tenets established in this discipline to the achievement of a better understanding of the mechanisms of human disease. Since a variety of diseases are mediated through immune mechanisms, the expertise of the clinical immunologist is essential to a number of subspecialists regarding the diagnosis and treatment of their patients' problems. Thus, there is little doubt that immunology has and will continue to make a major impact on health care.

With the growth of clinical immunology as a discipline, challenges have been presented to both the busy medical student and practicing physician. Medical students, who have little time to master complex biologic and physiologic concepts, are attracted early to immunology as a new and exciting science. They therefore need a textbook that will satisfy their intellectual curiosities. In addition, doctors in practice, who may not have had extensive teaching in immunology during their undergraduate or postgraduate years, seek resource material that will provide them with a complete, yet expeditious, introduction to the scope of clinical immunology. To meet both demands, a textbook of clinical immunology that will be useful to both the medical student and practicing physician is required. This text is designed to meet these demands.

This book is based upon a series of lectures making up the Clinical Immunology course taught to 2nd-year medical students at the University of Wisconsin Medical School. We have divided the book into five sections. The first section reviews the basic concepts of clinical immunology. In this section, we have chosen to vary the format of the individual chapters to provide the reader with (*a*) a general framework upon which future developments in the discipline can be appreciated and (*b*) more in-depth reviews on monocytes and macrophages, neutrophil function, and components of hypersensitivity reactions. These topics have not been well developed in the existing literature yet they have a tremendous impact on multiple components of the immune system.

The four sections that follow the Basic Concepts section are Immune Deficiency, Pulmonary Disease, Allergic Disease, and Rheumatic Diseases, areas which at present most typify where clinical immunol-

ogy has been most insightful into disease pathogenesis. Chapters in these sections review clinical problems that have immunologic implications or documented mechanisms. In discussing these disorders, we have attempted to describe the process, review immunologic mechanism(s) in the disease, and provide an introduction to therapy.

The individuals who have contributed to this work represent a number of disciplines at our medical school. This fact alone underscores the scope of clinical immunology within our institution. All of the contributors have taught in our Clinical Immunology course. This textbook, therefore, will provide a unique opportunity for us to expand the enrollment of our immunology lecture series to include individuals (students and physicians) who wish to increase their knowledge base in the immunologic sciences.

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Contents

1

Basic Concepts

Fortunately for us (and unfortunately for bacteria, viruses, fungi, and parasites), we possess a remarkable, flexible, and powerful protective system that can destroy organisms attempting to use our bodies as their personal universe for procreation. This system, collectively denoted our host defense system, includes lymphocytes and macrophages (the immune system), polymorphonuclear leukocytes, fluid substances used to augment and amplify cellular activities (complement and cytokines), and mechanical barriers such as the skin and cilia.

The components of the immune system are distributed throughout the body and can be compared to a military force. Like the militia, the immune system may have to kill to protect. Therefore, its activities have to be carefully regulated; unfortunately, however, innocent bystanders may be harmed during an altercation. This pervasive and transcending character of immune reactions requires that all physicians, regardless of their personal commitment to a system or discipline, be aware of basic immune principles.

The pivotal role of the immune system in medical phenomena is shown by the awarding of the Nobel Prize in Medicine to immunologists in 3 of the last 8 years. The stunning scientific advances of recent years, exemplified by interplanetary space travel, computer technology, and genetic engineering, reflect an awesome level of understanding of physics and biology. Our ability to explain biology has now extended to the most elemental level—that of DNA analysis. The application of our newfound knowledge to enhance diagnosis and engender novel therapy has revolutionized the field of medicine and immunology in particular. The word impossible is being used more and more infrequently in regard to medical practice.

In the following chapters, we will deal primarily with the basic concepts concerning the immune system and the fluid products required for its optimal function. To obtain an overview and comprehend the integration of the various facets of the immune system as presented in these chapters one also should understand the following regarding the immune response.

Anatomy of the Immune Response. A productive immune response to antigen requires a series of events that must be orchestrated exquisitely. Five major steps occur:

1. Relevant mononuclear cell lines (macrophages and lymphocytes) are generated from the multipotential stem cells of the bone marrow.
2. Maturation and differentiation of the cell lines occur in either the bone marrow (B-lymphocytes and macrophages) or the thymus (T-cells). Generation of cell lines of appropriate diversity and heterogeneity leads to development of an adequate repertoire of immune elements capable of responding to over a million different antigenic stimuli in a specific and unique manner.
3. An antigenic stimulus addresses the repertoire that can now respond specifically because the cells express on their surface receptors able to recognize and react to a unique signal that is destined to excite them into preparation for the subsequent phases. In order to be appropriately stimulatory to the T- and B-cells, antigen must be processed appropriately by the macrophages and presented to the lymphocytes.

   A special requirement of T-cell immune responses is that the antigen be recognized in association with a transplantation antigen, both at the time of the initial stimulation and at the time when the T-cell uses the antigen as a target for cell lysis. In other words, the antigens expressed by viruses, bacteria, or fungi are not enough to excite an immune response from the T-cells. The surface proteins of the infectious agents are not antigenic until they are combined with a transplantation antigen expressed by our own tissues. This phenomenon is known as genetic restriction and illustrates one facet of the genetic influence upon the immune response. Many of the immune responses are controlled and heavily influenced by the products of a region on chromosome 6 known as the major histocompatibility complex.
4. Proliferation and further differentiation occur to generate the fully mature immune T- or B-cells that now can react with the immunologic vigor required for the elimination of the antigen.
5. Effector molecules react with the antigen. There may be secretion of the B-cell product (immunoglobulin) or, in the case of the T-cell, a physical combination of the mature cell with the antigen. T-cell reactions are associated with the release of cellular products that aid in the formation of granulomata. A key component to granuloma formation is the accumulation of macrophages. Thus, macrophages are important in the beginning phases of the immune reaction to process antigen and also in the later phases to aid in its elimination or containment. Alternatively, T-cell activation can result in a lytic reaction against a target bearing the immunizing antigen on its surface (e.g., a virally infected cell). If these events occur in the appropriate sequence and with sufficient vigor, the individual survives in his germ-laden environment.

Chapters 1–3 and 6–9 are devoted to these aspects of the immune response and describe the various cellular, genetic, and fluid components in greater detail.

Price of Protection. As mentioned previously, the immune reaction is both powerful and potent and may be associated with damage to neighboring structures. IgE responses cause clogged nasal passages and sinuses and wheezing lungs (immediate hypersensitivity or allergy). Years ago, allergic responses were extracted as the price for protection from parasites. There is no longer any significant need for this aspect of the immune response in modern countries, but until sufficient evolutionary pressure removes IgE from our immune apparatus, we will continue to

be charged unfairly for services not received. This phenomenon and the role of the eosinophil are discussed in Chapters 4 and 5.

In summary, existence in the sea of infectious agents in which we live is not possible without a functioning immune system. The extreme versatility and capability of this system require a complex developmental process and continuous productive cellular interactions. These extraordinary demands of competent immune respones set the scene for many potential errors. The immune response, whether beneficial or harmful, can occur in virtually all organs of the body, and thus, knowledge of the workings of this system must comprise a part of the fundamental basic knowledge of all physicians.

RICHARD HONG, M.D.

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B and T Lymphocytes

INTRODUCTION

The immune system is charged with the containment or elimination of foreign materials (antigens) that gain entrance into the body. This is accomplished by the development of two kinds of immune elements, immunoglobulins (Igs) and cytotoxic T-cells. The former are derived from lymphocytes known as B (bone marrow-derived)-lymphocytes and the latter from lymphocytes that differentiate in the thymus gland and are hence known as T-lymphocytes.

Specific immune responses are initiated by binding of antigen to receptors (protein molecules having a shape that is complementary to the antigen) expressed on the surface of the responding T- or B-cell. Encounter with the antigen causes an expansion of these cells; the resultant descendants all express the same receptor gene and hence the process is one of *clonal* expansion. Antigens are composed of a group of separable units known as epitopes. An epitope represents the smallest moiety that can generate an immune response. Each epitope induces a different clone. Our immune response is considered to be the sum total of all of our clonal responses; it is *polyclonal*. Since we can respond to over one million antigens with specific antibodies, the immune response is inordinately complex and an appropriate response requires an extremely well-coordinated cellular apparatus. It is impossible to survive if a significant deficiency

of both T- and B-cells exists. Deficiency of only the B-cell system is compatible with life if the infectious processes that usually ensue can be controlled. In recent years, methods to replace the various missing facets of the immune system have become available.

The effector mechanisms of the immune system (immunoglobulins and cytotoxic T-cells) are extremely potent and as long as this destructive capability is directed against unwanted intruders, all is well. If perchance this force becomes directed against normal body constituents, serious illness or even death can result. Thus, the immune elements must be closely regulated and controlled. Failure of these modulating influences results in the production of autoimmune disorders.

B-LYMPHOCYTES

The five major Ig proteins (isotypes) produced by B-cells include IgG (immunoglobulin G), IgA, IgM, IgE, and IgD. In addition to these five major isotypes, subgroups of IgG and IgA have been well described; slightly different behavioral characteristics are exhibited by these antibody subpopulations. Subgroups of the other isotypes are less well studied. IgD antibody is regularly found on the surface of young B-cells and always in association with another Ig. Trace amounts present in the serum probably represent shed receptors. Whether IgD is an immunoglobulin that provides protection by combining to antigen in the fluid phase is unknown. The other four Igs are secreted by B-cells and, from their site of manufacture in organized lymphoid tissues located in lymph nodes, spleen, lungs, and gastrointestinal tract, they are transported throughout the body. In various regions of the body they provide protection by slightly different mechanisms. In the intravascular space, Ig molecules combine with organisms and in this milieu they need to be especially effective in promoting phagocytosis and clearance. Molecules that are effective in gastrointestinal tract secretions appear to operate primarily by acting as a mechanical barrier to prevent adherence of organisms to the epithelial lining. Ability to resist proteolytic digestion is an important attribute of secretory antibodies. Specific functions of immunoglobulins are shown in Table 1. See also Chapter 10, "B-Cell Deficiency States."

ONTOGENY

B-cells arise from a stem cell that shares a common lineage with the hematopoietic system. The very first stages of B-cell development occur in the fetal liver during the 8th to 9th weeks of gestation. Shortly thereafter migration to the spleen and bone marrow occurs. In later life the bone marrow becomes the main repository for precursor B-cells. The capability for synthesis of all isotypes is present by the 20th week. Thus, the fetus can respond to antigenic stimuli received in utero. By the time of birth, the newborn human can respond to nearly all antigens; a notable exception is the polysaccharide antigen of pneumococcus. The mechanisms that control the hierarchical responses to antigens are not known but in general, except for the delayed ability to respond to certain polysaccharide antigens, immunological immaturity in the sense of a delayed B-cell response is not a significant clinical problem.

Serum Ig values increase with age. As the antigenic experience of the individual progresses, the total amount of Ig increases but at a different rate for each isotype. For a given antigenic stimulus, the IgM clones respond initially. With further exposure to the immunogen, the isotype response switches to produce IgG and IgA. The total serum levels of the major isotypes reflect this pattern. Serum IgM values rise rapidly and attain adult values by 9 months while adult levels of IgG and IgA are seen at 4 and 13 years, respectively.

There are small changes in serum Ig levels with advanced age. An interesting