

allergic Diseases

**DIAGNOSIS AND
MANAGEMENT**

ALLERGIC DISEASES

Diagnosis and Management

Edited by

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Preface

This book covers those clinical problems that are commonly seen in the daily practice of the speciality of Allergy. Because of the high incidence of hypersensitivity disease of the immediate type in the general population, reagin-mediated disease is responsible for the majority of clinical immunologic problems seen in medical practice. The theoretical and practical aspects of these IgE-mediated diseases are discussed in detail. Diseases that have clinical manifestations similar to the reagin-mediated reactions but are probably not IgE-mediated are included, because they are commonly referred to the specialist in Allergy. These diseases may include certain types of asthma, urticaria and rhinitis. The complex problem of drug reactions, most of which are probably not IgE-mediated, is discussed in detail, because it is a common and growing problem in the clinical practice of allergy.

The remarkable advances made in basic and clinical immunology in the past 15 years have extended the range of diseases now considered to be of immunologic origin. We have decided not to attempt to review the basic and clinical information relating to the immunology of hematology, nephrology, rheumatology, transplantation, infectious diseases and other major areas of current interest. The consultant in the specialty of Allergy and Immunology must be familiar with these problems, but detailed information regarding them is already available in a variety of recent texts and reviews. The comprehensive practice of modern clinical allergy requires knowledge and training separate from immunology because of the importance of such aspects as pulmonary physiology in asthma, the pharmacology of therapeutic agents, and the botany and aerobiology of antigenic materials. These areas, relevant to the common allergic diseases seen in practice are reviewed in some detail because they are less frequently encountered in recent texts dealing primarily with nonreaginic immunologic diseases.

It is the opinion of many practitioners and teachers in the field of allergy that the recent advances in basic and clinical immunology must not lead to a decline in emphasis on the common allergy problems, if only because of the high incidence of allergy and the lack of appropriate care patients may receive.

This book has been written by a group of authors, who have worked

together, either during their training period in Allergy, or as faculty members of the Allergy-Immunology Section of the Department of Medicine at Northwestern University Medical Center. Although they were selected because of their unified approach to teaching and clinical care in allergy, they have either trained or are currently working in other medical centers; so their opinions and approaches are not restricted to those of one small group.

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Classification of Hypersensitivity Reactions

James D. Lakin, PH.D., M.D.

The rapid expansion of the immunologic literature has been apparent to immunologists and to interested clinicians who have found this area relevant to their own fields of interest. It is the purpose of this chapter to review briefly some of the more recent and significant findings of immunology and immunochemistry as they relate to the subject of clinical hypersensitivity phenomena. Obviously such a broad subject does not permit detailed examination, and throughout this discussion the reader is referred to a number of excellent review articles which have recently appeared.

Clinical allergy or hypersensitivity processes embrace a wide range of disease states including such diverse entities as bronchial asthma, a number of dermatologic disorders, the connective tissue syndromes, transplantation, tumor and auto-immunity. However, throughout this seeming potpourri of clinical and pathological entities, a common denominator of pathophysiology must be either objectively demonstrable or reasonably inferred: allergy or hypersensitivity is immunologically mediated, through interaction of antigen, of exogenous or endogenous origin, with specific humoral antibodies or specifically sensitized lymphocytes. The consequences of this interaction may be quite diverse, accounting for a variety of clinical manifestations.

Historically the definition of allergy has been based on the acquisition by the individual of an altered reactivity to a normally innocuous substance. This older concept has been shown not to be strictly applicable to clinical observation. For example, allergic rhinitis due to reaginic antibody against ragweed pollen is an immunologically mediated disease. However, a very similar clinical picture occurs in vasomotor rhinitis due to increased reactivity of the microvasculature to cold temperatures. In the first instance the reaction is immunologic; in the second, idiosyncratic. In other situations the differentiation of the immunologic from the nonimmunologic may be even more difficult. Indeed with increasingly sensitive techniques for the detection of immunoglobulin and anti-

body activity, a number of diseases, such as ulcerative colitis, pernicious anemia and some forms of hepatitis, are being associated with the presence of immunoglobulin (presumably antibody) deposits in the area of pathology. In some cases, however, these presumed auto-allergic processes are results rather than causes of the basic lesion of the disease, merely representing a secondary response of the immune system to tissue breakdown. The classification of hypersensitivity diseases has often proved to be as problematic as the differentiation of the allergic from the nonallergic. The traditional subdivisions of immediate and delayed allergy are inadequate to encompass the quite diverse reactions accepted as manifestations of hypersensitivity. Classification according to antigen type, as in drug allergy, or according to organ involvement has produced the grouping of rather dissimilar conditions in common company.

As more basic immunologic data has been correlated with clinical experience, a workable system of general classification has been produced.³⁰ It is based on four general reaction types originally proposed by Gell and Coombs. Type I hypersensitivity is mediated by reaginic antibody which is predominately, if not exclusively, of the IgE class in man (anaphylaxis and allergy). Type II hypersensitivity reactions are produced by reaction of antibody with cell-bound antigen followed secondarily by complement fixation. Type III reactions are effected by soluble antigen-antibody complex deposition at a reaction site (toxic-complex reactions). Following complex formation, complement fixation occurs mediating many of the biologic consequences of Type III reactions. Type IV reactions (delayed or cellular hypersensitivity) refer to that group of allergic disorders caused by the reaction of specifically sensitized small lymphocytes with antigen. The remainder of this chapter will be devoted to a more detailed examination of these reaction types.

TYPE I OR ANAPHYLACTIC REACTIONS

The first type of hypersensitivity reaction considered in the Gell and Coombs classification is termed anaphylactic hypersensitivity. This reaction group is also referred to as immediate type hypersensitivity (atopy or allergy) or reaginic hypersensitivity. The clinical conditions in which Type I hypersensitivity appears to play a role include extrinsic bronchial asthma, seasonal allergic rhinitis or hayfever, some cases of urticaria, certain food and drug allergies, reactions to stinging insects, systemic anaphylaxis and possibly atopic dermatitis or eczema. The mediation of these reactions is accomplished by a distinct group of antibodies termed reagin, or skin-sensitizing antibodies. The work of Ishizaka and others has

demonstrated that the majority, if not all reaginic activity in humans is confined to a class of immunoglobulins separate from the better characterized IgG, IgM, IgA and IgD categories. Antibody of this immunoglobulin class, IgE, has been shown to possess the classic characteristics of reagin.³⁹ Reagin can circulate in serum or bind to certain cells including those of the respiratory or gastrointestinal mucosa or circulating leukocytes. Unlike most other antibodies, its biologic activity is destroyed upon heating to 56° C. It does not cross the placental barrier. When cell-bound reagin combines with antigen, it initiates the characteristic events of immediate type allergy within minutes. Histamine, slow reacting substance and possibly kinins (discussed in succeeding sections) are thought to be released by human reagin-bearing cells causing vasodilation, increased capillary permeability and smooth muscle contraction. This in turn leads to the clinical manifestations of urticaria, angioedema, hypotension, bronchospasm, spasm of gastrointestinal musculature or uterine contractions, depending on the location and severity of the reaction.

The IgE class of immunoglobulins which possess reaginic activity has been found to have a molecular weight of approximately 200,000 and a sedimentation coefficient of 8S. With the discovery of the IgE type of myeloma, structural studies of the protein have been possible. Prior to the availability of these IgE myelomas, the normal concentrations of IgE of from 6 to 780 nanograms per ml. had technically precluded such investigations.^{43, 66, 34} In common with the other immunoglobulins, IgE molecules are composed of two light chains of either kappa or lambda type. Its heavy chains are antigenically unique to IgE, being termed epsilon chains. IgE is a glycoprotein, its epsilon chain containing a very large amount of the sulfur-containing amino acids, methionine and cystine. Although IgE can sensitize both human and monkey skin, it will not sensitize guinea pig skin. Complement fixation by IgE antibodies has not been detected, consistent with the lack of complement fixation and anaphylatoxin formation observed in Type I reactions. Further structural studies have revealed that the Fc portion of the IgE molecule contains the structures essential for attaching to the cell sites. Binding of reaginic antibody to cells has been shown to be inhibited by pretreatment of the cells with Fc fragment.

The IgE molecule has been shown to contain two antigen binding sites, and thus IgE is divalent in analogy to IgG. However, it has been further noted that two IgE molecules are required for the formation of skin reactive complexes. It has been suggested that induction of skin reactive properties by the formation of cell-bound, antigen-antibody complexes may involve interaction between the IgE antibody molecules, structural changes in the molecules or both. The induction of this al-

losteric phenomenon by combination with antigen may effect the cell membrane in some manner, leading to the release of effector molecules (histamine, slow reacting substance etc.).⁷⁸

In clinical practice, correlation of specific IgE type antibody with atopic disease has been suggested in a number of instances.^{44, 74} It has been observed that IgE fixes to basophilic leukocytes and mast cells that can release mediators of inflammation upon exposure to specific antigen. A number of investigators have speculated regarding a protective function for IgE. In intestinal parasitic infestations markedly elevated levels of IgE have been documented although their significance is not known.^{38, 45} A protective function for IgE in the respiratory tree has been suggested (10); however, more recent reports have failed to support a relation between increased susceptibility to sinopulmonary infection and a deficiency of IgE.⁷⁵ Indeed, IgE deficiency has been documented in a 28-year-old female in good health.⁵⁶ Further studies of the relation of IgE to the immune defenses are necessary before meaningful conclusions can be made.³⁴

TYPE II OR CYTOTOXIC REACTIONS

The second major type of hypersensitivity reaction described in the classification of Gell and Coombs is termed cytotoxic or cytolytic. Alternately, this reaction group is referred to as complement dependent cytotoxicity. This should not be confused with Type IV reactions which also result in cytotoxicity, although by quite a different mechanism. Also, the distinction between Type II and Type III reactions should be stressed, each reaction pattern involving secondary complement fixation, after different primary reactions. The distinctive primary event of Type II reactions is that of antibody combining with an antigenic determinant which is present on tissue cells. The antigen may be part of the internal structure of the cell involved or it may be an exogenous antigen or hapten which is absorbed on or combined with tissue cells. Complement usually, but not always, is necessary to produce cellular damage.

The Complement System

It may be surmised that complement is an important effector system *in vivo*. It is involved in Type II reactions after combination of cell-bound antigen with antibody has occurred and in Type III reactions after deposition of antigen-antibody complexes at the reaction site has occurred.

The biologic consequences of the interaction of antigen, antibody and the complement system are diverse. Phenomena which have been de-