

Introduction to Allergic Diseases

27430

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I. INTRODUCTION

An allergy is the immune-mediated state of hypersensitivity that results from exposure to an allergen. An allergen, in turn, is a biological or chemical substance that causes an allergic reaction.¹ The most common allergic reaction is mediated by immunoglobulin E (IgE) and involves activation of effector cells, mainly mast cells and basophils, which lead to an inflammatory response and clinical manifestations.

Allergic diseases affect a significant portion of the general population, estimated at 10 to 25% in developed countries, although food allergies are much less prevalent. Clinical disease requires both genetic predisposition and environmental allergen exposure. It is unclear why some people develop allergies and others do not. It is known, however, that people with a genetic predisposition to allergy (a condition called atopy) produce significantly greater quantities of total and specific IgE compared to nonallergic individuals.

An IgE-mediated response occurs in all normal individuals, but the presence of certain genes may be needed for antigen specificity and clinical manifestations of the atopic state. The genetic influence is evidenced by the known epidemiological findings which indicate that if one parent has allergies, the chances are 1:3 that each of their children will have allergies. If both parents have allergies, it is even more likely (60 to 70%) that their children will exhibit some allergic symptoms.

Allergic diseases result in major clinical and public health problems due to their high prevalence. For example, about 20% of Americans suffer from allergic rhinitis. Eight to 12% of the Ameri-

can population has asthma. Among chronic diseases, asthma is the leading cause of school absenteeism and is responsible for approximately 4000 deaths per year in the U.S. In 1990, the estimated cost of asthma-related illness in the U.S. was 6.2 billion dollars.¹ It is therefore obvious that the economic and social impact of allergic diseases in developed countries is significant.

II. CELLS OF THE IMMUNE RESPONSE

A normal immune system is essential for health; a dysfunctional system leads to disease. A deficiency in immune cell production or defective immune function may lead to a wide spectrum of immune-deficiency diseases. Overactivity of various components of the immune system leads to the development of allergic or autoimmune diseases. Multiple cells are included in the immune system, as is shown in Table 1. The cells, which are directly involved in the induction and/or elicitation of the allergic response, will be discussed in more detail below.

A. B Lymphocytes

B cells constitute one of the principal components of the immune system. They provide both cognitive and effector functions in the humoral immune response. Membrane Ig-expressing B cells are cognitive cells, because they recognize and respond to various antigens. Following antigenic stimulation, they differentiate into effector cells and secrete Ig. The vast array of antibodies produced by B cells belong to five Ig classes (isotypes), namely IgM, IgD, IgG, IgA, and IgE.² The basic structure of an Ig is shown in Figure 1.

Table 1
CELLS OF THE IMMUNE RESPONSE

	Location	Function
LYMPHOCYTES (% normal range)		
T	Blood (65-75), thymus (>95) lymph nodes (70-80), spleen (20-30) lymphoid organs (i.e. Peyer's patches, etc.)	Cell mediated cytotoxicity Cell mediated immunity Regulatory effects on other immune cells
B	Blood (10-20), (Thymus <1) lymph nodes (10-20) spleen (40-50)	Immunoglobulin production & secretion Antigen presentation
Natural Killer (NK)	Blood, bone marrow spleen	Killing of certain tumor cells; defense against viral infection; regulatory effects on other immune cells
Macrophages	Various tissues (i.e. lymph nodes, spleen, thymus, liver, lung, central nervous system, skin)	Phagocytosis and processing of antigens. Antigen presenting cell (APC)
GRANULOCYTES		
Neutrophils	Blood	Phagocytosis and bacterial killing; proinflammatory effects via extra-cellular degranulation (i.e. complement activation, degradation of connective elements), increased vascular permeability
Eosinophils	Blood	Parasite killing; effector cell in allergic inflammation (i.e. induces histamine release from mast cells, bronchospasm, damage to respiratory epithelia)
Basophils	Blood	Allergic/anaphylactic reactions; immune response against ticks
MAST CELLS	Tissues (connective and mucosal)	Major effector cell in the allergic response

The life history of the B-cell lineage in the bone marrow is divided into two main stages: an initial antigen-independent phase (pre-B cells to mature B lymphocytes) and an antigen-dependent phase (B lymphocytes to antibody-secreting plasma cells).³ The pre-B-cell stage begins with a multipotent hemopoietic stem cell. Primitive B-cell precursors have μ chains (heavy chain of IgM) in their cytoplasm and no Ig on their surface. At the next identifiable stage in B-cell maturation, kappa or lambda light chains are also produced. These associate with the μ heavy chains and then assembled IgM molecules are expressed on the cell surface. Thus, more differentiated B cells (but still immature) have intact cytoplasmic and surface IgM. The cells in this stage of development do not proliferate and differentiate in response to antigens. In fact, their encounter with some antigens such as self antigens may lead to unresponsiveness (tolerance) rather than activa-

tion. Once a B cell expresses a complete heavy or light chain of the Ig molecule, it cannot produce another heavy or light chain containing a different variable region (antigen specificity). Mature B cells lose their cytoplasmic IgM and add surface IgD to the surface IgM. Both classes of membrane Ig have the same variable region and hence the same antigen specificity. Once the mature B cells are stimulated by antigens (or other signals) they proliferate and differentiate, producing an increasing proportion of their Ig in a secreted form and progressively less in a membrane-bound form. After activation, B cells in any given clone can switch Ig production from IgM to antibodies of different heavy-chain classes (isotypes), but with identical antigen-binding specificity. Thus, these cells begin to express Ig heavy-chain classes other than μ , e.g., γ , α , or ϵ . This crucial step of isotype switching facilitates the diversity of B-cell responses in Ig production and involves splicing

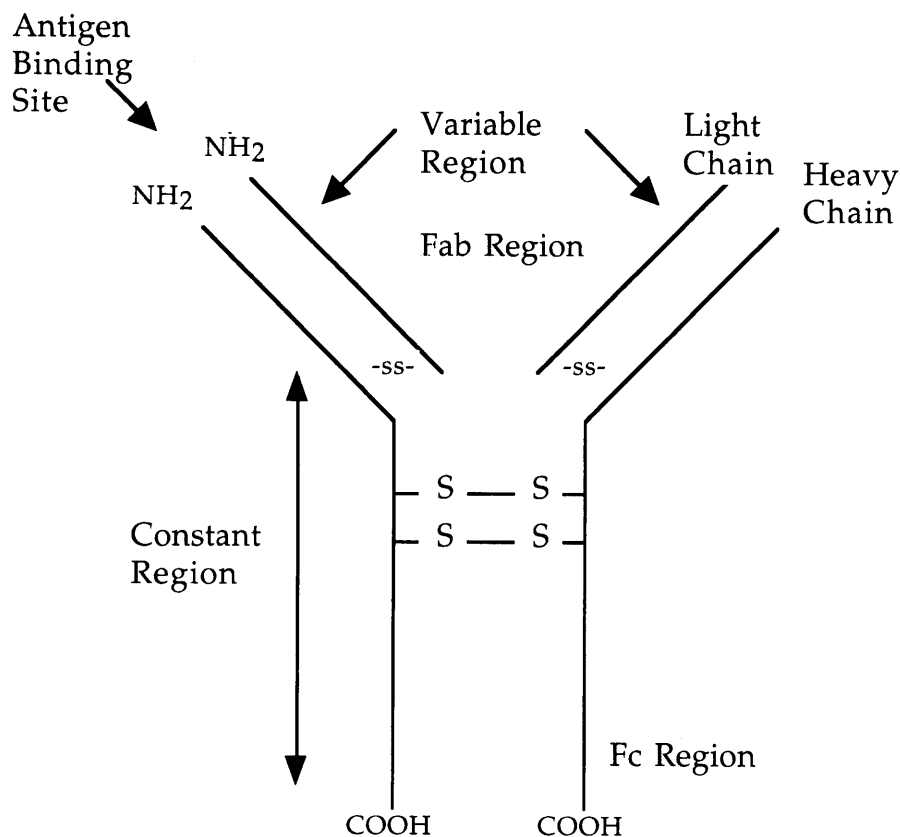


FIGURE 1. The basic structure of an Ig.

and deletion of exons in the C μ gene (the gene for the constant region of IgM) located on chromosome 14. Other activated B cells may not secrete antibodies, but may instead persist as membrane Ig-expressing memory cells that survive for months without further antigenic stimulation and actively recirculate between the blood and lymphoid organs. Their stimulation by an antigen will lead to a secondary antibody response. Antigen-induced differentiation of mature or memory B lymphocytes culminates in the development of antibody-secreting cells, some of which can be morphologically identified as plasma cells. The primary function of an antibody is to bind specifically to an antigen and bring about inactivation or removal from the body, of the offending toxin, microbe, parasite, or other foreign substance. The biological characteristics of human Ig are presented in Table 2.

Surface-bound Ig may thus be perceived as antigen receptors. Antigens or other multivalent ligands that cross-link Ig molecules are able to

induce the resting B cell to enter the cell cycle, enlarge, develop synthetic machinery, and begin DNA synthesis in preparation for division. Antigen molecules that bind to surface Ig receptors are internalized and partially digested. The antigen fragments are then recycled to the B-cell surface and expressed in association with class II molecules of the major histocompatibility complex (MHC). This combination of antigen fragments and the class II molecule on the B-cell surface may then be recognized by a T cell by means of its antigen receptor. In this way the B cell presents antigen to helper T cells and stimulates production of T-cell-secreted factors (lymphokines) that in turn will promote proliferation and differentiation of the antigen-presenting B cell. Other antigen-presenting cells (APC) of importance include macrophages and Langerhans cells. Lymphokines which are known to affect B-cell differentiation include interleukin-4 (IL-4), which controls the switch to IgE production,⁴ interleukin-5 (IL-5) and the transforming growth

TABLE 2
Human Ig

	IgG	IgA	IgM	IgD	IgE
Mol wt (kDa)	150	160 (390) ^a	900 ^b	175	190
Serum half-life (d)	23	6	5	3	2.5
Average serum concentrations (mg/dl)	1250 ± 300	200 ± 50	125 ± 50	3–4	0.03
Function	Secondary antibody response	Antibody in mucous secretions	Primary antibody response	Primary lymphocyte surface molecule	Mediates allergic responses
Antiviral activity	+	+++	+	?	?
Antibacterial activity	+	+	+++	?	?
Binding cells via Fc	Macrophages, neutrophils, eosinophils, LGL ^c	Lymphocytes	Lymphocytes	None	Mast cells, basophils, B cells, eosinophils, Langerhans

^a Secretory IgA appears in saliva and GI secretion is a dimer.

^b IgM circulates as a pentameric molecule.

^c Large granular lymphocytes.

factor- β (TGF- β), which are responsible for IgA production, and interferon- γ (IFN- γ), which inhibits IgE synthesis.

B. T Lymphocytes

T lymphocytes (T cells) are critical components of the immune system. Unlike B cells, they predominantly recognize antigen when it is associated with membrane-bound products of the MHC. This dual recognition of antigen and MHC is important for activation of both effector T cells, including cytotoxic T cells, and immunoregulatory T cells.⁵

T cells arise from stem cells and are “educated” in the thymus, hence the name “T” cells. The central role of the thymus is related to the rearrangement and productive expression of the T-cell receptor (TCR) genes and the subsequent selection of the antigen receptor repertoire that enables mature T cells to recognize foreign but not self antigens. In the thymus, primitive T cells (pro-T cells) develop T-cell-specific surface antigens (or markers), such as CD2 and CD7.* Pro-

T cells differentiate into pre-T cells, which begin to express CD1, CD4, and CD8 markers, usually within the thymic cortex. A proportion of the relatively immature CD4⁺8⁺ cells then lose expression of either CD4 or CD8 to become CD4⁺8⁺ or CD4⁺8⁺. The amount of CD3/TCR on the cell surface is increased, and the CD1 molecule is lost. T cells develop into a variety of clones, each bearing a different CD3/TCR molecule specific for a particular antigen-MHC complex. Only a minority of pre-T cells in the thymus successfully differentiate into mature T lymphocytes and migrate to the lymphoid organs and blood. In the peripheral blood, about 70% of lymphocytes are T cells.

T cells are heterogeneous with regards to their function. They initiate the immune response, mediate antigen-specific effector responses, and regulate the activity of other leukocytes by secreting soluble factors termed lymphokines. A correlation exists between the expression of membrane antigen markers and the functional activities of T cells. Effector functions of T cells include cell-mediated cytotoxicity where T cells recognize antigens associated with class I MHC or class II

* CD-cluster of differentiation (nomenclature of cell surface molecules of human leukocytes).

MHC alone. These T cells destroy virally infected class I-bearing cells and are major effectors in allograft rejection. They bear the CD8 marker and appear to affect their targets directly.⁶ Other T cells carry out delayed-type hypersensitivity reactions (DTH). These cells react with antigen-class II MHC on the APC and create effects mainly via lymphokine production and activation of other cells. These cells are usually CD4⁺.

Regulator T cells augment or suppress immune responses through a variety of T cell-T cell and T cell-B cell interactions. T-helper cells (usually CD4⁺) control many B-cell functions, including proliferation, maturation, and isotype switching, as well as proliferation and activation of other T cells. Most of these cells react with antigen-class II MHC. Two types of helper T cells have recently been identified according to their profile of cytokine production.⁷ T-helper 1 (TH1) cells mainly produce IL-2 and IFN- γ and are active in DTH reactions. The T-helper 2 (TH2) cells produce IL-4, IL-5, IL-6, and IL-10, mainly affecting antibody production and allergic inflammatory responses. Suppressor T cells, most of which are CD8⁺, down-regulate immune responses and are believed to be critical in various phases of immunoregulation, tolerance, and autoimmunity. They operate in part by secreting various mediators including free TCRs.

As mentioned above, T cells recognize antigens only when these are present on the cell surface of an APC, where they must be associated with polymorphic cell surface polypeptides encoded within the MHC. This dual specificity focuses the attention of T cells on cell-bound antigens. Hence, unlike B cells whose secreted antibodies act at a distance, T cells regulate or kill other cells through cell-cell contact. This contact is mediated through the TCR where its ligand is composed of a fragment of the foreign antigen complexed to some residues within an MHC molecule. The receptor appears to contact portions of both the antigen fragment and the MHC.

The TCR is a disulfide heterodimer composed of α and β glycoprotein chains with constant regions close to the cell surface that anchor the receptor to the T-cell membrane, and the polymorphic variable part (V region) away from the cell surface. It is the difference in the structure of the variable region (similar to antibodies) of the α

and β chains that allows the development of different T-cell clones that will eventually recognize the different antigens. The complete molecule has a transmembrane region and a cytoplasmic tail that is responsible for transmitting signals to the cell interior. The TCR is noncovalently associated on the cell surface with CD3, a complex of at least five polypeptides that may participate in mediating activation signals.⁸

Like Ig genes, the genes that encode TCR α and β chains are formed from the joining of separate genetic elements. These gene segments rearrange during T-cell ontogeny within the thymus by deletion of intervening DNA to form a contiguous V gene. The rearrangement of the gene segments to form the TCR gene allows the generation of a diversity of receptors.

Recently, a smaller set of T cells were identified that express a receptor that is a disulfide-linked heterodimer composed of γ and δ chains (instead of α and β). These chains also consist of V and constant (C) regions and are encoded by rearranging gene segments. These cells resemble the regular α/β T cells, but are distinguished by having a smaller repertoire of V gene segments in their receptor. Their function and the ligand for the receptor are unknown, although many demonstrate non-MHC-restricted killing of target cells.

When an α/β -TCR on a CD4 lymphocyte binds to a specific peptide antigen-class II MHC molecule combination on an APC, a trimolecular complex is formed that transmits a signal to the cell. This signal initiates a series of biochemical reactions within the cell, resulting in subsequent biological responses such as proliferation and lymphokine production. The critical biochemical events are (1) hydrolysis of phosphatidyl inositol biphosphate to form inositoltriphosphate (IP3) and diacylglycerol (DAG); (2) influx of calcium into the cell cytoplasm; and (3) activation of protein kinase C (PKC). Calcium and PKC act as a second messenger, probably with other signals to induce transcription of IL-2 and other cytokine genes,⁹ which in turn activate T cells and other immunocompetent cells.

C. Mast Cells and Basophils

In humans, mast cells are usually found in the loose connective tissues of all organs, notably

around blood vessels, nerves, and lymphatics. Basophils circulate in the blood stream. Both contain multiple prominent granules that stain from purple to red with blue aniline dyes, thus exhibiting metachromasia. This staining property is attributed to highly sulfated proteoglycans within mast cells and basophils. Both cells also synthesize and store histamine and proteases complexed to these proteoglycans. These substances are then released when mast cells or basophils are activated by an antigen that is recognized by antigen-specific IgE bound to high-affinity (Fc ϵ RI) receptors located on the surface of these cells.

All mast cells are derived from progenitor cells present in the bone marrow. Normally, mast cells are not found in the circulation. Progenitors are believed to migrate to the peripheral tissues as immature cells and undergo differentiation *in situ* under microenvironmental influences. Four interleukins have been shown to sustain and promote the growth and development of murine mast cell populations, e.g., IL-3, IL-4, IL-9, and IL-10.¹⁰ IL-3 is a necessary factor to maintain mast cell viability. IL-4 has little or no ability to sustain the proliferation of murine mast cells in the absence of IL-3. In the presence of IL-3, IL-4 promotes mouse mast cell maturation *in vitro*. Granulocyte macrophage-colony stimulating factor (GM-CSF), on the other hand, inhibits the growth of IL-3-dependent mast cells,¹¹ as does TGF- β .¹²

A significant advance in the understanding of mast cell biology is the appreciation that mast cells may assume one of two phenotypes.¹³ Mucosal mast cells are found mainly in the mucosa of the gastrointestinal (GI) tract. Their main arachidonic acid metabolite is leukotriene (LT) C₄ and their viability *in vivo* appears to depend on T cells, the presumed source of IL-3 and IL-4. The second phenotype of mast cells has been found in the skin, lungs, and serosal cavities. These connective tissue mast cells contain heparin as their main proteoglycan, produce prostaglandin (PG) D₂, and depend on stromal cell-produced stem cell factor (SCF) for their maturation *in vivo*.^{14,15} The gene encoding SCF has been cloned and SCF has been shown to be a product of the Sl locus in the mouse and the ligand for the proto-oncogene c-kit tyrosine kinase receptor (allelic with W locus).¹⁵ However, mucosal and connective tissue phenotypes are not fixed, and bidirectional changes

may be possible in suitable microenvironments. It is likely, however, that in normal development there is a maturational sequence of bone marrow precursors to mucosal type mast cells to connective tissue mast cells. Thus, the precise nature of the mast cell and its mediators varies with anatomic location.¹³

In humans, the factors that regulate mast cell growth and differentiation are less defined. In addition, human mast cells are not as clearly differentiated as mouse mast cells. Major differences between types of human mast cells reside in the composition of serine proteases found in the granule that are trypsin like or chymotrypsin-like in substrate specificity, and in the ultrastructural morphology of the granules. For example, in the skin, the predominant mast cell contains tryptase, chymase, and cathepsin G (MC_{Tc} mast cell type). The granules in these cells have a pattern described as lattice like or crystalline, and the cells degranulate in response to neuropeptides such as substance P or opiates. By contrast, GI mucosa mast cells (MC_I type) contain tryptase, but not other proteases, have a granule pattern described as scroll-like, and do not respond to substance P or opiates with degranulation. Nevertheless, it does appear that in humans as well as in mice, the pattern of mediators produced by mast cells may vary with anatomic location.¹⁶

Indeed, CD34⁺ mononuclear cells that are cultured in the presence of IL-3 over agarose surfaces for 3 weeks yield cultures with 1 to 3% mast cells.¹⁷ Mast cell granules in such cultures appear as homogeneous dense structures, but without the scroll, lattice, or reticular pattern seen in mature skin or lung mast cells. For human mast cells to express a more mature phenotype, coculture with fibroblasts is required. In these cocultures, CD34⁺ progenitor cells give rise to mast cells that have IgE receptors and granules containing tryptase. More strikingly, cocultured mast cells have a variety of granule morphologies including scroll, reticular, and dense-core patterns found in mature human mast cells within tissues.

The human homolog of SCF has been cloned and its effects on human mast cells have been examined. Thus, mast cells cultured in IL-3 plus SCF, but not in IL-3 alone, are berberine sulfate positive, suggesting the presence of heparin proteoglycans within the granules.^{10,17} Also, elec-

tron microscopic examination of cultures supplemented with IL-3 and SCF, but not with IL-3 alone, reveals that after 3 weeks in culture, mast cell granules contain tryptase and exhibit scroll and reticular patterns as seen previously in CD34/3T3 fibroblast cocultures. Thus, CD34⁺ cells cultured in the presence of both IL-3 and SCF give rise to cultures containing mast cells (and basophils), with mast cells showing evidence of maturation. Bone marrow-derived IL-3-dependent murine mast cells undergo programmed cell death

(apoptosis) upon removal of IL-3, an event that is prevented by the addition of SCF through its ligand c-kit. This demonstrates how these principal mast cell growth factors may act in concert to regulate mast cell number under physiologic or pathologic conditions.¹⁸

Activation of mast cells (or basophils) upon interaction of an antigen (allergen) with its specific membrane-bound IgE will result in an allergic response, to be discussed later in this article (Figures 2 and 3).

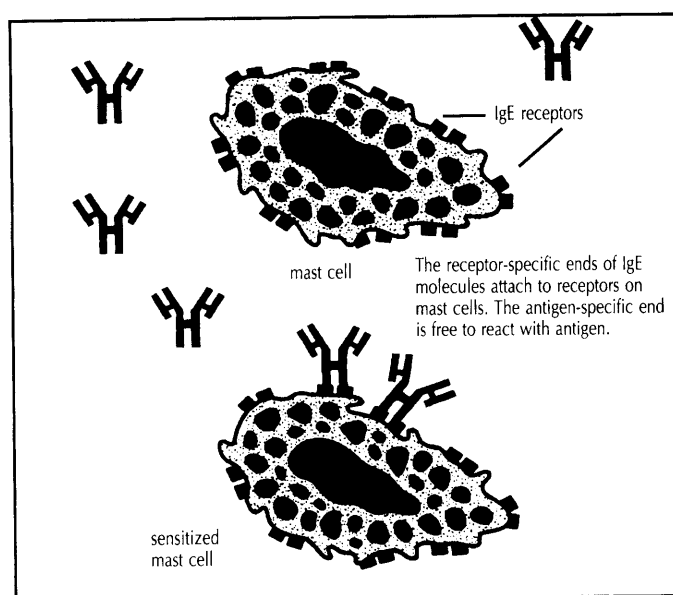


FIGURE 2. Sensitization of mast cells. (Reprinted from ILSI Europe Concise Monograph on Food Allergy. With permission from the International Life Sciences Institute.)

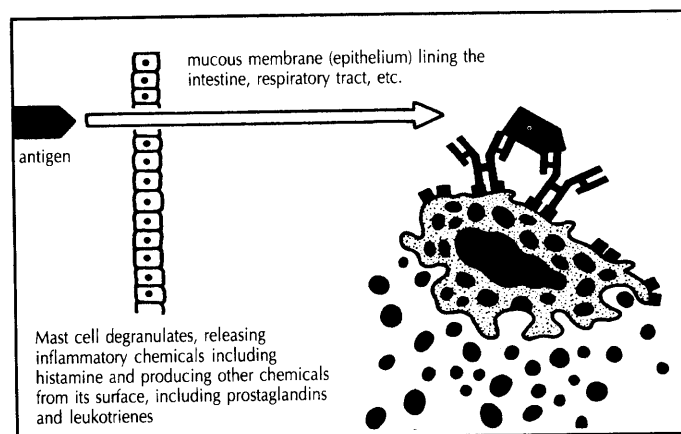


FIGURE 3. Inflammatory reaction initiated by mast cells. (Reprinted from ILSI Europe Concise Monograph on Food Allergy. With permission from the International Life Sciences Institute.)

III. IMMUNOLOGIC MECHANISMS OF TISSUE DAMAGE

When an adaptive immune response occurs in an exaggerated or inappropriate form causing tissue damage, the term hypersensitivity is applied.¹⁹ Clinical allergy or hypersensitivity phenomena are associated with a wide range of processes. However, in each of these entities a common denominator of pathophysiology is either objectively demonstrable or reasonably inferred. Hypersensitivity is immunologically mediated through the interaction of an antigen of exogenous or endogenous origin with specific antibodies or lymphocytes. The consequence of this interaction may be quite diverse, and may account for a variety of clinical manifestations, including allergic reactions such as rhinitis or anaphylaxis; and autoimmune phenomena, including hemolytic anemia and connective tissue disorders, vasculitides, or graft rejection. As more basic immunologic data have been correlated with clinical manifestations, a workable system of general classification has been developed. Gell and Coombs²⁰ have classified the mechanisms of tissue injury due to hypersensitivity reactions into four distinct types. In practice these types do not necessarily occur in isolation from each other. These reactions are basically expressions of the beneficial immune responses acting inappropriately, and sometimes causing inflammatory reactions and tissue damage. The first three types are antibody mediated, whereas the fourth is mediated primarily by T cells and macrophages.

A. Type I or Immediate Hypersensitivity Reactions

These reactions occur when antigens such as certain proteins from pollens or foods bind to specific preformed IgE antibodies attached to the surface of basophils in the blood or mast cells in tissues. This interaction results in the release of various mediators such as histamine, PG, LT, and cytokines, which produce an acute inflammatory reaction with symptoms such as rhinitis, asthma, or anaphylaxis.

B. Type II or Antibody-Dependent Cytotoxic Hypersensitivity Reactions

These reactions involve the binding of antibodies to cell-bound antigen. This may lead to phagocytosis, cell destruction by killer cell activity, or complement-mediated cytolysis of the cells to which the antibody is bound. Examples of tissue injury by this mechanism include immune hemolytic anemia and Rh hemolytic disease of the newborn. It should be noted that antibody interaction with membrane-bound antigen may lead in certain cases not to cell destruction, but to inappropriate (exaggerated) function of the target cell as found in hyperthyroidism.

C. Type III or Immune Complex-Mediated Hypersensitivity Reactions

These reactions develop when antibody-antigen complexes are formed in large quantities or cannot be cleared adequately by the reticuloendothelial (or mononuclear phagocyte) system. Deposition of these complexes in tissues or on vascular endothelium results usually in complement activation, which leads to polymorphonuclear cell infiltration and activation. This cascade of events produces the tissue injury which is found in conditions such as serum sickness and vasculitis.

D. Type IV or DTH

DTH is manifested when antigen-sensitized T cells are stimulated with the specific antigen introduced to T cells in a specific manner by APCs. This interaction leads to the activation of the T cells and to lymphokine production that mediates a range of inflammatory responses due to the ability of lymphokines to attract and activate various cells with proinflammatory effects. The classic examples of this response are the tuberculin skin test reaction and contact dermatitis. DTH is particularly relevant in understanding the pathogenesis of gluten-sensitive enteropathy (see "Allergic Reactions to Foods" by J. Anderson in this issue).

IV. THE IMMEDIATE HYPERSENSITIVITY RESPONSE

The clinical and pathologic manifestations of immediate hypersensitivity (type I) reactions are the net result of the actions of the mediators released from sensitized mast cells upon their interaction with specific antigens. Thus, three essential components are involved in the elicitation of immediate hypersensitivity. These are the antigen (allergen), IgE antibodies directed at antigenic determinants on the allergen, and the effector cell, namely, the mast cell or basophil. Thus, the typical sequence of events in immediate hypersensitivity is as follows: (1) production of IgE by B cells in response to exposure to the antigen; (2) binding of IgE to its receptors on the surface of mast cells and basophils (Figure 2); (3) interaction of the reintroduced antigen with the bound-specific IgE; (4) activation of mast cells and basophils with the release of mediators that affect the various target organs resulting in the clinical and pathologic manifestations of disease (Figure 3).

A. The Antibody

IgE is central to the induction of immediate hypersensitivity through its binding to high-affinity receptors on mast cells and basophils. The critical difference between atopic and normal individuals is that the former produce high levels of IgE in response to particular antigens, whereas the latter generally synthesize other Ig isotypes and only small amounts of IgE. IgE is the least prevalent of the five antibody classes in terms of serum levels, which range in normal human subjects from 17 to 250 ng/ml and comprise approximately 0.002% of total serum Ig (Table 2). In pathologic conditions, such as severe atopy, this level can rise to over 1000 ng/ml. IgE circulates as a bivalent antibody and contains a relatively high proportion of carbohydrates (approximately 12%) giving it a mol wt of around 200,000. The IgE heavy-chain V (variable) regions and IgE light chains are products of the same genes as other Ig molecules. The heavy-chain C (constant) regions are encoded by the ϵ gene located in the heavy-chain gene cluster. Thus, IgE is produced as a result of heavy-chain isotype switching.

B. IgE Receptors

Despite the minuscule fraction that IgE constitutes in the serum, its action is amplified by the activities of the receptors to which it binds. The "high-affinity" receptor Fc ϵ RI on mast cells and basophils (affinity constant at about 10^{-9} to 10^{-10} M) binds the Fc region of the ϵ heavy chain of IgE and is responsible for sensitization. When a multivalent allergen associates with Fc ϵ RI-bound IgE, it cross-links these receptor molecules on the cell membrane. This triggers degranulation of the cell resulting in acute allergic inflammation in the surrounding tissues (Figure 3). Fc ϵ RI has been discovered recently on Langerhans cells (in the skin), eosinophils, and activated monocytes. Its biological functions in these cells have not been identified, except that in eosinophils Fc ϵ RI does mediate IgE-dependent killing of parasites *in vitro*.²¹ B cells, eosinophils, and macrophages express various forms of a second lower affinity receptor for IgE termed Fc ϵ RII, and also known as CD23. This receptor mediates phagocytosis of immune complexes by monocytes *in vitro*, and on the surface of B cells it plays a part in IgE-dependent antigen presentation to T cells and in adhesion of B cells to each other.²¹ It is also expressed on follicular dendritic cells in the lymph nodes and may thus be involved in the homing of B cells to the germinal centers in the lymphatic organs. Soluble fragments of Fc ϵ RII stimulate the growth and differentiation of the precursors of plasma cells, T cells, and basophils, thereby initiating both humoral and cellular immune responses. The soluble form of Fc ϵ RII has also been found to up-regulate IgE synthesis by B cells.²¹ IgE itself closes a negative feedback loop by switching off its own synthesis through interaction with Fc ϵ RII. These observations are now interpreted in terms of a system of interacting proteins that are designated as the IgE network.²¹

C. Regulation of IgE Synthesis in Humans

Cytokines are essential for B-cell proliferation and differentiation. They not only determine Ig secretion quantitatively, they also direct Ig isotype switching. IL-4 is a crucial factor for

isotype switching to IgE. It provides a necessary but insufficient condition for the induction of IgE synthesis by B cells. In humans, a variety of second IgE-inducing signals synergize with IL-4 in the induction of IgE synthesis.²² In addition to cytokines, contact-mediated signals delivered by CD4⁺ T cells are required for B-cell proliferation and Ig production. Recently, the ligand for CD40, which is expressed on activated CD4⁺ T cells, was shown to be one such membrane-associated molecule that acts as a stimulatory signal for IL-4-dependent IgE production by both murine and human B cells.²³ CD40 is a 50-kDa surface glycoprotein expressed on all human B cells. It is now clear that mast cells secrete IL-4²⁴ and express CD40-ligand,²⁵ allowing them to play a key role in allergy by producing inflammatory mediators, and by directly regulating IgE production. IL-4 up-regulates FcεRII on B and inflammatory cells, providing in turn a local source of contact stimulation and of soluble growth factors. Moreover, several cytokines, including IL-5 and IL-6, up-regulate the IgE response induced by IL-4 in mononuclear cells.²² Recently, IL-13 induced IgE and IgG4 synthesis by human B cells, an effect that was found to be IL-4 independent.²⁶ Thus, IL-13 is another T-cell-derived cytokine that, in addition to IL-4, efficiently directs native human B cells to switch to IgE production. IFN-γ has been reported to inhibit IL-4-dependent IgE synthesis in both humans and mice.²² Of particular interest is the finding that the expression of IFN-γ is down-regulated by IL-4, both at the protein and at the mRNA level. Induction of IgE synthesis by IL-4 may reflect not only the ability of this cytokine to induce isotype switching, but also its ability to simultaneously suppress a major functional IL-4 antagonist.

D. The Antigen

Antigens that elicit immediate hypersensitivity reactions are called allergens and are proteins or chemicals bound to proteins. Materials such as venoms, food, pollens, animal danders, and hormone extracts function as complete antigens and are capable of eliciting a complete IgE response. On the other hand, low-molecular-weight substances, including some drugs, function as hap-

tens that by themselves cannot elicit an IgE response. These substances usually bind to self proteins (carriers), forming hapten-carrier conjugates that function as complete neoantigens. It is not known why some antigens cause strong type I responses, whereas other antigens, which may be encountered by the same route of administration, result in non-IgE humoral or cell-mediated immune responses. The property may reside in the antigen itself, perhaps in epitopes recognized by certain T cells. Some protein antigens are naturally encountered with adjuvant substances that favor IgE synthesis. The nature of the adjuvant may determine the type of APC that is activated or recruited and is likely to present the antigen to T cells. A particular type of APC may provide costimulators that favor the activation of helper T cells that are especially potent at stimulating IgE synthesis.⁹ Also, genetic predisposition may determine the T-cell response to allergens. Atopic individuals produce larger numbers of allergen-specific IL-4-producing T cells than nonatopic persons. Moreover, allergen-specific CD4 T cells obtained from atopic patients produce high levels of IL-4 compared with CD4 T cells from the same patients not specific for this allergen or with CD4 cells from healthy individuals. These high IL-4-producing cells strongly support the induction of IgE synthesis.²⁷ These data suggest that chronic stimulation by allergens selects for allergen-specific T cells in individuals whose T cells are intrinsically prone to secrete large amounts of IL-4 on activation (TH2 cells).

In general, repeated exposure to a particular allergen is necessary to develop an atopic reaction to that allergen. For example, individuals with respiratory allergic reactions to pollens may benefit from a geographic change of residence with a change in indigenous plant pollens. Food allergies are common during childhood, perhaps because the mucosal barrier of the GI tract is not mature. A dramatic example of the influence of the natural history of exposure to allergen is seen in cases of bee sting anaphylaxis. The protein toxins in the venom are usually not of concern on the first exposure because the atopic individual has no preexisting specific IgE antibodies. However, a large IgE response may occur after a second sting.

Thus, to initiate a type I response, exposure to an appropriate antigen and a genetically determined capacity to respond with IgE production are required. Antigen presentation requires access of antigen to the mucus membranes, uptake by APC, antigen processing, and stimulation of local antibody production. IgE production occurs in the same local environment as antigen presentation, probably in the draining lymph nodes. As stated earlier, IgE production is regulated by locally produced cytokines including IL-4 secreted by local TH2 cells. The IgE that is produced sensitizes mast cells by binding to FcεRI on the cell surface (Figure 2).

E. Mast Cell Activation and Mediator Release

As mentioned, the event that initiates the immediate hypersensitivity reaction is the binding of allergen to IgE on the mast cell or basophil surface. Mast cells or basophils are activated by cross-linking of FcεRI molecules, which is thought to occur by binding of multivalent allergens to the attached IgE (Figure 3). Individuals subject to type I reactions are more likely to have greater amounts of IgE specific for a given allergen. There is a high probability that the allergen will bridge two adjacent IgE molecules specific for its antigenic determinants, and a cross-linking will occur.

Activation of mast cells (and basophils) results in three types of biological responses: secretion of preformed contents of their granules by exocytosis; synthesis of lipid mediators derived from precursors stored in the cell membrane and lipid bodies; and initiation of transcription, translation, and secretion of cytokines.⁹

Mast cells reach maturity within tissues and are the first cells activated in allergic inflammation. Basophils circulate in the blood as mature cells and are capable of migrating into tissues during an allergic inflammatory response. Through the release and production of a variety of proinflammatory molecules, both cells set in motion a series of events that result in both immediate and late-phase responses (LPR). Activation of mast cells and basophils involves a complex series of biochemical events that lead to degranu-

lation and mediator release. Briefly, the cross-linking of FcεRI results in activation of a G protein that activates a membrane-bound phospholipase C to catalyze phosphatidyl inositol biphosphate to IP3 and DAG. IP3 causes elevation of cytoplasmic calcium and DAG activates PKC. These events are similar to those observed in T cell activation via the TCR. These events lead to phosphorylation of myosin chains, which is thought to result in disassembly of actin-myosin complexes beneath the plasma membrane, thus allowing fusion of the granules with the plasma membrane and resulting in exocytosis of the granule contents.⁹

In addition to the known ability of mast cells and basophils to degranulate in response to cross-linking of FcεRI, they may also be activated and degranulated by a variety of other stimuli. These include the complement-derived anaphylatoxins C3a and C5a produced by complement activation during humoral immune responses; IL-8 or other mononuclear-derived cytokines produced as part of cell-mediated immunity; neurotransmitters such as substance P, drugs such as codeine and drugs that create hyperosmolar conditions.

After mast cell and/or basophil activation, a number of chemical mediators are released from storage granules (preformed mediators) or newly generated. The best known mediator of the former group is histamine. Histamine is formed *in vivo* by the decarboxylation of the amino acid histidine, a process that takes place in the Golgi apparatus of mast cells and basophils. It is then stored as a complex with the highly charged sulfate groups of proteoglycan side chains in the secretory granules. Approximately 3 to 8 pg histamine per cell is found in mast cells isolated from human lungs, skin, and small intestine. Histamine exerts its biological effects on a variety of tissues in large part via two receptors, termed H-1 and H-2. H-1 receptors mediate such effects as bronchoconstriction, intestinal peristalsis, and pruritus. H-2 receptor-mediated effects include increased gastric acid secretion, increased mucous secretion, and increased gastric mucosal blood flow. H-1 and H-2 receptors act in concert to promote uterine contraction and vasodilation. Specific histamine-receptor blockers are now in use for the treatment of histamine-mediated effects. H-1 receptors are blocked by classic antihistamines such as chlorpheniramine and the newer nonsedative

antihistamines, including astemizole, loratadine, and terfenidine. H-2 receptor antagonists include cimetidine and ranitidine.

A second group of preformed mediators includes those that stay firmly associated with the granule after release. The proteoglycans comprise one such group of mediators. Heparin is the prototype proteoglycan mediator in mast cells, but it has become apparent that not all mast cells contain significant amounts of the compound.¹³ Instead, mucosal mast cells are known to contain proteoglycans of the chondroitin sulfate class, which are less highly charged than the heparin molecule, or contain a mixture of both forms. Proteoglycans are a major granule constituent and may, by virtue of their charge density, provide a storage matrix for other mediators. After their release, proteoglycans may exert a variety of effects. Heparin binds to various enzymes as well as growth factors, thus influencing their function. Both heparin and oversulfated chondroitin sulfates inhibit lymphocyte blastogenesis. Heparin also acts as an anticoagulant.

A third group of preformed (granule-associated) mediators are the proteolytic enzymes. The most important enzymes in human mast cell granules are proteases. In humans, tryptase is found in both mucosal and connective tissue mast cells, with chymotrypsin limited to connective tissue mast cells.¹⁶ A variety of substrates for these proteases have been documented including collagen, bradykinin, and structural connective tissue proteoglycans. Tryptase isolated from human lung mast cells cleaves the complement component C3 to generate C3a anaphylatoxin *in vitro*. The long half-life of tryptase in the serum makes measurement of this mediator a reliable test to document the type I nature of a reaction such as anaphylaxis, but is less useful in food-induced reactions.^{28,29}

The activation of mast cells not only causes the secretion of preformed granule-associated mediators, but initiates the *de novo* synthesis of certain lipid-derived substances.¹⁰ Of particular importance are mediators derived from arachidonic acid, itself a cleavage product of membrane phospholipids. Arachidonic acid may be metabolized by two main enzymes: cyclooxygenase, leading to PG and thromboxanes (TX); and lipoxygenase, leading to hydroxyeicosatetraenoic acids

(HETE) and LT. These lipid mediators exhibit potent effects on a variety of cells and tissues. For example, LTB₄ has potent chemotactic activity for neutrophils, enhances lysosomal enzyme release, and augments superoxide anion production. It has also been suggested as a modifier of lymphocyte function by inducing specific suppressor lymphocytes and augmenting human natural cytotoxic cell activity. Other LT such as LTC₄ are potent bronchoconstrictors and increase vascular permeability. PGD₂ is generated within 15 s of immunologic activation of rat serosal mast cells and is the primary PG synthesized by mast cells. It is a potent inhibitor of platelet aggregation, causes bronchoconstriction, and induces chemokinesis of various cell types. In conjunction with LTD₄, it will mediate accumulation of neutrophils in human skin. High levels of these mediators have been detected in the urine of mastocytosis patients, and contribute to hypotension observed in such patients. A final generated mediator is platelet-activating factor (PAF), which has been detected after activation of mouse bone marrow-derived mast cells, rabbit basophils, and human mast cells, but not following activation of human basophils. It is a potent mediator causing platelet aggregation and degranulation, eosinophil accumulation, bronchoconstriction, mucous secretion, and increased vascular permeability and vasodilation, leading to clinical manifestations such as systemic anaphylaxis.

Mast cells are a significant source of cytokines,³⁰ including tumor necrosis factor- α (TNF- α), IL-1, IL-4, IL-5, IL-6, GM-CSF, and IL-3. They may also produce chemokines such as T-cell activation gene 3 (TCA-3) and macrophage inflammatory protein α (MIP-1 α) and MIP-1 β . The relative contribution of mast cells vs. T cells or macrophages to the production of these cytokines *in vivo* is not yet clear. Nevertheless, it is obvious that this capability of mast cells enables them to play an important effector role in various inflammatory processes. These cytokines have multiple proinflammatory effects, including growth-promoting activity (GM-CSF; IL-5), stimulation of IgE synthesis (IL-4), chemotaxis (chemokines and TNF- α), and modulation of the biological functions of a number of immunologic effector cells, including neutrophils and lymphocytes. The biological functions affected by such

cytokines include cell adhesion to endothelial surfaces and to extracellular matrix components, cell migration to the site of inflammation, cellular activation, and cytokine release.³¹

The consequences of mediator release usually occur within minutes, thus the term "immediate" hypersensitivity. The mediators interact with the surrounding tissues and elicit the allergic responses, the nature of which is determined by the local environment. Many, but not all, hypersensitivity reactions result in a second LPR. These reactions begin 2 to 4 h after the original challenge and peak between 6 and 12 h afterward.

Unlike the immediate response, this late event is characterized by a local inflammatory process consisting of accumulation of cells including neutrophils, eosinophils, and in a later phase mononuclear cells, which are mainly lymphocytes. It now appears likely that cytokines, released after mast cell activation, contribute to the LPR. TNF- α in particular may account for the sequential polymorphonuclear and mononuclear cell infiltrates.³¹ LPR is believed to be the major pathogenic mechanism that underlies chronic diseases such as asthma.

V. CLINICAL MANIFESTATIONS

The clinical and pathologic features of type I reactions are the result of the cumulative effects of mast cell mediators on the surrounding tissues. These features vary with the anatomic site because of various factors, including the nature and the point of contact with the antigen; the local mast cell phenotype; and the sensitivity of the target organs to the mast cell-derived mediators.⁹ The clinical manifestations of food allergy are the focus of "Allergic Reactions to Foods."

The most common forms of type I disease are allergic rhinitis, asthma, atopic dermatitis (AD), and GI allergy. A diffuse multisystemic reaction is termed anaphylaxis.

A. Respiratory Manifestations

1. Rhinitis

Rhinitis is a manifestation of an immunologic response to allergens, such as pollen grains and

mold spores, that are deposited on the nasal mucosa. Symptoms may include paroxysms of sneezing, itching of the nose, eyes and palate, and nasal stuffiness. Runny nose (rhinorrhea) with watery discharge is another typical feature of allergic rhinitis that is often accompanied by postnasal drip. A personal history of other atopic diseases, a strong family history of allergy, or a regular seasonal pattern of compatible symptoms is strongly suggestive of an allergic cause.³² Most patients develop symptoms before the age of 30 years. Once symptoms have started, they can be exacerbated by various nonspecific irritants such as cigarette smoke, air pollution, strong odors, and climatic changes.

2. Asthma

Particles with an aerodynamic equivalent diameter of less than 4 μ m are likely to reach the lower respiratory tract. Asthma is the clinical result of an immunologic response that takes place in the lower respiratory tract. It can be defined clinically as recurrent airflow obstruction causing intermittent wheezing, breathlessness, and sometimes cough with sputum production. Pathologically, the airflow obstruction of asthma is due to a combination of bronchial smooth muscle contraction, mucosal edema, inflammation, and mucus secretion. The disease involves large and small airways but not alveoli, and the processes leading to airflow obstruction are in general reversible.³²

B. Dermatologic Manifestations

The two most common type I allergic diseases of the skin are urticaria and AD. These skin reactions may be provoked either directly by contact of the allergen with the skin surface or indirectly by mast cell activation by an allergen that is systemically spread via the circulation after ingestion or injection, such as allergic skin response to food, drugs, and stings.

1. Urticaria (Hives)

Urticaria consists of blanchable, erythematous, edematous papules and plaques, usually

pruritic and ranging from 1 to 2 mm to several centimeters in diameter.³³ Individual lesions usually last several hours. Acute episodes of urticaria are commonly of brief duration, resolving within several days. Most cases of acute urticaria are IgE dependent, whereas an IgE-dependent mechanism can only rarely be implicated in chronic urticaria that is defined as urticaria that lasts more than 6 weeks. Cutaneous mast cells may also be activated and thus cause urticaria via local nonimmunologic mechanisms such as physical stimuli, including dermatographism, pressure, and cold.

2. AD

AD is a chronic inflammatory skin disease in which the role of activated mast cells has not yet been elucidated. It is characterized by pruritus, erythema, edema, and vesiculation. The chronic lesions become scaly and lichenified. The importance of IgE-mediated hypersensitivity is suggested by the clinical findings that 80% of patients with AD have significantly elevated IgE levels, allergens exacerbate AD, and a personal or family history of AD is usually present.³³ Recently, receptors for IgE have been found on the surface of Langerhans cells in the skin that serve as APC for T cells.

C. GI Manifestations

GI manifestations of IgE-mediated allergic responses (see "Allergic Reactions to Foods") are more frequent than the respiratory or cutaneous manifestations. These symptoms result from local effects of mast cell-derived mediators on the GI mucosa. Mast cells in the GI tract may be activated by either local direct stimuli such as foods or as a part of a generalized response to an antigen spread by the circulation. These GI symptoms usually include nausea, cramping, bloating, vomiting, and diarrhea.

D. Anaphylaxis

Anaphylaxis refers to the constellation of signs and symptoms that result from IgE-mediated mast cell- and basophil-activation and degranulation. The target tissues for the mast cell and basophil derived mediators are primarily blood vessels and smooth muscles.

The sites of responses to mediators are both local and remote from the site of the antigen deposition. This is a diffuse response and may be fatal if not treated. The clinical manifestations of anaphylactic reactions are specific, depending on the particular target systems affected. For example, reactions involving the skin are manifested by pruritus, flushing, urticaria, and angioedema. Involvement of the upper airways is exhibited by hoarseness, stridor, and laryngeal edema. The lower airway manifestations of anaphylaxis include dyspnea, tachypnea, wheezing, bronchorrhea, and ultimately respiratory arrest. Cardiac manifestations include tachycardia, arrhythmias, hypotension, and ultimately cardiac arrest. Finally, GI signs and symptoms include nausea, vomiting, cramping, and diarrhea.³⁴

VI. DIAGNOSTIC APPROACH

The patient's medical history is the primary diagnostic procedure in allergy practice. Laboratory studies, including skin and *in vitro* tests for specific IgE antibodies, have relevance only when correlated with the patient's medical history.¹ The specific diagnostic approaches for the diagnosis of food allergies is detailed in "Allergic Reactions to Foods."

A. History

History of a possible allergic disease should include specific information such as: (1) seasonal, weekly, or diurnal variations of the symptoms; (2) relationship of symptoms to location (home, work); (3) exacerbating factors (e.g., dust, molds, animals); (4) medications and their efficacy in the treatment of the current symptoms; (5) occupational history; (6) family and past history of allergic diseases; (7) environmental survey that describes specific features of the patient's indoor or outdoor environment and the effects of specific environmental agents on symptoms.

B. Diagnostic Tests

The diagnostic tests currently employed verify the presence of specific IgE and point to the possibility of a type I allergic etiology to the patient's symptoms. These tests in and of themselves are

not diagnostic of IgE-mediated allergic disease, but provide evidence of immunologic sensitization.

1. Allergy Skin Testing (ST)

ST has been a primary diagnostic tool since the end of the nineteenth century. It is performed by introducing the allergen by prick or intradermal injection into the skin, although for foods, the prick skin test is preferred. For a skin test to be considered positive, a diluent control must be negative and a histamine control must be positive. A positive skin test is the culmination of a number of events that begin with the interaction of the allergen with IgE on the surface of cutaneous mast cells. This interaction is followed by mediator release and the subsequent biological effects on the surrounding tissues. These include vasodilation, increased vascular permeability, plasma leakage, and neuronal stimulation. These events lead to a "wheal" (leakage of fluid) and "flare" (vasodilation) response which is associated with local itching (neuronal response). The skin test indicates not only the presence of specific IgE, but also the sensitivity of mast cells and the biological effects of the mediators on tissues.

2. In Vitro Testing

In vitro tests detect the presence of specific IgE in the serum. A solid-phase immunoassay is widely used in which the allergen is bound to a solid phase and then incubated first with the patient serum and then with radiolabeled anti-human IgE antibody. In reports comparing *in vivo* and *in vitro* testing, *in vivo* testing (e.g., skin tests) is more specific for most antigens.³⁵

3. Challenge Tests

This diagnostic procedure involves the introduction of the allergen in the "natural" way by inhalation or ingestion. Ingestion would be the most natural route for foods. Signs and symptoms are thereafter monitored. These tests diagnose disease, identify etiologic agents, and study patho-

genesis. These challenge tests, including the double-blind placebo-controlled food challenge (DBPCFC), should be conducted by experienced medical personnel under careful conditions.

VII. PRINCIPLES OF THE THERAPEUTIC APPROACH

Three basic therapeutic techniques should be considered in treating an allergic disease: (1) avoidance of the offending allergens; (2) use of appropriate pharmacologic agents; and (3) allergy immunotherapy. Specific details on the therapeutic approach for food allergies are provided in "Allergic Reactions to Foods." (Also see International Consensus Report on the Diagnosis and Management of Asthma, U.S. Department of Health and Human Services publication 92-3091, June 1992.)

A. Allergen Avoidance

Whenever feasible, avoidance is the preferred form of treatment. It is the only treatment necessary in most cases of allergy to drugs, foods, animals, and some of the physical allergies.

B. Pharmacologic Therapy

Generally, the pharmacologic treatment of allergic diseases may be divided into two categories. The first is symptomatic control. Here, treatment mainly affects target organs involved in the clinical manifestations of the allergic response such as smooth muscles, blood vessel walls, and mucus glands. This category includes the use of H-1 and H-2 histamine receptor antagonists and the β_2 adrenergic agents albuterol and salmeterol. The latter agents are specific for the β_2 receptors that mediate a potent bronchodilating effect due to smooth muscle relaxation. These agents also reduce vascular permeability and plasma leakage. Also in this group are the anticholinergic drugs such as ipratropium bromide. Their anticholinergic effects include bronchodilation as well as inhibition of mucus secretion. Lastly, in this category of drugs are the methylxanthines such as

theophylline. Their major pharmacologic activity is relaxation of bronchial smooth muscles. Theophylline also improves contractility of the diaphragm, reverses mucosal edema, and accelerates mucociliary transport. Theophylline also antagonizes the effects of adenosine on mast cells and may thereby reduce mediator release.³⁶

The second category of therapy affects the cellular components of the inflammation and may be referred to as anti-inflammatory. Drugs in this category include cromolyn sodium, an agent whose mode of action relates to its ability to reduce mast cell reactivity. Therefore, early administration may prevent allergen-induced early and late allergic responses in the lungs and upper airways. Nedocromil sodium, a pyranoquinoline, is another nonsteroid anti-inflammatory agent for the treatment of asthma. Its pharmacologic effects include inhibition of human mast cell and eosinophil activation, as well as inhibition of the mobilization of inflammatory cells such as eosinophils and neutrophils. Nedocromil also inhibits both immunologic and nonimmunologic activation of monocytes and macrophages.³⁷ These cumulative effects may be relevant to the treatment of allergic diseases such as asthma, given the role of airway inflammation in this disease process. Finally, corticosteroids are known for their impressive therapeutic effects on a variety of allergic diseases. They are useful in treating allergic diseases such as asthma, rhinitis, and AD. Among the most relevant effects are a reduction in microvascular permeability, mucus secretion, and PD production; inhibition of eosinophil migration and proliferation, cytokine production by inflammatory cells; an enhanced β -adrenergic receptor expression; and a reduction in mast cell number and reactivity *in vivo*.³⁶ These actions together lead to a range of therapeutic benefits including inhibition of late-phase allergic responses.

C. Immunotherapy

This is the process by which increasing doses of the specific allergens to which the patient has been found to be allergic are injected subcutaneously over time to prevent IgE-mediated allergic symptoms. This therapeutic mode affects several immunologic processes in the allergic responses

and is the only treatment reported to have long-lasting preventive effects. Immunotherapy is effective in the treatment of allergy to Hymenoptera venom and in allergic rhinitis. The effectiveness of this treatment depends on several factors including delivery of an adequate dose of the respective allergens and the length of time of immunotherapy. Insufficient clinical data justify the use of immunotherapy in the treatment of food allergy.

The multiple effects of immunotherapy on cellular events, inflammatory responses, and immunologic changes that occur in IgE-mediated allergic processes have been reviewed.³⁸ Briefly, these effects include (1) an initial rise in specific IgE with subsequent significant decrease below treatment levels; (2) a drop in IgE that is inversely correlated with the rise of specific IgG antibodies capable of blocking the passive transfer of the allergic response, termed blocking antibodies; (3) an increase in IgG and IgA antibodies in the nasal secretions; (4) a decrease in basophil releasability where larger amounts of allergen are required for degranulation; (5) a decrease in antigen-induced eosinophil migration into the nasal cavity; (6) prevention of increased responsiveness of the nasal and bronchial mucosa to histamine in allergic patients during the season; and (7) effects on allergen-specific T cells such as a decrease in proliferation and suppression of cytokine production observed in response to the allergens. Recent works have demonstrated that the production of histamine-releasing factors by mononuclear cells is also decreased by immunotherapy.

VIII. SUMMARY

Allergic diseases result from IgE-mediated immune responses to foreign protein (allergens). The majority of such reactions are IgE-mediated (type I) reactions. Individuals who develop such reactions are allergic. Those predisposed on a genetic basis to synthesize IgE to environmental allergens are atopic. Most allergic reactions are precipitated when a specific allergen aggregates several IgE molecules attached to IgE receptors on the surfaces of mast cells and basophils. Chemical mediators are released which lead to the immediate signs and symptoms associated with

allergic diseases including hives, asthma, and anaphylaxis. More prolonged reactions follow if significant numbers of other cells including eosinophils, macrophages, and lymphocytes are drawn into sites of mast cell activation. Therefore, allergic diseases result from a complex interplay of immune cells, foreign proteins, and tissue inflammation.

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