Clinical Immuno-dermatology

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Foreword

MARION SULZBERGER SHOULD BE CONSIDERED the father of immunodermatology. His studies of delayed hypersensitivity and immunologic tolerance in the 1920s and 1930s—along with his classic 1940 book, *Dermatologic Allergy,* and his continued studies in allergy and immunology—attest to this. It was, however, not until the mid-1960s, when R. Jordon and E. Beutner discovered autoantibodies in pemphigus and pemphigoid, that immunology became important to the practicing dermatologist.

In the past two decades, we have witnessed an incredible expansion in our knowledge of fundamental immunologic principles and their relation to clinical disease. Dermatologists and their patients have reaped enormous benefits from these advances because diseases are diagnosed earlier, treated more rationally, and investigated in greater depth. It has become literally impossible to keep up with the "science" of dermatology, as its limits overlap those of many scientific subdisciplines. In the broad area of immunology, it is not possible for the busy practitioner, dermatology resident, or, for that matter, academician to keep up with new information related to clinical dermatologic problems. No longer is immunofluorescence all that is important to know. There have been a plethora of basic and clinical immunologic textbooks, as well as an increasing number of in-depth dermatologic works. However, none have provided the requisite balance of clinical dermatology and basic clinical immunologic principles in a primer for dermatologists and other physicians interested in skin diseases. This book fulfills that requirement.

Mark Dahl has simplified basic immunologic principles and has related them to the many dermatologic diseases with potentially immunologic associations. To many, this presentation may not seem "simplified"; but concepts such as HLA-disease associations, and the role of complement and other mediators in skin diseases and cellular interactions in the immune response are difficult to present in a way that physicians without an immunologic background can easily understand. Dr. Dahl's experience in immunologic research, his chairmanship of the American Academy of Dermatology Committee on Allergy and Immunology, his enthusiasm for teaching, and his talents as a writer have provided him with the tools required to meet the needs of the busy resident and practitioner.

It gives me great pleasure to recommend the book of a former colleague and a good friend.

Stephen I. Katz, M.D., Ph.D.
Bethesda, Maryland

Preface

THIS BOOK was written for clinicians treating patients with inflammatory skin diseases. The goal has been to provide a readable, clear, relevant, concise text applying immunologic principles to clinical dermatology. It is not intended to be a comprehensive text on immunology and inflammation but, rather, a primer.

Knowledge of the varied mechanisms of immunity and inflammation has increased at a rapid pace, providing insights into the pathobiology of many skin disorders. It is now recognized that the immune system plays an integral role in the initiation of inflammation and in the control and direction of most inflammatory events, including normal and abnormal immune responses. This realization has led to the development of new subgroups of clinical diseases and new diagnostic tests. Techniques for evaluating abnormalities of immune function are available to most physicians, and these tests provide new ways to measure severity, response to treatment, and prognosis. In order to properly apply this new knowledge to treatment of patients, an understanding of immunologic principles is necessary. I have written this text to provide this basic understanding in the framework of specific skin diseases.

Specifically, this book lays the foundation for understanding the mechanisms of inflammatory skin diseases. It underscores the use of immunologic tests for evaluation and treatment of these disorders. The first chapters introduce the fundamentals. Topics include humoral and cell-mediated immunity, complement, mediators of inflammation, role of phagocytic cells, and immunogenetics, including HLA. The second portion of the book contains discussions of individual clinical skin disorders, such as psoriasis, allergic contact dermatitis, atopic dermatitis, and bullous diseases. Emphasis is placed on pathophysiologic immune mechanisms and clinical laboratory tests. The appendix on immunofluorescence repeats some information contained in the chapters on clinical diseases. However, it provides a handy review of the uses of immunofluorescent techniques in clinical dermatology and discusses practical aspects, including when and where to perform biopsies and how to interpret results. A short glossary precedes each of the early chapters; especially important concepts are highlighted in boxes throughout the text.

Because this book is intended as a primer, specific references are not

cited. References are a convenient way to signal knowledge of a study that contradicts a prevailing idea, and they establish a clear separation of hypothesis from fact. However, they also force introduction of extraneous information and detract from the train of thought. Thus, I opted for simplification. References at the end of each chapter direct readers to appropriate reviews, should they need additional, specific information.

To provide a readable, unified presentation, I decided to write this book alone. My approach focuses on simplification of basic principles and practical application of these principles in a clinical setting. Simplification forces generalization, and I hope that any bias introduced by this generalization does not detract from the value of the text to clinicians.

Because it is impossible for an individual to be an expert in all areas of immunology and inflammation, I am fortunate to have had the benefit of advice from two outstanding immunodermatologists, Stephen Katz and Thomas Provost, and an outstanding immunologist, Ira Green. I thank them for their reviews of my manuscript. I would also like to express my appreciation to many other friends and associates who reviewed selected chapters. Their comments and suggestions resulted in a clearer, more accurate and relevant text.

Finally, I want to thank my family for their encouragement and patience, Dr. Robert Goltz for academic freedom, and Pearl Homiak for typing and assistance.

MARK V. DAHL

Contents

1 • Overview of the Immune System

Glossary

antibody—an immunoglobulin produced during an immune response to an antigen, capable of combining with the antigen that stimulated its production.

antigen—a substance capable of inducing an immune response.

cell-mediated immunity—an immune response involving lymphocytes and macrophages not primarily mediated by antibodies.

complement—a series of serum proteins that mediate antigen-antibody reactions.

delayed hypersensitivity reaction—a specific type of cell-mediated immune reaction with certain features, including maximum response occurring within 24 to 48 hours and infiltration with lymphocytes.

HLA antigen—a glycoprotein on a cell surface, produced under direction of specific genes within the major histocompatibility complex in man, which can act as an antigen when the cells are transplanted into another person.

humoral immunity—an immune response mediated by antibodies.

immunoglobulin—a protein that can act as an antibody, or a protein of similar composition without known antibody activity composed of at least two light and two heavy chains.

lymphokines—nonantibody substances with various functions elaborated by lymphocytes during an immune response.

major histocompatibility complex—a set of linked genetic loci that contains genes coding for cell surface antigens which are primarily responsible for control of tissue graft rejection.

monokines—nonantibody substances with various functions elaborated by macrophages during an immune response.

opsonin—a substance that can coat a particle to promote its phagocytosis.

phagocyte—a cell that can ingest particulate matter.

THE IMMUNE SYSTEM and its inflammatory limb are complex models of biologic activity and interaction. There is a great tendency to dissect the

immune response into its individual components; and, indeed, such close inspection is necessary in order to understand its function. However, manipulation of one component influences all others (Fig 1–1).

This chapter serves as a tour of the immune and inflammatory systems. It is an attempt to survey components of the immune system before each is examined in detail.

Immune Response

The concept of immune response implies a reaction to something. The initiator is called an antigen. This can be an infectious agent but is often a protein or other molecule. The antigen contacts certain cells, which initiate the complex series of events that lead toward its eventual destruction, degradation, or elimination. The series of events is the immune response.

The immune response, in turn, can be divided into two segments. First there are those events between the time the cells contact the antigen and the time the animal has developed hypersensitivity (become immune) to it. This sequence of events is called the afferent limb. The second half of

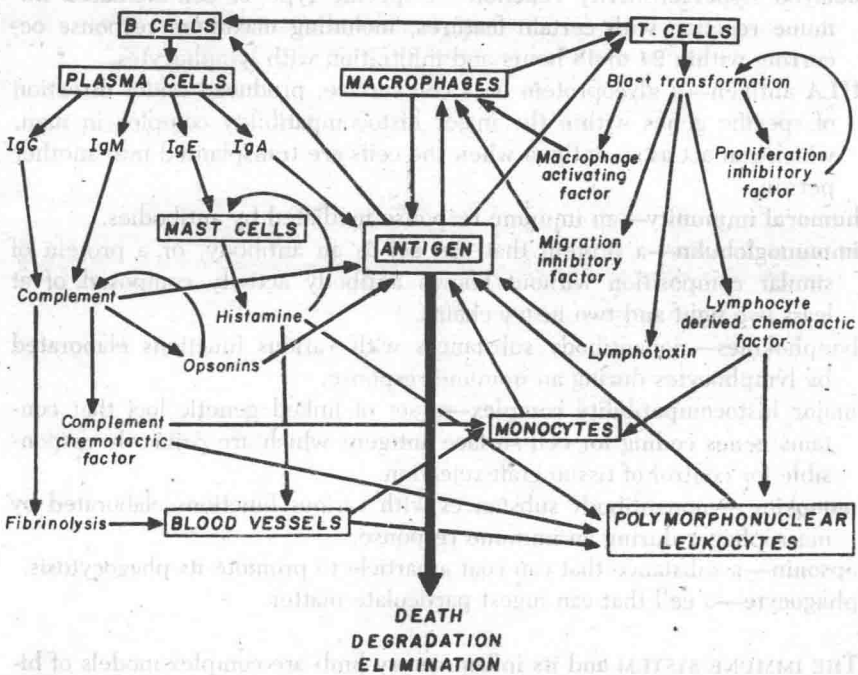

Fig 1–1.—The immune system—a complex system of interrelated components. Activity of one component often affects others.

the immune response is the sequence of events between development of hypersensitivity and elimination of the antigen. This sequence of events, called the efferent limb, includes the sequence of events that produce clinical inflammation.

An immune response is not obligatory for inflammation to develop. Said another way, antigens are not always ultimately responsible for inflammation. Chemical irritation, trauma, or other mechanisms produce inflammation without activating the afferent limb. Nor is inflammation always evoked by an immune response. The afferent limb can be activated without activation of the efferent limb.

The immune system is divided into two components. The humoral immune response involves certain gamma globulins called immunoglobulins (some of which are specific antibodies). The cell-mediated immune response may cause delayed hypersensitivity reactions mediated by lymphocytes and their products, called lymphokines.

The immune system is activated when an appropriate lymphocyte encounters an antigen. An antigen is a substance which is capable of initiating the immune response. It is usually a protein or carbohydrate, but it may be a lipid. Some nonimmunogenic substances (haptens) can act as antigens when coupled to other substances (carriers).

Humoral Immunity

There are two major types of lymphocytes: the T-cell and the B-cell. The T-cell will be discussed later. Both are derived from a precursor stem cell which is thought to exist in fetal liver or bone marrow. B-cells constitute the majority of lymphocytes in the bone marrow but only 10–20% of peripheral blood lymphocytes. They synthesize immunoglobulin and are identified by the presence of immunoglobulins on their cell surfaces as detected by direct immunofluorescence staining. B-cells also possess other receptors on their surfaces which allow them to be differentiated from T-cells.

B-lymphocytes differentiate into plasma cells, each capable of producing much more immunoglobulin than the precursor B-lymphocyte. There are five major classes of immunoglobulins, namely, IgG, IgA, IgM, IgD, IgE.

All immunoglobulins are polypeptides. Antigen combines with antibody at either of two antigen binding sites on one end of the antibody molecule. The other end of the antibody is called the Fc end, and it is involved in complement fixation and binding to Fc receptors on certain cells.

The major and most abundant immunoglobulin is IgG. It provides long-lasting immunity to a variety of infectious agents. The normal concentration of IgG in adult human beings is about 1,200 mg/100 ml of serum

(range 500–1,600 mg/100 ml). These immunoglobulins are produced by plasma cells in response to bacteria, viruses, and toxins. Their half-life is 23 days. IgG antibodies have been divided into four subclasses: IgG1, IgG2, IgG3, and IgG4. Except IgG4, each is capable of fixing complement. The major subclass is IgG1, which constitutes approximately 65% of the total IgG. The IgG molecule consists of two heavy and two light polypeptide chains.

IgM antibodies are usually pentamers and therefore more than five times the size of IgG antibodies. Each pentimeric IgM molecule consists of ten heavy chains and ten light chains. The concentration of IgM in the normal adult is approximately 100 mg/100 ml (range 48–414 mg/100 ml). These immunoglobulins have a half-life of about five days and do not cross the placenta, but they do fix complement. They are often the first-antibodies detectable after immunization or other antigenic challenge. Like IgG, IgM antibodies are produced in response to and react with infectious agents such as bacteria and viruses. Isohemagglutinin antibodies such as anti-red blood cell A or anti-red blood cell B are of the IgM class, as are cold agglutinins, most rheumatoid factors, and the heterophile antibodies which characterize infectious mononucleosis.

IgA antibodies are synthesized by B-lymphocytes and plasma cells in the gastrointestinal tract as well as in the bone marrow and peripheral blood. Approximately 90% of all IgA is synthesized in the gastrointestinal tract. When secreted into the gastrointestinal tract, IgA may act as a sort of "protective paint" to prevent absorption of certain dietary protein and toxins. IgA immunoglobulins are approximately the size of the IgG immunoglobulins and, like IgG, consist of two heavy chains and two light chains. However, the IgA secreted into the gut is dimeric; that is, it consists of two IgA molecules joined together by a J-chain and a small secretory piece (also called T-piece). The normal serum concentration of IgA is about 200 mg/100 ml (range 40–468 mg/100 ml). IgA has a half-life of about six days and is capable of neither complement fixation nor transfer across the placenta. However, *aggregated* IgA can activate complement.

IgD is present in the serum only in very small amounts. It consists of two heavy chains and two light chains and does not fix complement or cross the placenta. Its role is primarily that of a receptor on lymphocyte surfaces. It appears on the surfaces of B-cells during differentiation. The function of IgD in serum and on cells is unknown.

IgE is present only in minute amounts in the serum. It cannot cross the placenta or fix complement. IgE binds to the surface of mast cells and basophils. When the mast-cell-bound IgE encounters antigen, the mast cell degranulates and liberates histamine, heparin, and other mediators.

Antibodies can produce at least three different types of immune reactions: type I anaphylactic reactions, type II cytotoxic reactions, and type

III immune complex reactions. Type I anaphylactic reactions are caused by the combination of allergens with IgE molecules on mast cells and basophils and their subsequent liberation of histamine and other mediators. An example of a type I reaction is urticaria.

The type II cytotoxic response requires the binding of IgG or IgM to specific antigens. When the complement system is activated, it initiates a series of reactions which result in lysis or phagocytosis of the virus, bacterium, or other antigen. An example of a type II cytotoxic reaction in dermatology may be bullous pemphigoid.

A type III immune complex reaction is produced by aggregations of antigen, antibody, and complement. These can be formed in tissue or in the circulation. At least some immune complexes of a certain size are not easily removed by the mononuclear phagocyte system. These can interact with blood vessel walls or other tissues. Activation of complement and influx of polymorphonuclear leukocytes can provoke tissue damage. An example of a type III reaction is cutaneous necrotizing vasculitis.

Complement

Complement refers to a group of at least nine nonantibody plasma proteins that are necessary for certain antigen-antibody reactions to produce tissue damage or microbial death. As has been mentioned, complement can cause cell lysis. However, the major function of complement in the immune response is probably to mediate various aspects of inflammation, including vasodilatation, leakage of fluid, chemotaxis of phagocytic cells, opsonization, and metabolic events within inflammatory cells.

To reemphasize, activation of complement is often necessary before immune injury can occur. It is an integral component of both type II and type III reactions. As depicted in Figure 1–2, it can be activated in two major ways, by the classical complement pathway and the alternative complement pathway. Certain components of the complement system, however, can be activated from precursors by tissue proteases in the absence of antigen-antibody reaction. Immunologically, complement is activated by antigen-antibody reactions involving IgG, IgM, or aggregated IgA.

There are nine major complement components. Each acts sequentially to activate the next component. Activation of the classical complement pathway is initiated when IgG or IgM combines with antigen. A subunit of C1, called C1q, can then attach to the antigen-antibody complex to initiate the complement cascade. The alternative complement pathway can be activated by aggregated IgA and sometimes, in addition, by aggregated IgG and IgM. In the alternative pathway C1, C4, and C2 are bypassed and the initiators act instead on factor D to start the complement cascade. The alternative pathway is therefore a separate set of proteins which activate

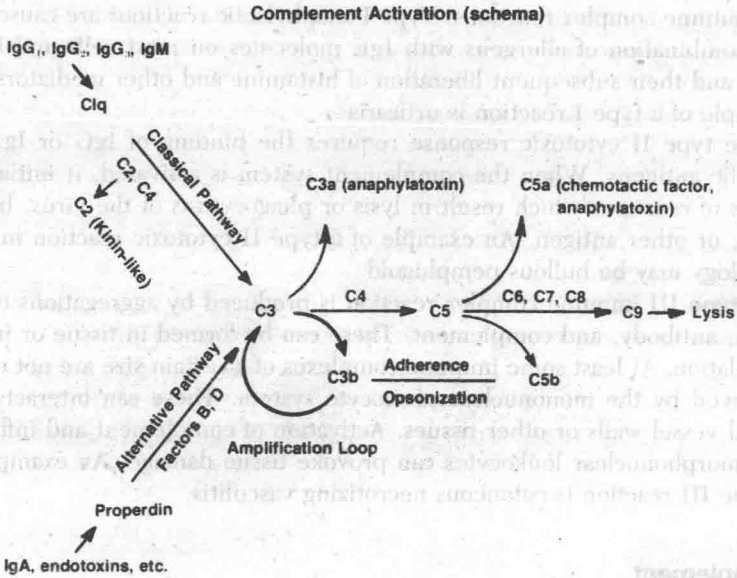

Fig 1–2.—Two ways of activating the complement system—classical pathway and alternative pathway. Complement activation mediates immune reactions by lysis of cell membranes or by generation of biologically active peptides. (Reprinted from Dahl, M. V.: Primary immunodeficiency diseases. *J. Contin. Educ. Dermatol.* 17:31–45, 1978. Used with permission.)

C3 without the involvement of C1, C4, or C2 that is needed in the classical pathway activation.

Both pathways ultimately lead to cleavage of the third component of complement, C3. C3 in turn can cleave C5 and activate terminal complement components C6, C7, C8, and C9. The cleavage of C3 also induces a tremendous amplification system in that numerous bystander C3 molecules can be activated by precursors and by-products of C3 cleavage.

C5 is in many ways like C3. Cleavage of C5 or C3 results in the production of small fragments of complement. C5a can cause mast cell degranulation and induce phagocytic cells to migrate toward the site of their generation (chemotaxis). Two other fragments of C3 and C5, C3b and C5b, can function to prepare particulate matter for ingestion by phagocytic cells (opsonization).

Cell-Mediated Immune System

Whereas the humoral immune system involves B-cells and their immunoglobulin products, the cell-mediated immune system involves T-cells

and their lymphokine products. The T-cell constitutes approximately 80–90% of peripheral blood lymphocytes and approximately 90% of lymphocytes in the thymus. While T-lymphocytes may have tiny amounts of immunoglobulins on their cell surfaces, these T-cells have far less immunoglobulin molecules on their surfaces than do B-cells. Consequently, under ordinary circumstances, T-cells do not fluoresce when incubated with fluorescein-labeled antihuman immunoglobulins and examined under the immunofluorescence microscope. However, in contrast to B-cells, T-cells have a receptor on their cell surfaces which combines with sheep red blood cells. Rosettes of red cells around T-cells are formed when T-cells are incubated with sheep red blood cells. The importance of these E-rosettes is that they identify T-cells.

Before a T-cell can respond to an antigen, the antigen must be "processed" and "presented" to the T-cell by a macrophage. Once the appropriate interaction of macrophage, antigen, and T-cell occurs, the T-cell undergoes a blastogenic transformation which results in increased metabolic activity (lymphocyte activation). Also, during the process of blastogenic transformation the T-cell elaborates a number of soluble substances called lymphokines which can evoke and influence the inflammation of cell-mediated immune reactions. Numerous lymphokines have been identified, including such substances as macrophage migration inhibitory factor (MIF), macrophage activation factor (MAF), macrophage chemotactic factor, leukocyte inhibitory factor (LIF), interferon, and lymphotoxin. These mediators are capable of affecting macrophages, polymorphonuclear leukocytes, lymphocytes, and other cells in such a way as to produce type IV delayed hypersensitivity reactions. An example of a type IV delayed hypersensitivity reaction in dermatology is allergic contact dermatitis.

The sequence by which lymphokines induce an inflammatory reaction is not well established. Lymphocytes activated by contact with specific antigens could liberate lymphokine chemotactic factors, bringing inflammatory cells into the area. They could be immobilized at the site of lymphocyte activation by macrophage migration inhibitory factor and leukocyte inhibitory factor. Macrophages could then be activated by macrophage activating factor to become killer cells to produce tissue injury. A recruitment amplification loop involving lymphocyte mitogenic factor could cause other uncommitted lymphocytes to participate in this delayed hypersensitivity response. Macrophages can also amplify the immune response by elaboration of monokines, such as interleukin 1 (LAF; lymphocyte-activating factor), to stimulate uncommitted lymphocytes to participate in the inflammatory reaction that ensues.

The cell-mediated immune system is controlled by helper and suppres-