# Allergic Diseases

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# Allergic Diseases

## *Diagnosis and Treatment*

## *Third Edition*

*Edited by*

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*To Barbara*

*P. L.*

*and*

*To Nicole*

*J. A. A.*

# Preface

*Allergic Diseases: Diagnosis and Treatment, 3rd Edition* is intended for the "front-line" physician who cares for the allergic patient. We have tried, once again, to make it as "user friendly" and clinically oriented as possible.

Our approach to the principles of pathophysiology is intended to allow them to be easily applied to the rationale for therapy. The major intent therefore is still to help the primary care physician deal with the day-to-day management of the allergic patient.

The arrangement of this text is similar to that of the first edition, with the major emphasis being on common allergic diseases and the pharmacologic tools we use to control them. To this end two new chapters have been added, one on antihistamines and the other on antileukotrienes. In addition, a new chapter has been added to help the physician deal with the child who experiences recurrent respiratory tract infections.

Many of the authors, because of the superb job they did with their first contributions, have been asked for an encore. However, to keep our approach fresh, some of these authors have been asked to write different chapters, and new contributors have been solicited.

Regardless of these changes, the thrust of the text remains the same—to disseminate the practical knowledge that we have accumulated in almost 70 years of practice and teaching in the field of allergy and immunology. As with the first and second editions of *Allergic Diseases: Diagnosis and Treatment*, our greatest hope is that the message has been delivered clearly, effectively, and in a manner that allows its easy application by the physician caring for those who suffer with allergic disease.

***Phil Lieberman,*** *MD*
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# 1 Allergic Disease

## *Pathophysiology and Immunopathology*

*Gloria E. Akan, MD*
*and Robert F. Lemanske, Jr., MD*

***CONTENTS***



## SUMMARY

The incidence of asthma and allergic disease is rising. However, primary care physicians have dealt with allergic conditions far more often than they may expect even before the development of these recent epidemiological trends. Some examples of immunological disease that the primary care physician has encountered include asthma, allergic rhinitis, and atopic dermatitis.

This chapter will review the role of atopy in the development and clinical manifestations of allergy. The two-step process of sensitization will be described. The role of the mast cell, the primary cell involved in allergic disease, will be delineated on a molecular and clinical level. Examples of allergic sensitization and presentation of disease will be provided using an example of food allergy. Descriptions of the early- and late-phase responses will be provided using the nasal tissue and skin as examples. The overall goal is to give the reader a good foundation and understanding of the mechanisms involved in allergic sensitization and the presentation of allergic diseases in a genetically predisposed individual.

**Key Words:** Immunoglobulin E (IgE) antibody; mast cell; basophil; late-phase response; early-phase response; anaphylaxis; allergy; immediate hypersensitivity.

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## INTRODUCTION

The incidence of asthma and allergic disease is rising. However, primary care physicians have dealt with allergic conditions far more often than they may expect even before the recent increase in allergic conditions. Some examples of immunological disease that the primary care physician sees include asthma, allergic rhinitis, and atopic dermatitis. To illustrate the importance of allergic disorders in clinical medicine, consider that physicians obtain an allergy history before prescribing any antibiotic because of the high incidence of drug reactions in the population.

Armed with the knowledge of the mechanisms mediating allergic reactions, a clinician can readily appreciate the pathophysiological changes caused by an exposure to a foreign antigen to a normally well-balanced system. This knowledge enables the physician to recognize and anticipate adverse reactions. Knowing that some asthmatics might experience a late-phase allergic response, for example, compels the physician to continue intensive therapy until the reaction has completely subsided.

Atopy, the genetic predisposition to the development of antigen-specific immunoglobulin E (IgE) antibody formation, involves complex genetic and environmental influences that are not fully understood. In other words, simple Mendelian inheritance patterns do not predict which individuals will develop allergies. Nevertheless, there appears to be a higher incidence of allergies among children of allergic parents.

One becomes "allergic" to a substance through a two-step process. The first step begins with sensitization and is outlined in Fig. 1. During the initial stage of sensitization, one develops significant amounts of IgE antibodies against an inhaled, ingested, or injected substance. Memory B-cells appear that are capable of immediately producing more specific IgE antibody when stimulated. The second stage involves adherence of this newly formed IgE antibody to circulating blood basophils or to tissue mast cells located in the mucosal surfaces of the skin, the gastrointestinal tract, and the respiratory system. These tissue mast cells were previously coated with IgE antibodies directed specifically against other potentially allergenic substances. The new exposure simply added to the existing population. There are millions of IgE molecules of different specificities (directed against different allergens) on the surface of each mast cell and basophil. An individual is "sensitized" only after IgE antibodies against a specific substance have been produced and are bound to the surface of mast cells and basophils. The process of sensitization does not produce any of the symptoms that we equate with allergic disease. In fact, a person is usually unaware of these initial molecular and cellular changes. It is not until re-exposure to the allergen that allergic symptoms begin to appear once this immunological response has been programmed to "target" a given organ system. Thus, the process of allergic sensitization does not necessarily equate with the development of allergic disease.

The second step in the two-step process of developing allergic disease involves the re-exposure of a sensitized person to the allergen. Symptoms range from negligible rhinorrhea to sudden death. Most cases lie somewhere in the middle of the two extremes. The biochemical events that lead to allergic symptoms will be discussed in some detail later, using an anaphylactic reaction to peanuts as an example. However, one should keep in mind that although the cellular and molecular events for all immediate hypersensitivity reactions are similar, differences in target organ responses ultimately dictate the clinical patterns of disease activity once a reaction has been induced. The mechanisms underlying differential target organ responses (i.e., rhinitis, atopic dermatitis, urticaria, asthma, and/

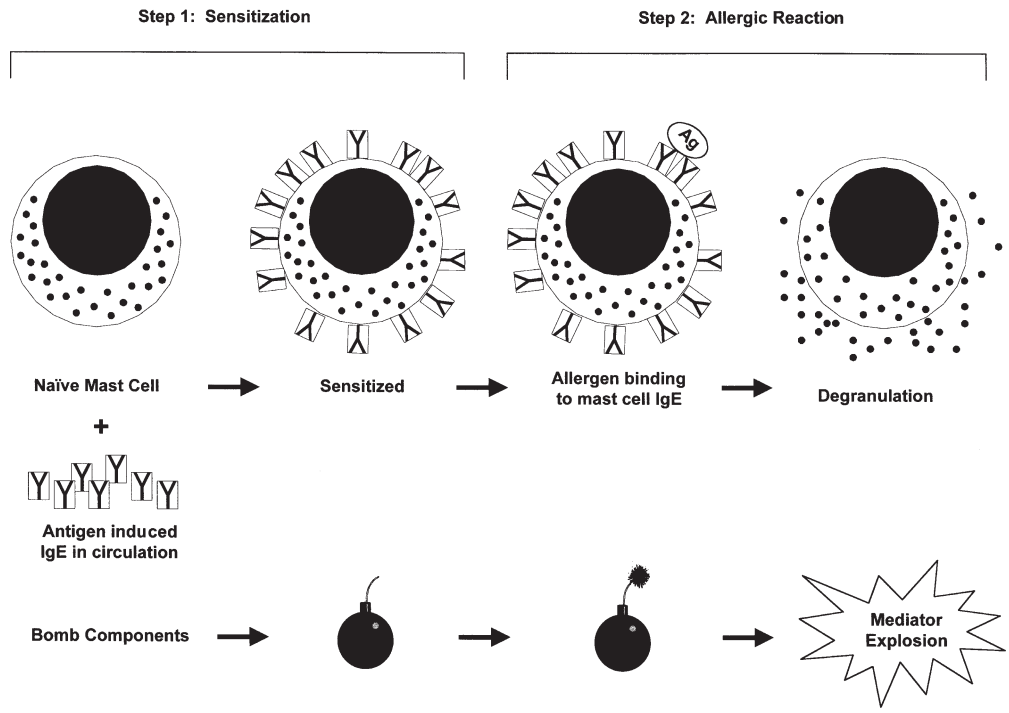


**Fig. 1.** Allergic sensitization and degranulation. The process of sensitization and degranulation in mast cells is analogous to the construction and detonation of a bomb. Initial binding of specific IgE to the naive mast cell surface "primes" the cell for activity, in effect building the bomb. Subsequent binding of allergen to the mast cell is akin to lighting the fuse of the bomb. Intracellular biochemical events lead to the ultimate "explosion"—a cellular degranulation leading to mediator release.

or anaphylaxis) in relationship to "atopic," immunological, genetic backgrounds, subsequent environmental exposures, and the development of these disease states have not been defined.

## THE ALLERGIC REACTION: A SCENARIO

An 8-mo-old girl was in the care of her aunt. Unfortunately, peanut butter crackers were given to the girl as part of a snack. She ingested the crackers without incident. While she was enjoying playtime with her cousins, the peanut proteins were being absorbed in her gut and filtered through the bloodstream and lymphatics, and lodging in the regional lymph nodes. The antigens encountered T- and B-cells and were recognized as foreign proteins. The interaction with lymphocytes leads to IgE production in genetically predisposed or atopic individuals. This IgE was specifically directed against the peanut protein and circulated briefly through the bloodstream before binding to IgE receptors on the tissue mast cells and blood basophils. These receptors bound the antibody at the $F_c$ end of the molecule, leaving the $F_{ab}$ (antigen-binding) region exposed and free to bind circulation antigen. By this time the peanut protein had been cleared by the reticuloendothelial system. The only evidence that the girl was sensitized to the peanut protein was the presence of the specific peanut IgE on her mast cells and the presence of a few memory B-cells capable of producing more specific peanut IgE if they encounter the protein again.

One year later the girl attended a birthday party and ate a cookie containing peanuts. Within minutes, she developed urticaria around her mouth, wheezing, and cough. She was gasping for air as paramedics were summoned and was cyanotic by the time they arrived. Fortunately, prompt treatment allowed her to recover. At the molecular level, her immune system made her a living time bomb, ready to detonate when she came in contact with the peanut antigen "trigger." Despite the 12-mo gap, the immune system never forgot its initial exposure to the peanut. On being exposed to peanuts the second time, the peanut antigen circulated through the blood stream and lymphatics. This time, the antigen flowed past the IgE peanut-specific antibodies already situated on the surface of the mast cells. These IgE molecules, like hands, grabbed the antigen as it passed by. When the number of peanut antigen molecules bound to the IgE on the mast cell surface was sufficient, some IgE antibodies crosslinked and caused a chain reaction. The mast cells released preformed chemicals that were quiescent in their intracellular granules. These chemicals cause bronchoconstriction, vasodilatation, and upper airway edema. Additionally, the triggering and degranulation of mast cell caused the *de novo* production of other substances that also contributed to the reaction. The effect of the re-exposure to the peanut antigen in this girl's case is called anaphylaxis and represents the most severe type of allergic reaction. Fortunately, such a reaction is rare and can often be prevented, or at least attenuated. We will now explore the pathophysiology of such a reaction in greater detail, starting with the effector cell in immediate hypersensitivity, the mast cell. We will also mention the basophil, a granulocyte that releases mediators similar to those of the mast cell.

## ASPECTS OF IgE PRODUCTION

The key intermediary in allergic conditions is IgE antibody. As discussed previously, it is the individual's propensity to produce IgE in response to an "allergic antigen" (also known as an allergen) that makes one atopic. The same allergen that stimulates B-cells to produce IgG or IgM in a nonallergic person may stimulate IgE antibody production in an atopic individual.

Why does the body respond to an allergen exposure by making IgE as opposed to other classes of antibodies? Antibody molecules consist of a variable region responsible for recognizing and binding the offending antigen and a constant region whose purpose is to dictate the fate of the antigen–antibody complex. For example, a person may make both IgA and IgG antibodies against a virus. Both are capable of binding to that virus, but the IgA is found mainly in secretions (as in the nasal mucosa), whereas the IgG predominates in the bloodstream. The mechanisms by which a particular antigen favors the production of one class of antibody over another are not firmly established; nevertheless, several factors that may favor IgE formation are worth discussing.

All antigens initially elicit the production of IgM antibodies against an injected or inhaled allergen. With repeated exposure, the antigen may stimulate an event known as class switching, whereby the constant portion of the antibody will "switch" to another class (i.e., IgG, IgA, or IgE). The new antibody will still have the same antigen-recognition region, but it will now be sitting on another constant region (e.g., IgG or IgA). IgE production by B-cells as a result of class switching is regulated by T-cells and macrophages, predominantly, and the cytokines they produce. Cytokines are small molecular-

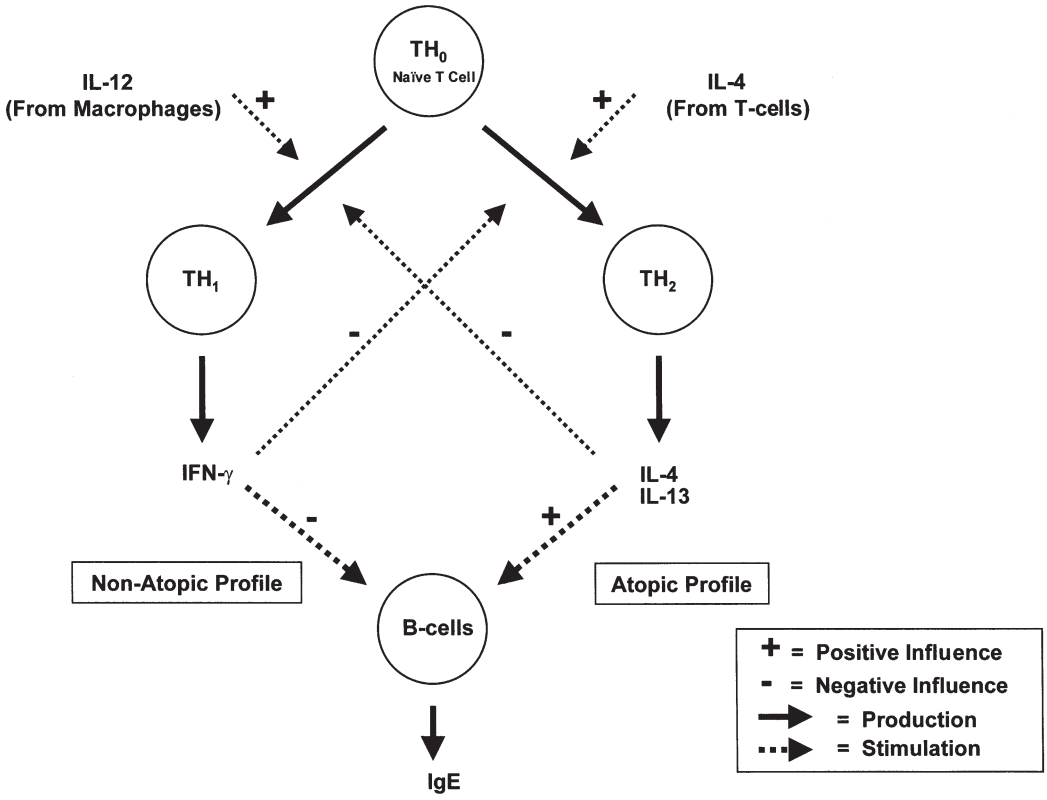


**Fig. 2.** The $TH_1$ and $TH_2$ paradigm. T-helper cells uncommitted to an atopic or nonatopic cytokine profile ($TH_0$) receive stimulation from cytokines IL-4 and IL-12 to polarize to a $TH_1$ or $TH_2$ phenotype. The $TH_1$ profile is consistent with a nonatopic phenotype, whereas the $TH_2$ profile is consistent with an atopic phenotype. $TH_1$ cells produce IFN-γ, which inhibits IgE production from B-cells and $TH_0$ differentiation into $TH_2$ cells. $TH_2$ cells, on the contrary, produce IL-4 and IL-13, both potent stimulators of IgE production from B-cells. IL-4 also feeds back to inhibit $TH_0$ differentiation into $TH_1$ cells; it can also further self-promote $Th_0$ differentiation into $TH_2$ cells to perpetuate the cycle of an atopic cytokine response.

weight molecules that affect cell function at the local level. Two primary cytokines that favor IgE class switching are interleukin (IL)-4 and IL-13. IL-4 and IL-13 are produced by a subset of $CD4^+$ T-cells, also known as T-helper 2 ($TH_2$) cells.

IL-4 is such an essential signal for IgE production that mice that have been genetically engineered to be devoid of IL-4 (IL-4 knockout mice) are unable to synthesize IgE. In contrast, the primary cytokine that inhibits IgE class switching is called interferon (IFN)-γ. IFN-γ is produced by a subset of T-cells that have a T-helper 1 ($TH_1$) cytokine profile. The cytokines produced by $TH_1$ and $TH_2$ cells reciprocally inhibit the other's development. These stimulatory and inhibitory interactions are outlined in Fig. 2. In atopic individuals the balance of $TH_1$ and $TH_2$ responses seems to favor the $TH_2$ response and IgE production. In nonatopic individuals, the balance between $TH_1$ and $TH_2$ favors a $TH_1$ dominant response.

The ability to produce polyclonal IgE antibody is present as early as 8–10 wk of gestation. Because IgE antibody cannot cross the placenta, any IgE present in cord blood has been produced entirely by the fetus. During the first year of life, antigen-specific IgE antibody is directed primarily against food antigens; by age 2–3 yr, aeroallergen sensitivity begins to become more prevalent.

The biochemical structure of an antigen appears to play a role in determining the isotype response. A polysaccharide antigen, from the surface of *Streptococcus*, for instance, will prompt B-cells to produce IgG but not IgE antibodies. In contrast, certain proteins from parasites can cause the B-lymphocytes (with help from the T-cells and IL-4) to cease production of IgG or IgM and to churn out vast quantities of IgE. However, exactly what it is about the structure of proteins that preferentially leads them to become allergens, thus stimulating IgE synthesis, remains unresolved.

## THE MAST CELL

A medical student, named Paul Ehrlich, first described the mast cell in 1877. He chose the name *Mastzellen* (well-fed cells) based on the cells' characteristic cytoplasmic granules (he incorrectly thought that the mast cells were phagocytes and that the granules were ingested debris). We now recognize the central role that mast cells play in the immediate hypersensitivity response.

As with all hematopoietic cells, the mast cells are formed by the action of soluble factors on a pluripotent stem cell (progenitor cell) in the bone marrow. The cells emerge from the bone marrow and migrate to the connective tissues, where they mature, acquiring both cytoplasmic granules and a coating of high-affinity IgE receptors (called FcεRI-α) on their cell surface. Despite gross morphological homogeneity, it is now apparent that mast cells are a heterogeneous cell population. Most pulmonary mast cells contain primarily one neutral protease, tryptase. Skin mast cells, on the other hand, contain large amounts of both tryptase and another protease, chymase (described below). Mast cells in humans are divided and named on the basis of this biochemical difference and are termed $MC_T$ (for mast cells containing tryptase) or $MC_{TC}$ (for mast cells containing chymase). The tissue distribution of these subtypes of mast cells is shown in Table 1. The relative numbers of $MC_T$ or $MC_{TC}$ may change locally with tissue inflammation, fibrosis, or the cytokine microenvironment. There are no accurate means of discerning from what tissue an isolated mast cell population is derived, because mixtures of both $MC_T$ and $MC_{TC}$ cells are found in all tissues.

## MEDIATORS OF THE ALLERGIC RESPONSE

The mediators released by mast cells and basophils can be grouped into two categories: (1) preformed substances contained within granules and (2) newly generated chemicals synthesized following cellular activation. These mediators comprise the effector function of the mast cell. Together they are able to increase vascular permeability, dilate vessels, cause bronchospasm, contract smooth muscle, and summon inflammatory cells, as summarized in Fig. 3. Few cells in the body produce compounds with such a large and varied spectrum of activity.

Histamine is a prominent preformed vasoactive amine contained within the mast cell granule. It is formed by the action of histidine decarboxylase on the amino acid histidine. Histamine is the only preformed mediator of the human mast cell with direct vasoactive

**Table 1**
**Relative Distribution of the Two Predominant Human Mast Cell Phenotypes in Immunologically Relevent Tissues and Cell Population**

| *Organ* | *% $MC_T$ Cells* | *%$MC_{TC}$ Cells* |
|---|---|---|
| Skin | 5 | 95 |
| Intestinal mucosa | 80 | 20 |
| Intestinal submucosa | 30 | 70 |
| Alveolar wall | 95 | 5 |
| Bronchial subepithelium | 40 | 60 |
| Dispersed lung mast cells | 90 | 10 |
| Tonsils | 40 | 60 |
| Nasal mucosa | 65 | 35 |

Adapted from Holgate and Church, Allergy. London: Gower Medical Publishing, 1993.

and smooth muscle spasmogenic effects. It can increase mucus production from airway epithelial cells and contract airway smooth muscle, thus contributing to both mucous plugging and bronchospasm. Histamine also acts to increase vascular permeability as well as to promote vasodilatation, thus causing extravasation of fluid into the tissues. In extreme cases, such intravascular fluid shifts can lead to hypotension and shock.

Neutral proteases are compounds that catalyze the cleavage of certain peptide bonds in proteins and facilitate protein degradation. Their activity is optimum at a neutral pH, hence the name. The two major proteases of human mast cells and basophils are tryptase and chymase. Basophils have negligible but detectable levels of proteases. Maintaining the interior of the granules at an acidic pH, thus inhibiting protease activity, controls the potentially dangerous proteolytic activity of these compounds.

Other accessory molecules have prominent roles in the allergic response. Proteoglycans, including heparin and chondroitin sulfate A, are important in mast cell and basophil biochemistry, respectively. Their exact function is unclear, although many believe that proteoglycans stabilize the enzymes to which they are bound until degranulation occurs.

Two predominant classes of mediators are synthesized *de novo* following activation of the mast cells and basophils: (1) lipid derivatives and (2) cytokines. The lipid derivatives include leukotrienes and prostaglandins. They represent byproducts of the metabolism of arachidonic acid formed upon activation of the mast cell. The mast cell is able to catabolize essential membrane components and convert them into biologically active mediators through a complex cascade of membrane-bound and soluble enzymes. The overall pathway is seen in Fig. 4. The leukotrienes, produced by the action of the 5-lipoxygenase system on arachidonic acid, demonstrate many different activities, of which the most prominent is immediate bronchoconstriction. They also can cause vasoconstriction in both the pulmonary and vascular beds. The primary leukotrienes made by human mast cells are $B_4$, $C_4$, $D_4$, and $E_4$. The leukotrienes, especially $D_4$, are greater than 10 times more potent than histamine.

Arachidonic acid is also broken down by the action of the cyclooxygenase pathway, resulting in the formation of prostaglandins, prostacyclins, and thromboxanes. These compounds generally function as local hormones and produce many of the same symptoms as the leukotrienes, such as bronchoconstriction, cough, and vasodilatation. The

**MEDIATORS OF ALLERGIC REACTIONS**

Molecules released from activated mast cells and basophils account for many allergic symptoms. This list includes a sampling of those chemicals and some of their effects, which can be redundant.

| | CHEMICAL | ACTIVITY | SYMPTOMS |
|---|---|---|---|
| MEDIATORS FROM GRANULES | Histamine | Constricts bronchial airways | Wheezing; difficulty breathing |
| | | Dilates blood vessels | Local redness at sites of allergen delivery· widespread dilation can contribute to potentially lethal hypotension (shock) |
| | | Increases permeability of small blood vessels | Swelling of local tissue; if widespread, increased permeability can contribute to shock |
| | | Stimulates nerve endings | Itching and pain in skin |
| | | Stimulates secretion of mucus in airways | Congestion of airways |
| | Platelet-activating factor | Constricts bronchial airways | *Same as for histamine* |
| | | Dilates blood vessels | *Same as for histamine* |
| LIPID MEDIATORS | Leukotrienes | Constricts bronchial airways | *Same as for histamine* |
| | | Increase permeability of small blood vessels | *Same as for histamine* |
| | Prostaglandin D | Constricts bronchial airways | *Same as for histamine* |

**Fig. 3.** Mast cell mediators and their effects. (Adapted from Lichtenstein L. Allergy and the immune system. Sci Am 1993;369:117–124, with permission.)

main prostaglandin produced by human mast cells is $PGD_2$, a compound at least 30 times as potent as histamine in causing bronchoconstriction. Thromboxane $A_2$ and prostacyclin ($PGI_2$) produce bronchoconstriction and bronchodilatation, respectively. Together they function as a mechanism to maintain bronchial and vascular tone.

Platelet-activating factor (PAF) is a phospholipid. PAF is produced by mast cells (as well as macrophages, neutrophils, and eosinophils) and functions to activate platelets and neutrophils and vasoconstrict smooth muscle. Perhaps most importantly, PAF stimulates chemoattraction of eosinophils to endothelial surfaces and eosinophil release of other cell mediators. PAF is rapidly inactivated in vivo, suggesting that it serves as a trigger of inflammatory events rather than a major mediator itself.

The identification of cytokines synthesized by mast cells and basophils is currently an area of intense investigation. Cytokines represent the primary mechanism by which cells

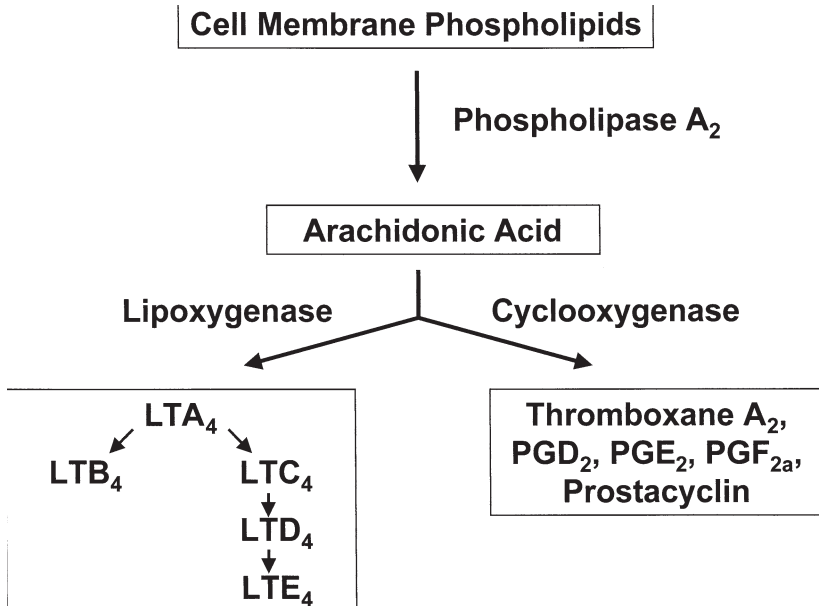


**Fig. 4.** Arachidonic acid metabolic pathways. Arachidonic acid, released as a result of phospholipase on the cellular membrane, is broken down by two distinct biochemical pathways: The lipoxygenase pathway results in formation of the leukotrienes (LT), whereas the cyclooxygenase pathway generates prostacyclin, thromboxane, and the prostaglandins (PG).

can influence the activity and development of unrelated cells and related cells in an exocrine and autocrine fashion. Human mast cells produce IL-4 and IL-5 as well as tumor necrosis factor (TNF)-α. The IL-4 stimulates mast cell differentiation and promotes immunoglobulin class switching to the IgE isotype. IL-5 is the most influential cytokine involved in eosinophil production and survival in humans. TNF-α increases vascular permeability and leukocyte migration.

Basophils have long been incorrectly viewed as the bloodborne equivalent of mast cells with analogous granules and functions. However, these cells represent a hematopoietic lineage distinct from mast cells, can also infiltrate tissues, and contain neither tryptase nor chymase. In addition, basophils seem to have a different role in the allergic reaction scenario. They tend to release abundant amounts of histamine but little, if any, $PGD_2$. This finding has been cited as evidence of their contribution to late-phase allergic inflammatory events in the nose, skin, and lung. The presence of increased histamine, but undetectable $PGD_2$, during late responses implies that basophils are recruited to sites of allergic inflammation (*see* Early- and Late-Phase Responses).

## ACTIVATION OF THE MAST CELL

The mechanism by which the external signal of IgE crosslinking is translated into cellular activation, granule release, and *de novo* synthesis of new molecules is a fascinating tale of cellular adaptation and biochemistry. An overview of the reactions is illustrated in Fig. 5.

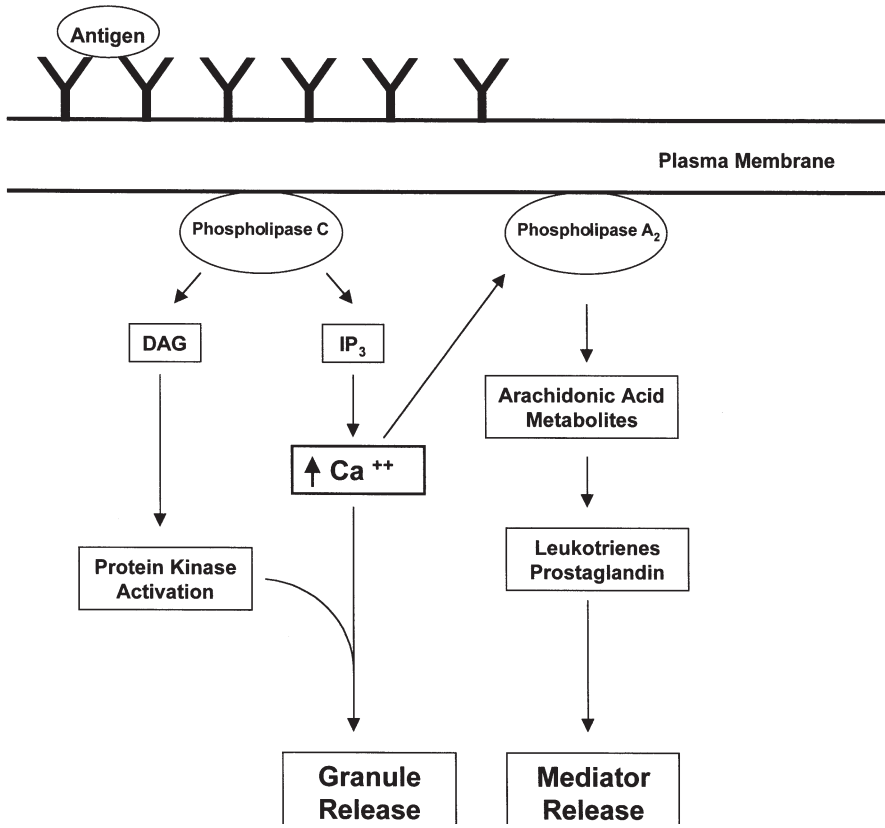


**Fig. 5.** Mast cell activation: biochemical reactions. Following IgE crosslinking by antigen, a series of protein kinase reactions culminate in the activation of phospholipase C, releasing diacylglycerol (DAG) and inositol triphosphate ($IP_3$) from the plasma membrane. The $IP_3$ releases calcium stores from the endoplasmic reticulum, which, along with DAG-stimulated kinases, leads to granule release. The intracellular calcium also activates phospholipase $A_2$, which generates arachidonic acid, a compound metabolized to form leukotrienes and prostaglandins.

The process begins with the crosslinking of two or more IgE molecules on the mast cell surface. This requires a multivalent antigen (i.e., more than one IgE-binding site on the same molecule). Monovalent antigens will not trigger mast cell activation. Once the antigen is attached to the mast cell by more than one IgE molecule, a series of cytoplasmic signals occur causing activation. This process is called signal transduction and is a method of cellular communication with the external environment. In this case, the signal enters the cell via a conformational change in the FcεRI-α receptor.

Once the antigen is bound to the mast cell via the IgE molecules, the cell begins a series of biochemical events that culminates in the release of its granules and the production of lipid mediators (arachidonic acid metabolites). The production of the lipid mediators requires effective intracellular scavenging by the mast cell. The principle is to cannibalize lipids from the membrane and transform them into potent mediators. $PLA_2$, activated by the calcium released from the endoplasmic reticulum, starts degrading phosphatidyl choline. In turn, arachidonic acid is formed and metabolized via the two pathways men-

tioned earlier: the lipoxygenase pathway (which produces leukotrienes) and the cyclooxygenase pathway (which produces prostaglandins). As stated previously, the main prostaglandin produced by mast cells is $PGD_2$. Leukotrienes $B_4$ and $C_4$ are the primary leukotrienes made. Leukotriene $C_4$ is subsequently converted to active compounds $LTD_4$ and $LTE_4$. The activities of these lipid mediators are described elsewhere.

In summary, the mast cell needs to accomplish two functions following activation: to release its granules with their associated biologically active compounds and to synthesize additional mediators of the allergic reaction using its cell membrane constituents as precursors. These activities utilize a great deal of cellular energy, most of which is obtained from the high-energy phosphate bonds generated by the action of protein kinases. The initiation of these cascades depends on interaction of the mast cell with antigen. The prerequisite crosslinking of the IgE molecules probably evolved as a safety mechanism to prevent premature activation of the cell. A sufficient quantity of specific IgE must be bound to the mast cell to achieve a crosslink, which is possible only if sensitization had occurred previously.

Allergic (IgE-mediated) activation of the mast cell was summarized earlier, but there is an alternate, IgE-independent mechanism of mast cell degranulation that should be mentioned. This degranulation is the result of mast cell membrane perturbation at a molecular level, often requiring calcium influx. This nonimmunological degranulation may be triggered by opioids, anaphylatoxins (complement components), and radiological contrast dyes. In fact, the majority of patients who report a history of "allergic reactions" to contrast dyes have experienced non-IgE-mediated reactions.

## EFFECTS OF MAST CELL MEDIATORS ON TARGET ORGANS

The examination of the mechanisms contributing to the release of mast cell mediators is only half the story of allergic pathophysiology. The spectrum of symptoms that prompts a visit to the allergist begins only after these substances are released from mast cells and interact with resident and infiltrating cells in various target organs. In the case involving the 8-mo-old girl sensitized to peanut, these mediators combined to cause anaphylaxis. Histamine was liberated from the mast cell granules and was quickly dispersed through the bloodstream. Histamine receptors are located on many target organs, including the skin, the nasal mucosa, the smooth muscle of the lungs and gastrointestinal tract, and vascular epithelial cells. Once bound to its receptor, histamine causes such diverse effects as vasodilatation of small vessels with subsequent exudation of fluid into surrounding tissue; smooth muscle contraction, an effect of particular import when one is considering the muscles surrounding the bronchial airways; and increased glandular mucus secretion, an annoyance in the nasal mucosa but dangerous in the small bronchioles. Extremely high doses of histamine cause these effects to occur on a systemic level, possibly leading to hypotensive shock in the case of massive vasodilatation.

The lipid mediators cause symptoms that are very similar to histamine; however, their effects are more persistent. Histamine is rapidly degraded in the serum with a half-life of 1 min, but the lipid mediators are slowly metabolized. As you recall, both leukotrienes and prostaglandins are synthesized only after an allergic reaction has begun, thus accounting for the delay in onset of action. Historically, leukotrienes were collectively termed the slow-reacting substance of anaphylaxis because of this delay in activity. Once released in the serum, the prostaglandins bind to specific receptors and lead to bronchial smooth

muscle contraction in the lungs, vasodilatation in the skin, and nasal blockage. Leukotrienes are also highly potent bronchoconstrictors but utilize distinct receptors on the smooth muscle cells. They also increase permeability at postcapillary venules, leading to localized tissue edema.

## ALLERGIC INFLAMMATION: A $TH_2$-MEDIATED RESPONSE

Just as IgE production and mast cell activation are key components to the initial allergic response, several other cells play a role in propagating this allergic inflammatory response. After the immediate release of mast cell mediators following allergen exposure, leukocytes influx into affected tissues. This occurs approx 2–8 hr after allergen exposure and has been termed the late-phase reaction (LPR) or the late allergic response (LAR). It is explained in detail later. The primary cell types recruited to sites of LPR include basophils, eosinophils, neutrophils, lymphocytes, and macrophages. The main attractants for these cells are cytokines secreted by mast cells, T-cells, and epithelial cells. Cells present during the initial allergic response, such as mast cells, as well as cells that migrate into tissues following an increase in vascular permeability, generate cytokines. Many cytokines contribute to this influx; however, IL-4, IL-5, TNF-$\alpha$, and chemotactic cytokines termed chemokines play major roles. TNF-$\alpha$ and IL-4 attract basophils. IL-5 is a potent eosinophil activator, and C-C chemokines such as RANTES (regulated on activation, normal T-cell expressed and secreted) promote eosinophil migration into tissues. These responses collectively parallel the $TH_2$ cytokine profile shown in Fig. 2. In cases of perennial allergic rhinitis, perennial asthma, and acute atopic dermatitis, T-cells isolated from the affected tissues (nose, lung, or skin, respectively) exhibit a predominantly $TH_2$ cytokine profile. However, it is important to remember that any T-cell population will express heterogeneity and not uniformly possess one cytokine profile.

## EARLY- AND LATE-PHASE RESPONSES

An important aspect of allergic disease, with scientific and clinical implications, is the concept of the late-phase IgE-mediated reaction. The mast cell activation pathway (described above) occurs within minutes of allergen exposure. All mechanisms and components of the system are designed for almost instantaneous responses. Once the initial surge of mediator release is completed, there is regeneration of the mast cell granules, although this process may take days to weeks to be completed. If one were to speculate that an allergic reaction represents an exaggerated host response to a foreign invader (or allergen), then it might make sense to have a backup system in place in case the immediate response is not completely successful. In the teleological sense, that is precisely what the late-phase response does.

The late-phase response is a delayed-in-time inflammatory response that occurs following mast cell activation. It may function to amplify an initial signal resulting from the first wave of allergen "attack." In response to a barrage of chemotactic and differentiative cytokines, multiple cell lineages (e.g., eosinophils, neutrophils) are summoned to the site of this breach of the immune system. Together, these summoned cells constitute the inflammatory or late allergic response (LAR). The LAR lacks the speed of the immediate response, but it more than makes up for this in terms of magnitude. The LAR typically occurs 2–8 h after initial allergen exposure. Subtle differences in the

nature and effect of the mediators involved in the LAR have been observed in each anatomical location in which it has been described. We will consider two such environments: the skin and the nose.

The cutaneous early reactions are well described: a characteristic wheal-and-flare reaction is seen with a positive skin test in an atopic individual. It resembles a mosquito bite in that it consists of a pale, circumscribed central area of edema surrounded by an erythematous diffuse border. This typical early-phase reaction will peak in 15 min and resolve in 30–60 min. In some cases, however, the early-phase response will persist for hours and progress into a late-phase response that peaks 6–8 h following allergen exposure and lasts up to 24 h. The cellular infiltrate observed 6–12 h after a cutaneous allergen challenge consists of a mixed population of neutrophils, eosinophils, and lymphocytes. Mediators produced in the cutaneous LAR reflect the nature of the cells summoned to the area and include various interleukins (IL-1, IL-4, IL-6).

The nasal late-phase response is characterized by a cellular infiltrate of eosinophils, mononuclear cells, and neutrophils and is often accompanied by fibrin deposition. The mediators produced in the nasal LAR are identical to those present in the early response with one exception: $PGD_2$ is absent. As mentioned earlier, the presence of histamine without $PGD_2$ suggests that basophils may play a prominent role in the nasal LAR. They characteristically produce negligible amounts of $PGD_2$ while maintaining a high histamine content. Nasal congestion is the predominant symptom associated with the nasal LAR (rhinorrhea and sneezing are generally associated with the early response).

## CONCLUSION

Several generalities apply to all tissues in which an allergic reaction can occur. The immediate result of an interaction between a sensitized mast cell and a specific allergen, also known as the early-phase response, results in the release of preformed mediators. Both local and distal target organ effects are exhibited as a result of the early-phase response. Although the cellular effects of these mediators are similar on each tissue, the clinical symptoms produced may differ. For example, increases in vascular permeability may present as angioedema in the skin or as congestion in the nose. The presence of a late-phase response is also seen in various issues and represents the inflammatory response. Because the goal of the late-phase response is to attract inflammatory cells, the cytokine profile differs slightly from the immediate response.

How does this relate to the 8-mo-old girl with the allergy to peanuts? Her primary care physician wisely sent her to a specialist. The girl was skin-tested to peanuts and had a positive testing indicating sensitization. In combination with her history, this confirmed the suspected diagnosis of peanut allergy. Her family was instructed on avoidance measures, and Epipen Jr was prescribed and instructions given on its use. She diligently avoids peanuts without other sweeping food restrictions. As we will see in later chapters, there are many immunological and pharmacological interventions that may be useful in preventing both immediate and late-phase allergic reactions. An appreciation of the pathophysiology of the allergic reaction is essential to the proper use of these treatments.

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# 2 Approach to the Allergic Patient

*Bruce L. Wolf, MD*

***CONTENTS***



**SUMMARY**

Allergic disease is protean in its manifestations, affecting single or multiple organ systems. It may also mimic other conditions. The clinician must be prepared to take an in-depth history, make a comprehensive physical examamination, and seek appropriate objective measures in order to adequately consider the differential diagnosis and arrive at a proper diagnosis.

No less important is the conference with the patient once the diagnosis has been established. At that meeting, findings and impressions should be summarized in language understandable to the patient. Terminology should be carefully chosen and prognosis phrased optimistically whenever possible. Likewise, medication regimen (including inhaler technique) and rationale, environmental and lifestyle modifications, and/or follow-up may be discussed.

**Key Words:** Allergic; asthma; atopic; diagnostic; examination; history; rhinitis; skin testing.

## INTRODUCTION

Although it often is remarked that everyone is allergic to something, in truth, only about 25–30% of the population is allergic to anything. This frequency is enough to make the allergic patient a common visitor in every medical setting. In addition, many disorders mimic allergy symptoms. Therefore, the differential diagnoses of various disease states must include allergy as a possibility.

Allergy can affect virtually any organ system. Common types of presentation include conjunctivitis (eyes), rhinitis (nose), urticaria and angioedema or atopic (allergic) dermatitis (skin), asthma (lungs), and anaphylaxis (multiorgan). Evaluation of suspected allergy must include a detailed medical history, comprehensive physical examination, and appropriate diagnostic tests.

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## HISTORY

The most important component of the evaluation of a possible allergic problem is the patient's history. It is from the history that salient physical examination and tests follow. An allergy history is made up of a chief complaint, determination of seasonality or diurnal variation of symptoms, identification of triggers, occupational exposure, response to medication, family history, and other pertinent medical history. It may not be obvious to the patient what historical factors are important; thus, it is recommended that a questionnaire that screens for contributory factors be used (Fig. 1).

The history is the most important element in the evaluation of allergy. Key features of the history are:

- Worsening of symptoms on exposure to aeroallergens
- Seasonal variation in symptoms related to pollination of trees, grasses, and weeds
- A family history of atopic disease
- An environmental history assessing exposure at workplace and home
- The presence of associated allergic conditions

An allergy history seeks to define the patient's chief complaint(s) and focuses on the details concerning those complaints. If the chief complaint is narrow in scope, for instance, "I sneeze all the time," then the clinician may be tempted to direct the majority of the questions toward a given organ system. This approach should be avoided and the patient given ample opportunity to expound on the extent of the complaint.

There is a lexicon common to patients with allergy complaints. Many state that they have "sinus" or "hay fever." They describe a wide array of symptoms ranging from itchy nose, eyes, or palate to runny nose or postnasal drainage to nasal congestion. Sinus pressure and headaches are frequently cited as symptoms. "Popping or fullness of the ears," implying eustachian tube dysfunction, is an often heard complaint. Asthma symptoms may be overt and present as wheezing, but descriptions my be more subtle, such as cough, tightness in the chest, or inability to get a good breath or let all the air out of the lungs.

The history taker should be attuned to the patient's perspective as a potential allergy sufferer. Where and when do the symptome occur? Do they interfere with daily activities, school or work, or exercise? Is there seasonal variation to the symptoms, or are they of a perennial nature? Are the symptoms worse at a particular time of day? During sleep?

At first, questions searching for triggers should be open-ended. For instance, "What seems to trigger your symptoms?" rather than "Does this or that bother you?" If patients are reticent or rambling in their responses, direct questions may be appropriate. In most cases, the patient will stipulate if symptoms are worse inside the house or outdoors.

Increasingly, indoor allergens are recognized as important triggers and sensitizers of the allergic patient. Type of home and the presence of a basement may be important. For example, a wet environment tends to produce growth of molds and dust mites. House dust mite is likely the most common allergen in our society. It is found in greatest abundance in bedding, pillows, carpet, and upholstered furniture. Therefore, the kind of bedding and

type of flooring may be relevant to understanding a given patient. Mold sensitivity has been popularized in the press, but there is little scientific data to support the hysteria of mold causation. Cockroach is another allergen increasingly implicated with public housing, inner-city asthma, and allergic respiratory disorders. Particular attention should be given to any exposure to pets. Do the pets sleep in the bedroom or on the bed?

It may be difficult to distinguish between an irritant and an allergen. Irritants are often misconstrued as allergens because they can cause the same cascade of symptoms. Examples of irritants include cigarette smoke, perfume, cold air, strong odors, and cleaning solvents.

Outdoors, the allergic patient faces pollution (irritant) and pollens (allergens). Trees, grasses, and weeds can wreak havoc on an allergic sufferer. Likewise, different pollens may predominate in a particular region. For example, Bermuda grass may be prevalent in Florida but not in Montana. A given allergen can have its particular season, as in the case of pollen, or be perennial in its presence like the dust mite. One pollen season can also overlap another; that is, grass pollination can coincide with pollination of ragweed. This is often important because one allergen can prime a person to have heightened sensitivity to another. Growing seasons may vary according to residential area. In summary, the history taker is always confronted with the puzzle of microcosm vs macrocosm. Although television pollen counts may report elm pollen, those same reports do not anticipate which trees predominate outside a bedroom window or in a given neighborhood or in the courtyard where the patient takes a work break.

Occupational exposure must always be considered. If indicated, material safety data information sheets may be requested to better overview what the patient may be breathing in their work environment. Day-care facilities can be an insidious source of recurrent viral and bacterial exposure for children.

Family history of an allergic diathesis should be sought. The genetics of allergy are not entirely understood, but a parent with atopy roughly doubles a patient's chance of being atopic. Risk of atopy is increased from 25% in the general population to about 75% when both parents are atopic. In one study, 90% of allergic asthmatic children had one or both parents who were atopic.

In asthma, objective measures such as spirometry and peak flow measurements paint only part of the picture. History should help to delineate the asthma as mild, moderate, or severe. Questions to determine the extent of asthma control include type and amount of inflammatory medication used (type of delivery system and quality of inhaler technique), frequency of respiratory symptoms and need for β-agonists, interference with daily activities or sleep, and diurnal peak flow variability if known. In some practices, a quality-of-life survey is now employed to address subjective parameters that contribute to asthma severity.

Degree of severity will ultimately dictate choice and intensity of treatment. Emergency room visits or hospitalization for asthma in the past year or use of oral steroids in the last 6 mo identify the more severe asthmatic. Psychosocial problems, lower socioeconomic status, and history of previous intubation are potential risk factors for increased asthma morbidity and mortality.

Confounders of asthma must always be kept in mind. For instance, a history of recurrent use of antibiotics, frequent colds, or cough in a supine position may point to chronic sinusitis. Gastroesophageal reflux can present solely as cough and sometimes mimic or exacerbate asthma. Irritation of the skin presenting as pruritus or rash is frequently attributable to soaps that are too drying.

**Primary reason for coming to Allergy & Asthma Specialists:**

_____

**Check your main symptoms** - those that prompted your visit here:

| **Head or Nose** | **Chest** | **Skin** | **Insect Stings** |
|---|---|---|---|
| ☐ Sneezing | ☐ Cough | ☐ Eczema | ☐ Hives |
| ☐ Runny Nose | ☐ Wheezing | ☐ Itching | ☐ Swelling |
| ☐ Postnasal drainage | ☐ Shortness of breath | ☐ Swelling | ☐ Shortness of breath |
| ☐ Nose Blocking | ☐ Hoarseness | ☐ Hives | ☐ Itching |
| ☐ Sinus Infections | ☐ Chest Infections | | ☐ Dizziness |
| ☐ Sore Throat | ☐ Voice Loss | | ☐ Fainting |
| ☐ Ear Blocking | | | |
| ☐ Headache | | | |
| ☐ Snoring | | | |
| ☐ Nosebleeds | | | |
| ☐ Eye Symptoms | | | |

How many years have you suffered from the chief complaints of:

Head or Nose symptoms _____ Chest symptoms _____

Skin symptoms _____ Insect Sting reactions _____

Please indicate pattern of symptoms:

| | **Head/Nose** | **Chest** |
|---|---|---|
| Year round, no seasonal change | _____ | _____ |
| Year round, worse seasonally | _____ | _____ |
| Seasonally only | _____ | _____ |

If seasonal, list months: _____

Are your symptoms worse at night? Yes ☐ No ☐

**Do you note increased symptoms from any of the following?**

| **Allergens** | **Irritants** | **Ingestants** | **Weather** |
|---|---|---|---|
| ☐ Mown grass | ☐ Perfumes | ☐ Alcoholic beverages | ☐ Windy days |
| ☐ Dead grass | ☐ Soap | ☐ Drugs | ☐ Cold fronts |
| ☐ Dead leaves | ☐ Detergent | ☐ Foods | ☐ Temperature change |
| ☐ Hay | ☐ Cleaning agents | ☐ Other (list): | ☐ Damp weather |
| ☐ House dust | ☐ Smoke | _____ | |
| ☐ Cats | ☐ Paint | _____ | |
| ☐ Dogs | ☐ Hair spray | _____ | |

Please check the ones that best describe your home:

☐ House (Age:_____) ☐ Apartment ☐ City ☐ Country

Do you have a basement? ☐ Yes ☐ No

Type of heating system: ☐ Central ☐ Floor ☐ Electric ☐ Other:_____

Type of mattress: ☐ Conventional ☐ Waterbed

Type of pillow: ☐ Synthetic ☐ Down

Do you have stuffed animals? ☐ Yes ☐ No

Do you have carpet in your home? ☐ Yes Type: _____ ☐ No

Are your symptoms worse anywhere in your home? ☐ Yes Location: _____ ☐ No

Do you have pets at home? ☐ Yes What Kind: _____ ☐ No

Are your pets kept: ☐ Inside ☐ Outside

**Fig. 1.** Screening for contributory factors.

Are your symptoms worse at your workplace / school? ☐ Yes ☐ No
Have your symptoms been so severe as to cause you to miss work or school? ☐ Yes ☐ No
If so, how many days? _____
Has travel affected your symptoms? ☐ Yes ☐ No
Do you have hobbies that expose you to allergens or irritants? ☐ Yes ☐ No
If yes, explain briefly: _____

List medicines you use for the relief of allergy symptoms (including nose drops or sprays):

_____
_____

List other drugs you take for any reason (include all over-the-counter drugs, creams, suppositories, eye drops, etc.):

_____
_____

Can you take aspirin? ☐ Yes ☐ No
Are you allergic to any medications? ☐ Yes ☐ No
If yes, please list: _____
What type of reaction occurs? _____

Have you ever taken hypo-sensitization shots (allergy shots) before? ☐ Yes ☐ No

Have you ever had a chest x-ray? ☐ Yes ☐ No If yes, when? _____ Where? _____
Have you ever had a sinus x-ray? ☐ Yes ☐ No If yes, when? _____ Where? _____
Do you smoke? ☐ Yes ☐ No
If yes, how many packs per day? _____ How long? _____
Have you ever smoked? ☐ Yes ☐ No
If yes, how many packs per day? _____ How long? _____
Does anyone you live with smoke? ☐ Yes ☐ No
If yes, who? _____
Are you exposed to smoke at work or school? ☐ Yes ☐ No

Is there a history of any of the following in your family?
☐ Asthma ☐ Hay fever ☐ Nasal polyps ☐ Eczema ☐ Hives
If so, which family member? _____

Have you ever been treated in an emergency room? ☐ Yes ☐ No
If yes, how many times? _____
For what were you treated? _____
List all hospitalizations in order of most recent:

| Cause of Hospitalization | Age |
|---|---|
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |
| _____ | _____ |

Circle any of the following that you might have had:
Stomach ulcer Diabetes Glaucoma High Blood Pressure
Circle any of the problems that you might have had with the following:
Blood Bones Heart Nervous system Urinary tract
List any medical problems you have not noted above: _____

**Fig. 1.** *(continued)*

A good drug history is necessary because medications often contribute to the allergic presentation. There are many examples. Frequent use of decongestant nasal spray can lead to rebound nasal congestion, also called rhinitis medicamentosa. Over-the-counter preparations (such as aspirin or nonsteroidal anti-inflammatory compounds, vitamins, and alternative remedies and herbal supplements), often not considered medication by the patient, may be causal factors in urticaria. Likewise, angiotensin-converting enzyme inhibitors and oral or ocular β-blockers may lead to cough or worsening of asthma.

The physical examination may be entirely normal at the time of the examination, because allergy symptoms and signs are often evanescent. The examination should emphasize the organs involved with allergy symptoms.

## PHYSICAL EXAMINATION

An allergic patient's history may direct the clinician's examination to a particular area or organ system. A specific allergic symptom, however, should not divert the examiner's attention from the patient as a whole. Each patient should be approached in a systematic way. Often physical examination may be normal; lack of findings does not rule out allergy.

Vital signs are a starting point in any examination. Pulse rate and pulsus paradoxicus greater than 10 mmHg are two of the most sensitive indicators of severe airway obstruction. Respiratory rate is important as well, but hyperventilation is more a reflection of minute ventilation (respiratory rate × tidal volume) than respiratory rate alone. Fever (>100°F) is an infrequent manifestation of allergy and points the differential elsewhere.

With the worldwide increase in the use of inhaled corticosteroids for the treatment of allergic respiratory disease, growth in children has been more closely scrutinized. Height and weight should be measured in children on a periodic, at least annual, basis. Although growth in children may often occur in spurts, change in growth velocity or decremental change in height or weight percentile should alert the physician to consider reasons for change in growth with the knowledge that growth in atopic and asthmatic children is generally delayed and usually not strictly linear.

Clues to allergic propensity are often seen in the patient's face. Discoloration of the infra-orbital skin or "allergic shiners" may imply nasal congestion and subsequent lymph stasis. Extension of the mid-face or adenoid facies in children with adenoid hypertrophy, an infra-orbital crease or Dennie's line, and a transverse crease along the lower half of the nose are frequent but not absolute indicators of underlying allergy.

The eye examination is concerned principally with the state of the tarsal (lower lids) or palpebral (upper lids) and bulbar conjunctivae. Degree of injection is noteworthy. In vernal conjunctivitis and giant papillary conjunctivitis, the superior palpebral conjunctivae show papillary hypertrophy or cobblestoning and may be accompanied by a stringy, fibrinous secretion. Horner-Trantas dots, small white spots at the limbus, are sometimes seen in association with vernal conjunctivitis. Cataracts are found with increased incidence in atopic individuals; pingueculae are not.

Tympanic membranes should be visualized. Tympanosclerosis implies previous recurrent otitis and/or a history of myringotomy. If the light reflex is not well appreciated or